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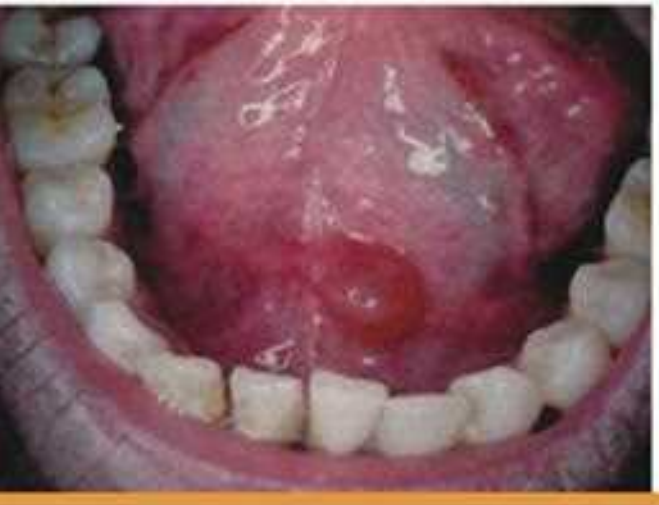
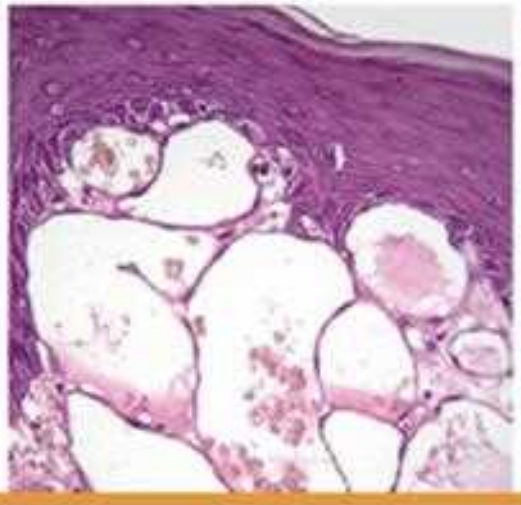
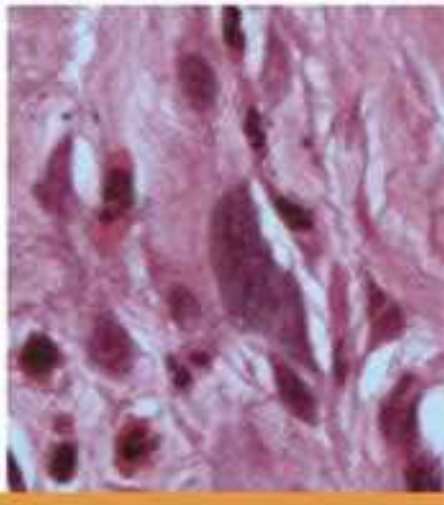
Shafer's Textbook of ORAL PATHOLOGY

Editors | R Rajendran
B Sivapathasundharam

Shafer's Textbook of ORAL PATHOLOGY

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Shafer's Textbook of ORAL PATHOLOGY

Seventh Edition

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Shafer's Textbook of Oral Pathology, 7/e
Rajendran and Sivapathasundharam

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Fifth Edition 2006 © Elsevier
Sixth Edition 2009 © Elsevier
Seventh Edition 2012 © Elsevier

This adaptation of *Textbook of Oral Pathology, 4/e* by William G. Shafer, Maynard K. Hine and Barnet M. Levy is published by an arrangement with Elsevier Inc.

Original ISBN: 978-07-216-8128-3
Indian Adaptation ISBN: 978-81-312-3097-8

Published by Elsevier, a division of Reed Elsevier India Private Limited
Registered Office: 305, Rohit House, 3 Tolstoy Marg, New Delhi-110 001
Corporate Office: 14th Floor, Building No. 10B, DLF Cyber City, Phase II, Gurgaon-122 002, Haryana, India

Publishing Manager: Ritu Sharma
Commissioning Editor: Nimisha Goswami
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Manager-Publishing Operations: Sunil Kumar
Production Manager: NC Pant
Cover Designer: Raman Kumar

Typeset by Chitra Computers, New Delhi

Printed and bound at Thomson Press (India) Ltd.

Dedicated
to

Prof Mansour Faris Hussein, PhD, FRCPath
Department of Pathology
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King Saud University, Riyadh, Saudi Arabia
For being a source of inspiration to me during this arduous journey

R Rajendran

my wife Dr S Rohini

B Sivapathasundharam

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Foreword

It is a distinct honor and privilege to have been asked to write the foreword for this edition of Shafer's Textbook of Oral Pathology. Dr Shafer, through the text that he co-authored with Drs Maynard Hine and Barnet Levy, made a tremendous impact on the practice of dentistry from the first edition, published in 1958, to the last edition, published in 1983. It is likely that no other text has ever had such a widespread influence on the perception of a specialty of dentistry, essentially establishing that the clinical and histopathologic diagnosis of oral disease belonged to the practice of dentistry, and the practice of oral and maxillofacial pathology specifically.

I was fortunate to have been one of more than 60 individuals who were trained under 'the Chief', as he was widely known by the people who passed through his department. Understand that he was a stern taskmaster, and he was serious about the practice of oral pathology. When a resident made a diagnosis, Dr Shafer expected that resident to know everything about that disease, and we spent hours in the library (this was in the days before computers!) tracking down who first reported that specific disease, in what year, and in what journal, as well as the most recent references related to the disease. He never allowed any of his residents to use his text as a reference, either. Perhaps he imparted the most significant concept, consciously or unconsciously, to us: knowledge and understanding of disease is an ever-changing, evolving process, and the practitioner must continually keep up with the dental and medical literature in order to remain current and provide the most accurate, up-to-date patient care.

This textbook, then, provides the dental clinician with some of the most current viewpoints related to the vast spectrum of disease that is encountered in the oral and maxillofacial region. The editors are to be commended on continuing Dr Shafer's legacy to the dental and oral pathology communities. By updating and amplifying the textbook, the authors will ensure that this knowledge will be handed down to future generations of practitioners. Future editions will include the inevitable advances in our understanding of disease processes, and hopefully will provide the stimulus for new investigators wishing to advance the science of oral and maxillofacial pathology. Undoubtedly, this textbook will maintain the tradition of excellence in oral pathology education that was established by Dr Shafer and will serve as a valuable resource for students, instructors and clinicians alike.

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Preface to the Seventh Edition

The periodic and timely revisions of *Shafer's Textbook of Oral Pathology* have brought out a treatise, well conceived and written with the aim of updating the student all necessary nuances of the specialty. The scope of the present edition is an extension of this goal aimed at understanding the disease processes at a more fundamental level, the impetus being those in the maxillofacial region. While the subject appears more of loco-regional nature, as the text unfolds, its wider ramifications become more apparent and the disease entities described here appear wider in scope and nature. As in the past, this edition has also undergone an extensive revision and new topics have been included. A well thought out decision of incorporating 'cutting edge' technologies of relevance such as molecular markers and disease profiling, continues to be incorporated in the text with the aim of updating the subject and making it more contemporary. Scattered throughout the text one finds highlighted 'boxes' which stand out, yet merge imperceptibly with the rest, denoting advanced information perhaps beyond the ambit of the undergraduate curriculum. In this way, the text has been user friendly, though discriminatory of the scope and choice of its contents. We believe this approach is sensible and will be well taken by the readership. This textbook represents a treasury of information based for the most part, on the publications of our contemporaries and predecessors. In order to present the material in an informal manner, continuous referencing to these sources have been discarded. However, the reader will find a list of suggested references of wider scope at the end of each chapter.

This edition is peculiar in having new pieces of four-color art schematics, flowcharts and diagrams primarily aimed at comprehension of its contents and to facilitate reasoning of concepts such as the molecular basis of cancer. A change which is far reaching and marked is the hard copy format of the text which intends to minimize structural fatigue and maximize ease of usage. Finally, as was true of the fifth and sixth editions, all of our associations with the publisher, Elsevier India were pleasant and helpful. We want to thank the editorial staff of Elsevier India for their skilled and friendly assistance in helping us publish this project to completion successfully.

Deficiencies and shortcomings are rather inevitable in an effort of this magnitude and for which we shall be solely responsible. This textbook is dedicated to our contemporaries and predecessors who have made this effort a reality.

R Rajendran
B Sivapathasundharam

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Preface to the First Edition

ORAL PATHOLOGY represents the confluence of the basic sciences and clinical dentistry. Since it has no methods of its own, knowledge in this field is acquired through the adaptation of methods and disciplines of those sciences basic to dental practice, such as gross and microscopic anatomy, chemistry, microbiology and physiology, and through information obtained by clinical histories and observation of patients. Through the science of oral pathology, an attempt is made to correlate human biology with the signs and symptoms of human disease. The oral pathologist attempts to understand oral disease so that it can be properly diagnosed and adequately treated.

In this text we have attempted to bring the reader to an understanding of the patient and his problems through applied basic science. We have tried to explain clinical signs and symptoms in the light of known histologic, chemical and physiologic alterations. Where possible, the prognosis of each disease is considered as a reflection of the underlying tissue changes and what we know can be done about them today.

In numerous sections of the text we have attempted to integrate information from many of the basic sciences for adequate diagnosis of oral disease. This approach is a departure from that of the usual textbook of oral pathology, representing an effort to place more emphasis on the physiologic and chemical aspects of oral disease.

The references at the end of each chapter are extensive enough to be of value to those interested in additional reading. Only those papers which constitute good review articles or exceptional discussions or which are of historical importance are included. Because the field of oral pathology is large, much of the bibliographic material has had to be curtailed or omitted. The highlights alone have been stressed. It is our hope that this book will prove to be a stimulus to study as well as a guide for undergraduate and postgraduate students and practitioners of both dentistry and medicine.

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Acknowledgements

The editors wish to acknowledge, with extreme gratitude, the unstinted support provided by way of literature and photograph search, website browsing, proof correction and data entry by the following friends and colleagues: Anisha Cynthia Sathyasekar, Anirudh Acharaya, Balasundaram T, Dulkanti Santhosh Reddy, Einstein T Bertein, Helen James, Jose Joy Idicula, Karthigakannan S, Kavitha B, Liza Thakur Suchdeva, Manikandhan R, Capt. Neelakandan RS, Poornima Kumar, Pritham Panja, Ramakrishnan T, Ramya Ganesh, Sriram G, Sujatha G, Saraswathi TR, Saravanakumar, Surapaneni Sunilkumar, Spencer Lilly D, Anna P Joseph, C Venugopal, PK Rajeesh Mohammad, Sabu Paul, Saleem Shaikh, Sivakumar G, Sunil Kumar Kothawar, S Sunil, Twinkle S Prasad, Vidyarani Bhat. Without their active participation and help, this edition would have been impossible to complete.

In addition, Dr B Sivapathasundharam would especially like to thank Dr Rohini Sivapathasundharam, his wife for her continuous help, support and encouragement, and postgraduate students of department of oral pathology, Meenakshi Ammal Dental College for correcting the proofs; Thiru AN Radhakrishnan, Chancellor, Dr E Munirathnam Naidu, Former Vice Chancellor, Meenakshi University; and Dr P Jayakumar, Principal, Meenakshi Ammal Dental College for their constant encouragement and support. The editor also wishes to thank Dr Kavitha Bottu, Dr Thubashini Kannan, Dr M Preethi, Dr B Sabari, Dr Manoj Prabhakar, Dr M Sivaramakrishnan, Dr K Karthik and Dr R Kalpana.

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SECTION I

Disturbances of Development and Growth

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CHAPTER 1

Developmental Disturbances of Oral and Paraoral Structures

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CHAPTER OUTLINE

CRANIOFACIAL ANOMALIES

Craniofacial anomalies (CFA) are a diverse group of deformities in the growth of the head and facial bones. Anomaly is a medical term meaning 'irregularity' or 'different from normal'. These abnormalities are congenital (present at birth) and have numerous variations: some are mild, others are severe and require surgery.

There is no single factor that causes these abnormalities. Instead, there are many factors that may contribute to their development, including the following:

- **Combination of genes.** A child may receive a particular combination of gene(s) from one or both parents, or there may be a change in the genes at the time of conception, which results in a craniofacial anomaly.
- **Environmental.** There is no data that shows a direct correlation between any specific drug or chemical exposure causing a craniofacial anomaly. However, any prenatal exposure should be evaluated.
- **Folic acid deficiency.** Folic acid is a B vitamin found in orange juice, fortified breakfast cereals, enriched grain products, and green, leafy vegetables. Studies have shown that women who do not take sufficient folic acid during pregnancy, or have a diet lacking in folic acid, may have a higher risk of having a baby with certain congenital anomalies, including cleft lip and/or cleft palate.

Some of the most common types of craniofacial anomalies (Table 1-1) include:

- **Cleft lip and/or cleft palate.** A separation that occurs in the lip or the palate or both. Cleft lip and cleft palate are the most common congenital craniofacial anomalies seen at birth.

  Cleft lip. An abnormality in which the lip does not completely form. The degree of the cleft lip can vary greatly, from mild (notching of the lip) to severe (large opening from the lip up through the nose).
  Cleft palate. Occurs when the roof of the mouth does not completely close, leaving an opening that can extend into the nasal cavity. The cleft may involve either side of the palate. It can extend from the front of the mouth (hard palate) to the throat (soft palate). The cleft may also include the lip.

- **Craniosynostosis.** A condition in which the sutures in the skull of an infant close too early, causing problems with normal brain and skull growth. Premature closure of the sutures may also cause the pressure inside the head to increase and the skull or facial bones to change from a normal, symmetrical appearance.
- **Hemifacial microsomia.** A condition in which the tissues on one side of the face are underdeveloped, affecting primarily the ear (aural), mouth (oral), and jaw (mandibular) areas. Sometimes, both sides of the face

Table 1-1: Examples of most common craniofacial anomalies

	Prevalence at birth: per 10,000
Cleft lip ± palate	
Caucasian	10
Japanese	20
Native (North) Americans	36
African-American population	3
Cleft palate	
Average across races	5
Craniosynostosis	3
Crouzon syndrome	0.4
Apert syndrome	0.15
Otomandibular anomalies	1.2
Treacher Collins syndrome	0.2
CHARGE association	1
Holoprosencephaly	1.2
Stickler syndrome	1
Fetal alcohol syndrome	2

Source: Rovin et al, 1964; Temple, 1989; Cohen et al, 1992; Lewanda et al, 1992; Croen et al, 1996; Derijcle et al, 1996; Sampson et al, 1997; Blate et al, 1998.

can be affected and may involve the skull as well as the face. Hemifacial microsomia is also known as Goldenhar syndrome, brachial arch syndrome, facio-auriculovertebral syndrome (FAV), oculo-auriculovertebral spectrum (OAV), or lateral facial dysplasia.

- **Vascular malformation.** A birthmark or a growth, present at birth, which is composed of blood vessels that can cause functional or esthetic problems. Vascular malformations may involve multiple body systems. There are several different types of malformations, named after the type of blood vessel that is predominantly affected. Vascular malformations are also known as lymphangiomas, arteriovenous malformations, and vascular gigantism.
- **Hemangioma.** A type of birthmark; the most common benign (noncancerous) tumor of the skin. Hemangiomas may be present at birth (faint red mark) or appear in the first month after birth. A hemangioma is also known as a port wine stain, strawberry hemangioma, and salmon patch.
- **Deformational (or positional) plagiocephaly.** A misshapen (asymmetrical) shape of the head (cranium) from repeated pressure to the same area of the head. Plagiocephaly literally means 'oblique head' (from the Greek '*plagio*' for oblique and '*cephale*' for head).

Collectively they affect a significant proportion of the global society (Table 1-1).

GLOBAL EPIDEMIOLOGY

The frequency of occurrence of cleft lip, with or without cleft palate, has been computed on a global scale and is estimated to be 1 in every 800 newborn babies (Tables 1-2 and 1-3). A child is therefore born with a cleft somewhere in the world approximately every two-and-half minutes. Accurate data on the frequency of occurrence of these disorders is relevant for implementing strategies aimed at primary prevention and effective management of these disabled children (Table 1-2). Like anywhere else, the epidemiological data in this situation is also inherently handicapped by:

- The heterogeneity of orofacial clefting,
- The lack of standard criteria for collection of data, and
- In particular, the lack of and/or failure to apply an internationally comparable classification for orofacial clefting.

Defining the affected population is also problematic because, on many occasions, the terminology is so vague that it is not clear whether it denotes all birth, or all live births. The word 'births' is again somewhat ambiguous because it usually includes stillbirths, a term which lacks clarity.

REGISTRATION OF TARGETED CRANIOFACIAL ANOMALIES IN INDIA

1. Three multicenter studies in India have provided almost similar frequency of CFA: meta-analysis of 25 early studies from 1960–1979, involving 407,025 births, showed:
   CL/P = 440 cases, 1.08 per 1,000 births,
   CP = 95 cases, 0.23 per 1,000 births.
2. A prospective national study of malformations in 17 centers from all over India from September 1989 to September 1990 involving 47,787 births showed:
   CL/P = 64 cases, 1.3 per 1,000 births,
   CP = 6 cases, 0.12 per 1,000 births.
3. The latest three-center study, conducted in 1994–1996, involved 94,610 births in Baroda, Delhi and Mumbai, and showed a frequency of:
   CL/P = 0.93 per 1,000 births,
   CP = 0.17 per 1,000 births.
   This was the most rigorously conducted study and it found the number of infants born every year with CLP to be 28,600; this means 78 affected infants are born every day, or three infants with clefts are born every hour (Table 1-4)!

CFA are not lethal but they are disfiguring, and thus cause a tremendous social burden. However, these disorders have an excellent outcome if surgical repair is carried out competently. Recent information regarding the etiology of CFA provides the means to carry out primary or secondary prevention. Maintaining a registry would be very useful as a benefit to the community and in reducing the burden of these anomalies, either by prevention or surgical repair.

Another reason why a registry would be desirable is the changing pattern of morbidity and mortality in India emerging as a result of the achievements in immunization, the success in providing primary health care and the existence of a well-developed health infrastructure. In many university and city hospitals congenital malformations and genetic disorders have become important causes of illness. All these reasons show that starting a registry of these disorders deserves high priority in India.

Table 1-2: Cleft lip with or without cleft palate

	Live and stillbirths	Induced abortions	Total cases	Total births	Rates (per 10,000)	
Argentina	99	–(*)	99	73,942	13.4	↑
Australia						
South Australia	–	–	19	19,801	9.6	
Victoria	26	47	73	65,182	11.2	
Belarus	–	–	–	–	–	
Belgium						
Hainaut Namur	30	1	31	24,856	12.5	
Brazil	51	–(*)	51	36,689	13.9	
Chile	20	–(*)	20	22,276	9.0	
Czech Republic	113	–	113	107,153	10.5	
Denmark						
Odense	17	0	17	12,054	14.1	
France						
Bouches du Rhone	33	3	36	44,704	8.1	
Central East	74	4	78	100,074	7.8	↓
Paris	47	16	63	71,319	8.8	
Strasbourg	29	5	34	27,200	12.5	
Ireland						
Dublin	31	–(*)	31	38,000	8.2	
Italy						
Campania	38	2	40	43,325	9.2	
Emilia Romagna	25	–	25	25,924	9.6	
Ioscana	42	1	43	48,991	8.8	
Japan	172	–(*)	172	113,702	15.1	↑
Mexico	81	–(*)	81	65,670	12.3	
Netherlands						
North	52	6	58	38,670	15.0	↑
Norway	99	2	101	60,584	16.7	↑
Spain						
Basque Country	114	2	16	31,248	5.1	↓
Switzerland	101	4	105	148,000	7.1	↓
United Kingdom						
Belfast	10	1	11	49,482	2.2	↓
Glasgow	19	1	20	22,570	8.9	
North Thames	43	10	53	47,274	11.2	
USA						
Atlanta	34	0	34	39,856	8.5	
Hawaii	–	–	22	20,596	10.7	
Uruguay	17	–(*)	17	21,332	8.0	
Venezuela	21	–(*)	21	36,377	5.8	↓

Source: WHO (1998), World Atlas of Birth Defects (1st Edition).
** Abortion for birth defect not permitted.*
↑ = 99% significantly higher than the mean.
↓ = 99% significantly lower than the mean.

EXISTING EPIDEMIOLOGICAL DATA ON CFA

The epidemiological information that exists on CFA anomalies in India needs to be examined to decide what data should be collected for the registry:

- Higher frequency of CL+CP among Indian males is similar to that observed among Caucasians. The ratio is more than that observed in Africans and Japanese.
- The higher prevalence of CL+CP as compared with CL among Indians is like that observed in Africans, and is more than that observed in Caucasians.
- Children born prematurely are more frequently affected in India, as elsewhere.
- About 10.9% of 459 cases of all clefts are syndromic in Chennai. Of these, about 50 % are due to single-gene disorders, about 18% due to chromosomal disorders, and the rest due to undetermined causes.

Table 1-3: Cleft palate without cleft lip

	Live and stillbirths	Induced abortions	Total cases	Total births	Rates (per 10,000)	
Argentina	43	–(*)	43	73,942	5.8	
Australia						
South Australia	18	–	18	19,801	9.1	
Victoria	39	0	39	65,182	6.0	
Belarus	–	–	–	–	–	
Belgium						
Hainaut Namur	15	2	17	24,856	6.8	
Brazil	19	–(*)	19	366,689	5.2	
Chile	13	–(*)	13	22,276	5.8	
Czech Republic	66	–	66	107,153	6.2	
Denmark						
Odense	11	0	11	12,054	9.1	
France						
Bouches du Rhone	23	5	28	44,704	6.3	
Central East	72	7	79	100,074	7.9	↑
Paris	36	14	50	71,319	7.0	
Strasbourg	21	2	23	27,200	8.5	
Ireland						
Dublin	13	–(*)	13	38,000	3.4	
Italy						
Campania	24	–	24	43,325	5.5	
Emilia Romagna	12	–	12	25,924	4.6	
Ioscana	10	2	12	48,991	2.4	↓
Japan	52	–(*)	52	113,702	4.6	
Mexico	27	–(*)	27	65,870	4.1	
Netherlands						
North	32	1	33	38,670	8.5	
Norway	26	0	26	60,584	4.3	
Spain						
Basque Country	17	1	18	31,248	5.8	
Switzerland	63	3	66	148,000	4.5	
United Kingdom						
Belfast	6	1	7	49,482	1.4	↓
Glasgow	19	3	22	22,570	9.7	
North Thames	20	2	22	47,274	4.7	
USA						
Atlanta	12	1	13	39,856	3.3	
Hawaii	12	–	12	20,596	5.8	
Uruguay	10	–(*)	10	21,332	4.7	
Venezuela	14	–(*)	14	36,377	3.8	
Total			789	1,457,051	5.4	

Source: WHO (1998), World Atlas of Birth Defects (1st Edition).

* *Abortion for birth defect not permitted.*

↑ *= 99% significantly higher than the mean.*

↓ *= 99% significantly lower than the mean.*

- Chromosomal studies would be desirable in cases with associated abnormalities.
- Syndromes are more commonly associated with CP than with CL, as elsewhere.
- Lateralization (more clefts on the left side) in India is similar to that observed in other races.
- In one study in India, the intake of drugs was observed in 18% of parents — mostly steroidal compounds (progestogens as tests for pregnancy).
- A greater history of terminated pregnancies has been observed among cases, as compared with controls.
- History of severe vomiting has been observed to be about six times more common among case mothers than among controls.
- There is some difference in the frequency of orofacial clefts in different states in India; however, this needs verification. The state of origin (or mother tongue) of the parents should be recorded.

Table 1-4: Number of infants with common malformations born every year in India

Malformation	Rate per 10,000	Total number per year
Neural tube defects	36.3	88,935
Talipes equinovarus	14.5	35,525
Polydactyly	11.6	28,420
Hydrocephalus alone	9.5	23,275
Cleft lip with cleft palate (CLP)	9.3	22,786
Congenital heart disease	7.1	17,395
Hypospadias	5.0	12,250
Cleft palate alone (CP)	1.7	4,145

Source: Global registry and database on craniofacial anomalies: Report of a WHO registry on craniofacial anomalies, 2001.

- Clefts are more commonly found in certain caste groups among Hindus.
- In India CP has less frequency in those with blood group A.
- CL occurs more in those with group O and AB.
- Association of clefts with certain HLA types has been documented in India.
- In a study in Chennai, significantly more consanguinity was observed among couples having children with clefts as compared with controls.

GENETICS: PRINCIPLES AND TERMINOLOGY

Genotype and Phenotype

The science of genetics is concerned with the inheritance of traits, whether normal or abnormal, and with the interaction of

Table 1-5: Genes involved in craniofacial and dental disorders, sorted by acronym gene name

Acronym	Full name
ACTC	Actin, Alpha, Cardiac Muscle
APP	Amyloid Beta A4 Precursor Protein (APP)
ARVCF	Armadillo Repeat Gene Deleted in VCFS
ATP&E	ATPhase, H+ Transporting, Lysosomal, Subunit E
CA1	Carbonic Anhydrase 1
CLTCL1	Clathrin, Heavy Polypeptide-Like 1
COL01A1	Collagen, Type I, Alpha-1
COL01A2	Collagen, Type I, Alpha-2
COL02A1	Collagen, Type II, Alpha-1
COL04A4	Collagen, Type IV, Alpha-4
COL04A5	Collagen, Type IV, Alpha-5
COL05A1	Collagen, Type V, Alpha-1
COL06A1	Collagen, Type VI, Alpha-1
COL10A1	Collagen, Type X, Alpha-1
COMT	Catechol-O-Methyltransferase
CYLN2	Cytoplasmic Linker 2
DCN	Decorin
DGSI	DiGeorge Syndrome Critical Region Gene
ELN	Elastin
FBLN2	Fibulin 2
FBN1	Fibrillin 1
FGF8	Fibroblast Growth Factor 8
FGFR1	Fibroblast Growth Factor Receptor 1
FGFR2	Fibroblast Growth Factor Receptor 2
FGFR3	Fibroblast Growth Factor Receptor 3
GNAS1	Guanine Nucleotide-Binding Protein, Alpha-Stimulating Activity Polypeptide
GOLGA1	Golgi Autoantigen, Golgin Subfamily A, 1
GP1BB	Glycoprotein Ib, Platelet, Beta Polypeptide
GPC3	Glypican 3
GPC4	Glypican 4
GPR1	G Protein-Coupled Receptor 1
GTF2I	General Transcription Factor II-I
HIP1	Huntingtin-interacting Protein 1
HIRA	Histone Cell Cycle Regulation Defective, S. Cerevisiae, Homolog of, A
HOXD10	Homeo Box D10
ITGB2	Integrin, Beta-2
KRT04	Keratin 4
KRT06A	Keratin 6A
KRT06B	Keratin 6B
KRT13	Keratin 13
KRT16	Keratin 16
KRT17	Keratin 17
LAMB1	Laminin, Beta-1
MEOX2	Mesenchyme Homeo Box 2
MSX1	MSH, Drosophila, Homeo Box, Homolog of, 1
MSX2	MSH (Drosophila) Homeo Box Homolog 2
PNUTL1	Peanut-Like 1
PTHR1	Parathyroid Hormone Receptor 1
RO60	Autoantigen Ro/SSA, 60–KD
SCZD	Schizophrenia
SCZD4	Schizophrenia 4
SCZD8	Schizophrenia 8
SRC	V-SRC Avian Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene
SRY	Sex-Determining Region Y
SSA1	Sjögren Syndrome Antigen A1
SSB	Sjögren Syndrome Antigen B
TNFRSF11B	Tumor Necrosis Factor Receptor Superfamily, Member 11B
TTPA	Tocopherol Transfer Protein, Alpha
TWIST	Twist, Drosophila, Homolog of
WBSCR1	Williams-Beuren Syndrome Chromosome Region 1

Source: Report of the National Institutes of Dental and Craniofacial Research Genetics Workgroup, Meeting held November 14–16, 1999.

genes and the environment. This latter concept is of particular relevance to medical genetics, since the effects of genes can be modified by the environment.

Consideration of the heritability of a particular feature or trait requires a consideration of the relationship between genotype and phenotype. Genotype is defined as the genetic constitution of an individual, and may refer to specified gene loci or to all loci in general. An individual's phenotype is the final product of a combination of genetic and environmental influences. Phenotype may refer to a specified character or to all the observable characteristics of the individual. The proportion of the phenotypic variance attributable to the genotype is referred to as heritability.

Genetic variation in man may be observed at two levels:

In specific traits, individual genotypes are readily identified and differences are qualitative (discrete), for example, the ABO blood antigen system. Gene frequencies can be estimated and the Mendelian type of analysis can be applied.

In continuous traits such as height, weight or tooth size, differences are characterized quantitatively between individuals. These quantitative traits in man are more elusive to study because they are determined by the alleles of many gene loci, and therefore, the Mendelian type of analysis is not appropriate. They are further modified by environmental conditions which obscure the genetic picture. If the genetic variation of a particular phenotypic trait is dependent on the simultaneous segregation of many genes and affected by environment it is referred to as being subject to multifactorial inheritance. Genetic differences caused by the segregation of many genes is referred to as polygenic variation and the genes concerned are referred to as polygenes. These genes are, of course, subject to the same laws of transmission and have the same general properties as the single genes involved in qualitative traits, but segregation of genes is translated into genetic variations seen in continuous traits through polygenes.

Different types of genetic 'product' can be thought of as being different distances from the fundamental level of gene activity. Enzymes, for instance, are almost direct products of gene action, and in most cases where genetic variation of enzyme structure has been demonstrated, it has been shown that a single locus is responsible for the structure of a single enzyme. The structure, and consequently, the activity of an enzyme is therefore usually simply and directly related to allele substitutions at a single locus.

Morphological characters, on the other hand, such as the numerous dimensions used to describe the shape of the face and jaws, are furthest removed from the fundamental genetic level and are the end results of a vast complexity of interacting, hierarchical, biochemical, and developmental processes. Each gene is therefore likely to influence many morphological characters so that a deleterious mutation, although producing a unitary effect at the molecular level, almost always results in a syndrome of morphological abnormalities. When a gene is known to affect a number of different characters in this way its action is said to be pleiotropic. A reverse hierarchy also exists, making each morphological character dependent on many different genes (Mossey, 1999).

Modes of Inheritance

Population genetics deals with the study of the mode of inheritance of traits and the distribution of genes in populations.

All chromosomes exist in pairs so our cells contain two copies of each gene, which may be alike or may differ in their substructure and their product. Different forms of genes at the same locus or position on the chromosome are called alleles. If both copies of the gene are identical, the individual is described as homozygous, while if they differ, the term used is heterozygous.

The exception to the rule that cells contain pairs of chromosomes applies to the gametes, sperm and ovum, which contain only single representatives of each pair of chromosomes, and therefore, of each pair of genes. When the two gametes join at fertilization, the new individual produced again has paired genes, one from the father and one from the mother. If a trait or disease manifests itself when the affected person carries only one copy of the gene responsible, along with one normal allele, the mode of inheritance of the trait is called dominant (Fig. 1-1A). If two copies of the defective gene are required for expression of the trait, the mode of inheritance is called recessive (Fig. 1-1B).

The special case of genes carried on the X chromosome produces yet different pedigrees. Since male-to-male transmission is impossible and since females do not express the disease when they carry only one copy of the diseased gene (since it is modified by the homologous X chromosome), the usual pedigree consists of an affected male with clinically normal parents and children, but with affected brothers, maternal uncles, and other maternal male relatives (Fig. 1-1C). This mode of inheritance is described as X-linked recessive.

It has been long appreciated that many normal traits, such as height, intelligence, and birth weight, have a significant genetic component, as do a number of common diseases, such as diabetes mellitus, schizophrenia, hypertension, and cleft lip and palate. However, the pattern of inheritance of these traits does not follow the simple modes just described. Mathematical analysis of many of these has led to the conclusion that they follow the rules of polygenic inheritance, i.e. determined by a constellation of several genes, some derived from each parent.

The determination of heritability for polygenic or multifactorial characters is difficult, as a feature of continuous variation is that different individuals may occupy the same position on the continuous scale for different reasons. Using mandibular length as an example, micrognathia can occur in chromosomal disorders, such as Turner's syndrome, in monogenic disorders such as Treacher Collins syndrome or Stickler syndrome, or due to an intrauterine environmental problem, such as fetal alcohol syndrome. Combined with this the concept of etiological heterogeneity encompasses the principle of the same gene defect producing different phenotypic anomalies, and syndromes can be due to defective gene activity in different cells. Conversely, different gene defects or combinations of defective genes can produce a similar phenotypic abnormality. Genetic lethality or reduced reproductive fitness can also complicate the diagnostic picture

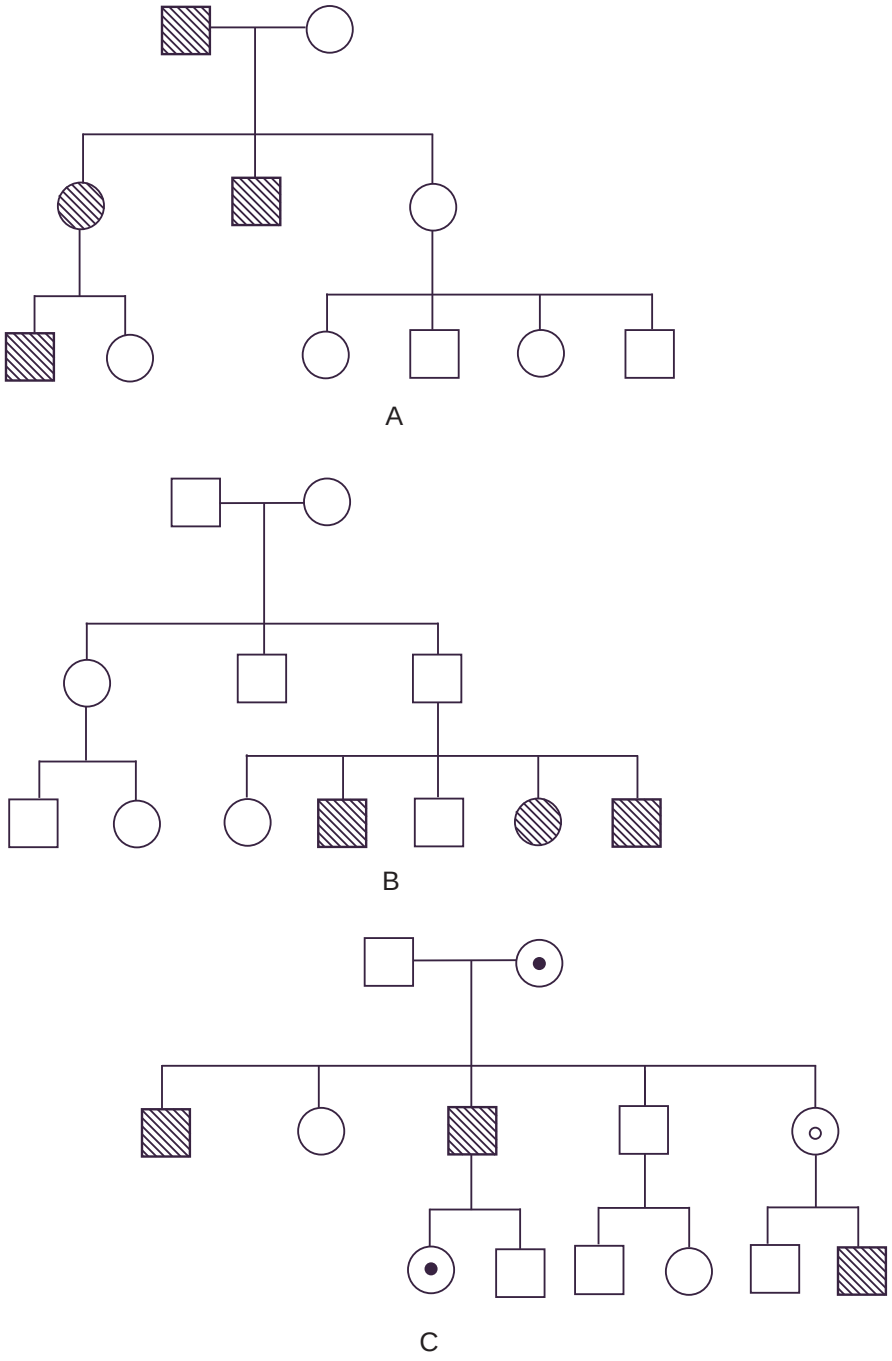


Figure 1-1. (A) Autosomal dominant pedigree. (B) Autosomal recessive pedigree. (C) X-linked recessive pedigree.
(Courtesy of PA Mossey, 1999).

and genomic imprinting can result in a gene defect 'skipping' a generation. These complexities serve to hamper progress in the understanding of polygenic or multifactorial disorders such as orofacial clefting (Mossey, 1999).

Multifactorial Inheritance. In contrast to single-gene inheritance, either autosomal or sex-linked, the pedigree pattern does not afford a diagnosis of multifactorial inheritance. In multifactorial traits, the trait is determined by the interaction of a number of genes at different loci, each with a small, but additive effect, together with environmental factors (i.e., the genes are rendering the individual unduly susceptible to the environmental agents). Many congenital malformations (Table 1-6) and common diseases of adult life are inherited as multifactorial traits and these are categorized as either continuous or discontinuous.

Molecular Genetics in Dental Development. The first sign of tooth development is a local thickening of oral epithelium, which subsequently invaginates into neural crest derived mesenchyme and forms a tooth bud. Subsequent epithelial folding and rapid cell proliferation result in first the cap, and then the bell stage of tooth morphogenesis. During the bell stage, the dentine producing odontoblasts and enamel

Table 1-6: Causes of deformations

Extrinsic
Mechanical
Unstretched uterine and abdominal muscles
Small maternal size
Amniotic tear
Unusual implantation site
Uterine leiomyomas
Unicornuate uterus
Bicornuate uterus
Twin fetuses
Intrinsic
Malformational
Spina bifida
Other central nervous system malformations
Bilateral renal agenesis
Severe hypoplastic kidneys
Severe polycystic kidneys
Urethral atresia
Functional
Neurologic disturbances
Muscular disturbances
Connective tissue defects

Source: MM Cohen Jr, The Child with Multiple Birth Defects. Raven Press, New York, 1982, p 10. Cited by RJ Gorlin, MM Cohen, LS Levin. Syndromes of the Head and Neck, 3rd Ed, Oxford University Press; 1990, New York.

secreting ameloblasts differentiate. Tooth development, like the development of all epithelial appendages, is regulated by inductive tissue interactions between the epithelium and mesenchyme (Thesleff, 1995).

There is now increasing evidence that a number of different mesenchymal molecules and their receptors act as mediators of the epithelial-mesenchymal interactions during tooth development. Of the bone morphogenetic proteins (BMPs) 2, 4, and 7 mRNAs shift between the epithelium and mesenchyme in the regulation of tooth morphogenesis (Aberg et al, 1997). The fibroblast growth factor (FGF) family have also been localized in epithelial and mesenchymal components of the tooth by immunohistochemistry (Cam et al, 1992); and in dental mesenchyme tooth development and shape is regulated by FGF8 and FGF9 via downstream factors MSX1 and PAX9 (Kettunen and Thesleff, 1998).

Control of Tooth Development. Homeobox genes have particular implications in tooth development. Muscle specific homeobox genes Msx-1 and Msx-2 appear to be involved in epithelial mesenchymal interactions, and are implicated in craniofacial development, and in particular, in the initiation developmental position (Msx-1) and further development (Msx-2) of the tooth buds (MacKenzie et al, 1991; Jowett et al, 1993). Further evidence of the role of Msx-1 comes from gene knock-out experiments which results in disruption of tooth morphogenesis among other defects (Satokata and Maas, 1994). Pax-9 is also transcription factor necessary for tooth morphogenesis (Neubuser et al, 1997). BMPs are members of the growth factor family (TGF) and they function in many aspects of craniofacial development with tissue specific functions. BMPs have been found to have multiple roles not only in bone morphogenesis, (BMP 5, for example, induces endochondral osteogenesis *in vivo*), but BMP 7 appears to induce dentinogenesis (Thesleff, 1995).

Disorders in Tooth Morphogenesis. Advances in the field of molecular genetics have made great progress in the understanding of a number of dental anomalies with a genetic component.

CONGENITAL DEFORMATIONS OF HEAD AND NECK

These are common, and mostly resolve spontaneously within the first few days of postnatal life. When they do not, further evaluation may be necessary to plan therapeutic interventions that may prevent long-term consequences. Approximately 2% of infants are born with extrinsically caused deformations that usually arise during late fetal life from intrauterine causes. Approximately 30% of deformed infants have two or more deformations. Deformed infants tend to show catch-up growth during the first few postnatal months after release from the intrauterine environment. The common deformations considered under the craniofacial category are nasal, auricular and mandibular deformities.

Teratogenic Agents

Teratogens are agents that may cause birth defects when present in the fetal environment. Included under such a definition are a wide array of drugs, chemicals, and infectious, physical, and metabolic agents that may adversely affect the intrauterine environment of the developing fetus. Such factors may operate by exceedingly heterogeneous pathogenetic mechanisms to produce alterations of form and function as well as embryonic and/or fetal death (Gorlin et al, 1990).

The mechanisms of teratogenesis are selective in terms of the target and effect. Thus, characteristic patterns of abnormalities can be expected to be associated with particular teratogenic agents. However, the extent to which an individual may be adversely affected by exposure to a given teratogen varies widely. This depends on the following four factors:

1. Differences in dose
2. Developmental timing of exposure
3. Differences in susceptibility
4. Interactions among environmental exposures.

It is of considerable interest to the dental profession that experimental studies of teratogenic agents have almost invariably revealed a variety of head, neck and oral malformations. Conway and Wagner have compiled a list of the most common malformations of the head and neck as shown in Table 1-7.

Table 1-7: Classification of cleft lip

Type	Occurrence (%)
Unilateral incomplete	33
Unilateral complete	48
Bilateral incomplete	7
Bilateral complete	12

Source: V Veau: Division palatine; anatomie, chirurgie, phonetique. Paris, Masson et Cie, 1931.

Stem cells

Stem cells are clonogenic cells that have the capacity for self-renewal and multilineage differentiation. The microenvironment in which stem cells reside is called a stem cell niche and is composed of heterologous cell types, extracellular matrix and soluble factors to support the maintenance and self-renewal of the stem cells. Stem cells have been isolated and characterized from a wide variety of sources. Adult progenitor cellular populations have been isolated from distinctive tissues and fluids, such as bone marrow, peripheral blood, umbilical cord blood, Wharton's jelly, placenta, amniotic fluid and membrane, adipose tissue, dermis, hair follicles, synovial membrane, skeletal muscle, central nervous system, olfactory bulb, retina, and liver among others. From these biological sources, progenitors of the mesenchymal, epithelial, hematopoetic (discussed elsewhere), neural, endothelial and trophoblastic lineages have been identified (Fig. 1-2).

In tissue engineering applications, mesenchymal stem cells are among the most used populations because of the wide variety of sources from which they can be harvested, their ability to self-renew, and their multilineage potential following adequate induction. Moreover, the vast majority of the tissues relevant in surgical repair / regeneration are of mesenchymal origin. This is of particular relevance in the craniofacial area because during development cells originating from the neural crest are known to migrate, differentiate, and participate in the morphogenesis of virtually all structures of the region including muscle, ligament, bone, cartilage, periodontal tissues and teeth.

There are two major categories of stem cells, which are of relevance to dentistry:

1. Embryonic stem cells
2. Adult or somatic stem cells.

Totipotent embryonic stem cells are derived from the inner cell mass of mammalian blastocyst and can be maintained indefinitely in culture. Somatic stem cells have a limitation in their potential of differentiation. The differentiation potential of dental stem cells lies in the formation of dentin or periodontium associated tissues, whether these cells are derived from pulp, periodontal ligament or dental follicle. It is obvious that dental ectomesenchymal stem cells can be classified into two different groups with respect to their differentiation potential. The first group is associated with the dental pulp, consisting of dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SCEDs), and stem cells from apical papilla (SCAPs); the second group contains periodontal ligament stem cells (PLSCs) and dental follicle progenitor cells (DFPCs), related to the periodontium.

The odontogenic stem cells are further divided into:

1. Epithelial stem cells (ESCs)
2. Mesenchymal stem cells (MSCs).

Dental epithelial stem cells

Embryonic dental epithelium is capable of inducing the development of a tooth germ in combination with non-dental ectomesenchymal tissue. However, oral ectomesenchyme in combination with non-dental epithelium did not induce tooth development. Later steps in tooth development are driven by a complex interaction of both ectodermal and ectomesenchymal tissues along with growth promoting factors of bone morphogenic protein-4 (BMP-4) and fibroblast growth factor-8 (FGF-8), produced by the oral ectoderm for the initiation of tooth development.

Oral ectoderm derived ameloblasts are unable to proliferate or regenerate once they have reached the maturation stage of development. Continuously growing mouse incisors and molars in some mammalian species show replenishing populations of enamel organs composed of stellate reticulum, stratum intermedium and enamel epithelial cells which provide models for dental epithelial stem cells. Mice have an epithelial stem cell niche located at their incisor labial apical ends, known as the cervical loop. The cervical loop has been considered to be a determinative region in odontogenesis due to its ability to produce enamel and dentin. One specialized structure found at the apical region of the labial cervical loop in mouse incisors, "apical bud" (Ohshima H et al, 2003), is suggested as stem cell compartment that could differentiate into ameloblast through interaction with mesenchymal cells and growth factors.

In humans, these dental epithelial stem cells are lost after tooth eruption; therefore, are not available for studies on dental development. In contrast to dental epithelial stem cells, undifferentiated cells of the oral ectomesenchyme are not entirely lost after tooth eruption in humans. It became possible to isolate precursor cells from the dental pulp and ectomesenchymal stem cells were isolated from the dental pulp of extracted wisdom teeth.

Dental mesenchymal stem cells

They are a heterogeneous population of multipotent self-renewal cells that possess clonogenic competence and the capacity to differentiate into all cell lineages of the mesenchymal and connective tissue elements. They also seem to be able to differentiate into epithelial cells and lineages derived from neuroectoderm. Mesenchymal stem cells have been shown to produce a wide range of bioactive molecules capable of immunomodulatory functions along with the ability to modulate the regenerative processes in the human body (Ohshima H et al, 2001).

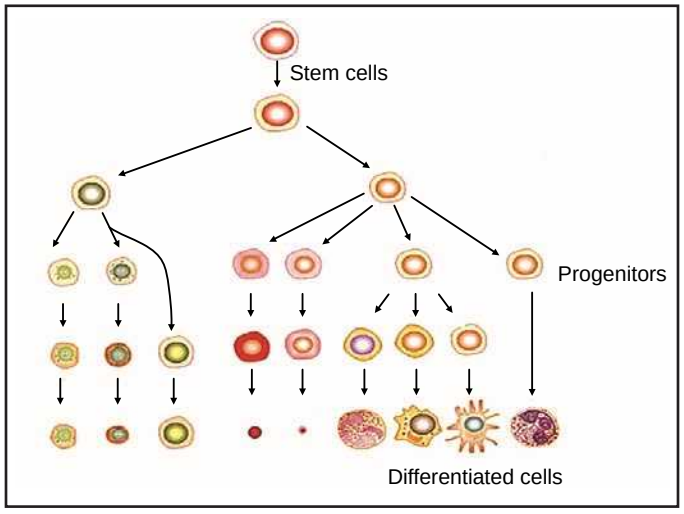


Figure 1-2. Mandibular micrognathia.
(Courtesy: Prof Anil Sukumaran, Prof R Rajendran. King Saud University, Riyadh, KSA).

DEVELOPMENTAL DISTURBANCES OF JAWS

Agnathia

(Otocephaly, holoprosencephaly agnathia)

Agnathia is a lethal anomaly characterized by hypoplasia or absence of the mandible with abnormally positioned ears having an autosomal recessive mode of inheritance. More commonly, only a portion of one jaw is missing. In the case of the maxilla, this may be one maxillary process or even the premaxilla. Partial absence of the mandible is even more common. The entire mandible on one side may be missing, or more frequently, only the condyle or the entire ramus, although bilateral agenesis of the condyles and of the rami also has been reported. In cases of unilateral absence of the mandibular ramus, it is not unusual for the ear to be deformed or absent as well. It is probably due to failure of migration of neural crest mesenchyme into the maxillary prominence at the fourth to fifth week of gestation (postconception). The prevalence is unknown and less than 10 cases are described. The prognosis of this condition is very poor and it is considered to be lethal.

Micrognathia

Micrognathia literally means a small jaw, and either the maxilla or the mandible may be affected. Many cases of apparent micrognathia are not due to an abnormally small jaw in terms of absolute size, but rather to an abnormal positioning or an abnormal relation of one jaw to the other or to the skull, which produces the illusion of micrognathia.

True micrognathia may be classified as either congenital, or acquired. The etiology of the *congenital* type is unknown, although in many instances it is associated with other congenital abnormalities, including congenital heart disease and the Pierre Robin syndrome (q.v.) This form of the disease has been discussed by Monroe and Ogo. It occasionally follows a hereditary pattern. Micrognathia of the maxilla frequently occurs due to a deficiency in the premaxillary area, and patients with this deformity appear to have the middle third of the face retracted. Although it has been suggested that mouth-breathing is a cause of maxillary micrognathia, it is more likely that the micrognathia may be one of the predisposing factors in mouth-breathing, owing to the associated maldevelopment of the nasal and nasopharyngeal structures.

True mandibular micrognathia of the congenital type is often difficult to explain. Some patients appear clinically to have a severe retrusion of the chin but, by actual measurements, the mandible may be found to be within the normal limits of variation. Such cases may be due to a posterior positioning of the mandible with regard to the skull or to a steep mandibular angle resulting in an apparent retrusion of the jaw. Agenesis of the condyles also results in a true mandibular micrognathia.

The acquired type of micrognathia is of postnatal origin and usually results from a disturbance in the area of the temporomandibular joint. Ankylosis of the joint, for example, may be caused by trauma or by infection of the mastoid, of the middle ear, or of the joint itself. Since the normal growth of the mandible depends to a considerable extent on normally developing condyles as well as on muscle function, it is not difficult to understand how condylar ankylosis may result in a deficient mandible.

The clinical appearance of mandibular micrognathia is characterized by severe retrusion of the chin, a steep mandibular angle, and a deficient chin button (Fig. 1-3).

Micrognathia may be caused by or may be a feature of several conditions (Table 1-8).

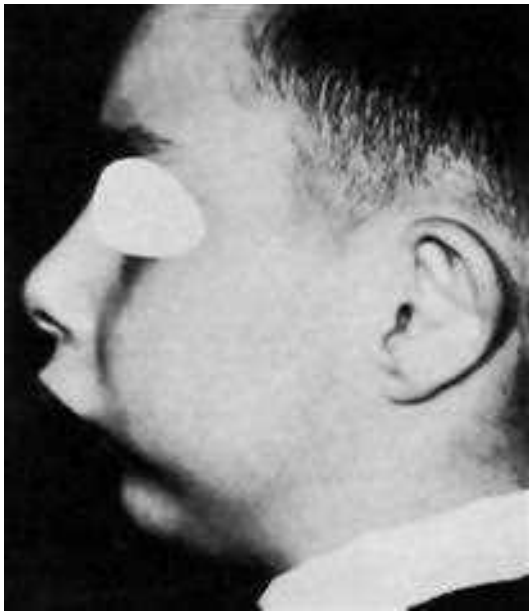


Figure 1-3. Mandibular micrognathia.
(Courtesy of Dr G Thaddeus Gregory and Dr J William Adams).

Table 1-8: Causes of micrognathia

Congenital conditions
• Catel-Manzke syndrome
• Cerebrocostomandibular syndrome
• Cornelia de Lange syndrome
• Femoral hypoplasia—unusual facies syndrome
• Fetal aminopterin-like syndrome
• Miller-Dieker syndrome
• Nager acrofacial dysostosis
• Pierre Robin syndrome
• Schwartz-Jampel-Aberfeld syndrome
• van Bogaert-Hozay syndrome
Intrauterine acquired conditions
• Syphilis, congenital
Chromosomal abnormalities
• 49, XXXXX syndrome
• Chromosome 8 recombinant syndrome
• Cri du chat syndrome 5p
• Trisomy 18
• Turner's syndrome
• Wolf-Hirschhorn syndrome
Mendelian inherited conditions
• CODAS (cerebral, ocular, dental, auricular, skeletal) syndrome
• Diamond-Blackfan anemia
• Noonan's syndrome
• Opitz-Frias syndrome
Autosomal dominant conditions
• Camptomelic dysplasia
• Cardiofaciocutaneous syndrome
• CHARGE syndrome
• DiGeorge's syndrome
• Micrognathia with peromelia
• Pallister-Hall syndrome
• Treacher Collins-Franceschetti syndrome
• Trichorhinophalangeal syndrome type 1
• Trichorhinophalangeal syndrome type 3
• Wagner vitreoretinal degeneration syndrome
Autosomal recessive conditions
• Bowen-Conradi syndrome
• Carey-Fineman-Ziter syndrome
• Cerebrohepatorenal syndrome
• Cohen syndrome
• Craniomandibular dermatodysostosis
• De la Chapelle dysplasia
• Dubowitz syndrome
• Fetal akinesia-hypokinesia sequence
• Hurst's microtia-absent patellae-micrognathia syndrome
• Kyphomelic dysplasia
• Lathosterolosis
• Lethal congenital contracture syndrome
• Lethal restrictive dermopathy
• Marden-Walker syndrome
• Orofaciodigital syndrome type 4
• Postaxial acrofacial dysostosis syndrome
• Rothmund-Thomson syndrome
• Smith-Lemli-Opitz syndrome
• ter Haar syndrome
• Toriello-Carey syndrome
• Weissenbacher-Zweymuller syndrome
• Yunis-Varon syndrome
X-linked inherited conditions
• Atkin-Flaitz-Patil syndrome
• Coffin-Lowry syndrome
• Lujan-Fryns syndrome
• Otopalatodigital syndrome type 2
Autoimmune conditions
• Juvenile chronic arthritis

Source: www.diseasesdatabase.com, Health on the Net Foundation, 2005.

Macrognathia

Macrognathia refers to the condition of abnormally large jaws. An increase in size of both jaws is frequently proportional to a generalized increase in size of the entire skeleton, e.g. in pituitary gigantism. More commonly only the jaws are affected, but macrognathia may be associated with certain other conditions, such as:

- Paget's disease of bone, in which overgrowth of the cranium and maxilla or occasionally the mandible occurs,
- Acromegaly, in which there is progressive enlargement of the mandible owing to hyperpituitarism in the adult, or
- Leontiasis ossea, a form of fibrous dysplasia in which there is enlargement of the maxilla.

Cases of mandibular protrusion or prognathism, uncomplicated by any systemic condition, are a rather common clinical occurrence (Fig. 1-4). The etiology of this protrusion is unknown, although some cases follow hereditary patterns. In many instances the prognathism is due to a disparity in the size of the maxilla in relation to the mandible. In other cases the mandible is measurably larger than normal. The angle between the ramus and the body also appears to influence the relation of the mandible to the maxilla, as does the actual height of the ramus. Thus prognathic patients tend to have long rami which form a less steep angle with the body of the mandible. The length of the ramus, in turn, may be associated with the growth of the condyle. It may be reasoned, therefore, that excessive condylar growth predisposes to mandibular prognathism.

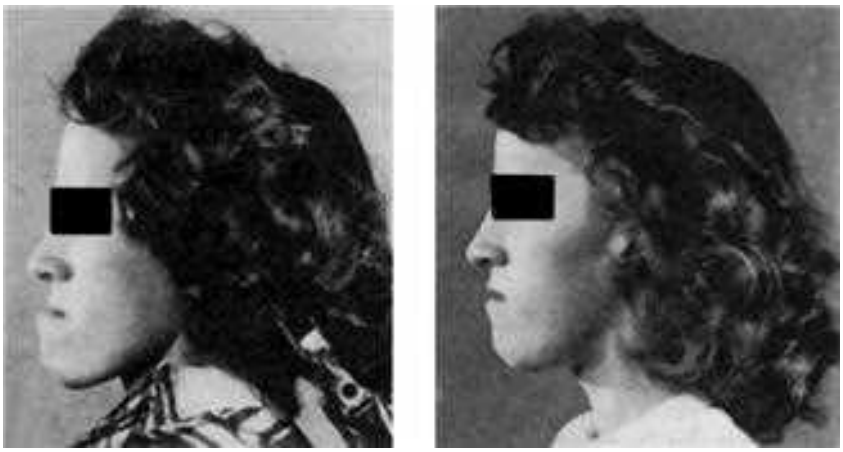
General factors which conceivably would influence and tend to favor mandibular prognathism are as follows:

- Increased height of the ramus
- Increased mandibular body length
- Increased gonial angle
- Anterior positioning of the glenoid fossa
- Decreased maxillary length
- Posterior positioning of the maxilla in relation to the cranium
- Prominent chin button
- Varying soft-tissue contours.

Surgical correction of such cases is feasible. Ostectomy, or resection of a portion of the mandible to decrease its length, is now an established procedure, and the results are usually excellent from both a functional and a cosmetic standpoint.

Facial Hemihypertrophy
(Hyperplasia)

Hemihyperplasia is a rare developmental anomaly characterized by asymmetric overgrowth of one or more body parts. Although the condition is known more commonly as hemihypertrophy, it actually represents a hyperplasia of the tissues rather than a hypertrophy. Hemihyperplasia can be an isolated finding, but it also may be associated with a variety of malformation syndromes (Table 1-9). Almost all cases of isolated hemihyperplasia are sporadic.



A B

Figure 1-4. Macrognathia (prognathia) of the mandible.
(A) The protrusion of the mandible is obvious. **(B)** The same patient after surgical correction (ostectomy) *(Courtesy of Dr G Thaddeus Gregory and Dr J William Adams).*

Table 1-9: Malformation syndromes associated with hemihyperplasia

• Beckwith-Wiedemann syndrome
• Neurofibromatosis
• Klippel-Trenaunay-Weber syndrome
• Proteus syndrome
• McCune-Albright syndrome
• Epidermal nevus syndrome
• Triploid/diploid mixoploidy
• Langer-Giedion syndrome
• Multiple exostoses syndrome
• Maffucci's syndrome
• Ollier syndrome
• Segmental odontomaxillary dysplasia

Source: HE Hoyme et al, 1998.

Hoyme et al (1998) provided an anatomic classification of hemihyperplasia:

- Complex hemihyperplasia is the involvement of half of the body (at least one arm and one leg); affected parts may be contralateral or ipsilateral,
- Simple hemihyperplasia is the involvement of a single limb, and
- Hemifacial hyperplasia is the involvement of one side of the face.

Etiology. The cause is unknown, but the condition has been variously ascribed to vascular or lymphatic abnormalities; CNS disturbances; and chromosomal abnormalities.

Clinical Features. Patients affected by facial hemihypertrophy exhibit an enlargement which is confined to one side of the body, unilateral macroglossia and premature development, and eruption as well as an increased size of dentition. Familial occurrence has been reported on a few occasions, according to the excellent review of the condition by Rowe, who described four additional cases. Of all reported cases, females are affected somewhat more frequently than males (63% versus 37%), according to the review by Ringrose. There is an almost equal involvement of the right and left sides.

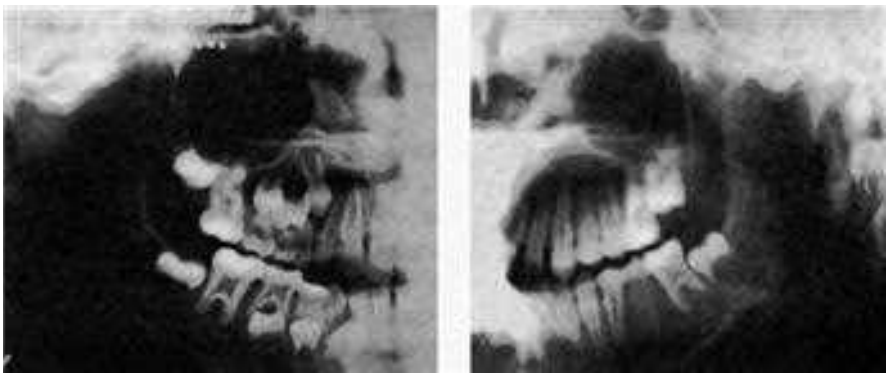
Oral Manifestations. The dentition of the hypertrophic side, according to Rowe, is abnormal in three respects: crown size, root size and shape, and rate of development. Rowe has also pointed out that not all teeth in the enlarged area are necessarily affected in a similar fashion. There is little information about the effects on the deciduous dentition, but the permanent teeth on the affected side are often enlarged, although not exceeding a 50% increase in size. This enlargement may involve any tooth, but seems to occur most frequently in the cuspid, premolars, and first molar. The roots of the teeth are sometimes proportionately enlarged but may be short.

Characteristically, the permanent teeth on the affected side develop more rapidly and erupt before their counterparts on the uninvolved side (Fig. 1-5). Coincident to this phenomenon is premature shedding of the deciduous teeth. The bone of the maxilla and mandible is also enlarged, being wider and thicker, sometimes with an altered trabecular pattern.

The tongue is commonly involved by the hemihypertrophy and may show a bizarre picture of enlargement of lingual papillae in addition to the general unilateral enlargement and contralateral displacement. In addition, the buccal mucosa frequently appears velvety and may seem to hang in soft, pendulous folds on the affected side.

Histologic Features. Tissue examination has been infrequently reported but is generally uninformative. In those cases reported, true muscular hypertrophy was not found.

Treatment and Prognosis. There is no specific treatment for this condition other than attempts at cosmetic repair. Cosmetic surgery is advised after cessation of growth. Effect on life expectancy is not certain, but in some cases patients have lived a normal life span. Periodic abdominal ultrasound/MRI is recommended to rule out tumors.



A B

Figure 1-5. Facial hemihypertrophy.
The difference in the eruption pattern of the teeth on each side is apparent. The teeth on the affected side, where all deciduous teeth have already been lost, are not appreciably larger than those on the unaffected side *(Courtesy of Dr John B Wittgen)*.

Differential Diagnosis. There are certain diseases of the jaws, such as neurofibromatosis and fibrous dysplasia of the jaws, that may give the clinical appearance of facial hemihypertrophy, but these can usually be differentiated readily by the lack of effect on tooth size and rate of eruption.

Facial Hemiatrophy

(Parry-Romberg syndrome, Romberg-Parry syndrome, progressive facial hemiatrophy, progressive hemifacial atrophy)

Hemifacial atrophy remains almost as much an enigma today as it was when first reported by Romberg in 1846. Hemifacial atrophy, originally described by Parry and Henoch and Romberg consists of slowly progressive atrophy of the soft tissues of essentially half the face, which is characterized by progressive wasting of subcutaneous fat, sometimes accompanied by atrophy of skin, cartilage, bone and muscle. Although the atrophy is usually confined to one side of the face and cranium, it may occasionally spread to the neck and one side of the body and it is accompanied usually by contralateral Jacksonian epilepsy, trigeminal neuralgia, and changes in the eyes and hair. Evidence of a mendelian basis is lacking. Lewkonia and Lowry reported the case of a 16-year-old boy who developed facial changes at age seven and had localized scleroderma on one leg and the trunk. The presence of antinuclear antibodies in his serum suggested that the Parry-Romberg syndrome may be a form of localized scleroderma. Hemifacial atrophy is a form of localized scleroderma and is supported by its concurrence with scleroderma.

Hemifacial atrophy is a rare condition that occurs sporadically although some familial distribution has been found. The majority of cases are sporadic with no definite inheritance being proven in the literature.

Etiology. The etiology has been the subject of considerable debate. Wartenburg considered the primary factor to be a cerebral disturbance leading to increased and unregulated activity of sympathetic nervous system, which in turn produced the localized atrophy through its trophic functions conducted by way of sensory trunks of the trigeminal nerve. Other workers suggested extraction of teeth, local trauma, infection and genetic factors could also be a cause. In a paper published in 1973, Poswillo attributed the development of facial deformities to the disruption of the stapedial artery. Poswillo fed pregnant rats with triazine and pregnant monkeys with thalidomide and showed the consistent maldevelopment of first and second branchial arch structures. Robinson, in 1987, supported Poswillo's theory by demonstrating carotid flow abnormalities in two and defects related to vascular disruption in a third child with craniofacial microsomia.

Clinical Features. Hemifacial atrophy is a syndrome with diverse presentation. The most common early sign is a painless cleft, the 'coup de sabre,' near the midline of the face or forehead. This marks the boundary between normal and atrophic tissue. A bluish hue may appear in the skin overlying atrophic fat.

The affected area extends progressively with the atrophy of the skin, subcutaneous tissue, muscles, bones, cartilages, alveolar bone and soft palate on that side of the face. In addition to facial wasting that may include the ipsilateral salivary glands and hemiatrophy of the tongue, unilateral involvement of the ear, larynx, esophagus, diaphragm, kidney and brain have been reported.

It starts in the first decade and lasts for about three years before it becomes quiescent. The final deformity varies widely, burning itself out in some patients with minimal atrophy, while in others progressing to marked atrophy.

Neurological disorders are found in 15% of patients, while ocular findings occur in 10–40%, the most common being enophthalmos.

Rarely, one half of the body may be affected. This condition may be accompanied by pigmentation disorders, vitiligo, pigmented facial nevi, contralateral Jacksonian epilepsy, contralateral trigeminal neuralgia and ocular complications.

The disease occurs more frequently in women; female to male ratio is 3 : 2. It has a slight predilection for the left side and appears in the first or second decades of life. It progresses over a period of two and 10 years, and atrophy appears to follow the distribution of one or more divisions of the trigeminal nerve. The resulting facial flattening may be mistaken for Bell's palsy (Fig. 1-6).

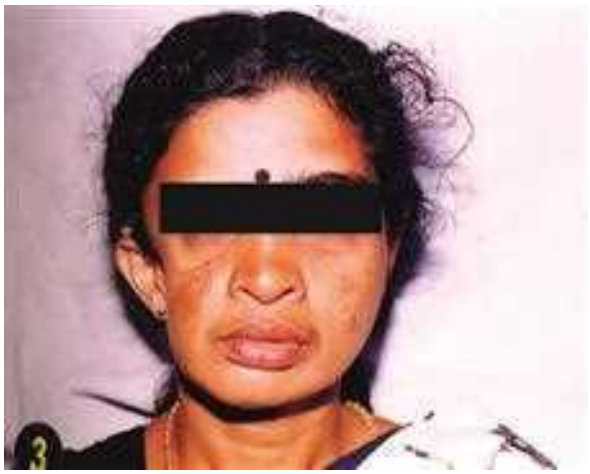


Figure 1-6. Facial hemiatrophy.

Oral Manifestations. Dental abnormalities include incomplete root formation, delayed eruption and severe facial asymmetry, resulting in facial deformation and difficulty with mastication. Hemiatrophy of the lips and the tongue is reported, as are dental effects. Foster has reported that growth of the teeth may be affected just as other tissues are involved. Eruption of teeth on the affected side may also be retarded.

Differential Diagnosis. Post-traumatic fat atrophy, hemifacial microsomia (first and second branchial arch syndrome), Goldenhar's syndrome, and partial lipodystrophy which is; however, always bilateral.

Treatment and Prognosis. There is no specific treatment for the condition. It has been found that, typically, the disease will be progressive for a period of several years and then remain unchanged for the remainder of the patient's life.

ABNORMALITIES OF DENTAL ARCH RELATIONS

In the preceding sections the conditions discussed are those in which there is an actual or apparent abnormal variation in size of one or both jaws. Of far greater importance than a simple disparity in size is the disparity in relation of one jaw to the other and the difficulties in occlusion and function that result.

A great many different types of malocclusion exist, and many classifications have been evolved in an attempt to unify methods of treatment. The classification of Angle, proposed in 1899, is the most universally known and used. That classification, with the approximate percentage occurrence as determined by Angle in a large group of orthodontic patients, is as follows:

Class I. Arches in normal mesiodistal relations 69.0%.

Class II. Mandibular arch distal to normal in its relation to the maxillary arch.
Division 1. Bilaterally distal, protruding maxillary incisors 9.0.
Subdivision. Unilaterally distal, protruding maxillary incisors 3.5.
Division 2. Bilaterally distal, retruding maxillary incisors 4.0.
Subdivision. Unilaterally distal, retruding maxillary incisors 10.0.

Class III. Mandibular arch mesial to normal in its relation to the maxillary arch.
Division. Bilaterally mesial 3.5.
Subdivision. Unilaterally mesial 1.0.

Since these abnormal jaw relations constitute a separate course of study, no further allusion to this subject will be made here.

DEVELOPMENTAL DISTURBANCES OF LIPS AND PALATE

Congenital Lip and Commissural Pits and Fistulas

Congenital lip pits and fistulas are malformations of the lips, often following a hereditary pattern, that may occur alone or in association with other developmental anomalies such as various oral clefts. Both Taylor and Lane and McConnel and his associates have emphasized that in 75–80% of all cases of congenital labial fistulas, there is an associated cleft lip or cleft palate, or both. The association of pits of the lower lip and cleft lip and/or cleft palate, termed van der Woude's syndrome, has been reviewed by Cervenka and his associates.

Commissural pits are an entity probably very closely related to lip pits, but occur at the lip commissures, lateral to the typical lip pits. Everett and Wescott have described this entity and noted that it is also frequently hereditary, possibly a dominant characteristic following a Mendelian pattern, and may be associated with other congenital defects.

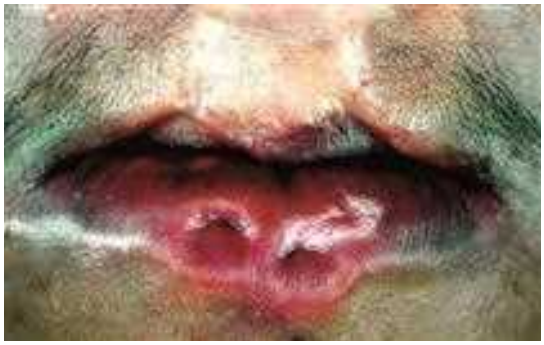
Etiology. Many theories of the etiology of congenital lip pits have been offered, but none has been universally accepted. Pits may result from notching of the lip at an early stage of development, with fixation of the tissue at the base of the notch, or from failure of complete union of the embryonic lateral sulci of the lip, which persist and ultimately develop into the typical pits.

Commissural pits are also difficult to explain, but they occur at the site of the horizontal facial cleft and may represent defective development of this embryonic fissure.

Clinical Features. The lip pit or fistula is a unilateral or bilateral depression or pit that occurs on the vermilion surface of either lip but far more commonly on the lower lip (Fig. 1-7A). In some cases a sparse mucous secretion may exude from the base of this pit. The lip sometimes appears swollen, accentuating the appearance of the pits.

Commissural pits appear as unilateral or bilateral pits at the corners of the mouth on the vermilion surface (Fig. 1-7B). An actual fistula may be present from which fluid may be expressed. Whether this tract, either in lip or commissural fistulas, represents a true duct is not clear. Interestingly, in several cases preauricular pits have been reported in association with commissural pits.

A



B

Figure 1-7. (A) Congenital lip pits. (B) Congenital commissural pits.
(Courtesy of Dr Spencer Lilly, Meenakshi Ammal Dental College, Chennai).

Treatment. Surgical excision of these various pits has been recommended but primarily for academic information, since the pits are harmless and seldom manifest complications.

van der Woude Syndrome

(Cleft lip syndrome, lip pit syndrome, dimpled papillae of the lip)

van der Woude syndrome is an autosomal dominant syndrome typically consisting of a cleft lip or cleft palate and distinctive pits of the lower lips. The degree to which individuals carrying the gene are affected is widely variable, even within families. These variable manifestations include lip pits alone, missing teeth, or isolated cleft lip and palate of varying degrees of severity. Other associated anomalies have also been described.

Etiology. The most prominent and consistent feature of van der Woude syndrome is orofacial anomalies. They are due to an abnormal fusion of the palate and lips, at days 30–50 postconception. The van der Woude syndrome can be caused by deletions in chromosome band **1q32,** and linkage analysis has confirmed this chromosomal locus as the disease gene site. The gene has been localized to chromosome band **1q32**. Further studies have raised the possibility that the degree of phenotypic expression of a gene defect at this locus may be influenced by a second modifying gene that has been mapped to chromosome band **17p11**.

Clinical Features. In general, van der Woude syndrome affects about 1 in 100,000–200,000 people. About 1–2% of patients with cleft lip or palate have van der Woude syndrome. The van der Woude syndrome affects both genders equally and no difference among them have been reported. The severity of the van der Woude syndrome varies widely, even within families. About 25% of individuals with the van der Woude syndrome have no findings or minimal ones, such as missing teeth or trivial indentations in the lower lips. Others have severe clefting of the lip or palate. The hallmark of the van der Woude syndrome is the association of cleft lip and/or palate with distinctive lower lip pits. This combination is seen in about 70% of those who are overtly affected but in less than half of those who carry the gene. The cleft lip and palate may be isolated. They may take any degree of severity and may be unilateral or bilateral. Submucous cleft palate is common and may be easily missed on physical examination. Hypernasal voice and cleft or bifid uvula are clues to this diagnosis. It is possible as well that a bifid uvula is an isolated finding in certain individuals with the van der Woude syndrome. The lower lip pits seen in this syndrome are fairly distinctive (Fig. 1-8). The pits are usually medial, on the vermilion portion of the lower lip. They tend to be centered on small elevations in infancy, but are simple depressions in adults. These pits are often associated with accessory salivary glands that empty into the pits, sometimes leading to embarrassing visible discharge. Occasionally lip pits may be the only manifestation of the syndrome. Affected individuals may have maxillary hypodontia; missing maxillary incisors or missing premolars. Again, this may be the only manifestation of the syndrome. Although infrequently reported, other oral manifestations include syngnathia (congenital adhesion of the jaws); narrow, high, arched palate; and ankyloglossia (short glossal frenulum or tongue-tie).

Extraoral Manifestations. The reported incidence of extraoral manifestations are rare but include limb anomalies, popliteal webs, and brain abnormalities. Accessory nipples, congenital heart defects, and Hirschsprung disease have also been reported. It is uncertain whether these extraoral manifestations are unassociated additional anomalies or infrequently expressed aspects of van der Woude syndrome.

Treatment. Along with a thorough orofacial examination, a thorough general physical examination helps to determine if

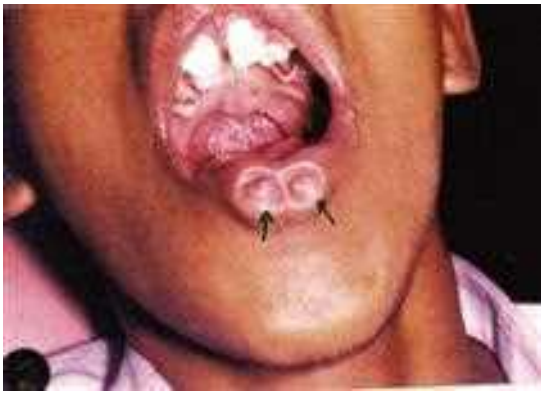


Figure 1-8. Bilateral lip pits.

there are other associated anomalies of the cardiovascular system, genitourinary system, limbs, or other organ systems. Examination and genetic counseling by a pediatric geneticist (dysmorphologist) is suggested for families that may be affected by the van der Woude syndrome. This should include an examination of as many potentially affected family members (probands) as possible. Surgical repair of the cleft lip and palate or other anomalies may be required, when planning surgical intervention, imaging studies of affected areas, such as CT scanning of the oropharynx, may be appropriate. Even among those less severely affected, surgical excision of lip pits is often performed, either to alleviate discomfort or for cosmetic reasons (e.g. improving the appearance of lip pits or reducing mucous discharge).

Cleft Lip and Cleft Palate

The term cleft lip and palate is commonly used to represent two types of malformation, i.e., cleft lip with or without cleft palate (CL/P) and cleft palate (CP). Cleft lip and palate are common congenital malformations. The reported incidence of clefts of the lip and palate varies from 1 in 500 to 1 in 2500 live births depending on geographic origin, racial and ethnic background and socioeconomic status. In general, Asian population have the highest frequencies, often at 1 in 500 or higher, with Caucasian population intermediate, and African-derived population the lowest at 1 in 2500.

An understanding of the normal human maxillofacial development is necessary before a discussion of cleft lip and palate. During the fourth week of gestation, the maxillary processes emerge from the first branchial arch on each side and the nasal placodes form from the frontal prominence. By the fifth week, all the primordia for the lip and palate are present. The medial, lateral nasal and the frontonasal processes are formed from the nasal placodes and the maxillary processes continue to enlarge. During the seventh week the medial nasal, frontonasal and maxillary processes fuse to form the primary palate, which becomes the medial portion of the upper lip, alveolus and the anterior part of hard palate up to the incisive foramen. When the primary palate is completely formed, the maxillary processes enlarge intraorally to form the palatine processes. During the 8th week of gestation, the palatal shelves fill up the space on both sides of the tongue. During the 9th and 10th weeks, the mandibular arch enlarges and the tongue drops. The palatal shelves transpose horizontally and fuse with each other and with the anterior part of the palate. Palatal fusion occurs anteroposteriorly and the process is completed by the 11th to 12th weeks (Shapiro, 1976).

Failure in the fusion of the nasal and maxillary processes leads to the cleft of the primary palate, which can be unilateral or bilateral. The degree of cleft can vary from a slight notch on the lip to complete cleft of the primary palate. Cleft of the secondary palate is medial. It varies from bifid uvula to complete cleft palate up to the incisive foramen. When it is associated with the primary palate, a complete uni- or bilateral cleft lip and palate is formed.

Etiology. It has been clearly established by Fogh-Andersen and confirmed by numerous other investigators that two separate and distinct entities exist:

- Cleft lip with or without associated cleft palate, and
- Isolated cleft palate.

Heredity is undoubtedly one of the most important factors to be considered in the etiology of these malformations. However, there is increasing evidence that environmental factors are important as well. According to Fogh-Andersen, slightly less than 40% of the cases of cleft lip with or without cleft palate are genetic in origin, whereas slightly less than 20% of the cases of isolated cleft palate appear to be genetically derived. Most investigations indicate that the inheritance pattern in cleft lip with or without cleft palate is different from that in isolated cleft palate. The mode of transmission of the defect is uncertain. This has been discussed by Bhatia, who pointed out that the possible main modes of transmission are either by a single mutant gene, producing a large effect, or by a number of genes (polygenic inheritance), each producing a small effect which together create this condition. It should be pointed out that cytogenetic studies have failed to reveal visible alterations in chromosomal morphology of the affected individuals.

Bixler more recently has expanded upon this concept and reiterated that there are two forms of clefts. The most common is hereditary, its nature being most probably *polygenic* (determined by several different genes acting together). In other words, when the total genetic liability of an individual reaches a certain minimum level, the threshold for expression is reached and a cleft occurs. Actually, it is presumed that every individual carries some genetic liability for clefting, but if this is less than the threshold level, there is no cleft. When the individual liabilities of two parents are added together in their offspring, a cleft occurs if the threshold value is exceeded. However, even though this is the most common form of cleft, the threshold value is sufficiently high that it is a low-risk type. The second form of cleft is **monogenic** or **syndromic** and is associated with a variety of other congenital anomalies. Since these are monogenic, they are of a high-risk type. Bixler has pointed out that, fortunately, the clefting syndromes are rare and probably make up only 5% of all cleft cases even though, according to Cohen, there are now over 300 clefting syndromes reported in the literature.

Although there is insufficient evidence that nutritional disturbances cause cleft palates in human beings, abnormal dietary regimens have caused developmental clefts in animals. Cleft palate has been experimentally produced in newborn rats by feeding diets either deficient or excessive in vitamin A to maternal rats during pregnancy. Riboflavin-deficient diets fed to pregnant rats have also produced offspring with a high incidence of cleft palate. The administration of cortisone to pregnant rabbits has induced similar clefts in their young.

Strean and Peer reported that physiologic, emotional, or traumatic stress may play a significant role in the etiology of human cleft palate, since stress induces increased function of the adrenal cortex and secretion of hydrocortisone. Their study,

based on histories of 228 mothers of children with cleft palate, confirms the experimental findings of cleft palate in animals due to the action of stressor agents or the administration of cortisone. However, Fraser and Warburton have reported data which indicate that neither maternal emotional stress nor the lack of a prenatal nutritional supplement was causally related to the occurrence of cleft lip or cleft palate.

Other factors that have been suggested as possible causes of cleft palate include:

- A defective vascular supply to the area involved
- A mechanical disturbance in which the size of the tongue may prevent the union of parts
- Circulating substances, such as alcohol and certain drugs and toxins
- Infections
- Lack of inherent developmental force.

Despite the numerous clinical and experimental investigations, the etiology of cleft palate in the human being is still largely unknown. It must be concluded; however, that heredity is probably the most important single factor.

Clinical Features. Cleft lip with or without palate is more common in males than in females. Males have also been reported to have more severe defects, whereas the isolated cleft palate is more common in females.

Clefts can be divided into nonsyndromic and syndromic forms. Syndromic forms of clefts include those cases that have additional birth defects like lip pits or other malformations, whereas nonsyndromic clefts are those cases wherein the affected individual has no other physical or developmental anomalies and no recognized maternal environmental exposures. At present, most studies suggest that about 70% of cases of cleft lip with or without palate and 50% of isolated cleft palate are nonsyndromic. The remaining syndromic cases can be subdivided into chromosomal anomalies, teratogens and uncategorized syndromes.

Cleft lip can occur as a unilateral (on the left or right side) or as a bilateral anomaly. The line of cleft always starts on the lateral part of the upper lip and continues through the philtrum to the alveolus between the lateral incisor and the canine tooth. The clefting anterior to the incisive foramen (i.e. lip and alveolus) is also defined as a cleft of primary palate. Cleft lip may occur with a wide range of severity, from a notch located on the left or right side of the lip to the most severe form, bilateral cleft lip and alveolus that separates the philtrum of the upper lip and premaxilla from the rest of the maxillary arch. When cleft lip continues from the incisive foramen further through the palatal suture in the middle of the palate, a cleft lip with palate (either unilateral or bilateral) is present (Figs. 1-9, 1-10). A wide range of severity may be observed. The cleft line may be interrupted by skin or mucosa bridges, hard (bone) bridges, or both, corresponding to a diagnosis of an **incomplete cleft**. This occurs in unilateral and bilateral CLP.

Isolated cleft palate is etiologically and embryologically different from cleft lip with or without cleft palate. Several subtypes of isolated cleft palate can be diagnosed based on severity. The uvula is the place where the minimal form of clefting of the palate is observed (Fig. 1-11). A more severe form is a cleft of the soft palate. A complete cleft palate constitutes a cleft of the hard palate, soft palate, and cleft uvula. The clefting posterior to the incisive foramen is defined as a cleft of secondary palate.

Classification of CLP

Various classification schemes have been devised in the last 70 years, but few have received widespread clinical acceptance. Four of the more accepted schemes are depicted:

Davis and Ritchie classification. Each of the following subgroups is further subdivided into the extent of the cleft (1/3, 1/2, etc.):

- Group I: Clefts anterior to the alveolus (unilateral, median, or bilateral CL)
- Group II: Postalveolar clefts (CP alone, soft palate alone, soft palate and hard palate, or submucous cleft).

Veau classification. The Veau classification system is illustrated in:

- Group I (A): Defects of the soft palate only
- Group II (B): Defects involving the hard palate and soft palate
- Group III (C): Defects involving the soft palate to the alveolus, usually involving the lip
- Group IV (D): Complete bilateral clefts.

Kernahan and Stark symbolic classification. This classification highlights the anatomic and embryonic importance of the incisive foramen formed during weeks 4–7 GA. The secondary palate forms the roof of the mouth from the incisive foramen to the uvula during weeks 7–12 GA.

This system provides a graphic classification scheme using a Y-configuration, which can be divided into 9 areas:

- Areas 1 and 4: Lip
- Areas 2 and 5: Alveolus
- Areas 3 and 6: Palate between the alveolus and the incisive foramen
- Areas 7 and 8: Hard palate
- Area 9: Soft palate.

International confederation of plastic and reconstructive surgery classification. This system uses an embryonic framework to divide clefts into 4 groups, with further subdivisions to denote unilateral or bilateral cases.

- Group I: Defects of the lip or alveolus
- Group II: Clefts of the secondary palate (hard palate, soft palate, or both)
- Group III: Any combination of clefts involving the primary and secondary palates.

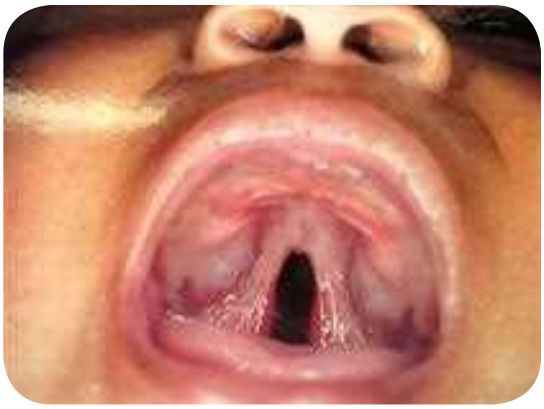


Figure 1-9. Cleft involving both the hard and the soft palates.
(Courtesy of Dr R Manikandan, Meenakshi Ammal Dental College, Chennai).

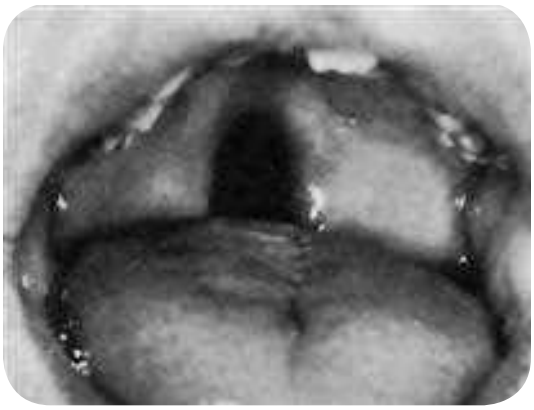


Figure 1-10. Cleft involving the soft palate only.
(Courtesy of Dr John M Tondra and Harold M Trusler).

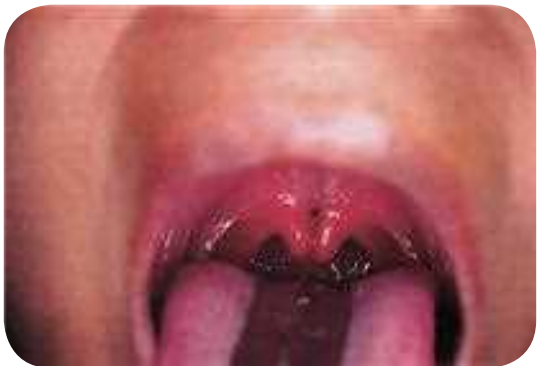


Figure 1-11. Cleft or bifid uvula.
(Courtesy of Dr Manikandan R, Meenakshi Ammal Dental College, Chennai).

A **median maxillary anterior alveolar cleft** is a relatively common defect, occurring in approximately 1% of the population, according to Stout and Collett, but this is unrelated to cleft lip or cleft palate. This type of cleft has been discussed by Gier and Fast, who suggested that it might be due to precocious limitation of the growth of the primary ossification centers on either side of the midline at the primary palate, or to their subsequent failure to fuse. In addition, Miller and his coworkers have suggested that at least some cases may represent an incomplete manifestation of the median cleft-face syndrome (hypertelorism, median cleft of the premaxilla and palate, and cranium bifidum occultum). This syndrome has no clinical manifestations and is usually detected only on routine intraoral radiographic examination (Fig. 1-12).

Clinical Significance. Most cases of cleft lip can be surgically repaired with excellent cosmetic and functional results. It is customary to operate before the patient is one month old or when he has regained his original birth weight and is still gaining.

Both the physical and psychologic effects of cleft palate on the patient are of considerable concern. Eating and drinking are difficult because of regurgitation of food and liquid through the nose. The speech problem is also serious and tends to increase the mental trauma suffered by the patient.

Most individuals with CL, CP, or both, require the coordinated care of providers in many fields of medicine and dentistry, as well as those in speech pathology, otolaryngology, audiology, genetics, nursing, mental health, and social medicine.

Treatment. Treatment of CLP anomalies requires years of specialized care. Although successful treatment of the cosmetic and functional aspects of orofacial cleft anomalies is now

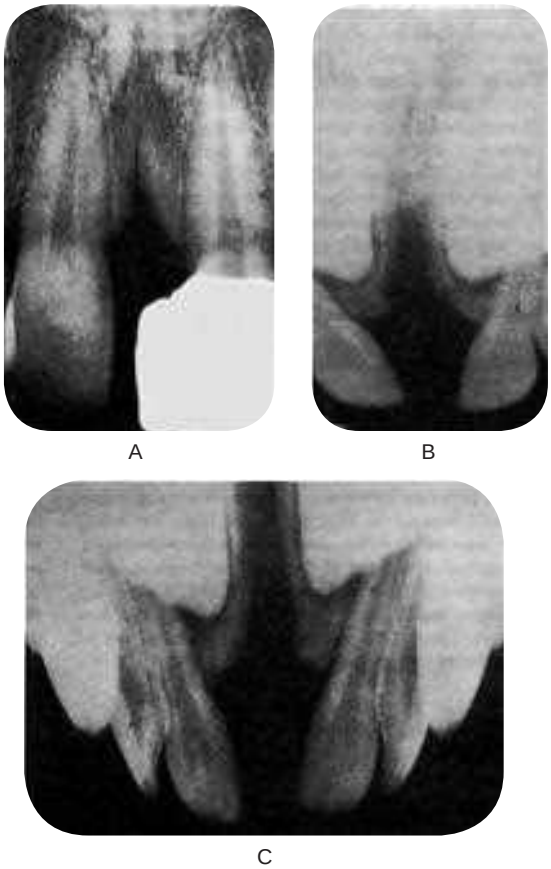


Figure 1-12. Median maxillary anterior alveolar cleft.
All degrees of severity of the cleft may occur *(Copyright by the American Dental Association. Reprinted by permission and by courtesy of Dr Arthur S Miller. From AS Miller, JN Greeley and DL Catena: Median maxillary anterior alveolar cleft: report of three cases. J Am Dent Assoc, 79: 896, 1969).*

possible, it is still challenging, lengthy, costly, and dependent on the skills and experience of a medical team. This especially applies to surgical, dental, and speech therapies. Undoubtedly, closure of the CL is the first major procedure that tremendously changes children's future development and ability to thrive. Variations occur in timing of the first lip surgery; however, the most usual time occurs at approximately three months of age. Pediatricians used to strictly follow a rule of 'three 10s' as a necessary requirement for identifying the child's status as suitable for surgery (i.e. 10 lb, 10 mg/L of hemoglobin, and age 10 weeks). Although pediatricians are presently much more flexible, and some surgeons may well justify a neonatal lip closure, the rule of three 10s is still very useful.

Anatomical differences predispose children with CLP and with isolated CP to ear infections. Therefore, ventilation tubes are placed to ventilate the middle ear and prevent hearing loss secondary to otitis media with effusion (OME). In multidisciplinary teams with significant participation of an otolaryngologist, the tubes are placed at the initial surgery and at the second surgery routinely. The hearing is tested after the first placement when ears are clear with tubes. If no cleft surgery is planned early, placing the tubes by age six months and monitoring hearing with repeated testing is recommended. Complications include eardrum perforation and otorrhea, particularly in patients with open secondary palates in which closure is planned for a later date.

Cheilitis Glandularis

(Actinic cheilitis, squamous cell carcinoma)

Cheilitis glandularis (CG) is a clinical diagnosis that refers to an uncommon and poorly understood inflammatory disorder of the lip. The condition is characterized by progressive enlargement and eversion of the lower labial mucosa that results in obliteration of the mucosal-vermilion interface. With externalization and chronic exposure, the delicate labial mucous membrane is secondarily altered by environmental influences, leading to erosion, ulceration, and crusting. Most significantly, susceptibility to actinic damage is increased. Therefore, CG can be considered a potential predisposing factor for the development of actinic cheilitis and squamous cell carcinoma.

Etiology. CG is an unusual clinical manifestation of cheilitis that evolves in response to one or more diverse sources of chronic irritation. Lip enlargement is attributable to inflammation, hyperemia, edema, and fibrosis. Surface keratosis, erosion, and crusting develop consequent to long-standing actinic exposure, unusual repeated manipulations that include self-inflicted biting or other factitial trauma, excessive wetting from compulsive licking, drying (sometimes associated with mouth-breathing, atopy, eczema, and asthma), and any other repeated stimulus that could serve as a chronic aggravating factor.

Clinical Features. In 1870, von Volkman introduced the term cheilitis glandularis. He described a clinically distinct, deeply suppurative, chronic inflammatory condition of the lower lip characterized by mucopurulent exudates from the ductal orifices of the labial minor salivary glands. In 1914, Sutton proposed that the characteristic lip swelling was attributable to a congenital adenomatous enlargement of the labial salivary glands. This remained the prevailing hypothesis until 1984 when Swerlick and Cooper reported five new cases and a retrospective analysis of all cases of CG reported until that time. Their studies revealed no evidence to support the assertion that salivary gland hyperplasia is responsible for CG.

Cheilitis glandularis is a chronic progressive condition. Patients typically present for diagnostic consultation within 3–12 months of onset. Complaints vary according to the nature and the degree of pain, the enlargement and the loss of elasticity of the lip, and the extent of evident surface change. Asymptomatic lip swelling initially occurs with clear viscous secretion expressible from dilated ductal openings on the mucosal surface. Some patients report periods of relative quiescence interrupted by transient or persistent painful episodes associated with suppurative discharge. A burning discomfort or a sensation of rawness referable to the vermilion border may be reported. This is associated with atrophy, speckled leukoplakic change, erosion, or frank ulceration with crusting. CG affects the lower lip almost exclusively. In more suppurative cases, application of gentle pressure can elicit mucopurulent exudate. Prolonged exposure to the external environment results in desiccation and disruption of the labial mucous membrane, predisposing it to inflammatory, infectious, and actinic influences. This is an uncommon condition. CG has been associated with a heightened risk for the development of squamous cell carcinoma. In many cases, dysplastic (premalignant) surface epithelial change is evident, and frank carcinomas have been reported in 18–35% of cases. The disorder appears to favor adult males; however, cases have been reported in both genders. The condition most frequently occurs between the fourth and seventh decades of life; however, the age range is wide. The risk of dysplasia and carcinoma increases with age, especially in fair-skinned individuals with sun-damaged skin. This is because the characteristic eversion of the lower lip results in long-term chronic exposure of the thinner, more vulnerable labial mucosa to actinic influence.

Classification. CG had historically been subclassified into three types, now believed to represent evolving stages in the severity of a single progressive disorder.

- In the **simple type,** multiple, painless, papular surface lesions with central depressions and dilated canals are seen.
- The **superficial (suppurative) type** (also referred to as **Baelz disease**) consists of painless, indurated swelling of the lip with shallow ulceration and crusting.
- CG of the **deep suppurative type** (CG apostematosa, CG suppurativa profunda, myxadenitis labialis) comprises a deep-seated infection with formation of abscesses, sinus tracts and fistulas, and potential for scarring.

The latter two types of CG have the highest association with dysplasia and carcinoma, respectively.

Histologic Findings. Lip biopsy is indicated to rule out specific granulomatous diseases that predispose to lip enlargement and aid in establishing a definitive diagnosis. A

representative incisional biopsy specimen should consist of a wedge (or punch) of lip tissue that includes surface epithelium and is of adequate depth to ensure inclusion of several submucosal salivary glands. The term cheilitis glandularis is a provisional descriptive designation rather than a definitive diagnosis. It refers to a constellation of clinical findings that can reflect a broad scope of possible histologic changes; therefore, no consistent or pathognomonic features of this disorder are seen at the microscopic level. Instead, a diverse array of possible alterations can be seen in both the surface epithelium and the submucosal tissues. These findings best enable the clinician to presumptively determine the etiology and the nature of individual cases.

The minor salivary glands may appear normal under the microscope, or they may exhibit various changes indicative of nonspecific sialadenitis. These changes can include atrophy or distention of acini, ductal ectasia with or without squamous metaplasia, chronic inflammatory infiltration and replacement of glandular parenchyma, and interstitial fibrosis. Suppuration and sinus tracts may be present in cases that involve bacterial infection. Other possible histologic findings include stromal edema, hyperemia, surface hyperkeratosis, erosion, or ulceration.

Differential Diagnosis. Differential diagnoses of this condition include actinic keratosis, atopic dermatitis, cheilitis granulomatosa (Miescher-Melkersson-Rosenthal syndrome), sarcoidosis and squamous cell carcinoma.

Treatment. The approach to treatment is based on diagnostic information obtained from histopathologic analysis, the identification of likely etiologic factors responsible for the condition, and attempts to alleviate or eradicate those causes. In cases with acute or chronic suppuration, bacterial culture and sensitivity testing is indicated for selection of appropriate antibiotic therapy. Given the relatively small number of reported cases of CG, neither sufficient nor reliable data exist with regard to medical approaches to the condition. Therefore, treatment varies accordingly for each patient. In cases where a history of chronic sun exposure exists (especially if the patient is fair skinned or the everted lip surface is chronically eroded, ulcerated, or crusted), biopsy is strongly recommended to rule out actinic cheilitis or carcinoma.

Cheilitis Granulomatosa
(Miescher-Melkersson-Rosenthal syndrome)

Cheilitis granulomatosa is a chronic swelling of the lip due to granulomatous inflammation. Miescher cheilitis is the term used when the granulomatous changes are confined to the lip. Miescher cheilitis is generally regarded as a monosymptomatic form of the Melkersson-Rosenthal syndrome, although the possibility remains that these may be two separate diseases. Melkersson-Rosenthal syndrome is the term used when cheilitis occurs with facial palsy and plicated tongue. Melkersson-Rosenthal syndrome is occasionally a manifestation of Crohn's disease or orofacial granulomatosis.

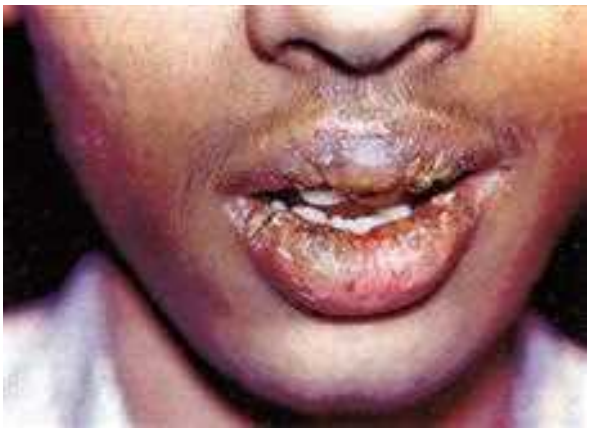


Figure 1-13. Cheilitis granulomatosa.

Etiology. The cause is unknown. A genetic predisposition may exist in Melkersson-Rosenthal syndrome; siblings have been affected, and a plicated tongue may be present in otherwise unaffected relatives. Crohn's disease, sarcoidosis, and orofacial granulomatosis may present in a similar clinical fashion, and with identical histologic findings. Dietary or other antigens are the most common identified causes of orofacial granulomatosis. Contact antigens are sometimes implicated.

Clinical Features. Cheilitis granulomatosa is episodic with nontender swelling and enlargement of one or both lips (Fig. 1-13). Occasionally, similar swellings involve other areas, including the periocular region. The first episode of edema typically subsides completely in hours or days. After recurrent attacks, swelling may persist and slowly increase in degree, eventually becoming permanent. Recurrences can range from days to years. Attacks sometimes are accompanied by fever and mild constitutional symptoms (e.g. headache, visual disturbance).

The earliest manifestation is sudden diffuse or occasionally nodular swellings of the lip or the face involving (in decreasing order of frequency) the upper lip, the lower lip, and one or both cheeks. The forehead, the eyelids, or one side of the scalp may be involved (less common). The upper lip is involved slightly more often than the lower lip, and it may feel soft, firm, or nodular on palpation. Once chronicity is established, the enlarged lip appears cracked and fissured with reddish brown discoloration and scaling. The fissured lip becomes painful and eventually acquires the consistency of firm rubber. Swelling may regress very slowly after some years. Regional lymph nodes are enlarged (usually minimally) in 50% of patients. A fissured or plicated tongue is seen in 20–40% of patients. Its presence from birth (in some patients) may indicate a genetic susceptibility. Patients may lose the sense of taste and have decreased salivary gland secretion. Facial palsy of the lower motor-neuron type occurs in about 30% of patients. Facial palsy may precede attacks of edema by months or years, but it more commonly develops later. Facial palsy is intermittent at first, but it may become permanent. It can be unilateral or bilateral, partial or complete. Other cranial nerves

(e.g. olfactory, auditory, glossopharyngeal, hypoglossal) are occasionally affected. Poorly defined association of psychiatric and neurologic features are reported. Autonomic disturbances may occur. In granulomatous cheilitis, normal lip architecture is eventually altered by the presence of lymphedema and noncaseating granulomas in the lamina propria. The frequency is unknown; the condition is rare. Morbidity depends on whether underlying organic disease, such as Crohn's disease or sarcoidosis, is present. There is no racial and sexual predilection. The age of onset is usually young adulthood.

Differential Diagnosis. Differential diagnoses include insect bites and sarcoidosis. Serum angiotensin-converting enzyme test, chest radiography or gallium or positron emission tomography (PET) scanning may be performed to help exclude sarcoidosis. Gastrointestinal tract endoscopy and radiography may be used to help exclude Crohn's disease.

Histologic Features. The histologic features of cheilitis granulomatosa and the swellings of the syndrome are rather characteristic, consisting of a chronic inflammatory cell infiltrate — particularly peri- and para-vascular aggregations of lymphocytes, plasma cells, and histiocytes—and focal noncaseating granuloma formation with epithelioid cells and Langhans type giant cells. The microscopic findings are suggestive of sarcoidosis, but as yet there is insufficient evidence to relate cheilitis granulomatosa with sarcoid.

Treatment. Patch tests may be used to help exclude reactions to metals, food additives, or other oral antigens. Some cases may be associated with such sensitivities. If found, avoidance of the implicated allergen is recommended. This condition can be conservatively managed by intralesional corticosteroid injections, nonsteroidal anti-inflammatory agents, mast cell stabilizers, clofazimine and tetracycline (used for anti-inflammatory activity). Surgery and radiation have been reported to be used.

HEREDITARY INTESTINAL POLYPOSIS SYNDROME

(Peutz-Jeghers syndrome, intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules)

The Peutz-Jeghers syndrome is an autosomal dominantly inherited disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. A 15-fold elevated relative risk of developing cancer exists in this syndrome over that of the general population; cancer primarily is of the GI tract, including the pancreas and luminal organs, and of the female and male reproductive tracts and the lung. The syndrome was named after Peutz, who noted a relationship between the intestinal polyps and the mucocutaneous macules in 1921, and after Jeghers, who is credited with the definitive descriptive reports in 1944 and later in 1949.

Etiology. The cause of the Peutz-Jeghers syndrome appears to be a germline mutation of the **STK11** (serine threonine kinase 11) gene in most cases, located on band **19p13.3**. Penetrance of the gene is variable, causing varied phenotypic manifestations among patients with Peutz-Jeghers syndrome (e.g. inconsistent number of polyps, differing presentation of the macules) and allowing for a variable presentation of cancer. Because the signaling pathway of the *STK11* gene product currently is not identified, the mechanism of hamartomatous polyp formation and mucocutaneous pigmentation is not known. In cancer formation, *STK11* inactivation appears to occur early and might be followed by interruption of the APC/β-catenin and p53 pathways, but this has not been fully elucidated. *STK11* may be a tumor suppressor gene in that its overexpression can induce a growth arrest of a cell at the G1 phase of the cell cycle and that somatic inactivation of the unaffected allele of *STK11* often is observed in polyps and cancers from patients with the Peutz-Jeghers syndrome.

Clinical Features. The Peutz-Jeghers syndrome has been described in all races. The occurrence of cases in males and females is about equal. The average age at diagnosis is 23 years in men and 26 years in women. The affected individuals usually have a positive family history of the Peutz-Jeghers syndrome. The principal causes of morbidity stem from the intestinal location of the polyps (i.e. small intestine, colon, stomach). Morbidity includes small intestinal obstruction and intussusception (43%), abdominal pain (23%), hematochezia (14%), and prolapse of a colonic polyp (7%), and these typically occur in the second and third decades of life.

The presenting complaints include repeated bouts of abdominal pain in patients younger than 25 years, unexplained intestinal bleeding in a young patient, or menstrual irregularities in females (due to hyperestrogenism from sex cord tumors with annular tubules). Cutaneous pigmentation (1–5 mm macules) of the perioral region crossing the vermilion border (94%), perinasal, and perioral areas is seen; pigmentation may also be present on the fingers and toes, on the dorsal and ventral aspects of the hands and feet, and around the anus and genitalia. This pigmentation may fade after puberty. Mucous membrane pigmentation primarily affects the buccal mucosa (66%) and the intestinal mucosa rarely. Other manifestations of this syndrome include precocious puberty, prolapse of tissue from the rectum, rectal mass (rectal polyp), testicular mass, gynecomastia and growth acceleration (due to Sertoli cell tumor).

Histologic Features. Characteristic pathology of Peutz-Jeghers polyps includes extensive smooth muscle arborization throughout the polyp, with the appearance of pseudoinvasion because some of the epithelial cells, usually from benign glands, are surrounded by the smooth muscle.

Treatment. Surgical treatment for cancers detected by surveillance has been recommended.

Labial and Oral Melanotic Macule

The oral mucosa is usually not pigmented despite the fact that it has the same density of melanocytes as the skin. Occasional patients; however, will show a focal area of melanin

deposition, either as a response to local chronic conditions (mechanical trauma, tobacco smoking, chronic autoimmune mucositis), racial background (the darker a person's skin color the more likely they are to have oral pigmentation), or systemic medications, especially chloroquine. Moreover, certain syndromes and systemic diseases have oral pigmentation as part of their spectrum.

Most focal melanin deposits of the oral mucosa which are not associated with race or an appropriate syndrome are innocuous surface discolorations called oral melanotic macule (focal melanosis). This entity represents not only a focal increase in melanin deposition but a concomitant increase in the number of melanocytes. Unlike the cutaneous ephelis (freckle), the oral melanotic macule is neither dependent on sun exposure, nor does it show the elongated rete ridges of actinic lentigo. Some authorities have questioned the purported lack of an association with actinic irradiation for melanotic macule located on the vermilion border, preferring to consider the lesion at this site to be a distinct entity called labial melanotic macule. Melanotic macules are found in the mouths of 1 of every 1,000 adults.

Clinical Features. The oral melanotic macule has a 2:1 female predilection with an average age of 43 years at the time of diagnosis, although it can develop at any age. One-third of lesions occur on the vermilion border of the lower lip, but the buccal mucosa, gingiva and palate are other sites of common occurrence. Almost one fifth of the lesions are multiple.

The typical macule is a well-demarcated, uniformly tan to dark brown, asymptomatic, round or oval discoloration less than 7 mm in diameter. The lesion is not thickened and has the same consistency as surrounding mucosa. It tends to have an abrupt onset and seldom enlarges after diagnosis.

A special case of oral melanosis, called **smoker's melanosis** is found on the gingival or buccal mucosa in heavy smokers. It has an adult onset and is often associated with a concomitant superficial white/gray keratosis. The keratosis may become thick enough to mimic *leukoplakia,* although it is not known whether or not it is a true precancer. Both the pigmentation and the keratosis diminish or disappear once the tobacco habit is stopped.

While the melanotic macule is an innocuous lesion, it must be remembered that focal oral and oropharyngeal pigmentation might represent an internal malignancy (usually lung), an oral manifestation of a systemic disease or one facet of a genetic syndrome.

Histologic Features. The oral melanotic macule is characterized by an otherwise normal stratified squamous epithelium with abundant melanin deposits within the keratinocytes of the basal and parabasal layers. Deposits may also be seen within subepithelial stroma (melanin incontinence), perhaps within macrophages or melanophages. There is no underlying inflammatory response. The melanin can be distinguished from iron deposits with melanin stains or by the loss of brown color after bleaching. Brown formalin deposits can be differentiated by their association with erythrocytes rather than with basal layer epithelial cells.

Treatment and Prognosis. No treatment is required for oral melanotic macule except for esthetic considerations. The intraoral melanotic macule has no malignant transformation potential, but an early melanoma could have a similar clinical appearance. For this reason, pigmented macular lesions of recent onset, large size, irregular pigmentation, unknown duration, or with a history of recent enlargement should be excised and examined histopathologically.

DEVELOPMENTAL DISTURBANCES OF ORAL MUCOSA

Fordyce's Granules
(Fordyce's disease)

This is not a disease of the oral mucosa, as the name might indicate, but rather a developmental anomaly characterized by heterotopic collections of sebaceous glands at various sites in the oral cavity. It has been postulated that the occurrence of sebaceous glands in the mouth may result from inclusion in the oral cavity of ectoderm having some of the potentialities of skin in the course of development of the maxillary and mandibular processes during embryonic life. A complete review of Fordyce's granules was published by Miles, and a superb investigation of the sebaceous glands of the lips and oral cavity was carried out by Sewerin.

Clinical Features. Fordyce's granules appear as small yellow spots, either discretely separated or forming relatively large plaques, often projecting slightly above the surface of the tissue (Fig. 1-14). They are found most frequently in a bilaterally symmetrical pattern on the mucosa of the cheeks opposite the molar teeth but also occur on the inner surfaces of the lips, in the retromolar region lateral to the anterior faucial pillar, and occasionally on the tongue, gingiva, frenum, and palate. Ectopic sebaceous glands have been discussed in an excellent review by Guiducci and Hyman and are recognized to occur,

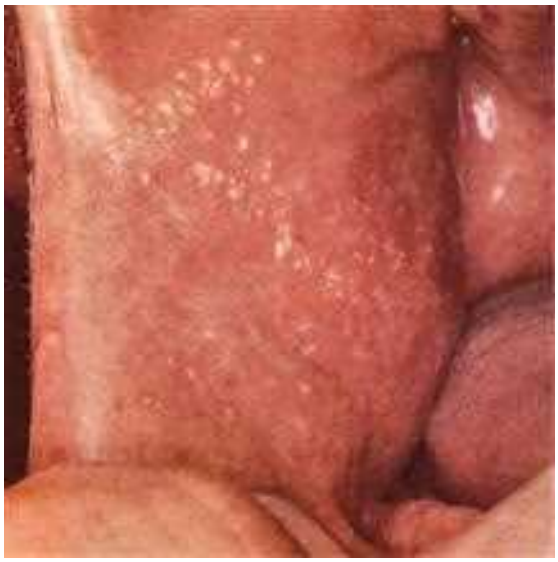


Figure 1-14. Fordyce's granules.

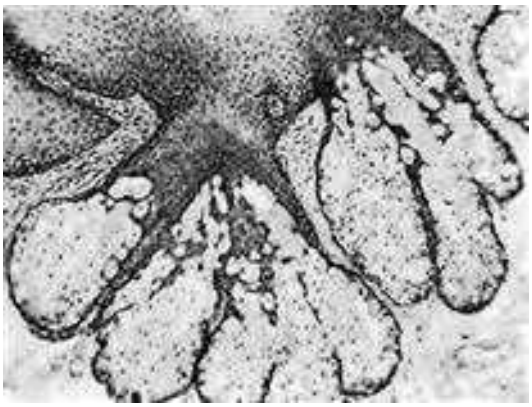


Figure 1-15. Fordyce's granules.
Heterotopic collections of sebaceous glands.

besides in the oral cavity, in the esophagus, the female genitalia including the cervix uteri, the male genitalia, the nipples, the palms and soles, the parotid gland, the larynx, and the orbit.

Studies by Halperin and coworkers, confirmed by Miles, have indicated that the oral condition is present in approximately 80% of the population, with apparently no significant differences in occurrence between the genders or races. Fewer children than adults exhibit Fordyce's granules, probably because the sebaceous glands and hair system do not reach maximal development until puberty. Nevertheless, Miles has reported that large numbers of sebaceous glands in the cheeks and lips may sometimes be found in children long before the age of puberty. Because of the high incidence of these glands in the oral cavity, Knapp has suggested that they be regarded as sebaceous nevi rather than ectopic glandular tissue.

Histologic Features. These heterotopic collections of sebaceous glands are identical with those seen normally in the skin, but are unassociated with hair follicles, although a single hair follicle and hair shaft growing from the gingiva—an extremely rare occurrence—has been reported recently by Baughman (Fig. 1-15). The glands are usually superficial and may consist of only a few or a great many lobules, all grouped around one or more ducts which open on the surface of the mucosa. These ducts may show keratin plugging.

Treatment. These glands are innocuous, have no clinical or functional significance, and require no treatment. However, very rarely a benign sebaceous gland adenoma may develop from these intraoral structures, such as in the case involving the buccal mucosa reported by Miller and McCrea. Sewerin has also reported the occasional development of keratin-filled pseudocysts from the ducts of these sebaceous glands.

Focal Epithelial Hyperplasia
(Heck's disease)

One of the most contagious of the oral papillary lesions is focal epithelial hyperplasia or Heck's disease, another HPV-induced epithelial proliferation first described in 1965 in Native Americans. The level of contagion is exemplified by the fact that in some isolated population up to 40% of children have been affected. Today, it is known to exist in numerous populations and ethnic groups and to be produced by one of the subtypes of the human papillomavirus, HPV-13, and possibly HPV-32. Where the infection is endemic among children, adults seem to have minimal evidence of residual oral lesions and so the lesions are presumed to eventually disappear on their own.

Focal epithelial hyperplasia is somewhat different from other HPV infections in that it is able to produce extreme acanthosis or hyperplasia of the prickle cell layer of the epithelium with minimal production of surface projections or induction of connective tissue proliferation. The mucosa may be 8–10 times thicker than normal.

Clinical Features. Heck's disease primarily occurs in children, but lesions may occur in young and middle-aged adults. There is no gender predilection. Sites of greatest involvement include the labial, buccal and lingual mucosa, but gingival and tonsillar lesions have also been reported.

Individual lesions are broad-based or so slightly elevated as to present as well demarcated plaques. Lesions are frequently papillary in nature, but relatively smooth-surfaced, flat-topped lesions are more commonly seen. Papules and plaques are usually the color of normal mucosa, but may be pale or, rarely, white. Hyperplastic lesions are small (0.3–1.0 cm), discrete, and well-demarcated, but they frequently cluster so closely together that the entire mucosal area takes on a **cobblestone** or **fissured appearance.**

Histologic Features. Epithelial hyperplasia in this disease presents microscopically as an abrupt and sometimes considerable focal acanthosis of the oral epithelium. The thickened mucosa extends upward, not down into underlying connective tissues, hence the lesional rete ridges are at the same depth as the adjacent normal rete ridges. The ridges themselves are widened, often confluent and sometimes club-shaped; they are not long and thin as in *psoriasis* and other diseases. Some superficial keratinocytes show a koilocytic change similar to that seen in other HPV infections, while occasionally others demonstrate a collapsed nucleus which resembles a mitotic figure (mitosoid cell). These presumably result from viral alteration of the cells. Virus-like particles have been noted ultrastructurally within both cytoplasm and nuclei of cells within the spinous layer, and this layer is positive for HPV antigen with *in situ* hybridization.

The lesion is usually easily differentiated from squamous papilloma, verruca vulgaris and condyloma by its lack of pronounced surface projections; the presence of mitosoid cells, and the lack of connective tissue cores in the surface projections, when present. The sessile nature of focal epithelial hyperplasia also serves to separate it from the former two lesions, although this is not a guaranteed distinction.

Focal epithelial hyperplasia also tends to lack the pronounced elongation of thin rete ridges seen in keratoacanthoma and pseudoepitheliomatous hyperplasia, and it lacks the central keratin-filled core of the keratoacanthoma. It also lacks the subepithelial foamy or granular histiocyte-like cells required for the diagnosis of verruciform xanthoma.

Treatment and Prognosis. Conservative excisional biopsy may be required to establish the proper diagnosis, but additional treatment is unnecessary, except perhaps for esthetic reasons relating to visible labial lesions. Spontaneous regression has been reported after months or years, and the disease is rather rare in adults. No case of focal epithelial hyperplasia has been reported to transform into carcinoma. It should be remembered that focal epithelial hyperplasia may be an oral manifestation of AIDS.

DEVELOPMENTAL DISTURBANCES OF GINGIVA

Hereditary gingival fibromatosis is a benign, idiopathic condition affecting both arches. It affects males and females equally and is usually autosomal dominant. The gingiva are markedly enlarged, asymptomatic, nonhemorrhagic, nonexudative. It may be an isolated finding or associated with other syndromes (see below). A relationship with growth hormone deficiency has been suggested. The condition is either of a nodular form or, more commonly, a symmetric form. Onset of the condition usually begins with eruption of the permanent teeth. This condition predisposes one to malpositioning of the teeth, retention of deciduous teeth, esthetic and functional problems. Treatment is gingivectomy in one or several appointments. Recurrence is possible after some years.

Fibromatosis Gingivae

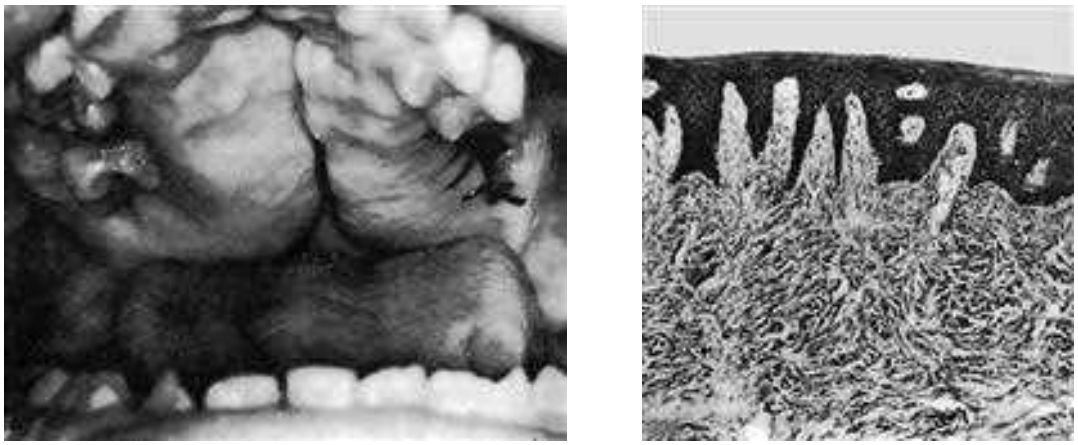
(Elephantiasis gingivae, hereditary gingival fibromatosis, congenital macrogingivae)

Fibromatosis gingivae is a diffuse fibrous overgrowth of the gingival tissues, described for many years under a variety of terms. In the majority of reported cases, the condition was hereditary, being transmitted through a dominant autosomal gene. Zackin and Weisberger have reviewed this condition and presented a family of 11 affected children and 10 normal children from six marriages over four generations, while Emerson has reported the pedigree of a family over four generations in which nine marriages between affected and unaffected persons resulted in seven affected and all 11 normal offsprings. But many cases have appeared to be sporadic, with no familial background. Occasionally other abnormalities have been reported in association with fibromatosis gingivae, but of these, only hypertrichosis has been noted more than a few times. Even this association, in terms of total number of reported cases, is rare.

Clinical Features. This condition is manifested as a dense, diffuse, smooth, or nodular overgrowth of the gingival tissues of one or both arches, usually appearing about the time of eruption of the permanent incisors. It has been reported; however, in even very young children and, in a few instances, at birth (Fig. 1-16A). The tissue is usually not inflamed, but is of normal or even pale color, and it is often so firm and dense that it may prevent the normal eruption of teeth. It is not painful and shows no tendency for hemorrhage. The extent of the tissue overgrowth may be such that the crowns of the teeth are nearly hidden even though they are fully erupted with respect to the alveolar bone (Fig. 1-17).

Histologic Features. The microscopic picture of the tissue in fibromatosis gingivae is similar to that of any fibrous hyperplasia. The epithelium may be somewhat thickened with elongated rete pegs, although the bulk of the tissue is composed of dense fibrous connective tissue. The bundles of collagen fibers are coarse and show few interspersed fibroblasts or blood vessels. Inflammation is an unrelated and variable finding (Fig. 1-16B).

Treatment and Prognosis. When tooth eruption is impeded, surgical removal of the excessive tissue and exposure of the teeth are indicated. The cosmetic appearance may also require surgical excision. The lesion sometimes recurs. It has been reported that tooth extraction alone will cause the tissues to shrink almost to normal and that recurrences can be prevented by this means.



A B

Figure 1-16. Fibromatosis gingivae.
(A) The palatal vault is nearly filled with a dense fibrous mass of tissue. The apparent midline cleft extends only to the bone and is not a true cleft. The maxillary gingiva is also involved. **(B)** The photomicrograph reveals that the mass is made up only of a dense mass of fibrous connective tissue covered by normal epithelium.

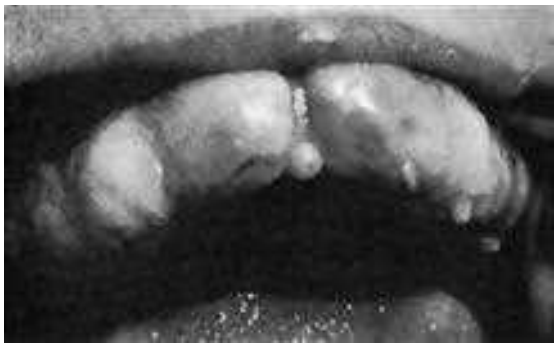


Figure 1-17. Fibromatosis gingivae.
The firm fibrous tissue mass has covered all but the incisal edges and the tips of the cusps of the maxillary teeth.

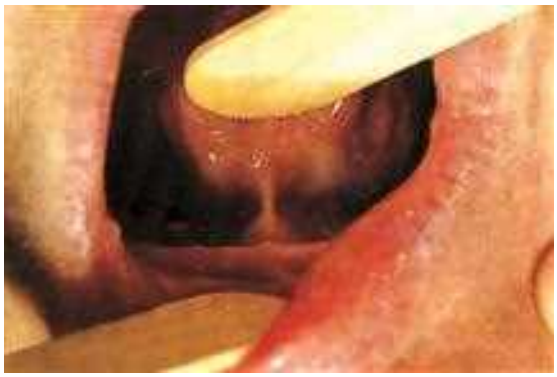


Figure 1-18. Congenital short lingual frenum of the tongue with microglossia.

Retrocuspid Papilla

The retrocuspid papilla, first described by Hirshfeld in 1933 but not reported until 1957, is a small, elevated nodule located on the lingual mucosa of the mandibular cuspids.

Clinical Features. This soft, well-circumscribed, sessile, mucosal nodule, commonly bilateral, is located lingual to the mandibular cuspid, between the free gingival margin and the mucogingival junction.

It is exceedingly common in children, occurring in 99% of those between the ages of eight and 16 years, according to the original report of Hirshfeld, but decreases in incidence with age, occurring in 38% of those between the ages of 25 and 39 years and in 19% of those between the ages of 60 and 80 years. Thus there appears to be regression of the structure with maturity. In addition, most studies have found a greater occurrence bilaterally than unilaterally. A study by Berman and Fay, who have reviewed the studies dealing with the retrocuspid papilla, reported from their own data that the structure was consistently more common in females than in males.

Histologic Features. The structure appears as an elevated mucosal tag often showing mild hyperorthokeratosis or hyperparakeratosis, with or without acanthosis. The underlying connective tissue is sometimes highly vascularized and may exhibit large stellate fibroblasts as well as occasional epithelial rests.

Treatment. Because of its frequency of occurrence, the retrocuspid papilla is often considered to be a 'normal' anatomic structure which regresses with age and requires no treatment.

DEVELOPMENTAL DISTURBANCES OF TONGUE

Aglossia and Microglossia Syndrome

This malformation is very rare, since the first publication which was attributed by Gaillard and Nogué to Antoine De Jussieu in 1718, to present till date there have been less than 35 cases reported (Grinspan, 1976). This anomaly is almost always associated to malformations in the extremities, especially the hands and feet, cleft palate and dental agenesia. Aglosia syndrome is, in reality, a microglossia with extreme glossoptosis. What is commonly observed is a rudimentary, small tongue. As a consequence of the lack of muscular stimulus between the alveolar arches, these do not develop transversely and the mandible does not grow in an anterior direction, producing as a result a severe dentoskeletal malocclusion (Fig. 1-18). This syndrome shows no predilection for gender and has no genetic implications. Its etiology must be searched for in some sort of fetal cell traumatism in the first few weeks of gestation. Neither language nor swallowing are sensibly affected by this condition.

Macroglossia

(Tongue hypertrophy, prolapsus of the tongue, enlarged tongue, pseudomacroglossia)

Macroglossia, meaning large tongue, has been a documented anatomical anomaly for several centuries. The earliest known written description of tongue lesions comes from the Egyptian Papyrus Ebers, originally thought to be from around 1550 BC. Obviously, tongue lesions have since been categorized by their etiologies. Macroglossia has an extensive list of possible causes. Its treatment has been largely surgical in the modern era.

Although the exact incidence of macroglossia is unknown (because the etiologies are too numerous to quantify), some congenital syndromes often express macroglossia in their phenotypes, most commonly Down syndrome (1 per 700 live births) and **Beckwith-Wiedemann syndrome** (0.07 per 1,000 live births). In Beckwith-Wiedemann syndrome, 97.5% of patients have macroglossia.

Reports on the etiology of macroglossia are extensive. Historically, Virchow described it as a form of elephantiasis. In the last 100 years, Butlin and Spencer attributed it to the dilation of lymphatics, muscle hypertrophy, or inflammation. Because of the large number of possible etiologies, multiple classification schemes have been used to list the causes.

The two broadest categories under the heading of macroglossia are **true macroglossia** and **pseudomacroglossia.**

Physical examination of the oral cavity and head morphology is helpful to deduce true macroglossia from pseudomacroglossia. Severe retrognathia and unusually small maxillary and/or mandibular size may indicate the latter. In addition, check tongue tone and mobility to rule out simple

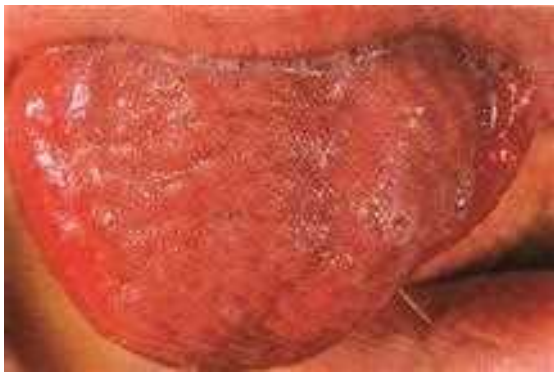


Figure 1-19. Macroglossia.

atonia or hypotonia indicating poor posturing of the tongue—as is commonly observed in Down syndrome (Fig. 1-19).

In addition to the oral cavity and airway, assess other features in the patient that may indicate congenital or systemic syndromes. Certain vitamin deficiencies may present with angular stomatitis, nonpitting edema of the lower extremities may indicate hypothyroidism, and unusual body morphologies may indicate the early signs of diseases-like acromegaly.

Treatment. The goal of nearly all surgery is to return the patient to an anatomically and physiologically normal condition; and this applies to macroglossia as well. The goal is to reduce tongue size and thereby improve function. Those main functions include articulation, mastication, deglutition, protection of the airway, and gustation. Of these, only gustation is not often improved with surgical intervention.

Ankyloglossia or Tongue-tie

Ankyloglossia, or tongue-tie as it is more commonly known, is said to exist when the inferior frenulum attaches to the bottom of the tongue and subsequently restricts free movement of the tongue. At one time, such restriction was believed to cause speech problems and it was routine to clip the membranous frenulum (frenulectomy) to free the tongue tip. Ankyloglossia occurs in approximately 1.7% of all neonates without preference for either gender and is reported to be transitory. With growth, the frenulum lengthens so normal tongue function is established. The criterion for diagnosis is based upon observation of lingual mobility; no current specific indications for surgery are emphasized in either the dental or medical literature reviewed. Simple incision of the frenulum may result in the development of scar tissue and further restriction of tongue movement (Schuller and Schleuning, 1994). Some authors indicate that if the tongue is able to touch the lower incisor teeth or just beyond the lower teeth, articulation will not be adversely affected. In some cases the frenulum is reported to tear spontaneously during infancy. Tongue-tie can cause feeding problems in infants; if this is the case, feeding difficulties are usually noticed early in an infant's life. Feeding difficulties may be a reason to consider early surgery to cut the lingual frenulum and loosen the tongue. In some children, tongue-tie may also cause speech defects, especially articulation of the sounds: l, r, t, d, n, th, sh, and z. Preventing speech defects or improving a child's articulation may be another reason to consider surgical intervention. The tongue is remarkably able to compensate; however, many children have no speech impediments due to ankyloglossia. Tongue-tie may contribute to dental problems as well, causing a persistent gap between the mandibular incisors.

Treatment. Frenulectomy is recommended.

Cleft Tongue

A completely cleft or bifid tongue is a rare condition that is apparently due to lack of merging of the lateral lingual swellings of this organ. A partially cleft tongue is considerably more common and is manifested simply as a deep groove in the midline of the dorsal surface (Figs. 1-20, 1-21). The partial cleft results because of incomplete merging and failure of groove obliteration by underlying mesenchymal proliferation. Interestingly, it is often found as one feature of the oral-facial-digital syndrome in association with thick, fibrous bands in the lower anterior mucobuccal fold eliminating the sulcus and with clefting of the hypoplastic mandibular alveolar process.

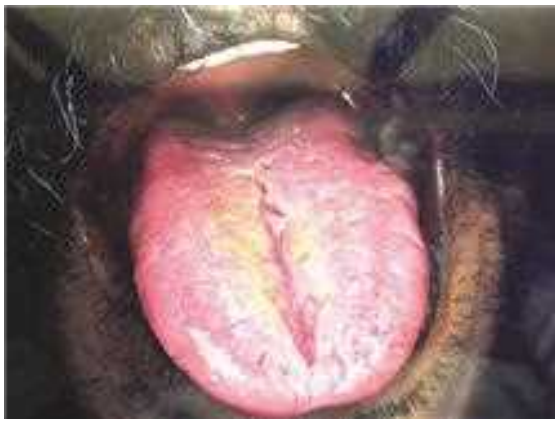


Figure 1-20. Cleft tongue.
(Courtesy Dr N Gururaj, CSI Dental College, Madurai, Tamil Nadu).

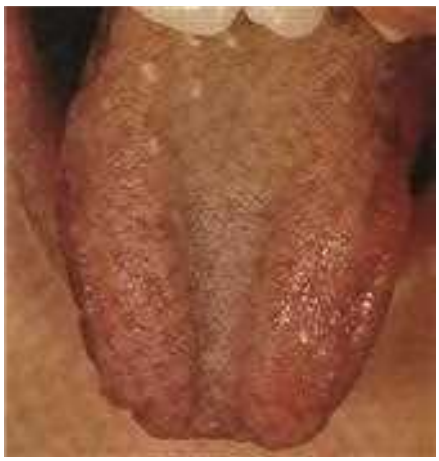


Figure 1-21. Bifidness of the tip of tongue.

Pseudomacroglossia includes any of the following conditions, which force the tongue to sit in an abnormal position:

- Habitual posturing of the tongue
- Enlarged tonsils and/or adenoids displacing tongue
- Low palate and decreased oral cavity volume displacing tongue
- Transverse, vertical, or anterior/posterior deficiency in the maxillary or mandibular arches displacing the tongue
- Severe mandibular deficiency (retrognathism)
- Neoplasms displacing the tongue
- Hypotonia of the tongue

True macroglossia can be subdivided into two main subcategories, congenital causes and acquired causes:

- **Congenital causes**
  - Idiopathic muscle hypertrophy
  - Gland hyperplasia
  - Hemangioma
  - Lymphangioma
  - Down syndrome
  - Beckwith-Wiedemann syndrome
  - Behmel syndrome
  - Lingual thyroid
  - Gargoylism
  - Transient neonatal diabetes mellitus
  - Trisomy 22
  - Laband syndrome
  - Lethal dwarfism of Blomstrand
  - Mucopolysaccharidoses
  - Skeletal dysplasia of Urbach
  - Tollner syndrome
  - Autosomal dominant inheritance
  - Microcephaly and hamartoma of Wiedemann
  - Ganglioside storage disease type I
- **Acquired causes** (categories have been assigned to simplify the list, but there can be overlap of a particular etiology into more than one of these categories)
- Metabolic/endocrine
  - Hypothyroidism
  - Cretinism
  - Diabetes
- Inflammatory/infectious
  - Syphilis
  - Amebic dysentery
  - Ludwig angina
  - Pneumonia
  - Pemphigus vulgaris
  - Rheumatic fever
  - Smallpox
  - Typhoid
  - Tuberculosis
  - Actinomycosis
  - Giant cell arteritis
  - Candidiasis
  - Scurvy
  - Pellagra
- Systemic/medical conditions
  - Uremia
  - Myxedema
  - Hypertrophy
  - Acromegaly
  - Neurofibromatosis
  - Iatrogenic macroglossia
- Traumatic
  - Surgery
  - Hemorrhage
  - Direct trauma (e.g. biting)
  - Intubation injury
  - Radiation therapy
- Neoplastic
  - Lingual thyroid
  - Lymphangioma
  - Hemangioma
  - Carcinoma
  - Plasmacytoma
- Infiltrative
  - Amyloidosis
  - Sarcoidosis

It is of little clinical significance except that food debris and microorganisms may collect in the base of the cleft and cause irritation.

Fissured Tongue

(Scrotal tongue, lingua plicata)

Fissured tongue is a condition frequently seen in the general population and it is characterized by grooves that vary in depth and are noted along the dorsal and lateral aspects of the tongue (Fig. 1-22). Although a definitive etiology is unknown, a polygenic mode of inheritance is suspected because the condition is seen clustering in families who are affected. Patients are usually asymptomatic, and the condition is initially noted on routine intraoral examination as an incidental finding. Fissured tongue is also seen in **Melkersson-Rosenthal syndrome** and **Down syndrome** and in frequent association with benign migratory glossitis (geographic tongue).

Melkersson-Rosenthal syndrome is a rare condition consisting of a triad of persistent or recurring lip or facial swelling, intermittent seventh (facial) nerve paralysis (Bell's palsy), and a fissured tongue. The etiology of this condition is also unknown. The orofacial swelling usually manifests as pronounced lip enlargement. It may or may not affect both lips,

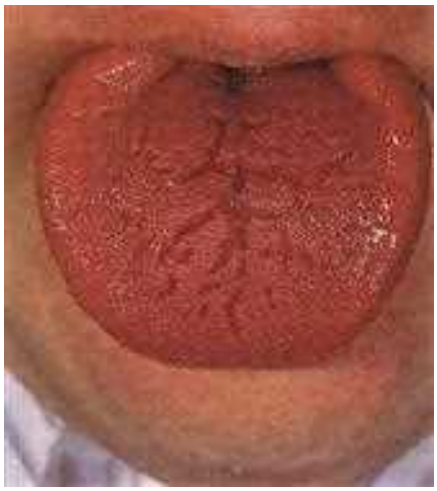


Figure 1-22. Large fissured tongue.

and it may be tender or erythematous. Histologic examination of this tissue exhibits characteristic noncaseating granulomatous inflammation. Therapy for these lesions is often intralesional steroid injections. The facial paralysis is indistinguishable from Bell's palsy, and it may be an inconsistent and intermittent finding with spontaneous resolution. The presence of fissured tongue in association with these other features is diagnostic of the condition.

This condition affects only the tongue and is a finding in Melkersson-Rosenthal syndrome, which consists of a triad of fissured tongue, cheilitis granulomatosa, and cranial nerve VII paralysis (Bell's palsy).

Clinical Features. The prevalence worldwide varies by geographic location and has been reported to be as high as 21%. Fissured tongue is a totally benign condition and is considered by most to be a variant of normal tongue architecture. No predilection for any particular race appears to exist. Some reports have shown a slight male predilection. Although fissured tongue may be diagnosed initially during childhood, it is diagnosed more frequently in adulthood. The prominence of the condition appears to increase with increasing age.

The lesions are usually asymptomatic unless debris is entrapped within the fissure or when it occurs in association with geographic tongue (a common finding). On clinical examination, fissured tongue affects the dorsum and often extends to the lateral borders of the tongue. The depth of the fissures varies but has been noted to be up to 6 mm in diameter. When particularly prominent, the fissures or grooves may be interconnected, separating the tongue dorsum into what may appear to be several lobules. Although a specific etiology has not been elicited, a polygenic or autosomal dominant mode of inheritance is suspected because this condition is seen with increased frequency in families with an affected proband.

Histologic Features. A biopsy is rarely performed on a fissured tongue because of its characteristic diagnostic clinical appearance; however, histologic examination has shown an increase in the thickness of the lamina propria, loss of filiform papillae of the surface mucosa, hyperplasia of the rete pegs, neutrophilic microabscesses within the epithelium, and a mixed inflammatory infiltrate in the lamina propria.

Treatment. No definitive therapy or medication is required.

Median Rhomboid Glossitis

Embryologically the tongue is formed by two lateral processes (lingual tubercles) meeting in the midline and fusing above a central structure from the first and second branchial arches, the tuberculum impar. The posterior dorsal point of fusion is occasionally defective, leaving a rhomboid-shaped, smooth erythematous mucosa lacking in papillae or taste buds. This median rhomboid glossitis (central papillary atrophy, posterior lingual papillary atrophy) is a focal area of susceptibility to recurring or chronic atrophic candidiasis, prompting a recent shift towards the use of **posterior midline atrophic candidiasis** as a more appropriate diagnostic term.

The latter term has certain difficulties; however, because not all cases improve with antifungal therapy or show initial evidence of fungal infection. The erythematous clinical appearance; moreover, is due primarily to the absence of filiform papillae, rather than to local inflammatory changes, as first suggested in 1914 by Brocq and Pautrier. The lesion is found in one of every 300–2,000 adults, depending on the rigor of the clinical examinations. It is seldom biopsied unless the red discoloration is confused with precancerous erythroplakia or its surface shows pronounced nodularity.

Clinical Features. Median rhomboid glossitis presents in the posterior midline of the dorsum of the tongue, just anterior to the V-shaped grouping of the circumvallate papillae (Fig. 1.23A, B). The long axis of the rhomboid or oval area of red depapillation is in the anteroposterior direction. Most cases are not diagnosed until the middle age of the affected patient, but the entity is, of course, present in childhood. There appears to be a 3 : 1 male predilection.

Those lesions with atrophic candidiasis are usually more erythematous but some respond with excess keratin production, and therefore, show a white surface change. Infected cases may also demonstrate a midline soft palate erythema in the area of routine contact with the underlying tongue involvement; this is commonly referred to as a **kissing lesion.**

Lesions are typically less than 2 cm in greatest dimension and most demonstrate a smooth, flat surface, although it is not unusual for the surface to be lobulated. Occasional lesions are located somewhat anterior to the usual location. None have been reported posterior to the circumvallate papillae.

Prior to biopsy, the clinician should be certain that the midline lesion does not represent a lingual thyroid, as it may be the only thyroid tissue present in the patient's body. Differential diagnoses include the gumma of tertiary syphilis, the granuloma of tuberculosis, deep fungal infections, and granular cell tumor.

Histologic Features. Median rhomboid glossitis shows a smooth or nodular surface covered by atrophic stratified squamous epithelium overlying a moderately fibrosed stroma

A B

Figure 1-23 (A, B) Median rhomboid glossitis.
(Courtesy of Dr S Rohini, Ambattur, Chennai).

with somewhat dilated capillaries. Fungiform and filiform papillae are not seen, although surface nodules may mimic or perhaps represent anlage of these structures. A mild to moderately intense chronic inflammatory cell infiltrate may be seen within subepithelial and deeper fibrovascular tissues.

Chronic candida infection may result in excess surface keratin or extreme elongation of rete processes and premature keratin production with individual cells or as epithelial pearls (dyskeratosis) deep in the processes. Silver staining for fungus will often reveal candida hyphae and spores in the superficial layers of the epithelium. This **pseudoepitheliomatous hyperplasia** may be quite pronounced, and the tangential cutting of such a specimen may result in the artifactual appearance of cut rete processes as unconnected islands of squamous epithelium, leading to a mistaken diagnosis of well differentiated squamous cell carcinoma. Because of this difficulty, it is recommended that the patient be treated with topical antifungals prior to biopsy of a suspected median rhomboid glossitis.

Treatment and Prognosis. No treatment is necessary for median rhomboid glossitis, but nodular cases are often removed for microscopic evaluation. Recurrence after removal is not expected, although those cases with pseudoepitheliomatous hyperplasia should be followed closely for at least a year after biopsy to be certain of the benign diagnosis. Antifungal therapy (topical troches or systemic medication) will reduce clinical erythema and inflammation due to candida infection. This therapy, as stated earlier, should ideally be given prior to the biopsy, in order to reduce the candida-induced pseudoepitheliomatous hyperplasia features. Some lesions will disappear entirely with antifungal therapy.

Benign Migratory Glossitis
(Geographic tongue)

Benign migratory glossitis is a psoriasiform mucositis of the dorsum of the tongue. Its dominant characteristics is a constantly changing pattern of serpiginous white lines surrounding areas of smooth, depapillated mucosa. The changing appearance has led some to call this the wandering rash of the tongue, with the depapillated areas have reminded others of continental outlines on a globe, hence the use of the popular term geographic tongue (Fig. 1-24). As with psoriasis, the etiology of benign migratory glossitis is unknown, but it does seem to become more prominent during conditions of psychological stress and it is found with increased frequency (10%) in persons with psoriasis of the skin. The great majority of those with oral involvement; however, lack psoriatic skin involvement. Approximately 1–2% of the population are affected, although most cases are so mild that they are never formally diagnosed.

Histologic Features. All of the microscopic features of psoriasis are present in benign migratory glossitis and migratory stomatitis, but these will not be obvious unless the biopsy is

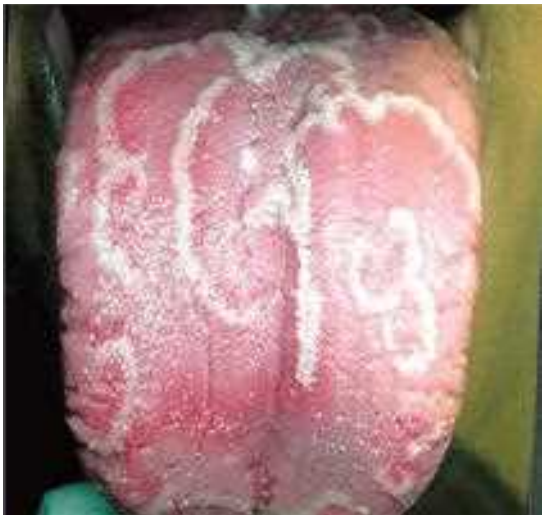


Figure 1-24. Benign migratory glossitis.
(Courtesy of Dr Spencer Lilly, Meenakshi Ammal Dental College, Chennai).

taken from a prominent serpiginous line at the periphery of a depapillated patch. A thickened layer of keratin is infiltrated with neutrophils, as are lower portions of the epithelium to a lesser extent. These inflammatory cells often produce small microabscesses, called **Monro's abscesses,** in the keratin and spinous layers. Rete ridges are typically thin and considerably elongated, with only a thin layer of epithelium overlying connective tissue papillae. When rete ridges are not elongated, the pathologist should consider **Reiter's syndrome** as a diagnostic possibility. Chronic inflammatory cells can be seen in variable numbers within the stroma and silver or PAS staining will often demonstrate candida hyphae or spores in the superficial layers of the epithelium. There is no liquefactive degeneration of basal cells, as seen in lichenoid lesions, and there is no ulceration except in cases of Reiter's syndrome.

Treatment and Prognosis. No treatment is usually necessary for benign migratory glossitis and stomatitis. Symptomatic lesions can be treated with topical prednisolone and a topical or systemic antifungal medication can be tried if a secondary candidiasis is suspected. Occasional symptomatic cases respond well to topical tetracycline or systemic, broad-spectrum antibiotics, but this should not be expected.

Hairy Tongue

(Lingua nigra, lingua villosa, lingua villosa nigra, black hairy tongue)

Hairy tongue (lingua villosa) is a commonly observed condition of defective desquamation of the filiform papillae that results from a variety of precipitating factors (Fig. 1-25). The condition is most frequently referred to as **black hairy tongue** (lingua villosa nigra); however, hairy tongue may also appear brown, white, green, pink, or any of a variety of hues depending on the specific etiology and secondary factors (e.g. use of colored mouthwashes, breath mints, candies).

Figure 1-25. Hairy tongue.
(Courtesy of Dr S Rohini, Ambattur, Chennai)

Etiology. The basic defect in hairy tongue is the hypertrophy of filiform papillae on the dorsal surface of the tongue, usually due to a lack of mechanical stimulation and debridement. This condition often occurs in individuals with poor oral hygiene (e.g. lack of toothbrushing, eating a soft diet with no roughage that would otherwise mechanically debride the dorsal surface of the tongue). Contributory factors for hairy tongue are numerous and include tobacco use and coffee or tea drinking. These factors account for the various colors associated with the condition.

Clinical Features. Normal filiform papillae are approximately 1 mm in length, whereas filiform papillae in hairy tongue are more than 15 mm in length. Hairy tongue has been reported with greater frequency in males, patients infected with human immunodeficiency virus (HIV), and those who are HIV negative and use intravenous drugs. Hairy tongue is rarely symptomatic, although overgrowth of *Candida albicans* may result in glossopyrosis (burning tongue). Patients frequently complain of a tickling sensation in the soft palate and the oropharynx during swallowing. In more severe cases, patients may actually complain of a gagging sensation. Retention of oral debris between the elongated papillae may result in halitosis. No racial predilection is associated with hairy tongue. Because hairy tongue is usually asymptomatic, the history is often irrelevant. In most cases, lesions are noted as part of an intraoral examination, although patients may complain of a tickling or gagging sensation. The tongue has a thick coating in the middle, with a greater accentuation towards the back. Bacterial and fungal overgrowth play a role in the color of the tongue. The only complication associated with hairy tongue is an occasional candidal overgrowth, which often results in an uncomfortable glossopyrosis (burning tongue). Altered taste sensation is a rare complication.

Differential Diagnosis. This condition has to be differentiated from candidiasis, leukoplakia, oral lichen planus and oral hairy leukoplakia. Culture of the tongue's dorsal surface may be taken if a superimposed oral candidiasis or other specific oral infection is suspected. Distinguishing between oral hairy leukoplakia and hairy tongue is important if patients are found or suspected to be HIV positive. This can be accomplished by a simple mucosal punch biopsy and appropriate immunostaining of the specimen for the presence of Epstein-Barr virus, the causative agent of oral hairy leukoplakia. However, in most cases, the diagnosis is made retrospectively on the basis of the clinical response to mechanical debridement.

Histologic Features. Histopathologic findings in hairy tongue consist of elongated filiform papillae, with mild hyperkeratosis and occasional inflammatory cells. Debris accumulation among the papillae and candidal pseudohyphae is not unusual finding. No other specific microscopic findings are associated with this entity.

Treatment. The treatment of hairy tongue is variable. In many cases, brushing of the tongue with a toothbrush or

using a commercially available tongue scraper is sufficient to remove elongated filiform papillae and retard the growth of additional ones. Surgical removal of the papillae by using electrodesiccation, carbon dioxide laser, or even scissors is the treatment of last resort when less complicated therapies prove ineffective. The prognosis for hairy tongue is excellent. If the precipitating factors cannot be adequately controlled or compensated for, patients may have to make tongue brushing or scraping part of their daily oral hygiene regimen.

Lingual Varices

(Lingual or sublingual varicosities)

A varix is a dilated, tortuous vein, most commonly a vein which is subjected to increased hydrostatic pressure but poorly supported by surrounding tissue. Varices involving the lingual ranine veins are relatively common, appearing as red or purple shotlike clusters of vessels on the ventral surface and lateral borders of the tongue as well as in the floor of the mouth. However, varices also do occur in other oral sites such as the upper and lower lip, buccal mucosa, and buccal commissure.

There has been no direct association established between these varicosities and other specific organic diseases. However, Kleinman has concluded that these varicosities represent an aging process and that, when they occur prior to 50 years of age, they may indicate premature aging. In his study, lingual varicosities were not related to cardiac pulmonary disease. In an investigation of 1,751 persons (755 males and 996 females) ranging in age from 7 to 99 years, Ettinger and Manderson found that 68% of the persons over 60 years of age had sublingual varices. In this study, there appeared to be a significant relationship between the presence of leg varicosities and sublingual varices.

Thrombosis of any of these varices is a relatively frequent occurrence, as indicated in a report of 12 such cases by Weathers and Fine, but is apparently of little clinical significance.

Lingual Thyroid Nodule

The thyroid gland develops in the embryo from the ventral floor of the pharynx by means of an endodermal invagination or diverticulum. The tongue forms at the same time from this pharyngeal floor and is anatomically associated with the thyroid gland by connection through the thyroglossal tract, the lingual remnant of which is known as the foramen caecum.

The lingual thyroid is an anomalous condition in which follicles of thyroid tissue are found in the substance of the tongue, possibly arising from a thyroid anlage that failed to 'migrate' to its predestined position or from anlage remnants that became detached and were left behind. Baughman has reviewed and discussed in detail the various theories on the development of lingual thyroglossal remnants and the lingual thyroid nodule.

Etiology. The benign enlargement of lingual thyroid tissue is thought to be due in some cases to functional insufficiency of the chief thyroid gland in the neck, since some patients with such a lingual lesion are without a demonstrable main thyroid gland. Other cases of lingual thyroid nodules occur in patients residing in goitrous areas, but it is not certain that the condition is a form of goiter. In addition, it has been suggested that the failure of the primitive thyroid anlage to descend is the cause of the majority of cases of nongoitrous sporadic cretinism.

Clinical Features. The incidence of this benign condition is not known, since a routine autopsy seldom includes an examination of the base of the tongue. Montgomery, in an exceptionally complete and thorough review of the entire subject of the lingual thyroid, analyzed 144 acceptable previously reported cases, pointing out that these represented only cases showing hypertrophy of the lingual thyroid tissue. Though information is inadequate about racial and geographic distribution of lingual thyroid nodules, a difference in gender incidence does appear to be significant. Of 135 cases in which the gender was recorded, 118 patients were female and only 17 were male. The majority of patients had their onset of symptoms relatively early in life, chiefly during puberty, adolescence, and early maturity, though cases have been recorded as early as birth and as late as the seventh decade.

In contrast, Sauk carried out a study to determine the frequency with which ectopic thyroid tissue occurred in the tongue of 'normal' persons, i.e. those without a definite symptomatic mass for which treatment was sought. In a series of 200 consecutive necropsies, ectopic thyroid tissue was found in 10% of the cases, with an equal distribution between the sexes. Nearly identical data have been reported by Baughman in his own investigation of 184 tongues from human cadavers. Since the condition is more often clinically apparent in females, Sauk suggested that hormonal factors may be involved in the genesis of symptoms. Most cases appear to arise in females during puberty, adolescence, pregnancy, or menopause.

The lingual thyroid may be manifested clinically as a nodular mass in or near the base of the tongue in the general vicinity of the foramen caecum and often, but not always, in the midline (Fig. 1-26). This mass, which more commonly appears as deeply situated rather than as a superficial exophytic lesion, tends to have a smooth surface. In some cases it may appear vascular, while in others the color of the mucosa is not atypical. The size of the lesion in many of the reported

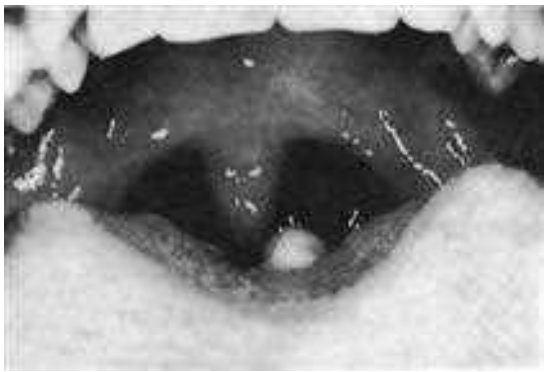


Figure 1-26. Lingual thyroid nodule.
(Courtesy of Dr Ronald A Baughman).

cases has been approximated 2–3 cm in diameter. The chief symptoms of the condition may vary, but the presenting complaint is often dysphagia, dysphonia, dyspnea, hemorrhage with pain, or a feeling of tightness or fullness in the throat.

Histologic Features. The benign lingual thyroid nodules may present a variety of microscopic patterns, but in the majority of cases they resemble either normal thyroid tissue or thyroid tissue of an embryonal or fetal type. In some instances the nodules exhibit colloid degeneration or goiter.

Great care must be taken to distinguish these lesions from lesions derived from accessory salivary glands in the same location. Both the lingual thyroid and these salivary glands may give rise to adenomas and adenocarcinomas in the tongue.

Treatment. Care must be exercised in handling the lingual thyroid lesion. It has been emphasized by Hung and his associates that a careful physical examination should be performed to demonstrate the presence of a normally located thyroid gland in patients presenting with midline masses in the lingual or sublingual area. If the thyroid gland cannot be palpated, a scintiscan with a tracer dose of radioactive iodine, ^{131}I, should be carried out to determine whether there is a normally located thyroid gland and if the lingual mass is ectopic thyroid. It is usually recommended that a patient with an ectopic thyroid gland should have a trial of replacement thyroid hormone therapy before excision is contemplated, since this will often decrease the size of the lesion and make surgery unnecessary. Occasionally, the clinical manifestations of the lesion and its size necessitates surgical excision.

DEVELOPMENTAL DISTURBANCES OF ORAL LYMPHOID TISSUE

Reactive Lymphoid Aggregate
(Reactive lymphoid hyperplasia)

The lingual tonsil, one of the largest oral lymphoid aggregates, is located on the posterior portion of the tongue on the dorsolateral aspect. It is typically surrounded by a crypt lined by stratified squamous epithelium. It frequently becomes inflamed and enlarged so that it is clinically evident. Such enlargement is usually bilateral but, if unilateral, may easily be mistaken clinically for early carcinoma. This reactive lingual tonsil has often been called 'foliate papillitis,' referring to the vestigial foliate papilla in this area.

Similar reactive hyperplasia may occur in the lymphoid aggregates in the other locations mentioned previously, the buccal mucosa being especially common. This presents clinically as a firm nodular submucosal mass which may be tender. Since this lymphoid tissue may be the site for the development of lesions of the malignant lymphoma group, early microscopic diagnosis is essential whenever the lesions do not regress in a short period of time.

Hyperplastic lymphoid polyps have also been described as polypoid structures composed entirely of lymphoid tissue. They are reported to occur on the gingiva, buccal mucosa, tongue, and floor of the mouth.

Lymphoid Hamartoma
(Angiofollicular lymph node hyperplasia, angiomatous lymphoid, Castleman tumor, giant benign lymphoma, hamartoma of lymphatics, giant lymph node hyperplasia)

Castleman's disease is a rare disorder characterized by noncancerous benign growths that may develop in the lymph node tissue throughout the body (i.e. systemic disease of plasma cell type). Most often, they occur in the chest, stomach, and/or neck (i.e. localized disease of hyaline vascular type). Less common sites include the armpit (axilla), pelvis, and pancreas. Usually the growth represents abnormal enlargement of the lymph nodes normally found in these areas (lymphoid hamartoma). There are two main types of Castleman's disease: **hyaline vascular type** and **plasma cell type.** The hyaline vascular type accounts for approximately 90% of the cases. Most individuals exhibit no symptoms of this form of the disorder (asymptomatic) or they may develop noncancerous growths in the lymph nodes. The plasma cell type of Castleman's disease may be associated with fever, weight loss, skin rash, early destruction of red blood cells, leading to unusually low levels of circulating red blood cells (hemolytic anemia), and/or abnormally increased amounts of certain immune factors in the blood (hypergammaglobulinemia).

A third type of Castleman's disease has been reported in the medical literature. This type may affect more than one area of the body (**multicentric** or **generalized Castleman's disease**). Many individuals with multicentric Castleman's disease may exhibit an abnormally large liver and spleen (hepatosplenomegaly). Researchers' opinions in the medical literature differ as to whether multicentric Castleman's disease is a distinct entity or a multicentric form of the plasma cell type of Castleman's disease. The exact cause of Castleman's disease is not known. Some researchers speculate that increased production of interleukin-6 (IL-6) may be involved in the development of Castleman's disease. IL-6 is a substance produced by structures within the lymph nodes.

Angiolymphoid Hyperplasia with Eosinophilia
(Epithelioid hemangioma, histiocytoid hemangioma, pseudopyogenic granuloma, papular angioplasia, inflammatory angiomatous nodules)

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon idiopathic condition that presents with isolated or grouped plaques or nodules in the skin of the head and neck. Most patients present with lesions in the periauricular region, forehead, or scalp.

A distinct pathologic entity, ALHE is marked by a proliferation of blood vessels with distinctive large endothelial cells. These blood vessels are accompanied by a characteristic inflammatory infiltrate that includes eosinophils. The lesion is benign but may be persistent and difficult to eradicate. Whether ALHE represents a benign neoplasm or an unusual reaction to varied stimuli, including trauma, remains unclear. While ALHE shows some similarity to **Kimura disease,** it is a distinct condition.

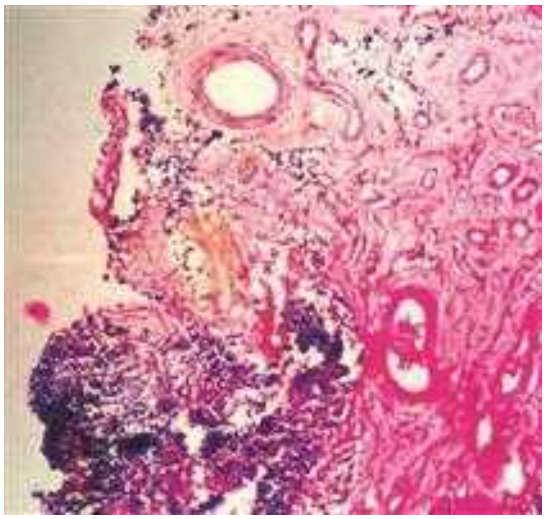


Figure 1-27. Angiolymphoid hyperplasia.
H and E section showing irregular clusters of blood vessels and intermixed lymphocytes and eosinophils in this example of ALHE.

Etiology. ALHE is idiopathic. Whether this condition is a neoplastic or reactive state is uncertain; a reactive cause is favored.

Clinical Features. Although ALHE may be a benign tumor, numerous factors suggest that it is an unusual reactive process. The condition may be multifocal. ALHE has occurred following various forms of trauma or infection. Hyperestrogenic states (e.g. pregnancy, oral contraceptive use) may foster lesion growth. Additionally, the distinctive inflammatory infiltrate in ALHE appears to be an intrinsic (not secondary) component of the lesion. Approximately 20% of patients have blood eosinophilia. Although frequency is unknown, cases have been reported worldwide. ALHE is uncommon but not rare; it may be more common in Japan than in other countries. ALHE can persist for years, but serious complications (e.g. malignant transformation) do not occur. ALHE is seen most commonly in Asians, followed by Caucasians. Although less commonly, blacks too can develop ALHE. ALHE is somewhat more common in females; however, a male predominance has been noted in selected Asian studies. ALHE presents most commonly in patients aged 20–50 years, with mean onset of 30–33 years. This condition is rare in elderly patients and in the non-Asian pediatric population.

Patients with ALHE typically present with an expanding nodule or group of nodules, usually in the vicinity of the ear. The lesion(s) may be associated with pain or pruritus. Uncommon symptoms include pulsation and spontaneous bleeding.

ALHE typically appears as dome-shaped, smooth-surfaced papules or nodules. Approximately 85% of lesions occur in the skin of the head and neck; most of them are on or near the ear or on the forehead or scalp. The lesions range from erythematous to brown in color and may be eroded or crusted. Approximately 80% of patients present with isolated lesions, while the remaining patients usually demonstrate grouped papules or nodules in a single region. Rarely, the lesions may be pulsatile. Most lesions are 0.5–2 cm in diameter, with a range of 0.2–8 cm. Larger nodules tend to be deeply centered within the subcutis.

Differential Diagnosis. Granuloma faciale, insect bites, pyogenic granuloma (lobular capillary hemangioma), angiosarcoma, hemangioendothelioma and hemangioma.

Histologic Features. The clinical presentation of papules around the ears may suggest ALHE, but a biopsy is required to establish the diagnosis. ALHE shows characteristic histologic features, including a proliferation of small blood vessels, many of which are lined by enlarged endothelial cells with uniform ovoid nuclei and intracytoplasmic vacuoles. These distinctive endothelial cells have been described as having a cobblestone appearance. In addition, a perivascular and interstitial infiltrate composed primarily of lymphocytes and eosinophils is present. Eosinophils typically comprise 5–15% of the infiltrate. Rarely, they can account for as much as 50% of the infiltrate. Occasionally, the infiltrate is devoid of eosinophils. Lymphoid aggregates with or without follicle formation are typical.

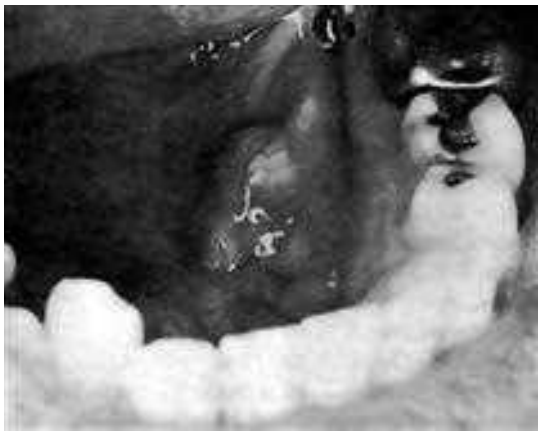
Treatment. Treatment is not mandatory. Intralesional corticosteroids and irradiation have been employed but are not very effective. Surgical removal of the lesions has demonstrated the best results, however, they may recur.

Lymphoepithelial Cyst

The oral lymphoepithelial cyst develops within a benign lymphoid aggregate or accessory tonsil of the oral or pharyngeal mucosa. The surface of such aggregates may be indented with tonsillar crypts, as are the much larger pharyngeal tonsils of the lateral pharyngeal walls. The crypts may become obstructed by keratin or other debris, or the surface opening may become constricted during episodes of inflammatory hyperplastic responses. Certain cases develop a complete disunion of the crypt epithelium from the surface epithelium, resulting in a subepithelial cyst lined by the old crypt epithelium. This cyst was first reported by Parmentier in 1857 as hydatid cyst. Outside of the head and neck region, lymphoepithelial cyst is found most frequently in the pancreas and testis.

A similar but much larger cervical lymphoepithelial cyst (**branchial cleft cyst**) most probably develops from entrapped salivary duct epithelium in the lymph nodes of the lateral neck, rather than from the branchial cleft. These are discussed in a separate section of the present book. Another similar cyst, the **parotid cyst,** is found in major salivary glands, especially in AIDS patients, although it often lacks a surrounding lymphoid aggregate in Chapter 3 on Tumors of the Salivary Gland.

Clinical Features. Oral lymphoepithelial cyst presents as a movable, painless submucosal nodule with a yellow or yellow-white discoloration. Occasional cysts are transparent. Almost all cases are less than 0.6 cm in diameter at the time of diagnosis, which is usually during the teen years or the third decade of life. Approximately half of all intraoral examples are found on the oral floor (Fig. 1-28A), but the lateral and ventral tongue are not uncommon sites of occurrence, nor is the soft



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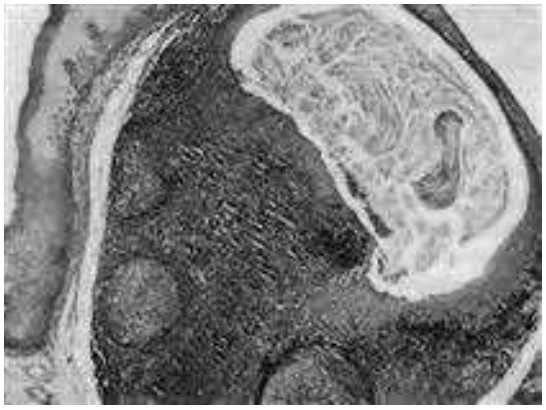


B

Figure 1-28. Oral lymphoepithelial cyst.
An elevated nodule in the floor of the mouth **(A)**. Histologically exhibited a keratin-filled epithelium-lined cyst in a lymphoid aggregate **(B)**. *(Courtesy of Dr Joseph A Regezi).*

palate, especially the mucosa above the pharyngeal tonsil. Of course, this cyst may also occur within the pharyngeal tonsils themselves. Occasional superficial cysts rupture to release a foul-tasting, cheesy, keratinaceous material.

This cyst has a clinical appearance similar to that of an epidermoid cyst or a dermoid cyst of the oral/pharyngeal mucosa, but its growth potential is much less than the other cysts. The lymphoepithelial cyst never occurs on the alveolar mucosa, hence, can easily be distinguished from a gingival cyst of adults or from an unruptured **parulis** or **'pus pocket'** at the terminus of a fistula (extending from the apical or lateral region of an abscessed tooth).

Histologic Features. The lymphoepithelial cyst is lined by atrophic and often degenerated stratified squamous epithelium, usually lacking rete processes and usually demonstrating a minimal granular cell layer. Orthokeratin is seen to be sloughing from the epithelial surface into the cystic lumen, often completely filling the lumen and sometimes showing dystrophic calcification. Rarely, mucus-filled goblet cells may be seen within the superficial layers of the epithelium, and occasional cysts will demonstrate an epithelium-lined communication with the overlying mucosal surface. The cyst is entrapped within a well-demarcated aggregate of mature lymphocytes. The aggregate or 'tonsil' will have a variable number of germinal centers, sometimes none at all. The lymphoid aggregate may be hyperplastic.

This combination of epithelium-lined cyst with lymphoid aggregates is unique enough to make the diagnosis an easy one (Fig. 1-28B), but the pathologist must differentiate this lesion from the Warthin tumor (papillary cystadenoma lymphomatosum). The latter lesion is lined not by squamous epithelium but by a bilayered cuboidal, columnar or oncocytic ductal epithelium. It is almost always found in the parotid gland, but rare oral examples have been reported.

Occasional cysts have very small lumina with degenerated epithelial linings and may mimic metastatic deposits of well differentiated squamous cell carcinoma. Deeper sections will reveal the true nature of the benign lesion.

Treatment and Prognosis. No treatment is usually necessary for the oral lymphoepithelial cyst unless its location is such that it is constantly being traumatized. Most lesions are, however, removed by conservative surgical excision in order to arrive at a definitive diagnosis. There is no malignant potential to this lesion but the lymphoid stroma, as with all lymphoid tissues, can become involved with an extranodal lymphoma.

DEVELOPMENTAL DISTURBANCES OF SALIVARY GLANDS

Aplasia
(Agenesis)

Any one or group of salivary glands may be absent, unilaterally or bilaterally. Aplasia becomes manifest with the development of xerostomia and its sequelae. A diagnosis of salivary gland aplasia is made after exclusion of the common causes of xerostomia medications, Sjögren's syndrome and radiation. The CT scan or MRI will indicate the gland's absence and its replacement by fat and fibrous tissue. Scintiscanning with a radioisotope will confirm the initial diagnosis. The absence of the salivary duct orifice/papilla is an additional clue.

Aplasia occurs for unknown reasons as an isolated finding or in conjunction with other developmental defects such as *hemifacial microsomia,* the *LADD syndrome* (see below) and *mandibulofacial dysostosis (Treacher Collins).* In the more severe cases, the ensuing xerostomia causes clinical problems. Salivary loss leads to increased caries, burning sensations, oral infections, taste aberrations and difficulty with denture retention.

Hemifacial microsomia, a relatively frequent entity (1 in 3,500 births), is characterized by an asymmetric mild to severe underdevelopment of the craniofacial skeleton, the external ear, and facial soft tissues including the parotid gland. It involves structures derived from the first and second branchial arches. The majority of cases occur sporadically but rare familial cases have been reported.

LADD is a hereditary autosomal dominant syndrome. The lacrimal (**L**) apparatus usually demonstrates occlusion of the lacrimal puncta, nasolacrimal duct obstruction with overflow of tears (epiphora), lacrimal sac inflammation (dacrocystitis) and lacrimal gland aplasia. The auricles (**A**) are deformed with the ear having a cup-shaped appearance. There is some hearing loss. Dentally (**D**), peg-shaped teeth, hypodontia, and enamel hypoplasia are noted. Various combinations of salivary gland agenesis, with varying degrees of xerostomia, are present. Digital (**D**) deformities are manifested by deviation of the fingers medially or laterally (clinodactyly).

Mandibulofacial dysostosis is familial in origin. Patients have a symmetric notching of the lower eyelids with the eyes slanting downward at the lateral borders. Maldevelopment of the mandible and maxilla, a defective development of the malar bones results in bird-like appearance and often salivary aplasia are seen.

Treatment. Treatment for salivary gland agenesis is supportive and directed at relieving xerostomia and its effects. Salivary substitutes, frequent mouth washes, comprehensive dental care, fluoride therapy, and good oral hygiene all play a role in successful management.

Xerostomia
(Dry mouth)

Xerostomia is not a disease but can be a symptom of certain diseases. It can produce serious negative effects on the patient's quality of life, affecting dietary habits, nutritional status, speech, taste, tolerance to dental prosthesis and increased susceptibility to dental caries. The increase in dental caries can be devastating in many patients and therefore special care must be made to control this condition.

Etiology. A convenient way of classifying the causes of xerostomia is as temporary or permanent.

Temporary Causes

Psychological. Anxiety and depression are well recognized as causes of reduced salivary flow, as many students become aware at examination times! However, these psychological problems are often treated with drugs, which may be salivary inhibitors.

Duct calculi. A blockage of the duct of a major salivary gland, commonly the submandibular, can produce dryness on the affected side, together with pain and swelling in the gland, especially on stimulation. If untreated, the obstruction may lead to progressive fibrosis of the gland and permanent xerostomia.

Sialoadenitis. Inflammation of the salivary glands can cause reduced secretion. Acute infections include mumps and postoperative parotitis, while chronic conditions include swellings related to nutritional deficiency and hypersensitivity to iodine. However, many cases of intermittent swelling of the salivary glands are idiopathic and are described as 'chronic nonspecific sialadenitis' and may be associated with duct calculi.

Drug therapy. A wide variety of drugs may cause xerostomia. Anticholinergic and sympathomimetic agents may be implicated and this group includes tricyclic antidepressants, bronchodilators and antihistamines. Diuresis produced by drugs or alcohol can result in dehydration and xerostomia. In most cases function recovers after the drug is withdrawn. **Zyban,** a newly introduced drug to aid smoking cessation can cause xerostomia and since the demand for the drug is likely to be high, its use may become a common etiological factor.

Permanent Causes

Salivary gland aplasia. Congenital absence of one or more of the major salivary glands is a rare but recognized condition of unknown etiology.

Sjögren's syndrome. This combination of dry mouth, dry eyes, and often rheumatoid arthritis, mainly affects women over 40 years of age and is often accompanied by a mild fever. About half of the patients with this syndrome also present with, or go on to develop swellings of the major salivary glands, which display similar histology to Mikulicz's disease.

Other systemic disorders. Xerostomia is associated with diabetes mellitus, probably as a consequence of polyurea, as well as Parkinson's disease, cystic fibrosis and sarcoidosis. It has been reported in cases of vitamin A, riboflavin and nicotinic acid deficiencies and anemia.

Radiotherapy. One of the most dramatic and distressing causes of xerostomia is therapeutic radiography for head and neck tumors. The effect on the glands of the irradiated side is often rapid and profound. Postradiation glandular atrophy is partly due to a reduction in the vascularity of the gland and partly to the direct effect of the X-rays on the highly specialized and sensitive secretory epithelial cells. While recovery of function can occur after several months, in many cases a permanent xerostomia develops. Radiation does not appear to damage the teeth or periodontal tissues directly, the effect on the dentition resulting solely from the reduction in salivary flow.

Surgical desalivation. Surgery or physical trauma to the salivary gland duct may result in damage to the gland, duct, blood or nerve supply and impair secretion.

Clinical Features. It is important to establish whether the dryness is continual or intermittent, whether it is accompanied by pain or swelling, if unilateral or bilateral and whether there is any relevant history of anxiety, stress or depression, a systemic disorder, irradiation, trauma, surgery or medication. The patient's occupation, diet and domestic situation are often relevant.

Unilateral dryness with pain or discomfort and swelling in the affected gland on stimulation is often an indication of a duct calculus. Sjögren's syndrome commonly produces bilateral swelling, often constant and accompanied by the other symptoms of the syndrome, and in many cases lymph node enlargement. A punch biopsy of labial glands and by serological tests may be needed to confirm the diagnosis. As well as looking for evidence of enlargement of salivary glands and lymph nodes and unilateral dryness, the palpation of the floor of the mouth for evidence of submandibular duct calculi and examination of the major duct openings,

as inflammation or swelling of the orifice may indicate the presence of a distally placed calculus. These are often revealed by simple radiography.

While the more dramatic forms of xerostomia are not common, a more typical case of nonspecific xerostomia is a postmenopausal woman, living alone with few family or other social contacts, surviving on a low income and a marginally inadequate diet, and wearing old ill-fitting dentures. The combination of atrophy of the oral mucosa due to hormonal changes and a mild chronic candidosis and reduced salivary flow due to age and depression for which she might have medication, together with a marginal iron deficiency anemia, is sufficient to produce a degree of discomfort which a cursory oral examination will not reveal.

All degrees of xerostomia exist. In some cases, the patient complains of a dry or burning sensation but the mucosa appears normal. In other cases there is a complete lack of saliva.

When the deficiency of saliva is pronounced, there may be severe alterations in the mucous membranes, and the patient may have extreme discomfort. The mucosa will appear dry and atrophic, sometimes inflamed or, more often, pale and translucent. The tongue may manifest the deficiency by atrophy of the papillae, inflammation, fissuring, and cracking and in severe cases by areas of denudation. Soreness, burning, and pain of the mucous membrane and tongue are common symptoms. Xerostomia, in all its aspects, has been discussed by Bertram.

Clinical Significance. Aside from annoyance to the patient, there is one feature of the condition that is serious. In many cases, chronic xerostomia predisposes to rampant dental caries and subsequent loss of teeth. Moreover, patients with xerostomia have difficulty with artificial dentures. Dental appliances are extremely disagreeable against dry mucosa and cannot be tolerated by some patients.

Treatment. The basic principles of management are first to eliminate or address any etiological factors such as drugs, calculi and emotional problems. It is also advisable to promote salivary stimulation by using sugar-free chewing gum which is effective and convenient. Salivary substitutes can also be given. The relief that can be given to many sufferers is limited. However, patience and consideration, especially towards the elderly, is as important as clinical intervention. Regular review to monitor the condition of teeth, gingivae and mucosa and to give support and reinforcement of preventive measures is advised.

Hyperplasia of Palatal Glands

An unusual localized hyperplasia or hypertrophy of minor accessory salivary glands in the palate has been described by Giansanti and his associates, although they have also accepted the view that this lesion may represent a benign adenoma of these glands. The cause of this focal enlargement is unknown although, according to these investigators, the following have been reported to result in salivary gland enlargement: (1) endocrine disorders, (2) gout, (3) diabetes mellitus, (4) menopause, (5) hepatic disease, (6) starvation, (7) alcoholism, (8) inflammation, (9) benign lymphoepithelial lesion, (10) Sjögren's syndrome, (11) adiposity, hyperthermia, oligomenorrhea, and parotid swelling syndrome, (12) aglossia-adactylia syndrome, (13) Waldenstrom's macroglobulinemia, (14) uveoparotid fever, (15) Felty's syndrome, (16) certain drugs, and (17) the aging process.

A series of 10 cases has been reported recently by Arafat and her associates. They could also find no associated abnormalities and had to consider the cases idiopathic. Interestingly, one of their cases involved the glands of the retromolar area rather than the palate.

Clinical Features. Palatal gland hyperplasia presents as a small localized swelling, measuring from several millimeters to 1 cm or more in diameter, usually on the hard palate or at the junction of the hard and soft palates. The lesion has an intact surface and is firm, sessile, and normal in color. It is usually asymptomatic and the patient may be unaware of the lesion. Too few cases have been reported to determine whether there is any age or gender predilection.

Histologic Features. The mass appears microscopically as closely packed collections of normal-appearing mucous acini with the usual intermingling of normal ducts. There is no inflammation, no spillage of mucin, and no fibrosis.

Treatment. Because hyperplasia of palatal glands cannot be differentiated clinically from a small salivary gland neoplasm in this area, it is essential that they be excised for microscopic examination. No further treatment is necessary and the condition is not reported to recur.

Atresia

Congenital occlusion or absence of one or more of the major salivary gland ducts is an exceedingly rare condition. When it does occur, it may result in the formation of a retention cyst or produce a relatively severe xerostomia. Such a case has been reported by Foretich and his associates.

Aberrancy

Because of the widespread distribution of normal accessory salivary glands in the oral cavity, it is difficult to define the condition of aberrancy. Since such accessory glands may be found in the lips, palate, buccal mucosa, floor of the mouth, tongue, and retromolar area, aberrancy may be construed as simply that situation in which these glands are found farther than normal from their usual location. In any event, there is no clinical significance to be attached to aberrant salivary glands other than that they may be the site of development of a retention cyst or neoplasm.

Occasional cases have been reported in the literature of salivary gland tissue present within the body of the mandible. It has been found, in many instances, that this glandular tissue anatomically communicated with the normal submaxillary or sublingual gland, generally through a stalk or pedicle of tissue which perforated the lingual cortical plate. For this reason, this

aberrancy of salivary gland tissue probably represents only an extreme example of the condition known as the 'developmental lingual mandibular salivary gland depression' described next.

Developmental Lingual Mandibular Salivary Gland Depression

(Static bone cavity or defect of the mandible, lingual mandibular bone cavity, static bone cyst, latent bone cyst, Stafne cyst or defect)

A Stafne bone cyst is an unusual form of slightly aberrant salivary gland tissue wherein a developmental inclusion of glandular tissue is found within or, more commonly, adjacent to the lingual surface of the body of the mandible within a deep and well-circumscribed depression. The oldest described occurrence of this phenomenon is in a skull dated to the sixth to fourth centuries BC. The phenomenon was first recognized by Stafne in 1942, hence the eponym. However, this cyst has been referred to by many other names, including static bone cavity, defect of the mandible, lingual mandibular bone cavity, static bone cyst, latent bone cyst, and Stafne bone defect. The incidence of occurrence has been reported as 0.1–1.3% in various studies. The general consensus is that this is a congenital defect, although it rarely has been observed in children. These lesions generally may be regarded as developmental rather than pathologic defects. A predilection for males over females seems to exist.

Radiographically, the lesion usually appears as an ovoid radiolucency located between the inferior alveolar canal and the inferior border of the mandible in the region of the second or third molars. It can be differentiated from the traumatic or hemorrhagic bone cyst, which by location almost invariably lies superior to the inferior alveolar canal.

Although the classic Stafne cyst is described in the posterior mandible, an anterior variant presenting as a round or ovoid radiolucency in the area between the central incisors and first premolars exists; however, it is far less common.

Anterior Lingual Depression

It has also been recognized that a similar asymptomatic round or ovoid radiolucency may occur in the anterior segment of the mandible, generally appearing as a rather poorly circumscribed lesion somewhere between the central incisor and the first premolar area. This anterior radiolucency also represents a cavity or depression on the lingual surface of the mandible. It has been reviewed by Miller and Winnick and more recently by Connor. Langlais and his coworkers examined 12 dried mandibles with such anterior depressions and concluded that these might represent either anatomic variants related to the digastric or sublingual fossa or developmental anomalies caused by impingement of the sublingual gland. These are far less common than the posterior lesion (Fig. 1-29).

Complications. A complication occasionally reported in the literature is the development of a true central salivary gland neoplasm from the included salivary gland tissue, but this is rare. This has been discussed in Chapter 3 on Tumors of the Salivary Glands (q.v.) in the section on mucoepidermoid carcinoma.

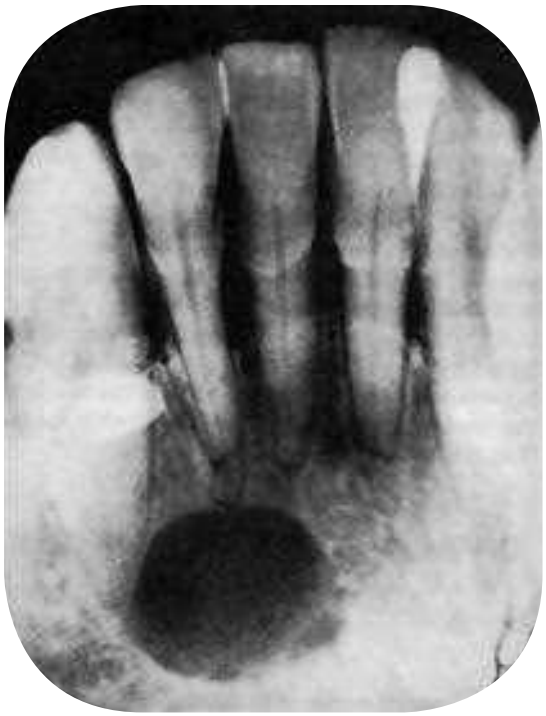


Figure 1-29. Developmental lingual mandibular salivary gland depression of sublingual gland.
(Courtesy of Dr Michael J Freeman).

Treatment. These lesions generally represent benign developmental anomalies that normally do not require any treatment. A complication occasionally reported in the literature is the development of a true salivary gland neoplasm in the tissue associated with one of the cortical defects. Therefore, recording the finding of these lesions and periodically observing them radiographically seem prudent. Clinical or radiographic changes may indicate the need for further investigation.

DEVELOPMENTAL DISTURBANCES IN SIZE OF TEETH

Microdontia

This term is used to describe teeth which are smaller than normal, i.e. outside the usual limits of variation. Three types of microdontia are recognized: (1) true generalized microdontia, (2) relative generalized microdontia, and (3) microdontia involving a single tooth.

In **true generalized microdontia,** all the teeth are smaller than normal. Aside from its occurrence in some cases of pituitary dwarfism, this condition is exceedingly rare. The teeth are reportedly well formed, merely small.

In **relative generalized microdontia,** normal or slightly smaller than normal teeth are present in jaws that are somewhat larger than normal, and there is an illusion of true microdontia.

Since it is well recognized that a person may inherit the jaw size from one parent and the tooth size from the other parent, the role of hereditary factors in producing such a condition is obvious.

Microdontia involving only a single tooth is a rather common condition (Fig. 1-30). It affects most often the maxillary lateral incisor and the third molar. These two teeth are among those that are most often congenitally missing. It is of interest to note; however, that other teeth which are often congenitally absent, the maxillary and mandibular second premolars, seldom exhibit microdontia. Supernumerary teeth; however, are frequently small in size.

One of the common forms of localized microdontia is that which affects the maxillary lateral incisor, a condition that has been called the **'peg lateral'** (Fig. 1-31). Instead of exhibiting parallel or diverging mesial and distal surfaces, the sides converge or taper together incisally, forming a peg-shaped or cone-shaped crown. The root of such a tooth is frequently shorter than usual.

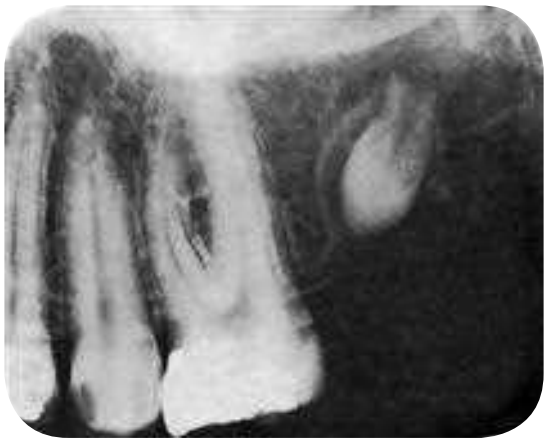


Figure 1-30. Microdontia.
The third molar is small and incompletely formed. The second molar had been previously extracted.

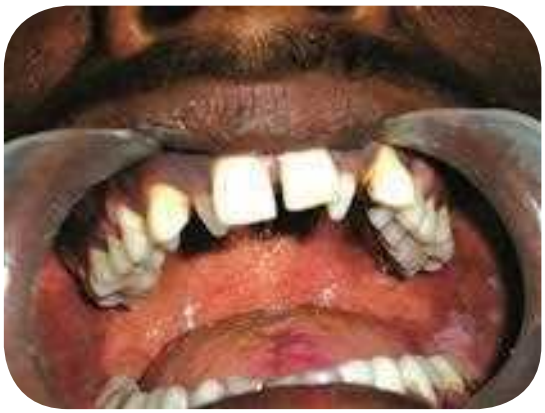


Figure 1-31. Microdontia.
Peg-shaped maxillary lateral incisor *(Courtesy of Dr Gururaj N, CSI Dental College, Madurai, Tamil Nadu).*

Macrodontia

Macrodontia is the opposite of microdontia and refers to teeth that are larger than normal. Such teeth may be classified in the same manner as microdontia.

True generalized macrodontia, the condition in which all teeth are larger than normal, has been associated with pituitary gigantism, but is extremely rare.

Relative generalized macrodontia is somewhat more common and is a result of the presence of normal or slightly larger than normal teeth in small jaws, the disparity in size giving the illusion of macrodontia. As in microdontia, the importance of heredity must be considered.

Macrodontia of single teeth is relatively uncommon, but is occasionally seen. It is of unknown etiology. The tooth may appear normal in every respect except for its size. True macrodontia of a single tooth should not be confused with fusion of teeth, in which, early in odontogenesis, the union of two or more teeth results in a single large tooth.

A variant of this localized macrodontia is the type that is occasionally seen in cases of hemihypertrophy of the face, in which the teeth of the involved side may be considerably larger than those of the unaffected side.

DEVELOPMENTAL DISTURBANCES IN SHAPE OF TEETH

Gemination

Geminated teeth are anomalies which arise from an attempt at division of a single tooth germ by an invagination, with resultant incomplete formation of two teeth. The structure is usually one with two completely or incompletely separated crowns that have a single root and root canal. It is seen in deciduous as well as permanent dentition, and in some reported cases, appears to exhibit a hereditary tendency. It is not always possible to differentiate between gemination and a case in which there has been fusion between a normal tooth and a supernumerary tooth (Fig. 1-32).

The term 'twinning' has sometimes been used to designate the production of equivalent structures by division resulting in one normal and one supernumerary tooth. These terms, as well as 'fusion' and 'concrescence,' have been discussed by Levitas.

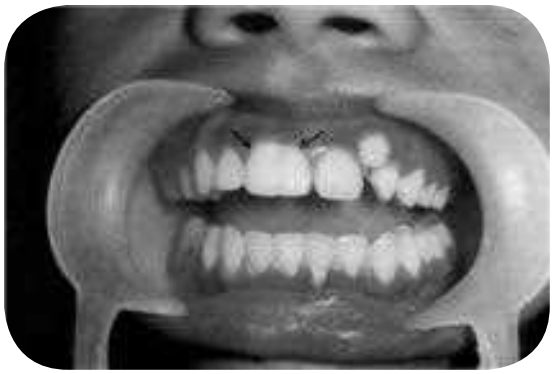
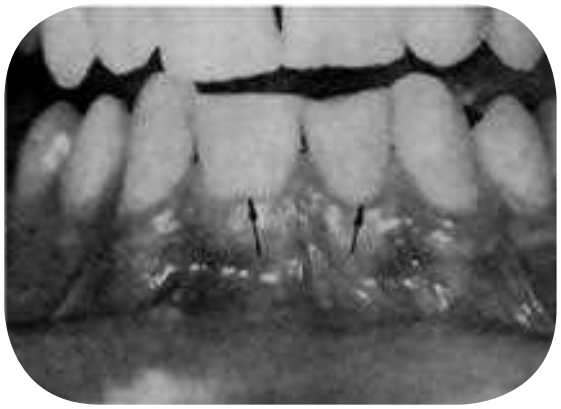


Figure 1-32. Gemination (with unpaired root canals).

Fusion

Fused teeth arise through union of two normally separated tooth germs. Depending upon the stage of development of the teeth at the time of the union, fusion may be either complete or incomplete. It has been thought that some physical force or pressure produces contact of the developing teeth and their subsequent fusion. If this contact occurs early, at least before calcification begins, the two teeth may be completely united to form a single large tooth (Fig. 1-33). If the contact of teeth occurs later, when a portion of the tooth crown has completed its formation, there may be union of the roots only. The dentin; however, is always confluent in cases of true fusion. The tooth may have separate or fused root canals, and the condition is common in the deciduous as well as in the permanent dentition. In fact, Grahnen and Granath have reported that fusion of teeth is more common in the deciduous than in the permanent dentition.



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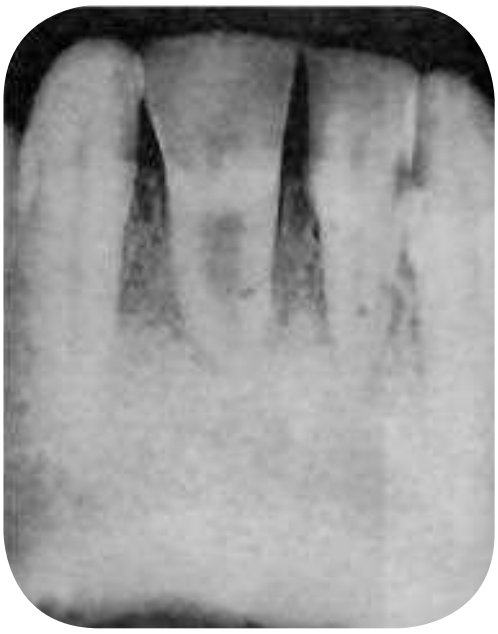


B

Figure 1-33. Fusion of teeth.
(A) There has been complete fusion between the mandibular left central and lateral incisors and the right central and lateral incisors. **(B)** The intraoral radiograph showing a common pulp chamber and root canal in each pair of fused teeth.

Figure 1-34. Fusion of right lower central and a supernumerary tooth.
(Courtesy of Dr Spencer Lilly, Meenakshi Ammal Dental College, Chennai).

In addition to affecting two normal teeth, fusion may also occur between a normal tooth and a supernumerary tooth such as the mesiodens or the distomolar (Fig. 1-34). In some cases the condition has been reported to show a hereditary tendency.

The possible clinical problems related to appearance, spacing, and periodontal conditions brought about by fused teeth have been discussed by Mader, who has also reported several illustrative cases.

Concrescence

Concrescence of teeth is actually a form of fusion which occurs after root formation has been completed. In this condition, teeth are united by cementum only. It is thought to arise as a result of traumatic injury or crowding of teeth with resorption of the interdental bone so that the two roots are in approximate contact and become fused by the deposition of cementum between them. Concrescence may occur before or after the teeth have erupted, and although it usually involves only two teeth, there is at least one case on record of union of three teeth by cementum.

The diagnosis can frequently be established by radiographic examination. Since with fused teeth the extraction of one may result in the extraction of the other, it is desirable that the dentist be forewarned of the condition and advices the patient.

Dilaceration

The term 'dilaceration' refers to an angulation, or a sharp bend or curve, in the root or crown of a formed tooth (Fig. 1-35). The condition is thought to be due to trauma during the period in which the tooth is forming, with the result that the position of the calcified portion of the tooth is changed and the remainder of the tooth is formed at an angle. The curve or bend may occur anywhere along the length of the tooth, sometimes at the cervical portion, at other times midway along the root or even just at the apex of the root, depending upon the amount of root formed when the injury occurred. It has been emphasized by van Gool that such an

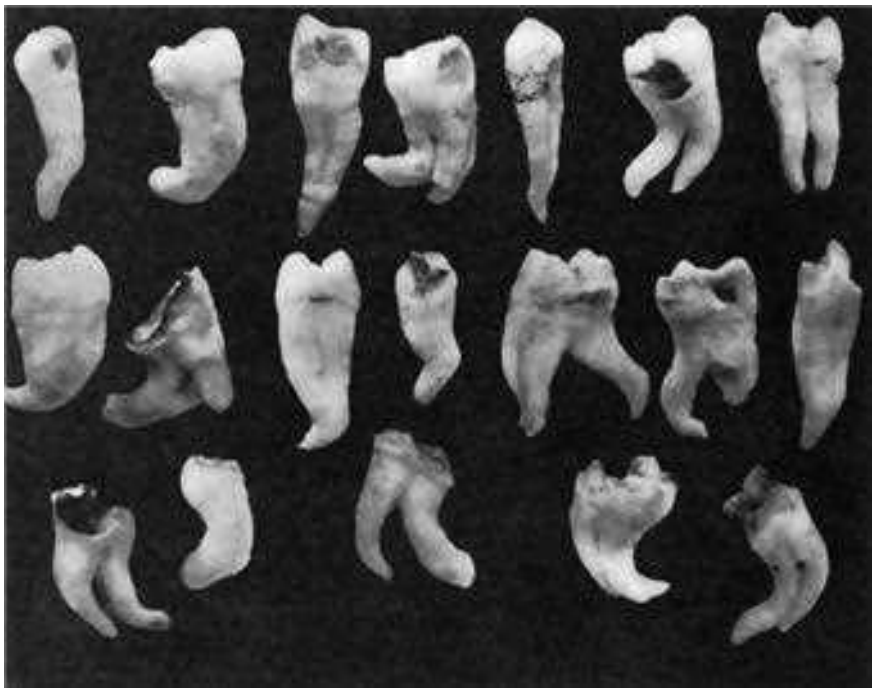


Figure 1-35. Dilaceration.
Examples of various types of curves and angles involving roots of teeth.

injury to a permanent tooth, resulting in dilaceration, often follows traumatic injury to the deciduous predecessor in which that tooth is driven apically into the jaw. He has discussed this condition in detail, reporting 18 such cases.

Since dilacerated teeth frequently present difficult problems at the time of extraction if the operator is unaware of the condition, the need for preoperative radiographs before any surgical procedures are carried out is self-evident.

Talon Cusp

The talon cusp, an anomalous structure resembling an eagle's talon, projects lingually from the cingulum areas of a maxillary or mandibular permanent incisor. This cusp blends smoothly with the tooth except that there is a deep developmental groove where the cusp blends with the sloping lingual tooth surface (Fig. 1-36). It is composed of normal enamel and dentin and contains a horn of pulp tissue.

This anomaly has been discussed by Mellor and Ripa, who have emphasized the problems it poses for the patient in terms of esthetics, caries control, and occlusal accommodation. They have recommended prophylactically restoring the groove to prevent caries. If there is occlusal interference, it should be removed but exposure of the pulp horn, necessitating endodontic therapy, is almost certain to occur. Fortunately, this anomaly is quite uncommon among the general population. However, it has been reported by Gardner and Girgis that it appears to be more prevalent in persons with the **Rubinstein-Taybi syndrome** (developmental retardation, broad thumbs and great toes, characteristic facial features, delayed or incomplete descent of testes in males, and stature, head

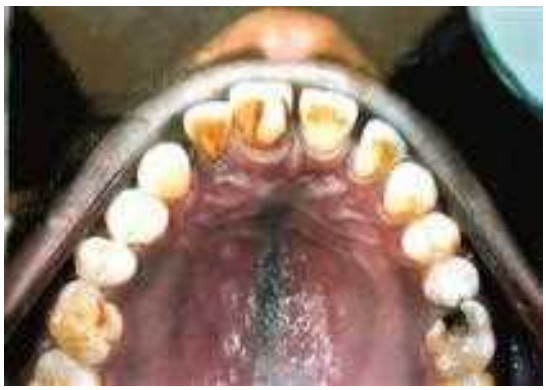


Figure 1-36. Talon cusp.
(Courtesy of Dr Spencer Lilly D, Meenakshi Ammal Dental College, Chennai).

circumference, and bone age below the fiftieth percentile). The talon cusp has not been reported as an integral part of any other syndrome, although Mader, in his thorough review, suggested that it may be associated with other somatic and odontogenic anomalies.

Dens in Dente

(Dens invaginatus, dilated composite odontome)

The 'dens in dente' is a developmental variation which is thought to arise as a result of an invagination in the surface of tooth crown before calcification has occurred (Fig. 1-37). Several causes of this condition have been proposed. These include an increased localized external pressure, focal growth

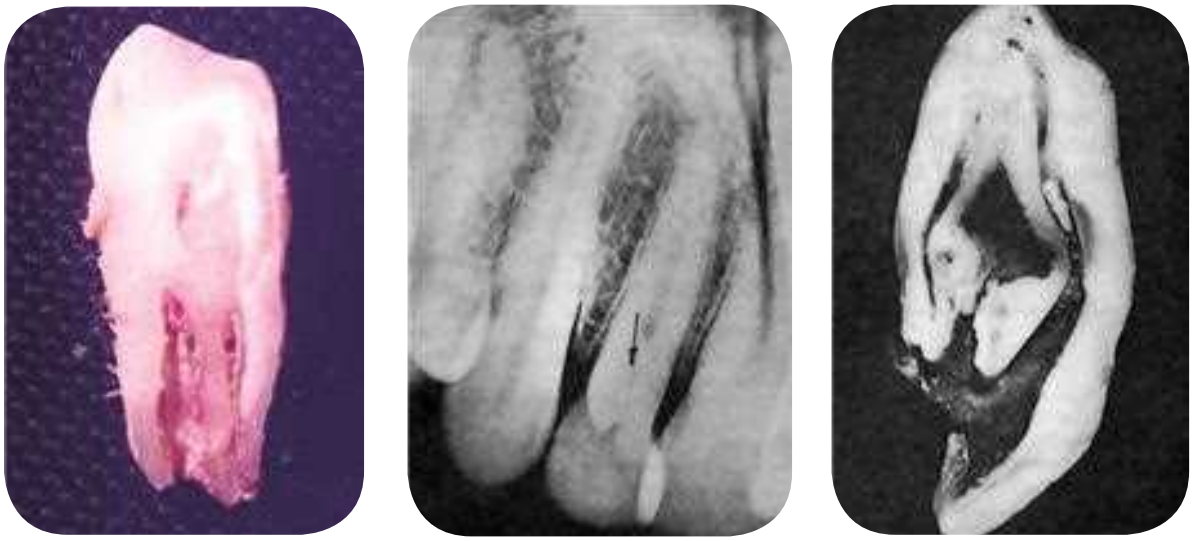


Figure 1-37. Dens in dente.
(A) Dens invaginatus. **(B)** A slight invagination may be seen in the lingual pit area of the maxillary lateral incisor on the radiograph. **(C)** The ground section of tooth represents a severe form of 'dens in dente' and illustrates how the anomaly may resemble a tooth within a tooth (*Courtesy of Dr Twinkle S Prasad*).

retardation, and focal growth stimulation in certain areas of the tooth bud.

The permanent maxillary lateral incisors are the teeth most frequently involved, and in the majority of cases the 'dens in dente' appears to represent simply an accentuation in the development of the lingual pit (Fig. 1-37A). The maxillary central incisors are sometimes involved, and the condition is frequently bilateral. Oehlers has presented an excellent discussion of this condition and emphasized that not only are posterior teeth sometimes affected but also an analogous form of invagination occasionally occurs in the roots of teeth. This radicular variety of 'dens in dente' has been discussed by Bhatt and Dholakia, who pointed out that the radicular invagination usually results from an infolding of Hertwig's sheath and takes its origin within the root after development is complete.

The cases that have been reported in the literature indicate that the condition is fairly common and that an extremely wide range in degree of variation can exist. The term 'dens in dente,' originally applied to a severe invagination that gave the appearance of a tooth within a tooth, is actually a misnomer, but it has continued in usage (Fig. 1-37B). In the mild form, there is a deep invagination in the lingual pit area, which may not be evident clinically. Radiographically, it is recognized as a pear-shaped invagination of enamel and dentin with a narrow constriction at the opening on the surface of the tooth and closely approximating the pulp in its depth. Food debris may become packed in this area with resultant caries and infection of the pulp, occasionally even before the tooth has completely erupted. The more severe forms of 'dens in dente' may exhibit an invagination that extends nearly to the apex of the root, and these present a bizarre radiographic picture (Fig. 1-38),

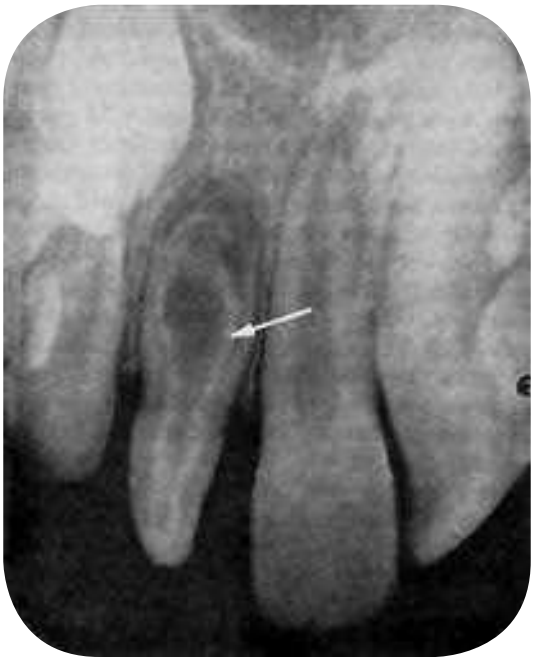


Figure 1-38. Dens in dente.
A nearly complete invagination in a maxillary lateral incisor.

reflecting a severe disturbance in the normal anatomic and morphologic structure of the teeth.

It is important to realize that this condition, particularly in its mild form, is fairly common. The clinical studies of Amos have shown that if the minor invaginations are included, the incidence may be as high as 5% of all patients examined (Table 1-10). The more severe forms; however, are much less common.

Table 1-10: Investigations on the prevalence of dens invaginatus

Author/Country	Year	Sample	Frequency
Muhlreiter(Austria)	1873	500 extracted lateral maxillaryincisors (histological investigation)	2.8% of teeth
Atkinson(USA)	1943	500 lateral maxillary incisors	10% of teeth
Boyne(USA)	1952	1,000 maxillary incisors	0.3% of teeth
Stephens	1953	150 full-mouth surveys	8%
(unknown)	1953	1,000 patients	3.6% (cited by Hovland & Block 1977)
Shafer(USA)	1953	2,542 full-mouth surveys	1.3% of patients (cited by Hovland & Block 1977)
Hallet(unknown)	1953	586 full-mouth surveys	6.6% of maxillary lateral incisors 0.5% of maxillary central incisors (cited by Hovland & Block 1977)
Amos(USA)	1955	1,000 full mouth surveys 203 full mouth surveys	5.1% of patients 6.9% (students of dentistry)
Grahnen et al (*Sweden*)	1959	3,020 right maxillary incisors	2.7% of patients
Ulmansky & Hermel (Israel)	1964	500 full mouth surveys	2% of patients
Poyton & Morgan (Canada)	1966	5,000 full mouth surveys	0.25% of patients (cited by Hovland& Block 1977)
Miyoshi et al (*Japan*)	1971	extracted maxillary lateral incisors	38.5% of teeth (cited by Gotoh et al, 1979)
Fujiki et al (*Japan*)	1974	2,126 lateral maxillary incisors	4.2% of teeth (cited by Gotoh et al, 1979)
Thomas (USA)	1974	1,886 full mouth surveys	7.74% of patients
Gotoh et al (*Japan*)	1979	766 lateral maxillary incisors	9.66% of teeth
Ruprecht et al (Saudi Arabia)	1986	1,581 full mouth surveys	1.7% of patients
Ruprecht et al (Saudi Arabia)	1987	300 full mouth surveys	10% of patients

Source: Hulsmann. Int Endod J, 30: 79-90, 1997.

To prevent caries, pulp infection, and premature loss of the tooth, the condition must be recognized early and the tooth prophylactically restored. Fortunately, the defect may be recognized radiographically even before the teeth erupt.

Dens Evaginatus

(Occlusal tuberculated premolar, Leong's premolar, evaginated odontome, occlusal enamel pearl)

The dens evaginatus is a developmental condition that appears clinically as an accessory cusp or a globule of enamel on the occlusal surface between the buccal and lingual cusps of premolars, unilaterally or bilaterally, although it has been reported to occur rarely on molars, cuspids, and incisors (Fig. 1-39). It has been thought to develop only in persons of Mongoloid ancestry: Chinese, Japanese, Filipinos, Eskimos, and American Indians. Its prevalence in a group of 2,373 Chinese schoolchildren in Singapore, reported by Yip, was 2.2%. However, Palmer has reported a series of cases in Caucasians in England.

The pathogenesis of the lesion is thought to be the proliferation and evagination of an area of the inner enamel epithelium and subjacent odontogenic mesenchyme into the dental organ during early tooth development. Thus, it has been considered to be the antithesis of the mechanism of development of the dens in dente or dens invaginatus.

The clinical significance of the condition is similar to that of the talon cusp, which it may physically resemble. This 'extra' cusp may contribute to incomplete eruption, displacement of teeth and/or pulp exposure with subsequent infection following occlusal wear or fracture. This phenomenon has been discussed by Senia and Regezi, who have reported periapical infection of caries-free premolars affected by dens evaginatus.

Figure 1-39. Dens evaginatus.
(Courtesy of Dr Charles E Tomich).

Taurodontism

The term 'taurodontism' was originated by Sir Arthur Keith in 1913 to describe a peculiar dental anomaly in which the body of the tooth is enlarged at the expense of the roots. The term means 'bull-like' teeth and its usage is derived from the similarity of these teeth to those of ungulate or cud-chewing animals. Shaw further classified taurodont teeth into hypotaurodont, mesotaurodont, and hypertaurodont forms, with hypertaurodontism being the extreme form in which the bifurcation or trifurcation occurs near the apices of the roots and hypotaurodontism being the mildest form.

A variety of possible causes of taurodontism have been enumerated by Mangion as follows: (1) a specialized or retrograde character, (2) a primitive pattern, (3) a mendelian recessive trait, (4) an atavistic feature, and (5) a mutation resulting from odontoblastic deficiency during dentinogenesis of the roots. Hammer and his associates believe that the taurodont is caused by failure of Hertwig's epithelial sheath to invaginate at the proper horizontal level. The heritability of this condition requires further study, although after finding 11 cases of taurodontism among members of three families, Goldstein and Gottlieb have stated that the condition appears to be genetically controlled and familial in nature.

This condition is of anthropologic interest in as much as it has been found commonly in fossil hominids, especially in the Neanderthal man, with a very high prevalence during the neolithic period. At one time it was thought to be confined to these early populations, but it is now known to be widespread in many modern races. Hammer and his associates have discussed these anthropologic aspects in detail, while Blumberg and his coworkers have carried out a biometric study of the condition. A case of taurodontism occurring concomitantly with amelogenesis imperfecta has been reported by Crawford. In addition, it has been reported that many patients with the Klinefelter syndrome (males whose sex chromosome constitution includes one or more extra X chromosomes) exhibit taurodontism, but it is not a constant feature of this syndrome. For this reason, Gardner and Girgis have recommended that male patients exhibiting taurodontism should have chromosomal studies performed, especially if there is any nonspecific diagnosis of mental retardation and if the patient has a tall, thin appearance with long arms and legs and a prognathic jaw.

Clinical Features. Taurodontism may affect either the deciduous or permanent dentition, although permanent tooth involvement is more common. The teeth involved are almost invariably molars, sometimes only a single tooth, at other times several molars in the same quadrant. The condition may be unilateral or bilateral or may exhibit any combination of quadrant involvement. The teeth themselves have no remarkable or unusual morphologic clinical characteristics.

Radiographic Features. The unusual nature of this condition is best visualized on the radiograph. Involved teeth frequently tend to be rectangular in shape rather than taper toward the roots. The pulp chamber is extremely large with a much greater apico-occlusal height than normal. In addition, the pulp lacks the usual constriction at the cervical of the tooth and the roots are exceedingly short. The bifurcation or trifurcation may be only a few millimeters above the apices of the roots (Fig. 1-41). This radiographic picture is quite striking and characteristic.

Treatment. No special treatment is necessary for this anomaly.

Supernumerary Roots

This developmental condition is not uncommon and may involve any tooth (Fig. 1-42). Teeth that are normally single-rooted, particularly the mandibular bicuspids and cuspids, often have two roots. Both maxillary and mandibular molars, particularly third molars, also may exhibit one or more supernumerary roots. This phenomenon is of considerable significance in exodontia, for one of these roots may be broken off during extraction and, if unrecognized and allowed to remain in the alveolus, may be the source of future infection.

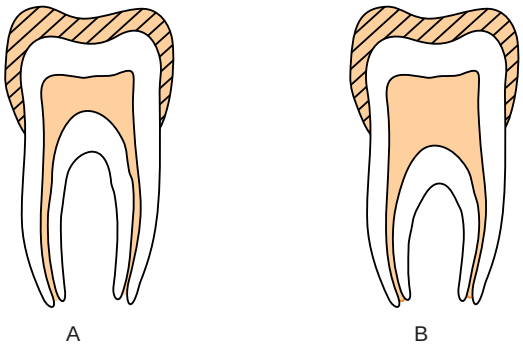


Figure 1-40. Normal tooth (A), taurodontism (B). Note increased pulpal width in B.
(Courtesy of Paulsen, Alvin C, Plymate SR. 'Klinefelter's syndrome.' The Genetic Basis of Common Diseases. Editors: King et al. Oxford Monograph on Medical Genetics, Chapter 44, 885: 1992.)

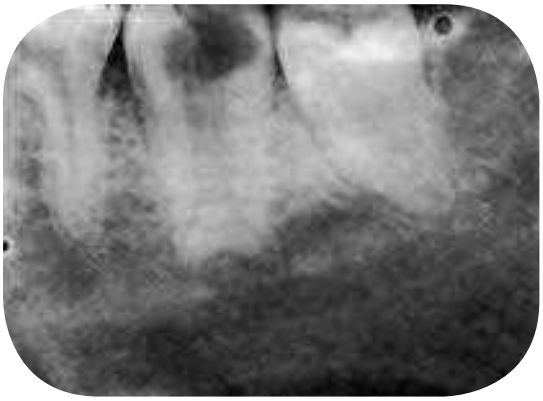


Figure 1-41. Taurodontism.

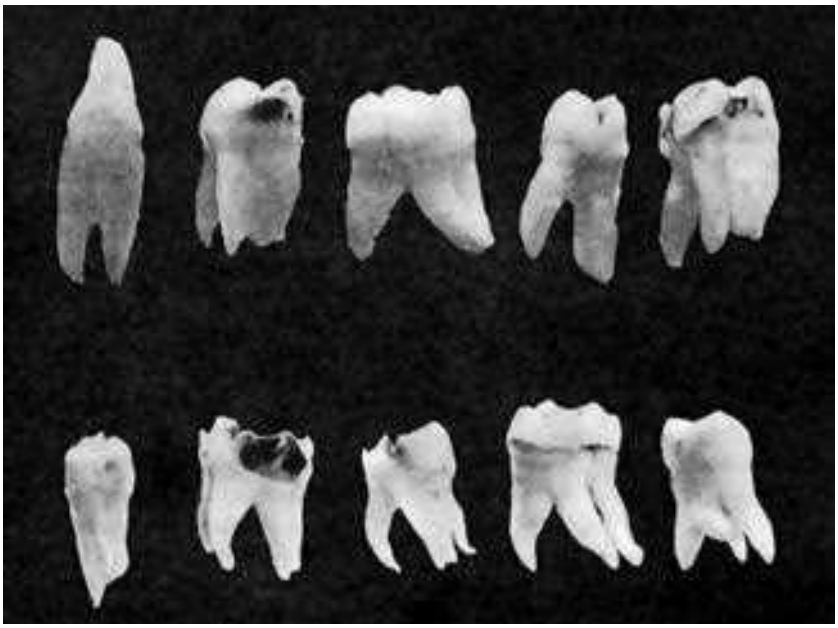


Figure 1-42. Supernumerary roots.

DEVELOPMENTAL DISTURBANCES IN NUMBER OF TEETH

Anodontia

True anodontia, or congenital absence of teeth, may be of two types, total and partial. Total anodontia, in which all teeth are missing, may involve both deciduous and permanent dentition (Fig. 1-43). This is a rare condition; when it occurs, it is frequently associated with a more generalized disturbance, hereditary ectodermal dysplasia (q.v.).

Induced or false anodontia occurs as a result of extraction of all teeth, while the term pseudoanodontia is sometimes applied to multiple unerupted teeth. The condition under discussion here is a true failure of odontogenesis and should not be confused with false or pseudoanodontia.

True partial anodontia (hypodontia or oligodontia) involves one or more teeth and is a rather common condition (Fig. 1-42). Although any tooth may be congenitally missing, there is a tendency for certain teeth to be missing more frequently than others (Table 1-11). Studies on the frequency of missing third molars have shown this tooth to be congenitally absent in as many as 35% of all subjects examined, with a frequent absence of all four third molars in the same person (Table 1-12). Other studies have shown that the maxillary lateral incisors and maxillary or mandibular second premolars are commonly missing, often bilaterally (Fig. 1-44). In severe partial anodontia, the bilateral absence of corresponding teeth may be striking. An outstanding review of this subject has been reported by Graber, who showed that the overall frequency of patients with congenitally missing teeth (excluding third molars) has ranged from 1.6–9.6% in various series of studies in different countries.

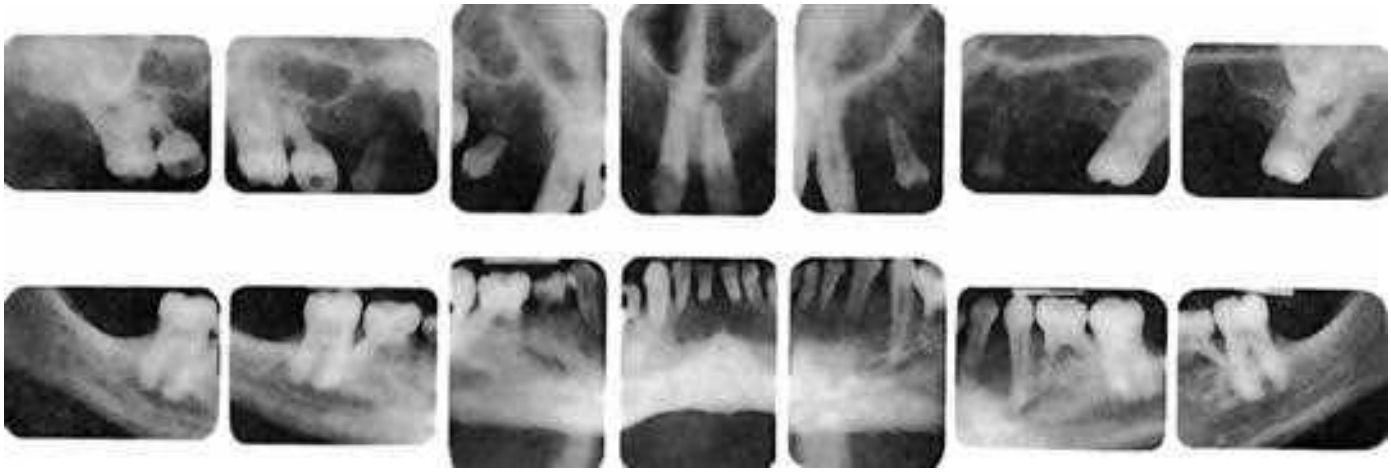


Figure 1-43. Anodontia.
There is congenital absence of nearly all permanent teeth with retention of many deciduous teeth.

Table 1-11: Prevalence of dental agenesis by continent, race and gender in percentages (and 95% CI)

	Males	Females	Total
Europe (White)	4.6 (4.5–4.8)	6.3 (6.1–6.5)	5.5 (5.3–5.6)
North America (White)	3.2 (2.9–3.5)	4.6 (4.2–4.9)	3.9 (3.7–4.1)
North America (African American)	3.2 (2.2–4.1)	4.6 (3.5–5.8)	3.9 (3.1–4.6)
Australia (White)	5.5 (4.4–6.6)	7.6 (6.0–9.2)	6.3 (5.4–7.2)
Saudi Arabia (White)	2.7 (2.0–3.4)	2.2 (1.2–3.1)	2.5 (1.9–3.1)
Chinese (Mongoloid)	6.1 (4.0–8.1)	7.7 (5.4–10.0)	6.9 (5.3–8.4)

Source: Polder BJ et al. Community Dent Oral Epidemiol 32: 217–26, 2004.

Table 1-12: Prevalence in percentages and 95% CI of dental agenesis of individual teeth derived from 48, 274 persons

	Maxilla		Mandible	
	n	Prevalence	n	Prevalence (95% CI)
I1	3	0.00–0.01	143	0.25–0.35
I2	804	1.55–1.78	102	0.17–0.25
C	47	0.07–0.13	8	0.01–0.03
P1	100	0.17–0.25	66	0.10–0.17
P2	722	1.39–1.61	1479	2.91–3.22
M1	17	0.02–0.05	6	0.00–0.02
M2	21	0.03–0.06	47	0.07–0.13

Source: Polder BJ et al. Community Dent Oral Epidemiol 32: 217–26, 2004.

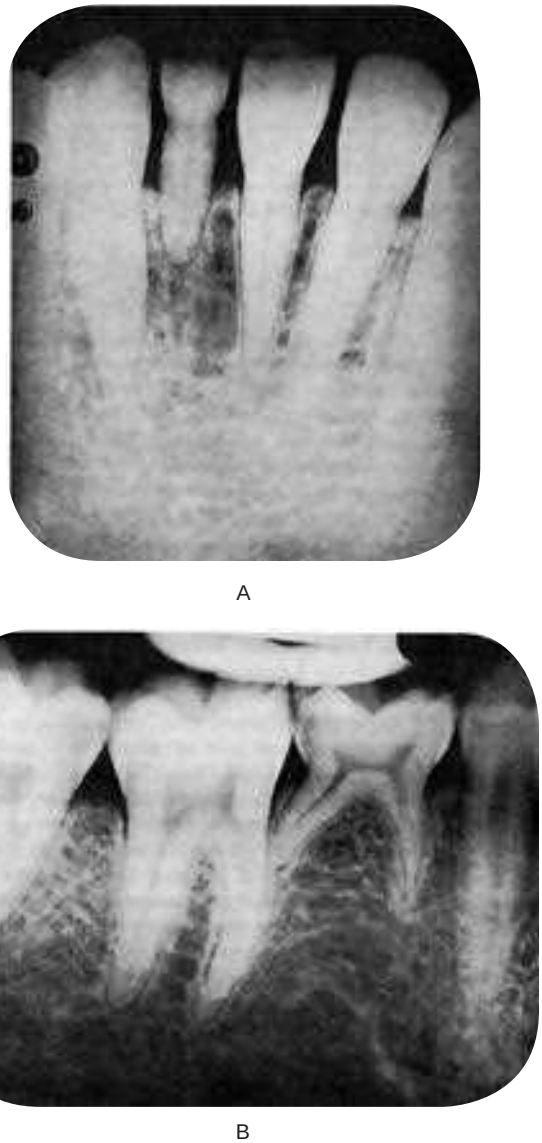
Congenitally missing deciduous teeth are uncommon but, when occurring, usually involve the maxillary lateral incisor. Mandibular lateral incisors and mandibular cuspids may also be missing, according to the study of Grahnen and Granath. Their studies also showed a close correlation between congenitally missing deciduous teeth and their permanent successors; suggesting, at least in some instances, a genetic factor.

Although the etiology of a single missing tooth is unknown, a familial tendency for this defect is present in many instances. Graber, in reviewing congenital absence of teeth, reported the accumulating evidence that it is actually the result of one or more point mutations in a closely linked polygenic system, most often transmitted in an autosomal dominant pattern with incomplete penetrance and variable expressivity. Some investigators believe cases of missing third molars to be an evidence of an evolutionary trend towards fewer teeth. Hereditary ectodermal dysplasia may be associated with partial anodontia, and in these instances the few teeth that are present may be deformed or misshapen, frequently cone-shaped.

Occasionally one sees children with teeth of one quadrant or both quadrants on the same side missing owing to X-ray radiation of the face at an early age. Tooth buds are extremely sensitive to X-ray radiation and may be destroyed completely by relatively low dosages. Teeth already forming and partially calcified may be stunted by X-ray radiation.

Supernumerary Teeth

A supernumerary tooth may closely resemble the teeth of the group to which it belongs, i.e. molars, premolars, or anterior teeth, or it may bear little resemblance in size or shape to the teeth with which it is associated. It has been suggested that supernumerary teeth develop from a third tooth bud arising from the dental lamina near the permanent tooth bud, or



A

B

Figure 1-44. Partial anodontia.
The mandibular permanent left central incisor is congenitally missing. The deciduous incisor is retained **(A)**. There is congenital absence of the mandibular second bicuspid with retention of the deciduous molar **(B)**.

possibly from splitting of the permanent bud itself. Another theory, well supported in the literature, is the hyperactivity theory, which suggests that supernumeraries are formed as a result of local, independent, conditioned hyperactivity of the dental lamina. In some cases there appears to be a hereditary tendency for the development of supernumerary teeth.

A supernumerary tooth is an additional entity to the normal series and is seen in all the quadrants of the jaw. The etiology of supernumerary teeth is not completely understood. The anomaly does not follow a simple mendelian pattern. In a survey of 2,000 schoolchildren, Brook found that supernumerary teeth were present in 0.8% of primary dentition and in 2.1% of permanent dentition. Occurrence may be single or multiple, unilateral or bilateral, erupted or impacted, and in one or both jaws. Multiple supernumerary teeth are rare in individuals with no other associated diseases or syndromes. The conditions commonly associated with an increased prevalence of supernumerary teeth include cleft lip and palate, cleidocranial dysplasia, and Gardner syndrome. Supernumerary teeth associated with cleft lip and palate result from fragmentation of the dental lamina during cleft formation. The frequency of supernumerary permanent teeth in the cleft area in children with unilateral cleft lip or palate or both was found to be 22.2%. The frequency of supernumeraries in patients with cleidocranial dysplasia ranged from 22% in the maxillary incisor region to 5% in the molar region. While there is no significant gender predilection in primary supernumerary teeth, males are affected approximately twice as frequently as females in the permanent dentition.

Classification. Supernumerary teeth are classified according to morphology and location. In the primary dentition, morphology is usually normal or conical. There is a greater variety of forms presenting in the permanent dentition.

Four different morphological types of supernumerary teeth have been described:

- Conical
- Tuberculate
- Supplemental
- Odontome.

Conical. This small peg-shaped conical tooth is supernumerary and most commonly found in the permanent dentition. It develops with root formation ahead of or at an equivalent stage to that of permanent incisors and usually presents as a mesiodens. It may occasionally be found high and inverted into the palate or in a horizontal position. In most cases; however, the long axis of the tooth is normally inclined. The conical supernumerary can result in rotation or displacement of the permanent incisor, but rarely delays eruption.

Tuberculate. The tuberculate type of supernumerary possesses have more than one cusp or tubercle. It is frequently described as barrel-shaped and may be invaginated. Root formation is delayed compared to that of the permanent incisors. Tuberculate supernumeraries are often paired and are commonly located on the palatal aspect of the central incisors. They rarely erupt and are frequently associated with delayed eruption of the incisors.

Supplemental. The supplemental supernumerary refers to a duplication of teeth in the normal series and is found at the end of a tooth series. The most common supplemental tooth is the permanent maxillary lateral incisor, but supplemental premolars and molars also occur. The majority of supernumeraries found in the primary dentition are of the supplemental type and seldom remain impacted.

Odontome. Odontome has been listed as the fourth category of supernumerary teeth by Howard. However, this category is not universally accepted. The term 'odontoma' refers to any tumor of odontogenic origin. Most authorities; however, accept the view that the odontoma represents a hamartomatous malformation rather than a neoplasm. The lesion is composed of more than one type of tissue and consequently has been called a composite odontoma. Two separate types have been described, the diffuse mass of dental tissue which is totally disorganized is known as a **complex composite odontoma,** whereas the malformation which bears some superficial anatomical similarity to a normal tooth is referred to as a **compound composite odontoma.**

Gardner syndrome is an interesting disease complex, reviewed by Fader and his associates and by Duncan and his associates. It is also characterized by the occurrence of multiple impacted supernumerary teeth. This syndrome consists of: (1) multiple polyposis of the large intestine, (2) osteomas of the bones, including long bones, skull, and jaws, (3) multiple epidermoid or sebaceous cysts of the skin, particularly on the scalp and back, (4) occasional occurrence of desmoid tumors, and (5) the impacted supernumerary and permanent teeth (Figs. 1-45, 1-46).

It is due to a single pleiotropic gene and has an autosomal dominant pattern of inheritance, with complete penetrance and variable expression. Indicative of its inheritability is a report by Watne and his associates, who studied 280 patients from 11 families with Gardner syndrome. They found that 126 of the 280, or 45% of the patients at risk, exhibited some part of the syndrome. Significantly, the intestinal polyps in this disease were premalignant, and polyps were found to be present in 85 of the 126 patients. In 41 of the patients, carcinoma of the intestine subsequently developed and only 27% survived. This disease is of interest to the dental profession, since the impacted teeth and osteomas of the jaws may lead to early diagnosis of the entire syndrome.

Predeciduous Dentition

(Premature eruption, natal teeth, neonatal teeth)

Infants occasionally are born with structures which appear to be erupted teeth, usually in the mandibular incisor area. These structures must be distinguished from true deciduous teeth, or the so-called natal teeth described by Massler, which may have erupted by the time of birth. The predeciduous teeth have been described as hornified epithelial structures without roots, occurring on the gingiva over the crest of the ridge, which may be easily removed. Prematurely erupted true deciduous teeth, of course, are not to be extracted. These predeciduous

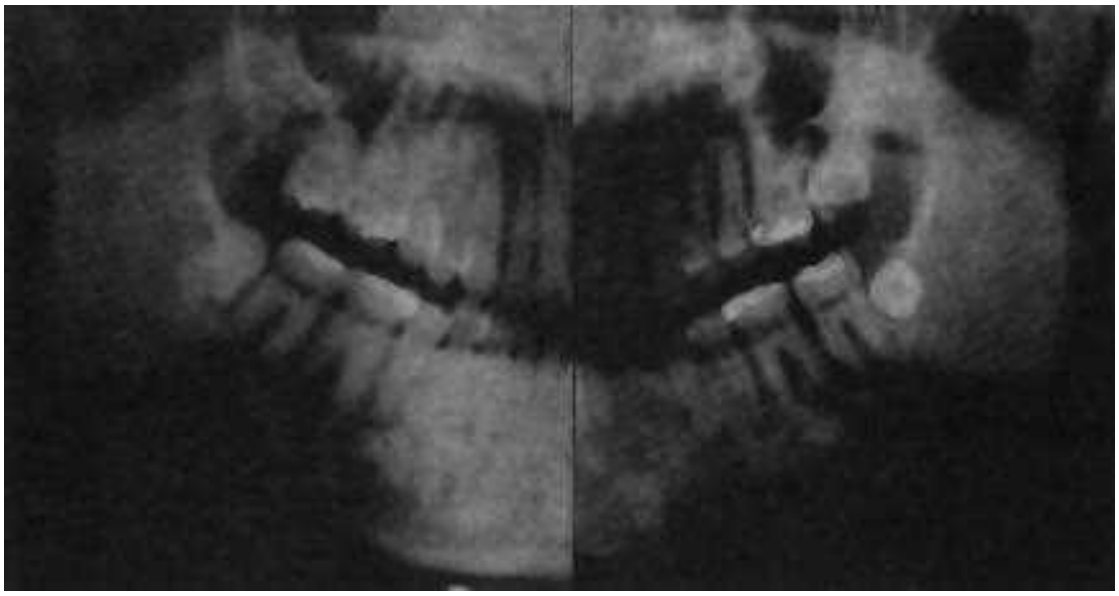


Figure 1-45. Gardner syndrome.
Multiple diffuse osteomas of the maxilla and mandible are present, although the patient does not have supernumerary teeth *(Courtesy of Dr Wesley P Titterington, Dr William M Wade, Jr).*

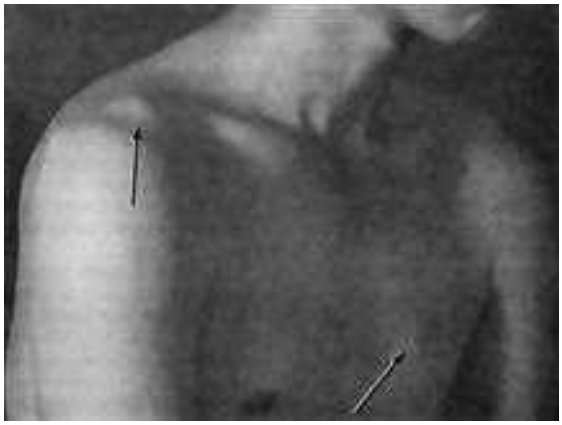


Figure 1-46. Gardner syndrome.
Sebaceous cysts of the skin are present over the shoulder and chest *(Courtesy of Dr Wesley P Titterington, Dr William M Wade, Jr).*

teeth have been thought to arise either from an accessory bud of the dental lamina ahead of the deciduous bud or from the bud of an accessory dental lamina.

The concept of predeciduous teeth has been questioned by Spouge and Feasby; however. They are probably correct in believing that considering predeciduous teeth as an entity is a misinterpretation and that such structures, present at birth, undoubtedly represent only the dental lamina cyst of the newborn (q.v.). This cyst does commonly project above the crest of the ridge, is white in color and is packed within keratin, so that it appears 'hornified' and can be easily removed.

Post Permanent Dentition

A few cases are recorded of persons who have had all their permanent teeth extracted and yet have subsequently erupted several more teeth, particularly after the insertion of a full denture. The majority of such cases are the result of delayed eruption of retained or embedded teeth. A small number of cases; however, do appear to represent examples of a post permanent or third dentition, although it probably would be better to classify these as simply multiple supernumerary unerupted teeth, since they probably develop from a bud of the dental lamina beyond the permanent tooth germ.

DEVELOPMENTAL DISTURBANCES IN STRUCTURE OF TEETH

Amelogenesis Imperfecta

(Hereditary enamel dysplasia, hereditary brown enamel, hereditary brown opalescent teeth)

A complex inheritance pattern gives rise to amelogenesis imperfecta (AI), a structural defect of the tooth enamel. It may be differentiated into three main groups: **hypoplastic (HP), hypocalcified (HC),** and **hypomature (HM),** depending on the clinical presentation of the defects and the likely stage of enamel formation that is primarily affected (Table 1-13). Each main clinical group of AI may be further divided into several subgroups depending on the mode of inheritance, as well as the clinical appearance of the defective enamel, although in some cases, overlapping clinical features may make distinction difficult. The prevalence of this condition has been

Table 1-13: Classification of amelogenesis imperfecta according to Witkop (1989)

Type I	Hypoplastic
IA	Hypoplastic, pitted autosomal dominant
IB	Hypoplastic, local autosomal dominant
IC	Hypoplastic, local autosomal recessive
ID	Hypoplastic, smooth, autosomal dominant
IE	Hypoplastic, smooth X-linked dominant
IF	Hypoplastic, rough autosomal dominant
IG	Enamel agenesis, autosomal recessive
Type II	Hypomaturation
IIA	Hypomaturation, pigmented autosomal recessive
IIB	Hypomaturation, X-linked recessive
IIC	Snow-capped teeth, autosomal dominant
Type III	Hypocalcified
IIIA	Autosomal dominant
IIIB	Autosomal recessive
Type IV	Hypomaturation-hypoplastic with taurodontism
IVA	Hypomaturation-hypoplastic with taurodontism, autosomal dominant
IVB	Hypoplastic-hypomaturation with taurodontism, autosomal dominant

Source: CJ Witkop: J Oral Pathol, 17: 547–53, 1989.

Table 1-14: Gene(s) mutated in amelogenesis imperfecta (known and unknown)

Type I	Hypoplastic AI
IA	Pitted hypoplastic AD The gene defect for this AI type is unknown at this time
IB	Local hypoplastic AD A mutation in the enamelin gene (ENAM) has been identified as causing this AI type
IC	Local hypoplastic AR The gene defect for this AI type is unknown at this time
ID	Smooth hypoplastic AD Multiple mutations in the enamelin gene (ENAM); have been identified as causing this AI type
IE	Smooth hypoplastic X-linked dominant A variety of different mutations in the gene coding for the amelogenin protein (AMELX); cause this AI type
IF	Rough hypoplastic AD The gene defect for this AI type is unknown at this time
IG	Enamel agenesis AR (rough hypoplastic AR) The gene defect for this AI type is unknown at this time
Type II	Hypomaturation AI
IIA	Pigmented hypomaturation AR The gene defect for this AI type is unknown at this time
IIB	Hypomaturation AI X-linked recessive Multiple mutations in the AMELX gene have been identified in this AI type
IIC	Snow capped teeth AD The gene defect for this AI type is unknown at this time
Type III	Hypocalcified AI
IIIA	Hypocalcified AI AD The gene defect for this AI type is unknown at this time
IIIB	Hypocalcified AI AR The gene defect for this AI type is unknown at this time
Type IV	Hypomaturation-Hypoplastic with taurodontism
IVA	AD Hypomaturation-hypoplastic with taurodontism The gene defect for this AI type is unknown at this time
IVB	AD Hypoplastic-hypomaturation with taurodontism The gene defect for this AI type is unknown at this time

Source: Modified from the website data of School of Dentistry, University of North Carolina, 2005.

estimated to range from (1 in 718) to (1 in 14,000), depending on the population studied. Hypoplastic AI represents 60–73% of all cases, hypomaturation AI represents 20–40%, and hypocalcification AI represents 7%. Disorders of the enamel epithelium also can cause alterations in the eruption mechanism, resulting in the anterior open bite.

Molecular Genetic Studies. Molecular genetic studies have shown that the etiology of AI is related to the alteration of genes involved in the process of formation and maturation of the enamel (Table 1-14). Although the genetic origin of the autosomal forms is less understood, analysis of X-linked AI has shown the defective gene for this specific AI type to be closely linked to the locus **DXS85 at Xp22**. Interestingly, this also has been identified as the general location of the human gene for **amelogenin,** the principal protein in developing enamel. Information from molecular genetic studies will ultimately lead to identification of the genes involved in normal and pathological enamel formation and provide a basis for definitive diagnostic tests.

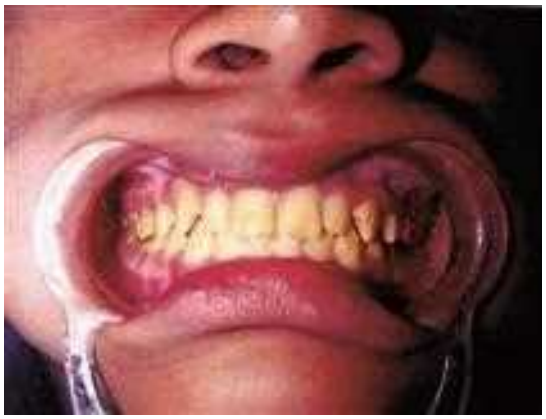
Radiographic Features. The overall shape of the tooth may or may not be normal, depending upon the amount of enamel present on the tooth and the amount of occlusal and incisal wear. The enamel may appear totally absent on the radiograph, or when present, may appear as a very thin layer, chiefly over the tips of the cusps and on the interproximal surfaces (Fig. 1-47). In other cases the calcification of the enamel may be so affected that it appears to have the same approximate radiodensity as the dentin, making differentiation between the two difficult (Fig. 1-48).

Histologic Features. The general histologic features of the enamel also parallel the general type of amelogenesis imperfecta that has been diagnosed. There is a disturbance in the differentiation or viability of ameloblasts in the hypoplastic type, and this is reflected in defects in matrix formation up to and including total absence of matrix. In the hypocalcification types there are defects of matrix structure and of mineral deposition. Finally, in the hypomaturation types there are alterations in enamel rod and rod sheath structures.

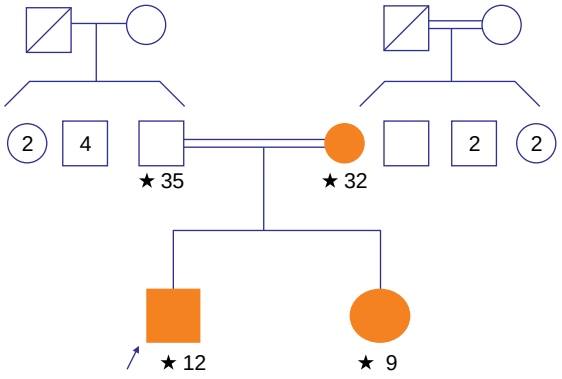
Treatment. There is no treatment except for improvement of cosmetic appearance. However, in some cases, these teeth do not appear markedly abnormal to the casual observer.

Environmental Enamel Hypoplasia

Enamel hypoplasia may be defined as an incomplete or defective formation of the organic enamel matrix of teeth.



A



B

Figure 1-47. Smooth hypoplastic AI with autosomal dominant inheritance pattern.
(Courtesy of Dr Bijo Alexander).

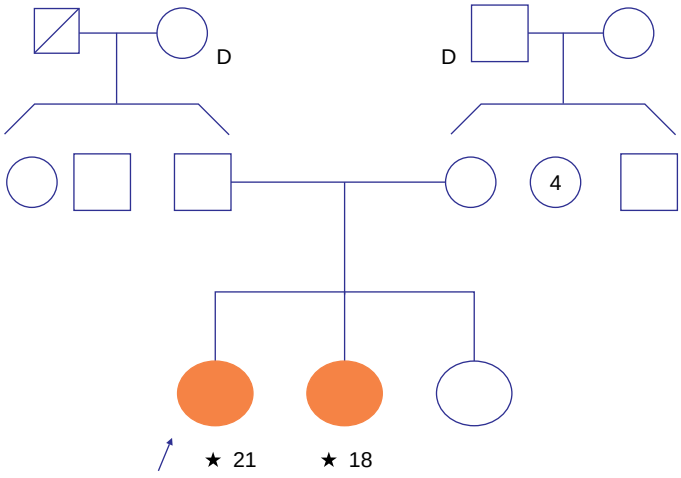


Figure 1-48. Hypocalcified AI with autosomal recessive inheritance pattern.

Two basic types of enamel hypoplasia exist: (1) a hereditary type, described previously under amelogenesis imperfecta, and (2) a type caused by environmental factors. In the hereditary type, both the deciduous and permanent dentitions usually are involved and generally only the enamel is affected. In contrast, when the defect is caused by environmental factors, either dentition may be involved and sometimes only a single tooth; both enamel and dentin are usually affected, at least to some degree.

Many studies, both experimental and clinical, have been carried out in an attempt to determine the cause and nature of environmental enamel hypoplasia. It is known that a number of different factors, each capable of producing injury to the ameloblasts, may give rise to the condition, including: (1) nutritional deficiency (vitamins A, C, and D); (2) exanthematous diseases (e.g. measles, chickenpox, scarlet fever); (3) congenital syphilis; (4) hypocalcemia; (5) birth injury, prematurity, Rh hemolytic disease; (6) local infection or trauma; (7) ingestion of chemicals (chiefly fluoride); and (8) idiopathic causes.

In mild environmental hypoplasia, there may be only a few small grooves, pits, or fissures on the enamel surface (Fig. 1-49). If the condition is more severe, the enamel may exhibit rows of deep pits arranged horizontally across the surface of the tooth (Fig. 1-50). There may be only a single row of such pits or several rows indicating a series of injuries. In the most severe cases, a considerable portion of enamel may be absent, suggesting a prolonged disturbance in the function of the ameloblasts.

Hypoplasia results only if the injury occurs during the time the teeth are developing, or more specifically, during the formative stage of enamel development. Once the enamel has calcified, no such defect can be produced. Thus, knowing the chronologic development of the deciduous and permanent teeth,

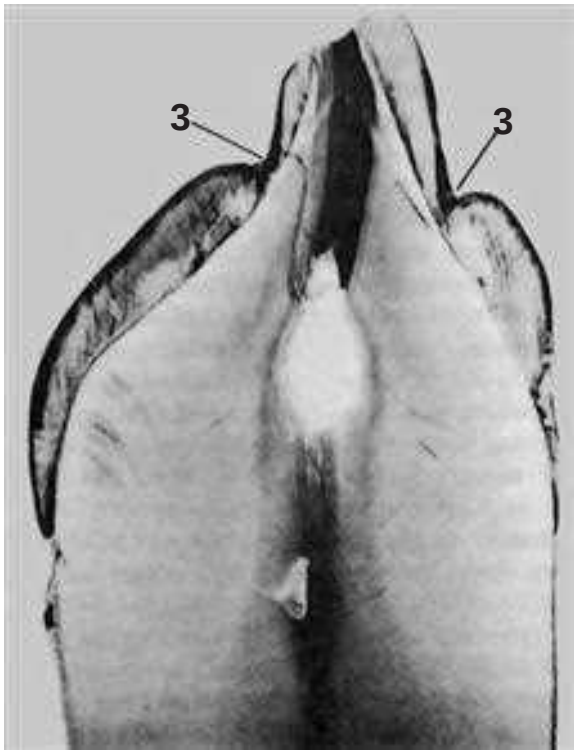


Figure 1-49. Enamel hypoplasia, environmental type.
The ground section of tooth shows a pit like defect on both the labial and lingual surfaces (1).

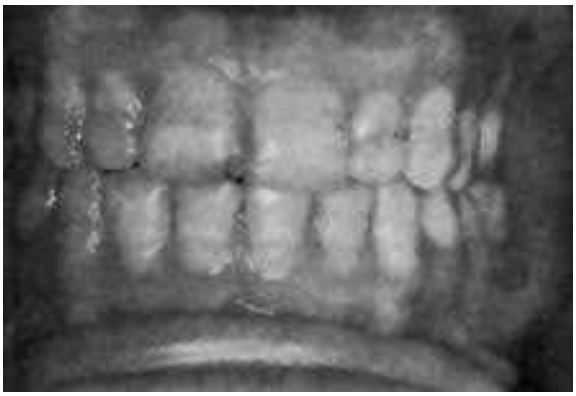


Figure 1-50. Enamel hypoplasia, environmental type.
Several rows of irregular, stained pits cover much of the labial surfaces of the teeth.

it is possible to determine from the location of the defect on the teeth the approximate time at which the injury occurred.

Hypoplasia due to Nutritional Deficiency and Exanthematous Fevers. Some studies have shown that rickets during the time of tooth formation is the most common known cause of enamel hypoplasia. For example, in a series of rachitic children reported by Shelling and Anderson, 43% of teeth showed hypoplasia. At present; however, rickets is not a prevalent disease. Deficiencies of vitamin A and C have also been named as causes.

Some studies have indicated that the exanthematous diseases, including measles, chickenpox and scarlet fever, are etiologic factors, but other investigators have been unable to confirm this finding. In general, it might be stated that any serious nutritional deficiency or systemic disease is potentially capable of producing enamel hypoplasia, since the ameloblasts are one of the most sensitive groups of cells in the body in terms of metabolic function.

The type of hypoplasia occurring from these deficiency or disease states is usually of the pitting variety described above. Since the pits tend to stain, the clinical appearance of the teeth may be very unsightly.

Clinical studies indicate that most cases of enamel hypoplasia involve those teeth that form within the first year after birth, although teeth that form somewhat later may be affected. Thus the teeth most frequently involved are the central and lateral incisors, cuspids, and first molars. Since the tip of the cuspid begins formation before the lateral incisor, some cases involve only the central incisor, cuspid, and first molar. Premolars and second and third molars are seldom affected, since their formation does not begin until about the age of three years or later.

There has been considerable controversy as to whether there is any relation between enamel hypoplasia and dental caries experience, and clinical reports have given conflicting results. It is most reasonable to assume that the two are not related, although hypoplastic teeth do appear to decay at a somewhat more rapid rate once caries has been initiated.

Enamel Hypoplasia due to Congenital Syphilis. The hypoplasia due to congenital syphilis is most frequently not of the pitting variety previously described but instead presents a characteristic, almost pathognomonic, appearance. This hypoplasia involves the maxillary and mandibular permanent incisors and the first molars. The anterior teeth affected are sometimes called 'Hutchinson's teeth,' while the molars have been referred to as 'mulberry molars' (Moon's molars, Fournier's molars).

Characteristically, the upper central incisor is 'screw-driver' shaped, the mesial and distal surfaces of the crown tapering and converging toward the incisal edge of the tooth rather than toward the cervical margin (Fig. 1-51). In addition, the incisal edge is usually notched. The mandibular central and lateral incisors may be similarly involved, although the maxillary lateral incisor may be normal. The cause of the tapering and notching of the maxillary incisor has been explained on the basis of the absence of the central tubercle or calcification center. The crowns of the first molars in congenital syphilis are irregular and the enamel of the occlusal surface and occlusal third of the tooth appears to be arranged in an agglomerate mass of globules rather than in well-formed cusps (Fig. 1-52). The crown is narrower on the occlusal surface than at the cervical margin.

It has been reported by Fiumara and Lessell that between 1958 and 1969 there has been over a 200% increase in reported cases of primary and secondary syphilis in the United States

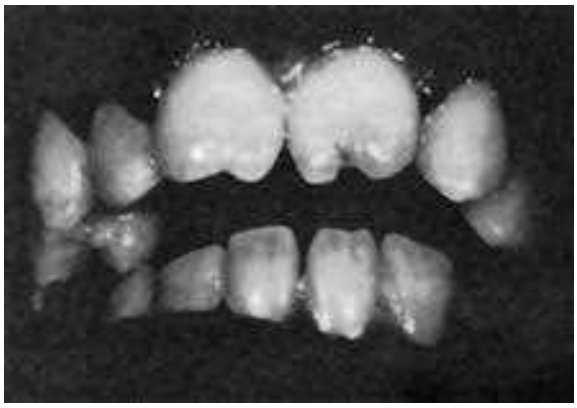


Figure 1-51. Enamel hypoplasia of congenital syphilis (mulberry molars).
The mandibular first molars show many small globular masses of enamel on the occlusal portion of the tooth.

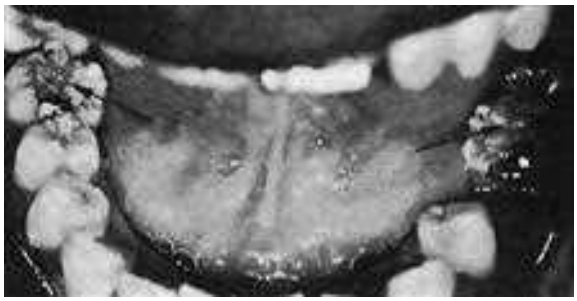


Figure 1-52. Enamel hypoplasia of congenital syphilis (Hutchinson's incisors).
There is characteristic notching of the incisal edges of the maxillary central incisors as well as tapering of the mesial and distal surfaces toward the incisal portion.

and that, consequently, congenital syphilis in children under one year of age increased 117% during the 10–year period from 1960 to 1969. Investigating 271 patients with congenital syphilis, they found that over 63% had Hutchinson's teeth but they pointed out that this may not be the true incidence, since some of the patients had their teeth extracted. In addition, approximately 65% of this group of patients with congenital syphilis also had the characteristic 'mulberry molars.'

Not all patients with congenital syphilis will exhibit these dental findings. Also, occasional patients will appear to have Hutchinson's teeth without having a history of congenital syphilis. Therefore, one must not be hasty in making the diagnosis of syphilis, particularly in the absence of the other conditions of Hutchinson's triad (q.v.).

Enamel Hypoplasia due to Hypocalcemia. Tetany, induced by a decreased level of calcium in the blood, may result from several conditions, the most common being vitamin D deficiency and parathyroid deficiency (parathyroprivic tetany). In tetany the serum calcium level may fall as low as 6–8 mg per 100 ml, and at this level enamel hypoplasia is frequently produced in teeth developing concomitantly. This type of enamel hypoplasia is usually of the pitting variety and thus does not differ from that resulting from a nutritional disturbance or exanthematous disease.

Hypoplasia due to Birth Injuries. The neonatal line or ring, described by Schour in 1936 and present in deciduous teeth and first permanent molars, may be thought of as a type of hypoplasia because there is a disturbance produced in the enamel and dentin, which is indicative of trauma or change of environment at the time of birth. In traumatic births the formation of enamel may even cease at this time. In addition, Miller and Forrester have reported a clinical study with evidence that enamel hypoplasia is far more common in prematurely born children than in normal term infants. In this same study they not only drew attention to the widely recognized staining of teeth in children who had suffered from Rh hemolytic disease at birth (q.v.) but also reported enamel hypoplasia in these cases. Grahnen and Larsson have also shown an increased incidence of enamel hypoplasia in premature children, but interestingly no differences in caries incidence between this group and a control group of children.

Although the literature indicates that most cases of enamel hypoplasia of deciduous teeth involve enamel formed after birth, it is seen also in prenatal enamel. In such instances a gastrointestinal disturbance or some other illness in the mother may be responsible.

Enamel Hypoplasia due to Local Infection or Trauma. A type of hypoplasia occasionally seen is unusual in that only a single tooth is involved, most commonly one of the permanent maxillary incisors or a maxillary or mandibular premolar. There may be any degree of hypoplasia, ranging from a mild, brownish discoloration of the enamel to a severe pitting and irregularity of the tooth crown (Fig. 1-53). These single teeth are frequently referred to as **'Turner's teeth,'** and the condition is called 'Turner's hypoplasia.'

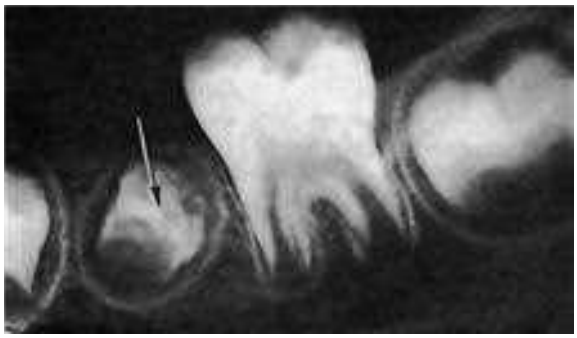


Figure 1-53. Enamel hypoplasia due to local infection (Turner's hypoplasia). The crown of the unerupted bicuspid is extremely irregular, owing to disruption of the forming tooth by infection through the preceding deciduous tooth *(Courtesy of Dr Ralph E McDonald).*

If a deciduous tooth becomes carious during the period when the crown of the succeeding permanent tooth is being formed, a bacterial infection involving the periapical tissue of this deciduous tooth may disturb the ameloblastic layer of the permanent tooth and result in a hypoplastic crown. The severity of this hypoplasia will depend upon the severity of the infection, the degree of tissue involvement, and the stage of permanent tooth formation during which the infection occurred.

A similar type of hypoplasia may follow trauma to a deciduous tooth, particularly when the deciduous tooth has been driven into the alveolus and has disturbed the permanent tooth bud. If this permanent tooth crown is still being formed, the resulting injury may be manifested as a yellowish or brownish stain or pigmentation of the enamel, usually on the labial surface, or as a true hypoplastic pitting defect or deformity. This form of dental injury has been discussed by Via, who has pointed out that a disturbance either in matrix formation or in calcification can occur, depending chiefly upon the stage of tooth formation at the time of injury.

Enamel Hypoplasia due to Fluoride: Mottled Enamel. Mottled enamel is a type of enamel hypoplasia that was first described under that term in this country by GV Black and Frederick S McKay in 1916. Earlier reference to the condition is known in the foreign literature; however. Black and McKay recognized that this lesion exhibited a geographic distribution and even suggested that it was a result of some substance in the water supply, although it was not until some years later that fluorine was shown to be the causative agent.

Etiology. It is now recognized that the ingestion of fluoride-containing drinking water during the time of tooth formation may result in mottled enamel. The severity of the mottling increases with an increasing amount of fluoride in the water. Thus there is little mottling of any clinical significance at a level below 0.9–1.0 part per million of fluoride in the water, whereas it becomes progressively evident above this level.

Pathogenesis. This type of hypoplasia is due to a disturbance of the ameloblasts during the formative stage of tooth development. The exact nature of the injury is not known, but since there is histologic evidence of cell damage, it is

Table 1-15: Distribution (percentage) of dental mottling by age groups

Age group (in yrs.)	Vellore		Dharmapuri		Krishnagiri		Salem		Erode		Pooled	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1–4	130	1.5	114	0.9	143	0.7	113	2.7	46	0.0	546	1.3
5–14	308	33.8	725	53.3	478	45.2	450	41.8	210	24.8	2171	18.1
15–19	106	37.7	287	60.3	235	37.9	177	61.0	64	32.8	869	10.0
>	786	9.6	1239	24.4	1087	14.0	1321	28.1	705	18.0	5138	16.0
Pooled	1330	13.4	2365	18.3	1943	14.3	2061	14.1	1025	15.3	8724	15.3

Source: Kumar RH et al. J Human Ecology 21 (1): 27– 32, 2007.

likely that the cell product, the enamel matrix, is defective or deficient. It also has been shown that, with somewhat higher levels of fluoride, there is interference with the calcification process of the matrix.

Epidemiologic studies have reported that not all children born and reared in an area of endemic fluorosis exhibit the same degree of mottling even though they all have used the same water supply. Furthermore, a few persons may exhibit mild mottling even when exposed to a very low concentration of fluoride (Table 1-15). These findings may be related to individual variation in total water consumption and thus to total fluoride intake.

Clinical Features. Depending upon the level of fluoride in the water supply, there is a wide range of severity in the appearance of mottled teeth, varying from: (1) questionable changes characterized by occasional white flecking or spotting of the enamel (Fig. 1-54A), through (2) mild changes manifested by white opaque areas involving more of the tooth surface area (Fig. 1-54B), to (3) moderate and severe changes showing pitting and brownish staining of the surface (Fig. 1-54C), and even (4) a corroded appearance of the teeth (Fig. 1-54D). Those teeth which are moderately or severely affected may show a tendency for wear and even fracture

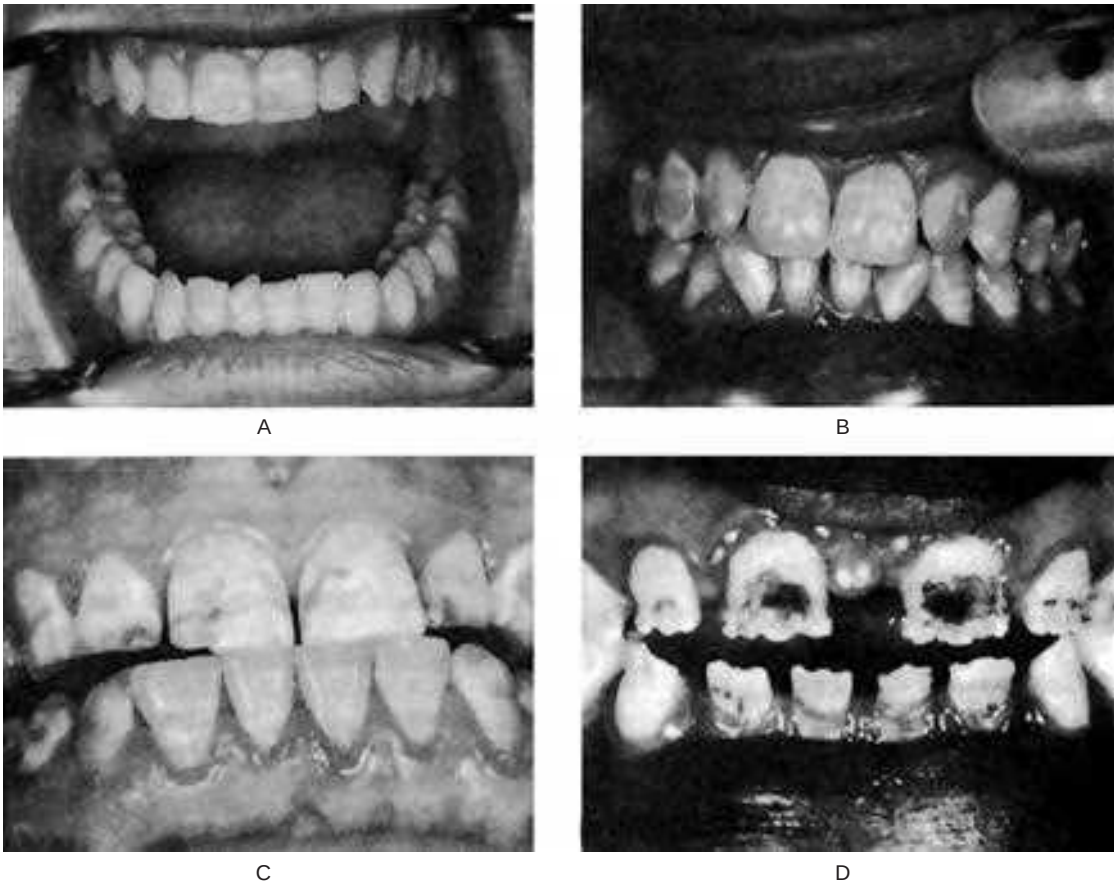


Figure 1-54. Enamel hypoplasia due to excessive fluoride (mottled enamel).
There is **(A, B)** flecking of the enamel surface by white opaque spots, **(C)** involvement of most of the tooth surface by opaque white areas, and **(D)** severe pitting and staining of the tooth surface.

of the enamel. Early studies actually noted the difficulty of retaining restorations in such teeth.

Geographic Distribution. Mottled enamel has been reported in many parts of the world, including Europe, Africa, and Asia as well as the United States. In this country, persons in at least 400 areas in 28 states have shown dental evidence of endemic fluorosis, and undoubtedly more communities remain to be reported. Most of the areas affected are west of the Mississippi River, the largest single area being the Texas Panhandle, but there are numerous communities east of the Mississippi River in which fluorosis is present, the most notable being in Illinois.

The well-known relation between mottled enamel (or actually fluoride intake) and dental caries will be discussed in Chapter 9 on Dental Caries.

Treatment. Mottled enamel frequently becomes stained an unsightly brown color. For cosmetic reasons, it has become the practice to bleach the affected teeth with an agent such as hydrogen peroxide. This is frequently effective, but the procedure must be carried out periodically, since the teeth continue to stain.

Hypoplasia due to Idiopathic Factors. Although numerous factors have been reported as being possibly responsible for causing enamel hypoplasia, clinical studies have shown that, even with careful histories, the majority of cases are of unknown origin. Since the ameloblast is a sensitive type of cell and easily damaged, it is likely that in those cases in which the etiology cannot be determined, the causative agent may have been some illness or systemic disturbance so mild that it made no impression on the patient and was not remembered. Even relatively severe cases of enamel hypoplasia arise with no pertinent past medical history to account for their occurrence.

DENTINOGENESIS IMPERFECTA

Dentinogenesis imperfecta is an autosomal dominant condition affecting both deciduous and permanent teeth. Affected teeth are gray to yellowish-brown and have broad crowns with constriction of the cervical area resulting in a **'tulip'** shape. Radiographically, the teeth appear solid, lacking pulp chambers and root canals. Enamel is easily broken leading to exposure of dentin that undergoes accelerated attrition. The gene maps to **chromosome number 4.** It encodes a protein called **dentin sialophosphoprotein (DSPP).** This protein constitutes about 50% of the noncollagenous component of dentin matrix. It is not known how the mutant protein causes near obliteration of the pulp. A clinically and radiographically indistinguishable dental condition is seen sometimes in patients with osteogenesis imperfecta. Dentin defect associated with osteogenesis imperfecta was earlier listed as dentinogenesis imperfecta type I (**Sheilds classification**). Extensive studies have proven that dentinogenesis imperfecta is clearly a disorder distinct from osteogenesis imperfecta hence the following **revised classification** is proposed.

Dentinogenesis imperfecta I: Dentinogenesis imperfecta without osteogenesis imperfecta (opalescent dentin): this corresponds to dentinogenesis imperfecta type II of Shields classification.

Dentinogenesis imperfecta II: Brandywine type dentinogenesis imperfecta: this corresponds to dentinogenesis imperfecta type III of Shields classification.

There is no substitute in the present classification for the category designated as DI type I of the previous classification (Shields).

Dentinogenesis imperfecta II is even more rare and paradoxically characterized by too little rather than too much dentin resulting in 'shell teeth.' Dentinogenesis imperfecta II may be an allelic variant of dentinogenesis imperfecta I (a different mutation in the same gene), both genes map to the same region on chromosome number 4.

Dentinogenesis Imperfecta I

(Opalescent dentin, dentinogenesis imperfecta without osteogenesis imperfecta, opalescent teeth without osteogenesis imperfecta, dentinogenesis imperfecta, Shields type II, Capdepont teeth)

Dentinogenesis imperfecta II is caused by mutation in the **DSPP** gene (**gene map locus 4q21.3**), encoding **dentin phosphoprotein** and **dentin sialoprotein.** Dentinogenesis imperfecta is an entity clearly distinct from osteogenesis imperfecta with opalescent teeth, and affects only the teeth. There is no increased frequency of bone fractures in this disorder. The frequency may be 1 in 6,000–8,000 children. Witkop and Rao (1971) preferred the term opalescent dentin for this condition as an isolated trait, reserving dentinogenesis imperfecta for the trait when it is combined with osteogenesis imperfecta. The teeth are blue-gray or amber brown and opalescent. On dental radiographs, the teeth have bulbous crowns, roots that are narrower than normal, and pulp chambers and root canals that are smaller than normal or completely obliterated. The enamel may split readily from the dentin when subjected to occlusal stress. Sauk et al (1976) noted an increase in glycosaminoglycans in EDTA soluble dentin in the teeth from patients with this disorder as compared to controls, and less glycosaminoglycan in EDTA insoluble residue.

Shields et al (1973) proposed that the variety of dentinogenesis imperfecta (dentinogenesis imperfecta type III) described in the Brandywine isolate by Hursey et al (1956) was distinct from dentinogenesis imperfecta type II.

A deficiency of dentin sialophosphoprotein had been suggested as a causative factor in dentinogenesis imperfecta. Zhang et al (2001) studied a Chinese family with dentinogenesis imperfecta Shields type II. Affected members in three generations showed discoloration and severe attrition of their teeth, with obliterated pulp chambers.

Dentinogenesis Imperfecta II

(Shields type III, Brandywine type dentinogenesis imperfecta)

This disorder was found in the Brandywine triracial isolate in southern Maryland. The crowns of the deciduous and permanent teeth wear rapidly after eruption and multiple pulp exposures may occur. The dentin is amber and smooth

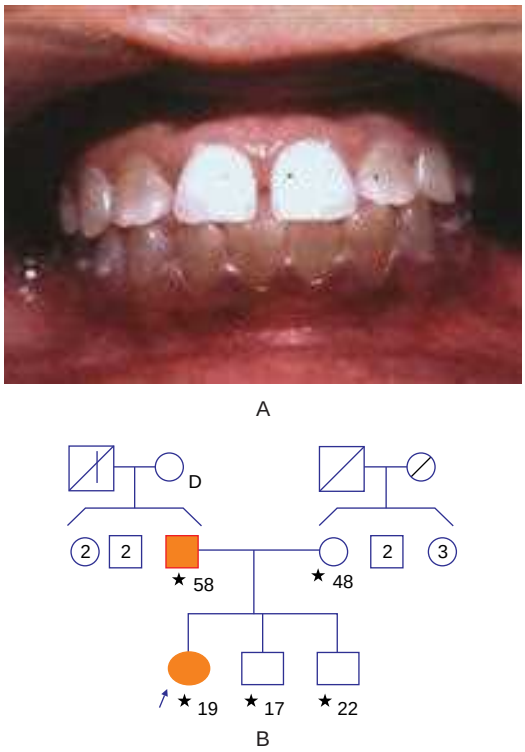


Figure 1-55. Dentinogenesis imperfecta type II with autosomal dominant inheritance pattern.

(Fig. 1-55). Radiographs of the deciduous dentition show very large pulp chambers and root canals, at least during the first few years, although they may become reduced in size with age. The permanent teeth have pulpal spaces that are either smaller than normal or completely obliterated. Patients with Shields type III, or the Brandywine type, do not have stigmata of osteogenesis imperfecta. This disorder may be a separate mutation from dentinogenesis imperfecta I. Shields et al (1973) stated that multiple pulp exposures and markedly enlarged pulp chambers in the deciduous teeth do not occur in DGI-1; however, Witkop (1975) suggested that the two disorders are the same. Recent studies are consistent with the hypothesis that DGI-1 and DGI-2 are allelic or the result of mutations in two tightly linked genes. MacDougall (1998) provided information on the intervals separating four genes that map to this same region, all four of which are involved in dental development: **DSPP, DMP-1, IBSP,** and **SPP1.** MacDougall et al (1999) stated that the manifestations of DGI-2 can differ from those of DGI-1 by the presence of multiple pulp exposures, normal nonmineralized pulp chambers and canals, and a general appearance of **'shell teeth.'** They illustrated the amber discoloration of the teeth, attrition, and fractured enamel, as well as the classic 'shell teeth' appearance on radiographs.

Histologic Features. The histologic appearance of the teeth in dentinogenesis imperfecta I emphasizes the fact that this is purely a mesodermal disturbance. The appearance of the enamel is essentially normal except for its peculiar shade, which is actually a manifestation of the dentinal disturbance. The dentin, on the other hand, is composed of irregular tubules, often with large areas of uncalcified matrix (Fig. 1-56). The tubules tend to be larger in diameter and thus less numerous than normal in a given volume of dentin (Fig. 1-57). In some areas there may be complete absence of tubules. Cellular inclusions, probably odontoblasts, in the dentin are not uncommon, and as pointed out previously, the pulp chamber is usually almost obliterated by the continued deposition of dentin. The odontoblasts have only limited ability to form well-organized dentinal matrix, and they appear to degenerate readily, becoming entrapped in this matrix.

The histopathology of the teeth in type III has not been adequately documented.

Chemical and Physical Features. Chemical analysis explains many of the abnormal features of the teeth of dentinogenesis imperfecta I. Their water content is greatly increased, as much as 60% above normal, while the inorganic content is less than that of normal dentin. As might be expected, the density, X-ray absorption, and hardness of the dentin are also low. In fact, the micro-hardness of the dentin closely approximates that of cementum, thus explaining the rapid attrition of affected teeth. There is no significant information available on teeth in type III.

Treatment. The treatment of patients with dentinogenesis imperfecta is directed primarily towards preventing the loss of enamel and subsequent loss of dentin through attrition. Cast metal crowns on the posterior teeth and jacket crowns on the anterior teeth have been used with considerable success, although care must be taken in the preparation of the teeth for such restorations. Caution must also be exercised in the use

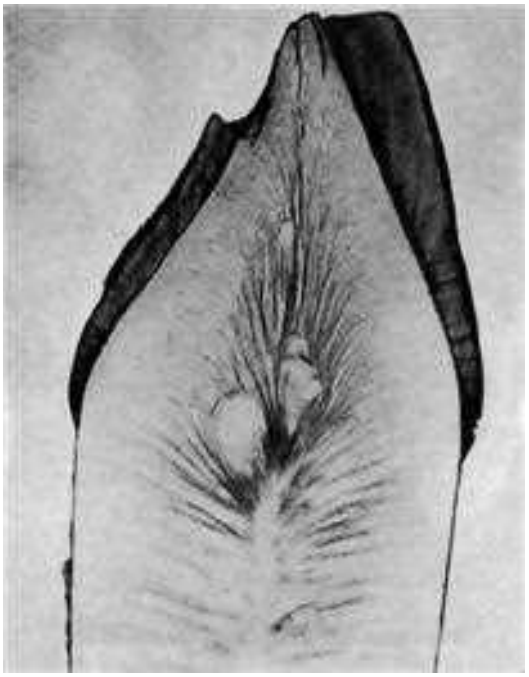
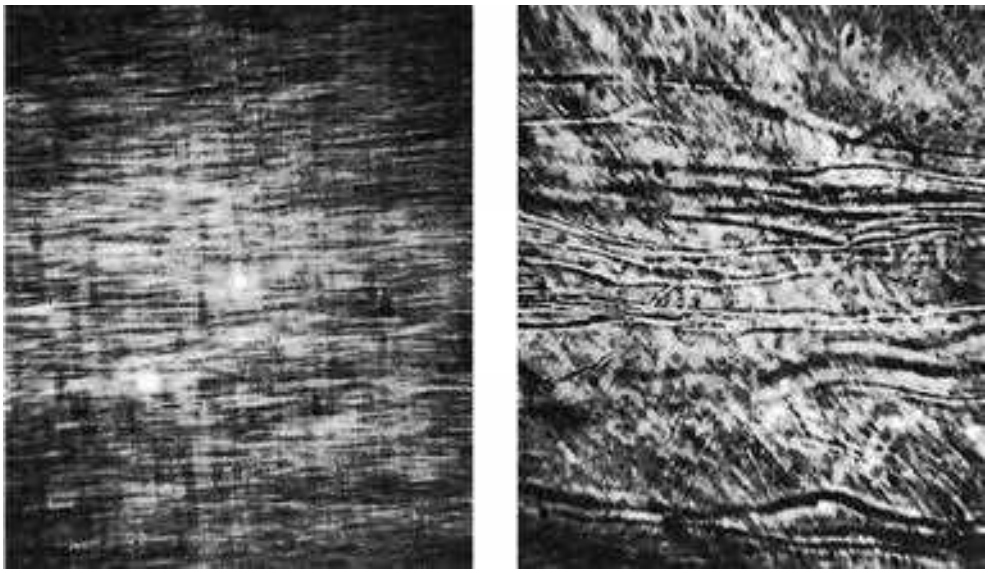


Figure 1-56. Dentinogenesis imperfecta.
Ground section of tooth.



A B

Figure 1-57. Dentinogenesis imperfecta.
(A) Normal dentin showing regular dentinal tubules. (B) large irregular dentinal tubules in dentinogenesis imperfecta. Both photomicrographs taken at same magnification.

of partial appliances which exert stress on the teeth, because the roots are easily fractured. Experience has further shown that fillings are not usually permanent because of the softness of the dentin.

Dentin Dysplasia
(Rootless teeth)

Dentin dysplasia is a rare disturbance of dentin formation characterized by normal enamel but atypical dentin formation with abnormal pulpal morphology.

At one time this was thought to be a single disease entity, but it now has been separated by Shields and his associates into type I (dentin dysplasia) and type II (anomalous dysplasia of dentin). However, Witkop has suggested that as a guide to the clinician, these conditions be referred to as **radicular dentin dysplasia (type I)** *and* **coronal dentin dysplasia (type II).** It has been found that type I is by far the more common.

The first description of the disease was that of Ballschmiede, who in 1920 reported the spontaneous exfoliation of multiple teeth in seven children of one family and called this phenomenon 'rootless teeth.' The first concise description of the disease was published in 1939 by Rushton, who was also the first to designate it as 'dentin dysplasia.'

Etiology. Dentin dysplasia, both type I and type II, appears to be a hereditary disease, transmitted as an autosomal dominant characteristics. Nothing is known of the mutation rate, but it must be extremely low.

Clinical Features

Type I (radicular). Both dentitions are affected, although the teeth appear clinically normal in morphologic appearance and color. Occasionally there may be a slight amber translucency. The teeth generally exhibit a normal eruption pattern, although delayed eruption has been reported in a few cases. However, the teeth characteristically exhibit extreme mobility and are commonly exfoliated prematurely or after only minor trauma as a result of their abnormally short roots.

Type II (coronal). Both dentitions are also affected in this form of dentin dysplasia, although the involvement of each dentition is different clinically, radiographically, and histologically. The deciduous teeth have the same yellow, brown, or bluish-gray opalescent appearance as seen in dentinogenesis imperfecta. However, the clinical appearance of the permanent dentition is normal.

Radiographic Features

Type I (radicular). In both dentitions, the roots are short, blunt, conical, or similarly malformed (Fig. 1-58). In the deciduous teeth, the pulp chambers and root canals are usually completely obliterated, while in the permanent dentition, a crescent-shaped pulpal remnant may still be seen in the pulp chamber. This obliteration in the permanent teeth commonly occurs pre-eruptively. Of significant interest is the discovery of periapical radiolucencies representing granulomas, cysts, or abscesses involving apparently otherwise intact teeth.

Type II (coronal). The pulp chambers of the deciduous teeth become obliterated as in type I and in dentinogenesis imperfecta. This does not occur before eruption. The permanent teeth; however, exhibit an abnormally large pulp chamber in the coronal portion of the tooth, often described as **'thistle-tube'** in shape, and within such areas radiopaque foci resembling pulp stones may be found. Periapical radiolucencies do not occur unless for an obvious reason.

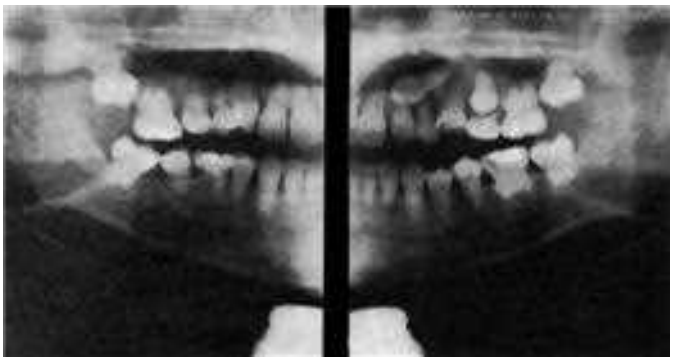


Figure 1-58. Dentinal dysplasia, type I (radicular).
The exceptionally short roots and obliteration of pulp chambers and root canals are clearly evident.*(Courtesy of Dr Arthur S Miller; from AS Miller and K Brookreson: Pa, Dent J, 37: 134, 1970).*

Histologic Features

Type I (radicular). A portion of the coronal dentin is usually normal. Apical to this may be areas of tubular dentin, but most of that which obliterates the pulp is calcified tubular dentin, osteodentin, and fused denticles. Normal dentinal tubule formation appears to have been blocked so that new dentin forms around obstacles and takes on the characteristic appearance described as ***'lava flowing around boulders'*** (Fig. 1-59). Electron microscopic studies by Sauk and his coworkers have suggested that this pattern of 'cascades of dentin' results from repetitive attempts to form root structure. Interestingly, the dentin itself is histologically normal but is simply disoriented.

Figure 1-59. Dentin dysplasia, type I (radicular).
The atypicality of root dentin and dentin filling the pulp chamber is seen in this ground section of tooth *(Courtesy of Dr Richard K Wesley and George Wysocki. From Oral Surg, 41: 516, 1976).*

Type II (coronal). The deciduous teeth exhibit amorphous and atubular dentin in the radicular portion, while coronal dentin is relatively normal. The permanent teeth also show relatively normal coronal dentin, but the pulp has multiple pulp stones or denticles.

Excellent scanning electron microscopic studies of both types I and II dentin dysplasia have been reported by Melnick and his associates, and these have added appreciably to our knowledge of the atypical structure of this dentin.

Treatment and Prognosis. There is no treatment for the disease, and its prognosis depends upon the occurrence of periapical lesions necessitating tooth extraction as well as upon the exfoliation of teeth due to increased mobility.

Regional Odontodysplasia
(Odontodysplasia, odontogenic dysplasia, odontogenesis imperfecta, ghost teeth)

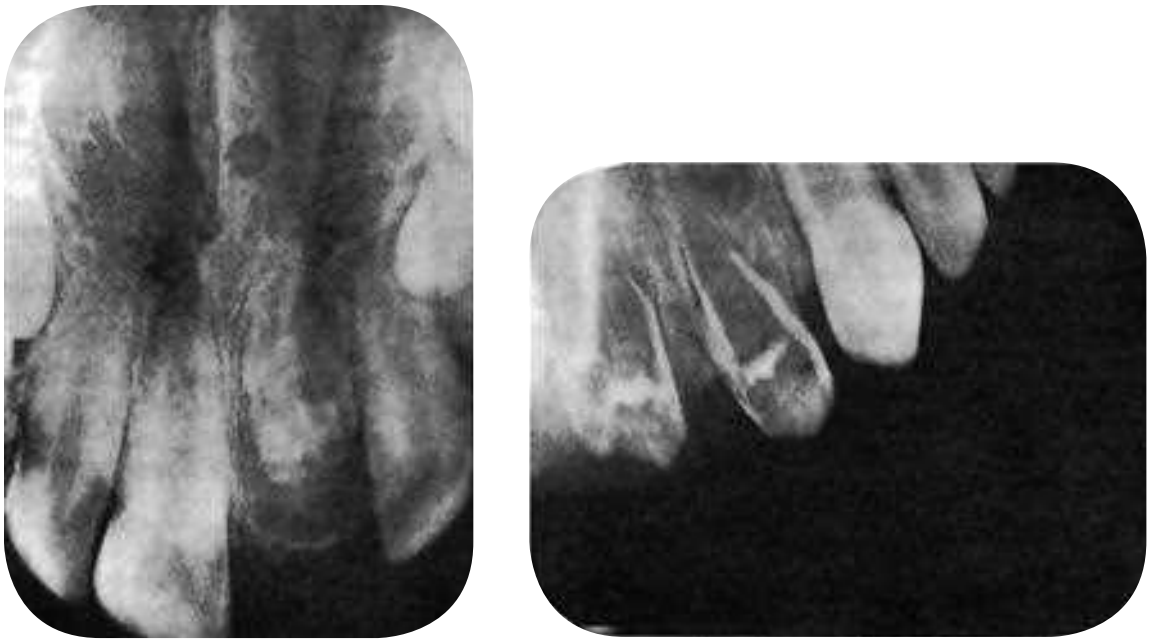
This is an unusual dental anomaly in which one or several teeth in a localized area are affected in an unusual manner. Apparently the maxillary teeth are involved more frequently than the mandibular, the most frequently affected teeth being the maxillary permanent central incisor, lateral incisor, and cuspid. In the mandible, the same three anterior teeth are most often affected. The deciduous teeth as well as the permanent may be involved.

The etiology of this disease is unknown inasmuch as there is no history of trauma or systemic illness. It has been suggested that the condition may represent a somatic mutation, although the possibility has also been raised that it could be due to a latent virus residing in the odontogenic epithelium, which subsequently becomes active during the development of the tooth. In an excellent review of cases in the literature and a discussion of the condition, Walton and his coworkers observed that in three cases of regional odontodysplasia that they reported, all three patients had vascular nevi of the overlying facial skin as infants. They reported similar involvement in three additional cases in the literature, and these findings suggested to them that local vascular defects are involved in the pathogenesis of the condition. An early comprehensive account was also reported by Rushton.

Clinical Features. The teeth affected by odontodysplasia exhibit either a delay or a total failure in eruption. Their shape is markedly altered, being generally very irregular in appearance, often with evidence of defective mineralization.

Radiographic Features. The radiographs are uniquely characteristic, showing a marked reduction in radiodensity so that the teeth assume a **'ghost'** appearance (Fig. 1-60A, B). Both the enamel and dentin appear very thin and the pulp chamber is exceedingly large. The enamel layer often is not evident.

Histologic Features. The most characteristic features of the disease are the marked reduction in the amount of dentin, the



A B

Figure 1-60. Regional odontodysplasia.
The unusually large pulp, thin enamel, and dentin are evident ((A) *Courtesy of Dr E Jefferson Burkes, and* (B) *of Dr Joseph L Bigelow*).

widening of the predentin layer, the presence of large areas of interglobular dentin, and an irregular tubular pattern of dentin. Characteristically, the reduced enamel epithelium around non-erupted teeth shows many irregular calcified bodies. Ultrastructural studies by Sapp and Gardner have proved enlightening in detailing some of the fine components of both the soft and calcified tissues in regional odontodysplasia.

Treatment. Because of the poor cosmetic appearance of these teeth, extraction with restoration by a prosthetic appliance is usually indicated.

Dentin Hypocalcification

Normal dentin is calcified by deposition of calcium salts in the organic matrix in the form of globules, which increase in size by further peripheral deposition of salts until all the globules are finally united into a homogeneous structure. In dentinal hypocalcification there is failure of union of many of these globules, leaving interglobular areas of uncalcified matrix. This globular dentin is easily detected in both ground sections and decalcified histologic sections of teeth, but there is no alteration in the clinical appearance.

Many clinicians believe that they can detect areas of globular dentin by the softness of the dental structure. Although this remains to be proved, it is logical that hypocalcified dentin would be softer than well-calcified dentin.

The causes of dentin hypocalcification are similar to those of environmental enamel hypocalcification and enamel hypoplasia. Obviously, any factor which interferes with normal calcification, such as parathyroid deficiency or rickets, could produce hypocalcification.

DISTURBANCES OF GROWTH (ERUPTION) OF TEETH

It is recognized that a broad range of variation exists in the normal eruption times of the deciduous and permanent teeth in different persons. A valuable modification of the usually accepted chronology of the calcification and eruption times of the deciduous teeth has been published by Lunt and Law. Because of this inherent biologic variation, which is particularly notable in the human being, it is difficult to determine when the eruption dates of the teeth of a given person are outside the limits of the normal range. Nevertheless, certain cases do occur in which the eruption time is grossly beyond the extremes of normality and may be considered a pathologic state. The significance of this is frequently not apparent.

Premature Eruption

Deciduous teeth that have erupted into the oral cavity are occasionally seen in infants at birth. These are called **natal teeth** in contrast with **neonatal teeth**, which have been defined as those teeth erupting prematurely in the first 30 days of life. Usually only one or two teeth erupt early, most often the deciduous and mandibular central incisors. The etiology of this phenomenon is unknown, although in some instances it follows a familial pattern. It is well recognized in experimental animals that the secretion of several endocrine organs (e.g. thyroid, adrenals, and gonads) may alter the eruption rate of teeth, and it has been suggested that in some cases of early eruption in humans a poorly defined endocrine disturbance may be present. In cases of the adrenogenital syndrome (q.v.) developing early in life, premature eruption of teeth is sometimes seen. Most cases; however, defy explanation.

Spouge and Feasby have pointed out that prematurely erupted teeth are often well formed and normal in all respects except that they may be somewhat mobile. These teeth should be retained even though nursing difficulties may be experienced. A series of 18 cases of natal and neonatal teeth has been studied clinically and histologically by Berman and Silverstone, who reported that these were essentially normal teeth compatible with their chronologic age of development.

The premature eruption of permanent teeth is usually a sequela of the premature loss of deciduous teeth. This is best demonstrated in the situation in which only a single deciduous tooth has been lost, with subsequent eruption of the succedaneous tooth. Occasionally, cases occur involving the entire dentition, and here again the possibility of an endocrine dysfunction (e.g. hyperthyroidism) must be considered.

Eruption Sequestrum

The eruption sequestrum, an anomaly associated with the eruption of teeth in children, was first described by Starkey and Shafer.

Clinical Features. The eruption sequestrum is a tiny irregular spicule of bone overlying the crown of an erupting permanent molar, found just prior to or immediately following the emergence of the tips of the cusps through the oral mucosa. The spicule directly overlies the central occlusal fossa but is contained within the soft tissue. As the tooth continues to erupt and the cusps emerge, the fragment of bone completely sequestrates through the mucosa and is lost. For a few days, the fragment of bone may be seen lying on the crest of the ridge in a tiny depression from which it may easily be removed (Fig. 1-61A).

Radiographic Features. It is possible to recognize the eruption sequestrum radiographically even before the teeth begin to erupt into the oral cavity or before the bony spicule perforates the mucosa. It appears as a tiny irregular opacity overlying the central occlusal fossa but separated from the tooth itself (Fig. 1-61B).

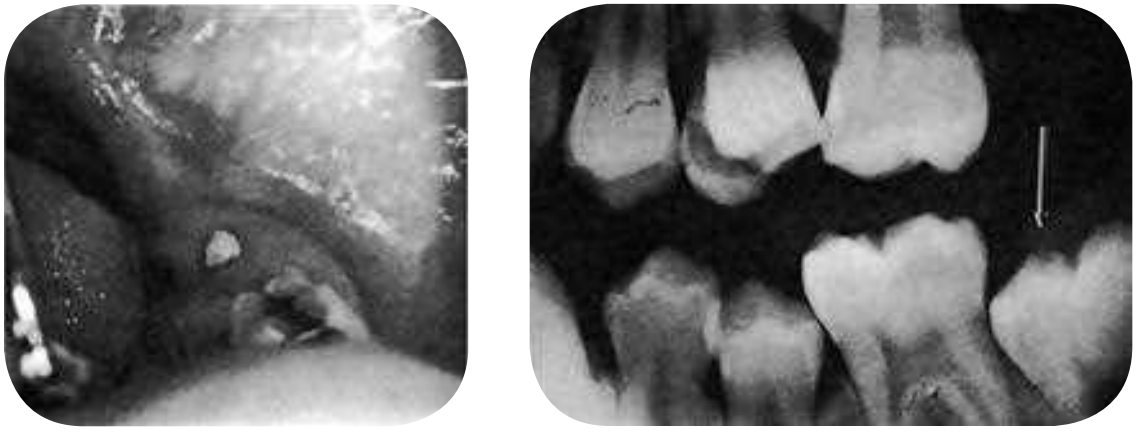
Etiology. The explanation of this phenomenon is relatively simple. As the molar teeth erupt through the bone, they will occasionally separate a small osseous fragment from the surrounding contiguous bone, much in the fashion of a corkscrew. In most cases, this fragment probably undergoes total resorption prior to eruption. If the bony spicule is larger or eruption is fast, complete resorption cannot occur and the eruption sequestrum is observed.

Clinical Significance and Treatment. The clinical significance associated with this condition is that, occasionally, a child may complain of a slight soreness in the area, probably produced by compression of the soft tissue over the spicule during eating and just prior to its breaking through the mucosa, or by the movement of the spicule in the soft tissue crypt during mastication and following eruption through the mucosa. No treatment is necessary, since the condition corrects by itself.

Delayed Eruption

Retarded or delayed eruption of the deciduous teeth is difficult to establish unless the eruption is grossly overdue. In many cases the etiology is unknown, although in some instances it may be associated with certain systemic conditions, including rickets, cretinism, and cleidocranial dysplasia (q.v.). Local factors or circumstances may also delay eruption, as in the case of fibromatosis gingivae, in which the dense connective tissue will not permit eruption.

When the local factors can be established as the cause, their treatment may alleviate the condition. In cases of generalized or systemic disturbances in which the dental problem is of secondary importance, treatment of the primary condition, if possible, will frequently bring about tooth eruption.



A B

Figure 1-61. Eruption sequestrum.
The bony sequestrum is lying on the crest of the ridge **(A)** and may be seen as a small radiopacity **(B).** *(From PE Starkey, WG Shafer. Eruption sequestra in children. J Dent Child, 30: 84, 1963).*

Delayed eruption of the permanent dentition as a whole may be associated with the same local or systemic conditions causing the retardation of deciduous tooth eruption. Since there is a wider range of variation in the time of eruption of the permanent teeth, it is frequently difficult to state exactly when a case of retardation exists.

Multiple Unerupted Teeth

There is an uncommon condition in which there is a more or less permanently delayed eruption of teeth. The person affected may have retained his/her deciduous teeth, or more commonly the deciduous teeth may have been shed but the permanent teeth have failed to erupt. The term 'pseudoanodontia' is sometimes applied to this latter circumstance. In many instances, the clinical and radiographic examinations reveal apparently normal jaws and teeth. What seems to be lacking is eruptive force.

If this condition is due to an endocrine dysfunction, proper treatment may result in the eruption of teeth; if it is associated with cleidocranial dysplasia (q.v.), there is no known therapy.

Embedded and Impacted Teeth

Embedded teeth are individual teeth which are unerupted usually because of a lack of eruptive force. Impacted teeth are those prevented from erupting by some physical barrier in the eruption path. Some writers do not differentiate between the two terms and call all unerupted teeth impacted.

Lack of space due to crowding of the dental arches or to the premature loss of deciduous teeth with subsequent partial closure of the area they occupied is a common factor in the etiology of partially or completely impacted teeth (Fig. 1-62). Even more common; however, is the rotation of tooth buds resulting in teeth which are 'aimed' in the wrong direction because their long axis is not parallel to a normal eruption path.

Any tooth may be impacted, but certain ones are more commonly affected than others. Thus the maxillary and mandibular third molars and the maxillary cuspids are most frequently impacted, followed by the premolars and supernumerary teeth. Of the third molars, the mandibular teeth are more apt to exhibit severe impaction than the maxillary teeth.

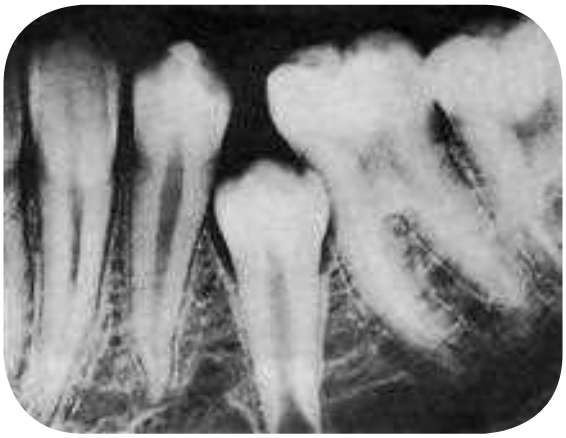


Figure 1-62. Partial tooth impaction due to premature loss of deciduous molar.

Dachi and Howell have published the results of a study of 3,874 routine full-mouth radiographs of patients over 20 years of age. They found that 17% of these persons had at least one impacted tooth. The incidence of impaction of maxillary and mandibular third molars was 22% and 18%, respectively, while the incidence of impacted maxillary cuspids was 0.9%.

Impacted mandibular third molars may exhibit a great variety of positions (Fig. 1-63). A simple classification of the types of impactions of mandibular third molars, based upon position, has been devised by Winter as follows:

Mesioangular impaction. The third molar lies obliquely in the bone, the crown pointing in a mesial direction, usually in contact with the distal surface of the root or crown of the second molar. This is the most common type of impaction.

Distoangular impaction. The third molar lies obliquely in the bone, the crown of the tooth pointing distally toward the ramus, the roots approximating the distal root of the second molar.

Vertical impaction. The third molar is in its normal vertical position, but is prevented from erupting by impingement on the distal surface of the second molar or the anterior border of the ramus. Thus, in most cases of this type, there is simply lack of space for eruption.

Horizontal impaction. The third molar is in a horizontal position with respect to the body of the mandible, and the crown may or may not be in contact with the distal surface of the second molar crown or roots. In this type of impaction, the third molar may lie at any level within the bone from the crest of the ridge to the inferior border of the mandible.

In addition to these types of impaction in which there is variation of angulation in the sagittal plane, the impacted third molars may also be deflected either buccally or lingually in any case of the foregoing circumstances. Cases also have been recorded of complicated impactions in which the third molar is inverted, the crown pointing toward the inferior border of the mandible, or in which the third molar has been situated completely within the ramus of the mandible.

In the case of impaction of any tooth, but particularly of the mandibular third molar, it is important to determine whether the tooth is completely or only partially impacted. By definition, a completely impacted tooth is one which lies completely within the bone and has no communication with the oral cavity. A partially impacted tooth is not completely encased in bone but lies partially in soft tissue. Although there may be no obvious communication of the tooth with the oral cavity, one may exist (e.g. through a periodontal pocket on the distal of the second molar) and create an ideal situation for infection and even dental caries of the impacted tooth crown. A completely embedded or impacted tooth cannot become infected or carious.

Impacted maxillary third molars may be impacted in a manner similar to the mandibular third molar (Fig. 1-64). Thus they may show a mesioangular, distoangular, vertical, or even a horizontal position and may be deflected buccally or lingually.

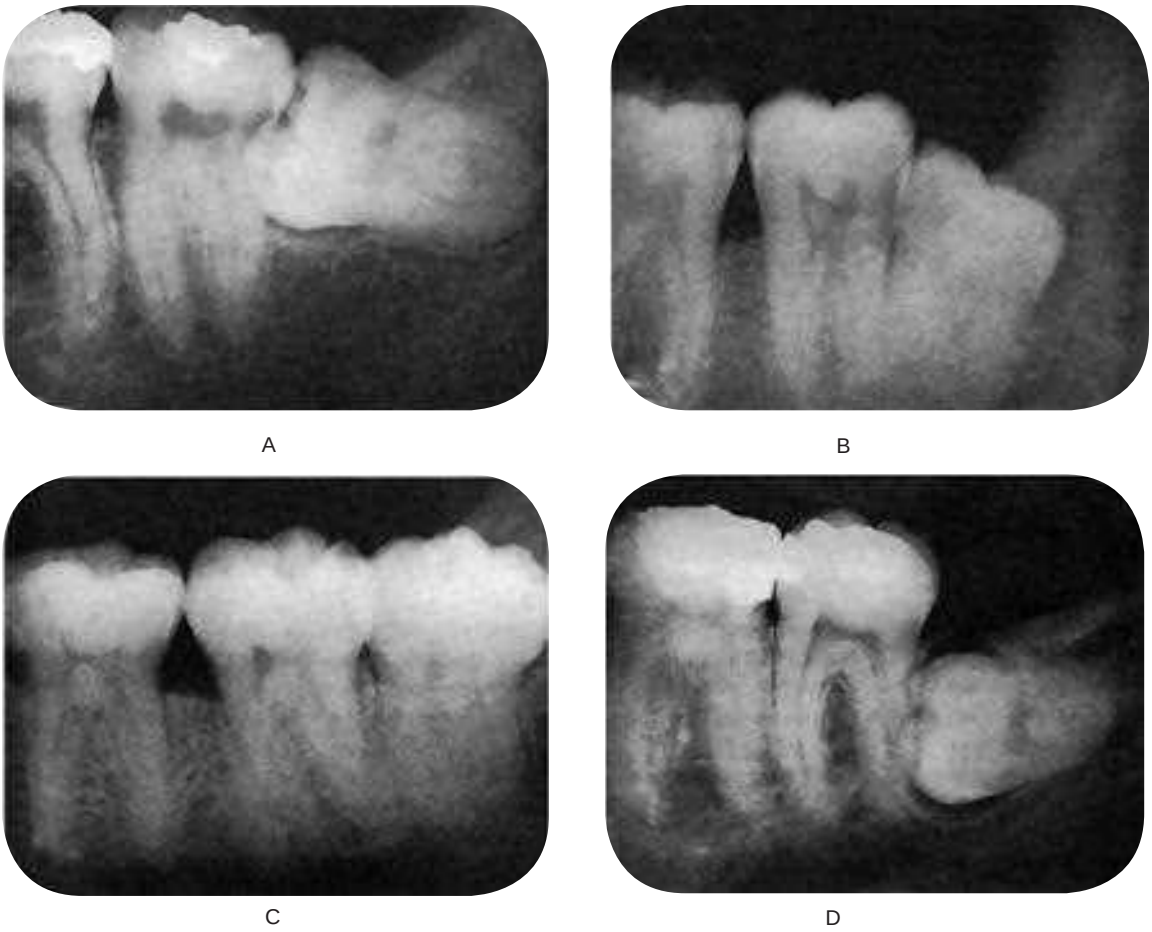


Figure 1-63. Impacted mandibular third molars.
(A) Mesioangular impaction. **(B)** Distoangular impaction. (C) Vertical impaction. (D) Horizontal impaction *(Courtesy of Dr Wilbur C Moorman).*

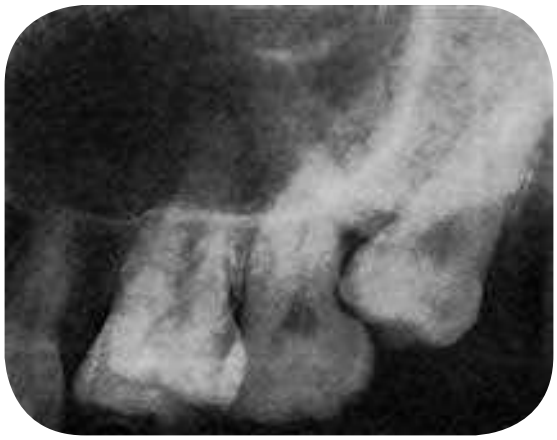


Figure 1-64. Partially impacted maxillary third molar (mesioangular type).

Impacted maxillary cuspids also assume a variety of positions ranging from horizontal to vertical (Fig. 1-65). In horizontally impacted cuspids the crown usually points in an anterior direction and may impinge on the roots of any of the incisors or premolars. The horizontal tooth may lie either labial or lingual to the associated teeth. The vertically impacted cuspid is usually situated between the roots of the

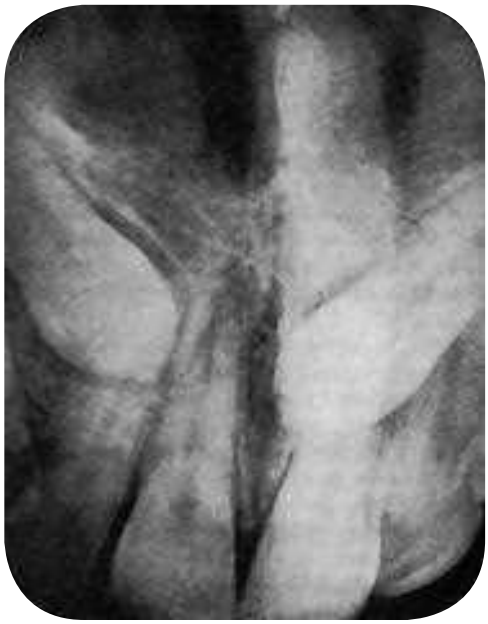


Figure 1-65. Bilateral impacted maxillary cuspids.
(Courtesy of Dr Wilbur C Moorman).

lateral incisor and first premolar and is prevented from eruption simply by lack of space.

The treatment of an impacted tooth depends to a great extent upon the type of tooth involved and the individual circumstances. In some cases, such as the impacted cuspid, it is possible by a suitable orthodontic appliance to bring the tooth into normal occlusion. The majority of impacted teeth; however, must be surgically removed. Because of their location, impacted teeth frequently cause resorption of the roots of adjacent teeth. They may also cause periodic pain and even trismus, particularly when infection occurs around partially impacted teeth. Referred pain from impacted teeth has also been described.

A dentigerous cyst may develop around the coronal portion of an impacted tooth and may cause displacement of the tooth and destruction of bone. In the study of Dachi and Howell, 37% of impacted mandibular third molars and 15% of impacted maxillary third molars exhibited an area of radiolucency about the crown. About 10% of these radiolucencies were of such a size that they could be considered dentigerous cysts. Furthermore, cases of ameloblastoma have been reported developing in the wall of such a cyst (dentigerous cysts are discussed in more detail in Chapter 4 on Cysts and Tumors of Odontogenic Origin).

Occasionally, impacted teeth allowed to remain *in situ* may undergo resorption. The reason that some teeth are resorbed whereas others are not is unknown. The process usually begins on the crown of the tooth and results in destruction of the enamel and dentin, a well as of the cementum, with subsequent replacement by bone. Radiographically, early resorption resembles a carious lesion of the crown and has often been mistakenly called caries of an impacted tooth. Obviously, caries is impossible in a tooth that is completely impacted.

Ankylosed Deciduous Teeth
(Submerged teeth)

'Submerged' teeth are deciduous teeth, most commonly mandibular second molars, that have undergone a variable degree of root resorption and then have become ankylosed to the bone. This process prevents their exfoliation and subsequent replacement by permanent teeth (Fig. 1-66). After the adjacent permanent teeth have erupted, the ankylosed tooth appears to have submerged below the level of occlusion. This illusion is explained by the fact that there has been continued growth of the alveolar process and also that the crown height of the deciduous tooth is less than that of the adjacent permanent teeth, so that the relative level of occlusion has been changed, not the position of the deciduous tooth. This relation between submersion and ankylosis of human deciduous molars has been studied in detail by Darling and Levers.

The diagnosis of ankylosis of a tooth is usually suspected clinically and confirmed by radiographic examination. The teeth affected lack mobility even though root resorption is far advanced. Upon percussion, an ankylosed tooth imparts a characteristic solid sound in contrast to the dull, cushioned sound of a normal tooth. Radiographically, at least partial absence of the periodontal ligament is seen, with areas of apparent blending between the tooth root and bone. The process is basically one of resorption of tooth substance and bony repair with the result that the tooth is locked in bone.

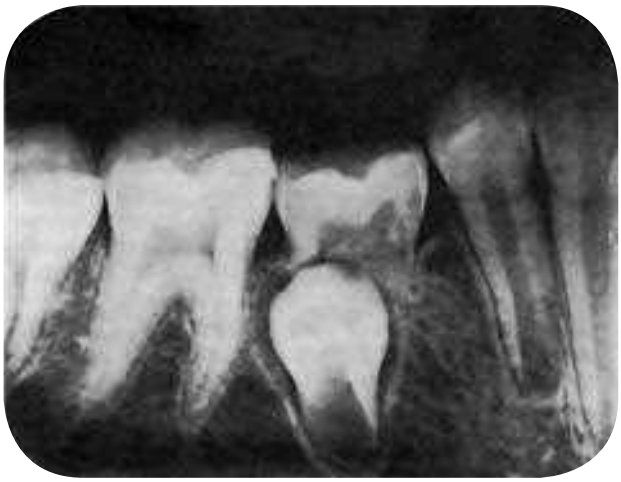


Figure 1-66. Ankylosed (submerged) deciduous second molar.
The ankylosed deciduous tooth appears submerged because of the difference in crown height between the deciduous and permanent teeth and continued growth of the alveolar process.

The cause of ankylosis is not known, although in some cases trauma, infection, disturbed local metabolism, or a genetic influence has been considered an important etiologic factor. These influences have been discussed by Henderson, who also emphasized that a patient who has had one or two ankylosed teeth is very likely to have other teeth ankylosed over a period of time. This condition is usually treated by the surgical removal of the ankylosed tooth to prevent the development of a malocclusion, a local periodontal disturbance, or dental caries.

FISSURAL (INCLUSION, DEVELOPMENTAL) CYSTS OF ORAL REGION

A number of different types of fissural (or inclusion) cysts of bone occur in the jaws and have generally been considered arising, as the name would indicate, along the lines of fusion of various bones or embryonic processes. These are true cysts (i.e. pathologic cavities lined by epithelium, usually containing fluid or semisolid material), the epithelium being derived from epithelial cells which are entrapped between embryonic processes of bones at union lines. These fissural cysts may be classified: (1) median anterior maxillary cyst, (2) median palatal cyst, (3) globulomaxillary cyst, and (4) median mandibular cyst.

There are several additional developmental cysts derived from embryologic structures or faults which involve the oral or adjacent soft tissue structures. These may be listed as: (1) nasoalveolar cyst, (2) palatal cysts of the neonate, (3) thyroglossal tract cyst, (4) benign cervical lymphoepithelial cyst, (5) epidermoid and dermoid cyst, and (6) heterotopic oral gastrointestinal cyst.

Nasopalatine Duct Cyst

(Nasopalatine canal cyst, incisive canal cyst)

The most common of the nonodontogenic cyst, the nasopalatine duct cyst (NPDC) is a developmental cyst, non-neoplastic in nature. Its location is peculiar and specific in that it affects the midline anterior maxilla.

The nasopalatine ducts ordinarily undergo progressive degeneration; however, the persistence of epithelial remnants may later become the source of epithelia that gives rise to NPDC, from either spontaneous proliferation or proliferation following trauma (e.g. removable dentures), bacterial infection, or mucous retention. Genetic factors have also been suggested. The mucous glands present among the proliferating epithelium can contribute to secondary cyst formation by secreting mucin within the enclosed structure. NPDC can form within the incisive canal, which is located in the palatine bone and behind the alveolar process of the maxillary central incisors, or in the soft tissue of the palate that overlies the foramen, called the cyst of the incisive papilla.

Etiology. The cause of NPDC is essentially unknown. Trauma, infection, and mucous retention within associated salivary gland ducts have all been suggested as possible pathogenic factors; however, most believe that spontaneous cystic degeneration of residual ductal epithelium is the most likely etiology.

Clinical Features. No data currently available on the international frequency of this type of cyst. No racial predilection is known. Males are affected 18–20 times more often than females. NPDCs occur over a wide age range (8–84 year), although they also occur in fetuses. Most patients who are affected are aged 40–60 years.

Small cysts in the early stages of their development are frequently asymptomatic. Large cysts can be responsible for a variety of symptoms, including swelling (52–88%), discharge (25%), and pain (20–23%). About 70% of patients experience a combination of these symptoms. Paradoxically, patients with small cysts may have disproportionately severe symptoms, whereas patients with large ones may experience few or no symptoms. A salty taste in the mouth and devitalization of the pulps of associated teeth have been reported. Large and more destructive cysts that have perforated the labial and palatal bony plates may present as expansile, fluctuant swellings of the anterior palate and the palate. Extrabony cysts that develop within the soft tissues of the incisive papilla area of the anterior hard palate (called the **cyst of the incisive papilla**) may present as a translucent or bluish colored, dome-shaped swelling. The clinically apparent discoloration is due to the accumulation of fluid contents within the cyst. NPDCs clinically demonstrate slow and progressive growth, sometimes exceeding 60 mm in diameter. Tooth displacement is common finding, having been reported to occur in 78% of patients, whereas bony expansion is noted in only 1.4% of patients.

Histologic Features. Histopathologic examination discloses a cavity lined by epithelium and surrounded by a connective tissue wall. A reported 71.8% of NPDCs have squamous, columnar, cuboidal, or some combination of these epithelial types; respiratory epithelium is seen in 9.8%. The type of epithelium depends on the localization of the cyst, and it may also be reflective of the pluripotential character of the embryonic epithelial remnants. Rarely, dendritic melanocytes have been reported within the epithelium. Malignant transformation of the lining epithelium has not been reported. Often (81% of cases), a chronic inflammatory reaction consisting of lymphocytes and plasma cells is observed in the cyst wall; hemorrhage has been noted in 71% of the cases. Also helpful in the microscopic diagnosis of NPDC are the presence of structural elements in the cyst wall that are native to the nasopalatine canal (e.g. moderately sized peripheral nerves, arteries and veins, mucous glands, adipose tissue). A clear or straw-colored fluid aspirate is suggestive of NPDC; however, other cystic processes (e.g. lateral radicular cyst, cystic ameloblastoma) cannot be excluded on the basis of this finding alone. The cyst fluid has been reported to contain erythrocytes, leukocytes, desquamated epithelial cells, tissue debris, and bacteria.

Treatment. NPDCs are treated by enucleation via a palatine or buccal approach.

Median Palatal Cyst

The median palatal cyst arises from epithelium entrapped along the line of fusion of the palatal processes of the maxilla.

Clinical Features. The median palatal cyst is located in the midline of the hard palate between the lateral palatal processes. It may become large over a prolonged period of time and produce a definite palatal swelling that is visible clinically (Fig. 1-67A). The cause the epithelial proliferation and subsequent cyst formation is unknown.

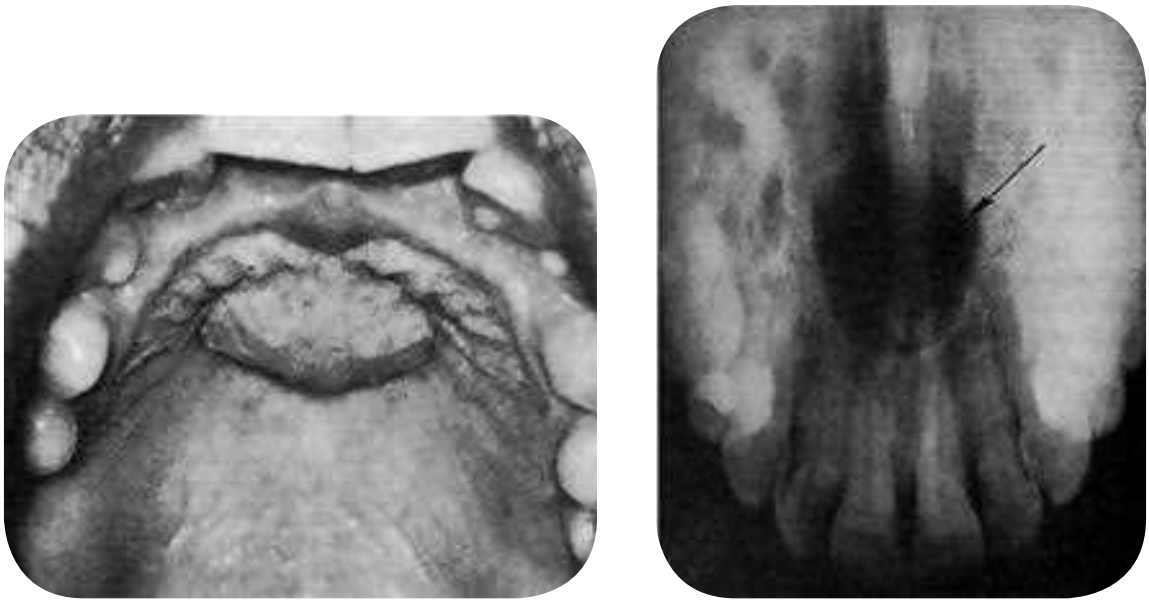
Radiographic Features. On the palatal radiograph a well-circumscribed radiolucent area is seen opposite the bicuspid and molar region, frequently bordered by a sclerotic layer of bone (Fig. 1-67B).

Histologic Features. The lining of such a cyst usually consists of stratified squamous epithelium overlying a relatively dense fibrous connective tissue band which may show chronic inflammatory cell infiltration. However, occasional cases have been reported to be lined by pseudostratified ciliated columnar epithelium or even a 'modified' squamous epithelium, as pointed out by Courage and his associates in a review of this lesion.

Treatment. The treatment, as for most of the fissural cysts, is surgical removal and thorough curettage.

Globulomaxillary Cyst

The globulomaxillary cyst has traditionally been described as a fissural cyst found within the bone between the maxillary lateral incisor and canine teeth. Radiographically, it is a well-defined radiolucency which frequently causes the roots of the adjacent teeth to diverge. While there can be no doubt that cyst do occur in this region and that the pulps of the adjacent teeth



A B

Figure 1-67. Median palatal cyst.
A large swelling **(A)** and underlying defect in the bone **(B)** are present in the midline of the palate. This cyst is not associated with the teeth and is posterior to the area of the incisive canal.

may give positive vitality responses, there is now a considerable body of opinion against the idea that they are fissural cysts. The evidence against their being fissural cysts is, in fact, more substantial than the evidence in favor (Shear, 1996).

The WHO classification of cyst of the jaws (1992) considered this entity under the rubric 'of debatable origin.' We have included here a description of this cyst due to the cited reason.

The globulomaxillary cyst is found within the bone at the junction of the globular portion of the medial nasal process and the maxillary process, the globulomaxillary fissure, usually between the maxillary lateral incisor and cuspid teeth. However, there are reports of evidence that the cyst actually forms in the bone suture between the premaxilla and maxilla, the incisive suture, so that its location may be different from the cleft ridge and palate. Because of this, Ferenczy has suggested the term **'premaxilla-maxillary cyst'** as more accurately describing its origin. The cause of the proliferation of epithelium entrapped along this line of fusion is unknown. Virtanen and Laine have carried out an extensive review and discussion of the globulomaxillary cyst.

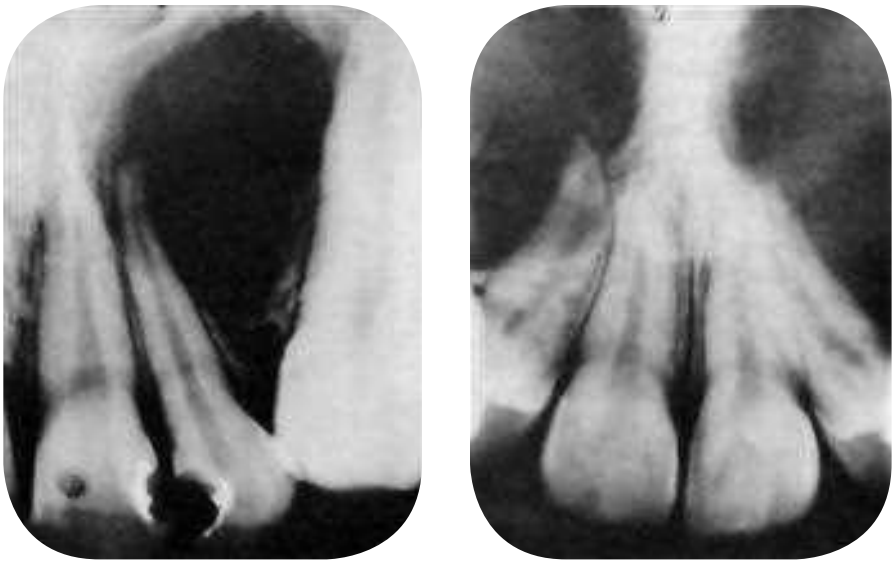
Christ has also thoroughly evaluated the literature dealing with globulomaxillary cysts and has concluded that, embryologically, facial processes *per se* do not exist, and therefore, ectoderm does not become entrapped in the facial fissures of the nasomaxillary complex. Thus, he believes that this cyst should be removed from the category of orofacial fissural cysts, since modern embryologic concepts do not support such a view. Instead, he suggests that an odontogenic origin for this cyst is far more likely, the clinical and radiographic appearance being entirely compatible with a lateral periodontal, lateral dentigerous, or primordial cyst. In addition, numerous reported cases have had the histologic features of the odontogenic keratocyst (q.v.), while nests of odontogenic epithelium in the wall of globulomaxillary cysts are not rare. Furthermore, there is at least one case, reported by Aisenberg and Inman, of an ameloblastoma developing in a globulomaxillary cyst, which suggests an odontogenic origin.

Clinical Features. The globulomaxillary cyst seldom if ever presents clinical manifestations. Nearly every recorded case has been discovered accidentally during routine radiographic examination. Rarely, the cyst does become infected, and the patient may complain of local discomfort or pain in the area.

Radiographic Features. This cyst, on the intraoral radiograph, characteristically appears as an inverted, pear-shaped radiolucent area between the roots of the lateral incisor and cuspid, usually causing divergence of the roots of these teeth (Fig. 1-68A). Interestingly, there are several known cases of bilateral globulomaxillary cyst (Fig. 1-68B).

Care must be exercised not to confuse this lesion with an apical periodontal cyst arising as a result of pulp involvement or trauma to one of the adjacent teeth. The teeth associated with a globulomaxillary cyst are vital unless coincidentally infected.

It has been emphasized recently by Wysocki, reviewing 37 cases of 'globulomaxillary radiolucencies' that many different types of lesions may present radiographically with features characteristic of a globulomaxillary cyst and that these must be included in any differential diagnosis of such a radiolucency in this area. He cited as examples such lesions as the periapical granuloma, apical periodontal cyst, lateral periodontal cyst, odontogenic keratocyst, central giant cell granuloma, calcifying odontogenic cyst, and odontogenic myxoma. He also concluded, in agreement with Christ, that cysts in the globulomaxillary region are odontogenic rather than fissural in origin.



A B

Figure 1-68. Globulomaxillary cyst.
There is a large cyst between the maxillary lateral incisor and cuspid teeth with a characteristic inverted pear shape **(A)**. The same type of cyst may occur bilaterally **(B)**. Note the divergence of the roots of these teeth *(Courtesy of Dr Michael J Freeman and Richard Oliver)*

Histologic Features. The globulomaxillary cyst classically has been described as being lined by either stratified squamous or ciliated columnar epithelium. However, Christ has emphasized that, in the literature, there is no accepted case of globulomaxillary cyst that is lined by pseudostratified ciliated columnar epithelium. The remainder of the wall is made up of fibrous connective tissue, usually showing inflammatory cell infiltration.

Treatment. This type of cyst should be surgically removed, preserving the adjacent teeth if possible.

Median Mandibular Cyst

The median mandibular developmental cyst is an extremely rare lesion occurring in the midline of the mandible. It is of disputed origin. Some authorities consider it a true developmental condition originating from proliferation of epithelial remnants entrapped in the median mandibular fissure during fusion of the bilateral mandibular fissure during fusion of the bilateral mandibular arches. The possibility does exist; however, that the lesion may represent some type of odontogenic cyst such as a primordial cyst originating from a supernumerary enamel organ in the anterior mandibular segment, particularly since the bones uniting at the mandibular symphysis originate deep within the mesenchyme and thereby provide little opportunity for inclusion and subsequent proliferation of epithelial rests deep within the bone. It is also conceivable that this lesion represents a lateral periodontal cyst occurring in the midline, although the origin of this latter lesion is also obscure. The pertinent literature about this unusual type of cyst has been reviewed by White and his coworkers.

Clinical Features. Most of the median mandibular developmental cysts are clinically asymptomatic and are discovered only during routine radiographic examination. They seldom produce obvious expansion of the cortical plates of bone, and the associated teeth; unless otherwise involved, they react normally to pulp vitality tests.

Radiographic Features. The radiographic appearance of the cyst is generally that of a unilocular, well-circumscribed radiolucency, although it may also appear multilocular (Fig. 1-69).

Histologic Features. Histologic examination of the lesion shows a thin, stratified squamous epithelium, often with many folds and projections, lining a central lumen. But in some reported cases, the cyst has been lined by a pseudostratified ciliated columnar epithelium.

Treatment and Prognosis. Too few cases have been reported to be certain of the prognosis of the median mandibular developmental cyst, but conservative surgical excision with preservation of associated teeth, if possible, is deemed advisable.

Nasoalveolar Cyst
(Nasolabial cyst, Klestadt's cyst)

The nasoalveolar cyst is not found within bone, but is usually described as a rare fissural cyst that may involve bone secondarily. It has been thought to arise at the junction of the globular process, the lateral nasal process, and the maxillary

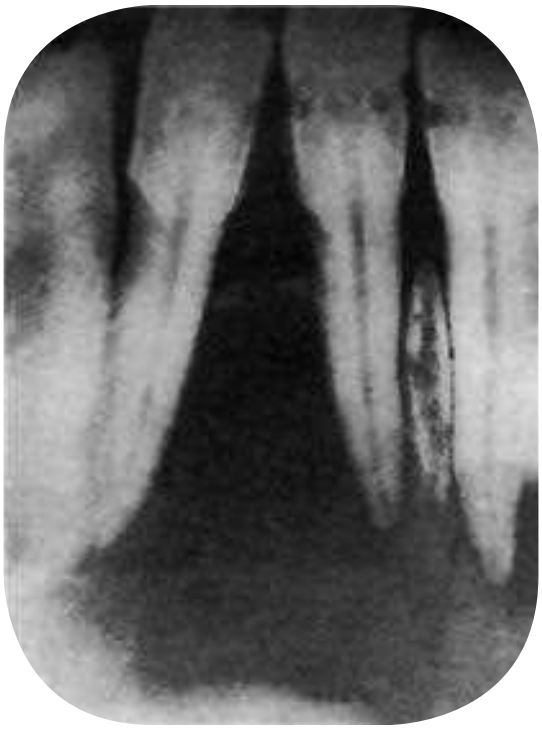


Figure 1-69. Median mandibular cyst.
All teeth in the anterior segment were vital *(Courtesy of Dr Howard H Morgan).*

process as a result of proliferation of entrapped epithelium along the fusion line.

Clinical Features. The nasoalveolar cyst may cause a swelling in the mucolabial fold as well as in the floor of the nose, being located near the attachment of the ala over the maxilla. Superficial erosion of the outer surface of the maxilla may be produced by pressure of the nasoalveolar cyst, but it should be noted that they are not primarily central lesions and therefore may not be visible on the radiograph. Bilateral cases, such as reported by Brandao and his associates, are very rare.

Roed-Petersen, in a discussion of this lesion, reviewed 160 reported cases and noted that slightly over 75% of cases occurred in women. The mean age of occurrence was between 41 and 46 years, although cases have been reported in persons from 12–75 years of age.

Excellent reviews of the nasoalveolar cyst, with recapitulations of its etiology and pathogenesis, have been published by Moeller and Philipsen and by Campbell and Burkes. It has been suggested by Roed-Petersen and emphasized by Christ that this cyst probably originates from the lower anterior part of the nasolacrimal duct rather than from epithelium entrapped in the naso-optic furrow.

Histologic Features. Histologically, the nasoalveolar cyst may be lined by pseudostratified columnar epithelium which is sometimes ciliated, often with goblet cells, or by stratified squamous epithelium.

Treatment. The cyst should be surgically excised, although care must be exercised to prevent perforation and collapse of the lesion.

Palatal and Alveolar Cysts of Newborns
(Epstein's pearls, Bohn's nodules, gingival cysts of the newborn)

A special form of odontogenic cyst is found in as many as 80% of newborn infants. Although this gingival cyst of the newborn has the microscopic appearance of an epidermoid cyst, it arises from epithelial remnants of the deeply budding dental lamina during tooth development, after the fourth month *in utero,* and is, therefore, discussed with the odontogenic lesions in the present text. A similar palatal cyst of the newborn is commonly found in the posterior midline of the hard palate, where it arises from epithelial remnants remaining in the stroma after fusion of the palatal processes which meet medially to form the palate. As originally described, the cysts along the median raphe of the palate were called Epstein's pearls and the term Bohn's nodules was used for cysts which originated from palatal gland structures and were scattered more widely over the hard and soft palates. Today these two terms are used interchangeably for both palatal and gingival cysts of newborns.

Clinical Features. Palatal cysts of the newborn typically present as multiple (usually less than six) 1–4 mm yellow-white, sessile mucosal papules of the posterior hard palate, and occasionally of the anterior soft palate. Occasional cysts are located at some distance from the midline. The cysts are usually somewhat larger and less numerous than the gingival cysts of the alveolar processes in newborns, but the two entities are, otherwise, clinically identical. Both types of cysts are so superficial that several may be ruptured at the time of examination (Fig. 1-70).

Histologic Features. Both gingival and palatal cysts of the newborn show a thin, stratified squamous epithelium cyst lining with a routine fibrovascular connective tissue stroma,

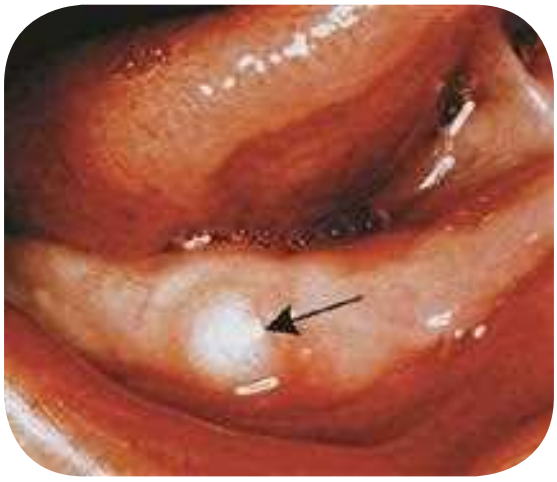


Figure 1-70. Alveolar cysts of newborn.

usually without an inflammatory cell infiltrate. The cystic lumen is filled with degenerated keratin, usually formed into concentric layers or **onion rings** and the epithelium lacks rete processes. Occasional cysts will demonstrate a communication with the surface.

Treatment and Prognosis. No treatment is required for gingival or palatal cysts of the newborn. The cysts are very superficial and within weeks will rupture to harmlessly spill their contents into the oral or pharyngeal environment. The cyst lining then fuses with the overlying mucosa and becomes part of it. Occasionally, a larger cyst or a cyst situated more deeply in the submucosal stroma will remain for six to eight months before rupturing.

Thyroglossal Duct Cyst

The thyroglossal duct cyst is a rare but occasional cause of a benign midline neck mass. The cyst is usually located at the midline of the neck. The duct extends upward from the cyst with varying numbers of branches and secretory glands. These ducts or branches merge into a single duct at the level of the hyoid bone.

Thyroglossal duct cysts result from the dilatation of a remnant at the site where the primitive thyroid descended from its origin at the base of the tongue to its permanent location, low in the neck. Failure of subsequent closure and obliteration of this tract predisposes to thyroglossal cyst formation.

It most often occurs before age 20, but may be found in the older population as well.

Clinical Features. Thyroglossal duct cysts most often present with a palpable (able to be felt) asymptomatic midline neck mass at or below the level of the hyoid bone. The neck mass moves with swallowing. Some patients will have neck or throat pain, or dysphagia (difficulty in swallowing). The spectrum of clinical symptoms may be as varied.

Since the persistent duct or sinus can promote oral secretions, such cysts can become infected. Up to one half of thyroglossal cysts are not diagnosed until adult life. The tract may lie dormant for years or decades until some stimulus leads to cystic dilatation. Infection sometimes causes transient appearance of a mass or enlargement of the cyst, at times with periodic recurrences. Spontaneous drainage occurs in some instances.

Diagnosis is usually made clinically.

Histologic Features. The thyroglossal tract cyst may be lined by stratified squamous epithelium, ciliated columnar epithelium, or intermediate transition type, since it is actually derived from cells originating from the embryonic pharyngeal floor (Fig. 1-71 A–D). With increased intracystic pressure, the cells may become flattened. The connective tissue wall of the cyst will frequently contain small patches of lymphoid tissue, thyroid tissue, and mucous glands. Interestingly, nodular collections of sebaceous glands in association with thyroglossal duct like structures of the tongue occasionally have been reported. Leider and his associates have described such a case as a sebaceous choristoma of the lingual thyroglossal duct.

Treatment and Prognosis. Antibiotics are indicated if there is infection. Definitive surgical management requires excision not only of the cyst but also of the path's tract and branches. The intimate association of the tract with hyoid bone mandates simultaneous removal of the central portion of the hyoid bone to ensure complete removal of the tract (Sistrunk procedure). Recurrence is unlikely after such an operation except with skin involvement and intraoperative cyst rupture.

Before thyroglossal duct cysts are excised, it is important to demonstrate that normally functioning thyroid tissue is in its usual location. Thyroid scans and thyroid function studies are ordered preoperatively.

Epidermal Inclusion Cyst

(Epidermal cyst, epidermoid cyst, epithelial cyst, keratin cyst, sebaceous cyst, milia)

The terminology and nomenclature of jaw cysts varies. Epidermal inclusion cysts are the result of implantation of epidermal elements and its subsequent cystic transformation. The term epidermoid cysts is used in a general context in that, irrespective of the source of the epithelium, the term persists. Milia merely represent miniature epidermoid cysts. Sebaceous cyst is a misnomer, and the term should not be used at all because these cysts are not of sebaceous origin.

Etiology. The origin of epidermoid cyst is varied. They may form by the sequestration and implantation of epidermal rest during embryonal period, occlusion of the pilosebaceous unit, or iatrogenic or surgical implantation of epithelium into the jaw mesenchyme. HPV infection and eccrine duct occlusion may be additional factors in the development of palmoplantar epidermoid cysts. Epidermoid cysts result from the proliferation of epidermal cells within a circumscribed space of the dermis. They have been shown not to be of sebaceous origin based on the analysis of their lipid pattern, which demonstrates similarities to the epidermis. In addition, epidermoid cysts express cytokeratins 1 and 10, which are constituents of the suprabasilar layers of the epidermis. The source of this epidermis is often the infundibulum of the hair follicle. Inflammation is in part mediated by the horny material contained in epidermoid cysts. Extracts of this material have been shown to be chemotactic for polymorphonucleocytes.

Clinical Features. The epidermoid cysts are indolent in nature, slow to progress and remains asymptomatic until or unless secondarily infected. The occurrence of secondary malignancies of the types basal cell carcinoma, Bowen disease, SCC and even mycosis fungoides have been reported albeit rarely. In one study, epidermoid cysts were approximately twice as common in men as in women. Epidermoid cysts may occur at any time in life, but they are most common in the third and fourth decades of life. Gardner syndrome is an exception; the average patient age at onset is 13 years. Discharge of a foul-smelling cheese-like material is a common complaint. Less frequently, the cysts can become inflamed or infected, resulting in pain and tenderness. In the uncommon event of

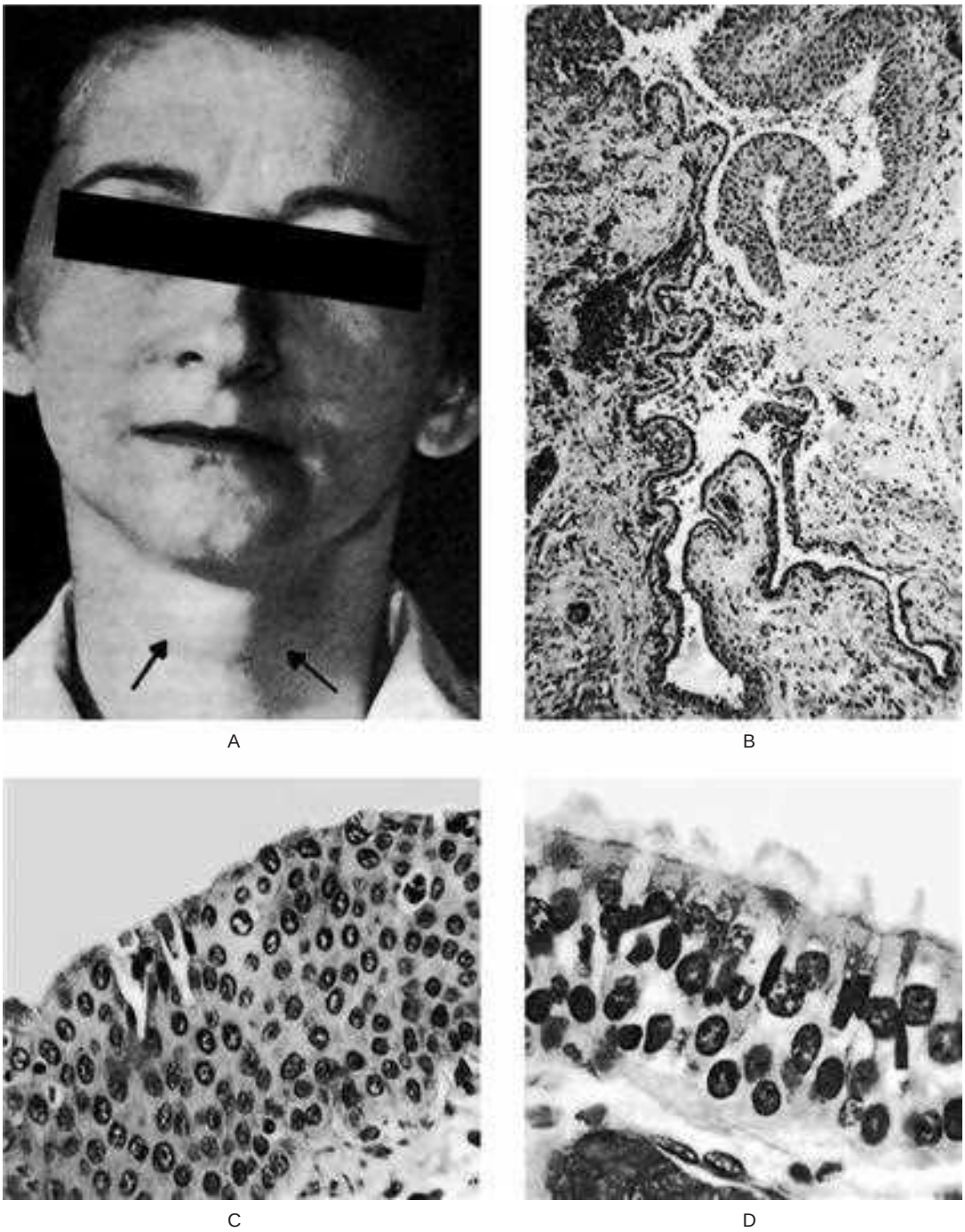


Figure 1-71. Thyroglossal tract cyst.
Patient demonstrates a midline palpable fluctuant lesion **(A)**, which was found to be an epithelium-lined cyst **(B)** composed of both stratified squamous epithelium **(C)** and pseudostratified, ciliated columnar epithelium **(D)**. *(Courtesy of Dr James O Beck Jr)*.

malignancy, rapid growth, friability, and bleeding have been reported. When located orally, the cysts can cause difficulty in feeding, swallowing, or even speaking (Fig. 1-72). Epidermoid cysts appear as firm, round, mobile, flesh-colored to yellow or white subcutaneous nodules of variable size. A central pore or punctum is an inconsistent finding that may adhere the cyst to the overlying epidermis and from which a thick cheesy material can sometimes be expressed. In individuals with dark pigmentation, epidermoid cysts may also be pigmented. In a study of Indian patients with epidermoid cysts, 63% of the cysts contained melanin pigment.

This cyst is mainly reported from sites of face, the trunk, the neck, the extremities, and the scalp. While facial involvement is also frequent in Gardner syndrome, the extremities tend to be affected more than the trunk. The ocular and oral mucosae can also be affected, and cysts have been reported on the palpebral

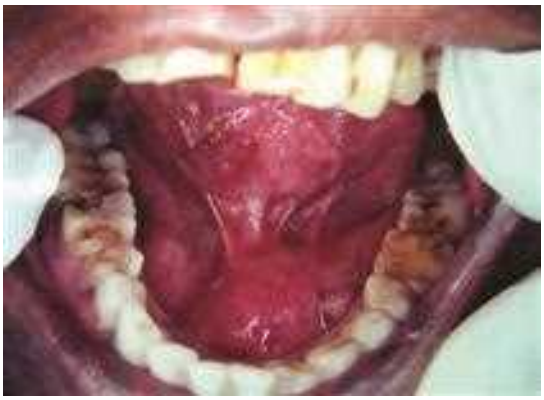


Figure 1-72. Epidermoid cyst.
Lesion appears as a symmetrical swelling in the floor of the mouth *(Courtesy of Dr N Gururaj, CSI Dental College, Madurai, Tamil Nadu)*.

conjunctivae, on the lips, on the buccal mucosa, under the tongue, and even on the uvula. The anterior fontanelle is an unusual location where epidermoid cysts have been found.

Certain hereditary syndromes have epidermoid cysts as part of their features. Examples include **Gardner syndrome, basal cell nevus syndrome,** and **pachyonychia congenita.** An epidermoid cyst may be a feature of pachyonychia congenita.

Histologic Features. The cystic lining is comprised of stratified squamous epithelium with glandular differentiation and is filled with desquamated keratin disposed in a laminar pattern. Dystrophic calcification and reactive foreign body reaction are seen associated with the cystic capsule. Malignant transformation of the cystic lining is noticed not infrequently.

Pigmented epidermoid cysts may demonstrate melanin pigment in the wall and a keratin mass. A surrounding infiltrate of melanocytes and melanophages may also be observed. Palmoplantar epidermoid cysts that are infected with HPV show characteristic histologic changes. The findings include intracytoplasmic eosinophilic inclusion bodies in the cyst wall, vacuolated cells and cells with condensed keratohyalin granules in the granular layer, elongated rete ridges, and vacuolated structures and parakeratotic nuclei in the keratinous mass. Structures resembling eccrine ducts are also observed in some lesions.

Treatment and Prognosis. Surgical removal seems to be the mainstay in the management protocol and recurrence is seldom noticed. Malignancies have been identified in epidermoid cysts. An unusual complication reported from an oral epidermoid cyst was sialadenitis due to pressure on the submandibular salivary duct.

Dermoid Cyst

(Dermoid cystic tumor, cystic teratoma, ovarian cystic teratoma, cystic tumor of ovary, cystic tumors of omentum, congenital cyst of spine, spinal dermoid cysts)

A hamartomatous tumor containing multiple sebaceous glands and almost all skin adnexa, this may contain substances such as nails and dental, cartilage like, and bone like structures. If limited to the skin or subcutaneous tissue, dermoid cysts are thin-walled tumors that contain different amounts of fatty masses; occasionally, they contain horny masses and hairs. The origin of this cyst is probably by sequestration of skin and subsequent implantation of it along the lines of embryonic closure.

Clinical Features. Dermoid cyst occurs mostly on the face, neck, or scalp. In addition to the skin, dermoid cysts can be intracranial, intraspinal, or perispinal. Intra-abdominal cysts, such as cystic tumors of the ovary or omentum, occur as well. No racial predilection appears to exist; however, most cases of dermoid cysts in the literature occurred in whites. Dermoid cysts of the ovary or omentum are gender restricted, that is, they occur only in the female population. In other dermoid cysts, no gender predilection has been found. Dermoid cysts are described in persons of all ages. Intracranial or perispinal dermoid cysts are most often found in infants, children, or young adolescents. Intra-abdominal dermoid cysts are described in females aged 15–40 years. For example, cystic teratoma is a relatively rare tumor that most often occurs in females aged 15–40 years. Most dermoid cysts on the floor of the mouth occur in individuals aged 10–30 years. Only a few cases describe oral dermoid cysts in newborns or children. Dermoid cysts that are congenital and localized on the neck, head, or trunk are usually visible at birth. Occasionally, they occur on the neck or in a midline region. When on the head, dermoid cysts are often adherent to the periosteum. The usual diameter of the lesions is 1–4 cm. In many patients, dermoid cysts occur on the floor of the mouth or elsewhere in the mouth. Three subclasses of congenital mouth cysts are described in the literature: **epidermoid (simple) cysts, dermoid (complex) cysts, and teratoid (complex) cysts.** Most of these lesions occur in individuals aged 10–30 years. Other rare dermoid cysts in the oral cavity are those on the tongue. As of early 2000, 17 patients with intralingual dermoid cysts are described in the English-language literature. All cases occurred in young patients.

Histologic Features. In contrast to epidermal cysts, dermoid cysts in the skin are lined by an epidermis that possesses various epidermal appendages. As a rule, these appendages are fully mature. Hair follicles containing hairs that project into the lumen of the cyst are often present. The dermis of dermoid cysts usually contains sebaceous glands; eccrine glands; and, in many patients, apocrine glands. Occasionally, the lining epithelium may proliferate as papillary boundaries extend externally or inward toward the lumen of the cyst. This proliferation may have some superficial resemblance to epidermal carcinomatous proliferation, and the growth may be misdiagnosed as a cancer.

Treatment and Prognosis. Surgical excision is the treatment of choice in any localization.

Heterotopic Oral Gastrointestinal Cyst

Heterotopic islands of gastric mucosa have been found in the esophagus, small intestine, thoracic cysts, omphalomesenteric cysts, pancreas, gallbladder, and Meckel's diverticulum,

according to the review by Gorlin and Jirasek. In addition, Harris and Courtemanche cited at least 17 cases of cysts lined by gastric or intestinal mucosa occurring in the oral cavity, in the tongue, or in the floor of the mouth, probably from misplaced embryonal rests.

Clinical Features. This choristomatic cyst can be found in patients at any age, although the majority have been infants or young children. It may be significant that the lesion occurs overwhelmingly in males.

The cyst presents as a small nodule entirely within the body of the tongue, either anterior or posterior, or in the floor of the mouth, in the neck, or adjacent to the submaxillary gland. It may be asymptomatic or may cause difficulty in eating or speaking. Some cysts communicate with the surface mucosa by a tube or duct like structure.

Histologic Features. This cyst is usually lined partly by stratified squamous epithelium and partly by gastric mucosa similar to that found in the body and fundus of the stomach, with both parietal and chief cells. Sometimes intestinal epithelium is found, including Paneth, goblet and argentaffin cells. A muscularis mucosa may or may not be present.

Treatment. Surgical excision is the treatment of choice, although this lesion cannot be diagnosed clinically and is seldom suspected.

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CHAPTER 2

Benign and Malignant Tumors of the Oral Cavity

■ T"TCLGPFTCP

CHAPTER OUTLINE

The study of tumors of the oral cavity and adjacent structures constitutes an important phase of dentistry because of the role which the dentist plays in the diagnosis and treatment of these lesions. Although tumors constitute only a small number of the pathologic conditions seen by the dentist, they are of great significance since they have the potential ability to jeopardize the health and longevity of the patient. Many of the great variety of oral tumors will seldom be seen by the general practitioner of dentistry. Yet, it is of utmost importance that he/she be familiar with them so that when one does present itself, he/she may either institute appropriate treatment or refer the patient to the proper therapist.

A tumor, by definition, is simply a swelling of the tissue in the strict sense, the word does not imply a neoplastic process. Many of the lesions to be discussed in this chapter are called tumors only because they are manifested as swellings; they are in no way actually related to true neoplasms.

Neoplasia is a poorly understood biological phenomenon which, in some instances, cannot be clearly differentiated from other processes or tissue reactions. A neoplasm can be defined as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change (Willis 1952).

BENIGN TUMORS OF EPITHELIAL TISSUE ORIGIN

Squamous Papilloma

The oral squamous papillomas are seemed to be associated with papilloma virus, the one commonly incriminated as causative in skin warts. It is the fourth most common oral mucosal mass and is found in 4 of every 1,000 and accounts for 3–4% of all biopsied oral soft tissue lesions.

The HPV types 6 and 11, commonly associated with squamous papillomas, failed to be demonstrated in oral malignancies as well as potentially malignant oral lesions. Even though all HPV lesions are infective, the squamous papilloma appears to have an extremely low virulence and infectivity rate; it does not seem to be contagious.

Since the squamous papilloma may be clinically and microscopically indistinguishable from verruca vulgaris, the virus-induced focal papillary hyperplasia of the epidermis, it is briefly discussed in this section.

Clinical Features. The papilloma is an exophytic growth made up of numerous, small finger like projections which result in a lesion with a roughened, verrucous or 'cauliflower like' surface. It is nearly always a well circumscribed pedunculated tumor, occasionally sessile. It is painless, usually white but sometimes pink in color. Intraorally it is found most commonly on the tongue, lips, buccal mucosa, gingiva and palate, particularly that area adjacent to the uvula (Fig. 2-1). The majority of papillomas are only a few millimeters in diameter, but lesions may be encountered which measure several centimeters. These growths occur at any age and are seen even in young children. A series of 110 cases has been reported by Greer and Goldman, while a series of 464 cases has been studied by Abbey and his coworkers; this is somewhat indicative of the prevalent nature of the lesion.

The common wart or verruca vulgaris, is a frequent tumor of the skin analogous to the oral papilloma. It is uncommon

Figure 2-1. Papilloma.
Large **(A)** and small **(B)** papillomas of the tongue illustrate the variation in clinical appearance of the lesion. The photomicrograph **(C)** illustrates the many finger like projections (1), each containing a thin, central connective tissue core (2), of which the lesion is composed.

on oral mucous membranes but extremely common on the skin. The associated viruses in verruca are the subtypes HPV-2, HPV-4 and HPV-40. Clinically it shows pointed or verruciform surface projections, a very narrow stalk, appears white due to considerable surface keratin, and presents as multiple or clustered individual lesions. It enlarges rapidly to its maximum size, seldom achieving more than 5 mm in greatest diameter. Verruca vulgaris is contagious and capable of spreading to other parts of an affected person's skin or membranes by way of autoinoculation. Lesions that are histologically identical to the verruca vulgaris of the skin are frequently found on the lips and occasionally intraorally (Fig. 2-2). These are often seen in patients with verrucae on the hands or fingers, and the oral lesions appear to arise through autoinoculation by finger sucking or fingernail biting.

Papilloma like or papillomatous lesions as well as 'pebbly' lesions and fibromas of various sites in the oral cavity are recognized as one of the many manifestations of the multiple hamartoma and neoplasia syndrome (Cowden's syndrome). This is an autosomal dominant disease characterized by facial trichilemmomas associated with the gastrointestinal tract, the thyroid, CNS and musculoskeletal abnormalities as well as oral lesions. It is also considered a cutaneous marker of breast cancer.

Figure 2-2. Verruca vulgaris.
These verrucae of the lips occurred in a girl, with similar lesions on the fingers, who habitually bit her fingernails *(Courtesy of Dr Paul E Starkey)*.

Histologic Features. The microscopic appearance of the papilloma is characteristic and consists of many long, thin, finger-like projections extending above the surface of the mucosa, each made up of a continuous layer of stratified squamous epithelium and containing a thin, central connective tissue core which supports the nutrient blood vessels (Fig. 2-1C). Some papillomas exhibit hyperkeratosis, although this finding is probably secondary to the location of the lesion and the amount of trauma or frictional irritation to which it has been subjected. The essential feature is a proliferation of the spinous cells in a papillary pattern; the connective tissue present is supportive stroma only and is not considered a part of the neoplastic element. Occasional papillomas demonstrate pronounced basilar hyperplasia and mild mitotic activity which should not be mistaken for mild epithelial dysplasia. **Koilocytes** (HPV altered epithelial cells with perinuclear clear spaces and nuclear pyknosis) may or may not be found in the superficial layers of the epithelium. The presence of chronic inflammatory cells may be variably noted in the connective tissue.

Treatment and Prognosis. Treatment of the papilloma consists of excision, including the base of the mucosa into which the pedicle or stalk inserts. Removal should never be accomplished by an incision through the pedicle. If the tumor is properly excised, recurrence is rare. The possibility of malignant degeneration in the oral papilloma is quite unlikely, although fixation of the base or induration of the deeper tissues should always be viewed with some suspicion.

Intraoral verruca vulgaris is also treated effectively by conservative surgical excision or curettage, but liquid nitrogen cryotherapy and topical application of keratinolytic agents (usually containing salicylic acid and lactic acid) are also effective. Recurrence is seen in a small proportion of treated cases.

Squamous Acanthoma

The squamous acanthoma is an uncommon lesion which probably represents a reactive phenomenon of the epithelium rather than a true neoplasm. It bears no known relationship to the clear cell acanthoma, which occurs with considerable frequency on the skin and may also be found on the lips, as in the two cases reported by Weitzner.

The squamous acanthoma has no distinctive clinical appearance by which it may be identified or even suspected, and may occur at virtually any site on the oral mucosa, usually in older adults. It is generally described as a small flat or elevated, white, sessile or pedunculated lesion on the mucosa. The lesion is histologically distinctive and consists of a well-demarcated elevated and/or umbilicated epithelial proliferation with a markedly thickened layer of orthokeratin and underlying spinous layer of cells. Tomich and Shafer, who originally described this lesion, postulated that it was caused by trauma and developed its characteristic morphology through a series of epithelial alterations beginning with a localized pseudoepitheliomatous hyperplasia. It is not known to recur after excision.

Keratoacanthoma

(Self-healing carcinoma, molluscum pseudocarcinomatosum, molluscum sebaceum, verrucoma)

A lesion which clinically and pathologically resembles squamous cell carcinoma, keratoacanthoma is a relatively common low-grade malignancy that originates in the pilosebaceous glands. It is considered to be a variant of invasive squamous cell carcinoma.

The definite cause of this lesion remains unclear but similarity in epidemiologic data with squamous cell carcinoma and Bowen disease supports sunlight as an important etiologic factor. Industrial workers exposed to pitch and tar have been well established as having a higher incidence of keratoacanthoma, thus chemical carcinogens may be one of the etiologic factors. Trauma, human papilloma virus (specifically types 9, 11, 13, 16, 18, 24, 25, 33, 37, and 57), genetic factors and immunocompromised status also have been implicated as etiologic factors. Recent studies identified that up to one-third of keratoacanthomas harbor chromosomal aberrations such as gains on 8q, 1p, and 9q with deletions on 3p, 9p, 19p, and 19q. One other report identified a 46, XY, t (2;8) (p13; p23) chromosomal aberration.

Clinical Features. Keratoacanthoma has been reported in all age groups, but incidence increases with age. It occurs twice as frequently in men as in women and is less common in darker skinned individuals. Most keratoacanthomas occur on sun-exposed areas. The face, neck, and dorsum of the upper extremities are common sites; 8.1% of the cases occurred on the lips and the vermilion border of both the upper and lower lip are affected with equal frequency. Intraoral lesions are quite uncommon, a total of four cases were reviewed by Freedman and his associates.

Lesions typically are solitary and begin as firm, round, skin-colored or reddish papules that rapidly progress to dome-shaped nodules with a smooth shiny surface and a central crateriform ulceration or keratin plug that may project like a horn. The lesion appears as an elevated umbilicated or crateriform one with a depressed central core or plug (Fig. 2-3). It is seldom over 1.0 to 1.5 cm in diameter. The lesion is often painful and regional lymphadenopathy may be present.

The clinical course of the lesion is one of its unusual aspects. It begins as a small, firm nodule that develops to full size over a period of four to eight weeks, persists as a static lesion for another four to eight weeks, then undergoes spontaneous regression over the next six- to eight-week period by expulsion of the keratin core with resorption of the mass. However, lesions with an overall duration of as long as two years have been reported. Recurrence is rare.

The differential diagnoses include actinic keratosis, molluscum contagiosum, Muir-Torre syndrome, squamous cell carcinoma, and verrucous carcinoma.

Histologic Findings. The lesion consists of hyperplastic squamous epithelium growing into the underlying connective tissue. The surface is covered by a thickened layer of parakeratin

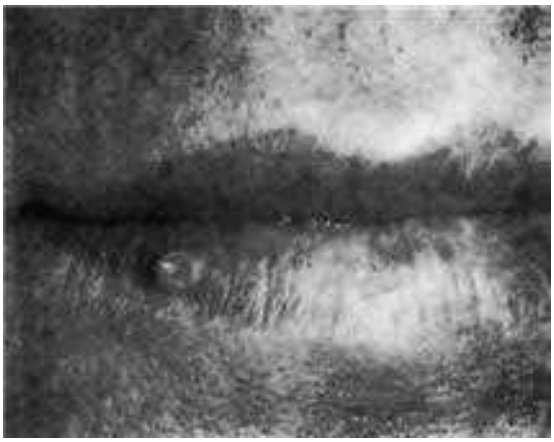


Figure 2-3. Keratoacanthoma.
This small keratoacanthoma of the lip illustrates the typical elevated, umbilicated appearance of the lesion *(Courtesy of Dr Charles E Huttom)*.

or orthokeratin with central plugging. The epithelial cells do not usually show atypia but occasionally dysplastic features are found. At the deep leading margin of the tumor, islands of epithelium often appear to be invading and frequently this area cannot be differentiated from epidermoid carcinoma. Lapins and Helwig, among others, have also reported that the keratoacanthoma on occasion may invade perineural spaces, but this does not adversely affect the biologic behavior of the lesion; neither can it be used as a distinguishing characteristic between keratoacanthoma and epidermoid carcinoma. Pseudocarcinomatous infiltration typically presents a smooth, regular, well-demarcated front that does not extend beyond the level of the sweat glands. The connective tissue in the area shows chronic inflammatory cell infiltration. The most characteristic feature of the lesion is found at the margins where the normal adjacent epithelium is elevated towards the central portion of the crater; then an abrupt change in the normal epithelium occurs as the hyperplastic acanthotic epithelium is reached. For this reason, the diagnosis may be impossible if the adjacent border of the specimen is not included in the biopsy.

The term squamous cell carcinoma, keratoacanthoma type has been introduced for otherwise classic keratoacanthomas that reveal a peripheral zone formed by squamous cells with atypical mitotic figures, hyperchromatic nuclei, and loss of polarity to some degree. These marginal cells also may penetrate into surrounding tissue in a more aggressive pattern.

Treatment. The lesion is usually treated by surgical excision. Spontaneous regression does not occur in every case; where it has occurred, residual scar may be present. Prognosis is excellent following excisional surgery. Recurrent tumors may require more aggressive therapy. Patients with a history of keratoacanthoma should be followed for the development of new primary skin cancers (squamous cell carcinoma, in particular).

Oral Nevi

(Oral melanocytic nevus, nevocellular nevus, mole, mucosal melanocytic nevi)

Categorized as hamartomas, developmental malformations, the nevi are benign proliferations of nevus cells in either epithelium or connective tissue. In 1943, Ackermann and Field have reported the first case of an oral nevus. King et al, adopted the less anatomically specific term, intramucosal nevus. Adult whites harbor this lesion rather commonly but intraoral lesions are much less common.

Nevi may also be classified as **congenital** or **acquired** (Buchner and Hansen). On the basis of the histologic location of the nevus cells, cutaneous acquired nevi can be classified into three categories:

- **Junctional nevus**—when nevus cells are limited to the basal cell layer of the epithelium
- **Compound nevus—**nevus cells are in the epidermis and dermis
- **Intradermal nevus** (common mole)—nests of nevus cells are entirely in the dermis.

Oral nevi follow the same classification where the term intradermal is replaced by intramucosal.

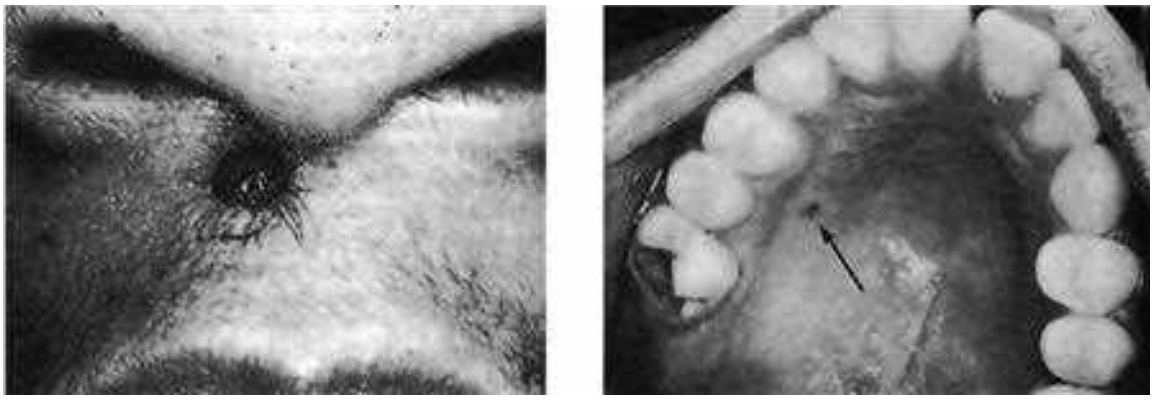
Oral acquired melanocytic nevi evolve through stages similar to those of nevi on the skin. Junctional nevi that are first noted in infants, children and young adults typically mature into compound nevi. Then, during later adulthood, the lesions mature into intramucosal nevi. As the nevus cells penetrate into the dermis, their pigmentation diminishes; approximately 15% of intramucosal nevi are nonpigmented.

The most common mucosal type is the intramucosal nevus, which accounts for more than one half of all reported oral nevi. The common **blue nevus** is the second most common type found in the oral cavity. The blue nevi is commoner in the mouth than in the skin; which account for 25–36% of all oral nevi, according to different studies. Junctional and compound nevi account for only 3–6% of all oral nevi.

Clinical Features. Ainsworth and her colleagues separate the congenital nevi of the skin into 'small' and 'garment' nevi. The 'small' nevi are greater than 1 cm in diameter and usually 3–5 cm. The 'garment' nevi are greater than 10 cm in diameter and can cover large areas of the skin. The congenital nevi occur in 1–2.5% of neonates and, with the passage of time, may change from flat, pale tan macules to elevated, verrucous, hairy lesions. Approximately 15% occur on the skin of the head and neck. Intraoral occurrence is extremely rare.

Acquired nevi are extremely common. They appear in about the eighth month of life and increase in number with age, apparently reaching their peak numerically in the late third decade of life. Clark has stated that the number of nevi which a person has is genetically determined. Interestingly, the number of nevi begin to decrease as one ages, so that elderly persons average far fewer nevi than younger adults.

The **intradermal nevus** (common mole) is one of the most common lesions of the skin, most persons exhibiting several, often dozens, scattered over the body. The common



A B

Figure 2-4. Pigmented cellular nevus.
Typical examples of nevi of the skin **(A)** and palate **(B)** are illustrated.

mole may be a smooth flat lesion or may be elevated above the surface; it may or may not exhibit brown pigmentation, and it often shows strands of hair growing from its surface (Fig. 2-4). This form of mole seldom occurs on the soles of the feet, the palms of the hands or the genitalia.

The **junctional nevus** may appear clinically similar to the intradermal nevus, the distinction being chiefly histologic. It is extremely important; however, that a distinction be drawn, since the prognosis of the two lesions is different, as will be pointed out later.

The **compound nevus** is a lesion composed of two elements: an intradermal nevus and an overlying junctional nevus.

The **spindle cell and/or epithelioid cell nevus (Spitz nevus)** occurs chiefly in children, only about 15% appearing in adults, and may appear histologically similar to malignant melanoma in the adult. Seldom; however, does this lesion exhibit clinically malignant features. Essentially, this lesion is clinically benign, but histologically malignant. Weedon and Little have reviewed 211 cases of spindle cell and epithelioid cell nevi while Allen has reviewed 262 cases, and none of these authors have found any nevus of this type on a mucous membrane surface, including the oral cavity.

The **blue nevus** is a true mesodermal structure composed of dermal melanocytes which only rarely undergo malignant transformation. It occurs chiefly on the buttocks, on the dorsum of the feet and hands, on the face and occasionally on other areas. The majority of blue nevi are present at birth or appear in early childhood and persist unchanged throughout life. The lesion is smooth, exhibits hairs growing from its surface and varies in color from brown to blue or bluish black. Scofield reviewed this lesion in 1959 and reported two intraoral cases, the first recorded occurrence of the lesions in the mouth. Since then, numerous intraoral lesions have been reported.

Histologic variants of acquired nevi such as neural, balloon cell and halo nevi occur. Only the halo nevus is clinicopathologically distinctive. The neural and balloon cell nevi are histologic variants of intradermal or compound nevi.

Oral Manifestations. Eight-five percent of oral nevi are found in patients younger than 40 years. Oral nevi are found in all races and more frequently in whites, in whom 55% of reported oral nevi occurred. Approximately 23% of oral nevi occurred in black patients. Patients with junctional or compound nevi were relatively young; they were aged 22 and 24 years, respectively, whereas the mean age of patients with intramucosal nevi and blue nevi was 35 years and 38 years, respectively. Studies have revealed that oral mucosal nevi are slightly predominant in women rather than men. Oral nevi most commonly occur on the hard palate, with almost 40% presenting in that location. The second most common location is the buccal mucosa (20% of cases). Other common locations include the vermilion border of the lip and the labial mucosa. Roughly 10% of all types of oral nevi are found on the gingiva. Only one mucosal nevus has been reported on the tongue or floor of the mouth.

Most oral nevi are asymptomatic, and the lesions are usually detected as an incidental finding on routine dental examination. Nevi are often mistaken for melanotic macules, amalgam tattoos, physiologic ethnic pigmentation, smoker's melanosis, or other vascular or pigmented lesions.

An aid in differential diagnosis is that melanotic macules and amalgam tattoos are usually flat while the majority of nevi elevate from the mucosal surface. Ethnic pigmentation is nearly always symmetric and rarely affects the surface topography or disturbs the normal stippling in the gingiva. Smoker's melanosis involves only the anterior gingiva and most often occurs in women who smoke and take oral contraceptives. Vascular lesions can be mistaken for melanocytic proliferations; the former usually blanch with compression, and aspiration may be helpful in differentiating a nevus from a vascular process. Malignant melanoma is frequently associated with diffuse areas of pigmentation, possible ulceration, nodularity, variegation in color, and an irregular outline.

Approximately 85% of oral nevi are pigmented. Pigmentation usually varies from brown to black or blue. Nevi are well circumscribed, round, or oval, and are raised or slightly raised

in 65–80% of cases. Approximately 15% of nevi are amelanotic. Many amelanocytic lesions appear as sessile growths that resemble fibromas or papillomas or excrescences of normal color.

The anatomic distribution of nevi closely follows its histologic type. Almost two-thirds of blue nevi occur in hard palate. Intramucosal nevi are distributed almost equally between the hard palate and buccal mucosa, with almost 25% in each location. Approximately 17% of intramucosal nevi are on the gingiva, 12% on the vermilion border of the lip, and almost 9% on the labial mucosa.

Histologic Features. The nevus cells are assumed to be derived from neural crest and their envisaged relationship with true melanocytes remains uncertain. Nevus cells are large ovoid, rounded, or spindle-shaped cells with pale cytoplasm; and may contain granules of melanin pigment in their cytoplasm. The nucleus is vesicular and lacks the dendritic processes typical of melanocytes. In addition, they either lack contact inhibition or lose it shortly after the proliferation process begins. Melanosomes are retained by nevus cells and are not transferred to adjacent keratinocytes. They tend to be grouped in sheets or cords which are called nest or thèque. Nevus cells also have the ability to migrate from the basal cell layer into the underlying connective tissue.

Multinucleated giant nevus cells are sometimes seen, but are of little prognostic significance. Mitotic figures are not common.

In the **intradermal nevus,** the nevus cells are situated within the connective tissue and are separated from the overlying epithelium by a well defined band of connective tissue. Thus, in the intradermal nevus, the nevus cells are not in contact with the surface epithelium (Fig. 2-5A).

In the **junctional nevus,** this zone of demarcation is absent, and the nevus cells contact and seem to blend into the surface epithelium. This overlying epithelium is usually thin and irregular and shows cells apparently crossing the junction and growing down into the connective tissue—the so-called *abtropfung* or 'dropping off' effect. This 'junctional activity' has serious implications because junctional nevi have been known to undergo transformation into malignant melanomas (Fig. 2-5D).

The **compound nevus** shows features of both the junctional and intradermal nevus. Nests of nevus cells are dropping off from the epidermis, while large nests of nevus cells are also present in the dermis (Fig. 2-5B, C).

The **spindle cell** and/or **epithelioid cell nevus** is commonly composed of pleomorphic cells of three basic types: spindle cells, oval or 'epithelioid' cells, and both mononuclear and multinucleated giant cells. These are arranged in well-circumscribed sheets and there is generally considerable junctional activity.

The **blue nevus** is of two types: the common blue nevus and the cellular blue nevus. In the common blue nevus, elongated melanocytes with long branching dendritic processes lie in bundles, usually oriented parallel to the epidermis, in the middle and lower third of the dermis. There is no junctional activity. The melanocytes are typically packed with melanin granules, sometimes obscuring the nucleus, and these granules may extend into the dendritic processes. In the cellular blue

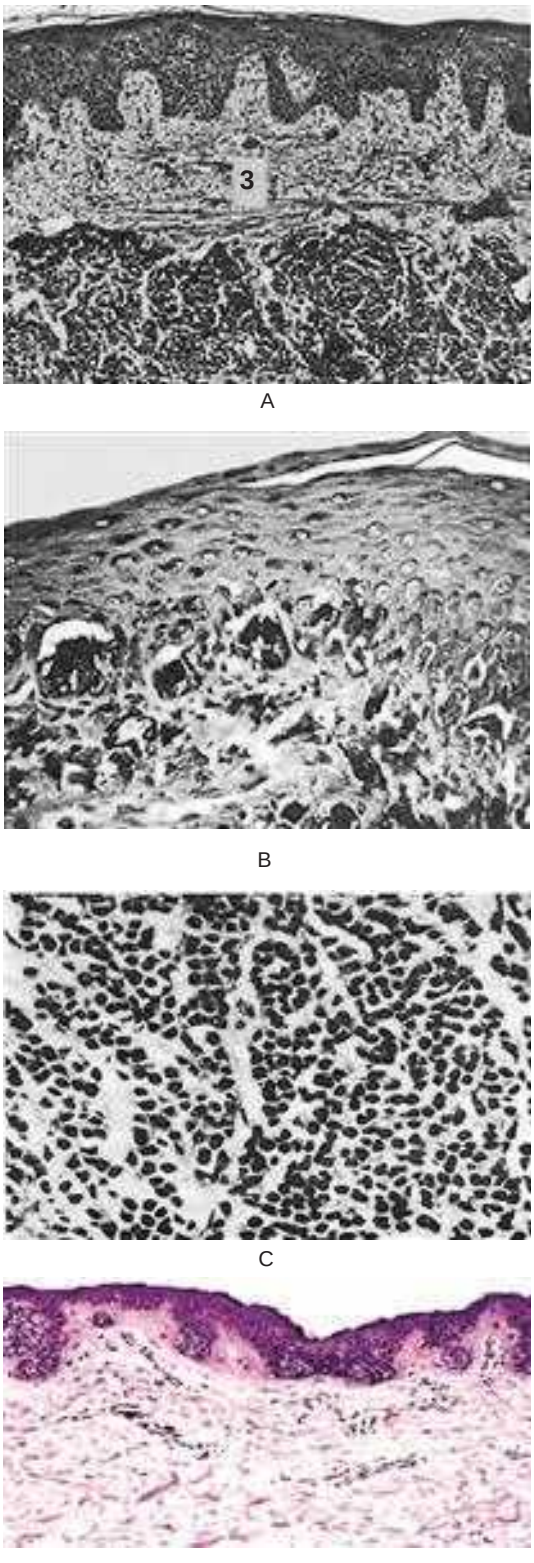


Figure 2-5. Pigmented cellular nevus.
The intradermal nevus **(A)** demonstrates a thick band of connective tissue (1) separating the nevus cells from the overlying epithelium. In the compound nevus **(B)**, the nevus cells are in contact with the overlying epithelium and are in the underlying connective tissue. The nevus cells are shown under high magnification **(C)**, Pigmented cellular nevus—nevus cells are in contact with the overlying epithelium and appear to blend into the epithelium **(D)**. *(Courtesy of Dr Hari S,Noorul Islam College of Dental Science,Trivandrum)*

nevus, an additional cell type is present: a large, round or spindle cell with a pale vacuolated cytoplasm. These cells commonly are arranged in an alveolar pattern.

Treatment and Prognosis. Since the acquired pigmented nevus is of such common occurrence, it would obviously be impossible to attempt to eradicate all such lesions. It has become customary to recommend removal of pigmented moles if they occur in areas which are irritated by clothing, such as at the belt or collar line, or if they suddenly begin to increase in size, deepen in color, or become ulcerated. Allen and Spitz have stated that it is fairly certain that trauma to an intradermal nevus will not induce malignancy. Whether simple trauma to a junctional nevus will produce malignancy is not known.

On the other hand, it is now well recognized that the congenital nevi have a great risk for transformation to malignant melanoma. Kaplan reported seven cases which were seen at the Stanford University Hospital and discussed 49 other cases. It is estimated that 14% of the large congenital nevi may undergo malignant transformation. Of particular interest is the occurrence of the B-K mole syndrome described by Clark and coworkers. This autosomal dominant condition is characterized by large pigmented nevi and a high risk for the development of melanoma. Its occurrence; however, has not been documented intraorally.

Surgical excision of all intraoral pigmented nevi is recommended as a prophylactic measure because of the constant chronic irritation of the mucosa in nearly all intraoral sites occasioned by eating, toothbrushing, etc.

'PREMALIGNANT' LESIONS/CONDITIONS OF EPITHELIAL TISSUE ORIGIN

Several lines of evidence, including clinical, experimental, and morphological data, support the concept that squamous cell carcinoma of the upper aerodigestive tract arises from noninvasive lesions of the squamous mucosa. These lesions encompass a histological continuum between the normal mucosa at one end and high grade dysplasia/carcinoma *in situ,* at the other, establishing a model of neoplastic progression. This continuum of preinvasive neoplasia is encountered in many other epithelia, including the lower respiratory tract and the cervix uteri.

The identification of preneoplastic lesions of the upper aerodigestive tract, through clinical, morphological and more recently, molecular means, helps in the early detection and treatment of head and neck squamous cell carcinoma. Moreover, understanding and documenting the morphological and molecular abnormalities associated with this progression may shed light on the biology of these tumors.

Historically, the definition of an oral premalignant lesion dates back to 1978, when it was defined by the World Health Organization (WHO) as "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart." The precancerous condition in its turn is "a generalized state associated with a significantly increased risk of cancer". Examples of precancerous conditions are sideropenic dysphagia, submucous fibrosis and possibly, lichen planus.

Cancer being a genetic disorder involves multiple alterations of the genome progressively accumulated during a protracted period, the overall effects of which surpass the inherent reparative ability of the cell. In the course of its progression, visible physical changes are taking place at the cellular level (atypia) and at the resultant tissue level (dysplasia). These alterations include genetic changes, epigenetic changes, surface alterations and alterations in intercellular interactions. The sum total of these physical and morphological alterations are of diagnostic and prognostic relevance and are designated as 'precancerous' changes. In many situations, the relationship between these changes and the progression towards neoplasia is not understood. Nevertheless, it seems probable that these changes are ultimately involved in driving cells further along the path to neoplastic transformation.

The diagnosis of precancers is primarily based on morphology and its grading on histology (dysplasia). Despite the fact that this estimation is subjective and therefore carries a low prognostic value of an impending malignancy, it is still widely practiced to assess the risk of malignant potential of such lesions. Because of this inherent discrepancy such lesions may well be designated as potentially malignant.

A premalignant phase in the development of oral cancer is predicted by the classic model of experimental epithelial carcinogenesis. Virtually all oral squamous cell carcinomas arise from a premalignant precursor, but it is difficult to specifically define the term 'premalignant'. Oral pathologists use the term epithelial dysplasia to indicate microscopic features in a biopsy specimen that are associated with a risk of malignant change and then assign a grade of severity. There is good correlation between higher grades of dysplasia and increasing risk of cancer but less so with the lower grades.

DYSPLASIA

The histologic connotation to premalignancy is marked by aberrant and uncoordinated cellular proliferation depicted basically at cellular level (atypia), reflections of which could be discerned at tissue levels too (dysplasia). Frequently it is the forerunner of cancer, the causation of this twilight zone in cellular transformation is by no means clear. Dysplasia is encountered principally in the epithelia. "It comprises a loss in the uniformity of the individual cells, as well as a loss in their architectural orientation." Dysplastic cells exhibit considerable pleomorphism (variation in size and shape) and often possess deeply stained (hyperchromatic) nuclei, which are abnormally large for the size of the cell. The nuclear: cytoplasmic ratio increases from 1:4 to 1:1, at the expense of the cytoplasmic volume. Mitotic figures are more abundant than usual, although almost invariably they conform to normal pattern. Frequently, the mitoses appear in abnormal locations within the epithelium and may appear at all levels rather than in its usual basal location. The usual proliferative organization of the epithelium (see below) is lost and is replaced by a disorderly arranged scramble of cells with varying degrees of differentiation arrest.

"Dysplasia is characteristically associated with protracted chronic irritation or inflammation", of which oral cavity is a common site. Due to its peculiar anatomic location and its constant presence of endogenous and exogenous micro-organisms, a sustained state of chronic subclinical infection is maintained at the oral cavity. Overlying physical trauma consistently inflicted on the oral mucosa, compounds the existing situation.

"Dysplasia is a reversible, and therefore presumably a controlled, cellular alteration. When the underlying inciting stimulus is removed, the dysplastic alterations revert to normal." However, there is an important and significant cellular change discerned at the morphological level which cautions its likelihood of subsequent neoplastic transformation. The line of demarcation when the cell surpasses the point of no return is rather faint and the underlying mechanism poorly defined. In short, dysplasia giving rise to neoplasia is akin to cellular changes in response to a noxious stimulus. As it is evident it traverses the stage of cellular adaptation, reversible damage, and finally, irreversible cell death. When a susceptive cell is exposed to a carcinogen it probably tries to adapt to it, depending on the extent and duration of stimuli. An increase in cell proliferation, diminishing the cytosolic volume and the associated organellar load, could be an attempt in this direction. In the context of oral epithelium, an accelerated growth phase depicted by broadening the progenitor compartment (hyperplasia) is the earlier sequela of exposure to an irritant. When the irritant persists, the epithelium shows features of cellular atrophy, again a well characterized feature of adaptation (atrophy). At a later stage when the stages of adaptation and reversible cell damage surpass, the cells progressively slip into a stage of irreversible cell damage; manifests either as cell death or neoplastic transformation. It appears that some mysterious line is crossed, whereby dysplastic cells escape the normal homeostatic controls and assume the autonomy of a tumor cell. The accelerated pace of cell division noted at the earlier stages of transformation as part of an adaptive response (to replace the damaged cell pool) is, in a way, facilitative of the accumulation of further genetic damage, thereby driving the cells further along the path of transformation. As it is apparent from the foregoing discussion, there is considerable overlap between the stages of cellular adaptation, reversible damage and atypia. Precise morphologic and genetic criteria delineating this line of demarcation between atypia (reversible damage) and neoplasia is unfortunately unknown and is the scope of the study of tumor biology.

Proliferative Organization of Oral Epithelium

Advances in our understanding of the proliferative organization of the oral epithelium has been a slow process for several reasons. These include a lack of suitable experimental models to test hypotheses, difficulty in extrapolating from other renewing cell systems and the need for new investigative techniques (Hume, 1991). The earlier rather mechanistic concept envisages a uniform progenitor compartment occupying the basal layer, retained in a state of sustained replication readiness with roughly equal cell cycle times and their migration towards the surface layers is simply by physical process of forward push induced during waves of cell division. Experimental work to elucidate these underpinned concepts and radical revisions are made (Leblond et al, 1964).

Between 1969 and 1975, a number of workers showed that these concepts were too simple, which suggested that a complex pattern of migration from the basal layer to the surface had to occur to maintain this highly ordered and non-random cell stacking. This, in turn, focused attention on the pattern of cell proliferation in the basal layer and led to the concept of the existence of a number of proliferative subpopulations, of which the stem cell population seemed to be of particular importance for tissue homeostasis and disease. This concept envisages that not all cells in the basal layer can divide, that a number are instead already differentiating, that cells capable of division comprise a number of subpopulations and finally, that cell migration is not caused by cell proliferation pressure but is an independent biological process.

The use of oral epithelium as a model for the investigation of the behavior of proliferative subpopulations followed on from the work that had already begun in rodent skin, it is also true that because of its particular morphological structure and marked circadian (diurnal) variation in cell proliferation, it has contributed significantly to the development of an integrated cell proliferation model applicable also to bone marrow, intestine, testis, nematodes and also to developmental situations (Hume, 1991).

Staging of Oral Precancerous Lesions

The value of histology as an indicator of cancer risk is time-tested not only in the oral cavity or other head and neck regions, but also in other sites, including the uterine cervix, lung, breast, skin, and esophagus. More likely, the future will see gradual extension of the classical histological and clinical approaches to include an evaluation of molecular markers.

An increase in abnormality in either histology or genetic markers was associated with an increase in cancer risk (Fig. 2-6). More recently, studies reported an association of ploidy status (DNA content) in dysplastic lesions with progression risk of oral precancers. The lowest risk was associated with diploid dysplastic lesions (3% progressed into oral squamous cell carcinoma), tetraploid lesions had an intermediate risk (60% showed progression), and aneuploid dysplasia showed the greatest risk (84% progressed). (Lippmann SM, Hong WK, 2001). With time, more such studies will accrue. A future goal will be to determine which combinations of histological and molecular markers best predict risk.

How can such information best be handled? One possibility is to develop staging systems that incorporate different risk factors into risk models. One such model is presented in Table 2-1. For the sake of simplicity, this hypothetical model only includes pathological and molecular markers (clinical features such as appearance, site, and size of the lesion, are not included but should be part of an eventual screening system). In this model, the majority of lesions would be placed into

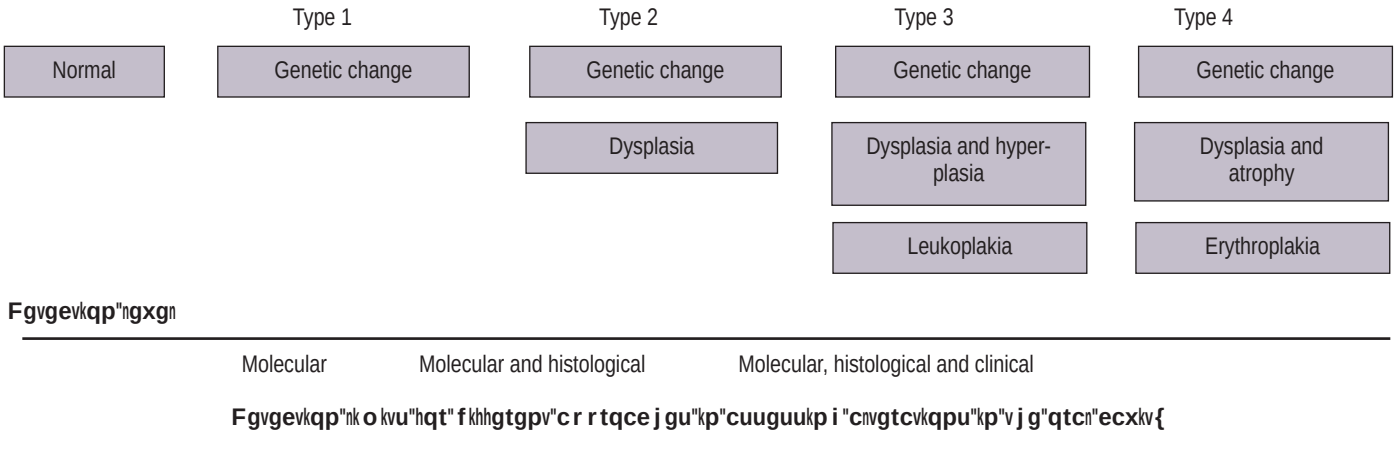


Figure 2-6. Types of alterations to oral cavity.

Table 2-1: Staging of oral premalignant lesions with both pathologic and genetic indices[a]

Stage (cancer risk)	Pathology (P)[b] and genetic (G)[c] patterns
1	$P_1 + G_1$
2	$P_1 + G_2$
	$P_2 + G_1$
	$P_2 + G_2$
3	$P_3 + G_1$
	$P_3 + G_2$
	$P_1 + G_3$
	$P_2 + G_3$
	$P_3 + G_3$

a Adapted from Zhang and Rosin (2001).

b Pathological indices: P_1, no dysplasia or mild dysplasia; P_2, moderate dysplasia and P_3, severe dysplasia/CIS.

c Genetic patterns, categorized by increasing risk: G_1, low risk; G_2, intermediate risk, and G_3, high risk.

stage 1, with the lowest probability of progressing to cancer. Such lesions would contain both low-risk pathology (P_1) and genetic patterns (G_1). The emergence of intermediate-risk patterns in either histology (P_2) or genetic profile (G_2) would place a lesion into stage 2. Stage 3 would contain lesions with a high-risk genetic or histology pattern. It should be noted that the greatest impact of such a staging system would be on lesions in stage 3. Such lesions would now include cases with a relatively benign phenotype (without or with minimal dysplasia) but a high-risk genotype (e.g. $P_1 + G_3$).

LEUKOPLAKIA (LEUKOKERATOSIS)

Leukoplakia (white patch) is the most common potentially malignant lesion of the oral mucosa. However, its usage should be limited exclusively to the clinical context by the exclusion of other lesions, which present as oral white plaques. Such lesions are lichen planus (hypertrophic), chronic cheek-bite (morsicatio), frictional keratosis, tobacco-induced keratosis (nicotine stomatitis), leukoedema and white sponge nevus. When a biopsy is taken, the term leukoplakia should be replaced by the diagnosis obtained histologically. In other words, leukoplakia denotes a negative diagnosis based on exclusion criteria. It represents an area localized in distribution, hyperkeratotic in nature and white in appearance due to wetting of the keratotic patch while in contact with saliva. It should be stressed that the diagnosis of leukoplakia denotes mainly, that

- The mucosa is irritated by either mechanical, chemical or galvanic means, and
- The mucosa is trying to adapt to the noxious stimuli by undergoing hyperkeratinization of its surface (good example of tissue adaptation—see earlier paragraphs).

Since leukoplakia is an adaptive response, offered by a viable and healthy oral mucosa against some forms of sustained, low-grade irritant, it is irrational to consider it as a disease entity (hence its assumption of a negative diagnostic state).

Definition and Terminology

Oral leukoplakia has recently been redefined as "a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakia will transform into cancer" (Axell T, 1996). A provisional diagnosis is made when a lesion at clinical examination cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance. A definitive diagnosis is made when it is histopathologically examined. The term preleukoplakia is sometimes used when the whiteness is not very distinct and should not be confused with leukoedema (a hereditary malformation of the oral mucosa).

Definable White Lesions. Examples include:

- ***Hyperplastic candidiasis (candidal leukoplakia).*** When dealing with a hyperplastic epithelial lesion in which the presence of *Candida albicans* is demonstrated, it is referred to as candida-associated leukoplakia or others prefer the term hyperplastic candidiasis. In the absence of clinical response to antifungal treatment, it seems preferable to consider such lesion as leukoplakia (van der Waal, 1997).

- ***Hairy leukoplakia (Greenspan lesion).*** The term 'hairy leukoplakia' is a misnomer due to several reasons. First of all, hairy leukoplakia is a definable lesion. Furthermore, the lesion is not premalignant in nature. Therefore, the use of the term should be abandoned. As an alternative, the term 'Greenspan lesion' has been suggested.
- ***Tobacco-induced white lesions.*** Smoker's palate (leukokeratosis nicotina palati), palatal keratosis in reverse smokers and snuff dippers lesions are clearly related to tobacco use and, therefore, are usually listed as 'tobacco-induced lesions'. These lesions are being regarded as 'definable lesions' and are traditionally not described as leukoplakia. Nevertheless, some of these lesions may transform into cancer.
- ***Tobacco-associated leukoplakia.*** The etiological role of tobacco in patients who smoke cigarettes, cigars or pipes is less obvious. Therefore, preference has been given to the term 'tobacco-associated leukoplakia' (leukoplakia in smokers) over the term 'tobacco-induced white lesions'.
- ***Idiopathic leukoplakia.*** One also recognizes nontobacco-associated leukoplakia (leukoplakia in nonsmokers), often referred to as idiopathic leukoplakia.

Premalignant/Potentially Malignant Lesion. In two studies from India (Gupta PC et al, 1980, Silverman S et al, 1976), rather low annual malignant transformation rates of oral leukoplakia have been reported, 0.3% and 0.06%, respectively. In reports from western countries, usually based on hospital material, somewhat higher figures have been mentioned (Axell T, 1987). One must take the following into account, when studying percentages of malignant transformation rates of oral leukoplakia:

- The length of observation period
- The type of study population
- The therapeutic approach.

On the basis of the lowest reported annual malignant transformation rate of oral leukoplakia, it can be calculated that patients with oral leukoplakia carry a five fold higher risk of developing oral cancer than controls. Recently the role(s) of dietary factors in determining the precancerous nature of oral leukoplakia among tobacco habitues revealed interesting results (Gupta PC et al, 1998). A population-based case control study in the Bhavnagar district, Gujarat, India estimated nutrient intake in blinded, house-to-house interviews. Among 5,018 male tobacco users, 318 were diagnosed as cases. An equal number of controls matched on age (± 5 years), gender, village, and use of tobacco were selected. Odd ratio (OR), a measure of the relative risk of malignant transformation of individual lesions were calculated from multiple logistic regression analysis controlling for relevant variables (type of tobacco use and economic status), a protective effect of fiber was observed for both oral submucous fibrosis (OSF) and leukoplakia; with 10% reduction in risk per gm day ($p<0.05$). Ascorbic acid (vitamin C) appeared to be protective against leukoplakia with the halving of associated risk of malignant transformation (OR=0.46; $p<0.10$). It is apparent that in addition to tobacco use, intake of specific nutrients and their deficiency may have a role in the development and progression of oral precancerous lesions.

Epidemiology. The *prevalence* of this lesion in Ernakulam district (Kerala, India) was 17 per 1,000; it was highest (61 per 1,000) among people with mixed habits. The annual age adjusted incidence rate was 2.1 per 1,000 among men and 1.3 per 1,000 among women; the highest incidence (6.0 per 1,000) was among men who both chewed and smoked. In an adult Swedish population a 3.6% prevalence rate was recorded (Axell T, 1976). Almost all leukoplakia in India occur in tobacco users. A definite dose-response relationship between leukoplakia and various forms of tobacco use in this area has been demonstrated. The dose-response relationship was stronger for the smoking habit than for the chewing habit and remained significant after taking account of age, gender and type of tobacco habit.

Age and Gender. The onset of leukoplakia usually takes place after the age of 30 years; resulting in a peak incidence above the age of 50 years. The gender distribution in most studies varies, ranging from a strong male predominance in different parts in India, to almost 1 : 1 in the western world.

Etiology. Leukoplakia occurs more frequently in smokers of tobacco than in nonsmokers. There is a dose-response relationship between tobacco usage and the prevalence of oral leukoplakia. Reducing or cessation of tobacco use may result in the regression or disappearance of oral leukoplakia (Gupta et al, 1995). On the other hand, disappearance of oral leukoplakia has occasionally been reported in patients who continued to smoke (Silverman and Rozen, 1968). Tobacco was most often chewed as an ingredient in betel quid (smokeless tobacco or *paan*) in India. The *paan*-chewers' lesion consists of a thick, brownish-black encrustation on the buccal mucosa at the site of the placement of betel quid. It is often seen in heavily addicted betel quid chewers. It could be scraped off with a piece of gauze (leukoplakia); it regresses spontaneously when the habit is discontinued. Due to these reasons the *paan*-chewer's lesion does not deserve the designation of leukoplakia. This is a specific entity and rarely progresses to leukoplakia. Whether the use of alcohol by itself is an independent etiological factor in the development of oral leukoplakia, is still questionable. Its effect, at best, may be synergistic to other well-known etiological factors (physical irritants). The role of *Candida albicans* as a possible etiological factor in leukoplakia and its possible role in malignant transformation is still unclear. About 10% of oral leukoplakias satisfy the clinical and histological criteria for chronic hyperplastic candidiasis (candidal leukoplakia). Epithelial dysplasia is reported to occur four to five times more frequently in *Candida leukoplakia* than in leukoplakia in general. However, this change is more common in the speckled variant than in homogeneous leukoplakia and carcinomatous change is more a characteristic of the speckled lesion than that of candidal superinfection. Various kinds of evidence has been presented to justify an etiologic role for candida in neoplastic transformation, which includes, among others, the catalytic transformation *in vitro* of the carcinogenic

Table 2-2: Forms of leukoplakia

1. Homogeneous	Lesions that are uniformly white
2. Nonhomogeneous	Lesions in which part of the lesion is white and rest appears reddened
Alternatively, a more elaborate subdivision may be used such as:	
1. Homogeneous	(a) Smooth (b) Furrowed (fissured) (c) Ulcerated
2. Nonhomogeneous nodulospeckled: Well demarcated raised white areas, interspersed with reddened areas	
When recording leukoplakia, space has been allowed in the recording form for three different subdivisions	
1. Homogeneous	Smooth and fissured
2. Homogeneous	Ulcerated
3. Nonhomogeneous	Nodulospeckled

Adapted from Comm Denti and Oral Epidemiol 1980; 8: 1–26.

nitrosamine, N-nitrosobenzyl-methylamine, by strains of *C. albicans* demonstrated to be selectively associated with leukoplakia. The possible contributory role of viral agents (human papilloma virus strains 16, 18) in the pathogenesis of oral leukoplakia has also been discussed, particularly with regard to exophytic verrucous leukoplakia (Palefsky JM et al, 1995). In a study from India, serum levels of vitamin A, B_{12}, C, beta-carotene and folic acid were significantly decreased in patients with oral leukoplakia compared to controls, whereas, serum vitamin E was not (Ramaswamy G et al, 1996). Relatively little is yet known with regard to possible genetic factors in the development of oral leukoplakia.

Clinical Aspects. Preleukoplakia is defined as a low-grade or very mild reaction of the oral mucosa, appearing as a gray or grayish-white, but never completely white area with a slightly lobular pattern and with indistinct borders blending into the adjacent normal mucosa (Pindborg et al, 1968).

Clinical Classification. It is desirable to record, separately the various forms of leukoplakia and for this purpose subdivisions are recommended (WHO, 1980) (Table 2-2).

The adjective 'nonhomogeneous' is applicable both to the aspect of color, i.e. mixture of white and red changes (erythroleukoplakia) and to the aspect of texture, i.e. exophytic, papillary or verrucous. With regard to the latter lesions, no reproducible clinical criteria can be provided to distinguish (proliferative) verrucous leukoplakia from the clinical aspect of verrucous hyperplasia or verrucous carcinoma. The homogeneous type is usually otherwise asymptomatic, whereas the nonhomogeneous (mixed white and red) leukoplakia are often associated with mild complaints of localized pain or discomfort. In the presence of redness or palpable induration, malignancy may already be present (Fig. 2-7).

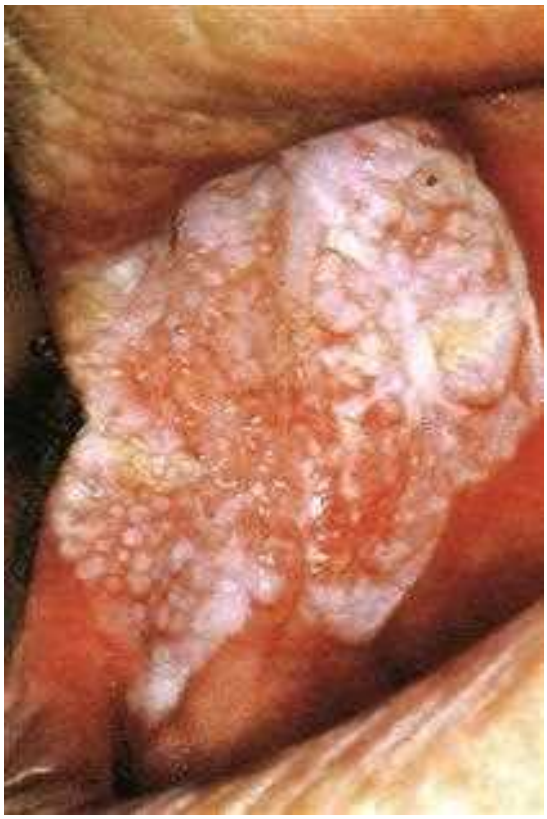


Figure 2-7. Speckled leukoplakia.
This mixed white and red lesion of the buccal mucosa showed moderate epithelial dysplasia *(Courtesy of Dr Crispian Scully)*.

Proliferative Verrucous Leukoplakia and its Related Lesions

Proliferative verrucous leukoplakia (PVL) and verrucous hyperplasia (VH) are two related oral mucosal lesions. The terms; however, are not clinically or pathologically interchangeable. The term PVL is preferably a clinical one, but the diagnosis of VH, on the other hand, must be made histologically.

PVL. First described by Hansen et al, in 1985, PVL continues to be recognized as a particularly aggressive form of oral idiopathic leukoplakia that has a considerable morbidity and a strong potential for malignant transformation. Diagnosis is often made late in the protracted course of PVL with the disease in an advanced stage when it is especially refractory to treatment. The histologic spectrum that is seen in PVL are:

- Verrucous hyperplasia (VH), a histologically defined lesion
- Varying degrees of dysplasia
- Three forms of squamous cell carcinoma: verrucous, conventional and according to some, papillary squamous cell carcinoma.

VH. This is a forerunner of verrucous carcinoma and the transition is so consistent that the hyperplasia, once diagnosed, should be treated like verrucous carcinoma.

Histopathological Aspects. It should be emphasized that leukoplakia is a clinical term, and its use carries no implications with regard to the histological findings. However, it is recommended that a histological report should always include a statement on the presence or

Table 2-3: Histopathological features of epithelial dysplasia

1.	Loss of polarity of the basal cells
2.	Presence of more than one layer of cells having a basaloid appearance
3.	Increased nuclear cytoplasmic ratio
4.	Drop-shaped rete processes
5.	Irregular epithelial stratification
6.	Increased number of mitotic figures (a few abnormal mitoses may be present)
7.	Presence of mitotic figures in the superficial half of the epithelium
8.	Cellular pleomorphism
9.	Nuclear hyperchromatism
10.	Enlarged nucleoli
11.	Reduction of cellular cohesion
12.	Keratinization of single cells or cell groups in the prickle layer

Adapted from Krammer et al., 1978.

absence of epithelial dysplasia, and if present, the assessment of its severity. The hallmarks of the histopathological aspects of leukoplakia are epithelial hyperplasia and surface hyperkeratosis. Epithelial dysplasia, if present, may range from mild to severe. In some instances, carcinoma *in situ* and even squamous cell carcinoma are encountered histologically. The various cellular changes that may occur in epithelial dysplasia are listed in Table 2-3. The clinical significance of human papilloma virus-associated epithelial dysplasia, so-called 'koilocytic dysplasia' remains to be investigated. The term 'lichenoid dysplasia' is sometimes used when the dysplastic epithelium may show features that, to some extent, resemble those of lichen planus. The term 'chevron' type of keratinization is used when it is associated with use of tobacco. Microabscesses may be observed in the superficial layers of the epithelium in the presence of *C. albicans* and inflammatory cell infiltration is commonly seen. Some of the exophytic, verrucous or papillomatous lesions, in spite of the absence of epithelial dysplasia, may in time progress to squamous cell carcinoma and that long-term follow-up should be considered. The final diagnosis of a white lesion of the oral mucosa can often only be made through a close dialogue between the clinician and the pathologist. Even then, cases may remain unsettled.

Grading of Epithelial Dysplasia. Epithelial dysplasia is usually assessed subjectively and considerable interobserver variability exists in its interpretation. Principally, what is lacking in this exercise is objectivity and lack of reproducibility. A consensus decision is, by and large, adopted in the management of individual lesions and based on the presence of dysplastic features, epithelial dyplasia is usually divided into three categories: mild, moderate and severe. It is recommended that the histological report of a leukoplakia should include a statement on the absence or presence of epithelial dysplasia and an assessment of its severity. The practical value of the grading of epithelial dysplasia is questionable. Although leukoplakia with moderate or severe epithelial dysplasia shows a greater disposition for malignant transformation than in the absence of dysplastic features, carcinomatous transformation may also take place in non-dysplastic leukoplakias.

Modified Classification and Staging System for Oral Leukoplakia

A proposal for a modified classification and staging system for oral leukoplakia (OLEP) has been presented by Van der Waal et al, 2000 in which the size of the leukoplakia and the presence or absence of epithelial dysplasia are taken into account. Altogether four stages are recognized:

L1 — Size of leukoplakia <2 cm
L2 — Size of leukoplakia 2–4 cm
L3 — Size of leukoplakia >4 cm
Lx — Size not specified
P — Pathology
P0 — No epithelial dysplasia
P1 — Distinct epithelial dysplasia
Px — Dysplasia not specified in the pathology report.

OLEP Staging System

Stage I — L1 P0
State II — L2 P0
Stage III — L3 P0 or L1 L2 P1
Stage IV — L3 P1

The proposed system should facilitate uniform reporting of treatment or management results of OLEPs in which a biopsy has become available. The system can easily be adjusted by replacing the histopathological criteria of epithelial dysplasia by a clinical subdivision in homogeneous and nonhomogeneous leukoplakia for cases in which no biopsy is available. It also could serve as a means for epidemiological studies. It has yet to be shown whether such a staging system may also be helpful in providing guidelines for the management of oral leukoplakias.

Diagnostic Procedures

Elimination of Possible Cause(s). The clinician should first try to rule out any of the definable white lesions before accepting a definitive clinical diagnosis of leukoplakia.

Biopsy. In homogeneous leukoplakia, the value of histological examination might, to some extent, be questioned. The occurrence of epithelial dysplasia is rather low in this clinical subtype, as is the risk of future malignant transformation. However, this cannot be taken as the dictum in all cases since at least in few cases it proves to be otherwise. Therefore, the taking of a biopsy in homogeneous leukoplakia should be the standard rule. If treatment consists of CO_2-laser evaporation, it is mandatory to have a biopsy taken prior to such treatment. In nonhomogeneous leukoplakia, biopsy should be taken at the site of symptoms, if present, and/or at a site of redness or induration. Diagnostic methods other than histological examination, such as the use of toluidine blue staining or Lugol's iodine and exfoliative cytology are of limited value when dealing with leukoplakia.

Treatment Modalities. Apart from the surgical excision, various treatment modalities are available, such as cryosurgery, CO_2- laser surgery, retinoids and other drugs, and recently, photodynamic therapy. The last is a rather recent application with regard to oral leukoplakia, therefore does not deserve comment on long-term results.

Possible Solutions. This overview demonstrates that tobacco smoking and betel quid chewing are detrimental to oral health, as they are strongly associated with oral leukoplakia, oral cancer and other mucosal pathologies. In view of these findings, specific studies for primary and secondary prevention of these lesions are warranted. Prevention was found to be feasible and effective (Gupta et al, 1980) by timely diagnosis and management of oral precancerous lesions like leukoplakia and by measures like habit alleviation. Effort in this direction will take us a long way into the overall control and management of potentially malignant oral mucosal lesions.

Leukoedema

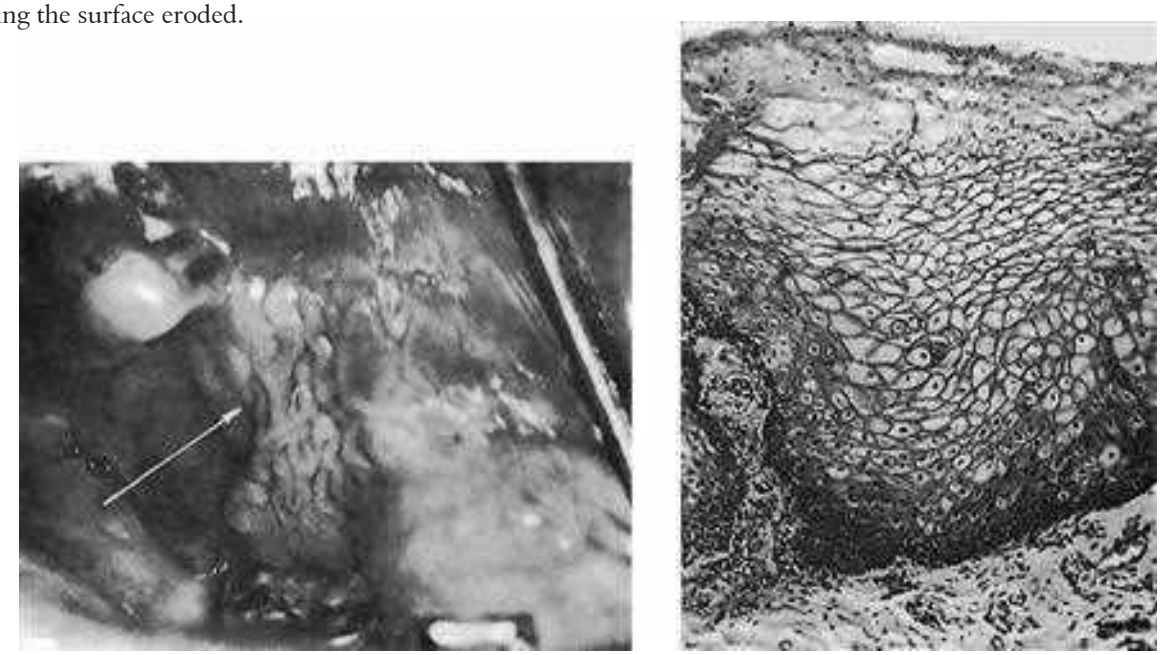
Leukoedema is an abnormality of the buccal mucosa which clinically resembles early leukoplakia, but appears to differ from it in certain respects.

Clinical Features. The gross appearance of leukoedema varies from a filmy opalescence of the mucosa in the early stages to a more definite grayish-white cast with a coarsely wrinkled surface in the later stages (Fig. 2-8A). Lesions occur bilaterally in the majority of cases and frequently involve most of the buccal mucosa, extending onto the oral surface of the lips. Leukoedema is most noticeable along the occlusal line in the bicuspid and molar region. In some cases, desquamation occurs, leaving the surface eroded.

Etiology. The etiology of leukoedema is unknown. An extensive study of this condition was carried out in the United States by Sandstead and Lowe, who found no apparent correlation between the incidence of the condition and the use of tobacco, the pH of the saliva, oral bacterial infection, syphilis or galvanic irritation. In their study, the incidence of leukoedema was approximately 45% in Caucasian men and 40% in Caucasian women, while it was 94% in Negro men and 86% in Negro women, all adults with an average age of 45 years.

It has now been identified in many countries around the world with a remarkable variation in prevalence that suggests some ethnic association. The different reported epidemiological studies have been reviewed by Axell and Henricsson, who also noted an incidence of occurrence of nearly 50% in a survey of over 20,000 persons aged 15 years and above in Sweden. Their data suggested that tobacco smoking was closely correlated with the occurrence of the leukoedema, although studies from India, where tobacco use is extremely prevalent, have shown a very low incidence of leukoedema.

Histologic Features. The microscopic features of leukoedema consist of an increase in thickness of the epithelium, intracellular edema of the spinous or malphigian layer, a superficial parakeratotic layer of several cells in thickness, and broad rete pegs which appear irregularly elongated (Fig. 2-8B). The characteristic edematous cells appear extremely large and pale, and they present a reticular pattern. The cytoplasm appears lost, and the nuclei appear absent, clear or pyknotic. Inflammatory cell infiltration of the subjacent connective tissue is not a common finding.



A B

Figure 2-8. Leukoedema.
The opaque appearance of the buccal mucosa **(A)** is somewhat different from that in leukoplakia. The photomicrograph **(B)** shows only acanthosis with intracellular edema of the spinous cells.

In a review and discussion of leukoedema, Archard and his coworkers have concluded that the clinical appearance of the lesion is due to a retained superficial layer of parakeratotic cells.

Clinical Significance. It has been suggested that leukoedema may represent a lesion of the oral mucosa in which leukoplakia is more apt to develop than in normal epithelium. This conclusion is based upon the fact that nearly all patients examined who manifested leukoplakia also exhibited leukoedema in the adjacent mucosa. However, Archard and his coworkers have concluded, on the basis of their studies, that there is no evidence to support this contention. Furthermore, they concluded that there is no evidence that this lesion is premalignant or in any way associated with potential malignant alteration.

Since leukoedema appears to be simply a variant of normal mucosa, no treatment is necessary.

Intraepithelial Carcinoma
(Carcinoma in situ)

Intraepithelial carcinoma is a condition which arises frequently on the skin, but occurs also on mucous membranes including those of the oral cavity. Some authorities believe that this disease represents a precancerous dyskeratotic process, but others say that it is a laterally spreading, intraepithelial type of superficial epithelioma or carcinoma. As Chandler Smith has expressed in a discussion on the concept of the term carcinoma *in situ*, it "does not reveal whether the lesion is a cancer now but has not yet become invasive, or whether it is not a cancer now but will become a cancer at some later time". Nevertheless, in this stage, it does not exhibit invasive malignant properties. Since metastasis cannot occur without infiltration of tumor cells into connective tissue and consequent accessibility to lymphatic or blood vessels, metastasis is impossible in intraepithelial carcinoma.

Bowen's disease is a special form of intraepithelial carcinoma occurring with some frequency on the skin, particularly in patients who have had arsenic therapy, and is often associated with the development of internal or extracutaneous cancer. On rare occasions, as reported by Gorlin, Bowen's disease may occur in the oral cavity.

Clinical Features. In a study of 82 lesions of carcinoma *in situ* in 77 patients reported by Shafer, he found that the clinical appearance was that of a leukoplakia in 45% of the lesions, an erythroplakia in 16% of the lesions, a combination of leukoplakia and erythroplakia in 9%, an ulcerated lesion in 13%, a white and ulcerated lesion in 5%, a red and ulcerated lesion in 1% and not stated in 11%.

These lesions have been reported to occur at all intraoral sites but the most common in the study of Shafer were floor of mouth (23%), tongue (22%) and lips in males (20%). This distribution is roughly comparable to that found in a series of 158 lesions of asymptomatic early oral epidermoid carcinoma reported by Mashberg and his associates. They appear to be somewhat more common in men than in women (1.8 : 1) and tend to occur principally in elderly persons.

Histologic Features. Intraepithelial carcinoma is characterized by a remarkable range of variation in histologic appearance. Keratin may or may not be found on the surface of the lesion but, if present, is more apt to be parakeratin rather than orthokeratin. Individual cell keratinization and epithelial or keratin pearl formation are exceedingly rare. In fact, these appear to be a hallmark of transformation of carcinoma *in situ* into invasive carcinoma, so that if these are found, a further search should be made for carcinomatous invasion. In some instances, there appears to be hyperplasia of the altered epithelium, while in others there is atrophy.

Certain cytologic alterations may also occur. An increased nuclear/cytoplasmic ratio and nuclear hyperchromatism are sometimes seen, but many cases do not show these. Cellular pleomorphism is quite uncommon. One of the most conspicuous and consistent alterations is loss of orientation of cells and loss of their normal polarity. Mitotic activity is extremely variable and of little significance unless overwhelming (Fig. 2-9).

It has also been found that sometimes a sharp line of division between normal and altered epithelium extends from the surface down to the connective tissue rather than a blending of epithelial changes. It is also not unusual to find multiple areas of carcinoma *in situ* interspersed by essentially normal appearing epithelium, producing multifocal carcinoma *in situ*.

All of the above changes occur within the surface epithelium, which remains confined by the basement membrane.

Treatment and Prognosis. There is no uniformly accepted treatment for intraepithelial carcinoma. The lesions have been surgically excised, irradiated, cauterized and even exposed to solid carbon dioxide. If the condition is left untreated, carcinomatous invasion is thought to occur eventually. Spontaneous regression of carcinoma *in situ* without treatment is known to occur in certain sites, chiefly the uterine cervix, in a significant percentage of cases. However, it is doubtful that this happens in the oral cavity; although progression into invasive carcinoma may take years in some instances, in others it apparently develops within months.

Erythroplakia
(Erythroplasia of Queyrat)

Whilst leukoplakia is a relatively common condition, erythroplakia is rare. In contrast to leukoplakia, erythroplakia is almost always associated with premalignant changes histologically and is, therefore, the most important precancerous lesion. The term 'erythroplakia' is used analogously to leukoplakia to designate lesions of the oral mucosa that present as bright red velvety plaques which cannot be characterized clinically or pathologically as due to any other condition. Just as there are many oral lesions that present clinically as white patches on the mucosa, so there are a number of conditions that appear as red areas. These include some dermatoses, inflammatory conditions due to local infection, or a more general subacute

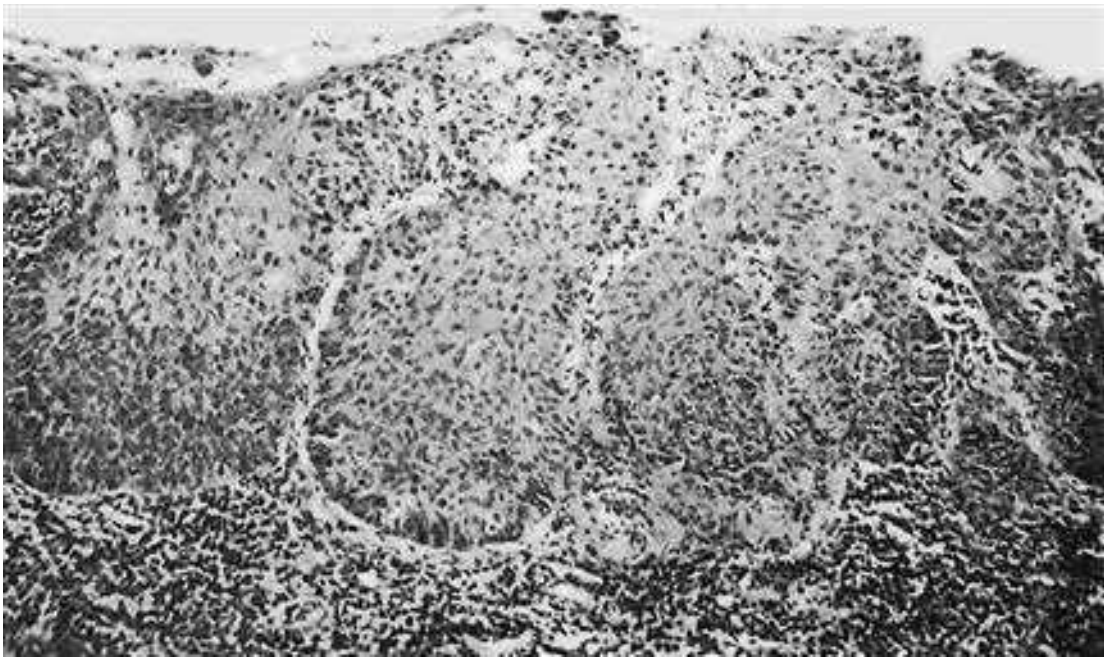


Figure 2-9. Intraepithelial carcinoma or carcinoma in situ.
The epithelial cells exhibit all the features of malignant cells, but invasion of the connective tissue has not begun.

or chronic stomatitis associated with the presence of dentures, tuberculosis, fungus infection and other conditions. Some red plaques prove to be early squamous cell carcinomas. The red patches that cannot be classified in any of these classes fall into the group of erythroplakia (a negative diagnosis— refer leukoplakia). The term 'erythroplasia' was originally used by Queyrat to describe a precancerous red lesion that develops on the penis. Oral erythroplakia is clinically and histopathologically similar to the genital process. Whereas red lesions of the oral mucosa have been noted for many years, the use of the term **erythroplakia** in this context was rare. Erythroplakia lesions are easily overlooked and the true prevalence of the condition is not known. This blatant underreporting probably reflects the fact that leukoplakias are more likely to be biopsied and emphasizes the lack of appreciation of the significance of erythroplakia clinically. Several clinical variants of erythroplakia have been described by different investigators, but there is no general agreement on classification. Shear, in 1972, described "homogeneous erythroplakia, erythroplakia interspersed with patches of leukoplakia, and granular or speckled erythroplakia" (the last category identical to speckled leukoplakia). The suggestion has also been made to change the term **speckled leukoplakia** to **speckled erythroplakia**, to emphasize the frequency with which this particular lesion is associated with cellular atypia. Many of these lesions are irregular in outline, and some contain islands of normal mucosa within areas of erythroplakia, a phenomenon that has been attributed to coalescence of a number of precancerous foci. The high rate of premalignant and malignant changes noticed in erythroplakia is true for all clinical varieties of this lesion and not solely a feature of speckled erythroplakia. Different studies have demonstrated that 80–90% of erythroplakias are histopathologically either severe epithelial dysplasia, carcinoma *in situ*, or invasive carcinoma. Erythroplakia has no apparent sex predilection; most cases reported have occurred in the sixth and seventh decades. The etiology of erythoplakia is unknown, although it seems likely that smoking and alcohol abuse are important etiological factors.

Histopathologic Features. The epithelium shows lack of keratin production and is often atrophic, but it may be hyperplastic. This lack of keratinization, especially when combined with epithelial thinness, allows the underlying microvasculature to show through, thereby causing the red color. The underlying connective tissue often demonstrates chronic inflammation. Differentiation of erythroplakia with malignant change and other early squamous cell carcinomas from benign inflammatory lesions of the oral mucosa can be enhanced by use of 1% toluidine blue (tolonium chloride) solution applied topically with a swab or as an oral rinse. This technique gives excellent results in detecting epithelial dysplasia with false-negative (underdiagnosis) and false positive (overdiagnosis) rates of well below 10%.

Treatment. It should follow the same principles outlined for leukoplakia. Observation for one to two weeks following elimination of suspected irritants is acceptable. Prompt biopsy is thereafter mandatory for lesions that persist. Surgical excision gives excellent results and a recurrence rate of less than 5% is reported.

Leukokeratosis Nicotina Palati

This lesion commonly seen among conventional smokers, consists of a grayish-white palate with small nodular excrescences having small central red spots corresponding to the inflamed orifices of the minor salivary glands (Murti et al, 1992).

Epidemiology. The prevalence of this lesion among Indians was 0.3%; 52% of the 31 lesions occurred among *bidi* smokers (Mehta FS et al, 1971). The annual age adjusted incidence rate among smokers was 1.7 per 1,000; 0.7 per 1,000 in those who smoked and chewed (Gupta PC et al, 1980).

Natural History. Over a longer period 66% of the 44 lesions remained stationary, 34% regressed spontaneously and none showed malignant transformation. Palatal changes in reverse smokers (smoke with the burning end of a cigar/cigarette within the oral cavity), on the other hand, must be distinguished from this lesion and are multimorphic and precancerous, whereas leukokeratosis nicotina palati exhibits neither great variability nor malignant transformation (Table 2-4).

Palatal Changes Associated with Reverse Smoking

Reverse *chutta* (crude form of cigar) smoking practiced especially among females of Srikakulam district of Andhra Pradesh, recorded a prevalence of 8.8% of leukoplakia, 4.6% preleukoplakia and 17.9% leukokeratosis nicotina palati (Daftary et al, 1992). Palatal involvement was noted in 422 (85%) of the 497 leukoplakia cases and in 168 (57%) of the 296 preleukoplakias, and of course in all of the cases of leukokeratosis nicotina palati. Palatal changes associated with reverse smoking thus exhibited a spectrum of clinical changes, and it was not satisfactory to group them under leukoplakia, preleukoplakia or leukokeratosis nicotina palati. Accordingly, a new classification for palatal changes encompassing the entire spectrum of clinical components was proposed by Mehta FS et al, 1977.

Epidemiology. The annual age-adjusted incidence rates of palatal changes (encompassing all components) was 24.9 per 1,000 among men and 39.6 per 1,000 among women and the peak incidence was in the 55–64 year age group (Srikakulam data).

Clinical Aspect. Palatal changes comprise several components:

- ***Keratosis***—diffuse whitening of the entire palatal mucosa
- ***Excrescences***—1–3 mm elevated nodules, often with central red spots
- ***Patches***—well defined, elevated white plaques
- ***Red areas***—well defined reddening of the palatal mucosa
- ***Ulcerated areas***—crater-like areas covered by fibrin
- ***Nonpigmented areas***—areas of palatal mucosa that are devoid of pigmentation.

Histological Features. Hyperorthokeratosis, epithelial dysplasia and inflammatory cells in the connective tissue were observed in 87%, 23% and 55% of the biopsies collected from Srikakulam district (Daftary et al, 1992). Melanin deposits were noted in the lamina propria of most of them. The epithelium was atrophic in 60% of biopsies from red areas. Epithelial dysplasia was observed in 52% of red areas, 25% of excrescences, 20% of ulcerations, 10% of patches and in 19% of nonpigmented areas.

Natural History. In a six-year follow-up study, palatal changes remained stationary in 75% of individuals; regressed in 14% and were variable in 11%, i.e. they regressed, recurred and regressed again (Gupta PC et al, 1980). The regression rates were higher when the habit was discontinued or reduced substantially. Malignant transformation was observed for 0.3% of the palatal lesions. In a 10-year intervention study in the same area, the malignant potential of various components of palatal changes was evaluated: red areas and patches were found to exhibit a high potential for malignant transformation.

Palatal Erythema

This lesion is marked by a diffused erythematous hard palate, occasionally extending to the soft palate.

Epidemiology. Of the 69 lesions observed among 7,216 tobacco users, 87% occurred among smokers, especially *bidi* smokers.

Clinical Aspects. This lesion occurs either independently or sometimes with other lesions. About 10% of the lesions were associated with palatal papillary hyperplasia and 25% with central papillary atrophy of the tongue and bilateral commissural leukoplakias. This triad of lesions is comparable to the **multifocal candidiasis** described in western literature.

Natural History. The highest percentage of persistent lesions (60%) was seen among people who did not give up their smoking habits, while the highest percentage (75%) of regressed lesions occurred among those who discontinued or reduced smoking substantially. These observations clearly indicate that palatal erythema is caused by smoking, particularly *bidi* smoking. None of the lesions progressed to cancer.

Table 2-4: Classification of oral mucosal lesions

Based on different habits the lesions can be grouped broadly as shown:
Predominantly associated with smoking
Leukoedema
Leukokeratosis nicotina palati
Palatal erythema
Central papillary atrophy of tongue
Predominantly associated with chewing
Paan chewer's lesion
Oral lichen planus-like lesion
Oral submucous fibrosis
Associated with smoking and chewing (mixed habit)
Leukoplakia and preleukoplakia
Oral lichen planus
Oral squamous carcinoma

Central Papillary Atrophy of the Tongue

This lesion has also been described in the literature as median rhomboid glossitis and localized atrophy of the tongue papillae. It consists of a well-defined, oval, pink area in the center of the dorsum of the tongue devoid of lingual papillae.

Epidemiology. The prevalence of this lesion in the general population was 1%; it was present among 2.2% *bidi* smokers, 1.6% cigarette smokers and 0.3% of nonsmokers of tobacco. In a 10-year follow-up study from India, the annual age-adjusted incidence rate among smokers was 1.5 per 1000 as compared to 0.8 per 1,000 among nonsmokers.

Etiology. It is considered to be due to candidal infection, smoking or both (bidi smoking). Interestingly, very few women had this lesion due perhaps to the rarity of smoking among women.

Histologic Features. This lesion was marked by the absence of tongue papillae, the presence of slight parakeratinization of the epithelial surface, long slender rete ridges and occasional pseudoepitheliomatous hyperplasia. Chronic inflammatory cell infiltrate, chiefly of lymphocytes, was usually present within the epithelium and in the lamina propria. Candidal hyphae were observed in the superficial layers of epithelium in the majority of cases.

Natural History. The highest percentage of regressed lesions (87%) was seen in those who stopped their habits. None of the lesions progressed to cancer.

Lesions Associated with Betel Quid Chewing
(Paan-chewer's lesion)

This lesion consists of a thick brownish black encrustation on the buccal mucosa at the site of placement of the buccal quid (Fig. 2-10). It is often seen among heavily addicted betel quid chewers. It could be scrapped off with a piece of gauze; it regresses spontaneously; more frequently when the habit is discontinued.

Epidemiology. The annual age-adjusted incidence rate of this lesion was 28 per 1,000 among male chewers and 17.4 per 1,000 among female chewers (Gupta PC et al, 1980).

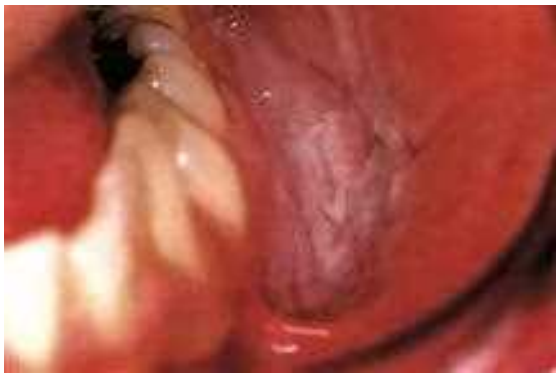


Figure 2-10. Tobacco pouch keratosis.
A white, wrinkled change of the mucosa in the mandibular buccal vestibule secondary to the use of chewing tobacco *(Courtesy of Dr Regazi JA, Dr Sciubba JJ and Dr Pogrd MA).*

Histologic Features. These lesions showed pale staining parakeratin-like surface layers of epithelium, containing round nuclear remnants, ballooning and vacuolated cells and epithelial hyperplasia.

Natural History. It is a specific entity and rarely progresses to leukoplakia. Malignant transformation was not observed in these lesions.

Oral Lichen Planus-like Lesion
(Lichenoid reaction)

A characteristic lesion consisting of white, wavy, parallel, nonelevated striae that do not criss-cross (as in lichen planus) is observed in habitual betel quid chewers. Sometimes, these striae radiate from a central erythematous area at the site of placement of the betel quid.

Epidemiology. The prevalence of this lesion among 5,099 individuals in Ernakulam, Kerala was 0.7%. About 89% of the lesions occurred among betel quid chewers and 11% among people with mixed habits. The annual age-adjusted incidence rates among men and women were 0.7 and 2.2 per 1,000 respectively. The peak incidence for women was in the 45–54 year age group. The incidence was zero among smokers and nonusers of tobacco; and 4.3 per 1,000 among women who chewed. This lesion is thus entirely associated with betel quid chewing.

Clinical Aspects. The lesion always occurs on the buccal mucosa and mandibular groove, areas which are in intimate contact with the betel quid.

Histologic Features. The lesion shows parakeratinized, atrophic epithelium, liquefaction degeneration of the basal cell layer and a band-like inflammatory cell infiltrate containing lymphocytes and plasma cells. Unlike lichen planus, this lesion shows hyperparakeratosis, and plasma cells in the juxtaepithelial region.

Natural History. Although the histological features are similar to those of oral lichen planus, in view of its complete association with betel quid chewing, it is regarded as a specific entity. No malignant transformation has been reported.

Oral Submucous Fibrosis

Oral submucous fibrosis (OSF) is a chronic, progressive, scarring disease, that predominantly affects people of South-East Asian origin. This condition was described first by Schwartz (1952) while examining five Indian women from Kenya, to which he ascribed the descriptive term "atrophia idiopathica (tropica) mucosae oris". Later in 1953, Joshi from Bombay (Mumbai) redesignated the condition as oral submucous fibrosis, implying predominantly its histological nature. The WHO definition for an oral precancerous condition—a generalised pathological state of the oral mucosa associated with a significantly increased risk of cancer—accords well with the characteristics of OSF.

Clinical Features. The onset is insidious, over a two to five years.

Prodromal Symptoms (Early OSF). This includes a burning sensation in the mouth when consuming spicy food, appearance of blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa, excessive salivation, defective gustatory sensation and dryness of the mouth. There are periods of exacerbation manifested by the appearance of small vesicles in the cheek and palate. The intervals between such exacerbation vary from three months to one year. Focal vascular dilatations manifest clinically as petechiae in the early stages of the disease. This may be part of a vascular response due to hypersensitivity of the oral mucosa towards some external irritant like arecanut products. Petechiae are observed in about 22% of OSF cases (Rajendran, 1994), mostly on the tongue followed by the labial and buccal mucosa with no sign of blood dyscrasias or systemic disorders. Pain in areas where submucosal fibrotic bands are developing when palpated is a useful clinical test. Histologically, they revealed a slightly hyperplastic epithelium, sometimes atrophic with numerous dilated and blood-filled capillaries juxtaepithelially (Figs. 2-11, 2-12). The inflammatory cells seen are mainly lymphocytes, plasma cells and occasional eosinophils. The presence together of large numbers of lymphocytes and fibroblasts as well as plasma cells in moderate numbers, suggests the importance of a sustained lymphocytic infiltration in the maintenance of the tissue reaction in OSF.

Advanced OSF. As the disease progresses, the oral mucosa becomes blanched and slightly opaque, and white fibrous bands appear. The buccal mucosa and lips may be affected at an early stage, although it was thought that the palate and the faucial pillars are the areas involved first. The oral mucosa is involved symmetrically (with possible exception) and the fibrous bands in the buccal mucosa run in a vertical direction. The density of the fibrous deposit varies from a slight whitish area on the soft palate, causing no symptoms, to a dense fibrosis, causing fixation and shortening or even deviation of the uvula and soft palate. The fibrous tissue in the faucial pillars ranges from a slight submucosal accumulation in both pillars to a dense fibrosis extending deep into the pillars with strangulation of the tonsils. It is this dense fibrosis, involving the tissues around the pterygomandibular raphae, that causes varying degrees of difficulty in mouth opening. A factor which seems to be overlooked by many investigators while recording the extent of mouth opening is the acuteness of oral symptoms (persistent/recurrent glossitis and stomatitis) at the time of recording. Sometimes the fibrosis spreads to the

Figure 2-11. Advanced OSF with difficulty in opening the mouth.
Note the bilateral pouching-in of cheek while opening mouth.

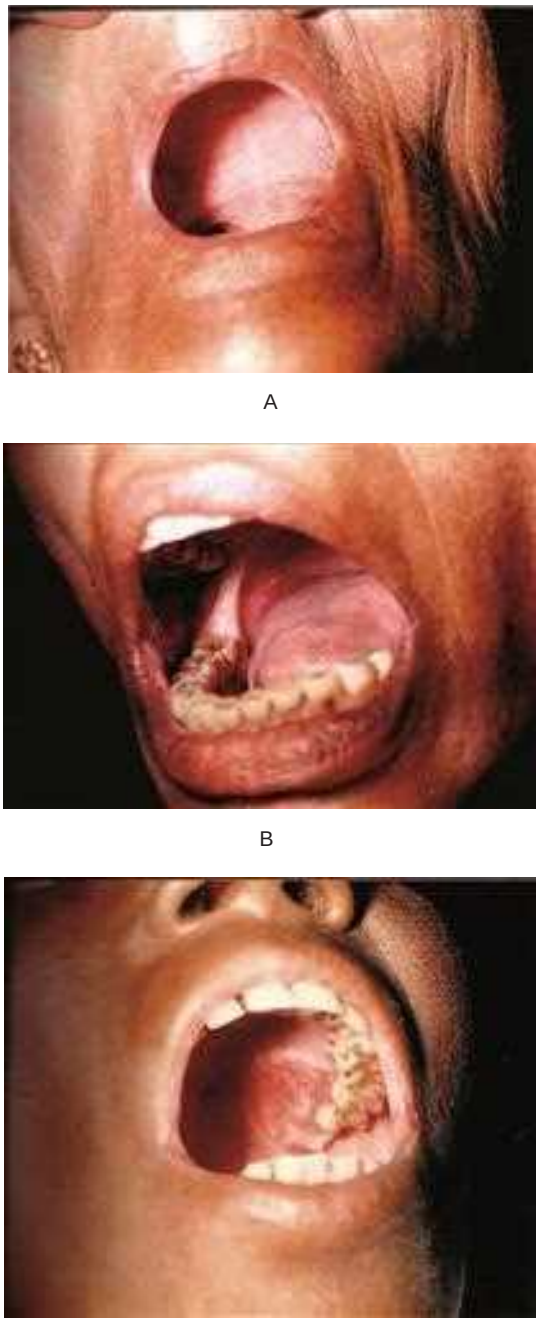


Figure 2-12. Advanced oral submucous fibrosis.
(A) Horizontal fibrosis traversing at the junction of hard and soft palate. **(B)** Involvement of pterygomandibular raphae compounding the difficulty of mouth opening. **(C)** Carcinoma developed on the palate.

pharynx and down to the piriform fossae. Upon palpation, a circular band can be felt around the entire *rima oris* (mouth orifice), and these changes are quite marked in the lower lip. All observers have noted impairment of tongue movement in patients with advanced OSF with significant atrophy of the tongue papillae. With progressing fibrosis, the stiffening of certain areas of the mucosa occurs leading to difficulty in opening the mouth, inability to whistle or blow out a candle and difficulty in swallowing. When the fibrosis involves the nasopharynx, the patient may experience referred pain to the ear and a nasal voice as one of the later signs in some patients.

Epidemiology. Numerous published reports on OSF allow an informed appraisal of its geographic distribution, together with data on the percentage prevalence. An epidemiological assessment of the prevalence of OSF among Indian villagers, based on baseline data, recorded a prevalence of 0.2% (n = 10,071) in Gujarat, 0.4% (n = 10,287) in Kerala, 0.04% (n = 10,169) in Andhra Pradesh, and 0.07% (n = 20,388) in Bihar. The prevalence among 101,761 villagers in the state of Maharashtra (central India) was 0.03%. In a 10-year follow-up study of oral precancer, Gupta et al, in 1980, calculated the incidence rate of OSF in Ernakulam, Kerala: 8 for men and 19 for women per 100,000. Variations in the prevalence figures are common between different studies, probably because of differences in the clinical criteria for diagnosis. While some investigators adhere to the earlier signs and symptoms, others looked for fibrous bands as the diagnostic criterion. According to Pindborg 1989, if only the fibrous band was the criterion for diagnoses, the prevalence rate would have been about 1.6%. Prevalence by gender varies widely in the different published studies. The general female preponderance may be related to factors like oral habits, deficiency states of iron, vitamin B complex among many other conditions prevalent in Indian women.

Etiology. There is compelling evidence to implicate the habitual chewing of arecanut with the development of OSF. It occurs predominantly in the Indian subcontinent where the habit is more prevalent. The frequency of this habit in population affected by OSF ranged from 34–100% (Bhonsle RB et al, 1987). This has been reported to be higher among OSF patients than in the general population. In a study of 100,000 villagers in Maharashtra (India), 4.2% of females who chewed areca nut and did not use tobacco suffered from OSF. Thus chewing areca nut may be an important factor in the etiology of OSF. Previous studies on the pathogenesis of OSF have suggested that the occurrence may be due to:

- Clonal selection of fibroblasts with a high amount of collagen production during the long-term exposure to areca quid ingredients (Meghji S et al, 1987).
- Stimulation of fibroblast proliferation and collagen synthesis by arecanut alkaloids (Harvey W et al, 1986).
- By fibrogenic cytokines secreted by activated macrophages and T lymphocytes in the OSF tissues (Haque MF et al, 2000).
- By decreased secretion of collagenase (Shieh TY et al, 1992).
- Deficiency in collagen phagocytosis by OSF fibroblasts (Tsai CC et al, 1999).
- By production of collagen with a more stable structure (collagen type I trimer) by OSF fibroblasts (Kuo MYP et al, 1995).
- By stabilization of collagen structure by (+) catechin and tannins from the areca nut (Scutt A et al, 1987).
- And by an increase in collagen cross-linkage as caused by upregulation of lysyl oxidase by OSF fibroblasts (Ma RH et al, 1995).

Genetic susceptibility may also be associated with OSF because raised frequencies of HLA-A10, – B7 and – DR3 are found in OSF patients compared to normal subjects. Further HLA-typing done by the use of the polymerase chain reaction (PCR) also demonstrates significantly increased frequencies of HLA-A24, DRB1-11 and DRB3-0202/3 antigens in 21 OSF patients when compared with the English controls (Saeed B et al, 1997).

Pathology

Structural and microstructural changes. The epithelial changes in the different stages of OSF are predominantly hyperplasia (early) and atrophy (advanced), associated with an increased tendency for keratinizing metaplasia. The epithelial atrophy reported by Pindborg et al, (1966) is the marked epithelial change in advanced OSF, which contrasts with the predominantly hyperplastic epithelium (Figs. 2-13, 2-14) of early OSF. Lesions involving the palate showed predominantly orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitotic count in parakeratotic epithelium, which is more common with OSF, and the association with parakeratotic leukoplakia and atrophic epithelial changes predisposes OSF to malignancy.

Subepithelial changes. On the basis of the histopathological appearance of stained (H&E) sections, OSF can be grouped into four clearly definable stages: very early, early, moderately advanced and advanced. These stages are based not only on the amount and nature of the subepithelial collagen, but also on the following criteria taken together:

Figure 2-13. Advanced stage with fibrosis of lamina propria and submucosa: Van Gieson stain.

Figure 2-14. Early oral submucous fibrosis.
Note the sparing of lamina propria from fibrosis: Van Gieson stain.

- Presence or absence of edema
- Physical state of the mucosal collagen
- Overall fibroblastic response (number of cells and age of individual cells)
- State of the blood vessels
- Predominant cell type in the inflammatory exudate.

A vascular response due to inflammation, apart from the connective tissue repair process, has been very commonly found in OSF. Normal, dilated and constricted blood vessels have been seen often in combination, in the same section. The apparent narrowing of the smaller vessels appears first in the upper mucosa and spreads gradually to the larger, deeper vessels. Persistent dilatation has also been seen in many moderately advanced and advanced biopsies. A rise in mast cells occurs in the earlier stages of the tissue reaction but in advanced stages, the counts are fewer in number.

The inflammatory cells seen are mainly lymphocytes and plasma cells. The connective tissue in advanced stages is characterized by the submucosal deposition of extremely dense and avascular collagenous tissues with variable numbers of chronic inflammatory cells. Epithelial dysplasia without carcinoma is found in 10–15% of cases submitted for biopsy and carcinoma is found in at least 5% of sampled cases. The excessive fibrosis in the mucosa seems to be the primary pathology in OSF. The atrophic changes in the epithelium are secondary.

Biological Studies on Individuals and Tissues from OSF

Blood chemistry and hematological variations. Deficiency of vitamin B_{12}, folate and iron can affect the integrity of the oral mucosa. Significant hematological abnormalities have been reported in OSF, including an increased erythrocyte sedimentation rate (ESR), anemia and eosinophilia, increased gammaglobulin, a decrease in serum iron and an increase in total iron binding capacity (TIBC). The percentage saturation of transferrin also decreased and a significant reduction in total serum iron and albumin was found. The role of iron deficiency anemia as the cause or the effect of the disorder is doubtful. A rise in serum mucoproteins, mucopolysaccharides and antistreptolysin titer 'O' (measured in Todd's unit) has also been reported. A significant depression of the lactate dehydrogenase isoenzyme ratio (LDH IV/LDH II) is reported at the tissue level in OSF. A significant alteration in the serum copper and zinc ratio is also reported with a reduction in zinc content.

Chromosomal instability has long been associated with the neoplastic process and the quantitative assay of sister chromatid exchange (SCE) provides an easy, rapid and sensitive method for studying chromosome/DNA instability and its subsequent repair processes. This increase may be attributed to the genotoxic effect of the constituents of betel quid. The role of areca nut alkaloids in this regard may be significant.

AgNOR. Silver-binding nucleolar organizer region proteins (AgNORs) comprise a simple and reproducible cytological test indicative of the proliferative status of cells, particularly of epithelial and hematopoetic origin. It was found that the pooled mean AgNOR count in clinically advanced OSF was higher than in moderately advanced cases. Counting of AgNORs may be useful as a predictor of the biological behavior of OSF.

Immunological studies. Because of a possible immunological connection, the fact that the disease has been reported in subjects who do not practice the betel habit and the inability to prove a dose and effect relationship in all cases, the question arose whether there is a predisposition for the disease. In this respect, the finding by Canniff et al (1981) that the human leukocyte antigens (HLA) A10, B7 and DR3 occurred significantly more frequently in OSF, is important. Later van Wyk et al (1994), investigated the frequency of HLA in areca nut chewers with and without OSF and comparing them to a control comprising people with a similar background (South African Indians) they were unable to detect specific frequencies as was found by Canniff and coworkers. Thus, the problem of a possible predilection remains unanswered. In addition, studies on the relationship between systemic disease and OSF also proved negative.

Cell kinetic studies. Investigations carried out in the UK and South Africa found that the growth of OSF fibroblasts is normal. However, when fibroblasts are exposed to the alkaloids of areca nut their proliferation rate, according to certain workers, increases; a finding in contrast to others' results. The second group found a dose-dependent inhibition of growth by alkaloids (van Wyk et al, 1995). These studies prompt one to propose that the connective tissue changes in OSF are probably not due to increased fibroblast proliferation. On the other hand, OSF fibroblasts can play a role in overproduction of collagen. The UK group (Scutt A et al, 1987) found that collagen formation by fibroblasts increases when exposed to nut extracts and alkaloids, a finding which has been questioned recently by Jeng et al (1996), whose findings were contradictory. Thus it would seem that OSF fibroblasts have the capability to produce collagen in excess, but what triggers it, is controversial. Ma et al (1995) discovered increased lysyl oxidase activity in fibroblasts cultured from OSF patients. Lysyl oxidase, an extracellular metalloenzyme of copper, is secreted by fibroblasts and initiates cross-linking of collagen

which makes it relatively resistant to digestion by mammalian collagenase. Therefore, increased lysyl oxidase activity can result in collagen accumulation. Recently Trivedy et al (1997) demonstrated that the copper content in areca nut is relatively high and that it is released in the mouth with chewing. Other reasons proposed for an excessive accumulation of collagen are decreased collagenase activity in OSF mucosa and reduced phagocytosis by OSF fibroblasts, recently shown by Taiwanese researchers. In both instances, accumulation of collagen is enhanced. Unfortunately, none of these findings give an answer for the persistence of the disease, or for the continuing deposition of excessive collagen after stoppage of the habit. To conclude, the effect of the areca nut on cells is the trigger resulting, initially among others, in excessive accumulation of collagen which is followed by a permanent change possibly in the fibroblast population, characterized by a continued abnormal accumulation of collagen. The mechanism of this permanent change is not known at present.

Management. The reduction or even elimination of the habit of areca nut chewing is an important preventive measure. At least in the early stages of OSF, it could probably slow the progress of the disease. To improve current treatment regimens of OSF, the following strategies have been proposed:

1. ***Nutritional support.*** Mainly for high proteins and calories and for vitamin B complex and other vitamins and minerals.
2. ***Immunomodulatory drugs.*** Local and systemic applications of glucocorticoids and placental extracts are commonly used. These also prevent or suppress inflammatory reaction, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen.
3. ***Physiotherapy.*** This includes measures such as forceful mouth opening and heat therapy. Heat has been commonly used and the results have been described as satisfactory.
4. ***Local drug delivery.*** Local injections of corticosteroids and placental extract have been tried, in addition to hyaluronidase, collagenase and similar substances which break down intercellular cement substances and also decrease collagen formation.
5. ***Combined therapy.*** With peripheral vasodilators (nylidrin hydrochloride), vitamins D, E and 'B' complex, iodine, placental extract, local and systemic corticosteroids and physiotherapy claim a high success rate in OSF management. The evaluation of the merits and disadvantages of individual items in treatment is not possible due to the use of combined treatment protocols; unavoidable at present because of the empirical nature of each approach.
6. ***Surgical management.*** Measures such as forcing the mouth open and cutting the fibrotic bands have resulted in more fibrosis and disability. Submucosal resection of fibrotic bands and replacement with a partial thickness skin or mucosal graft have also been attempted along with procedures such as bilateral temporalis myotomy. At a retrospective glance, surgery seems to be a poor option in the overall management of the disease. Controlled studies of different regimens in the management of OSF are needed. They will not be easy to organize because of the

Interventions for the management of OSF

Objectives. To assess the effectiveness of interventions for the management of pain and restricted jaw opening or movement occurring as a result of oral submucous fibrosis.

Selection Criteria. Randomised controlled trials comparing surgical interventions, systemic or topical medicines or other interventions to manage the symptoms of OSF.

Data Collection and Analysis. Two authors independently assessed trial quality and extracted trial data. Disagreements were resolved by consultation with a third author. Attempts were made to contact study authors where necessary for clarification and for additional information.

Main Results. Two trials, involving 87 participants, evaluated lycopene in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth stretching exercises and heat. Only two of the primary but none of the secondary outcomes of this review were considered in these trials and provided a limited amount of reliable data. The data in one trial were based on inadequately defined evaluations of outcomes, and in the other trial are likely to be skewed due to a substantial number of withdrawals and therefore were not entered into the RevMan analyses. There were no reports of toxicity to the interventions but some side effects, which were mostly gastric irritation to pentoxifylline, were noted.

Authors' Conclusions. The lack of reliable evidence for the effectiveness of any specific interventions for the management of OSF is illustrated by the paucity, and poor methodological quality, of trials retrieved for this review.

The review authors found two studies which evaluated the effectiveness of lycopene, an extract of tomato, in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth exercises and heat. These studies provided a limited amount of reliable data which did not permit any firm conclusions to be made.

Future research should aim to provide evidence for people to make informed decisions about whether these treatments are effective and should also explore treatment plans which include patient education aimed at cessation of the chewing habit.

Source: Fedorowicz Z et al. Interventions for the management of oral submucous fibrosis (Review). The Cochrane Collaboration, John Wiley Sons, 2009.

number of items in current management protocols, but they should greatly increase our understanding of OSF.

MALIGNANT TUMORS OF THE EPITHELIAL TISSUE ORIGIN

Basal Cell Carcinoma

(Basal cell epithelioma, BCC, rodent ulcer)

The most common malignancy in humans, basal cell carcinoma develops most frequently on the exposed surfaces of the skin, the face and the scalp in middle-aged or elderly persons. People with fair complexion who have spent much of their lives out of doors are often victims of this lesion, but it is by no means confined to such persons. It is slow growing and rarely metastasizes, but it can cause significant local destruction and disfigurement if neglected or treated inadequately.

Etiology. Ultraviolet radiation is the most important and common cause of BCC. Shorter wavelength ultraviolet (UV) radiation (290–320 nm, sunburn rays) is believed to play a greater role than the longer wavelength ultraviolet A (UVA) radiation (320–400 nm, tanning rays). Thus chronic sun exposure is important in the development of BCC. A long latency period of 20–50 years is typical between the time of UV damage and clinical onset of BCC. X-ray exposure as well as chemical like arsenic has been associated with basal cell carcinoma development. A modest role has been ascribed to immunosuppression as well.

Syndromes like xeroderma pigmentosum (due to an inability to repair UV-induced DNA damage), and nevoid BCC syndrome are characterized by multiple basal cell carcinomas occurring in early age.

Ultraviolet-induced mutations in the TP53 tumor suppressor gene, which resides on chromosome 17p, have been implicated in some cases of BCC. In addition, data support mutation of a tumor suppressor gene on band 9q22 as causing nevoid BCC syndrome, an autosomal-dominant condition characterized by early and continued appearance of many BCCs.

Basal cell carcinoma is believed to arise from the pluripotential stem cell compartments of the basal layer of epidermis as well as follicular structures (hair follicle stem cells residing just below the sebaceous gland duct).

Clinical Features. Basal cell carcinoma occurs most frequently in persons in the fourth decade of life or later, but it has been reported as occurring in younger persons, even children. The male-to-female ratio is approximately 3:2. It is a disorder of white individuals, especially those with very fair skin. It is rare in individuals with dark skin.

Basal cell carcinoma is most frequently seen in the middle third of the face, but may occur anywhere on the sun-exposed part of skin. It is important to realize that this form of carcinoma does not arise from oral mucosa and thus is never seen in the oral cavity unless it arrives there by invasion and infiltration from a skin surface.

The subtypes of basal cell carcinoma are:

Nodular basal cell carcinoma. This is the most common variety of basal cell carcinoma. It begins as a small, slightly elevated papule with a central depression which ulcerates, heals over and then breaks down again. Very mild trauma may cause bleeding. One or more telangiectatic blood vessels are usually seen coursing over the borders around the central depression. It enlarges, but still evidences periods of attempted healing. Eventually, the crusting ulcer which appears superficial, develops a smooth, rolled border representing tumor cells spreading laterally beneath the skin. Untreated lesions continue to enlarge, infiltrate adjacent and deeper tissues and may even erode deeply into cartilage or bone.

Pigmented basal cell carcinoma. In addition to features seen in lesions of nodular basal cell carcinoma, lesions of pigmented BCC contain increased brown or black pigment and are seen more commonly in individuals with dark skin.

Cystic basal cell carcinoma. These lesions are translucent blue-gray cystic nodules that may mimic benign cystic lesions.

Superficial basal cell carcinoma. This variety presents as scaly patches or papules that are pink to red-brown in color, often with central clearing. A thread like border is common. Erosion is less common than in nodular variety. Superficial BCC is common on the trunk and has little tendency to become invasive. The papules may mimic psoriasis or eczema but are slowly progressive and not prone to fluctuate in appearance. The occurrence of numerous superficial BCCs may indicate arsenic exposure.

Micronodular basal cell carcinoma. This is an aggressive variety. It is less prone to ulceration, may appear yellow-white when stretched, and is firm to touch. It may have a seemingly well-defined border.

Morpheaform and infiltrating basal cell carcinoma. These are aggressive basal cell carcinoma subtypes with sclerotic (scar like) plaques or papules. The border is usually not well defined and often extends well beyond clinical margins. Ulceration, bleeding, and crusting are uncommon. It may be mistaken for scar tissue.

The differential diagnoses include actinic keratosis, Bowen's disease, keratoacanthoma, melanocytic nevi, sebaceous hyperplasia, seborrheic keratosis, squamous cell carcinoma.

Histologic Features. Tumor cells of nodular basal cell carcinoma, sometimes called basalioma cells, typically have large, hyperchromatic, oval nuclei with little cytoplasm and arranged in nests of varying size. Cells appear rather uniform, and mitotic figures are usually few in number. The cells at the periphery of these nests show palisading. Early lesions usually exhibit some connection to the overlying epidermis, but such contiguity may be difficult to appreciate in more advanced

lesions. Increased mucin is often present in the surrounding dermal stroma.

Cleft formation, known as retraction artifact, commonly occurs between BCC nests and stroma because of shrinkage of mucin during tissue fixation and staining. Some lobules may exhibit areas of pseudoglandular change, and this is the predominant change in adenoid basal cell carcinoma. In the nodulocystic variant, larger tumor lobules may degenerate centrally, forming pseudocystic spaces filled with mucinous debris.

In pigmented basal cell carcinoma, benign melanocytes in and around the tumor produce large amounts of melanin. These melanocytes contain many melanin granules in their cytoplasm and dendrites.

Superficial basal cell carcinoma appears as buds of basaloid cells attached to the undersurface of the epidermis. Nests of various sizes often are seen in the upper dermis which show typical palisading periphery.

The more aggressive morpheaform and infiltrating basal cell carcinomas exhibit growth patterns resulting in strands of cells rather than round nests. Morpheaform BCC arises as thin strands of tumor cells that are embedded in a dense fibrous stroma. The strands of infiltrating type tend to be somewhat thicker than those seen in morpheaform basal cell carcinoma, and have a spiky irregular appearance. Infiltrating basal cell carcinoma usually does not exhibit the scar like stroma seen in morpheaform type. Peripheral palisading and retraction are much less pronounced in morpheaform and infiltrating basal cell carcinoma and subclinical involvement is often extensive.

Another aggressive variant, micronodular basal cell carcinoma, appears as small nodular aggregates of basaloid cells. Retraction artifact tends to be less pronounced than in the nodular form and subclinical involvement is often significant.

Treatment and Prognosis. Each lesion must be considered separately when contemplating the choice of therapy. In general, equally good results may be expected from surgical excision of the tumor or from X-ray radiation. There is probably an equal number of failures or recurrences subsequent to each type of treatment. Some lesions stubbornly resist treatment and exhibit great propensity for recurrence and subsequent destruction of tissue.

The prognosis of basal cell lesions is good, since the neoplasm grows slowly, does not tend to metastasize and responds well to treatment. Most difficulties, which may lead to death by local invasion, are due to neglect on the part of the patient who fails to seek medical aid until the lesion is in a far-advanced state.

Epidermoid Carcinoma
(Squamous cell carcinoma)

Squamous cell carcinoma is defined as "a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges" (Pindborg JJ et al, 1997).

The epidermoid carcinoma is the most common malignant neoplasm of the oral cavity. Although it may occur at any intraoral site, certain sites are more frequently involved than others. Because of the differences in clinical appearance, the nature of the lesion and particularly the prognosis, it is well to describe the tumors individually, as they may arise in these various areas.

Epidemiology. The incidence of squamous cell carcinomas of the oral cavity differs widely in various parts of the world and ranges from approximately 2–10 per 100,000 population per year. Such differences can, to some extent, be explained on the basis of environmental differences or lifestyle and habits among certain populations, such as betel quid chewing, snuff dipping or the habit of reverse smoking. High incidence countries include those in South Asia such as Sri Lanka, India, Pakistan and Bangladesh; Bas-Rhin and Calvados regions in France; countries in central and eastern Europe; and Brazil. The incidence of oral carcinoma in blacks is somewhat lower than in whites, which is mainly due to the low incidence of lower lip cancer in blacks.

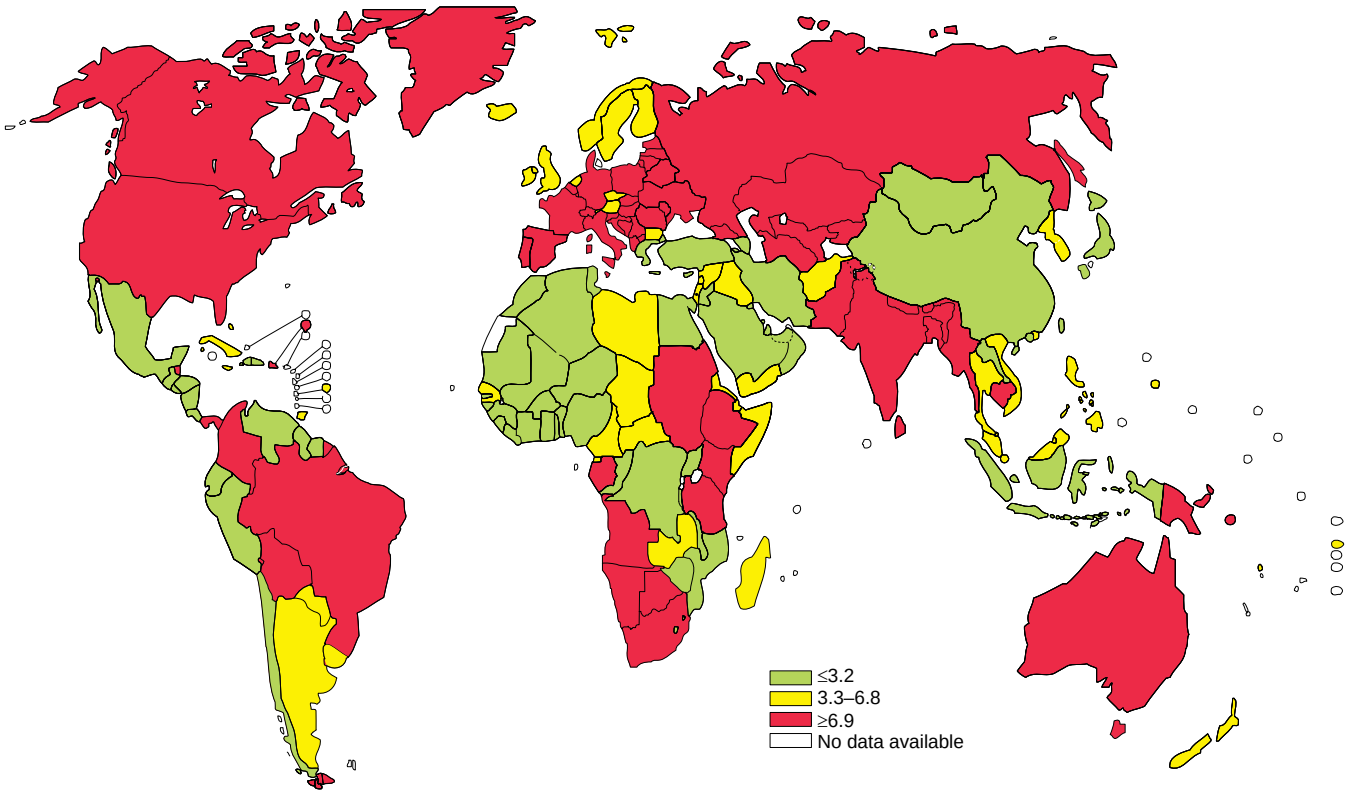
In most parts of the world the male-female ratio is approximately 2 : 1 for oral carcinoma, except for carcinoma of the vermilion border of the lower lip. In the latter site there is a strong male predominance. Oral squamous cell carcinomas are mainly found after the fourth decade.

South-East Asian scenario. In India, oral cancer, constituting 9.8% of an estimated 644,600 incident cancer cases in 1992, ranks first among all cancer cases in males and is the third most common among females in many regions, with age-standardized incidence rates from 7–17/100,000 persons/ year; the incidence rate being higher than the western rate of 3–4/100,000/ year (Fig. 2-15).

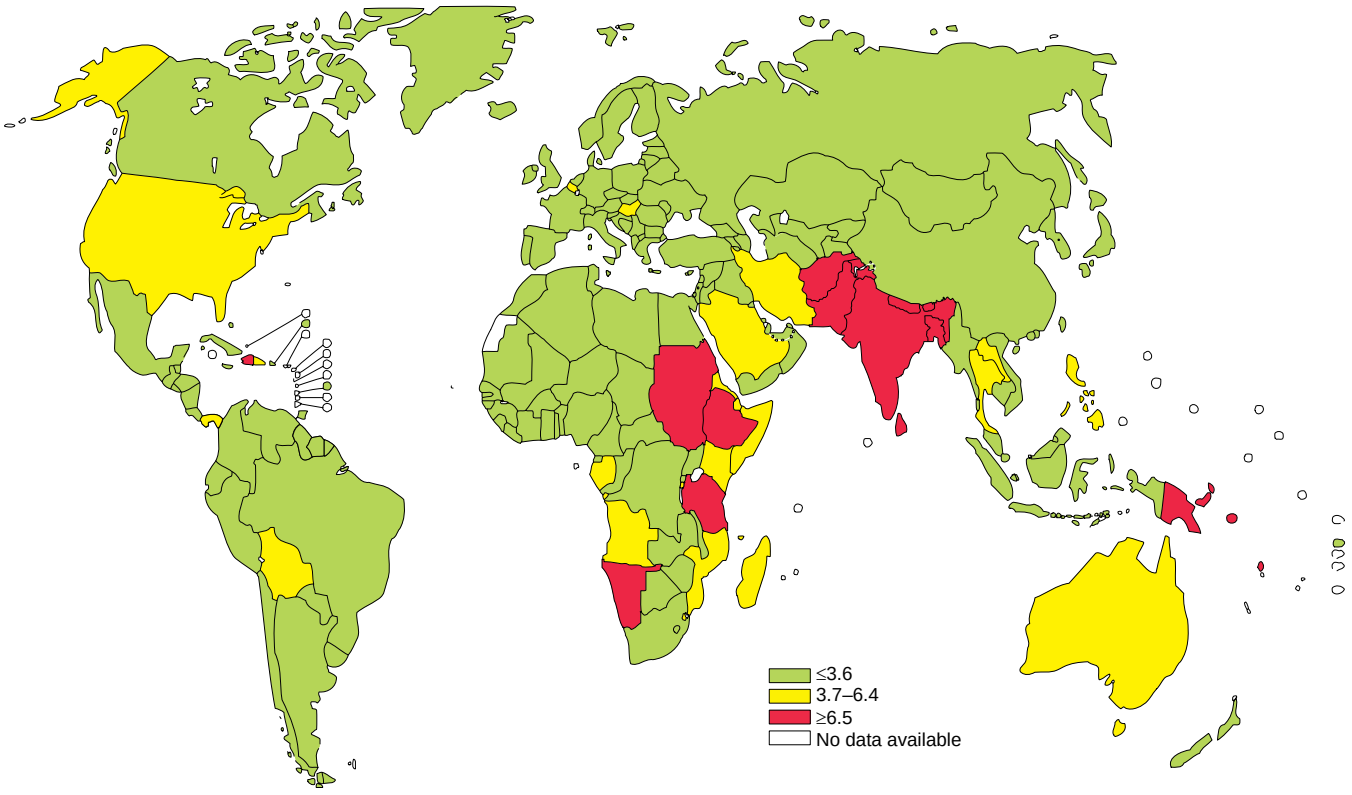
Significant geographic variation is noted in the incidence of oral cancer, with high rates reported for the Indian subcontinent and parts of Asia (male incidence rates in excess of 10 per 100,000 per annum). In India, cancer of the oral cavity (ICD-9, 141, 143–145) is one of the five leading sites of cancer in either gender. The age standardized incidence rates (ASR) vary from 6.2 per 100,000 in Bangalore to 16.1 per 100,000 in Bhopal among urban males, and from 3.5 in Delhi to 7.8 per 100,000 in Chennai among urban females. On the basis of the cancer registry data, it is estimated that annually 75,000–80,000 new oral cancer cases develop in India. In India, the majority of oral cancers are unequivocally associated with tobacco-chewing habits, and usually preceded by premalignant lesions, most often a persistent leukoplakia or oral submucous fibrosis (SMF). Oral leukoplakias and SMF have been reported to show an increased risk of conversion to malignant transformation varying from 0.13–6%, and the risk further increased to 14% or higher in dysplastic lesions.

Of the areas of the oral cavity, the mortality rate is lowest for lip cancer (0.04 per 100,000) and highest for the tongue (0.7 per 100,000). More than 90% of oral cancers occur in patients over the age of 45. The incidence increases steadily with age until 65, when the rate levels off.

However, studies have shown that between 16 and 62% of oral carcinomas are associated with leukoplakic lesions when diagnosed, and an Indian house-to-house survey



A



B

Figure 2-15. Incidence of oral cavity cancer among males (A) and (B) females (age standardized rate (ASR) per 100 000 world population, December 2004.
Source: World Cancer Report. Lyon: IARC 2003.

showed that about 80% of oral cancers were preceded by oral precancerous lesions or conditions. Others consider the vast majority of oral cancers to arise from otherwise clinically normal mucosa.

National Cancer Registry Programme. The National Cancer Registry Programme (NCRP) was initiated in 1982, with three population-based (existing Mumbai registry and new registries at Bangalore and Chennai), and three hospital-based registries (at Chandigarh, Dibrugarh and Thiruvananthapuram). Further expansion saw the initiation of urban population-based cancer registries at Bhopal and Delhi; rural population-based cancer registry at Barshi (Maharashtra); and hospital cancer registries at Mumbai, Bangalore and Chennai. The Chandigarh registry functioned till 1992. At present the network has six population-based and five hospital-based cancer registries. Coordinating units at Bangalore and Delhi, with the help of a steering committee, carry out the monitoring and coordination of activities. Data from cancer registries helped in highlighting the magnitude and common sites of cancer in India, and was useful in planning the National Cancer Control Programme (Table 2-7).

Network of National Cancer Registry Programme. In 1994, the crude incidence rates of cancer in India varied between 57.5 and 78.6 per 100,000 men (Fig. 2-16); and between 57.7 and 89.7 per 10,000 women in urban registry areas (Fig. 2-17).

The age standardized incidence rates range from 98.7–138.3 per 100,000 men (Fig. 2-18); and from 08.0–143.4 per 100,000 women in urban areas (Fig. 2-19). The crude incidence rate for cancers at all sites in rural Barshi was reported to be 32.9 per 100,000 men and 49.7 per 100,000 women. The age standardized incidence rate in Barshi was 41.1 and 56.3 per 100,000 men and women, respectively (Tables 2-5, 2-6, 2-7).

Etiology. The use of tobacco in its various forms, including smokeless tobacco, is regarded as the main cause of oral cancer, particularly when associated with the use of excess alcohol. High exposure to ultraviolet light increases the chance of developing cancer of the lower lip. Diets with low levels of vitamins A and C or inadequate consumption of vegetables and fruits may contribute to the risk of oral cancer.

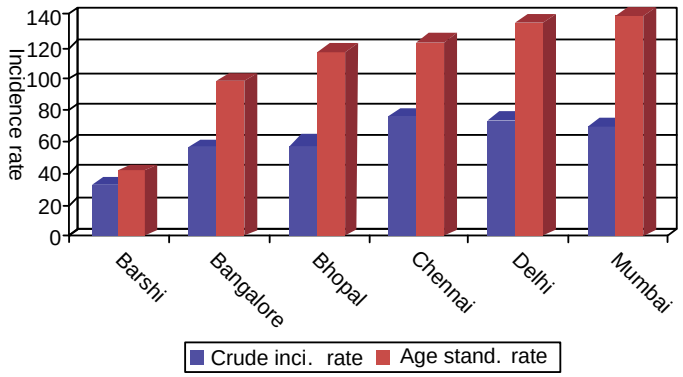


Figure 2-16. Incidence rate of cancer in India, men (1994).

Patients who are immunosuppressed, e.g. renal and homograft recipients and HIV-infected patients, have a higher incidence of subsequent cancer development, particularly of the lower lip. Furthermore, a number of rare conditions predispose to the development of oral cancer, such as xeroderma pigmentosum, Fanconi's anemia, and Bloom's syndrome.

In some patients with oral cancer, especially in females, none of the aforementioned factors or cofactors seem to be present, which makes the etiology of the development of oral cancer incompletely understood.

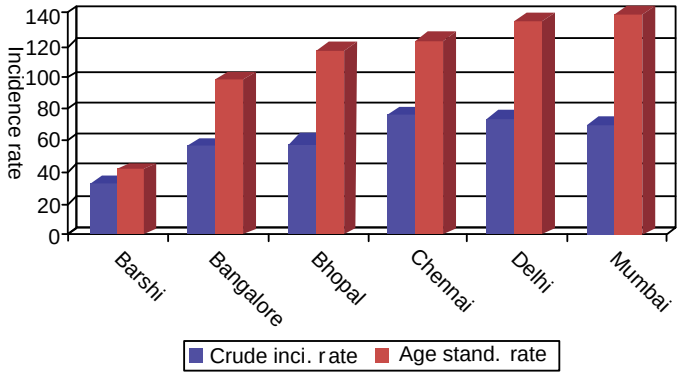


Figure 2-17. Incidence rate of cancer in India, women (1994).

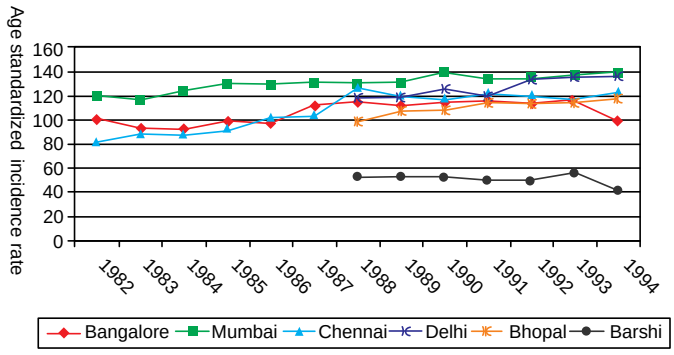


Figure 2-18. Trends in age standardized cancer incidence rate among men in India (1982–1994).

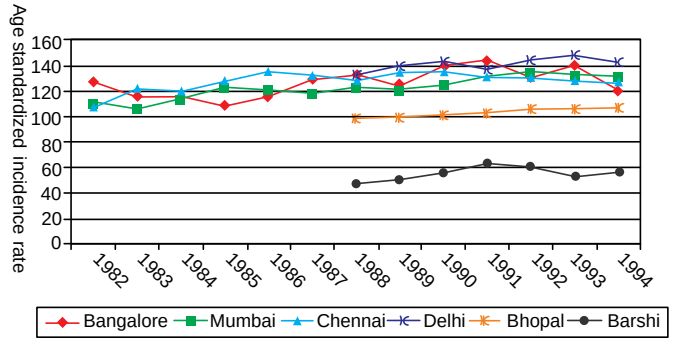


Figure 2-19. Trends in age standardized cancer incidence rate among women in India (1982–1994).

Source (for Figures 2-18 and 2-19): National Cancer Registry Programme, ICMR, New Delhi, 1994.

Table 2-5: Common cancers among men in India

Rank	Bangalore	Bhopal	Chennai	Delhi	Mumbai	Barshi
1	Stomach 10.9	Lung 14.5	Stomach 15.4	Lung 13.2	Lung 14.3	Hypopharynx 6.1
2	Esophagus 9.4	Tongue 10.6	Lung 10.9	Larynx 9.7	Esophagus 11.0	Esophagus 4.9
3	Lung 9.2	Hypopharynx 8.5	Esophagus 9.2	Prostate 7.1	Larynx 8.5	Penis 3.4
4	Hypopharynx 6.4	Esophagus 8.3	Mouth 7.3	Esophagus 6.6	Hypopharynx 8.2	Mouth 3.1
5	Prostate 5.1	Mouth 7.5	Hypopharynx 5.7	Urinary bladder 6.3	Prostate 7.5	Larynx 2.7

Table 2-6: Common cancers among women in India

Rank	Bangalore	Bhopal	Chennai	Delhi	Mumbai	Barshi
1	Cervix 30.8	Cervix 24.9	Cervix 41.9	Breast 29.0	Breast 27.1	Cervix 27.7
2	Breast 21.4	Breast 22.2	Breast 22.4	Cervix 29.0	Cervix 19.5	Breast 8.0
3	Mouth 9.9	Ovary 6.1	Mouth 8.0	Gall bladder 8.4	Esophagus 8.2	Esophagus 2.1
4	Esophagus 9.0	Mouth 5.8	Stomach 7.0	Ovary 8.4	Ovary 7.2	
5	Stomach 5.8	Esophagus 5.8	Esophagus 6.4	Lymphoma 4.9	Mouth 4.6	

Figures are age standardized rates for the specific cancer sites.
Figures for Bangalore, Chennai and Mumbai are for the years 1982–94. For other registries the figures are for the years 1988–94.

Table 2-7: Oral cancer (Trivandrum data 1993–97)

Site	Male						Female					
	No. of cases	Freq. (percentage)	Crude rate	ASR world	Cum, 0–64	rates 0–74	No. of cases	Freq. (percentage)	Crude rate	ASR world	Cum, 0–64	rates 0–74
			(per 100,000)		(percentage)				(per 100,000)		(percentage)	
Lip	11	0.6	0.4	0.5	0.03	0.05	9	0.4	0.3	0.4	0.02	0.05
Tongue	124	6.3	4.5	5.4	0.38	0.66	70	3.4	2.5	2.7	0.17	0.34
Mouth	207	10.5	7.6	9.3	0.66	1.13	118	5.7	4.2	4.7	0.25	0.56
Tonsil	19	1.0	0.7	0.8	0.06	0.09	8	0.4	0.3	0.3	0.02	0.05
Other oropharynx	48	2.4	1.8	2.2	0.17	0.28	2	0.1	0.1	0.1	0.00	0.01
Nasopharynx	14	0.7	0.5	0.6	0.05	0.06	6	0.3	0.2	0.2	0.02	0.02
Hypopharynx	46	2.3	1.7	2.1	0.12	0.25	7	0.3	0.2	0.3	0.02	0.04
Pharynx unspecified	1	0.1	0.0	0.0	0.00	0.00	0	0.0	0.0	0.0	0.00	0.00

Adapted from: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, Volume VIII; IARC Scientific Publications No. 155 2002, IARC, Lyon, France.

Although much circumstantial evidence currently exists, the literature still lacks unequivocal evidence linking HPV and oral cancer. When all anatomic sites are considered, the prevalence of HPV in oral cancer does not appear to be higher than the prevalence of HPV in clinically normal mucosa.

Epidemiological findings also lend further support to a causal relationship between HPV and oral cancer, particularly for oropharyngeal tumors:

- The risk of oral cancer has been shown to increase in the presence of HPV infection.
- Certain sexual risk factors known to be associated with cervical cancer for women have been shown to be associated with oral cancer in men.
- HPV positive oropharyngeal tumors appear to represent a distinct clinical and histopathological entity with improved prognosis.

However, it is difficult to ignore the highly preferential association of HPV with tonsillar carcinoma, as well as the finding of high-risk HPV type 16 in these tumors. It is also possible that this area is more predisposed to epithelial injury which facilitates the subsequent viral infection.

Sunlight, in cases of lip cancer, appeared to be of only minor etiologic significance. This is the generally accepted reason for its occurrence preponderantly in fair-skinned outdoor male workers who are affected by exposure of the lower lip to the sun, whereas the upper lip is partially protected. The lesser rate of occurrence in females may be due to lower exposure to sunlight and the partial protection of their lips by lipstick.

Trauma and dental irritation were not found to be significant etiologic factors in oral cancer. In this regard, Monkman and his associates have also carried out a thorough review of the literature relating cancer to trauma and found no evidence to suggest that single uncomplicated trauma can cause cancer. They also found it debatable whether trauma can aggravate or accelerate existing malignancies. However, they concluded that trauma, in combination with other factors, may act as a co-carcinogen and that there was adequate evidence suggesting that metastatic spread of malignant tumors can be affected by trauma.

Genetic Basis of Oral Cancer

Evidence suggests that oral cancer results from genetic damage.There is increased risk of oral cancer associated with exposure to genetic mutagens in tobacco, alcohol and betel quid. Gene mutations have been detected in oral SCC in chromosomes 3p, 4q, 6p, 8p, 9p, 11q, 13q (retinoblastoma [Rb] tumor suppressor gene), 14q, 17p (p53 tumor suppressor gene), 18q (deleted in colon cancer [DCC] tumor suppressor gene) and 21q.1113 The genetic hypothesis predicts a role for hyperactive oncogenes (growth promoting genes) in oral carcinogenesis. Oncogenes encode many of the signal-transmitting proteins (for example, EGFr, ras, cytoplasmic kinases, c-myc) via which cells respond to external growth signals. Normal cells, with normal oncogenes, will not commit themselves to another round of DNA replication and cell division without stimulation from such external signals. However, with oncogene mutation, the mutant oncoprotein may send a growth-stimulatory signal to the nucleus, regardless of events taking place in the cell's

As discussed, the ras oncoprotein lies on the internal aspect of the membrane-bound EGFr and is involved in the transmission of the EGF growth-stimulatory signal to the nucleus (Fig. 2-20). In the inactive state, ras binds guanosine diphosphate (GDP).When cells are stimulated by EGF, inactive ras becomes activated by exchanging GDP for guanosine triphosphate (GTP). Active ras activates the Raf protein and subsequently the other cytoplasmic kinases (MEK, MAPK) in a cascade-like manner (Fig. 2-20). After activating Raf, active ras returns to the inactive state due to its intrinsic guanosine triphosphatase (GTPase) activity. GTPase hydrolyses GTP to GDP, thereby releasing a phosphate group and returning the ras protein to its inactive GDP-bound state. The intrinsic GTPase activity of activated ras is amplified by binding of GTPase- activating proteins (GAPs). Under normal circumstances, this mechanism ensures that ras is active for only a brief period of time following EGF stimulation and that cell proliferation is tightly regulated by EGF. However, the control of ras activity changes dramatically with mutation of the ras oncogene. Mutant ras protein can bind GAPs, however GTPase activity is not amplified. Hence, mutant ras is trapped in its active GTP-bound form which continues to activate Raf, thus sending a proliferation signal to the nucleus even in the absence of binding between EGF and its receptor on the cell surface. In addition, hyperactive ras may stimulate the transcription of bcl-2 which blocks caspase 3 activation and hence blocks apoptotic cell death. Many studies have shown ras oncogene mutation and ras oncoprotein overexpression in oral SCC. Furthermore, oral premalignant lesions and oral cancer may be associated with upregulated EGF receptor expression. Oral cancer may, therefore, result from mutation of an oncogene in the EGF pathway. The mutant oncoprotein sends a continuous growth signal to the nucleus resulting in continuous oral keratinocyte proliferation and tumor development.

Under normal circumstances, the p53 tumor suppressor protein detects DNA damage (such as ras oncogene mutation) and halts progression through the cell cycle. Following DNA damage, there is an increase in the level of p53 which, in turn, stimulates the transcription of p21 (Fig. 2-20). The p21 tumor suppressor protein is a CDK inhibitor and blocks the phosphorylation of pRb, thereby blocking the release of E2F transcription factors and blocking DNA replication.The p21 tumor suppressor protein also binds and deactivates proliferating cell nuclear antigen (PCNA) (Fig. 2-20). PCNA is a toroidal-shaped protein that encircles and slides along DNA. PCNA tethers the DNA polymerase catalytic unit to the DNA template and is therefore essential for DNA replication. Binding of p21 to PCNA inhibits the interaction between PCNA and DNA polymerase, thereby, blocking DNA replication. Hence p53, acting via p21, puts the brakes on DNA replication and cell division in cells with damaged DNA. In some instances, p53 will trigger apoptosis (programmed cell death) in cells with damaged DNA. p53 stimulates the transcription of Bax which blocks the activity of bcl-2 (Fig. 2-20). bcl-2 normally blocks the activation of caspase 3, a central mediator of the apoptosis cell death pathway. When bcl-2 activity is blocked by Bax, caspase 3 activity is unchecked and apoptotic cell death proceeds (Fig. 2-20). p53 also represses the transcription of bcl-2 which

further contributes to caspase 3 activity and apoptosis in cells with damaged DNA.

However, if the p53 gene is mutated, the protection offered by the p53 tumor suppressor protein against DNA damage (for example, ras oncogene mutation) is lost. Both alleles of the tumor suppressor gene must be mutated for the tumor suppressor protein to become non-functional. A cell which is 'heterozygous' for a tumor suppressor gene has one normal allele and one mutant allele and the cell is clinically normal. If a cell becomes homozygous for the mutant allele, that is 'loses heterozygosity', cancer may develop. In familial cases of retinoblastoma, children inherit one mutant allele of the Rb tumor suppressor gene and the other allele is normal. Only one somatic mutation is required to inactivate the single normal allele of the Rb gene and for retinoblastoma to develop. In sporadic cases, both normal alleles of the Rb tumor suppressor gene in a single retinoblast are lost by somatic mutation resulting in retinoblastoma. In the Li–Fraumeni cancer susceptibility syndrome, children inherit one mutant allele of the p53 tumor suppressor gene and the other allele is normal. Again, only one somatic mutation is required to inactivate the single normal allele of the p53 gene and patients with this syndrome are at high risk of developing carcinomas, sarcomas, lymphomas and brain tumors. Most oral cancers are sporadic and therefore both normal alleles of the p53 tumor suppressor gene in a single oral keratinocyte are lost by somatic mutation. In this context, the tumor suppressor genes are 'recessive', as both alleles must be damaged for transformation to occur. In contrast, the oncogenes (for example, ras) are 'dominant', as mutation of only one allele results in transformation.

Mutation of the p53 tumor suppressor gene is the most common genetic lesion in human neoplasia and p53 is mutated in up to 80% of oral cancers. In oral SCC, p53 mutation correlates with a history of heavy smoking and is associated with increased epithelial cell proliferation. Mutation of p53 may precede or accompany the transition from oral precancer to cancer. A common p53 mutation in many tumors is deletion of one allele accompanied by a mutation in the central DNA-binding domain of the remaining allele. Consequently, the mutant p53 protein is unable to stimulate p21 or Bax transcription and cells with damaged DNA (for example, mutated ras oncogene) continue to divide, passing on their gene mutations to subsequent generations (Table 2-8).

By way of a simple example, oral cancer may result from an activating mutation of the ras oncogene and a simultaneous deactivating mutation of the p53 tumor suppressor gene in an oral keratinocyte. In this scenario, oral cancer would evolve from an oral keratinocyte that has received three genetic 'hits' from mutagens in tobacco, alcohol, betel quid or some other source. The first 'hit' would inactivate one allele of the p53 tumor suppressor gene. The second 'hit' would inactivate the other allele of the p53 tumor suppressor gene. The third 'hit' would activate apoptosis. As discussed, oral cancer may result from mutation in other oncogenes in the EGFr/ras/kinase cascade/c-myc signalling pathway and cumulative tumor suppressor gene the ras oncogene.The order of these 'hits' is probably important, as ras oncogene mutation in the mutations, presence of at least one functional allele of p53 would be expected to result in cell cycle arrest and which correlates with the stages of carcinogenesis from normal mucosa, to squamous hyperplasia (9p), to dysplasia (3p, 17p) to carcinoma *in situ* (11q, 13q, 14q) to invasive carcinoma (6p, 8 and 4q).

Adapted from: Sugerman PB, Savage NW. Aust Dent J 1999; 44 (3): 147–156.

Table 2-8: Proteins required for DNA replication

Enzymes required in nucleotide synthesis
• Initiator proteins: bind at replication origin
• DNA helicase: binds initiator proteins and opens the double helix
• Single strand DNA binding proteins (helix destabilizing proteins): stabilizes unwound single strand DNA
• DNA polymerase: polymerizes deoxyribonucleoside triphosphates (5'–3') on a single strand DNA template
• PCNA (proliferating cell nuclear antigen) - tethers DNA polymerase to the DNA template
• DNA primase: makes RNA primers for lagging strand replication
• DNA ligase: joins Okazaki fragments during lagging strand replication
• Proofreading exonuclease: provides base-paired terminus that primes DNA synthesis
• DNA topoisomerase: transient nick in DNA to allow free rotation during replication

Most of these proteins are enzymes which are newly transcribed with each round of cell division. Many of these proteins are transcribed by the E2F family of transcription factors (Fig.2-20).

Source: Sugerman PB, Savage NW. Aust Dent J 1999; 44 (3): 147–156.

surroundings. The subsequent autonomous proliferation of mutant oncogene-bearing cells result in tumor formation.

Clinical Presentations of Oral Cancer. Clinically, almost all oral cancers, except those in the earliest stages have two very characteristic features in the form of ulceration and an indurated margin. In different sites; however, there are certain variations.

Histologic Features. Considerable histologic variation is presented in intraoral epidermoid carcinomas, although in general they tend to be moderately well-differentiated neoplasms with some evidence of keratinization (Fig. 2-21 and Table 2-9). Highly anaplastic lesions do occur, but are uncommon; such lesions tend to metastasize early and widely and cause death quickly. The well-differentiated epidermoid carcinoma consists of sheets and nests of cells with obvious origin from squamous epithelium. These cells are generally large and show a distinct cell membrane, although intercellular

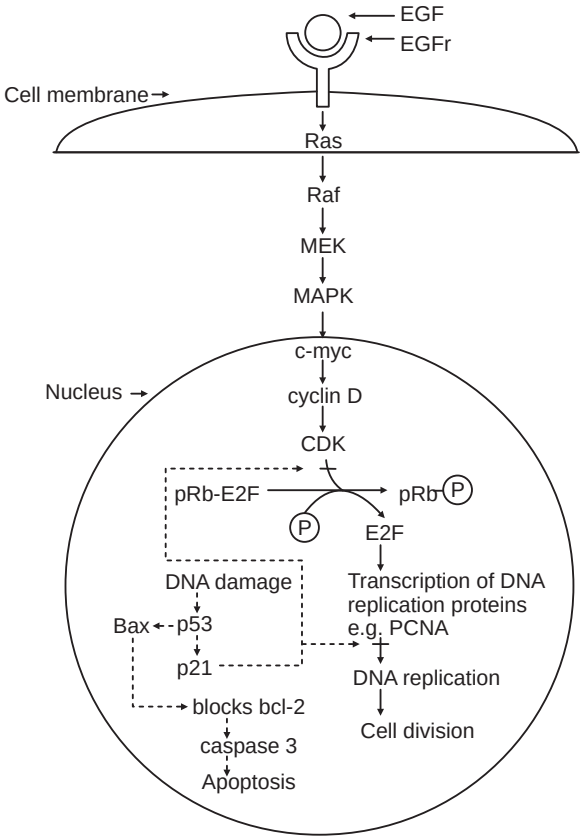


Figure 2-20. Oral cancer: Genetic basis
Normal oral keratinocyte division is stimulated by epidermal growth factor (EGF) binding the EGF receptor (EGFr) which activates ras. Active ras triggers the kinase cascade (Raf, MEK, MAPK) resulting in increased levels of c-myc in the nucleus. c-myc stimulates the transcription of cyclin D which activates cyclin-dependent kinase (CDK). Active CDK catalyzes the phosphorylation of the retinoblastoma tumor suppressor protein (pRb). Phosphorylated pRb releases the E2F transcription factors which are required for the transcription of DNA replication proteins including proliferating cell nuclear antigen (PCNA). DNA replication proceeds, followed closely by cell division.Cyclin D and most of the DNA replication proteins are degraded and must be newly transcribed with each round of cell division. DNA damage in oral keratinocytes is detected by p53. As a result, there is an increase in the level of p53 which stimulates the transcription of p21, a CDK inhibitor which blocks the phosphorylation of pRb. p21 also binds and deactivates PCNA. p53 stimulates the transcription of Bax which blocks the activity of bcl-2. Caspase 3 activity is therefore unchecked and apoptotic cell death proceeds. The dotted lines represent the apoptotic cell death pathway following DNA damage.
Source: Sugerman PB, Savage NW. Aust Dent J 1999; 44 (3): 147- 156.

Pathophysiology

Allelic imbalances (loss of heterozygosity [LOH]) have been identified in tumor suppressor genes on the short arm of chromosome 3, p16 on chromosome 9, p53 on chromosome 17.

Damage to tumor suppressor genes may also involve damage to other genes involved in growth control, mainly those involved in cell signaling (oncogenes), especially some on chromosome 11 (PRAD-1) and chromosome 17 (Harvey *ras* [H-*ras*]). Changes in oncogenes can disrupt cell growth control, leading ultimately to the uncontrolled growth of cancer.

The molecular changes found in oral squamous cell carcinoma from Western countries (United Kingdom, United States, Australia), particularly p53 mutations, are infrequent in Eastern countries (India, South-East Asia), where the involvement of ras oncogenes is more common, suggesting genetic differences that might be involved in explaining the susceptibility of certain groups to oral squamous cell carcinoma.

The rare syndrome (Li–Fraumeni syndrome) is associated with defects in p53.

bridges or tonofibrils often cannot be demonstrated. The nuclei of the neoplastic cells are large and may demonstrate a good deal of variability in the intensity of the staining reaction. Nuclei which stain heavily with hematoxylin are referred to as hyperchromatic. In the well-differentiated lesion mitotic figures may be found, but they often do not appear to be especially numerous (Fig. 2-22). Many of these mitotic figures are atypical, although this may be obvious only to an experienced histopathologist. One of the most prominent features of the well-differentiated epidermoid carcinoma is the presence of individual cell keratinization and the formation of numerous epithelial, or keratin pearls of varying sizes. In a typical lesion, groups of these malignant cells can be found actively invading the connective tissue in a vagarious pattern.

Less well-differentiated epidermoid carcinomas lose certain features, so that their resemblance to squamous epithelium is less pronounced. The characteristic shape of the cells and their arrangement may be altered. The growth rate of the individual cells is more rapid, and this is reflected in the greater numbers of mitotic figures, the even greater variation in sizes, shape and tinctorial reaction and the failure to carry out the function of a differentiated squamous cell, the formation of keratin.

The poorly differentiated carcinomas bear little resemblance to their cell of origin and will often present diagnostic difficulties because of the primitive and uncharacteristic histologic appearance of the malignant, rapidly dividing cells. These cells show an even greater lack of cohesiveness and are extremely vagarious.

The recognition that different degrees of differentiation occur in the epidermoid carcinoma prompted Broders to suggest a system of grading tumors in which a grade I lesion was highly differentiated (its cells were producing much keratin), while grade IV was very poorly differentiated (the cells were highly anaplastic and showed practically no keratin formation). The fact that the same tumor may show different degrees of differentiation in varying areas has prompted the discontinuation of the grading system. Instead, most pathologists now modify the diagnosis of the neoplasm by a descriptive adjective indicative of its differentiation. The one advantage of grading a tumor is that the grade reflects the anaplasticity of the lesion, which in turn indicates the general rapidity of growth, the rapidity of metastatic spread, the general reaction to be expected after X-ray radiation and the prognosis.

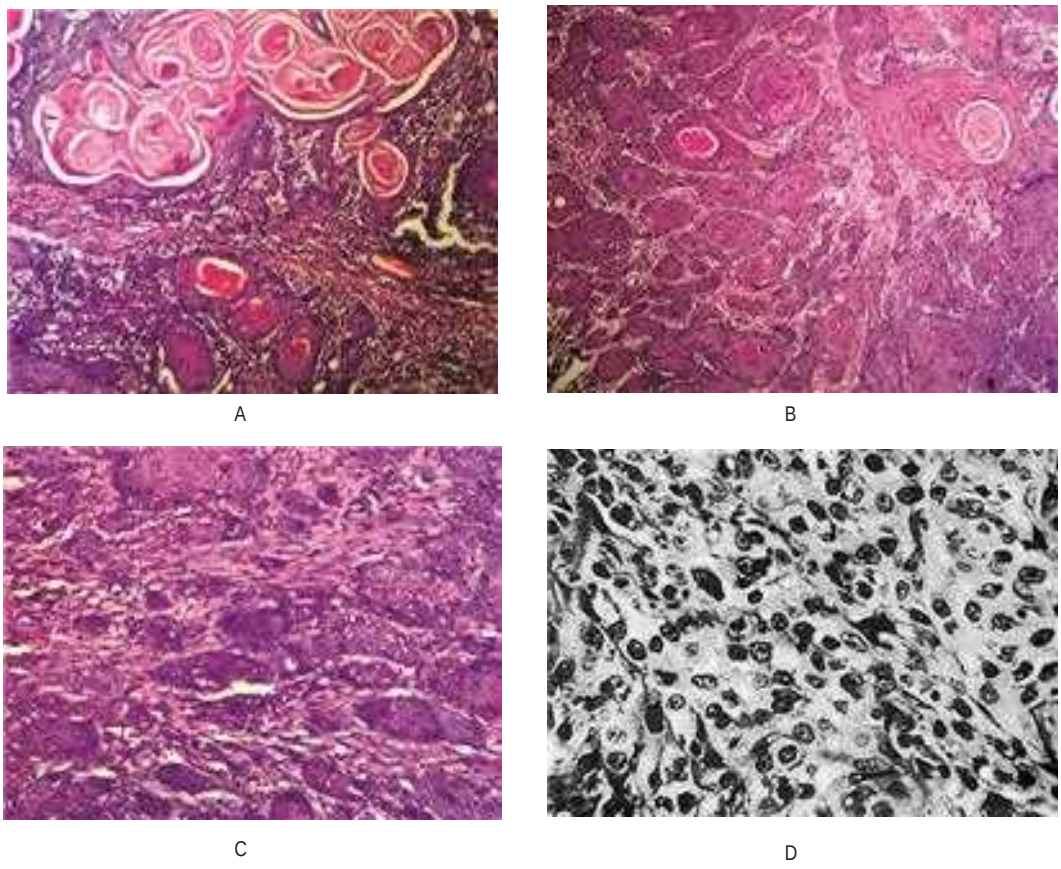


Figure 2-21. Epidermoid carcinoma.
Photomicrographs of various cases of epidermoid carcinoma illustrate **(A)** a highly differentiated carcinoma, **(B)** a well differentiated carcinoma, **(C)** a moderately differentiated carcinoma, and **(D)** a poorly differentiated carcinoma *(Courtesy of Dr G Sriram, Department of Oral and Maxillofacial Pathology, Meenakshi Ammal Dental College, Chennai).*

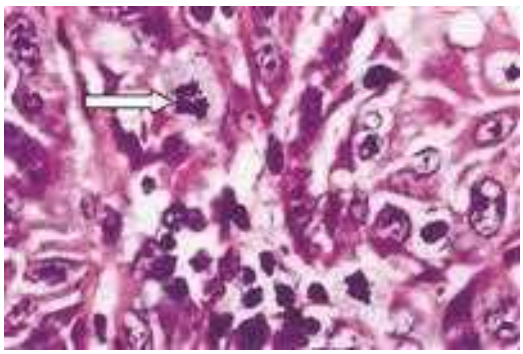


Figure 2-22. Increased number of mitotic figures per field (H&E stain).

This great advantage is still retained in the descriptive grading which is replacing the numerical grading system.

Metastases from intraoral carcinoma of different sites involve chiefly the submaxillary and superficial and deep cervical lymph nodes (Figs. 2-23–2-26). Occasionally, other nodes such as the submental, preauricular and postauricular nodes and supraclavicular nodes may be involved, but blood stream metastasis from oral cancer is uncommon. However, Gowen and de Suto-Nagy have reported on a series of 59 patients who died of carcinoma of the head and neck and were autopsied, with distant metastases being specifically sought. Surprisingly, 57% of these patients did have distant metastases; in the lung in 82% of the cases, in the liver in 45%, and in the bones in 23%.

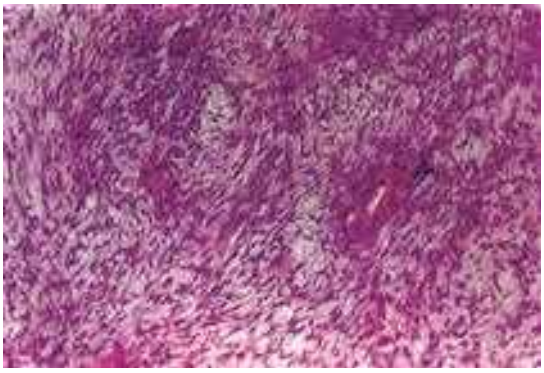


Figure 2-23. Squamous cell carcinoma with spindle metaplastic features.

Table 2-9: Histological classification of cancer and precancer of the oral mucosa

1. Carcinomas
   - Squamous cell carcinoma
   - Verrucous carcinoma
   - Basaloid squamous cell carcinoma
   - Adenoid squamous cell carcinoma
   - Spindle cell carcinoma
   - Adenosquamous carcinoma
   - Undifferentiated carcinoma
2. Benign lesions capable of microscopically resembling oral squamous cell carcinoma and oral verrucous carcinoma
   - Papillary hyperplasia
   - Granular cell tumor
   - Discoid lupus erythematosus
   - Median rhomboid glossitis
   - Keratoacanthoma
   - Necrotizing sialometaplasia
   - Juxtaoral organ of Chievitz
   - Chronic hyperplastic candidiasis
   - Verruciform xanthoma
   - Verruca vulgaris
   - Condyloma acuminatum
3. Precancerous lesions (clinical classification)
   - Leukoplakia
   - Erythroplakia
   - Palatal keratosis associated with reverse smoking
4. Precancerous lesions (histological classification)
   - Squamous epithelial dysplasia
   - Squamous cell carcinoma in situ
   - Solar keratosis
5. Benign lesions capable of resembling oral precancerous lesions
   - White lesions resembling leukoplakia
   - Red lesions resembling erythroplakia
   - Focal epithelial hyperplasia
   - Reactive and regenerative atypia
6. Precancerous conditions
   - Sideropenic dysphagia
   - Lichen planus
   - Oral submucous fibrosis
   - Syphilis
   - Discoid lupus erythematosus
   - Xeroderma pigmentosum
   - Epidermolysis bullosa

Carcinogen-metabolizing enzymes are implicated in some patients

1. Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde, which is cytotoxic and results in the production of free radicals and DNA hydroxylated bases; alcohol dehydrogenase type 3 genotypes appear predisposed to oral squamous cell carcinoma.
2. Cytochrome p450 can activate many environmental procarcinogens. Ethanol is also metabolized, to some extent, by cytochrome p450 IIEI (CYP2E1) to acetaldehyde. Mutations in some tumor suppressor genes may be related to cytochrome p450 genotypes and predispose to oral squamous cell carcinoma.
3. Glutathione S transferase (GST) genotypes may have impaired activity; for example, the null genotype of GSTM1 has a decreased capacity to detoxify tobacco carcinogens. Some GSTM1 and GSTP1 polymorphic genotypes and GSTM1 and GSTT1 null genotypes have been shown to predispose to oral squamous cell carcinoma.
4. N-acetyltransferases NAT1 and NAT2 acetylate procarcinogens. N-acetyl transferase NAT1*10 genotypes may be a genetic determinant of oral squamous cell carcinoma, at least in some populations.
5. DNA repair genes are clearly involved in the pathogenesis of some rare cancers such as are seen in xeroderma pigmentosum but, more recently, evidence of defective DNA repair has also been found to underlie some oral squamous cell carcinoma.

   Immune defects may predispose to OSCC, especially lip cancer.

Courtesy of Scully Crispian et al. 2004; Cancers of the Oral Mucosa (eMedicine).

Metastatic Carcinoma

Mustard and Rosen have reported on the influence of lymph node metastasis on the survival rate of patients with oral cancer. In a series of 1,177 patients who did not have regional lymph node involvement at the time of diagnosis of their lesion,

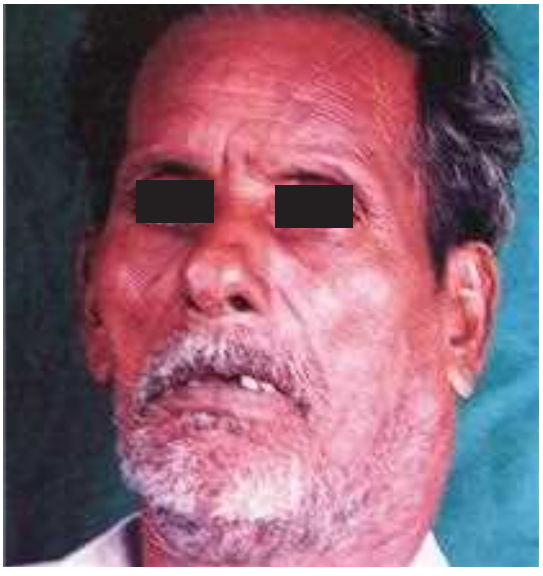


Figure 2-24. Metastatic epidermoid carcinoma.
There is massive involvement of the cervical lymph nodes, which are firm, fixed and matted.

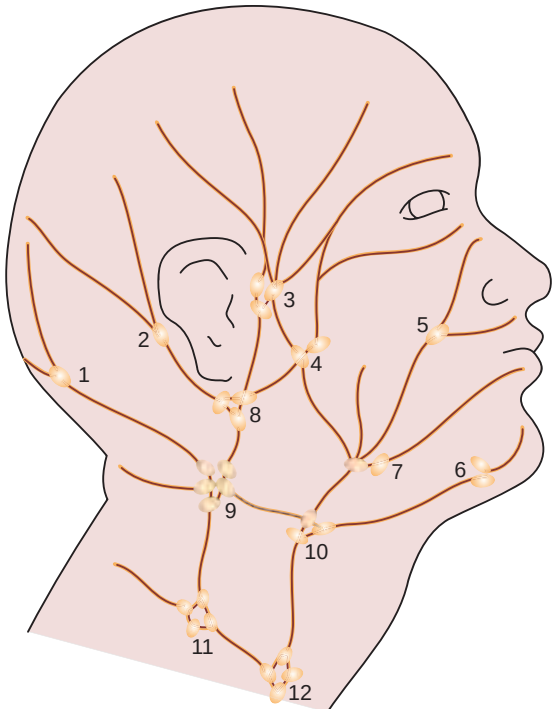


Figure 2-25. Regional lymphatic system of the head and neck, showing the various groups of lymph nodes.
1. Occipital nodes, 2. posterior auricular nodes, 3. anterior auricular (preauricular) nodes, 4. parotid nodes, 5. facial nodes, 6. submental nodes, 7. submaxillary nodes, 8. inferior auricular nodes, 9. lateral upper deep cervical nodes, 10. medial upper deep cervical nodes, 11. lateral lower deep cervical nodes and 12. medial lower deep cervical nodes.

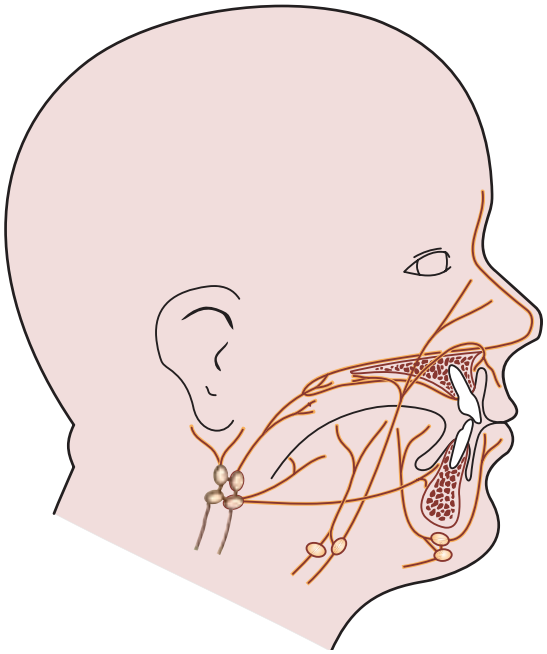


Figure 2-26. Regional lymphatic drainage of the oral structures.

64% lived for five years. However, of the group who did have lymph node involvement at the time of admission, only 15% survived for the same period.

TNM CLASSIFICATION OF LIP AND ORAL CAVITY CARCINOMAS

Rules for Classification

The classification applies only to carcinomas of the vermilion surfaces of the lips and of the oral cavity, including those of minor salivary glands. There should be histological confirmation of the disease. The following are the procedure for assessment of the T, N and M categories:

T category Physical examination and imaging
N category Physical examination and imaging
M category Physical examination and imaging.

Anatomical Sites and Subsites

Lip (ICD Coding)

1. External upper lip (vermilion border) (C00.0)
2. External lower lip (vermilion border) (C00.1)
3. Commissures (C00.6)

Oral Cavity

1. Buccal mucosa
   i. Mucosa of upper and lower lips (C00.3,4)
   ii. Cheek mucosa (C06.0)
   iii. Retromolar areas (C06.2)
   iv. Buccoalveolar sulci, upper and lower (vestibule of mouth) (C06.1)
2. Upper alveolus and gingiva (upper gum) (C03.0)
3. Lower alveolus and gingiva (lower gum) (C03.1)
4. Hard palate (C05.0)
5. Tongue
   i. Dorsal surface and lateral borders anterior to vallate papillae (anterior two-thirds) (C02.0,1)
   ii. Inferior (ventral) surface (C02.2)
6. Floor of mouth (C04).

Regional Lymph Nodes. The regional lymph nodes are the cervical nodes.

TNM Clinical Classification

T—Primary tumor

TX Primary tumor cannot be assessed
TO No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Lip: Tumor invades adjacent structures, e.g. through cortical bone, tongue, skin of neck
Oral cavity: Tumor invades adjacent structures, e.g. through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin.

N—Regional lymph nodes

NX Regional lymph nodes cannot be assessed

NO No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node, more than 6 cm in greatest dimension
Note: Midline nodes are considered ipsilateral nodes.

M—Distant metastasis
MX Presence of distant metastasis cannot be assessed
MO No distant metastasis
M1 Distant metastasis.

(pTNM pathological classification: The pT, pN and pM categories correspond to the T, N, and M categories).

Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 T2 T3	N1 N1 N0, N1	M0 M0 M0
Stage IV	T4 Any T Any T	N0, N1 N2, N3 Any N	M0 M0 M1

Source: Hermanek, P, Sobin LH (eds). TNM Classification of Malignant Tumors, 4th edn, 2nd revision. International Union against Cancer. Springer, Berlin, 1992.

HISTOPATHOLOGICAL GRADING OF ORAL SQUAMOUS CELL CARCINOMA

Classic microscopic histopathologic alterations observed with squamous cell carcinoma include:

a. Enlarged nuclei as well as cell size
b. Large and prominent nucleoli
c. Increased nuclear/cytoplasmic ratio
d. Hyperchromatic (dark staining) nuclei
e. Dyskeratosis (premature keratinization of cells)
f. Increased and/or aberrant mitotic activity.

Based upon the above mentioned histopathologic features, squamous cell carcinoma can then be histologically graded. Although the grade of tumor does not substitute the staging protocol, it does serve as an important adjunctive in predicting the overall biological behavior of the tumor. In general, tumors that more closely resemble their native tissues are considered to be well differentiated and tend to have a better long-term prognosis. In contrast, tumors with abundant amounts of cellular and nuclear alterations with little or no resemblance to squamous epithelium or those that lack keratin production may be classified as poorly differentiated tumors. These lesions, also termed as anaplastic or high grade, have an increased propensity for regional metastasis and correlate to a poor prognosis. Additional features that favor a more aggressive nature include perineural spread, lymphatic invasion, and tumor extension beyond the lymph node capsule. Hematogenous spread is an uncommon mode of spread for carcinomas.

Criteria for the Diagnosis of Oral Epithelial Dysplasia

The diagnosis and grading of oral epithelial dysplasia is based on a combination of architectural and cytological changes (Barnes L et al, 2005), but evaluation of these is subjective and has been subject to considerable inter-and intra-observer variations in the grading of lesions. More recently, there has been an attempt to more carefully define the criteria for grading of epithelial dysplasia (Bouquot J et al, 2006, Brothwell DJ et al, 2003). The WHO classification (2005) recommends a more objective grading which does, to some extent, take account of levels of involvement of involved epithelium. The criteria for grading of oral epithelial dysplasia are summarized as follows:

Mild dysplasia (Grade-1). Demonstrates proliferation or hyperplasia of cells of the basal and parabasal layers which does not extend beyond the lower third of the epithelium. Cytological atypia is generally slight with only mild pleomorphism of cells or nuclei. Mitoses are not prominent, and when present are usually basally located and normal. Architectural (gross) changes are minimal.

Moderate dysplasia (Grade-2). Demonstrates a proliferation of atypical cells extending into the middle one third of the epithelium. The cytological changes are more severe than in mild dysplasia and changes such as hyperchromatism, and prominent cell and nuclear pleomorphism may be seen. Increased and abnormal mitoses may be seen, but these are usually located at the basal layers of the epithelium. Architectural changes may be seen in the lower half of the epithelium where there may be loss of basal polarity and hyperplasia leading to bulbous rete pegs. However, stratification and maturation are relatively normal, often with hyperkeratosis of the surface epithelium.

Severe dysplasia (Grade 3): There is abnormal proliferation from the basal layer into the upper third of the epithelium. Cytological and architectural changes can be very prominent. All the changes seen in mild and moderate dysplasia are present but in addition there is marked pleomorphism often with abnormal large nuclei and prominent or even multiple nucleoli present. Prominent and suprabasal mitoses are usually evident and abnormal tripolar or star shaped forms may be seen. Apoptotic bodies (cell death) may also be prominent. Architectural changes are severe, often with complete lack of

stratification and with deep abnormal keratinization and even formation of keratin pearls. Abnormal forms of rete pegs are usual and bulbous rete pegs are particularly significant in the diagnosis of severe dysplasia. Abnormal shaped rete pegs may also be seen, with lateral extensions or small branches. These are quite abnormal and may be the earliest signs of invasion. Occasional lesions may show prominent acantholysis with severe disruption of the architecture. Although the epithelium may be thickened, severe dysplasia is sometimes accompanied by marked epithelial atrophy (thinning). This is especially prominent in lesions from the floor of the mouth, ventral tongue or soft palate and may be a feature of lesions which have presented clinically as erythroplakia (red patch). In these cases there may be minimal evidence of stratification or keratinization, and atypical cells may be extended to the surface.

Carcinoma *in situ*. It is the most severe form of epithelial dysplasia and is characterised by full thickness cytological and architectural changes. In the oral cavity such changes are rare, and often, even in the presence of the most severe atypia, there is still an intact keratinised surface layer. Carcinoma *in situ* is thought by some to be a premalignancy but others regard it as evidence of actual malignant change but without invasion (Speight PM, 2010).

Histological Models and Scoring Systems

Many such models and scoring systems have been developed for predicting the biological behavior of oral squamous cell carcinoma. Broder's system (1920) was first established on the basis of the proportion of highly differentiated cells in the tumor. Although Broder's system was simple and widely used, it was a poor predictor for survival or metastasis. In 1973, Jakobsson et al, developed a multifactorial grading system which had the advantage of scoring tumor–host interactions and tumor characteristics, but eventually proved to be useful only when applied to tongue cancers. Later, Anneroth et al (1984) proposed a modification of Jakobsson system based on the assessment of six histomorphological parameters including degree of keratinization, nuclear pleomorphism, pattern of invasion, host response and mitotic activity. Bryne et al (1989) modified Anneroth's grading system and developed a malignancy grading focusing on the invasive front of the tumor. This method of grading appeared to be less time consuming in assessment of the neoplasm than that of Jakobsson et al, and Anneroth et al. Neverthless, this system was not sufficiently homogeneous to allow grading parameters to be assessed individually.

EMERGING TRENDS

An interesting pursuit in tumor biology would be studying the biologic behavior of neoplasms in general and follow the subtle differences that exists with individual tumors. Among the many variables would be consideration of the site, size, histologic grades, etiologic factors and stage of progression of individual neoplasms. This newer approach of carefully monitoring tumors comprise a separate area of 'biologic staging', which is currently gaining acceptance in clinical practice (Table 2-10). Another interesting trend currently being investigated is the use of the polymerase chain reaction (PCR) to determine if surgical margins obtained at the time of surgery that are histopathologically free of tumor contain a small amount of histologically undetectable tumor cells. Specifically, the use of PCR to detect specific p53 mutations identified in the primary tumor in the histopathologically negative surgical margin could be very useful, as these mutations would indicate the presence of residual (histopathologically undetected) tumor cells. It will be very important to establish whether the presence of submicroscopic tumor cells contributes to prognosis and clinical outcome. The recent development of *in situ* PCR will allow amplification of both DNA and RNA directly in tissue section; this technique should be extremely helpful in the future to localize tumor cells containing altered oncogenes or tumor suppressor genes. An improved understanding of the molecular biology of head and neck cancer may also contribute to future therapeutic improvements. Finally, molecular probes may be used to facilitate the early detection of secondary malignancies.

Table 2-10: Biomarker predictors in oral precancerous and cancerous lesions

Marker method	Detection	Target
Proliferation PCNA, Ki67, BrU Histone AgNORs	 IHC mRNA ISH Silver stain	 Cycling cells
Genetic Ploidy	 FC	 Aneuploid cells
Oncogenes C-myc	 IHC	 Cycling cells
Tumor suppressor p53 mutations	 IHC, PCR	 Cycling cells
Cytokeratin 8/19	IHC	Anaplasia
Blood group antigens	IHC	Anaplasia
Integrins/ECM ligands	IHC	Invasion and metastatic potential

IHC: immunohistochemistry, FC: flowcytometry, PCR: polymerase chain reaction, ISH: in-situ hybridization.

Under the current management, the strategy for head and neck cancer includes specialists from many disciplines and their concerted effort will promote the use of increasingly refined laboratory techniques for improved diagnosis and therapy. A good deal of current laboratory and clinical research is focusing on identifying the relative contributions of certain oncogenes and tumor suppressor genes on carcinogenesis, tumor stage, and clinical outcome. Although abnormalities of some oncogenes and tumor suppressor genes have been identified, their relative contribution and optimal use in diagnosis, prognosis, or treatment remain unknown. The same might be said for the role of Epstein-Barr, hepatitis, and herpes simplex viruses; further clinicolaboratory studies will be needed to define which are clinically relevant and when they should be

investigated. Genetic analysis at a molecular/chromosomal level is emerging as a science that may aid in identifying risk and possibly prevention as well. Finally, a reliable and predictable histopathology grading system should be developed to include, in addition to differentiation of tumor cells, such factors as basement membrane protein expression and invasion patterns, perineural invasion, and immunologic responses.

Carcinoma of Lip

Epidermoid carcinoma of the lip is a disease that occurs chiefly in elderly men. Furthermore, the lower lip is involved by this neoplasm far more commonly than the upper lip. Great numbers of cases have been reported in the literature, and the data of Cross, Guralnick and Daland on 563 patients with lip cancer may be cited to illustrate certain typical characteristics. In this large series, it was found that 98% of the patients were men and that the age of these patients at the onset of the disease ranged from 25–91 years, with the greatest incidence between 55 and 75 years and a mean of 62 years of age. Of the total group of lip cancers, 88.3% occurred on the lower lip, 3.3% on the upper lip and 8.3% on the labial commissures. The right and left sides were affected with equal frequency. In 636 cases reviewed by Schreiner, similar findings were reported. In his series 97% of the lesions occurred in men, and 96% were found on the lower lip. Nearly one-third of his cases occurred between the ages of 60 and 70 years.

Etiology. A number of possible etiologic factors have been suggested by the review of the records of many patients. One of the most common of these has been the use of tobacco, chiefly through pipe-smoking. The data of Cross and his coworkers indicate that 64% of their patients with lip cancer were pipe smokers, while a total of 94% habitually used tobacco in some form. These observations are in agreement with the data of Widmann, who, in a review of 363 cases of lip cancer, estimated an incidence of approximately 40% pipe smokers. Schreiner reported that 87% of his lip cancer patients were tobacco users. Although no conclusions may be drawn from such data because of the widespread use of tobacco in the general population, it appears suggestive that the heat, the trauma of the pipe stem and possibly the combustion end-products of tobacco may be of some significance in the etiology of lip cancer.

Syphilis is probably not as significant an etiologic factor in lip cancer as in certain other oral sites, since the incidence of lip cancer has been found to be low in syphilitic patients: 7.2% by Cross and his associates, 8% by Widmann and 3.6% by Schreiner. As indicated previously; however, the data of Wynder and his group indicated that syphilis was of etiologic significance in lip cancer.

Sunlight is generally considered to be important, as discussed previously, because the alterations which occur in skin and lips as a result of prolonged exposure to sun are characterized as preneoplastic. Ju has discussed this problem and constructed a profile of the lip cancer patient.

Poor oral hygiene is an almost universal finding in patients with lip cancer. Cross and his group pointed out that only approximately 8% of their entire series of patients had good or even fair oral hygiene. In addition, some patients indicate a history of trauma before the appearance of a lesion. They report not only a single traumatic experience, such as a cigarette burn or a cut, but also chronic trauma from jagged teeth and so forth. Unfortunately, it is difficult to assess scientifically the role of such factors in the etiology of cancer.

Leukoplakia has often been associated with the development of carcinoma. Since clinical leukoplakia is a fairly common lesion of the lip, it was only natural that the relationship should be investigated. Schreiner found leukoplakia present in only 2.4% of his 636 cases of lip cancer, while Cross and coworkers found leukoplakia associated with carcinoma in 14.5% of the cases in their series. This would indicate that the simultaneous occurrence of the two conditions is probably due to chance and that leukoplakia is not a common predecessor of lip cancer. However, in light of more recent studies dealing with the frequency of preneoplastic and neoplastic transformation in lesions of leukoplakia of the lip (q.v.), the interpretation of the above findings is uncertain.

Clinical Features. There is considerable variation in the clinical appearance of lip cancer, depending chiefly upon the duration of the lesion and the nature of the growth. The tumor usually begins on the vermilion border of the lip to one side of the midline. It often commences as a small area of thickening, induration and ulceration or irregularity of the surface. As the lesion becomes larger it may create a small crater like defect or produce an exophytic, proliferative growth of tumor tissue. Some patients have large fungating masses in a relatively short time, while in other patients the lesion may be only slowly progressive.

Carcinoma of the lip is generally slow to metastasize, and a massive lesion may develop before there is evidence of regional lymph node involvement. Some lesions; however, particularly the more anaplastic ones, may metastasize early. When metastasis does occur, it is usually ipsilateral and involves the submental or submaxillary nodes. Contralateral metastasis may occur, especially if the lesion is near the midline of the lip where there is a cross drainage of the lymphatic vessels.

Histologic Features. Most lip carcinomas are well-differentiated lesions, often classified as grade I carcinoma. This type of cancer tends to metastasize late in the course of the disease. In the series of Widmann, the following approximate distribution of graded lesions was found: grade I, 60%; grade II, 26%; grade III, 13%; grade IV, 2%.

Treatment and Prognosis. Carcinoma of the lip has been treated by either surgical excision or X-ray radiation with approximately equal success, depending to some degree upon the duration and extent of the lesion and the presence of metastases. Interestingly, in the series of Cross the overall cure rate of patients with lip cancer treated by surgery was approximately 81%, while in the series of Widmann the cure rate of patients with the same type of neoplasm treated by X-ray radiation was approximately 83%. This would indicate that either form of therapy, in skilled hands, will produce equally good results.

Many factors may influence the success or failure of treatment of lip carcinoma. The size of the lesion, its duration, the presence or absence of metastatic lymph nodes and the histologic grade of the lesion must all be considered carefully by the therapist in planning his/her approach to the neoplastic problem.

Carcinoma of Tongue

Cancer of the tongue comprises between 25 and 50% of all intraoral cancer. It is less common in women than in men except in certain geographic localities, chiefly the Scandinavian countries, where the incidence of all intraoral carcinoma in women is high because of the high incidence of a preexisting Plummer–Vinson syndrome. In a series of 441 cases of tongue cancer reported by Ash and Millar, 25% occurred in women and 75% in men, with an average age of 63 years. In a series of 330 cases of cancer of the tongue reported by Gibbel, Cross and Ariel the average age of the patient was 53 years, with a range of 32–87 years. Thus it is essentially a disease of the elderly, but it may occur in relatively young persons. To exemplify this latter point, a series of 11 patients less than 30 years of age, four of them less than 20 years, with carcinoma of the tongue has been reported by Byers. This group of patients represented approximately 3% of all patients seen at MD Anderson Hospital with epidermoid carcinoma of the tongue between 1956 and 1973 (418 cases).

Etiology. A number of causes of cancer of the tongue have been suggested, but in our present state of knowledge no precise statements can be made. A definite relation does appear to exist; however, between tongue cancer and certain other disorders. Many investigators have found syphilis, either an active case or at least a past history of it, coexistent with carcinoma of the tongue. In the series of Gibbel et al, 22% of patients with lingual cancer demonstrated a positive complement fixation or Kahn reaction, while in the general admission at their hospital only 5% of the patients had a positive reaction for syphilis. Martin reported that 33% of his patients with cancer of the tongue also had syphilis. The relationship can be explained on the basis of a chronic glossitis produced by the syphilis, chronic irritation long being recognized as carcinogenic under certain circumstances. This explanation implies a local effect of syphilis rather than a generalized or systemic effect. It should be pointed out that some studies do not confirm the theory of a relationship between syphilis and tongue cancer. Wynder has confirmed this relationship, but questioned whether the neoplasm might be related to the arsenic therapy, the treatment of choice before the advent of antibiotics, rather than to the syphilis itself. Meyer and Abbey have also questioned this relationship since they found only 15 patients (6%) who showed positive evidence of a history of syphilis in a survey of 243 cases of primary carcinoma of the tongue.

Leukoplakia is a common lesion of the tongue which has been observed many times to be associated with tongue cancer. Martin noted that 46% of his series of cancer patients had leukoplakia of the tongue, while Gibbel et al, found only a 10% incidence of leukoplakia in his series. It is not unusual to see typical lesions of carcinoma in leukoplakic areas; on the other hand, many lesions of leukoplakia appear to persist for years without malignant transformation, and many cases of carcinoma of the tongue develop without evidence of preexisting leukoplakia.

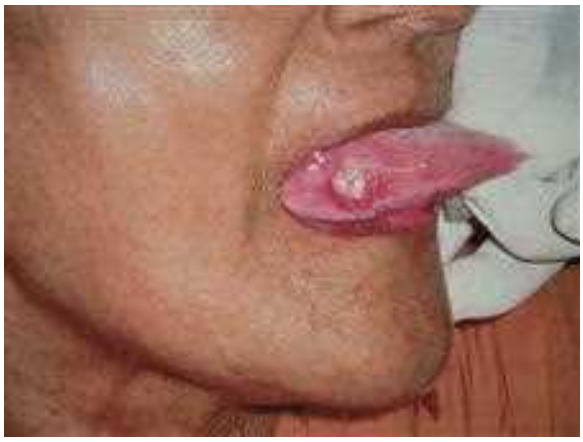
Other factors which have been thought to contribute to the development of carcinoma of the tongue include poor oral hygiene, chronic trauma and the use of alcohol and tobacco. Poor hygiene and the use of alcohol and tobacco are so prevalent as nearly to preclude the possibility of drawing conclusions about a possible cause and effect relation. A considerable number of cases have been observed in which cancer of the tongue developed at a site exactly corresponding to a source of chronic irritation such as a carious or broken tooth or an ill-fitting denture. The work of Wynder and his group; however, suggests that these findings may be fortuitous.

Clinical Features. The most common presenting sign of carcinoma of the tongue is a painless mass or ulcer, although in most patients the lesion ultimately becomes painful, especially when it becomes secondarily infected. The tumor may begin as a superficially indurated ulcer with slightly raised borders and may proceed either to develop a fungating, exophytic mass or to infiltrate the deep layers of the tongue, producing fixation and induration without much surface change (Fig. 2-27A–C).

The typical lesion develops on the lateral border or ventral surface of the tongue. When, in rare cases, carcinoma occurs on the dorsum of the tongue, it is usually in a patient with a past or present history of syphilitic glossitis. In a series of 1,554 cases of carcinoma of the tongue reported by Frazell and Lucas, only 4% occurred on the dorsum. The lesions on the lateral border are rather equally distributed between the base of the tongue, the anterior third and the mid portion, although in the above series 45% of cases occurred on the middle third. Lesions near the base of the tongue are particularly insidious, since they may be asymptomatic until far advanced. Even then the only presenting manifestations may be a sore throat and dysphagia. The specific site of development of these tumors is of great significance, since the lesions on the posterior portion of the tongue are usually of a higher grade of malignancy, metastasize earlier and offer a poorer prognosis, especially because of their inaccessibility for treatment.

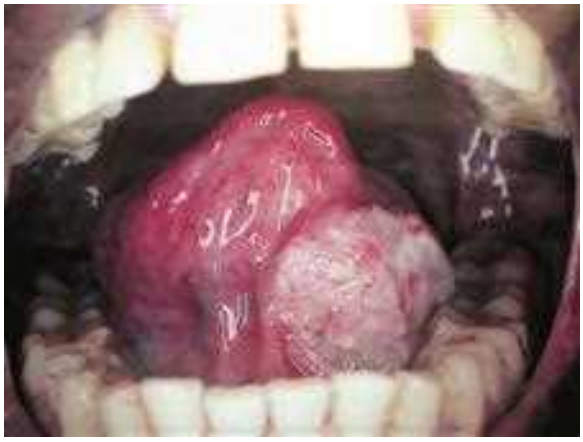
Metastases occur with great frequency in cases of tongue cancer. In 302 patients on whom information was available, Gibbel and his group reported that cervical metastases from tongue lesions were present in 69% at the time of admission to the hospital. The metastatic lesions may be ipsilateral, bilateral, or because of the cross lymphatic drainage, contralateral in respect to the tongue lesion.

Treatment and Prognosis. The treatment of cancer of the tongue is a difficult problem, and even now no specific statements can be made about the efficacy of surgery in comparison to that of X-ray radiation. As in other areas, it will probably be found that the judicious combination of surgery and X-ray will be of greatest benefit to the patient.



A

B



C

Figure 2-27. Epidermoid carcinoma of tongue.
Early to advanced.

Many radiotherapists prefer the use of radium needles or radon seeds to X-ray radiation because they are able with these devices to limit the radiation to the tumor, sparing adjacent normal tissue. Metastatic nodes are highly complicating factors, but treating them without controlling the primary lesion is useless.

The prognosis of cancer in this location is not good. Although statistics vary between series, the five-year cure rate is generally conceded to be below 25%. Martin reported a 22% survival in 556 patients with tongue cancer, while Gibbel et al, found only a 14% survival among 213 patients. Frazell and Lucas reported an overall five-year cure rate of 35% on a series of 1,321 patients with tongue cancer.

The most significant factor affecting prognosis of these patients is the presence or absence of cervical metastases. Thus the studies of Gibbel and his associates showed an 81% survival rate if no metastases ever developed, 43% if no metastases were present at the time of hospital admission, and only 4% if metastases were present at the time of admission or developed subsequent to admission. The necessity for early diagnosis thus becomes obvious, and the role of the dentist in recognizing cancerous lesions is, of course, of paramount importance.

Carcinoma of Floor of Mouth

Carcinoma of the floor of the mouth represents approximately 15% of all cases of intraoral cancer and occurs in the same age group as other oral cancers. The average age of the patient was 57 years in the series of Tiecke and Bernier, 67 years in the series of 110 cases reported by Ash and Millar and 63 years in the group of 100 cases reported by Ballard and his associates. In the latter report, 81% of the lesions occurred in men, while 93% of the patients were men in the series of Ash and Millar.

Smoking, especially a pipe or cigar, has been considered by some investigators to be important in the etiology of cancer in this location. In the series of Ballard and his coworkers, 50% of the patients were classified as heavy smokers, 33% as heavy drinkers and 28% as heavy smokers and heavy drinkers. Nevertheless, little evidence has been gathered to suggest an obvious cause-and-effect relation with regard to tobacco or other factors such as alcohol, poor oral hygiene or dental irritation. Leukoplakia does occur in this location and there is evidence to indicate that epithelial dysplasia and malignant transformation in the leukoplakia occur here with greater frequency than in other oral sites.

Clinical Features. The typical carcinoma in the floor of the mouth is an indurated ulcer of varying size situated on one side of the midline. It may or may not be painful. This neoplasm occurs far more frequently in the anterior portion of the floor than in the posterior area. Because of its location, early extension into the lingual mucosa of the mandible and into the mandible proper as well as into the tongue occurs with considerable frequency (Fig. 2-28). Carcinoma of the floor of the mouth may invade the deeper tissues and may even extend into the submaxillary and sublingual glands. The proximity of this tumor to the tongue, producing some limitation of motion of that organ, often induces a peculiar thickening or slurring of the speech.

Metastases from the floor of the mouth are found most commonly in the submaxillary group of lymph nodes, and since the primary lesion frequently occurs near the midline where a lymphatic cross drainage exists, contralateral metastases

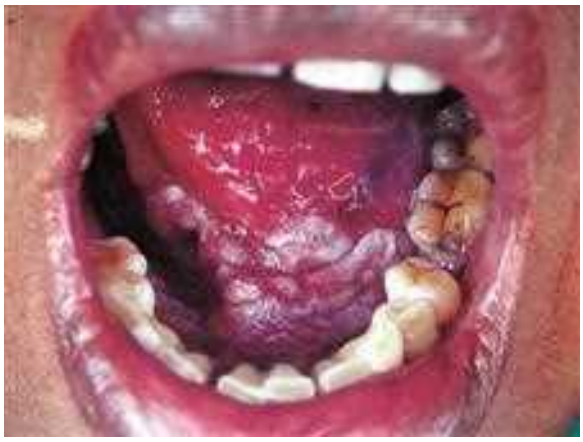


Figure 2-28. Epidermoid carcinoma of floor of mouth.

are often present. Of 95 cases of carcinoma of the floor of the mouth reviewed by Ash and Millar, 21% presented lymph node involvement at the time of admission, while an additional 23% subsequently developed lymphadenopathy. Thus the total incidence of metastasis was 44%. This corresponds to the incidence of 42% metastatic lymph node involvement in the series reported by Tiecke and Bernier and 58% by Martin and Sugarbaker. Fortunately, distant metastases are rare.

Treatment and Prognosis. The treatment of cancer of the floor of the mouth is difficult and all too frequently unsuccessful. Large lesions, because of the anatomy of the region, usually are not a surgical problem. Even small tumors are apt to recur after surgical excision. For this reason, X-ray radiation and the use of radium often give far better results than surgery. The problem is complicated, however, if there is concomitant involvement of the mandible.

The prognosis for patients with carcinoma of the floor of the mouth is fair. The net five-year survival of 86 patients with cancer in this location reviewed by Ash and Millar was 43%. All patients in this series were treated by some form of radiation. Martin and Sugarbaker reported a five-year survival rate of 21% in their series of 103 patients.

Carcinoma of Buccal Mucosa

Reported studies of carcinoma of the buccal mucosa reveal exceptional variation in incidence, the widest differences being accounted for by studies from countries other than the United States. In the series of Krolls and Hoffman, cancer of the buccal mucosa comprised 3% of the total cases of intraoral carcinoma. Like most cancers of the oral cavity, cancer of the buccal mucosa is approximately 10 times more common in men than in women and occurs chiefly in elderly persons. In the study of Tiecke and Bernier, the average age at occurrence of carcinoma of the buccal mucosa was 58 years.

Etiology. The etiology of carcinoma of the buccal mucosa is no better understood than that of carcinoma of other areas of the oral cavity. Several factors appear to be of indisputable significance, however; these include the use of chewing tobacco and the habit of chewing betel nut, which is widespread in many countries in the Far East. It is a fairly common clinical observation that carcinoma of the buccal mucosa develops in the area against which a person has habitually carried a quid of chewing tobacco for years while the opposite cheek may be normal, the patient never having rested the tobacco there. Although this is only presumptive evidence of a cause-and-effect relation; it has been recognized so frequently that it appears to be more than a coincidental finding. A special form of neoplasm known as 'verrucous carcinoma' (q.v.) occurs almost exclusively in elderly patients with a history of tobacco chewing. Since the betel nut quid contains tobacco as well as other substances, including slaked lime, the high incidence of cancer in persons addicted to its use may be explained on a similar basis.

Leukoplakia is a common predecessor of carcinoma of the buccal mucosa. It is usually of extremely long duration and may or may not necessarily be associated with the use of tobacco. Chronic trauma in the form of cheek biting and dental irritation such as that from jagged teeth does not appear to be associated with the development of carcinoma, although focal areas of leukoplakia sometimes occur when these conditions exist.

Clinical Features. There is considerable variation in the clinical appearance of carcinoma of the buccal mucosa. The lesions develop most frequently along or inferior to a line opposite the plane of occlusion. The anteroposterior position is variable, some cases occurring near the third molar area, others anteriorly towards the commissure.

The lesion is often a painful ulcerative one in which induration and infiltration of deeper tissues are common. Some cases, however, are superficial and appear to be growing outward from the surface rather than invading the tissues. Tumors of this latter type are sometimes called exophytic or verrucous growths.

The incidence of metastases from the usual epidermoid carcinoma of the buccal mucosa varies considerably, but is relatively high. Tiecke and Bernier reported that 45% of the patients in their study exhibited metastases at the time of presentation for treatment. This is similar to the incidence of approximately 50% reported by Richards. The most common sites of metastases are the submaxillary lymph nodes.

Treatment and Prognosis. The treatment of carcinoma of the buccal mucosa is just as much of a problem as that of cancer in other areas of the oral cavity. In early cases, it is probable that similar results may be obtained by either surgery or X-ray radiation. The combined use of these two forms of treatment undoubtedly also has a place in the therapy of this tumor.

The prognosis of this neoplasm depends upon the presence or absence of metastases. The findings of Modlin and Johnson indicate that the five-year survival rate for patients with cancer of the buccal mucosa approximates 50%, but in another series Martin reported only a 28% survival.

Carcinoma of Gingiva

Carcinoma of the gingiva constitutes an extremely important group of neoplasms. The similarity of early cancerous lesions of the gingiva to common dental infections has frequently led to delay in diagnosis or even to misdiagnosis. Hence institution of treatment has been delayed, and the ultimate prognosis of the patient is poorer.

Martin reported that approximately 10% of all malignant tumors of the oral cavity occur on the gingiva. In the study of Krolls and Hoffman, 11% of the intraoral carcinomas occurred on the gingiva, while Tiecke and Bernier found a similar incidence of 12% in their series. In the group reported by Martin, one patient was only 22 years old, but the average age of the patients was 61 years. This is essentially a disease of elderly persons, since only 2% of the tumors occurred in patients under the age of 40 years. In the same group of patients, 82% were men and only 18% were women. This is similar to the gender distribution found in oral cancer in other locations.

Etiology. The etiology of carcinoma of the gingiva appears to be no more specific or defined than that in other areas of the oral cavity. Syphilis does not appear to be as significant a factor here as it is in carcinoma of the tongue, and the relation to the use of tobacco is indefinite. Since the gingiva, because of calculus formation and collection of microorganisms, is in nearly all persons the site of a chronic irritation and inflammation lasting over a period of many years, one may speculate the possible role of chronic irritation in the development of cancer of the gingiva. Occasionally, cases of gingival carcinoma appear to arise after extraction of a tooth. If such cases are carefully examined, however, it may usually be ascertained that the tooth was extracted because of a gingival lesion or disease or because the tooth was loose. In fact, the tooth was extracted because of the tumor, which, at the time of surgery, went unrecognized or undiagnosed.

An unusual situation arises in some instances after extraction of a tooth in that a carcinoma appears to develop rapidly and proliferate up out of the socket. Those cases which appear to represent such a phenomenon probably are due to carcinoma of the gingiva growing down along the periodontal ligament and then proliferating suddenly after the dental extraction.

Clinical Features. It is generally agreed that carcinoma of the mandibular gingiva is more common than the involvement of the maxillary gingiva, although the distribution of cases varies considerably between different series. In 47 cases reported by Tiecke and Bernier, 81% of the tumors were found on the mandibular gingiva and only 19% on the maxillary gingiva. Martin, however, reported a more equal distribution of 54% on the mandibular gingiva and 46% on the maxillary gingiva. Data on the exact position in the dental arch at which carcinoma is most apt to develop are insufficient to draw valid conclusions.

Carcinoma of the gingiva usually is manifested initially as an area of ulceration which may be a purely erosive lesion or may exhibit an exophytic, granular or verrucous type of growth (Fig. 2-29). Many times, carcinoma of the gingiva does not have the clinical appearance of a malignant neoplasm. It may or may not be painful. The tumor arises more commonly in edentulous areas, although it may develop in a site in which teeth are present. The fixed gingiva is more frequently involved primarily than the free gingiva.

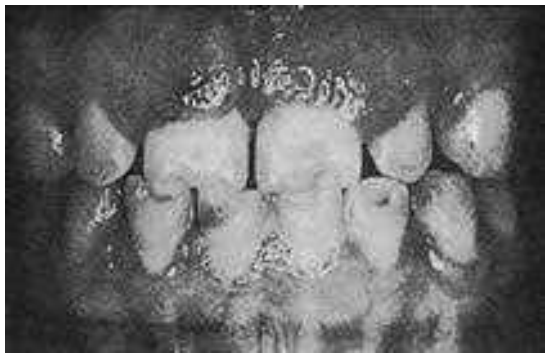


Figure 2-29. Carcinoma of the gingiva.
The mild overgrowth of the gingiva over the maxillary central incisors in this 25-year-old girl resembled inflammatory gingival hyperplasia. Microscopic examination of the gingivectomy specimen revealed epidermoid carcinoma. This is an unusual clinical appearance, age and location for this neoplasm, but many early cases are difficult to recognize *(Courtesy of Harold R Schreiber and Charles A Waldron. J Periodontol, 29: 196, 1958)*.

The proximity of the underlying periosteum and bone usually invites early invasion of these structures. Although many cases exhibit irregular invasion and infiltration of the bone, superficial erosion arising apparently as a pressure phenomenon sometimes occurs. In the maxilla, gingival carcinoma often invades into the maxillary sinus, or it may extend onto the palate or into the tonsillar pillar. In the mandible, extension into the floor of the mouth or laterally into the cheek as well as deep into the bone is rather common. Pathologic fracture sometimes occurs in the latter instance (Fig. 2-30).

Metastasis is a common sequela of gingival carcinoma. Cancer of the mandibular gingiva metastasizes more frequently than cancer of the maxillary gingiva. In most series of cases, metastases to either the submaxillary or the cervical nodes eventually occur in over 50% of the patients regardless of whether the involvement is maxillary or mandibular.

Treatment and Prognosis. The use of X-ray radiation for carcinoma of the gingiva is fraught with hazards because of the well-known damaging effect of the X-rays on bone. In general, treatment of carcinoma in this location is a surgical problem.

The prognosis of cancer of the gingiva is not particularly good. In the series of 105 cases reported by Martin, only 26% of the patients were alive and free of the disease five years after treatment. It is of great significance that in this same series there were no five-year survivals if the patient presented lymph node metastases at the time of admission. This again illustrates the great need for early diagnosis of these neoplasms.

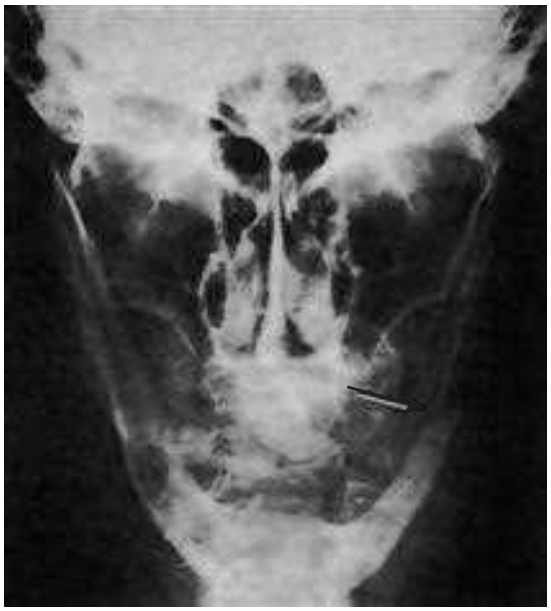


Figure 2-30. Pathologic fracture of mandible caused by the invasion of epidermoid carcinoma arising on the alveolar ridge.

Carcinoma of Palate

Epidermoid carcinoma of the palate is not a particularly common lesion of the oral cavity. It exhibits approximately the same percentage of occurrence as carcinoma of the buccal mucosa, floor of the mouth and gingiva. The palate was the primary site of 9% of the intraoral epidermoid carcinomas reported by Krolls and Hoffman. In a study by Tiecke and Bernier, of 38 palatal tumors in which the site was specific, 53% occurred on the soft palate, 34% on the hard palate and 13% on both. Ackerman, however, stated that epidermoid carcinoma of the hard palate is a rare finding. New and Hallberg found an incidence of only 0.5% of cases of epidermoid carcinoma of the hard palate among approximately 5,000 cases of intraoral carcinoma. (Accessory salivary gland tumors of the hard palate appear to be three to four times more common than epidermoid carcinoma).

Clinical Features. Palatal cancer usually manifests itself as a poorly defined, ulcerated, painful lesion on one side of the midline (Fig. 2-31). It frequently crosses the midline, however, and may extend laterally to include the lingual gingiva or posteriorly to involve the tonsillar pillar or even the uvula. The tumor on the hard palate may invade into the bone or occasionally into the nasal cavity, while infiltrating lesions of the soft palate may extend into the nasopharynx.

The epidermoid carcinoma is almost invariably an ulcerated lesion, whereas the tumors of accessory salivary gland origin, even the malignant lesions, are often not ulcerated, but are covered with an intact mucosa. This fact may be of some aid in helping to distinguish clinically between these two types of neoplasms.

Metastases to regional lymph nodes occur in a considerable percentage of cases, but there is little evidence to indicate whether such metastases are more common in carcinoma of the soft palate or in that of the hard palate.

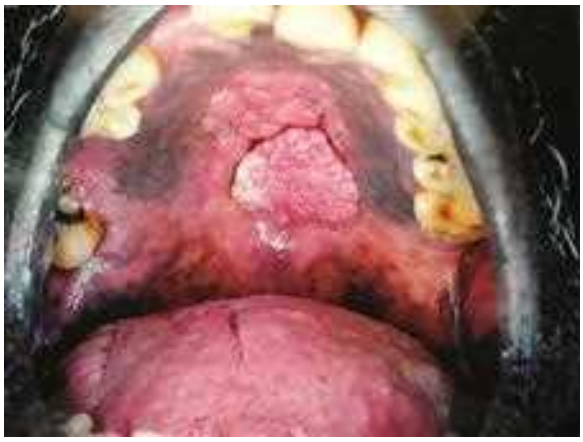


Figure 2-31. Epidermoid carcinoma of palate.

Treatment and Prognosis. Both surgery and X-ray radiation have been used in the treatment of epidermoid carcinoma of the palate. Few large series of cases are available for analysis to aid in determining which form of therapy may be expected to give the greatest survival. Nor are any significant series of purely palatal carcinomas available to aid in the determination of overall survival rate of patients with this lesion. It does appear that the prognosis is somewhat comparable to that of carcinoma of the gingiva.

Carcinoma of Maxillary Sinus

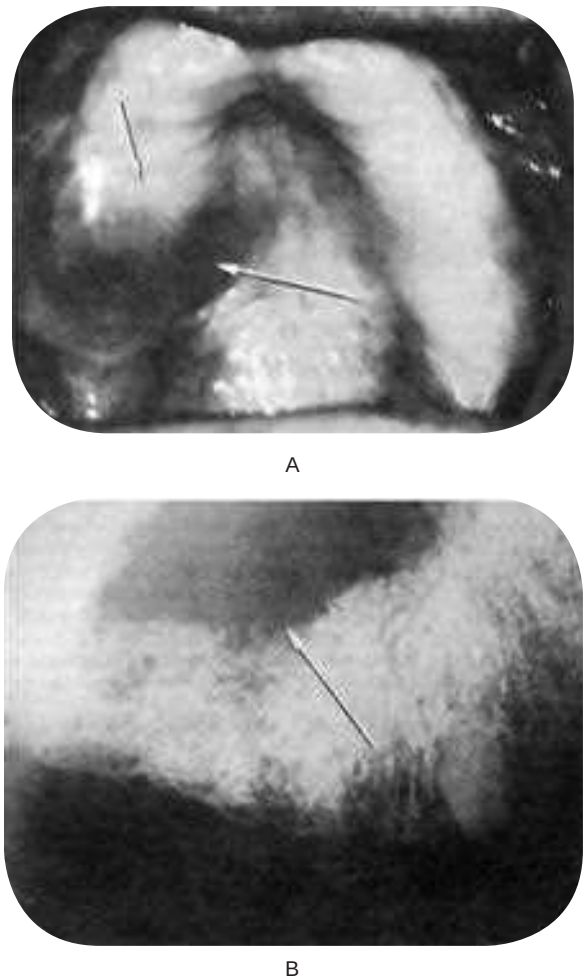
Antral carcinoma is an exceedingly dangerous disease. Although the actual incidence of the disease in respect to intraoral carcinoma cannot be determined, it does appear to be considerably less frequent than any other form of oral cancer. Seelig presented an excellent 10-year survey of the literature and described the chief findings in 624 cases of antral carcinoma; a review of this disease has also been reported by Chaudhry and his associates. Although nothing is known of the etiology of this particular neoplasm, Ackerman stated that chronic sinusitis does not seem to predispose to the development of carcinoma of the maxillary sinus. It might be pointed out here that, although most cases of carcinoma of the maxillary sinus are of the epidermoid type, occasional cases of adenocarcinoma occur, apparently originating from the glands in the wall of the sinus.

Clinical Features. One of the features which contribute to the deadly nature of this disease is that it is often hopelessly advanced before the patient is conscious of its presence. The dentist must be fully aware of the potentialities of this neoplasm and the various ways in which it may manifest itself clinically.

Available studies indicate that carcinoma of the antrum is somewhat more common in men and that, though it is chiefly a disease of elderly persons, occasional cases occur in young adults.

The first clinical sign of antral carcinoma is frequently a swelling or bulging of the maxillary alveolar ridge, palate or mucobuccal fold, loosening or elongation of the maxillary molars or swelling of the face inferior and lateral to the eye (Fig. 2-32). Unilateral nasal stuffiness or discharge is sometimes a primary complaint. In edentulous patients wearing maxillary dentures, loosening of or inability to tolerate the prosthetic appliance may occur before there is any visible clinical evidence of the disease.

The actual spread of the neoplasm which determines the clinical manifestations of the disease is reflected by the extent of involvement of the various walls of the antrum. In some cases, only the floor of the sinus is invaded so that the manifestations of the disease are associated solely with oral structures. If the medial wall of the sinus is involved, nasal obstruction may result. The involvement of the superior wall or roof produces displacement of the eye, while invasion of the lateral wall produces bulging of the check. Ulceration either into the oral cavity or on the skin surface may occur, but only late in the course of the disease.



A

B

Figure 2-32. Epidermoid carcinoma of the maxillary sinus.
(A) The alveolar ridge shows thickening, reddening and deformity, although there is no ulceration of the mucosa. **(B)** The radiograph reveals raggedness of the maxillary sinus and obvious bony alteration.

Metastases usually do not occur until the tumor is far advanced, but when they appear they involve the submaxillary and cervical lymph nodes. The lack of metastasis does not indicate a favorable course, since many patients die from local infiltration alone.

Treatment and Prognosis. Both surgery and X-ray radiation have been used to treat this form of neoplastic disease. If the cancer is confined to the antrum and inferior structures, hemimaxillectomy gives favorable clinical results in some cases. Radiation treatment frequently takes the form of radium needles inserted into the antrum or the tumor mass. This has proved effective in some cases, even though considerable invasion of adjacent structures has occurred.

The overall prognosis of patients with antral carcinoma is not good. In the series of Chaudhry and his associates, only 10% of 49 patients with carcinoma of the antrum lived for more than five years.

Verrucous Carcinoma

A warty variant of squamous cell carcinoma characterized by a predominantly exophytic overgrowth of well-differentiated keratinizing epithelium having minimal atypia and with locally destructive pushing margins at its interface with underlying connective tissue.

Verrucous carcinoma was originally described as a distinct entity on account of its clinical and microscopic features and its mode of behavior. Well differentiated, hyperplastic stratified squamous epithelium is organized into bulbous rete-ridges that exhibit little or no cytological atypia or mitotic activity. There may be a significant endophytic component and the invading margin is usually below the level of the surrounding mucosa. Deep surface invaginations are filled with keratin. The advancing epithelial border is broad and the basement membrane is generally intact. There is usually a heavy inflammatory cell reaction in the adjacent connective tissue. Local destruction of connective tissue occurs in advance of the deep epithelial border. Growth is generally slow and metastatic spread occurs late, if at all. There is a view that verrucous carcinomas may become more aggressive if irradiated.

Although most verrucous carcinomas can be distinguished from squamous cell carcinomas on the basis of their mode of growth, infrequent dysplasia and absence of metastases, there are occasionally foci of conventional squamous cell carcinomas within a verrucous carcinoma. Such lesions should be classified and treated as squamous cell carcinomas. Thorough sectioning of specimens is therefore, necessary to eliminate this possibility. Another hazard in diagnosis occurs when the extremely thick layers of keratin and hyperplastic epithelium are biopsied at insufficient depth to include underlying connective tissue.

The term verrucous hyperplasia describes an exophytic overgrowth of well differentiated keratinizing epithelium that is similar to verrucous carcinoma but without the destructive pushing border at its interface with the underlying connective tissue. Areas of verrucous hyperplasia may be encountered in association with verrucous carcinoma, squamous cell carcinoma or proliferative verrucous leukoplakia.

Exophytic papillary lesions that show epithelial dysplasia, possibly even carcinoma *in situ,* and relatively inconspicuous areas of invasive squamous cell carcinoma separate from the surface epithelium, should be distinguished from verrucous carcinomas and classified as papillary squamous cell carcinomas (Pindborg JJ et al, 1997).

Clinical Features. Verrucous carcinoma is generally seen in elderly patients, the mean age of occurrence being 60–70 years, with nearly 75% of the lesions developing in males, according to a review by Shafer of nearly 300 reported cases. The vast majority of cases occur on the buccal mucosa and gingiva or alveolar ridge, although the palate and floor of the mouth are occasionally involved.

The neoplasm is chiefly exophytic and appears papillary in nature, with a pebbly surface which is sometimes covered by a white leukoplakic film. The lesions commonly have rugae-like folds with deep clefts between them. Lesions of the buccal mucosa may become quite extensive before the involvement of deeper contiguous structures. Lesions on the mandibular ridge or gingiva grow into the overlying soft tissue and rapidly become fixed to the periosteum, gradually invading and destroying the mandible (Fig. 2-33A–C). Regional lymph nodes are often tender and enlarged, simulating metastatic tumor, but this node involvement is usually inflammatory. Pain and difficulty in mastication are common complaints, but bleeding is rare.

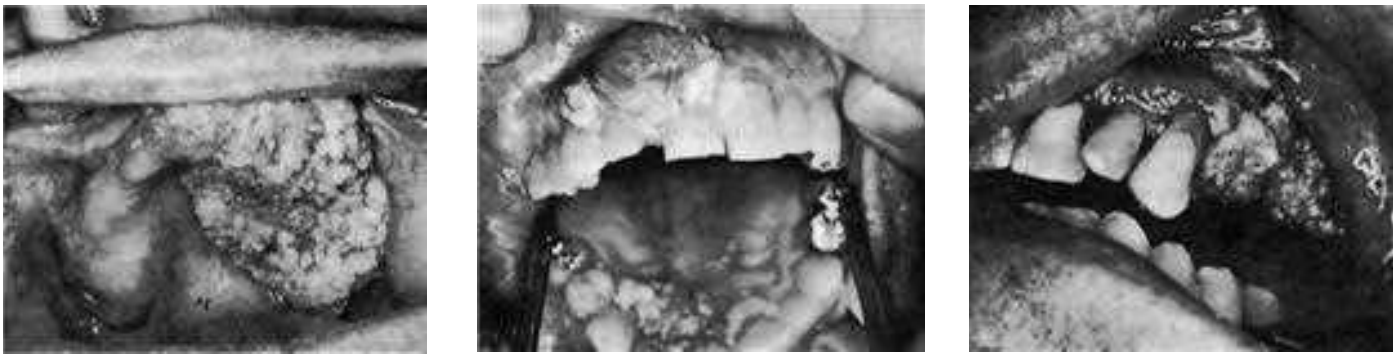
The term oral florid papillomatosis has been used by dermatologists to describe a lesion with not only a clinical and microscopic appearance similar to verrucous carcinoma but also a similar biologic behavior. For this reason, many authorities now believe that oral florid papillomatosis and verrucous carcinoma represent one and the same disease with no justification for continued use of the former term, since it fails to imply the neoplastic nature of the disease.

It is consistently reported that a very high percentage of patients with this disease are tobacco chewers. A small number of patients give no such history but, instead, use snuff or smoke tobacco heavily. Occasional patients deny the use of tobacco and these usually have ill-fitting dentures.

Histologic Features. The histologic features may be extremely deceptive, and many cases have been diagnosed originally as simple papillomas or benign epithelial hyperplasia because of the orderly and harmless appearance of the specimen. There is generally marked epithelial proliferation with downgrowth of epithelium into the connective tissue but usually without a pattern of true invasion. The epithelium is well differentiated and shows little mitotic activity, pleomorphism or hyperchromatism. Characteristically, cleft like spaces lined by a thick layer of parakeratin extend from the surface deeply into the lesion. Parakeratin plugging also occurs extending into the epithelium. The parakeratin lining the clefts with the parakeratin plugging is the hallmark of verrucous carcinoma. Even though the lesion may be very extensive, the basement membrane will often appear intact. When the lesions become infected, focal intraepithelial abscesses are often seen. Significant chronic inflammatory cell infiltration in the underlying connective tissue may or may not be present (Fig. 2-34).

Unfortunately, the diagnosis of verrucous carcinoma is often difficult even when the biopsy specimen is generous, and the pathologist will sometimes request a second biopsy.

Treatment and Prognosis. Verrucous carcinoma has been treated in several ways in the past, usually by surgery, X-ray radiation or a combination of the two. However, there have been some reports of anaplastic transformation of lesions occurring in patients treated by ionizing radiation. While the radiation appears to be the triggering mechanism, other factors contributing to or related to the transformation are unknown. Even though such an occurrence is uncommon, many investigators believe the treatment should be entirely surgical. Since the lesion is so slow-growing and late to metastasize, many cases can be treated by relatively conservative excision without a mutilating procedure. The prognosis is much better than for the usual type of oral epidermoid carcinoma.



A B C

Figure 2-33. Verrucous carcinoma.
The exophytic, verrucous nature of the lesion is evident *(A and B, Courtesy of Dr Charles A Waldron, and C, of Dr George G Blozis and Dr Mirdza E Neiders).*

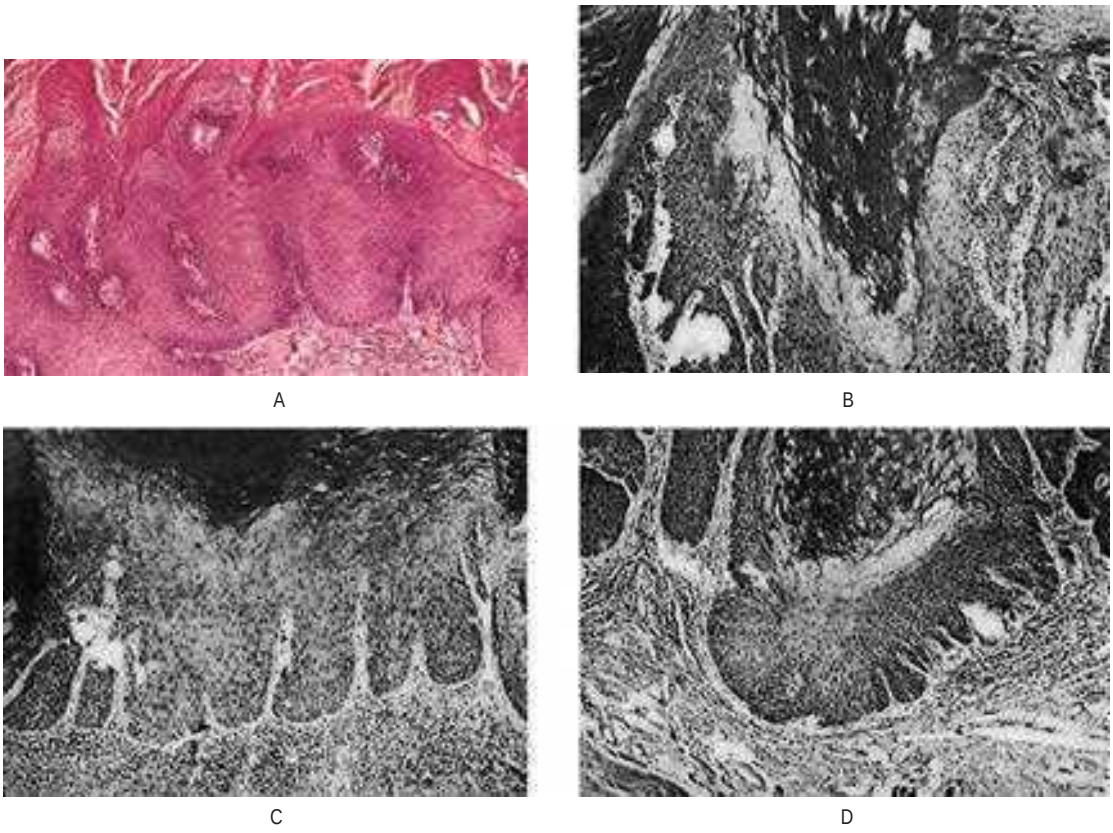


Figure 2-34. Verrucous carcinoma.
The tumor is exophytic and has a papilliferous surface. It is composed of proliferating sheets and groups of stratified squamous epithelium, which exhibit few cytological features of malignancy. There is a round cell infiltrate in the fibrous tissue stroma. It may turn invasive at a later stage. *(A, Courtesy of Dr Hari S, Noorul Islam College of Dental Science,Trivandrum)*

Spindle Cell Carcinoma

(Carcinosarcoma, pseudosarcoma, polypoid squamous cell carcinoma, Lane tumor)

A carcinoma within which there are some elements resembling a squamous cell carcinoma that are associated with a spindle cell component.

In a true spindle cell carcinoma, the malignant spindle shaped cells should be demonstrably of epithelial origin and derived from the squamous cell component of the carcinoma. This must be distinguished both from a squamous cell carcinoma that has provoked a reactive fibroblastic stromal proliferation and from a carcinosarcoma in which a squamous cell carcinoma is accompanied by a sarcoma of fibroblastic or other connective tissue cell type. Care should also be taken not to confuse a spindle cell carcinoma with a spindle cell malignant melanoma or with sarcomas of various types. Often the squamous cell carcinoma component in a spindle cell carcinoma is inconspicuous and multiple sections or blocks may be necessary to find it. Most of the neoplasm comprises of thin elongated cells amongst which there may be occasional pleomorphic cells. Mitotic figures, including abnormal forms, are usually not difficult to find. The behavior is similar to that of the more frequent and usual type of squamous cell carcinoma (Pindborg JJ et al, 1997).

Clinical Features. A series of 59 cases of the oral cavity has been reported by Ellis and Corio, who noted a predilection for occurrence in males, although this finding was somewhat biased because of the number of military cases involved. The mean age of occurrence of the lesion was 57 years, with a range of 29–93 years. The lesions developed with the greatest frequency on the lower lip (42%), tongue (20%) and alveolar ridge or gingiva (19%) with the remainder scattered at other sites.

The most common presenting findings were swelling, pain and the presence of a nonhealing ulcer. The initial lesion appeared either with a polypoid, exophytic or endophytic configuration. It is perhaps significant that 13 patients in this series were known to have a history of prior therapeutic radiation to the region where the tumor subsequently developed. The time interval from radiation to diagnosis of the tumor ranged from 1.5–10 years with a mean of about seven years.

Histologic Features. Spindle cell carcinoma is a bimorphic or biphasic tumor which, although almost always ulcerated, will show foci of surface epidermoid carcinoma or epithelial dysplasia of surface mucosa, usually just at the periphery and often quite limited. Proliferation and 'dropping-off' of basal cells to spindle cell elements is a common phenomenon. The tissue patterns making up the bulk of the tumor have

been categorized as either fasciculated, myxomatous or streaming. The cells, particularly in the fasciculated form, are elongated with elliptical nuclei, although pleomorphic cells are also common. The number of mitoses may vary from few to many. Giant cells, both benign-appearing of the foreign body type and the bizarre, pleomorphic, atypical cells may be found. Finally, an inflammatory cell infiltrate is often present. Osteoid formation within the tumor component is sometimes seen. Microscopic invasion of subjacent structures is evident, as it is with most epidermoid carcinomas of the oral cavity.

Numerous ultrastructural studies of the spindle cell carcinoma, such as those of Leifer and his associates, have been carried out in clarification of the histogenesis and pathogenesis of this lesion.

Treatment and Prognosis. Surgical removal of the tumor, with or without radical neck dissection, alone or in combination with radiation, or radiation therapy alone all have been used in the treatment of this disease. In the series reported by Ellis and Corio, those treated by surgery had the best survival rate although only nine of 18 patients treated in this fashion were alive and well. Radiation therapy appears ineffective. The presence of metastasis signals a poor prognosis, since 81% of the patients with recorded metastases in this study died of their disease. The value of chemotherapy is not known.

Adenoid Squamous Cell Carcinoma

(Adenoacanthoma, pseudoglandular squamous cell carcinoma)

A squamous cell carcinoma containing pseudoglandular spaces or lumina is an interesting tumor of the skin which also occurs with considerable frequency on the lips. It was originally described by Lever in 1947. This variant is produced as a result of acantholysis and degeneration within islands of a squamous cell carcinoma. The result is a pseudoadenocarcinomatous appearance, but there is no evidence of glandular differentiation or of secretory activity or products. There are insufficient reported cases to establish likely behavior.

Clinical Features. Adenoid squamous cell carcinoma is reported to occur as early as 20 years of age, although in the series of Johnson and Helwig, nearly 75% of the patients were 50 years of age or older. In their series, only 2% of the patients were females. Significantly, they found that 93% of the lesions were in the head and neck region.

The lesions on the skin appear as simply elevated nodules that may show crusting, scaling or ulceration. Sometimes there is an elevated or rolled border to the lesion.

A series of 15 cases of adenoid squamous cell carcinoma of the lips (11 lower, three upper, one unstated) has been reported by Jacoway and his associates, while Tomich and Hutton have reported two cases and discussed the lesion in detail. These lip lesions often appear clinically similar to epidermoid carcinoma, being described frequently as ulcerated, hyperkeratotic or exophytic.

There have been four cases of this lesion reported intraorally, two on the gingiva. The latter includes the first case reported from India by Sivapathasundharam B and Rohini S. However three of these lesions behaved in a very aggressive fashion, metastasized in at least two instances and the patient died in all three cases as a result of the tumor. Because of the aggressive nature of the lesions, these intraoral cases may not be identical to those of the skin and lips.

Histologic Features. There is a proliferation of surface dysplastic epithelium into the connective tissue as in the typical epidermoid carcinoma. However, the lateral or deep extensions of this epithelium show the characteristic solid and tubular ductal structures which typify the lesion. These duct like structures are lined by a layer of cuboidal cells and often contain or enclose acantholytic or dyskeratotic cells.

Treatment and Prognosis. The adenoid squamous cell carcinoma is generally treated by surgical excision. On only rare occasions does it metastasize or cause death of the patient. However, recurrence is relatively common (38% in the series of lip lesions reported by Jacoway and his coworkers, although it is possible that some of these may have been second lesions, since multiple adenoid squamous cell carcinomas in the same patient often occur).

Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma is a form of carcinoma with a mixed composition of basaloid and squamous cells. This is a form of oral carcinoma in which the basaloid component comprises small cells with hyperchromatic nuclei and scant cytoplasm that are crowded together into lobulated sheets or strands focally connected to the surface epithelium. Cells at the periphery of the lobules are often palisaded; more centrally there may be cystic spaces, sometimes containing material resembling mucin, and focal squamous differentiation. Mitotic figures, including abnormal forms, and areas of necrosis are commonly seen. There is often hyalinization of the surrounding stroma and chronic inflammatory cell infiltration is variable. Confusion with ameloblastoma and adenoid cystic carcinoma is to be avoided; a focal squamous cell carcinoma component among the basaloid areas is the most important distinguishing feature. Most cases have been described in the larynx, hypopharynx and base of the tongue (Pindborg JJ et al, 1997).

Adenosquamous Carcinoma

A malignant tumor with histological features of both adenocarcinoma and squamous cell carcinoma. This tumor may arise from the ducts of minor salivary glands or from the overlying surface epithelium. The component identified as squamous cell carcinoma may be *in situ* or invasive, and the adenocarcinomatous component comprises glandular structures lined by basaloid, columnar or mucin-secreting cells. A distinction between adenosquamous carcinoma and high-grade mucoepidermoid carcinoma may be difficult, though in the former the glandular and squamous components are generally more distinct. Care must also be taken to distinguish

adenosquamous carcinoma from adenoid squamous cell carcinoma (Pindborg JJ et al, 1997).

Undifferentiated Carcinoma

Undifferentiated carcinoma is carcinoma that lacks evidence of squamous, glandular or other types of differentiation. Accurate diagnosis is almost certainly dependent upon the use of adjunctive diagnostic techniques.

Lymphoepithelioma and Transitional Cell Carcinoma

There is an unusual group of malignant neoplasms exhibiting many features in common which involves nasopharynx, oropharynx, tongue, tonsil and anatomically associated structures such as the nasal chamber and paranasal sinuses. These tumors arise from the mucosa of these areas, exhibit a relatively specific histologic pattern and react in a rather atypical fashion to X-ray radiation. This group of neoplasms consists of the lymphoepithelioma, transitional cell carcinoma and undifferentiated squamous cell carcinoma.

Regaud, and later Schminke as well as Ewing, described the lymphoepithelioma as a lesion occurring chiefly in the nasopharynx of young or middle-aged persons. It was found to be usually a small lesion which often did not manifest itself clinically before regional lymphadenopathy was apparent. Death of the patient was the frequent outcome of the disease even though the lesion was found to be radiosensitive.

Under the term 'transitional cell epidermoid carcinoma', Quick and Cutler reported a series of cases in which the lesions arose chiefly from the tonsil, base of the tongue and nasopharynx. It is in these areas that a transitional type of stratified epithelium is found, the schneiderian membrane. These tumors, then, occurred in areas similar to the sites of the lymphoepithelioma. It was noted, however, that this transitional cell carcinoma was extremely malignant, running a rapid clinical course, metastasizing widely and causing very early death.

Clinical Features. The primary lesion of the lymphoepithelioma or transitional cell carcinoma is usually very small, often completely hidden, usually slightly elevated and either frankly ulcerated or presenting a granular, eroded surface. The tumor is indurated and, in some instances, appears as an exophytic or fungating growth. Since the primary lesion usually remains small, the patient may not seek advice until metastasis to the regional lymph nodes has already occurred.

Scofield carried out an excellent study of 214 cases of malignant nasopharyngeal lesions, comprising transitional cell carcinoma, lymphoepithelioma and undifferentiated squamous cell carcinoma. He found that swelling of the regional lymph nodes was the most common presenting symptom of the observed patients, followed by sore throat, nasal obstruction, defective hearing or ear pain, headache, dysphagia, epistaxis and ocular symptoms. Differences in the median age of the patients were found, patients with transitional cell carcinoma averaging 44 years of age, those with lymphoepithelioma averaging only 26 years and those with undifferentiated squamous cell carcinoma, 56 years. Bloom published a review of cancer of the nasopharynx with particular reference to the significance of the histopathology of the lesions.

Histologic Features. The diagnosis of these neoplasms and their differentiation depends solely upon their microscopic structure.

Transitional cell epidermoid carcinoma consists of cells growing in solid sheets or in cords and nests. The individual cells are moderately large, round or polyhedral, and exhibit a lightly basophilic cytoplasm and indistinct cell outlines. The nuclei appear large and round, and they exhibit varying degrees of mitotic activity. Although a slight degree of intercellular bridging may be present, keratinization and pearl formation are completely lacking. The stroma exhibits little or no lymphocytic infiltration.

The lymphoepithelioma is made up of cells growing in a syncytial pattern with the stroma infiltrated by varying numbers of lymphocytes. The individual cells are large and polyhedral with indistinct outlines. The cytoplasm stains lightly eosinophilic. The nuclei appear large, oval and vesicular, and characteristically contain one or two large eosinophilic nucleoli.

Treatment and Prognosis. Because of the general inaccessibility of the majority of these lesions and their unusual property of being highly radiosensitive, X-ray radiation has been the most commonly accepted treatment. The response of this tumor to radiation is different from that of the epidermoid carcinoma found in these locations. Regional lymph node metastases also respond well to X-ray radiation. The complicating factor lies in the relative inability to treat the widespread metastases in the various organs.

The outlook for patients with these forms of neoplastic disease is poor. Since widespread metastases frequently occur before there is any clinical manifestation of disease, the unfavorable prognosis can be readily understood. In the series of Scofield the probability of five-year survival was calculated. He found that, after onset of symptoms, only 30% of treated patients suffering from transitional cell carcinoma or lymphoepithelioma would be alive in five years, while only 11% with squamous cell carcinoma in these areas would survive.

Nasopharyngeal Carcinoma

A tumor of the nasopharynx involving squamous epithelium, malignant in nature is widely prevalent in parts of south China (Cantonese) (98 per 100,000 of the population); where it is the commonest tumor in men and the second commonest in women. The tumor is rare in most parts of the world, though pockets occur in north and central Africa, Malaysia, Alaska, and Iceland. The most undifferentiated form of the tumor is always associated with EBV whereas the rarer, more differentiated forms are not consistently so. The evidence that EBV is involved in the pathogenesis is based on detection of multiple copies of the EBV genome can be detected in the malignant cells of 100% of undifferentiated

NPC. All the malignant cells express EBNA-1. Furthermore, infectious EBV particles can be recovered from NPC cell lines. And also 100% of sera from undifferentiated NPC patients have high-titer antibodies to EB-viral antigens.

Clinical Features. NPC is a tumor proven to have a genetic background mainly restricted to southern China, with intermediate frequency in some Negro and Mongoloid races and rare in Caucasians. Studies have shown that first-generation immigrants from south China retain the high incidence of the disease, with the later generations showing a decline in incidence. This suggests that environmental as well as genetic factors are involved. NPC is especially associated with certain HLA haplotypes, e.g. HLA A2. More genetic linkage studies demonstrated the presence of NPC susceptibility genes near the MHC locus. Environmental factors are thought to play a role, particularly the consumption of salted fish and foods containing nitrosamines.

The EBV associated undifferentiated type arises mainly in younger patients whereas the more differentiated types occur in older patients and constitute the bulk of the sporadic cases. The tumor most commonly arises in the posterior wall of the nasopharynx in the *fossa of Rosenmuller*, where it often remains silent and metastasize to the local lymph nodes. The most common presentation of NPC is bilateral enlargement of the glands in the neck. The primary tumor may be very small and difficult to locate. Less frequently, the patient may present with the symptoms of invasion by the primary tumor, e.g. nasal obstruction, postnasal discharge, epistaxis, partial deafness and cranial nerve palsies. If untreated, the disease is rapidly fatal due to the development of laryngeal and pharyngeal obstruction.

Histologic Features. Three types of NPC are recognized on histological appearance:

- Well differentiated squamous cell carcinoma
- Nonkeratinizing carcinoma
- Undifferentiated carcinoma.

Serum antibodies to EBV antigens can be used to confirm the diagnosis and monitor the progress of the disease.

Treatment. NPC is difficult to treat surgically because of the early metastasis to regional lymph nodes. The tumor is resistant to chemotherapy, and radiotherapy is the treatment of choice. However, because the tumor usually presents late, the prognosis is poor with a five-year survival rate of 20%. It may be possible to prevent the development of NPC with the use of an EBV vaccine at an early age.

Malignant Melanoma

Malignant melanoma is a neoplasm of epidermal melanocytes. It is one of the more biologically unpredictable and deadly of all human neoplasms. Although it is the third most common cancer of the skin (basal and squamous cell carcinomas are more prevalent), it accounts for only 3% of all such malignancies. However, it results in over 83% of all deaths due to skin cancer in the United States.

Cutaneous melanoma is increasing in incidence. The frequency of its occurrence is closely associated with the constitutive color of the skin, and depends on the geographical zone. Incidence among dark skinned ethnic groups is 1 per 100,000 per year or less, but among light-skinned Caucasians up to 50 and higher in some areas of the world. The highest incidence rates have been reported from Queensland, Australia with 56 new cases per year per 100,000 for men and 43 for women. In contrast, for Africans and Asians the annual incidence rate of malignant melanoma is only 0.2–0.4 per 100,000 population, affecting mainly the palms, soles, and mucous membranes. Cutaneous malignant melanoma is the most rapidly increasing cancer in whites. The annual increase in incidence rates has been estimated to be between 3 and 7%. These estimates suggest a doubling of rates every 10–20 years. These epidemiologic studies have supported the belief that sunlight is an important etiologic factor in cutaneous melanoma.

For many years, it was believed that many melanomas developed in preexisting pigmented nevi, particularly junctional nevi. However, Clark and his colleagues are of the opinion that junctional nevi are not histogenetically related to melanomas. It is quite possible that lesions which were interpreted as junctional nevi were, in fact, premalignant melanocytic dysplasias of some type, thus leading to the erroneous concept of malignant transformation of nevi. In support of this is a study by Jones and his colleagues in which 169 cases diagnosed as junctional nevi were studied retrospectively. Only 74 were actually junctional nevi, whereas 41 were actually melanomas in various phases of growth. The remainder were nevoid and non-nevoid pigmented lesions of various types. Melanomas may develop in or near a previously existing precursor lesion or in healthy-appearing skin. A malignant melanoma developing in healthy skin is said to arise de novo, without evidence of a precursor lesion. Certain lesions are considered to be precursor lesions of melanoma, including the common acquired nevus, dysplastic nevus, congenital nevus, and cellular blue nevus.

The following environmental and genetic factors are described in the etiology of malignant melanoma.

Environmental Factors

Sun exposure. The highest incidence of melanoma has been reported from areas with long hours of sunlight throughout most of the year. Studies reported lower risk for melanoma among people who resided in a low ultraviolet environment in childhood compared with those who resided in a high UV environment. Intermittent exposure to high intensity UV seems to be more detrimental than continual exposure in its causation. Exposure in childhood appears to be particularly important. Recreational activity leading to sunburns in adulthood, such as sailing, has also been incriminated as an etiological factor.

Artificial UV sources. Several case-control studies of melanoma risk and tanning lamp use have demonstrated a positive relation, suggesting that longer wave artificial UVA may play a part in the etiology of melanoma in addition to exposure to natural sunlight. The association of melanoma with PUVA (combination of psoralen (P) and long wave

ultraviolet radiation (UVA)) therapy has also been reported. This topic is still controversial, though, and further studies are needed.

Socioeconomic status. Several studies have reported that melanoma is more prevalent in those of high socioeconomic status. An explanation of this finding may be the fact that the latter can better afford holidays in areas of high UV intensity, as well as expensive outdoor hobbies like sailing, which increase the risk of melanoma due to intermittent intense sun exposure.

Fair skin, freckles, red hair. These phenotypic characteristics increase the risk of melanoma.

Number of melanocytic nevi. The total number of melanocytic nevi, dysplastic or bland, has been reported by several groups as a strong risk factor.

Genetic Factors

Familial melanoma. Between 2 and 5% of melanoma patients have a positive family history of melanoma in at least one first-degree relative. In approximately 30% of melanoma patients abnormalities on chromosome 9p21 are seen.

Xeroderma pigmentosum. In this genetically determined disorder, defective DNA repair mechanisms lead to excessive chronic UV damage and subsequent development of different sun-related skin tumors, including melanoma, in sun-exposed areas.

Risk factors for oral mucosal melanomas are unknown. These melanomas have no apparent relationship to chemical, thermal, or physical events (e.g. smoking, alcohol intake, poor oral hygiene, irritation from teeth, dentures, or other oral appliances) to which the oral mucosa is constantly exposed. Although benign, intraoral melanocytic proliferations (nevi) occur and are potential sources of some oral melanomas; the sequence of events is poorly understood in the oral cavity. Currently, most oral melanomas are thought to arise de novo.

In 1975, Clark and his coworkers presented an interesting concept regarding the developmental biology of cutaneous melanoma. They documented two phases in the growth of melanoma: the *radial-growth phase* and the *vertical-growth phase.*

Many genes are implicated in the development of melanoma, including CDKN2A (p16), CDK4 (chromosome 12q15), RB1, CDKN2A (p19), PTEN/MMAC1, and ras. CDKN2A (p16) appears to be especially important in both sporadic and hereditary melanomas. This tumor suppressor gene is located on band 9p21, and its mutation plays a role in various cancers. Variations in the melanocortin-1 receptor gene can also increase the risk of melanoma. The gene plays an important role in determining hair and skin color, and sensitivity to UV radiation. Interestingly, people who had olive and darker skin and who carried one or more variations of the gene had a higher than average risk for melanoma.

The radial-growth phase is the initial phase of growth of the tumor. During this period, which may last many years, the neoplastic process is confined to the epidermis. Neoplastic cells are shed with normally maturing epithelial cells and although some neoplastic cells may actually penetrate the basement membrane, they are destroyed by a host-cell immunologic response. The vertical-growth phase begins when neoplastic cells populate the underlying dermis. This takes place because of increased virulence of the neoplastic cells, a decreased host-cell response, or a combination of both. Metastasis is possible once the melanoma enters the vertical-growth phase. It is recognized that not all melanomas have both radial- and vertical-growth phases. Nodular melanoma (q.v.) exists only in the vertical-growth phase.

Cutaneous melanoma has been classified into a number of types. However, the most common types are: superficial spreading melanoma; nodular melanoma; lentigo maligna melanoma (Hutchinson's freckle); and acral lentiginous melanoma.

Clinical Features

Superficial spreading melanoma is the most common cutaneous melanoma in Caucasians. It accounts for nearly 65% of cutaneous melanomas. It exists in a radial-growth phase which has been called premalignant melanosis or pagetoid melanoma *in situ.* The lesion presents as a tan, brown, black or admixed lesion on sun-exposed skin, especially the back. It also occurs on the skin of the head and neck, chest and abdomen and the extremities. The radial-growth phase may last for several months to several years. The vertical-growth phase is characterized by an increase in size, change in color, nodularity and, at times, ulceration.

Nodular melanoma accounts for approximately 13% of cutaneous melanomas. It apparently has no clinically recognizable radial-growth phase, existing solely in a vertical-growth phase. It presents as a sharply delineated nodule with varying degrees of pigmentation. They may be pink (amelanotic melanoma) or black. They have a predilection for occurrence on the skin of the back and head and neck skin of men. In other cutaneous sites, there is an even gender distribution.

Lentigo maligna melanoma accounts for approximately 10% of cutaneous melanomas. It exists in a radial-growth phase which is known as **lentigo maligna** or **melanotic freckle of Hutchinson**. The melanotic freckle has been recognized as a clinicopathologic entity for nearly 100 years. However, the concept that it represents a melanoma in a radial-growth phase is much more recent. The lesion occurs characteristically as a macular lesion on the malar skin of middle-aged and elderly Caucasians. It occurs more often in women than in men. In an extensive series of 85 cases, Wayte and Helwig found an average age of 58 years in men and 55 in women. In a series studied by Clark and his colleagues, the median age was 70 years. Both studies showed a female gender predilection. The lesion can remain in the radial-growth phase for years. In Wayte and Helwig's study, the average duration in which an accurate history was possible was 14 years. Clark and Mihm

have documented a lentigo maligna for 50 years prior to the development of a vertical-growth phase. Nearly 53% of the lesions evolved into lentigo maligna melanoma, the vertical-growth phase of this form of melanoma.

Melanoma may occur as a primary lesion not only on the skin but also in the eye and on mucous membranes. It has also been reported as a primary lesion in the parotid gland, although melanomas in this site are usually metastatic to lymph nodes in the parotid region.

Acral lentiginous melanomas. Melanoma developing on the palms and soles, as well as on toes and fingers, represents only 10% of cases in whites, but over 50% of all melanomas on Black and Asian skin. The tumor is characterized by a macular, lentiginous pigmented area around a nodule. Mechanical stress may lead to erosion and ulceration. Subungual melanomas present as pigmentations of the nail bed and are often mistaken for subungual hematomas, and are thus commonly diagnosed at a late stage in development. They are extremely aggressive, with rapid progression from the radial to vertical growth phase.

Mucosal lentiginous melanomas develop from the mucosal epithelium that lines the respiratory, gastrointestinal, and genitourinary systems. These lesions account for approximately 3% of the melanomas diagnosed annually and may occur on any mucosal surface, including the conjunctiva, oral cavity, esophagus, vagina, female urethra, penis, and anus. Noncutaneous melanomas are commonly diagnosed in patients of advanced age. When compared to cutaneous melanomas, mucosal lentiginous melanomas appear to have a more aggressive course, although this may be because they are commonly diagnosed at a later stage of disease than the more readily apparent cutaneous melanomas.

Amelanotic melanoma presents as an erythematous or pink, sometimes eroded, nodule. This tumor is often confused for other tumors, and only the histological examination provides the right diagnosis.

The following criteria aid clinical diagnosis of melanoma **(ABCDE-rule):**

- Asymmetry—in which one half does not match the other half
- Border irregularity—with blurred, notched, or ragged edges
- Color irregularity—pigmentation is not uniform. Brown black, tan, red, white, and blue—can all appear in a melanoma
- Diameter—greater than 6 mm. Growth in itself is also a sign
- Elevation—a raised surface can also be a sign.

Oral Manifestations. Malignant melanoma is an uncommon neoplasm of the oral mucosa. Pliskin reviewed the literature on oral melanoma and found that they accounted for 1.6% of over 7,500 reported melanomas. Other authors have reported rates of 0.2–8%. Conley and Pack reported 26 cases of primary oral melanoma and McCaffrey, Neel and Gaffey reported on the 10 cases treated at the Mayo Clinic. Of epidemiologic interest is the fact that melanoma of the oral mucosa is one of the most common sites for the neoplasm in Japanese. Melanomas in Blacks are seldom found in the skin yet occur on mucous membranes and on the plantar skin.

Primary oral melanoma is nearly twice as common in men as in women. The overall age of occurrence is approximately 55 years, with most cases occurring between 40 and 70 years.

The oral melanoma exhibits a definite predilection for the palate and maxillary gingiva/alveolar ridge. Seventy-seven% of the cases in Pliskin's review occurred in these two sites. Cases are also recorded on the buccal mucosa, mandibular gingiva, tongue, lips and floor of the mouth. The lesion usually appears as a deeply pigmented area, at times ulcerated and hemorrhagic, which tends to increase progressively in size (Fig. 2-35A–C). Amelanotic melanoma accounts for 5–35% of oral melanomas which appear as a white, mucosa-colored, or red mass.

Significantly, focal pigmentation preceding the development of the actual neoplasm frequently occurred several months

A B C

Figure 2-35. Malignant melanoma.
Typical lesions involve the plate **(A)** and **(B)**, and the alveolar ridge **(C)** *(Courtesy of Sivakumar G, Sivapathasundharam B, Karthiga KS. Malignant melanoma of the oral cavity–case reports and review of literature. Indian J Dent Res, 2004, 15(2): 70–73).*

to several years before clinical symptoms appeared. For this reason it has been suggested that the appearance of melanin pigmentation in the mouth and its increase in size and in depth of color should be viewed seriously.

Although clinicopathologic correlation is well established for cutaneous melanomas, it is unfortunate that such correlation does not exist for oral melanomas. It is now apparent that melanomas of the oral mucosa can exist in radial- and vertical-growth phases but only a few such cases have been reported. Takagi and his coworkers were able to document a preexisting or concurrent melanosis in 62 of 94 cases of oral melanomas which they studied. Regezi, Hayward and Pickens evaluated three cases of oral melanoma in accordance with the established clinicopathologic parameters of cutaneous melanomas. They were able to classify one as a superficial spreading melanoma which had a preexisting melanosis for 11 years. The other two had histologic features consistent with lentigo maligna melanoma. However, since these lesions behaved much more aggressively, they were termed *acral-lentiginous melanomas* as suggested by Clark and his colleagues and by Reed.

Most dermatopathologists recognize the existence of lentigo maligna (melanotic freckle of Hutchinson) only on sun-damaged skin and do not accept its occurrence intraorally. It follows that lentigo maligna melanoma (melanoma arising in melanotic freckle of Hutchinson) cannot occur on oral mucosa, although such a case has been reported by Robinson and Hukill. In light of present knowledge, such a case would be called acral-lentiginous melanoma because of the clinicopathologic similarity of the oral lesion to those on palmar and plantar skin (Table 2-11).

Thus, oral melanomas may be expected to exist in superficial spreading, acral-lentiginous and nodular types. Batsakis and his associates and Hansen and Buchner have recently discussed the current concepts of oral mucosal melanomas relative to their cutaneous counterparts.

Table 2-11: Differential diagnosis for melanoma

Condition	Distinguishing characteristics
Seborrheic keratosis	"Stuck-on" appearance, symmetric, often multiple
Traumatized or irritated nevus	Returns to normal appearance within 7–14 days
Pigmented basal cell carcinoma	Waxy appearance, telangiectasias
Lentigo	Prevalent in sun-exposed skin, evenly pigmented, symmetric
Blue nevus	Darkly pigmented from dermal melanocytes, no history of change from melanoma
Angiokeratoma	Vascular tumors, difficult to distinguish
Traumatic hematoma	May mimic melanoma but resolves in 7–14 days
Venous lake	Blue, compressible, found on ears and lips
Hemangioma	Compressible, stable
Dermatofibroma	Firm growths of fibrous histiocytes, 'button-hole' when pinched
Pigmented actinic keratosis	Sandpapery feel; sun-exposed area

Source: Beth G Goldstein, and Adam O Goldstein. American Academy of Family Physicians, News and Publications, 2001.

Histologic Features. The malignant cells often nest or cluster in groups in an organoid fashion; however, single cells can predominate. The melanoma cells have large nuclei, often with prominent nucleoli, and show nuclear pseudoinclusions due to nuclear membrane irregularity. The abundant cytoplasm may be uniformly eosinophilic or optically clear. Occasionally, the cells become spindled or neurotized in areas. This finding is interpreted as a more aggressive feature, compared with findings of the round or polygonal cell varieties.

The intraepithelial component (radial-growth phase) of superficial spreading melanoma is characterized by the presence of large, epithelioid melanocytes distributed in a so-called 'pagetoid' manner (Figs. 2-36, 2-37 A). This pagetoid spread within the epidermis is sometimes known as 'buckshot scatter'. As long as the malignant cells are confined to the epithelium, there is no host-cell response in the underlying connective tissue. When melanocytes penetrate basement membrane, a florid host-cell response of lymphocytes develops. Macrophages and melanophages may be present. The tumor cells are often destroyed by this cellular response. The vertical-growth phase is characterized by the proliferation of malignant epithelioid melanocytes in the underlying connective tissues (Fig. 2-37B). The cells may be arranged singly or in clusters. Melanin pigment is usually scanty.

Nodular melanoma also is characterized by large, epithelioid melanocytes within the connective tissue. However, small ovoid and spindle-shaped cells may be present. Melanin pigment is usually but not invariably present. The tumor cells may invade and ulcerate the overlying epithelium and penetrate the deep soft tissues.

Lentigo maligna (melanotic freckle of Hutchinson) has well-defined histologic features which have been discussed by Wayte and Helwig and by Clark and Mihm. The lesion is characterized

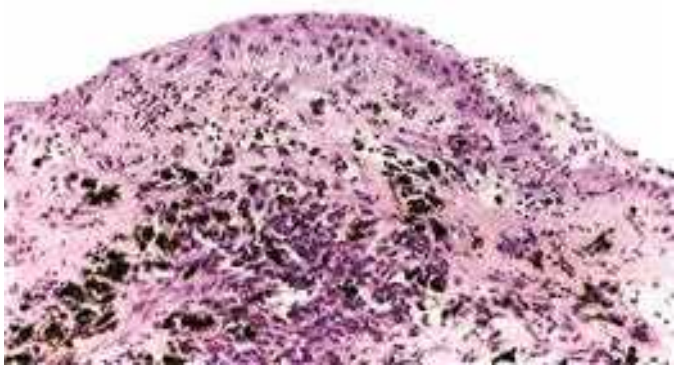
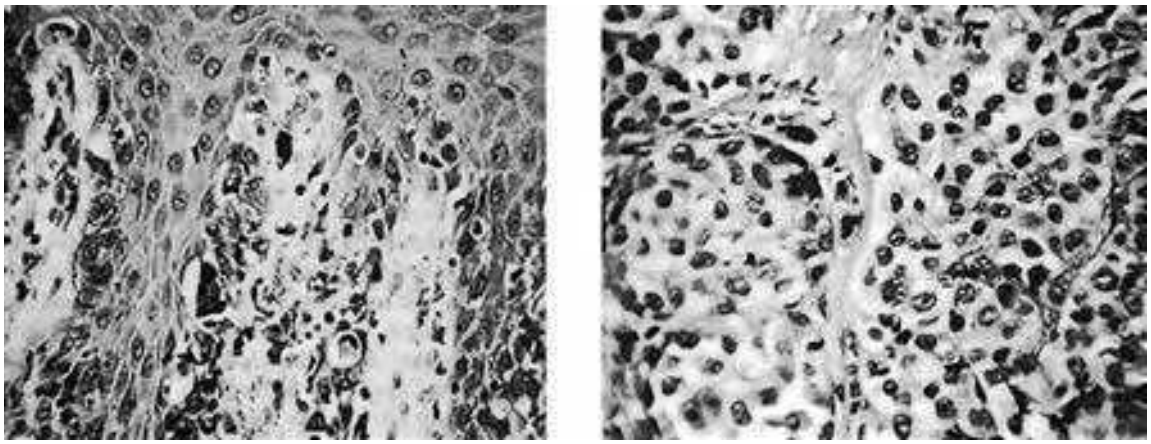


Figure 2-36. Vertical growth phase characterized by malignant melanocytes invading the underlying connective tissue
(Courtesy of Dr Hari S, Noorul Islam College of Dental Science,Trivandrum).



A B

Figure 2-37. Malignant melanoma.
(A) The radial-growth phase or premalignant melanosis is characterized by atypical melanocytes within the epithelium. **(B)** The vertical-growth phase is characterized by malignant epithelioid melanocytes invading the underlying connective tissue.

by increased numbers of atypical melanocytes within the basal epithelial layer. The epithelium is generally atrophic and the dermal collagen shows the effects of sun-damage (basophilic degeneration). If skin appendages are present, they are often involved with atypical melanocytes as well. In time, cords and nests of atypical melanocytes may be evident. Lentigo maligna melanoma is characterized by invasive spindle-shaped cells into the underlying dermis. A lymphohistiocytic infiltrate is usually present.

The acral-lentiginous melanoma is histologically similar to lentigo maligna melanoma. Coleman and his coworkers have studied 35 cases and have pointed out the salient histologic features. These are:

- A lentiginous radial-growth phase
- A deep vertical-growth phase composed predominantly of spindle-shaped cells
- Psoriasiform epidermal hyperplasia
- An intense host-cell response
- A prominent desmoplasia associated with the vertical-growth phase.

Although the majority of melanomas are diagnosed by routine light microscopy, ultrastructural study can be of value in diagnosing and distinguishing between various types of melanoma. As pointed out by Klug and Gunther, the three main types of cutaneous melanoma differ ultrastructurally in the number and size of melanosomes. Regezi, Hayward and Pickens studied an oral acral-lentiginous melanoma ultrastructurally and found premelanosomes and melanosomes similar to those found in normal melanocytes and nevus cells.

Less common histologic variants of melanoma such as desmoplastic, neurotropic, spindle cell and balloon cell melanomas exist. These have been discussed by Ainsworth and her colleagues.

Although immunohistochemical stains are usually not necessary for diagnosis, they are generally performed for confirmation. Both S-100 and homatropine methylbromide (HMB45) stains are positive in melanoma. The S-100 is highly sensitive, although not specific, for melanoma, while the HMB45 is highly specific and moderately sensitive for melanoma. The 2 stains, in concert, can be useful in diagnosing poorly differentiated melanomas. Vimentin is positive in most cases. Recently, microphthalmic transcription factor, tyrosinase, and melano A immunostains have been used to highlight melanocytes.

The lymph node metastasis is identified by using lymphoscintigraphy and a radioactive tracer (technetium-labeled sulfur colloid or human serum albumin).

Treatment and Prognosis. The treatment of cutaneous malignant melanoma is surgical excision. Although regional lymph node dissection is indicated when nodes are involved, prophylactic lymph node dissection is very controversial. The decision of the surgeon relative to elective node dissection should be based upon the thickness of the lesion and its specific anatomic location. In this regard, tumors greater than 0.75 millimeters in thickness and located in the so-called BANS (back, arm, neck and scalp) sites have a greater tendency to metastasize. On the other hand, melanomas of the skin of the face have a much more favorable prognosis.

Chemotherapy, immunotherapy and radiation therapy have been used in the treatment of cutaneous melanoma. The role of these modalities is discussed in the monograph on melanoma edited by Clark, Goldman and Mastrangelo.

The treatment of oral melanoma has been and still is surgical excision. Jaw resection and lymph node dissection is indicated in cases involving bone and regional lymph nodes. Other forms of therapy such as cryosurgery, radiation, chemotherapy and

immunotherapy have been employed on occasion but none have significantly improved the dismal prognosis of melanoma in the oral cavity.

There are both clinical and histologic factors which are of great prognostic significance in cutaneous melanomas. According to McGovern, clinical features with prognostic significance are the gender and age of the patient and the site of the lesion. Women have a much better survival rate up to the age of 50 years and then the rate declines.

Histologic features which are of prognostic significance are histologic type and depth of invasion. Nodular melanoma and superficial spreading melanoma have much poorer prognosis than lentigo maligna melanoma. In fact, McGovern believes that lentigo maligna melanoma should be considered as a separate entity because of its better prognosis. In 1999, Clark and his colleagues related prognosis to the anatomic level of invasion at the time of diagnosis. In 1970, Breslow proposed that the actual thickness of the tumor as measured in millimeters by an ocular micrometer correlated well with prognosis. It is now recognized that tumors less than 0.75 mm in thickness rarely metastasize or cause death, regardless of the location on skin.

Unfortunately, oral mucosal melanomas have a far worse prognosis than cutaneous melanomas. According to Pliskin, the five-year survival rate for such tumors is approximately 7%. Batsakis and his colleagues have pointed out that establishment of prognostic indicators for oral mucous membrane melanomas has not kept pace with those which have been established for cutaneous melanomas.

The level of tumor invasion is another important indicator of the prognosis of MM. The **Clark system** is generally used to grade tumor invasion based on the deepest histologic cutaneous structure the tumor infiltrates. Table 2-12 depicts five-year survival (FYS) rates for MM based on the Breslow and Clark grading systems.

Table 2-12: Malignant melanoma classification and five-year survival (FYS) rates

Clark system	FYS rate (percentage)
Level I: Tumor *in situ* Tumor is confined to the epidermis and is entirely above the basement membrane	100–98
Level II Invasive cells are only present in the papillary dermis. The tumor is usually still considered to be in the radial growth phase	96–72
Level III Tumor cells are found throughout the papillary dermis with impingement on the reticular dermis. The tumor has entered the vertical growth phase	90–46
Level IV Tumor cells are clearly seen between the collagen bundles of the reticular dermis	67–31
Level V	
Tumor cells show invasion of the subcutaneous fat.	48–12

Breslow system*	FYS rate (in percentage)
0.00 – 0.76 mm	98 – 99
0.76 – 1.49 mm	85
1.50 – 2.49 mm	84
1.50 – 2.49 mm	84
4.00 mm	44

** Total tumor thickness as measured from the outermost layer of the stratum granulosum to the deepest identifiable point of tumor invasion in the dermis.*

BENIGN TUMORS OF CONNECTIVE TISSUE ORIGIN

Oral Fibroma and Fibromatoses Fibroma
(Irritation fibroma, focal fibrous hyperplasia)

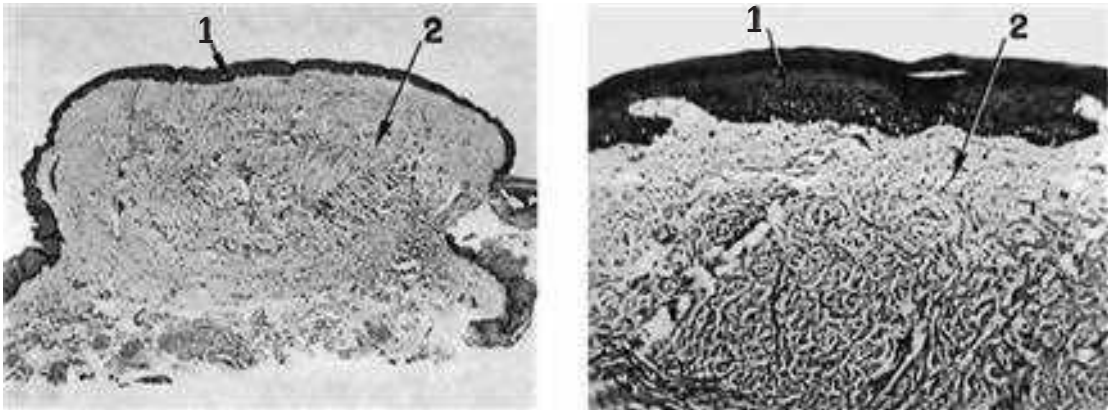
This connective tissue tumor is the most common benign soft tissue neoplasm occurring in the oral cavity. Most fibromas represent reactive focal fibrous hyperplasia due to trauma or local irritation. Although the term focal fibrous hyperplasia more accurately describes the clinical appearance and pathogenesis of this entity, it is not commonly used. It is intimately related to fibrous hyperplasia and, in many instances, is histologically indistinguishable from it.

Clinical Features. A fibroma may occur at any oral site, most commonly it is seen on the buccal mucosa along the plane of occlusion. Other frequent sites are the gingiva, buccal mucosa, the tongue, lips and the palate.

The fibroma appears as an elevated nodule of normal color with a smooth surface and a sessile or, occasionally, pedunculated base. The tumor may be small or, in rare instances, may range up to several centimeters in diameter. Projecting above the surface, the tumor sometimes becomes irritated and inflamed and may even show superficial ulceration or hyperkeratosis. It is nearly always a well-defined, slowly growing lesion that occurs at any age, but is most common in the third, fourth and fifth decades. Females are affected twice as frequently as males.

The clinical differential diagnosis of a fibroma includes giant cell fibroma, neurofibroma, peripheral giant cell granuloma, mucocele, and benign and malignant salivary gland tumors.

Histologic Features. The fibroma consists of bundles of interlacing collagenous fibers interspersed with varying numbers of fibroblasts or fibrocytes and small blood vessels. The surface of the lesion is covered by a layer of stratified squamous epithelium which frequently appears stretched and shows shortening and flattening of the rete pegs (Fig. 2-38). If trauma to the tissue has occurred, vasodilatation, edema and inflammatory cell infiltration are variably present. Areas of diffuse or focal calcification or even ossification are found in some fibromas, chiefly those occurring on the gingiva, and these lesions have sometimes been called 'peripheral ossifying fibroma', 'ossifying fibroid epulis', 'peripheral cementifying fibroma' or 'peripheral odontogenic fibroma' (q.v.).



A B

Figure 2-38. Fibroma.
(A) The low-power photomicrograph illustrates the typical sessile base, the thin surface epithelium (1) and coarse bundles of collagen (2) comprising the bulk of the tumor. **(B)** The high-power photomicrograph shows the relative acellularity of the connective tissue.

It is interesting to note that the fibroma, a true neoplasm of connective tissue origin, is microscopically similar to the condition known as inflammatory hyperplasia, an increased bulk of connective tissue which forms as part of an inflammatory reaction. In few situations is the distinction between the two general processes, hyperplasia and neoplasia, as poorly defined as it is here. Hyperplasia is usually considered to be a self-limiting process which is not etiologically related to neoplasia. Both processes, however, are typified by an increase in the number of cells brought about by increased mitotic activity. Hyperplastic tissue sometimes, but not invariably, regresses after the removal of the stimulus or irritant. Neoplastic tissue shows no such regression.

This distinction between hyperplasia and neoplasia is not clearcut, and cases occur intraorally in which there is focal or diffuse proliferation of tissue obviously due to irritation which does not regress after removal of the irritant. The tissue appears identical with that in other cases which do regress when the irritant is removed. This suggests that the processes of hyperplasia and neoplasia may not be as completely dissociated as previously considered and that a true oral neoplasm may result from chronic irritation.

Many persons think, however, that a great number of the lesions of the oral cavity diagnosed as fibromas are, in reality, simply examples of focal or localized hyperplasia, resulting from inflammation, and that the true fibroma is much rarer than is presently believed. There is no doubt that the pyogenic granuloma (q.v.), if left untreated, will undergo eventual healing by sclerosis and will then microscopically resemble the fibroma.

Treatment and Prognosis. The treatment for the fibroma, or focal inflammatory hyperplasia as the case may be, is conservative surgical excision. Seldom does the lesion recurs.

Fibromatoses

Fibromatoses, sometimes referred to as juvenile or aggressive fibromatoses, represent a group of infiltrating fibrous proliferations with a biologic behavior and microscopic appearance intermediate between those of benign lesions and fibrosarcomas.

Clinical Features. The head and neck region, particularly the submandibular area, is a common site of involvement. However, intraoral lesions are rare. The age of affected patients varies from 0–51 years, but in 74% of patients, fibromatosis is diagnosed before they are aged 10 years. No significant gender predilection is apparent.

A desmoplastic fibroma is considered to be the intraosseous counterpart of the soft-tissue fibromatosis. A desmoplastic fibroma appears as a firm, painless, poorly demarcated mass that is either rapidly or slowly growing. The mass is locally aggressive, blends into surrounding structures, and causes resorption of the underlying bone when it is present.

Fibromatosis has to be differentiated clinically from low-grade fibrosarcoma, nodular fasciitis, reactive fibrous hyperplasia, fibrous histiocytoma, and neurofibroma.

Histologic Features. Histologically, fibromatosis is characterized by a poorly delineated, infiltrating cellular proliferation of mature spindle cells arranged in streaming and interlacing fascicles. Collagen production is prominent. Infiltration of the adjacent structures is common at the periphery, but cellular atypia is not present.

Treatment and Prognosis. The treatment is wide excision. The recurrence rate of 24% for intraoral fibromatoses is recorded.

Giant Cell Fibroma

Giant cell fibroma is an oral tumor first described in 1974 by Weathers and Callihan as a distinctive entity. The distinctive histologic appearance sets it apart from a conventional fibroma.

Clinical Features. It appears as an asymptomatic sessile or pedunculated nodule that is less than 1 cm in diameter. Often, it has a bosselated or somewhat papillary surface. Most cases are diagnosed in persons aged 10–30 years, and no gender

predilection exists. The most common site is the mandibular gingiva, followed by the maxillary gingiva, the tongue, and the palate.

The clinical differential diagnoses include squamous papilloma, irritation fibroma, pyogenic granuloma, and peripheral giant cell granuloma.

Histologic Features. Microscopically, a giant cell fibroma is an unencapsulated mass of loose fibrous connective tissue that contains numerous characteristic large, plump, spindle-shaped and stellate fibroblasts, some of which are multinucleated. These cells are easily observed in the peripheral areas of the lesion, whereas the more central areas contain typical fusiform fibroblasts. The surface epithelium is corrugated and atrophic; in contrast to an irritation fibroma, a giant cell fibroma has thin, elongated rete ridges.

The origin of stellate and multinucleate cells is not well known. Few studies showed positive immunostaining for vimentin. This suggests that the stellate and multinucleate cells of GCF have a fibroblast phenotype.

Treatment and Prognosis. Conservative excisional biopsy is curative, and its findings are diagnostic. Recurrence is rare.

Myofibroma and Myofibromatosis

The terms myofibroma (if solitary) or myofibromatosis (if multicentric) are applied to the tumors which show predominant myofibroblasts. Myofibroblasts have features of both fibroblasts and smooth muscle cells.

Clinical Features. The tumors are benign and similar to fibromatosis but less aggressive. Tumors of the myofibroblasts may occur in either gender and in patients of all ages, with a mean patient age of 26.6 years.

Myofibroblastic tumors are most common in the head and neck region, including oral and perioral sites, than in other areas. Intraoral lesions occur mainly on the tongue, lips, and buccal mucosa. Tumors have also been described in the dermis, soft tissues, viscera, and bone. Jaw lesions, usually mandibular lesions, generally appear as well-defined unilocular or multilocular radiolucencies. Oral lesions appear as firm submucosal nodules or exophytic masses with a diameter of 0.3–5.0 cm. Although lesions are most often asymptomatic, they may be tender or even painful.

The clinical differential diagnosis for oral myofibroma includes irritation fibroma, peripheral giant cell fibroma, neurofibroma, leiomyoma, and benign and malignant neoplasms of the minor salivary glands.

Histopathologic Features. Histologically, all cases showed a biphasic pattern that consisted of fascicles of spindle cells with abundant eosinophilic cytoplasm that resembled smooth muscle, in addition to a population of more primitive spindled cells associated with a hemangiopericytoma like vascular pattern.

Treatment and Prognosis. Treatment for oral myofibromas is conservative excision. The recurrence rate is low, and spontaneous regression is reported.

Peripheral Ossifying Fibroma

(Peripheral odontogenic fibroma, peripheral cementifying fibroma, calcifying or ossifying fibroid epulis, peripheral fibroma with calcification)

There are numerous histologically different types of focal overgrowths which may occur on the gingiva, such as the peripheral giant cell granuloma, the giant cell fibroma, the pyogenic granuloma, the simple fibroma (which may be simply a healed pyogenic granuloma in many cases) and the present lesion, which in the past has been known by a variety of names indicated above. The terms most frequently used have been the 'peripheral ossifying fibroma' and the 'peripheral odontogenic fibroma'. In as much as the latter term has been used for a lesion described by the World Health Organization in their classification of odontogenic tumors as a totally different entity, the term peripheral ossifying fibroma will be used here for that relatively common gingival lesion characterized by a high degree of cellularity usually exhibiting bone formation, although occasionally cementum-like material or rarely dystrophic calcification may be found instead.

Some investigators believe that the lesion is nevertheless odontogenic in origin, being derived from the periodontal ligament, especially since it only occurs on the gingiva and may contain oxytalan fibers. At the present time, however, its exact derivation is still uncertain. Despite the similarity in terminology, it is not considered to be the extraosseous counterpart of the central ossifying fibroma. An attempt at clarification of the terms 'peripheral ossifying fibroma' and 'peripheral odontogenic fibroma' has been published recently by Gardner.

Clinical Features. The peripheral ossifying fibroma can occur at any age, although it appears to be somewhat more common in children and young adults. In a study of 365 cases by Cundiff, 50% of the lesions occurred between the ages of five and 25 years with the peak incidence at 13 years, while the mean age was 29 years. Most reported series of cases show a predilection for occurrence in females by a ratio ranging from 2 : 1 to 3 : 2. In addition, the lesions are approximately equally divided between the maxilla and the mandible. In the series reported by Cundiff, over 80% of the lesions in both jaws occurred anterior to the molar area. A series of 185 cases of 'peripheral fibroma with calcification' were also reported by Bhaskar and Jacoway with very similar clinical data.

The clinical appearance of the lesion is characteristic but not pathognomonic. It is a well-demarcated focal mass of tissue on the gingiva, with a sessile or pedunculated base (Fig. 2-39A). It is of the same color as normal mucosa or slightly reddened. The surface may be intact or ulcerated. It most commonly appears to originate from an interdental papilla.

Radiographic Features. In the vast majority of cases, there is no apparent underlying bone involvement visible on the radiograph. However, on rare occasions, there does appear to be superficial erosion of bone.

Histologic Features. The surface of the peripheral ossifying fibroma exhibits either an intact or, more frequently, an

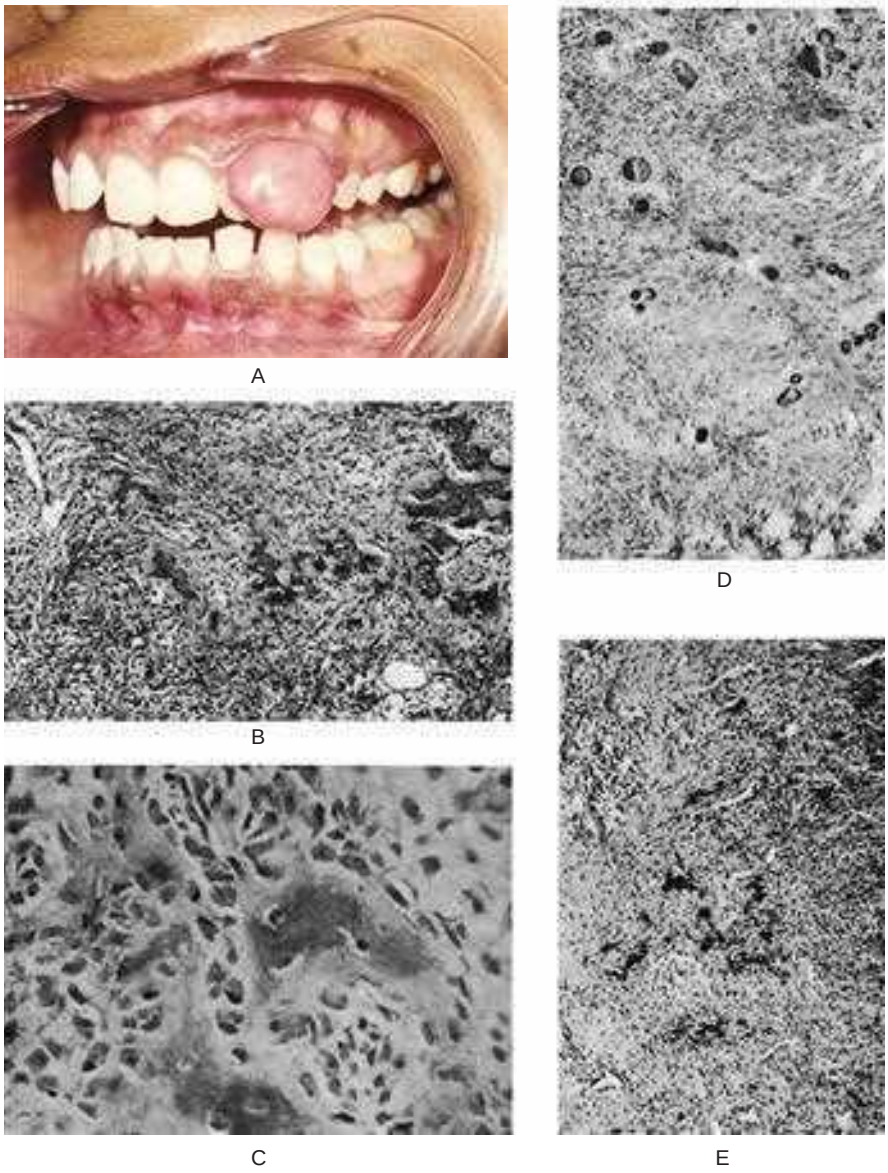


Figure 2-39. Peripheral ossifying fibroma.
The sessile lesion on the gingiva **(A)** is histologically a very cellular lesion which also exhibits most frequently irregular trabeculae of osteoid or bone (**[B]** in low power, **[C]** high power), but occasionally presents cementum-like droplets **(D)** or even dystrophic calcification **(E)**. *(A, Courtesy of Dr Vandhana KL, Department of Periodontics, College of Dental Sciences, Davangere)*.

ulcerated layer of stratified squamous epithelium. The bulk of the lesion is composed of an exceedingly cellular mass of connective tissue comprising large numbers of plump proliferating fibroblasts intermingled throughout a very delicate fibrillar stroma. The lesion is quite characteristic in its high degree of cellularity in contrast to the usual simple fibroma. In addition, vascularity is not nearly as prominent a feature of this lesion as in the pyogenic granuloma. Several forms of calcification occur in this particular lesion and will vary in amount from case to case. The calcification may be in the form of single or multiple interconnecting trabeculae of bone or osteoid (either mature lamellar bone or immature cellular bone), although less commonly globules of calcified material closely resembling acellular cementum, or a diffuse granular dystrophic calcification may be found (Fig. 2-39B, C, D, and E). Significantly, the degree of cellularity of the lesions is usually greatest in the areas of the bone cementum of calcification.

On occasion, areas will be found containing multinucleated giant cells which, with the surrounding tissue, bear considerable resemblance to some areas of the peripheral giant cell granuloma.

Treatment and Prognosis. The lesions should be surgically excised and submitted for microscopic examination for confirmation of diagnosis. The extraction of adjacent teeth is seldom necessary or justified. However, the lesions do recur with some frequency and, in fact, repeated recurrences are not uncommon. In the series of Cundiff, 16% of the cases

recurred, while in a series of 50 cases reported by Eversole and Rovin, the recurrence rate was 20%.

Central Ossifying Fibroma of Bone
(Central fibro-osteoma)

The ossifying fibroma of bone is a central neoplasm of bone which has caused considerable controversy because of confusion of terminology and criteria of diagnosis. It now appears that this represents a definite entity which should be separated from fibrous dysplasia of bone and the other fibro-osseous lesions which do not represent true neoplasms. This concept has been discussed by Pindborg, by Waldron and by many others.

There is a remarkable similarity in clinical features between this lesion and the central cementifying fibroma, a tumor accepted by most investigators as being odontogenic in origin. There is also considerable similarity and even overlap in the histologic features of these two lesions. For these reasons, it has been suggested that:

- These are two separate benign tumors, identical in nature except for the cell undergoing proliferation, the osteoblast with bone formation in one case, or the cementoblast with cementum formation in the other case; or
- These represent simply two facets of the same basic tumor. Further investigation will be necessary to clarify the relationship, or lack of it, between the central ossifying fibroma and the central cementifying fibroma.

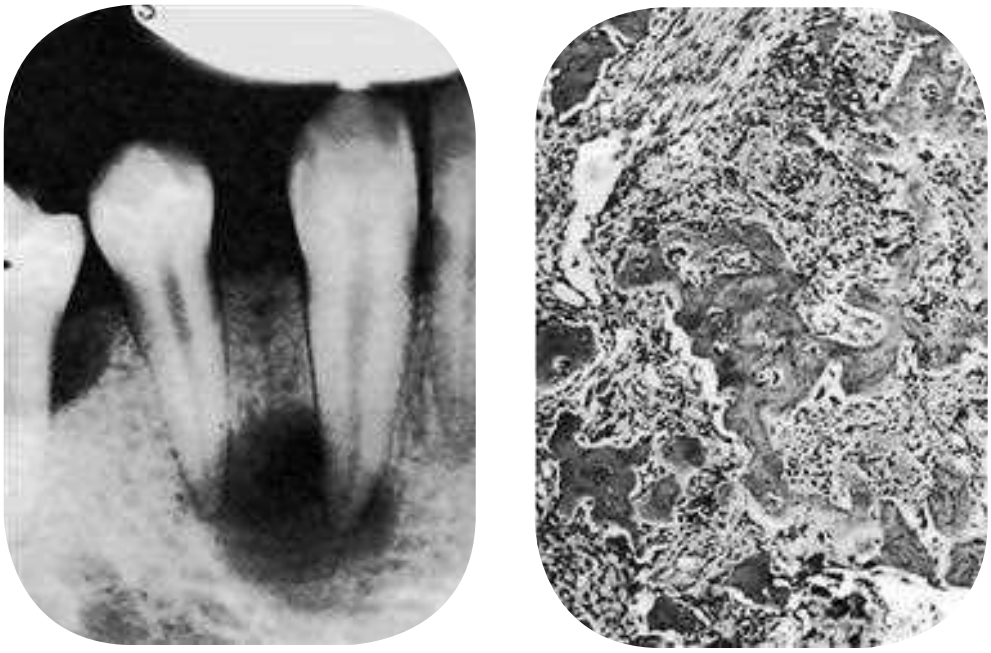
Clinical Features. The central ossifying fibroma may occur at any age, but is far more common in young adults. The age range of occurrence in a series of 31 cases presented by Shafer was nine to 52, with a mean of 33 years of age. Langdon and his associates reported similar findings. Either jaw may be involved, but there appears to be a predilection for the mandible. In the series of Shafer, there were 26 cases in the mandible but only five in the maxilla. A marked predilection for occurrence in females was also noted: 26 cases compared to only five in males. In addition, there was an unusually high incidence of lesions in blacks; 13 cases contrasted to 18 cases in white patients.

The lesion is generally asymptomatic until the growth produces a noticeable swelling and mild deformity; displacement of teeth may be an early clinical feature. It is a relatively slow growing tumor and may be present for some years before discovery. Because of the slow growth, the cortical plates of bone and overlying mucosa or skin are almost invariably intact.

Radiographic Features. The neoplasm presents an extremely variable radiographic appearance depending upon its stage of development. Yet despite the stage of development, the lesion is always well circumscribed and demarcated from the surrounding bone, in contrast to fibrous dysplasia.

In its early stages, the central ossifying fibroma paradoxically appears as a radiolucent area with no evidence of internal radiopacities (Fig. 2-40A). As the tumor bone apparently matures, there is increasing calcification, so that the radiolucent areas becomes flecked with opacities until, ultimately, the lesion appears as a relatively uniform radiopaque mass. Displacement of adjacent teeth is common, as well as impingement upon other adjacent structures.

Histologic Features. The lesion is composed basically of many delicate interlacing collagen fibers, seldom arranged in discrete bundles, interspersed by large numbers of active,



A B

Figure 2-40. Central ossifying fibroma of bone.

proliferating fibroblasts. Although mitotic figures may be present in small numbers, there is seldom any remarkable cellular pleomorphism. This connective tissue characteristically presents many small foci of irregular bony trabeculae (Fig. 2-40B) which may bear some similarity to the bizarre Chinese-character shape of the bony trabeculae in fibrous dysplasia of bone (q.v.).

As the lesion matures, the islands of ossification increase in number, enlarge and ultimately coalesce. This, with the probable increase in degree of calcification, accounts for increasing radiopaqueness of the lesion on the radiograph.

Treatment and Prognosis. The lesion should be excised conservatively, and recurrence is rare.

Peripheral Giant Cell Granuloma

(Peripheral giant cell epulis, peripheral giant cell reparative granuloma)

Peripheral giant cell granuloma has an unknown etiology, with some dispute as to whether this lesion represents a reactive or neoplastic process. However, most authorities believe peripheral giant cell granuloma is a reactive lesion. Since the lesion does not appear to be truly a 'reparative' one, this term reparative granuloma has been deleted from the name in the past few years.

The use of the term 'epulis' in connection with this or any other oral tumor is to be deplored. By definition, the word means only a growth on the gingiva and is entirely nonspecific. Since it gives no hint as to the true nature of a lesion, the term should be discarded.

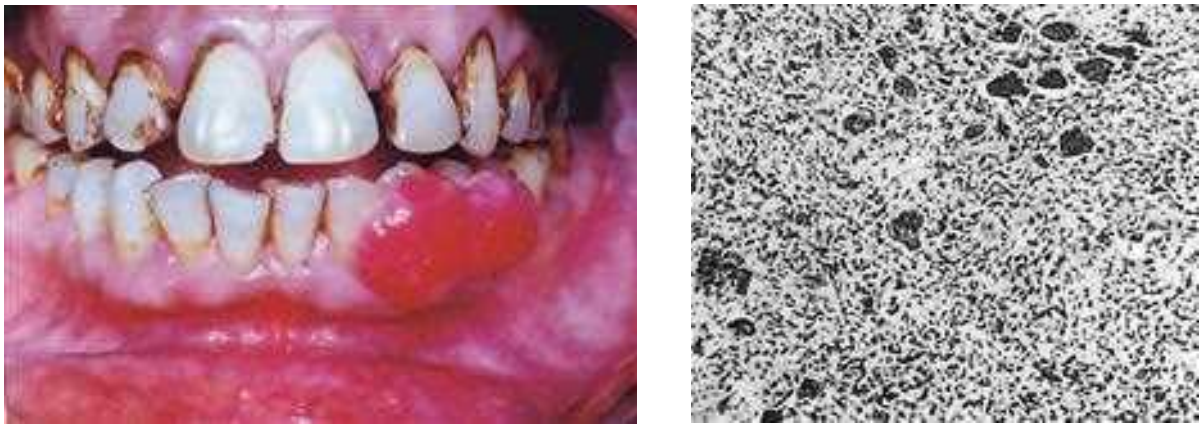
The etiology of peripheral giant cell granuloma is unknown, but local irritation due to dental plaque or calculus, periodontal disease, poor dental restorations, ill-fitting dental appliances, or dental extractions has been suggested to contribute to the development of the lesion.

Clinical Features. Although the lesion may be found in very young children as well as in dentulous or edentulous elderly persons, most patients were in fourth to sixth decades of life and the mean age of patients at the time of diagnosis is typically 38–42 years. It was found that females were affected almost twice as frequently as males — 65% compared to 35%. A similar gender predilection has been found for the central giant cell granuloma. Lesions are generally asymptomatic and have a relatively rapid growth rate, often attaining a size of 1 cm within a few months.

Peripheral giant cell granuloma may vary considerably in clinical appearance. It always occurs on the gingiva or alveolar process, most frequently anterior to the molars, and presents itself as a pedunculated or sessile lesion that seems to be arising from deeper in the tissue than many other superficial lesions of this area such as the fibroma or pyogenic granuloma, either of which it may resemble clinically. Thus it seems to originate from either periodontal ligament or mucoperiosteum. The lesion also varies widely in size, but usually is between 0.5 and 1.5 cm in diameter. It is most often dark red, vascular or hemorrhagic in appearance, and it commonly exhibits surface ulceration.

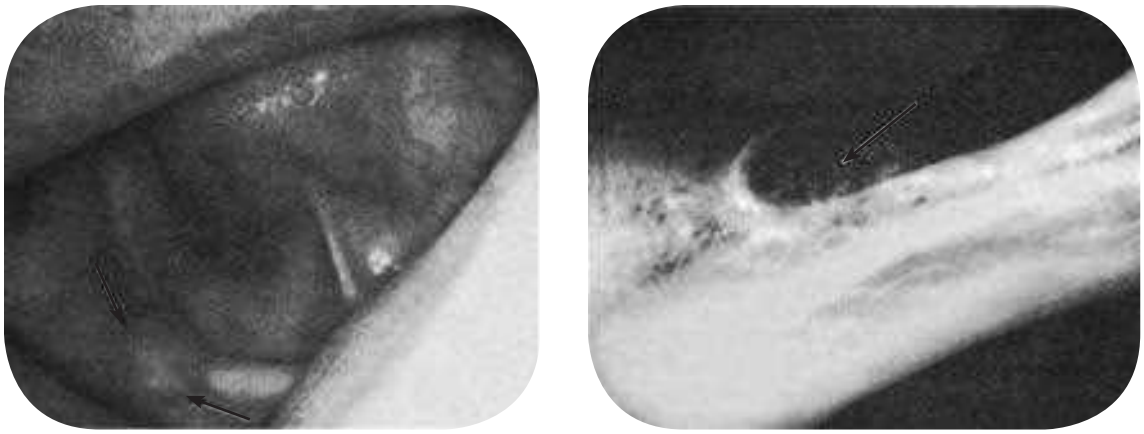
In the edentulous patient, the lesion may appear sometimes as a vascular, ovoid or fusiform swelling of the crest of the ridge, seldom over 1–2 cm in diameter (Fig. 2-41A). Or there may be a granular mass of tissue which seems to be growing from the tissue covering the slope of the ridge. The color of these lesions varies, but is usually similar to that of lesions in dentulous patients. Ulceration is less common in the edentulous situation. A slight predilection for the mandible is observed in most reported series.

Histologic Features. The microscopic appearance of the giant cell lesion is unique. It consists of a nonencapsulated mass of tissue composed of a delicate reticular and fibrillar connective tissue stroma containing large numbers of ovoid or spindle-shaped young connective tissue cells and multinucleated giant cells. The giant cells in some instances resemble osteoclasts and in other cases are considerably larger than the typical osteoclast. Capillaries are numerous, particularly around the periphery of the lesion, and the giant



A B

Figure 2-41. Peripheral giant cell granuloma of gingiva.
(A, Courtesy of Dr Vandhana KL, Department of Periodontics, College of Dental Sciences, Davangere).



A B

Figure 2-42. Peripheral giant cell granuloma.
The lesion in edentulous patients produces a circumscribed growth, causing expansion of the alveolar ridge, **(A)**. The radiograph shows ragged loss of bone with peripheral 'cuffing', **(B)**.

cells sometimes may be found within the lumina of these vessels. Foci of hemorrhage, with liberation of hemosiderin pigment and its subsequent ingestion by mononuclear phagocytes, as well as inflammatory cell infiltration, are also characteristic features. Spicules of newly formed osteoid or bone are often found scattered throughout the vascular and cellular fibrous lesion (Fig. 2-42B).

A histochemical study of this lesion has been reported by Shklar and Cataldo with distinct differences observed in different multinucleated giant cells with respect to the distribution of tyrosine and sulfhydryl groups.

The origin of the giant cells has never been established. Although their resemblance to osteoclasts is sometimes striking, seldom are they seen carrying out the ascribed normal resorptive function of such cells. Geschickter and Copeland suggested that the giant cells might be derived from proliferating giant cells associated with the resorption of deciduous tooth roots. Thus they suppose the lesion to be concerned with the transition from the deciduous to the permanent dentition. Unfortunately, such association of lesions is present in only a few cases even though the tumor is a rather common one in youngsters. Such a theory would account for the predominance of the lesions anterior to the permanent molars.

There has been considerable support for another theory of origin from endothelial cells of capillaries. There is some basis in fact for such an idea, the chief being the common occurrence of the giant cells within vascular channels, suggesting that they arise here through fusion of endothelial cell. This suggested to earlier workers that the tumor was a malignant metastasizing one, and they applied to it the term 'giant cell sarcoma' or, in some cases, 'myeloid sarcoma'.

A recent study of the giant cells in the peripheral giant cell granuloma by electron microscope has been reported by Sapp. He found that these giant cells ultrastructurally contained a sufficient number of features in common with osteoclasts to conclude that they represent a slightly modified form of that cell. In addition, he reported that the stromal cells were structurally compatible with the various stages of differentiating osteoprogenitor cells.

Laboratory studies are generally not necessary. Serum calcium level or a parathyroid hormone assay may be indicated to rule out the rare possibility of brown tumor for lesions that are particularly large and recurrent, may be associated with systemic signs of hyperparathyroidism.

Radiographic Features. The intraoral radiograph may or may not exhibit evidence of involvement of the bone underlying the lesion. In edentulous areas the peripheral giant cell granuloma characteristically exhibits superficial erosion of the bone with pathognomonic peripheral 'cuffing' of the bone as seen in the radiograph (Fig. 2-41B). When the tumor occurs in areas in which teeth are present, the radiograph may reveal superficial destruction of the alveolar margin or crest of the interdental bone, but this is by no means invariably present.

Treatment and Prognosis. Conservative excision is typically curative, although the lesion must be completely removed to prevent recurrence. Prognosis is excellent. A recurrence rate of 10–15% has been reported in most series; however, recurrences are typically managed easily with additional surgery.

Central Giant Cell Granuloma and Giant Cell Tumor of Bone

Central giant cell granuloma (CGCG) is an uncommon, benign, and proliferative lesion whose etiology is not defined. It was Jaffe who first introduced the term central giant cell reparative granuloma to distinguish this lesion from the giant cell tumor of long bones. However, since a reparative response was quite rare and most of these lesions were found to be destructive rather than reparative, the word 'reparative' was omitted from that term.

Clinical Features. Though central giant cell granuloma may be seen in all age group, it is much more common in the young, especially those under 30 years of age. It is somewhat more common in females than in males. The gender distribution of 38 cases reported by Waldron and Shafer was approximately 2 to 1, females over males. A study of 34 cases

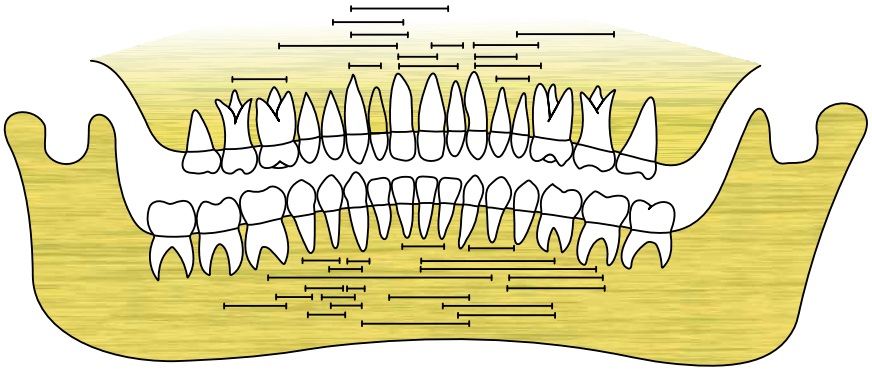


Figure 2-43. Central giant cell granuloma.
Distribution of sites of lesions.
(*Source: Waldron CA, Shafer WG: The central giant cell reparative granuloma of the jaws. Am J Clin Pathol, 45: 437, 1966*).

by Austin, over 60% of the cases occurred before the age of 30 years. Furthermore, 60% of their cases were under the age of 20 years. Either jaw may be involved, but the mandible is affected more often. Two-thirds of their cases occurred in the mandible, and only one-third in the maxilla. The lesions are more common in the anterior segments of the jaws and, not uncommonly, cross the midline (Fig. 2-43).

The lesion may present no signs or symptoms and may be discovered accidentally, but sometimes, central giant cell granuloma may lead to an expansion of the cortex and perforation, mobility, displacement, and root resorption of associated tooth. The borders of the lesions may be regular or diffuse.

Depending on clinical and radiographic features, central giant cell granuloma can be classified into two types. The first type of lesion is **nonaggressive,** slow growing, does not show root resorption or cortical perforation, and often shows new bone formation. The second type is an **aggressive** type which grows quickly, shows pain, cortical perforation, and root resorption. On the other hand, although the clinical, radiographic and histologic features of CGCG have been extensively evaluated, the dimensional features of these lesions have not been clearly defined.

Radiographic Features. Central giant cell granuloma is essentially a destructive lesion, producing a radiolucent area with either a relatively smooth or a ragged border, and sometimes showing faint trabeculae. Definite loculations are often present, particularly in larger lesions. The cortical plates of the bone are often thin and expanded and may become perforated by the mass. Displacement of the teeth by the lesion is seen with some frequency. The appearance of the giant cell granuloma is not pathognomonic and may be confused with that of many other lesions of the jaw, both neoplastic and non-neoplastic (Fig. 2-44 A–F).

Histologic Features. Central giant cell granuloma is made up of a loose fibrillar connective tissue stroma with many interspersed proliferating fibroblasts and small capillaries. The collagen fibers are not usually collected into bundles; however, groups of fibers will often present a whorled appearance. Multinucleated giant cells are prominent throughout the connective tissue, but not necessarily abundant (Fig. 2-45). These giant cells vary in size from case to case and may contain only a few or several dozen nuclei. In addition, there are usually numerous foci of old extravasated blood and associated hemosiderin pigment, some of it phagocytized by macrophages. Foci of new trabeculae of osteoid or bone also are often seen, particularly around the periphery of the lesion.

There is a debate whether the giant cells are fibroblast origin or from monocyte/macrophages. Recent study by Itonaga et al, indicate that the giant cells in CGCG of the jaw are osteoclast like and formed from monocyte/macrophage precursors which differentiate into osteoclasts.

Treatment and Prognosis. The treatment of the giant cell granuloma is curettage or surgical excision. The lesions so treated almost invariably fill in with new bone and heal with no difficulty. Occasional lesions recur, but this is seldom sufficient cause for more radical procedures. X-ray radiation is contraindicated.

Giant Cell Tumor of Bone
(Osteoclastoma)

Giant cell tumor of bone is a distinctive neoplasm of undifferentiated cells. Multinucleated giant cells apparently result from fusion of the proliferating mononuclear cells, and although they are a constant and prominent part of this tumor, the giant cells are probably of less significance than the mononuclear cells. The exact cell of origin of this neoplasm is still unknown. Several immunohistochemical studies have suggested that the mononuclear cells are of histiocytic origin and that the giant cells arise from their fusion.

Malignant giant cell tumor cannot be diagnosed with assurance unless evidence of ordinary benign giant cell tumor exists within the lesion or has been demonstrated previously at the same site. If the stromal cells of a tumor that has many benign giant cells are malignant throughout with features of osteosarcoma, malignant fibrous histiocytoma, or fibrosarcoma, the tumor probably has no relationship to giant cell tumor.

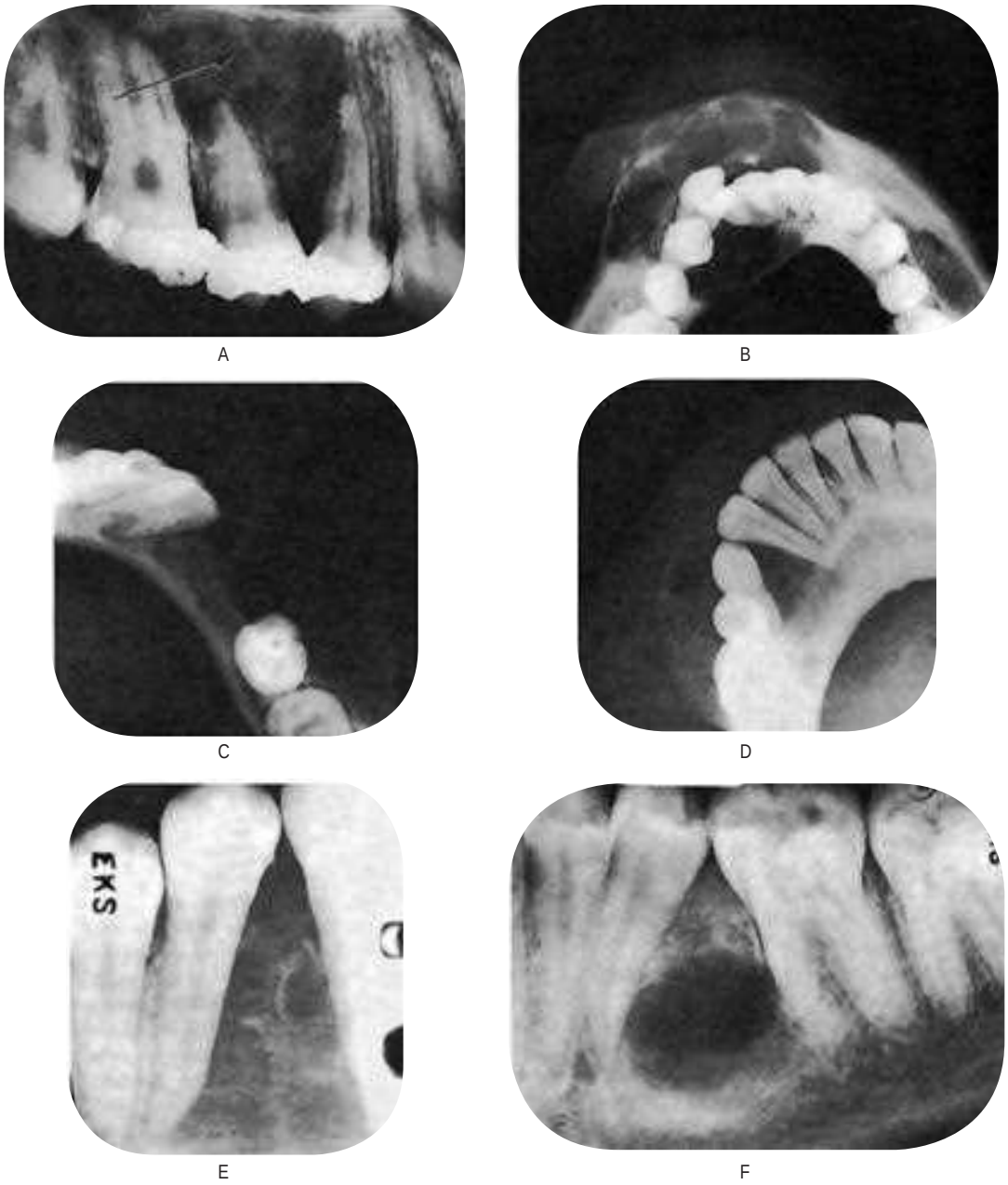


Figure 2-44. Central giant cell granuloma.
Various cases all show the radiolucent, expansile, multilocular nature of the lesion.

The benign giant cells are but an incidental and confusing component. The clinical correlative studies reported by Troup and coworkers in 1960 have fortified this concept.

Clinical Features. The 568 cases of giant cell tumor reported from Mayo Clinic files represented 5.12% and 22.7% of the benign tumors. In many series, female patients are predominant. Approximately 84% of the neoplasms occurred in patients older than 19 years, with a peak incidence in the third decade of life (Unni KK, 1996). Pain of variable severity is almost always predominant symptom. More than three-fourths of the patients had noted swelling of the affected region. Less common symptoms were weakness, limitation of motion of the joint and pathologic fracture.

Histologic Features. The basic proliferating cell has round-to-oval or even spindle-shaped nucleus in the field that is diagnostic of true giant cell tumor. The nucleus is surrounded by an ill-defined cytoplasmic zone, and discernible intercellular substance is absent. Mitotic figures can be found, sometimes numerous. Mitotic activity has no prognostic significance. The giant cells are usually scattered uniformly throughout the lesion. They usually contain 40–60 nuclei. Areas of infarct-like necrosis are common in giant cell tumors. Some tumors are almost completely necrotic. The necrosis is not associated with an inflammatory response. Small collections of foam cells are common. Grading of giant cell tumors has no prognostic significance (Fig. 2-46).

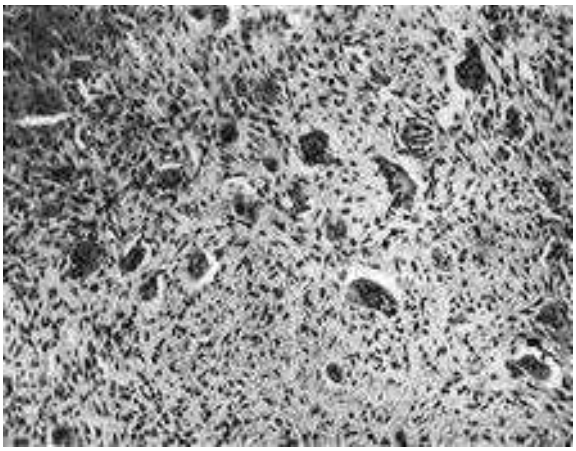


Figure 2-45. Central giant cell granuloma.

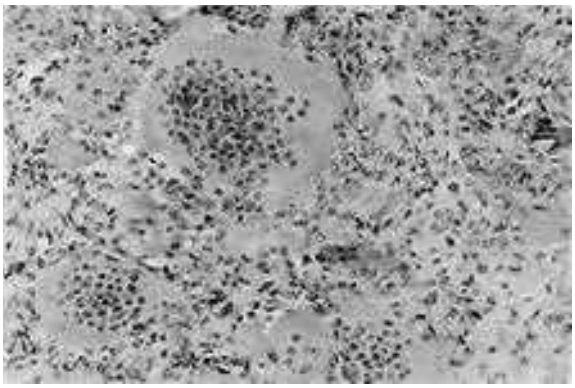


Figure 2-46. Giant cell tumor.
Typical appearance of a benign giant cell tumor. Giant cells with varying numbers of nuclei are arranged more or less uniformly within a background of mononuclear cells *(Courtesy of Dr KK Unni).*

Treatment. Removal of the tumor by curettage is the most widely accepted therapy. Recurrence may be seen as late as seven years. Secondary malignant change is usually to pure fibrosarcoma or osteosarcoma.

Aneurysmal Bone Cyst

The aneurysmal bone cyst is an interesting solitary lesion of bone which was separated as a distinct entity in 1942 by Jaffe and Lichtenstein. Since their original account, many cases have been reported in the literature, although the first cases occurring in the jaws were not described until 1958.

Features that make it logical to exclude aneurysmal bone cyst from the neoplastic category include the observation that the lesion has been known to regress after incomplete removal. The cause of this strange process in bone is unknown but several examples apparently arose after a fracture. It is similar to and probably related to other reactive non-neoplastic processes, including giant cell reparative granuloma of the jaws, traumatic reactions in periosteum and bone and even florid heterotopic ossification. Aneurysmal bone cyst may arise de novo in bone; that is, a definite preexisting lesion cannot be demonstrated in the tissue. Rarely malignant tumors of bone contain such benign areas as well. Obviously, recognition of an underlying process is important.

Clinical Features. The aneurysmal bone cyst is generally a lesion of young persons, predominantly occurring under the age of 20 years, with no significant predilection for either gender. The lesion can be encountered in adults. A history of traumatic injury preceding development of the lesion may often be obtained.

Cases of aneurysmal bone cyst have been observed in nearly every part of the skeleton, although over 50% of all cases occur in the long bones and vertebral column. Lesions are also seen frequently in the clavicle, rib, innominate bone, skull and bones of the hands and feet as well as other sites.

The lesions are usually tender or painful, particularly upon motion, and this soreness may limit movement of the affected bone. Swelling over the area of bone involvement is also common.

Gross findings at the time of operation are characteristic. Upon entering the lesion, excessive bleeding is encountered, the blood 'welling up' from the tissue. The tissue has been described as resembling a blood-soaked sponge with large pores representing the cavernous spaces of the lesion. In manometric studies by Biesecker and his associates, some of the cysts had elevated vascular pressures as high as arteriolar levels.

Four phases of pathogenesis are recognized, as follows:

- Osteolytic initial phase.
- Active growth phase, which is characterized by rapid destruction of bone and a subperiosteal blow out pattern.
- Mature stage, also known as stage of stabilization, which is manifested by the formation of a distinct peripheral bony shell and internal bony septa and trabeculae that produce the classic soap-bubble appearance.
- Healing phase, with progressive calcification and ossification of the cyst and its eventual transformation into a dense bony mass with an irregular structure.

Oral Manifestations. The aneurysmal bone cyst occurs with some frequency in the jaws, although many probably are misdiagnosed as some other bone lesion (Fig. 2-47A). In a review of the literature, Neumann-Jensen and Praetorius found 26 reported cases in the jaws, 17 in the mandible and nine in the maxilla. Of these, the average age of occurrence was 18 years with a range of 6–69 years, although only two patients were over 22 years of age. There was a slight predilection for occurrence in females, 14–19, where the gender was known.

Radiographic Features. The radiographic picture of the lesion is often distinctive. The bone is expanded, appears cystic with a honeycomb or soap-bubble appearance in many cases, and is eccentrically ballooned (Fig. 2-47B). The cortical bone may be destroyed, and a periosteal reaction may be evident.

Histologic Features. The aneurysmal bone cyst consists of a fibrous connective tissue stroma containing many cavernous or sinusoidal blood-filled spaces. These spaces may or may not show thrombosis. Young fibroblasts are numerous in

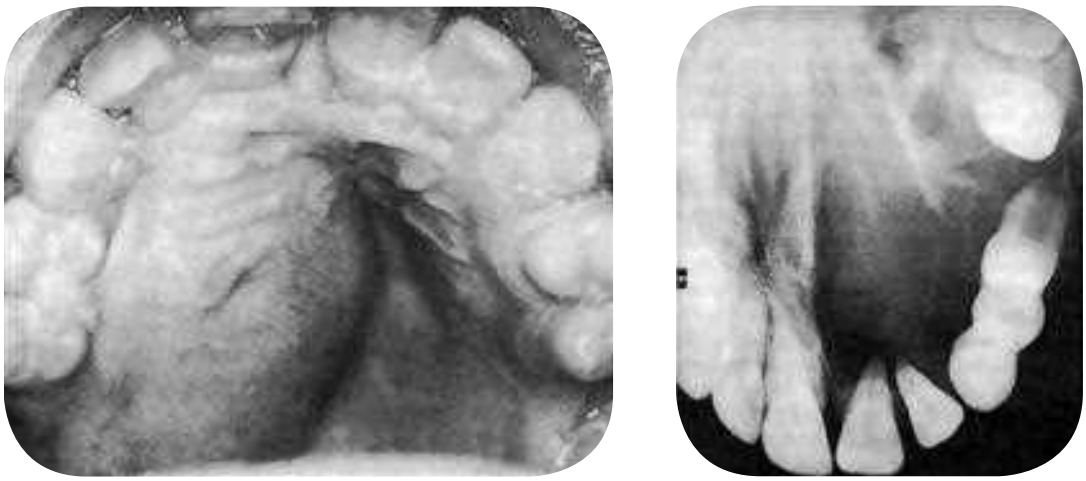


Figure 2-47. Aneurysmal bone cyst.
The large palatal swelling is a result of the underlying destructive, expansile mass *(Courtesy of Dr Jack Todd)*.

the connective tissue stroma, as well as multinucleated giant cells with a patchy distribution similar to that in the giant cell granuloma. But in the latter lesion the cavernous spaces are not found. Varying amounts of hemosiderin are present and, invariably, new osteoid and bone formation (Fig. 2-48A–D).

Pathogenesis. The nature of this lesion is still controversial despite the many cases that have been studied and reported. Lichtenstein has proposed that the aneurysmal bone cyst arises as a result of a persistent local alteration in hemodynamics, leading to increased venous pressure and subsequent development of a dilated and engorged vascular bed in the transformed bone area. Resorption of bone then occurs, to which the giant cells are related, and this is replaced by connective tissue, osteoid and new bone.

An alternative explanation of the lesion is that it represents an exuberant attempt at repair of a hematoma of bone, similar to the central giant cell granuloma. But in the case of the aneurysmal bone cyst, it is postulated that the hematoma maintains a circulatory connection with the damaged vessel. This would produce a slow flow of blood through the lesion and account for the clinical 'welling' of blood when the lesion is entered. Thus the only real difference between this aneurysmal cyst and the giant cell granuloma is that in the latter lesion damaged blood vessels fail to retain a circulatory connection with the lesion.

It is most significant that Biesecker and his associates have reported that 32% of their series of aneurysmal bone cysts had an accompanying benign primary lesion of bone. On this basis, they have proposed a new hypothesis for the etiology and pathogenesis of this lesion—namely, that a primary lesion of bone initiates an osseous, arteriovenous fistula and thereby creates, via its hemodynamic forces, the secondary reactive lesion of bone, the aneurysmal bone cyst.

This occurrence of aneurysmal bone cyst secondary to or in association with other osseous lesions has been confirmed by other investigators. For example, Levy and his associates reported 57 cases of aneurysmal bone cyst with which the most commonly associated lesion was the solitary or unicameral bone cyst (16 cases), the osteoclastoma or benign giant cell tumor (14 cases) and osteosarcoma (12 cases). Other associated lesions included the nonosteogenic fibroma, benign osteoblastoma, hemangioendothelioma and hemangioma of bone. Five aneurysmal bone cysts were secondary to fracture or other bone trauma.

Hillerup and Hjrting-Hansen have summarized the different theories on the etiology and pathogenesis of the aneurysmal bone cyst, simple bone cyst and central giant cell granuloma of the jaws. They suggested that these three lesions have a common dysvascular etiology and that local environmental factors within the bone may differentiate the pathogenesis.

Treatment and Prognosis. Surgical curettement or excision is the treatment of choice, although low doses of radiation have also been used. The possibility of radiation sarcoma is always a potential hazard, however, and the propriety of treatment of benign lesions by radiation has been seriously questioned on this basis. Recurrence in bones other than the jaws has been reported variously in between 21 and 59% of cases. However, no lesion in the jaws is known to have recurred.

Lipoma

It is a relatively rare intraoral tumor, although it occurs with considerable frequency in other areas, particularly in the subcutaneous tissues of the neck.

This is a benign, slow-growing neoplasm composed of mature fat cells. It appears that the cells of the lipoma differ metabolically from normal fat cells even though they are histologically similar. Thus a person on a starvation diet will lose fat from normal fat depots in the body, but not from the lipoma. Furthermore, fatty acid precursors are incorporated at

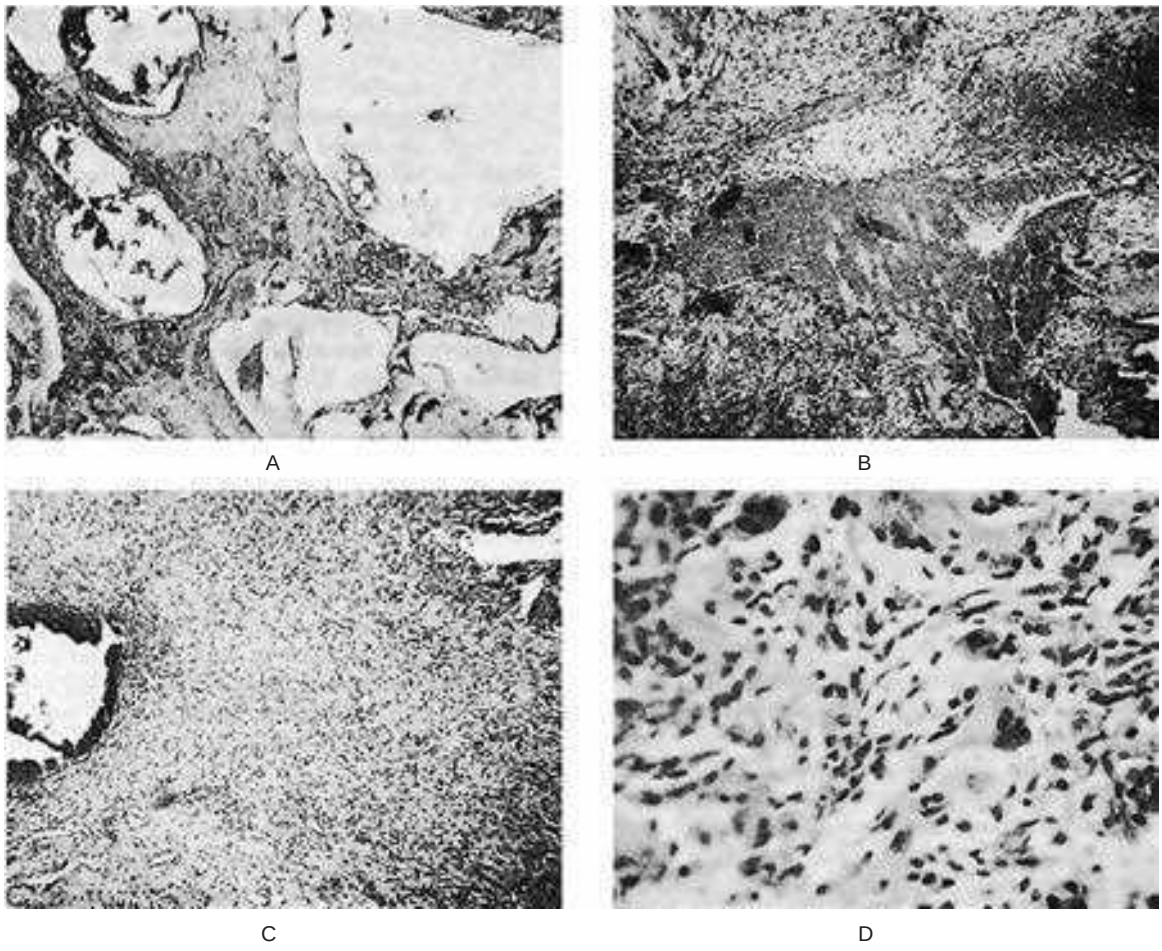


Figure 2-48. Aneurysmal bone cyst.
The photomicrographs illustrate the sinusoidal blood spaces, connective tissue, osteoid and giant cells.

a more rapid rate into lipoma fat than into normal fat while lipoprotein lipase activity is reduced.

The lipoma is a very common benign tumor of adipose tissue, but its presence in the oral and oropharyngeal region is relatively uncommon, with a prevalence rate of only 1/5,000 adults. The first description of an oral lesion was provided in 1848 by Roux in a review of alveolar masses; he referred to it as a 'yellow epulis'. While most lesions are developmental anomalies, those which occur in the maxillofacial region usually arise late in life and are presumed to be neoplasms of adipocytes, occasionally associated with trauma. Few lipomas show rearrangement of **12q, 13q, 6p** chromosomes.

Clinical Features. It is usually found in adults and there is no gender predilection. In most cases the size of the lesion is less than 3 cm at the time of diagnosis, but can increase up to 5–6 cm over a period of years. The tumor has been reported to occur in a variety of locations, including the tongue, floor of the mouth, buccal mucosa, gingiva, and mucobuccal or labial folds. Morphologically intraoral lipomas can be classified as **diffuse form** affecting the deeper tissues, and a **superficial** and **encapsulated form**.

Superficial form appears as a single or lobulated, painless lesion attached by either a sessile or a pedunculated base (Fig. 2-49A). There is a yellow surface discoloration and well-encapsulated, lipoma are freely movable beneath the mucosa. The epithelium is usually thin, and the superficial blood vessels are readily visible over the surface. The lipoma is yellowish, and relatively soft to palpation. Lesions in deeper tissues produce only a slight surface elevation which tend to be more diffuse than the superficial type of lipoma. When palpated, the diffuse form feels like fluid, sometimes leading to a mistaken tentative diagnosis of 'cyst'. Since this diffuse form often occurs in areas in which some fat is normally present, the diagnosis of lipoma depends upon the recognition of simply an overabundance of this tissue. Thus the diagnosis is essentially a clinical one.

Multiple head and neck lipomas have been observed in neurofibromatosis, Gardner syndrome, encephalocraniocutaneous lipomatosis, multiple familial lipomatosis, and Proteus syndrome. Generalized lipomatosis has been reported to contribute to unilateral facial enlargement in hemifacial hypertrophy.

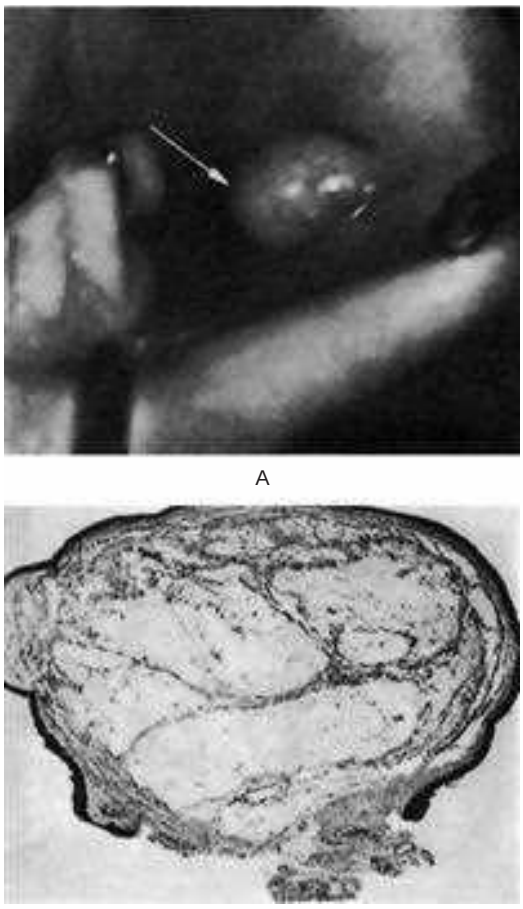


Figure 2-49. Lipoma.
The circumscribed mass on the buccal mucosa **(A)** is composed chiefly of adult fat cells with occasional connective tissue septa coursing through the lesion **(B)**.

Histologic Features. The lipoma is composed predominantly of mature adipocytes, possibly admixed with collagenic streaks, and is often well demarcated from the surrounding connective tissues. A thin fibrous capsule may be seen and a distinct lobular pattern may be present. Quite often, however, lesional fat cells are seen to 'infiltrate' into surrounding tissues, perhaps producing long, thin extensions of fatty tissue radiating from the central tumor mass. When located within striated muscle this infiltrating variant is called intramuscular lipoma **(infiltrating lipoma)**, but extensive involvement of a wide area of fibrovascular or stromal tissues might best be termed **lipomatosis**.

Occasional lesions exhibit excessive fibrosis between the fat cells **(fibrolipoma)**, excess numbers of small vascular channels **(angiolipoma)**, a myxoid background stroma **(myxoid lipoma, myxolipoma)**, or areas with uniform spindle-shaped cells interspersed between normal adipocytes (spindle cell lipoma). When spindle cells appear somewhat dysplastic or mixed with pleomorphic giant cells with or without hyperchromatic, enlarged nuclei, the term **pleomorphic lipoma** is applied. When the spindled cells are of smooth muscle origin, the term **myolipoma** may be used, or **angiomyolipoma** when the smooth muscle appears to be derived from the walls of arterioles.

Rarely, chondroid or osseous metaplasia may be seen in a lipoma (**osteolipoma,** ossifying lipoma, chondroid lipoma, ossifying chondromyxoid lipoma). When bone marrow is present, the term **myelolipoma** is used. Also on rare occasions, isolated ductal or tubular adnexal structures are scattered throughout fat lobules, in which case the term **adenolipoma** is applied. **Perineural lipoma** has also been reported.

On occasion, lipoma of the buccal mucosa cannot be distinguished from a herniated buccal fat pad, except by the lack of a history of sudden onset after trauma. Otherwise, lipoma of the oral and pharyngeal region is not difficult to differentiate from other lesions, although spindle cell and pleomorphic types must be distinguished from liposarcoma. When metaplastic calcified tissue is present, the lesion may be confused with soft tissue chondroma or soft tissue osteoma.

The benign neoplasm of brown fat, **hibernoma,** has been reported in the oral/pharyngeal region only rarely.

Lipoblastoma

This is a rare related lesion originally described by Vellios and his associates in 1958. It is probably not a true neoplasm but rather a continuation of the normal process of fetal fat development carried into postnatal life. It is characterized clinically by the occurrence in infants of solitary or multiple soft-tissue masses developing at various sites such as the buttock, chest, axilla or neck. The lesions are benign but may recur if inadequately excised. Diffuse lipoblastoma involving deeper soft tissue is called **lipoblastomatosis**.

Histologically, the central core of mature adipocytes and a peripheral envelope of cells containing variably sized fat vacuoles are noticed. Affected cells are smaller than normal, with 1–4 vacuoles, with a light, wispy cytoplasm between vacuoles. Some cells have nuclei centrally located, as seen in the moderately-sized cells of hibernoma, while others show the nucleus to be pushed toward the cytoplasmic membrane (signet-ring cell). Mitotic activity is extremely rare and fibrous septa separate fat lobules in this tumor. An abnormality of the long arm of chromosome **8q11-13** is a rather consistent finding in the lesional cells.

Treatment and Prognosis. Conservative surgical removal is the treatment of choice for oral lipoma, with occasional recurrences expected. An infiltrating lipoma often must be debulked.

Verruciform Xanthoma

(Verrucous xanthoma, inflammatory papillary hyperplasia with foam cell response)

Verruciform xanthoma is an uncommon lesion that usually occurs on the oral mucosa of unknown etiology and uncertain nature, first described as an entity by Shafer in 1971. Numerous cases have now been reported in the literature, including on the vulva, penis, on the skin of the thigh and perineum. Many authors consider it to be a reactive process rather than a true neoplasm.

The etiopathogenesis of verruciform xanthoma is unknown. It is thought that damage to the squamous cells with increased epithelial cell turnover, leading to the deposition of epithelial cell debris that is engulfed by macrophages in the corium may lead to the development of this lesion. An immunologic etiology has also been proposed.

Most commonly, the lesion has a verruciform appearance, but it may appear polypoid, papillomatous, or sessile. Rare lesions have been found to occur in cysts. The chief distinguishing feature of verruciform xanthoma is the presence of large numbers of lipid-laden foamy histiocytes in, and essentially limited to, the connective tissue papillae in the lesion.

Clinical Features. Verruciform xanthoma is uncommon, accounting for 0.025–0.05% of all pathology cases. The age of occurrence varies widely from 2 to 89 years. But most oral cases occur in middle-aged persons with mean age of 40–50 years, and no gender predilection is apparent. Most cases are reported in whites, but blacks are also affected. Verruciform xanthoma may occur at any site but its most preferred site is the alveolar ridge, or gingiva, followed by the buccal mucosa and then the palate, floor of the mouth, lip and lower mucobuccal fold with equal frequency.

Verruciform xanthoma occurs as a solitary lesion, either normal or reddish in color but sometimes pale or 'hyperkeratotic', with a rough, pebbly surface and either a sessile or pedunculated base. It may be as small as 2 mm or as large as 1.5 cm in diameter, and is invariably asymptomatic. In the oral cavity lesions can be found in association with lichen planus, pemphigus vulgaris, oral bullae, carcinoma *in situ,* or frank squamous cell carcinoma.

Depending on the nature of the individual lesion, it may clinically resemble any verrucous, papillary, or lichenoid oral lesion, particularly any such lesion that is also hyperkeratotic. It is frequently misdiagnosed at clinical examination as a papilloma.

Verruciform xanthoma outside oral mucosa is usually associated with other conditions like lymphoedema, epidermal nevi and congenital hemidysplasia with ichthyosiform erythroderma and limb defect (CHILD) syndrome.

Histologic Features. Verruciform xanthomas may appear verrucous, papillary, or cauliflower like, or they may show a lichenoid pattern histologically. A mixture of the above patterns may also be observed. A variable degree of parakeratosis is observed that is usually more marked in verrucous and papillary lesions, with hyperparakeratosis present in the crypts between papillae. The rete pegs are extremely elongated and uniform, although no increased mitoses or pseudoepitheliomatous hyperplasia are found. The connective tissue papillae are of variable length and thickness; they often extend close to the surface. Rarely, the entire process may occur in a cyst like structure.

The most striking and characteristic feature is the presence of large foam cells in the connective tissue papillae between the epithelial pegs. These are confined to the papillae and do not extend into the dermis beneath the pegs. Almost all of the papillae are involved with these cells, which occasionally may also be seen in the epithelium (i.e. epidermis, mucosa).

A slight inflammatory infiltrate may be present beneath the lesion. Occasional lesions have been associated with a massive or lichenoid infiltrate. No granulomatous change has been described other than the presence of the foamy macrophages. Microorganisms are not characteristically present. Although bacteria and fungal hyphae are occasionally described, they appear to play no role in the etiopathogenesis. Attempts to incriminate a viral role have been counterproductive.

Ultrastructurally, most studies have concluded that the foam cells in verruciform xanthoma are fat-laden macrophages, although other cell types, including Langerhans cells and even fibroblasts have been proposed.

Treatment. Local surgical excision is almost always curative. Recurrence is rare.

Immunohistochemical analysis revealed these cells to be positive for LCA and CD68 and negative for S100, a marker pattern also characteristic of macrophages. A few S100 negative dendritic or granular cells have been reported in these lesions as well and may represent Langerhans cells. The contents of the cells stain with lipid stains, and the vacuoles that contain this material are decorated with antihuman lysosome antibody. They are also periodic acid-Schiff (PAS) positive and diastase resistant, indicating that the PAS-positive material is not glycogen.

At electron microscopy, this material also demonstrates the appearance of lipid. Chemical studies by gas chromatography of extracted material show a preponderance of cholesterol esters. In addition to the lipid material, few researchers noted the presence of what they interpreted as degenerating epithelial cells in the foam cells. Cobb et al. described myelin figures, reduplication of the overlying basal lamina and fibroblasts, in addition to macrophage like cells, which contained lipid inclusions.

Oral Hemangiomas and Vascular Malformations
(Oral vasoformative tumor)

Hemangiomas are lesions that are not present at birth. They manifest within the first month of life, exhibit a rapid proliferative phase, and slowly involute to nonexistent. Hemangiomas are tumors identified by rapid endothelial cell proliferation in early infancy, followed by involution over time; vascular malformations result from anomalous development of vascular plexuses. The malformations have a normal endothelial cell growth cycle that affects the veins, the capillaries, or the lymphatics, and they do not involute. Vascular malformations are more stable and fail to regress.

Hemangiomas of the oral cavity are not common pathologic entities, but the head and neck are common sites. Most true hemangiomas involute with time, but 10–20% of true hemangiomas incompletely involute and require postadolescent ablative treatment.

Hemangiomas are associated with the following syndromes:

- Rendu-Osler-Weber syndrome (autosomal dominant inheritance, multiple telangiectasias, occasional GI tract involvement, occasional CNS involvement).
- Sturge-Weber-Dimitri syndrome (noninherited and nonfamilial, port-wine stain, leptomeningeal angiomas).
- Kasabach-Merritt syndrome (thrombocytopenic purpura associated with hemangioma, consumptive coagulopathy, microangiopathic hemolysis, intralesional fibrinolysis).
- Maffucci syndrome (hemangiomas of the mucous membranes, dyschondroplasia).
- von Hippel-Lindau syndrome (genetic transmission variable, hemangiomas of the cerebellum or the retina, cysts of the viscera).
- Klippel-Trenaunay-Weber syndrome (port-wine stain, angiomatosis of the extremities).

In 1982, Mulliken and Glowacki classified the vasoformative tumors into two broad groups: **hemangiomas and vascular malformations** (Table 2-13). Vascular malformations can be further subdivided into **venous, capillary, arteriovenous and lymphatic malformations.**

A simple classification is that proposed by Watson and McCarthy based upon a series of 1,308 blood vessel tumors, and is as follows: (1) capillary hemangioma, (2) cavernous hemangioma, (3) angioblastic or hypertrophic hemangioma, (4) racemose hemangioma, (5) diffuse systemic hemangioma, (6) metastasizing hemangioma, (7) nevus vinosus, or port-wine stain, and (8) hereditary hemorrhagic telangiectasia.

Clinical Features. By their definition, hemangiomas occur in infants and children. The incidence of hemangiomas increases to 23% in premature infants with a birthweight of less than 1,000 gm. The peak incidence of central hemangiomas of the jaws is in the second decade of life. But vascular malformations have a much broader range of incidence.

Hemangioma affects as many as 12% infants in whites, but it rarely occurs in darker-skinned individuals. Vascular malformations are also more common in whites. Hemangiomas are about three times more common in females than in males. But for venous malformations gender ratio is reported to be 1:1.

The most commonly affected facial bones are the mandible, the maxilla, and the nasal bones. Intraosseous lesions affect the mandible more often than the maxilla, with a ratio of 2:1. Involvement of the zygoma is rare. Intramuscular hemangiomas in the oral region are most commonly seen in the masseter, comprising 5% of all intramuscular hemangiomas.

Patients with multiple lesions have rates of resolution similar to those with single lesions; however, separate lesions in the same individual do not necessarily grow or involute simultaneously.

Vascular malformations are present at birth and continue to grow with the child. The growth may become accelerated when the patient undergoes puberty or pregnancy, with the attendant hormonal changes.

Oral Manifestations. The hemangioma of the oral soft tissue is similar to the hemangioma of the skin and appears as a flat or raised lesion of the mucosa, usually deep red or

Etiology. The causes of vasoformative tumors are unknown. One hypothesis postulates that placental cells, such as the trophoblast, may be the cell of origin for hemangiomas. Therefore, hemangiomas may arise secondary to some event *in utero.* However, conflicting evidence supports this hypothesis. The relationship between hemangiomas and placental tissues needs further investigation.

Pathophysiology. Vascular malformations need to be understood in terms of their embryology and development. The classic sequence of events usually falls into three stages:

- The undifferentiated capillary network stage
- The retiform developmental stage
- The final developmental stage.

In the undifferentiated capillary network stage, the primitive mesenchyme is nourished by an interlacing system of blood spaces without distinguishable arterial and venous channels. Separate venous and arterial stems appear on either side of the capillary network in the retiform developmental stage. The retiform developmental stage begins at about 48 days of embryonic development. The final developmental stage begins at two months of development and involves the gradual replacement of the immature plexiform network by the mature vascular channels.

The more common capillary hemangioma represents an arrest in the development of the mesenchyme primordia in the undifferentiated capillary network stage. As differentiation progresses, primitive vessels penetrate deeper into the subcutaneous layer, the muscle, or the bone tissue and give rise to capillary hemangiomas. Termination of development in the retiform developmental stage may produce venous, arterial, or capillary malformations because this stage is characterized by an established venous, arterial, and capillary system. In the final developmental stage, the maturation of the venous and lymphatic systems predominates. Aberrations in this mature stage of development result in venous malformations and lymphangiomas.

Proliferating hemangiomas have been shown to have estradiol-17 beta receptors in the cytoplasm, and corticosteroid treatment has been theorized to block these receptors. Thus steroid treatment is the first line of treatment for proliferating lesions. Estradiol receptors are absent in stable or involuting lesions.

Takahashi has outlined a number of cellular markers that distinguish the phases of hemangiomas; these markers include tissue metalloproteinase (TIMP-1), bFGF, proliferating cell nuclear antigen, type IV collagenase, VEGF, and urokinase.

Table 2-13: Classification of vasoformative tumors

Vasoformative tumor	New nomenclature	Old nomenclature
Hemangiomas	Capillary hemangioma Cavernous hemangioma Mixed hemangioma	Strawberry hemangioma Juvenile hemangioma Parotid hemangioma
Vascular malformations	Venous malformation	Cavernous hemangioma Hemangiomatosis
	Intramuscular venous malformation	Intramuscular hemangioma
	Capillary malformation	Capillary hemangioma Port-wine stain Arteriovenous hemangioma Arterial angioma
	Arteriovenous malformation	Arteriovenous aneurysm Cirsoid angioma Red angioma Serpentine aneurysm Capillary lymphangioma Cavernous lymphangioma
	Lymphatic malformation	Lymphangioma Cystic hygroma

Source: Randall Wilk. eMedicine Speciaities. Diseases of the Oral Mucosa, 2003.

bluish red and seldom well circumscribed. They are readily compressible and fill slowly when released. The most common sites of occurrence are the lips, tongue, buccal mucosa and palate (Fig. 2-50). The tumor often is traumatized and undergoes ulceration and secondary infection.

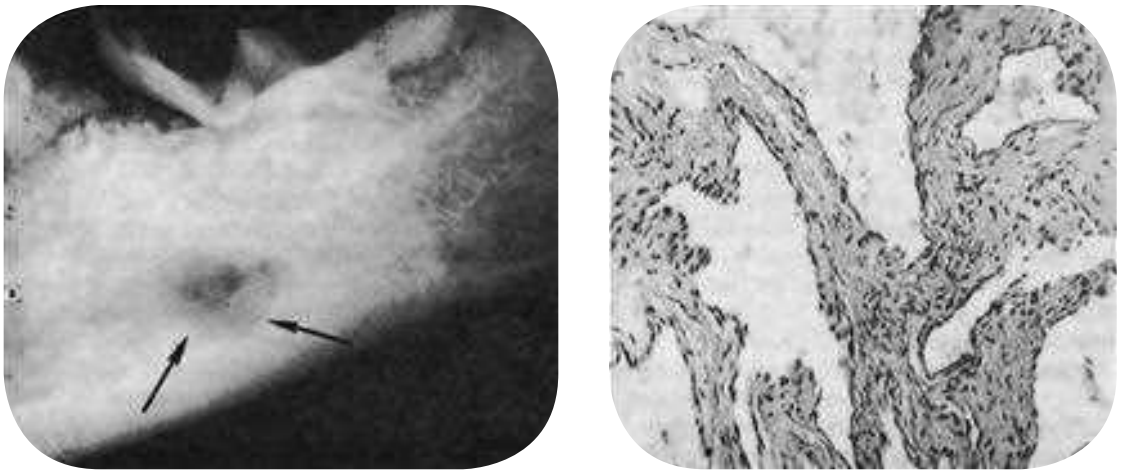
Certain tiny vascular formations of lip vessels called 'microcherry', 'glomerulus' and 'venous lake' have been described by Gius and his associates as lesions encountered with increasing frequency in the later decades of life and occurring with greater frequency in patients with gastric and duodenal ulcers.

The **intramuscular hemangioma** is one special form of hemangioma which is quite rare in the head and neck region. It arises within normal skeletal muscle, comprises less than 1% of all hemangiomas and is important chiefly because of the problem in differential diagnosis and of treatment of the lesion. Intramuscular hemangiomas represent a challenge on diagnosis because they exhibit few signs on clinical examination. Often times, the extent of the lesion is not clinically apparent on examination, and imaging studies frequently define more extensive lesions than suspected.

Central hemangiomas of the maxilla or mandible occasionally occur and frequently present difficulty in differential diagnosis. Lund and Dahlin reviewed 35 cases of hemangioma of the jaws and found that over 50% of the cases occurred in the first two decades of life and that two-thirds of the lesions were located in the mandible. Here the tumor is a bone-destructive lesion which may be of varying size and

A B

Figure 2-50. Hemangioma
(A) Congenital bilateral hemangioma of the face and lip. The lesion follows the distribution of the beard. **(B)** The hemangioma of the tongue is superficial but diffuse.



A B

Figure 2-51. Central hemangioma of bone.

appearance, but is often suggestive of a cyst (Fig. 2-51). Root resorption of the teeth has been reported in 30% of cases, but the vitality of the teeth is usually not affected. Some central hemangiomas present a honeycombed appearance on the radiograph, sometimes with radiating spicules at the expanded periphery forming a 'sunburst' appearance reminiscent of that effect seen in osteosarcoma. Radiographic appearance is also similar to that of a giant cell lesion or an ameloblastoma.

The attempt at radical surgical excision of such central lesions has often resulted in severe loss of blood, which has occasionally led to exsanguination of the patient to the point of death. In such bony lesions, it is always advisable to attempt to aspirate fluid contents through a needle before surgically opening the area. When the hemangioma is entirely central within bone, Gamez-Araujo and his associates have stated that the prognosis is excellent with adequate surgical intervention, in contrast to those lesions where soft tissue is also involved by capillary hemangioma. In these latter instances, the lesions become aggressive, invade locally and often recur if not totally eradicated.

The **arteriovenous aneurysm**, or arteriovenous fistula, is an uncommon lesion which often has been mistaken clinically for a hemangioma. It represents a direct communication between an artery and a vein through which the blood bypasses the capillary circulation. The arteriovenous aneurysm may be congenital or acquired, the latter usually being traumatic in origin. It may occur either in the soft tissues, such as in the case of the palate reported by Ingram and Coker, and on the alveolar ridge as reported by McComb and Trott, or central in the jaw as reported by Cook and Zbar. These aneurysms typically are classified as:

- A **cirsoid aneurysm** which is a tortuous mass of small arteries and veins linking a larger artery and vein.
- A **varicose aneurysm** which consists of an endothelium-lined sac connecting an artery and a vein.
- An **aneurysmal varix** representing a direct connection between an artery and a dilated vein.

The arteriovenous aneurysm has been reviewed in detail by Gomes and Bernatz, while Orbach has discussed the entire gamut of congenital arteriovenous malformations of the head and neck. He has emphasized the histogenesis and pathogenesis of these abnormalities, stressing the fact that they range from the most trivial angioma to the large-bore arteriovenous fistula.

Radiographic Features. Imaging should be considered to determine their extent and flow characteristics. Angiography is considered the most definitive of the studies, although the angiographic appearance of intraosseous lesions is less well defined than that of soft tissue lesions. Ultrasonography can be used to determine angiomatous in nature (i.e. hemangioma, lymphangioma), but it cannot differentiate a hemangioma from a lymphangioma. Contrast-enhanced MRI can be used to differentiate a hemangioma from a lymphangioma in the oral cavity. MRI appears to be highly reliable for lesions of either soft tissue or bone. Radiographically, intraosseous hemangioma shows honeycombed pattern that is well demarcated from normal bone. CT scans often show an expansile process with a high-density amorphous mass that may be suggestive of fibrous dysplasia.

Histologic Features. The usual hemangioma is composed of many small capillaries lined by a single layer of endothelial cells supported by a connective tissue stroma of varying density. It bears considerable resemblance to young granulation tissue and is nearly identical with some cases of pyogenic granuloma. Some cases show rather remarkable endothelial cell proliferation (Fig. 2-52). In fact, one common form is referred to as a juvenile hemangioendothelioma because it occurs in very early life and is characterized by an extremely cellular pattern. It is generally believed that this lesion is an immature stage of a capillary hemangioma and that, in time, it will either develop into a simple hemangioma or regress.

The cavernous form of hemangioma consists of large dilated blood sinuses with thin walls, each showing an endothelial lining. The sinusoidal spaces usually are filled with blood,

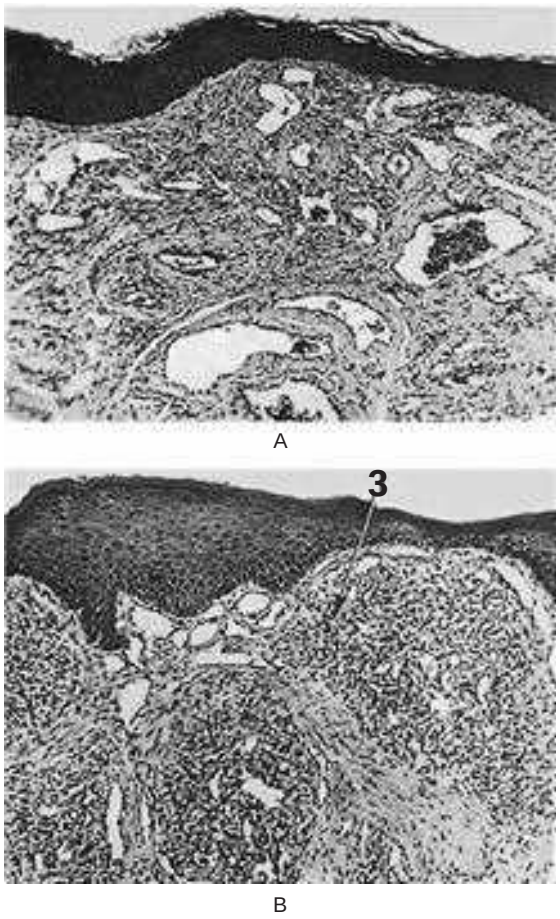


Figure 2-51. Hemangioma.
Some lesions **(A)** are characterized by the presence of many small dilated capillaries and a minimum of endothelial cells, while others **(B)** show large numbers of proliferating endothelial cells (1), but only moderate numbers of patent capillaries.

although an admixture with occasional lymphatic vessels occurs in some instances.

Intravascular angiomatosis, also referred to in the literature most commonly under the terms hemangioendotheliome vegetant intravasculaire of Masson, Masson's pseudoangiosarcoma, and intravascular papillary endothelial hyperplasia, is actually an unusual form of an organizing thrombus, although it is often mistaken for a vascular tumor, especially a malignant one such as angiosarcoma. This lesion has been discussed by McClatchey and his associates, who described perioral cases, including two on the lips which clinically resembled mucoceles, and emphasized that angiosarcoma could best be excluded as a diagnosis by the intravascular localization, the absent to rare mitoses and necrosis, and the rare solid cellular areas without vascular differentiation.

Treatment and Prognosis. Many congenital hemangiomas have been found to undergo spontaneous regression at a relatively early age. Cases which do not show such remission or those which arise in older persons have been treated in a variety of ways, including: (1) surgery, (2) radiation therapy (external radiation or radium), (3) sclerosing agents, such as sodium morrhuate or psylliate, injected into the lesion, (4) carbon dioxide snow, (5) cryotherap and (6) compression. Each form of treatment has its proponents and antagonists, but it appears that in skilled hands each has its proper place.

Salient histopathologic findings of vasoformative tumors (hemangioma and vascular malformations) are as follows:

- Hemangiomas (proliferative phase)
  - Endothelial cell hyperplasia forming syncytial masses
  - Thickened (multilaminated) endothelial basement membrane
  - Ready incorporation of tritiated thymidine in endothelial cells
  - Presence of large number of mast cells
- Hemangiomas (involuting phase)
  - Less mitotic activity
  - Little or no uptake of tritiated thymidine in endothelial cells
  - Foci of fibrofatty infiltration
  - Normal mast cell counts
- Vascular malformations
  - No endothelial cell proliferation
  - Contain large vascular channels lined by endothelium
  - Unilamellar basement membrane
  - Does not incorporate tritiated thymidine in endothelial cells
  - Normal mast cell counts

The prognosis of the hemangioma is excellent, since it does not become malignant or recur after adequate removal or destruction.

Hereditary Hemorrhagic Telangiectasia

(Osler-Weber-Rendu syndrome, Rendu-Osler-Weber syndrome, heredofamilial angiomatosis, familial hemorrhagic angiomatosis, Osler's disease)

Osler-Weber-Rendu syndrome, also known as hereditary hemorrhagic telangiectasia, is an autosomal dominant disorder identified typically by the triad of telangiectasia, recurrent epistaxis, and a positive family history for the disorder. The major cause of morbidity and mortality due to this disorder lies in the presence of multiorgan arteriovenous malformations (AVMs) and the associated hemorrhage that may accompany them.

Clinical Features. The disease most commonly occurs in white patients, but it has been described in patients of Asian, African and Arabic descent. The spider-like telangiectases are occasionally present at or shortly after birth, although in the majority of cases they do not become conspicuous until after puberty. They appear to increase in number and prominence as the patient ages. The skin lesions are most common on

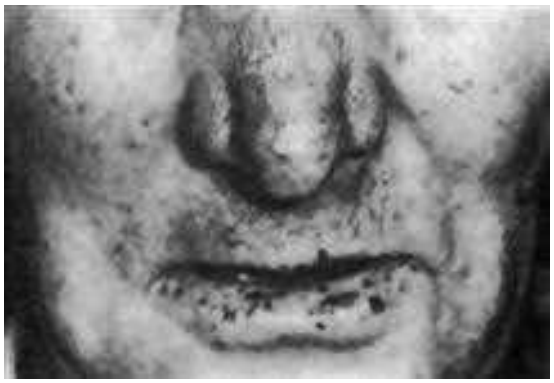


Figure 2-53. Hereditary hemorrhagic telangiectasia.
(Courtesy of Dr Theodore Century).

the face, neck, and chest, although any area may be involved (Fig. 2-53). Involvement of the oral mucous membrane constitutes an important feature of the disease, the most commonly affected areas being the lips, gingiva, buccal mucosa and palate, as well as the floor of the mouth and the tongue.

One of the earliest signs of the disease, often occurring in childhood and preceding the appearance of telangiectasia, is epistaxis as well as bleeding from the oral cavity, both of which may be difficult to control. The diagnosis may be established if a history of epistaxis dating from childhood, the presence of the telangiectatic areas and the familial history are ascertained. The main areas of involvement are the nasal mucosa, skin, the GI tract, the pulmonary vasculature, and the brain.

Etiopathogenesis

The disease is caused by an inherited defect. Currently 2 loci have been identified associated with Osler-Weber-Rendu syndrome, one on chromosome arm 9q33–q34 and a second on chromosome arm 12q. Chromosome arm 9q34 harbors the endoglin gene, which encodes for a homodimeric integral membrane glycoprotein expressed at high levels on human vascular endothelial cells. Several mutations of the endoglin gene have been reported in family members affected with Osler-Weber-Rendu syndrome. Chromosome arm 12q harbors the activin receptor like kinase 1 (ALK1), which encodes for a surface receptor for the transforming growth factor beta superfamily of ligands. Several families with Osler-Weber-Rendu syndrome harbor mutations of ALK1.

Transforming growth factor beta has a role in tissue repair and angiogenesis. Thus, the development of abnormal vasculature, defects in the endothelial cell junctions, endothelial cell degeneration, and weakness of the perivascular connective tissue are thought to cause dilation of capillaries and postcapillary venules, which manifest as telangiectases, AVMs, and aneurysms.

Similar telangiectases of skin and oral mucous membranes may occur in a variety of other situations, however, and these include progressive systemic sclerosis (scleroderma) and the CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), lupus erythematosus, sarcoid and other rarer diseases. The differential diagnoses are important and have been discussed by Donaldson and Myall.

Histologic Features. The disease is due primarily to defects in the small blood vessels of the skin and mucosa. Hashimoto and Pritzker have shown, in an electron microscope investigation, that the actual cause of the hemorrhage is either a primary intrinsic defect of the endothelial cells permitting their detachment, or a defect in the perivascular supportive tissue bed which weakens the vessels, rather than a lack of elastic fibers as was thought at one time. Both clotting and bleeding times are normal, as are the blood elements, although with severe bleeding mild anemia and thrombocytopenia may result.

Treatment and Prognosis. The treatment of the disease is varied, depending upon its severity. The spontaneous hemorrhages may be controlled by pressure packs, particularly the nasal bleeding. The angiomatous or telangiectatic areas are sometimes cauterized, treated with X-ray radiation or surgically excised.

The disease is seldom so severe that life is endangered. Nevertheless a considerable number of deaths from severe hemorrhage have been reported.

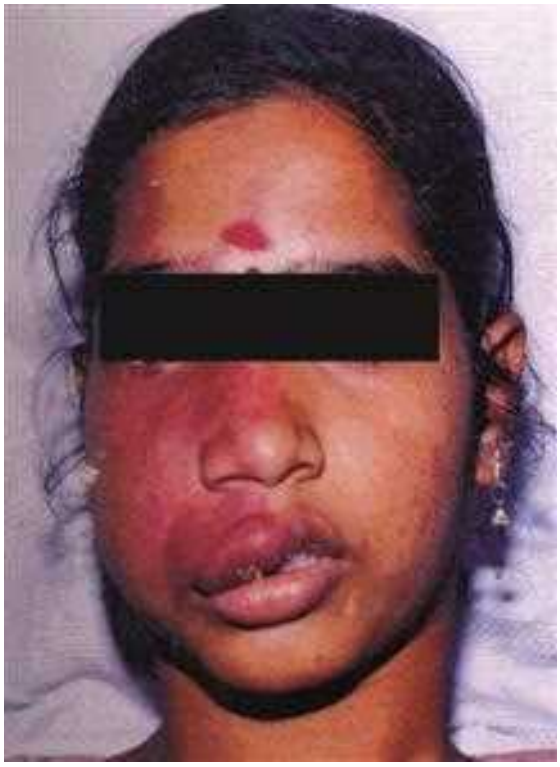
Encephalotrigeminal Hemangiomatosis
(Sturge-Weber syndrome)

Sturge-Weber syndrome is a rather uncommon congenital condition. It consists of congenital hamartomatous malformations that may affect the eye, the skin, and the central nervous system at different times, characterized by the combination of a venous angioma of the leptomeninges over the cerebral cortex with ipsilateral angiomatous lesions of the face, and sometimes, of the skull, jaws and oral soft tissues. Sturge-Weber syndrome (SWS) belongs to a group of disorders collectively known as the phakomatoses (mother-spot diseases—Fig. 2-54).

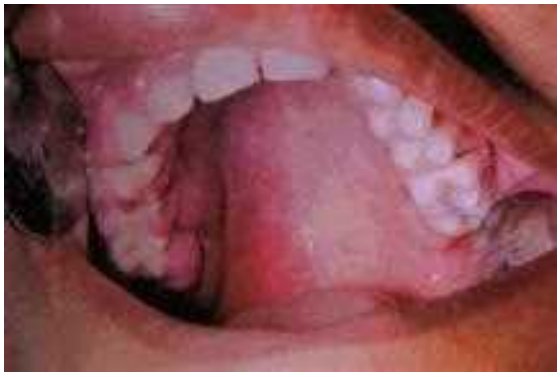
Etiology. The clinical manifestations of SWS have a common embryological basis. The primary defect is a developmental insult affecting precursors of tissues that originate in the promesencephalic and mesencephalic neural crest. Then, these affected precursors give rise to vascular and other tissue malformations in the meninges, the eye, and the dermis.

Although the exact nature of the insult is unknown, it has been postulated that a somatic mutation in these precursors may lead to overproduction of an angiogenic factor. Others have suggested that SWS may be due to a lethal gene surviving by mosaicism. The influence of heredity in SWS has not been documented. To date, no gene defect has been associated with the syndrome. Several types of chromosomal abnormalities have been reported, but most patients with SWS have normal karyotypes. Most patients with SWS have a sporadic, nonfamilial disease.

Clinical Features. The facial cutaneous capillary venous angiomas (or port-wine nevi) are usually the first component of the syndrome to be observed, at birth, and are confined



A



B

Figure 2-54. Sturge-Weber syndrome.
(A) The unilateral distribution of angiomatous malformations which never cross the midline is pathognomonic of the syndrome. **(B)** Unilateral involvement of palate with angiomatous malformation.

almost exclusively to the skin area supplied by the trigeminal nerve. A second common feature is the presence of typical intracranial convolutional calcifications discernible in cranial radiographs. Ocular involvement occurs in some patients, consisting generally of glaucoma, exophthalmus, angioma of the choroid or other abnormalities.

Neurologic manifestations are among the most characteristic features of the disease and consist of convulsive disorders and spastic hemiplegia with or without mental retardation. These manifestations are directly related to the leptomeningeal angioma and calcifications, the latter being also related to the vascular disturbance.

Oral Manifestations. Occasionally, angiomatous lesions also involve the gingiva and buccal mucosa. There is generally no difficulty in diagnosis because of the presence of the facial lesions.

Treatment. The treatment of the disease is essentially a neurosurgical problem, although the convulsions can sometimes be controlled by anticonvulsant drugs.

Nasopharyngeal Angiofibroma
(Juvenile nasopharyngeal fibroma)

The nasopharyngeal angiofibroma is a relatively uncommon benign neoplasm occurring almost exclusively in the nasopharynx of adolescent males. Occasional cases have extended to involve the oral cavity, however, and for this reason the entity deserves consideration here.

Hippocrates described the tumor in the 5th century BC, but Friedberg first used the term angiofibroma in 1940. Other terms (e.g. nasopharyngeal fibroma, bleeding fibroma of adolescence, fibroangioma) also have been used.

Etiopathogenesis. A hormonal theory has been suggested due to the lesion's occurrence in adolescent males. Other theories include a desmoplastic response of the nasopharyngeal periosteum or the embryonic fibrocartilage.

Clinical Features. Nasopharyngeal angiofibroma accounts for 0.05% of all head and neck tumors. A frequency of 1: 5,000–1: 60,000 in otolaryngology patients have been reported. It occurs exclusively in males. Females diagnosed with nasopharyngeal angiofibroma should undergo genetic testing. Onset most commonly happens in the second decade; the range is 7–19 years, and it is rare in patients older than 25 years.

The lesion is generally manifested by nasal obstruction (80–90%), epistaxis (45–60%), sinusitis (25%), and facial swelling (10–18%). On examination, nasal mass (80%), orbital mass (15%), proptosis (10–15%) may be noticed. Other findings may include serous otitis due to eustachian tube blockage. Zygomatic swelling and trismus denote spread of the tumor to the infratemporal fossa. Decreasing vision due to optic nerve involvement has rarely been reported. Care must be taken to differentiate this lesion from ordinary nasal polyps, which it may resemble superficially. As the tumor mass enlarges, inferior depression of the palate and facial deformity may occur.

Oral Manifestations. The oral manifestations of the nasopharyngeal angiofibroma are generally those of a palatal or tonsillar mass, often with nasal obstruction. Occasionally, however, lesions of the posterior portion of the maxilla and even of the mandible have been seen which are microscopically identical with the nasopharyngeal lesions, and they may be considered similar in nature.

Radiographic Features. Radiograph of sinuses may demonstrate nasopharyngeal polyp, bowing of the posterior wall of the maxillary sinus and maxillary sinus opacification is very suggestive of JNA. CT scan can demonstrate extent of the tumor. Magnetic resonance imaging (MRI) is indicated

to delineate and define the extent of the tumor, especially in cases of intracranial involvement.

Histologic Features. On gross examination, the tumor is usually sessile, lobulated, rubbery, and red-pink to tan-gray in appearance. In rare cases, the tumor is polypoid or pedunculated.

The tumor is encapsulated and consists essentially of two basic and characteristic components: a vascular network and a connective tissue stroma. The vessels comprising the vascular network are of varying caliber, irregular in shape and generally consisting of a simple endothelial lining. The vascular element is generally most pronounced at the periphery of the lesion where active growth is occurring. Thrombosis and occlusion are frequently seen, usually in association with vasculitis.

The connective tissue stroma consists of both fine and coarse collagen fibrils, usually with an irregular, unoriented pattern, interspersed with plump, stellate cells arranged in a haphazard fashion (Fig. 2-55). An abundance of mast cells in the stroma and a lack of other inflammatory cells exist. Hyalinized foci are sometimes present, as well as areas resembling myxomatous degeneration. When the stromal cells are abundant, the resemblance to the sclerosing hemangioma may be pronounced. Multinucleated stromal cells are sometimes present, and with the occasional atypical nuclear and cellular changes that may be found, the lesion may be mistaken for a sarcoma.

When examined under electron microscope, stromal cells mostly are fibroblasts and show intensive immunostaining for vimentin. However, myofibroblasts may occur focally in connection with fibrotic areas and are characterized by the coexpression of vimentin and smooth muscle actin.

Treatment. Spontaneous regression is rare. Surgical resection with preoperative embolization is the preferred treatment. The testosterone receptor blocker flutamide was reported to reduce the size of the tumor in early stages. External beam irradiation is most often reserved for intracranial, unresectable, or recurrent disease. Complications are related to intracranial extension, uncontrolled hemorrhage and death, iatrogenic injury to vital structures. Postoperative radiographic surveillance is important due to high rates of recurrence (6–60%). Recurrences can occur as early as three or four months after surgery.

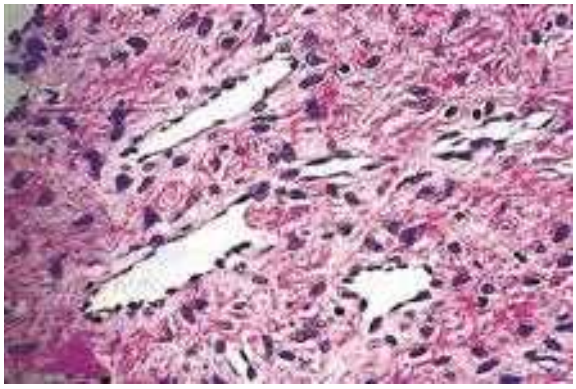


Figure 2-55. Nasopharyngeal angiofibroma.
The dense fibrous quality of the stroma and the numerous thin-walled vessels are characteristic of this entity *(Courtesy of Dr Juan Rosai)*.

Lymphangioma

The lymphangioma is a benign hamartomatous hyperplasia of lymphatic vessels, with three-fourths of all cases occurring in the head and neck region. While occasional adult-onset cases occur, this tumor is thought to be a developmental malformation of vessels which have poor communication with the normal lymph system. Diagnosed cases are typically superficial but may extend deeply into underlying connective tissues. Rarely, multiple lesions are seen in infancy and childhood in **lymphangiomatosis,** the lymphatic counterpart to angiomatosis of blood vessels and a potentially life-threatening disease when visceral involvement occurs.

A classification of the lymphangiomas has been suggested by Watson and McCarthy based upon their study of 41 cases. In this classification the following divisions are proposed: (1) simple lymphangioma, (2) cavernous lymphangioma, (3) cellular or hypertrophic lymphangioma, (4) diffuse systemic lymphangioma, and (5) cystic lymphangioma or hygroma. Very large cystic spaces may be seen in lesions proliferating in loose connective tissues and fascial spaces.

Clinical Features. The majority of cases of lymphangioma are present at birth, according to Watson and McCarthy, in whose series 95% of the tumors had arisen before the age of 10 years. In the series of 132 patients reported by Hill and Briggs, 88% of the lesions had developed by the end of the second year of life. In contrast to that of the hemangioma, the gender distribution of the lymphangioma is nearly evenly divided. The head and neck area in the series of Watson and McCarthy was the site of the tumor in 52% of the cases.

The most common head and neck location is the lateral neck, where this lesion typically contains large cystic spaces and is commonly called cystic lymphangioma or cystic hygroma.

Oral Manifestations. The intraoral lymphangioma most commonly occurs on the tongue, but is seen also on the palate, buccal mucosa, gingiva and lips (Fig. 2-56). The superficial lesions are manifested as papillary lesions which may be of the same color as the surrounding mucosa or of a slightly redder hue. The deeper lesions appear as diffuse nodules or masses without any significant change in surface texture or color. In some cases relatively large areas of tissue may be involved. If the tongue is affected, considerable enlargement may occur, and to this clinical feature the term 'macroglossia' may be applied. A series of 46 cases of lymphangioma of the tongue has been reviewed by Litzow and Lash. They pointed out that the anterior dorsal part of the tongue was most frequently affected. The irregular nodularity of the surface of the tongue with gray and pink projections is the commonest sign of the disease, and when associated with macroglossia, is pathognomonic of lymphangioma.

Lip involvement and its attendant deformity are referred to as macrocheilia. The cystic hygroma is a common and distinct

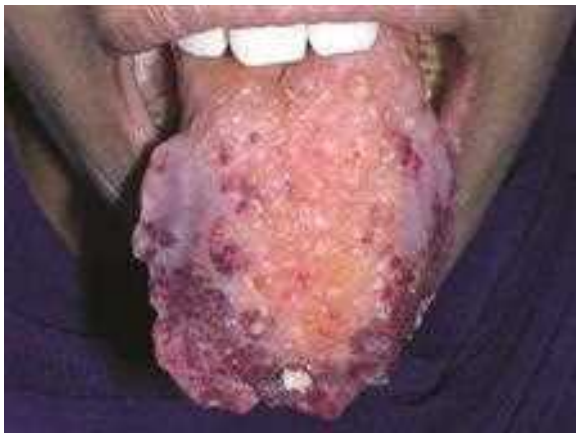


Figure 2-56. Lymphangioma of tongue.
(Courtesy of Dr Ravindra Shetty, Dr G Sriram, Dr Vaishali Natu, Department of Oral Pathology, Nair Hospital Dental College, Mumbai).

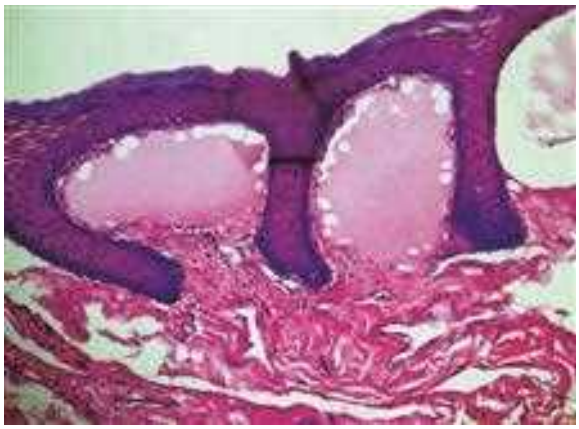


Figure 2-57. Lymphangioma of buccal mucosa.
(Courtesy of Dr Ravindra Shetty, Dr G Sriram, Dr Vaishali Natu, Department of Oral Pathology, Nair Hospital Dental College, Mumbai).

entity that is not manifested in the oral cavity but occurs in the neck as a large, deep, diffuse swelling. This has been discussed in particular by Bill and Sumner and by Paletta.

An unusual form of lymphangioma termed *lymphangioma of the alveolar ridge in neonates* has been reported by Levin and his associates. They found small blue domed fluid-filled lesions on the alveolar ridges in 55 (3.7%) of 1,470 normal black newborns; none were found in whites. Histologically, those biopsied were lymphangiomas. The natural history of this lesion is unknown, although spontaneous regression was noted in several cases.

Occasional cases of central lymphangioma of bone are also known to occur such as that in the tibia reported by Bullough and Goodfellow, as well as in the jaw.

Histologic Features. The lymphangioma consists of multiple, intertwining lymph vessels in a loose fibrovascular stroma. The lymphangioma, of which the cavernous type is the most common, consists of numerous dilated lymphatics, single layer of endothelial cells with flattened, occasionally plump, nuclei and containing lymph (Fig. 2-57). Those vessels just beneath the surface epithelium tend to fill or replace the connective tissue papillae, perhaps producing a papillary surface change. It is not unusual for a superficial lesion to have little or no fibrous stroma separating it from the overlying epithelium. Occasional channels may be filled with blood, a mixed **hemangiolymphangioma**. Occasional lesions demonstrate proliferation of lymphatic channels with another connective tissue component, primarily smooth muscle cells called **lymphangiomyoma**.

No encapsulation of even the tumors which appear well-circumscribed clinically. Deeper lesions show vessels interspersed between adipocytes and striated muscle bundles.

Lymphangioma can be subclassified into four categories:

1. **Lymphangioma simplex** (capillary lymphangioma, lymphangioma circumscriptum), composed of small, thin-walled lymphatics.
2. **Cavernous lymphangioma,** comprised of dilated lymphatic vessels with surrounding adventitia.
3. **Cystic lymphangioma** (cystic hygroma), consisting of huge, macroscopic lymphatic spaces with surrounding fibrovascular tissues and smooth muscle.
4. **Benign lymphangioendothelioma** (acquired progressive lymphangioma), lymphatic channels appear to be dissecting through dense collagenic bundles.

These categories are somewhat artificial and many lesions are combinations of categories.

Treatment and Prognosis. The treatment of the lymphangioma is considerably different from that of the hemangioma. Surgical excision is probably the treatment of choice, since the lymphangioma is more radioresistant and insensitive to sclerosing agents, such as sodium morrhuate, than the hemangioma. Spontaneous regression, according to most studies is rare. Because of the nonencapsulated and 'infiltrating' nature of the lymphangioma, complete removal is often impossible without excessive removal of surrounding normal structures. Surgical debulking of the tumor is, the typical treatment provided, and additional debulking procedures will most likely be required as the affected child grows.

Myxoma

Myxoma is a heterogeneous group of soft tissue tumors which have a common histologic appearance of abundant myxoid ground substance. This is composed of mucopolysaccharides, mainly hyaluronic acid. The myxoma of the soft tissues is a tumor which has been described by Stout as a true neoplasm made up of tissue resembling primitive mesenchyme. Thus it is composed of stellate cells arranged in a loose mucoid stroma which also contains delicate reticulin fibers. The lesion is benign and does not metastasize, although it frequently infiltrates adjacent tissues.

Clinical Features. Most soft-tissue myxomas are deeply situated lesions, occurring in the skin or the subcutaneous tissues, the genitourinary tract, the gastrointestinal tract or in organs such as the liver, the spleen, or even the parotid gland.

This tumor may make its appearance at any age, approximately equal numbers of cases having been reported in every decade of life. There is no definite gender predilection of this neoplasm. A detailed study of 58 patients with 64 tumors has been reported by Ireland and his associates.

Oral Manifestations. The intraoral soft-tissue myxoma is an extremely rare lesion. The majority of oral cases undoubtedly represent only myxomatous degeneration in a fibrous tumor, and these cannot be considered true myxomas, although Elzay has presented 15 intraoral cases which he accepted as bona fide examples.

Other cases occurring centrally within the bone of the jaws have been classified, particularly in the dental literature, as odontogenic myxomas, i.e. as tumors derived from odontogenic tissue. Even though such tumors are sometimes associated with missing or displaced teeth, their dental origin is difficult, is not impossible, to establish. Nevertheless, for the sake of convenience, the central myxoma of bone is discussed under the odontogenic myxoma in the odontogenic tumor section (q.v.).

The **nerve sheath myxoma** is a benign tumor thought to arise from perineural cells of peripheral nerves and is characterized by the occurrence of stellate cells in a prominent mucoid matrix. A few cases have been reported in the oral cavity on the tongue, buccal mucosa and retromolar area and these have been reviewed by Sist and Greene. Their ultrastructural studies, along with those of Webb, supported the perineural origin of these lesions. They are treated by local excision and do not recur.

Oral focal mucinosis, the oral counterpart of a dermal lesion known as cutaneous focal mucinosis and/or cutaneous myxoid cyst, is the lesion most commonly misdiagnosed as an intraoral soft tissue myxoma, according to the study of Tomich. In fact, he has stated that most, if not all, cases diagnosed as oral soft-tissue myxomas are in reality lesions of this entity. He reported eight cases of oral focal mucinosis, including the histologic and histochemical findings, postulating that the lesion develops because of a fibroblastic overproduction of hyaluronic acid due to an unknown stimulus.

Histologic Features. The soft-tissue myxoma is characteristically a loose-textured tissue containing moderate numbers of delicate reticulin fibers and mucoid material, probably hyaluronic acid. Oral focal mucinosis lacks this reticulin network. Interspersed throughout are varying numbers of stellate cells which occasionally assume a spindle shape. The tumor is not encapsulated and may invade surrounding tissue. This invasiveness is not characteristic of oral focal mucinosis.

Tomich has listed the 'myxoid' appearing lesions to be considered in the differential diagnosis as including: soft- tissue myxoma, odontogenic myxoma, myxomatous degeneration in a fibrous lesion, oral focal mucinosis, nerve sheath myxoma, myxoid neurofibroma, mucous retention phenomenon, and localized myxedema.

Treatment and Prognosis. The treatment of the myxoma is essentially surgical, since X-ray radiation is of little benefit. Recurrence is common, but this is not of grave concern, since the tumor does not metastasize. The attempt to avoid recurrence may necessitate the sacrifice of an appreciable amount of apparently uninvolved surrounding tissue, although this is generally not true of the intraoral lesion. In contrast, oral focal mucinosis has no tendency to recur.

Chondroma

The chondroma, a benign central tumor composed of mature cartilage, is a well-recognized entity in certain areas of the bony skeleton, but is uncommon in the bones of the maxilla or mandible. Reported cases were reviewed by MacGregor in 1952. A later review by Chaudhry and his coworkers contained only 18 cases from English scientific literature between 1912 and 1959. The lesion is of considerable clinical importance because of the propensity of the tumor to undergo malignant degeneration in some instances, even after remaining quiescent for long periods of time.

The chondroma seldom develops in membrane bones, particularly if no vestigial cartilaginous rests are present, but since both the maxilla and mandible may contain such remnants, the tumor certainly may occur in these bones. Miles pointed out that areas of 'secondary cartilage', cartilage not related to recognized parts of the chondrocranium, occur in the mandible in the mental region, coronoid process and condyle. At least in the embryo, cartilage is found in the maxilla on the lateral aspects near the malar process close to the molar teeth, as well as in the premaxillary area.

Clinical Features. This neoplasm may develop at any age and shows no apparent gender predilection. The chondroma usually arises as a painless, slowly progressive swelling of the jaw which, like many other neoplasms, may cause loosening of the teeth. The overlying mucosa is seldom ulcerated. The anterior portion of the maxilla is the most frequent site of involvement by this tumor because it is here that vestigial cartilage rests are found, particularly in the midline lingual to or between the central incisors. In the mandible the most common site of occurrence is posterior to the cuspid tooth, involving the body of the mandible, or the coronoid or condylar processes. It is also documented in the nasal septum and nasal spine and has been discussed here by Tomich and Hutton.

Occasional peripheral cases, outside bone, have been reported, such as that on the soft palate described by Gardner and Paterson or the relatively common chondroma or osteochondroma of the tongue. However, these may represent only islands of chondroid metaplasia or even a choristoma rather than a true neoplasm. Thus, they would be analogous to **osteoma mucosae** (q.v.). The relationship of these intraoral peripheral chondromas, especially those of the tongue, to the well-recognized **chondroma of soft parts**, reviewed by Chung and Enzinger, is not clearly established.

Radiographic Features. The radiograph shows an irregular radiolucent or mottled area in the bone. The chondroma is a

destructive lesion and, in addition, has been shown to cause root resorption of teeth adjacent to it.

Histologic Features. The distinction between chondroma and chondrosarcoma is a narrow one and may offer a serious problem to the pathologist confronted with only a small biopsy specimen. The chondroma is made up of a mass of hyaline cartilage which may exhibit areas of calcification or of necrosis. The cartilage cells appear small, contain only single nuclei and do not exhibit great variation in size, shape or staining reaction. Cartilaginous tumors vary considerably in appearance from area to area, so that some malignant lesions present regions of apparent benignity. For this reason, care must be exercised in the unequivocal diagnosis of such a tumor from a small biopsy specimen.

Treatment and Prognosis. The treatment of the chondroma is surgical, since the tumor is resistant to X-ray radiation. The fact that sarcomatous change is not an unlikely occurrence suggests that somewhat more than a conservative enucleation should be carried out, although radical resection cannot be justified unless the tumor is of unusual size. Because of the dearth of reported cases, the prognosis of this disease in the jaws is not known, but to judge from cases in other parts of the body, it is probably good.

Benign Chondroblastoma

(Epiphyseal chondromatous giant cell tumor, Codman's tumor)

The benign chondroblastoma of bone, named by Jaffe and Lichtenstein in 1942 but described earlier by Ewing in 1928 and Codman in 1931, is a distinct entity usually involving long bones but sometimes occurring in the cranial bones. Of 13 such cranial tumors reviewed by Al-Dewachi and his coworkers, nine occurred in the temporal bone, one in the parietal, two in the mandible and one in the maxilla.

Clinical Features. This benign, primary central bone tumor occurs predominantly in young persons, nearly 90% of a series of 69 cases reported by Schajowicz and Gallardo ranging between the ages of five and 25 years. Identical findings were reported in a series of 125 cases by Dahlin and Ivins. Males are involved more than females, usually in a ratio of about 2 to 1. The vast majority of cases involve the long bone of the upper and lower limbs. However, cases involving the mandibular condyle have been reported by Goodsell and Hubinger and by Dahlin and Ivins, while a case involving the anterior maxilla of a 13-year-old girl has been reported by Al-Dewachi and his associates. In addition, an extraskeletal chondroblastoma of the ear has been reported by Kingsley and Markel.

Histologic Features. The tumor is composed of relatively uniform, closely packed, polyhedral cells with occasional foci of chondroid matrix. A scattering of multinucleated giant cells may be found, usually associated with areas of hemorrhage, necrosis or calcification of the chondroid material. Formation of bone and osteoid also occurs, and as pointed out by Gravanis and Giansanti, is probably more common than is generally accepted. In addition, occasional cases have histologic features overlapping those of the chondromyxoid fibroma of bone.

Treatment. Conservative surgical excision is the usually accepted treatment, although recurrence is not uncommon. In a series of 25 cases reported by Huvos and his associates, an aneurysmal bone cyst was found engrafted on the primary bone lesion in 6–24% of the cases, and recurrence rate was higher in this group than in the group without the associated aneurysmal cysts.

Chondromyxoid Fibroma

The chondromyxoid fibroma is an uncommon benign tumor of cartilage derivation first described as an entity in 1946 by Jaffe and Lichtenstein.

Clinical Features. This central bone tumor has a predilection for occurrence in young persons, approximately 75% of patients being under the age of 25 years. There is no definite gender predilection. The majority of cases occur in long bones but it is also found in the small bones of the hands and feet, in the pelvic girdle and elsewhere sporadically. A case in the anterior mandible extending on either side of the symphysis of a 10-year-old girl has been reported by Schutt and Frost. It is extremely rare here, however, considering the relatively large series of cases of chondromyxoid fibroma in other bones reported, such as the 189 cases by Feldman and his associates, the 32 cases by Schajowicz and Gallardo, and the 76 cases by Rahimi and his associates. The possible cases in the jaws have been reviewed by Grotepass and his associates, adding an additional case, as have Davis and Tideman as well as Browne and Rivas.

Pain is the outstanding clinical characteristics of the lesion. Evident swelling is uncommon but does occur.

Histologic Features. This tumor characteristically exhibits lobulated myxomatous areas, fibrous areas and areas having a chondroid appearance, i.e. cells resembling chondroblasts and chondrocytes in lacunae in a chondroid matrix. In addition, foci of calcification are sometimes found. Care must be taken not to make a mistaken diagnosis of chondrosarcoma or mesenchymal chondrosarcoma.

Treatment. Conservative surgical excision is the preferred treatment for this benign tumor. However, recurrence of this tumor in other bones is not uncommon, particularly in young patients in whom the lesions appear to act somewhat more aggressively. Too few cases in the jaws have been reported to draw valid conclusions regarding biologic behavior here.

Osteoma

The osteoma is a benign neoplasm characterized by a proliferation of either compact or cancellous bone, usually in an endosteal or periosteal location. In many parts of the body it is not difficult to establish an incontrovertible diagnosis of osteoma. In the jaws, however, where infection is common it is not always possible to differentiate a bony mass induced by irritation or inflammation from one of a true neoplastic nature. In addition, the so-called exostoses and enostoses further complicate the picture, since they may produce a similar

clinical, radiographic and histologic picture. Although their nature is unknown, they might more properly be considered developmental lesions.

Clinical Features. The osteoma is not a common oral lesion. Although it may arise at any age, it seems to be somewhat more common in the young adult. The lesion of periosteal origin manifests itself as a circumscribed swelling on the jaw producing obvious asymmetry, but it must not be confused with Garre's nonsuppurative sclerosing osteomyelitis or proliferative periostitis. The osteoma is a slow-growing tumor, and so the patient does not usually become alarmed. The osteoma of endosteal origin is slower to present clinical manifestations, since considerable growth must occur before there is expansion of the cortical plates (Fig. 2-58A and B). There is seldom any pain associated with this tumor. Multiple osteomas of the jaws, as well as of long bones and skull, are a characteristic manifestation of Gardner syndrome (q.v.).

The **soft-tissue osteoma** of the oral cavity is a relatively uncommon lesion, a total of 25 cases from the literature being reviewed and reported by Krolls and his coworkers. The lesion is also known as 'osteoma mucosae,' analogous to the well-recognized dermal lesion 'osteoma cutis' and as 'osseous choristoma' after Krolls. These lesions occur almost exclusively in the tongue, although occasional cases are found in the buccal mucosa. They occur at any age and present as a firm nodule ranging up to 2 cm in diameter. Of the 25 reported cases, 18 occurred in females and only seven in males but the significance of this is not known. The bone itself is normal, well-circumscribed lamellar bone, usually compact but sometimes showing fatty marrow (Fig. 2-59B).

Radiographic Features. The central lesion usually appears within the jaw as a well-circumscribed radiopaque mass which is indistinguishable from scar bone (Fig. 2-58B). Sometimes this osteoma is diffuse, but it must be differentiated from chronic sclerosing osteomyelitis. The periosteal form of the disease also is manifested as a sclerotic mass.

Histologic Features. The osteoma is composed either of extremely dense, compact bone or of coarse cancellous bone. In any given area the bone formed appears normal (Fig. 2-58C). The lesion is most often well circumscribed, but not encapsulated. In some tumors foci of cartilage may be found, in which case the term 'osteochondroma' is often used. Myxomatous tissue also may be intermingled on rare occasions.

Treatment and Prognosis. Treatment consists of surgical removal if the lesion is causing difficulty or if a prosthetic appliance is to be constructed, particularly when the tumor lies close to the surface of the alveolar bone. The osteoma does not recur after surgical removal.

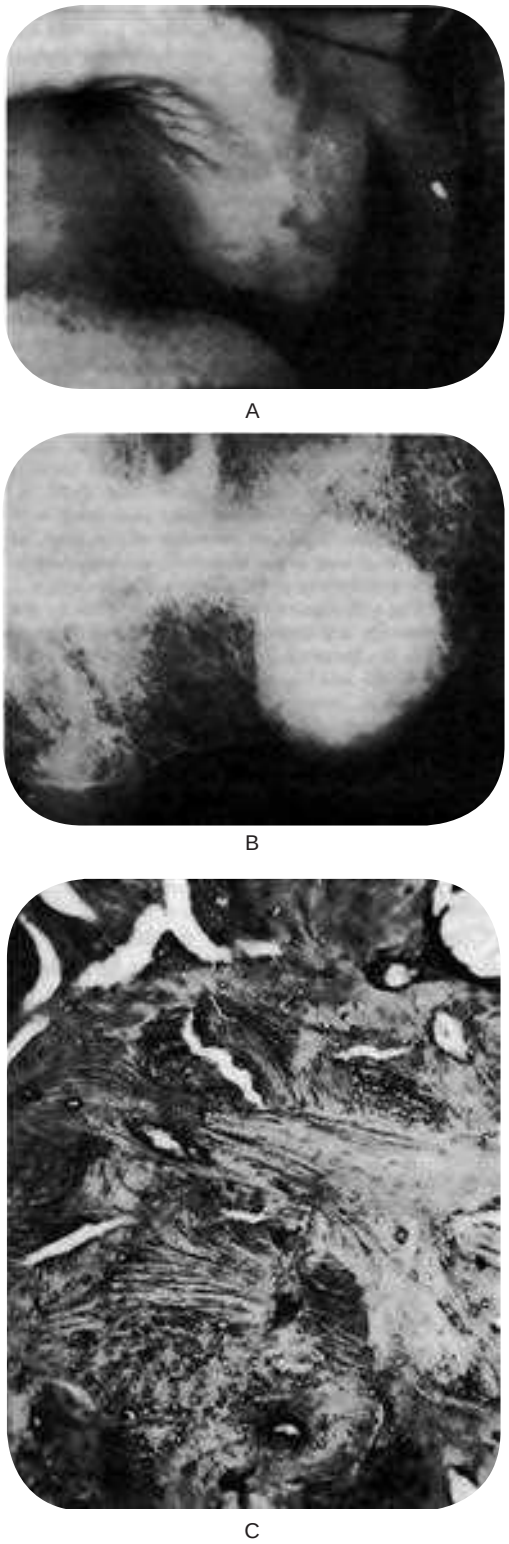
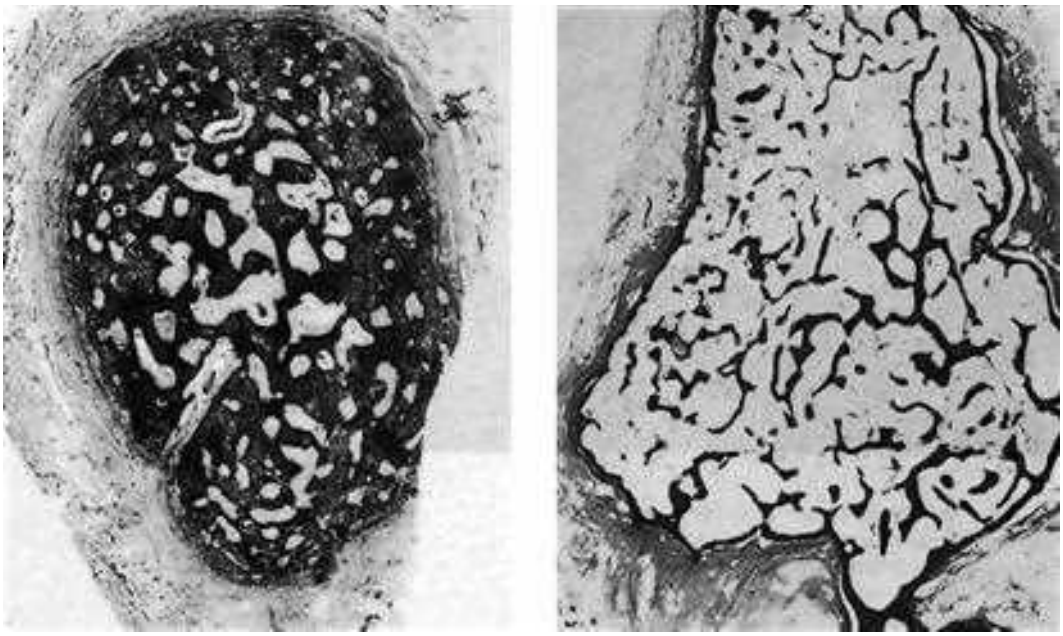


Figure 2-58. Osteoma.
The clinical expansion of the alveolar ridge, **(A)** is seen on the radiograph, **(B)** to be due to a well-circumscribed radiopaque mass. Microscopically, this was composed entirely of dense, compact bone **(C)**.

Osteoid Osteoma

The osteoid osteoma is a benign tumor of bone which has seldom been described in the jaws. The true nature of this lesion is unknown. Jaffe and Lichtenstein have suggested that the lesion is a true neoplasm of osteoblastic derivation, but other workers have reported that the lesion occurs as a result



A B

Figure 2-59. Soft-tissue osteoma.
The osteoma mucosae may be composed of quite dense bone **(A)**, or very loose trabecular bone **(B)**.

of trauma or inflammation. In some instances it has been confused with chronic sclerosing osteomyelitis, and the osteoid osteoma may actually represent a form of this osteomyelitis. A review of the literature with an additional report of 80 cases by Freiberger and his associates has supported the neoplastic theory.

Clinical Features. The osteoid osteoma usually occurs in young persons, seldom developing after the age of 30 years. Young children under the age of 10 years or even five years are frequently affected. In most series, males predominate over females by a ratio of at least 2 to 1. It has been reported most frequently in the femur or in the tibia, although other bones throughout the body have occasionally been involved. One of the chief symptoms of the condition is severe pain out of all proportion to the small size of the lesion. The pain of osteoid osteoma is described as unrelenting and sharp, worse at night. Classically, the pain is relieved by aspirin. Localized swelling of the soft tissue over the involved area of bone may occur and may be tender.

Oral Manifestations. Greene and his associates have reviewed the literature and added one more case, bringing the total number of cases of osteoid osteoma of the jaws to seven. Of these, four have occurred in the mandible and three in the maxilla. Of the mandibular lesions, three were in the body and one in the condyle, while one maxillary lesion involved the antrum.

Radiographic Features. Radiographically, the osteoid osteoma presents a pathognomonic picture characterized by a small ovoid or round radiolucent area surrounded by a rim of sclerotic bone. The central radiolucency may exhibit some calcification. The lesion seldom is larger than 1 cm in diameter, but the overlying cortex does become thickened by subperiosteal new bone formation.

Histologic Features. The microscopic appearance of the osteoid osteoma is characteristic and consists of a central nidus composed of compact osteoid tissue, varying in degree of calcification, interspersed by a vascular connective tissue. Formation of definite trabeculae occurs, particularly in older lesions, outlined by active osteoblasts. Osteoclasts and foci of bone resorption are also usually evident. The overlying periosteum exhibits new bone formation, and in this interstitial tissue collections of lymphocytes may be noted (Fig. 2-60).

Ultrastructural investigation of five cases of osteoid osteoma by Steiner has revealed the morphology of the osteoblasts to be similar to that of normal osteoblasts although atypical

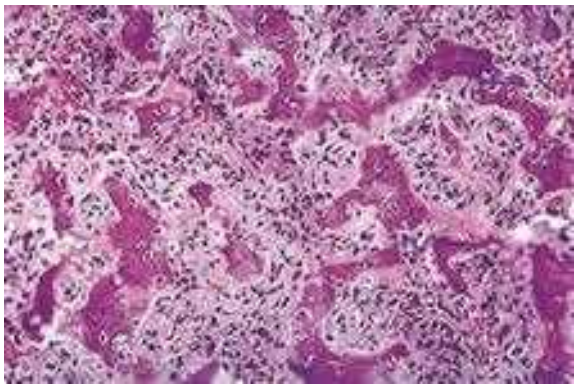


Figure 2-60. Osteoid osteoma.
This is the central nidus of an osteoid osteoma composed of irregular reactive new bone.

mitochondria could be seen. For comparison, the osteoblasts of a benign osteoblastoma were studied and were found to be essentially identical, including the atypical mitochondria. The author concluded that his observations supported the idea that the osteoid osteoma and the osteoblastoma are closely related lesions. Unlike in osteoblastoma, neural staining techniques reveal many axons throughout an osteoid osteoma, which probably accounts for the pain (the nidus). Levels of prostaglandin E_2 are markedly elevated in the nidus; this is presumably the cause of pain and vasodilatation.

Treatment. The treatment of the osteoid osteoma consists of surgical removal of the lesion. If the lesion is completely excised, recurrence is not to be expected. There is fairly good circumstantial evidence that spontaneous regression may occur in at least some untreated cases.

Benign Osteoblastoma
(Giant osteoid osteoma)

The osteoblastic nature of the tumor often results in zones similar to those of an osteoid osteoma producing a histologic resemblance that cannot be ignored. Benign osteoblastoma differs, however, in that it does not share the markedly limited growth potential of the average osteoid osteoma. Furthermore, the benign osteoblastoma frequently lacks the characteristic pain and the halo of sclerotic bone associated with osteoid osteoma. McLeod and coworkers resolved this problem by arbitrarily regarding an equivocal lesion as an osteoblastoma when the lesion was more than 1.5 cm in its greatest dimension.

The term **giant osteoid osteoma,** introduced several years ago, was an attempt to recognize the pathologic similarity of this lesion to osteoid osteoma, at the same time indicating a difference, especially in the size of the average tumor. **Benign osteoblastoma,** nevertheless, has become the most widely accepted designation for this tumor (Unni KK, 1996).

One can logically question whether benign osteoblastoma is correctly classed with true neoplasms because some osteoblastomas regress or become arrested after incomplete surgical removal. Fields within some of these tumors resemble portions of an aneurysmal bone cyst. This resemblance, coupled with the pronounced clinical similarity, suggests that both tumors may be different manifestations of a reaction to some as yet unknown agent.

There are rare well documented examples of osteoblastoma undergoing malignant change to osteosarcoma (Unni KK, 1996). The lesion called **cementoblastoma,** at or around the root of a tooth, is similar, and has been included with osteoblastoma.

The benign osteoblastoma was first described under the name 'giant osteoid osteoma' by Dahlin and Johnson in 1954 and under the presently more accepted name by Jaffe and by Lichtenstein in 1956 in separate reports. The lesion is not common but is nevertheless very important in as much as it is frequently mistaken for a malignant bone tumor even though it is actually entirely benign.

Clinical Features. This central bone tumor occurs most frequently in young persons, approximately 75% of the patients being under 20 years of age and 90% under 30 years of age. However, it does occur even in elderly adults. In most reported series, there is a definite predilection for occurrence in males. The lesion is characterized clinically by pain and swelling at the tumor site, the duration being just a few weeks to a year or more. Unlike osteoid osteoma, the pain of osteoblastoma is more generalized and less likely to be relieved by salicylates.

The most common site of occurrence is the vertebral column. Other frequently affected sites include the sacrum, long tubular bones and calvarium. The first case in the jaws was reported by Borello and Sedano in 1967, but it is now recognized that the benign osteoblastoma occurs in both the maxilla and mandible with some frequency, and a number of cases have been reported. These have been reviewed by Greer and Berman, and more recently, by Miller and his coworkers, who tabulated 26 cases: 14 mandible, 11 maxilla, and one unstated.

Radiographic Features. The lesion is not distinctive but, on the radiograph, appears rather well circumscribed. In some instances, there is purely bone destruction, while in other cases there is sufficient bone formation to produce a mottled, mixed radiolucent-radiopaque appearance (Fig. 2-61). A periosteal counterpart has been described by Goldman and such a case in the mandible is reported by Farman and his associates. The spectrum of the osteoblastoma is discussed by McLeod and his associates.

Histologic Features. There may be considerable variation in the microscopic appearance of the benign osteoblastoma. Nevertheless, the hallmark of the benign osteoblastoma consists of:

- The vascularity of the lesion with many dilated capillaries scattered throughout the tissue
- The moderate numbers of multinucleated giant cells scattered throughout the tissue, and
- The actively proliferating osteoblasts which pave the irregular trabeculae of new bone (Fig. 2-62).

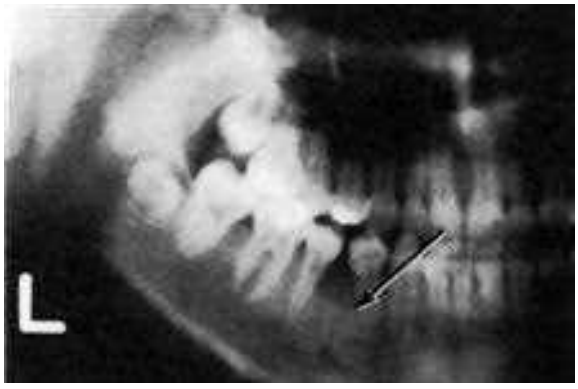
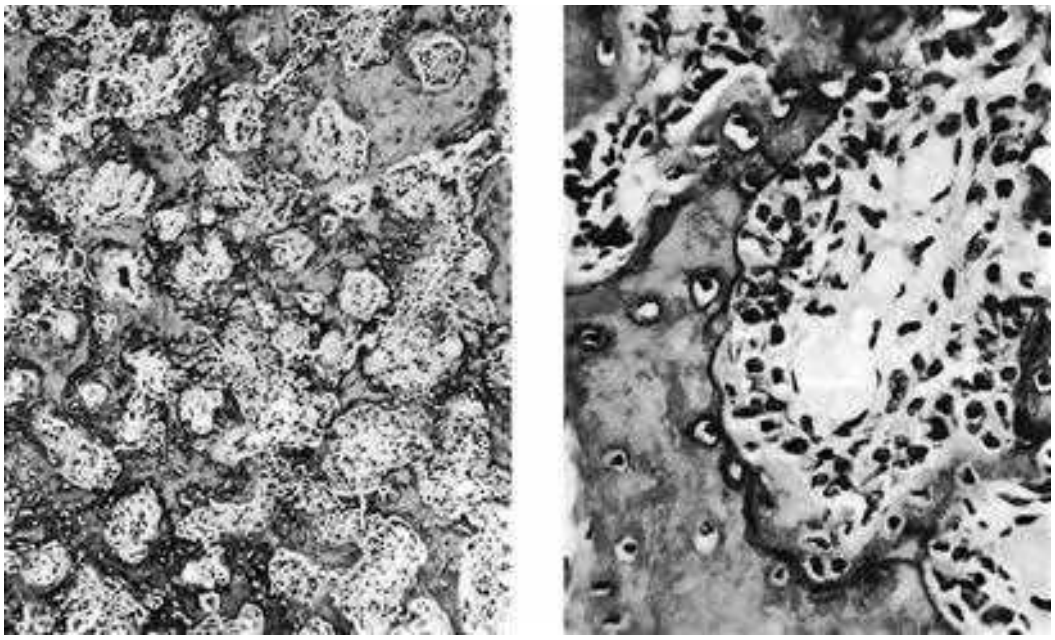


Figure 2-61. Benign osteoblastoma.
(Courtesy of Dr Ronald Vincent).



A B

Figure 2-62. Benign osteoblastoma.

These osteoblasts often appear so active and are present in such numbers that, in the past, mistaken diagnosis of osteosarcoma have often been rendered. In addition, some cases bear remarkable resemblance to an aneurysmal bone cyst.

The osteoblastoma has been studied ultrastructurally by Steiner who noted that, with a few exceptions, the tumor osteoblasts resembled normal osteoblasts. Comparative differences of osteosarcoma cells from osteoblastoma cells also did not appear pathognomonic, so he concluded that the final diagnosis of osteoblastic tumors rested at the light microscope level.

A **malignant osteoblastoma** has been described by Schajowicz and Lemos on the basis of a histologically more bizarre pattern of cells: more abundant and often plump hyperchromatic nuclei, greater nuclear atypia, and numerous giant cells. While locally more aggressive than the benign osteoblastoma, it has a better prognosis than a conventional osteosarcoma.

Finally, malignant transformation of a previously benign osteoblastoma into an osteosarcoma has also been reported, such as the case discussed by Merryweather and his coworkers.

Treatment. Conservative surgical excision is the preferred treatment for this tumor. Recurrence is rare.

Torus Palatinus

The torus palatinus is a slowly growing, flat-based bony protuberance or excrescence which occurs in the midline of the hard palate. Numerous theories have been suggested, but a plausible and thoroughly convincing explanation for this common oral lesion is still lacking. A study by Suzuki and Sakai offered evidence that both the torus palatinus and torus mandibularis are hereditary conditions, thought to follow a mendelian dominant pattern.

Clinical Features. The incidence of torus palatinus reported in the United States varies between 20 and 25%. Women are affected more frequently than men, the approximate ratio found by Kolas and his associates being 2 to 1. Although the palatine torus may occur at any age, including the first decade, it appears to reach its peak incidence shortly before the age of 30 years. Certain races, such as the American Indian and the Eskimo, are reported to exhibit a much higher incidence of torus palatinus than the general population in this country, including blacks.

The torus palatinus presents itself as an outgrowth in the midline of the palate and may assume a variety of shapes (Fig. 2-63). It has been classified clinically on this basis as flat, spindle-shaped, nodular or lobular. The mucosa overlying the torus is intact, but occasionally appears blanched. It may become ulcerated if traumatized. The torus itself may be composed either of dense compact bone or of a shell of compact bone with a center of cancellous bone, and thus it is often visible on an intraoral palatal radiograph.

Treatment and Prognosis. There is little clinical significance attached to this lesion, since it is benign and never becomes malignant. The torus is usually not treated, although occasionally it may be of such size and shape that it is impossible or impractical to construct a full or partial denture over the structure because of undercuts, the probability of trauma

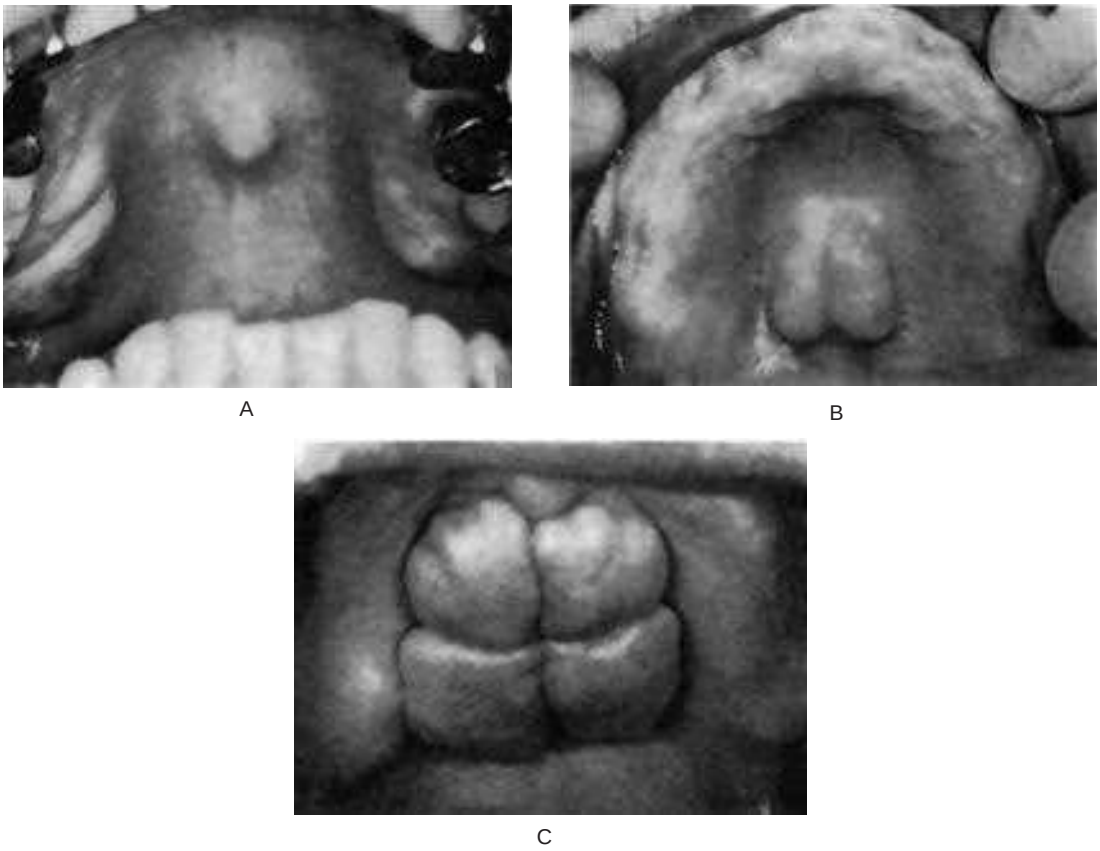


Figure 2-63. Torus palatinus.
This lesion may be a small outgrowth in the midline of the palate **(A)**, a larger lobed mass **(B)**, or may nearly completely fill the palatal vault **(C)**.

to the overlying mucosa or inability to seat the denture, owing to rocking. In such cases the situation must be appraised and the torus removed surgically before the construction of the prosthetic appliance.

Torus Mandibularis

The torus mandibularis is an exostosis or outgrowth of bone found on the lingual surface of the mandible. Just as in the case of the palatine torus, numerous causes have been suggested, but the etiology of the torus mandibularis is actually still unknown.

A genetic or ethnic background is suggested, for example, by the high frequency of occurrence in Mongoloid groups and a low frequency in Caucasoid groups, as pointed out by Sellevold. Supporting this idea through familial investigations, Suzuki and Sakai have commented on its apparent hereditary nature. Essentially, their studies showed that when one or both parents had either type of torus, the frequency of occurrence of a torus in the children ranged between 40 and 64%. When neither parents had a torus, the incidence of a torus in the children was only 5–8%. In contrast, some studies seem to favor an environmental background as the more important factor. For example, it has been found that groups of the same population living in different environments have different frequencies of occurrence of this torus, while different racial groups living in approximately the same environment have similar frequencies of occurrence. It has been an idea held for many years that a torus mandibularis will develop as a reinforcement of bone in this bicuspid area in response to the torsional stress created by heavy mastication.

Clinical Features. This growth on the lingual surface of the mandible occurs above the mylohyoid line, usually opposite the bicuspid teeth (Fig. 2-64). Like the palatine torus, it may

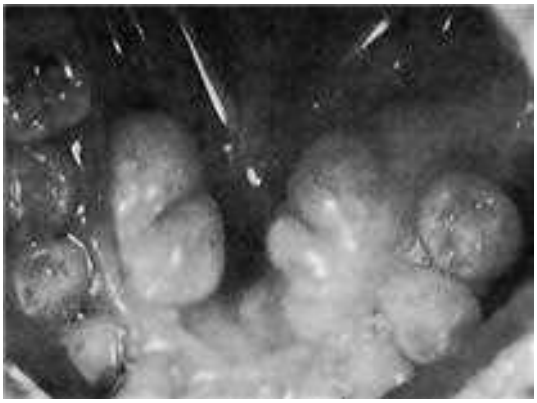


Figure 2-64. Torus mandibularis.

vary considerably in size and shape. Although the mandibular tori are usually bilateral, they are seen as a unilateral condition in about 20% of the cases. Both unilateral and bilateral protuberances may be single or multiple, and they are frequently visible on dental periapical radiographs. There is no correlation in the frequency of simultaneous occurrence of torus palatinus and torus mandibularis, according to the studies of Kolas and coworkers, suggesting that the two conditions are not related. Suzuki and Sakai reported a highly significant correlation in the frequency of simultaneous occurrence of the two tori, however.

The bilateral bony growths on the lingual of the mandible may be lobed or multiple.

The reported incidence in the United States varies between 6 and 8%, with no differences between the genders noted. Some races, such as the Alaskan Eskimos and Aleuts, are reported to have a much higher incidence of mandibular tori. Among the general population in this country the torus mandibularis is infrequently seen in the first decade of life, but it usually has its onset by the age of 30 years.

Treatment and Prognosis. Surgical removal of the torus mandibularis may be necessary because of difficulties encountered in attempting to construct a denture over the outgrowth. The lesion is comparable to the torus palatinus in its benignity.

Multiple Exostoses

Multiple exostoses of the jaws are somewhat less common than the maxillary and mandibular tori and are usually found on the buccal surface of the maxilla below the mucobuccal fold in the molar region. Clinically, these exostoses appear as small nodular protuberances over which the mucosa may appear blanched (Fig. 2-65).

There are numerous small excrescences part of bone on the buccal surface of the maxilla above the teeth and below the mucobuccal fold.

Their etiology is unknown, and no figures are available as to their incidence or disposition. They are of no clinical significance except that, if large, they may interfere with the preparation or insertion of a prosthetic appliance.

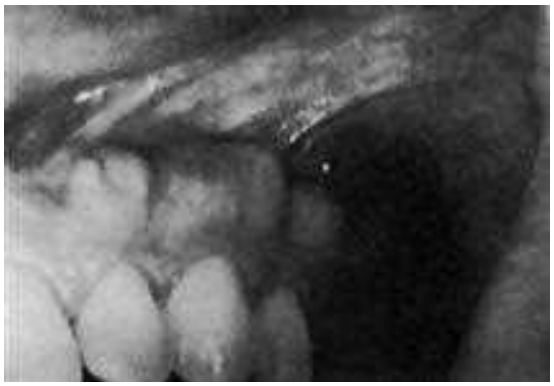


Figure 2-65. Multiple exostoses.

MALIGNANT TUMORS OF CONNECTIVE TISSUE ORIGIN

Fibrosarcoma

Fibrosarcoma is a tumor of mesenchymal cell origin that is composed of malignant fibroblasts in a collagenous background. It can occur as a soft tissue mass or as a primary or secondary bone tumor. The fibrosarcoma was once considered to be one of the most common of the malignant soft-tissue neoplasms. However, the gradual separation of other tumors from this group as our knowledge of fibrous lesions increased has in effect reduced the apparent frequency of the disease, so that nowadays fibrosarcoma, particularly of the head and neck area, is a quite uncommon neoplasm.

The sarcomas as a group differ from malignant epithelial neoplasms by their typical occurrence in relatively younger persons and their greater tendency to metastasize through the blood stream rather than the lymphatics, thereby producing more widespread foci of secondary tumor growth.

Two main types of fibrosarcoma of bone exist, **primary** and **secondary**. Primary fibrosarcoma is a fibroblastic malignancy that produces variable amounts of collagen. It is central, arising within the medullary canal, or peripheral, arising from the periosteum. Secondary fibrosarcoma of bone arises from a preexisting lesion or after radiotherapy to an area of bone or soft tissue. This is a more aggressive tumor with poorer prognosis.

Etiopathogenesis. Fibrosarcoma, like other soft tissue sarcomas, has no definite cause.

Several inherited syndromes like multiple neurofibromas may have a 10% risk over a lifetime of developing a neurosarcoma or fibrosarcoma.

Current research indicates that many sarcomas are associated with genetic mutations. Recently, a unique fusion transcript has been detected in 10 out of 11 cases (Jacqueline M et al., 2000). This fusion results from the translocation **t(12;15)(p13;q25)** giving rise to ETV6-NTRK3 (ETS variant gene 6; neurotrophic tyrosine kinase receptor type 3) gene fusion. It is absent in other spindle cell tumors of childhood as well as adult fibrosarcoma.

Fibrosarcoma also has been noted to arise from preexisting lesions, such as fibrous dysplasia, chronic osteomyelitis, bone infarcts, Paget's disease, and in previously irradiated areas of bone. These lesions are very aggressive and are associated with much poorer outcome than the primary fibrosarcoma of bone.

Clinical Features. Fibrosarcoma represents only about 10% of musculoskeletal sarcomas and less than 5% of all primary tumors of bone. No known racial predilection exists. Fibrosarcoma of bone occurs slightly more commonly in men than in women. Fibrosarcoma of bone is seen more commonly in patients of fourth decade of life and is usually in the lower extremities, especially the femur and the tibia. Fibrosarcoma of the soft tissues usually affects a wider age

spectrum of patients than fibrosarcoma of the bone, with an age range of 35–55 years. It often arises in the soft tissues of the thigh and the posterior knee. It is generally a large painless mass deep to fascia and has an ill-defined margin.

An infantile form (in children <10 years) of fibrosarcoma exists. Unlike fibrosarcoma in adults, it has an excellent prognosis, even in the face of metastatic disease at presentation, when treated with a combination of neoadjuvant and adjuvant chemotherapy and resection.

Sarcomas involving bone often present with pain and swelling after a long duration of symptoms. They may even grow large enough to threaten the structural integrity of the bone and cause pathologic fracture as the initial presentation. A prior history of bone infarct, irradiation, or other such risk factors should alert the physician to the possibility of a secondary fibrosarcoma.

Soft tissue sarcomas most often present as painless masses. The duration, however, is often shorter than with lesions involving bone. Because these lesions often arise deep in the muscular fascia, they may become extremely large tumors prior to diagnosis.

Differential diagnoses include fibrous dysplasia, fibrous histiocytoma, osteosarcoma, Paget's sarcoma, malignant fibrous histiocytoma, malignant neurosarcoma.

Histologic Features. Fibrosarcomas are tumors of malignant fibroblasts. They vary in histologic grade.

Well-differentiated forms have multiple plump fibroblasts with pale eosinophilic cytoplasm and deeply staining spindled nuclei with tapered ends. The malignant cells are dispersed in a rich collagen background. The lesion is typically scattered, histologically normal mitotic figures are seen in small numbers, but cells and nuclei are not pleomorphic (Fig. 2-66).

Intermediate grade tumors are cellular and have the typical **herringbone** pattern showing the diagnostic parallel sheets of cells arranged in intertwining whorls. Quite cellular with slight degree of cellular pleomorphism but moderate amounts of mature collagen may be produced, perhaps with areas of hyalinization (Fig. 2-67).

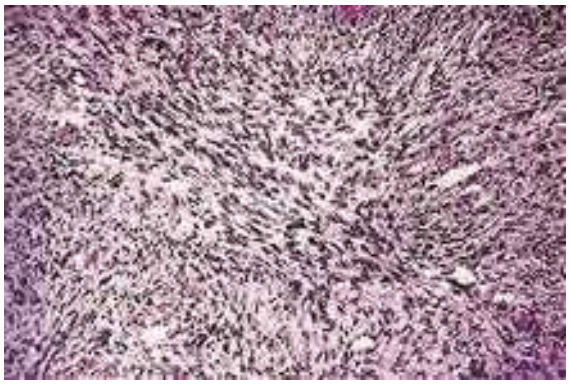


Figure 2-66. Low power appearance of well-differentiated fibrosarcoma. The tumor has a monotonous hypercellular look with regimentation of nuclei. Mitotic figures are common.

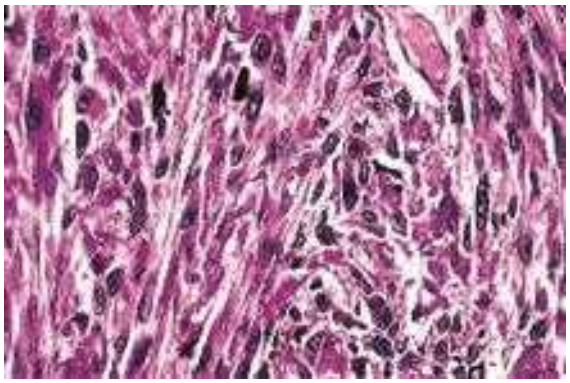


Figure 2-67. Fibrosarcoma showing moderate degree of nuclear pleomorphism.

High-grade lesions are very cellular with marked cellular atypia and mitotic activity. The matrix is sparse. Multinucleated giant cells are rarely seen. No malignant osteoid formation should be present. Higher grades are extremely anaplastic and pleomorphic with bizarre nuclei that bring to mind the histologic features of malignant fibrous histiocytoma. In fact, some pathologists believe that the division between malignant fibrous histiocytoma, high-grade osteosarcoma, and fibrosarcoma may be artificial. Immunohistochemical studies reveal positivity for smooth muscle actin, desmin, S100 protein, and CD34.

Sclerosing epithelioid fibrosarcoma is an uncommon tumor of deep soft tissues. Histologically, sclerosing epithelioid fibrosarcoma composed predominantly of small to moderate size, round to ovoid, relatively uniform cells, often with clear cytoplasm, embedded in a hyalinized fibrous stroma. The only consistent immunohistochemical finding was a strong, diffuse reactivity of tumor cells for vimentin.

Treatment and Prognosis. Tumors require radical surgery, including removal of potentially invaded muscle and bone. The use of chemotherapy is controversial, but is generally used in bone lesions. Radiation therapy is used in conjunction with surgery for soft tissue fibrosarcomas, with or without additional chemotherapy. Fibrosarcoma seldom metastasizes except late in its clinical course, but when this does occur the metastatic deposits are usually blood-born and carried to distant sites, especially the lungs, liver and bones. Radiotherapy may be used as salvage for recurrences.

If all grades are included, primary fibrosarcoma of the bone has a worse prognosis than osteosarcoma, with a five-year survival rate of 65%. Specifically, in high-grade primary fibrosarcoma, the 10-year survival rate is less than 30%. Secondary fibrosarcoma is associated with a very poor outcome, with a less than 10% survival rate at 10 years.

Miscellaneous Locally Aggressive Fibrous Lesions

There is a sizable of locally aggressive but nonmetastasizing fibrous lesions which must always be differentiated type. In the past, many of these benign but locally aggressive lesions

have been confused with sarcoma, and it is only in recent years that the pathologist has been able to separate these lesions with any assurance.

All of these lesions are quite uncommon in the oral cavity, and for this reason, no detailed description of them will be made here. This group consists chiefly of the following:

1. Nodular fasciitis (pseudosarcomatous fibromatosis)
2. Aggressive fibromatosis (extra abdominal desmoid)
3. Proliferative myositis
4. Fibrous histiocytoma (fibroxanthoma)
5. Atypical fibroxanthoma (and malignant variant)
6. Desmoplastic fibroma of bone.

Each of these lesions has been described in detail in the Atlas of Tumor Pathology Fascicle on Tumors of the Soft Tissues (AFIP) by Stout and Lattes and in the World Health Typing of Soft Tissue Tumors by Enzinger, Lattes and Torloni.

Definitions of each of the above lesions have been proposed in this WHO monograph and are reproduced as follows:

1. Nodular fasciitis. "A benign and probably reactive fibroblastic growth extending as a solitary nodule from the superficial fascia into the subcutaneous fat, or less frequently, into the subjacent muscle. Confusion with a sarcoma is possible because of its cellularity, its mitotic activity, its richly mucoid stroma, and its rapid growth. Other fibroblastic proliferations, such as proliferative myositis, are probably akin to this lesion. Nodular fasciitis is most common in the upper extremity, the trunk and the neck region of young adults."

Nodular fasciitis of the head and neck has been described in detail by Werning, who reported 41 cases in this area and reviewed the pertinent literature. In his series, lesions occurred in every age group but were most common in the third through the fifth decade of life. These lesions developed most often within subcutaneous tissues overlying the mandible and zygoma, although intraoral lesions of buccal mucosa, tongue and alveolar mucosa also occurred. Since so many of the cases occurred in areas which serve as sites of origin or insertion of muscles of mastication and which are particularly vulnerable to trauma, Werning has emphasized that this lends support to the theory that nodular fasciitis is a pseudoneoplastic exuberant fibroblastic or myofibroblastic reactive process. These were usually firm, painless masses but, on occasion, there was pain, tenderness and a history of rapid growth. The treatment for this lesion is surgical excision and recurrence is rare.

2. Aggressive fibromatosis. "A nonmetastasizing tumor like fibroblastic growth of unknown pathogenesis involving voluntary muscle as well as aponeurotic and fascial structures. Histologically, it is indistinguishable from an abdominal fibromatosis. The lesion has a strong tendency to local recurrence and aggressive, infiltrating growth. It is most common in the shoulder girdle, the thigh, and the buttock of young adults."

Aggressive fibromatosis of the oral or paraoral structures has been reported on occasion but it is quite uncommon in this location. Melrose and Abrams, reporting three cases involving the jaws of children, have discussed the protean nature of this group. For example, some are rapidly enlarging while others are of quite slow growth. Pain may or may not be present. When in apposition to bone, destruction of the bone occurs. The microscopic appearance of their lesions was quite uniform, however, consisting of cellular interlacing bundles of elongated fibroblasts showing no pleomorphism, little or no mitotic activity and no giant cells but typically with numerous slit-like vascular spaces not associated with inflammation. Treatment consists of complete surgical excision with generous margins of normal tissue. Recurrence is always a strong possibility and some workers recommend prolonged indefinite follow-up.

3. Proliferative myositis. "A rapidly growing, poorly circumscribed, probably reactive proliferation of fibroblasts and ganglion cell-like giant cells involving chiefly the connective tissue framework of striated muscle tissue. In contrast to myositis ossificans, a history of preceding trauma is infrequent and the lesion occurs chiefly in patients older than 45 years. The lesion is benign and should not be mistaken for a rhabdomyosarcoma or some other malignant neoplasm. Proliferative myositis has been discussed in Chapter 20 on Diseases of the Nerves and Muscles (q.v.).

4. Fibrous histiocytoma. "A benign, unencapsulated and often richly vascular growth made up of histiocytes and collagen-producing fibroblast-like cells, which are arranged in a whorled or cartwheel pattern. Frequently, the growth contains lipid-carrying macrophages. It may occur anywhere but is most common in the dermis."

5. Atypical fibroxanthoma. "A probably benign growth, which is closely related to fibroxanthoma but shows a much greater degree of cellular pleomorphism with multinucleated giant cells and occasional giant cells of the Touton type as well as numerous mitotic figures, including atypical forms. The relatively small size of the lesion (generally less than 3 cm), its prevalence in the sun-damaged or irradiated skin of elderly individuals, and the fact that it is usually well-circumscribed, help in the difficult differential diagnosis from malignant fibroxanthoma. It probably does not occur in the oral cavity.

6. Desmoplastic fibroma of bone. This is a lesion of bone, including the jaws, which is histologically indistinguishable from aggressive fibromatosis or the extra abdominal desmoid. Although there is a wide spread in the age of occurrence, the vast majority of cases have occurred in the second decade. The lesion does not metastasize but often shows local recurrence. Wide local excision is, therefore, the treatment of choice.

The desmoplastic fibroma of the jaws has been reviewed by Freedman and his associates, who have analyzed and discussed 26 cases described in the literature. They found also that nearly all cases in this location occurred in the first three decades of life with the vast majority involving the mandible, particularly the molar-ramus-angle area. Swelling of the jaw was the common presenting complaint, pain or tenderness rarely being present. In a high percentage of cases, the lesions appeared as well-delineated radiolucencies, either unilocular or multilocular. The broadening of the microscopic

parameters of this lesion was also emphasized by Freedman, who summarized the concept of the desmoplastic fibroma of bone as being composed of cells that may be either small and uniform, plump and uniform, or both in the same lesion, set in a variably collagenized stroma. The cells lack anaplastic forms or significant numbers of mitotic figures. Treatment of this lesion appears to be surgical excision or thorough curettage. Recurrence of jaw lesions has been uncommon.

Fibrous Histiocytoma

Fibrous histiocytoma represents a benign but diverse group of neoplasms which exhibit both fibroblastic and histiocytic differentiation. The cell of origin is believed to be the histiocyte, but the varied microscopic appearance of the lesion has led to the use of numerous alternative diagnostic terms, including dermatofibroma, sclerosing hemangioma, xanthogranuloma, fibroxanthoma, and nodular subepidermal fibrosis. A malignant variant of this neoplasm is discussed in the following section.

Clinical Features. The most common site of occurrence is the skin of the extremities, where it usually presents as a small, firm nodule. Oral and perioral lesions are uncommon, but when seen they occur predominantly on the buccal mucosa and vestibule (Fig. 2-68). The oral lesion is typically found in middle-aged and older adults, where it presents as a painless submucosal nodule which can vary in size from a few millimeters to several centimeters. Deeper tumors tend to be larger and most lesions cannot be easily moved about beneath the epithelium.

Histological Features. Fibrous histiocytoma is characterized by a submucosal, cellular aggregation of spindle-shaped, fibroblast like cells with relatively pale, oval nuclei; scattered rounded histiocytic cells are also present. Foamy histiocytes and **Touton-type** multinucleated giant cells, with nuclei pushed to the periphery, may be seen to contain phagocytosed lipid or hemosiderin; these cells sometimes are so numerous that they form xanthomatous aggregates. A background stroma of variably dense collagenous tissue and vascularity is seen. The spindled cells may be arranged randomly but usually there are large areas with tumor cells streaming in interlacing fascicles from a central nidus and intersecting with cells from adjacent aggregates, imparting a **storiform** or crisscross pattern on low power magnification.

Figure 2-68. Benign fibrous histiocytoma of cheek (intraoperative view).

The fibrous histiocytoma is poorly demarcated from surrounding tissues and is separated from the overlying mucosa by a zone of fibrovascular connective tissue (grenz zone). The overlying epithelium often demonstrates considerable acanthosis, with regular elongation of rete processes. Chronic inflammatory cells, especially lymphocytes, are usually scattered throughout the tumor in small numbers. The lesional stroma is occasionally very densely fibrotic or hyalinized, leading some in the past to use the diagnostic misnomer **sclerosing hemangioma**. Deeper lesions may contain focal areas of dystrophic calcification or metaplastic osteoid.

Benign fibrous histiocytoma is often confused with other benign fibrous lesions and must be differentiated from nodular fasciitis, myofibroma, palisading encapsulated neuroma, neurofibroma, leiomyoma and the spindle cell type of myoepithelioma. It is important, moreover, to separate this tumor from aggressive forms of fibrous and fibrohistiocytic neoplasms such as dermatofibrosarcoma protuberans, malignant fibrous histiocytoma and fibrosarcoma.

Treatment and Prognosis. Benign fibrous histiocytoma is treated by wide surgical excision, with 5–10% of cases recurring locally. Deeper and larger lesions have a higher rate of recurrence. More aggressive examples usually show the microscopic features of dysplasia, such as marked cellularity, mitotic activity, focal necrosis, even atypical giant cells. It is sometimes, however, very difficult to predict biological behavior on the basis of cellular features alone. This warrants the need for extensive follow-up of cases.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) was first described in 1964 under the name malignant fibrous xanthoma. Since then several major variants have been identified and it has become the most commonly diagnosed of all the sarcomas of adults. Oral and maxillofacial sites are seldom involved, however, and the tumor occurs primarily in the soft tissues of the extremities and retroperitoneum.

Clinical Features. The MFH occurs primarily in adults, especially those 50–70 years of age, but rare cases have been described in children. Regardless of the histopathologic subtype, men are affected almost twice as frequently as women.

Within the maxillofacial region the most common complaint is a moderately firm submucosal mass expanding slowly or moderately fast, with or without pain and surface ulceration. The irregular nodular lesion is typically unencapsulated and attached to surrounding tissues and adjacent structures. It is usually less than 4 cm in greatest diameter at the time of biopsy. The myxoid variant often has a soft consistency and the angiomatoid variant is often found in a location more superficial than that of the other variants.

Histologic Features. MFH has a wide spectrum of cellular and tissue alterations. The cellular differentiation and density vary markedly, even within the same tumor. The classic histopathologic features, however, include at least mild cellular and nuclear pleomorphism, an admixture of fibroblastic and histiocytic elements, and focal areas with a storiform or cartwheel pattern of streaming spindle cells. This classic pattern is the one most frequently encountered in head and neck sites and is often referred to as the **storiform-pleomorphic MFH**.

Most lesional cells are spindled fibroblast like cells which tend to be arranged in short woven fascicles or bundles. The spindle cells may be long and thin with minimal atypia, but there are usually areas with plump cells containing enlarged, hyperchromatic and irregular nuclei. Varying numbers of rounded, polygonal and irregularly shaped histiocyte like cells may dominate some areas of the lesion, often with very pleomorphic, multinucleated giant cells interspersed. The histiocytic cells have either abundant eosinophilic cytoplasm or pale foamy cytoplasm, and cell membranes are not easily visualized. Areas with histiocytic predominance usually have a haphazard structural appearance.

Chronic inflammatory cells are often scattered sparsely throughout the tumor, including foamy histiocytes, lymphocytes and plasma cells. Mitotic activity varies widely and is directly related to the degree of cellular pleomorphism.

The fibrous stroma of MFH varies in density, being less pronounced in areas of lesser cellular differentiation. Myxoid stroma may be found, and rarely, foci of osteoid or cartilage metaplasia are present. While blood vessels are usually inconspicuous, some lesions present with numerous dilated, branching vessels. Depending on the dominant morphology, MFH is currently subclassified as one of several major variants: **pleomorphic-storiform, myxoid, angiomatoid (aneurysmal), and giant cell MFH**.

Treatment and Prognosis. MFH of the oral region is usually treated by radical surgical resection, but at least 40% of lesions recur locally and a similar proportion metastasize within two years. Five-year survival is no more than 30%, although it is somewhat better for the myxoid variant.

Synovial Sarcoma

Synovial sarcoma comprises 8–10% of all sarcomas and most commonly affects adults in the third-to-fifth decades of life. The malignancy most commonly involves the extremities, especially the lower extremities around the knees. Synovial sarcoma frequently is misdiagnosed as benign often because of its small size, slow growth, and well-defined appearance.

Etiopathogenesis. Synovial sarcoma is so named because of its resemblance to developing synovial tissue under light microscope. It arises from pluripotential mesenchymal cells near joint surfaces, tendons, tendon sheaths, juxta-articular membranes, and fascial aponeuroses.

Clinical Features. Synovial sarcoma can occur in patients with a wide age range, but it is most common in patients in the third-to-fifth decades of life. In one series of 121 cases, 83.6% of tumors occurred in patients aged 10–50 years, with a median age of 31.3 years (Lewis JJ et al, 2000). A slight male predilection is seen with the male-to-female ratio of 3 : 2. The region around the knee is the most common site of involvement. In head and neck area this tumor is very rare. Other head and neck locations include the cervical or parapharyngeal regions, masticator space, soft palate, tongue, suboccipital and infratemporal fossa regions, and sinonasal space. Most synovial sarcomas are found within 5 cm of a joint; only 10% of cases are intraarticular.

The clinical features of synovial sarcoma are nonspecific. No features to distinguish synovial sarcoma from other sarcomas. Most commonly, patients notice a slowly enlarging, deep-seated mass, which is painful in slightly more than one half of patients. In head and neck involvement, patients complain of symptoms such as dyspnea, dysphagia, hoarseness, and headache.

Specific cytogenetic abnormalities have been identified. More than 90% of patients have a **t(X;18)** translocation mutation, which is not associated with other sarcomas. The **t(X;18)(p11;q11)** translocation fuses the SYT gene from chromosome 18 to either of two homologous genes at Xp11, either SSX1 or SSX2. The fusion proteins SYT-SSX1 and SYT-SSX2 are believed to function as aberrant transcriptional regulators, resulting in either activation of protooncogenes or inhibition of tumor suppressor genes. The downstream targets of these fusion proteins that lead to transformation have not been identified.

Radiographic Features. Plain radiograph may aid in the diagnosis as synovial sarcoma typically produces spotty calcification (**snowstorm**) within the matrix of the soft-tissue tumor. CT scan or MRI is used to confirm the presence of a mass, its size, and its location.

Histologic Features. Gross specimens are usually well-demarcated, pink, fleshy masses with a heterogeneous appearance, and specimens may display solid, hemorrhagic, or cystic components on sectioning. Calcification foci are occasionally noted. Heavy calcification tends to indicate less aggressive lesions and offers a more favorable prognosis.

Typical morphology is that of two strikingly distinct well-differentiated cell populations. Depending on which cell type predominates, overall histologic appearances can be described as **biphasic** (epithelioid and spindle cell), **monophasic** spindle cell, or monophasic epithelioid. Marked cellular pleomorphism and atypia are uncommon, and when present, the appearance overlaps with that of high-grade malignant fibrous histiocytoma and fibrosarcoma.

The histologic appearance is that of large polygonal cells (epithelioid) which show an organization suggestive of microscopic joint spaces (cleft like or slit like spaces lined by cuboidal epithelial-like cells). The spaces may contain a PAS-positive mucoid material. These cells are surrounded

by spindle cells that simulate subsynovial mesenchymal cells. Punctate areas of calcification may be observed. The second pattern is comprised of a fibrosarcoma like proliferation of cells with associated collagen and reticulin. A monophasic pattern without the slit like spaces exists but is very uncommon.

Treatment. The treatment is wide resection with negative margins, which often include surrounding muscle groups or total amputation. Resection is commonly followed by localized irradiation. Synovial sarcomas have been shown to be markedly chemosensitive, multidrug adjuvant chemotherapy is currently recommended for systemic control of the tumor. The prognosis of head and neck synovial sarcoma is better than that of sarcoma involving the extremities, with five-year survival rates of 47–82%.

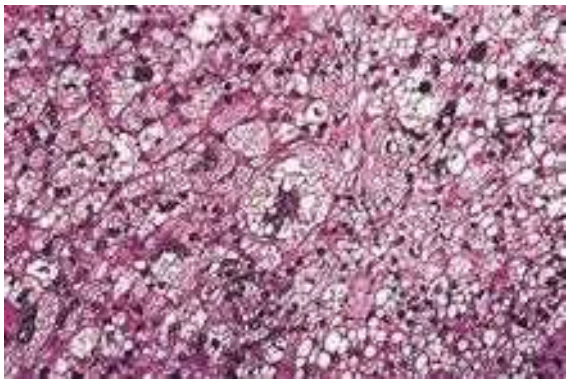


Figure 2-69. Liposarcoma.
Numerous tumor giant cells and malignant cells showing features of lipoblasts *(Courtesy of Dr Juan Rosai).*

Liposarcoma

Liposarcoma is a malignancy of fat cells. Virchow first described liposarcoma in the 1860s.

The most recent World Health Organization classification of soft-tissue tumors recognizes five categories of liposarcomas:

- Well differentiated, which includes the adipocytic, sclerosing, and inflammatory subtypes
- Dedifferentiated
- Myxoid
- Round cell
- Pleomorphic.

In rare circumstances, lesions can have a combination of morphologic types; these are classified as **combined or mixed-type** liposarcomas.

Chromosomal reciprocal translocation **t(12;16) (q13;p11.2)** is seen to be associated with the development of liposarcomas. The 12q13–15 region encodes for important protooncogenes including MDM2, CDK4, HMGI-C, SAS, GLI, CHOP, OS1, and OS9 which play varying roles in oncogenesis.The most common chromosomal translocation is the CHOP-FUS, TLS or EWS fusion gene, which encodes a transcription factor necessary for adipocyte differentiation.

Etiopathogenesis. No well-established causative factor has been identified, although trauma has been implicated. The development of a liposarcoma from a preexisting benign lipoma is rare. Most cases arise de novo. Liposarcomas most frequently arise from the deep-seated connective tissue stroma rather than the submucosal or subcutaneous fat.

Clinical Features. Liposarcoma is the most common soft-tissue sarcoma, accounting for approximately 17% of all soft-tissue sarcomas with an annual incidence of 2.5 cases per million population, and 3% of all liposarcomas occur in the head and neck region.

Although there is a wide range, from children to the very elderly, the liposarcoma of the head and neck region occurs most frequently in adults. Liposarcomas are slightly more common in males than in females. No association with race or geography is known. Oral involvement is rare; a fewer than 50 oral cases has been reported.The most commonly affected site was the tongue; other sites are the submandibular area, cheek, tongue, floor of mouth and soft palate. Most cases present as a slowly growing, painless, nonulcerated submucosal mass. But some lesions grow rapidly and become ulcerated early. The clinical impression seems to be lipoma or fibroma in the majority of cases. Tumor size ranged from 0.6–8.0 cm.

Histologic Features. The recognition of lipoblasts is the key finding in the diagnosis of liposarcoma. A lipoblast has the ability to produce and accumulate nonmembrane-bound lipid within its cytoplasm (Fig. 2-69).

Well-differentiated liposarcomas usually contain a predominance of mature fat cells with relatively few, widely scattered lipoblasts. A misdiagnosis of lipoma can result from inadequate sampling. In the **sclerosing subtype** of a well-differentiated liposarcoma, collagen fibrils that encircle fat cells and lipoblasts make up a prominent part of the matrix.

Myxoid liposarcoma, the most common type, is diagnosed by the observation of a delicate plexiform (chicken wire) pattern of capillary network that is associated with both primitive mesenchyme-like cells (spindle cells) and a variable number of lipoblasts. The stroma contains a large proportion of myxoid ground substance (i.e. hyaluronic acid), in which numerous microcysts may form.

In the **round-cell** type, lipoblasts with very little lipid are interspersed among sheets of poorly differentiated round cells. The round cells have a small to moderate amount of finely vacuolated or granular cytoplasm and may appear epithelioid or pericytoid.

Poorly differentiated **pleomorphic liposarcoma** is recognized by an extreme cellularity, mixture of bizarre, often multivacuolated lipoblasts and atypical stromal cells, many of which contain highly abnormal mitotic figures including bizarre giant cells. Lesional cells may be polygonal or stellate

with pale eosinophilic cytoplasm and poorly-demarcated cell boundaries. Hemorrhagic and necrotic areas are common. The characteristic lipoblast distinguishes pleomorphic liposarcoma from malignant fibrous histiocytosis (MFH). The round-cell and pleomorphic types are the high-grade liposarcomas.

However, it has been noted by Baden and Newman that the majority of liposarcomas of the head and neck area were myxoid liposarcomas and that the majority of these were well-differentiated neoplasms.

Stains for lipids are often useful in the diagnosis of liposarcoma, but this material may be scarce and is sometimes produced by unrelated mesenchymal and epithelial neoplasms. The mucinous matrix, when present, will stain with alcian blue and is metachromatic with toluidine blue and cresyl violet stains; it is weakly positive with Meyer's mucicarmine stain. Intracellular glycogen (diastase-sensitive, PAS positive) may be seen in some lesional cells. Adipocytes and lipoblasts react positively for vimentin and S100 protein immunostains, but these vary in intensity and may not be expressed in poorly differentiated lesions.

Treatment and Prognosis. Liposarcoma of the oral region is typically treated by wide local excision. Radiotherapy may be used to control local recurrence and lessen the risk of metastasis.

Hemangioendothelioma

Hemangioendothelioma is a varied group of proliferative and neoplastic vascular lesions, which have a biological behavior that falls somewhere between the benign hemangioma and malignant angiosarcoma. Approximately 10% of cases are associated with other developmental anomalies or syndromes, including early onset varicose veins, lymphedema, Klippel-Trenaunay-Weber syndrome, and Maffucci's syndrome.

Chromosomal translocation involving chromosomes 1 and 3 **[t(1;3)(p36.3;q25)]** was detected in few cases of epithelioid hemangioendothelioma.

Clinical Features. The tumor is usually seen during the second and third decades of life and there is no gender predilection. This neoplasm may occur anywhere in the body, but is most commonly found in the skin and subcutaneous tissues. Primary lesions of the oral cavity, though not common, have been reported in a variety of locations, including the lips, palate, gingiva, tongue and centrally within the maxilla and mandible. The literature pertaining to malignant hemangioendotheliomas of the oral cavity was reviewed by Wesley and his associates and Zachariades and his coworkers, who tabulated 46 reported oral cases.

The hemangioendothelioma arises at any age and has been found present even at birth. Females appear to be affected almost twice as often as males. Localized swelling may be the primary manifestation of the lesion, although pain is occasionally present as well.

The malignant hemangioendothelioma is similar to the hemangioma in appearance and is usually manifested clinically as a flat or slightly raised lesion of varying size, dark red or bluish red, sometimes ulcerated and showing a tendency to bleed after even slight trauma. Bone may be involved by the tumor, producing a destructive process.

Histologic Features. The hemangioendothelioma is a poorly circumscribed, usually biphasic proliferation of venous or capillary vessels. There are dilated and congested veins with inactive endothelial cell nuclei and with occasional thrombi or phleboliths. These vessels are intermixed with solid sheets of epithelioid (**epithelioid hemangioendothelioma**) or spindle-shaped (**spindle cell hemangioendothelioma**) mesenchymal cells with minimal dysplasia, few mitotic figures, and minimal differentiation toward a vascular lumen or channel.

The epithelioid cells have abundant eosinophilic cytoplasm, may contain vacuoles (primitive lumina), and may be admixed with smooth muscle bundles. These cells stain positively with *Ulex europaeus* and many will show cytoplasmic factor VIII-associated antigen reactivity with immunohistochemistry. Tumor cells also stain for endothelial markers such as CD31 and CD34 in approximately one-fifth of cases.

The lesional cells of the spindle cell hemangioendothelioma are rather bland, bipolar mesenchymal fibroblast like cells which may contain vacuoles, presumed to be abortive or primitive vascular lumina. Epithelioid cells are usually seen in small numbers in scattered areas and the associated dilated venous channels are more prone to contain thrombi and phleboliths than are those of the epithelioid hemangioendothelioma. **Kaposiform hemangioendothelioma,** histopathologically an admixture of tissues similar to both capillary hemangioma and Kaposi's sarcoma, has been reported from an oral or pharyngeal location (Zukerberg LR et al, 1993). Uniform spindle cells with pale eosinophilic cytoplasm and elongated nuclei associated with slit like vascular channels, similar to those of Kaposi's sarcoma, with mild extravasation of erythrocytes and hemosiderin deposition within or outside of macrophages. Mitotic figures and atypia are rare.

Polymorphous hemangioendothelioma consists of mixture of solid and primitive vascular and angiomatous endothelial areas.

The pathologist must be careful to rule out metastatic carcinoma or melanoma, which typically display much more dysplasia than hemangioendothelioma. The various epithelioid sarcomas must also be ruled out, especially the epithelioid angiosarcoma.

Treatment and Prognosis. Hemangioendothelioma is treated with wide surgical excision, with more than half of all cases recurring at the operative site or near by. Almost one third of epithelioid hemangioendotheliomas develop metastases to regional lymph nodes, the lungs, liver or bones.

Hemangiopericytoma

Stout and Murray in 1942 were the first to suggest hemangiopericytoma as a distinctly different vascular neoplasm. Stout also was the first to report an oral hemangiopericytoma, just a few years after its initial reporting. It is a neoplasm which is usually benign but has a definite malignant counterpart.

Head and neck lesions represent 16–25% of all reported hemangiopericytomas, and the tumor represents 2–3% of all soft tissue sarcomas in humans. Chromosomal translocations **t(12;19) and t(13;22)** have been observed in lesional cells.

Clinical Features. The oral hemangiopericytoma is typically a rapidly enlarging red or bluish mass which arises in all age groups but is rare prior to the second decade or after the seventh decade. There is no gender predilection. It is soft or rubbery, is usually painless and is relatively well demarcated from the surrounding mucosa. The lesion may be sessile or somewhat pedunculated, and may demonstrate a surface lobularity or telangiectasia. Intraosseous examples have been reported.

The oral/pharyngeal mucosa is, additionally, one of the most common locations for the rarely reported **infantile hemangiopericytoma.** This lesion is usually multiple and congenital, and often demonstrates an alarmingly rapid rate of enlargement after birth. Although this entity tends to recur after surgical excision, there is no potential for metastasis.

Histologic Features. On gross examination, hemangiopericytomas may be well circumscribed and appear grayish white. The appearance is much less hemorrhagic than endothelial tumors. The consistency is variable and may be solid or spongy, friable or granular (Fig. 2-70).

Hemangiopericytoma is a tumor thought to be derived from pericytes. Hemangiopericytoma consists of numerous vascular channels with plump endothelial nuclei and a surrounding, tightly packed proliferation of oval and spindled cells, hyerchromatic nuclei and a moderate amount of cytoplasm. The cells have indistinct cytoplasmic borders. The tumor cells do not arise from endothelial cells even though they surround irregular vascular spaces. The branching vascular channels

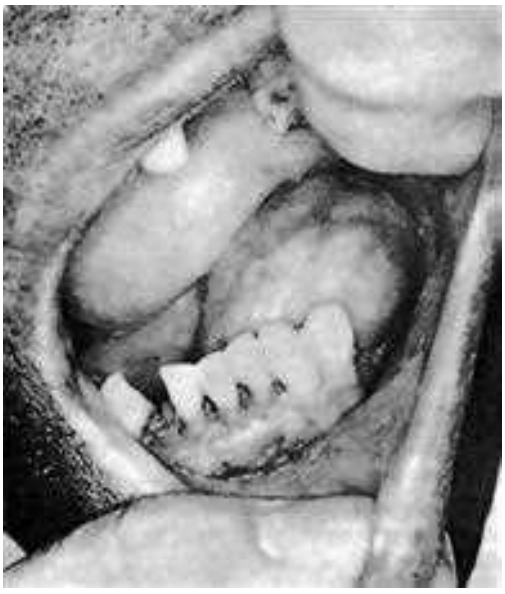


Figure 2-70. Hemangiopericytoma of floor of mouth.
(Courtesy of Dr Irwin A Small).

Figure 2-71. Dilated, thin-walled vessels as shown here are common. These vessels simulate 'staghorns' that are often associated with hemangiopericytoma.

of varying sizes is often described as a **'staghorn'** pattern (Fig. 2-71). Older, less aggressive lesions tend to have less cellularity and may have a largely mucoid interstitial appearance, which can be mistaken for myxoid lipoma or myxoid liposarcoma. Focal cartilage production may rarely be seen and such lesions must be differentiated from mesenchymal chondrosarcoma.

Reticulin staining will demonstrate lesional vessels lined by a single layer of endothelial cells, with the pericytes lying outside the basal lamina. Lesional cells are immunoreactive for vimentin (variable intensity), factor XIIIa antigen, HLA-DR antigen and QBEND10 (CD34). They do not stain for or react with factor VIII-related antigen, *Ulex europaeus* I lectin, alpha-smooth muscle actin, desmin, myoglobin, low-molecular weight cytokeratin, high-molecular weight cytokeratin, or epithelial membrane antigen.

The differential diagnosis of this lesion includes, in addition to the tumors named above, fibrous histiocytoma, MFH, synovial sarcoma, other stromal sarcomas, vascular leiomyoma, and juvenile hemangioma.

Treatment and Prognosis. The treatment of hemangiopericytoma is dependent on the amount of cellular dysplasia and mitotic activity. The more bland lesions with minimal mitotic activity are treated by wide local excision, but the more active and dysplastic lesions are treated by radical surgical excision, with or without adjunctive radiotherapy.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi
(Kaposi's sarcoma, angioreticuloendothelioma)

Kaposi's sarcoma is a multicentric proliferation of vascular and spindle cell components, which was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist, who described skin tumors in five men in their sixth and seventh decades of life as **'idiopathic multiple pigmented sarcoma of the skin'**. Now considered to be a viral-induced or viral-associated tumor, it is unclear whether the lesion is a true neoplasm or a simple hyperplasia. This tumour is currently incriminated with HIV/AIDS and its clinical stage depends greatly on the

immune status of the patient. Although found predominantly in HIV-infected persons, HIV does not seem to be the direct cause of the tumorous proliferation and HIV amino acid sequences have not been identified within lesional cells.

Clinical Features. Kaposi's sarcoma has four major clinical presentations: **classic (chronic), endemic (lymphadenopathic; African), immunosuppression-associated (transplant), and AIDS-related.**

The classic variant is often associated with altered immune states as well as lymphoreticular and other malignancies. Cutaneous multifocal blue-red nodules develop on the lower extremities and slowly increase in size and numbers, with some lesions regressing while new ones are forming on adjacent or distant skin. Oral involvement in this form of the disease is quite unusual but when it occurs it does so as soft, bluish nodules of the palatal mucosa or gingiva.

Lymphadenopathic Kaposi's sarcoma is endemic to young African children and presents as a localized or generalized enlargement of lymph node chains, including the cervical nodes. The disease follows a fulminant course with visceral involvement and minimal skin or mucous membrane involvement. In the head and neck region, salivary glands may be affected. This variant does not appear to be HIV related.

Transplantation-associated Kaposi's sarcoma is seen in 1–4% of renal transplant patients, usually becoming manifested one or two years after transplantation. The extent and progression of the disease correlates directly with the loss of cellular immunity of the host. Sarcomatous involvement occurs on the skin as well as internal organs, but oral mucosal lesions are decidedly rare.

AIDS-related Kaposi's sarcoma. Approximately 40% of homosexual AIDS patients will develop Kaposi's sarcoma, often as an early sign of the disease. Affected patients are usually young adults or early middle-aged males, with the average age at diagnosis being 39 years in the US. Individual lesions occur in many cutaneous locations, especially along lines of cleavage and on the tip of the nose. Oral lesions can also occur on any mucosal surface but have a strong predilection for palatal and gingival mucosa.

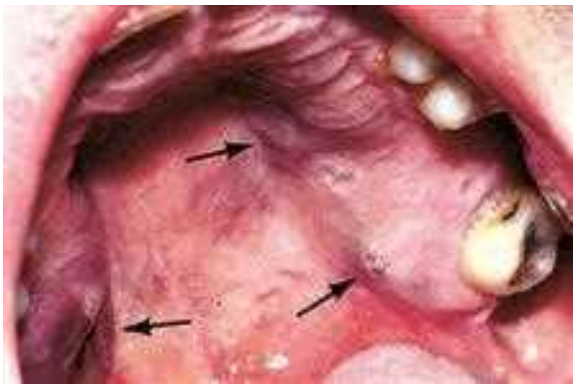


Figure 2-72. Kaposi's sarcoma.

Early oral mucosal sarcomas are flat and slightly blue, red or purple plaques, either focal or diffuse, may be completely asymptomatic and easily overlooked. With time, lesions become more deeply discolored and surface papules and soft nodules develop, or may become exophytic and ulcerated, and may bleed, usually remaining less than 2 cm *in size* (Fig. 2-72). Individual lesions may coalesce and occasional patients never develop the nodular variant. Cervical lymph nodes and salivary gland enlargement may also be seen. The patient may have oral candidiasis and AIDS-related gingivitis as well. Other oral sites of KS involvement include the gingiva, tongue, uvula, tonsils, pharynx, and trachea. These lesions

Etiology. The etiology of Kaposi's sarcoma remains unknown. While immunosuppression is highly associated with Kaposi's sarcoma, it cannot be considered an etiology. Immunosuppression is believed to create an environment that allows an opportunistic factor to cause Kaposi's sarcoma. A causal model to explain the occurrence of Kaposi's sarcoma has been developed by Wahman et al., 1991. Their cofactor model suggests that "the combined effects of numerous infectious agents, host factors, and environmental factors encourage Kaposi's sarcoma proliferation".

The evidence also suggests that the disease is promoted by the effects of immunosuppression and immune activation, possibly combined with a sexually transmissible infectious agent.

In two recently published studies (Chang et al., 1994, Moore et al., 1995), herpes virus like DNA sequences, dubbed **human herpes virus 8 (HHV8 or KSHV),** have been isolated from lesions and in Kaposi's sarcoma-derived cell cultures.

There is increasing evidence that circulating growth factors appear to play a key role in the pathogenesis of HIV-related Kaposi's sarcoma. A number of cytokines and viral products produced by retrovirally infected cells (or by the Kaposi's sarcoma cells themselves) are potent growth factors for lesional cells *in vitro.* These include the HIV-1 tat protein, basic fibroblast growth factor (bFGF), the cytokines IL-1, TNF and IL-6, and others. HIV-infected lymphocytes are also capable of producing their own set of similar cytokines.

Friedman-Kien et al., 1990 have suggested a genetic predisposition to the disease as a result of studies implicating increased incidence of the histocompatibility marker HLA-DR5 in 62% of classic Kaposi's sarcoma cases. Windle-Taylor and Shah 1983 suggested an environmental etiology due to the overall geographical distribution of the disease.

Some evidence suggests that Kaposi's sarcoma may not, in fact, be a true malignancy but rather an angiogenic disorder with widespread cellular proliferation occurring in response to circulating growth factors (reactionary).

may interfere with mastication × phonation and cause tooth loss and airway obstruction (eating and speaking, cause tooth loss, or compromise the airways).

Histologic Features. Kaposi's sarcoma has a similar histopathologic appearance in all of its clinical subtypes. The early lesion **(patch stage)** is characterized by proliferation of small veins and capillaries around one or more preexisting dilated vessels. The slit like vessels are present around preexisting blood vessel, skin adnexa and between collagen fibers. Vessels are lined by plump, mildly atypical endothelial cells. The features resemble granulation tissue. A pronounced mononuclear inflammatory cell infiltrate, including mast cells, scattered erythrocytes and hemosiderin deposits may be present. There may be an inconspicuous perivascular proliferation of spindle cells, but cellular atypia is minimal.

More advanced lesions **(plaque stage)** are nodular and show increased numbers of small capillaries or dilated vascular channels interspersed with proliferating sheets of sarcomatous or atypical spindle cells, often with large numbers of extravasated erythrocytes and abundant hemosiderin deposition. Slit like vascular channels without a visible endothelial lining are typically interspersed with the spindle cells. Lesional cells have somewhat enlarged, hyperchromatic nuclei with mild to moderate pleomorphism. Mitotic activity is quite variable but is usually minimal. Infiltration by chronic inflammatory cells is also variable. In the **nodular stage,** all the histologic features are more prominent than plaque stage.

Treatment and Prognosis. Various treatments have been used in oral Kaposi's sarcoma with variable success. Small or localized lesions can be surgically excised with a small surrounding margin of clinically normal tissue, but more recent therapies have concentrated on low-dose irradiation and intralesional chemotherapy and sclerosing solutions. For larger and multifocal lesions, systemic chemotherapy is often effective.

Immunoreactivity is somewhat variable, but the spindle cells are consistently reactive for CD34 and the delicate, flattened endothelial cells lining the vascular clefts are reactive for both CD31 and CD34. The vascular channels are often reactive for *Ulex europaeus* agglutinin, but nonreactive for factor XIIIa (Fig. 2-73).

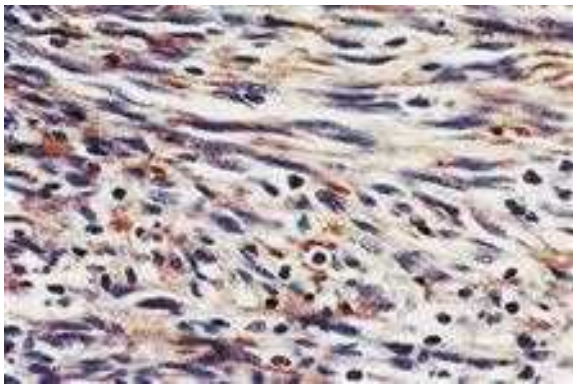


Figure 2-73. Immunoreactivity for factor VIII-related antigen in Kaposi's sarcoma.
(Courtesy of Dr Juan Rosai).

Ewing's Sarcoma
(Endothelial myeloma, 'round cell' sarcoma)

Ewing's sarcoma is a sarcoma of the bone, classically described under small round cell tumors. There is considerable clinical and histologic overlap between this tumor and the primitive neuroectodermal tumor (PNET). Now with sophisticated molecular biological analysis, it turns out that both tumors share a common and unique chromosomal translocation. Most investigators now believe that Ewing's sarcoma and PNET are different morphological expressions of one tumor type. In general, Ewing's sarcoma arises within the bone while PNET arises within soft tissues. However, there are overlap cases of Ewing's sarcoma arising within soft tissue (extraosseous Ewing's sarcoma) and PNET arising within the bone. Under the microscope, the tumors share a considerable homology though there are usually more **neuroendocrine** features with PNET. Ewing's sarcoma is thought to be a more undifferentiated tumor. Though data is conflicting, some investigators believe Ewing's sarcoma to have a slightly better prognosis.

A practical working definition is to consider all highly malignant, small round-to-oval cell sarcomas with the clinical and radiographic characteristics of a primary osseous lesion to be Ewing's tumor (Unni KK, 1996). Inherent in this concept is the exclusion of cytologically incompatible lesions such as myeloma, malignant lymphoma, and histiocytosis X. Production of a chondroid or osteoid matrix by the neoplastic cells likewise excludes Ewing's sarcoma. Similarly, true spindling of the nuclei is incompatible with the diagnosis of Ewing's sarcoma. It is sometimes impossible to differentiate a biopsy specimen of a metastatic malignant tumor such as neuroblastoma, small cell carcinoma of the lung, or even a leukemic infiltrate from a specimen of Ewing's tumor, even after critical histologic study according to modern concept. Immunoperoxidase stains, however, can effectively rule out metastatic carcinomas and lymphomas and leukemias.

Clinical Features. This neoplastic disease occurs predominantly in children and young adults between the ages of five and 25 years, the median age of occurrence is 13 years, 80% occur within first two decades of life, but is seen on occasion in older patients also. In the series of 107 cases reported by Bhansali and Desai, six patients were over the age of 40 years, the oldest being an 83-year-old woman. Thus it arises in the same general age group in which osteogenic sarcoma is most prevalent. It is approximately twice as common in males as in females, and uncommon in blacks.

It is noteworthy that an episode of trauma often precedes the development of the tumor, although it must not be inferred that this is in any manner important in the etiology of the neoplasm.

Pain, usually of an intermittent nature, and swelling of the involved bone are often the earliest clinical signs and symptoms of Ewing's sarcoma. The bones most commonly affected are the long bones of the extremities, although the skull, clavicle, ribs and shoulder and pelvic girdles may be involved, as well as the maxilla and mandible. The jaws were involved in 13% of a series of 126 cases reported by Geschickter and Copeland. Nine additional cases, eight in the mandible and one in the maxilla, have been reported by Potdar.

Facial neuralgia and lip paresthesia have been reported in cases of jaw involvement. The appearance of the jaw swelling is often a relatively rapid one, and the intraoral mass may become ulcerated. The patient may have a low-grade fever and an elevated white blood cell count, and these findings have often given rise to an erroneous tentative diagnosis of an infection.

An extraskeletal form of this tumor has been described by Angervall and Enzinger and termed **Ewing's sarcoma of soft tissues**. The ultrastructural characteristics of the cells constituting this tumor, studied by Gillespie and his associates, among others, are identical to those of the typical Ewing's cells.

Radiographic Features. The radiographic appearance of Ewing's sarcoma has been described as being suggestive but not pathognomonic of the disease. The lesion is a destructive one and produces an irregular, diffuse radiolucency, although lesions of the jaw resembling sclerosing osteomyelitis have been described.

A common characteristic radiographic feature is the formation of layers of new subperiosteal bone producing the so-called 'onion skin' appearance on the film. This thickened cortex is usually infiltrated by tumor. Osteophyte formation may also be visible on the radiograph and, in such cases, may be similar to the 'sun-ray' appearance of osteosarcoma.

Histologic Features. Ewing's sarcoma is an extremely cellular neoplasm composed of solid sheets or masses of small round cells with very little stroma, although a few connective tissue septa may be present (Fig. 2-74). The cells themselves are small and round, with scanty cytoplasm and relatively large round or ovoid nuclei with dispersed chromatin and hyperchromasia. The cell borders are indistinct. The sarcoma cells are arranged in Filigree pattern. Mitotic figures are common. The cells are positive for glycogen and are diastase resistant. The importance of intracytoplasmic glycogen in the diagnosis of Ewing's sarcoma has been reaffirmed by Telles and his coworkers 1978, who also emphasized that therapy did not alter the presence of this glycogen. Rosettes present in 10% of cases. Many tiny vascular channels may also be present. Hemorrhage with vascular lakes or sinuses may be seen. Geographic necrosis with perivascular sparing is a common feature. However, as Telles and his associates pointed out in an autopsy study of 26 cases of Ewing's sarcoma, increased cellular pleomorphism and increased numbers of bizarre giant cells may be found in the lesions in patients treated with radiation and adjuvant chemotherapy.

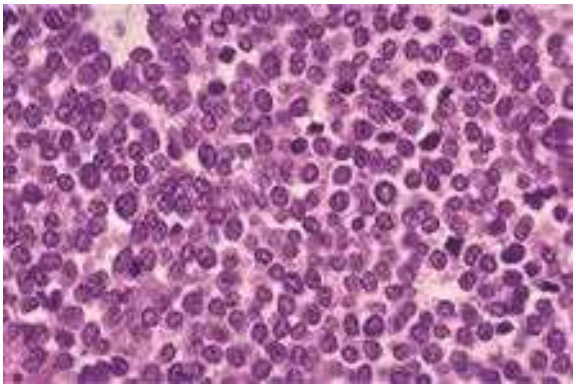


Figure 2-74. Ewing's sarcoma.
Ewing's sarcoma is one of the 'small round blue cell' tumors histologically. Note the many mitotic figures in the field.

Encroachment of tumor cells on a bone trabecula causing its ragged resorption is apparent. Necrosis is also present on the opposite side of the fragment of bone (Fig. 2-75).

The cells of Ewing's sarcoma can generally be differentiated from reticulum cell sarcoma with little difficulty. In some cases of Ewing's sarcoma, however, the cells are larger and may simulate the malignant lymphoma. Schajowicz has reported that tumor cells of Ewing's sarcoma contain histochemically demonstrable glycogen, which is absent in cells of the reticulum cell sarcoma, thus providing an easy method of differentiation. Other tumors which have to be differentiated from Ewing's sarcoma are small cell osteosarcoma, PNET (peripheral neuroectodermal tumor of infancy), metastatic neuroblastoma, mesenchymal chondrosarcoma.

Cytogenetic studies of the Ewing's sarcoma have identified a consistent alteration of the Ewing's sarcoma locus on chromosome 22 band q12 that may involve other chromosomes, including 11 or 21. Characteristically, the amino terminus of the Ewing's sarcoma gene is juxtaposed with the carboxy terminus of another gene. In most cases (90%), the carboxy terminus is provided by *FL1,* a transcription factors gene located on chromosome 11 band q24. Other genes which may combine with the Ewing's sarcoma gene in order of frequency are *ERG* (located on chromosome 21), *ETV 1* (located on chromosome 7), and *E1AF* (located on chromosome 17), which result in the following translocations: t(21;22), t(7;22), and t(17;22) respectively. Besides these consistent aberrations involving the Ewing's sarcoma gene at 22q12, additional numerical and structural aberrations have been observed in Ewing's family of tumors, including gains of chromosomes 2, 5, 7, 8, 9, and 12, the nonreciprocal translocation t(1;16)(q12;q11.2), and deletions at the short arm of chromosome 1.

Characteristic translocation is seen with Ewing's sarcoma of the bone. The fusion gene is designated as **EWS/FLI-1(t(11;22)(q24q12)).** Monoclonal antibodies to the fusion gene protein product are termed CD99.

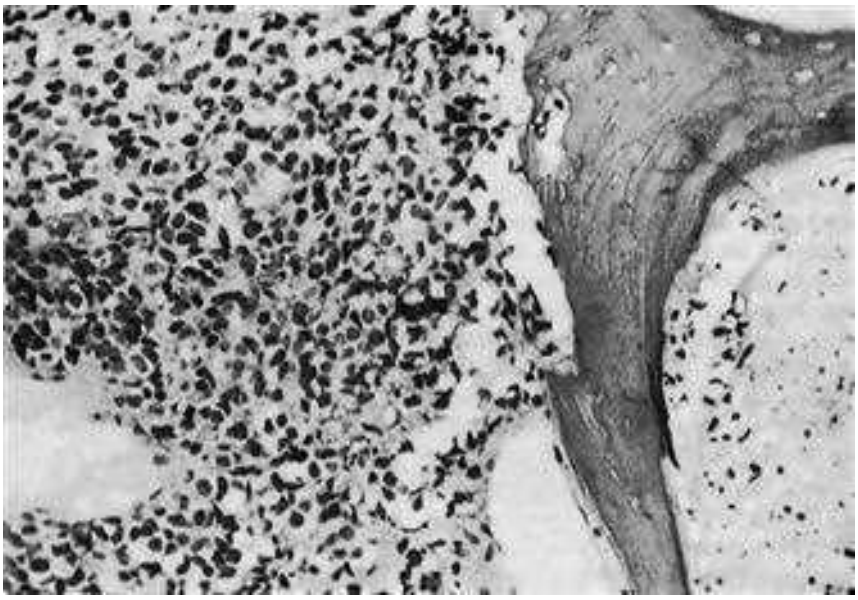


Figure 2-75. Ewing's sarcoma.

Treatment and Prognosis. This neoplasm is radiosensitive, but unfortunately, in the past, has seldom been cured by X-ray radiation. Radical surgical excision has been done, alone and coupled with X-ray radiation, but it has been common for metastatic foci to appear in other bones and organs, such as lungs and lymph nodes, within a matter of a few weeks or months. Five-year survival with a combination of surgery and chemotherapy is 74%.

Chondrosarcoma

The chondrosarcoma is the malignant counterpart of the chondroma, and like the benign lesion, may occur in either the maxilla or the mandible, as well as in many other bones in the body.

The exact origin of chondrosarcoma is obscure, but the salient pathologic fact is that its basic proliferating tissue is cartilage throughout. Large portions of these tumors may become myxomatous, calcified or even ossified. Sometimes at the periphery of the lobules of a high-grade chondrosacroma, a few fibrosarcoma like spindled tumor cells occur. Osseous trabeculae, when present, are seen at the periphery of the lobules and appeared to be rimmed with osteobalsts, however, when the malignant cells produce an osteoid lacework or osteoid trabeculae directly, even in small foci, the neoplasm has clinical characteristics of osteosarcoma and belongs in that category (Unni KK, 1996).

Chondrosarcoma usually has a slow clinical evolution. Metastasis is relatively rare and often occurs late. Chondrosarcomas can arise de novo (primary chondrosarcoma) in extraskeletal tissues or in teratomas and other mixed tumors. Chondrosarcomas composed of hyaline cartilage are extremely rare in the somatic soft tissues; most of the lesions are **myxoid chondrosarcomas**. Their general characteristics are similar to those of the skeletal examples.

Secondary chondrosarcomas arise most commonly in osteochondromas (osteocartilaginous exostoses), especially in the mutiple familial type. The primary and secondary chondrosarcomas may, on occasion, give rise to more highly malignant tumors—osteosarcomas, fibrosarcomas, or malignant fibrous histiocytomas—and these are called **dedifferentiated chondrosarcomas.**

Clinical Features. There are no pathognomonic signs or symptoms presented by the chondrosarcoma, nor may it be differentiated from the chondroma purely on the basis of the clinical findings. The tumor can occur at any age between 10 and 80 years. However, in the series of 288 cases reported by Henderson and Dahlin, the peak incidence was between 30 and 60 years, while in the series of 151 cases of McKenna and his associates, it was between 30 and 50 years. The secondary chondrosarcoma occurs at an earlier age than the primary chondrosarcoma, by an average of about 10 years. In general, chondrosarcomas occur more often in males, in a ratio of about 2 to 1. The presentation of chondrosarcoma depends on the grade of the tumor. A high-grade, fast growing tumor can present with excruciating pain. A low grade, more indolent tumor is likely to be present in an older patient complaining of pain and swelling. Chondrosarcoma usually has a slow clinical evolution. Metastasis is relatively rare and often occurs late.

Rare variants with distinctive microscopic and clinical features are discerned: clear cell chondrosarcoma (1%), mesenchymal chondrosarcoma (2%), juxtacortical chondrosarcoma (2%), extraskeletal myxoid chondrosarcoma (5%) and dedifferentiated chondrosarcoma (Table 2-14).

Mesenchymal chondrosarcoma is a characteristic and distinctive type of chondrosarcoma in which the majority of cases occur between the ages of 10 and 30 years, and in which there is an approximately equal gender distribution. In

Table 2-14: Chondrosarcoma of bone and variants

Conventional chondrosarcoma
Borderline
Low grade
High grade
Secondary chondrosarcoma (originate from preexisting benign tumor)
Solitary exostoses
Multiple exostoses
Multiple chondromas
Synovial chondromatosis
Post radiation
Fibrous dysplasia
Peripheral chondrosarcoma
Chondrosarcoma of upper respiratory (excluding larynx)
Clear cell chondrosarcoma
Dedifferentiated chondrosarcoma
Mesenchymal chondrosarcoma
Chondrosarcoma of small bones

addition, the most common sites of origin are the jaws and ribs, according to Salvador and his associates.

Clear cell chondrosarcoma is a recognized variant of the usual chondrosarcoma from which it should be separated because of its slow growth pattern and its favorable clinical course with low metastatic potential and high probability of cure. Without radical excision, however, death can result. It may occur in the jaws, and such a case has been reported by Slootweg.

Dedifferentiated chondrosarcoma is the most malignant form of chondrosarcoma. This tumor is a mix of low grade chondrosarcoma and high grade spindle cell sarcoma where the spindle cells are no longer identifiable as having a cartilage origin. The dedifferentiated portion of the lesion may have histological features of malignant fibrous histiocytoma, osteosarcoma, or undifferentiated sarcoma. Dedifferentiated chondrosarcoma has a five-year survival of 10%.

Oral Manifestations. Chaudhry and his associates have reviewed all cartilaginous tumors of the jaws reported in the English literature between 1912 and 1959. Both primary and secondary jaw chondrosarcomas appear as an expanding lesion which is frequently painless (Fig. 2-76A). The mucosa is often intact. The tumor may occur in the mandible or the maxilla with primary involvement of the alveolar ridge, or sometimes in the maxilla near the antrum. Resorption and exfoliation of teeth sometimes occur. In general, these lesions are invasive and destructive and metastasize readily.

Radiographic Features. Radiographic findings do not differ remarkably from those seen in the benign chondroma unless the lesion is of relatively long standing and has produced considerable destruction of bone. Occasional tumors will appear as radiopaque lesions because of calcification of the neoplastic cartilage (Fig. 2-76B, C).

Histologic Features. Chondrosarcoma is one of the most difficult of the malignant tumors of the bone for the pathologist to diagnose. The criteria that differentiate a low-grade chondrosarcoma from a chondroma are very subtle. However, some lesions may appear to be malignant by conventional criteria but are benign. The features proposed by Lichtenstein and Jaffe are very helpful when viable fields are studied. These include many cells with plump nuclei, more than an occasional cell with two such nuclei, and especially, giant cartilage cells with large single or multiple nuclei or with clumps of chromatin. The correct diagnosis depends on correct interpretation of the subtle qualitative characteristics. Furthermore, malignant foci may be obscured by necrotic regions or by zones with insufficient cytologic evidence for the diagnosis of sarcoma.

Most chondrosarcomas have sheets of chondrocytes, which may have a lobulated growth pattern under low power. Some chondrosarcomas, however, have pronounced cluttering of the chondrocytes similar to the classic appearance in synovial chondromatosis. Chondrosarcoma is not a spindle cell neoplasm, because chondrocytes lie within lacunae. Occasionally, however, the nuclei appear spindle shaped (Fig. 2-77).

Most of the **secondary chondrosarcomas** are extremely undifferentiated, so that a clear histologic diagnosis of chondrosarcoma is usually not possible. In osteochondroma, there is a columnar arrangement of the chondrocytes towards the base. This orderly arrangement is lost when chondrosarcoma supervenes. Nodules of cartilage apparently permeating soft tissues and separated from the main mass of the tumor also are evidence of chondrosarcoma. Mitotic figures are uncommon in chondrosarcoma.

The **mesenchymal chondrosarcoma** consists of sheets of small, round or ovoid, undifferentiated cells interspersed by small islands of well-differentiated cartilage which often show calcification and metaplastic bone formation. Ultrastructural studies by Steiner and his associates have confirmed the presence of two cell types: a poorly differentiated mesenchymal cell and a cell with cartilaginous differentiation in an early stage of maturation.

The **clear cell chondrosarcoma** consists of single or clustered benign giant cells and tumor cells with clear cytoplasm. Conventional low-grade chondrosarcoma may sometimes be found in areas.

Dedifferentiated chondrosarcoma consists of a mix of low grade chondrosarcoma and high grade spindle cell sarcoma where the spindle cells are no longer identifiable as having a cartilage origin. The dedifferentiated portion of the lesion may have histological features of malignant fibrous histiocytoma, osteosarcoma, or undifferentiated sarcoma.

Grading. Chondrosarcomas are graded mainly based on the cellularity of the neoplasm and the cytologic atypia. Because mitotic activity is uncommon in chondrosarcomas, it is not used in grading these tumors. Grade 1-chondrosarcomas are relatively hypercellular compared with enchondromas and have moderate cytologic atypia. Grade 2-chondrosarcomas are more cellular than grade 1, and similarly, cytologic atypia is more pronounced. Grade 3-chondrosarcomas are extremely uncommon. They are characterized by extreme cellularity, large

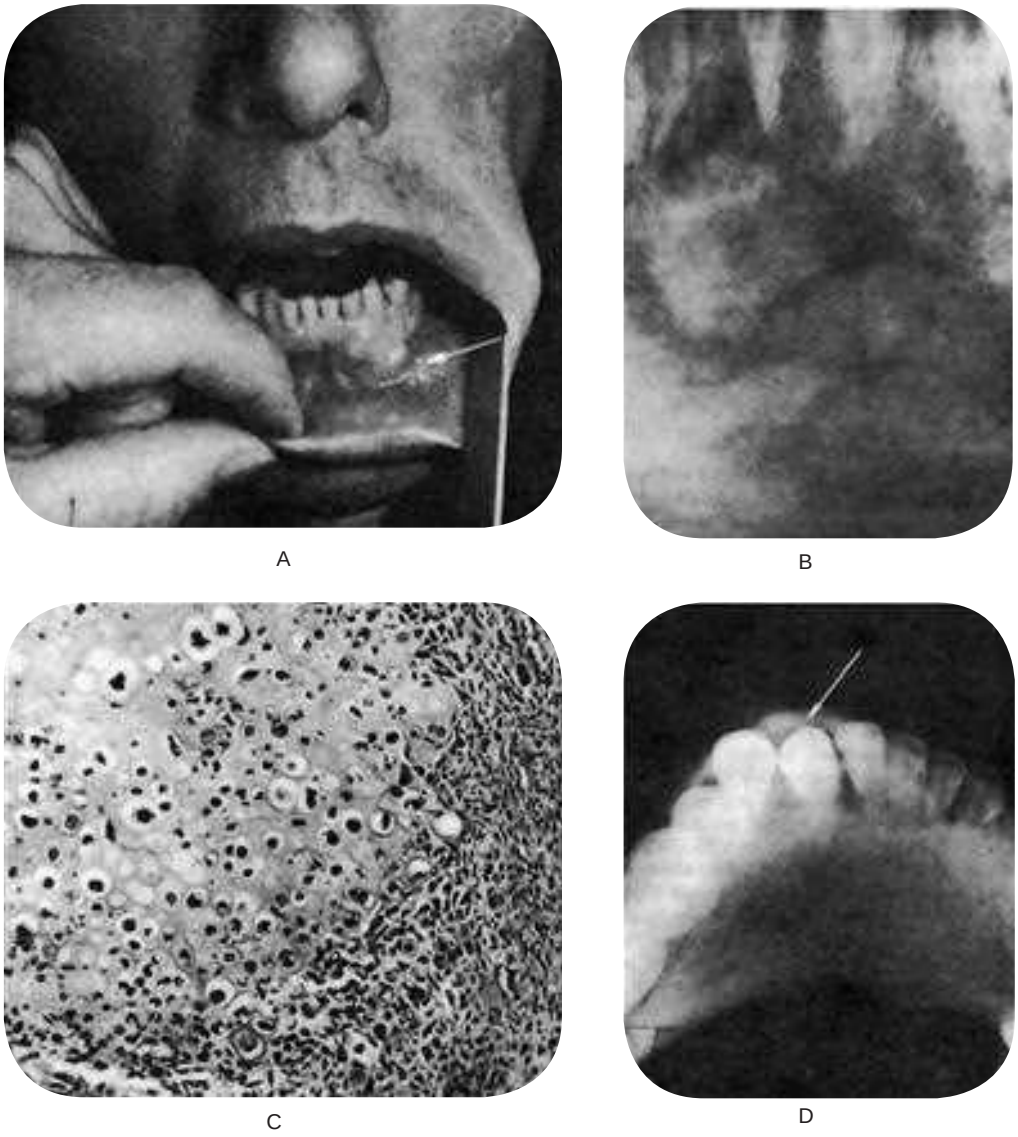


Figure 2-76.Chondrosarcoma.
The clinical expansion of the mandible **(A)** manifests obvious changes in the dental radiographs **(B, C)**. The photomicrograph **(D)** illustrates malignant cartilage cells comprising the neoplasm *(Courtesy of Dr Charles A Waldron)*.

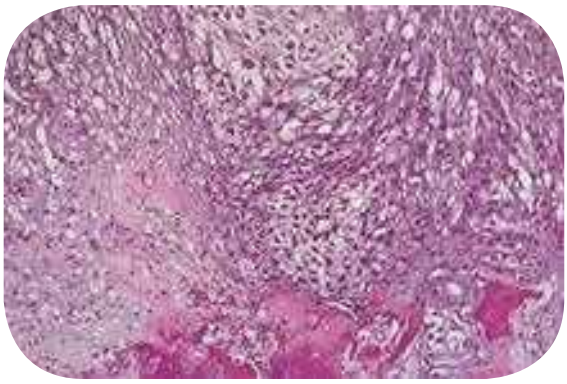


Figure 2-77. Low power chondrosarcoma.
This is the low power microscopic appearance of a chondrosarcoma. The tissue is recognizable as cartilage, and there are chondrocytes in clear spaces, but there is no orderly pattern. At the bottom, this neoplasm can be seen invading and destroying bone.

bizarre nuclei, and small foci of spindling at the periphery of the lobule. Sheets of spindle cells are not seen in chondrosarcoma.

Approximately 10% of the tumors that recur have an increase in the degree of malignancy.

Treatment and Prognosis. The only beneficial treatment of the chondrosarcoma is surgery. The malignant nature of this tumor demands wide excision to ensure the greatest possibility for cure. X-ray radiation is of little value, since this type of neoplasm is resistant to such therapy. Neither does chemotherapy appear to be of significant benefit.

Data gathered from known cases of chondrosarcoma of the jaws indicate that the tumor in this location is exceedingly dangerous and often results in death, either from local invasion or from metastasis to distant sites. Although the lesion tends to grow slowly, surgical intervention often stimulates the growth rate and increases the tendency for metastasis.

The **mesenchymal chondrosarcoma** is even more variable in its clinical course, since metastasis may occur many years after the original surgical procedure and death is markedly delayed. Expression of 'five-year survival' is of little significance in the case of this tumor.

Osteosarcoma
(Osteogenic sarcoma)

Osteosarcoma is the third most common cancer in adolescence, occurring less frequently than only lymphomas and brain tumors. It is thought to arise from a primitive mesenchymal bone-forming cell and is characterized by production of osteoid.

Clinical Features. Osteosarcoma is a bone tumor that can occur in any bone. It most commonly occurs in the long bones of the extremities near metaphyseal growth plates. The most common sites are femur (42%, with 75% of tumors in the distal femur), tibia (19%, with 80% of tumors in the proximal tibia), and humerus (10%, with 90% of tumors in the proximal humerus). Other significant locations are the skull or jaw (8%) and pelvis (8%).

Incidence is slightly higher in males than in females (1.25: 1). Osteosarcoma occurs chiefly in young persons, the majority between 10–25 years with decreasing incidence as the age advances. It is very rare in young children and the incidence increases steadily with age; a more dramatic increase in adolescence corresponds with the growth spurt.

The exact cause of osteosarcoma is unknown. However, a number of risk factors exist. Rapid bone growth appears to predispose patients to osteosarcoma, as suggested by the increased incidence during the adolescent growth spurt, and osteosarcoma's typical location near the metaphyseal growth plate of long bones. Exposure to radiation is the only known environmental risk factor. A genetic predisposition may exist, for example:

- Familial cases where the deletion of chromosome **13q14** thus inactivating the retinoblastoma gene (RB gene) leading to development of retinoblastoma and is associated with a particularly high risk of osteosarcoma to develop.
- Bone dysplasias, including Paget's disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses, increase the risk of osteosarcoma.
- Li–Fraumeni syndrome (germline TP53 mutation) is a predisposing factor for osteosarcoma development.
- Rothmund–Thomson syndrome (i.e. autosomal recessive association of congenital bone defects, hair and skin dysplasias, hypogonadism, cataracts) is associated with increased risk of osteosarcoma.

A number of variants of osteosarcoma are: **conventional types (i.e. osteoblastic, chondroblastic, fibroblastic); multifocal; telangiectatic; small cell; intraosseous well-differentiated; intracortical; periosteal; paraosteal; high-grade surface; and extraosseous** (Table 2-15).

Swelling and pain, particularly with activity of the involved bone, are the early features of the neoplasm. Patients may complain of a sprain, arthritis, or so-called grawing pain. Systemic symptoms, such as fever and night sweats, are rare. Sometimes the presenting signs and symptoms are indistinguishable from those of osteomyelitis. Often, the patient has a history of trauma, though pathologic fractures are not particularly common. (The exception is the telangiectatic type of osteosarcoma, which is commonly associated with pathologic fractures). If in an extremity, the pain may result in a limp. Regional lymphadenopathy is unusual.

Oral Manifestations. Several large series of cases of osteosarcoma of the jaws have been published in recent years, contributing greatly to our knowledge of this tumor. The largest series was that of Garrington and his associates who analyzed 56 cases and found that the most common presenting symptoms of the patients were swelling of the involved area, often producing facial deformity and pain, followed by loose teeth, paresthesia, toothache, bleeding, nasal obstruction and a variety of other manifestations (Fig. 2-78).

The median age of the patients at the time of appearance of the first related symptoms was about 27 years, nearly a decade older than patients with osteosarcoma of other bones of the skeleton. Of 44 cases of osteosarcoma of the jaws and facial bones reported by Kragh and his associates, the mean age of occurrence was 33 years. In all series, mandibular tumors are more common than those in the maxilla, and there is usually a predilection for occurrence in males.

As indicated previously, it has been reported on numerous occasions that trauma to other sites in the skeleton has preceded the development of osteosarcoma at that site. Furthermore, it is recognized that osteosarcoma develops with considerable frequency in bone affected by osteitis deformans, or Paget's disease, as in the 80 cases studied by Price and Goldie. Finally, bone that has been subjected to therapeutic X-ray radiation may undergo malignant transformation, as in the 50 cases studied by Arlen and his associates. Surprisingly, in nearly all cases of osteosarcoma of the jaws, there is no preceding history of trauma or of Paget's disease. However, cases of osteosarcoma developing after X-ray radiation for benign jaw lesions such as fibrous dysplasia and giant cell granuloma are adequately documented; 43 such cases were discussed by De Lathouwer and Brocheriou in their review of the literature.

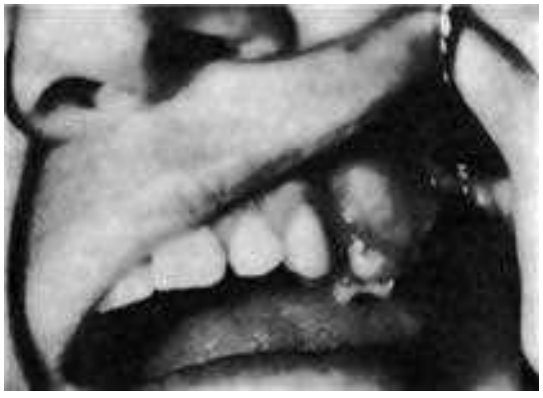


Figure 2-78. Osteosarcoma of maxilla.
(Courtesy of Dr Wilbur C Moorman).

Table 2-15: Variants of osteosarcoma

1.	Multifocal synchronous	Divided into synchronous and asynchronous – Pulmonary metastasis is absent usually – Childhood form is most common in 10 years of age with tumors confined to the medullary cavity with minimal extraosseous extension – Adult form less common with mean 37 years Histology – Usually osteoblastic with high grade histology – Adult forms usually better differentiated – Lesions discovered within 6 months of each other – Often symmetric appearance with similar size and not a dominant lesion: osseous metastasis is rare
	Asynchronous	– Develop less than 24 months after the initial lesion
2.	Telangiectatic	– 0.4–12% of all the osteosarcomas is seen commonly in adolescence and early adulthood – Pathologic fractures seen in 25% of cases – May be confused radiographically with an aneurysmal bone cyst or giant cell tumor – Hemorrhagic and necrotic areas seen in tumor Histology – Contains large, blood filled spaces
3.	Small cell	– 1–4% of all the osteosarcomas – Presentation is simillar to conventional osteosarcomas – 70% in first or second decades of life – 90% have at least focal osteoblastic features Histology – Small round cells with at least focal osteoid – Focal hemangiopericytoma-like pattern may be common – May have a Ewing's sarcoma-like pattern in 2/3rd of cases and lymphoma-like pattern in 1/3rd of cases
4.	Intraosseous well-differentiated	– 1–2% of osteosarcomas – Peak incidence in third decade, may affect older adults also – Metaphyseal regions of long bones are commonly affected site – In radiograph 85% cases appear as central medullary lesions Histology – Well differentiated mature appearing bone with small central osteocytes within fibroblastic stroma with mild atypia – Mitotic figures 1–2/10 hpf
5.	Intracortical	– Very rare – Diaphyses of lower extremity long bone – Radiographically presents as intracortical radiolucency surrounded by sclerosis Histology – Osteoblastic sclerotic tumors
6.	Periosteal	– < 2% of osteosarcomas – Subtype of surface osteoscaroma – Which most often occurs in older patients who have a long history of symptoms, reflecting its indolent nature – Predilection for diaphyseal region of long bones – Arises from the cortex but usually encircles the bone – Located on the external surface of the cortex and extends into the surrounding soft tissue – May not invade the medullary cavity Histology – Chondromatous foci predominate with focal malignant osteoid
7.	Paraosteal	– 5% of all osteosarcomas – Can be seen in childhood or adulthood – Arises from the juxtacortical region of the long bones – Striking predilection for the distal femur, especially the posterior aspect – Dense mushroom shaped mass attached to the outer metaphyseal cortex by broad base, as it grows it may encircle the involved bone-separated from the cortex by a narrow lucent zone Histology – Long narrow trabeculae or ill-defined islands of osteoid and woven bone separated by a fibrous stroma – Trabeculae may undergo a maturation resulting in the formation of lamellar bone – Spaces between bony trabeculae filled with spindled cells with minimal cytologic atypia – May contain foci of dedifferentiation and these tumors have a very poor prognosis; may occur in 16% of cases
8.	High-grade surface	– Arises from the outer cortex of the bone with minimal or absent intramedullary expansion – Very rare – Median age 20 years – Involves the diaphyseal or less commonly the diaphyseal-metaphyseal regions, distal femur being most common site of occurrence – Partially mineralized mass attached to the outer cortical surface with some cortical erosion – High grade neoplasms with microscopic foci of intramedullary extension in 60% of cases

Source: Modified from www.thedoctor'sdoctor.com, 2004.

Parosteal (juxtacortical) osteosarcoma is a very uncommon form of osteosarcoma which occurs in many bones throughout the skeleton and is characterized by its slow growth and good prognosis because of its lower tendency for metastasis. It is exceedingly rare in the jaws, although two cases have been reported in a series of 20 osteosarcomas of the maxilla and mandible by Roca and his coworkers. A total of seven cases in the jaws have now been reported, according to a recent review by Bras and his coworkers (Fig. 2-79).

Figure 2-79. Osteosarcoma of the maxilla.
(Courtesy of Dr Twinkle S Prasad).

Periosteal osteosarcoma appears to be an aggressive variant of the parosteal osteosarcoma and has been separated out as an entity by Unni and his associates because of its more active biologic behavior. Nevertheless, it still has a much better prognosis than the conventional intramedullary osteosarcoma.

Extraosseous osteosarcoma involving extraskeletal osteosarcoma of soft tissue in the absence of a primary skeletal tumor occasionally occurs but is rare. Osteosarcoma occurring in certain organs, such as the breast, liver and kidney, may only represent malignant teratoma but, excluding these, a true soft-tissue osteosarcoma does exist. It is a highly malignant tumor and has been discussed by Miller and his associates.

Radiographic Features. As with many bone tumors, both benign and malignant, the radiographic appearance is variable and depends on the amount of tumor bone synthesized by the malignant osteoblasts. In those tumors with little tumor bone, the radiographic appearance will be radiolucent; whereas those tumors with much tumor bone will be radiodense. Mixed lucent-dense lesions indicate an intermediate degree of tumor bone formation. *Cumulus cloud* densities form within the intramedullary and soft tissue components caused by mineralizing tumor osteoid.

There are three features of osteosarcoma that are classics:

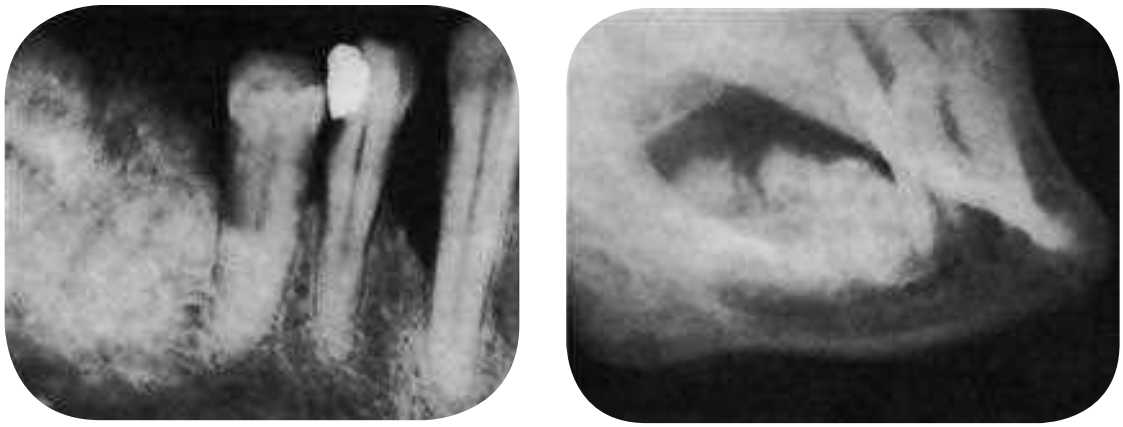
- Small streaks of bone radiate outward from approximately 25% of these tumors. This produces a **sunray (sunburst)** pattern.
- This tumor may grow within the periodontal membrane space causing resorption of the adjacent bone resulting in uniform widening of the space. Widening of the periodontal membrane space may also be seen in other conditions such as chondrosarcoma and scleroderma, and so it is not pathognomonic.
- In the long bones affected with osteosarcoma, the periosteum is elevated over the expanding tumor mass in a tent-like fashion. At the point on the bone where the periosteum begins to merge (edge of the tent), an acute angle between the bone surface and the periosteum is created. This is called **Codman's triangle** and is highly suspicious for osteosarcoma.

Histologic Features. Gross tissue of osteoblastic osteosarcoma show white-tan, yellow in color and firm in consistency. The chondroblastic elements appear as translucent lobules and fibroblastic elements appear as tan colored, with soft, or firm consistency. Hemorrhage and necrosis are common.

Osteosarcoma is characterized by the proliferation of both atypical osteoblasts and their less differentiated precursors. In general, the characteristic feature of osteosarcoma is the presence of osteoid formed by malignant osteoblasts in the lesion, even at sites distant from bone (e.g. the lung). Stromal cells may be spindle shaped and atypical with irregularly shaped nuclei.

A number of distinct histologic types of osteosarcoma exist. The conventional type is the most common in childhood and adolescence, and has been subdivided on the basis of the predominant features of the cells (i.e. osteoblastic, chondroblastic, fibroblastic), though the subtypes are clinically indistinguishable.

In the osteoblastic type of osteosarcoma atypical, neoplastic osteoblasts exhibit considerable variation in size and shape, show large, deeply staining nuclei and are arranged in a disorderly



A B

Figure 2-80. Osteogenic sarcoma of mandible.
(A) Intraoral radiograph. **(B)** Lateral jaw radiograph.

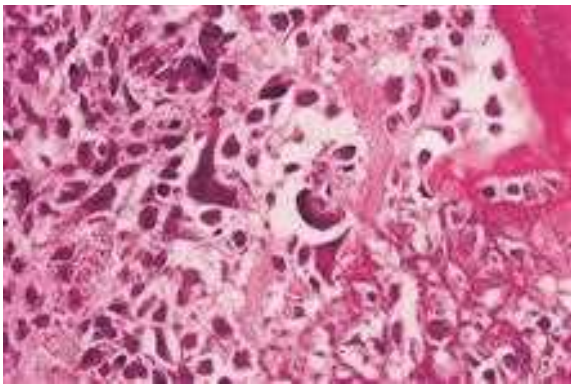


Figure 2-81. The neoplastic spindle cells of osteosarcoma are seen to be embedded in a matrix of osteoid (tumor osteoid) produced by these cells.

fashion about trabeculae of bone. In addition, there is a great deal of new tumor osteoid and bone formation, mostly in an irregular pattern and sometimes in solid sheets rather than in trabeculae. This comprised nearly 60% of the jaw lesions of Garrington's group. Varying degrees of proliferation of anaplastic fibroblasts are also found, and in the absence of significant amounts of tumor osteoid or bone, when these cells predominate, the lesion is designated as a fibroblastic type of osteosarcoma. This type comprised about 34% of the above group of jaw tumors. Some tumors show occasional areas of neoplastic myxomatous tissue and cartilage. Most authorities currently believe that even though a lesion is composed chiefly of malignant cartilage, it should be diagnosed as osteosarcoma if significant malignant osteoblasts and tumor osteoid or bone can be identified since the course of the lesion will probably be that of an osteosarcoma rather than of a chondrosarcoma (Fig. 2-81). However, when only limited chondroid is present, it is termed chondroblastic type and this form accounts for less than 10% of jaw osteosarcomas.

Staging. The purpose of staging tumors is to stratify risk groups. The conventional staging system used for other solid tumors is not appropriate for skeletal tumors because these tumors rarely involve lymph nodes or spread regionally.

The osteosarcoma staging system can be summarized as follows:

- Stages
  - Stage I – Low-grade lesions
  - Stage II – High-grade lesions
  - Stage III – Metastatic disease
- Substages
  - A – Intramedullary lesion
  - B – Local extramedullary spread
- Site of primary
  - Distal extremity – Best prognosis
  - Distal femur – Intermediate prognosis
  - Axial skeleton – Worst prognosis

Treatment. In the case of long bone involvement, amputation is a prime requisite. Neoplasms in other sites must be treated by radical resection, but, especially in the jaws, it is difficult to perform adequate and complete excision. Primary X-ray radiation is of no avail. Neoadjuvant (preoperative) chemotherapy has been found to facilitate subsequent surgical removal by shrinking the tumor. More recently, adjuvant chemotherapy in combination with surgery, including resection of pulmonary metastases, has appeared to offer promise of increased survival from this disease.

Patients who have a good histopathologic response to neoadjuvant chemotherapy (>95% tumor cell killed or necrosed) have a better prognosis than those whose tumors do not respond as favorably. The prognosis depends considerably upon the condition of the patient and the duration of the lesion when treatment is instituted. Under favorable conditions, when skeletal osteosarcoma was treated by proper radical means, the five-year cure rate of a series of 183 cases of sclerosing osteosarcoma reported by Geschickter and Copeland was 21%, while the five-year cure rate for their series of 149 cases of osteolytic osteosarcoma was 16%.

Of 45 cases of osteosarcoma of the jaws available for follow-up in the Garrington series, 50% developed clinical evidence of metastasis, most commonly to the lung. The overall five-year survival rate for maxillary osteosarcoma was 25% and for mandibular osteosarcoma, 41%. There was no correlation between histologic characteristics of the tumor and prognosis.

The overall five-year survival rate for patients diagnosed between 1974 and 1994 was 63% (59% for males, 70% for females).

Malignant Lymphoma

The malignant lymphomas constitute a group of neoplasms of varying degrees of malignancy which are derived from the basic cells of lymphoid tissue, the lymphocytes and histiocytes in any of their developmental stages. For this reason these diseases are intimately related to each other, and a concise distinction cannot always be drawn even on histologic grounds. Lukes has rendered the following excellent definition of this disease process, "Malignant lymphoma is a neoplastic proliferative process of the lymphopoietic portion of the reticuloendothelial system that involves cells of either the lymphocytic or histiocytic series in varying degrees of differentiation and occurs in an essentially homogeneous population of a single cell type. The character of histologic involvement is either diffuse (uniform) or nodular and the distribution of involvement may be regional or systemic (generalized); however, the process is basically multicentric in character. Lymphomas and leukemias of lymphocytes and histiocytes are identical, and the variation in the frequency of cells appearing in the peripheral blood appears to be related to differences in distribution and is dependent usually upon the occurrence of bone marrow involvement."

The malignant lymphomas, with the exception of Hodgkin's disease which is well established nosologically, are currently in

a state of change relative to a universally accepted classification. The non-Hodgkin's lymphomas as they are known nowadays, were called lymphosarcomas for many years. In the late 1930s and early 1940s, Gall and Mallory and Jackson and Parker developed classifications for the malignant lymphomas including Hodgkin's disease. These classifications were generally accepted, but in 1956, Rappaport and his colleagues presented a new classification of the malignant lymphomas. Rappaport revised this classification in 1966 and currently it is used by many pathologists because of its clinicopathologic relevance. However, many authorities claim that the modified Rappaport classification is scientifically inaccurate. In 1974, Lukes and Collins developed an immunologic classification of the non-Hodgkin's lymphomas which was scientifically accurate but difficult to use in a clinical situation. During the ensuing years, a number of classifications of non-Hodgkin's lymphomas have evolved. These too have not been based upon extensive clinicopathologic correlation and in addition have required modifications as new entities or variants of lymphomas were recognized.

At the present time, there are six well-described classifications of the non-Hodgkin's lymphomas. Each has its proponents, advantages and disadvantages. As a result, the US-based National Cancer Institute sponsored an international study of nearly 1,200 cases of non-Hodgkin's lymphoma. The panel consisted of six 'expert' proponents of the respective classifications as well as six other pathologists with experience and expertize in lymph node pathology. The study was designed "to assess the clinical applicability and reproducibility of six major histopathologic systems of classification for the non-Hodgkin's lymphomas and to evaluate whether any classification was superior to others in these regards." Based upon morphologic criteria only, without the use of immunologic methods, a working classification of 10 major types of non-Hodgkin's lymphoma was devised. This working classification has provided a means for translating a lymphoma into the various classifications but most importantly has reaffirmed the prognostic significance of a follicular architecture in the non-Hodgkin's lymphomas. Unfortunately, there is no unanimity of opinion as to whether this system is superior to the others or to the revised Rappaport classification as far as clinical significance, scientific accuracy and reproducibility is concerned. Because these current classifications of the non-Hodgkin's lymphomas are as yet not finalized and universally accepted, only a division of the non-Hodgkin's lymphomas and Hodgkin's disease will be used here until there is unification of the lymphoma concept.

Over the years, classifications have evolved from purely morphologic systems combined with prognostic categories (working classification) to one which integrate immunohistochemical data (Revised European American Lymphoma and WHO Classifications).

Non-Hodgkin's Lymphoma

The American Cancer Society predicted that approximately 23,000 cases of non-Hodgkin's lymphomas would occur in the United States in 1982. This accounts for approximately 70% of all new cases of malignant lymphoma. The non-Hodgkin's lymphomas are a heterogeneous group of lymphoproliferative malignancies which can involve both lymph nodes and lymphoid organs as well as extranodal organs and tissues. The lymph nodes of the head and neck are commonly involved as well as the extranodal tissues of this area.

Classification. The treatment of patients with non-Hodgkin's lymphoma (NHL) has been hampered by lack of a uniform classification system. In 1982, results of a consensus study were published as the Working Formulation. **The Working Formulation** combined results from six major classification systems into one classification. This allowed comparison of studies from different institutions and countries. The **Rappaport classification,** which also follows, is no longer in common use (Table 2-16).

The WHO modification of the Revised European American Lymphoma (REAL) classification recognizes three major categories of lymphoid malignancies based on morphology and cell lineage (Table 2-17). The categories include **B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin lymphoma**. Both lymphomas and lymphoid

Table 2-16: Comparison of working formulation and Rappaport classification

Working Formulation	Rappaport classification
Low-grade	
A. Small lymphocytic, consistent with chronic lymphocytic leukemia (SL)	Diffuse lymphocytic, well-differentiated (DLWD)
B. Follicular, predominantly small cleaved cell (FSC)	Nodular lymphocytic, poorly differentiated (NLPD)
C. Follicular, mixed small cleaved and large cell (FM)	Nodular mixed, lymphocytic and histiocytic (NM)
Intermediate-grade	
D. Follicular, predominantly large cell (FL)	Nodular histiocytic (NH)
E. Diffuse, small cleaved cell (DSC)	Diffuse lymphocytic, poorly differentiated (DLDP)
F. Diffuse mixed, small and large cell (DM)	Diffuse mixed, lymphocytic and histiocytic (DM)
G. Diffuse, large cell cleaved or noncleaved cell (DL)	Diffuse histiocytic (DH)
High-grade	
H. Immunoblastic, large cell (IBL)	Diffuse histiocytic (DH)
I. Lymphoblastic, convoluted or nonconvoluted cell (LL)	Diffuse lymphoblastic (DL)
J. Small noncleaved cell, Burkitt's or non-Burkitt's (SNC)	Diffuse undifferentiated Burkitt's or non-Burkitt's (DU)

Source: Adapted from Med News, National Cancer Institute, 2004.

Table 2-17: Updated Revised European American Lymphoma (REAL)/ WHO Classification (2001)

	B-cell neoplasms
1.	Precursor B-cell neoplasm: precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL, LBL)
2.	Peripheral B-cell neoplasms (a) B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (b) B-cell prolymphocytic leukemia (c) Lymphoplasmacytic lymphoma/immunocytoma (d) Mantle cell lymphoma (e) Follicular lymphoma (f) Extranodal marginal zone B-cell lymphoma of MALT type (g) Nodal marginal zone B-cell lymphoma (± monocytoid B-cells) (h) Splenic marginal zone lymphoma (± villous lymphocytes) (i) Hairy cell leukemia (j) Plasmacytoma/plasma cell myeloma (k) Diffuse large B-cell lymphoma (l) Burkitt's lymphoma
	T-cell and putative NK-cell neoplasms
1.	Precursor T-cell neoplasm: precursor T-cell lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL, LBL)
2.	Peripheral T-cell and NK-cell neoplasms (a) T-cell chronic lymphocytic leukemia/prolymphocytic leukemia (b) T-cell granular lymphocytic leukemia (c) Mycosis fungoides/Sézary syndrome (d) Peripheral T-cell lymphoma, not otherwise characterized (e) Hepatosplenic gamma/delta T-cell lymphoma (f) Subcutaneous panniculitis-like T-cell lymphoma (g) Angioimmunoblastic T-cell lymphoma (h) Extranodal T-/NK-cell lymphoma, nasal type (i) Enteropathy-type intestinal T-cell lymphoma (j) Adult T-cell lymphoma/leukemia (HTLV 1+) (k) Anaplastic large cell lymphoma, primary systemic type (l) Anaplastic large cell lymphoma, primary cutaneous type (m) Aggressive NK-cell leukemia
	Hodgkin's lymphoma (Hodgkin's disease)
1.	Nodular lymphocyte-predominant Hodgkin's lymphoma
2.	Classical Hodgkin's lymphoma (a) Nodular sclerosis Hodgkin's lymphoma (b) Lymphocyte-rich classical Hodgkin's lymphoma (c) Mixed-cellularity Hodgkin's lymphoma (d) Lymphocyte-depleted Hodgkin's lymphoma

Source: Adapted from Med News, National Cancer Institute, 2004.

leukemias are included in this classification because both solid and circulating phases are present in many lymphoid neoplasms and distinction between them is artificial. Within B-and T-cell categories, two subdivisions are recognized: precursor neoplasms, which correspond to the earliest stages of differentiation, and more mature differentiated neoplasms.

Etiology. Genetic abnormalities like nonrandom chromosomal and molecular rearrangements play an important role in the pathogenesis of many lymphomas and correlate with histology and immunophenotype (Table 2-18). Most lymphomas do not have a familial pattern; however, coexistence of multiple breast cancers, ovarian cancer, sarcomas, and lymphomas in a family may suggest an inherited abnormality in tumor suppressor genes.

The most common chromosomal abnormality associated with NHL is the **t(14;18)(q32;q21)** translocation that is found in 85% of follicular lymphomas and 25–30% of intermediate-grade NHLs. This translocation results in the juxtaposition of the bcl-2 apoptotic inhibitor oncogene at chromosome band 18q21 to the heavy-chain region of the immunoglobulin (Ig) locus within chromosome band 14q32, resulting in its overexpression. The **t(11;14)(q13;q32)** translocation results in overexpression of bcl-1 (cyclin-D1/PRAD1), a cell cycle control gene on chromosome band 11q13, and is diagnostic of mantle cell lymphoma.

Environmental factors also seem to play a role in the development of NHL. Certain chemicals have been linked to the development of NHL include a variety of pesticides and herbicides (e.g. organophosphates, chlorophenols), solvents and organic chemicals (e.g. benzene, carbon tetrachloride), and wood preservatives. Thus certain workers like pesticide applicators, workers in the petroleum, rubber, plastics, and synthetic industries have a slightly increased risk of NHL. Patients who receive cancer chemotherapy and/or radiation therapy are at increased risk of developing NHL.

Several **viruses** have been implicated in the pathogenesis of NHL, including the Epstein-Barr virus in Burkitt's lymphoma (especially in endemic areas of Africa), sinonasal lymphoma in Asia and South America, and lymphomas in immunocompromised patients; HTLV-1 in adult T-cell lymphoma/leukemia; and human herpesvirus 8 (HHV 8) in body cavity-based lymphomas in patients with HIV infection.

Immunodeficiency states that seem to predispose to NHL include congenital immunodeficiency states (e.g. ataxia telangiectasia, Wiskott–Aldrich syndrome, common variable hypogammaglobulinemia, severe combined immunodeficiency (SCID) as well as acquired immunodeficiency states (e.g. HIV infection, iatrogenic immunosuppression for solid organ or bone marrow transplant recipients).

Connective-tissue disorders, including Sjögren syndrome, rheumatoid arthritis, chronic lymphocytic thyroiditis, and systemic lupus erythematosus (SLE) are also associated with increased risk of NHL.

Clinical Features. The median age at presentation for all subtypes of NHL is older than 50 years. High-grade lymphoblastic and small noncleaved cell lymphomas are the only subtypes of B-cell NHL that are observed more commonly in children and young adults. NHL is more common in male subjects, with a reported incidence of 19.2 cases per 100,000 population as compared with 12.2 cases per 100,000 population in women. Certain endemic geographical factors appear to influence the development of NHL in specific areas, e.g. follicular lymphomas are more common in North America and Europe but are rare in the Caribbean, Africa, China, Japan, and the Middle East. HTLV-1-associated adult T-cell lymphoma/ leukemia occurs commonly in Japan and in the Caribbean.

Table 2-18: Chromosomal abnormalities in B-cell NHL

Cytogenetic abnormality	Histology	Antigen rearrangement	Oncogene expression
t(14;18)(q32;q21)	Follicular, diffuse large cell	IgH*	bcl-2
t(11;14)(q13;q32)	Mantle cell	IgH	bcl-1
t(1;14)(p22;q32)	Extranodal marginal zone B-cell lymphoma of MALT type	IgH	bcl-10
t(11;18)(q21;q21)	Extranodal marginal zone B-cell lymphoma of MALT type	IgH	API2, MLT
t(9;14)(p13;q32)	Lymphoplasmacytic lymphoma	IgH	PAX-5
t(14;19)(q32;q13.1)	B-cell CLL	IgH	bcl-3
8q24 translocations			
t(8;14)(q24;q32)	Burkitt and small	IgH	
t(2;8)(p11–12;q24)	Noncleaved lymphoma	Ig-8	c-myc
t(8;22)(q24;q11)		Ig-6	
t(3;22)(q27;q11)	Diffuse large cell	Ig-6	–
Trisomy 12	Small lymphocytic B-cell CLL	–	–
t(6;14)(p25;q32)	Myeloma	–	mum1

**Immunoglobulin H.*
Source: Modified from Ajeet Gajra, eMedicine Specialities. Haematology, 2005.

Lymphadenopathy is the most common manifestation of lymphoma. Systemic symptoms like fevers, night sweats, weight loss, and fatigue, pruritus are noticed. Sometimes waxing and waning lymphadenopathy may be seen. Spontaneous remissions have been documented in some patients with low-grade lymphomas.

Organ-specific symptoms such as shortness of breath, chest pain, cough, abdominal pain and distention, or bone pain, may lead to identification of specific sites of involvement. Neurological symptoms are important because CNS involvement may occur with aggressive lymphomas.

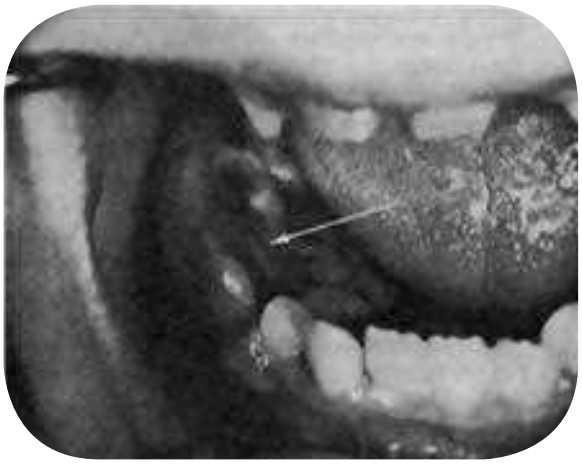
Oral Manifestations. Numerous cases of non-Hodgkin's lymphoma of the oral cavity have been reported. In many instances, the oral involvement is simply a manifestation of disseminated disease. On the other hand, many lesions are the sole expression of the disease or the initial manifestation of generalized disease.

The oral lesions are characterized by swellings which may grow rapidly and then ulcerate. In some cases, these become large, fungating, necrotic, foul-smelling masses (Fig. 2-82). Pain is a variable feature. When underlying bone is involved, tooth mobility and pain may develop. A number of cases have been reported in which paresthesia of the mental nerve developed.

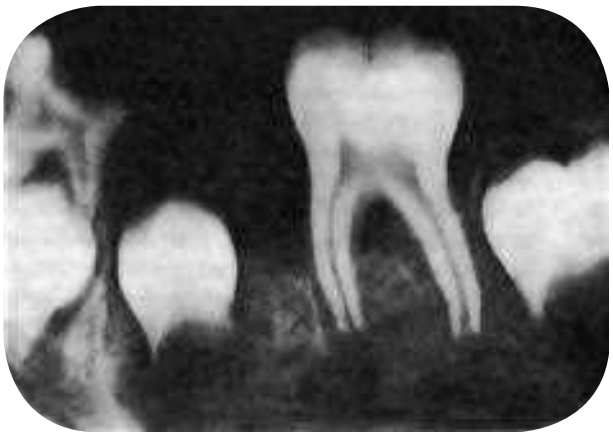
Tomich and Shafer reported 21 cases of malignant lymphomas in the hard palate. Reported as *lymphoproliferative disease of the hard palate,* all proved to be non-Hodgkin's lymphomas. These lesions occurred primarily in elderly men and women with an average age of 70 years. They presented as soft, fluctuant swellings which were occasionally bilateral. The swellings were ulcerated or discolored in some cases (Fig. 2-83). Although lymphoid lesions in the hard palate are very likely to be lymphomas, follicular lymphoid hyperplasia can present in this anatomic location and therefore careful histologic examination is of paramount importance. Harsany and his associates described such a condition and discussed the histologic differentiation between lymphoid hyperplasia, non-Hodgkin's lymphoma and benign lymphoepithelial lesion (q.v.).

Histologic Features. The non-Hodgkin's lymphomas present a histologic pattern which is described as either nodular or diffuse. In the nodular pattern, the neoplastic cells tend to aggregate in such a way that large clusters of cells are seen (Fig. 2-84A). In contrast, the diffuse pattern is characterized by a monotonous distribution of cells with no evidence of nodularity or germinal center formation. The diffuse lymphomas produce an entire effacement of normal lymph node architecture (Fig. 2-84B). The histologic pattern of involvement is very important, since there is clinicopathologic and prognostic correlation between the two types. The nodular pattern is seen in lymphomas in adults more often than in children and is associated with a more favorable prognosis than the diffuse type. The histologic pattern of involvement, therefore, has been a basis for the classification of non-Hodgkin's lymphoma. A diagnosis of nodular or diffuse lymphoma is highly reproducible among pathologists, and it has definite clinical significance.

The actual cell type involved in the non-Hodgkin's lymphoma has proven to be an enigma for histopathologists. Immunologic cell surface marking studies have shown that the nodular lymphomas are of B-cell origin. Many of the diffuse lymphomas are likewise of B-cell origin but some diffuse lymphomas prove to be of T-cell origin. From a purely morphologic observation, without the use of immunologic markers, the determination of the cell of origin is difficult. This has resulted in cells being interpreted as lymphocytes, reticulum cells and histiocytes in various degrees of differentiation. Currently, cells formerly interpreted as 'reticulum cells' or 'histiocytes' are known to represent large lymphocytes.



A



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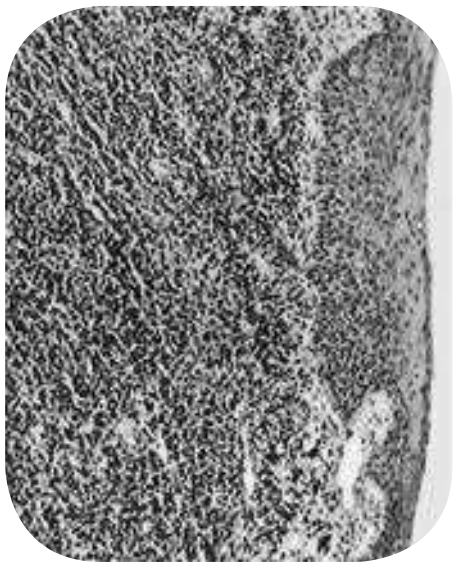


C

Figure 2-82. Non-Hodgkin's lymphoma.
(A) The child has a fungating tissue mass after extraction of the second deciduous molar because of sudden looseness. **(B)** The intraoral radiograph demonstrates loss of supporting bone around the first permanent molar, an unusual and serious finding in a child. **(C)** The photomicrograph shows dense diffuse infiltration of the tissues by abnormal lymphocytes.

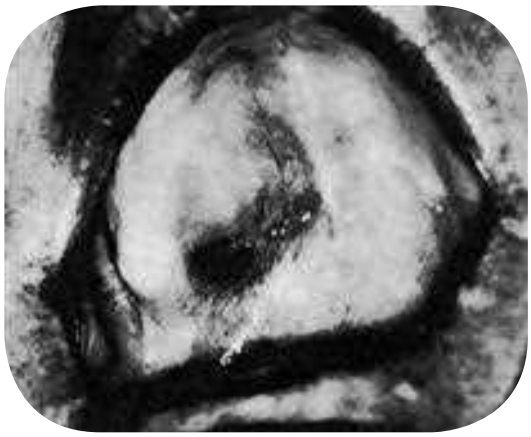


Figure 2-83. Lymphoproliferative disease of the hard palate.

A

B

Figure 2-84. Non-Hodgkin's lymphoma.
The nodular pattern is characterized by large clusters of cells **(A)** while the diffuse pattern shows no such clustering but rather a monotonous population of cells **(B)**.

However, it is thought that a histiocytic lymphoma does exist, albeit uncommon. The problem of cell identification on a morphologic, nonimmunologic basis is one of the major obstacles in arriving at a universally acceptable classification of the non-Hodgkin's lymphomas.

The **Ann Arbor staging system** is commonly used for patients with NHL. In this system, stages I, II, III, and IV, adult NHL can be subclassified into A and B categories: B for those with well-defined generalized symptoms and A for those without such symptoms. The B designation is given to patients with any of the following symptoms:

- Unexplained loss of more than 10% of body weight in the six months before diagnosis
- Unexplained fever with temperatures above 38° C
- Drenching night sweats.

Stage I
Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II
Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved may be indicated by a subscript (e.g. II3).

Stage III
Involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E).

Stage IV

Disseminated (multifocal) involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

The histologic findings in B-cell NHL are varied. The salient features of the most common subtypes are:

Follicular lymphoma (nodular). Represents 22% of all non-Hodgkins lymphomas. At low magnification, a predominantly nodular growth pattern is observed in lymph nodes. Two principal cell types are observed in varying proportions: small cells with irregular or cleaved nuclear contours and scant cytoplasm that are referred to as **centrocytes** (small cleaved cells) and larger cells with open nuclear chromatin, several nucleoli, and modest amounts of cytoplasm that are referred to as **centroblasts**. In most follicular lymphomas, small cleaved cells comprise the majority of the cellularity. Peripheral blood involvement sufficient to produce lymphocytosis (usually <20,000/dl) is observed in about 10% of patients. Bone marrow involvement occurs in 65% of patients and characteristically takes the form of paratrabecular lymphoid aggregates. Splenic white pulp and hepatic portal triads are also frequently involved (Fig. 2-85).

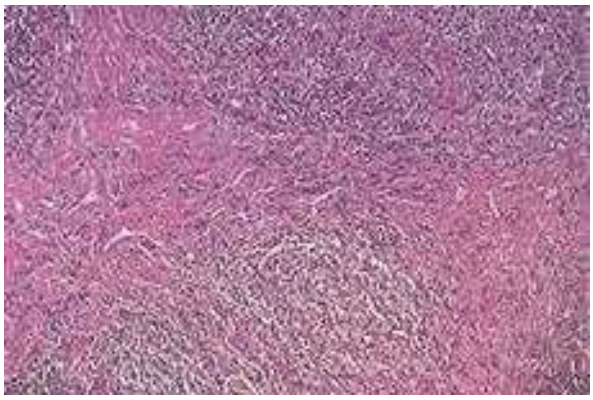


Figure 2-85. Follicular non-Hodgkin's lymphoma.

Diffuse large B-cell lymphoma. Represents 31% of all non-Hodgkin's lymphomas. The common morphologic features that unite this group are the relatively large cell size (usually four or five times that of a small lymphocyte) and a diffuse pattern of growth. In other respects, a fair degree of morphologic variation exists. In most cases, the tumor cells have a round or oval nucleus that appears vesicular because of margination of chromatin at the nuclear membrane, but large multilobed or cleaved nuclei predominate in some cases. Nucleoli may be two or three in number and located adjacent to the nuclear membrane, or they may be single and centrally placed. Cytoplasm is usually present in moderate abundance and may be pale or basophilic. Other more anaplastic tumors may contain multinucleated cells with large inclusion like nucleoli that closely resemble Reed–Sternberg cells, and phenotyping is often necessary to distinguish these two entities.

Treatment and Prognosis. NHL can be treated with radiotherapy, chemotherapy (forms the cornerstone of therapy in lymphoma and has a curative, as well as a palliative role) or biologic therapy (comprised of interferon therapy and monoclonal antibodies). The NHLs can be divided into two prognostic groups: the **indolent** lymphomas and the **aggressive** lymphomas. Indolent NHL types have a relatively good prognosis, with median survival as long as 10 years, but they usually are not curable in advanced clinical stages. Early-stage (I and II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at five years is approximately 50–60%. 30–60% of patients with aggressive NHL can be cured. The vast majority of relapses occur in the first two years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease.

Although significant advances in lymphoma treatment have been made, the disease is still a serious one, and the prognosis for any particular patient should be considered individualistic.

Primary Lymphoma of Bone

(Primary lymphocytic lymphoma, reticulum cell sarcoma of bone)

Primary lymphoma of bone (PLB) is a rare malignant neoplastic disorder of the skeleton. In 1939, it was described as a distinct clinical condition by Parker and Jackson. In 1963, the term primary lymphoma of bone was introduced by Ivins and Dahlin.

Most (94%) primary lymphoma of bone cases result from non-Hodgkin's lymphoma and 6% resulted from Hodgkin's disease. Primary lymphoma of bone tumors produce osteoclast-stimulating factors that cause lytic bone destruction.

The etiology of bone lymphoma is unknown. Viral agents and immunosuppression are implicated in some cases. Primary lymphoma of bone has been documented as a post-transplant lymphoproliferative disorder in patients who were immunosuppressed. Bone has also been documented as a site for primary lymphoma in patients with AIDS. Rarely, patients with Paget's disease of bone may develop malignant lymphoma in the involved bone. However, these associations are not commonly documented and are the subject of a few case reports in the literature.

Clinical Features. The incidence of disease is distributed fairly evenly in the second through eighth decades. This disease is rare in children younger than 10 years, as are most primary bone malignancies. Male-to-female ratio ranges from 1.5–2 : 1. Patients of all races are affected.

The most common presenting feature of bone lymphoma is pain, which occurs in 60–100% of patients. Other presenting features are palpable swelling or mass and pathologic fracture. Pediatric patients may present with functional deficits in involved bone. Systemic symptoms such as weight loss, fever, and night sweats are seen in fewer than 10% of patients. Regional lymph node involvement is more common in cases of bone involvement in patients with systemic lymphoma.

The diagnostic criteria (Coley et al, 1950) by WHO are:

- A primary focus in a single bone
- Histologic confirmation
- At the time of diagnosis, no evidence of distant soft tissue or distant lymph node involvement.

Regional lymph node involvement at diagnosis is not considered exclusionary using these criteria. Currently, it is recognized that PLB may involve multiple bones, as long as the other two criteria are met.

Oral Manifestations. Primary lymphoma of bone is not a common disease of the jaws, but it appears to be somewhat more frequent in the mandible than in the maxilla. Of the 150 primary cases of Dahlin, 22 or 15% occurred in the mandible. There were no cases in the maxilla. It occurs in the jaws with a predilection for the male gender.

Gerry and Williams collected all the reported cases of primary lymphoma of the mandible and noted that the principal presenting symptom of the disease was pain, usually present for a period of several months to a year or more before the patient sought advice and treatment. Demonstrable swelling or enlargement of the bone was often noted.

The oral mucosa in this disease seldom is ulcerated over the involved bone, although there may be minor change in the texture or hue, sometimes, appearing diffusely inflamed (Fig. 2-86A, B). The teeth often become exceedingly loose, owing to destruction of bone. When the neoplasm involves the maxilla, there may be evidence of expansion of the bone as well as symptoms of nasal obstruction due to superior growth of the tumor into the floor of the nasal cavity. Aside from this local discomfort, the patient seldom exhibits systemic signs or symptoms of the disease.

Radiographic Features. The most common radiographic features, reported in a review of 237 cases by Mulligan et al, included the following: permeative lytic pattern of bone destruction (74%), metadiaphyseal location (69%), periosteal reaction (58%), soft tissue mass (80–100%).

Sometimes variable findings such as no detectable abnormal findings on initial conventional radiographs (<5%), focal geographic lesions that may have a mixed or blastic appearance (11%), pathologic fracture (22%), varied periosteal reactions, ranging from a single continuous layer to interrupted multiple layers are found. Interrupted single or multiple layers were the most common type of periosteal reaction (52%).

Laboratory Findings. Most patients have elevated lactate dehydrogenase (LDH) levels, this is directly proportionate to the disease load. Erythrocyte sedimentation rate (ESR) also is frequently elevated in systemic disease involvement. Hypercalcemia is seen in some patients and has been associated with a poorer prognosis.

Histologic Features. The primary cell of this osseous lesion is identical with that of the soft-tissue tumor, and diagnosis depends upon adequate biopsy with microscopic examination of the tissue by a competent and qualified pathologist (Fig. 2-86C, D). Since the oral tissues frequently exhibit considerable inflammatory cell infiltration, confusion of this tumor with an inflammatory lesion sometimes occurs.

The most common subtype seen as primary lymphoma of bone is diffuse large B-cell lymphoma, which accounts for 60–90% of cases. These cases show a diffuse population of large lymphoid cells, sometimes with convoluted nuclear contours. Admixed fibrosis is present with a background population of reactive small lymphocytes.

Other types of lymphoma seen in primary bone lesions include follicular lymphoma, Burkitt's lymphoma, precursor B-lymphoblastic lymphoma, and B-cell small lymphocytic lymphoma. T-cell lymphomas are distinctly uncommon. Cases of anaplastic large cell lymphoma, peripheral T-cell lymphoma, and adult T-cell lymphoma have been reported, the latter associated with human T-cell lymphotrophic virus type I (HTLV-I) infection.

Histologic differential diagnoses include Ewing's sarcoma, osteolytic osteosarcoma, neuroblastoma and other small round cell tumors, bone metastasis, granulocytic sarcoma, and Langerhans cell histiocytosis.

Treatment and Prognosis. The consensus now favors radiation for control of the primary lesion. Sometimes surgical

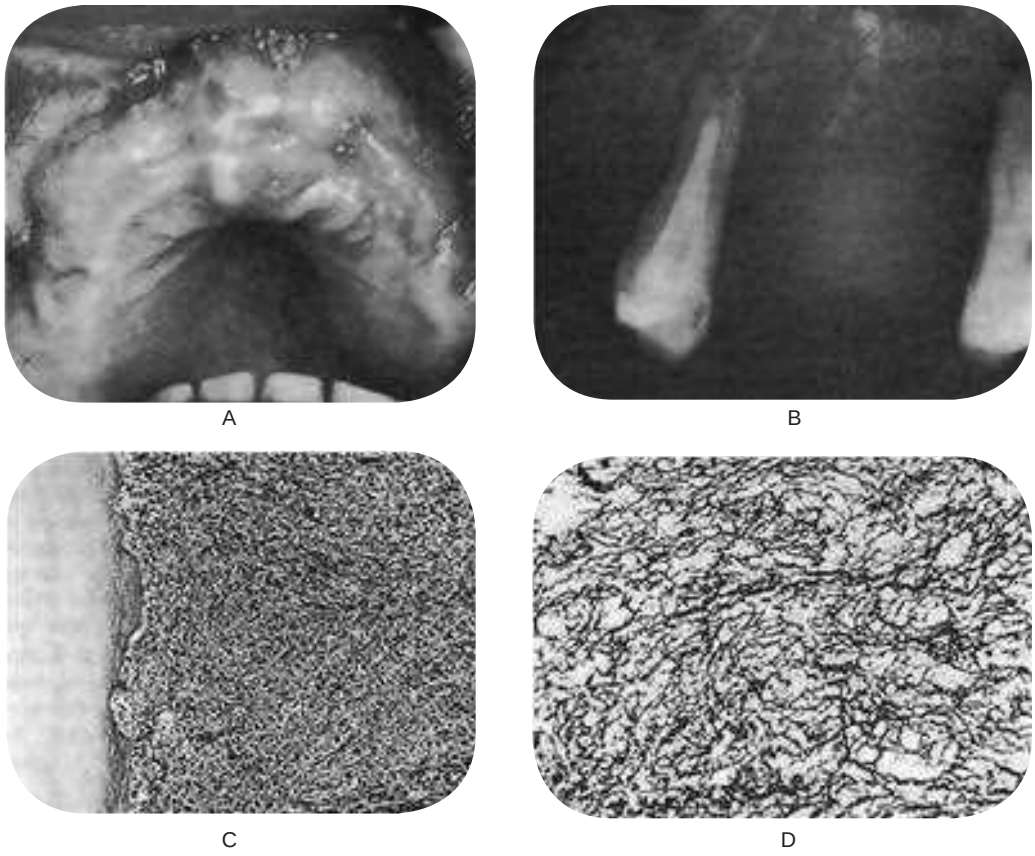


Figure 2-86. Primary lymphoma of bone.
(A) The maxilla is diffusely involved by the neoplasm, but presents no remarkable changes in the oral mucosa. **(B)** The intraoral radiograph, taken just before extraction of the few remaining teeth, shows bone destruction causing loosening of the teeth. **(C)** The photomicrograph illustrates the cellular nature of the neoplasm in an area of tissue attached to one tooth. **(D)** A special silver stain shows the profusion of reticulin fibers produced by the lesion.

ablation becomes necessary because radiation either results in local necrosis that is disabling or fails to halt the growth of the primary tumor. Regional lymph nodes require attention, and radiation therapy is likely to be the most efficacious for these. Chemotherapy is indicated for disseminated disease.

Many reports indicate that malignant lymphoma has the best prognosis of all the primary malignant tumors of bone. Five-year survival rates of 40–50% and even higher have been reported. Patients with involvement of multiple bones but without involvement of nonskeletal sites had a surprisingly good survival rate of 42% at five years (Unni KK, 1996).

Most of the small group of patients with mandibular tumors in the series of KK Unni (1996) reported long-term survival. A gratifying percentage of patients with locally invasive and basically inoperable lymphomas of the maxillary region, can be cured by appropriate radiation therapy.

African Jaw Lymphoma
(Burkitt's lymphoma)

A tumor peculiar to the children of tropical central Africa was reported by Denis Parsons Burkitt (1958–59), which later became named after him. Burkitt's lymphoma (BL) occurs endemically in parts of Africa and Papua, New Guinea and is restricted to areas with endemic malaria. BL also occurs sporadically throughout the world.

It is a high-grade B-cell neoplasm and has two major forms: the endemic (African) form and the nonendemic (sporadic) form. Burkitt's lymphoma is a childhood tumor but it is observed in adult patients too. Burkitt's lymphoma is one of the fastest growing malignancies in humans, with a very high growth fraction.

Clinical Features. The African form most often involves the maxilla or mandible. The involvement of abdominal organs, such as the kidneys, ovaries, or retroperitoneal structures, is slightly less common. In contrast, the sporadic form usually involves abdominal organs, with the most common involvement of the distal ileum, cecum, or mesentery, and less common involvement of other abdominal organs, pelvic organs, and facial bones.

The exact causes and mechanisms of Burkitt's lymphoma are not known. EBV is closely associated with the African form of Burkitt's lymphoma. Some have postulated that, because of immunosuppression caused by coexistent malaria or another infection, the host is unable to generate an adequate T-lymphocyte response (i.e. EBV-specific cytotoxic T cells)

against B cells that are infected latently with EBV. This subsequently results in excessive B cell proliferation.

About 90% of Burkitt's lymphomas carry a translocation of the c-myc oncogene from chromosome 8 to either the immunoglobulin (Ig) heavy-chain region on chromosome **14 [t(8;14)]** or one of the light-chain loci on chromosome 2 (kappa light chain) **[t(8;2)]** or chromosome 22 (lambda light chain) **[t(8;22)].** Overproduction of the c-myc product may change the lymphocytes into cancer cells.

In the African form of Burkitt's lymphoma, patients most often present with swelling of the affected jaw or other facial bones, loosening of the teeth, and swelling of the lymph nodes, which are nontender and rapidly growing, in the neck or below the jaw. Abdominal presentation is slightly less common (Fig. 2-88).

Patients with the sporadic form of Burkitt's lymphoma most commonly present with abdominal tumors causing swelling and pain in the affected area. Some patients present with symptoms of bowel obstruction secondary to an ileocecal intussusception caused by tumor growth.

Because of the rapid growth of the Burkitt tumor, patients may quickly manifest significant metabolic derangement and renal function impairment. Less common presentations of Burkitt's lymphoma include an epidural mass, skin nodules, CNS symptoms, and bone marrow involvement. Rare cases of Burkitt's lymphoma can present as acute leukemia (L3-ALL) with fever, anemia, bleeding, and adenopathy.

Major signs of Burkitt's lymphoma include a soft tissue mass associated with the involvement of the jaw or other facial bones, enlarged cervical lymph nodes, abdominal masses, and ascites.

Histologic Features. Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes characterized by small noncleaved cells that are uniform in appearance and that produce a diffuse pattern of tissue involvement.

Burkitt cells are homogeneous in size and shape, with round to oval nuclei and slightly coarse chromatin, with multiple nucleoli, and with intensely basophilic vacuolated cytoplasm that contains neutral fat. Frequent mitotic figures usually are observed. A characteristic **starry sky** appearance is imparted by scattered macrophages with an abundant clear cytoplasm, often containing phagocytic cellular debris (Fig. 2-89).

Treatment and Prognosis. Before the advent of specific therapies, children with Burkitt's lymphoma died rapidly. With combination chemotherapy and CNS prophylaxis (intrathecal chemotherapy), the survival rate is now at least 60%. Patients with limited disease have a survival rate of 90%. Those with bone marrow and CNS involvement have a poor prognosis. Adults with the disease, especially those in the advanced stage, do more poorly than affected children.

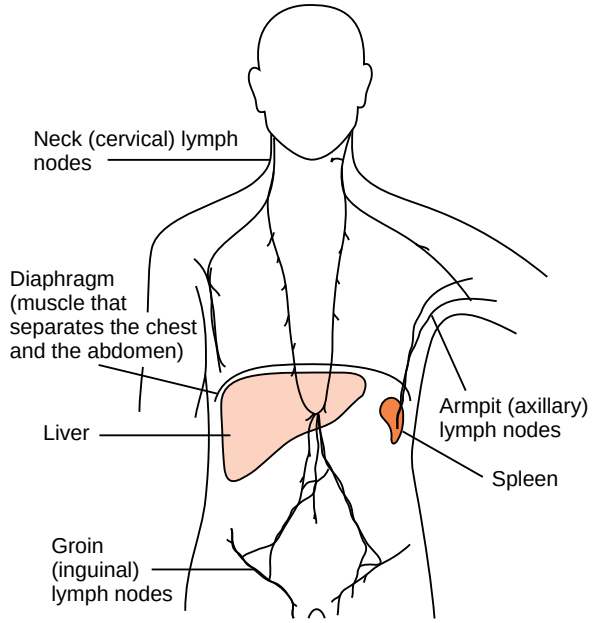


Figure 2-87. A diagram showing the main groups of lymph nodes in the body.
(Courtesy of Cancer BACUP 2003).

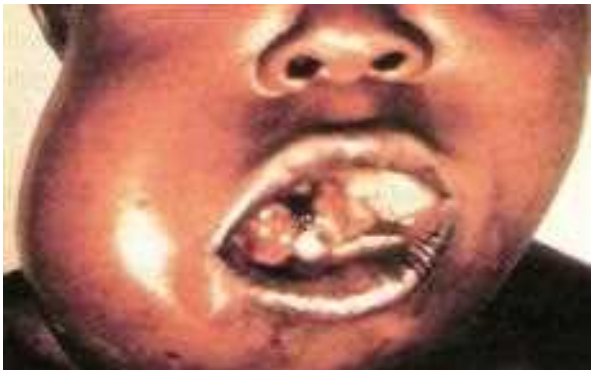


Figure 2-88. Burkitt's lymphoma presenting as a large tumor of the jaw in an African child.
(Courtesy of WHO, World Cancer Report, 2003).

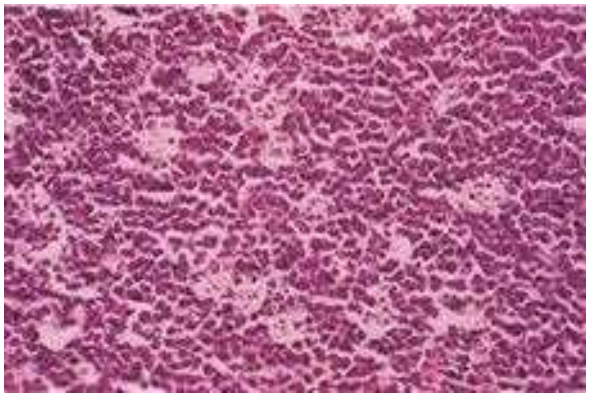


Figure 2-89. Starry sky appearance.
Appearance of Burkitt's lymphoma.

Staging. Various staging systems have been proposed.

- **Stage I.** The lymphoma is only in one group of lymph nodes in one particular area of the body.
- **Stage II.** More than one group of lymph nodes is affected, but all the affected nodes are contained within either the upper half or the lower half of the body. The upper half of the body is above the sheet of muscle underneath the lungs (the diaphragm) and the lower half is below the diaphragm.
- **Stage III.** Lymphoma is present in lymph nodes in both the upper and lower parts of the body (i.e. in lymph nodes both above and below the diaphragm). Spleen is considered as a lymph node in this staging system.
- **Stage IV.** The lymphoma has spread beyond lymph nodes to other organs, i.e. to sites such as the nervous system, bone marrow, liver or lungs.

The tumour can be stained with antibodies to lambda light chains which should reveal a monoclonal tumor of B-cell origin. In over 90% of cases, the cells express IgM at the cell surface. The lymphoma cells are CD20+, CD5–, CD10+, bcl-2+.

Hodgkin's Disease

(Hodgkin's lymphoma, malignant lymphoma)

Hodgkin's disease (HD) is considered as one of the two main types of malignant lymphomas. Thomas Hodgkin first described Hodgkin's disease in 1832. it is a potentially curable malignant lymphoma with distinct histology, biologic behavior, and clinical characteristics.

The etiology of HD is unknown. Infectious agents, especially the Epstein-Barr virus (EBV), may be involved in the pathogenesis. In as many as 50% of HD cases, the tumor cells are EBV-positive. EBV positivity is higher with mixed cellularity Hodgkin disease (60–70%) than the nodular sclerosis Hodgkin disease (15–30%). Almost 100% of HIV-associated HD cases are EBV-positive.

Patients with HIV infection have a higher incidence of HD compared to the population without HIV infection. However, HD is not considered an AIDS-defining neoplasm.

Genetic predisposition may play a role in the pathogenesis. Approximately 1% of patients with HD have a family history of the disease. Siblings of an affected individual have a three- to seven-fold increased risk for developing HD. This risk is higher in monozygotic twins. HLA-DP alleles are more common in HD.

Clinical Features. Age-specific incidence rates have a bimodal distribution in both genders, peaking in young adults (aged 15–34 years) and older individuals (>55 years). HD is more common in males than in females, with an age standardized incidence of 1.8 cases per 100,000 population in males and 0.8 cases per 100,000 population in females. This male predominance is particularly evident in children, where 85% of the cases are in males. HD is more common among whites and less common among Asians. In developing countries, the incidence of the mixed-cellularity subtype in children is higher. On the other hand, in developed countries, young adults have the highest incidence of the nodular sclerosis subtype. Also, socioeconomic class is associated with a higher risk of HD. HD had a worldwide incidence of 59,000 cases annually (0.7% of all cancers) and accounts for 26,000 deaths (0.5% of all cancers).

The clinical signs and symptoms of Hodgkin's disease are extremely protean. The first manifestation in the majority of cases is painless enlargement of one or more cervical lymph nodes, not uncommon finding in other lymphomas or in cases of simple upper respiratory tract or oral infection. Palpable painless lymphadenopathy occurs in the cervical area (60–80%), axilla (6–20%), and, less commonly, in the inguinal area (6–20%) and Waldeyer ring or occipital nodes. The nodes are usually firm and rubbery in consistency, and the overlying skin is normal (Fig. 2-90).

Constitutional symptoms such as unexplained weight loss, fever, night sweats are present in about 40% of patients. Chest pain, cough, and/or shortness of breath may be present due to a large mediastinal mass or lung involvement. Rarely, hemoptysis is observed. Alcohol-induced pain at sites of nodal disease is specific for HD and occurs in less than 10% of patients. Patient may present with pruritus or intermittent fever. Back, abdomen or bone pain may occur rarely due to splenomegaly, hepatomegaly, pressure from enlarged lymph nodes, involvement of bone or vertebrae.

Oral Manifestations. Hodgkin's disease is primarily a disease of lymph nodes, and for this reason, seldom occurs as a disease primarily in the oral cavity. It is conceivable that the oral cavity could be involved secondarily, but this appears to be an exceedingly rare happening. A case of Hodgkin's disease secondarily involving the mandible and overlying alveolar mucosa has been reported by Forman and Wesson.

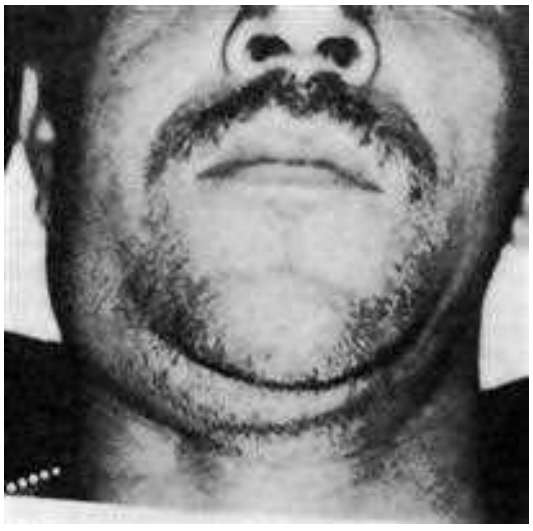


Figure 2-90. Hodgkin's disease.
There is cervical lymphadenopathy which is more pronounced on one side *(Courtesy of Dr Cesar Lopez).*

Histologic Features

1. ***Nodular sclerosis (NS) Hodgkin's disease*** comprises 60–80% of all cases. The morphology shows a nodular pattern. The broad bands of fibrosis divide the node into 'nodules'. The capsule is thickened. The characteristic cell is the lacunar-type RS cell, which has a monolobated or multilobated nucleus and a small nucleolus with abundant and pale cytoplasm. NS frequently is observed in adolescents and young adults and usually involves the mediastinum and other supradiaphragmatic sites.
2. ***Mixed-cellularity Hodgkin's disease*** comprises 15–30%. Histologically, the infiltrate is usually diffuse. RS cells are of the classic type (large, with bilobate, double or multiple nuclei, and a large eosinophilic inclusion like nucleolus). It commonly affects the abdominal lymph nodes and spleen. Patients with this histology typically have advanced-stage disease with systemic symptoms and immunodeficiency.

Characteristics of typical Reed–Sternberg cell

Characteristic malignant cells of Hodgkin's diseases are large cells known as Reed–Sternberg (RS) cells (typical and variant), 20–50 micrometers in diameter, abundant, amphophilic, finely granular/homogeneous cytoplasm; two mirror-image nuclei (owl eyes) each with an eosinophilic nucleolus and a thick nuclear membrane (chromatin is distributed at the cell periphery). One or two percent of these malignant cells are admixed within a reactive cell infiltrate composed of variable proportions of lymphocytes, histiocytes, eosinophils, and plasma cells. The Reed–Sternberg cells are identified as large often binucleated cells with prominent nucleoli and an unusual CD15+, CD30+ immunophenotype. In approximately 50% of cases, the Reed–Sternberg cells are infected by the Epstein-Barr virus. There are five recognized histologic types of Hodgkin's disease which form the basis for its classification (Fig. 2-91).

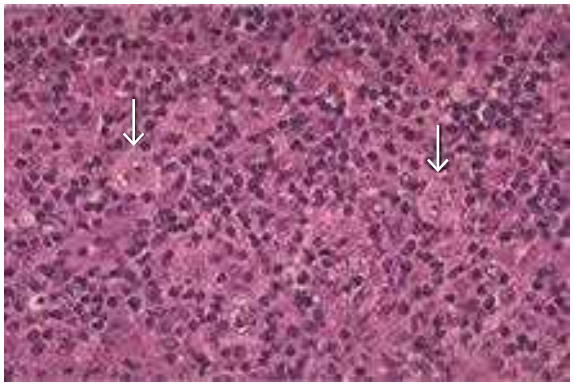


Figure 2-91. Reed-Sternberg cell.
Cells with large, pale nuclei containing purple nucleoli at the arrowheads. These are Reed–Sternberg cells that are indicative of Hodgkin's disease. Most of the cellular content of foci of Hodgkin's disease consists of reactive lymphoid cells.

3. ***Lymphocyte-depleted Hodgkin's disease*** makes up less than 1%. The infiltrate in lymphocyte-depleted Hodgkin disease (LDHD) is diffuse and often appears hypocellular. Large numbers of RS cells and bizarre sarcomatous variants are present. It is associated with older age and HIV positivity. Patients usually present with advanced-stage disease. EBV proteins are expressed in many of these tumors. Many cases of LDHD diagnosed in the past actually were non-Hodgkin's lymphomas, often of the anaplastic large-cell type.
4. ***Lymphocyte-rich classic Hodgkin's disease*** comprises 5%. In this type of HD, RS cells of the classic or lacunar type are observed, with a background infiltrate of lymphocytes. It requires immunohistochemical diagnosis. Some cases may have a nodular pattern. Clinically, the presentation and survival patterns are similar to those for mixed-cellularity Hodgkin's disease.
5. ***Nodular lymphocyte-predominant Hodgkin's disease*** constitutes 5%. In contrast to the other histological subtypes, the typical RS cells in nodular lymphocyte-predominant Hodgkin disease are not observed or appear infrequently. Instead, a variant of RS cells, the lymphocytic and histiocytic cells (L&H), or *popcorn cells* (their nuclei resemble an exploded kernel of corn), are seen within a background of inflammatory cells, predominantly benign lymphocytes. The L&H cells are positive for B-cell antigens, such as CD19 and CD20, but generally are negative for CD15 and CD30.

Treatment and Prognosis. It is now recognized that proper treatment of Hodgkin's disease can lead to long-term remission and even cure. Radiation therapy and combination chemotherapy have been clearly shown to be effective in the management of Hodgkin's disease. The most important prognostic determinants are the histologic type and the clinical stage of the disease. The lymphocyte predominant type has the most favorable prognosis, followed by nodular sclerosis, mixed cellularity and lymphocyte depletion, the least favorable. Localized (stage I) disease has a much better prognosis than disseminated (stage IV) disease. Patchefsky and his associates have reported that male gender, older age and systemic symptoms also are associated with poor prognosis. The five-year disease-specific survival for patients with stages I and II, III, and IV is 90%, 84%, and 65%, respectively.

Multiple Myeloma and other Plasma Cell Neoplasms

Multiple myeloma is the most common primary neoplasm of the skeletal system. The disease is a malignancy of plasma cells. Plasma cells are a subset of B-cells, which are the producers of humoral immunity factors termed antibodies. However, if malignant transformation occurs in a single plasma cell, its clones produce only a single type of immunoglobulin, and electrophoresis demonstrates a monoclonal peak corresponding to this particular immunoglobulin.

Pathogenesis. Multiple myeloma has been the prototype of monoclonal malignancies, in this case, of plasma cells; the

disease may result from a mutation of terminally differentiated B cells or even from early but committed B cells that manifest clinically as more differentiated plasma cells. The expression of multiple markers of different cell lineages (B and T) by plasma cells supports the possibility of either an aberrant expression of unexpected phenotypes, as in other malignancies, or a stem-cell precursor from which all hematopoietic cells arise.

No predisposing events appear to be important in the etiology of multiple myeloma. Some events that have been suggested include radiation exposure (in radiologists and radium-dial workers), occupational exposure (in agricultural, chemical, metallurgical, rubber plant, pulp, and paper workers and leather tanners), and chemical exposure to benzene, formaldehyde, hair dyes, paint sprays, and asbestos. None of these associations has proven to be statistically significant, and all have been contradicted by negative correlations. The initial report that survivors of the atomic bombings in Japan had an increased risk of developing myeloma has been refuted by longer follow-up.

Multiple studies have described the cytogenetics of myeloma. Although no karyotypic abnormalities are specific, frequent aberrations of chromosomes 1 and 14, the latter containing the heavy-chain immunoglobulin gene, have been noted. In addition, specific translocations have been described, including **t(11;14), t(14;18),** and **t(8;14).** Other chromosomal abnormalities include 6q-, 7q-, 5q-, **t(9;22)**, and 17p+. Abnormal expression of the bcl-2 protein has also been noted in patients without a t(14;18) translocation. Mutations of the ras oncogene and ***p53*** gene mutations have been reported, especially in patients with late disease. The ras mutation correlates with a low treatment response rate, and the p53 gene mutation has been noted in patients with extramedullary proliferation of plasma cells.

A variety of cytokines stimulate the growth of malignant plasma cells *in vitro*. Interleukin-6 (IL-6), considered the most important myeloma growth factor, binds to the IL-6 receptor on plasma cells, which is made up of an alpha chain (IL-6R) and a beta-transducer chain (gp130). IL-6 acts in concert with an extensive cytokine network (IL-1, IL-3, IL-7, IL-11, 6-colony-stimulating factor [CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF, sargramostim (Leukine)], and tumor-necrosis factor [TNF]) to promote the growth of malignant plasma cells. Other factors (alpha interferon [IFN-alfa], gamma interferon [IFN-gamma], and IL-4) appear to inhibit plasma-cell growth, and some of these cytokines may play a role in therapy.

Although myeloma is not an inherited disease, there have been numerous case reports of it in the same family. However, a case-control study revealed no significant increase in myeloma among relatives of patients with multiple myeloma, other hematologic malignancies, or other cancers.

Clinical Features. Multiple myeloma is a disease of older people. Most patients who receive the diagnosis are aged 60–65 years. Only 3–5% of patients with multiple myeloma are younger than 45 years. The disease is rare in children. Men appear to be at increased risk of multiple myeloma compared to women. The annual incidence per 100,000 population is 6.4 among white men and 4.1 among white women. Among black men and women, the frequency doubles to 12.7 and 10.0, respectively, per 100,000 population. This racial difference is not explained by socioeconomic or environmental factors and is presumably due to unknown genetic factors.

Multiple myeloma is a diffuse disease of the bone marrow. Almost 90% of patients with myeloma have osseous involvement. The predominant sites of involvement are within the axial skeleton and include the vertebral column, ribs, skull, pelvis, and femur bone. Most patients have either a number of lytic foci or diffuse demineralization at the time of diagnosis. The underlying pathology of multiple myeloma is expansion of a single line of plasma cells that replace normal bone marrow and produce monoclonal immunoglobulins.

The clinical presentation of multiple myeloma is quite variable. Bone pain, especially from compression fractures of vertebrae or ribs, is the most common symptom. Findings that suggest a diagnosis of multiple myeloma include lytic bone lesions, anemia, azotemia, hypercalcemia, and recurrent infections. However, approximately 20% of patients with multiple myeloma are free of symptoms and are diagnosed by chance.

Extramedullary plasmacytoma. Patients with isolated plasma cell tumors of soft tissues, most commonly occurring in the tonsils, nasopharynx, or paranasal sinuses, should have skeletal X-rays and bone marrow biopsy. If these tests are negative, the patient has extramedullary plasmacytoma. About 25% of patients have serum and/or urine M-protein; this should disappear following adequate irradiation.

Macroglobulinemia. Macroglobulinemia is a proliferation of plasmacytoid lymphocytes secreting an IgM-protein. Patients often have lymphadenopathy and hepato-splenomegaly, but bony lesions are uncommon. There is no universally accepted staging system.

Oral Manifestations. Involvement of the jaws in cases of multiple myeloma has been reported on many occasions. Bruce and Royer studied a series of patients with this disease and concluded that the mandible is far more frequently involved than the maxilla, since nearly 95% of their cases evidenced mandibular lesions. Furthermore, the ramus, angle and molar region of the mandible were the most frequent sites of the lesions. These correspond to the most active hematopoietic areas. Conversely, in the Mayo series, 20 of the 28 cases with jaw lesions had maxillary involvement. Interestingly, two of the patients were only in the third decade of life. Cataldo and Meyer have confirmed the high frequency of jaw involvement in a series of 44 cases of multiple myeloma in which 70% of the patients who had jaw radiographs taken had maxillary or mandibular lesions.

Other signs and symptoms of jaw involvement include pain, swelling, expansion of the jaw, numbness and mobility of teeth. In addition, extraosseous lesions occur which may resemble gingival enlargements or epulides. Extension of the

disease to other sites outside the skeleton such as lymph nodes, skin and viscera also occurs.

It is impossible to compute the overall incidence of jaw involvement in patients with multiple myeloma, since most patients suffering from this disease do not receive a thorough oral examination with radiographs. Nevertheless, studies indicate that the incidence may be somewhat higher than formerly believed because many such lesions may be asymptomatic.

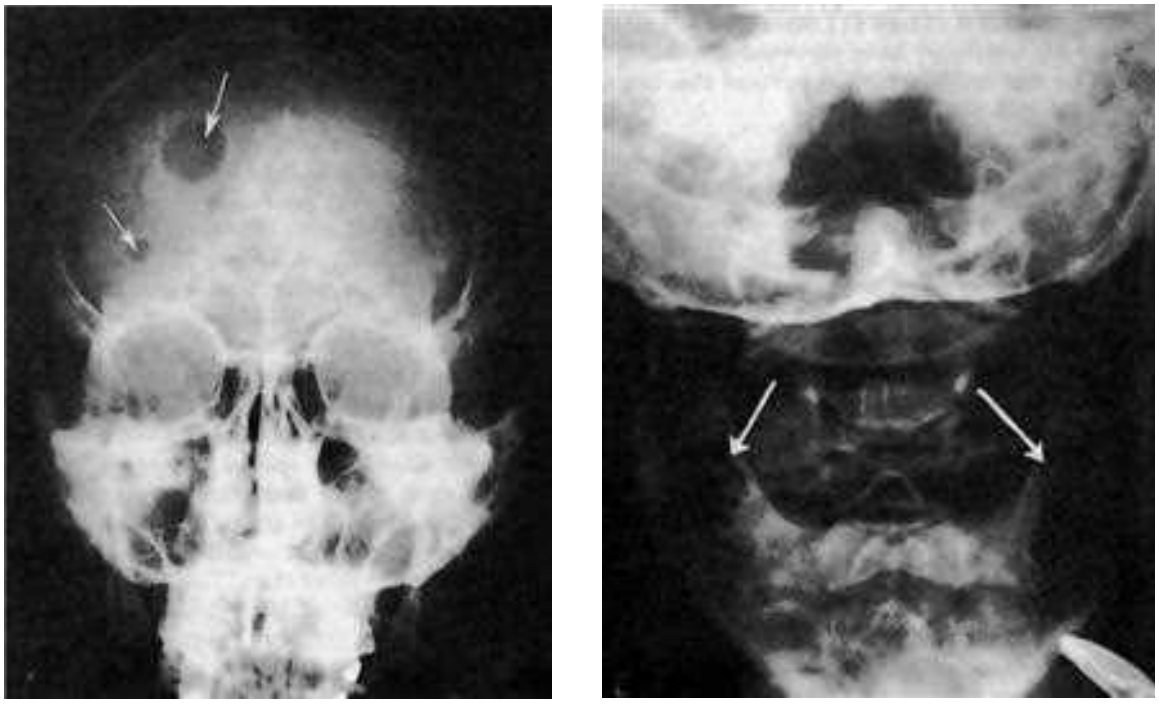
Radiographic Features. Radiographic examination will usually reveal numerous sharply punched-out areas in a variety of bones, which may include the vertebrae, ribs, skull, jaws and ends of long bones (Fig. 2-92). Note that these are all sites of active hematopoiesis. These lesions may vary in size from a few millimeters to a centimeter or more in diameter, but there is usually no peripheral bone reaction. Diffuse destructive lesions of bone may also occur.

Laboratory Features. Certain laboratory findings are of considerable importance in establishing the diagnosis of multiple myeloma. Many patients, but not all, exhibit a hyperglobulinemia **(monoclonal gammopathy)** resulting in a reversal of the serum albumin-globulin ratio and an increase in total serum protein to a level of 8–16 gm%. In addition, the presence of Bence Jones protein in the urine is noted in 60–85% of myeloma patients. This is an unusual protein which coagulates when the urine is heated to 40°–60° C and then disappears when the urine is boiled. It reappears as urine is cooled. Occasionally, Bence Jones protein is found in the urine of patients with diseases other than multiple myeloma, such as leukemia and polycythemia. Furthermore, its absence does not rule out the presence of multiple myeloma. Anemia is also a common finding in multiple myeloma. Kyle has thoroughly discussed the laboratory findings in the Mayo clinic cases.

The diagnostic laboratory finding in myeloma is monoclonal hypergammaglobulinemia. IgG myeloma is the most common, followed by IgA myeloma. As a result of bone destruction, hypercalcemia is a common manifestation and can be difficult to manage. Other laboratory abnormalities include hyperuricemia (resulting from elevated cell turnover), elevated sedimentation rate, and increased levels of alkaline phosphatase.

Monoclonal gammopathy of undetermined significance (MGUS). Patients with MGUS have an M-protein in the serum without findings of multiple myeloma, macroglobulinemia, amyloidosis, or lymphoma and with fewer than 10% plasma cells in the bone marrow. These patients are asymptomatic and should not be treated. They must, however, be followed carefully since about 2% per year will progress to develop one of the symptomatic B-cell neoplasms and may then require therapy.

Histologic Features. The usual lesion is composed of sheets of closely packed cells resembling plasma cells. These are round or ovoid cells with eccentrically placed nuclei exhibiting chromatin clumping in a 'cartwheel' or 'checkerboard' pattern (Figs. 2-93, 2-94). Two nuclei within a single cell membrane are seen occasionally, but mitotic activity is not great. A perinuclear halo may be present. Russell bodies are common



A B

Figure 2-92. Multiple myeloma.
(A) Numerous sharply punched-out areas are found in the skull film. **(B)** The anteroposterior radiograph of another patient shows multiple bilateral radiolucent jaw lesions *(B, Courtesy of Dr Clifford Brown)*.

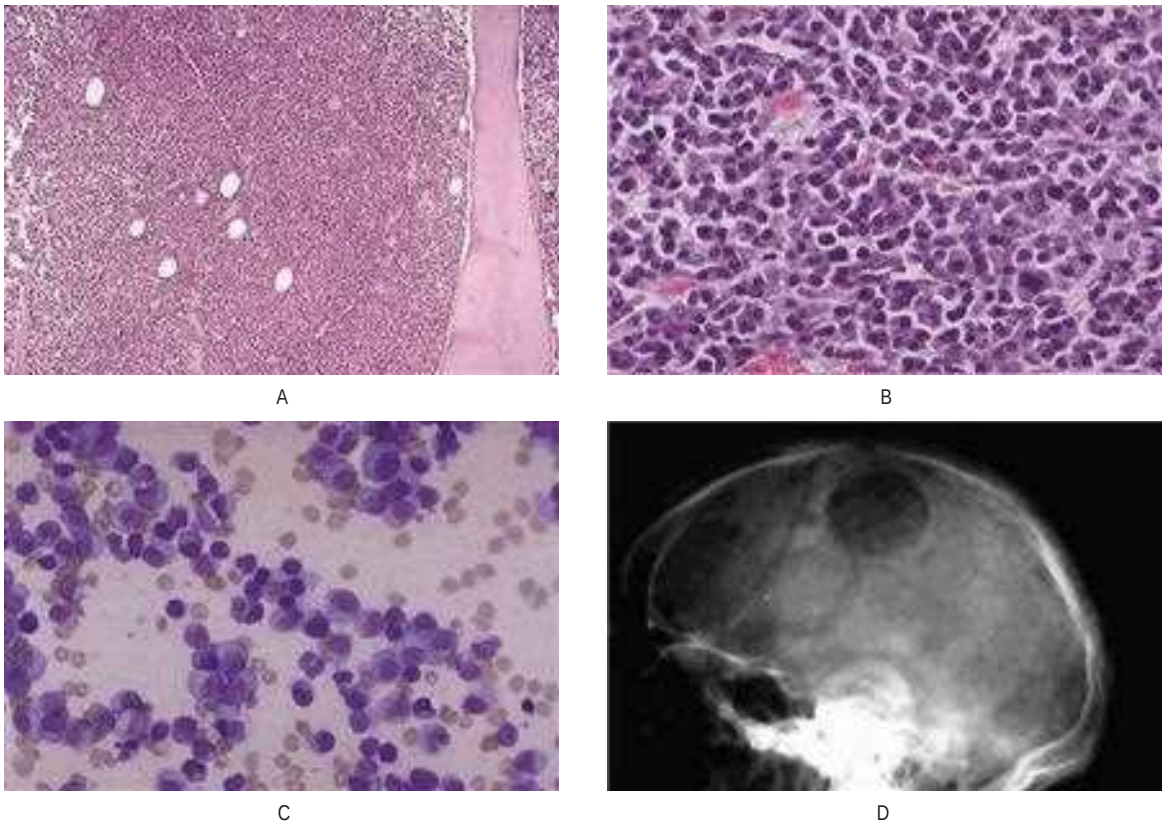


Figure 2-93. Multiple myeloma.
(A) At low power, the abnormal plasma cells of multiple myeloma fill the marrow. **(B)** At medium power, the plasma cells of multiple myeloma here are very similar to normal plasma cells, but they may also be poorly differentiated. Usually, the plasma cells are differentiated enough to retain the function of immunoglobulin production. Thus, myelomas can be detected by an immunoglobulin 'spike' on protein electrophoresis, or the presence of Bence Jones proteins (light chains) in the urine. Immunoelectrophoresis characterizes the type of monoclonal immunoglobulin being produced. **(C)** Here is a smear of bone marrow aspirate from a patient with multiple myeloma. Note that there are numerous plasma cells with eccentric nuclei and a perinuclear halo of clearer cytoplasm. **(D)** The rounded 'punched-out' lesions of multiple myeloma appear as lucent areas with this skull radiograph.

as in chronic inflammatory lesions with numerous typical plasma cells, although it was once thought that their absence in myeloma was noteworthy.

Chen has studied the ultrastructure of a mandibular plasma cell myeloma. He noted numerous mitochondria in a perinuclear distribution as well as prominent Golgi complexes. The latter are most likely responsible for the perinuclear halo which is observed by light microscopy. Wright and his coworkers have discussed the diagnostic value of the immunoperoxidase technique in distinguishing between inflammatory and neoplastic lesions of the jaws which are composed of plasma cells. Inflammatory plasma cell lesions are characterized by polyclonal staining, whereas monoclonal staining is indicative of neoplasia.

Treatment and Prognosis. The role of prophylactic bisphosphonate therapy in the reduction of osteoclastic activity and bone mineralization maintenance is under study.

Treatment choice is determined largely by the age and general health of the patient. Concurrent with the management of specific complications, chemotherapy should be instituted promptly to reduce the number of malignant plasma cells. However, despite the development of many different chemotherapeutic regimens, there has been little improvement in outcome during the past 25 years. Only 5–10% of patients live longer than 10 years. Infection, anemia and kidney failure are the most common immediate causes of death.

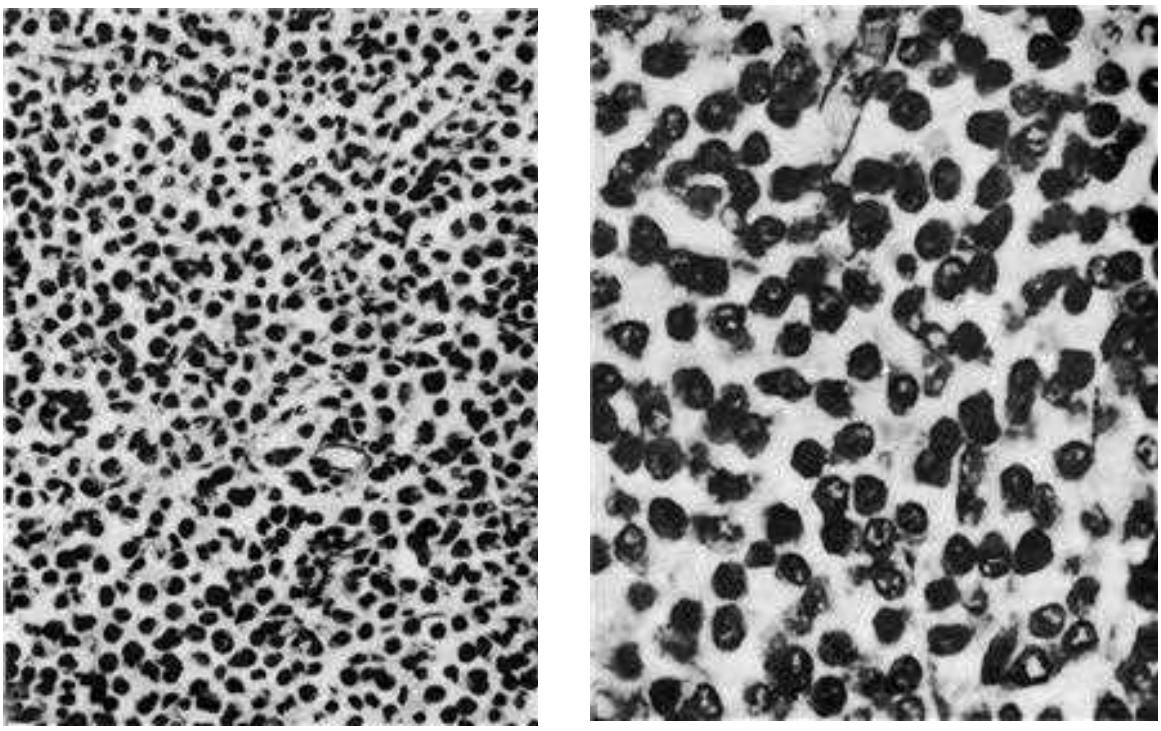
Extramedullary plasmacytoma is a highly curable disease, with progression-free survivals ranging from 70–87% at 10–14 years using radiation therapy (with or without previous resection).

Solitary Plasma Cell Myeloma
(Plasmacytoma)

A plasmacytoma is a discrete, solitary mass of neoplastic monoclonal plasma cells in either bone marrow or a soft tissue site. Solitary plasmacytomas can be divided into two groups according to location:

- Plasmacytoma of the skeletal system (solitary bone plasmacytoma).
- Soft tissue plasmacytoma (extramedullary plasmacytoma).

Clinical Features. The mean age for solitary bone plasmacytoma and soft tissue plasmacytoma is 55 years (range, 50–60 years), which is 10 years younger than multiple myeloma. Different studies show two-thirds of patients were men in plasmacytoma and three-fourths of soft tissue plasmacytoma



A B

Figure 2-94. Multiple myeloma.
(A) The uniform distribution of cells with very little stroma is characteristic of myeloma. **(B)**, Under high magnification, the resemblance of myeloma cells to inflammatory plasma cells is obvious.

cases were males. Solitary bone plasmacytoma may involve any bone, but it has a predisposition for the red marrow containing axial skeleton. Spinal disease is observed in 34–72% of cases. The thoracic vertebrae are most commonly involved, followed by lumbar, sacral, and cervical vertebrae. The rib, sternum, clavicle, or scapula is involved in 20% of cases.

Cytogenetic studies of solitary plasmacytoma have shown recurrent losses in chromosome **13,** chromosome arm **1p,** and chromosome arm **14q** and gains in chromosome arms **19p, 9q,** and **1q.** Interleukin 6 is still considered the principal growth factor in the progression of plasma cell disorders (Dimopoulos, 2000). The specific role of surface markers, adhesion molecules, and angiogenesis in solitary plasmacytoma need to be studied further. Solitary plasmacytoma could be considered an intermediate step in the evolution from monoclonal gammopathy of undetermined significance to multiple myeloma.

The most common symptom is pain at the site of the skeletal lesion due to bone destruction by the infiltrating plasma cells. In other cases, solitary bone plasmacytoma may be discovered during radiographic studies for another condition, or the patient presents with a painless swelling of the sternum, rib, or other bone.

Patients with vertebral involvement may also have evidence of spinal cord or nerve root compression. A few patients present with symptoms and signs of demyelinating polyneuropathy. Compression fractures of the thoracic and lumbar vertebral bodies usually result in severe spasms and back pain.

Although soft tissue plasmacytoma can occur in any site, 90% of tumors develop in the head and neck area, especially in the aerodigestive tract, without apparent primary bone involvement. Approximately 80% of cases involve the paranasal sinuses, pharynx, nasal cavity, or gums and oral mucosa. Soft tissue plasmacytoma presents as a mass growing in the aerodigestive tract (80% of the cases) with spread to lymph nodes, although other sites are affected as well. Because of the usual presentation as submucosal lesions of the upper aerodigestive tract, swelling, headache, nasal discharge, epistaxis, nasal obstruction, sore throat, hoarseness, dysphonia, dysphagia, dyspnea, epigastric pain, and hemoptysis are common symptoms. Symptoms from plasmacytomas in other tissues are associated with the site of the tumor, tumor size, and to compression and/or involvement of the surrounding structures. The etiology is thought to be due to long-term stimulation by inhaled irritants or viral infection.

Oral Manifestations. Occasional cases of solitary plasma cell myeloma of bone have been reported in the jaws, both maxilla and mandible. Caution must be exercised, however, in diagnosing a lesion of the jaws as solitary myeloma, since the finding of large numbers of plasma cells in granulomas associated with dental infection is common. It is in such cases that immunoperoxidase techniques may be of diagnostic value.

Extramedullary plasmacytoma may be situated on the gingiva, palate, floor of the mouth, tongue, tonsils and pillars

as well as the nasal cavity, nasopharynx and paranasal sinuses. The lesions are described as sessile or polypoid reddish masses in the mucous membranes, which become lobulated as they enlarge, but do not tend to ulcerate.

The nature of the extramedullary plasmacytoma is as obscure as that of the other forms of plasma cell lesions. It is undoubtedly different from the common plasma cell-containing granulomas and polyps which are commonly found in the upper air passages and oral cavity. Yet, though the majority of the reported cases of plasma cell tumors in this location remain localized lesions in the soft tissue, metastases have occurred to lymph nodes, bones and other sites. In a discussion of this disease by Kotner and Wang, it was pointed out that only 10–20% of patients develop regional lymph node metastases.

Corwin and Lindberg studied 12 patients with extramedullary plasmacytoma. Two of the 12 developed multiple myeloma. Thus these tumors should be regarded as serious and potentially fatal, although they have a much more favorable prognosis than multiple myeloma.

Radiographic Features. Radiographic examination of the bones in solitary plasma cell myeloma reveals one of the two types of lesions. One type is a purely destructive intramedullary lesion suggestive of metastatic carcinoma. The other type of lesion is an expansile one suggestive of a giant cell tumor. There is nothing pathognomonic or even characteristic of the radiographic picture of solitary myeloma.

Computed tomographic scan is used to depict the extent of the infiltrating lesion more clearly, but MRI is the best imaging study. The appearance of solitary bone plasmacytoma on MRI resembles that of other primary or secondary malignancies that produce lytic destruction of the bone with a focal area of bone marrow replacement, but MRI also may show unanticipated foci of bone marrow involvement.

Laboratory Features. Laboratory findings are interesting because few (24–72%) of the patients exhibit Bence Jones protein in the urine or serum. With disease progression, monoclonal protein may be found in the serum or urine in some patients. Furthermore, the characteristic hyperglobulinemia and anemia, so characteristic of multiple myeloma, are absent in solitary myeloma and extramedullary plasmacytoma.

Histologic Features. It has been stated previously that the histologic features of the solitary and multiple myeloma are similar. In the well-differentiated lesions of multiple myeloma it is impossible to distinguish between the two. The extramedullary plasmacytoma is also microscopically identical with the solitary myeloma. Nevertheless some cases of multiple myeloma present a variegated histologic picture which is not seen in solitary myeloma or the extramedullary plasmacytoma.

Treatment and Prognosis. Definitive local radiotherapy is the treatment of choice for solitary bone plasmacytoma. Treatment fields should be designed to encompass all disease shown by MRI or CT scanning and should include a margin of normal tissue.

The accepted treatment for extramedullary plasmacytoma is radiotherapy. When a lesion can be completely resected, surgery provides the same results as radiotherapy. Combined therapy (surgery and radiotherapy) also is an accepted treatment depending on the resectability of the lesion.

BENIGN TUMORS OF MUSCLE TISSUE ORIGIN

Leiomyoma

The leiomyoma is a benign tumor derived from smooth muscle and is found in a variety of anatomic sites, including the skin, subcutaneous tissues and the oral cavity. Most leiomyomas occur in the uterus, the so-called fibroids. Under the microscope, they are nearly identical in every site. Clinically, they are soft tissue tumors that present with pain. They are uncommon in the oral cavity probably because of the general absence of smooth muscle there except in blood vessel walls and, occasionally, in the circumvallate papillae of the tongue.

Clinical Features. The majority of cases of leiomyoma have occurred on the posterior portion of the tongue, although others have been found on the palate, cheeks, gingiva, lips and salivary glands. Of the reported cases, the majority of oral leiomyomas occur in adults in the middle decades of life, over 65% being found in patients older than 30 years of age, although cases are described in young children in the first decade.

The oral leiomyoma is a slow-growing, painless lesion which is superficial and often pedunculated. The presenting symptoms of some of the patients in the reported cases have been 'sore throat' or 'tumor in the throat'. The tumor does not ulcerate and resembles the normal mucosa in color and texture.

A **central leiomyoma** of the jaw is also known to occur but is exceedingly rare. A case in the mandible, with ultrastructural confirmation, has been reported by Goldblatt and Edesess, who have also reviewed the literature on the central lesions of bone.

Histologic Features. The leiomyoma is composed of interlacing bundles of smooth muscle fibers interspersed by varying amounts of fibrous connective tissue. The muscle nuclei are typically spindle-shaped with blunt ends and quite vesicular. The bundles of fibers appear to form whorls because of their fascicular arrangement in varying planes. Intracytoplasmic myofibrils are present and can be demonstrated by phosphotungstic acid-hematoxylin special stain. Masson's trichrome stain is also commonly used to differentiate between collagen and smooth muscle. Leiomyoma cells are positive for smooth muscle markers like desmin, vimentin, actin, myosin and alpha smooth muscle actin.

Treatment and Prognosis. This smooth muscle neoplasm is best treated by conservative surgical excision, since it does not tend to recur or become malignant.

Angiomyoma
(Vascular leiomyoma, angioleiomyoma)

Leiomyomas and angiomyomas have commonly been treated as two forms of the same basic lesion in the past and reported

together as an entity. Thus, some lesions are quite vascular, being composed of large numbers of blood vessels of an atypical nature with disoriented smooth muscle layers (the angiomyoma), while others are relatively avascular. The suggestion has even been made that there may be a progression of lesions: hemangioma, angioma with much nonstriated muscle, vascular leiomyoma, leiomyoma with many vessels and solid leiomyoma. Thus, it has been proposed that the vascular leiomyoma may be only a stage in the continuous process of smooth muscle proliferation. Most investigators nowadays believe that the angiomyoma probably represents a hamartomatous malformation, while the solid leiomyoma represents a true neoplasm and that, therefore, these two entities should be clearly separated. This has been discussed in detail by Damm and Neville. Since the two lesions have been combined in the literature, separation of their clinical characteristics at this time is not possible, although Reichart and Reznik-Schuler have reported the ultrastructure of an oral angiomyoma and discussed some of the cases classified under this term.

Rhabdomyoma

The term rhabdomyoma was introduced by Zenker (1864) to indicate a benign tumour showing skeletal muscle cell with varying degree of differentiation and maturity. Rhabdomyomas are currently defined as benign neoplasm of striated muscle tissue, consisting usually of polygonal frequently vacuolated glycogen containing cells with a fine granular deeply acidophilic cytoplasm resembling myofibril in cut section.

The term 'rhabdomyoma' was used for benign tumor, arising from the cardiac muscle, often associated with a hamartoma complex, including sebaceous adenomas, tuberous sclerosis, and hamartomas of the kidney and other organs. Seventy to 90% of extra cardiac rhabdomyomas are found in the head and neck region but it is still a rare neoplasm of the maxillofacial region. They are subdivided into adult, fetal and genital histological subtypes.

The etiology is unknown. However, clonal balanced translocation (reciprocal) has been found in chromosomes 15 and 17 in adult rhabdomyoma tumors of head and neck.

Clinical Features. The adult form of rhabdomyoma occurs primarily in the middle-aged in the 16–82 years old (mean age 52 years). There is a marked male predominance of almost 5:1. The most frequent head and neck sites of involvement are the pharynx and the oral cavity, although laryngeal lesions have also been reported. Within the mouth, the oral floor is most often affected, pharyngeal lesions occur most frequently in the base of the tongue and the soft palate.

Fetal rhabdomyoma usually occurs in newborns and young children, but the lesion has been reported in patients as old as 50 years of age. This type also has a strong male predilection. The most common sites are post- or, preauricular region, or face, followed by nasopharynx but not in the mouth.

Both tumor types present as a nodule or submucosal mass which can become several centimeters in size. Multinodular tumors have been described, with two or more discrete nodules closely adjacent to one another. Rarely, separate tumors may be found at different anatomic sites.

Histologic Features. The tumor is composed of large, round cells that have a granular, eosinophilic vacuolated cytoplasm and show irregular cross-striations. This cytoplasm is rich in glycogen and glycoprotein. A fibrous stroma is present and mitotic activity is extremely low. Many cases demonstrate occasional degeneration vacuoles or clear spaces between the tumor cells.

The fetal rhabdomyoma is comprised of less mature, somewhat pleomorphic, polygonal muscle cells admixed with spindle-shaped cells. This type is typically more cellular than the adult type and often has a myxoid stroma. Mitotic activity is minimal but the more pleomorphic examples can be mistaken for rhabdomyosarcoma.

Cross-striations and crystalline structures are more readily identified with the phosphotungstic acid-hematoxylin (PTAH) stain, and oil red O staining will often reveal intracellular lipid. Lesional cells are immunoreactive with myoglobin, desmin and vimentin. Muscle specific actin, myoglobin may show focal positivity.

Treatment and Prognosis. Both variants of rhabdomyoma are treated by conservative surgical excision. Recurrence has been reported but is uncommon. Malignant transformation has not been reported.

Granular Cell Myoblastoma

(Myoblastic myoma, granular cell tumor, granular cell schwannoma)

It is not clear whether or not granular cell tumor is a true neoplasm, a developmental anomaly, or a trauma-induced proliferation. The original interpretation of the tumor being of muscle origin (granular cell myoblastoma) has been abandoned. The basic cell of origin is now thought to be neural, although past reports frequently indicated an origin from striated muscle, or less frequently an origin from histiocytes, fibroblasts or pericytes. The tumor is widely distributed throughout the body, but more than half of all cases occur in the oral cavity. The other head and neck site likely to be involved is the larynx.

Clinical Features. The lesion is typically diagnosed between the ages of 30 and 60, but it can arise at any age. There is no gender predilection for oral cases, but overall almost twice as many cases are diagnosed in women as in men.

More than one third of all granular cell tumors occur on the lingual dorsum, usually as a sessile, painless, somewhat firm, immovable nodule less than 1.5 cm in greatest diameter. Lesions often demonstrate pallor or yellowish discoloration and typically have a smooth surface.

Other oral and pharyngeal sites of involvement include the soft palate, uvula, labial mucosa, oral floor and gingiva. As many as 15% of patients will have granular cell tumors of multiple anatomic sites, with as many as 50 individual lesions in one patient.

Histologic Features. The granular cells are large polygonal, oval or bipolar cell of about 20–40 μ in diameter with abundant, fine or coarsely granular eosinophilic cytoplasm, and a small, pale-staining or vesicular nucleus eccentrically located in the cell. The cell membrane is moderately distinct (Fig. 2-95).

Granular cells often occur in ribbons separated by fibrous septa, giving the appearance of infiltrating or 'invading' into underlying tissues, especially muscle, with the bipolar shape being more frequently noted at the leading edge. The cells may also appear to be streaming off from or metaplastically arising from underlying muscle fibers. Older lesions tend to become desmoplastic with a few scattered nests of granular cells in a densely fibrotic background. Granular cells demonstrating nuclear enlargement, hyperchromatism and pleomorphism, or with mitotic activity or increased cellularity, are elements of the malignant variant of this tumor.

Ultrastructural studies have described the cytoplasmic granules as autophagic vacuoles containing cellular debris, including mitochondria and fragmented endoplasmic reticulum, as well as myelin. Background stroma is minimal.

Granular cells are positive for S100 protein, neuron-specific enolase (NSE), laminin and myelin basic proteins. Staining is negative for neurofilament proteins and glial fibrillary acidic protein (GFAP). Granules are PAS positive and diastase resistant.

It is particularly common for the surface of the lesion to be covered by a layer of stratified squamous epithelium exhibiting remarkable pseudoepitheliomatous hyperplasia which has been confused with epidermoid carcinoma.

Treatment and Prognosis. Conservative excision is the treatment of choice for granular cell tumor. Recurrence is seen in fewer than 7% of cases thus treated, even if granular cells extend beyond the surgical margins of the biopsy sample. A few reported metastasizing granular cell tumors have appeared to be histologically benign, and for this reason, tumors that recur, grow rapidly or reach a size greater than 5 cm should be viewed with grave suspicion.

Congenital Epulis of the Newborn

Congenital granular cell lesion or 'congenital epulis' is a rare lesion of the newborn. It is also known as **Neumann's tumor,** is benign in nature, mostly occurs as a single tumor but rarely as multiple. The histogenesis and natural clinical history of the lesion remain obscure. Even with the advent of modern histopathological techniques, it has not been possible to depict specific cellular features unique to this lesion.

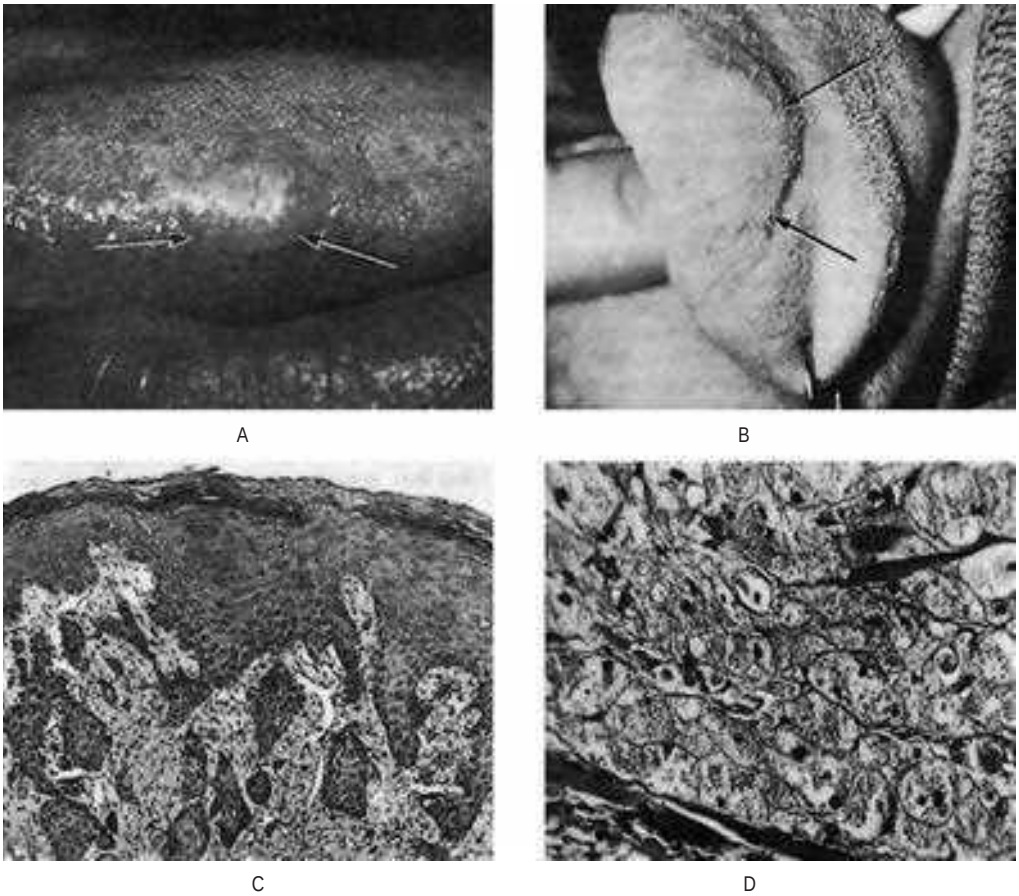


Figure 2-95. Granular cell myoblastoma.
(A) The lesion appears as a small nodular growth on the lateral border of the tongue. **(B)** The tumor may become quite large. **(C)** The low-power photomicrograph illustrates the remarkable overlying pseudoepitheliomatous hyperplasia, which may be mistaken for epidermoid carcinoma. **(D)** Under higher magnification the granular nature of the cells comprising the lesion can be seen. *(B, Courtesy of Dr Ronald Vincent)*.

A B

Figure 2-96. Congenital epulis of the newborn.
The nodular lesion of the maxilla **(A)**, present at birth, was composed of large, closely packed cells with an eosinophilic, granular cytoplasm **(B)**.

The congenital epulis of the newborn bears an unusual resemblance to the granular cell myoblastoma and is considered by some persons to be the same lesion. Nevertheless, there are certain features of the congenital epulis which are distinctly different from the granular cell myoblastoma, and as has been suggested by Custer and Fust, it is most likely a separate pathologic entity.

The congenital epulis is present at birth, as the name implies, and in this regard is distinctly different from the granular cell myoblastoma. It has been suggested that a protuberant mass of the maxilla, the typical site of the congenital epulis, would be more obvious than a lesion in the substance of the tongue, the usual site of the granular cell tumor, and thus would be apt to be discovered at a far earlier age than the tongue lesion. On this basis, it is conceivable that the two tumors are similar in nature, although actually the maxilla has been found to be the most unusual site for the occurrence of a granular cell tumor.

A number of workers have suggested that these congenital epulides are malformations of the dental blastema and should be regarded as a type of embryonal hamartoma and not a true neoplasm. The basis for such a belief is the presence of numerous epithelial rests in some sections of these tumors. Remember, however, that such epithelial inclusions are remnants of the dental lamina and may be found normally in most jaws of infants. Their occurrence in the congenital epulis is more likely to be coincidental than associated with the development of the lesion. Other theories of origin include the fibroblastic, histiocytic, myogenic and neurogenic. These have been discussed in a centennial review of the congenital epulis by Fuhr and Krogh.

Clinical Features. This tumor is present at birth and is located on the maxillary or mandibular gingiva, although it is somewhat more common on the maxilla than the mandible, by a ratio of approximately 2:1.

It is usually a pedunculated lesion found in the incisor region, apparently arising on the crest of the alveolar ridge or process (Fig. 2-96A). It may vary considerably in size from just a few millimeters in diameter to several centimeters. Of 40 cases reported in the literature and reviewed by Custer and Fust, only three occurred in males. Of the 113 cases reported since the original description of a congenial epulis by Neumann in 1871, 80.5% were females, 10.6% were males and 8.9% were of unstated sex, according to the review of Fuhr and Krogh.

Histologic Features. The congenital epulis is histologically similar to the granular cell tumor, although pseudoepitheliomatous hyperplasia does not occur in the former lesion. Thus sheets of large, closely packed cells showing fine, granular, eosinophilic cytoplasm comprise the tumor mass (Fig. 2-96B). Neither mitoses nor cross-striations are visible, but capillaries are numerous. In fact, the vascular component is much more prominent than in the granular cell tumor. Study by means of special staining techniques has not been highly informative.

An electron microscopic study of a congenital epulis by Kay and his associates revealed junctional complexes between some of the granular cells which suggested that they might be of epithelial origin, although the studies were not entirely conclusive. However, Lack and his associates reported that their ultrastructural findings strongly supported a mesenchymal histogenesis. In addition, their tissue assay for estrogen receptors was negative, but considering the marked predilection of the lesion for females, a hormonal factor could not be ruled out in its development. Congenital epulis is negative for S100 and other markers found in the granular cell tumor.

Treatment. The treatment for the congenital epulis is surgical excision with little possibility of recurrence. However, Welbury has suggested, on the basis of a few scattered reports, that the natural history of this lesion is one of spontaneous regression and that no treatment is required unless dictated by feeding or respiratory problems.

MALIGNANT TUMORS OF MUSCLE TISSUE ORIGIN

Leiomyosarcoma

The leiomyosarcoma is a malignant tumor of smooth muscle origin. It is very rare in the oral cavity and whether it develops through malignant transformation of a leiomyoma or de novo is not known. It probably arises at these sites from smooth

muscle cells, especially those found in blood vessel walls, and from undifferentiated mesenchymal cells.

Clinical Features. Leiomyosarcoma typically presents as painful, lobulated, fixed mass of the submucosal tissues in a middle-aged or older individual. It is exceedingly rare in children. Lesions are usually less than 2 cm in diameter at diagnosis and are slow-growing, but secondary ulceration of the mucosal surface has been reported. The cheek and floor of mouth were the most common sites. No gender predilection was apparent in these cases.

Histologic Features. Leiomyosarcoma is composed of fascicles of interlacing spindle-shaped cells with abundant eosinophilic cytoplasm and moderately large, centrally located, cigar-shaped or blunt-ended nuclei, often with mild atypia. Cellularity and cellular differentiation can vary considerably between tumors and between different areas of the same tumor. The well-differentiated lesion shows the spindled cells streaming or interweaving in fascicles in a fashion similar to that seen in leiomyoma. Nuclear palisading may be seen in several areas of the tumor, ischemic areas show stromal fibrosis and hyalinization (Fig. 2-97).

The epithelioid variant, called **malignant leiomyoblastoma** or **epithelioid leiomyosarcoma,** is most prevalent in the gastrointestinal and genitourinary tracts and has rarely been reported in oral or pharyngeal locations.

Treatment and Prognosis. Radical surgery is the treatment of choice for leiomyosarcoma, with adjunctive chemotherapy or radiotherapy used occasionally. The prognosis is poor, with numerous recurrences and distant metastases. Overall five-year survival is approximately 35–50%.

Intracellular myofibrils are readily discerned with the Masson trichrome stain, longitudinal striations of myofibrils may be seen within lesional cells with the PTAH stain and reticulin staining of well-differentiated lesions will demonstrate a delicate meshwork of reticulin fibers surrounding individual tumor cells (or clusters of tumor cells, in the case of epithelioid lesions). Well differentiated lesions are strongly positive for desmin, and alpha smooth muscle actin. Glycogen granules can be demonstrated with PAS staining.

The presence of mitoses is a hallmark of malignancy (at least 1 mitotic figure per 10 high power fields), lesions with 5 or more mitotic figures per 10 high-power fields should definitely be considered malignant.

Epithelioid leiomyosarcoma demonstrates numerous rounded epithelioid cells with either eosinophilic or clear cytoplasm. These cells seldom display obvious myoblastic differentiation and are easily demonstrated with the PAS-diastase reaction; electron microscopy will usually show the classic features of leiomyoblasts.

The study done by Wang R et al. suggest that **13q14–q21** loss and **5p14** gain at diagnosis could be used to identify patients with leiomyosarcoma who are likely to have a shorter survival time and who might benefit from early treatment intensification.

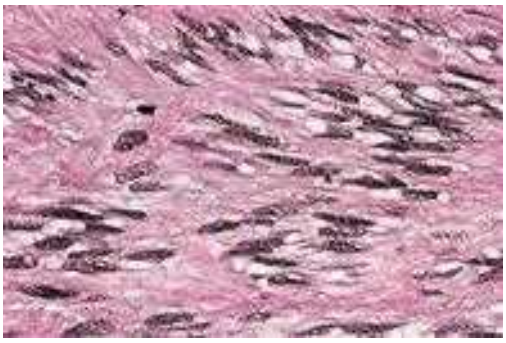


Figure 2-97. Leiomyosarcoma of oral cavity.
Note the prominent cytoplasmic vacuoles indenting to the nuclear poles *(Courtesy of Dr Juan Rosai)*.

Rhabdomyosarcoma

The rhabdomyosarcoma, the malignant tumor of striated muscle, is a relatively uncommon tumor in the oral cavity. According to Rubin, it is derived from primitive mesenchyme that retained capacity for skeletal muscle differentiation. The first published example of rhabdomyosarcoma was probably a tongue lesion reported in 1854.

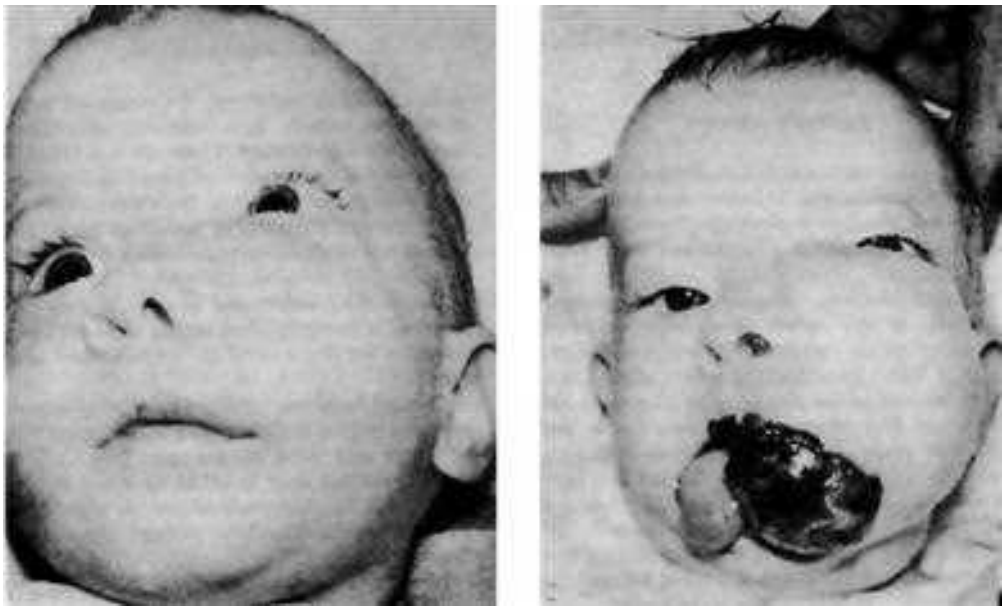
There are four separate types of rhabdomyosarcoma based on histologic appearance, and many of the clinical features are quite characteristic of certain of these. The four forms of rhabdomyosarcoma are:

- Pleomorphic
- Alveolar
- Embryonal
- Botryoid.

The embryonal form of rhabdomyosarcoma is recognized as having a marked predilection for occurrence in the head and neck area.

Clinical Features

Embryonal rhabdomyosarcoma. This is the most common subtype observed in children, accounting for 60–70% of all rhabdomyosarcoma cases in this age group. These tumors can occur at any site, but they are most commonly observed either in the genitourinary region or the head and neck region. They occur more commonly in the head and neck area than any of the other forms. Stobbe and Dargeon have pointed out that this neoplasm arises chiefly from the orbital, facial, and cervical musculature. Of 15 cases reported by Stobbe and Dargeon, the sites of occurrence included the orbit and inner canthus, the tonsil, soft palate, mastoid, internal ear and parotid, zygoma, and temporal and cervical regions. The average age of this group of patients was six years, ranging from 16 months to 16 years, with no gender predilection. In another review of 37 cases of this tumor by Moore and Grossi, the cheek, mandible and gingiva were found to be additional sites of occurrence. The youngest patient in this series was seven weeks, although there is one case on record of an infant born with an embryonal



A B

Figure 2-98. Embryonal rhabdomyosarcoma.
The rapidity of growth of this type of neoplasm can be judged by the fact that the two illustrations of this lesion, originating in the buccal mucosa, were taken only 14 days apart.

rhabdomyosarcoma of the floor of the mouth. In a series of 48 patients with embryonal rhabdomyosarcoma reported by Lawrence and his associates, the ages at diagnosis ranged from 16 days to 14 years, with a mean of five years. Finally, a series of 11 cases of embryonal rhabdomyosarcoma of the oral soft tissues have been reported by O'Day and his associates. The age of these patients ranged between 2 and 41 years of age, with a mean of 16 years. Of these oral tumors, four were in the soft palate, three in the cheek and one each in the upper and lower labial folds, lower buccal fold and lateral aspect of the tongue (Fig. 2-98).

Botryoid rhabdomyosarcoma (sarcoma botryoides) has been long recognized as a malignant tumor of the vagina, prostate, and base of the bladder in young children. Today, it is generally accepted as a variant of embryonal rhabdomyosarcoma and has been reported also involving the maxillary sinus, nasopharynx, common bile duct and middle ear. This tumor accounts for 10% of all rhabdomyosarcoma cases. It was formerly separated out as an entity because of its unusual clinical growth pattern.

Alveolar rhabdomyosarcoma. This subtype making up about 20% of all rhabdomyosarcomas in an analysis of 110 cases by Enzinger and Shiraki, is reported to occur much earlier in life, generally between 10 and 20 years of age with a median of 15 years. However, the range in this group was five months to 58 years. While the majority of cases of this type also occurred in the extremities, approximately 18% were found in the head and neck region.

Pleomorphic rhabdomyosarcoma (least common of all rhabdomyosarcoma) is a form of the tumor which, according to Patton and Horn, occurs more frequently in the extremities than in other sites and is generally seen in older individuals. In a series of 19 cases reported by these authors, the average age was 53 years.

The chief presenting complaint of the patient with rhabdomyosarcoma, generally irrespective of the histologic type, is usually swelling, but pain may be present if there is nerve involvement. Depending upon the site of the lesion, the following phenomena may be recognized: divergence of an eye, abnormal phonation, dysphagia, cough, aural discharge or deviation of the jaw. The lesions are occasionally ulcerated and may invade underlying bone and develop distant metastases. The most common site of presentation is head and neck region (35 %).

In embryonal rhabdomyosarcoma, the loss of heterozygosity of chromosome **11p15** was identified and in alveolar type unique translocation occurs between the **FKHR** gene on chromosome **13** and either the **PAX3** gene on chromosome **2** (70%) or the **PAX7** gene on chromosome **1** (30%). Individuals with the **PAX7** translocation are younger and may have longer event-free survival than those with the **PAX3** translocation (Marcus KC, 2001).

Histologic Features

Embryonal rhabdomyosarcoma has been described by O'Day and his coworkers as exhibiting a mixture of four cell types:

- Eosinophilic spindle cells, usually arranged in interlacing fascicles.
- Round eosinophilic cells, large and intermediate in size, with a small nucleus and a granular eosinophilic cytoplasm, generally interspersed among other cell types.

- Broad elongated eosinophilic cells, occasionally with cross-striations.
- Small round and spindle cells with dark-staining nuclei and little cytoplasm (Fig. 2-99C).

The more well-differentiated tumors demonstrate elongated, strap-shaped or tadpole-shaped rhabdomyoblasts. The background stroma consists of moderately loose to dense fibrous tissue and may be quite scant, myxoid zones are commonly seen in the stroma.

Pleomorphic rhabdomyosarcoma is composed chiefly of spindle cells in a haphazard arrangement. These cells are generally large and show considerable variation in appearance. The nuclei are ovoid or elongated with packed chromatin. A characteristic feature of this form of tumor is the large bizarre cells, the nuclei situated often in an expanded end of the cell, the 'racquet' cell. 'Strap' and 'ribbon' cells typically show processes of long streaming cytoplasm. Mitoses, particularly atypical, are common. The cytoplasm is eosinophilic, and intracytoplasmic longitudinal fibrils as well as transverse cross-striations may be seen. Cytoplasmic vacuoles are also present as a result of large amounts of glycogen in the cell (Fig. 2-99A). This tumor is often so undifferentiated that the identification of the cell of origin is difficult or impossible. Positive immunostains for desmin and myoglobin are very helpful in such cases.

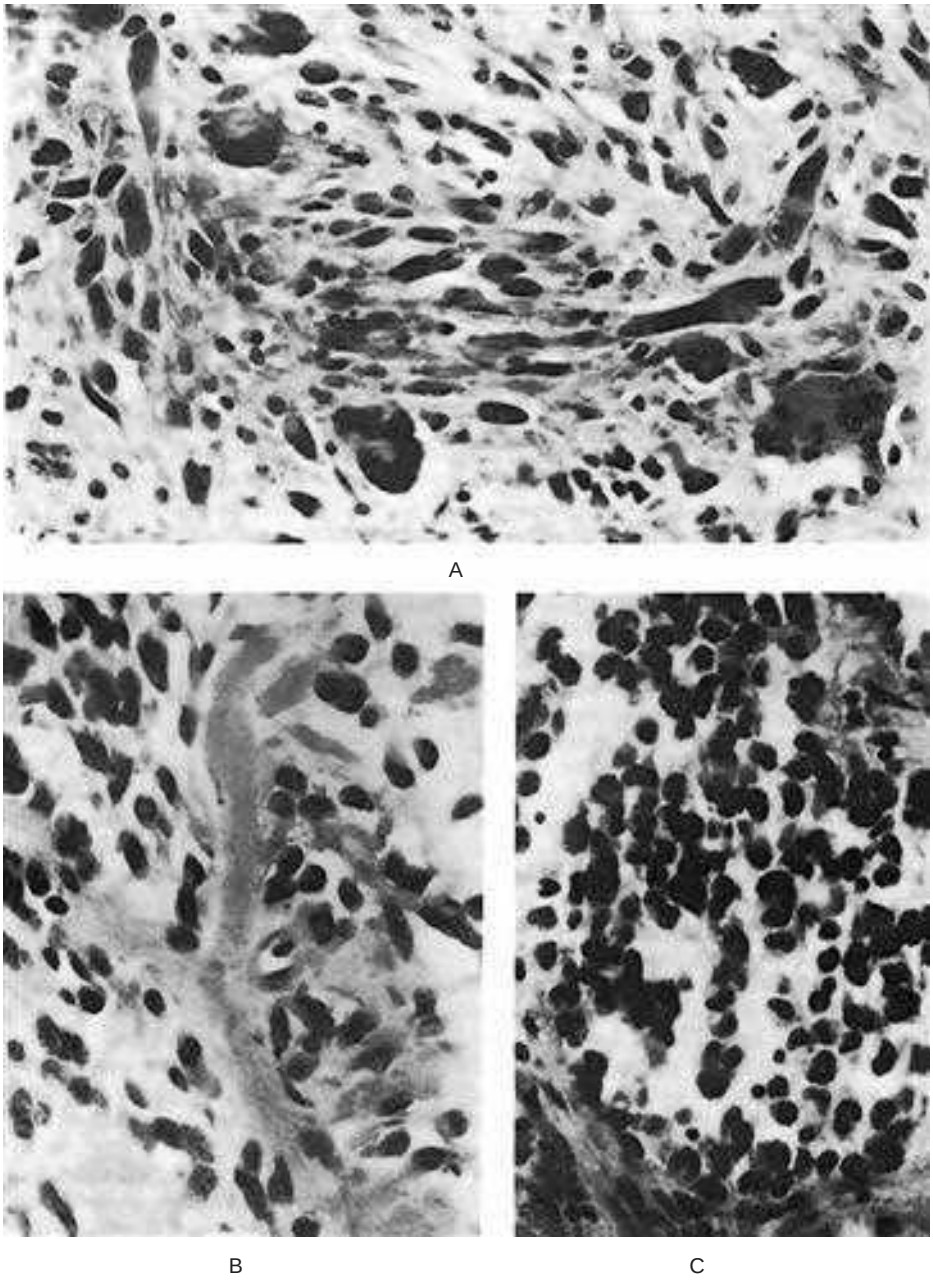


Figure 2-99. Rhabdomyosarcoma.
(A) Pleomorphic type. **(B)** Embryonal type. **(C)** Alveolar type.

Alveolar rhabdomyosarcoma is comprised of relatively small, poorly differentiated round and oval cells aggregated into irregular clusters or nests separated by fibrous septa. Degenerated cells in the center of the clusters show lack of cohesiveness, while the peripheral cells adhere in a single layer to the septal walls. Multinucleated giant cells may be seen and mitotic figures are common and sometimes bizarre. It is differentiated from the alveolar soft part sarcoma by its less regular tissue pattern and more pleomorphic cells.

An occasional variant, referred to as the **botryoid type,** demonstrates a diffuse myxoid or mucoid matrix with sparsely scattered primitive mesenchymal cells. The characteristic feature of this type is a peripheral zone of increased cellularity, sometimes known as the **'cambium layer'**.

Regardless of the histologic subtype, special stains are often quite useful for differentiating rhabdomyosarcoma from other neoplasms. The trichrome stain colors rhabdomyoblasts bright red while myofilaments and cross-striations are stained by PTAH (deep purple color). Myxoid stroma may be positive for hyaluronidase with acid mucopolysaccharide staining, although many other tumors also have positive stroma with these stains.

Treatment and Prognosis. Rhabdomyosarcoma is treated by radical surgical excision followed by multiagent chemotherapy. Postoperative radiotherapy is used for those cases which cannot be completely resected.

Alveolar Soft-Part Sarcoma
(Malignant granular cell myoblastoma)

The alveolar soft-part sarcoma is a tumor of uncertain histogenesis originally described under this name by Christopherson and his coworkers in 1952. It is a rare tumor, thought by some investigators to be of striated muscle origin, although it differs in some respects from the alveolar type of rhabdomyosarcoma. Other workers believe that it may be of neural origin and a variant of malignant granular cell tumor or a malignant nonchromaffin paraganglioma. Studies showed alveolar soft-part sarcomas are myogenic by immunophenotyping in a number of cases. In recent years, pathologists have shown this tumor to be a variant of a rhabdomyosarcoma, a sarcoma of skeletal muscle. Chromosome rearrangement at **17q25** and **Xp11.2** in alveolar soft-part sarcoma was demonstrated.

Clinical Features. The initial report of Christopherson indicated that this is predominantly a tumor of females, occurring usually in the teens or early 20s. A study of 53 cases by Lieberman and his associates has confirmed these findings. Of the 53 patients, 34 were female and 19 were male. The average age of their male patients was 30 years but that of their female patients, only 20 years. Occasional cases in older adults are reported.

Approximately one in four lesions occur in the head and neck region, usually the oral cavity, pharynx and orbit. However, the greatest predilection is for the muscles of the extremities, although lesions in the tongue and floor of the mouth have been reported by Caldwell and his associates. Only one of the 53 cases reported by Lieberman and his associates was intraoral and this occurred in the tongue. Font and his associates have reported 17 cases involving the orbit. The lesions are usually slow-growing, well-circumscribed masses with no distinguishing gross features.

Histologic Features. This tumor is composed of large cells with a finely granular cytoplasm that is not as eosinophilic as the cell of the rhabdomyosarcoma. The lesional cell is large and polygonal with a distinct cell border, a vesicular nucleus, and dense, abundant granular, eosinophilic or vacuolated cytoplasm. There is minimal variation in size and shape between cells and mitotic activity is sparse. These cells have a uniform pseudoalveolar or organoid pattern, arranged in relation to numerous delicate endothelium-lined vascular channels and septa (Fig. 2-100). The pattern is reminiscent of that seen in the nonchromaffin paraganglioma.

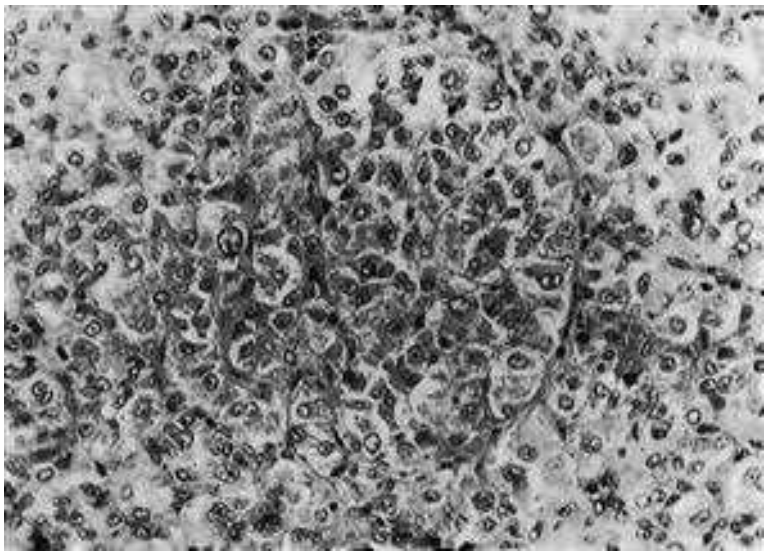


Figure 2-100. Alveolar soft-part sarcoma.

Vascular invasion is a frequent finding. Reticulin stains will enhance the organoid arrangement of the tumor cells.

Marshall and Horn reported that the alveolar soft-part sarcoma consistently showed a strongly positive periodic acid-Schiff (PAS) reaction before and after treatment with diastase, similar to the benign granular cell myoblastoma, but in contrast to the alveolar rhabdomyosarcoma in which the PAS-positive material is removed by digestion with diastase. This PAS-positive material in the cytoplasm of the alveolar soft-part sarcoma, described by Font and his coworkers as a highly characteristic and virtually pathognomonic finding of this lesion, represents crystalline structures composed of a protein-carbohydrate complex. They appear to form by coalescence of peculiar membrane-bound granules that exhibit acid-phosphatase activity.

Treatment and Prognosis. Radical surgical excision is the accepted treatment for this lesion because of the high frequency of recurrence, metastases and death of patients. Marshall and Horn reported the recurrence or metastatic rate as 70%, five-year survival being uncommon. Lieberman and his coworkers stated that they knew of no lifetime cures.

BENIGN TUMORS OF NERVE TISSUE ORIGIN

Traumatic Neuroma
(Amputation neuroma)

Traumatic (post-traumatic) or amputation neuroma is not a true neoplasm, but rather an exuberant attempt at repair of a damaged nerve trunk, i.e. a hyperplasia of nerve fibers and their supporting tissues. It most frequently follows accidental or purposeful sectioning of a nerve and may be incidental to difficult extraction. Cases also have occurred after an accident in which the lip or tongue was deeply lacerated by the teeth and nerve fibers were inadvertently severed.

Degeneration of the distal portion of the nerve after severance of the nerve fibers begins with swelling, fragmentation and disintegration of the axis cylinders and myelin sheaths. Macrophages serve to remove this tissue debris. The neurilemmal sheaths or tubes shrink until the distal degenerated fibers consist only of strands of connective tissue and the neurilemma. The nerve does not disappear completely.

Repair of a damaged nerve begins with proliferation of the axis cylinders, the cells of the neurilemmal sheaths and the endoneurium. Regeneration is facilitated by the persistence of the neurilemmal tubes, since new fibers proliferate through them and Schwann cells multiply around them.

Reinnervation usually occurs; unless the proliferating proximal end meets some obstruction, such as scar tissue or a malaligned bone, in which case the nerve continues to proliferate into an unorganized bulbous or nodular mass of nerve fibers and Schwann cells in varying proportions. This constitutes a traumatic neuroma. The pathogenesis of this lesion has been reviewed by Swanson.

Clinical Features. The oral traumatic neuroma usually appears as a small nodule or swelling of the mucosa, typically near the mental foramen, on the alveolar ridge in edentulous areas or on the lips or tongue (Fig. 2-101). A central lesion within the substance of the bone associated with a nerve trunk may also occur. This is a slowly growing lesion and seldom reaches a size greater than a centimeter in diameter (Fig. 2-101A, B).

Digital pressure may cause considerable pain locally, and in some instances along the course of the nerve involved. Reflex neuralgia with distant pain associated with the face, eyes and head has been recorded. Traumatic neuroma has been discussed in detail by Robinson and Slavkin and by Sist and Greene, who also reported 31 cases.

The **palisaded, encapsulated neuroma** is not a form of traumatic neuroma but may represent a primary hyperplasia of nerve fibers, the axons and their sheath cells. An alternative theory is that it represents a benign neoplasm. The lesion was first described by Reed and his coworkers as a clinically distinctive, solitary, benign cutaenous tumor occurring with equal frequency in both sexes and limited in its anatomic distribution (with rare exceptions) to areas bordering mucocutaneous junctions predominantly on the face. A case on the lower lip has been reported by Tomich and Moll.

Histologic Features. The histologic appearance of the neuroma is characteristic and shows a mass of irregular and often interlacing neurofibrils and Schwann cells situated in a connective tissue stroma scant or predominant. Much of this connective tissue is probably derived from the perineurium. The proliferating nerve fibers themselves may occur either in small discrete bundles or spread diffusely throughout the tissue (Fig. 2-101C, D). Care must be taken to differentiate this lesion from both the neurofibroma and neurilemmoma. The histologic, histochemical and ultrastructural aspects of wallerian degeneration of nerves have been described by Fisher and Turano and by Sist and Greene.

Treatment and Prognosis. Because of the progressive nature of this lesion and the associated pain, it is best treated by surgical excision along with a small proximal portion of the involved nerve. Recurrence is not common even though the sectioning of the nerve during treatment is similar to the injury that preceded the development of the tumor.

Multiple Endocrine Neoplasia Syndrome
(MEN syndrome [MEN III, MEN IIb])

The multiple endocrine neoplasia (MEN) syndromes are characterized by tumors of neuroendocrine origin. The type, MEN III syndrome, also called MEN IIb syndrome or multiple mucosal neuroma syndrome, was initially described by Wagenmann in 1922.

The disease is associated with adrenal pheochromocytoma, medullary thyroid carcinoma, diffuse alimentary tract ganglioneuromatosis, and multiple small submucosal neuroma nodules of the upper aerodigestive tract. The disease is inherited

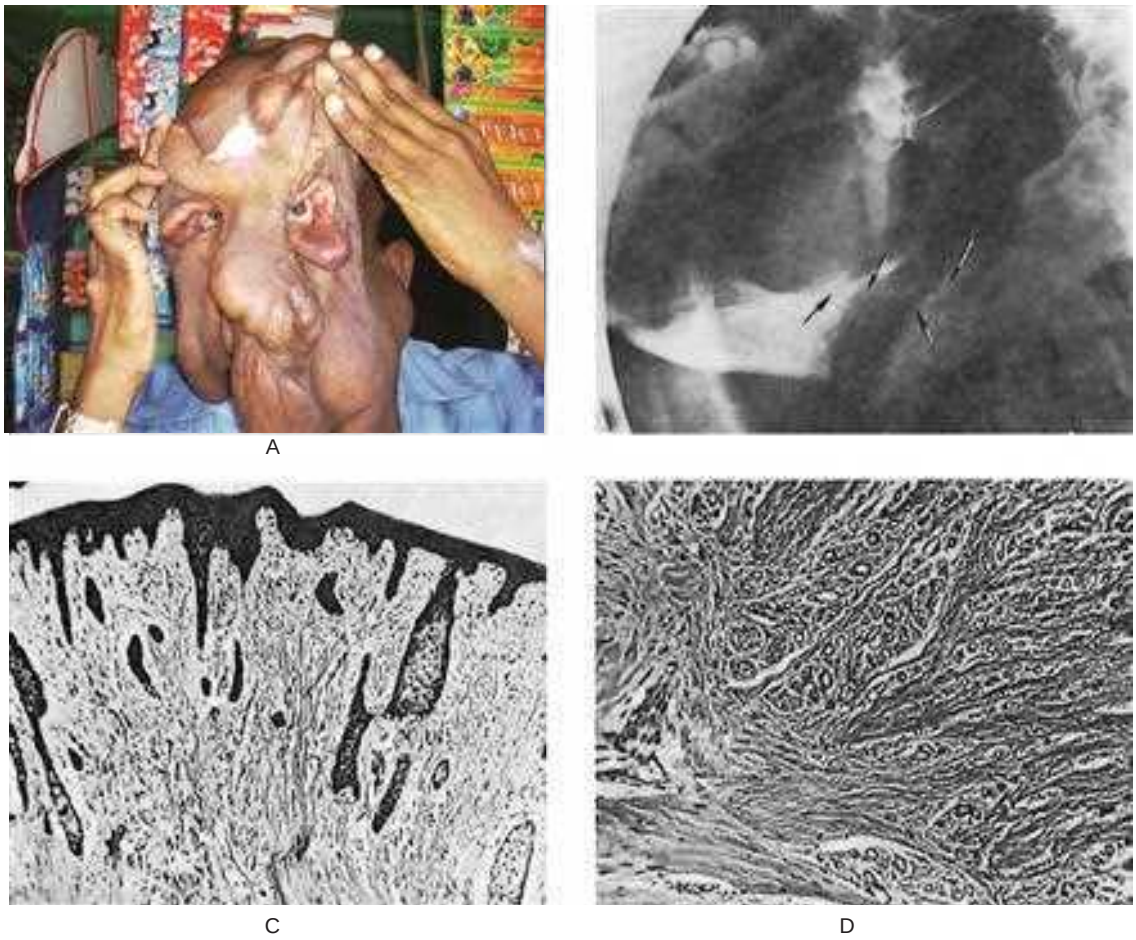


Figure 2-101. Traumatic neuroma.
(A) The patient presented with several pedulous tumour masses of the facial skin. The patient had sustained a fracture of the mandible many years previously that had resulted in the abnormal course of the mandibular nerve seen in the lateral jaw radiograph **(B)**. This nerve was subsequently sectioned for 'relief of pain'. The photomicrographs **(C, D)** reveal the hyperplasia of nerve fibers in a fibrous stroma. *(A, Courtesy of Dr K Murugesan, Maxillofacial Surgeon, Chennai)*

as an autosomal dominant trait, although many cases appear to be spontaneous mutations.

The affected individual has a tall, lanky, marfanoid body type, with a narrow face and perhaps with muscle wasting. The adrenal and thyroid tumors typically do not present until after puberty while the oral mucosal neuromas usually develop during the first decade of life. Mucosal neuromas are extremely rare, perhaps unheard of, outside of the MEN III syndrome. MEN syndromes are caused by mutations of the RET protooncogene, an important regulator of neural crest development and the receptor of glial derived neurotrophic factor (*GDNF)*.

Clinical Features. The oral mucosal neuroma of this disease presents as a 2–7 mm yellowish-white, sessile, painless nodule of the lips, anterior tongue and buccal commissures. Usually there are two to eight (or more) neuromas, with deeper lesions having normal coloration. There may be enough neuromas in the body of the lips to produce enlargement and a 'bumpy lip' appearance. Similar nodules may be seen on the eyelids, sometimes producing eversion of the lid, and on the sclera. Facial skin, especially around the nose, may also be involved.

Abnormal laboratory values are part of this syndrome. When a medullary thyroid carcinoma is present, serum and urinary calcitonin levels are elevated. When a pheochromocytoma is present, there often is an increase in the serum levels of vanillylmandelic acid (VMA) and altered epinephrine/norepinephrine ratios.

Histologic Features. The mucosal neuroma is comprised of a partially encapsulated aggregation or proliferation of nerves, often with thickened perineurium, intertwined with one another in a plexiform pattern. This tortuous pattern of nerves is seen within a background of loose endoneurium-like fibrous stroma. Individual nerves flow in fascicles of two or three fibers and are histologically normal except for occasional hyperplasias and bulbous expansions.

Inflammatory cells are not seen in the stroma and dysplasia is not present in the neural tissues. There may be close microscopic similarity with traumatic neuroma, but the streaming fascicles of mucosal neuroma are usually more uniform and the intertwining nerves of the traumatic neuroma lack the thick perineurium of the mucosal neuroma.

Luxol fast blue staining is used to identify myelin nerve fibers, and lesional cells react immunohistochemically for S100 protein, collagen type IV, vimentin, NSE, and neural filaments. More mature lesions will react also for EMA (epithelial membrane antigen), indicating a certain amount of perineurial differentiation. Early lesions have a stroma rich in acid mucopolysaccharides, hence, will stain positively with alcian blue.

Treatment and Prognosis. The mucosal neuromas of this syndrome are asymptomatic and self-limiting, and present no problem requiring treatment. They may, however, be surgically removed for esthetic purposes or if they are being constantly traumatized. It is strongly suggested that other family members may also be evaluated for MEN III.

Neurofibroma

(Neurofibromatosis, von Recklinghausen's disease of the skin, fibroma molluscum)

The neurofibroma is a benign tumor of nerve tissue origin, derived from the cells that constitute the nerve sheath. Neurofibroma is seen either as a solitary lesion or as part of the generalized syndrome of neurofibromatosis (von Recklinghausen disease of the skin). The solitary form does not differ from the disseminated form or the multiple form of the disease except that systemic and hereditary factors present in the disseminated form are absent in the solitary type.

The cell of origin for neurofibroma has not been definitively identified, but is generally believed to arise from the perineural fibroblasts which are neuroectodermal in origin. The cause of solitary neurofibroma is unknown. However, neurofibromatosis is inherited as an autosomal dominant trait with a high degree of penetrance but variable expressivity. As many as 50% of cases are reported to be the result of spontaneous mutation. Recently, two subsets have been defined: one is associated with the neurofibromatosis type 1 (NF1), gene mutations of the tumor suppressor genes coding for neurofibromin on chromosome 17q11.2, and the other is associated with the neurofibromatosis type 2 (NF2), gene mutations of the tumor suppressor genes coding for **schwannomin** on chromosome **22q12.1**.

Clinical Features. Neurofibromatosis, though not an exceedingly common disease, is by no means a clinical rarity. It has been reported in all races and does not exhibit a significant consistent sex predilection for occurrence. The hereditary nature of the disease has been recognized for many years and it is now known that it is inherited as a simple autosomal dominant trait with variable penetrance and a 50% mutation rate. It occurs with a frequency of one case in approximately 3,000 births in the general population. The birth incidence of NF1 lies between 1 in 2,500–3,300 and its prevalence in the population is 1 in 5,000. The birth incidence of NF2 lies between 1 in 33,000–40,000 with a prevalence within the population of 1 in 210,000.

The great clinical significance of neurofibromatosis, aside from the cosmetic problem, lies in the fact that in some patients malignant transformation subsequently occurs in one or more of their lesions. The incidence of sarcomatous transformation in neurofibromatosis has been placed at approximately 15% of all cases by Hosoi and by Preston and his coworkers. The type of sarcoma has been variously described as fibrosarcoma, spindle cell sarcoma and neurogenic sarcoma. However, solitary neurofibromas seldom undergo malignant transformation. Preston and his coinvestigators have reported other associated pathologic lesions, including osseous changes, mental disorders, congenital defects and ocular disease occurring in approximately 20% of their patients.

Oral Manifestations. Oral lesions occur in patients with von Recklinghausen's disease of skin, but the percentage of patients presenting such manifestations is not definitely known. In the series reported by Preston and his associates, intraoral neurofibromas were present in 7% of the patients. In contrast, Cherrick and Eversole reported that 20% of a series of 19 cases of intraoral neurofibroma occurred in association with von Recklinghausen's disease.

Discrete, nonulcerated nodules, which tend to be of the same color as the normal mucosa, may be noted, usually occurring on the buccal mucosa, palate, alveolar ridge, vestibule and tongue (Fig. 2-102A, B). Other cases exhibit diffuse masses of tissue which may involve the palate, buccal tissues and alveolar ridges and are composed of the same type of tissue as that seen in the isolated lesions. In addition, macroglossia due to diffuse involvement of the tongue is well recognized and has been reviewed by Ayres and his associates. Chen and Miller have also reported a series of 55 cases of benign nerve tumors of the oral cavity and noted the preponderance of neurofibroma over the neurilemmoma.

Occasional cases of neurofibroma located centrally within the jaw are seen. These are generally in the mandible, associated with the mandibular nerve, and radiographically show a fusiform enlargement of the mandibular canal. Involvement of the trigeminal nerve may cause facial pain or paresthesia. Ellis and his associates have also discussed central nerve sheath tumors of the jaws and found that very few of these reported were associated with multiple neurofibromatosis.

Histologic Features. The neurofibroma exhibits considerable variation in histologic structure but is generally composed of a proliferation of delicate spindle cells with thin, wavy nuclei intermingled with neurites in an irregular pattern as well as delicate, intertwining connective tissue fibrils. Cellular and myxoid patterns predominate; organoid features are not present. Melanocytes may sometimes be found in the tumor and mast cells are common. The lesions may or may not be well circumscribed.

In plexiform neurofibroma, the pattern may be that of distorted masses of myxomatous peripheral nerve tissue still within the perineural sheath are scattered within a collagen-rich matrix (Fig. 2-103). This histologic picture is considered to be virtually diagnostic of neurofibromatosis, even in the absence of other manifestations. There are reports of the existence of solitary plexiform neurofibromas unassociated with any

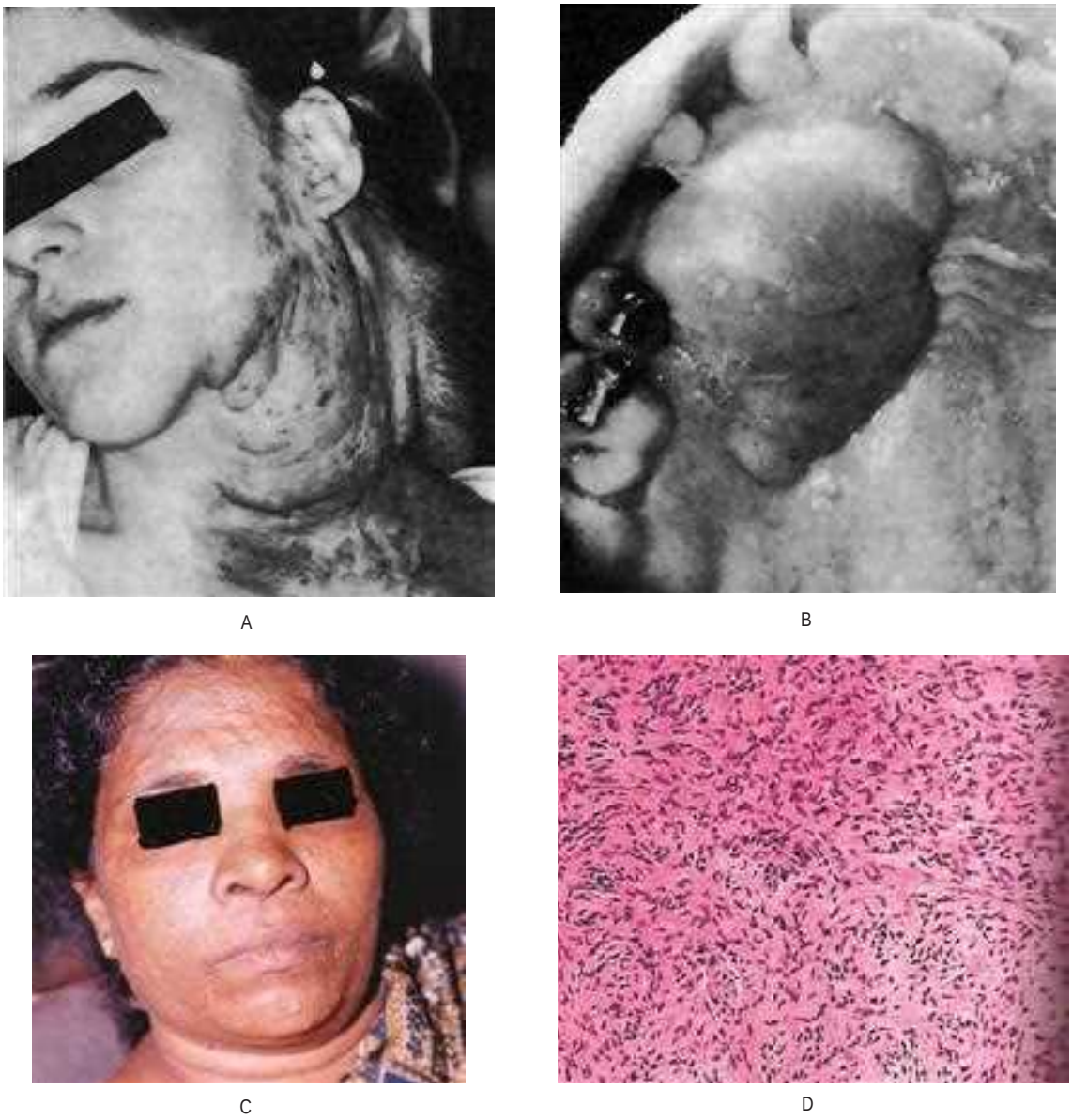


Figure 2-102. Neurofibroma.
(A) The patient presented several pendulous, pigmented tumor masses of the skin. **(B)** Neurofibroma of the palate in a patient without apparent neurofibromatosis. **(C)** Multiple neurofibromas of the face. **(D)** Neurofibromatosis showing spindled, wavy nuclei in fascicular form.

established syndromes, occurring in the oral cavity (tumors on the buccal mucosa and gingiva) (Alatli C et al, 1996).

The lesional cells are uniformly positive for S100 protein, signifying that they originate from neural crest-derived tissue. Antibodies to epithelial membrane antigen, CD57, and collagen IV are of secondary value and are used only when histologic differentiation with other neural tumors is difficult.

Treatment. Solitary oral neurofibromas are usually treated by surgical excision, depending on the extent and the site. Surgical removal may result in recurrence, and multiple recurrences have been associated with malignant transformation (5–15%). However, for neurofibromas associated with neurofibromatosis, surgical removal is attempted only for functional or cosmetic reasons. Genetic counseling and evaluation of other family members should be performed for those suspected to be affected by a syndrome.

Neurolemmoma

(Neurilemmoma, perineural fibroblastoma, schwannoma, neurinoma, lemmoma)

The neurolemmoma is a rather common tumor accepted by most investigators today to be derived from Schwann cells. Neurites are not a component of the tumor as in the neurofibroma but may be found on the surface of the tumor. Tissue culture studies by Murray and Stout, who cultivated this tumor *in vitro,* lend credence to the idea of the Schwann cells as the source of origin.

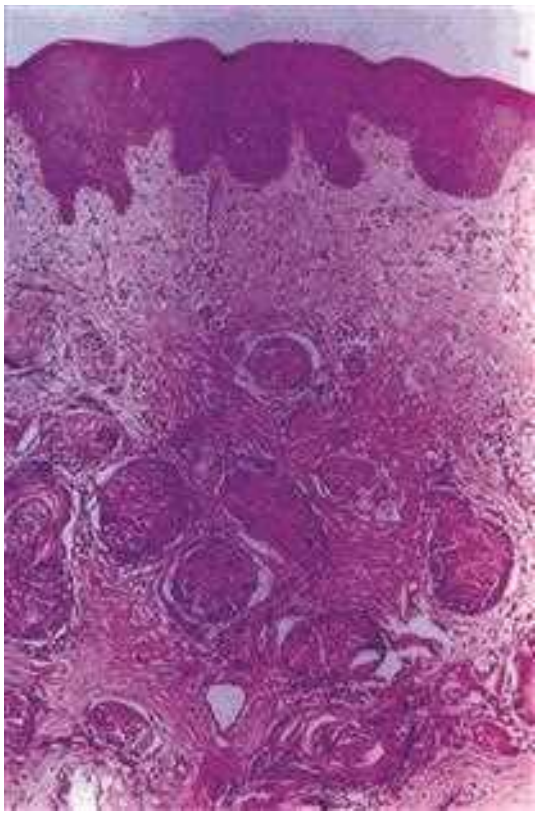


Figure 2-103. Plexiform neurofibroma of the gingiva.
Abundant nerve tissue in fascicles and collagenous fibrous stroma in ordered arrangement.

Clinical Features. Available clinical evidence indicates that the neurolemmoma is a slowly growing lesion and is usually of long duration at the time of presentation by the patient. An occasional tumor does exhibit a relatively rapid course, however, the lesion does occur with some frequency in patients with neurofibromatosis. It may arise at any age, cases having been reported even during the first year of life as well as in elderly patients. There is no gender predilection.

Despite the fact that these tumors originate from nerve tissue, they are usually painless unless they are causing pressure on adjacent nerves rather than on the nerve of origin. The presenting symptom of the majority of patients is only the presence of a tumor mass.

Oral Manifestations. The head and neck are rather common regions for the development of this neoplasm, as shown by the report of Ehrlich and Martin, and a variety of oral and paraoral locations have been the site of development of the neurolemmoma. Furthermore, in a series of 303 patients with benign solitary neurolemmomas reported by Das Gupta and his associates, 136 occurred in the head and neck. Reported cases of intraoral soft-tissue neurolemmomas have been reviewed by Hatziotis and Asprides with the following frequency of occurrence: tongue, 59 cases; palate, 11 cases; floor of mouth, 10 cases; buccal mucosa, 9 cases; gingiva, 6 cases; lip, 6 cases; and vestibule, 5 cases. Other cases have involved the maxillary sinus and salivary glands, as well as the retropharyngeal, nasopharyngeal and retrotonsillar areas.

In addition, the neurolemmoma has been reported as a central lesion within bone, chiefly the mandible, apparently arising from the mandibular nerve. Eighteen such cases have been reviewed by Eversole, which Ellis and his coworkers have added additional cases.

The soft-tissue lesion is usually a single, circumscribed nodule of varying size that presents no pathognomonic features (Fig. 2-104A, B). It may resemble any of a number of benign oral soft-tissue lesions. The central lesions in bone may produce considerable destruction of bone with expansion of the cortical plates and thus resemble a more serious lesion (Fig. 2-104C). Pain and paresthesia may accompany these central lesions of bone.

Histologic Features. The microscopic picture of the neurolemmoma is characteristic and can seldom be confused with that of other lesions. The tumor is classically described as being composed of two types of tissue, Antoni type A and Antoni type B. Antoni type A tissue is made up of cells with elongated or spindle-shaped nuclei which are aligned to form a characteristic palisading pattern, while the intercellular fibers are arranged in parallel fashion between rows of nuclei. These fibers in some planes will give the impression of occurring in whorls or swirls. Antoni type B tissue does not exhibit this characteristic palisading, but rather a disorderly arrangement of cells and fibers with areas of what appears to be edema fluid and with the formation of microcysts. Verocay bodies, small hyaline structures, are also characteristically present in this tumor (Fig. 2-104D). Of great importance is the fact that in nearly all instances the tumor is encapsulated.

Treatment and Prognosis. The treatment of the neurolemmoma is surgical excision. Like other nerve tumors, this lesion is not responsive to X-ray radiation. Since it is an encapsulated tumor, little difficulty is usually encountered in its complete removal, but it has been suggested that in instances in which complete removal cannot be accomplished, a portion of tumor may be left without risk of recurrence. Such a procedure is of poor clinical practice, however, except possibly in cases in which complete removal of the tumor would necessitate extensive sacrifice of structures and results in deformity. Recurrence is uncommon.

The neurolemmoma does not undergo malignant transformation, as may the neurofibroma after numerous episodes of surgical tampering.

Melanotic Neuroectodermal Tumor of Infancy

(Pigmented ameloblastoma, melanoameloblastoma, retinal anlage tumor, melanotic progonoma, melanotic epithelial odontoma, pigmented teratoma, atypical melanoblastoma, melanotic adamantinoma, pigmented epulis, retinal choristoma, retinoblastic teratoma, congenital melanocarcinoma)

The melanotic neuroectodermal tumor of infancy (MNTI) is a relatively uncommon osteolytic-pigmented neoplasm that primarily affects the jaws of newborn infants. Initially it was reported by Krompecker in 1918 as a congenital melanocarcinoma. Various theories suggested its origin from the odontogenic apparatus, the pigmented anlage of the retina, or the sensory neuroectodermal tissues.

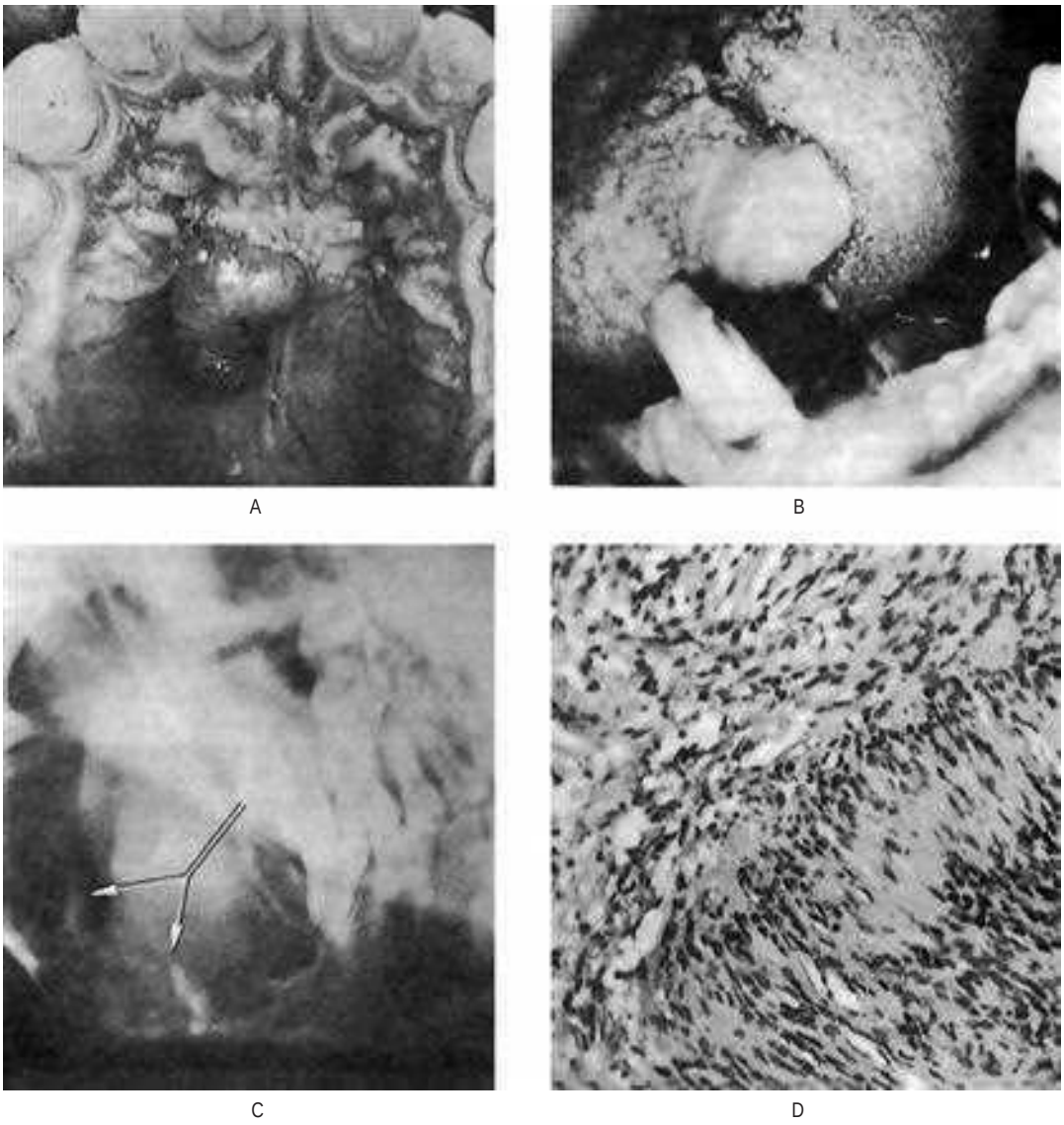


Figure 2-104. Neurolemmoma.
(A) Palate. **(B)** Tongue. **(C)** Central in bone, probably originating from mandibular nerve. **(D)** The microscopic features are characteristic *(A, Courtesy of Dr Charles A Waldron, and B, of Dr Robert Ewbank).*

In 1966, Borello and Gorlin reported a case with high urinary excretion of vanillylmandelic acid (VMA), suggesting a neural crest origin, and they proposed the term melanotic neuroectodermal tumor of infancy. Since then, numerous histochemical, immunohistochemical, electron microscopic, and tissue culture studies have supported the neural crest origin and confirmed the preferred term of melanotic neuroectodermal tumor of infancy.

Clinical Features. More than 90% of cases present within the first year of life, usually from age one to six months. The mean age of patients with MNTI is 4.3 months. Although extremely rare, cases of MNTI have been reported in adults. The sexual predilection is nearly equal, with a male-to-female ratio of 6 : 7.

More than 90% of MNTI occur in the head and neck region, with most on the anterior part of the maxillary ridge. Other common sites include the skull, the mandible, the epididymis, and the brain. Rare lesions have been reported in the shoulder, the skin, the femur, the mediastinum, and the uterus.

The majority of reported cases have been rapidly growing, nonulcerated, darkly pigmented lesions which have given a radiographic appearance of an invasive malignant neoplasm. In its typical premaxillary position, the tumor can displace or destroy the developing deciduous and permanent dentition. It can present as unilocular, or rarely as multiloculated radiolucency.

All the hematologic and blood chemistry values are within the normal range. The only finding in some but not all patients with MNTI is an increase in the urinary level of VMA, but shows no correlation with its clinical behavior. Elevated VMA has been reported in other tumors of neural crest origin, such as pheochromocytoma, ganglioneuroblastoma, retinoblastoma, and neuroblastoma.

Immunohistochemistry is of assistance in cases that are more difficult to diagnose. The cuboidal cells express cytokeratin as well as melanoma-associated antigen (HMB45), but they are usually negative for S100. Some cells are also positive for vimentin, epithelial membrane antigen, glial fibrillary acidic protein, neuron specific enolase (NSE), and synaptophysin.

Electron microscopic examination demonstrates ultrastructural evidence of neural, epithelial, and melanocytic features. Fine, delicate cytoplasmic fibers are suggestive of neurofibrils, reminiscent of glial tissue. Typically, some of the cells demonstrate neurosecretory granules. Evidence exists of basal laminae and interdigitating desmosomal attachments to adjacent cells, which is suggestive of epithelial features in some cells. Melanosomes are noted in many of the cuboidal cells.

When polygonal cells were cultured *in vitro* they developed long dendritic processes suggestive of their neural crest origin. However, no molecular or genetic basis to link MNTI to neuroblastoma is apparent.

Histologic Features. The microscopic appearance of this tumor is characteristic due to its distinct biphasic pattern. It is usually a nonencapsulated, infiltrating tumor mass of cells arranged in a pattern of alveolus-like spaces lined by cuboidal or large polygonal cells, which have pale abundant cytoplasm and nuclei with finely dispersed chromatin, many of which contain melanin pigment. Fontana stain can be used to demonstrate the melanin pigment. The central portions of the alveolar spaces contain many small round neuroblast-like cells which show little cytoplasm and exhibit a round, deeply staining nucleus. A moderately vascular fibrous stroma supports the tumor cells (Figs. 2-105, 2-106).

Treatment and Prognosis. The treatment of choice for MNTI is surgical excision, and it is usually curative. This treatment can usually be accomplished with a partial maxillectomy. Many clinicians advocate a 5 mm margin of healthy tissue to be included with the surgical specimen.

Local recurrence has been documented in 10–60% of patients. Overall, the average recurrence rate is 15–20%. Approximately 1% of tumors are malignant, with only rare tumors producing metastases.

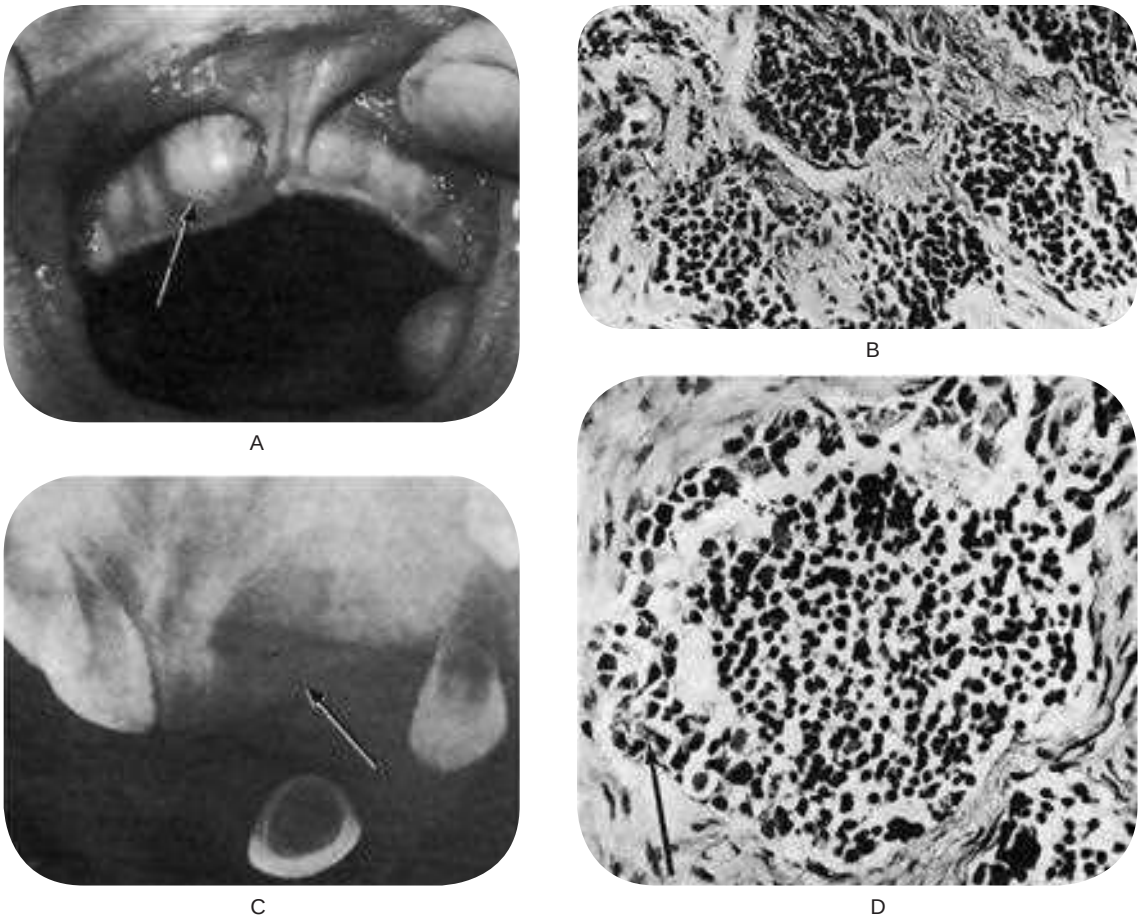


Figure 2-105. Melanotic neuroectodermal tumor of infancy.
There is a rapidly growing mass present on the anterior maxilla. **(A)** The radiograph shows diffuse destruction of bone, suggestive of a malignant neoplasm. **(B)** The photomicrographs demonstrate typical alveolus-like structures lined by an irregular layer of cuboidal cells containing melanin pigment, **(C)** and **(D)** *(A, Courtesy of Dr Jan L Silagi).*

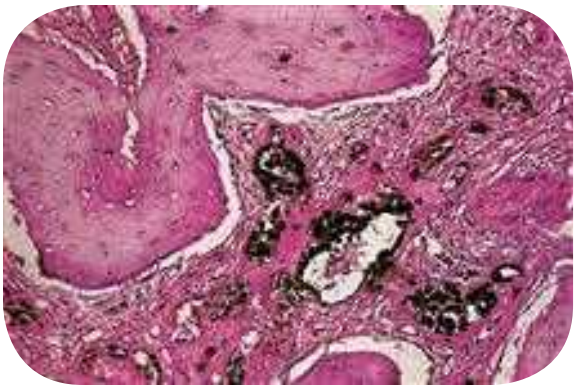


Figure 2-106. Pigmented neuroectodermal tumor of infancy.
The neoplastic islands located between the bone trabeculae contain abundant melanin pigment.

MALIGNANT TUMORS OF NERVE TISSUE ORIGIN

Malignant Peripheral Nerve Sheath Tumor

(Malignant schwannoma, malignant neurilemmoma, neurogenic sarcoma, neurofibrosarcoma)

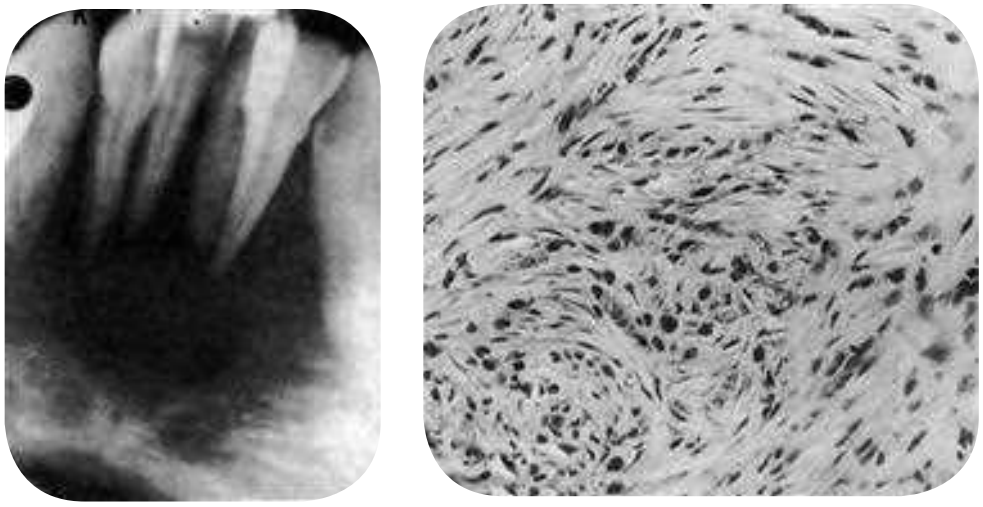
Malignant peripheral nerve sheath tumor (MPNST) is now the preferred name for the spindle cell malignancy of peripheral nerve Schwann cells. It represents approximately 10% of all soft tissue sarcomas and its diagnosis has been called 'one of the most difficult and elusive diagnoses in soft tissue diseases'. Up to half of all cases of MPNST are diagnosed in persons with neurofibromatosis I (4% of patients with neurofibromatosis I). About one in 10 cases are associated with irradiation. The preferred site is the lower extremities, but a small percentage of these lesions occur in the head and neck region, usually associated with the large cranial nerves, especially the trigeminal nerve.

Clinical Features. These tumors commonly occur in persons of 20–50 years of age, but children and elderly persons may also be affected. Lesions which develop in persons with neurofibromatosis I typically occur a decade or more earlier than those in nonsyndrome patients. There is a slight predilection toward males in sporadic cases, but within the subgroup of patients with neurofibromatosis I, 80% of lesions are found in males. The most common head and neck area of involvement is the neck, but its occurrence in oral cavity is extremely rare. When it occurs in the oral cavity it is usually seen arising from the tongue or soft palate. The lip, gingiva, palate and buccal muosa have been sites of involvement. In the central tumors, the mandible or mandibular nerve is more frequently affected than the maxilla.

In some instances there is no complaint other than the presence of a mass, although in other cases pain and/or paresthesia, muscle weakness are present. At surgery, attachment to a major nerve trunk is not unusual, and the surgeon may notice cystic degeneration or hemorrhage within the lesional stroma.

Radiographic Features. The radiograph may reveal a diffuse radiolucency characteristic of a malignant infiltrating neoplasm (Fig. 2-107). On the other hand, the appearance may be that of only a smooth radiolucency, such as dilatation of the mandibular canal when the tumor is originating from this nerve. When this appearance prevails, the lesion may be mistaken on the radiograph for a benign one.

Histologic Features. The MPNST resembles fibrosarcoma in its overall organization, but the spindled lesional cells demonstrate the wavy or comma-shaped outline and nuclear contour of Schwann cells. The cytoplasm of lesional cells is usually indistinct and slightly eosinophilic. Cellular and nuclear pleomorphism may be quite pronounced and mitotic activity is usually high. Spindle cells are arranged in sweeping fascicles interspersed with hypocellular and myxoid regions.



A B

Figure 2-107. Malignant schwannoma of the mandible.
(Courtesy of Dr Charles H Redish and Dr Norman S Klein).

Histologically MPNST may be classified into three major categories with **epithelioid, mesenchymal** or **glandular** characteristics.

The **epithelioid** variant demonstrates plump, rounded or ovoid epithelioid cells scattered throughout the spindled lesional cells, usually in rather small numbers and in well defined clusters. These cells may have vesicular or hyperchromatic nuclei and may bear slight resemblance to the cells of the amelanotic melanoma.

Some MPNST lesions show rhabdomyoblastic differentiation leading to the common use of the diagnostic term **Triton tumor.** The spindle cells are interspersed with large, plump, rounded or strap cells with eosinophilic, fibrillar cytoplasm and with cross-striations in the cytoplasm. These cells may be clustered and must be distinguished from simple entrapment of striated muscles fibers.

The **glandular** MPNST contains areas with usually well-differentiated ductal structures lined by simple, stratified, cuboidal or columnar epithelial cells with occasional goblet cells. The lumen may contain PAS-positive, diastase-resistant mucus.

Rare MPNST cases contain multiple sarcomatous tissue types, especially osteosarcoma, chondrosarcoma and angiosarcoma. These have sometimes been indistinguishable from the malignant mesenchymoma of soft tissue.

MPNSTs may resemble fibrosarcoma and may require immunohistochemistry and EM evaluation to discern useful diagnostic differences. The other sarcomas most closely resembling this tumor are leiomyosarcoma and monophasic synovial sarcoma. In the oral cavity, the synovial sarcoma is so rare as to be excluded from the differential diagnosis, while the spindle cell of the leiomyosarcoma has a more distinct eosinophilic cytoplasm and a quite blunted nucleus.

Distinguishing the MPNST from a benign nerve sheath tumor is usually not difficult, but some neurofibromas may be quite cellular and may contain occasional pleomorphic cells. In such cases, presence or absence of mitotic activity is usually the determining feature.

Treatment and Prognosis. The MPNST of the oral region is treated by wide surgical excision, but local recurrences are common and hematogenous metastasis occurs in at least half of treated cases. The tumor is resistant to radiotherapy and chemotherapy, and those occurring in neurofibromatosis I behave in a more aggressive fashion than those not associated with the syndrome. Overall, the five-year survival for MPNST is 40–75%.

Olfactory Neuroblastoma

(Esthesioneuroblastoma, esthesioneuroepithelioma)

The olfactory neuroblastoma is a rare tumor apparently originating from the olfactory apparatus, and therefore, found most frequently in the nasal cavity and nasopharynx. Occasional cases have been reported either originating in or invading the maxillary sinus. Such examples have been described by Church and Uhler and by Mashberg and his associates.

Clinical Features. The lesion generally appears as a painful swelling in the area of the nasal fossa. It is an invasive, destructive tumor, but only rarely metastasizes, chiefly to cervical lymph nodes and lungs. In contrast to other types of neuroblastoma, this lesion usually occurs in adults rather than children.

Histologic Features. The appearance of the tumor characteristically is one of densely packed masses of small darkly staining cells each with a poorly defined eosinophilic cytoplasm and a regular round vesicular nucleus, sometimes with stippled chromatin. Rosette formation is common. This is a pseudoglandular structure lined by a single layer of nonciliated columnar cells with a basal nucleus and a cuticular border at the apex of the cell. These resemble the sustentacular and olfactory cells of the olfactory mucosa. Eosinophilic neurofibrils extend into the lumen from the cell borders. Pseudorosettes also occur. Mitotic figures are often present, but not in large numbers. The stroma has a fibrillar neuroid pattern. The difficulty in microscopic diagnosis, however, has been emphasized by Oberman and Rice.

Treatment. The treatment is generally surgery, radiation or both in combination. Although recurrence of the lesion is rather common, its prognosis is generally fair. In a series of nearly 100 cases reviewed by Skolnik and his coworkers, the five-year survival rate was 52%.

Metastatic Tumors of Jaws

(Metastatic tumors to oral cavity, metastatic tumors to the oral mucosa)

Metastatic tumors to the oral region are uncommon and may occur in the oral soft tissues or jawbones. Because of their rarity, metastatic tumors to the oral region are challenging to diagnose. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to oral region.

Even though the oral region is not a preferred site for metastatic deposits, approximately 30% of oral metastases are the first sign of the disease. In such cases, tumor cells bypass the filtration of the lungs, probably through the valveless vertebral venous plexus.

The pathogenesis of the metastatic process in the jawbones is not clear. In the skeleton, bones with red marrow are the preferred sites for metastatic deposits. Jawbones have little active marrow, especially in elderly persons. Remnants of hematopoietic active marrow can be detected in the posterior areas of the mandible. Since the mode of spread is usually hematogenous, tumor cells tend to be deposited in this vascular medullary tissue.

In dentulous patients, 80% of the metastatic tumors to the oral soft mucosa are found in the attached gingiva, whereas in edentulous patients, metastatic lesions are equally distributed between the tongue and the alveolar mucosa, and with much less frequency, the remaining mucosa. The rich capillary network of chronically inflamed gingiva has been suggested as a mechanism that entraps malignant cells. The proliferating capillaries have

a fragmented basement membrane through which tumor cells can more easily penetrate.

Clinical Features. Most metastatic tumors to the oral region occur in patients aged 40–70 years. On average, patients with metastases to the jawbones are younger (aged 45 years) than those with metastases to the oral soft tissues (aged 54 years).

Metastatic tumors to the oral region are uncommon and account for approximately 1% of all malignant oral tumors. However, autopsies of patients with carcinoma reveal a higher frequency of metastatic deposits in the jawbones, which are not manifested clinically. Metastatic tumors to the jawbones are more frequently reported than those in the oral mucosa (Fig. 2-108).

The most common primary sources of metastatic tumors to the oral region are cancers in the breast, lung, kidney, bone, or colorectum. The breast is the most common primary site for tumors that metastasize to the jawbones, whereas the lung is the most common source for cancers that metastasize to the oral soft tissues (Tables 2-19, 2-20).

In female patients, the most common primary cancers that metastasize to the oral region are those in the breasts, followed with much lower frequency by those in the female genital organs, colorectum, bone, and kidneys (Table 2-20).

In its early manifestation, gingival metastasis resembles hyperplastic or reactive lesions (e.g. pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis) and in other oral soft tissue locations, especially in the tongue, the metastatic lesion manifests as a submucosal mass.

The metastatic lesions of the jaw may be completely asymptomatic. Usually, however, the patient is aware of slight discomfort or pain, followed in many cases by paresthesia or anesthesia of the lip or chin due to involvement of the mandibular nerve. The teeth in the affected area may become loose and extruded. Unfortunately, these teeth may be extracted simply because they are loose without an attempt by the dentist to learn the cause of this phenomenon. In such cases, the main symptom is a soft tissue mass extruding from a recent extraction wound and accompanied by pain. In some cases, pain described as a toothache has been the chief complaint of the patient. A definite swelling or expansion of the jaw is also an almost constant finding.

With the progression of the disease, oral metastatic lesions (especially those in soft tissues) cause progressive discomfort. Pain, bleeding, superinfection, dysphagia, interference with mastication, and disfigurement are some of the main patient complaints.

Radiographic Features. Metastatic lesions produce no pathognomonic radiographic appearance. Although most of such metastases produce osteolytic lesions and thus appear as a radiolucency on the radiograph, certain tumors produce

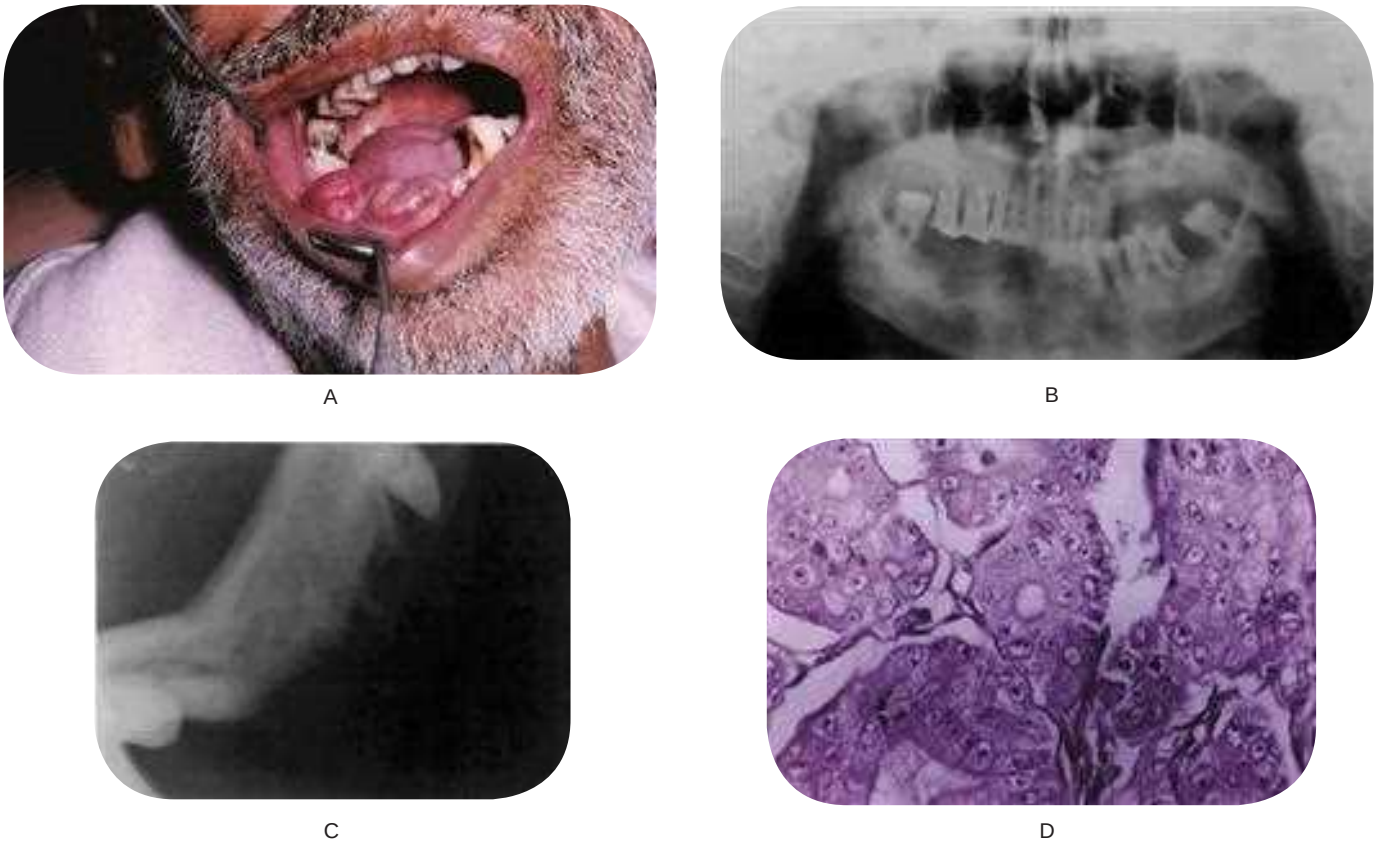


Figure 2-108. (A) Metastatic carcinoma of the lower alveolus. (B) Primary from prostate. (C) An osteolytic lesion of the mandible. (D) Photomicrograph of metastatic carcinoma of the alveolus.

Table 2-19: Metastatic tumors to the oral region in men

Metastatic site and origin	Percentage
Oral mucosa	
Lung	35.0
Kidney	16.0
Skin	15.0
Liver	7.0
Colorectum	5.5
Testis	5.5
Bone	3.0
Stomach	3.0
Rare tumors	10.0
Jawbones	
Lung	22.0
Prostate	12.0
Kidney	10.0
Bone	9.0
Adrenal gland*	9.0
Liver	7.0
Testis	5.5
Colorectum	4.0
Rare tumors	21.5

**Cases of neuroblastoma, including cases from retroperitoneum and mediastinum.*
Source: Adapted from: Abraham Hirshberg. eMedicine Speciaities. Diseases of the Oral Mucosa, 2002.

Table 2-20: Metastatic tumors to the oral region in women

Metastatic site and origin	Percentage
Oral mucosa	
Breast	24.0
Genital organs*	17.0
Lung	12.0
Kidney	10.0
Bone	10.0
Skin	7.0
Rare tumors	20.0
Jawbones	
Breast	42.0
Adrenal gland†	8.5
Colorectum	8.0
Kidney	6.0
Bone	6.0
Thyroid	6.0
Rare tumors	23.5

** Uterus, ovaries, cervix, fallopian tubes.*
† Cases of neuroblastoma, including cases from retroperitoneum and mediastinum.

osteoblastic lesions or lesions characterized by the production of bone. Such lesions are manifested as radiopaque or sclerotic areas and are most often associated with carcinoma of the prostate, and occasionally, of the breast and lung. The metastases in the radiograph may be relatively well demarcated and confined or they may exhibit diffuse, poorly outlined involvement of a considerable portion of bone. Because of the destruction of bone which may occur, pathologic fracture is occasionally seen. Lack of radiographic changes does not exclude the possible presence of a small metastatic deposit in the jawbone.

Histologic Features. The diagnosis is always based on histologic findings in the biopsy specimen. The clue to the diagnosis is the resemblance of the metastasis to the primary tumor. If history of a previous tumor exists, current histologic findings should compare with those of the preexisting primary malignant tumor. In some cases, histochemical staining, immunohistochemical tests, and electron microscopy should be performed to identify the primary source of the metastatic tumor.

Several primary intraoral malignancies (especially those originating from salivary glands) have histologic features similar to those of tumors in distant organs: for example, primary ductal carcinoma of a salivary gland origin versus metastatic breast carcinoma, primary intraoral clear cell carcinoma versus metastatic renal cell carcinoma, primary intraoral squamous cell carcinoma versus metastatic squamous cell carcinoma from the lung, or primary intraoral malignant melanoma versus metastatic malignant melanoma. Malignant soft tissue tumors may originate intraorally, but, because of their rarity, one should always consider a metastatic origin.

Treatment and Prognosis. Oral metastases usually indicate widespread disease. Treatment modalities are limited to palliation. In some cases, surgical treatment, sometimes combined with radiation therapy and/or chemotherapy, can improve the patient's quality of life. Adequate surgical treatment can improve the prognosis in some cases in which the oral region is the only metastatic site.

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CHAPTER 3

Tumors of the Salivary Glands

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CHAPTER OUTLINE

Tumors of the salivary glands constitute a heterogeneous group of lesions of great morphologic variation, and for this reason, present many difficulties in classification. Since these tumors are relatively uncommon, early investigators were handicapped by insufficient material for study. With the publication of several large series of cases, accompanied by serious discussions of the nature of tumors of the salivary glands based upon a cumulative clinical experience of many years, considerable progress has been made in broadening our knowledge of these lesions. Among these studies have been those of Evans and Cruickshank, Thackray and Lucas, and WHO.

Foote and Frazell were among the first investigators to provide a usable classification of salivary gland tumors. Spiro and his associates, Thackray and Sobin, and Batsakis have proposed classifications for practical use that are based on clinical behavior or specific histologic criteria. However, Eversole has proposed a histogenetic classification of salivary gland tumors, implicating two cell types as possible progenitors: the intercalated duct cell and the excretory duct reserve cell. The various types of salivary gland tumors are best distinguished by their histologic patterns. The clinical behavior of these various lesions may be based, as in most tumors, on the type of tumor as well as on the method of treatment utilized.

It is important to recognize that neoplasms may arise not only from the major salivary glands, but also from any of the numerous, diffuse, intraoral accessory salivary glands. Thus one may expect to see tumors originating from the glands in the lip, palate, tongue, buccal mucosa, floor of the mouth and retromolar area. Salivary gland tumors are much more common on the hard palate than on the soft, probably because there are a greater number of gland aggregates on the hard palate than on the soft palate. With only occasional exceptions, any type of tumor which occurs in a major salivary gland may also arise in an intraoral accessory gland. Thus, in the following discussion, the general features described under each tumor will hold true for both major and minor salivary gland lesions. There appear to be no truly specific, recognized tumors native only to the intraoral glands. Annual incidence of salivary gland tumors around the world is stated to be 1–6.5 cases per 100,000 people. Most studies have shown that minor salivary gland tumors are more common in females than males, with a ratio range from 1.2 : 1–1.9 : 1. Eneroth has presented data on over 2,300 tumors of the major salivary glands (Table 3-1), while a complete review of the intraoral minor salivary gland tumors has been published by Chaudhry and his coworkers, with much valuable information obtained from the analysis of over 1,300 cases (Table 3-2).

Benign tumors of the salivary gland need no treatment other than surgical removal. Malignant tumors, on the other hand, may require radiation or chemotherapy or both after surgery. Surgery for salivary gland tumors removes all or most of the affected glands, not just the tumor. When performing surgery on these glands, great care is taken to identify and protect the nerves that pass through or near these glands and supply the muscles of the face, mouth and tongue. These nerves are stretched during surgery, which results in a temporary weakness on part of the face in up to 15% of patients. This weakness is temporary and usually disappears in one to three months. Occasionally, malignant tumors invade the nerves that supply part or all of the muscles of the face. When this occurs, a portion of the nerve is surgically removed with the tumor, and a nerve graft is used to rebuild the nerve.

Table 3-1: Occurrence of major salivary gland tumors

	Parotid	Submaxillary	Total	
			No.	Percentage
Benign tumors				
Pleomorphic adenoma	1,658	102	1,760	75.6
Papillary cystadenoma lymphomatosum	101	4	105	4.5
Oxyphilic cell adenoma	21	1	22	0.9
Malignant tumors				
Carcinoma in pleomorphic adenoma	32	3	35	1.5
Mucoepidermoid carcinoma	88	6	94	4.0
Adenoid cystic carcinoma	49	26	75	3.2
Acinic cell carcinoma	66	1	67	2.9
Mucus-producing adenopapillary carcinoma	52	–	52	2.2
Solid undifferentiated carcinoma	84	15	99	4.3
Epidermoid carcinoma	7	12	19	0.8
Total	2,158	170	2,328	100.0

Data from CM Eneroth: Salivary gland tumors in the parotid gland, submandibular gland and the palate region. Cancer, 27: 1415, 1971.

Table 3-2: Occurrence of intraoral accessory salivary gland tumors

	Palate	Lip			Cheek	Tongue	Retromolar	Others	Total	
		Upper	Lower	NS					No.	Percenage
Benign tumors										
Pleomorphic adenoma	476	105	13	15	38	18	40	28	733	55.7
Simple adenoma	18	2	0	0	0	4	0	0	24	1.8
Myoepithelioma	12	1	0	0	4	0	0	0	17	1.3
Cystadenoma (incl. papillary)	12	1	0	0	4	1	1	1	20	1.5
Canalicular adenoma	1	0	0	2	1	0	0	0	4	0.3
Oxyphilic adenoma	0	0	0	0	0	1	1	0	2	0.2
Malignant tumors										
Malignant pleomorphic adenoma	13	1	0	0	5	0	5	2	26	2.0
Adenocarcinoma	104	6	1	5	17	62	12	8	215	16.3
Adenoid cystic carcinoma	2	1	0	0	0	0	2	2	7	0.5
Acinar cell adenocarcinoma	80	3	0	12	17	26	6	18	162	12.3
Miscellaneous forms	43	0	0	2	15	23	22	2	107	8.0
Mucoepidermoid carcinoma	1	0	0	0	2	0	0	0	3	0.2
Epidermoid carcinoma										
Total	762 (57.7%)	120 (9.1%)	14 (1.0%)	36 (2.7%)	103 (7.7%)	135 (10.2%)	89 (6.7%)	61 (4.6%)	1320	100.0

Data from AP Chaudhry, RA Vickers, and RJ Gorlin: Intraoral minor salivary gland tumors. Oral Surg, 14: 1194, 1961.

BENIGN TUMORS OF THE SALIVARY GLANDS

Pleomorphic Adenoma
(Mixed tumor)

Pleomorphic adenoma is a benign neoplasm consisting of cells exhibiting the ability to differentiate to epithelial (ductal and nonductal) cells and mesenchymal (chondroid, myxoid and osseous) cells. This tumor has been referred to by a great variety of names through the years (e.g. mixed tumor, enclavoma, branchioma, endothelioma, enchondroma), but the term 'pleomorphic adenoma' suggested by Willis characterizes closely the unusual histologic pattern of the lesion. It is almost universally agreed that this tumor is not a 'mixed' tumor in the true sense of being teratomatous or derived from more than one primary tissue. Its morphologic complexity is the result of the differentiation of the tumor cells, and the fibrous, hyalinized, myxoid, chondroid and even osseous areas are the result of metaplasia or are actually products of the tumor cells per se. Pleomorphic adenoma is the most common salivary gland tumor (Table 3-3).

Histogenesis. Numerous theories have been advanced in explaining the histogenesis of this bizarre tumor. Currently, these center around the myoepithelial cell and a reserve cell in the intercalated duct. Ultrastructural studies have confirmed the presence of both ductal and myoepithelial cells in pleomorphic adenomas. It follows that possibly either or both may play active roles in the histogenesis of the tumor. Hubner and his associates have postulated that the myoepithelial cell

Table 3-3: Histological classification of salivary gland tumors (WHO 1991)

1. Adenomas
   - Pleomorphic adenoma
   - Myoepithelioma (myoepithelial adenoma)
   - Basal cell adenoma
   - Warthin's tumor (adenolymphoma)
   - Oncocytoma (oncocytic adenoma)
   - Canalicular adenoma
   - Sebaceous adenoma
   - Ductal papilloma
     - Inverted ductal papilloma
     - Intraductal papilloma
     - Sialadenoma papilliferum
   - Cystadenoma
     - Papillary cystadenoma
     - Mucinous cystadenoma
2. Carcinomas
   - Acinic cell carcinoma
   - Mucoepidermoid carcinoma
   - Adenoid cystic carcinoma
   - Polymorphous low grade adenocarcinoma (terminal duct adenocarcinoma)
   - Epithelial-myoepithelial carcinoma
   - Basal cell adenocarcinoma
   - Sebaceous carcinoma
   - Papillary cystadenocarcinoma
   - Mucinous adenocarcinoma
   - Oncocytic carcinoma
   - Salivary duct carcinoma
   - Adenocarcinoma
   - Malignant myoepithelioma (myoepithelial carcinoma)
   - Carcinoma in pleomorphic adenoma (malignant mixed tumor)
   - Squamous cell carcinoma
   - Small cell carcinoma
   - Undifferentiated carcinoma
   - Other carcinomas
3. Nonepithelial tumors
4. Malignant lymphomas
5. Secondary tumors
6. Unclassified tumors
7. Tumor like lesions
   - Sialadenosis
   - Oncocytosis
   - Necrotizing sialometaplasia (salivary gland infarction)
   - Benign lymphoepithelial lesion
   - Salivary gland cysts
   - Chronic sclerosing sialadenitis of submandibular gland (Küttner tumor)
   - Cystic lymphoid hyperplasia in AIDS

Adapted from: Seifert G. Histological typing of salivary gland tumors, 2nd ed. Berlin, Springer-Verlag, 1991.

is responsible for the morphologic diversity of the tumor, including the production of the fibrous, mucinous, chondroid and osseous areas. Regezi and Batsakis postulated that the intercalated duct reserve cell can differentiate into ductal and myoepithelial cells and the latter, in turn, can undergo mesenchymal metaplasia, since they inherently have smooth muscle like properties. Further differentiation into other mesenchymal cells then can occur. Batsakis has discussed salivary gland tumorigenesis, and while still implicating the intercalated duct reserve cell as the histogenetic precursor of the pleomorphic adenoma, stated that the role of the myoepithelial cell is still uncertain and that it may be either an active or passive participant histogenetically. Finally, Dardick and his associates have questioned the role of both ductal reserve and myoepithelial cells. They state that a neoplastically altered epithelial cell with the potential for multidirectional differentiation may be histogenetically responsible for the pleomorphic adenoma.

Pleomorphic adenomas have shown consistent cytogenetic abnormalities, chiefly involving the chromosome region **12q13-15.** The putative pleomorphic adenoma gene (**PLAG1**) has been mapped to chromosome **8q12**. Many other genes have also been implicated; however, cytogenetic or molecular studies do not as yet have an established role in the diagnosis of pleomorphic adenoma.

Clinical Features. Pleomorphic adenoma is the most common tumor of salivary glands. The parotid gland is the most common site of the pleomorphic adenoma; 90% of a group of nearly 1,900 such tumors reported by Eneroth. It may occur in any of the major glands or in the widely distributed intraoral accessory salivary glands; however its occurrence in the sublingual gland is rare. In the parotid this tumor most often presents in the lower pole of the superficial lobe of the gland, about 10% of the tumors arise in the deeper portions of the gland. Approximately 8% of pleomorphic adenomas involve the minor salivary glands, the palate is the most common site (60–65%) of minor salivary gland involvement. It occurs more frequently in females than in males, the ratio approximating 6 : 4. The majority of the lesions are found in patients in the fourth to sixth decades with the average age of occurrence of about 43 years, but they are also relatively common in young adults and have been known to occur in children. The clinical behavior of this tumor in children is similar to that in adults (Table 3-4).

Table 3-4: TNM/AJCC 1997 staging (clinical staging)

TX: primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
- T2: Tumor > 2 cm but < 4 cm in greatest dimension without extraparenchymal extension*
- T3: Tumor having extraparenchymal extension* without seventh nerve involvement and/or more than 4 cm but no more than 6 cm in greatest dimension
- T4: Tumor invades base of skull, seventh nerve, and/or exceeds 6 cm in greatest dimension
- N0: No regional node metastasis
- Nx: Regional nodes cannot be assessed
- N1: Single ipsilateral node, < 3 cm
- N2a: Single ipsilateral node, > 3 cm and < 6 cm
- N2b: Multiple ipsilateral nodes, < 6 cm
- N2c: Contralateral or bilateral nodes, < 6 cm
- N3: Node > 6 cm
- M0: No distant metastasis
- Mx: Metastasis cannot be assessed

Minor salivary gland tumors are staged according to their site of origin.
Microscopic evidence alone does not constitute extraparenchymal extension for classification purpose.
**Extraparenchymal extension is clinical or macroscopic evidence of invasion of skin, soft tissues, bone or nerve.*

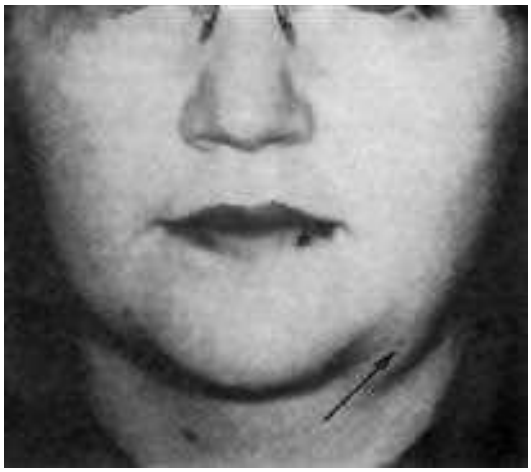


Figure 3-1. Pleomorphic adenoma of submaxillary gland.

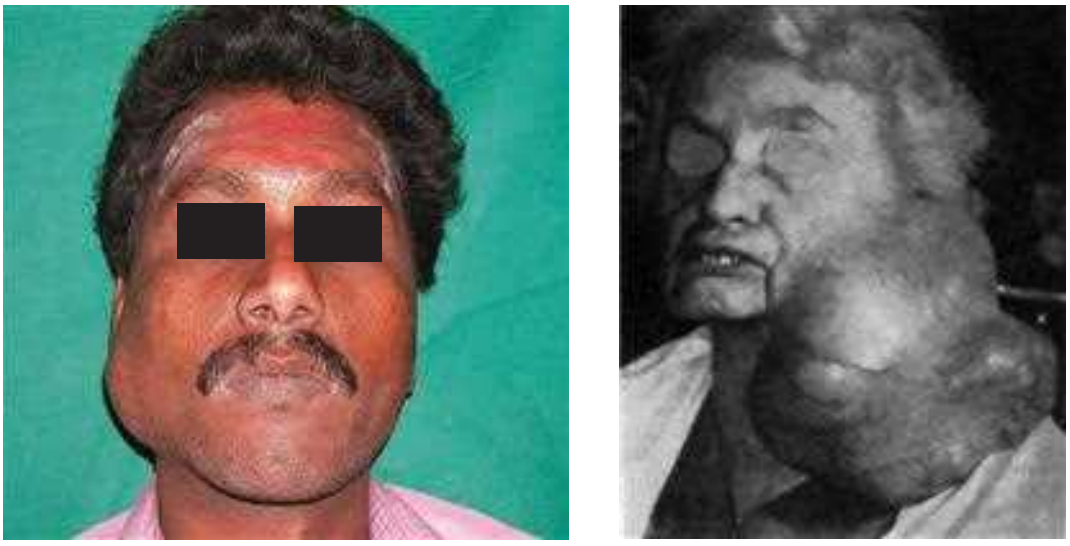
The history presented by the patient is usually that of a small, painless, quiescent nodule which slowly begins to increase in size, sometimes showing intermittent growth (Fig. 3-1). The pleomorphic adenoma, particularly of the parotid gland, is typically a lesion that does not show fixation either to the deeper tissues or to the overlying skin (Fig. 3-2 A). It is usually an irregular nodular lesion which is firm in consistency, although areas of cystic degeneration may sometimes be palpated if they are superficial. The skin seldom ulcerates even though these tumors may reach a fantastic size, lesions having been recorded which weighed several kilograms (Fig. 3-2 B). Pain is not a common symptom of the pleomorphic adenoma, but local discomfort is frequently present. Facial nerve involvement manifested by facial paralysis is rare.

The pleomorphic adenoma of intraoral accessory glands seldom is allowed to attain a size greater than 1–2 cm in diameter. Because this tumor causes the patient difficulties in mastication, talking and breathing, it is detected and treated earlier than tumors of the major glands. The palatal glands are frequently the site of origin of tumors of this type (Fig. 3-3), as are the glands of the lip (Fig. 3-4) and occasionally other sites. Except for size, the intraoral tumor does not differ remarkably from its counterpart in a major gland. The palatal pleomorphic adenoma may appear fixed to the underlying bone, but is not invasive. In other sites the tumor is usually freely movable and easily palpated. Recurrent lesions, however, occur as multiple nodules and are less mobile than the original tumor (Table 3-5).

Histologic Features

Macroscopic features. The mixed tumors generally appear as an irregular to ovoid mass with well-defined borders. The tumors in major glands have either an incomplete fibrous capsule or are unencapsulated whereas in the minor glands they are unencapsulated. The cut surface may be rubbery, fleshy, mucoid or glistening with a homogeneous tan or white color. Areas of hemorrhage and infarction may be noted occasionally.

Microscopic features. Morphologic diversity is the most characteristic feature of this neoplasm. Microscopically, benign mixed tumors are characterized by variable, diverse, structural histologic patterns, seldom do individual cases resemble each other, considerable variation is also seen within a single tumor. Pleomorphic adenomas demonstrate combinations of glandular epithelium and mesenchyme like tissue and the proportion of each component varies widely among individual tumors. Foote and Frazell (1954) categorized the tumor into the following types:



A B

Figure 3-2. Pleomorphic adenoma of parotid gland.
(A) Typical appearance of pleomorphic adenoma of parotid gland. **(B)** The lesion here is used not to illustrate the usual clinical appearance of a pleomorphic adenoma of the parotid gland, but to demonstrate the size which these tumors may attain. This lesion was present for eighteen years *(A, Courtesy of Dr Neelakandan RS, Department of Oral and Maxillofacial Surgery, Meenakshi Ammal Dental College, Chennai).*

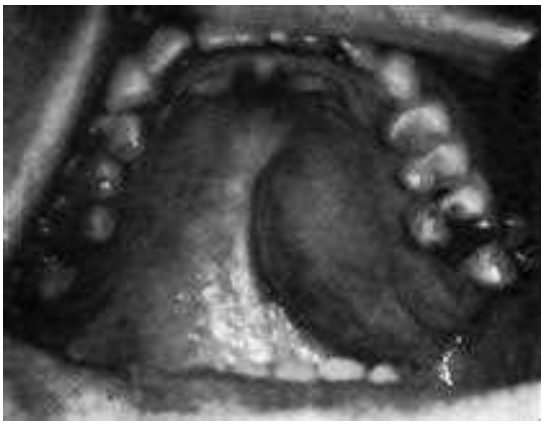


Figure 3-3. Pleomorphic adenoma of palate.

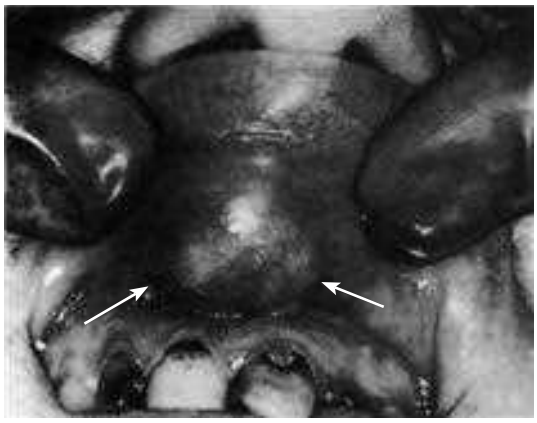


Figure 3-4. Pleomorphic adenoma of lip.

Table 3-5: Salivary gland tumors: comparative frequency of occurrence of tumors reported from eight tumor registries of India

City	Male						Female					
	No. of cases	Freq. (per-centage)	Crude ASR rate world (per 100,000)		Cum. rates (percentage)		No. of cases	Freq. (per-centage)	Crude ASR rate world (per 100,000)		Cum. rates (percentage)	
					0–64	0–74					0–64	0–74
Bangalore	35	0.5	0.3	0.4	0.02	0.04	28	0.3	0.2	0.3	0.02	0.03
Delhi	80	0.5	0.4	0.5	0.04	0.06	60	0.4	0.3	0.5	0.04	0.05
Karunagapally	3	0.3	0.3	0.3	0.02	0.02	2	0.3	0.2	0.2	0.01	0.01
Mumbai	100	0.5	0.3	0.5	0.03	0.06	59	0.3	0.2	0.3	0.02	0.03
Nagpur	12	0.5	0.4	0.6	0.04	0.07	13	0.6	0.5	0.7	0.05	0.05
Pune	28	0.6	0.4	0.6	0.04	0.07	12	0.2	0.2	0.2	0.02	0.03
Trivandrum	13	0.7	0.5	0.5	0.02	0.05	10	0.5	0.4	0.4	0.02	0.05
Ahmedabad	38	0.6	0.4	0.6	0.04	0.06	24	0.5	0.3	0.4	0.03	0.05

Modified from: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, Volume VIII, IARC Scientific Publications No. 155, 2002, IARC, Lyon, France.

Table 3-6: Typical features of benign and malignant salivary gland tumors

Benign salivary gland tumors	Malignant salivary gland tumors
• Slow growing	• Sometimes fast growing
• Soft or rubbery consistency	• Sometimes hard consistency
• 85% of parotid tumors are benign	• 45% of minor glands are malignant
• Do not ulcerate	• May ulcerate and invade bone
• No associated nerve signs	• May cause cranial nerve palsies (e.g. parotid tumor causes facial palsy, adenoid cystic carcinoma can cause multiple nerve lesions especially of lingual, facial or hypoglossal nerves)

- Principally myxoid
- Myxoid and cellular components present in equal proportion
- Predominantly cellular
- Extremely cellular.

The epithelial component forms ducts and small cysts that may contain an eosinophilic coagulum, the epithelium may also occur as small cellular nests, sheets of cells, anastomosing cords and foci of keratinizing squamous or spindle cells. Myoepithelial cells are a major component of pleomorphic adenoma. They have a variable morphology, sometimes appearing as angular or spindled, while some cells are more rounded with eccentric nuclei and hyalinized eosinophilic cytoplasm resembling plasma cells (earlier referred to as **hyaline cells**) (Fig. 3-5). Myoepithelial-cells are also responsible for the characteristic mesenchyme like changes; these changes are brought about by extensive accumulation of mucoid material around individual myoepithelial cells giving a myxoid appearance. Vacuolar degeneration of these myoepithelial cells then results in a cartilaginous appearance (Fig. 3-6). Foci of hyalinization, bone and even fat can be noted in the connective tissue stroma of many tumors. When the

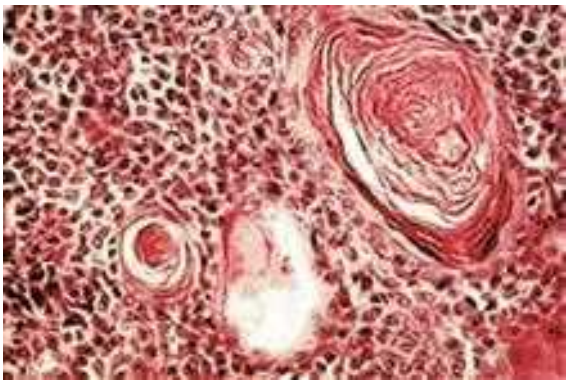
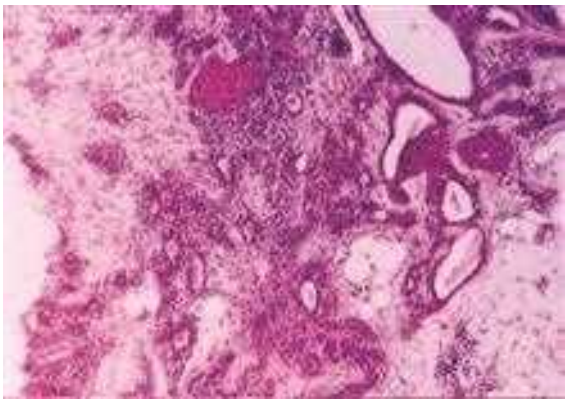
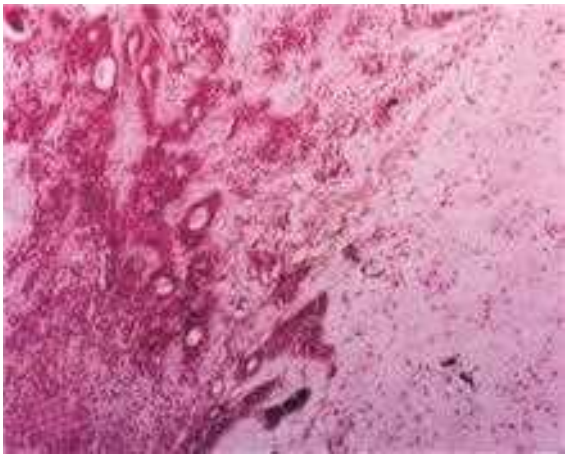


Figure 3-5. Pleomorphic adenoma.
Keratinizing epithelium in a background of plasmacytoid myoepithelial cells *(Courtesy of Dr Albert Abrams).*



A



B

Figure 3-6. Pleomorphic adenoma.
Neoplastic cells are seen arranged in ductal pattern, sheets and islands. Stroma is delicately collagenous with myxoid areas. Few cells show vacuolar degeneration and are chondroid in appearance **(A and B)**.

pleomorphic pattern of the stroma is absent, and the tumor is highly cellular, it is often referred to as a 'cellular adenoma'. When myoepithelial proliferation predominates, the diagnosis of 'myoepithelioma' (q.v.) is generally made.

Treatment and Prognosis. The accepted treatment for this tumor is surgical excision. The intraoral lesions can be treated somewhat more conservatively by extracapsular excision. Since these tumors are radioresistant, the use of radiation therapy is of little benefit and is therefore contraindicated.

Rarely, a malignant tumor may arise within this tumor, a phenomenon known as *carcinoma ex pleomorphic adenoma.* There is a second class of tumors which are called *metastasizing benign mixed tumors.* These tumors have a histologically benign appearance but usually have a history of multiple local recurrences. Metastases occur several years after the initial diagnosis and may occur to the lungs, regional lymph nodes, skin, and bone. The usual clinical course is good but there are cases which have an aggressive clinical course leading to death in 22% of cases. Fortunately this last category of tumors is very rare.

Myoepithelioma
(Myoepithelial adenoma)

The term myoepithelioma was first used by Sheldon in 1943. The myoepithelioma is an uncommon salivary gland tumor which accounts for less than 1% of all major and minor salivary tumors. Nonetheless, it is important in that the component cell constitutes a prominent place in salivary gland neoplasia. Many authorities, including Batsakis, consider the myoepithelioma to be a 'one-sided' variant at the opposite end of the spectrum from the pleomorphic adenoma.

Clinical Features. There are no clinical features which can serve to separate the myoepithelioma from the more common pleomorphic adenoma. It occurs in adults with an equal gender distribution. The parotid gland is most commonly involved and the palate is the most frequent intraoral site of occurrence. Sciubba and Brannon reported lesions in the retromolar glands and the upper lip.

Histologic Features. The tumor is composed exclusively, or almost exclusively, of neoplastic myoepithelial cells. The neoplastic cells are predominantly spindle-shaped or plasmacytoid. Epithelioid or clear cells may also be present (Figs. 3-7, 3-8). Either a single cell type predominates in a tumor or there may be a combination of cell types. The tumor is often difficult to diagnose definitively at the light microscopic level. Myoepithelioma does not contain the characteristic chondromyxoid stroma of pleomorphic adenoma. Myoepithelioma consisting predominantly of spindle cells tends to be more cellular than the tumor consisting of predominantly plasmacytoid cells. Definitive diagnosis lies in the ultrastructural identification of myoepithelial cells. The myoepithelial cell exhibits a basal lamina and fine intracytoplasmic myofilaments. Desmosomes are encountered between adjacent cells.

Treatment and Prognosis. The tumor is treated by surgical excision. The same surgical principles apply as in treating pleomorphic adenomas. Only one recurrence was noted in 16 cases in which follow-up was available.

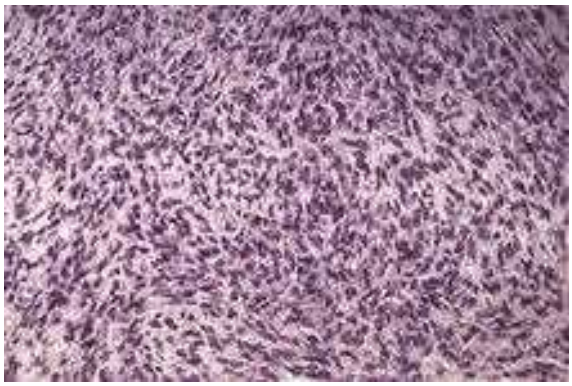


Figure 3-7. Myoepithelioma composed of spindle-shaped myoepithelial cells.

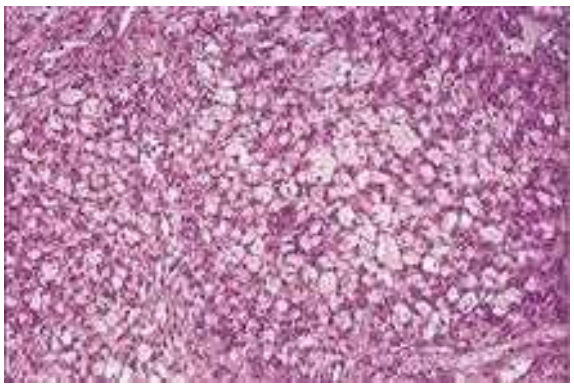


Figure 3-8. Myoepithelioma.
The cells are present in groups separated by a loose, myxoid stroma.

Basal Cell Adenoma

Basal cell adenoma is a neoplasm of a uniform population of basaloid epithelial cells arranged in solid, trabecular, tubular, or membranous patterns. The basal cell adenoma was first reported as distinct entity by Kleinsasser and Klein in 1967. Batsakis is credited with reporting the first case in the American literature in 1972, and suggested that the intercalated duct or reserve cell is the histogenetic source of the basal cell adenoma.

Clinical Features. Basal cell adenomas tend to occur primarily in the major salivary glands, particularly the parotid gland. In the series reported by Batsakis and associates, 48 of 50 tumors were in the parotid gland and two were in the submaxillary gland. The tumors are usually painless and are characterized by slow growth. They occur chiefly in adults, the average age of the patients is 57.7 years with the peak of incidence seen in the sixth decade. However, the tumor can occur in younger persons, Canalis and his coworkers reported a basal cell adenoma in the submaxillary gland of a newborn male. There is a 2 : 1 female predilection for the occurrence of this tumor. These tumors appear as a firm swelling which may be cystic and compressible. These tumors are clinically indistinguishable from mixed tumors and their greatest dimension is usually less than 3 cm.

Histologic Features

Macroscopic features. Basal cell adenoma occurs as a single well-defined nodule, the membranous type may be multifocal. Tumors in major salivary gland have a well defined capsule, whereas intraoral tumors are less well defined. The cut surface often is homogeneous with gray to brown in color, and may have cystic areas.

Microscopic features. The basal cells that make up this lesion are fairly uniform and regular; two morphologic forms can be seen. One is a small cell with scanty cytoplasm and round deeply basophilic nucleus. The other cell is large with eosinophilic cytoplasm and an ovoid pale staining nucleus. Basal cell adenomas can be divided on the basis of their morphologic appearances into four subtypes:

- Solid
- Tubular
- Trabecular
- Membranous.

Solid type. The most common type of basal cell adenoma is the solid variant. The basaloid cells form islands and cords that have a broad, rounded, lobular pattern. These cells are sharply demarcated from the connective tissue stroma by basement membrane. This feature contrasts with the melting type of growth characteristic of pleomorphic adenoma.

Tubular type. This pattern exhibits multiple small, round duct like structures. These tubules are lined by two distinct layers of cells, with inner cuboidal ductal cells surrounded by an outer layer of basaloid cells. The tubular variant is the least common; however, tubule formation either alone or with basal cell masses, can be found in most basal cell adenomas, at least focally (Fig. 3-9).

Trabecular type. This subtype has the same cytologic features as the solid type, but the epithelial islands are narrower and cord like and are interconnected with one another, producing a reticular pattern (Fig. 3-10).

Membranous type. This is a distinct subtype of basal cell adenoma characterized by the presence of abundant, thick, eosinophilic hyaline layer that surrounds and separates the epithelial islands. Electron microscopy has shown that this hyaline material is reduplicated basement membrane. The epithelial islands are arranged in large lobules and appear to mould to the shape of other lobules to resemble a jigsaw puzzle pattern.

Treatment and Prognosis. The tumor is treated by excision and recurrences are seldom seen.

Warthin's Tumor

(Papillary cystadenoma lymphomatosum, adenolymphoma)

Warthin's tumor is the second most common tumor in the salivary glands. This tumor was first recognized by Albrecht in 1910 (quoted by Ellis and Auclair 1991) and later described by Warthin in 1929. This unusual type of salivary gland tumor

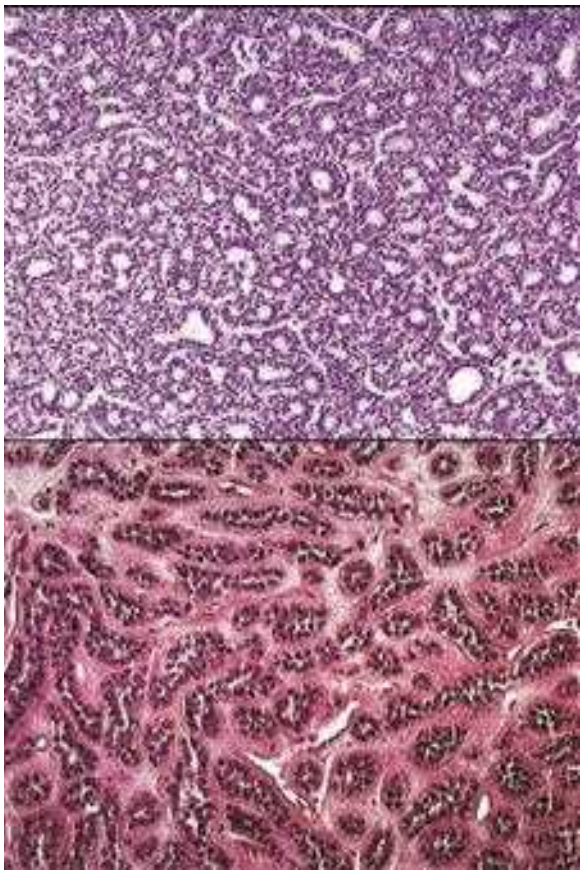


Figure 3-9. Basal cell adenoma — Tubular variant.

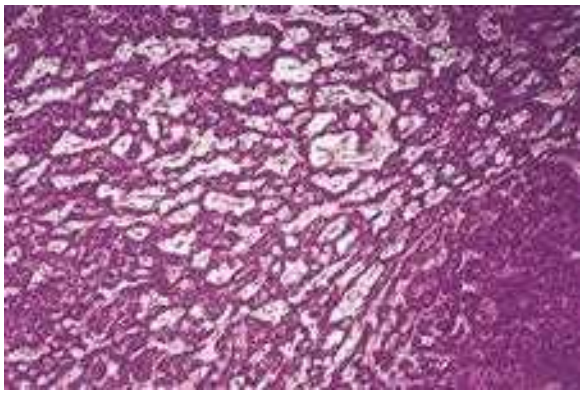


Figure 3-10. Basal cell adenoma has a trabecular pattern.

occurs almost exclusively in the parotid gland, although occasional cases have been reported in the submaxillary gland. The intraoral accessory salivary glands are rarely affected.

Histogenesis. Numerous theories have been advanced to account for the peculiar nature of this tumor. The currently accepted theory is that the tumor arises in salivary gland tissue entrapped within paraparotid or intraparotid lymph nodes during embryogenesis. However, Allegra has suggested that the Warthin's tumor is most likely a delayed hypersensitivity disease, the lymphocytes being an immune reaction to the salivary ducts which undergo oncocytic change. Hsu and coworkers recently studied the tumor immunohistochemically and have suggested that the lymphoid component of the tumor is an exaggerated secretory immune response.

A strong association between development of this tumor and smoking is documented. The exact mechanism by which smoking may predispose patients to Warthin's tumor is unclear. However, several studies have shown that a high percentage of Warthin's tumor patients smoke. Epstein-Barr virus has also been implicated in the pathogenesis of this tumor; however there are many conflicting reports.

Clinical Features. Warthin's tumor was traditionally considered a disease of men. However, recent reports have identified a substantial percentage of patients who are women. This tumor commonly presents in the sixth and seventh decades and average age of the patients at the time of diagnosis of the lesion was 62 years. The tumor is generally superficial, lying just beneath the parotid capsule or protruding through it. Seldom does the lesion attain a size exceeding 3–4 cm in diameter. It is not painful, is firm to palpation and is clinically indistinguishable from other benign lesions of the parotid gland.

Histologic Features

Macroscopic features. It is a smooth, somewhat soft parotid mass and is well encapsulated when located in the parotid. The tumor contains variable number of cysts that contains a clear fluid. Areas of focal hemorrhage may also be seen.

Microscopic features. This tumor is made up of two histologic components: epithelial and lymphoid tissue. As the name would indicate, the lesion is essentially an adenoma exhibiting cyst formation, with papillary projections into the cystic spaces and a lymphoid matrix showing germinal centers (Fig. 3-11). The cysts are lined by papillary proliferations of bilayered oncocytic epithelium. The inner layer cells are tall columnar with finely granular and eosinophilic cytoplasm due to presence of mitochondria and slightly hyperchromatic nuclei. The outer layer cells are oncocytic triangular and occasionally fusiform basaloid

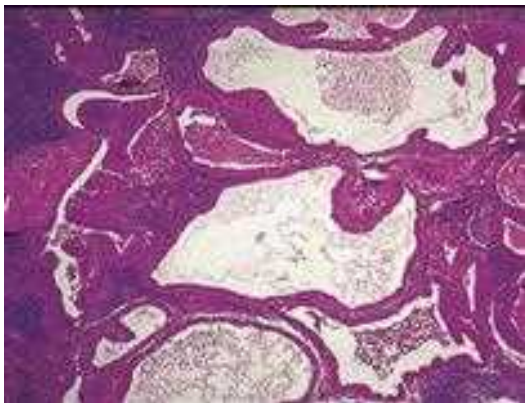


Figure 3-11. Warthin's tumor.
Figure shows cystic spaces partially filled with homogeneous fluid circumscribed by double rows of oncocytes having a stroma richly infiltrated by lymphoid tissue.

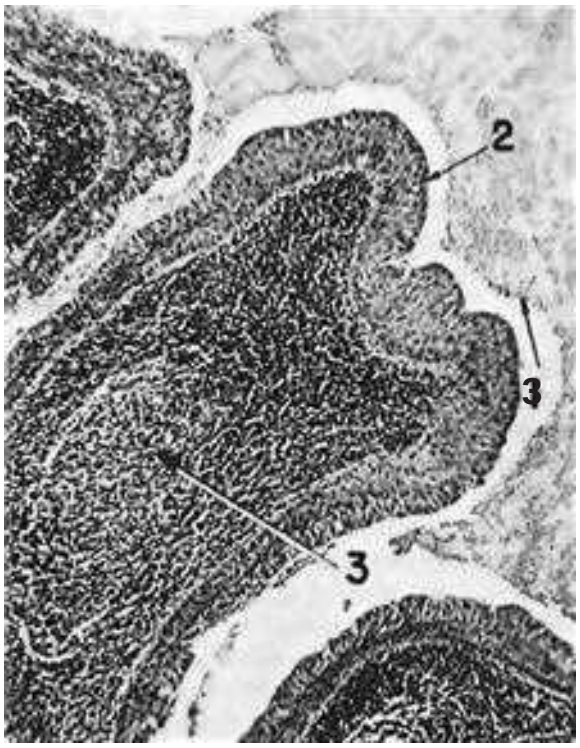


Figure 3-12. Papillary cystadenoma lymphomatosum.
Photomicrograph illustrating cystic cavity (1), epithelium (2), lymphocytes and (3), lymphoid follicle *(Courtesy of Dr Frank Vellios)*.

cells. Focal areas of squamous metaplasia and mucous cell prosoplasia may be seen. There is frequently an eosinophilic coagulum present within the cystic spaces, which appears as a chocolate-colored fluid in the gross specimen. The abundant lymphoid component may represent the normal lymphoid tissue of the lymph node within which the tumor developed or it may actually represent a reactive cellular infiltrate which involves both humoral and cell mediated mechanisms (Fig. 3-12).

Treatment and Prognosis. The accepted treatment of the papillary cystadenoma lymphomatosum is surgical excision. This can almost invariably be accomplished without injury to the facial nerve, particularly since the lesion is usually small and superficial. These tumors are well encapsulated and seldom recur after removal.

Malignant transformation is exceedingly rare in either the epithelial or lymphoid component. Cases of mucoepidermoid carcinoma involving Warthin's tumor of the parotid gland have been reported; however, a direct transition from Warthin's tumor to mucoepidermoid carcinoma was not identified.

Oncocytoma
(Oncocytic adenoma, oxyphilic adenoma, acidophilic adenoma)

Oncocytoma is a rare benign tumor composed of oncocytes with granular eosinophilic cytoplasm and a large number of atypical mitochondria. This rare salivary gland tumor is a small benign lesion, which usually occurs in the parotid gland. Except that it does not generally attain any great size, it does not differ in its clinical characteristics from other benign salivary gland tumors. For this reason, a clinical diagnosis is difficult if not impossible to establish. The name 'oncocytoma' is derived from the resemblance of these tumor cells to apparently normal cells which have been termed 'oncocytes' and which are found in a great number of locations, including the salivary glands, respiratory tract, breast, thyroid, pancreas, parathyroid, pituitary, testicle, fallopian tube, liver and stomach. These cells are predominantly seen in duct linings of glands in elderly persons, but little is actually known of their mode of development or significance (Fig. 3-13). Electron microscopic studies have shown that the cytoplasm of the oncocyte is choked with mitochondria. Ionizing radiation is the predisposing condition.

Clinical Features. The oncocytoma is somewhat more common in women than in men and occurs almost exclusively in elderly persons. Chaudhry and Gorlin, who reviewed the literature, found 29 cases of oncocytoma and added four new cases to those reported. Only occasionally does this tumor arise before the age of 60 years, 80% of cases occurring between the ages of 51 and 80 years. The tumor usually measures 3–5 cm in diameter and appears as a discrete, encapsulated mass which is sometimes nodular. Pain is generally absent.

An interesting condition called diffuse multinodular oncocytoma or 'oncocytosis' of the parotid gland has been described by Schwartz and Feldman. This condition is characterized by nodules of oncocytes which involve the entire gland or large portions of it.

Histologic Features. The oxyphilic adenoma is characterized microscopically by large cells which have an eosinophilic cytoplasm and distinct cell membrane and which tend to be arranged in narrow rows or cords (Fig. 3-13). The oncocytes are arranged in sheets or nests and cords, which form alveolar or organoid pattern. Some degree of cellular atypia, nuclear hyperchromatism and pleomorphism is accepted as compatible with benignancy in oncocytoma. These cells, exhibiting few mitotic figures, are closely packed, and there is little supportive stroma (Fig. 3-14). Lymphoid tissue is frequently present, but does not appear to be an integral part of the lesion. Ultrastructural studies of parotid oncocytomas by Tandler and associates and Kay and Still have shown that the cells are engorged with enlarged and morphologically altered mitochondria.

A variant of the oxyphilic adenoma is sometimes seen in intraoral salivary glands, particularly in the buccal mucosa and upper lip. This has been termed, an oncocytic cystadenoma since it is a tumor like nodule composed chiefly of numerous dilated duct like or cyst like structures lined with oncocytes. In recurrent tumors, there may be marked clear cell change and these tumors may be referred to as **clear-cell oncocytoma**.

Treatment and Prognosis. The treatment of choice is surgical excision, and the tumor does not tend to recur. Malignant transformation is uncommon, but malignant oncocytoma is now a well-established entity. Johns and associates reviewed the literature on malignant oncocytomas

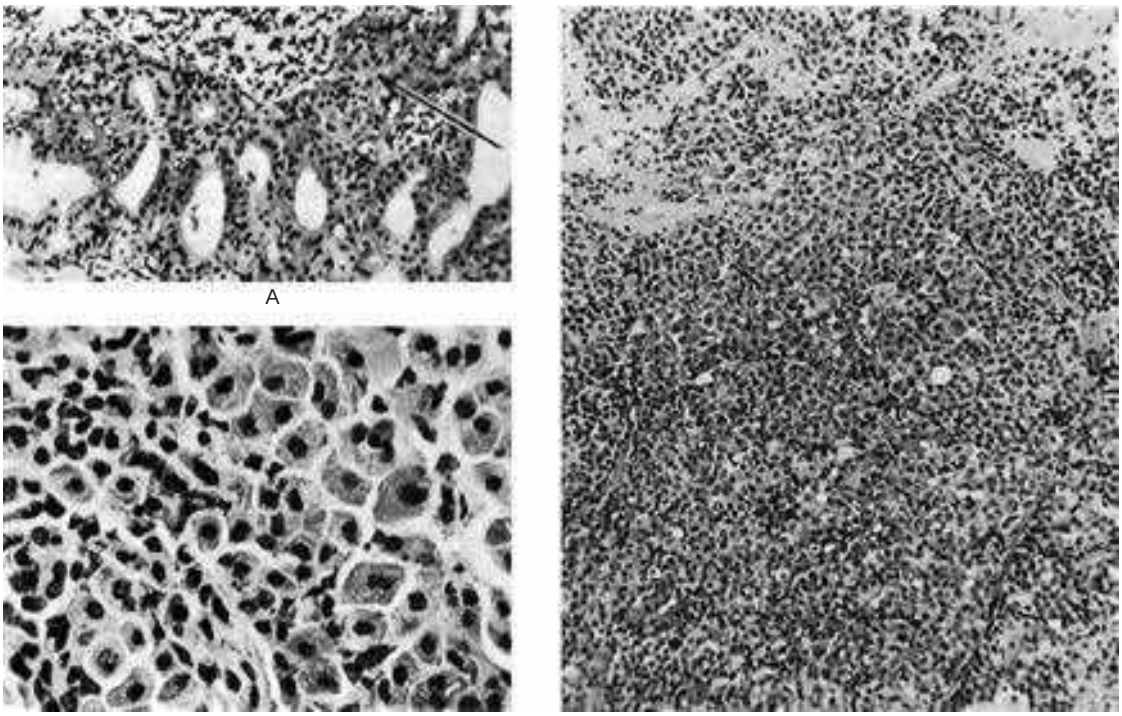


Figure 3-13. Oxyphilic adenoma.
(A) Normal oncocytes in accessory salivary gland ducts of elderly patient. **(B)** High-power photomicrograph. **(C)** Low-power photomicrograph of oncocytoma.

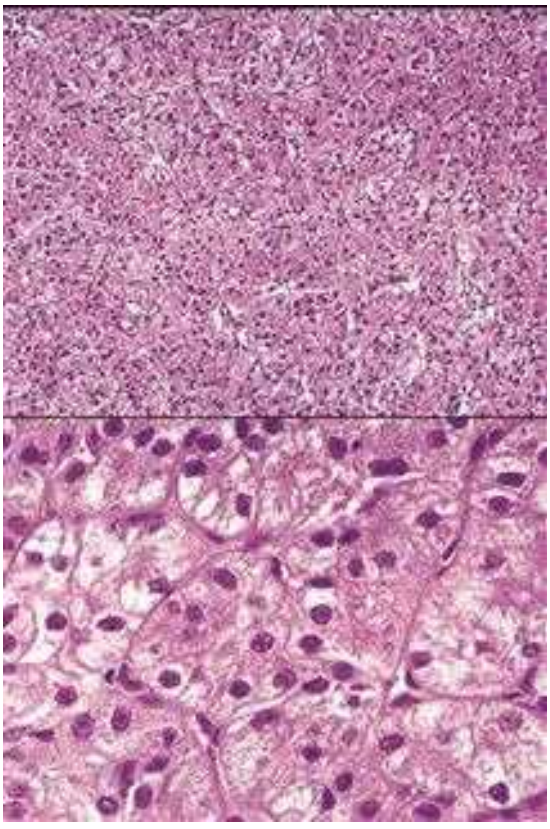


Figure 3-14. Oncocytoma alveolar pattern.
Illustrated by clusters of oncocytes that are supported by thin, fibrous connective tissue septa and small blood vessels. Note oncocytes have clear cytoplasm that is interspersed with cytoplasmic granularity.

and reported three additional cases. Other well-documented cases have been those of Lee and Roth, and Gray and his coworkers.

Canalicular Adenoma

Canalicular adenoma is an uncommon neoplasm composed of columnar epithelial cells arranged in a single or double layer forming branching cords in a loose stroma. The bilayer shows an intermittent separation, which forms structures resembling lumen or canaliculi.

Clinical Features. This lesion originates primarily in the intraoral accessory salivary glands, and in the vast majority of cases, it occurs in the upper lip. However, cases are known in which the lesion occurred in the palate, buccal mucosa and lower lip. Only one was noted in the parotid gland in the series reported by Nelson and Jacoway. The tumor occurs in adults far more common in patients of age 34–65 years; this tumor is seen more commonly in females with a ratio of 1.8 : 1. The tumor generally presents as a slowly growing, well-circumscribed, firm nodule which, particularly in the lip, is not fixed and may be moved through the tissue for some distance. Occasionally, two separate and distinct tumors may occur in the upper lip of an individual.

Histologic Features. The canalicular adenoma has a strikingly characteristic picture. It is composed of long columns or cords of cuboidal or columnar cells in a single layer. These single layers of cells are parallel, forming long canals. Sometimes rows of cells are closely approximated and appear as a double row of cells showing a 'party wall'. In some instances,

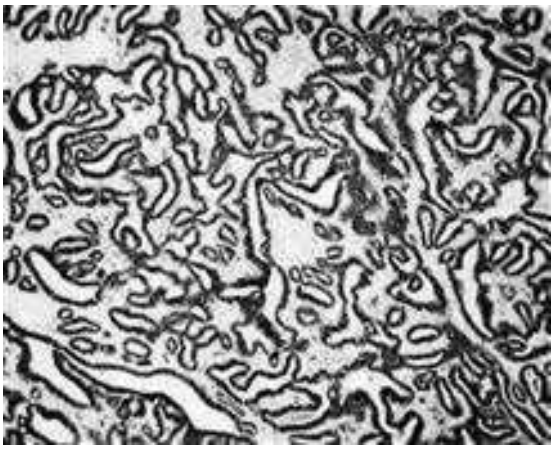


Figure 3-15. Canalicular adenoma.

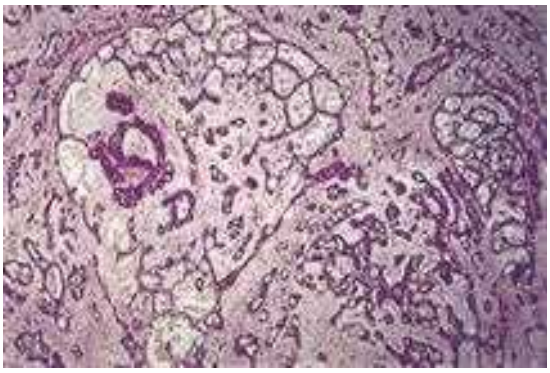


Figure 3-16. Canalicular adenoma.
The tumor shows single rows of cells that are arranged in parallel lines which form long lumina that have a 'canalicular' appearance.

cystic spaces of varying sizes are enclosed by these cords. The cystic spaces are usually filled with an eosinophilic coagulum. The supporting stroma is loose and fibrillar with delicate vascularity (Fig. 3-15). The tumor has, at times, been mistaken for an adenoid cystic carcinoma and care should be taken to prevent this error (Fig. 3-16). As Mader and Nelson have pointed out, the adenoid cystic carcinoma rarely occurs in the upper lip and is seldom freely movable. Occasionally the tumor may be multifocal and foci of tumor cells are found outside the main lesion.

Treatment and Prognosis. The tumor can be treated by enucleation or simple surgical excision; recurrence is rare.

Sebaceous Adenoma

Sebaceous adenoma is a rare benign tumor that accounts for 0.1% of all salivary gland neoplasms and slightly less than 0.5% of all salivary adenomas. The mean age at initial clinical presentation was 58 years (range 22–90 years). This tumor is more common in men. In a series of cases reported by Ellis et al (1991), 12 tumors were located in the parotid gland, 4 in the buccal mucosa, two in the submandibular gland, and three in the area of lower molars or retromolar region. The tumors ranged in size from 0.42–3.0 cm in diameter.

The tumors are commonly encapsulated or sharply circumscribed, and they vary in color from grayish-white to pinkish-white to yellow or yellowish gray. These tumors are composed of sebaceous cell nests with minimal atypia and pleomorphism and no tendency to invade local structures. Many tumors are microcystic or may be composed predominantly of ectatic salivary ducts with focal sebaceous differentiation. The sebaceous glands may vary markedly in size and in tortuosity and are usually embedded in a fibrous stroma. Occasionally tumors demonstrate marked oncocytic metaplasia, and histiocytes and/or foreign body giant cells may be seen focally. Lymphoid follicles, cytologic atypia, cellular necrosis, and mitosis are not observed in sebaceous adenomas.

Conservative excision seems to be the treatment of choice. No recurrences have been reported.

Ductal Papilloma

The term ductal papilloma is used to identify a group of three rare benign papillary salivary gland tumors. They represent adenomas with unique papillary features and arise from the salivary gland duct system. There are three types with unique histopathological features. These are inverted ductal papilloma, intraductal papilloma, and sialadenoma papilliferum.

Inverted Ductal Papilloma. Inverted ductal papilloma was first described by White et al, in 1982. It is a very rare tumor and has been described only in minor salivary glands of adults. The lower lip is the most frequently involved site followed by buccal vestibular mucosa. Inverted ductal papillomas appear to arise from the excretory ducts near the mucosal surface. Clinically, these tumors are seen as submucosal nodules which may have a pit or indentation in the overlying surface mucosa. These tumors do not show any gender predilection.

Histologically, it consists of basaloid and squamous cells arranged in thick, bulbous papillary proliferations that project into the ductal lumen. The lumen of the tumor is often narrow and in some tumors communicates with the exterior of the mucosal surface through a constricted opening.

Intraductal Papilloma. Intraductal papilloma is an ill-defined lesion that often is confused with papillary cystadenoma. It usually occurs in adults, with a mean age of occurrence being 54 years and is common in the minor salivary glands. The lower lip is the most frequently involved site followed by upper lip, palate and buccal mucosa. No gender predilection has been noted. Intraductal papilloma presents clinically as a submucosal swelling. These tumors appear to arise from the excretory ducts at a deeper level than the inverted ductal papilloma.

Microscopically, it exhibits a unicystic dilated structure. The cyst wall is lined by a single or double row of cuboidal and columnar cells, which extend into the cyst lumen as papillary projections having thin fibrovascular cores.

Sialadenoma Papilliferum. Sialadenoma papilliferum most commonly involves the minor salivary gland. This has a more complex histology, with a biphasic growth pattern of exophytic papillary and endophytic components. This tumor usually affects adults, the average age of the patients is 56 years. A male predilection is seen. The clinical presentation is unique as nearly all salivary gland neoplasms manifest as subsurface nodular swellings whereas sialadenoma papilliferum occurs as an exophytic, papillary surface lesion. The clinical impression in most cases is squamous papilloma of the mucosa.

Microscopically, these tumors display both an exophytic and an endophytic proliferation of ductal epithelium. The surface of the lesion is formed of papillary projections of epithelium supported by fibrovascular cores, covered by parakeratotic stratified squamous epithelium. The fibrovascular cores have an inflammatory cell infiltrate of lymphocytes, plasma cells and neutrophils. The ductal epithelium continues downwards into the deeper connective tissues. Multiple ductal lumina are seen, which are lined by a double row of cells consisting of a luminal layer of tall columnar cells resting on a cuboidal basal layer.

Treatment. Surgical excision is curative and these tumors are not known to recur.

Cystadenoma

Cystadenomas of the salivary glands are benign neoplasms in which the epithelium demonstrates adenomatous proliferation that is characterized by formation of multiple cystic structures. Several morphologic variants of cystadenoma have been described of which papillary cystadenoma and mucinous cystadenoma are important. The papillary cystadenoma (PC) is defined as a cystadenoma in which the cystic space is filled with papillary projections. WHO described papillary cystadenoma as "a tumor that closely resembles Warthin's tumor but without the lymphoid elements, constituting multiple papillary projections and a greater variety of epithelial lining cells." If mucous cells predominate in the cell population of the lining epithelial cells, the tumor is termed as mucinous cystadenoma.

Clinical Features. Cystadenoma is widely distributed among major and minor salivary glands. Most of the minor salivary gland tumors are seen in lips, buccal mucosa, palate and the tonsillar area. This is more common in females than males (2:1) and occurs in older age, most common in the eighth decade of life. Clinically, it presents as a slow growing painless slightly compressible swelling. Some of the nodules are clinically similar to mucocele.

Histologic Features. Epithelial proliferation (Fig. 3-17) results in various sized cystic structures. The lining of these cystic structures varies from flattened to tall columnar cells, and cuboidal, mucous and oncocytic cells may also be seen. The lining thickness varies from one to three epithelial cells. Limited papillary growth with central connective tissue core is seen. Eosinophilic or slightly hematoxyphilic secretions are seen in the stroma. Dense fibrous connective tissue stroma with scattered inflammatory cells is present.

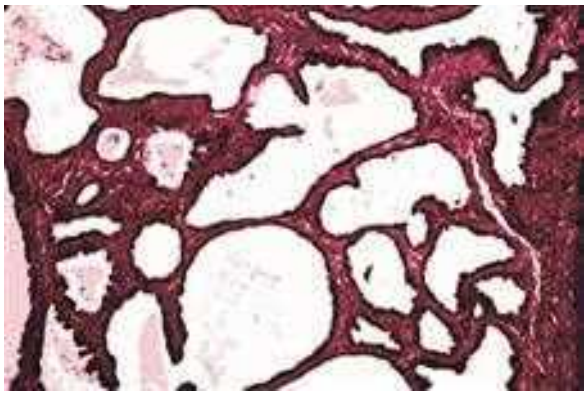


Figure 3-17. Cystadenoma.
Low-power photomicrograph of cystadenoma showing multicystic epithelial proliferation. The connective tissue stroma is scanty.

Treatment and Prognosis. No large series of cystadenoma with follow up information has been reported. At least one recurrence has been noted. The likelihood of recurrence is low. A conservative surgical procedure ensures complete removal.

MALIGNANT TUMORS OF THE SALIVARY GLANDS

Acinic Cell Carcinoma
(Acinar cell or serous cell adenoma, adenocarcinoma)

Most salivary gland tumors arise from the epithelium of the duct apparatus, but occasionally lesions seem to show acinar cell differentiation. Acinic cell carcinoma is a malignant epithelial neoplasm in which the neoplastic cells express acinar differentiation. Some authors advocate the existence of both benign and malignant acinic cell neoplasms, whereas others are of the opinion that all acinic cell neoplasms are malignant. Unfortunately, the criteria for distinguishing between benign and malignant acinar cell tumors, if such a distinction exists, have not been clearly established. In an extensive study of acinic cell tumors of the major salivary glands by Abrams and his coworkers, it was concluded that most investigators believe that all tumors of this type have at least a low-grade malignant potential. By conventional use, the term acinic cell carcinoma is defined by cytologic differentiation towards serous acinar cells (as opposed to mucous acinar cells), whose characteristic feature is cytoplasmic PAS-positive zymogen-type secretory granules. In AFIP data of salivary gland neoplasms, acinic cell carcinoma is the third most common malignant salivary gland epithelial neoplasm after mucoepidermoid carcinoma and adenocarcinoma. In this data, acinic cell carcinoma comprised 17% of primary malignant salivary gland tumors or about 6% of all salivary gland neoplasms (cited by Ellis GL, Auclair PL, Gnepp DR, 1991).

Clinical Features. The acinic cell carcinoma closely resembles the pleomorphic adenoma in gross appearance, tending to be encapsulated and lobulated. Although this tumor has been reported occurring chiefly in the parotid, with more than

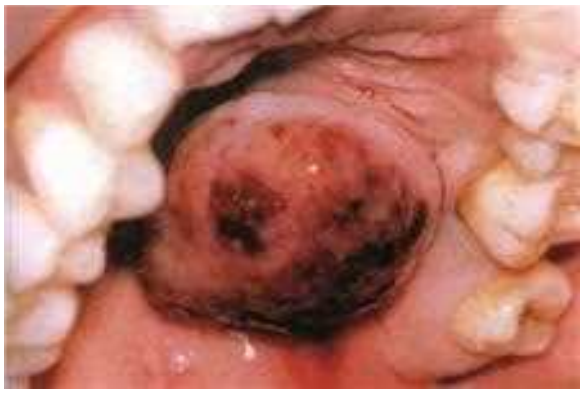


Figure 3-18. Acinic cell adenocarcinoma of the palate.

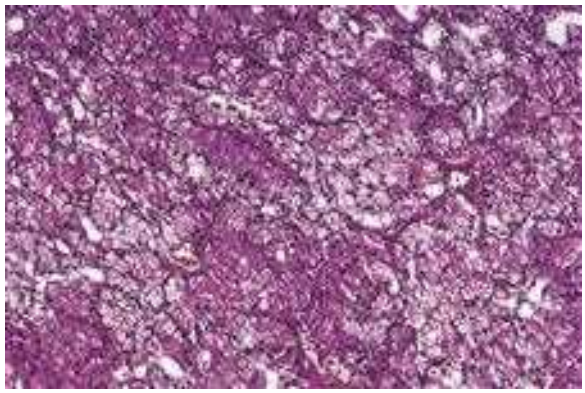


Figure 3-19. Acinic cell adenocarcinoma.

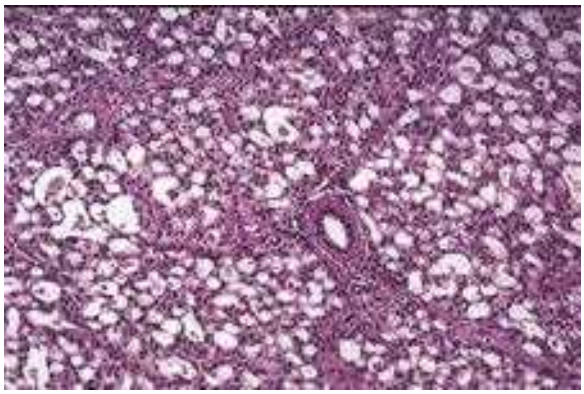


Figure 3-20. Acinic cell adenocarcinoma.
This group of moderately well differentiated acinar type cells in an acinic cell adenocarcinoma of the parotid gland have uniform, dark, round, eccentric nuclei and a basophilic cytoplasm. Occasional cells have cytoplasmic vacuoles.

80% of the cases occurring in the parotid gland, it does occur occasionally in the other major glands and in the accessory intraoral glands (Fig. 3-18). The most common intraoral sites are the lips and buccal mucosa. The acinic cell carcinoma occurs predominantly in persons in middle age or somewhat older, the mean age being 44 years. It has also been encountered in 12% of the patients before the age of 20 years. Women were affected more than men (3 : 2). This tumor presents as a slowly growing, mobile or fixed mass of various durations. Usually asymptomatic but pain or tenderness is seen in over one third of the patients. Facial muscle weakness may be seen. Patients with bilateral synchronous tumors have been reported.

Histologic Features. The acinic cell carcinoma, which is frequently surrounded by a thin capsule, may be composed of cells of varying degrees of differentiation. Well-differentiated cells bear remarkable resemblance to normal acinar cells, whereas less differentiated cells resemble embryonic ducts and immature acinar cells. Abrams and his associates have described four growth patterns: (1) solid, (2) papillary-cystic, (3) follicular, and (4) microcystic. In general, one pattern predominates, although combinations can occur. The most characteristic cell seen has the features of the serous acinar cells, with abundant granular basophilic cytoplasm and a round darkly stained eccentric nucleus. Other cells seen are the intercalated duct like cells, which are smaller and the vacuolated cells which seem to be unique to acinic cell carcinomas among salivary gland neoplasms.

Connective tissue stroma is delicately fibrovascular collagenous tissue. Lymphoid elements are commonly found in parotid acinic cell carcinomas, a feature which is helpful in the diagnosis. Such features are not found in the intraoral tumors. Apparently the acinic cell carcinoma can arise from embryologically entrapped salivary gland tissue in lymph nodes in or near the parotid compartment. Although 'clear cells,' have been described in acinic cell carcinomas, they most likely represent cells altered by fixation or they may actually represent the component cells of a clear cell carcinoma (q.v.), a recently recognized entity (Figs. 3-19, 3-20).

Treatment and Prognosis. The treatment of the acinic cell carcinoma in most cases has been surgical. Perzin and LiVolsi recommend total excision of parotid gland tumors with preservation of the facial nerve unless it is involved. Lymph node dissection is indicated only in the presence of clinical involvement and not as a routine procedure. Radiation therapy has not been shown to be of therapeutic value. Intraoral tumors are treated by surgical excision. Poor prognostic features included pain or fixation; gross invasion; and microscopic features of desmoplasia, atypia, or increased mitotic activity. Neither morphologic pattern nor cell composition was a predictive feature.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is a malignant epithelial tumor, first studied and described as a separate entity by Stewart, Foote and Becker in 1945. As the name implies, the tumor is composed of both mucus-secreting cells and epidermoid-type cells in varying proportions. Columnar and clear cells are also seen, and often demonstrate prominent cystic growth. It is the most common malignant neoplasm observed in the major and minor salivary glands. Mucoepidermoid carcinoma represents 29–34% of malignant tumors originating in both major and minor salivary glands. This carcinoma of the salivary glands accounts for 5% of all salivary gland tumors. The parotid

gland is the most common site of occurrence. Intraorally, mucoepidermoid carcinoma shows a strong predilection for the palate.

Clinical Features. Mucoepidermoid carcinoma occurs with a slight female predilection. It occurs primarily in the third or fifth decades of life, with an average age of 47 years, but can occur in virtually all decades. It is the most common malignant salivary gland tumor of children. Prior exposure to ionizing radiation appears to substantially increase the risk of developing mucoepidermoid carcinoma.

The tumor of low-grade malignancy usually appears as a slowly enlarging, painless mass which simulates the pleomorphic adenoma. Unlike the pleomorphic adenoma; however, the low-grade mucoepidermoid carcinoma seldom exceeds 5 cm in diameter, is not completely encapsulated and often contains cysts which may be filled with a viscid, mucoid material. In addition to palate intraoral tumors occur on the buccal mucosa, tongue and retromolar areas. Because of their tendency to develop cystic areas, these intraoral lesions may bear close clinical resemblance to the mucous retention phenomenon or mucocele, especially those in the retromolar area (Fig. 3-21).

The tumor of high-grade malignancy grows rapidly and does produce pain as an early symptom. Facial nerve paralysis is frequent in parotid tumors. The patient may also complain of trismus, drainage from the ear, dysphagia, numbness of the adjacent areas and ulceration, noted particularly in tumors of the minor salivary glands. The mucoepidermoid carcinoma is not encapsulated, but tends to infiltrate the surrounding tissue, and in a large percentage of cases, it metastasize to regional lymph nodes. Distant metastases to lung, bone, brain and subcutaneous tissues are also common.

Histologic Features. The mucoepidermoid carcinoma is composed of mucous secreting cells, epidermoid type (squamous) cells and intermediate cells. The mucous cells are of various shapes and have abundant, pale, foamy cytoplasm that stains positively for mucin stains. The epidermoid cells have squamoid features, demonstrate a polygonal shape, intercellular bridges and rarely keratinization. A population of cells that is often more important in recognizing mucoepidermoid carcinoma is a group of highly prolific, basaloid cells referred to as the intermediate cells. These cells are larger than basal cells and smaller than the squamous cells and are believed to be the progenitor of epidermoid and mucous cells. Occasionally clusters of clear cells can be present. These clear cells are generally mucin and glycogen free. Epidermoid cells, together with intermediate and mucous cells line cystic spaces or form solid masses or cords. Epidermoid and mucous cells may be arranged in a glandular pattern. The cysts may rupture liberating mucus which may pool in the connective tissue and evoke an inflammatory reaction (Fig. 3-22).

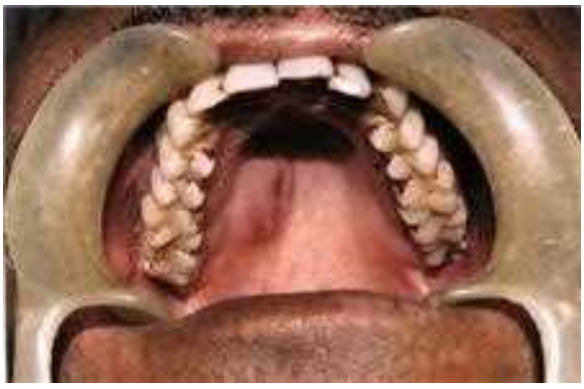


Figure 3-21. Mucoepidermoid carcinoma of palate.
(Courtesy of Dr Neelakandan RS, Department of Oral and Maxillofacial Surgery, Meenakshi Ammal Dental College, Chennai).

Mucoepidermoid carcinomas are graded as low-grade, intermediate-grade, and high-grade.

Low-grade tumors show well formed glandular structures and prominent mucin filled cystic spaces, minimal cellular atypia and a high proportion of mucous cells (Fig. 3-23).

Intermediate-grade tumors have solid areas of epidermoid cells or squamous cells with intermediate basaloid cells. Cyst formation is seen but is less prominent than that observed in low-grade tumors. All cell types are present, but intermediate cells predominate.

High-grade tumors consist of cells present as solid nests and cords of intermediate basaloid cells and epidermoid cells. Prominent nuclear pleomorphism and mitotic activity is noted. Cystic component is usually very less (<20%). Glandular component is rare although occasionally it may predominate. Necrosis and perineural invasion may be present.

Variants of Tumor

Sclerosing mucoepidermoid carcinoma. Although mucoepidermoid carcinoma is the most common primary malignancy of the salivary glands, the sclerosing morphologic variant of this tumor is extremely rare, with only six reported cases. As its name suggests, sclerosing mucoepidermoid carcinoma is characterized by an intense central sclerosis that occupies the entirety of an otherwise typical tumor, frequently with an inflammatory infiltrate of plasma cells, eosinophils, and/or lymphocytes at its peripheral regions.

The sclerosis associated with these tumors may obscure their typical morphologic features and result in diagnostic difficulties. Tumor infarction and extravasation of mucin resulting in reactive fibrosis are two mechanisms that have been suggested as the cause of this morphologic variant.

Intraosseous mucoepidermoid carcinoma. Mucoepidermoid carcinoma may originate within the jaws. This tumor type is known as central mucoepidermoid carcinoma. It is thought to form by the malignant transformation of the epithelial lining of odontogenic cysts. The tumor presents as an asymptomatic radiolucent lesion and is histologically of low-grade malignancy. The mandible is three times more commonly affected than the maxilla.

Treatment and Prognosis. Conservative excision with preservation of the facial nerve, if possible, is recommended for low- and intermediate-grade mucoepidermoid carcinomas of the parotid gland. The affected submandibular gland should

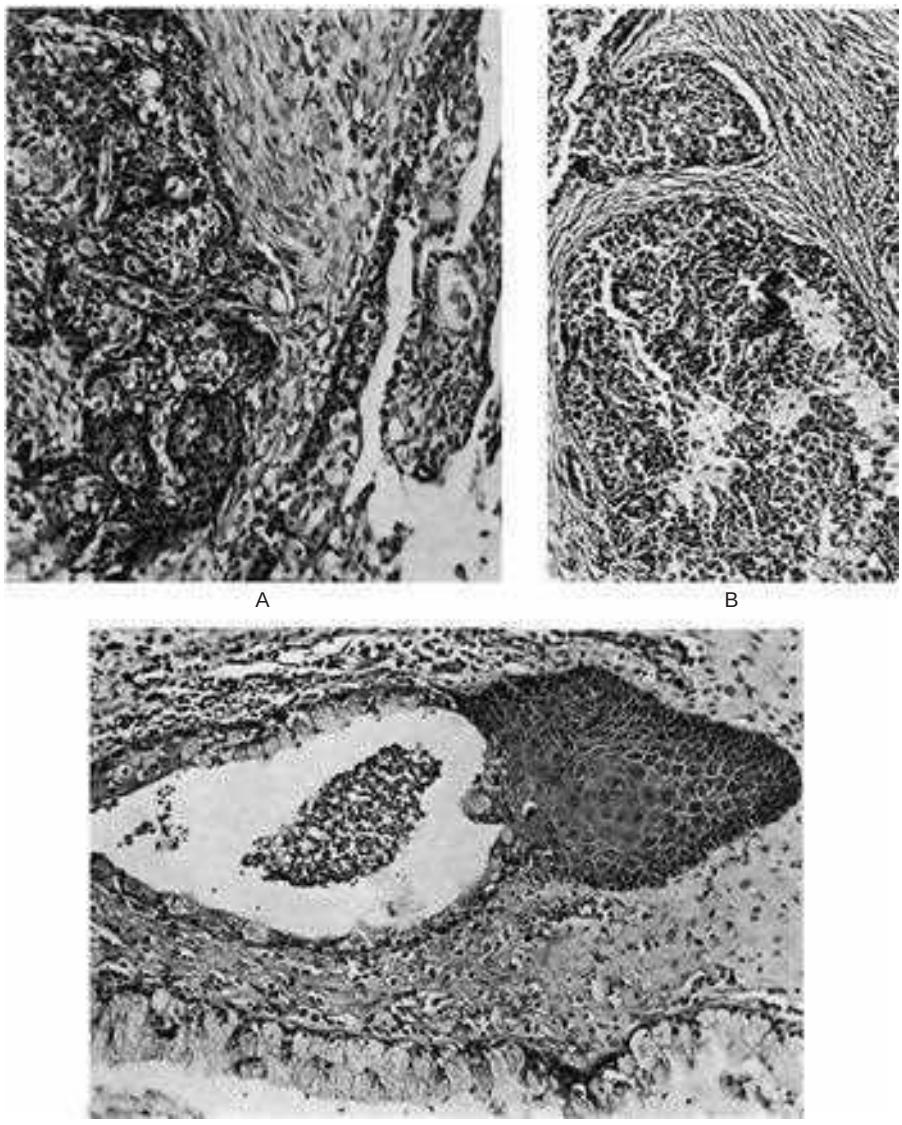


Figure 3-22. Mucoepidermoid carcinoma.
(A, B) Photomicrographs illustrate the association of the pale-staining, mucus-containing cells associated with darker staining epidermoid cells in a moderately high-grade mucoepidermoid carcinoma. **(C)** In one duct like structure the lining consists partially of squamous epithelium and partially of mucous cells *(From F Vellios: Am J Clin Pathol, 25: 147, 1955).*

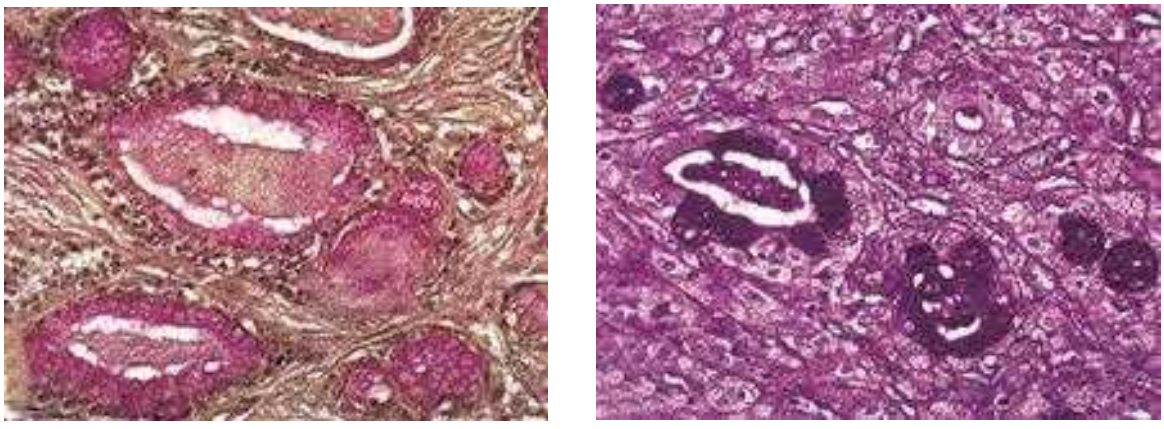


Figure 3-23. Mucoepidermoid carcinoma.
(A) Mucicarmine stain. **(B)** PAS stain. The two components of the tumor are large, pale, mucous secreting cells, which typically surround large or small cystic spaces and sheets of epidermoid cells.

be removed entirely. Radical neck dissection is performed in patients with clinical evidence of cervical node metastasis and is considered in any patient with a T3 lesion. Treatment for the minor glands is also primarily surgical. Some investigators have recommended postoperative irradiation only for high-grade malignancies, including high-grade mucoepidermoid carcinomas of the parotid glands. Few studies have assessed the role of chemotherapy and showed that high-grade mucoepidermoid carcinoma may show sensitivity similar to that of squamous cell carcinoma. Low-grade lesions had a five-year cure rate of 92%, whereas the intermediate-grade and high-grade lesions had a 49% 5-year cure rate.

Adenoid Cystic Carcinoma

(Cylindroma, adenocystic carcinoma, adenocystic basal cell carcinoma, pseudoadenomatous basal cell carcinoma, basaloid mixed tumor)

Adenoid cystic carcinoma (formerly known as 'cylindroma') is a slow-growing but aggressive neoplasm with a remarkable capacity for recurrence. It is characterized by proliferation of ductal (luminal) and myoepithelial cells in cribriform, tubular, solid and cystic patterns. In a review of its case files, the AFIP found adenoid cystic carcinoma to be the fifth most common malignant epithelial tumor of the salivary glands after mucoepidermoid carcinoma; adenocarcinoma, acinic cell carcinoma; and polymorphous low-grade adenocarcinoma (PLGA). However, other series report adenoid cystic carcinoma to be the second most common malignant tumor.

Clinical Features. The salivary glands most commonly involved by this tumor are the parotid, the submaxillary and the accessory glands in the palate and tongue (Fig. 3-24). The adenoid cystic carcinoma occurs most commonly during the fifth and sixth decades of life, but it is by no means rare even in the third decade. It is seen more commonly in females. Many of the patients exhibit clinical manifestations of a typical malignant salivary gland tumor: early local pain, facial nerve paralysis in the case of parotid tumors, fixation to deeper structures and local invasion. Some of the lesions, particularly the intraoral ones, exhibit surface ulceration. There may be clinical resemblance in some cases to the pleomorphic adenoma. Adenoid cystic carcinoma has a marked tendency to spread through perineural spaces and usually invades well beyond the clinically apparent borders.

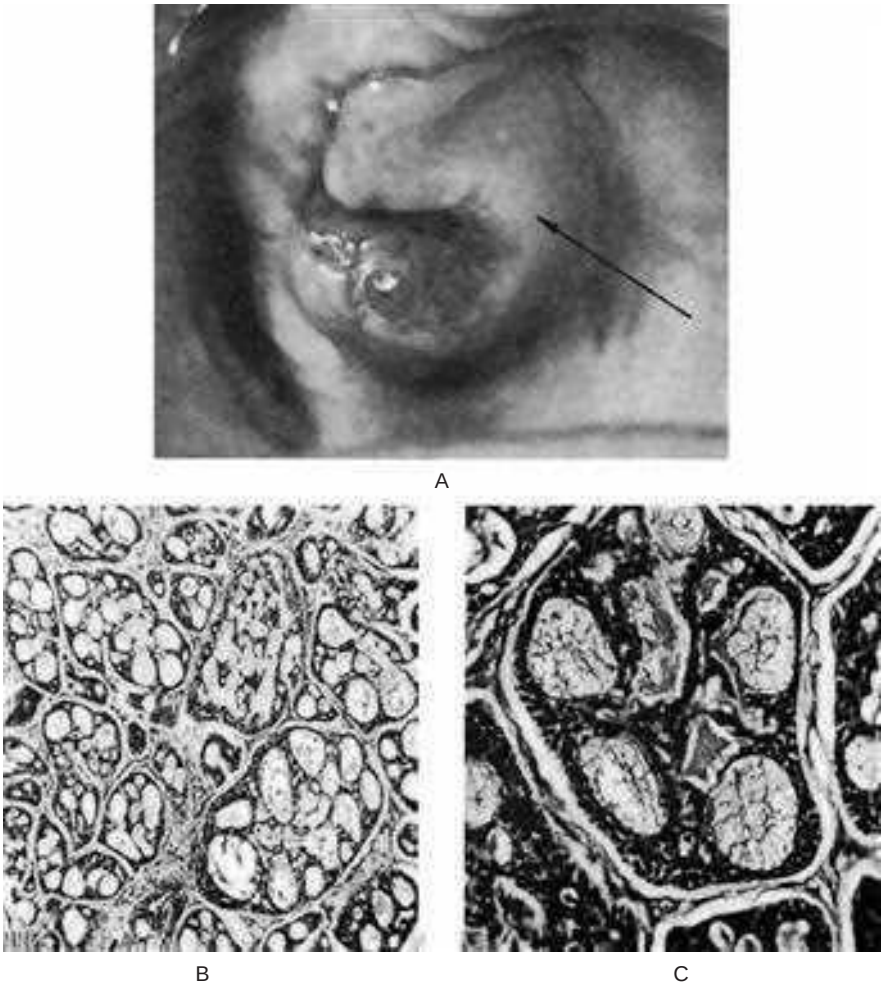


Figure 3-24. Adenoid cystic carcinoma of palate in edentulous patient.
(A) Clinical picture. **(B)** Low-power photomicrograph showing pattern of tumor. **(C)** High-power photomicrograph showing greater detail.

Histologic Features. Adenoid cystic carcinoma is composed of myoepithelial cells and ductal cells which have a varied arrangement. Morphologically, three growth patterns have been described: cribriform (classic), tubular, and solid (basaloid). The tumors are categorized according to the predominant pattern. The **cribriform pattern** shows basaloid epithelial cell nests that form multiple cylindrical cyst like patterns resembling a **Swiss cheese** or **honey comb** pattern, which is the most classic and best recognized pattern. The lumina of these spaces contain periodic acid-Schiff (PAS) positive mucopolysaccharide secretion. The **tubular pattern** reveals tubular structures that are lined by stratified cuboidal epithelium. The **solid pattern** shows solid groups of cuboidal cells with little tendency towards duct or cyst formation. The cribriform pattern is the most common, whereas the solid pattern is the least common. Solid adenoid cystic carcinoma is a high-grade lesion with reported recurrence rates of up to 100% compared with 50–80% for the tubular and cribriform variants.

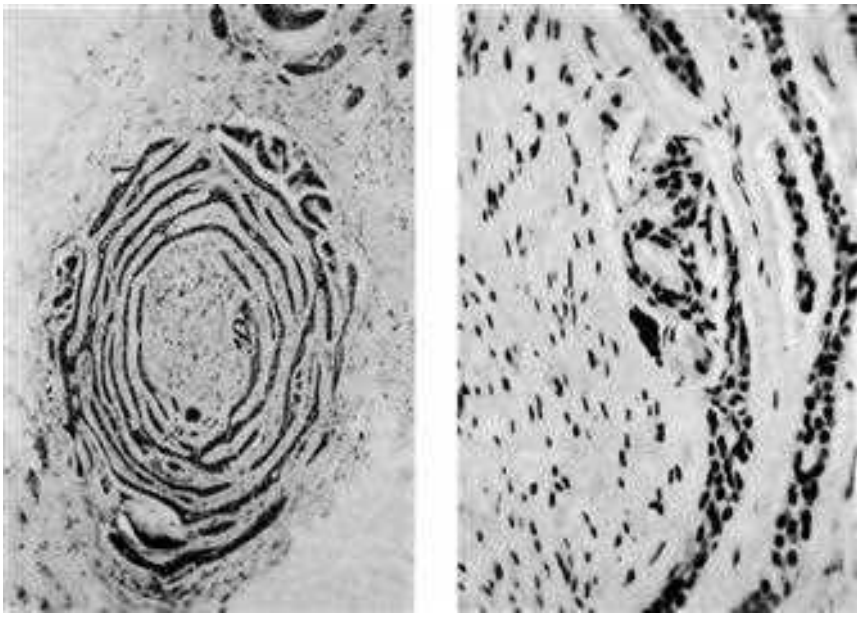
Variants

Dedifferentiation of adenoid cystic carcinoma. Dedifferentiated adenoid cystic carcinomas are a recently defined, rare variant of adenoid cystic carcinoma characterized histologically by two components: conventional low-grade adenoid cystic carcinoma and high-grade 'dedifferentiated' carcinoma. Because of frequent recurrence and metastasis, the clinical course is short, similar to that of adenoid cystic carcinomas with a predominant solid growth pattern. Histologically, the low-grade adenoid cystic carcinoma merges gradually into an extensive dedifferentiated component that is composed of solid sheets and cords of anaplastic tumor cells with focal gland formation. Immunohistochemically, the dedifferentiated component (but not the adenoid cystic carcinoma component) shows strong overexpression of p53 protein and cyclin D1, as well as a higher Ki67 index. Molecular studies confirmed the presence of p53 gene mutation selectively in the dedifferentiated component, suggesting a pivotal role of p53 gene alteration in the dedifferentiation process of adenoid cystic carcinoma.

Treatment and Prognosis. The treatment of the adenoid cystic carcinoma is chiefly surgical, although in some cases surgery has been successfully coupled with X-ray radiation. Radiation alone is not recommended. In general, this tumor is a slowly growing lesion which tends to metastasize only late in its course. The cure rate for patients with this disease, though varying somewhat from series to series, is discouragingly low. Factors influencing prognosis are the site of occurrence and the histologic pattern of the tumor (Fig. 3-25). Conley and Dingman (1974) found that there is a marked difference in the clinical behavior of major and minor gland adenoid cystic carcinomas. Only 28% of 78 patients with minor gland tumors were alive with no evidence of disease in a 4–14-year follow-up study. Sixty-four percent of 54 patients with major gland tumors studied over a comparable period were alive and free of disease.

Polymorphous Low-Grade Adenocarcinoma

Polymorphous low-grade adenocarcinoma (PLGA) is a malignant epithelial tumor that is essentially limited in occurrence to minor salivary gland sites and is characterized by bland, uniform nuclear features; diverse but characteristic



A B

Figure 3-25. Adenoid cystic carcinoma.
The perineural invasion by tumor cells is evident *(Courtesy of Dr James K Jacoby).*

architecture; infiltrative growth; and perineural infiltration. This is a recently recognized type of salivary gland tumor first described in 1983. Evans and Batsakis first used the term polymorphous low-grade adenocarcinoma in 1984 to describe this tumor. This tumor includes those entities, which were previously termed as terminal duct carcinoma, lobular carcinoma, papillary carcinoma and trabecular carcinoma.

Clinical Features. In minor gland sites polymorphous low-grade adenocarcinoma is twice as frequent as adenoid cystic carcinoma, and, among all benign and malignant salivary gland neoplasms, only pleomorphic adenoma and mucoepidermoid carcinoma are more common. The average age of patients is reported to be 59 years, with 70% of patients between the ages of 50 and 79 years. The female to male ratio is about 2 : 1. In the AFIP case files, over 60% of tumors occurred in the mucosa of either the soft or hard palates, approximately 16% occurred in the buccal mucosa, and 12% in the upper lip. Polymorphous low-grade adenocarcinoma typically presents as a firm, nontender swelling involving the mucosa of the hard and soft palates (often at their junction), the cheek, or the upper lip. Discomfort, bleeding, telangiectasia, or ulceration of the overlying mucosa may occasionally occur.

Histologic Features. Microscopically polymorphous low-grade adenocarcinoma is characterized by infiltrative growth with diverse morphology and uniform cytologic features. The tumors are well circumscribed but unencapsulated and infiltrate into adjacent structures. The polymorphic nature of the lesion refers to the variety of growth patterns it assumed which includes solid, ductal, cystic and tubular. In some tumors, a cribriform pattern can be produced, which resembles adenoid cystic carcinoma. The tumor is composed of cuboidal to columnar isomorphic cells that have uniform ovoid to spindle- shaped nuclei. Scant to moderate amounts of eosinophilic cytoplasm can be seen. The tumor stroma varies from mucoid to hyaline and in some cases, tumor nests are separated by fibrovascular stroma. Perineural invasion is common that makes this tumor mistaken as adenoid cystic carcinoma.

Treatment. Polymorphous low-grade adenocarcinoma is best treated by conservative wide surgical excision. This neoplasm typically runs a moderately indolent course. Although the tumor can recur, sometimes multiple times over many years, distant metastases have not been reported. The overall prognosis is good. Perineural invasion does not appear to affect the prognosis.

Epithelial-Myoepithelial Carcinoma

(Adenomyoepithelioma, clear cell adenoma, tubular solid adenoma, monomorphic clear cell tumor, glycogen-rich adenoma, glycogen-rich adenocarcinoma)

Epithelial-myoepithelial carcinoma is an uncommon, biphasic low-grade epithelial neoplasm composed of variable proportions of ductal and large, clear-staining, differentiated myoepithelial cells. It comprises approximately 1% of all epithelial salivary gland neoplasms.

Clinical Features. This is predominantly a tumor of the parotid gland. In the AFIP case files, the mean age of patients is about 60 years and women are more often affected than men. Localized swelling with a history of steady increase in size over a period of time is the common symptom, but occasionally patients experience facial weakness or pain. Nasal obstruction and facial deformity may represent major complaints of patients with maxillary involvement. Some studies have suggested that patients with these tumors are at increased risk for a second primary malignancy—either in the salivary glands or in a separate site (breast and thyroid have been reported).

Histologic Features. The histologic features of this tumor may vary greatly from solid lobules that are separated by bands of hyalinized fibrous tissue to irregular, papillary cystic arrangements with tumor cells which partially or completely fill cystic spaces but most tumors show a multinodular growth pattern with islands of tumor cells separated by dense bands of fibrous connective tissue. The islands of tumor cells are composed of small ducts lined by cuboidal epithelium that is surrounded by clear cells which interface with a thickened, hyaline-like basement membrane. The inner luminal cuboidal cells have finely granular, dense eosinophilic cytoplasm and central or basally located nucleus. The outer, clear myoepithelial cells vary in shape from columnar to ovoid and have a vesicular nucleus located towards the basement membrane.

Treatment. Surgery is considered the primary mode of treatment. Even with complete surgical resection recurrences and distant metastases remain a concern and may occur from a few months to years after initial surgery.

Basal Cell Adenocarcinoma

(Basaloid salivary carcinoma, carcinoma ex monomorphic adenoma, malignant basal cell adenoma, malignant basal cell tumor, basal cell carcinoma)

Basal cell adenocarcinoma of salivary glands is an uncommon and recently described entity occurring almost exclusively at the major salivary glands. It is a low-grade malignant neoplasm that is cytologically similar to basal cell adenoma, but is infiltrative and has a small potential for metastasis.

Clinical Features. In AFIP case files spanning almost 11 years, basal cell carcinoma comprised 1.6% of all salivary gland neoplasms and 2.9% of salivary gland malignancies. Nearly 90% of tumors occurred in the parotid gland. The average age of patients is reported to be 60 years. Basal cell adenocarcinoma predominantly occurs at the seventh decade without gender preference. The tumors affecting the minor salivary glands occur most frequently at the oral cavity (buccal mucosa, palate) and the upper respiratory tract. Similar to most salivary gland neoplasms, swelling is typically the only sign or symptom experienced. A sudden increase in size may occur in a few patients.

Histologic Features. As seen with basal cell adenoma, basal cell adenocarcinoma can also be histologically divided into four subtypes: (1) solid, (2) ductal, (3) trabecular, and (4) membranous.

The prevalent histologic tumor pattern is represented by solid neoplastic aggregates with a peripheral cell palisading arrangement frequently delineated by basement membrane like material. Few areas with trabecular or membranous arrangement may be seen. The neoplastic clusters are formed by two cell populations: the small dark cell type, which is predominant and a large pale cell type. Generally, the small dark cells are present peripherally to the larger paler cells. The tumor extends into the surrounding tissues by local infiltration as nodules, nests and cords. Perineural and vascular invasion is noticed in a few cases.

Treatment and Prognosis. Basal cell carcinomas are low-grade carcinomas that are infiltrative, locally destructive, and tend to recur. They only occasionally metastasize. Surgical excision with a wide enough margin to ensure complete removal of the tumor is the primary treatment. Regional lymph node dissection is recommended only if there is evidence of metastatic disease. The overall prognosis for patients with this tumor is good.

Sebaceous Carcinoma

Sebaceous carcinoma is a malignant neoplasm consisting chiefly of sebaceous cells, which are arranged in sheets and/or nests with different degrees of pleomorphism, nuclear atypia and invasiveness.

Clinical Features. This tumor shows bimodal age distribution, peak incidence of tumor occurrence is found in the third decade and seventh and eighth decades of life (range 17–93 years). The male and female incidence of occurrence is almost equal. Most of the reported cases have arisen in the parotid gland. The chief complaint is that of painful masses, with varying degrees of facial nerve paralysis, and occasionally, fixation of the skin is present. Tumors range in size from 0.6–8.5 cm in greatest dimension.

Histologic Features. Tumors are well circumscribed or partially encapsulated, with pushing or locally infiltrating margins. Cellular pleomorphism and cellular atypia are uniformly present and are more prevalent than in sebaceous adenomas. Tumor cells may be arranged in multiple large foci or in sheets and have hyperchromatic nuclei surrounded by abundant clear to eosinophilic cytoplasm (Fig. 3-26 A). Areas of cellular necrosis and fibrosis are commonly found. Perineural invasion has been observed in more than 20% of tumors. Vascular invasion is extremely unusual. Rare oncocytes and foreign body giant cells with histiocytes may be observed.

Treatment. It varies from local excision and parotidectomy to preoperative and postoperative radiotherapy, with or without chemotherapy. Patient survival ranged from 8 months to 13 years (mean is 4.5 years).

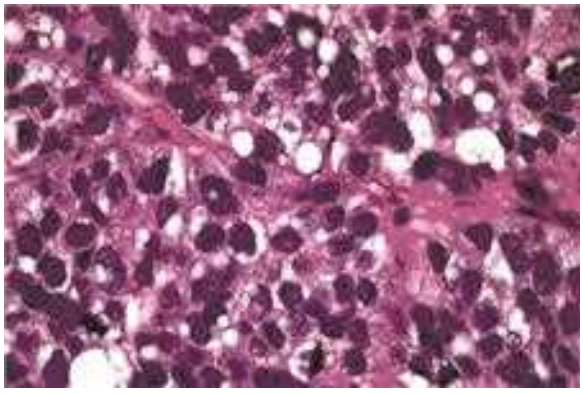
Papillary Cystadenocarcinoma

(Cystadenocarcinoma, malignant papillary cystadenoma, mucus-producing adenopapillary [nonepidermoid] carcinoma, low-grade papillary adenocarcinoma of palate, papillary adenocarcinoma)

Cystadenocarcinoma is the malignant counterpart of cystadenoma. It is a rare malignant epithelial tumor characterized histologically by prominent cystic and, frequently, papillary growth but lacking features that characterize cystic variants of several more common salivary gland neoplasms.

Clinical Features. Cystadenocarcinoma is considered to be a low-grade neoplasm. Most of the cases, about 65%, occurred in the major salivary glands (primarily in the parotid). Among the reported cases men and women are found to be affected equally and the average age at presentation is about 59 years. Patients present with a slowly growing asymptomatic mass. Clinically, this neoplasm is rarely associated with pain or facial paralysis.

Histologic Features. A cystic growth pattern must dominate the histologic appearance for the diagnosis to be considered (Fig. 3-26 B). These cystic spaces vary in size between tumors as well as within the same tumor. These neoplasms may appear circumscribed or reveal haphazard growth throughout the gland. The lumina often are filled with mucus and hemorrhage



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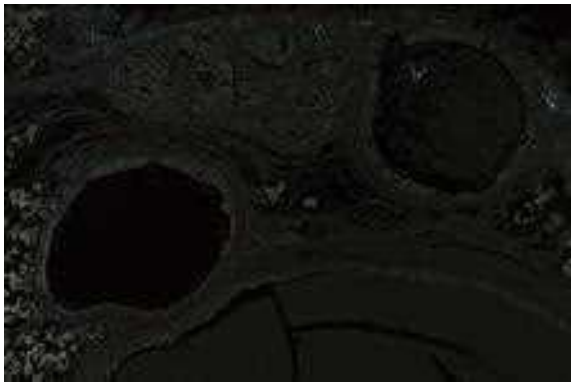


B

Figure 3-26. Sebaceous cell adenocarcinoma and cystadenocarcinoma.
(A) Sebaceous cell adenocarcinoma. Well differentiated sebaceous carcinoma composed of an area resembling sebaceous adenoma admixed with sheets of carcinoma cells. **(B)** Cystadenocarcinoma. Cystic neoplasm showing irregular cysts with great variation in size and frequent intraluminal papillary process. Invasion into the parotid parenchyma is noticed (upper field) *(Courtesy of Christopher DM Fletcher).*

and dystrophic calcifications are sometimes evident focally. The lining cells vary from cuboidal to tall columnar, and often a single tumor contains basaloid, oncocytic, clear, and occasionally, mucus cells that form adenomatous or nodular, solid epithelial areas. These solid areas usually occupy the space between the cystic structures. Nuclear hyperchromatism and nuclear variability are subtle, and only rare mitotic figures are present. Nucleoli may be obvious. Encapsulation is incomplete, and infiltration into either salivary gland parenchyma or fibrous or adipose tissue is seen. The tumor may infiltrate either as cyst like structures or as solid islands. Although the vast majority of cystadenocarcinomas are low-grade lesions, moderate/intermediate-grade tumors do exist.

Treatment and Prognosis. No information is currently available that pertains specifically to the prognosis of the salivary gland cystadenocarcinomas. Currently the treatment principles for low-grade cystadenocarcinomas are similar to the principles applied for other low-grade salivary gland adenocarcinomas. These include consideration of the site, the clinical extent of the disease and the histologic grade prior to institution of therapy. Radical neck dissection should be preserved only to deal with obvious metastases.

Mucinous Adenocarcinoma

Mucinous adenocarcinoma is a rare malignant neoplasm characterized by large amount of extracellular epithelial mucin that contains cords, nests, and solitary epithelial cells. The incidence is unknown. Limited data indicate that most, if not all, occur in the major salivary glands with the submandibular gland as the predominant site. These tumors may be associated with dull pain and tenderness. This neoplasm may be considered to be low-grade.

Clinical Features. Clinically, these lesions are soft, spongy masses that may be thought to be cysts.

Histologic Features. The gross specimens are very mucoid, with a slimy texture and they may actually ooze mucoid material. These tumors are circumscribed but not encapsulated. Low magnification reveals islands and cords of tumor cells that appear to be floating within pools of pale staining mucin. The pools of mucin may be divided into irregular lobules by fibrous connective tissue septa that course through the tumor, which is unencapsulated. The tumor cells are moderately large, cuboidal, and polygonal cells with eosinophilic to amphophilic cytoplasm. The nuclei are vesicular, and scattered mitotic figures may be found. The tumor islands are surrounded by pale-staining mucoid substance. The mucoid substance stains with mucicarmine, periodic acid-Schiff, and alcian blue at pH 2.0. Mucicarmine stain also reveals that many tumor cells contain intracytoplasmic mucin.

Treatment and Prognosis. Complete excision with the care to avoid seeding the surgical site would seem to be a satisfactory mode of treatment for these salivary gland tumors.

Oncocytic Carcinoma
(Oncocytic adenocarcinoma)

Oncocytic carcinoma is a rare, predominantly oncocytic neoplasm whose malignant nature is reflected both by its abnormal morphologic features and infiltrative growth. Bauer and Bauer reported the first case in 1953. Although focal oncocytic features are seen in a wide variety of salivary neoplasms, both benign and malignant oncocytic neoplasms are extremely rare.

Clinical Features. Oncocytic carcinoma may be considered to be a high-grade carcinoma. Most cases occur in the parotid gland but recent reports have described tumors that involved the submandibular gland and minor glands of the palate, nasal cavity, and ethmoid and maxillary sinuses. The average age of patients in one series was 63 years. Patients usually develop parotid masses that cause pain or paralysis. The skin overlying the gland is occasionally discolored or wrinkled.

Histologic Features. All types of benign or malignant salivary gland tumors may have foci of oncocytic cells, but the oncocytic component usually contains such a small portion that it is unlikely to be confused with oncocytic carcinoma. Tumors with a significant oncocytic component include Warthin's tumor, oncocytoma, and oncocytic carcinoma. They are characterized by oncocytes with marked cellular atypia, frequent mitosis, destruction of adjacent structures, perineural or vascular invasion, and distant or regional lymph node metastasis. Histochemical or electron microscopic confirmation of the oncocytic (mitochondrial) nature of the cytoplasm is necessary because cytoplasmic accumulation of smooth endoplasmic reticulum, lysosomes, or secretory granules may have a similar appearance.

Treatment and Prognosis. Oncocytic carcinoma is considered to be a high-grade neoplasm and aggressive initial surgery seems to have a significantly better overall prognosis. Radiation does not appear to favorably alter the biologic behavior of this tumor. Prophylactic neck dissection may be indicated for tumors that are larger than 2 cm in diameter.

Salivary Duct Carcinoma
(Salivary duct adenocarcinoma)

Salivary duct carcinoma is a rare, typically high-grade malignant epithelial neoplasm composed of structures that resemble expanded salivary gland ducts. A low-grade variant exists. Incidence rates vary depending upon the study cited. In the AFIP files, salivary duct carcinomas represent only 0.2% of all epithelial salivary gland neoplasms. More than 85% of cases involve the parotid gland and approximately 75% of patients are men. The peak incidence is reported to be in the seventh and eighth decades of life.

Clinical Features. Parotid swelling is the most common sign. Facial nerve dysfunction or paralysis occurs in over one-fourth of patients and may be the initial manifestation. The high-grade variant of this neoplasm is one of the most aggressive types of salivary gland carcinomas and is typified

by local invasion, lymphatic and hematogenous spread with poor prognosis.

Histologic Features. The infiltrative tumor elements are typically composed of clusters of tumor cells that may have small lumina or cribriform arrangements, but solid, irregularly shaped tumor cell aggregates are frequently present. The neoplastic epithelial cells are cuboidal and polygonal with a moderate amount of eosinophilic cytoplasm and are accompanied by a dense fibrous connective tissue stroma that may be hyalinized in some areas. Invasion of the nerves and blood vessels is frequent in addition to infiltration of salivary gland lobules and extra-salivary gland tissues, such as fat, muscle, and bone. Mucicarmine and Alcian blue stains are generally negative, except, perhaps, for a small amount of luminal staining. Immunohistochemical and ultrastructural studies have identified ductal cells but no myoepithelial cells.

Treatment and Prognosis. Salivary duct carcinoma is a high-grade malignancy that must be treated aggressively. Complete local excision with radical neck dissection and postoperative radiation therapy seems to offer the maximum benefit for the patient.

Adenocarcinoma

Adenocarcinomas of the salivary glands are rare but aggressive tumors.

Clinical Features. They tend to be present in patients over 40 years of age and occur with nearly equal frequency in men and women. About half of these tumors present in the parotid glands, the minor salivary glands, particularly the palate, lip and tongue are the next most commonly affected sites. Clinical presentation again most often involves an enlarging mass. Adenocarcinoma is different from other salivary gland neoplasms in that as many as 25% of patients will complain of pain or facial weakness at presentation.

Histologic Features. Gross pathology reveals a firm mass with irregular borders and infiltration into surrounding tissue. It is generally a solid tumor without any cystic spaces. These malignancies can demonstrate a wide range of growth patterns, and for this reason, can be somewhat difficult to classify. However, all adenocarcinomas have in common the formation of glandular structures and they are described as grades I, II or III based upon the degree of cellular differentiation. Grade I lesions have well formed ductal structures while grade III lesions have a more solid growth pattern with few glandular characteristics (Figs. 3-27, 3-28).

Treatment and Prognosis. Because these are more aggressive tumors, treatment for adenocarcinoma is aggressive. Complete local excision is the mainstay of therapy. In the parotid this may include facial nerve sacrifice. In the minor salivary glands, a portion of the maxilla or mandible may have to be resected with the tumor. Postoperative radiation therapy does seem to be of some benefit. Lymph node metastasis is not uncommon and in patients with palpable neck disease

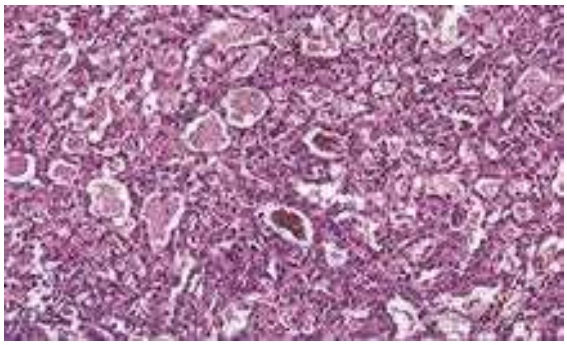


Figure 3-27. Adenocarcinoma.
Low-grade adenocarcinoma composed of a morphologically uniform population of cells showing formation of many ductal structures. Mitotic figures are rare which is typical for this group of tumors.

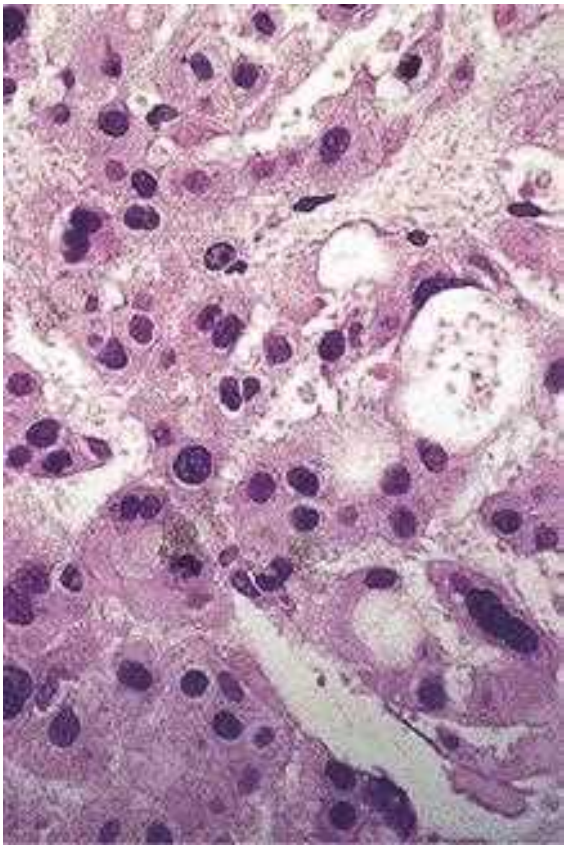


Figure 3-28. Adenocarcinoma.
High power view showing nuclear atypia.

neck dissection is warranted. Local recurrence rates vary in the literature but have been cited as high as 51%.

Malignant Myoepithelioma
(Myoepithelial carcinoma)

Ellis GL (1991) defined myoepithelial carcinoma as a malignant epithelial neoplasm whose tumor cells demonstrate cytologic differentiation towards myoepithelial cells and lack ductal

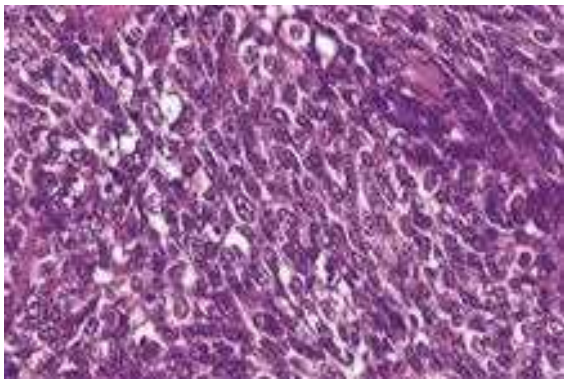


Figure 3-29. Malignant myoepithelioma.
Low magnification of malignant myoepithelioma shows sheets of tumor cells with round to ovoid nuclei and indistinct cytoplasm. Mitotic figures are evident in this field.

or acinar differentiation. Myoepithelial carcinoma is a rare, malignant salivary gland neoplasm in which the tumor cells almost exclusively manifest myoepithelial differentiation. This neoplasm represents the malignant counterpart of benign myoepithelioma. A majority of the tumors occur in the parotid gland. The mean age of patients is reported to be 55 years.

Clinical Features. The majority of patients present with the primary complaint of a painless mass. This is an intermediate- to high-grade carcinoma. Histologic grade does not appear to correlate well with clinical behavior; tumors with a low-grade histologic appearance may behave aggressively.

Histologic Features. The cytologic features of individual cells and the general morphologic features resemble tumor cells in benign myoepithelioma and the myoepithelial cells of mixed tumor. The tumor cells may be spindle shaped or plasmacytoid cells (Fig. 3-29). The cell types are often intermixed but usually one or the other cell type predominates. The tumors may be quite cellular and more suggestive of sarcoma than carcinoma. The stroma in other areas of the tumors may be more conspicuous and myxoid. These tumors are distinguished from benign myoepithelial neoplasms by their infiltrative, destructive growth. They usually demonstrate increased mitotic activity and cellular pleomorphism. Some tumor cell should be immunoreactive for cytokeratin, S100 protein, smooth muscle actin, and occasionally, glial fibrillary acidic protein.

Treatment. Wide surgical excision seems to be preferred.

Carcinoma in Pleomorphic Adenoma
(Malignant mixed tumor)

Malignant mixed tumors include three distinct clinicopathologic entities: carcinoma ex pleomorphic adenoma, carcinosarcoma, and metastasizing mixed tumor. Carcinoma ex pleomorphic adenoma constitutes the vast majority of cases, whereas carcinosarcoma (true malignant mixed tumor) and metastasizing mixed tumor are extremely rare.

Carcinoma ex Pleomorphic Adenoma (*Carcinoma ex mixed tumor*). Carcinoma ex pleomorphic adenoma is the most common of the three salivary neoplasms that are broadly referred to as malignant mixed tumors. It occurs when a carcinoma develops from the epithelial component of a preexisting pleomorphic adenoma. Diagnosis requires the identification of benign tumor in the tissue sample. The incidence or relative frequency of this tumor may vary considerably depending on the study cited. A review of material at the AFIP showed carcinoma ex pleomorphic adenoma to comprise 8.8% of all mixed tumors and 4.6% of all malignant salivary gland tumors, ranking it as the sixth most common malignant salivary gland tumor after mucoepidermoid carcinoma; adenocarcinoma; acinic cell carcinoma; polymorphous low-grade adenocarcinoma; and adenoid cystic carcinoma.

Clinical Features. The neoplasm occurs primarily in the major salivary glands. It occurs most often in the parotid, followed by the submandibular gland and palate. It presents in the sixth to eighth decade of life with patients averaging 10 years older than those with pleomorphic adenomas. Presentation is usually a painless mass but some patients will report recent rapid enlargement of a long-standing nodule. Approximately one-third of patients may experience facial paralysis.

Histologic Features. Gross pathology of carcinoma ex pleomorphic adenoma often shows a poorly circumscribed, infiltrative, hard mass. Microscopically malignant appearing cells are present adjacent to a typical appearing pleomorphic adenoma. The malignant portion of the tumor can take the form of any epithelial malignancy except acinic cell (Fig. 3-30). Most commonly this will be in the form of an undifferentiated carcinoma (30%) or adenocarcinoma (25%). This tumor tends to be more aggressive than other salivary malignancies and about 25% of patients will have lymph node metastasis on presentation.

Treatment and Prognosis. Treatment includes radical surgical resection, often in conjunction with neck dissection, and postoperative radiation therapy. Prognosis appears to be related to the local extent of disease and the histologic type of the carcinoma component.

Carcinosarcoma (*True malignant mixed tumor*). Carcinosarcoma is a rare malignant salivary gland neoplasm that

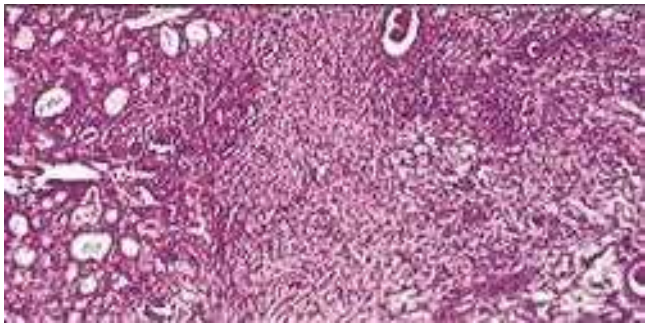


Figure 3-30. Malignant pleomorphic adenoma.
Demonstrates irregular foci of carcinoma composed of glandular structures with focal necrosis set in a mild desmoplastic background.

contains both carcinoma and sarcoma components. In a carcinosarcoma, the metastatic lesions contain both the stromal and epithelial elements. Some carcinosarcomas develop de novo while others develop in association with benign mixed tumor.

This neoplasm is rare in occurrence; there are only eight cases in the AFIP case files. Only 11 cases were recorded at MD Anderson over a 32-year period. The majority of tumors occur in the major salivary glands. The parotid is the most frequent site of occurrence. Average age at presentation is about 60 years and men and women appear to be equally affected. Clinically, swelling, pain, nerve palsy, and ulceration have been frequent findings.

Histologic Features. Microscopically, these tumors have both sarcomatous and carcinomatous elements. In the majority, the sarcoma is the dominating component and chondrosarcoma is the most common cell type. The carcinoma element is usually an undifferentiated or high-grade ductal adenocarcinoma.

Treatment and Prognosis. This is also an aggressive tumor. In the largest series reported (12 cases), the average survival period was 3.6 years and it is not uncommon for patients to have distant metastasis on presentation. Currently, recommended treatment includes radical surgery, neck dissection for palpable nodes and postoperative radiotherapy. Although efficacy has yet to be proven, chemotherapy is likely to have a role in the treatment of this disease given the high rate of distant metastasis.

Metastasizing Mixed Tumor. Metastasizing mixed tumor is a very rare histologically benign salivary gland neoplasm. The metastasizing mixed tumor refers to an otherwise benign acting pleomorphic adenoma that develops metastatic deposit. There is often a long interval between the diagnosis of the primary tumor and the metastases. The histologic features are within the spectrum of features that typify pleomorphic adenoma. The majority occur in the major salivary glands. The primary neoplasm is typically a single, well-defined mass. Recurrences, which may be multiple, have been reported to occur up to 26 years after excision of the primary neoplasm.

Squamous Cell Carcinoma

Primary squamous cell carcinoma is a malignant epithelial neoplasm of the major salivary glands that is composed of squamous (epidermoid) cells (Fig. 3-31). This diagnosis is not made in minor salivary glands because distinction from the more common mucosal squamous cell carcinoma is not possible. Primary squamous cell carcinoma of the salivary glands is quite rare, accounting for about 1.6% of salivary gland neoplasms. In order to make this diagnosis, high-grade mucoepidermoid carcinoma, metastatic squamous cell carcinoma to the gland or intraglandular nodes and direct extension of a squamous cell carcinoma must first be excluded.

Clinical Features. The reported frequency of this tumor among all major salivary gland tumors has varied from 0.9–4.7%. There is a 2 : 1 male-to-female ratio of occurrence and patients are usually over age 60. This neoplasm occurs in the parotid gland almost nine times more often than in the submandibular gland. This tumor is graded in a way similar to the extra salivary lesions according to the degree of differentiation (low, intermediate, and high). Previous exposure to ionizing radiation appears to increase the risk for developing this neoplasm. The median time between irradiation and diagnosis of the neoplasm is approximately 15.5 years. These tumors present as firm enlarging masses that are not uncommonly fixed to surrounding tissue and associated with pain or facial weakness.

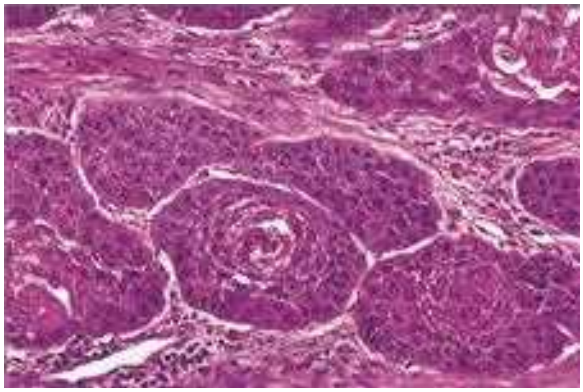


Figure 3-31. Squamous cell carcinoma.
Primary squamous cell carcinoma of salivary gland showing neoplastic squamous cells, metaplastic in origin, with varying degrees of nuclear atypia.

Histologic Features. The gross and microscopic appearance is similar to squamous cell carcinoma of other primary sites and varies from well-differentiated to poorly differentiated. Salivary gland squamous cell carcinoma displays aggressive behavior with rapid growth and early spread to regional lymph nodes (Fig. 3-32).

Treatment and Prognosis. Treatment consists of surgical resection, neck dissection and postoperative radiation. The prognosis for this neoplasm is poor. In a 30-year retrospective analysis of 50 cases of squamous cell carcinoma of the salivary glands, survival rates at five and 10 years were 24% and 18%, respectively.

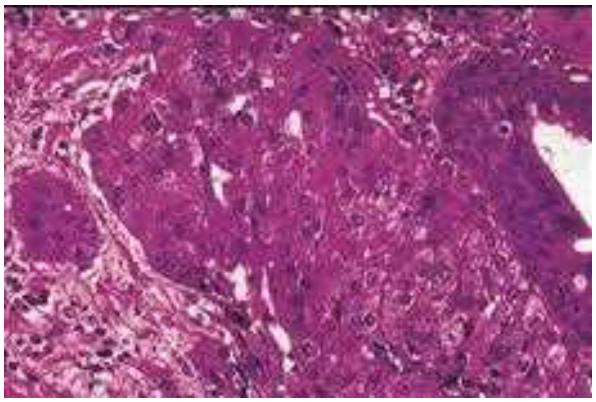


Figure 3-32. Primary squamous cell carcinoma of salivary gland (high power view).

Small Cell Carcinoma

Small cell carcinoma of the salivary gland was first described in 1972. Small cell carcinomas arising in salivary glands are extremely rare, high-grade malignant tumors and are subclassified into neuroendocrine and ductal types.

Histologic Features. Microscopically, the tumor cells have oval, hyperchromatic nuclei and scant amount of cytoplasm and are organized in sheets, strands, and nests. Small cell carcinoma of major salivary glands is a highly aggressive tumor, although the prognosis may be better than that for extra-salivary neoplasms. Studies also suggest that most salivary gland small cell carcinomas exhibit neuroendocrine differentiation. Neuroendocrine carcinomas are more frequently found in the minor salivary glands and have a better survival rate compared with small cell carcinomas of the lung. The undifferentiated counterpart of this neoplasm is the small cell undifferentiated carcinoma.

Treatment and Prognosis. The treatment of choice is wide surgical excision, possibly with radiation and/or chemotherapy. The prognosis for patients with small cell carcinomas arising in the major or minor salivary glands is better than that for patients with small cell carcinomas of the lung or larynx.

UNDIFFERENTIATED CARCINOMA

Undifferentiated carcinomas of salivary glands are a group of uncommon malignant epithelial neoplasms that lack the specific morphologic features of other types of salivary gland carcinomas. These carcinomas are histologically similar to undifferentiated carcinomas that arise in other organs and tissues. Accordingly, metastatic carcinoma is a primary concern in the differential diagnosis of these neoplasms. This group includes the following three tumors:

1. Small cell undifferentiated carcinoma
2. Large cell undifferentiated carcinoma
3. Lymphoepithelial carcinoma.

Small Cell Undifferentiated Carcinoma

(Extrapulmonary oat cell carcinoma)

Small cell undifferentiated carcinoma is a rare, primary malignant tumor that, with conventional light microscopy, is composed of undifferentiated cells, and with ultrastructural or immunohistochemical studies, does not demonstrate neuroendocrine differentiation. This is the undifferentiated counterpart of anaplastic small cell carcinoma.

Large Cell Undifferentiated Carcinoma

Large cell undifferentiated carcinoma is a tumor in which features of acinar, ductal, epidermoid, or myoepithelial differentiation are absent under light microscopy, although, occasionally, poorly formed duct like structures are found. Rapid growth of a parotid swelling is a common clinical presentation. This is a high-grade neoplasm that frequently metastasizes and has a poor prognosis.

Lymphoepithelial Carcinoma

(Undifferentiated carcinoma with lymphoid stroma, carcinoma ex lymphoepithelial lesion)

Lymphoephithelial carcinoma is an undifferentiated tumor that is associated with a dense lymphoid stroma. There is an exceptionally high incidence of this tumor in the Eskimo and Inuit populations. This neoplasm has been associated with Epstein-Barr virus infection. Over 80% occur in the parotid gland. In addition to the presence of a parotid or submandibular mass, pain is a frequent symptom, and facial nerve palsy occurs in up to 20% of patients. Over 40% of patients have metastases to cervical lymph nodes at initial presentation, and 20% develop distant metastases within three years following therapy.

Treatment and Prognosis. The treatment consists of surgery alone or of surgery in combination with radiotherapy. Very little data is available concerning the behavior of these rare tumors.

Salivary Adenocarcinoma, NOS

Adenocarcinoma, NOS, (not otherwise Specified) is a salivary gland carcinoma that shows glandular or ductal differentiation but lacks the prominence of any of the morphologic features that characterize the other, more specific carcinoma types. The diagnosis of adenocarcinoma, NOS, is essentially one of exclusion. In the Armed Forces Institute of Pathology (AFIP) review of cases, adenocarcinoma, NOS, was second only to mucoepidermoid carcinoma in frequency among malignant salivary gland neoplasms. Other series have reported an incidence of 4–10 % (Speight PM, Barret AW, 2002). In AFIP files, the mean patient age was 58 years. Approximately 40–60% of tumors occurred in the major and minor salivary glands, respectively. Among the major salivary gland tumors, 90% occurred in the parotid gland. Adenocarcinoma, NOS is graded in a similar way to extrasalivary lesions according to the degree of differentiation. Tumor grades include low grade, intermediate grade, and high grade categories (Ellis GL, Auclair PL, 1996).

Patients with tumors in the major salivary glands typically present with solitary, painless masses. Two retrospective studies indicate that survival is better for patients with tumors of the oral cavity than for those with tumors of the parotid and submandibular glands (Spiro RH, Huvos AG, Strong EW 1982, Matsuba HM, Mauney M et al, 1988). These studies differ regarding the prognostic significance of tumor grade.

OTHER CARCINOMAS

Adenosquamous Carcinoma

Adenosquamous carcinoma of the salivary gland is a controversial neoplasm that is not included in many classifications of salivary gland tumors. This is a malignant epithelial neoplasm that has histomorphologic features of both adenocarcinoma and squamous cell carcinoma.

Sebaceous Lymphadenocarcinoma

Sebaceous lymphadenocarcinoma is the malignant counterpart of sebaceous lymphadenoma and represents carcinoma arising in sebaceous lymphadenoma. These tumors appear to be low-grade malignant tumors that have the ability to recur locally. Lymph node or distant metastases may develop late in the clinical course of these tumors.

NONEPITHELIAL TUMORS

Mesenchymal Neoplasms

Mesenchymal neoplasms account for 1.9–5% of all neoplasms that occur within the major salivary glands. These classifications pertain to major salivary gland tumors. Because the minor salivary glands are small and embedded within fibrous connective tissue, fat, and skeletal muscle, it is impossible to determine the origin of a mesenchymal neoplasm from stroma. The types of benign mesenchymal salivary gland neoplasms include hemangioma, lipoma, and lymphangioma. Malignant mesenchymal salivary gland neoplasms include malignant schwannoma, hemangiopericytoma, malignant fibrous histiocytoma, rhabdomyosarcoma, and fibrosarcoma, among others; in the major salivary glands, these neoplasms represent approximately 0.5% of all benign and malignant salivary gland tumors and approximately 1.5% of all malignant tumors. It is important to establish a primary salivary gland origin for these tumors by excluding the possibilities of metastasis and direct extension from other sites. In addition, the diagnosis of salivary gland carcinosarcoma should be excluded. Primary salivary gland sarcomas behave like their soft tissue counterpart in which prognosis is related to sarcoma type, histologic grade, tumor size, and stage.

MALIGNANT LYMPHOMAS

Lymphomas of the major salivary glands are characteristically of the non-Hodgkin's type. In AFIP review of case files, non-Hodgkin's lymphoma accounted for 16.3% of all malignant tumors that occurred in the major salivary glands; disease in the parotid gland accounted for about 80% of all cases.

Patients with benign lymphoepithelial lesion (Mikulicz's disease), a manifestation of the autoimmune disease, Sjogren's syndrome, are at an increased risk for development of non-Hodgkin's lymphoma (Fig. 3-33).

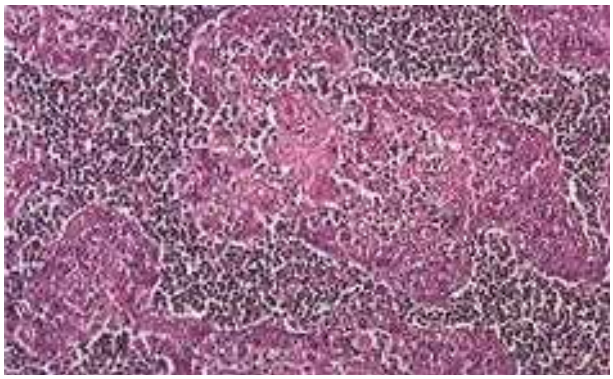


Figure 3-33. Malignant lymphoma—mucosa associated lymphoid tissue (MALT) type.
Note the myoepithelial islands suspended in a background of lymphoid tissue. The lymphoid element is neoplastic with varying degrees of malignancy.

Secondary Tumors

Malignant neoplasms whose origins lie outside the salivary glands may involve the major salivary glands by:

1. Direct invasion from cancers that lie adjacent to the salivary glands
2. Hematogenous metastases from distant primary tumors
3. Lymphatic metastases to lymph nodes within the salivary gland.

Direct invasion of nonsalivary gland tumors into the major salivary glands is principally from squamous cell and basal cell carcinomas of the overlying skin.

TUMOR LIKE LESIONS

Sialadenosis

Sialadenosis is the name given to nonneoplastic, noninflammatory enlargement of salivary glands, particularly the parotid gland. The enlargement is usually bilateral and may manifest recurrence or pain, or both. The condition is almost always found in association with systemic disorders; this association forms the basis for classification of sialadenosis.

Clinical Features. Characterized mainly by the presence of chronic, afebrile salivary gland enlargement, usually of the parotid glands. The enlargement is described as slowly evolving, indolent, undulating, and recurrent. Persons in the later decades of life (4th decade or beyond) are most afflicted. Decreased salivary secretion occurs, and sialochemistry generally demonstrates increased levels of potassium and decreased levels of sodium. Hypertrophy of acinar cells crowds and compresses the finer terminal ducts, thereby yielding the sialographic *'leafless tree'* pattern (Table 3-7).

Histologic Features. The parotid swelling is due to acinar enlargement. The diameter of the acinar cell increases two to three times that of normal. The nuclei tend to be basally situated, and the cytoplasm tends to be packed with granules. Inflammatory cells are absent but individual fat cells may be seen in the interstitial tissue. Batsakis (1988) suggests that long standing uncorrected autonomic neuropathy, such as occurs in alcoholism or diabetes mellitus eventually leads to acinar atrophy and replacement with fat.

Treatment. Treatment is generally unsatisfactory and depends on correcting the underlying cause. Subtotal parotidectomy may be considered as a last resort.

Table 3-7: Classification of sialadenosis

Hormonal sialadenosis
Sex hormonal sialadenosis
Diabetic sialadenosis
Thyroid sialadenosis
Hypophyseal and adrenal cortical disorders
Neurohumoral sialadenosis
Peripheral neurohumoral sialadenosis
Central neurogenous sialadenosis
Dysenzymatic sialadenosis
Hepatogenic sialadenosis
Pancreatogenic (exocrine) sialadenosis
Nephrogenic sialadenosis
Dysproteinemic sialadenosis
Malnutritional sialadenosis
Mucoviscidosis
Drug-induced sialadenosis

Oncocytosis

Oncocytosis is a metaplastic, sometimes hyperplastic, developmental or reactive process that is characterized by focal replacement of normal glandular tissue with enlarged eosinophilic epithelial cells with granular cytoplasm. These swollen epithelial cells were first described by Shafer (1897) and later the term 'onkocyte' was applied by Hamperl (1931) (cited by Ellis GL and Auclair PL, 1991). Oncocytosis is seen with greater frequency in older people and is considered a sequela of aging. The majority of cases occur in the parotid but it may be found in any major or minor gland. The histologic distinction between oncocytosis and oncocytoma, which is the benign neoplasm of oncocytes, may occasionally be difficult.

Histologic Features. Oncocytosis may present as scattered foci of enlarged, eosinophilic epithelial cells or a solitary focus of metaplastic oncocytes. The cells may retain an acinar arrangement and form sheets, trabeculae, or duct like structures surrounded by fine collagen septa. The cytologic features consist of large, eosinophilic, polyhedral epithelial cells with fine granular cytoplasm and a centrally placed pyknotic nucleus (Fig. 3-34). Oncocytes occasionally show transition to clear cells as a result of intracytoplasmic glycogen.

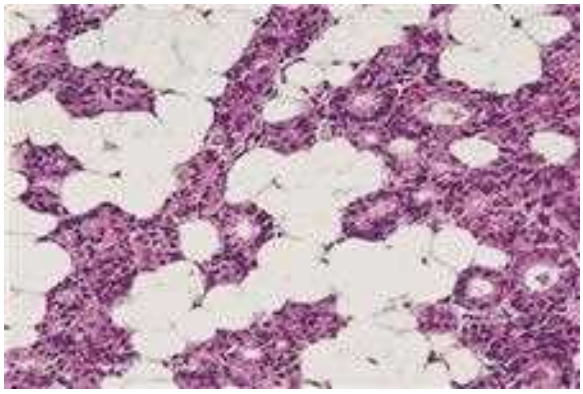


Figure 3-34. Oncocytic hyperplasia.
The granular oncocytes admixed with empty fat cells.

Ultrastructural findings are characterized by cytoplasm that is packed with large, pleomorphic mitochondria containing filamentous, tubular, and vesicular cristae. The oncocytes have been considered a product of degenerative changes.

Necrotizing Sialometaplasia
(Salivary gland infarction)

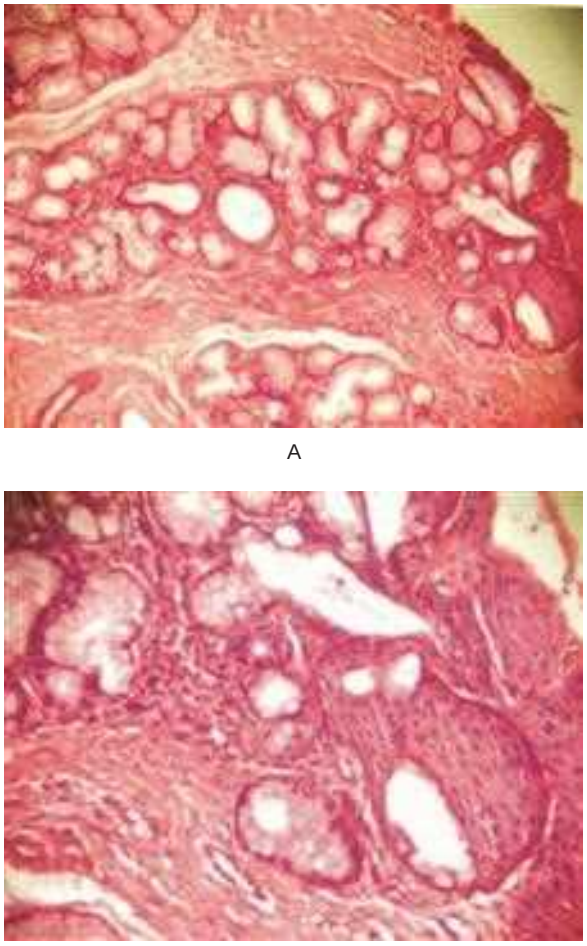
Necrotizing sialometaplasia (NS) is a non-neoplastic inflammatory condition of the salivary glands. In 1973, Abrams et al, first reported this condition. The clinical and histopathologic features of NS often simulate those of malignancies such as squamous cell carcinoma or mucoepidermoid carcinoma.

Etiology. Most cases of NS appear to arise spontaneously, whereas others are associated with a history of trauma, radiation therapy, or surgery. In most cases of NS, the etiology is believed to be related to vascular ischemia. The association of adjacent neoplasia that results in ischemic necrosis of the glandular elements and the histologic features of NS supports this pathogenic mechanism. Tobacco use is suggested as a possible etiologic risk factor for NS.

Clinical Features. NS is generally reported to involve the minor salivary glands of the oral cavity, particularly those of the palate. Reports of this entity in the minor glands of the retromolar pad area, buccal mucosa, tongue, incisive canal, and labial mucosa have also been reported. In addition, NS is recognized in the parotid and submandibular salivary glands, minor mucous glands in the lung, nasal cavity, larynx, trachea, nasopharynx, and maxillary sinus. Similar lesions are identified in the breast; the condition is referred to as post-traumatic lobular metaplasia of the breast. Lesions in the skin are referred to as syringometaplasia. The male-to-female ratio is approximately 2 : 1. The average age of patients with NS is 47.9 years, with a range of 17–80 years.

The lesions of NS often are painless; less frequently, they cause pain and numbness. NS manifests as a swelling with or without ulceration in anatomic sites that have mucous or serous glandular tissue. The typical clinical presentation of NS is that of a crateriform ulcer of the palate that simulates a malignant process. These ulcerated lesions are 1–3 cm and are usually unilateral, but bilateral synchronous lesions and metachronous lesions can occur. Some lesions of NS may present as a submucosal swelling, without ulceration of the overlying mucosa. An intact surface mucosa may be noted in an evolving lesion at the time of diagnosis, although most cases are accompanied by mucosal ulceration. Erosion of the palatal bone may occur in either ulcerated or nonulcerated lesions. Examination of a biopsy specimen is usually required to establish the correct diagnosis and to exclude a malignant or infectious process or an inflammatory condition such as Wegener granulomatosis. Extranodal lymphoma also may be considered in the clinical differential diagnosis of a palatal swelling or ulceration.

Histologic Features. The microscopic features of NS include coagulative necrosis of glandular acini and squamous metaplasia of its ducts. Mucin pooling is present, and an



A

B

Figure 3-35. Sialometaplasia.
Squamous metaplasia of salivary ducts. Lobular architecture of the glands is intact.

associated inflammatory infiltrate consists of macrophages, neutrophils, and less commonly, lymphocytes, plasma cells, and eosinophils (Fig. 3-35).

Pseudoepitheliomatous hyperplasia of the overlying mucosa can also be present, but the cytologic features of the epithelial atypia are usually absent. Occasionally, isolated mucous cells may be entrapped within the squamous islands; these cells should not be confused with those of mucoepidermoid carcinoma. The microscopic differential diagnosis for NS includes mucoepidermoid carcinoma and squamous cell carcinoma. Some believe that subacute necrotizing sialadenitis is yet another entity that occurs within the spectrum of NS; it should be distinguished from NS.

Treatment and Prognosis. NS resolves spontaneously. No treatment is necessary. Surgical care consists of incisional biopsy for diagnostic purposes. Periodic evaluation of the affected site is recommended until spontaneous resolution occurs. The prognosis for NS is excellent. Spontaneous resolution usually occurs within weeks. The average healing time for NS of the minor salivary glands of the hard and soft palates is approximately five weeks. The size of the lesion and whether or not bony perforation has occurred are clinical parameters that may influence the healing time.

Benign Lymphoepithelial Lesion

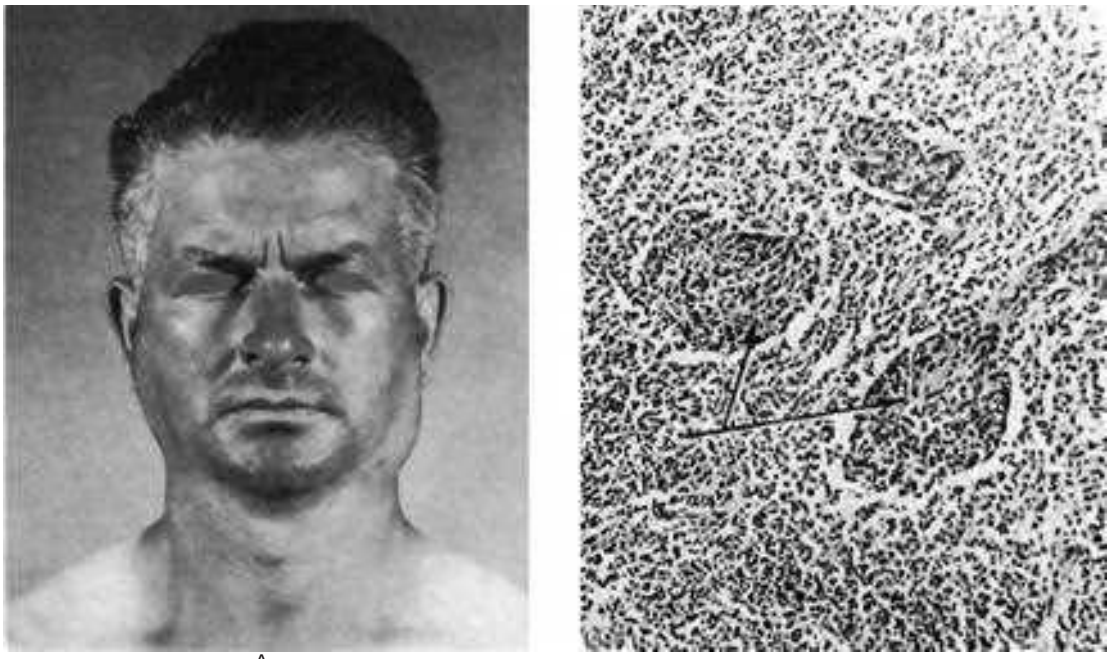
(Mikulicz syndrome, dacryosialoadenopathia, Mikulicz-Radecki syndrome, Mikulicz-Sjögren syndrome, von Mikulicz syndrome)

Mikulicz disease is a chronic condition characterized by the abnormal enlargement of the salivary and lacrimal glands. The tonsils and other glands in the soft tissue of the face and neck may also be involved. In 1888 Johann Mikulicz, a German surgeon first reported a case of chronic bilateral lacrimal gland enlargement associated with enlargement of the salivary glands. Subsequently many cases of bilateral salivary or lacrimal gland enlargement were reported as Mikulicz disease. But as most of these cases were caused by tuberculosis, sarcoidosis or lymphoma, this led to confusion regarding the terminology related to Mikulicz disease. Hence it was proposed that the term Mikulicz disease should be used if the cause is unknown and the Mikulicz syndrome be reserved for cases if the enlargement is associated with a known disease. People who have Mikulicz disease are at heightened risk for developing lymphomas.

Etiology. The exact cause of Mikulicz disease is not known, although it is suspected to be an autoimmune disorder. The symptoms of Mikulicz disease may occur due to the excessive accumulation of lymphocytes into the involved glands.

Clinical Features. Mikulicz disease affects more females than males and most often presents during the middle adult years. It often occurs in combination with Sjögren syndrome. Mikulicz disease is characterized by the sudden onset of xerostomia that may lead to difficulty in swallowing and result in tooth decay. Other symptoms include enlarged lacrimal glands, leading to absent or decreased tears; painless swellings (tumefactions) of the salivary glands (parotid, submaxillary) are noticed. The symptoms of Mikulicz disease are very similar to those of Sjögren syndrome and some researchers suspect that they may be the same disorder. Some people with Mikulicz disease may experience recurring fevers. The fever may be accompanied by dry eyes, diminished lacrimation, and uveitis. Lacrimal gland enlargement, parotid gland enlargement, dry mouth and dry eyes are the classic signs.

Histologic Features. The disease is characterized by an orderly lymphocytic infiltration of the salivary gland tissue, destroying or replacing the acini, with the persistence of islands of epithelial cells which probably represent residua of gland ducts (Fig. 3-36 B). Although the lymphoid element is usually diffuse, actual germinal centers are occasionally present. The epithelium may consist of ducts showing cellular proliferation and loss of polarity, or as the disease persists, solid nests or clumps of poorly defined epithelial cells which Morgan and Castleman termed 'epimyoepithelial islands'. These sometimes seem to form a syncytium. It has been suggested that such islands arise as a result of proliferation



A B

Figure 3-36. Benign lymphoepithelial lesion (Mikulicz's disease).
(A) There is enlargement of the parotid, submaxillary and lacrimal glands. **(B)** The photomicrograph illustrates the diffuse lymphocytic infiltrate and the typical epimyoepithelial islands *(Courtesy of Dr Frank Vellios).*

of both ductal cells and peripheral myoepithelial cells. A characteristic change also found in advanced lesions is the deposition of eosinophilic, hyaline material in the epithelial islands.

Great care must be taken in differentiating between the benign lymphoepithelial tumor and a malignant lymphoma involving the salivary glands. In the latter disease, epimyoepithelial islands are not present, the lymphoid element is atypical, and there is infiltration of the interlobular septa by lymphoid tissue. The epithelial islands, on the other hand, may be mistaken for metastatic carcinoma. Other histologically similar lesions which must be considered in the differential diagnosis are chronic sialadenitis, papillary cystadenoma lymphomatosum and uveoparotitis.

Treatment and Prognosis. Biopsy of one of the swollen glands is key to the diagnosis of Mikulicz disease. An ultrasonographic examination of the area may help to rule out other reasons for gland swelling. Treatment of this disorder is symptomatic. Artificial tears may be used to maintain moisture in the eyes, and artificial saliva may be used to treat oral symptoms. Some individuals with Mikulicz disease may be instructed to follow a soft moist diet. This may help to reduce the pain caused by chewing and swallowing.

Sjögren's Syndrome
(Sicca syndrome, Gougerot-Sjögren syndrome)

Sjögren's syndrome is a condition originally described by Henrik Sjögren in 1933, as a triad consisting of keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. Subsequently, it has been found that some patients present only with dry eyes and dry mouth (sicca complex or **primary Sjögren's syndrome**), while others also develop systemic lupus erythematosus, polyarteritis nodosa, polymyositis or scleroderma, as well as rheumatoid arthritis (**secondary Sjögren's syndrome**). As Sjögren pointed out, cases of xerostomia and arthritis without keratoconjunctivitis sicca have been observed.

Etiology. Various causes of this disease have been suggested: genetic, hormonal, infectious and immunologic, among others. It may well be that a combination of factors, both extrinsic and intrinsic, play a role in the etiology of this condition. Most authorities consider an altered immunologic response to be the main intrinsic factor which is responsible for the disease. Laboratory findings support the autoimmune etiologic role (q.v.). Bertram has reported that 75% of a series of 35 patients with Sjögren's syndrome had in their sera antisalivary duct antibody. Similar antibody was found in the sera of 24% of a group of 29 patients with systemic lupus erythematosus, a documented autoimmune disease. In addition, the sicca complex and Sjogren's syndrome have been found to be associated with the HLA system, specifically HLA-DR3 and HLA-B8 which are associated with primary form of the disease and HLA-DRw52 seen to be associated with both the forms of Sjögren's syndrome. Cytomegalovirus, paramyxovirus and Epstein-Barr virus have all been implicated in the pathogenesis of this condition but have not been proven conclusively.

Clinical Features. This disease occurs predominantly in women over 40 years of age, although children or young adults may be affected. The female: male ratio is approximately

10 : 1. The typical features of the disease are dryness of the mouth and eyes as a result of hypofunction of the salivary and lacrimal glands. This often results in painful, burning sensations of the oral mucosa. In addition, various secretory glands of the nose, larynx, pharynx and tracheobronchial tree (buccopharyngolaryngitis sicca), as well as of the vagina, are involved with this dryness. Schall and his associates have evaluated the degree of xerostomia by means of sequential salivary scintigraphy. Chisholm and Mason have quantified saliva production in patients with the sicca complex and Sjögren's syndrome. Reduced salivary flow was noted in both groups. Sialochemistry studies by Ben-Aryeh and coworkers have demonstrated significantly elevated levels of IgA, potassium and sodium in the saliva of patients with the sicca complex. Moutsopoulos has reported that 80% of patients with primary Sjögren's syndrome have parotid enlargement in contrast to only 14% with secondary Sjögren's syndrome. Lymphadenopathy is more than twice as common in the primary form of the disease.

Rheumatoid arthritis, as mentioned, is an integral part of secondary Sjögren's syndrome. It has been shown that patients with Sjögren's syndrome with rheumatoid arthritis have certain different clinical manifestations than patients with sicca complex, despite similar histologic findings and some laboratory findings. In this regard, patients without rheumatoid arthritis, that is, sicca complex or primary Sjögren's syndrome, more frequently manifest parotid gland enlargement, lymphadenopathy, purpura, Raynaud's phenomenon, kidney involvement and myositis.

Histologic Features. Three types of histologic alterations in the major salivary glands have been described. In one case, there may be intense lymphocytic infiltration of the gland replacing all acinar structures although the lobular architecture is preserved. In another, there may be proliferation of ductal epithelium and myoepithelium to form 'epimyoepithelial islands'. Both of these histologic changes are identical with those occurring in the benign lymphoepithelial lesion in Mikulicz's disease. The third alteration may be simply an atrophy of the glands sequential to the lymphocytic infiltration.

Interestingly, Bertram and Hjoting-Hansen have reported that 85% of a group of patients with Sjögren's syndrome exhibited alterations in the accessory salivary glands of the lip characteristically similar to those in the major glands; they also have suggested biopsy of the labial mucosa as an aid in establishing the diagnosis of the disease. Similar findings in accessory glands, as well as the demonstration of antisalivary duct antibody by an immunofluorescent technique, have been reported by Tarpley, Anderson and White.

Laboratory Findings. Over 75% of patients with primary Sjögren's syndrome have a polyclonal hyperglobulinemia and many develop cryoglobulins. Multiple organ- or tissue-specific antibodies are found, including antisalivary duct antibodies, rheumatoid factor and antinuclear antibodies. An increased sedimentation rate is present in 80% of these patients. Interestingly, the presence of antisalivary duct antibody is three times more common in those with secondary Sjögren's syndrome as compared to those with the sicca complex.

Radiographic Features. Sialography may be of diagnostic value in Sjögren's syndrome. Sialographs demonstrate the formation of punctate, cavitary defects which are filled with radiopaque contrast media. These filling defects have been said to produce a 'cherry blossom' or 'branchless fruit-laden tree' effect radiographically. Som and his associates have suggested that the contrast material actually extravasates through the weakened salivary gland ducts to produce the sialographic features. Poor elimination of contrast media is noted, as might be expected, with retention of the material for over a month.

Treatment and Prognosis. There is no satisfactory treatment for Sjögren's syndrome. Most patients are treated symptomatically. Keratoconjunctivitis is treated by instillation of ocular lubricants such as artificial tears containing methylcellulose, and xerostomia is treated by saliva substitutes such as those used in the treatment of person with xerostomia secondary to radiation therapy. Extensive dental caries is a complication which is quite common, and scrupulous oral hygiene and frequent fluoride application is indicated to reduce this problem. There is no specific treatment for enlargement of the salivary glands. Surgery has been employed but is generally recommended only in patients with discomfort. Although radiation therapy has been recommended in the past, its use is not advocated currently.

A major complicating factor in patients with Sjögren's syndrome is the development of pseudolymphoma and malignant lymphoma. In an extensive National Institutes of Health (NIH) study, 136 patients with Sjögren's syndrome were followed for an average period of over eight years. Nonlymphoma malignancies were no more common than would be expected, whereas lymphomas were observed in nearly 44 times the expected incidence rate. The risk of lymphoma in Sjögren's patients is 6.4 cases per 100 cases per year. Most lymphomas are non-Hodgkin's types and are B-cell in origin. Macroglobulinemia of Waldenstrom also has been noted to develop in these patients.

The relation between the benign lymphoepithelial lesion, Mikulicz's disease and Sjögren's syndrome is possibly a very close one. Mikulicz's disease, but not Mikulicz's syndrome, is probably identical with the lymphoepithelial lesion. This entity shares several features in common with Sjögren's syndrome. Both diseases are manifested, often but not invariably, by a swelling of the major salivary glands and lacrimal glands, singly or in pairs. In both diseases the patient has xerostomia, which probably is related to the displacement and destruction of acinar tissue. Finally, both diseases occur chiefly in middle-aged or elderly women.

It is likely that the benign lymphoepithelial lesion is a mild form of Sjögren's syndrome, but it should not be inferred that lymphoepithelial lesions will eventually terminate in Sjögren's

disease. More aptly, the two diseases may be considered two forms of the same disease with a probably common etiology.

SALIVARY GLAND CYSTS

Most cystic lesions of the major salivary glands are cystic neoplasms. Benign cyst is much less common and accounts for approximately 2–5% of parotid gland lesions. They are rare in the other major salivary glands. Benign cyst (sialocyst) of the parotid gland can be conveniently classified into the following three types: lymphoepithelial cyst, salivary duct cyst, and dysgenetic cyst. Polycystic (dysgenetic) disease of the parotid gland is considered a developmental malformation of the ductal system.

Lymphoepithelial Cysts

(Refer Chapter 1 Developmental Desturbances of Oral and Paraoral Structures)

Salivary Duct Cyst

Salivary duct cyst may be acquired or congenital. The majority; however, are acquired and most of these are probably secondary to obstruction. Some authors, therefore, prefer the term retention cyst to designate these lesions. Still others prefer the term simple cyst.

Clinical Features. Salivary duct cysts of the parotid gland are unilateral painless swellings with no involvement of facial nerve and no fixation to the overlying skin. The majority of the affected patients are over 40 years of age. The cysts range in size from 0.8–10.0 cm with an average size of approximately 1–3 cm.

Histologic Features. Typically, these unilocular cysts are lined by single or multilayered cuboidal or columnar epithelium. Occasional mucus containing goblet cells and areas of oncocytic differentiation may be seen. It may be completely or partially lined by squamous epithelium. A sparse to moderate lymphocytic infiltration is present in the cyst wall.

Treatment. Simple surgical resection is curative.

Chronic Sclerosing Sialadenitis of Submandibular Gland

(Küttner tumor)

Kuttner tumor or chronic sclerosing sialadenitis is a benign inflammatory condition of the submandibular gland that mimics a malignant neoplasm clinically because of presentation as a hard mass. This entity is poorly documented in the surgical pathology and cytology literature.

Histologic Features. Histologic examination of the excised submandibular glands revealed preserved lobular architecture, thickening of interlobular septa by sclerotic tissue, dense lymphoplasmacytic infiltrate, preservation of ducts with periductal fibrosis, and variable loss of acini. Fine-needle aspiration cytologic findings were characterized by scattered tubular ductal structures often enveloped by collagen bundles or lymphoplasmacytic infiltrate, isolated fragments of fibrous stroma, a background rich in lymphoid cells, and paucity or absence of acini.

Treatment and Prognosis. The treatment of sialadenitis includes appropriate antibiotic therapy and rehydration of the patient to stimulate salivary flow. Surgical drainage may be needed if there is abscess formation.

Cystic Lymphoid Hyperplasia in AIDS

Cystic lesions of the parotid gland have been reported in patients at risk for acquired immunodeficiency syndrome (AIDS). The cysts in many of these cases have features of lymphoepithelial cysts but differ from those described before the AIDS epidemic in that they are more frequently multiple and bilateral. In addition to the cysts, the parotid gland in many of the patients at risk of AIDS exhibits features suggestive of benign lymphoepithelial lesions. Such lesions, without associated cysts, may also occur in patients at risk of AIDS. The parotid lymphoid tissue in some of these cystic and noncystic lesions may exhibit features seen in the lymph nodes of patients with AIDS-related complex with persistent generalized lymphadenopathy. Transformation to malignant lymphoma may occur.

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CHAPTER 4

Cysts and Tumors of Odontogenic Origin

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CHAPTER OUTLINE

Tumors derived from the odontogenic tissues constitute an unusually diverse group of lesions. This multiformity reflects the complex development of the dental structures, since these tumors all originate through some aberration from the normal pattern of odontogenesis. An understanding of the pathogenesis of the odontogenic tumors is predicated upon an understanding of the histogenesis of the tooth.

Certain of the lesions discussed in this chapter represent only minor alterations in odontogenesis and not true neoplasms. The odontogenic cysts are included because they too represent an aberration at some stage of odontogenesis, and in fact, may be intimately associated with the development of certain of the odontogenic tumors. All of the various lesions are grouped here because of their common origin from a uniquely specialized group of tissues, and their classification is based upon this origin from the various germ layers.

Odontogenic Cysts

Cysts of the jaws can be classified as:

- Odontogenic (arising from tooth-forming tissues)
- Nonodontogenic (developmental or fissural).

The odontogenic cysts are derived from epithelium associated with the development of the dental apparatus. The type of epithelium can vary with most lesions having stratified squamous but some developmental or fissural cysts in the maxilla may have respiratory epithelium.

Several types of odontogenic cysts may occur, dependent chiefly upon the stage of odontogenesis during which they originate. Various investigators have attempted to devise a classification and system of nomenclature of the lesions. Some of these classifications have not been entirely satisfactory because they generally failed to recognize the mode of origin and development of the cysts and did not unite the views of the oral surgeon, the radiologist and the pathologist.

The following classification of odontogenic cysts (Table 4-1) is based on etiology and tissue of origin.

Dentigerous Cyst
(Follicular cyst)

Dentigenous cyst can be defined as an odontogenic cyst that surrounds the crown of an impacted tooth; caused by fluid accumulation between the reduced enamel epithelium and the enamel surface, resulting in a cyst in which the crown is located within the lumen. This is one of the most common types of developmental odontogenic cyst, estimated to be about 20% of all jaw cysts. It is estimated that about 10% of impacted teeth have formed a dentigerous cyst. Their frequency in the general population has been estimated at 1.44 cyst for every 100 unerupted teeth. The dentigerous cyst nearly always involves or is associated with the crown of a normal permanent tooth. Seldom is a deciduous tooth involved.

Clinical Features. This cyst is always associated initially with the crown of an impacted, embedded or unerupted tooth (Fig. 4-1). A dentigerous cyst may also be found enclosing a complex compound odontoma or involving a supernumerary tooth. The most common sites of this cyst are the mandibular and maxillary third molar and maxillary cuspid areas, since these are the most commonly impacted

Table 4-1: Classification of odontogenic cysts

Classification by etiology
Developmental: Unknown origin but are not the result of an inflammatory reaction
Dentigerous cyst Eruption cyst Odontogenic keratocyst Gingival cyst of newborn Gingival cyst of adult Lateral periodontal cyst Calcifying odontogenic cyst Glandular odontogenic cyst
Inflammatory: Result of inflammation
Periapical cyst Residual cyst Paradental cyst
Classification by tissue of origin
Derived from rests of Malassez
Periapical cyst Residual cyst
Derived from reduced enamel epithelium
Dentigerous cyst Eruption cyst
Derived from dental lamina (rests of Serres)
Odontogenic keratocyst Gingival cyst of newborn Gingival cyst of adult Lateral periodontal cyst Glandular odontogenic cyst
Unclassified
Paradental cyst Calcifying odontogenic cyst

Figure 4-1. Dentigerous cyst.
The cyst wall is attached to the cervical region of the associated unerupted tooth. The crown of the tooth projects into the cyst cavity and its roots exhibit hypercementosis.

teeth. Most lesions present in second and third decades, with slight male predilection (M:F–3:2). Most dentigerous cysts are solitary. Bilateral and multiple cysts are usually found in association with a number of syndromes including cleidocranial dysplasia and Maroteaux–Lamy syndrome. In the absence of these syndromes, bilateral dentigerous cysts are rare. The dentigerous cyst is potentially capable of becoming an aggressive lesion. Expansion of bone with subsequent facial asymmetry, extreme displacement of teeth, severe root resorption of adjacent teeth and pain are all possible sequelae brought about by continued enlargement of the cyst. Cystic involvement of an unerupted mandibular third molar may result in a 'hollowing-out' of the entire ramus extending up to the coronoid process and condyle as well as in expansion of the cortical plate due to the pressure exerted by the lesion. Associated with this reaction may be displacement of the third molar to such an extent that it sometimes comes to lie compressed against the inferior border of the mandible. In the case of a cyst associated with a maxillary cuspid, expansion of the anterior maxilla often occurs and may superficially resemble an acute sinusitis or cellulitis. There is usually no pain or discomfort associated with the cyst unless it becomes secondarily infected.

Radiographic Features. Radiographic examination of the jaw involved by a dentigerous cyst will reveal a radiolucent area associated in some fashion with an unerupted tooth crown (Fig. 4-2A). The impacted or otherwise unerupted tooth crown may be surrounded symmetrically by this radiolucency, although the distinction between a small dentigerous cyst and an enlarged dental follicle or follicular space is quite arbitrary, especially since the small cyst and the enlarged follicle would be histologically identical. While a normal follicular space is 3–4 mm, a dentigerous cyst can be suspected when the space is more than 5 mm. Only when the size of the radiolucency is grossly pathologic can the distinction be made with assurance.

Three radiological variations of the dentigerous cyst may be observed. In the *central* variety, the crown is enveloped symmetrically. In these instances, pressure is applied to the crown of the tooth and may push it away from its direction of eruption. In this way, mandibular third molars may be found at the lower border of the mandible or in the ascending ramus and a maxillary canine may be forced into the maxillary sinus as far as the floor of the orbit. The *lateral* type of dentigerous cyst is a radiographic appearance which results from dilatation of the follicle on one aspect of the crown. This type is commonly seen when an impacted mandibular third molar is partially erupted so that its superior aspect is exposed. The so-called *circumferential* dentigerous cyst results when the follicle expands in a manner in which the entire tooth appears to be enveloped by cyst. The dentigerous cyst is usually a smooth, unilocular lesion, but occasionally one with a multilocular appearance may occur. In actuality, the various compartments are all united by the continuous cystic membrane. Sometimes the radiolucent area is surrounded by a thin sclerotic line representing bony reaction. In cases of apparently multiple dentigerous cysts, care should be taken to rule out the possible occurrence of the odontogenic keratocyst, basal cell nevus, bifid rib syndrome (q.v.).

Histologic Features. There are no characteristic microscopic features which can be used reliably to distinguish the dentigerous cyst from the other types of odontogenic cysts.

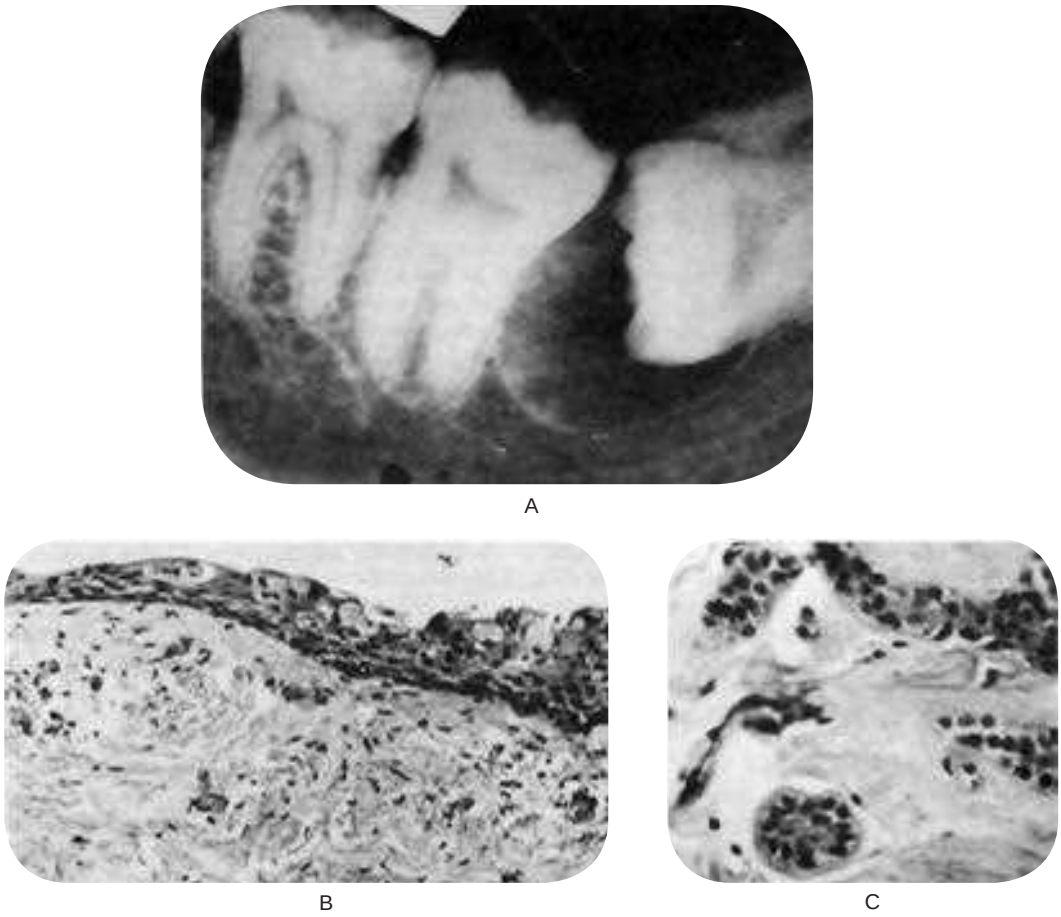

Figure 4-2. Dentigerous cyst.
The radiograph **(A)** demonstrates a large radiolucent area associated with the crown of the impacted mandibular third molar. The photomicrograph **(B)** shows this cyst to be lined by a thin layer of stratified squamous epithelium similar in appearance to the primordial cyst. Occasional mucus-containing cells are present in the epithelium. Small islands of odontogenic epithelium **(C)** are often present in the connective tissue wall.

It is usually composed of a thin connective tissue wall with a thin layer of stratified squamous epithelium lining the lumen (Fig. 4-2B). Rete peg formation is generally absent except in cases that are secondarily infected. The connective tissue wall is frequently quite thickened and composed of a very loose fibrous connective tissue or of a sparsely collagenized myxomatous tissue, each of which has been sometimes mistakenly diagnosed as either an odontogenic fibroma or an odontogenic myxoma. A hyperplastic dental follicle is not necessarily associated with inflammation. An additional feature of the connective tissue wall of both normal dental follicles and dentigerous cysts is the presence of varying numbers of islands of odontogenic epithelium (Fig. 4-2C). These are sometimes very sparse and obviously inactive, while at other times they are present in sufficient numbers to be mistaken for an ameloblastoma. While this latter odontogenic tumor can originate in this situation, care must be taken to differentiate between it and simply odontogenic epithelial rests. Inflammatory cell infiltration of the connective tissue is common although the cause for this is not always apparent. An additional finding, especially in cysts which exhibit inflammation, is the presence of Rushton bodies within the lining epithelium. These are peculiar linear, often curved, hyaline bodies with variable stainability which are of uncertain origin, questionable nature and unknown significance. Even electron microscopic studies, such as those of El-Labban, have only been of partial help in determining that the structures are probably of hematogenous origin, although it is not clear why they have such an intimate relationship to epithelium. The content of the cyst lumen is usually a thin, watery yellow fluid, occasionally blood tinged.

It was reported by Brannon in his excellent clinicopathologic study of 312 cases of odontogenic keratocysts that 8.5% of a series of 1,850 dentigerous cysts were odontogenic keratocysts (q.v.) with the characteristic histologic findings in the epithelium of a parakeratinized, corrugated surface, a remarkable uniformity of a 6- to 10-cell thickness without rete peg formation, and a polarized and palisaded basal layer of cells. This percentage of dentigerous cysts which are odontogenic keratocysts is in close agreement with the findings of Pindborg and his coworkers (7.1%) and Payne (8.5%).

The pluripotentialities of the epithelium in mandibular dentigerous cysts has been further emphasized by Gorlin, who described mucus-secreting cells in the lining stratified squamous epithelium, respiratory epithelial lining, sebaceous cells in the connective tissue wall, and lymphoid follicles with germinal centers.

Treatment. The treatment of the dentigerous cyst is usually dictated by the size of the lesion. Smaller lesions can be surgically removed in their entirety with little difficulty. The larger cysts which involve serious loss of bone and thin the bone dangerously are often treated by insertion of a surgical drain or marsupialization. Such a procedure is often necessary because of the potential danger of fracturing the jaw if complete surgical removal were attempted. Recurrence is relatively uncommon.

Potential Complications. Several relatively serious potential complications exist stemming from the dentigerous cyst, besides simply the possibility of recurrence following incomplete surgical removal. These include:

- The development of an ameloblastoma either from the lining epithelium or from rests of odontogenic epithelium in the wall of the cyst.
- The development of epidermoid carcinoma from the same two sources of epithelium.
- The development of a mucoepidermoid carcinoma, basically a malignant salivary gland tumor, from the lining epithelium of the dentigerous cyst which contains mucus-secreting cells, or at least cells with this potential, most commonly seen in dentigerous cysts associated with impacted mandibular third molars.

It is of great clinical significance that numerous cases of ameloblastoma have been reported developing in the wall of dentigerous cysts from the lining epithelium or associated epithelial rests (Fig. 4-3). Stanley and Diehl have reviewed a series of 641 cases of ameloblastoma and have found that at least 108 cases of this neoplasm, approximately 17%, were definitely associated with an impacted tooth and/or a follicular or dentigerous cyst. The disposition for neoplastic epithelial proliferation in the form of an ameloblastoma is far more pronounced in the dentigerous cyst than in the other odontogenic cysts. The formation of such a tumor manifests itself as a nodular thickening in the cyst wall, the mural ameloblastoma, but this is seldom obvious clinically. Therefore, it is not only good clinical practice, but also an absolute requisite that all tissue from dentigerous cysts be submitted to a qualified oral pathologist for thorough gross and microscopic examination. In reviewing the histologic changes sought by the oral pathologist which occur in the dentigerous cyst as a premonitory manifestation of ameloblastoma, Vickers and Gorlin have stressed that hyperchromatism of basal cell nuclei, palisading with polarization of basal cells and cytoplasmic vacuolization with intercellular spacing of the lining epithelium, **when observed together,** are manifestations of impending neoplasia. These findings may occur **individually** in other rather harmless conditions. The presence of sprouting or budding and protruding of epithelial islands from lining epithelium has been claimed to be evidence of neoplastic transformation, but this in itself was not considered such an indication by Vickers and Gorlin.

The development of epidermoid carcinoma from the lining epithelium of the dentigerous cyst also has been adequately

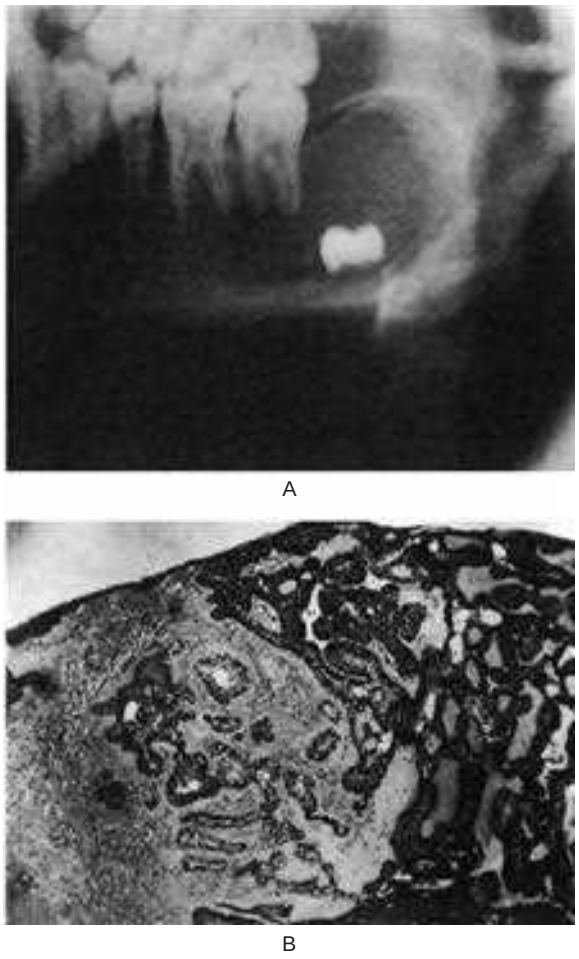

Figure 4-3. Ameloblastoma developing in wall of dentigerous cyst.

documented in the literature reviewed by Gardner, who reported eight acceptable cases among 25 cases of carcinoma developing in odontogenic cysts of all types combined. Browne and Gough have reported two additional cases of malignant transformation in dental cysts and suggested that keratin metaplasia in long-standing cyst lining appears to precede the development of the carcinomatous change, although there is little evidence that the odontogenic keratocyst is associated with malignant change more commonly than other types of odontogenic cysts. The predisposing factor and mechanism of development of this malignancy are unknown, but its occurrence appears unequivocal (Fig. 4-4).

Finally, the development of a mucoepidermoid carcinoma, a type of salivary gland tumor, is less well documented than the epidermoid carcinoma of this origin, but it also appears to be a potentiality. The inclusion of normal salivary gland tissue in the posterior portion of the body of the mandible has been reported, and undoubtedly, some central salivary gland tumors in this location originate from this source. However, cases of central mucoepidermoid carcinoma (q.v.) have been discovered in association with dentigerous cysts involving impacted mandibular third molars, and considering the frequency with which mucus-secreting cells are found

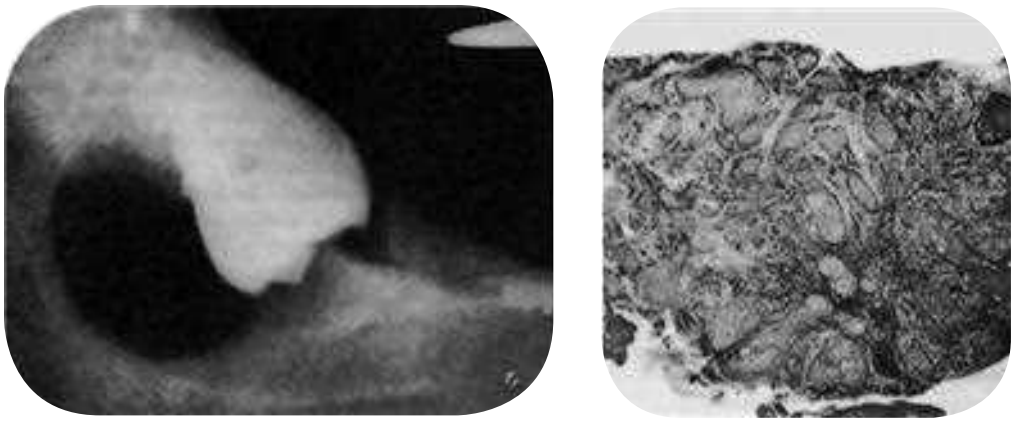

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Figure 4-4. Epidermoid carcinoma developing in dentigerous cyst.

in this lining epithelium indicative of the pluripotentiality of this epithelium, this very distinct possibility must always be considered. These findings comprise most of the medical rationale for removal of impacted third molars with pericoronal radiolucencies; however, impacted teeth with small pericoronal radiolucencies (suggesting the presence of normal dental follicle rather than dentigerous cyst) also may be monitored with serial radiographic examination. Any increase in the size of the lesion should prompt removal and histopathologic examination. Any lesion that appears larger than a normal dental follicle indicates removal and histopathologic examination.

Eruption Cyst

Eruption cyst is defined as an odontogenic cyst with the histologic features of a dentigerous cyst that surrounds a tooth crown that has erupted through bone but not soft tissue and is clinically visible as a soft fluctuant mass on the alveolar ridges.

An eruption cyst or 'eruption hematoma' is in fact a dentigerous cyst occurring in the soft tissues (Shear, 1992). Whereas the dentigerous cyst develops around the crown of an unerupted tooth lying in the bone, the eruption cyst occurs when a tooth is impeded in its eruption within the soft tissue overlying the bone. The pathogenesis is probably very similar to that of the dentigerous cyst. The difference is that the tooth in the case of the eruption cyst is impeded in the soft tissue of gingiva rather than in the bone. The presence of particularly dense fibrous tissue in the overlying gingiva could be responsible.

Clinical Features. Shear (1992) had recorded a 0.8% frequency. It is likely that they occur more frequent clinically and as some rupture spontaneously, these cysts go unnoticed and are not submitted for histological examination.

These cysts are found in children of different ages, and occasionally in adults if there is delayed eruption. Deciduous and permanent teeth may be involved, most frequently anterior to the first permanent molar. Clinically, the lesion appears as a circumscribed, fluctuant, often translucent swelling of the alveolar ridge over the site of the erupting tooth. When the circumcoronal cystic cavity contains blood, the swelling appears purple or deep blue; hence the term '**eruption hematoma'**. It is usually painless unless infected.

Sometimes more than one cyst may be present. There is often a brief history of about three to four weeks duration during which they enlarge to approximately 1–1.5 cm.

Radiographic Features. It may show a soft tissue shadow since the cyst is confined within it and there is usually no bone involvement.

Histologic Features. The superficial aspect is covered by the keratinized stratified squamous epithelium of the overlying gingiva. This is separated from the cyst by a strip of dense connective tissue of varying thickness which usually shows a mild chronic inflammatory cell infiltrate. Inflammatory cell infiltration is common. The follicular connective tissue is more densely cellular, less collagenous and has a basophilic hue, presumably because of a higher content of acid mucopolysaccharide in the ground substance. Odontogenic epithelial cell nests may be present in the connective tissue.

In noninflamed areas, the epithelial lining of the cysts is characteristically of reduced enamel epithelial origin, consisting of two or three cell layers of squamous epithelium with a few foci where it may be a little thicker. The adjacent corium is hyperemic and is the seat of a chronic inflammatory cell infiltrate (Fig. 4-5).

Treatment. No treatment is necessary as the cyst often ruptures spontaneously. Surgically exposing the crown of the tooth may aid the eruption process.

Odontogenic Keratocyst

A cyst derived from the remnants (rests) of the dental lamina, with a biologic behavior similar to a benign neoplasm, with a distinctive lining of six to 10 cells in thickness, and that exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratin.

This is the most interesting of jaw cysts. The term 'odontogenic keratocyst' was first used by Philipsen in 1956, while Pindborg and

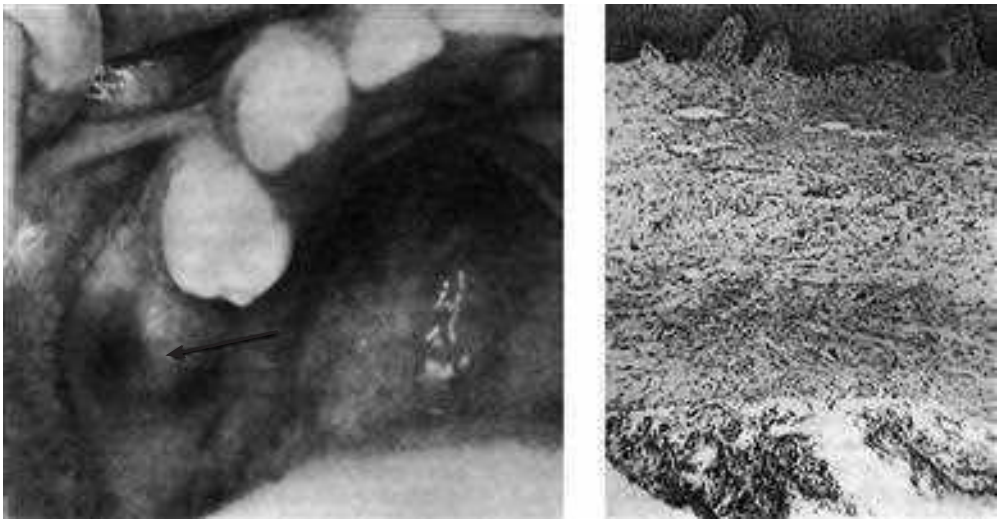

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Figure 4-5. Eruption cyst.
The cyst is lined by a thin layer of stratified squamous epithelium in which there are scattered inflammatory cells. Eruption cyst often shows marked secondary inflammatory changes from masticatory trauma.

Hansen in 1963 described the essential features of this type of cyst. It is named keratocyst because the cyst epithelium produces so much keratin that it fills the cyst lumen. Furthermore, flattening of the basement membrane and palisading of the basal epithelial cells, reminiscent of odontogenic epithelium, are characteristics of odontogenic keratocyst.

They are unique odontogenic lesions that have the potential to behave aggressively, that can recur, and can be associated with the nevoid basal cell carcinoma syndrome. Toller (1967) suggested that OKCs might be regarded as benign cystic neoplasms. Whether they are developmental or neoplastic continues to be debated.

Studies indicate that a significant number of OKCs show clonal loss of heterozygosity of common tumor suppressor genes. The finding of clonal deletion mutations of genomic DNA in these cysts supports the hypothesis that they are neoplastic rather than developmental in origin. The odontogenic keratocyst is regarded as a distinctive entity because of its characteristic histology, proliferation kinetics, and behavior. Therefore, although keratinization may be present in many other types of cysts, the specific histologic pattern of the odontogenic keratocyst separates it from all others.

Differences in cytokeratin, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) immunoreactivity between the parakeratinized OKC and the orthokeratinized variety have been demonstrated and the suggestion made that the latter having a considerably less aggressive behavior is different entity and should bear a different name **orthokeratinized odontogenic cyst** (Shear M, 2002).

There is general agreement that the origin of the odontogenic keratocyst comes from dental lamina remnants in the mandible and maxilla. However, the origin of this cyst from the extension of basal cells of the overlying oral epithelium has also been suggested.

Reclassification of the Odontogenic Keratocyst to Tumor: Keratocystic Odontogenic Tumor (KOT)

In 1967, Toller suggested that the OKC may best be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behavior. The WHO has reclassified the lesion as a tumor based on several factors, that formed the basis of this decision.

- ***Behavior:*** The KOT is locally destructive and recurrence rate is very high.
- ***Histopathology:*** The basal epithelial layer of KOT shows proliferation and budding into the underlying connective tissue in the form of daughter cysts and mitotic figures are frequently found in the suprabasal layers of the lesional epithelium.
- ***Genetics:*** PTCH (patched), a tumor suppressor gene involved in both syndrome associated and sporadic KOTs, occurs on chromosome 9q22.3 – q31. Normally, PTCH forms a receptor complex with the oncogene SMO (smoothened) for the SHH (sonic hedgehog) ligand. PTCH binding to SMO inhibits growth signal transduction. SHH binding to PTCH releases this inhibition. If normal functioning of PTCH is lost, the proliferation-stimulation effects of SMO are permitted to predominate.

Evidence has shown that the pathogenesis of syndrome associated and sporadic KOTs involves a 'two hit mechanism', with allelic loss at 9q22. The 'two hit mechanism' refers to the process by which a tumor suppressor gene is inactivated. The first hit is a mutation in one allele, which, although it can be dominantly inherited, has no phenotypic effect. The second hit refers to loss of the other allele and is known as 'loss of heterozygosity' (LOH). In KOTs, this leads to the dysregulation of the oncoproteins cyclin D1 and p53. LOH

in the 9q22.3–q31 region has been reported for many epithelial tumors, including basal cell carcinomas, squamous cell carcinomas, and transitional cell carcinomas; and LOH is by definition a feature of tumorigenic tissue.

Clinical Features. The largest and most detailed series of cases of odontogenic keratocyst has been published by Brannon, and his data are probably most representative of this lesion. The cyst may occur at any age, from the very young to the very elderly, although Brannon found it to be exceedingly rare under the age of 10 years, there being only two such patients in his series of 283 persons. The peak incidence is in the second and third decades of life, with a gradual decline thereafter. The data of Browne (104 patients) and of Forssell (119 patients) are virtually identical. In all series, there is a predilection for occurrence in males, ranging from 1.44:1 (Brannon), 1.46:1 (Browne) to 1.79:1 (Forssell).

The mandible is invariably affected more frequently than the maxilla: in the series of Brannon, 65% versus 35%, in the series of Browne, 79% versus 21%, and in that of Forssell, 78% versus 22%. In the mandible, the majority of the cysts occur in the ramus-third molar area, followed by the first and second molar area and then the anterior mandible. In the maxilla, the most common site is the third molar area followed by the cuspid region.

Multiple odontogenic keratocysts occur with some frequency. Lesions found in children are often reflective of multiple odontogenic keratocysts as a component of the nevoid basal cell carcinoma syndrome. However, at other times, these multiple cysts are independent of the syndrome. A rather remarkable parallelism between the odontogenic keratocyst and the ameloblastoma with respect to mean age of occurrence, predilection for site of occurrence, radiographic findings and recurrence rate has also been pointed out by Browne.

There are no characteristic clinical manifestations of the keratocyst, although about 50% of the patients in Brannon's series were symptomatic prior to seeking treatment. Among the more common features are pain, soft-tissue swelling and expansion of bone, drainage and various neurologic manifestations such as paresthesia of the lip or teeth. The maxillary OKC tends to be secondarily infected with greater frequency than the mandibular ones, due to its vicinity to the maxillary sinus.

Radiographic Features. Radiographically most OKCs are unilocular, presenting a well-defined peripheral rim. Scalloping of the border is also a frequent finding and this represents variations in the growth pattern of the cyst. Multilocular radiolucent OKC is also observed, generally representing a central cavity having satellite cysts. When it is multilocular and especially if located in the third mandibular molar area, it may be confused radiographically with an ameloblastoma. Occasionally OKC may mimic a dentigerous cyst and contain the crown of a retained tooth within its lumen. The final diagnosis of any cystic cavity within the jaw bones will be achieved only after biopsy of the surgical specimen. Multilocularity (20%) is often present and tends to be seen more frequently in larger lesions. Most lesions, however, are unilocular, with as many as 40% noted adjacent to the crown of an unerupted tooth (dentigerous cyst position). Approximately 30% of maxillary and 50% of mandibular lesions produce buccal expansion. Mandibular lingual enlargement is occasionally seen. Proximity to the roots of adjacent normal teeth sometimes causes resorption of these roots, although displacement is more common. Sometimes these cysts displace the neurovascular bundle.

Histologic Features. The odontogenic keratocyst wall is usually rather thin unless there has been superimposed inflammation. The lining epithelium is highly characteristic, and is composed of:

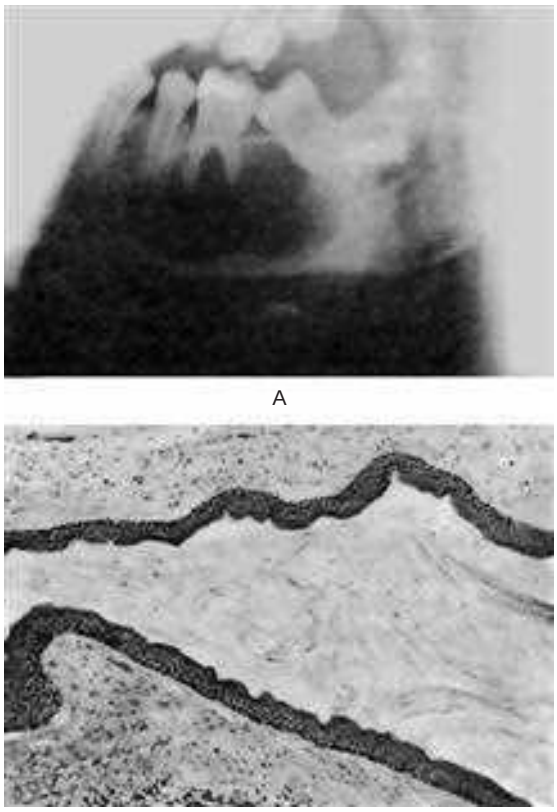
- A parakeratinized surface which is typically corrugated, rippled or wrinkled.
- A remarkable uniformity of thickness of the epithelium, usually ranging from 6 to 10 cells thick.
- A prominent palisaded, polarized basal layer of cells often described as having a 'picket fence' or 'tombstone' appearance.

Histologically, these cysts are formed with a stratified squamous epithelium that produces orthokeratin (10%), parakeratin (83%), or both types of keratin (7%). No rete ridges are present; therefore, the epithelium often sloughs from the connective tissue (94% of the time). The epithelium is thin, and mitotic activity is frequent; therefore, OKC grows in a neoplastic fashion and not in response to internal pressure. In the presence of an intense inflammatory process, the adjacent epithelium loses its keratinized surface, may thicken and develop rete processes or may ulcerate.

The connective tissue wall often shows small islands of epithelium similar to the lining epithelium; some of these islands may be small cysts. In at least some cases, the apparent islands of epithelium and small satellite or 'daughter' cysts actually represent the ends of folds of the lining epithelium of the main cystic cavity which have been cut in cross-section; the linings of these cysts are very commonly folded. Forssell and his associates have studied this problem using serial sections of cysts and found microcysts in the wall in 20% and epithelial islands in 50% of their cases. In 35% of the cases, apparent microcysts were found to be part of the main cyst by the serial sections while pseudo islands of epithelium were found in 75% of the cases.

The lumen of the keratocyst may be filled with a thin straw colored fluid or with a thicker creamy material. Sometimes the lumen contains a great deal of keratin, while at other times it has little. Cholesterol, as well as hyaline bodies at the sites of inflammation, may also be present. The electrophoretic measurement of fluid from these cysts has been reported by Toller to show that it contains a very low content of soluble protein compared with the patient's own serum (Fig. 4-6).

Dysplastic and neoplastic transformation of the lining epithelium in the odontogenic keratocyst is an uncommon occurrence but has been reported. Of the 312 keratocysts studied by Brannon, only two exhibited cellular atypia. Occasional other cases have also been described in the literature. Areen and his associates have recently reported a case of epidermoid carcinoma developing in an odontogenic keratocyst, and in reviewing the literature, have emphasized the necessity for careful microscopic examination of all such cysts.



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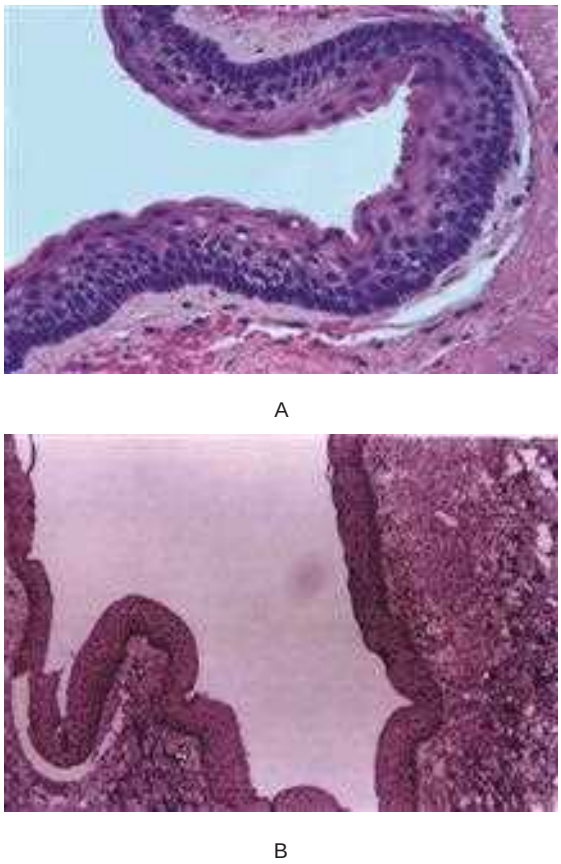
B

Figure 4-6. Odontogenic keratocyst.



A

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Figure 4-7. Odontogenic keratocyst.
(A) The epithelial lining is uniformly thin, generally ranging from 8–10 cell layers thick. The basal layer exhibits a characteristic palisaded pattern with polarized and intensely stained nuclei of uniform diameter. The luminal epithelial cells are parakeratinized and produce an uneven or corrugated profile. **(B)** Odontogenic keratocyst stained using proliferating cell nuclear antigen (PCNA) antibodies (x 10).

The variant of OKC that produces only orthokeratin acts somewhat differently than other OKCs. These almost always are found in a dentigerous association, usually around the mandibular third molar, and they are much less aggressive. They do not have a hyperchromatic basal layer; in fact, the basal layer is flattened. They are not associated with basal cell nevus syndrome (orthokeratinized odontogenic cyst).

Finally, the highly characteristic nature of the parakeratinized lining epithelium and its relationship to the high recurrence rate have been emphasized by a report dealing with orthokeratinized odontogenic cysts and their recurrence rate. Wright investigated 59 cases of orthokeratinized odontogenic cysts and found that they showed a predilection for occurrence in males, most commonly in the second to fifth decades. These cysts were located predominantly in the posterior mandible, where they most typically appeared as dentigerous cysts. The thin, uniform lining epithelium was covered with orthokeratin and showed a prominent granular layer and a cuboidal to flattened basal layer. Follow-up of 24 of these patients revealed only one case of recurrence. This difference in biologic behavior would further underscore the necessity for very strict application of the definition of the term odontogenic keratocyst in diagnosis of the lesion (Fig. 4-7).

Treatment and Prognosis. The odontogenic keratocyst should be surgically excised. However, clinical experience has shown that complete eradication of the cyst may be difficult because the wall of the cyst is very thin and friable and may easily fragment. In addition, perforation of cortical bone, particularly in lesions involving the ramus, is common and this complicates total removal.

The most important feature of the odontogenic keratocyst is its extraordinary recurrence rate. This has been reported as being between 13 and 60%. A review of 763 cases of odontogenic keratocysts in 13 different reported series of cases has shown the average recurrence rate to be 26%, with the majority occurring within five years of the surgical procedure. Forssell, Forssell and Kahnberg (1988) observed that recurrences were more frequent (63%) with cysts in patients with the nevoid basal cell carcinoma syndrome than with cysts in patients without the syndrome (37%). Keratocysts enucleated in one piece recurred significantly less often than cysts enucleated in several pieces, and the recurrence rate in cases with a clinically observable infection, a fistula or with a perforated bony wall was higher. The size of the cyst did not seem to influence its prognosis after surgery, but those whose radiographic appearance was multilocular had a higher recurrence rate than those with a unilocular appearance.

Browne found no significant differences in recurrence rate following three basic methods of treating the lesions:

- Marsupialization

- Enucleation and primary closure
- Enucleation and packing open.

Furthermore, recurrence does not appear related to the presence of satellite cysts. On this basis, Browne concluded that recurrence of the keratocyst is due to the nature of the lesion itself, i.e. the presence of additional remnants of dental lamina from which a cyst may develop, and is not related to its method of treatment. Since recurrence may be long delayed in this lesion, follow-up of any case of odontogenic keratocyst with annual radiographs is essential for at least five years after surgery. It is also essential that patients with an odontogenic keratocyst, especially if multiple, be evaluated medically to rule out the possibility of the jaw cyst-basal cell nevus-bifid rib syndrome (q.v.).

Jaw Cyst-Basal Cell Nevus, Bifid Rib Syndrome

(Basal cell nevus syndrome, hereditary cutaneomandibular polyoncosis, Gorlin and Goltz syndrome)

This syndrome, first described by Binkley and Johnson in 1951, has been thoroughly reviewed by Gorlin and his coworkers. A hereditary condition, it is transmitted as an autosomal dominant trait, with high penetrance and variable expressivity. It is caused by mutations in patched **(PTCH)**, a tumor suppressor gene that has been mapped to chromosome **9q22.3–q31**.

Clinical Features. The syndrome is very complex and includes a great variety of possible abnormalities. These may be briefly summarized as follows:

- **Cutaneous anomalies,** including basal cell carcinoma, other benign dermal cysts and tumors, palmar pitting, palmar and plantar keratosis and dermal calcinosis.
- **Dental and osseous anomalies,** including odontogenic keratocysts (often multiple), mild mandibular prognathism, rib anomalies (often bifid), vertebral anomalies and brachymetacarpalism (Fig. 4-8).
- **Ophthalmologic abnormalities,** including hypertelorism with wide nasal bridge, dystopia canthorum, congenital blindness and internal strabismus.
- **Neurologic anomalies,** including mental retardation, dural calcification, agenesis of corpus callosum, congenital hydrocephalus and occurrence of medulloblastomas with greater than normal frequency.
- **Sexual abnormalities,** including hypogonadism in males and ovarian tumors.

Some of these patients have shown a lack of response to parathormone as judged by the lack of phosphate diuresis which, coupled with shortened fourth metacarpals in some patients, has suggested that there may be some relationship to pseudohypoparathyroidism.

Oral Manifestations. The odontogenic keratocysts are indistinguishable from those previously described by that term which are not associated with this syndrome (Fig. 4-8). Because they often develop early in life, deformity and displacement of developing teeth may occur. However, they may not develop until middle age even though the basal cell skin tumors have occurred early in life.

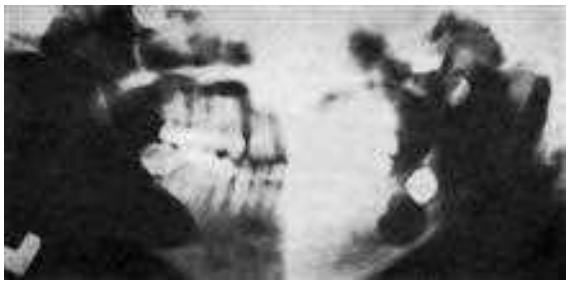


Figure 4-8. Odontogenic keratocysts in the basal cell nevus syndrome.

Treatment and Prognosis. Several cases of ameloblastoma have developed in cysts of this syndrome, thus emphasizing the importance of surgical removal of the cysts and their histologic examination. Whenever a diagnosis of odontogenic keratocyst is received by the dentist, he must be certain to rule out the presence of this syndrome because of the many associated problems which these patients ultimately will face.

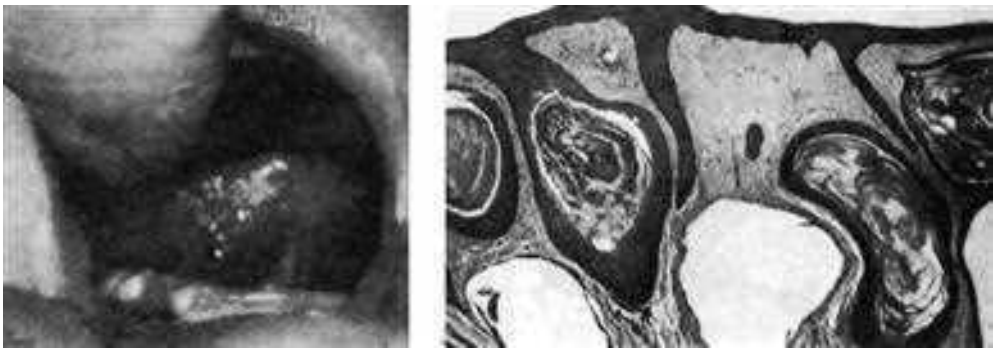
Dental Lamina Cyst of Newborn

(Gingival cyst of newborn, Epstein's pearls, Bohn's nodules)

Dental lamina cyst of the newborn are multiple, occasionally solitary, superficial raised nodules on edentulous alveolar ridges of infants that resolve without treatment; derived from rests of the dental lamina and consisting of keratin-producing epithelial lining. **Bohn's nodules** and **Epstein's pearls** are two similar lesions with which gingival cysts sometimes may be confused; however, the location and etiology of these lesions are somewhat different. As originally described, Epstein's pearls are cystic, keratin-filled nodules found along the midpalatine raphe, probably derived from entrapped epithelial remnants along the line of fusion (q.v.). Bohn's nodules are keratin-filled cysts scattered over the palate, most numerous along the junction of the hard and soft palate and apparently derived from palatal salivary gland structures (q.v.). Discussions of these various types of cysts in the newborn have been published by Fromm and by Cataldo and Berkman.

In studying sections of the maxillae and mandibles of 17 infants, Kreshover reported finding 65 examples of gingival cysts (38 multiple and 27 single). These cysts were localized in the corium below the surface epithelium. Those in the anterior portion of the jaws were usually displaced lingually with respect to the deciduous incisors and cuspids. Those in the posterior portion of the jaw were found occlusal to the crown of the molars. Kreshover stated that in all instances the cystic lesions were seen to arise from cells of the dental lamina. The etiology of these cysts has been thoroughly discussed by Maher and Swindle.

Clinical Features. Occasionally these dental lamina cysts in infants become sufficiently large to be clinically obvious as small discrete white swellings of the alveolar ridge, sometimes appearing blanched as though from internal pressure (Fig. 4-9A). These probably correspond to those structures described in the older literature as the 'predeciduous dentition'. These lesions appear to be asymptomatic and do not seem to produce discomfort in the infants.



A B

Figure 4-9. Gingival cyst of the newborn.
(Courtesy of Dr Ralph E McDonald and Dr Alfred Fromm).

Histologic Features. These are true cysts with a thin epithelial lining which lacks rete processes and show a lumen usually filled with desquamated keratin, occasionally containing inflammatory cells (Fig. 4-9B). Interestingly, dystrophic calcification and hyaline bodies of Rushton (q.v.), commonly found in dentigerous cysts, are also sometimes found in this lesion.

Treatment. No treatment is required inasmuch as these lesions almost invariably will disappear by opening onto the surface of the mucosa or through disruption by erupting teeth.

Gingival Cyst of Adult

A small developmental odontogenic cyst of the gingival soft tissue derived from the rests of the dental lamina, containing a lining of embryonic epithelium of cuboidal cells and distinctive focal thickenings similar to the lateral periodontal cyst.

The gingival cyst of the adult is an uncommon cyst of gingival soft tissue, occurring in either the free or attached gingiva.

The etiology and pathogenesis of this lesion have been reviewed by Ritchey and Orban, who suggested possible sources of cystic formation as:

- Heterotopic glandular tissue.
- Degenerative changes in a proliferating epithelial peg.
- Remnants of the dental lamina, enamel organ or epithelial islands of the periodontal membrane.
- Traumatic implantation of epithelium.

Of these possibilities, only the last two appear valid, and on this basis there do appear to be two recognizable forms of gingival cyst:

- That arising from cystic transformation of dental lamina or the 'glands' or rests of Serres.
- That arising from traumatic implantation of surface epithelium (and, therefore, not truly an odontogenic cyst).

The origin of the gingival cyst of the adult has been evaluated by Wysocki and his colleagues, who concluded that it does arise from postfunctional rests of dental lamina and thus represents the extraosseous counterpart of the lateral periodontal cyst, with which it shares a common histogenesis. Buchner and Hansen have reported essentially the same conclusions. The similarities between the lateral periodontal cyst and the gingival cyst of the adult in clinical behavior, morphologic appearance, anatomic site of occurrence and age predilection are too striking to be coincidental.

The vast majority of these gingival cysts appear to originate in the fashion described from dental lamina, including a soft tissue counterpart of the multilocular botryoid odontogenic cyst. However, an implantation type of cyst can occur lined by a more mature keratinizing stratified squamous epithelium lining derived from surface mucosal epithelium. Finally, as suggested by Buchner and Hansen, there is some evidence that a dental lamina cyst of the newborn may persist into adulthood, as judged by the finding of cysts packed with orthokeratin that appear identical to those in the newborn.

Clinical Features. The gingival cyst may occur at any age but is most common in adults. In the review of the literature by Reeve and Levy, the majority of patients were over 40 years of age. The mean age in the 33 cases reported by Buchner and Hansen was 48 years and that of the 10 cases reported by Wysocki and his associates was 51 years. The location of the lesion closely follows that of the lateral periodontal cyst. Thus, all except one cyst in the series of Wysocki and his coworkers were in the mandibular bicuspid-cuspid incisor area, the one exception being in the maxillary lateral incisor area. The locations in the series of Buchner and Hansen were virtually identical except that they had several cases also in the maxillary arch from cuspid to first molar.

This lesion presents generally as a small, well-circumscribed, painless swelling of the gingiva, sometimes closely resembling a superficial mucocele (Fig. 4-10). The lesion is of the same color as the adjacent normal mucosa and seldom measures over 1 cm in diameter, generally much less. Although this cyst may occur in either the free or attached gingiva, some gingival cysts occur in the gingival papilla itself.

Radiographic Features. The gingival cyst is a soft tissue lesion and does not generally manifest itself on the dental radiograph. If it enlarges to sufficient size, it may cause superficial erosion of the cortical plate of bone, but this is still generally not visible on the radiograph. If a circumscribed,

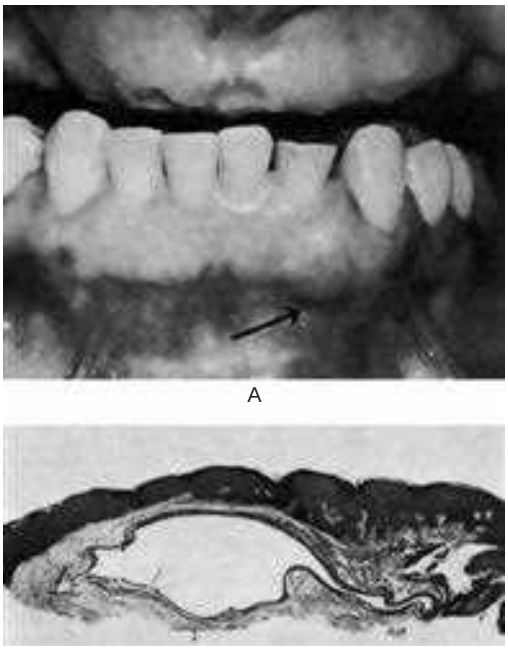


Figure 4-10. Gingival cyst of the adult.

radiolucent cystic lesion of alveolar bone with some swelling of the soft tissue is present, the cyst probably represents a lateral periodontal cyst rather than a gingival cyst.

Histologic Features. The gingival cyst of the adult is a true cyst, since it is a pathologic epithelium lined cavity which usually contains fluid (Fig. 4-10 B). The lining epithelium is generally identical to that found in the lateral periodontal cyst, with the occasional exceptions noted above. The epithelium ranges in thickness from simply one flattened cell to several cells, a thin stratified squamous epithelium. Glycogen-rich clear cells may be present, especially in the focal thickenings or plaques of the lining. Dental lamina rests may also be found in the connective tissue wall and these are commonly composed of the same type of glycogen-rich clear cells. As noted earlier, these lesions may be unicystic or polycystic. Since the cyst lies free in the connective tissue of the gingiva, it may or may not exhibit an associated inflammatory reaction.

In cases of the traumatic or implantation type of gingival cyst, calcification or even ectopic ossification on rare occasions may be associated with the cystic lesion, reminiscent of the ossification occurring after experimental implantation of bladder epithelium into subcutaneous tissues.

Treatment. Local surgical excision of the lesion in adults is usually recommended, and the lesions do not tend to recur. A neoplastic potential has never been reported.

Lateral Periodontal Cyst

A slow growing, nonexpansile developmental odontogenic cyst derived from one or more rests of the dental lamina, containing an embryonic lining of one to three cuboidal cells and distinctive focal thickenings (plaques).

The lateral periodontal cyst, as the name implies, occurs on a lateral periodontal location and it is of developmental origin arising from cystic degeneration of clear cells of the dental lamina. In order to establish the proper diagnosis, an inflammatory origin as well as exclusion of a possible odontogenic keratocyst must be ruled out clinically and histologically.

The lateral periodontal cyst is an uncommon but well-recognized type of developmental odontogenic cyst. The various theories concerning the etiology and pathogenesis of the lesion have been reviewed by Standish and Shafer. These cysts appear to arise in intimate association with the lateral root surface of an erupted tooth, with a predilection for the mandibular bicuspid area. The possibilities which have been offered to explain their origin and mode of development include:

- Origin initially as a dentigerous cyst developing along the lateral surface of the crown, and as the tooth erupts, the cyst assumes a position in approximation to the lateral surface of the root.
- Origin from proliferation of rests of Malassez in the periodontal ligament although the stimulus for this proliferation is unknown.
- Origin simply as a primordial cyst of a supernumerary tooth germ, since the predilection for occurrence of the lateral periodontal cyst in the mandibular bicuspid area corresponds well with the known high incidence of supernumerary teeth in this same region.
- Origin from proliferation and cystic transformation of rests of dental lamina, which are in a postfunctional state and therefore have only a limited growth potential that is in accordance with the usual small size of these cysts.

This latter theory, including the suggestion that the lateral periodontal cyst and the gingival cyst of the adult (q.v.) share this common histogenesis from postfunctional dental lamina rests and that these two cysts represent basically the central or intraosseous and peripheral or extraosseous manifestations of the same lesion, has been discussed in detail by Wysocki and his colleagues. At present, it seems the most appropriate one. They have also pointed out the important fact that in many reports of the lateral periodontal cyst in the previous literature, the term has been used to designate any cyst that may be positioned against the lateral root surface of a tooth (e.g. lateral radicular cyst related to pulp infection, odontogenic keratocyst, etc.). This positional use of the term should be avoided and the designation applied only to that specific developmental lesion with characteristic features.

An unusual form of cyst was reported in 1973 by Weathers and Waldron under the term **botryoid odontogenic cyst.** They described two cases of cysts which had a multilocular pattern apparent radiographically, histologically and even clinically at the time of surgical removal. Additional experience with this cyst, as indicated by Wysocki and his associates, now strongly suggests that this is simply a polycystic variant of the lateral periodontal cyst developing through cystic transformation of multiple islands of dental lamina rests. The epithelial lining in the two cysts is identical, as are its clinical features, including age of predilection and sites of occurrence.

In addition, a multilocular extraosseous form analogous to the gingival cyst of the adult also occurs.

Clinical Features. The lateral periodontal cyst occurs chiefly in adults, according to the series of 39 cases reported by Wysocki and his associates in which there was a mean age of 50 years and an age range of 22–85 years. In this series, there was a predilection for occurrence in males over females, 67: 28 with 5% unknown. The location of the lesion was extremely limited in this study: 67% of cases were in the mandibular bicuspid/cuspid/incisor area, while 33% were in the maxillary lateral incisor area. Lesions were found at no other sites and this has also been the experience of most other investigators. No rational explanation has been offered for this localization.

The majority of cases have presented no clinical signs or symptoms and have been discovered during routine radiographic examination of the teeth. Occasionally, when the cyst is located on the labial surface of the root, there may be a slight mass obvious, although the overlying mucosa is normal. Unless otherwise affected, the associated tooth is vital. If the cyst becomes infected, it may resemble a lateral periodontal abscess and even seek to establish drainage.

Radiographic Features. The periapical radiograph discloses the lateral periodontal cyst as a radiolucent area in apposition to the lateral surface of a tooth root (Fig. 4-11A–D). The lesion is usually small, seldom over 1 cm in diameter, and may or may not be well circumscribed. In most cases the border is definitive and is even surrounded sometimes by a thin layer of sclerotic bone. The botryoid odontogenic cyst appears similar except that its polycystic nature is often evident through its multilocular pattern on the radiograph (Fig. 4-12).

Histologic Features. Histologically, the lateral periodontal cyst is a distinct type of developmental cyst characterized by a thin, nonkeratinized epithelium usually one to five cell layers thick, which resembles the reduced enamel epithelium. Cuboidal or even columnar cells may be found composing the lining. Many of the lining cells have a clear, vacuolated, glycogen-rich cytoplasm (Fig. 4-13). This lining is incomplete and easily sloughs away. Focal thickened plaques of proliferating lining cells often project into the lumen in areas. These are especially prominent in the botryoid odontogenic cyst (Fig. 4-13). Rests of dental lamina are sometimes found in the connective tissue wall and these similarly are frequently composed of glycogen-rich clear cells. These also appear to be more common in the botryoid-type cyst. Papillary infoldings of the lateral periodontal cyst wall are sometimes seen and inflammatory cells may be present, but this is a secondary reaction. The histologic characteristics of these cysts have been detailed by Wysocki and his colleagues as well as by Shear and Pindborg. The connective tissue subjacent to the epithelium exhibits a zone of hyalinization, consisting of a thick fibrous noninflamed cyst wall. A different histologic appearance has been described for this cyst with the name of **botryoid**

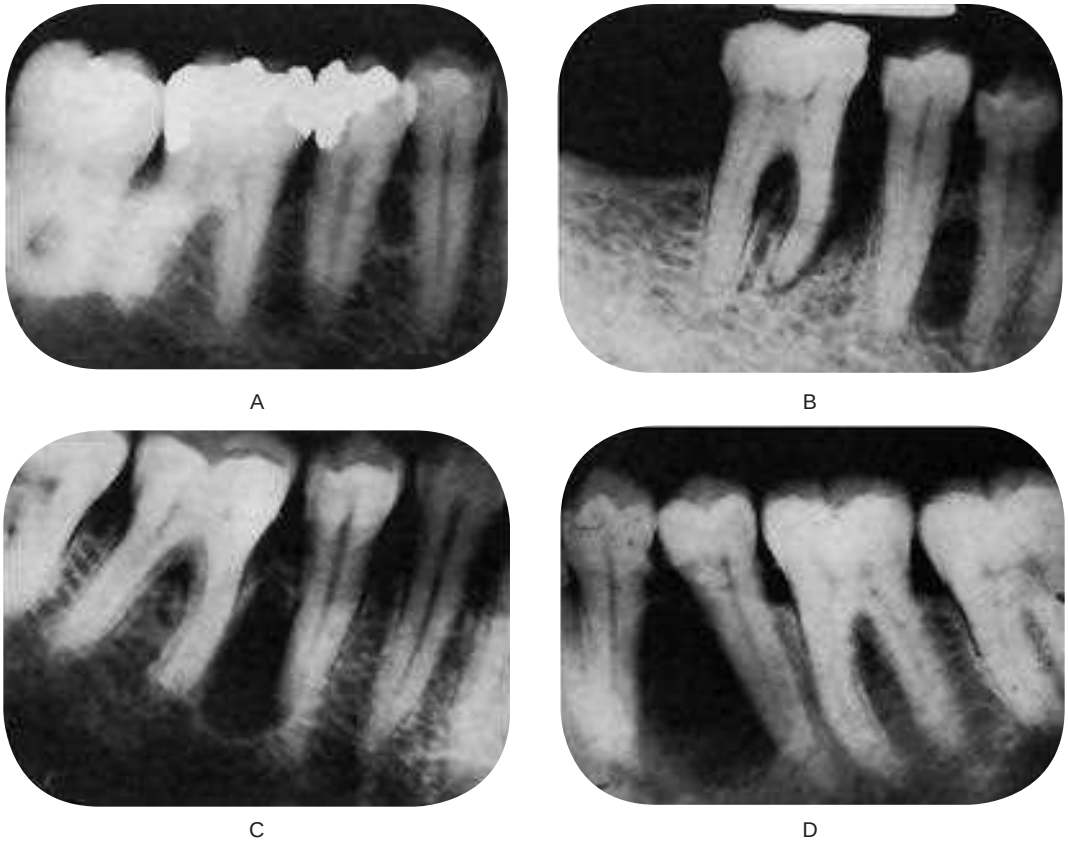


Figure 4-11. Lateral periodontal cysts.
A cyst lies in the periodontal tissues proximal to the roots of premolar and molar teeth. The pulp of the associated teeth appear normal.

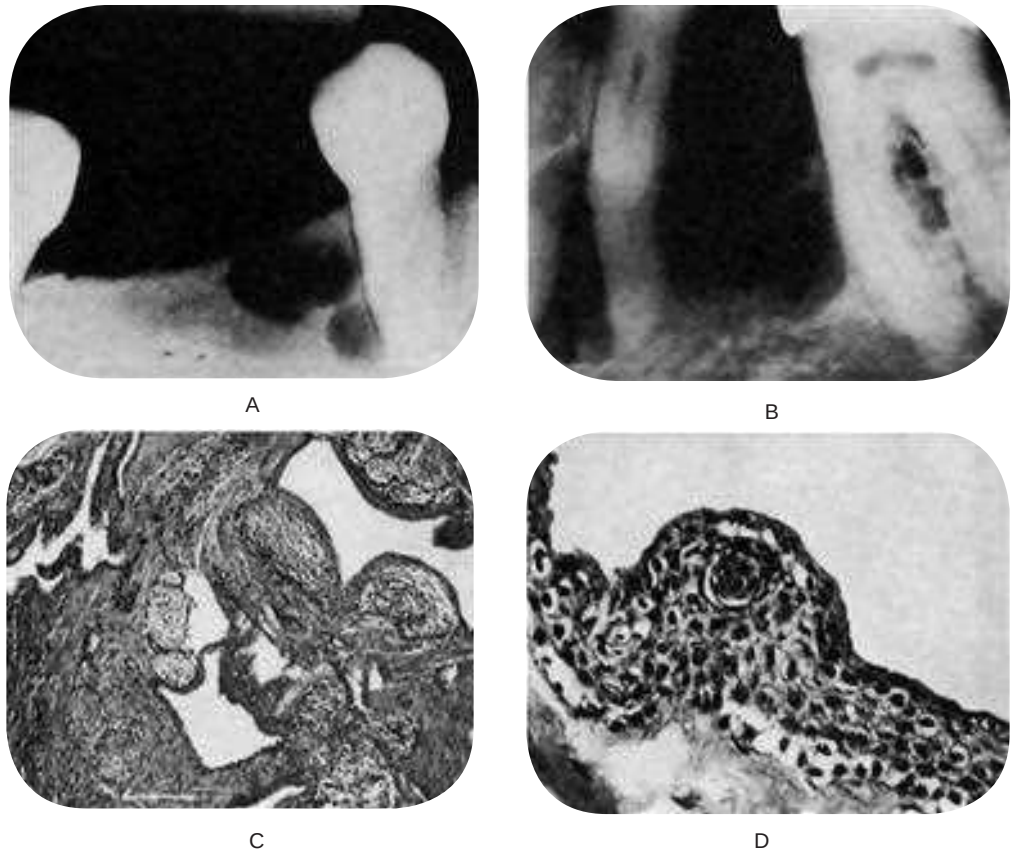


Figure 4-12. Botryoid odontogenic cysts.
The multilocular appearance **(A, B)** is indicative of their polycystic nature. The lining epithelium **(C, D)** of the numerous small cysts is thin and shows focal areas of thickening.

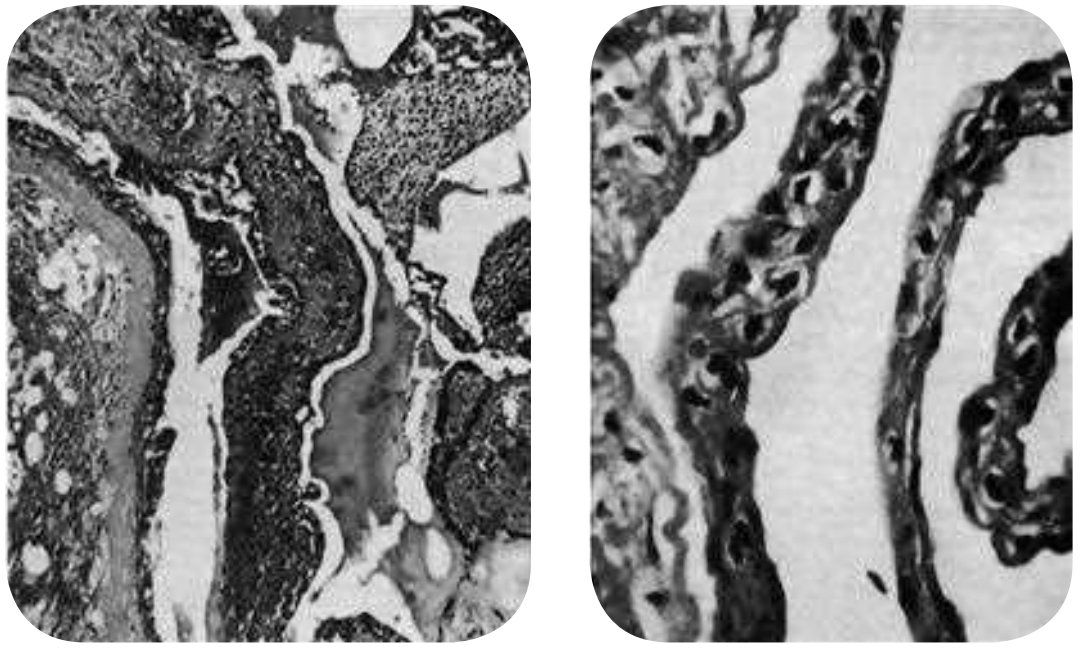


Figure 4-13. Lateral periodontal cysts.

odontogenic cyst. This name reflects the gross similarity of the cystic cavities to that of a cluster of grapes.

Treatment and Prognosis. Provided that the lesion is unilocular on radiographic examination the lateral periodontal cyst is treated by surgical enucleation. Attempts should be made to avoid sacrificing the associated tooth, but this may not always be possible. The botryoid variety, a lesion that is radiographically or histologically multilocular, has an increased risk of recurrence or persistence and patients treated for a botryoid odontogenic cyst should be followed periodically. It is especially important that the diagnosis be established because of the similarity in appearance between this cyst and other more serious lesions such as an early ameloblastoma.

Calcifying Odontogenic Cyst

(Keratinizing and/or calcifying epithelial odontogenic cyst, Gorlin cyst, cystic keratinizing tumor)

A rare, well-circumscribed, solid or cystic lesion derived from odontogenic epithelium that resembles follicular ameloblastoma but contains 'ghost cells' and spherical calcifications.

The so-called calcifying odontogenic cyst (COC) represents a heterogeneous group of lesions that exhibit a variety of clinicopathologic and behavioral features. Because of this diversity, there has been confusion and disagreement on the terminology and classification of these lesions. The term calcifying odontogenic cyst includes both non-neoplastic cyst and true neoplasms. **The 1992 WHO classification includes this cyst and all its variants in the category of odontogenic tumors.**

It has become obvious that it is not one lesion but really two—a cystic lesion and a solid neoplastic lesion. A third malignant counterpart of the neoplastic lesion may be added. The calcifying odontogenic cyst may present as an intraosseous cystic lesion or in association with an odontoma. On rare occasions, it may present as a peripheral (gingival) lesion. The neoplasm, more aptly termed a **dentinogenic ghost cell tumor**, is a rare lesion that may occur in bone or in the gingival soft tissue (for detailed description refer section on odontogenic tumors).

Glandular Odontogenic Cyst

(Sialo-odontogenic cyst, mucoepidermoid odontogenic cyst)

An unusually large solitary or multilocular odontogenic cyst probably derived from the rests of dental lamina, consisting of a stratified squamous epithelium containing numerous mucus-secreting cells.

The glandular odontogenic cyst (GOC), also known as **sialo-odontogenic cyst** has many similarities to the lateral periodontal cyst of which it is considered a variant by some authors. Glandular odontogenic cyst occurs in the same location as the lateral periodontal cyst but as a rule it has a multilocular radiolucent appearance. The name of the cyst is not yet established. The term most descriptive of the lesion is probably **mucoepidermoid odontogenic cyst** because of the presence of both secretory elements and stratified squamous epithelium (Sadeghi et al, 1991). The use of this name might, however, lead to confusion with the mucoepidermoid carcinoma, and is therefore unlikely to find favor (Shear, 1992).

Padayachee and van Wyk, 1987, indicated that the typical features of the cyst are that it is intrabony and multilocular radiographically; that it can recur if not adequately excised; that it is multicystic, with the cystic spaces lined by a nonkeratinized epithelium similar to reduced enamel epithelium, with epithelial thickenings or plaques; that mucous and cylindrical cells form an integral part of the epithelial component; and that mucinous material within the cystic spaces is a prominent feature. Gardner et al, (1988) who favored the name 'glandular odontogenic cyst' suggested that its histological features and biological behavior are sufficient for it to be regarded as an entity.

Clinical Features. The glandular odontogenic cyst occurs over a wide age range. A slight male predilection was reported. The common site affected was anterior mandible. The lesions showed slow progressive growth, were painless and locally destructive. The mandible seems to be affected more commonly (87.2%) than the maxilla. The age ranges from 10–90 years with the mean of 49.5 years.

Radiographic Features. The lesions appear well defined with a multilocular pattern but without specific diagnostic features.

Histologic Features. Histologically, glandular odontogenic cyst is lined in parts by a nonkeratinized stratified epithelium of varying thickness (Fig. 4-14). The epithelium has a glandular or pseudoglandular structure, with goblet mucous producing cells as well as intraepithelial crypts or microcysts containing mucus. These microcysts may open onto the surface of the epithelium giving a papillary or corrugated appearance. Some cells may also be ciliated. Occasionally the epithelium is thinner, similar to reduced enamel epithelium. Epithelial thickenings or plaques may be present either in this thin epithelium or in the stratified epithelium. Interface between epithelium and connective tissue is flat. The diagnosis of

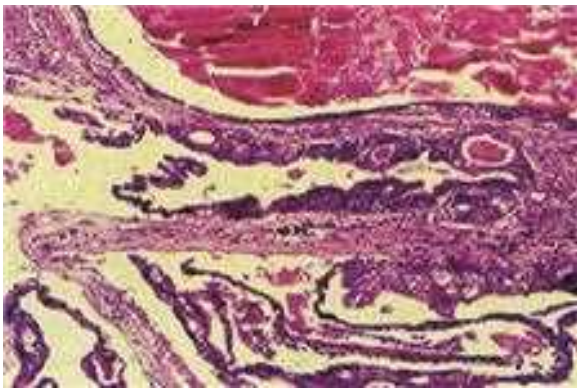


Figure 4-14. Sialo-odontogenic cyst.
Nonkeratinized stratified epithelium of varying thickness; cuboidal or columnar ciliated surface lining with goblet cells; polycystic with secretory and epithelial elements; microcysts may form duct like structures and are filled with a PAS-positive material surrounded by fibrous capsule.

glandular odontogenic cyst should be considered when observing a lateral periodontal multilocular radiolucency. The diagnosis is essentially microscopic.

Treatment. The treatment should be conservative but with a careful dissection of the margins in order to avoid recurrences. Patient should be followed-up periodically in order to assess early recurrences.

INFLAMMATORY CYSTS

Periapical Cyst

(Radicular cyst, apical periodontal cyst, root end cyst)

The periapical (radicular) cyst is the most common odontogenic cyst. The usual etiology is an infected tooth, leading to necrosis of the pulp. Toxins exit at the apex of the tooth, leading to periapical inflammation. This inflammation stimulates the epithelial rests of Malassez, which are found in the apical periodontal ligament, resulting in the formation of a periapical granuloma that may be infected or sterile. Eventually, this epithelium undergoes necrosis caused by a lack of blood supply, and the granuloma becomes a cyst (periapical cyst). The lesions are not usually clinically detectable when small but most often are discovered as an incidental findings on radiographic survey.

Pathogenesis. This cyst is classified as inflammatory, because in the majority of cases it is a consequence to pulpal necrosis following caries, with an associated periapical inflammatory response. Other causes include any event that may result in pulpal necrosis such as tooth fracture and improper restorations, among others. The first line of defense to pulpal necrosis in the periapical area is the formation of a granuloma. A granuloma is a highly vascularized tissue containing a profuse infiltrate of immunologically competent cells, i.e. lymphocytes, macrophages and plasma cells.

The epithelial rests of Malassez, which are pluripotential in nature can differentiate into any type of epithelium, under the proper stimuli. These rests play a central role in the formation of radicular cysts. In the midst of the rich vascular area provided by the periapical granuloma, the rests of Malassez proliferate and eventually form a large mass of cells. With continuous growth, the inner cells of the mass are deprived of nourishment and they undergo liquefaction necrosis. This leads to the formation of a cavity which is located in the center of the granuloma, giving rise to a radicular cyst.

Islands of squamous epithelium which have developed from odontogenic rests of Malassez can also be found in a periapical granuloma without cystic transformation. Endodontists refer to these granulomas as **'bay cyst'**.

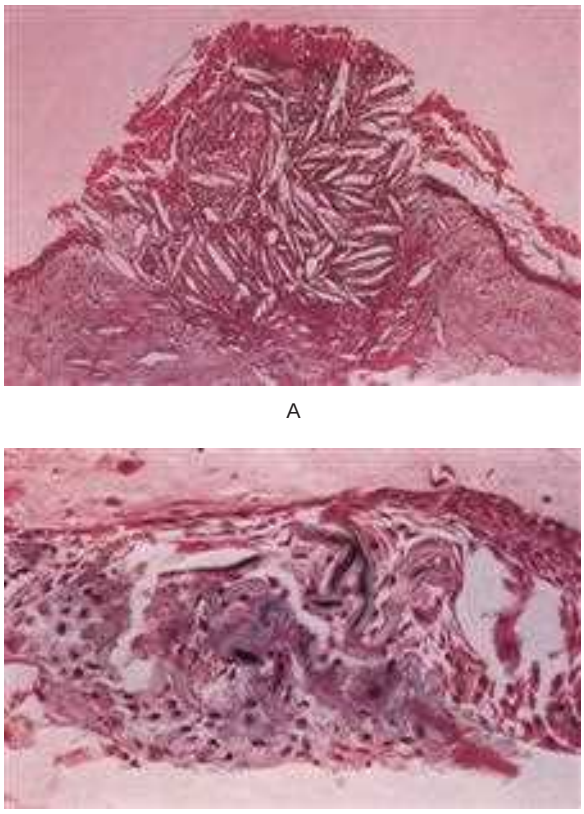
Clinical Features. Around 60% of all jaw cysts are radicular or residual cysts. Radicular cysts can occur in the periapical area of any teeth, at any age but are seldom seen associated with the primary dentition. The majority of cases of apical periodontal cysts are asymptomatic. The tooth is seldom painful or even sensitive to percussion. This type of cyst is only infrequently of such a size that it destroys much bone, and even more rarely does it produce expansion of the cortical plates. The apical periodontal cyst is a lesion that represents a chronic inflammatory process and develops only over a prolonged period of time. In some cases, such a cyst of long standing may undergo an acute exacerbation of the inflammatory process and develop rapidly into an abscess (periapical abscess) that may then proceed to a cellulitis or form a draining fistula. The cause of such a sudden flare up is not known, but it may be a result of loss of local or generalized tissue resistance.

Radiographic Features. The radiographic image of the radicular cyst is a peri- or para-apical, round or oval radiolucency of variable size which is generally well delineated and most likely with a marked radiopaque rim. Other lesions, such as granulomas, neoplasms of various origin and some diseases of bone can also present a similar radiolucent periapical appearance. Therefore, a periapical radiolucency cannot be automatically assumed to be a cyst. Several studies have indicated that it is not possible to rely on the radiographic size of a periapical radiolucency to establish the diagnosis of either cyst or granuloma unless the lesion is larger than 2 cm in diameter. Rarely radicular cysts will induce resorption of the root of the affected tooth.

Histologic Features. Microscopically a radicular cyst is limited by a mature collagenous connective tissue wall. Abundant fibroblasts can be identified within the cystic wall. The wall generally presents an inflammatory infiltrate of variable degree. Lymphocytes are generally the most prominent cells in the infiltrate and are characterized by their darkly stained nucleus, which occupies most of the cytoplasm. Plasma cells are also abundant in cysts' walls and mostly seen in long standing (chronic) cysts. They are characterized by an eccentric nucleus with a cartwheel arrangement of the nuclear chromatin. Plasma cells are considered repertoire of immunoglobulins. Other histological findings within the cystic wall are: erythrocytes and areas of hemorrhage, occasional spicules of dystrophic bone, multinucleated giant cells and cholesterol crystals (Fig. 4-15A).

The cavity of a radicular cyst is generally lined by stratified squamous epithelium. These cysts can be lined by respiratory epithelium, especially if they are in the vicinity of the maxillary sinus. The epithelial lining, many times, is discontinuous, frequently missing over areas of intense inflammation. Rarely radicular cysts may be lined by mucus producing epithelium in either maxillary or mandibular locations. The mucous epithelium is the result of metaplastic transformation of the epithelial rests of Malassez which are pluripotential. In rare instances, carcinoma has been reported developing from the lining epithelium of odontogenic cysts, including the radicular cyst. These have been reviewed by Gardner (1969).

An interesting and peculiar structure, originally described by Rushton and subsequently reported by Molyneux, Medak and Weinmann and Shear, is the hyaline body or Rushton body, often found in great numbers in the epithelium of apical, periodontal or residual cysts (Fig. 4-15 B). These hyaline bodies are tiny linear or arc-shaped bodies, generally associated with the lining epithelium, that appear amorphous



A

B

Figure 4-15. Radicular cyst.
(A) The cyst cavity is filled with an eosinophilic coagulum containing slit-like spaces which contain cholesterol. These cholesterols may form mucosal nodules; the epithelial lining becomes discontinued where such nodules have formed. **(B)** Hyaline bodies. Another feature that may be seen within the epithelial linings of radicular cyst is the peculiarly shaped structures which are eosinophilic, and typically, are described as lady's hairpin shaped *(Courtesy of Dr K W Lee)*.

in structure, eosinophilic in reaction and brittle in nature, since they evidence fracture in some cases. Their frequency of occurrence in cyst linings ranges between 2.6 and 9.5% of cysts, according to a review by Allison. The etiology, pathogenesis, and significance of these structures are unknown. The lumen of the cyst usually contains a fluid with a low concentration of protein that stains palely eosinophilic. Occasionally the lumen may contain a great deal of cholesterol, and in rare instances, limited amounts of keratin are present.

Treatment. The treatment of the radicular cyst consists of extraction of the involved teeth and careful curettage of the periapical tissue. Under some conditions, root canal therapy may be carried out with apicoectomy of the cystic lesion. The cyst does not recur if surgical removal is thorough. If the cystic sac is badly fragmented, leaving epithelial remnants, or if a periapical granuloma is incompletely removed with epithelial rests remaining, a residual cyst may develop in this area months or even years later. If untreated, the radicular cyst slowly increases in size at the expense of the surrounding bone. The bone undergoes resorption, but seldom is there a remarkable expansion of the cortical plates, as is frequently seen in the case of the dentigerous cyst.

Residual Cyst

Residual cyst is a term of convenience because no teeth are left by which to identify the lesion. Most commonly, these actually are retained periapical cysts from teeth that have been removed. The histology of the lining is a nondescript stratified squamous epithelium.

Theoretically, it could develop in a dental granuloma that is left after an extraction. The residual cyst may be found in any of the tooth bearing areas of the mandible or maxilla. Morphologically, the residual cyst may present as a fairly well defined radiolucency that can vary in size from a few mm to several cm. Clinically, these cysts are usually found on routine radiographic examination of patients. They may have been present for many months or years and only become symptomatic upon secondarily infected (Figs 4-16 A, B, and C). Usually, residual cysts do not expand bone. Treatment is surgical curettage (refer periapical cyst).

Paradental Cyst

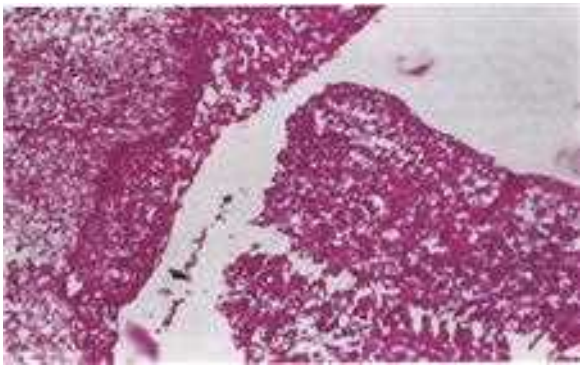
A cyst of uncertain origin found primarily on the distal or facial aspect of a vital mandibular third molar, consisting of intensely inflamed connective tissue and epithelial lining.

The paradental cyst is an inflammatory cyst which develops on the lateral surface of a tooth root. Some authors refer to this cyst as an inflammatory periodontal cyst or collateral cyst. This cyst is of rare occurrence and must be radiographically differentiated from the lateral periodontal cyst. It is treated by surgical ablation and does not have a tendency to recur.

It seems clear that the paradental cyst is of inflammatory origin and that it arises from odontogenic epithelium. Craig (1976) has suggested that either the cell rests of Malassez or the reduced enamel epithelium might provide the cell of origin. He favored the latter source, arguing that in his study the rests of Malassez always appeared inactive and that if the Malassez rests were responsible the lesions should be equally distributed around the root surface. His serial sections indicated that the development of paradental cyst may follow hyperplasia and cystic change in reduced enamel epithelium. He suggested that the presence of an extension of reduced enamel epithelium over the enamel projections might be the source, and could explain the frequent buccal location of the cyst.

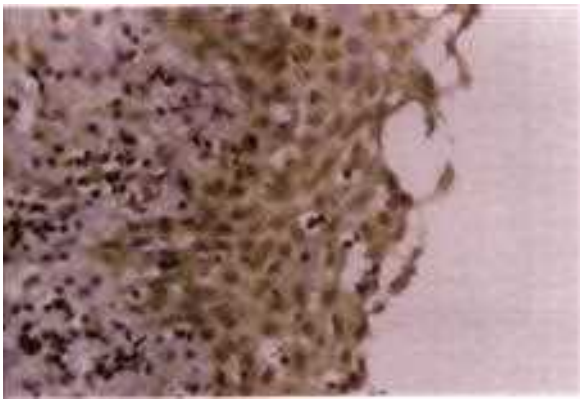
Pathogenesis. There is no unanimity with regard to pathogenesis. Ackerman, Cohen and Altini (1987) like Craig (1976), favored origin from reduced enamel epithelium but suggested that cyst formation occurs as a result of unilateral expansion of the dental follicle secondary to inflammatory destruction of periodontium and the alveolar bone. Fowler and Brannon (1989) suggested that it may be a variant of the dentigerous cyst or derived from an occluded periodontal pocket. Vedtofte and Praetorius (1989) were satisfied that the cyst was of inflammatory origin, initiated by a pericoronitis at the time of tooth eruption and considered rests of Malassez and reduced enamel epithelium the most likely source of the cyst epithelium.

Clinical Features. In the sample of 2,616 jaw cysts reported by Shear (1992), there were 65 paradental cysts classified over a 32-year period (2.5%). The series of 50 cases reported by



A

B



C

Figure 4-16. Residual cyst.
Histopathological features of **(A)**, residual cyst using H & E stain (x 10), **(B)** of residual cyst using PCNA antibody stain (x 10), and **(C)** of residual cyst using PCNA antibody stain (x 40).

Ackerman, Cohen and Altini (1987) represented the 3% of a sample of 1,852 odontogenic cysts observed over a 20-year period. Virtually all the cases in the study by Ackermann, Cohen and Altini occurred between the ages of 10 and 39 with two-thirds of their sample in the third decade; the same as in Craig's material (cited by Shear, 1992). There was a considerable preponderance of males reported by Ackermann, Cohen and Altini and by Fowler and Brannon but of Vedtofte and Praetorius. There was an equal gender distribution. Ackermann, Cohen and Altini found most of their cyst located distally and distobuccally to the third molar. All the papers emphasized that the involved teeth were vital. Bilateral examples occurred in a number of instances.

Radiographic Features. All authors reported a variable radiographic picture but there are some features which appeared consistently and which seem to be useful in contributing to the diagnosis. These are the non widening of the periodontal ligament space and that the lesion was superimposed on the buccal root face. When there was a distal as well as a buccal radiolucency, the distal element was separate from the distinct distal follicular space (Shear, 1992).

Histologic Features. Histologically, the cysts were lined by a hyperplastic nonkeratinized stratified squamous epithelium. An intense inflammatory cell infiltrate is present associated with the hyperplastic epithelium and in the fibrous capsule adjacent to the epithelium. Histologically the paradental cyst cannot be differentiated from a radicular cyst.

Treatment. Enucleation and extraction of associated molar.

TUMORS OF ODONTOGENIC ORIGIN

Odontogenic tumors represent a spectrum of lesions ranging from malignant (rare) and benign neoplasms to dental hamartomas, all arising from odontogenic residues, i.e. odontogenic epithelia and/or ectomesenchyme with variable amounts of dental hard tissues formed generally in the same sequence as in normal tooth development.

Occasionally an odontogenic tumor develops from a preexisting developmental cyst (e.g. adenomatoid odontogenic tumor from a dentigerous cyst) or dental primordium (e.g. ameloblastomas often take the place of lower third molars). In many instances the exact tissue of origin (histogenesis) of an odontogenic tumor may only be inferred from its site and structure.

Classification of Odontogenic Tumors. The WHO classification (1992) divides odontogenic tumors into benign and malignant, with major subdivisions in each category (White, 2004) (Table 4-2). The subdivisions for the benign neoplasms are based on types of odontogenic tissue involved in the process and include:

- Odontogenic epithelium without odontogenic ectomesenchyme.
- Odontogenic epithelium with odontogenic ectomesenchyme, with or without dental hard tissue formation.
- Odontogenic ectomesenchyme with or without included odontogenic epithelium.

The classic example of odontogenic tumor viz. ameloblastoma is an archetype of a neoplasm where the neoplastic component is epithelial only without contribution from the ectomesenchyme. In the second category, some of the neoplasms are pure epithelial tumors but are capable of inducing dysplastic enamel and dentin formation. Examples include adenomatoid odontogenic tumor, calcifying odontogenic cyst, and odontoameloblastoma. Other tumors in the category exhibit neoplastic cells of both odontogenic epithelium and

Table 4-2: Odontogenic tumors (modified WHO classification)

A. Benign
- I. Odontogenic epithelium without odontogenic ectomesenchyme
  1. Ameloblastoma
  2. Squamous odontogenic tumor
  3. Calcifying epithelial odontogenic tumor (Pindborg tumor)
  4. Adenomatoid odontogenic tumor*
- II. Odontogenic epithelium with odontogenic ectomesenchyme with or without hard tissue formation
  1. Ameloblastic fibroma
  2. Ameloblastic fibrodentinoma
  3. Ameloblastic fibro-odontoma
  4. Odontoameloblastoma
  5. Calcifying odontogenic cyst
  6. Complex odontoma
  7. Compound odontoma
- III. Odontogenic ectomesenchyme with or without included odontogenic epithelium
  1. Odontogenic fibroma
  2. Myxoma (myxofibroma)
  3. Cementoblastoma (benign cementoblastoma, true cementoma)

B. Malignant
- I. Odontogenic carcinomas
  1. Malignant ameloblastoma
  2. Primary intraosseous carcinoma
  3. Clear cell odontogenic carcinoma**
  4. Ghost cell odontogenic carcinoma
- II. Odontogenic sarcomas
  1. Ameloblastic fibrosarcoma
  2. Ameloblastic fibrodentinosarcoma
  3. Ameloblastic fibro-odontosarcoma

** Originally classified under II, but in a new revision of the WHO classification it will be classified under I.*

*** Originally classified as a benign tumor under I (clear cell odontogenic tumor), but it is now recognized as a malignant tumor (clear cell odontogenic carcinoma) and classified accordingly.*

ectomesenchyme and include ameloblastic fibroma and ameloblastic fibro-odontoma (mixed odontogenic tumors). Yet other entities represent hamartomatous proliferations of both tissues, including compound and complex odontomas. In the third category, odontogenic ectomesenchyme with or without included odontogenic epithelium, the neoplastic cells appears to be of connective tissue origin. Neoplasms include odontogenic fibroma and odontogenic myxoma. Any epithelial component is not considered to be neoplastic.

Ameloblastic carcinoma and odontogenic sarcomas are examples of odontogenic neoplasms which contain a malignant epithelial and connective tissue component as part of the tumor. Calcifying odontogenic cyst has been placed in the odontogenic tumors classification by the WHO because some variants consist of a solid tumor with ameloblastoma like areas, dentinoid, and ghost cells. This form has been designated as dentinogenic ghost cell tumor or odontogenic ghost cell tumor. Benign cementoblastoma has currently been delinked from the WHO classification of odontogenic tumors and is described along with benign osteoblastoma.

Ameloblastoma

(Adamantinoma, adamantoblastoma, multilocular cyst)

The ameloblastoma is a true neoplasm of enamel organ type tissue which does not undergo differentiation to the point of enamel formation. It has been described very aptly by Robinson as being a tumor that is 'usually unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent'.

The term 'ameloblastoma' as applied to this particular tumor was suggested by Churchill in 1934 to replace the term 'adamantinoma', coined by Malassez in 1885, since the latter term implies the formation of hard tissue, and no such material is present in this lesion. The first neoplasm of this nature reported in the scientific literature is credited to Broca in 1868, although Guzack reported a tumor of the jaw in 1826 which may be the first recorded instance of an ameloblastoma. In any event, the first thorough description of an ameloblastoma is that of Falkson in 1879.

It is the second most common odontogenic neoplasm, and only odontoma outnumbers it in reported frequency of occurrence. Excluding odontoma, the incidence of ameloblastoma is at least equal to the incidence of all the other odontogenic neoplasms combined. However G Sriram and Shetty RP based on an Indian institutional study on 250 odontogenic tumors reported ameloblastoma to be the most common (61.5%) odontoplasmic neoplasm in India. Its incidence, combined with its clinical behavior, makes ameloblastoma the most significant odontogenic neoplasm of concern to oral and maxillofacial surgeons.

Pathogenesis. The earlier workers noted the resemblance between the odontogenic apparatus and the ameloblastoma and suggested that the neoplasm was derived from a portion of this apparatus or from cells potentially capable of forming dental tissue. Malassez described small collections of epithelial cells adjacent to the roots of teeth in the periodontal ligament and suggested that the 'adamantine epithelioma' was produced by a proliferation of these cell rests.

Most authorities consider the ameloblastoma to be of varied origin, although the stimulus initiating the process is unknown. Thus the tumor conceivably may be derived from:

- Cell rests of the enamel organ, either remnants of the dental lamina or remnants of Hertwig's sheath, the epithelial rests of Malassez.
- Epithelium of odontogenic cysts, particularly the dentigerous cyst, and odontomas.
- Disturbances of the developing enamel organ.
- Basal cells of the surface epithelium of the jaws.
- Heterotopic epithelium in other parts of the body, especially the pituitary gland.

Presently, it is thought that it is likely the result of alterations or mutations in the genetic material of cells that embryologically preprogrammed for tooth development. Environmental factors and individual patient variables (e.g. general health status, nutritional status) also likely have a role in modulating the incidence of the disease. This theory is demonstrated by the finding that the average age of occurrence of ameloblastoma in industrialized nations is 10–15 years greater than that seen in developing countries (Kessler HP et al, 2003).

Cahn in 1933 reported a case of ameloblastoma originating in the wall of a dentigerous cyst, and numerous cases have subsequently been recognized as developing in this fashion.

It should be reiterated that Stanley and Diehl, in reviewing 641 cases of ameloblastoma, found that 108 of these tumors, approximately 17%, were definitely associated with an impacted tooth and/or a follicular (dentigerous) cyst. They also noted a marked reduction in the prevalence of such cases after the age of 30, presumably because of the loss of the ameloblastomatous potential of the odontogenic epithelium in impacted tooth follicles and follicular cysts as patients age. Such a significant finding emphasizes the dangerous potential of the dentigerous cyst and the need for careful microscopic examination of every such lesion. This is discussed in greater detail in the section on the dentigerous cyst. Since a dentigerous cyst may develop in association with an odontoma, as well as with an impacted tooth, it is suggested that these too be examined by the pathologist. There is apparently little tendency for the development of the ameloblastoma in the ordinary apical periodontal or radicular cyst.

Clinical Features. A wide age range of occurrence of the tumor from 10 years through 90 years has been reported. The average age at diagnosis is in the range of 33–39 years, and most cases cluster between ages 20 and 60 years. Only about 10% of cases are reported to arise in children, and less than one third of those occur in children younger than 10 years. No significant sex predilection has been reported. There is conflicting evidence on the incidence rates in different races. Although some reports claim an increased incidence of ameloblastoma in black individuals, a large study identifies Asians as the population with the greatest number of affected patients. Because sizeable numbers of cases are reported in every racial group, race does not seem to be a significant defining demographic characteristic of the disease (Reichart PA et al, 1995).

Ameloblastoma occurs in all areas of the jaws, but the mandible is the most commonly affected area (more than 80% of all cases). Within the mandible, the molar angle-ramus area is involved three times more commonly than are the premolar and anterior regions combined. Statistics on the location of maxillary ameloblastomas are more variable and more difficult to interpret. Some studies report a low incidence in the anterior maxilla, whereas other studies suggest that the incidence in the anterior maxilla is roughly equivalent to the incidence in the maxillary molar region. When comparing large studies, it appears that maxillary tumors tend to occur in slightly older patients than do mandibular lesions. The incidence of occurrence of ameloblastoma in different sites within the jaws has been shown to vary among racial groups. Asians seem to have fewer tumors involving the ramus than do whites or blacks, whereas blacks have an increased frequency of tumors in the anterior mandible compared with the other two groups (Kessler HP et al, 2003).

Peripheral (extraosseous) ameloblastoma. This is a tumor which histologically resembles the typical central or intraosseous ameloblastoma but which occurs in the soft tissue outside and overlying the alveolar bone. In addition, a number of cases of lesions in a similar location and with similar histologic features have been reported under the term 'basal cell carcinoma of the gingiva'. Many investigators consider these the same basic lesion, including Gardner, who has reviewed the literature, adding seven additional unpublished cases for a total of 21 examples of peripheral ameloblastoma. Occasional other cases have since been reported, such as those of Greer and Hammond and of Gould and his colleagues.

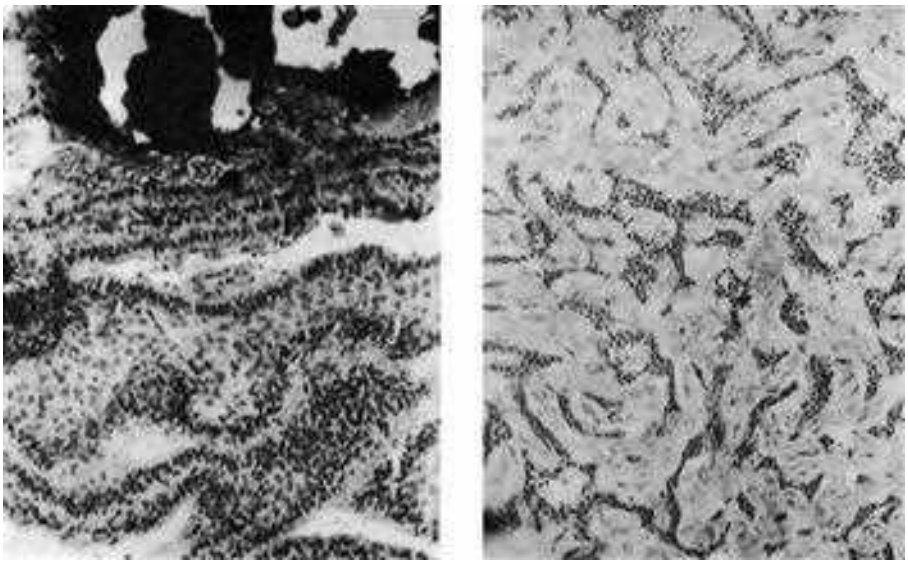
This tumor appears to originate from either surface epithelium or remnants of dental lamina. In some instances, the tumor exhibits one or more areas of continuity with the surface epithelium, while in other cases, even with serial sectioning, no evidence of continuity between the two can be found.

The ages of the patients in the 21 cases reviewed by Gardner ranged between 23 and 82 years, with 10 patients between 30 and 50 years of age. There was a slight predilection for occurrence in males, 13 cases to 8 cases in females. There was an approximately 2 : 1 ratio of occurrence in the mandible over the maxilla. The lesions, all of which appeared as nodules on the gingiva, varied in size from 3 mm to 2 cm in diameter. In only two cases was radiographically evident superficial erosion of bone present.

The peripheral ameloblastoma histologically may exhibit the same pattern seen in the intraosseous ameloblastoma. However, while some lesions appeared to be of the follicular type, the vast majority were acanthomatous, at least in areas. Greer and Hammond have studied the ultrastructural characteristics of their case and found the electron microscopic appearance to be similar to that of the intraosseous ameloblastoma and the cutaneous basal cell carcinoma. In a similar ultrastructural study, Gould and his associates found that the features of their tumor was characteristic of origin from either surface epithelium or odontogenic remnants, thereby precluding definitive conclusions regarding site of origin. In terms of differential diagnosis, one must always consider the possibility of the peripheral odontogenic fibroma, which is also a peripheral lesion of the gingiva with variable amounts of odontogenic epithelium. The distinction on the basis of the connective tissue parenchyma of the odontogenic fibroma is usually not difficult, although cases with features of both lesions may occur, such as that reported by Sciubba and Zola.

One of the most important aspects of the peripheral ameloblastoma, emphasizing the need for its careful identification as a peripheral lesion and separation from the intraosseous counterpart, is the difference in clinical behavior. The peripheral lesion is relatively innocuous, lacks the persistent invasiveness of the intraosseous lesion and has very limited tendency for recurrence. For this reason, it may be excised locally, although follow-up examination is always good practice.

Pituitary ameloblastoma (craniopharyngioma, Rathke's pouch tumor). This is a neoplasm involving the central nervous system which grows as a pseudoencapsulated mass, usually in the suprasellar area but occasionally in the intrasellar area, and often destroys the pituitary gland. The peak incidence is reported to be between 13 and 23 years of age. According to Zulch, the pituitary ameloblastoma is the most common tumor of childhood and adolescence. In his series of 6,000 CNS tumors, it constituted 2.5% of the total in all patients regardless of age.



A B

Figure 4-17. Ameloblastoma like tumors in other locations.
(A) Craniopharyngioma showing typical ameloblastoma like formation with calcification. **(B)** Adamantinoma of tibia *(Courtesy of Dr William G Sprague and Dr David C Dahlin).*

It is generally thought to originate from the unobliterated portions of the fetal craniopharyngeal duct, which itself is derived from Rathke's pouch. This pouch is a recess arising as a result of invagination of a portion of the stomodeal ectoderm, and the pituitary gland forms by fusion of this pouch with a process of the forebrain. Epithelial remnants of this craniopharyngeal duct are extremely common in the adult. These cell rests have a certain pluripotential and on occasion may give rise to tumors histologically similar to the ameloblastoma of the jaw.

Microscopic features of the craniopharyngioma, not generally found in the ameloblastoma, include the almost universal occurrence of irregular calcified masses as well as occasional foci of metaplastic bone or cartilage (Fig. 4-17 A). In addition, many investigators have noted the similarity between the craniopharyngioma and the calcifying odontogenic cyst because of the presence in the pituitary lesion of islands and nests of 'ghost' cells, as well as the calcifications and the fact that cyst formation is common. Several cases of craniopharyngioma with tooth formation have also been reported, such as that of Seemayer and his associates.

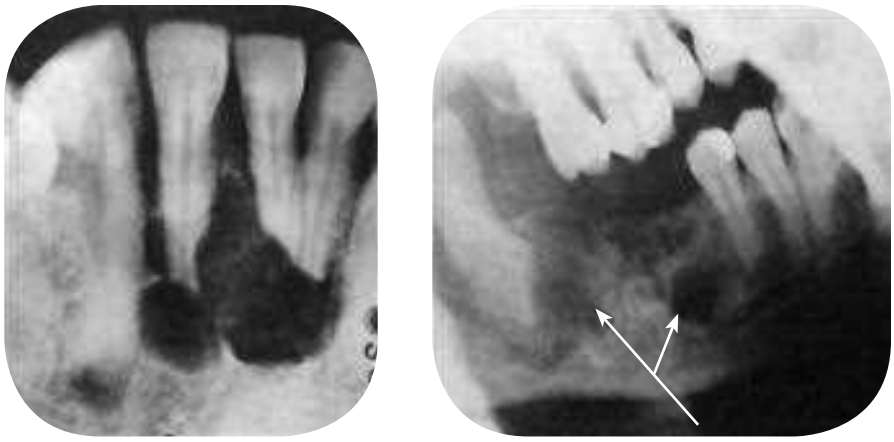
There is great variability in the rate of growth of the pituitary ameloblastoma. Depending upon its exact location, there may be a gamut of clinical features eventually manifested, such as evidence of endocrine disturbance, drowsiness or even toxic symptoms. The treatment of this neoplasm is a neurosurgical problem.

Adamantinoma of long bones. This tumor has been discussed by Baker, Dockerty and Coventry, who reviewed the literature and concluded that the true nature of the lesion is still unknown. The tumor, which bears a superficial microscopic resemblance to the ameloblastoma of the jaws, has occurred in the tibia in approximately 90% of the slightly over 100 reported cases, but also has been recorded in the ulna, femur and fibula (Fig. 4-17B). Changus and his coworkers suggested that the lesion is actually a malignant angioblastoma, and this view is supported by Huvos and Marcove in their investigation of 14 cases. In contrast, Unni and his coworkers studied 29 cases, with ultrastructural microscopy of three of the tumors, and concluded that this provided evidence that the islands of tumor cells were epithelial in origin. Thus, although the histogenetic origin of this tumor is unknown, most authorities agree that it is not related to the ameloblastoma of the jaws, even though they support retention of the term 'adamantinoma' because of its acceptance through usage and for lack of a better name.

Radiographic Features. The ameloblastoma has been described classically as a multilocular cyst like lesion of the jaw. This is especially true in advanced cases of ameloblastoma. Here, the tumor exhibits a compartmented appearance with septa of bone extending into the radiolucent tumor mass (Fig. 4-18A). In many cases, however, the lesion is a unilocular one and presents no characteristic or pathognomonic features (Figs. 4-18B, 4-19). The periphery of the lesion on the radiograph is usually smooth, although this regularity may not be borne out at the time of operation. In the advanced lesion producing jaw expansion, thinning of the cortical plate may be seen on the radiograph (Figs. 4-20, 4-21).

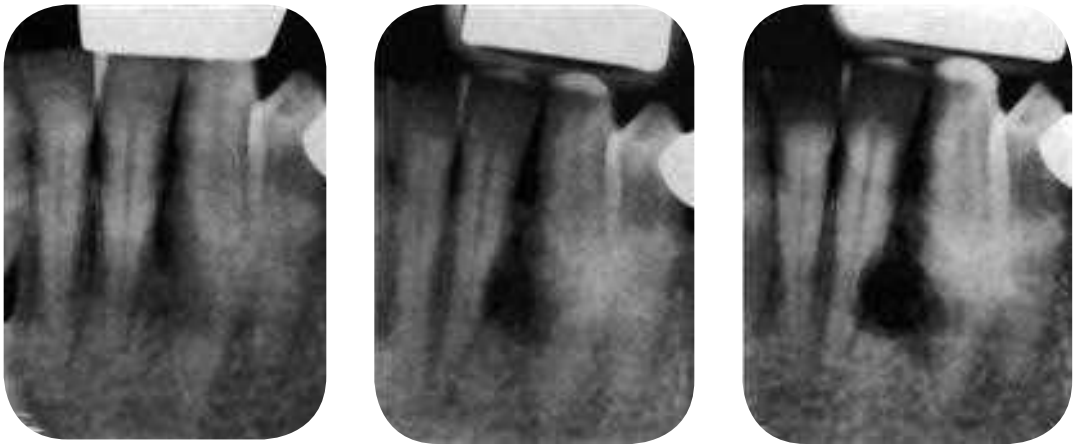
The term 'cystic ameloblastoma' is frequently used in referring to certain of these neoplasms. It is important to note that there is no correlation between the term thus used clinically and the appearance of the tumor on the radiograph. The radiographic film does nothing more than indicate the relative presence or absence of calcified tissue, and a variety of lesions may manifest themselves in manner similar to that of the ameloblastoma.

Histologic Features. Six histopathologic subtypes of ameloblastoma are recognized: follicular, acanthomatous, granular



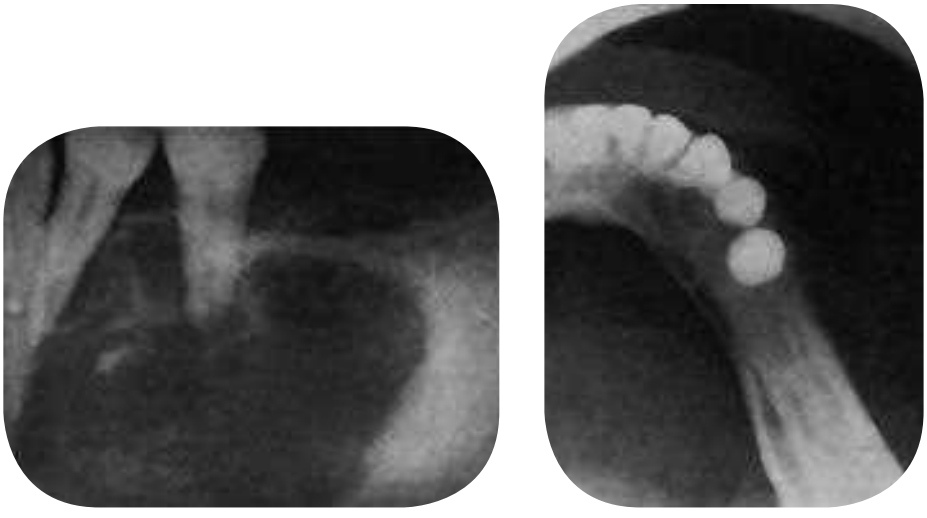
A B

Figure 4-18. Ameloblastoma.
(A) The typical loculations which often occur are clearly seen. **(B)** This lateral jaw radiograph reveals an early lesion with no loculations, but with several focal areas of bone destruction.



A B C

Figure 4-19. Developing ameloblastoma.
Each radiograph was taken at intervals of two years. The slow growth of the ameloblastoma over the four-year period is typical *(Courtesy of Dr Harry R Kerr Jr and Dr G Thaddeus Gregory).*



A B

Figure 4-20. Ameloblastoma.
The periapical **(A)** and occlusal **(B)** radiographs showing the destruction and expansion of bone which frequently occur.

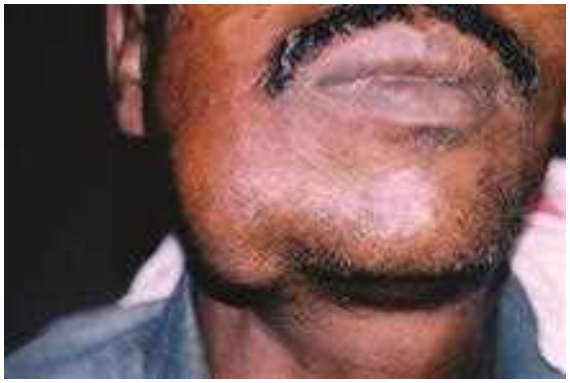


Figure 4-21. Ameloblastoma of the mandible.

cell, basal cell, desmoplastic, and plexiform. Most tumors show a predominance of one pattern, but few lesions are found to be composed purely of one histopathologic subtype. Mixtures of the different patterns commonly are observed. Lesions tend to be subclassified according to the predominant pattern that is present. The literature-based retrospective study by Reichart et al (1995) showed that the histologic subtype may have prognostic implications for recurrence. According to their study, the follicular type of ameloblastoma had the highest rate of recurrence at 29.5%. In contradistinction, the acanthomatous type of ameloblastoma showed only a 4.5% recurrence rate. The plexiform subtype was intermediate between the two extremes and showed a 16.7% recurrence rate. Studies have verified that desmoplastic ameloblastoma shows a tendency to recur, and the rate of recurrence is reported within the range of the other histologic subtypes of ameloblastoma.

A moderately to densely collagenized connective tissue characteristically constitute the stroma. The epithelial component of the neoplasm proliferates in what seems to be disconnected islands, strands, and cords within the collagenized fibrous connective tissue stroma. A prominent budding growth pattern often is seen, with small, rounded extensions of epithelium projecting from larger islands, recapitulating the various stages of enamel organ formation (Kessler HP et al 2003). The islands, strands, and cords may vary considerably in size. In high power magnification, the darkly staining periphery is composed of tall columnar cells with hyperchromatic nuclei. The nuclei tend to be round to oval in shape, and the nuclei of adjacent cells are in roughly the same location within the cytoplasm. This produces a characteristic palisading pattern. The palisaded nuclei are oriented away from the basement membrane area of the cell, and a small clear vacuole can be seen between the nucleus and the basement membrane. This peripheral layer of tall columnar cells with hyperchromasia, reverse polarity of the nuclei, and subnuclear vacuole formation mimic the normal embryologic development of the tooth bud at the stage of enamel matrix production. These classic features of ameloblastoma originally were described by Vickers and Gorlin in 1970 (criteria).

Focally in many ameloblastomas, the proliferating epithelium is seen to exert an inductive effect on the surrounding connective tissue stroma. In these areas, a zone of hyalinization of the collagen is present immediately adjacent to the epithelium. Fibroblasts are almost totally absent within the zone of hyalinization. It is theorized that the ameloblastic epithelium, in an attempt to complete its embryologic function and produce enamel matrix, signals the connective tissue to induce dentin formation; however, the fibroblastic cells in the connective tissue are unable to differentiate into odontoblasts, a required step in dentin and enamel formation. The hyalinized zone most likely represents the end result of this blockade in the normal embryologic sequence of odontogenesis (Kessler HP et al, 2003).

The ***follicular (simple) ameloblastoma*** is the most commonly encountered variant (Reichart PA et al, 1995), composed of many small discrete islands of tumor composed of a peripheral layer of cuboidal or columnar cells whose nuclei are generally well polarized. These cells strongly resemble ameloblasts or preameloblasts and these enclose a central mass of polyhedral, loosely arranged cells resembling the stellate reticulum. The terms 'solid' and 'cystic' have often been applied to the ameloblastoma and have variously referred to the clinical or histologic appearance of the tumor. Clinically, some cases exhibit tiny cysts that are grossly evident when the lesion is excised and examined carefully. In such instances, the stellate reticulum like tissue has undergone complete breakdown or cystic degeneration, and in such cases, there is often flattening of the peripheral columnar cells so that they resemble low cuboidal or even squamous cells. Cyst formation is relatively common in this follicular type of ameloblastoma.

In the ***plexiform ameloblastoma,*** the ameloblast like tumor cells are arranged in irregular masses, or more frequently, as a network of interconnecting strands of cells. Each of these masses or strands is bounded by a layer of columnar cells, and between these layers may be found stellate reticulum like cells. Sometimes double rows of columnar cells are lined up back to back. However, the stellate reticulum like tissue is much less prominent in the plexiform type than in the follicular type of ameloblastoma. Areas of cystic degeneration of stroma are also common.

In the ***acanthomatous ameloblastoma,*** the cells occupying the position of the stellate reticulum undergo squamous metaplasia, sometimes with keratin formation in the central portion of the tumor islands. This usually occurs in the follicular type of ameloblastoma. On occasion, epithelial or keratin pearls may even be observed.

In the ***granular cell ameloblastoma,*** there is marked transformation of the cytoplasm, usually of the stellate reticulum like cells, so that it takes on a very coarse, granular, eosinophilic appearance. This often extends to include the peripheral columnar or cuboidal cells as well. Ultrastructural studies, such as that of Tandler and Rossi, have shown that these cytoplasmic granules represent lysosomal aggregates with no recognizable cellular components. Hartman has reported a series of 20 cases of granular cell ameloblastoma and emphasized that this granular cell type appears to be an aggressive lesion with a marked proclivity for recurrence unless appropriate surgical measures are instituted at the first operation. In addition, several cases of this type have been reported as metastasizing. However, all other clinical features of the lesion appear similar to the other forms of ameloblastoma.

The ***basal cell type of ameloblastoma*** bears considerable resemblance to the basal cell carcinoma of the skin. It is believed that this is the rarest histologic subtype and the epithelial tumor cells are more primitive and less columnar, are generally arranged in sheets, more so than in the other tumor types (Fig. 4-22).

The ***desmoplastic ameloblastoma*****,** characteristically, is found in a dense collagen stroma that may appear hyalinized and hypocellular. The desmoplastic ameloblastoma has a greater tendency to grow in thin strands and cords of epithelium rather than in an island like pattern. The epithelial proliferation almost seems to be compressed and fragmented by the dense hyalinized

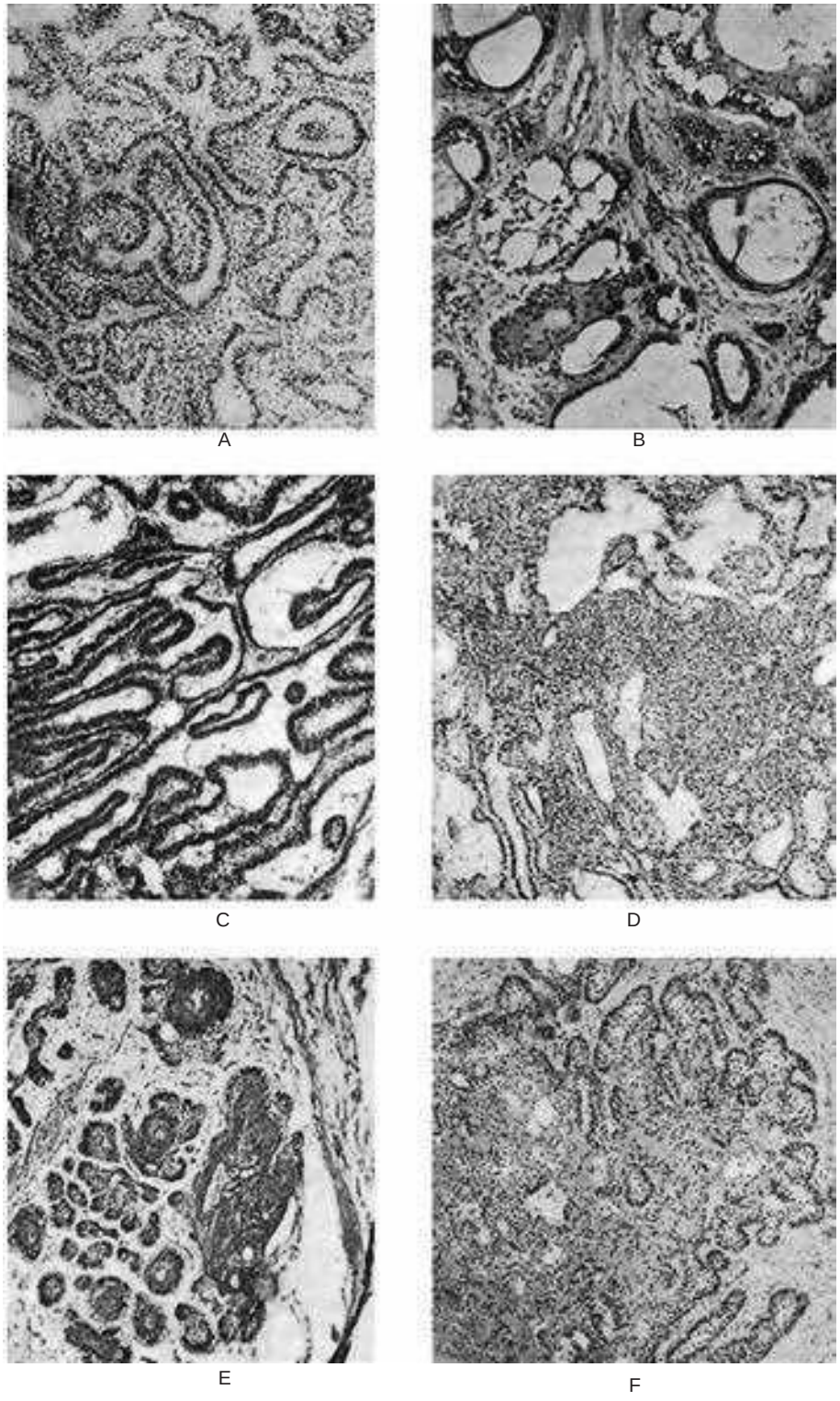


Figure 4-22. Ameloblastoma.
(A) Follicular type. **(B)** Follicular type showing cystic degeneration and squamous metaplasia. **(C)** Plexiform type. **(D)** Basal cell type. **(E)** Acanthomatous type. **(F)** Granular cell type.

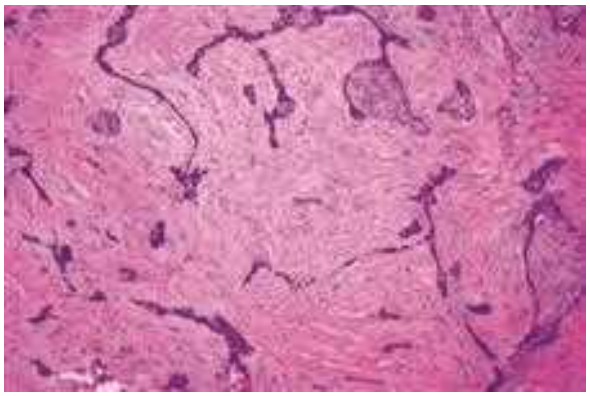


Figure 4-23. Desmoplastic ameloblastoma.
Higher magnification details the cord and strand like growth that is characteristic of this histologic subtype (hematoxylin-eosin, original magnification x5) *(Courtesy of Dr HP Kessler).*

stroma. Central cells are often scant in the epithelial proliferation, and the cells making up the periphery of the strands and cords often are flattened or cuboidal rather than tall columnar in appearance. Reverse polarity of nuclei and subnuclear vacuole formation may be difficult to recognize (Fig. 4-23).

Most desmoplastic ameloblastomas display occasional classic islands of follicular ameloblastoma among the predominant strands and cords. Without these classic islands of ameloblastoma, the diagnosis can be difficult.

The growth pattern of the neoplasm, categorized as conventional or unicystic, is more important than the histopathologic subtype in treatment decision. The desmoplastic ameloblasloma is more important than the histopathologic subtype in treatment decision. Desmoplasia of the stromal connective tissue can be argued to be a maturation stage of the tumor, as similar dense collagenization is seem during maturation of long tumors (Sivapathamundaram et al, 2007). However, these authors failed to explain the off occurrence of these variants in the anterior jaw, unlike in conventional forms.

Unicystic ameloblastoma, the second and far less frequent growth pattern seen in the intraosseous ameloblastoma is the unicystic type. This growth pattern is seen in approximately 6% of ameloblastomas. It tends to occur in a younger population (average age in one large study, 22.1 years) compared with the patient population with conventional ameloblastomas. A high percentage of these lesions are associated with an impacted tooth, and the most commonly cited provisional diagnosis is dentigerous cyst. Cystic areas nearly always are noted grossly at the time of surgery. Recognition of this growth pattern is important, because it is well accepted that the unicystic type has a considerably better overall prognosis and a much reduced incidence of recurrence compared with conventional ameloblastoma (Li TJ et al, 1998).

The unicystic ameloblastoma is characterized by one or more of the following features:

- Lining epithelium exhibiting alterations virtually identical with those described by Vickers and Gorlin as representing early ameloblastomatous changes in the dentigerous cyst (q.v.).

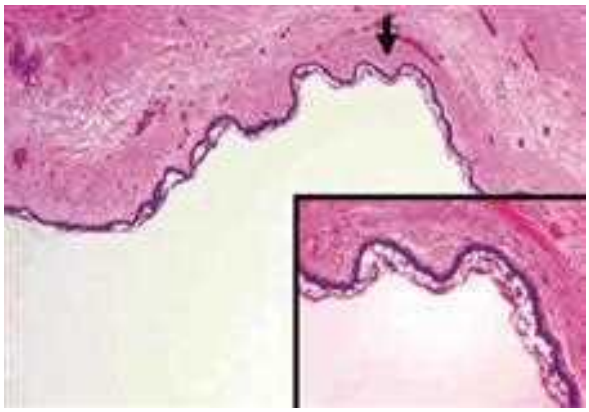


Figure 4-24. Unicystic ameloblastoma.
The ameloblastoma shows a cystic architecture with the typical ameloblastic changes confined to the cyst-lining epithelium. The arrow indicates the area enlarged in the inset at lower right (hematoxylin-eosin, original magnification x2). (Inset) Ameloblastic epithelium with hyperchromatic palisaded basal cell layer, thin layer of stellate reticulum like cells, and abrupt transition to a thin parakeratinizing luminal surface (hematoxylin-eosin, original magnification x10) *(Courtesy of Dr HP Kessler).*

- Nodules of tumor projecting intraluminally.
- Ameloblastomatous lining epithelium proliferating into the connective tissue wall.
- Islands of ameloblastoma occurring isolated in the connective tissue wall (Fig. 4-24).

The recurrence rate of this lesion is distinctly lower than that for the characteristic ameloblastoma, thus indicating a less aggressive type of lesion. The epithelium lining the cystic cavity of the neoplasm shows typical cytomorphologic features that are recognizable as ameloblastoma, with a basal cell layer composed of columnar cells displaying hyperchromatic, palisaded nuclei.

Reverse polarity of the nuclei is present, and a subnuclear vacuole is usually noted between the basement membrane and nucleus. A thin overlying layer of stellate reticulum-like cells is seen. A luminal parakeratin layer may or may not be present. When keratinization is present, an abrupt transition from the stellate reticulum-like layer is usually observed. In some instances, the ameloblastic epithelium may be proliferative, with extension of the ameloblastic epithelium into the lumen of the cystic cavity. This feature has been termed **intraluminal proliferation,** and in many instances, this growth resembles the plexiform type of ameloblastoma. Thus, some lesions have been referred to as plexiform **unicystic ameloblastoma** (Fig. 4-25).

Treatment and Prognosis. There are some differences of opinion about the preferable method of treatment of the ameloblastoma. The only unanimity centers around the fact that complete removal of the neoplasm, regardless of how it is accomplished, will result in a cure of the patient.

The types of treatment that have been used include both radical and conservative surgical excision, curettage, chemical and electrocautery, radiation therapy or a combination of surgery and radiation. The majority of workers today prefer

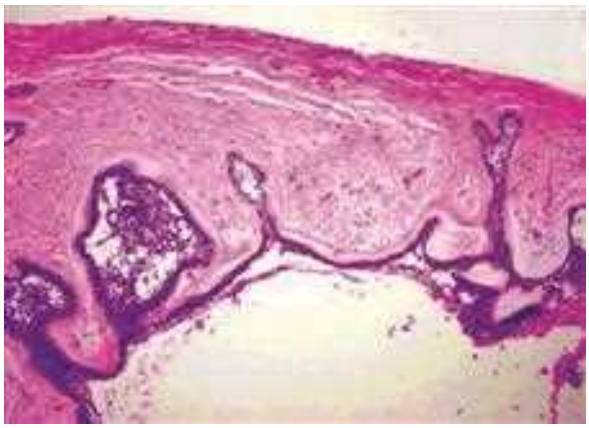


Figure 4-25. Ameloblastoma with mural growth.
Ameloblastic epithelium infiltrates the connective tissue of the cyst wall. The infiltrating ameloblastic epithelium remains in direct continuity with the ameloblastic epithelium lining the cystic lesion. The cyst lumen is seen at the bottom (hematoxylin-eosin, original magnification x5).

some form of surgical excision. Curettage is least desirable, since it is associated with the highest incidence of recurrence. The basic principles of treatment have been discussed in detail by Gardner and Mehlisch and his colleagues.

Frissell reviewed the reported cases in which radiation therapy was utilized and found that there was considerable variance of opinion as to its benefit. The report of Kimm, supported by study of serial biopsy, on the treatment of the ameloblastoma by radiation indicated that this neoplasm is generally highly radioresistant and that the use of this form of therapy is not warranted. Wide clinical experience has shown the truth of this finding. Regardless of the form of treatment, long-term follow-up of the patient is an absolute necessity.

Treatment decisions for ameloblastoma are based on the individual patient situation and the best judgment of the surgeon. The surgical plan should be influenced strongly by whether the lesion involves the mandible or maxilla. Maxillary lesions behave distinctly differently from mandibular lesions. The higher cancellous bone percentage in the maxilla facilitates the spread of the ameloblastoma, whereas the density of the cortical plates in the mandible tends to limit spread of the neoplasm. Regardless of which jaw is involved, once an ameloblastoma has recurred, retreatment becomes more challenging. Radical retreatment typically is performed even for suspected unicystic lesions during the initial phase of the disease.

Calcifying Epithelial Odontogenic Tumor
(Pindborg tumor)

The calcifying epithelial odontogenic tumor was first described in 1956 by the late Dr Jens J Pindborg. Pindborg tumor is now a universally recognized synonym for this neoplasm. An alternative abbreviation also commonly used is CEOT.

The Pindborg tumor is classified as an uncommon, benign, odontogenic neoplasm that is exclusively epithelial in origin. Some have suggested that the epithelial cells of the Pindborg tumor are reminiscent of the cells in the stratum intermedium layer of the enamel organ in tooth development. Some hypothesize that the Pindborg tumor arises from remnants of the primitive dental lamina found in the initial stage of odontogenesis, and these epithelial rests are the more likely true progenitor cell. The definite etiology of this neoplasm still remains enigmatic.

Clinical Features. A report by Franklin and Pindborg in 1976 shows that 113 cases of this intraosseous tumor have been described in the literature since Pindborg's original paper. As the number of reported cases continues to increase, we are rapidly improving our knowledge of this lesion.

This tumor occurs most frequently in middle-age. Of the reported cases, the mean age of occurrence at the time of diagnosis was 40 years of age in both men and women, with a range of 8–92 years. There is no significant difference in occurrence between the gender, since 49% of the cases were in men and 51% in women.

There is a predilection for occurrence of the tumor in the mandible over the maxilla by a ratio of 2 : 1, and the prevalence in the molar region is three times that in the bicuspid region, whereas in other sites in the jaws there is a relatively even distribution. If these two respects, i.e. age and site, the Pindborg tumor is very similar to the ameloblastoma.

Most patients with this lesion are asymptomatic and are aware only of a painless swelling. It is significant, however, that 52% of the reported cases have been definitely associated with an unerupted or impacted tooth.

An extraosseous calcifying epithelial odontogenic tumor is also known to occur but is quite rare, with only eight reported cases, according to the review by Wertheimer and his associates in 1977. This extraosseous lesion has had a mean age of occurrence of 35 years and an approximately equal sex distribution. With the exception of one equivocal lesion on the upper lip, all cases have occurred on the gingiva, five mandibular and two maxillary, and almost invariably in the anterior segment (Fig. 4-26). The extraosseous lesion is histologically identical with the intraosseous one.

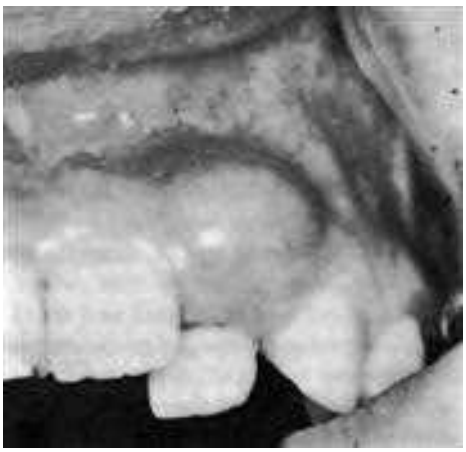


Figure 4-26. Extraosseous calcifying epithelial odontogenic tumor.
(Courtesy of Dr Jens J Pindborg: Acta Odontol Scand, 24: 419, 1966).

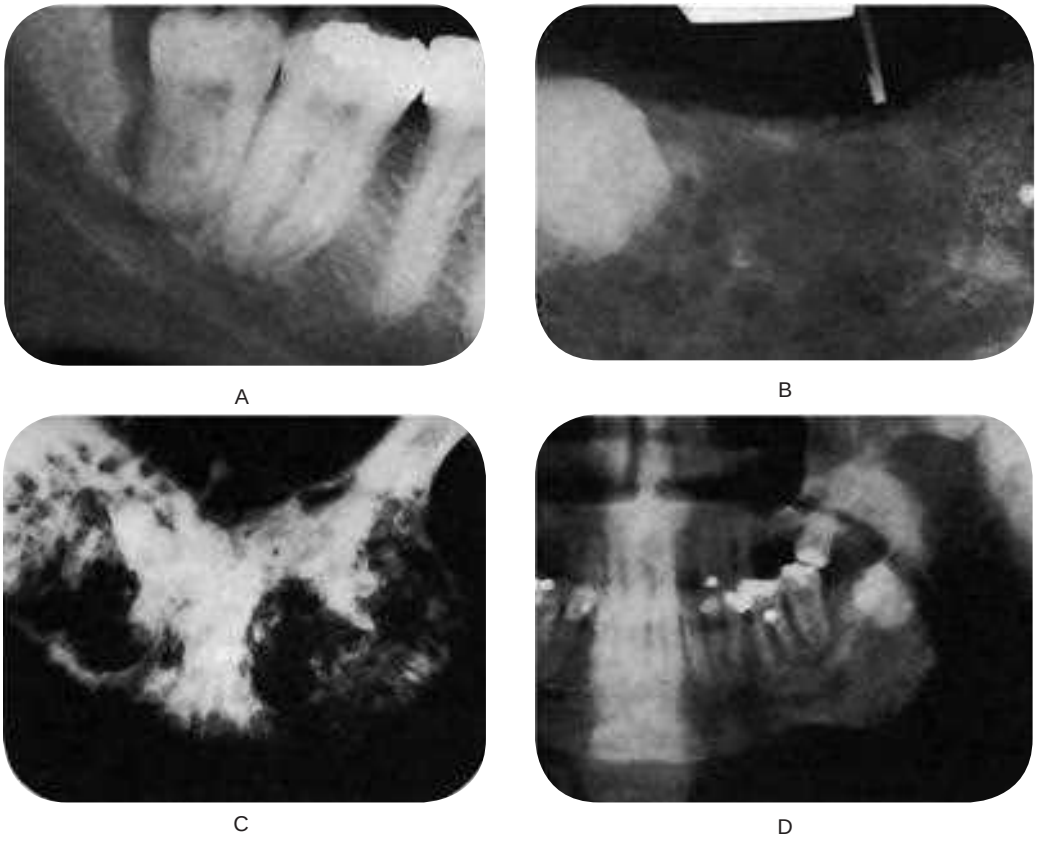


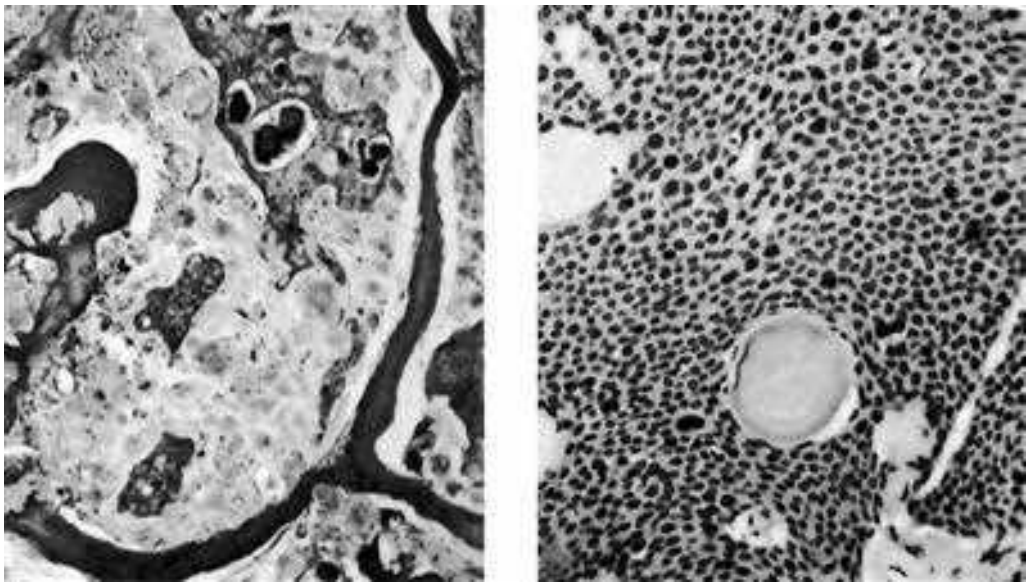
Figure 4-27. Calcifying epithelial odontogenic tumor of Pindborg.
(Courtesy of Dr Charles Redish, Dr Robert Bresick, Dr Charles Hutton, and Dr Ronald Vincent).

Radiographic Features. The tumor may show considerable radiographic variation. In some cases, the lesion appears as either a diffuse or a well-circumscribed unilocular radiolucent area, while in other cases there may appear to be a combined pattern of radiolucency and radiopacity with many small, irregular bony trabeculae traversing the radiolucent area in many directions, producing a multilocular or honeycomb pattern. Scattered flecks of calcification throughout the radiolucency have given rise to the descriptive term of a 'driven snow' appearance. In some instances, the lesion is totally radiolucent and is in association with an impacted tooth, thus leading to a mistaken clinical diagnosis of dentigerous cyst (Fig. 4-27).

On CT examination, calcifying epithelial odontogenic tumor in the mandible demonstrates expansion and thinning of buccal and lingual cortical bony plates by a well-defined mass containing scattered radiopaque areas of varying size and signal intensity. MRI reveals predominantly a hypointense lesion on T1-weighted images and a mixed hyperintense lesion on T2-weighted images.

Histologic Features. The calcifying epithelial odontogenic tumor is composed of polyhedral epithelial cells, sometimes closely packed in large sheets but other times consisting chiefly of scattered small islands of cells in a bland fibrous connective tissue stroma (Fig. 4-28). Occasionally, the cells are arranged in cords or rows, mimicking adenocarcinoma. The tumor cells have a well-outlined cell border with a finely granular eosinophilic cytoplasm, and intercellular bridges are often prominent. The nuclei are frequently pleomorphic, with giant nuclei and multinucleation being quite common but mitotic figures rare. The tumor cells in some lesions are characterized by extreme morphologic variation with severe cellular abnormalities, mimicking those often seen in some highly malignant neoplasms, while other cases of the calcifying epithelial odontogenic tumor are composed of very monomorphic, innocuous-appearing tumor cells; yet, to the best of our knowledge, the biologic behavior does not differ between the two.

A well-recognized form of this neoplasm is the **clear-cell variant.** In this type, the tumor cells exhibit a clear vacuolated cytoplasm rather than an eosinophilic cytoplasm. The nucleus may remain round or oval in the center of the cells or be flattened against the cell membrane. According to Krolls and Pindborg, who have discussed these histomorphologic variations, most of the clear cells are mucicarmine negative, although a few may show a faint tinge. In some tumors, the clear cells comprise the bulk of the tumor cells while, in others, they consist of only a few scattered foci. In as much as a variety of other types of tumors, both primary (e.g. mucoepidermoid carcinoma) and metastatic (e.g. hypernephroma), may exhibit clear cells, great care must be utilized in their interpretation and diagnosis.



A B

Figure 4-28. Calcifying epithelial odontogenic tumor of Pindborg.

This tumor has been investigated under the electron microscope by many researchers including Anderson and his coworkers, who have demonstrated that the tumor cells exhibit the features commonly seen in epidermal cells such as intercellular bridges with desmosomes, intracytoplasmic tonofilaments and well-developed hemidesmosomes.

One of the characteristic microscopic features of this tumor is the presence of a homogeneous, eosinophilic substance which has been variously interpreted as amyloid, comparable glycoprotein, basal lamina, keratin or enamel matrix. In at least some instances, this appears to form intracellularly and then is extruded into the extracellular compartment as a result of cell secretion or degeneration. This homogeneous eosinophilic material may be present in large or very limited quantities. In most cases, it stains metachromatically with crystal violet, positively with Congo red, and fluoresces under ultraviolet light with thioflavin T, all in a fashion similar to amyloid (Fig. 4-29). Ultrastructural studies have shown that this amyloid-like material is composed of at least three different types of fibrils, but that they have a smaller size than the fibers of 'conventional' amyloid, although this term is a rapidly expanding one. Some forms of amyloid are now suggested to arise from light chain fragments of immunoglobulin molecules, called immunamyloid, while another form is thought to originate from cells of certain endocrine tumors (e.g. medullary carcinoma of the thyroid) which may be derived from the endocrine polypeptide cells of neural crest origin of the amine precursor uptake and decarboxylation (APUD) system, called APUD-amyloid. On the evidence available at present, the exact nature of the amyloid like substance in the CEOT cannot be definitively assessed.

Another characteristic feature of the Pindborg tumor is the presence of calcification, sometimes in large amounts, and often in the form of Liesegang rings. This calcification

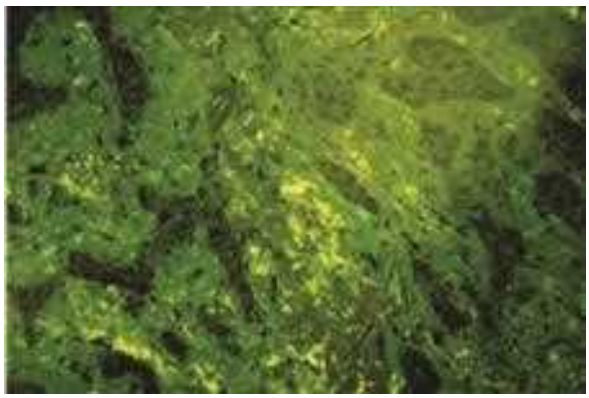


Figure 4-29. Calcifying epithelial odontogenic tumor of Pindborg.
Photomicrograph showing apple-green color birefringence of amyloid deposited in fibrous connective tissue stroma (Congo red stain under polarized light source, original magnification x20) *(Courtesy of Dr RK Goode).*

actually appears to occur in some instances in globules of the amyloid like material, many of which have coalesced and are transformed from being PAS (periodic acid-Schiff)-negative to PAS-positive during this calcification process. There does not appear to be necessarily a relationship between the amount of amyloid material formed in a given lesion and the amount of calcification occurring.

The source of the epithelial cells comprising this tumor was originally suggested by Pindborg to be the reduced enamel epithelium of the associated unerupted tooth. Today, most investigators believe that the cells originate from the stratum intermedium because of the morphologic similarity of the tumor cells to the normal cells of this layer of the odontogenic apparatus. Unfortunately, this does not explain those cases of tumor apparently occurring without an associated unerupted tooth or those extraosseous cases outside the jaw.

Treatment and Prognosis. There are a variety of alternative surgical treatment methods to successfully manage Pindborg tumors. Small, intrabony lesions with well-defined borders can be treated with enucleation or curettage followed by judicious removal of a thin layer of bone adjacent to the tumor. But some pathologists suggest that maxillary tumors should be treated more aggressively than a similar-sized lesion in the mandible.

Lesions designated recurrences, following conservative approaches like intrabony curettage, may in fact represent persistence of disease. Like ameloblastoma, small infiltrative foci of Pindborg tumor may insinuate along bony trabeculae and appear as uninvolved bone radiographically.

Recurrent or persistent tumors, which over an extended time have become larger and more extensive (greater than 4 cm), would require segmental resections such as partial or hemimandibulectomy or hemimaxillectomy.

Early intervention is advocated for the treatment of histopathologically atypical or frankly malignant calcifying epithelial odontogenic tumors before such a lesion could escape the confines of the involved mandible or maxilla. Radical resection of the affected jaw portion and any associated soft tissues with not less than 1 cm in every direction, as might be performed for any other variant of odontogenic carcinoma is adviced. Adjunctive external beam radiation therapy is advocated following determination of local spread to cervical lymph nodes and adjunctive chemotherapy may play some role in control of distant organ metastasis in some patients. Most studies of Pindborg tumor report a local recurrence rate of between 10 and 20% following conservative but complete removal of the lesion. The incidence of malignant transformation to odontogenic carcinoma ex-Pindborg tumor is so extremely low as to be considered distinctly rare; only three such cases being reported.

Adenomatoid Odontogenic Tumor

(Adenoameloblastoma, ameloblastic adenomatoid tumor)

Adenomatoid odontogenic tumor (AOT), generally considered to be an uncommon tumor, occurs mostly in association with an unerupted maxillary cuspid. Some investigators consider it as a benign neoplasm, while others have categorized it as a hamartomatous malformation due to the limited size and to the lack of recurrence of most cases (attributed perhaps to its minimal growth potential). Those who prefer to consider AOT to be a benign neoplasm believe that the limited size of most cases stems from early detection and removal of the lesion. They also point to the considerable size of some reported cases that had gone undetected or untreated for many years and resulted in facial asymmetry and distortion.

Histogenesis. Like all other odontogenic tumors, the specific stimulus that triggers proliferation of the progenitor cells of AOT is unknown. Because of its exclusive occurrence within the tooth-bearing areas of the jaws (most often associated closely with an unerupted or impacted tooth) and its cytologic resemblance to the dental lamina and components of the enamel organ, there is no disagreement that the AOT is of odontogenic origin (Rick GM, 2004).

Clinical Features. The mean age of these patients was approximately 18 years, with a range of 5–53 years. However, 73% of the patient were under 20 years of age. There is a marked predilection for occurrence of the tumor in females — 64% contrasted to 36% developing in males. The site of occurrence is greater in the maxilla (65%) than in the mandible (35%). In contrast to the ameloblastoma, this tumor occurs more frequently in the anterior part of the jaws with 76% developing anterior to the cuspid in the maxilla and mandible. Only very rarely does the lesion occur distal to the premolar area. It is of some interest that in at least 74% of the cases, the tumors were associated with an unerupted tooth, and in over two-thirds of the cases, this tooth was the maxillary or mandibular cuspid.

The vast majority of the lesions measured between 1.5 and 3.0 cm, although large lesions, exceeding 7.0 cm, have been reported. A large proportion of these tumors produced an obvious clinical swelling although they were generally asymptomatic. Five tumors reported in the literature have been extraosseous in their occurrence, according to Swinson.

Giansanti and his coworkers have pointed out that the high percentage of these lesions being associated with unerupted teeth and present as dentigerous cysts would strongly suggest that they are related to some late disturbance in odontogenesis. Since none of the associated teeth were described as morphologically defective, the disturbance must occur after odontogenesis is complete.

Adenomatoid odontogenic tumor may occur within the jaw bones or the gingiva. Peripheral lesions present as a painless, gingival colored mass that ranges from 1–1.5 cm in diameter. They are 10 times more prevalent in the maxillary gingiva than in the mandibular gingiva. The female to male ratio for the gingival lesion is 14: 1 (Philipsen HP et al, 1991).

Adenomatoid odontogenic tumor has to be clinically differentiated from central odontogenic cysts and tumors, benign fibro-osseous lesions and benign mesenchymal neoplasms. Gingival lesions cannot be differentiated clinically from gingival fibromas, peripheral cemento-ossifying fibromas, peripheral giant cell lesions, or from other peripheral odontogenic tumors, such as odontogenic fibroma, ameloblastoma, calcifying odontogenic cyst, and calcifying epithelial odontogenic tumor.

Radiographic Features. Central AOTs present as well-demarcated, almost always unilocular radiolucency that generally exhibit a smooth corticated (and sometimes sclerotic) border.

Most lesions are pericoronal or juxtacoronal but the radiolucency may extend apically beyond the cementoenamel junction on at least one side of the root. Rare, multilocular cases have been reported and a scalloped border is observed occasionally. Most cases are between 1 and 3 cm in greatest diameter. About 65% of reported cases also demonstrate faintly detectable radiopaque foci within the radiolucent lesion. Occasionally, a more obvious intralesional radiopacity may be identified, usually eccentrically positioned within the lesion. Divergence of roots and displacement of teeth occurs more frequently than root resorption. Orbital and maxillary sinus encroachment have been reported. Gingival lesions may cause slight erosion of the underlying alveolar bone cortex.

Histologic Features

Macroscopic features. Central AOTs macroscopically appears as a soft, roughly spherical mass with a distinct fibrous capsule. Upon gross sectioning, the tumor may exhibit white to tan, solid to crumbly tissue or one or more cystic spaces of varying sizes with yellowish brown fluid or semisolid material; fine, hard 'gritty' granular material; and one to several larger calcified masses. Additionally, intact specimens demonstrate the crown of an embedded tooth in the solid tumor mass or projecting into a cystic cavity.

Microscopic features. The AOT exhibits diverse histomorphologic features. The tumor is made up of a multinodular proliferation of spindle, cuboidal, and columnar cells in a variety of patterns comprising of scattered duct like structures, eosinophilic material, and calcifications in several forms; delimited by a fibrous capsule of variable thickness. Cytologic atypia is never a prominent feature.

Although not present in all tumors, the most distinctive microscopic feature of AOT is varying numbers of duct like structures with lumina of varying size that are lined by a single layer of cuboidal to columnar epithelial cells that have nuclei that frequently are polarized away from the lumen. These duct like or microcyst lumina frequently are lined by an eosinophilic rim of varying thickness (the so-called **hyaline ring**).

The stellate reticulum like spindle cells, and occasionally round or polygonal epithelial cells dominate the tissue between the cell-rich nodules. Small amounts of eosinophilic material or calcifications also may be present between these cells. Anastomosing strands of basaloid epithelial cells which resemble cell rests of the dental lamina, are arranged in a plexiform, trabecular, cribriform, or lattice like configuration. They occasionally extend between the cell-rich nodules and usually are present in the peripheral subcapsular area of most tumors. Many AOTs contain a few clusters of well defined calcifying epithelial odontogenic tumor like foci with eosinophilic polyhedral squamous epithelial cells and prominent intercellular bridges, and occasional mild nuclear pleomorphism (Fig. 4-30).

A considerable number of AOTs demonstrate cystic component. It is not clear whether this represents pooling of the mucoid stroma or if the tumor developed within or adjacent to a preexisting cyst. Although the cyst lining may occasionally resemble that seen in dentigerous cysts, it more often is similar to the basaloid cells that form the plexiform pattern that was described above. Some tumors exhibit pools of finely fibrillar eosinophilic material at the epithelial–connective tissue interface; this was immunoreactive for the basement membrane component laminin. Some AOTs contain varying amounts of dysplastic dentin, dentinoid, and osteodentin. Irregular to round calcified bodies which may exhibit areas with a concentric layered pattern (Liesegang rings) may be seen in parenchymal or stromal zones. The supporting stroma is loose, hypocellular, and fibrovascular that may show a prominent vascular component.

Treatment and Prognosis. The majority of tumors of this variety have been treated by conservative surgical excision and recurrence, if it ever occurs, is exceedingly rare.

Squamous Odontogenic Tumor
(Benign epithelial odontogenic tumor)

The squamous odontogenic tumor is a lesion which had been recognized as an apparent entity for a number of years but had not been named or reported until 1975, when Pullon and a small group of other oral pathologists combined their material and published six cases. Several additional cases have been reported since the original study, including five further cases by Goldblatt and his colleagues, who also reviewed the literature and commented further on this lesion.

The most important aspect of this lesion is its mistaken histologic identification as an acanthomatous ameloblastoma or as a well-differentiated epidermoid carcinoma. Most investigators believe that it represents a benign odontogenic neoplasm, probably arising from rests of Malassez, although a hamartomatous epithelial proliferation has also been considered.

The **histogenesis** of squamous odontogenic tumor may be varied. Rests of Malassez are the source of the epithelial proliferation for lesions that are associated with the alveolar process adjacent to the lateral root surface of the teeth, and dental lamina may be the source for lesions that developed in association with the crowns of unerupted or impacted teeth. Surface stratified squamous epithelium and rests of Serres have been cited as the sources of the extraosseous variant.

Clinical Features. The age at discovery of the 16 cases evaluated by Goldblatt and his coworkers ranged from 11 to 67 years with 10 cases being between 19 and 31 years of age. There were six males and 10 females in the series.

There is a slight male preponderance, and the mandible is commonly involved. In the maxilla, lesions centered around the incisor-cuspid area, whereas in the mandible, lesions had a predilection for the bicuspid-molar area. However, several cases exhibited multiple site involvement, including both maxillary and mandibular involvement in the same patient.

The lesions were often asymptomatic but presenting manifestations included mobility of involved teeth, pain, tenderness to percussion, and occasionally, abnormal sensations.

Radiographic Features. There are no radiographic features sufficiently characteristic to suggest the diagnosis of this condition. It presents as a semicircular or roughly triangular radiolucent area, with or without a sclerotic border, usually in association with the cervical portion of the tooth root (Fig. 4-31 A, B).

Histologic Features. The squamous odontogenic tumor is composed entirely of islands of mature squamous epithelium without a peripheral palisaded or polarized columnar layer (Fig. 4-31 C, D). This peripheral layer is usually quite flattened or at least cuboidal. The squamous cells are very uniform and exhibit no pleomorphism, nuclear hyperchromatism or mitotic activity. Occasionally, individual cell keratinization is present but no epithelial pearls. Intercellular bridges are usually seen with no difficulty. Three other variable findings are microcyst formation involving only small portions of the epithelial islands, laminar calcifications in the epithelium and globular, hyalin, eosinophilic structures within the islands, which are not amyloid. The fibrous stroma of the tumor is

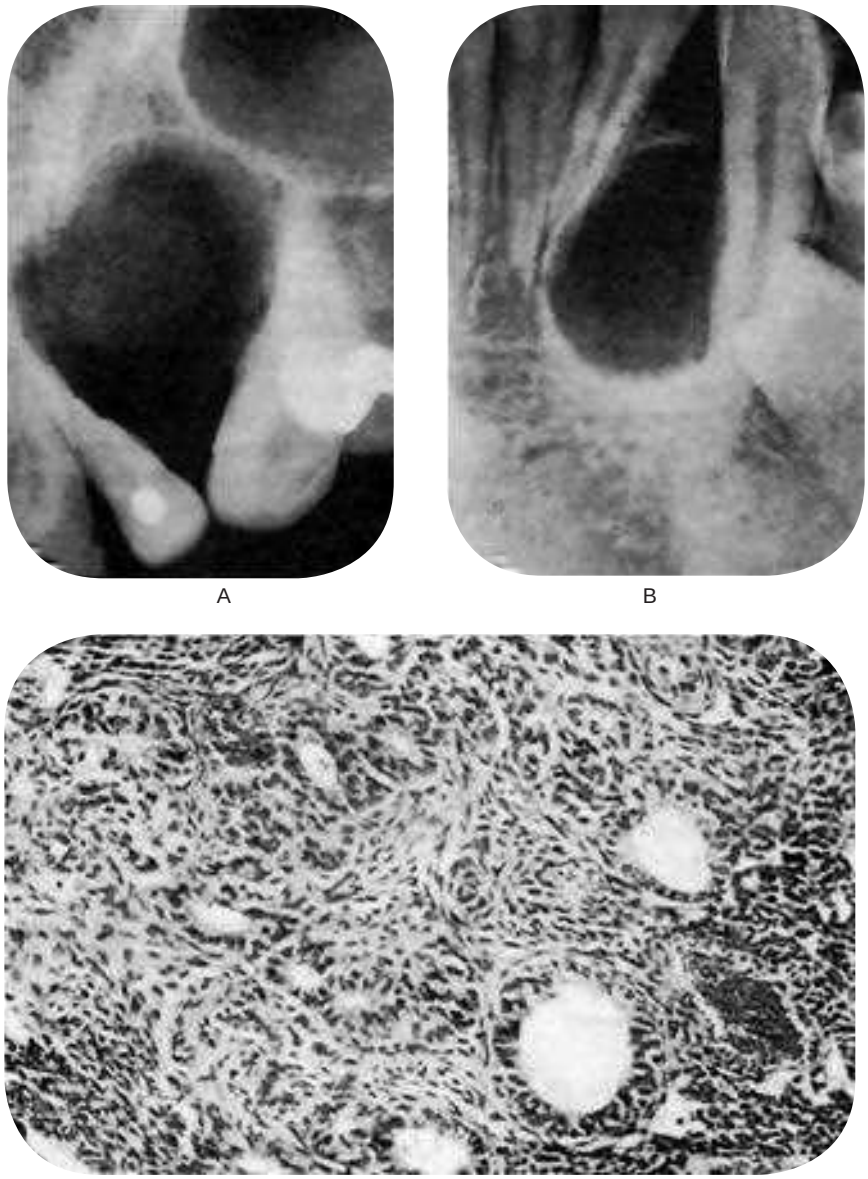


Figure 4-30. Adenomatoid odontogenic tumor.
The tumor in **(A)** radiographically resembled a globulomaxillary cyst. The tumor in **(B)** was associated with an impacted tooth and superficially resembled a dentigenous cyst. The photomicrograph **(C)** shows the typical duct like structures *(Courtesy of Dr Charles Redish and Dr Charles A Waldron).*

simply mature bundles of collagen fibers and is devoid of any peri-insular inductive effect.

Squamous odontogenic tumor like proliferations have been reported by Wright in the walls of odontogenic cysts, such as dentigerous or apical periodontal cysts. These proliferations may appear histologically nearly identical with those in the squamous odontogenic tumor, but they do not appear to cause any alteration in the usual biologic behavior of the cyst and do not appear to develop into the tumor. Care must be used, however, in differentiating between these proliferations and the tumor itself.

Although squamous odontogenic tumor exhibits a unique microscopic picture, it may be confused with other conditions, including ameloblastoma and squamous cell carcinoma. The acanthomatous and desmoplastic variants of ameloblastoma have been misdiagnosed as squamous odontogenic tumor. Both variants exhibit squamous differentiation within the tumor islands, but there is demonstrable ameloblastic change of the peripheral cells, including columnar shape, polarization of elongated nuclei away from the basement membrane, and a vacuolated or clear cytoplasm. These changes may be less evident in the desmoplastic variant but can be found on careful and thorough examination of the specimen. These changes are not seen in the squamous odontogenic tumor in which the peripheral cell layer is composed of flat to cuboidal cells. The islands and strands of desmoplastic ameloblastoma are often thin and compressed rather than rounded and broad-based, as seen in squamous odontogenic tumor.

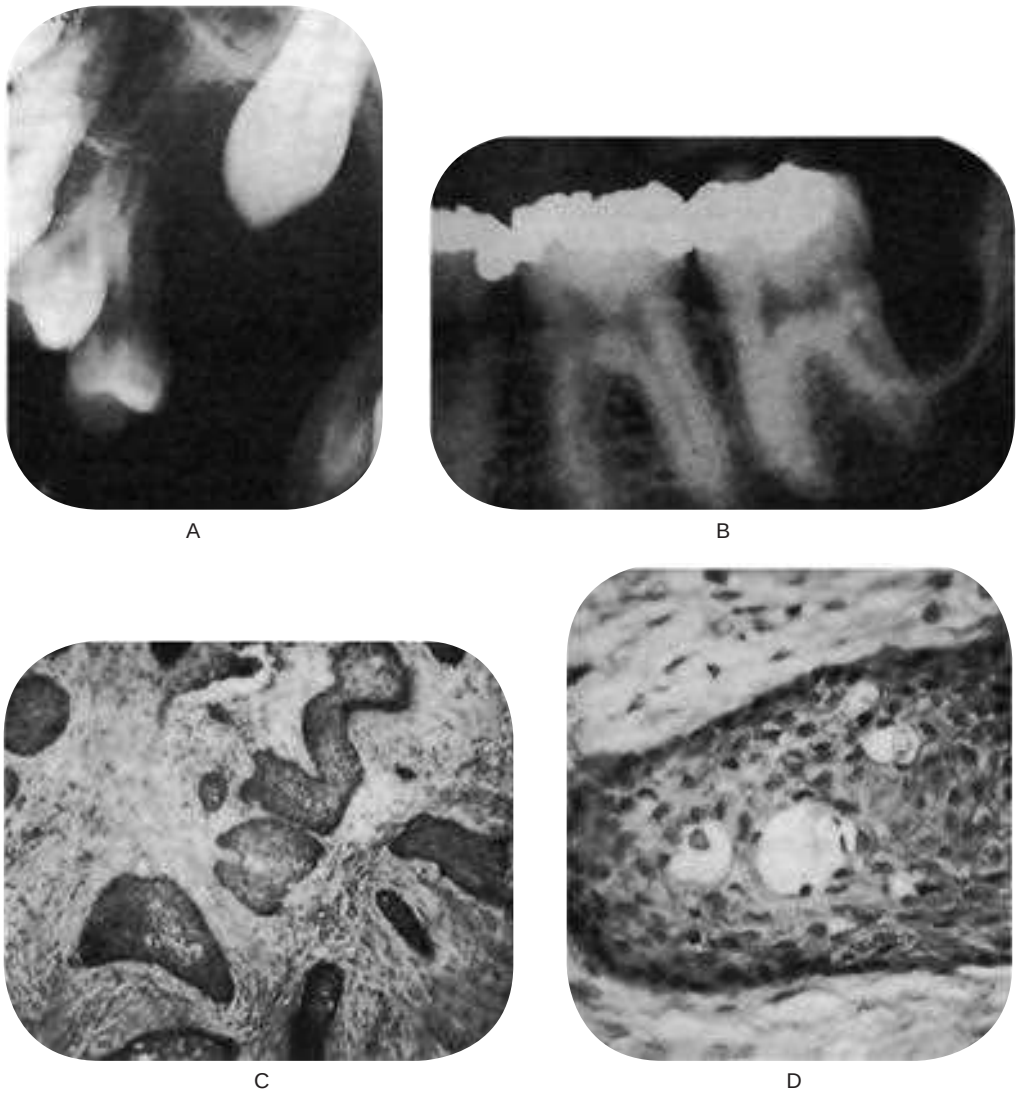


Figure 4-31. Squamous odontogenic tumor.
The radiographic appearance of the lesion **(A, B)** is nonspecific. However, the innocuous-appearing islands of squamous epithelium are quite characteristic (**C, D**) *(B, Courtesy of Dr Richard P Elzay and Dr Bennet Malbon).*

Squamous odontogenic tumor may be confused with well-differentiated squamous cell carcinoma; however, the islands in squamous odontogenic tumor are well defined, and the cells lack variation in cell size, shape and nuclear staining and mitotic figures that are characteristically seen in squamous cell carcinoma. Significant keratin formation also is not typical.

Occasionally, dentigerous and apical periodontal (radicular) cysts and periodontal granulation tissue exhibit foci of squamous odontogenic tumor like proliferation. This has been interpreted as a nonneoplastic, reactive process that is secondary to the cyst formation or inflammation. Foci of squamous odontogenic tumor within the connective tissue wall of odontogenic cysts do not seem to alter the prognosis of the primary cystic process.

Treatment. Enucleation, curettage, and local excision are treatment modalities that are most often described in case reports of squamous odontogenic tumor. Clinically aggressive lesions have been treated by en bloc excision.

ODONTOGENIC EPITHELIUM WITH ODONTOGENIC ECTOMESENCHYME WITH OR WITHOUT HARD TISSUE FORMATION

Ameloblastic Fibroma

(Soft mixed odontogenic tumor, soft mixed odontoma, fibroadamantoblastoma)

The ameloblastic fibroma is a relatively uncommon neoplasm of odontogenic origin which is characterized by the simultaneous proliferation of both epithelial and mesenchymal tissue without the formation of enamel or dentin. Thus this may be viewed as an example of a true mixed tumor.

Some investigators have suggested; however, that the ameloblastic fibroma represents an immature complex odontoma and that, if the tumor is left undisturbed, it will ultimately differentiate or mature further into a lesion known as an ameloblastic fibro-odontoma (q.v.) and then continue

maturation into a completely differentiated odontoma. In contrast, Eversole and his coworkers, in a discussion of the histogenesis of odontogenic tumors, have proposed that the mixed odontogenic tumors are solely and totally dependent upon the presence of differentiation factors which are or are not elaborated by a particular tumor. Thus, they have concluded that there is little probability of sequential differentiating events resulting in the progression of an immature entity such as the ameloblastic fibroma into a highly differentiated entity such as the complex odontoma. As Eversole and his associates discussed, and as Slootweg has emphasized, if these three lesions—the ameloblastic fibroma, the ameloblastic fibro-odontoma and the odontoma—were simply stages in a continuum, clinical data on each of the lesions should support this. For example, the ameloblastic fibroma should occur in younger patients, the odontoma in somewhat older patients and the ameloblastic fibro-odontoma in an intermediate age group. In addition, the gender predilection and distribution of all lesions should be the same. Slootweg has investigated this problem utilizing data from 55 reported cases of ameloblastic fibroma, 50 cases of ameloblastic fibro-odontoma, 77 cases of complex odontoma and 48 cases of compound odontoma. While correction had to be made for the fact that the odontogenic apparatus is active in various parts of the jaws at various ages, Slootweg concluded that the ameloblastic fibroma represents a separate specific neoplastic entity that does not develop into a more differentiated odontogenic lesion. He also concluded from his data that the ameloblastic fibro-odontoma does represent an immature complex odontoma, a hamartomatous rather than neoplastic odontogenic lesion.

Clinical Features. The ameloblastic fibroma, arising most commonly in the molar region of the mandible, is similar in location to the simple ameloblastoma. Nearly 75% of the 55 cases reviewed by Slootweg occurred in this location. There is a considerable difference, however, in the age group of patients most commonly affected. Whereas the simple ameloblastoma occurs typically in middle-aged persons, the average age of the patient at the time of discovery being approximately 33 years according to Small and Waldron, the ameloblastic fibroma occurs in much younger persons. In the review of 55 cases, Slootweg found that the average age of patients with the ameloblastic fibroma was 14.6 years, with 40% of the patients under the age of 10 years. He also reported that there was a very slight predilection for occurrence in males.

This tumor exhibits some what slower clinical growth than the simple ameloblastoma and does not tend to infiltrate between trabeculae of bone. Instead it enlarges by gradual expansion so that the periphery of the lesion often remains smooth. It will frequently cause no complaint on the part of the patient and has been discovered accidentally during radiographic examination. Pain, tenderness or mild swelling of the jaw may induce the patient to seek aid from the dentist, however.

Radiographic Features. No constant significant differences between the appearance of the simple ameloblastoma and that of the ameloblastic fibroma are found. The later is manifested as a unilocular or multilocular radiolucent lesion which has a rather smooth outline, often with a sclerotic border, and which may or may not produce evident bulging of bone (Fig. 4-32). In the study of 24 cases by Trodahl, most of the lesions were associated with unerupted teeth. In addition, he found considerable variation radiographically in the size of lesions, there being a range of 1–8.5 cm in diameter.

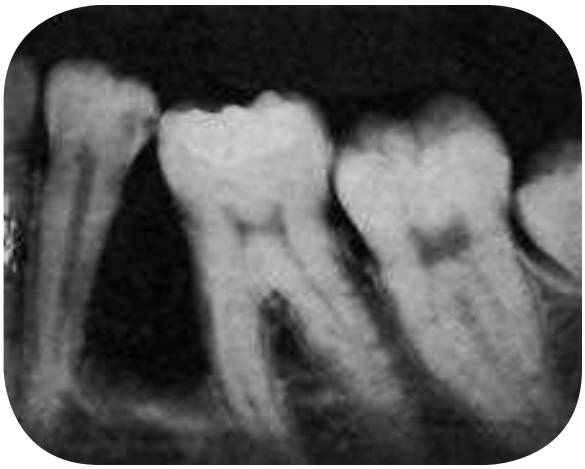


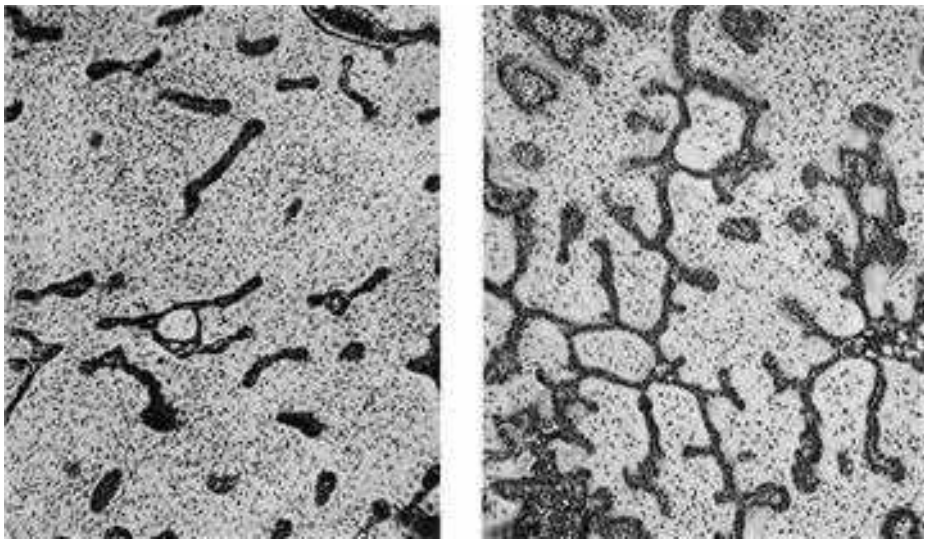
Figure 4-32. Ameloblastic fibroma.
The neoplasm was asymptomatic and was discovered during routine radiographic examination.

Histologic Features. The microscopic appearance of this odontogenic neoplasm is characteristic. The ectodermal portion consists of scattered islands of epithelial cells in a variety of patterns, including rosettes, long finger like strands, nest and cords. These epithelial cells are usually of a cuboidal or columnar type and bear close resemblance to primitive odontogenic epithelium. Mitotic activity is not common. Because the pattern of these cells is one of strands and cords, tissue resembling stellate reticulum is often not seen. However, occasional cases occur in which some of these tumor islands are found 'opening,' with the formation of stellate reticulum. The resemblance to the dental lamina is far more striking in this lesion than in the simple ameloblastoma (Fig. 4-33 A, B).

The mesenchymal component is made up of a primitive connective tissue that, in some cases, shows closely intertwining fibrils interspersed by large connective tissue cells closely resembling those of the dental papilla. There may be a paucity of blood vessels, and juxtaepithelial hyalinization of areas of the connective tissue occurs. On occasion, this may even resemble dysplastic dentin. Electron microscopic studies have suggested that this apparent hyalinization may, instead, actually represent exuberant basal lamina.

Treatment and Prognosis. The treatment of the ameloblastic fibroma has been somewhat more conservative than that of the simple ameloblastoma, since it does not appear to infiltrate bone as actively or as widely as the ameloblastoma. It also tends to separate from the bone more readily.

At one time the ameloblastic fibroma was regarded as exhibiting little tendency for recurrence, even following the



A B

Figure 4-33. Ameloblastic fibroma.
Within a stroma of primitive mesoderm there are interlacing thin strands of odontogenic epithelium, from which budding outgrowths arise. The epithelial buds have a peripherally placed row of more columnar cells and centrally placed more stellate cells.The septae of fibrous tissue may give the tumor a lobular pattern.

most conservative surgical removal. This was based on part on the review by Gorlin and his associates of 35 documented cases with only two instances of recurrence (approximately 6%). In contrast, Trodahl subsequently reported 10 recurrences in his series of 24 cases (approximately 44%). Since these two series, numerous other instances of recurrent lesions have been reported, and these have been reviewed and discussed by Zallen and his colleagues, who noted a total cumulative recurrence rate of 18.3% for this lesion. In addition, there have been a surprising number of cases reported of ameloblastic fibrosarcoma originating, at least in some instances, in a recurrent ameloblastic fibroma, as in the cases of Leider and his associates. Thus, it would seem that a somewhat more aggressive surgical removal, rather than simple curettage, should be considered for this lesion.

Ameloblastic Fibro-odontoma

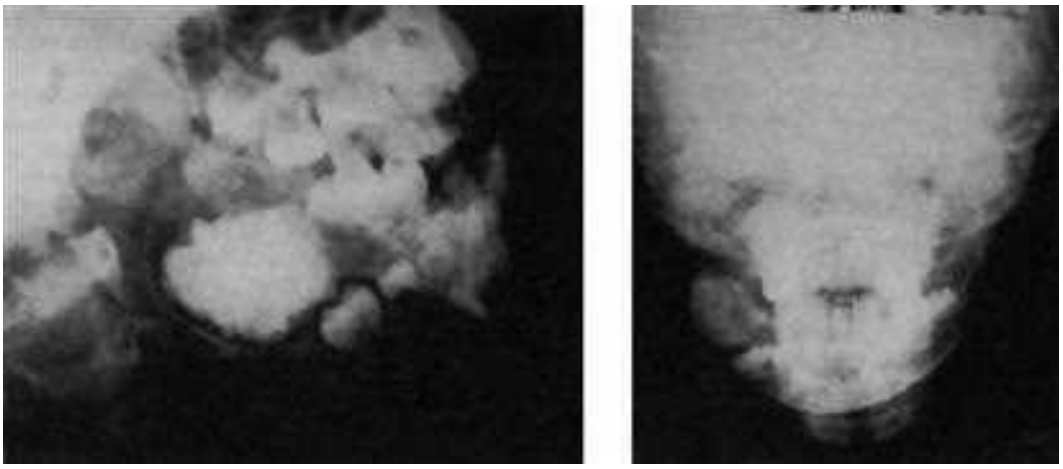
The ameloblastic fibro-odontoma (AFO) has been confused in the earlier literature with a lesion of similar nomenclature, the ameloblastic odontoma (q.v.), although a clear distinction between the two was finally drawn by Hooker in 1967 at the annual meeting of the American Academy of Oral Pathology. It has been emphasized that some investigators, furthermore, have believed that the ameloblastic fibroma (q.v.) represents an early, undifferentiated complex odontoma and that the ameloblastic fibro-odontoma is simply a further differentiated maturing odontoma. After investigating this problem, Slootweg concluded that the ameloblastic fibroma is a true neoplasm and does not differentiate into an ameloblastic fibro-odontoma. This evidence has been discussed in the section on ameloblastic fibroma. He also concluded that the ameloblastic fibro-odontoma to be discussed here did, in fact, represent an immature complex odontoma, and therefore, represented a hamartomatous rather than a neoplastic odontogenic lesion.

Clinical Features. The original report by Hooker consisted of 26 cases of ameloblastic fibro-odontoma. Of these 26 cases, there were 20 male and six female for a ratio of 3.3 : 1 in favor of the males. However, of the 50 cases reviewed by Slootweg, which did not include the 26 cases of Hooker, there were 28 males and 22 females. The age range of the cases in the series of Hooker was 0.5–39 years with the mean being 11.5 years of age. Nineteen of the 26 cases occurred under the age of 15, only two cases over the age of 20. In the Slootweg series, the mean age was 8.1 years, with 62% of the patients under the age of 10 years. Hooker's cases were evenly divided between the maxilla and mandible with 13 each. Nine of the 13 cases in the maxilla, and 10 of the 13 in the mandible occurred in the molar area. All cases were associated with an impacted tooth and three cases involved the maxillary sinus. Of Slootweg's cases, 38% were in the maxilla and 62% in the mandible, with 54% occurring in the posterior mandible.

Clinical manifestations of the lesion are often absent. The two most common presenting complaints are swelling and failure to tooth eruption.

Radiographic Features. The ameloblastic fibro-odontoma is almost invariably a well-circumscribed lesion, presenting as an expansile radiolucency generally containing either a solitary radiopaque mass or multiple small opacities representing the odontoma portion of the lesion (Fig. 4-34). Some of the lesions are relatively small when first detected, measuring not over 1–2 cm in diameter, while others may be exceedingly large, involving a considerable portion of the body of the mandible and even extending into the ramus. Occasionally, these lesions will become huge. A case was illustrated by Miller and his associates in their series that showed the calcified mass alone to measure 6 cm by 7 cm and that had produced a terrible facial deformity.

Histologic Features. The lesion consists of the same apparent type of tissue as seen in the ameloblastic fibroma.



A B

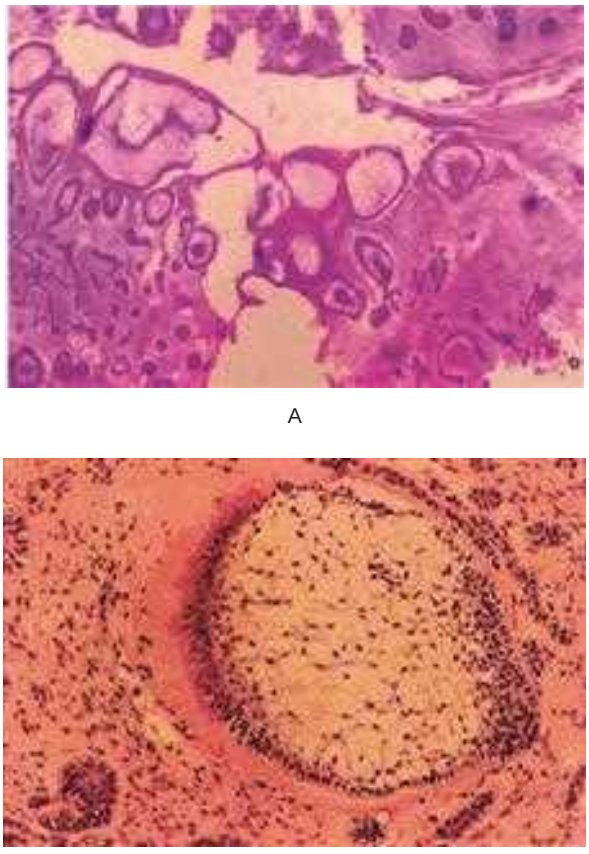
Figure 4-34. Ameloblastic fibro-odontoma.

Thus, cords, fingers, strands and rosettes of primitive odontogenic columnar or cuboidal epithelial cells, often resembling dental lamina, are found. The mesenchymal component is an embryonic fibrous connective tissue with delicate fibrils interspersed by large primitive fibroblasts, all resembling dental papilla. In addition, typical composite odontoma is found (Fig. 4-35 A, B).

Treatment and Prognosis. The ameloblastic fibro-odontoma is treated by curettage, since it does not appear to locally invade bone. There appears to be little tendency for recurrence of the ameloblastic fibro-odontoma. Tsagaris reviewed a total of 77 cases, including Hooker's 26 cases from the Armed Forced Institute of Pathology, and of 29 cases which he was able to follow up, found only one recurrence.

Odontoma

The term 'odontoma', by definition alone, refers to any tumor of odontogenic origin. Through usage, however, it has come to mean a growth in which both the epithelial and the mesenchymal cells exhibit complete differentiation, with the result that functional ameloblasts and odontoblasts form enamel and dentin. This enamel and dentin are usually laid down in an abnormal pattern because the organization of the odontogenic cells fails to reach a normal state of morphodifferentiation. Most authorities accept the view today that the odontoma represents a hamartomatous malformation rather than a neoplasm. This lesion is composed of more than one type of tissue, and for this reason, has been called a composite odontoma. In some composite odontomas the enamel and dentin are laid down in such a fashion that the structures bear considerable anatomic resemblance to normal teeth, except that they are often smaller than typical teeth. They have been termed *compound composite odontomas* when there is at least superficial anatomic similarity to normal teeth. On the other hand, when the calcified dental tissues are simply an irregular mass bearing no morphologic similarity even to rudimentary teeth, the term *complex composite odontoma* is used. The complex form of odontoma is less common than the compound type.



A

B

Figure 4-35. Ameloblastic fibro-odontoma.
(A) Ameloblastic fibro-odontoma exhibiting rudimentary tooth buds (H&E stain, original magnification x10). **(B)** AFO exhibiting dentinoid material around odontogenic epithelial island resembling a developing tooth bud (H&E stain, original magnification x 40) *(Courtesy of Dr DM Cohen)*.

Etiology. The etiology of the odontoma is unknown. It has been suggested that local trauma or infection may lead

to the production of such a lesion. This is entirely possible, but it would appear more likely that in such an event hypoplasia would be the end-result, depending upon the stage of odontogenesis. There is no seeming predilection for occurrence of the odontoma in particular sites of the oral cavity; it does not appear to be associated especially with supernumerary teeth, as might be suggested were it to occur with great frequency between the maxillary central incisors or distal to the maxillary third molar.

It has been suggested by Hitchin that odontomas are either inherited or are due to a mutant gene or interference, possibly postnatal, with the genetic control of tooth development. On the other hand, Levy has reported the experimental production of this lesion in the rat by traumatic injury.

Clinical Features. The odontoma may be discovered at any age in any location of this dental arch, maxillary or mandibular. Budnick has compiled an analysis of 149 cases of odontoma (76 complex and 73 compound) from the literature (65 cases) and from the files of Emory University (84 cases). While it may be discovered at any age, from the very young to the very elderly, he found the mean age of detection to be 14.8 years, with the most prevalent age for diagnosis and treatment being the second decade of life. He also found a slight predilection for occurrence in males (59%) compared with females (41%).

Of all odontomas combined, 67% occurred in the maxilla and 33% in the mandible. The compound odontoma had a predilection, in this study, for the anterior maxilla (61%), whereas only 34% of complex odontomas occurred here. In general, complex odontomas had a predilection for the posterior jaws (59%) and lastly the premolar area (7%). Interestingly, both types of odontomas occurred more frequently on the right side of the jaw than on the left (compound, 62%; complex 68%). The odontoma usually remains small, the diameter of the mass only occasionally greatly exceeding that of a tooth. Occasionally, it does become large and may produce expansion of bone with consequent facial asymmetry. This is particularly true if a dentigerous cyst develops around the odontoma.

Most odontomas are asymptomatic, although occasionally signs and symptoms relating to their presence do occur. These generally consist of unerupted or impacted teeth, retained deciduous teeth, swelling and evidence of infection.

Radiographic Features. The radiographic appearance of the odontoma is characteristic. Since most odontomas are clinically asymptomatic and are discovered by routine radiographic examination, the dentist should be familiar with their appearance. They are often situated between the roots of teeth and appear either as an irregular mass of calcified material surrounded by a narrow radiolucent band with a smooth outer periphery (Fig. 4-36), or as a variable number of tooth like structures with the same peripheral outline. This latter type of odontoma may contain only a few structures resembling teeth, or it may contain several dozen (Fig. 4-36). Both forms of odontoma are frequently associated with unerupted teeth. It is of interest that the majority of odontomas in the anterior segments of the jaws are compound composite in type, while the majority in the posterior areas are complex composite. This latter odontoma may appear also as a calcified mass overlying the crown of an unerupted or impacted tooth. A developing odontoma may be discovered on the routine radiograph and present difficulty in diagnosis because of the lack of calcification (Fig. 4-37).

Histologic Features. The histologic appearance of the odontoma is not spectacular. One finds normal-appearing enamel or enamel matrix, dentin, pulp tissue and cementum which may or may not exhibit a normal relation to one another (Fig. 4-38). If the morphologic resemblance to teeth does exist, the structures are usually single-rooted. The connective tissue capsule around the odontoma is similar in all respects to the follicle surrounding a normal tooth.

One additional interesting feature is the presence of 'ghost' cells in odontomas. These are the same cells described in the calcifying odontogenic cyst (q.v.) and have been reported by Levy to be present in nearly 20% of a series of 43 odontomas which he investigated. This has been substantiated by Sedano and Pindborg, although they could find no significance attached to the presence of these cells regarding prognosis or treatment of the odontoma.

Treatment and Prognosis. The treatment of the odontoma is surgical removal, and there is no expectancy of recurrence. Since both the ameloblastic odontoma and the ameloblastic fibro-odontoma bear great resemblance to the common odontoma, particularly on the radiograph, it is suggested that all odontomas be sent to a qualified oral pathologist for microscopic examination.

Ameloblastic Odontoma
(Odontoameloblastoma)

The ameloblastic odontoma is an odontogenic neoplasm characterized by the simultaneous occurrence of an ameloblastoma and a composite odontoma. As judged by the reported cases reviewed by Frissell and Shafer, it is a rare clinical entity. It should not be inferred that this tumor represents two separate neoplasms growing in unison; there exists, rather, a peculiar proliferation of tissue of the odontogenic apparatus in an unrestrained pattern, including complete morphodifferentiation, as well as apposition and even calcification. The lesion is unusual in that a relatively undifferentiated neoplastic tissue is associated with a highly differentiated tissue, both of which may show recurrence after inadequate removal.

Clinical Features. So few cases of this tumor have been reported that any statistical information may not be valid. However, the ameloblastic odontoma appears to occur at any age, but more frequently in children, and is somewhat more common in the mandible than in the maxilla. It is a slowly expanding lesion of bone which produces considerable facial deformity or asymmetry if left untreated. Since it is a central lesion, considerable destruction of bone occurs. Mild pain may be a presenting complaint, as well as delayed eruption of teeth.

Radiographic Features. Central destruction of bone with expansion of the cortical plates is prominent. The character-

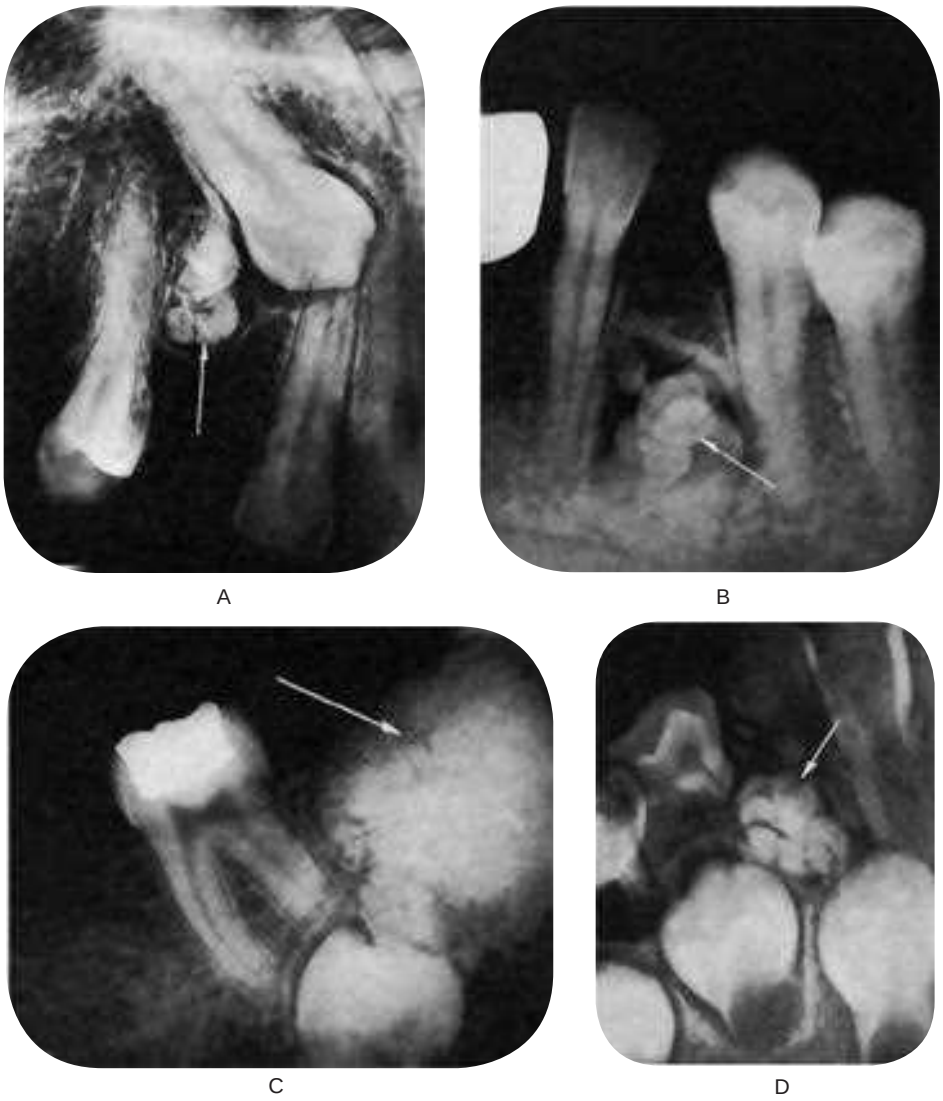


Figure 4-36. Odontoma.
Radiographs **(A)** and **(B)** illustrate two examples of compound composite odontoma, and **(C)** shows an example of a complex composite odontoma. The odontoma may also occur in young children, as seen in radiograph **(D)**. *(C, Courtesy of Dr Wilbur C Moorman).*

istic feature is the presence within the lesion proper of numerous small radiopaque masses which may or may not bear resemblance to formed, albeit miniature, teeth (Fig. 4-39 A). In other instances there is only a single, irregular radiopaque mass of calcified tissue present. Thus the radiographic appearance of the ameloblastic odontoma is identical with that of the composite odontoma of one form or another.

Histologic Features. The microscopic appearance of this tumor is both unusual and characteristic. It consists of a great variety of cells and tissue in a complex distribution, including columnar, squamous and undifferentiated epithelial cells, as well as ameloblasts, enamel and enamel matrix, dentin, osteodentin, dentinoid and osteoid material, stellate reticulum-like tissue, dental papilla, bone and cementum as well as stromal connective tissue (Fig. 4-39 B). Many structures resembling normal or atypical tooth germs may be found, with or without the presence of calcified dental tissues. In addition, an outstanding characteristic is the presence of sheets of typical ameloblastoma of one or another of the recognized types — usually basal cell, follicular or plexiform. Few mitotic figures are present even though the proliferative tendencies of the epithelial cells are obvious.

Treatment and Prognosis. The treatment of the ameloblastic odontoma is controversial, probably because there are few published cases. Some investigators believe that recurrence, associated with continued destruction of tissue, is common after conservative curettage or enucleation and that a more radical approach is necessary. Resection of the jaw, if possible preserving the inferior border of the mandible when this area is uninvolved, will certainly result in a permanent cure. The general behavior of this lesion is the same as that of the ameloblastoma component, and therefore, the same philosophy of management would also apply here as for the ameloblastoma.

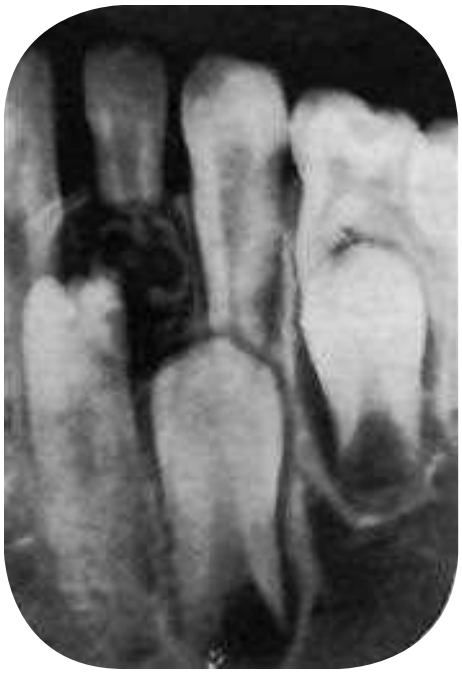
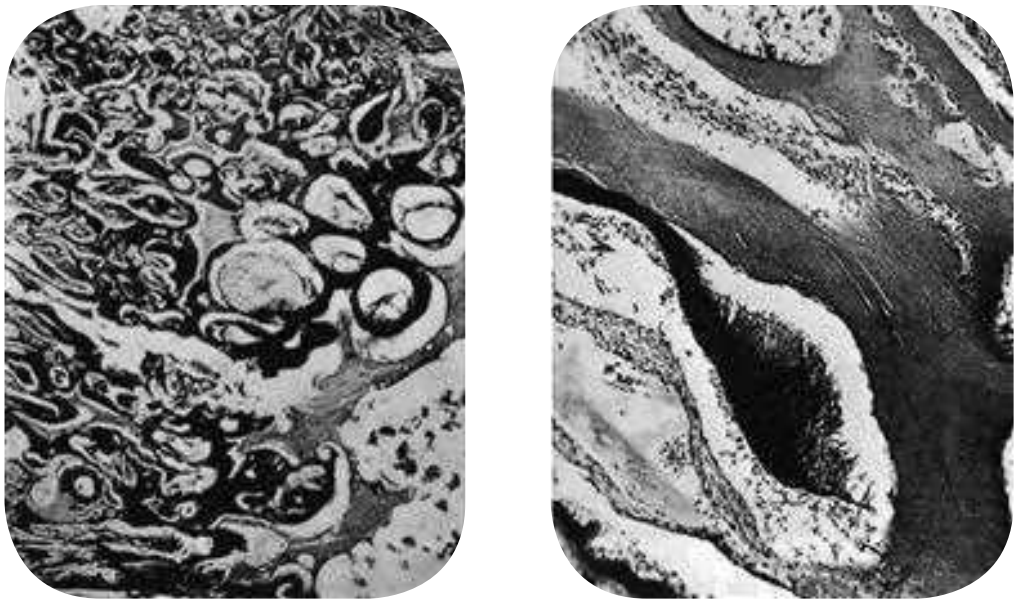


Figure 4-37. Developing odontoma.

Calcifying Odontogenic Cyst and Dentinogenic Ghost Cell Tumor

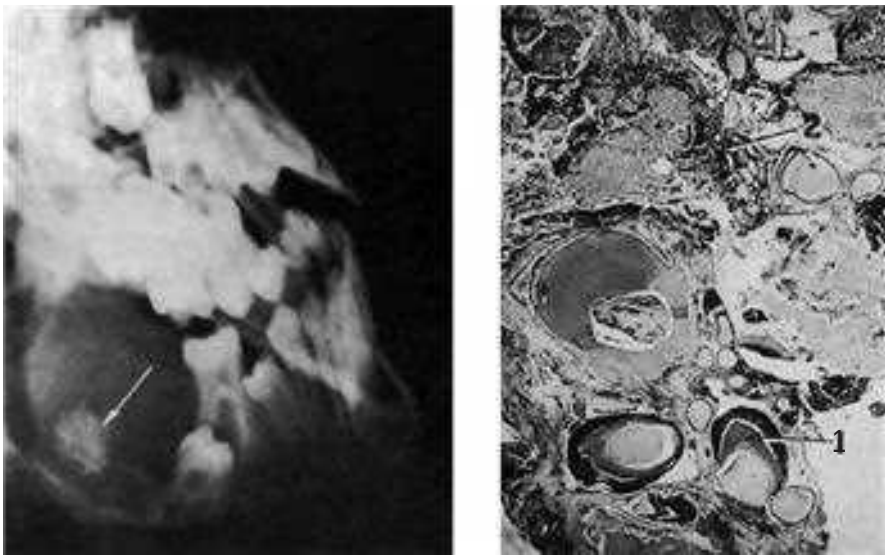
The calcifying odontogenic cyst was first described as a distinct clinicopathologic entity by Gorlin and his colleagues in 1962. Gold (1963) chose a similar, but not identical term for the lesion, namely **'keratinizing and calcifying odontogenic cyst'**. Perhaps the **Gorlin-Gold cyst** would be a fitting term for this interesting odontogenic lesion (Tomich CE, 2004). Kurt Thoma and Henry Goldman considered the lesions to be odontogenic tumors of ectodermal and mesodermal origin. They were not far from being correct. All of the investigators noted the unusual 'ghost cell' keratinization of the odontogenic epithelium which is the striking histologic feature of the entity. Gorlin and his associates suggested that the calcifying odontogenic cyst might be the oral analog of the 'calcifying epithelioma of Malherbe' (now preferably termed a 'pilomatricoma'); a well-recognized lesion of skin. The lesions have in common the peculiar abnormal keratinization of odontogenic and metrical (hair) epithelial cells that is termed 'ghost cell' or 'shadow cell' keratinization. Actually, the calcifying odontogenic cyst shares more histologic features with the rare, intracranial neoplasm known as 'craniopharyngioma.'

As more and more cases were studied, it became apparent that the lesion was not always a cyst; sometimes it was a solid lesion. Furthermore, it became apparent that the lesion could present centrally within the jaws or as an extraosseous gingival lesion. This raises the question: "Is the Gorlin cyst a cyst or is it a tumor that is frequently cystic?" In view of these findings, investigators suggested different names for this lesion. Fejerskov and Krogh suggested the term **'calcifying ghost cell odontogenic tumor'** and Freedman and his associates suggested the name **'cystic calcifying odontogenic tumor'**. Neither of these terms met with approval, possibly because of their similarity to the well-recognized lesion called the 'calcifying epithelial odontogenic tumor' or Pindborg tumor.



A B

Figure 4-38. Odontoma.
The admixture of dental tissues is illustrated in the photographs.



A B

Figure 4-39. Ameloblastic odontoma.
The radiograph **(A)** shows the destructive lesion of the mandible containing numerous small, irregular calcified masses. The photomicrograph **(B)** reveals that these are dental tissue, enamel and dentin (1), in association with an ameloblastoma (2).

The issue of 'cyst versus tumor' or 'cystic versus solid' has not been resolved totally. The calcifying odontogenic cyst can be classified mainly into two type:

- Cystic lesion
- Solid neoplastic lesion.

A third malignant counterpart of the neoplastic lesion may be added.

Clinical Features. The calcifying odontogenic cyst is not a common lesion; the dentinogenic ghost cell tumor is even less common and should be considered rare. Despite the uncommon occurrence of the calcifying odontogenic cyst and the rare dentinogenic ghost cell tumor, the former has gained wide recognition and a large series of cases have been reported in the literature. Although the calcifying odontogenic cyst may be seen in any decade of life, studies have shown predilection for persons in the second and third decades. The cyst occurs in both genders with almost equal frequency. Buchner's extensive review of 215 cases included 110 women and 105 men. The lesion has been seen in many racial groups. Buchner reported that in Asians there was a predilection for the maxilla, whereas in whites there was a 62% predisposition in the mandible.

Radiographic Features. The calcifying odontogenic cyst that occurs centrally in the jaws may present as a painless expansile lesion or it is discovered frequently on routine radiographic examination. The lesions may present as radiolucencies or radiolucencies with foci of opacification, particularly in the case of those that are associated with odontomas. Expansion may be evident in some cases. The dentinogenic ghost cell tumor is known to present as an expansile radiopacity. The lesions that occur peripherally (extraosseous) on the gingiva present as painless swellings or nodules. There are no pathognomonic clinical features that are diagnostic of the lesion.

Histologic Features. The main histopathologic criteria for the diagnosis of the calcifying odontogenic cyst are well established. The cyst lining should show proliferation to the point that it resembles ameloblastoma (i.e. columnar cells over which are stellate and spindled cells in an arrangement that suggest stellate reticulum). Within this proliferation of epithelium, cells undergo the characteristic 'ghost cell' keratinization. The calcifying odontogenic cyst is often encountered in association with an odontoma which may be identified in juxtaposition to the proliferative lining epithelium or intermixed with the ghost cells. This has been called 'dentinoid'. When this material is formed in abundance and the lesion is 'solid' rather than 'cystic', the lesion may be termed a 'dentinogenic ghost cell tumor'. Dystrophic calcification of the ghost cells may be seen; however, it is one of the less common and least important of the histologic features (Fig. 4-40). The presence of ghost cells within the proliferative odontogenic epithelium is the essential characteristic for the diagnosis. The presence of ghost cell keratinization alone is not sufficient enough for the diagnosis nor is it pathognomonic. Ghost cell keratinization may be observed in odontomas, ameloblastomas, ameloblastic fibro-odontomas, and in ameloblastic odontomas. Thus, one must observe ghost cells to make the diagnosis of the Gorlin cyst (Fig. 4-41).

The ghost cells contained nuclear remnants, remnants of cytoplasmic organelles, and numerous tonofilaments. The ghost cells differ from normal keratotic squames in that they are larger, often vacuolated, and the remnants of the nuclear membranes are more prominent. This may be due to intracellular edema and the presence of dilated degenerated membranous organelles.

Although Gorlin and his coworkers suggested that the calcifying odontogenic cyst is the oral counterpart of the

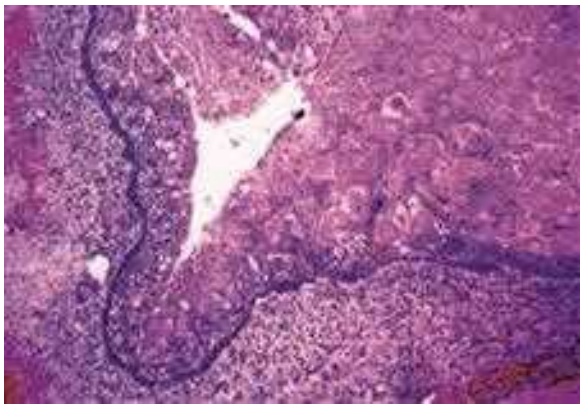


Figure 4-40. Calcifying odontogenic cyst.
This calcifying odontogenic cyst shows the proliferation of the lining epithelium with palisaded, hyperchromatic columnar nuclei, stellate reticulum like area, and sheets of ghost cells (100x H&E stain) *(Courtesy of Dr CE Tomich)*.

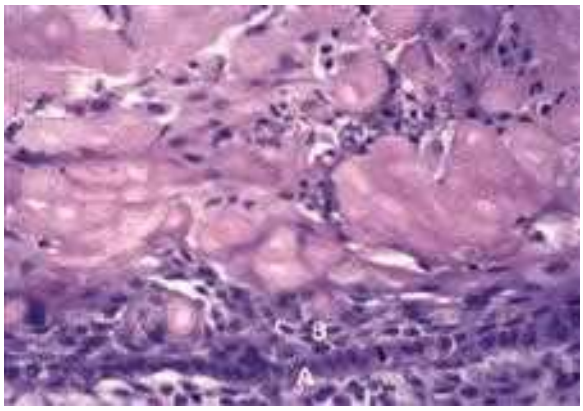


Figure 4-41. Dentinogenic ghost cell tumor.
Aggregates of ghost cells are seen in association with odontogenic epithelium. Low columnar cells (A) and spindle cells (B) are seen in association with groups of ghost cells (45 X, H&E stain) *(Courtesy of Dr CE Tomich)*.

cutaneous calcifying epithelioma of Malherbe (pilomatricoma), it is more likely to be the oral counterpart of the intracranial craniopharyngioma due to immunologic similarity. Both lesions demonstrated similar immunoreactivity to low and high molecular weight cytokeratins and involucrin—a protein that is characteristic of terminally-differentiated keratinocytes.

Treatment and Prognosis. The calcifying odontogenic cyst, with or without an associated odontoma, can be treated successfully by enucleation or thorough curettage. Peripheral lesions should be treated by conservative excision. The central (intraosseous) dentinogenic ghost cell tumor is treated by surgical excision. The removal of the tumor may require block excision or segmental resection, depending upon its size or anatomic extent. Recurrence following conservative treatment has been reported.

A rare malignant counterpart is recognized which was first reported in the Spanish language literature in 1965 by Astacio and Martinez. This tumor has been known by a variety of terms, including **malignant calcifying odontogenic cyst, odontogenic ghost cell carcinoma**, and **aggressive epithelial ghost cell odontogenic tumor**, to name a few. The designation **odontogenic ghost cell carcinoma** seems to be descriptive and specific. These tumors are unusual and rare lesions which develop in previously diagnosed calcifying odontogenic cysts or as de novo tumors. They are capable of locally aggressive behavior as well as distant metastasis.

ODONTOGENIC ECTOMESENCHYME WITH OR WITHOUT INCLUDED ODONTOGENIC EPITHELIUM

Peripheral Odontogenic Fibroma

There are a variety of different types of focal proliferative lesions which may occur on the gingiva, some neoplastic but others inflammatory, including such entities as the peripheral giant cell granuloma, pyogenic granuloma, giant cell fibroma, the simple fibroma, and the peripheral ossifying fibroma (q.v.). At one time, the terms 'peripheral ossifying fibroma' and 'peripheral odontogenic fibroma' were used quite interchangeably for one of these lesions. However, WHO, in its classification of odontogenic tumors, has used the term 'peripheral odontogenic fibroma' for a specific entity, quite separate from the peripheral ossifying fibroma, and designated specifically in the past also as an 'odontogenic gingival epithelial hamartoma' by Baden and his coworkers and as a 'peripheral ameloblastic fibrodentinoma' by numerous oral pathologists such as McKelvy and Cherrick.

The peripheral ossifying fibroma has been separated here from the peripheral odontogenic fibroma and is discussed in Chapter 2 in the Benign Connective Tissue Tumors section. The peripheral odontogenic fibroma, sometimes characterized as the 'WHO type', is considered here as an odontogenic tumor. An attempt at clarifying the distinction between these two conditions has been published recently by Gardner.

Clinical Features. The peripheral odontogenic fibroma, in distinct contrast to the peripheral ossifying fibroma, is a rare lesion. The largest series of cases reported has been that of Farman, who found only five cases in an extensive review of the English-language literature and added 10 new cases. There was no gender predilection in the 15 reported cases, while the ages of the patients ranged from five to 65 years, spaced throughout the various decades. There did seem to be a predilection for occurrence in the mandible, which was the site of 11 cases compared with only four cases in the maxilla.

The lesions appear to be slow growing, often present for a number of years. They are generally described as a solid, firmly attached gingival mass, sometimes arising, between teeth and sometimes displacing teeth (Fig. 4-42 A). Some lesions are found to contain a calcified stalk at the time of surgery and this, or other islands of calcified material, may be seen as radiopaque flecks on the radiograph.

Histologic Features. The peripheral odontogenic fibroma consists of a markedly cellular fibrous connective tissue

parenchyma, not the usual bland, acellular collagenous stroma of many tumors, with non-neoplastic islands, strands and cords of columnar or cuboidal, sometimes vacuolated odontogenic epithelium ranging from scanty to numerous. When numerous, the peripheral odontogenic fibroma has been occasionally mistaken for an epithelial neoplasm such as a peripheral ameloblastoma (Fig. 4-42B–E). This epithelium is usually deep in the lesion, away from the surface epithelium and is sometimes found 'cuffing' calcifications. Calcified tissue may or may not be present in the peripheral odontogenic fibroma. If found, it may resemble trabeculae of bone or osteoid, dentin or osteodentin (sometimes described as dysplastic dentin), or cementum like material. Mature fibrous connective tissue stroma is present and is sometimes highly vascularized, particularly in the less cellular areas. Myxomatous changes may also be found in the stroma, and the presence of inflammation is variable.

Treatment. The lesion is treated by surgical excision. In the series reported by Farman, no lesion was known to recur.

Central Odontogenic Fibroma

The odontogenic fibroma is a central tumor of the jaws which is seen so infrequently that little is known about this neoplasm. Of all the odontogenic tumors, this lesion has the most poorly defined parameters. The major explanation for the uncertainty regarding this tumor, as discussed by Gardner in his attempt at unification of the concept of the central odontogenic fibroma, is the lack of unanimity of definition of the lesion.

Three basic concepts have existed concerning this tumor:

- It is a lesion around the crown of an unerupted tooth resembling a small dentigerous cyst, although most investigators regard this as simply a hyperplastic dental follicle and not an odontogenic tumor.
- It is a lesion of fibrous connective tissue, with scattered islands of odontogenic epithelium, bearing some resemblance to the dental follicle but because of the size which it may attain appearing to constitute a neoplasm.
- It is a lesion which has been described by WHO as a fibroblastic neoplasm containing varying amounts of odontogenic epithelium, and in some cases, calcified material resembling

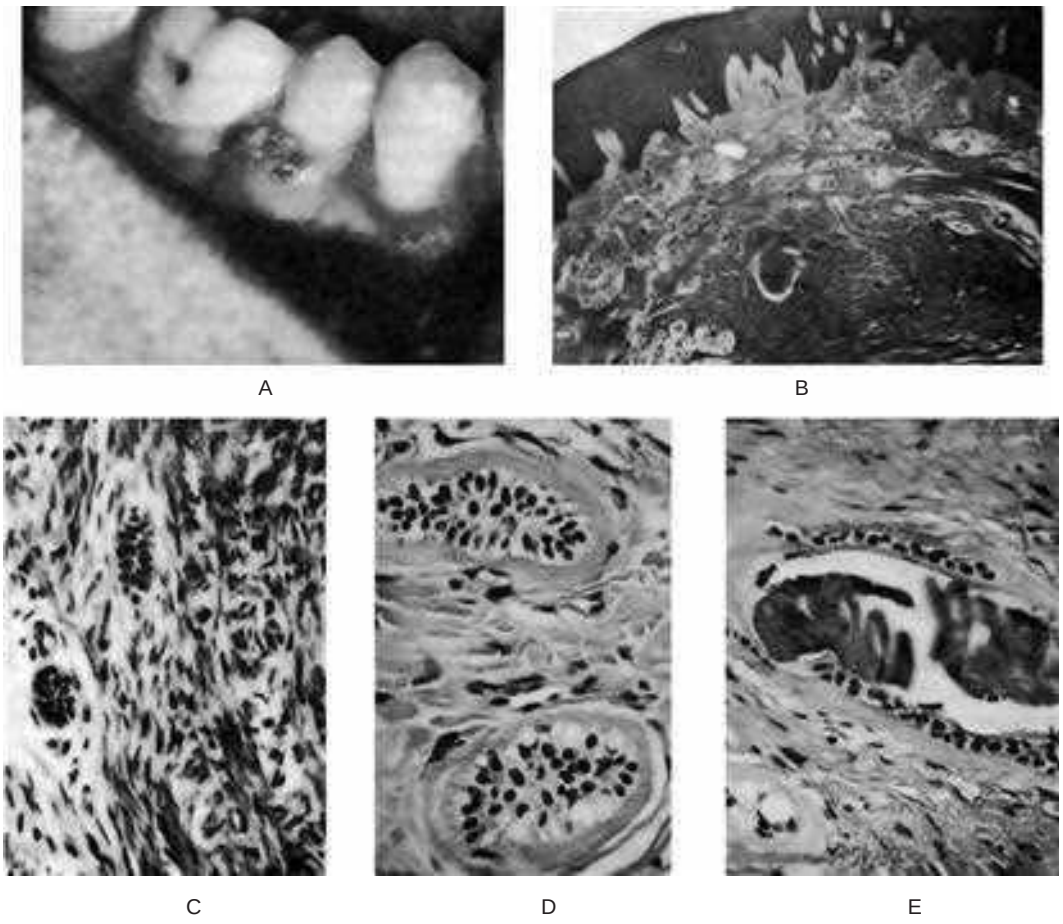


Figure 4-42. Peripheral odontogenic fibroma.
The mass on the gingiva **(A)** is characterized histologically by a cellular connective tissue containing islands of odontogenic epithelial cells, some of which show a clear vacuolated cytoplasm, and few foci of calcifications **(B, C, D, E)**. *(A, Courtesy of Dr Richard Henry; D and E, Courtesy of Dr Howard Goldstein).*

dysplastic dentin or cementum like material; thus, except for location, it is histologically identical to the peripheral odontogenic fibroma as described by the WHO group.

Since the occurrence of the latter two lesions in the jaws is undeniable even though their histogenesis is uncertain, Gardner has suggested referring to the tumor made up of connective tissue and odontogenic islands resembling dental follicle as the **simple central odontogenic fibroma** and to the tumor described by the WHO as the **WHO-type central odontogenic fibroma**. Until more cases of each are reported to clarify their histogenesis and their relationship, if any, this approach appears reasonable.

The simple central odontogenic fibroma has been discussed by Wesley and his associates, who reviewed eight cases, including one of their own, which they believed met the histologic criteria for this form of the lesion, while Dahl and her associates have added two more cases. Farman has reviewed eight cases of the WHO type of central odontogenic fibroma from the literature in his paper dealing basically with the peripheral form of this neoplasm. Thus, it may be seen that too few examples of either type of central odontogenic fibroma have been reported from which one may draw any significant conclusions regarding specific clinical features, treatment or prognosis.

Clinical Features. The odontogenic fibroma appears to occur more frequently in children and young adults, although a few cases have been reported in older persons, and has a predilection for occurrence in the mandible. It is generally asymptomatic except for swelling of the jaw.

Radiographic Features. This tumor sometimes produces an expansile, multilocular radiolucency similar to that of the ameloblastoma (Fig. 4-43 A).

Histologic Features. The odontogenic fibroma of both types has been described above. The **simple type** is characterized by a tumor mass made up of mature collagen fibers interspersed usually by many plump fibroblasts that are very uniform in their placement and tend to be equidistant from each other. Small nests or islands of odontogenic epithelium that appear entirely inactive are present in variable but usually in quite minimal amounts (Fig. 4-43 B).

The **WHO type** also consists of relatively mature but quite cellular fibrous connective tissue with few to many islands of odontogenic epithelium. Osteoid, dysplastic dentin or cementum like material is also variably present.

Care must be exercised not to misdiagnose other fibrous lesions of the jaws as an odontogenic fibroma. Lesions to be considered in the differential diagnosis include neurofibroma and desmoplastic fibroma.

Treatment and Prognosis. The treatment of this neoplasm is surgical excision. Little is known about recurrence.

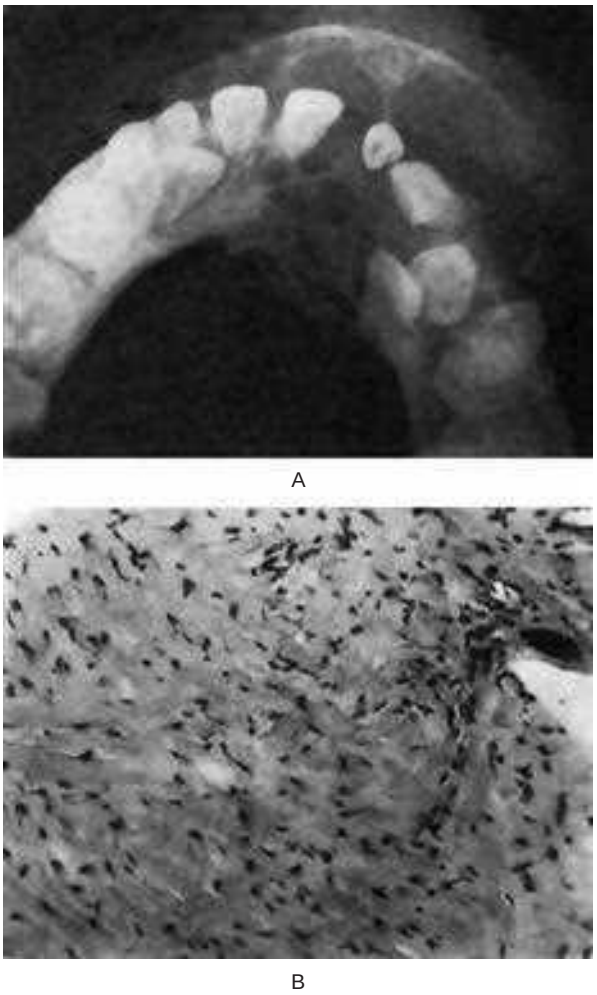


Figure 4-43. Central odontogenic fibroma.
The radiograph **(A)** exhibits expansion of the mandible with thinning of the cortical plates. The radiographic appearance is suggestive of ameloblastoma. The photomicrograph **(B)** shows the bundles of collagen fibers and an epithelial rest *(Courtesy of Dr Charles A Waldron).*

Odontogenic Myxoma
(Odontogenic fibromyxoma or myxofibroma)

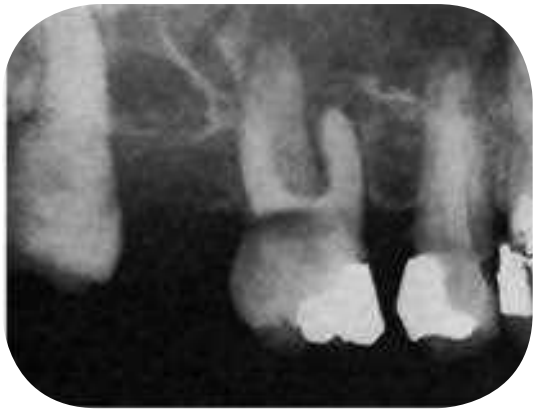
The odontogenic myxoma is a tumor of the jaws which apparently arises from the mesenchymal portion of the tooth germ, either the dental papilla, the follicle or the periodontal ligament. Previous reports of this tumor have been discussed by many investigators, most recently White and his colleagues, who summarized pertinent data on over 90 individual and series of cases of odontogenic myxoma of the jaws, including their own group of nine cases. Absolute proof of origin from the odontogenic apparatus is lacking for this lesion, but it appears most likely because of the frequent occurrence of this lesion in the jaws and almost universal absence in any other bone of the skeleton. For example, in a study by McClure and Dahlin of 6,000 cases of bone tumors at the Mayo Clinic up to 1976, no cases involving bones other than the jaws were found.

Clinical Features. The odontogenic myxoma occurs most frequently in the second or third decade of life, the average age in the various reported series ranging from 23–30 years. It rarely occurs before the age of 10 years or after the age of 50. There is no particular gender predilection in the

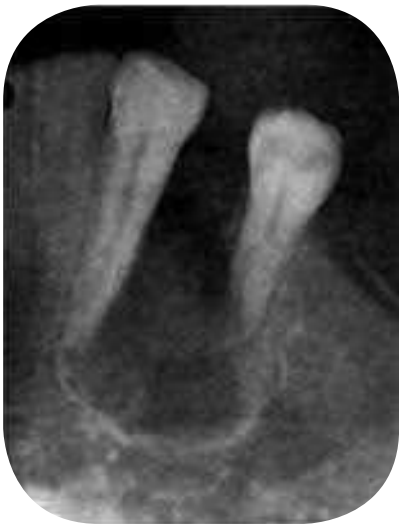
occurrence of this tumor, and there is a slight predilection for occurrence in the mandible. Occasional cases occur outside the tooth-bearing areas, several cases having been reported in the condyle or neck of the condyle. In the series reported by Thoma and Goldman, nearly every case was associated with missing or embedded teeth. However, in many instances this is not the case.

The odontogenic myxoma is a central lesion of the jaws which expands the bone and may cause destruction of the cortex. It is not a rapidly growing lesion, and pain may or may not be a feature.

Radiographic Features. The radiograph may present a mottled or honeycombed appearance of bone in some cases, while others may appear as a destructive, expanding radiolucency which sometimes has a multilocular pattern (Fig. 4-44 A, B). Displacement of teeth by the tumor mass is a relatively common finding, but root resorption is less frequent. The tumor is often extensive before being discovered. Invasion of the antrum occurs frequently in lesions of the maxilla.



A



B

Figure 4-44. Odontogenic myxoma.
(Courtesy of Dr Paul and Dr Emmett Jurgens).

Figure 4-45. Odontogenic myxoma.
High-power view of randomly arranged, spindle-shaped, stellate, and rounded cells in a loose myxoid stroma (hematoxylin and eosin, original magnification x10) *(Courtesy of Dr RB Brannon).*

Histologic Features. The myxoma is made up of loosely arranged, spindle-shaped and stellate cells, many of which have long fibrillar processes that tend to intermesh. The loose tissue is not highly cellular, and those cells present do not show evidence of significant activity (pleomorphism, prominent nucleoli or mitotic figures). The intercellular substance is mucoid. The tumor is usually interspersed with a variable number of tiny capillaries and occasionally strands of collagen. Nests of odontogenic epithelium may be found infrequently (Fig. 4-45).

Hodson and Prout have reported the presence of two acid mucopolysaccharides in the odontogenic myxoma: relatively large quantities of hyaluronic acid and lesser amounts of chondroitin sulfate. They have suggested that this high hyaluronic acid component may be a significant factor in the neoplastic behavior of the tumor.

Histochemical studies by Mori and his associates have shown that the tumor cells with long anastomosing processes in the odontogenic myxoma exhibited high alkaline phosphatase and lactate dehydrogenase activity, while there was low acid phosphatase, glucose-6-phosphate dehydrogenase and isocitrate dehydrogenase activity. These enzymatic reactions differed from those present in osteogenic sarcomas or even benign proliferating fibrous lesions such as osteogenic fibroma or a fracture callus. This suggested to the investigators that the tumor cells of the myxoma are not as biologically active as other tumors of the jaws.

Ultrastructural studies have also been reported by several investigators. White and his associates described 'pale' cells which probably represented active secretory cells, the 'secretion' actually representing transportation of synthesized material though to be nonsulfated mucopolysaccharide, the myxoid material, into the intercellular compartment. The other cell type, the 'dark' cell, contained collagen fibrils, and this suggested a disturbance in the secretory process of collagen molecules so that they became crystallized into fibrils intracellularly.

The ultrastructural studies of Goldblatt have also led him to conclude that the myxoma cell is not a typical fibroblast, that there is an attempt at collagen fibrillogenesis with little ultimate success and that prominent secretory activity within tumor cells appears to result in excess production of acid mucopolysaccharide matrix. He also pointed out that, according to other investigators, there may be actual phagocytosis by tumor cells of the small amount of collagen present. Finally, he concluded that, while the myxoma cells showed many characteristics of fibroblasts of the odontogenic apparatus, tumor origin from nonodontogenic mesenchyme cannot be ruled out by existing ultrastructural studies.

Care must be used in distinguishing the odontogenic myxoma histologically from a variety of other myxoid lesions, including myxoid neurofibroma, myxoid liposarcoma, and myxoid chondrosarcoma.

Treatment and Prognosis. The treatment of odontogenic myxomas is surgical excision, followed by cautery. Extensive lesions may require resection to eradicate the tumor. Although this is a benign neoplasm, it frequently exhibits insidious local invasion, making its complete removal difficult, a problem augmented by the loose, gelatinous nature of the tissue itself. The prognosis is good despite unpredictable recurrence. The tumor is not sensitive to X-ray radiation.

A frankly malignant form of this tumor, an odontogenic myxosarcoma, is known but is exceedingly rare.

Cementoblastoma
(Benign cementoblastoma, true cementoma)

Refer section on Bone Tumors

MALIGNANT ODONTOGENIC TUMORS

Odontogenic malignancies are very uncommon tumors. Presently the diagnosis of odontogenic malignancies is based on clinicoradiographic findings and subjective histopathologic evaluation. To be regarded as 'odontogenic', the tumor must arise in the gingiva or jaws (Table 4-3).

Table 4-3: Classification: Odontogenic malignancies

Odontogenic carcinomas
1. Metastasizing ameloblastoma
2. Ameloblastic carcinoma (a) Carcinoma ex ameloblastoma (b) De novo
3. Primary intraosseous carcinoma (a) Solid (b) Cystic (ex odontogenic cyst) (c) Central mucoepidermoid carcinoma
4. Ghost cell odontogenic carcinoma
5. Clear cell odontogenic carcinoma
Odontogenic sarcoma
1. Ameloblastic fibrosarcoma

Source: LJ Slater, Oral Maxfac Clin N Am, 16: 409-24, 2004.

ODONTOGENIC CARCINOMAS

Metastasizing Ameloblastoma

Traditionally, ameloblastoma has been regarded as a benign tumor that can be locally aggressive but occasionally can metastasize and kill the patient. The prospect that all ameloblastomas could represent low-grade malignant neoplasms deserves consideration. The term 'metastasizing ameloblastoma' is used to describe a tumor that shows histologic features of classic ameloblastoma in the gingiva or jaw and has metastatic deposits elsewhere.

Clinical Features. Typically, the primary ameloblastoma arises in the mandible of a young adult. The average age at presentation is 30 years, but 33% of patients are younger than 20 years of age. After a mean interval of approximately 11 years, metastatic nodules develop in the lung (80%), cervical lymph nodes (15%), or extragnathic bones. Typically, the pulmonary metastases are multifocal and involve both lungs. The median survival after discovery of the metastatic lesion is about two years. Innocuous lung 'granulomas' that are seen on routine chest films of a patient who has ameloblastoma can prove to be silent metastases. Kunze et al (1985) noted that most patients had multiple recurrences of the jaw ameloblastoma. The multiple recurrences could result from an intrinsically more aggressive tumor or from surgery-associated tumor 'spillage' into adjacent tissue or tumor embolization into lymphatic or blood vessels. The primary ameloblastoma can become locally aggressive (with parapharyngeal and cranial base invasion) before pulmonary metastases arise.

Histologic Features. Ameloblastoma with metastatic potential is histologically indistinguishable from conventional ameloblastoma. The metastatic ameloblastoma usually does not show any greater cytologic atypia or mitotic activity than that seen in the primary. Metastasizing ameloblastoma, ambiguously termed 'malignant ameloblastoma', clearly demonstrates the biologic behavior of a well-differentiated low-grade carcinoma.

Treatment. Metastatic ameloblastoma is managed best by surgery, but there is no evidence that it improves survival. Cervical lymph node metastases are managed by neck dissection. If adequate pulmonary function can be preserved, lung metastases can be excised by lobectomy. At surgery, more numerous pulmonary metastatic deposits are often identified than were apparent in diagnostic imaging studies. Generally, chemotherapy has been ineffective, but a short-term partial response is possible.

Ameloblastic Carcinoma

Ameloblastic carcinoma is a malignant epithelial proliferation that is associated with an ameloblastoma (carcinoma exameloblastoma) or histologically resembles an ameloblastoma (de novo ameloblastic carcinoma). Ameloblastic carcinoma subjectively demonstrates greater cytologic atypia and mitotic activity than ameloblastoma. Some ameloblastomas exhibit

basilar hyperplasia and an increased mitotic index. These findings might warrant a designation of 'atypical ameloblastoma' or 'proliferative ameloblastoma', but they are probably insufficient to permit a diagnosis of ameloblastic carcinoma in the absence of nuclear pleomorphism, perineural invasion, or other histologic evidence of malignancy.

Ameloblastic carcinoma is an aggressive neoplasm that is locally invasive and can spread to regional lymph nodes or distant sites, such as lung and bones. Usually, ameloblastic carcinoma is managed as a squamous cell carcinoma with attempted complete surgical excision, elective or therapeutic neck dissection, and postoperative radiation therapy. The prognosis is poor.

Carcinoma ex Ameloblastoma. A carcinoma directly contiguous with an ameloblastoma is appropriately termed a 'carcinoma arising from an ameloblastoma' (carcinoma ex ameloblastoma, carcinoma in ameloblastoma) (Fig. 4-46). The carcinoma arises when an ameloblastoma undergoes 'dedifferentiation' (i.e. when a less-differentiated proliferative clone arises within an ameloblastoma). This aggressive clone overgrows the ameloblastoma and becomes the dominant component. A follicular or plexiform ameloblastoma blends through a narrow transition zone with a hypercellular poorly differentiated carcinoma that demonstrates sheets of disordered mitotically active small basaloid cells with hyperchromatic nuclei, larger squamoid or polygonal cells with pale vesicular nuclei or elongated spindled epithelial cells. The carcinomatous cells show mild to moderate nuclear pleomorphism. A low-grade spindled ameloblastic carcinoma also has been described, in which ameloblastomatous epithelium is associated with hypercellular stroma that displays elongated fibroblastic cells that show little cytologic atypia and scattered mitotic figures; the 'fibroblastic cells' display immunoreactivity for cytokeratin (Slater LJ, 2004). Hamakawa et al (2000) reported a squamous cell carcinoma that arose adjacent to an ameloblastoma with no apparent transition between the two components. They interpreted it as a probable **collision tumor,** two separate primary tumors—a squamous cell carcinoma of gingival or odontogenic epithelial origin that abutted a conventional ameloblastoma.

De novo Ameloblastic Carcinoma. If a carcinoma lacks a component of conventional ameloblastoma, its unequivocal categorization as an ameloblastic carcinoma is considerably less secure (Fig. 4-47). The diagnosis of de novo ameloblastic carcinoma is based on subjective interpretation. The tumor should demonstrate vague ameloblastomatous features: a plexiform architecture that exhibits budding and anastomosing epithelial processes with peripheral palisaded cuboidal to columnar cells and central polygonal to angular cells. Tumors that lack evidence of reverse polarization, the so-called 'Vickers-Gorlin' changes that are indicative of ameloblastic differentiation, can be accepted as examples of de novo ameloblastic carcinoma; the stringent criterion of reverse polarity has not been required.

The possibility of a variant of squamous cell carcinoma that shows peripheral palisaded cells should be considered before a diagnosis of ameloblastic carcinoma is rendered. But the distinction is of academic interest only, because squamous cell carcinoma and ameloblastic carcinoma are treated the same way.

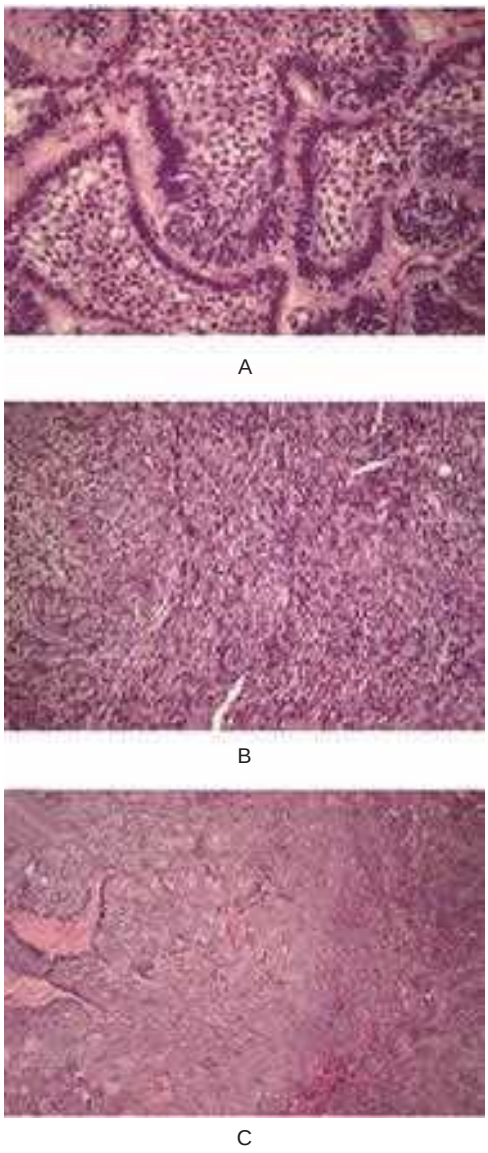


Figure 4-46. Carcinoma ex ameloblastoma.
(A) A 66-year-old woman who had a maxillary ameloblastoma that involved antrum; the ameloblastoma shows little cytologic atypia. **(B)** Pale islands and sheets of ameloblastoma (left and center) merge with dark sheets of spindled carcinoma cells (right). **(C)** Sheets of sarcomatoid spindled carcinoma cells at higher magnification *(Courtesy of Dr LJ Slater (Reprinted from Oral and Maxfac Surg Clin N Am 16: 411, 2004 with permission).*

Primary Intraosseous Carcinoma. Primary intraosseous carcinoma (PIOC) is a squamous cell carcinoma that occurs in the jaw bone. It is called 'primary' because it is not a secondary deposit; metastasis from a distant primary to the jaw must be excluded. It is termed 'intraosseous' because it develops centrally within bone; origin from surface stratified squamous or sinonasal epithelium must be ruled out. It lacks evidence of ameloblastic differentiation, otherwise it would be classified as a de novo ameloblastic carcinoma. If the intraosseous

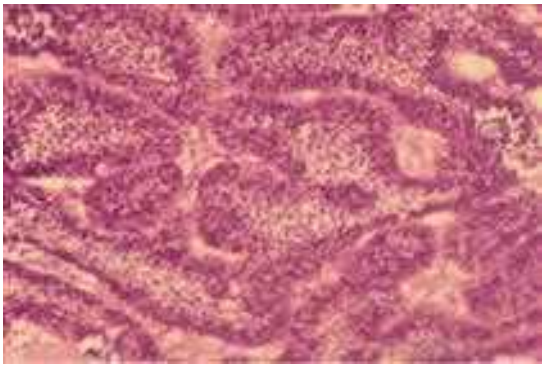


Figure 4-47. Ameloblastic carcinoma.
Budding and anastomosing epithelial trabecula that demonstrate peripheral palisaded tall cells, basilar hyperplasia (expansion of the proliferative compartment), and moderate nuclear pleomorphism; the central pale zones resemble stellate reticulum. It has the architecture of an ameloblastoma and sufficient cytologic atypia to warrant a diagnosis of carcinoma.

carcinoma demonstrates mucous cells, then a diagnosis of central mucoepidermoid carcinoma is appropriate.

Primary intraosseous carcinoma presents clinically as a diffuse enlargement of the jaw; if mucosal ulceration or mucosal tumefaction is present, the diagnosis of PIOC should be questioned. PIOC epithelium can become confluent with gingival surface stratified squamous epithelium after erosion of bone. Such confluence does not indicate necessarily that the carcinoma is of gingival origin if the tumor's overall growth pattern suggests an intraosseous origin. CT images can be useful in assessing whether a putative PIOC could have originated from a gingival squamous cell carcinoma, as well as buccal and lingual cortical destruction and trismus-inducing invasion of the masticator space before involving surface oral mucosa.

Primary intraosseous carcinoma is believed to arise from central odontogenic epithelium, but in rare cases, origin from incisive canal epithelium has been proposed. Cervical metastases have been identified synchronously or metachronously with a PIOC.

Solid Primary Intraosseous Carcinoma. Thomas et al, thoroughly reviewed the clinicoradiographic attributes of this rare tumor. The typical solid PIOC presents as a painful mass in the posterior mandible. Although the mean age at presentation is 52 years, 20% of patients are younger than 34 years and 39% are older than 65 years. Clinically, patients may present with pain, swelling and paresthesia.

Radiographically, 42% of patients demonstrate a cup-shaped radiolucent lesion, 26% demonstrate a poorly-circumscribed 'moth eaten' radiolucency, and 10% exhibit a well-circumscribed radiolucency. At presentation, 31% of patients have evidence of cervical metastases; however, the survival rate of patients who have regional metastases is apparently no worse than those who do not.

Most often, the tumor is treated by surgical excision and postoperative radiation therapy. Most deaths occur within two years of therapy. The overall five-year survival rate is 38%.

Cystic Primary Intraosseous Carcinoma. Cystic PIOC (PIOC arising in an odontogenic cyst, PIOC ex odontogenic cyst) is squamous cell carcinoma that demonstrates a cystic component with a lumen that contains fluid or keratin and a lining of stratified squamous epithelium that exhibits cytologic atypia (intraepithelial neoplasia, epithelial dysplasia). If the cystic component lacks cytologic atypia, the possibilities of a gingival carcinoma that eroded bone and collided with an odontogenic cyst or of a PIOC that arose adjacent to a benign cyst might be considered.

Intraosseous carcinomas that show a cystic and a solid component can mimic an odontogenic cyst radiographically.

Squamous cell carcinoma can exhibit a predominantly cystic architecture. The theoretic possibility of a squamous cell carcinoma metastasizing to the jaw as a cystic lesion, has not been reported.

Carcinoma ex Dentigerous Cyst. The most common odontogenic cyst to show carcinomatous changes is the dentigerous cyst. Intraepithelial neoplasia that involves sulcular gingival epithelium can mimic carcinoma ex dentigerous cyst histologically. It typically presents as an asymptomatic or painful pericoronal radiolucent lesion that is associated with an impacted mandibular third molar. The mean age of occurrence is 59 years with male predominance. Some lesions can cause osseous destruction. Most carcinomas that arise in dentigerous cysts occur in the mandibular molar area; occasionally they are associated with impacted canine teeth.

Histologically, the lesions demonstrate membranous connective tissue that is lined by stratified squamous epithelium that exhibits evidence of intraepithelial neoplasia (epithelial dysplasia) and is associated with an invasive well-differentiated or moderately-differentiated squamous cell carcinoma. The lining epithelium is derived from dental follicular epithelium or gingival sulcular epithelium (if the tooth is partially erupted).

Usually, the carcinoma is treated by surgical resection.

Carcinoma ex Odontogenic Keratocyst. Makowski et al (2001) identified 15 previously reported cases of squamous cell carcinoma that arose in an odontogenic keratocyst (OKC). In most cases, radiographic findings are those of a benign OKC.

In the maxilla, OKC lining epithelium can fuse with buccal vestibular surface stratified squamous epithelium to form a chronic sinus tract that drains pus-like keratinaceous material; this 'automarsupialized' cyst develops thickened nonkeratinized lining epithelium that is similar to that seen in a surgically decompressed OKC. PIOC that arises in a cyst that is lined by dysplastic thickened parakeratinized stratified squamous epithelium that lacks convincing features of classic OKC or orthokeratinized odontogenic cyst cannot be classified assuredly as carcinoma ex OKC.

Usually, the carcinomas have been treated by resection and postoperative radiation therapy, and infrequently with chemotherapy.

Intraosseous Mucoepidermoid Carcinoma. Intraosseous mucoepidermoid carcinoma (central mucoepidermoid carcinoma, PIOC with mucous cells) arises from odontogenic

epithelium or an odontogenic cyst. It represents a cystic primary intraosseous carcinoma that shows squamous differentiation and mucous cells. If a rare central mucoepidermoid carcinoma arises from ectopic salivary gland tissue that was enclaved within the mandible during development, it would be classified as a primary intraosseous carcinoma. A low-grade mucoepidermoid carcinoma that presents as a retromolar mucosal mass with an underlying broad 'cupped-out' radiolucency of the mandible may represent a conventional mucoepidermoid carcinoma derived from retromolar salivary glands that has secondarily eroded the mandible. With this presentation, a diagnosis of 'central mucoepidermoid carcinoma' should be questioned because central tumors do not present as mucosal masses. Some apparent maxillary intraosseous mucoepidermoid carcinomas probably arise from seromucous glands that are associated with sinonasal mucosa. Most tumors are low-grade cystic lesions that grow in a broad 'pushing' front and demonstrate a well-circumscribed unilocular or multilocular radiolucent lesion (Fig. 4-48). As for all neoplasms, the prognosis depends on the extent of disease (clinical stage) and the histologic grade of the tumor. High-grade tumors display a destructive permeative growth pattern and have metastatic potential. Typical low-grade tumors have a favorable prognosis. Death eventuates from uncontrolled local disease rather than from metastases (Slater LJ, 2004).

Varying surgical treatments have been used, including: curettage, partial resection, en bloc resection, and hemimandibulectomy. In several cases, curettage resulted in no evidence of disease after a follow-up period of 3–19 years.

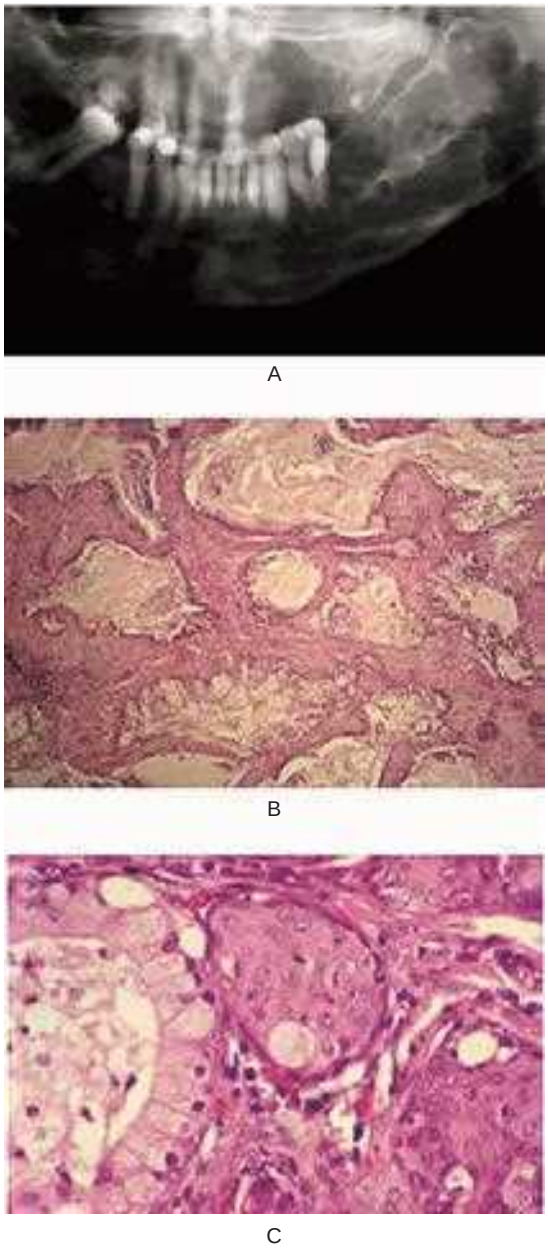


Figure 4-48. Central low-grade mucoepidermoid carcinoma.
(A) A 36-year-old woman had a painful expansile lesion of the left posterior mandible; radiographically, a multiloculated radiolucency is observed. **(B)** Multiple adjacent cystic structures contain mucus and are lined by epithelium that demonstrates numerous mucous cells. **(C)** At higher magnification, a cystic space is lined by mucous cells (left) and mural islands of epidermoid cells (center and right) are seen *(Courtesy of Dr LJ Slater) (Reprinted from Oral Maxfac Surg Clin N Am 16: 415, 2004 with permission).*

Ghost Cell Odontogenic Carcinoma

(Odontogenic ghost cell carcinoma, malignant epithelial odontogenic ghost cell tumor, aggressive [malignant] epithelial odontogenic ghost cell tumor, dentinogenic ghost cell tumor)

Ghost cell odontogenic carcinoma is an ameloblastic carcinoma that shows evidence of ghost cell keratinization. As such, it can be considered to be a variant of ameloblastic carcinoma. The biologic behavior of the lesion cannot be predicted from the presence of ghost cells. The tissue that surrounds the ghost cells gives the prognosis. For example, if a benign cyst contains ghost cells, its biologic behavior is that of a benign cyst; if an ameloblastoma contains ghost cells, its biologic behavior is that of an ameloblastoma; and if a carcinoma contains ghost cells, its biologic behavior is that of a carcinoma (Fukushima M, 1983).

Ghost cells are immunoreactive for amelogenin, a protein that is unique to enamel matrix; therefore, the presence of ghost cells in jaw tumors represents evidence of ameloblastic differentiation. As with all primary intraosseous carcinomas, the possibility of a metastasis should be excluded; carcinomas that demonstrate ghost cells include cutaneous pilomatrix carcinoma and visceral carcinomas.

The mean age at presentation was 38 years, but the age range was from 13–72 years; 75% arose in men. About 66% of cases occur in the maxilla. Ghost cell odontogenic carcinoma seems to be disproportionately more frequent in Asians.

Radiographically, it presents as an expansile multiloculated to poorly delineated radiolucent lesion; the radiographic features are not characteristic.

Ghost cell odontogenic carcinomas have a biologic behavior that is similar to that of an ameloblastoma or a low-grade

ameloblastic carcinoma. The tumor can be locally aggressive (e.g. maxillary tumors can invade the orbit). Apparently, the tumor has little metastatic potential.

Most of the ghost cell odontogenic carcinomas arise de novo. Most often, the carcinomas demonstrate sheets of small basaloid cells that show intraepithelial islands; stratified squamous epithelium that exhibit ghost cell keratinization. Approximately 50% have a prominent cystic component. Palisaded columnar cells at the periphery of tumor islands can create an ameloblastomatous pattern. Lesional tissue subjectively reveals features that warrant a malignant interpretation, including cytologic atypia, increased mitotic activity, an infiltrative growth pattern (perineural or intravascular invasion), and necrosis (Fig. 4-49), (Slater LJ, 2004).

It is treated by surgical excision, postoperative radiation therapy, and sometimes chemotherapy, as well.

Clear Cell Odontogenic Carcinoma

(Clear cell ameloblastic carcinoma, clear cell ameloblastoma, clear cell odontogenic tumor)

Clear cell odontogenic carcinoma is a low-grade carcinoma that is composed of cells that show uniform nuclei and clear cytoplasm. Approximately 90% of cases arise in the mandible—half in the anterior portion and half in the posterior segment. About 70% of patients are women with an age range of 17–89 years.

The tumor has a varied radiographic appearance. Often, it presents as a unilocular expansile radiolucent lesion with an indistinct periphery; however, some cases are multiloculated and well-circumscribed.

The classic case of clear cell carcinoma demonstrates budding and branching cords, islands, and sheets of neoplastic polygonal epithelial cells. Lesional cells exhibit central to eccentric small dark uniform nuclei; little evidence of nuclear pleomorphism or mitotic activity; abundant pale cytoplasm, 'clear cells'; and distinct cell borders. Tumor islands can display peripheral ameloblastomatous palisaded columnar cells; however, no evidence of central stellate reticulum, squamous differentiation, or cystic change is observed (Fig. 4-50). The clear cells contain periodic acid Schiff–positive diastase-sensitive glycogen, but they are mucicarmine negative. Recurrent lesions may be more proliferative than the original tumor, with cells showing greater mitotic index than those in the original tumor. The histologic differential diagnosis includes the clear cell variant of calcifying epithelial odontogenic tumor, metastatic renal cell carcinoma, the clear cell variant of mucoepidermoid carcinoma and clear cell squamous cell carcinoma. Salivary gland clear cell carcinomas are indistinguishable from clear cell odontogenic carcinoma based on histologic features, special stains, and immunohistochemical assays (Muramatsu T et al 1996).

The tumor is refractory to curettage. Resected tumors had a high recurrence rate; 10 of 21 (48%) resected tumors recurred following a median interval of 6.3 years.

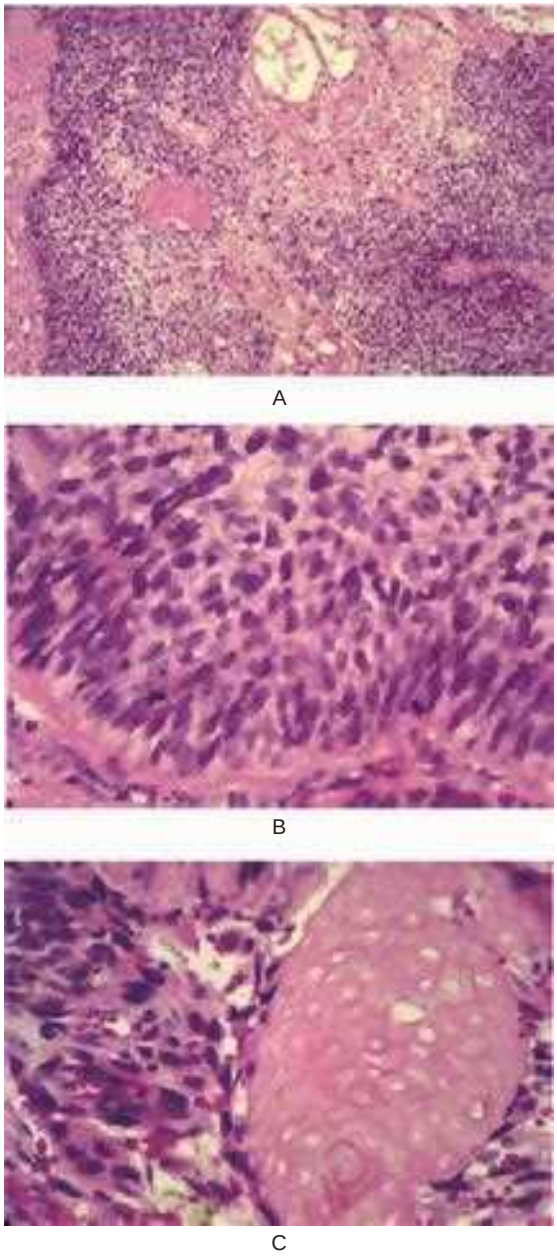


Figure 4-49. Ghost cell odontogenic carcinoma.
(A) Sheets of malignant epithelial cells demonstrate disordered dark basaloid cells at the periphery (left and right), central squamous differentiation with cystic change (top center), and an intraepithelial oval island of ghost cells (in center of left half of photograph). **(B)** Higher magnification of peripheral basaloid cells. **(C)** Higher magnification of an island of pink squamous epithelium that exhibits ghost cell keratinization (right half of photograph) *(Reprinted from Oral Maxfac Surg Clin N Am. 16: 416, 2004 with permission).*

Approximately 20% of tumors show cervical lymph node metastases; 17% display lung metastases; and about 20% of patients die of disease (after a median period of 14 years). In case of extensive extraosseous extension postoperative radiation therapy might be useful.

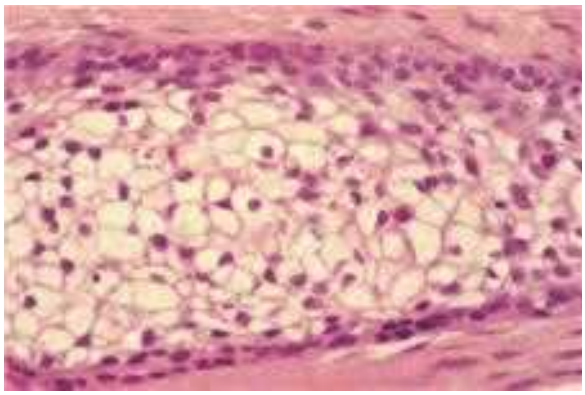


Figure 4-50. Clear cell odontogenic carcinoma.
Central large pale cells have abundant clear cytoplasm, small dark uniform nuclei, and distinct cytoplasmic borders. Peripheral basaloid cells display little cytologic atypia *(Courtesy of LJ Slater)*.

Ameloblastic Fibrosarcoma
(Odontogenic sarcoma, ameloblastic sarcoma)

Ameloblastic fibrosarcoma is a malignant proliferation of connective tissue cells that contains benign odontogenic epithelium that is similar to that seen in ameloblastic fibroma. Approximately 80% of cases occur in the mandible, predominantly the posterior segment; 60% occur in men. Often, it demonstrates an expansile radiolucency with indistinct margins and evidence of extraosseous soft tissue extension.

About 35% of cases arise in an ameloblastic fibroma. Although sarcoma ex ameloblastic fibroma presents in patients with a mean age of 33 years, de novo ameloblastic fibrosarcoma presents in younger patients with an average age of 22 years. Approximately 37% of patients have one or more recurrence and 19% die of disease. Typically, the patients do not develop metastases; they die of a locally aggressive neoplasm.

Varying radiographic patterns can be seen, that include destructive/permeative, unilocular, or multilocular sometimes, associated with an impacted molar.

Ameloblastic fibrosarcoma has the histologic architecture of an ameloblastic fibroma. Slender budding and branching epithelial cords of bland cuboidal to columnar cells with uniform nuclei or epithelial islands that are indistinguishable from those that are seen in follicular ameloblastoma are separated widely by hypercellular connective tissue that exhibits plump polygonal to fusiform stromal cells that show mild to moderate cytologic atypia and numerous mitotic figures in a pale hypocollagenous myxoid extracellular matrix. If the tumor recurs, it tends to display greater stromal cell cellularity, increased mitotic activity, more pronounced nuclear atypia, and less evidence of odontogenic epithelium with each recurrence. In some cases, the sarcomatous component completely overgrows the epithelial component; such recurrent tumors are devoid of epithelium (Fig. 4-51). Ameloblastic fibrosarcoma can demonstrate focal evidence of dentin formation or dentin and enamel formation; and this insignificant dental hard tissue component has resulted in the terms 'ameloblastic dentinosarcoma' and 'ameloblastic odontosarcoma', respectively. The histologic differential diagnosis includes a low-grade spindled ameloblastic carcinoma (Philips VM et al 1998).

The sarcoma is treated most often by a wide surgical excision and postoperative radiation therapy, without elective neck dissection.

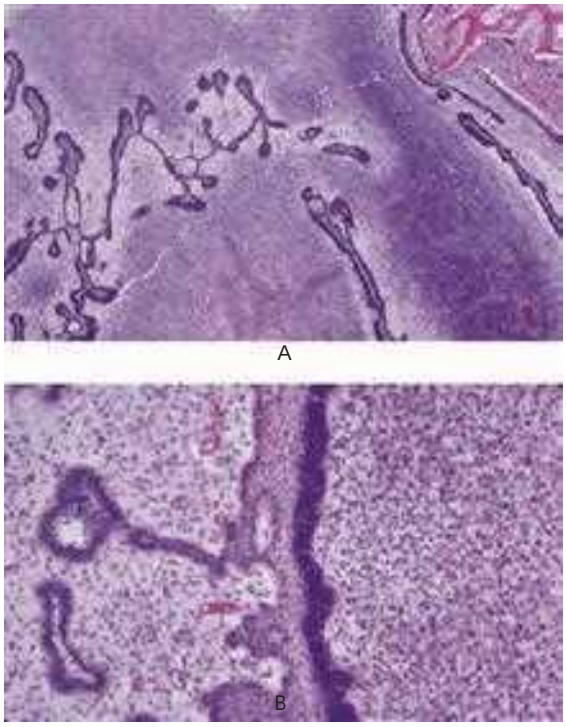


Figure 4-51. Ameloblastic fibrosarcoma.
(A) The neoplasm has the architecture of an ameloblastic fibroma that demonstrates slender budding and anastomosing cords that 'open up' to form central pale stellate reticulum; the dark band of sarcoma cells (lower right) is particularly hypercellular. **(B)** The pale connective tissue to the left of the epithelium is less cellular than the obviously sarcomatous dark polygonal cells at the right *(Courtesy of Dr LJ Slater)*.

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SECTION II

Diseases of Microbial Origin

SECTION OUTLINE

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CHAPTER 5

Bacterial Infections of the Oral Cavity

■ B SIVAPATHASUNDHARAM AND N GURURAJ

CHAPTER OUTLINE

Certain bacteria, viruses and fungi produce diseases, which are manifested in or about the oral cavity. Some of these diseases or lesions are of the specific nature and are produced by a specific microorganism. Others are clinically specific, but may be caused by any of the broad group of microorganisms. This microbial specificity or nonspecificity is characteristic of infectious diseases wherever they may occur in the body, and is necessarily confined to those of the oral cavity.

SCARLET FEVER

(Scarlatina)

Scarlet fever is a contagious systemic infection occurring predominantly in children, caused by β-hemolytic streptococci, *Streptococcus pyogenes* which produces a pyrogenic exotoxin. It is similar in many respects to acute tonsillitis and pharyngitis caused by streptococci, paralleling the occurrence of these conditions in its epidemiology. It is regarded as a separate entity because of the nature of the toxin. A number of different strains of streptococci may produce the disease. The rash occurs because of three exotoxins, A, B, C; previously described as erythrogenic or scarlet fever toxin. These organisms produce clear hemolysis around colonies in blood agar plates. Local erythematous reaction occurs in susceptible individuals injected with exotoxin, but no such reaction was found in those with specific immunity. Various studies suggest that development of scarlet fever may reflect a hypersensitivity reaction requiring prior exposure to the toxin.

Clinical Features. Scarlet fever is common in children. After the entry of the microorganisms into the body, which is believed to occur usually through the pharynx, there is an incubation period of three to five days; after which the patient exhibits severe pharyngitis and tonsillitis, headache, chills, fever, abdominal pain, and vomiting. Accompanying these symptoms may be enlargement and tenderness of the regional cervical lymph nodes. The diagnosis of scarlet fever is frequently not established until the characteristic diffused, bright, scarlet-skin rash appears on the second or third day of illness. This rash, which is particularly prominent in the areas of the skin folds, is a result of the toxic injury to the endothelium which produces dilatation of the small vessels and consequent hyperemia. These rashes blanch on pressure and typically begin first on the upper trunk, spreading to involve extremities but sparing the palms and soles. Small papules of normal color erupt through these rashes giving a characteristic 'sandpaper' feel to the skin. This rash that is particularly prominent in the areas of skin folds is called 'pastia lines.' The rash subsides after six or seven days followed by the desquamation of palms and soles. The color of the rash varies from scarlet to dusky-red.

Oral Manifestations. The chief oral manifestations of scarlet fever have been referred to as **stomatitis scarlatina**. Small punctate red macules may appear on the hard and

soft palate and uvula. These are called Forchheimer spots; however, these are not diagnostic since they may be present in other infectious conditions like rubella, roseola, infectious mononucleosis, and septicemia. The palate and the throat are often fiery red. The tonsils and faucial pillars are usually swollen and sometimes covered with a grayish exudate.

More important are the changes occurring in the tongue. Early in the course of the disease, the tongue exhibits a white coating and the fungiform papillae are edematous and hyperemic, projecting above the surface as small red knobs. This phenomenon has been described clinically as 'strawberry tongue'. The coating of the tongue is soon lost; beginning at the tip and lateral margins, and this organ becomes deep red, glistening and smooth except for the swollen, hyperemic papillae. The tongue in this phase has been termed as the 'raspberry tongue'. In severe cases, ulceration of the buccal mucosa and palate has been reported, but this appears to be due to secondary infection. Signaling the clinical termination of the disease is the desquamation of the skin, which usually occurs within a week or 10 days. Soon after, the tongue and the remainder of the mucosa assume a normal appearance. Scarlet fever should be differentiated from the other exanthematous diseases like measles and other viral exanthemas, Kawasaki disease, toxic shock syndrome, drug eruptions, and the like.

Complications. Occasional complications may arise referable to local or generalized bacterial dissemination or to hypersensitivity reactions to the bacterial toxins. These may include peritonsillar abscess, rhinitis and sinusitis, otitis media and mastoiditis, meningitis, pneumonia, glomerulonephritis, rheumatic fever, and arthritis.

Diagnosis. Diagnosis is usually based on clinical findings. Routine blood examination shows marked leukocytosis with increased neutrophilia. There is an elevation of ESR and C-reactive protein. Culturing the flora of intraoral lesions, pharynx, and saliva can be used to confirm the diagnosis.

Prevention and Treatment. There are no available methods for the prevention of scarlet fever. The administration of antibiotics like penicillin, dicloxacillin, and cephalexin will ameliorate the disease and also helps in controlling possible complications. Local applications like mupirocin topical ointment also can be used to relieve discomfort.

DIPHTHERIA

Diphtheria is an acute, life-threatening, infectious, and communicable disease of the skin and mucous membrane caused by toxemic strains of *Corynebacterium diphtheriae,* an anaerobic gram-positive organism. It is characterized by local inflammation and the formation of a grayish adherent pseudomembrane, which bleeds on removal. It occurs in the months of winter in temperate zones and throughout the year in the tropical region. Historically, it was described as Egyptian or Syrian ulcer in the second century.

It is a disease of the children. Humans are the principal reservoirs and the organisms may persist in discharges from the nose, throat, eye, and skin lesions for two to six weeks after infection. It is transmitted mainly by respiratory droplets, direct skin contact and from the skin to the respiratory tract through hands. In some instances carriers of the disease are responsible for dissemination of the microorganisms. Exposure to the diphtheria bacillus, particularly in the adult, may result in a subclinical infection, which is usually sufficient to establish immunity through the development of circulating antitoxins. Infection is most common in groups living in crowded conditions. It can occur in both immunized and partially immunized individuals.

Since 1990, this epidemic has occurred throughout the Russian Federation, Ukraine, Thailand, and Laos. These epidemics are largely due to decreasing immunization coverage among infants, waning immunity in adults, large-scale movement of population, and irregular supply of vaccine. Available data indicate a declining trend of diphtheria in India, due to increasing coverage of child population by immunization. Schick test surveys in India have shown that about 70% of children over the age of three and 99% over the age of five are already immune to diphtheria. Recent diphtheria outbreaks in a number of countries have demonstrated a shift in age distribution of cases to adults and old age people. The outbreaks warrant the need of booster immunization.

Pathogenesis. *C. diphtheriae* has an air-borne mode of transmission and localizes in the mucous membrane of the respiratory tract. It also invades open skin lesions resulting from insect bites or trauma. Diphtheria is, in fact, a toxemia, since the bacillus remaining at the site of entry multiplies and liberates toxins. These toxins induce initial edema and hyperemia followed by epithelial necrosis and acute inflammation.

Coagulation of the fibrin and purulent exudates produce pseudomembrane and the inflammatory reaction accompanied by vascular congestion extends into the underlying tissues. Thus the pseudomembrane consists of dead cells, leukocytes, erythrocytes, and bacteria. Systemically the toxin produces myocarditis, neuritis, and focal necrosis in various organs including kidneys, liver, and adrenal glands. Cutaneous diphtheria is caused by nontoxemic strains of diphtheria.

Clinical Features. Patients with *C. diphtheriae* in the respiratory tract are classified as diphtheria cases if the pseudomembrane is present and as diphtheria carriers if the pseudomembrane is absent. The pseudomembrane is seen on the tonsils. It is wash-leather, elevated grayish-green membrane with a well-defined edge surrounded by acute inflammation. The incubation periods for respiratory diphtheria are two to five days and rarely up to eight days. Cutaneous diphtheria is a secondary infection on pre-existing skin lesions, which develops at an average of seven days after the appearance of primary lesions. Various clinical types of diphtheria, classified by the location of the pseudomembrane are tonsillar, pharyngeal, laryngeal, tracheal, nasal, conjunctival, cutaneous, and genital. There may be swelling of the neck (bull neck) and tender enlargement of the lymph nodes.

Onset is gradual. It manifests as fever, sore throat, weakness, dysphagia, headache, and change of voice. Patients without toxicity exhibit discomfort and malaise associated with local

infection whereas toxic patients develop restlessness, pallor, and tachycardia and rapidly progressed to vascular collapse. Multiple sites may involve other than the primary site. The spread of infection from one site either upward or downward is common.

Initial findings include erythema of the posterior pharyngeal wall followed by white or gray spots that coalesce to form a thin veil-like membrane, which thickens and becomes gray. The larynx and trachea may be involved primarily or by extension from the pharynx and nose. It manifests as hoarseness of voice, respiratory stridor, and dyspnea, which may progress to severe respiratory obstruction and death in young children owing to the small airway size. Cutaneous manifestations include deep punched-out ulcers with a leathery discharge. Most lesions occur on the extremities but trunk and genital may also be affected.

Oral Manifestations. There is formation of a patchy 'diphtheritic membrane' which often begins on the tonsils and enlarges, becoming confluent over the surface. This false membrane is grayish-green, thick, and fibrinous, and is composed of dead cells, leukocytes and bacteria overlying necrotic, ulcerated areas of the mucosa tends to be adherent and leaves a bleeding surface if stripped away. The membrane is asymmetric and extends to involve the tonsil, soft palate and tongue, lips, gingiva, buccal mucosa and site of erupting teeth. Its advancing border is reddened and bleeding occurs on scraping the membrane. The submandibular and anterior cervical nodes are enlarged with soft tissue edema. Severely affected patients will give a bull neck appearance.

In the oral cavity, it appears as nonspecific ulcer. The soft palate may become temporarily paralyzed, usually during the third to fifth weeks of the disease. These patients have a peculiar twang, and may exhibit nasal regurgitation of liquids during drinking. The paralysis usually disappears in a few weeks or a few months at the most. If the infection spreads unchecked in the respiratory tract, the larynx may become edematous and covered by the pseudomembrane which results in a husky voice. This is especially serious because it produces a mechanical respiratory obstruction and the typical cough or diphtheritic croup. If the airway is not cleared, suffocation may result.

Complications. During or after this disease complications frequently arise in the cardiovascular and nervous systems as a result of toxemia. Thus both myocarditis and polyneuritis may develop, but usually there is complete recovery. Kidney lesions, particularly acute interstitial nephritis, are also possible serious sequelae. Obstruction of the airway, acute circulatory failure, post diphtheria paralysis, pneumonia, bleeding and otitis media are other complications.

The mortality rate is still of such proportions that diphtheria should be considered a serious disease. In the past this disease was a leading cause for death in children and was referred to as 'the strangling angel of children'. It should be differentiated from other conditions including streptococcal pharyngitis, Vincent's angina, Ludwig's angina, retropharyngeal and peritonsillar abscess, infectious mononucleosis, candidiasis, leukemia, and agranulocytosis.

Diagnosis is mainly based on clinical signs and symptoms but definite diagnosis is arrived by the isolation of organisms from the affected sites. Material should be obtained beneath the membrane or a portion of the membrane itself can be submitted for culture. Various media include Pai agar and cystine-tellurite agar and special stains like Albert's stain, Ponder's stain or Neisser's stains to demonstrate metachromatic granules.

Treatment. Administration of diphtheria antitoxin neutralizes the circulating diphtheria toxin and prevents the disease progression. Apart from antibiotic administration usually done by penicillin and erythromycin; maintaining the airway is also necessary.

Prevention. The disease may be prevented by prophylactic active immunization with diphtheria toxoid.

TUBERCULOSIS

Tuberculosis (TB) is a specific infectious granulomatous disease caused by *Mycobacterium tuberculosis.* It remains a major health problem in most developing countries. It commonly affects lungs but also affects the intestines, meninges, bones, joints, lymph glands, skin, and other tissues of the body. The disease also affects animals like cattle and is known as bovine tuberculosis; and is sometimes communicated to man.

Etiology. *M. tuberculosis* is a facultative intracellular parasite. Human strains are responsible for many cases, but the bovine strain may also produce illness through the ingestion of unpasteurized cow's milk. Rarely atypical or opportunistic mycobacteria can cause pulmonary or generalized infection in immunocompromised individuals.

M. tuberculosis is a rod-shaped, nonspore forming, and thin aerobic bacteria called acid-fast bacilli, due to the fact that once stained, it cannot be decolorized by acid alcohol. Its acid-fastness is due to the high content of mycolic acids, long chain cross-linked fatty acids and other cell wall lipids. Males are more affected than females in India though it affects all ages, from an average of 1% in the under-five age group.

Epidemiology. Developed countries have achieved spectacular results in the control of tuberculosis. Incidence has steadily declined in developing countries as well. This is due to early and accurate diagnosis of the disease through various tools and improved socioeconomic conditions. In developing countries, the Southeast region, the Western Pacific, and Africa accounts for 95% cases of TB. Among the world population, the Southeast Asian region carries a disproportionate 88% of the world's burden of TB.

India accounts for nearly one fifth (20%) of the global burden of TB. Every year 1.8 million persons develop tuberculosis of which about 0.8 million are new smear-positive highly infectious cases and about 0.32 million people die of TB every year. The vulnerability to TB in developing countries results from poverty, economic recession and malnutrition. Many new patients have multidrug resistance to TB. People with HIV infection are much more likely to develop TB. An increase in HIV prevalence represents a serious threat to TB control in India. WHO has launched a strategy for controlling TB called DOTS or Directly Observed Therapy Short-term,

a community based treatment protocol. Today in India it is recognized as fastest expanding program.

Pathogenesis. The interaction of the bacilli and the host begins when droplet nuclei from infectious patients are inhaled. The majority of the bacilli are trapped and exhaled by ciliary action and a fraction less than 10% enters alveoli.

In the initial stage of the host-bacterial interaction, either host's macrophages control the multiplication of the bacteria or the bacteria grow and kill the macrophages. Nonactivated monocytes attracted from blood stream to the site by various chemotactic factors ingest the bacilli released from the lysed macrophages. Initial stages are asymptomatic; about 2–4 weeks after infection tissue damaging and macrophage activating responses develop. With the development of specific immunity and accumulation of a large number of activated macrophages at the site of primary lesion, granulomatous reaction or tubercles are formed. The hard tubercle consists of epithelioid cells, Langhans giant cells, plasma cells, and fibroblasts. These lesions develop when host resistance is high. Due to cell-mediated immunity in the majority of individuals, local macrophages are activated and lymphokines are released, which neutralize the bacilli and prevent further tissue destruction. The central part of the lesion contains caseous, soft, and cheesy necrotic material (caseous necrosis). This necrotic material may undergo calcification at a later stage called Ranne complex, in the lung parenchyma and hilar lymph nodes in few cases. Caseous necrotic material undergoes liquefaction and discharges into the lungs leading to the formation of a cavity. Spontaneous healing of the cavity occurs either by fibrosis or collapse. Calcification of the cavities may occur in which bacteria persist.

In early stages, the spread of infection is mainly by macrophages to lymph nodes, other tissues, and organs. However, in children with poor immunity, hematogenous spread results in fatal military TB or tuberculous meningitis.

Clinical Features. The signs and symptoms of tuberculosis are often remarkably inconspicuous. The patient may suffer episodic fever and chills, but easy fatigability and malaise are often the chief early features of the disease. There may be gradual loss of weight accompanied by a persistent cough with or without associated hemoptysis.

Tuberculosis is either pulmonary or extrapulmonary. Pulmonary TB may be primary, secondary, or miliary. Extrapulmonary sites include lymph nodes, pleura, genitourinary tract, bones, joints, meninges, and peritoneum. As a result of hematogenous dissemination in HIV infected individuals, the extrapulmonary type is seen more commonly.

Primary pulmonary TB is usually seen in children but may also occur in adults. In a majority of cases, it is asymptomatic. A few may be present with febrile illness and cough, which may be dry or productive.

Symptoms of post-primary TB or secondary TB include fever, cough, chest pain, and hemoptysis.

Symptoms of miliary TB in children include acute febrile illness but in adults it is more insidious with gradual development of ill health, anorexia, loss of weight, and fever. Bilateral crackles on auscultation, hepatosplenomegaly, and lymphadenopathy may be present. Choroid tubercles are seen in children, but are rare in adults.

Tuberculous infection of submandibular and cervical lymph nodes, or scrofula, a tuberculous lymphadenitis, may progress to the formation of an actual abscess or remain as a typical granulomatous lesion. In either case, swelling of the nodes is obvious clinically. They are tender or painful, often show inflammation of the overlying skin, and when an actual abscess exists, typically perforate and discharge pus. It has been suggested that this specific form of tuberculosis probably arises as a result of lymphatic spread of organisms from a focus of infection in the oral cavity such as the tonsils. However, as Popowich and Heydt have stated, no published studies have confirmed the relationship between tuberculous cervical lymphadenitis and a primary source of infection elsewhere. For example, in the series of 22 cases reported by Ord and Matz, there was no history or clinical evidence of pulmonary tuberculosis in any patient. These investigators also emphasized that this disease can be caused by atypical mycobacteria and also that organisms frequently cannot be cultured from the lesions.

Primary tuberculosis of the skin or lupus vulgaris may occur either in children or adults and is a notoriously persistent disease. It appears as papular nodules, which frequently ulcerate. These are particularly common on the face, but may occur anywhere.

Oral Manifestations Tuberculous lesions of the oral cavity do occur, but are relatively uncommon. Reported studies on incidence vary considerably. The studies of Farber and his associates indicated that less than 0.1% of the tuberculous patients whom they examined exhibited oral lesions. Katz on the other hand, found that approximately 20% of a series of 141 patients examined at autopsy manifested such lesions, the majority of which occurred on the base of the tongue and were not discovered clinically. The obscure location of the tuberculous lesions found by Katz might account for the disparity in incidence of occurrence in these studies.

There is general agreement that lesions of the oral mucosa are seldom primary, but rather secondary to pulmonary disease. Although the mechanism of inoculation has not been definitely established, it appears most likely that the organisms are carried in the sputum and enter the mucosal tissue through a small break in the surface. It is possible that the organisms may be carried to the oral tissues by a hematogenous route, to be deposited in the submucosa and subsequently to proliferate and ulcerate the overlying mucosa.

The possibility that the dentist may contract an infection from his contact with living tubercle bacilli in the mouth of patients who have pulmonary or oral tuberculosis is a problem of great clinical significance. It has been shown on numerous occasions that the viable acid-fast microorganisms may be recovered from swabs or washings of the oral cavities of tuberculous patients. Abbott and his associates reported that tubercle bacilli were cultured from 45% of 300 samples of water used to wash the teeth and gingiva of 111 tuberculous patients.

Lesions of secondary tuberculosis may occur at any site on the oral mucous membrane, but the tongue is most commonly affected, followed by the palate, lips, buccal mucosa, gingiva, and frenula. The usual presentation is an irregular, superficial or deep, painful ulcer which tends to increase slowly in size (Fig. 5-1A,B,C). It is frequently found in areas of trauma and may be mistaken clinically for a simple traumatic ulcer or even carcinoma. Occasional mucosal lesions show swelling, granular, nodular or fissured lesions, but no obvious clinical ulceration. Primary oral tuberculosis usually involves gingiva and is present as diffuse, hyperemic, nodular, or papillary proliferation of the gingival tissues (Figs. 5-2, 5-3). Primary oral tuberculosis is usually associated with regional lymphadenopathy.

Tuberculosis may also involve the bone of the maxilla or mandible. One common mode of entry for the microorganisms is into an area of periapical inflammation by way of the blood stream; an anachoretic effect that has been noted in the oral cavity under other circumstances. It is conceivable also that these microorganisms may enter the periapical tissues

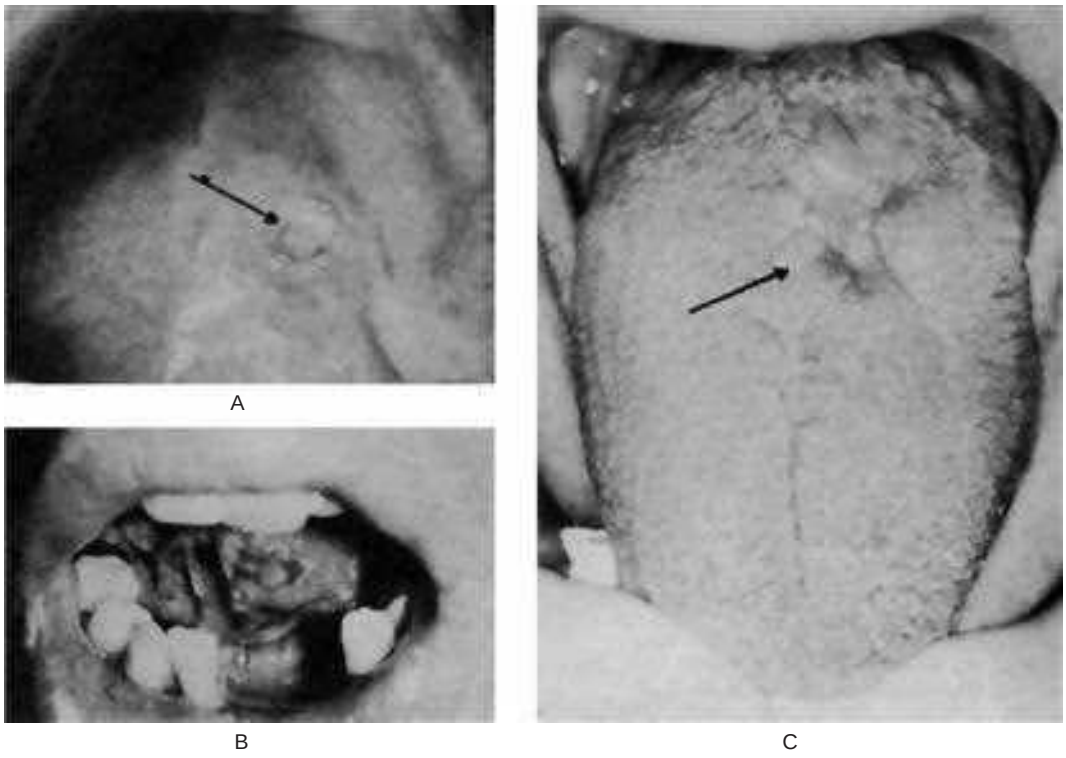


Figure 5-1. Tuberculous ulcer of the palate (A), ventral of tongue (B), and dorsum of tongue (C).

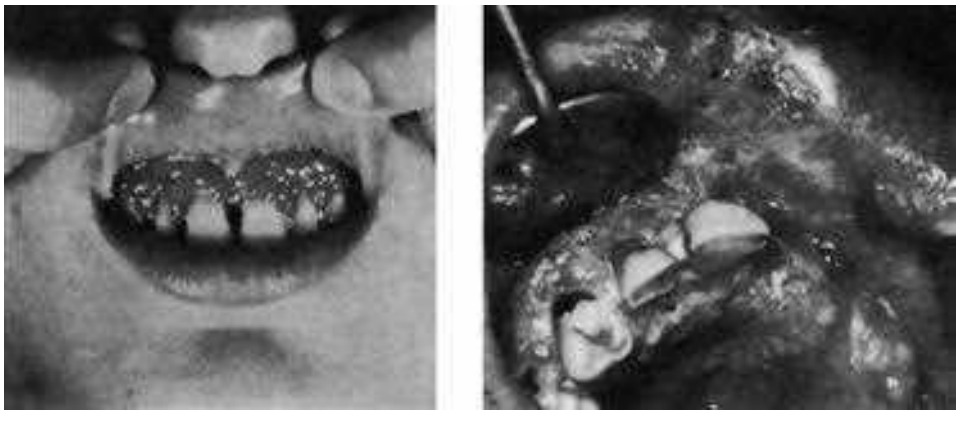


Figure 5-2. Tuberculous gingivitis.
The infection in **(A)** was restricted to the gingival tissues, but in **(B)** had extended to the palate and lip *(B, Courtesy of Dr Cesar Lopez)*.

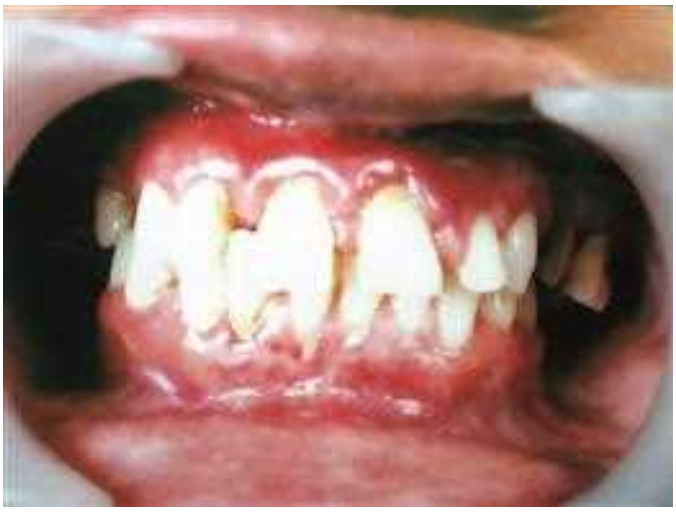


Figure 5-3. Primary tuberculous of gingiva.
Source: Anisha CR, Sivapathasundharam B. Primary tuberculosis of gingiva. J Indian Dent Assoc, 2000, 71: 144–45.

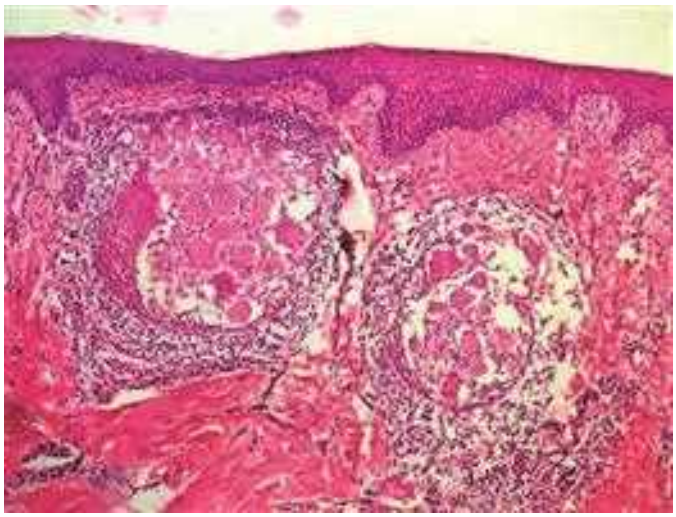


Figure 5-4. Oral tuberculosis.
Photomicrograph showing tuberculous granulomas with Langhans joint cells, epithelioid cells and lymphocytes *(Courtesy of Dr Leela Poonja, Dr G Sriram, Dr Vaishali Natu).*

by direct immigration through the pulp chamber and root canal of a tooth with an open cavity. The lesion produced is essentially a tuberculous periapical granuloma or tuberculoma. These lesions were usually painful and sometimes involve a considerable amount of bone by relatively rapid extension.

Diffuse involvement of the maxilla or mandible may also occur, usually by hematogenous spread, but sometimes by direct extension or even after tooth extraction. Tuberculous osteomyelitis frequently occurs in the later stages of the disease and has an unfavorable prognosis.

Histologic Features. Tuberculous lesions in the mouth do not differ microscopically from tuberculous lesions in other organs of the body. The characteristic histopathologic appearance is due to the cell-mediated hypersensitivity reaction. Formation of granuloma exhibiting foci of caseous necrosis surrounded by epithelioid cells, lymphocytes, and occasional multinucleated giant cells (Fig. 5-4). Caseous necrosis is not inevitably present, however.

Diagnosis. The diagnosis of active infection must be confirmed by demonstration of the organisms by special microbial stains and culture of the infected tissue or sputum. The presence of acid-fast bacilli (AFB) in sputum smear is the gold standard for the diagnosis of TB. Imaging techniques like radiograph of the affected part like chest and tuberculin test are most useful in supplementing the diagnosis of TB.

CT scan is used to diagnose mediastinal or hilar lymphadenopathy, cavities and intralesional calcification. Postcontrast peripheral enhancement of a lymph node is taken as indirect evidence of tuberculous etiology. A high resolution CT scan can be used to differentiate miliary TB and other diffuse forms of TB from other diffuse lung diseases. MRI is most useful for diagnosis of extrapulmonary TB.

Identification of Mycobacteria from Respiratory Specimens. The demonstration of tubercle bacilli in a respiratory specimen like sputum is a direct evidence of TB. WHO defines any patient whose sputum smear is positive for acid-fast bacilli as a case of pulmonary tuberculosis. Respiratory specimens can be subjected to smear and microscopy for acid-fast bacilli, as well as culture. The following respiratory specimens can be used to demonstrate *Mycobacterium*, sputum, spot samples collected early morning, laryngeal swab, bronchoalveolar lavage, transtracheal aspiration, or gastric contents aspirated by a nasogastric tube in children who swallow sputum.

Microscopical smears for acid-fast bacilli are stained by the following methods: Ziehl-Nielsen (Z-N) staining, Kinyoun's cold staining methods, and rhodamine staining for fluorescent microscopy. A minimum of five acid-fast bacilli on fluorescent microscopy and three on Z-N staining is reported as positive. A sputum smear examination is less than 60% sensitive.

Mycobacterial Culture. Conventional *Mycobacterium* cultures are done on Lowenstein-Jensen medium or one of the agar based media like Middlebrook medium. It takes four to six weeks for the growth of *M. tuberculosis.*

Other faster methods of culture:

- Rapid slide culture technique involves growing *Mycobacterium* on slides examining microcultures under a microscope.
- Radiometric culture method is based on the detection of utilization of a radioisotope of carbon by mycobacteria.

Tuberculin test or the **Mantoux test** involves subcutaneous injection of 0.1 ml of 5 tuberculin units of purified protein derivative of Siebert stabilized with Tween 80 or 1 tuberculin unit of PPDRT 23 into the forearm. It is positive if induration is seen after 48–72 hours. The maximum diameter of the induration measured by palpation and not redness, is recorded and interpreted as follows: more than 15 mm or ulceration, strongly positive; more than 10mm, positive; 5–9 mm, indeterminate; and less than 5mm, negative.

The tuberculin skin test has greater value in excluding tuberculosis than in diagnosing it. A positive reaction indicates that a *Mycobacterium* has replicated in the tissues of the individual at some time but does not indicate an active disease. A strongly positive test may indicate recent infection. The test is positive in 85% of infected individuals but may be falsely negative in tuberculosis pleurisy, miliary tuberculosis, immuno suppressed conditions, and viral fevers. 10% of recent tuberculin converters may develop active disease in their life time and 5% do so within the first two years of infection.

Extensively drug resistant tuberculosis (XDR TB)

A variant of tuberculosis which does not respond to one or more of the antituberculous drugs is known as multidrug resistant tuberculosis (MDR TB). Extensively drug resistant TB is relatively a rare form of MDR TB, which is resistant to almost all types of antituberculous drugs. Since XDR TB is resistant to most powerful first-line and second-line antituberculous drugs, the treatment outcome is usually worse, particularly in patients with impaired immune system, as in HIV infection.

Specific purified protein derivative (PPD) is available for the diagnosis of atypical mycobacterial strains. In HIV positive patients, when the CD4 count goes below 400, tuberculin energy is present and reflects the immune status of the host.

Newer methods of diagnosis of tuberculosis include radioimmunoassays (RIAs), soluble antigen fluorescent antibody (SAFA) test and enzyme linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) to detect the bacterial DNA, and antibody assays to detect the release of interferon gamma in response to mycobacteria.

Treatment. Multiple drug therapy is often recommended as *M. tuberculosis* mutates and resists single drug therapy. Isoniazid (INH) combined with rifampicin for nine months or INH, rifampicin and pyrazinamide for two months followed by INH and rifampicin for four months. Other drugs used are streptomycin and ethambutol.

LEPROSY

(Hansen's disease)

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae.* It multiplies very slowly and the incubation period is about five years. It may take as long as 20 years for the symptoms to develop. The disease is only slightly contagious. It mainly affects skin, peripheral nerves, the upper respiratory tract, eyes, and testes, but also affects muscles, bones, and joints. When untreated, it results in characteristic deformities. Nowadays because of early diagnosis and induction of appropriate therapy, major complications can be prevented. Binford et al, have published the most thorough and concise review of this disease. Recent studies and reports indicate that the incidence and prevalence is reduced due to multidrug therapy.

Etiology. *M. leprae* is an obligate intracellular, gram-positive, acid-fast bacillus. It is the only bacterium to infect peripheral nerve. It is unique in exhibiting dopa oxidase activity and acid fastness. It grows best in cooler tissues like skin, peripheral nerves, upper respiratory tract, anterior chamber of the eye, and testes; sparing warmer areas like axilla, groin, scalp, and midline of back. Taking smears from the skin, nasal mucosa of the affected persons, and staining with the Ziehl and Nielsen method can demonstrate the presence of bacilli. Living leprosy bacillus appears as solid staining pink rod whereas non-living leprosy bacilli may be granular or fragmented. It can be grown well in mouse footpad and nine banded armadillo and grows at 30–33° C with a doubling time of 12 days. It can remain viable in the environment for 10 days.

Epidemiology. Leprosy is almost exclusively a disease of developing countries. It is common in Asia, Africa, Latin America, and the Pacific. Africa has the highest disease prevalence and Asia has the most cases. More than 60% of the cases occur in India, China, Myanmar, Indonesia, Brazil, and Nigeria. Leprosy is still endemic in 28 countries. India accounts for 80% of the detection of leprosy cases in the world. The annual case detection rate in India is among the highest in the world (53 per 100,000).

In India prevalence is high in Bihar, Uttar Pradesh, Madhya Pradesh, Tamil Nadu, Andhra Pradesh, Orissa, and West Bengal. According to WHO, the official reports received from 109 countries and territories, the global registered prevalence of leprosy at the beginning of 2007 stood at 224,717 cases, while the number of new cases detected during 2006 were 259,017. Leprosy is very rare in infants and has a bimodal age distribution with peaks at 10–14 and 35–44 years. The mode of infection is not known but the probable spread could be through nasal secretion.

Pathogenesis. An immunologic and epidemiological study suggests most people develop a subclinical infection and very few develop infection. Once infected, both cell mediated and humoral responses are elicited by bacterial antigen DNA glycolipids. Lipoarabinomannan, a component of the cell membrane, induces immune suppression by inhibiting the interferon gamma mediated activation of macrophages.

The bacteria are taken by histiocytes in the skin and Schwann cells in the nerves. This usually results in an inflammatory response involving histiocytes and lymphocytes. It is clinically called indeterminate type represented as hypopigmented or erythematous macule. The clinical spectrum and ultimate outcome of disease depends upon the intensity of specific cell mediated immunity. Individuals prone to tuberculoid type have an intense cell mediated immune response and low bacillary load; whereas, patients with lepromatous type have low specific cell mediated immune response and a high bacillary load. These two different types are genetically controlled.

Clinical Features. Various types of clinical presentation occur in patients infected with this bacillus corresponding to patient's immune response. Leprosy manifests in two polar forms, namely, tuberculoid type and lepromatous type. Host resistance is high in tuberculoid type.

Between these two, the borderline and indeterminate forms occur depending upon the host response.

General features of leprosy are hypopigmented patches, partial or total loss of cutaneous sensation in the affected areas. The earliest sensation to be affected is usually light touch. The thickening of nerves and the presence of acid-fast bacilli in the skin or nasal smear are common. Tuberculoid lesions are characterized by single or multiple macular, erythematous eruptions, with dermal nerve and peripheral nerve trunk involvement resulting in the loss of sensation, often accompanied by the loss of sweating of the affected skin. The lepromatous lesions develop early erythematous macules or papules that subsequently lead to progressive thickening of the skin and characteristic nodules. These may develop in considerable numbers on any skin area and produce severe disfigurement.

Facial paralysis occurs with some frequency due to facial nerve involvement, and this has been discussed by Reichart et al. Features of advanced disease are nodules or lump in skin of the face and ears, plantar ulcers, loss of fingers and toes, nasal depression, foot drop, claw toe, and others. Although the disease is a crippling and disfiguring one, it runs a chronic course and seldom causes sudden death.

Oral Manifestations. The oral lesions that have been reported generally consist of small tumor like masses called lepromas, which develop on the tongue, lips, or hard palate. These nodules show a tendency to break down and ulcerate. Gingival hyperplasia with loosening of the teeth has also been described, but Reichart and his associates found that most of the gingival and periodontal changes occurring in a group of 30 leprosy patients were nonspecific.

Paralysis of facial and maxillary division of trigeminal nerve is reported. The dental manifestations are described as odontodysplasia leprosa. Premaxilla is affected in childhood due to granulomatous involvement. There will be a circumferential hypoplasia, shortening of roots, usually involving maxillary anterior teeth. Long standing lepromatous lesions may show granulomatous invasion of pulp and pinkish discoloration of crowns.

Histologic Features. The typical granulomatous nodule shows collections of epithelioid histiocytes and lymphocytes in a fibrous stroma. Langhans type giant cells are variably present. Sheets of lymphocytes with vacuolated macrophages called lepra cells are scattered throughout the lesions. In tuberculoid pattern, there is a paucity of organisms and they can be demonstrated only with acid-fast stains in contrast to lepromatous type where there is an abundance of organisms.

Diagnosis is based mainly on clinical and bacteriological examination. Culturing of the organism is difficult. So far the organism has been grown in the footpads of mice and armadillos.

Nasal smears and scrapings stained with modified Ziehl-Nielsen method to detect lepra bacilli at a concentration greater than 10^{11} gm of tissue. The morphological index is a measure of the number of AFB in skin scrapping that stain uniformly bright correlated with viability.

The bacteriologic index, a logarithmic scaled measure of density of *M. leprae* in the dermis, may be as high as 4t-6t in untreated patients falling by one unit per year during effective therapy.

Other investigations are skin biopsy, nerve biopsy, and foot culture histamine test. Tests for humoral response are monoclonal antibodies, ELISA, PCR, etc. In children, the sweat function test is used.

Leprosy should be differentiated from sarcoidosis, leishmaniasis, lupus vulgaris, lymphoma, syphilis, yaws, and other disorders having hypopigmentation.

Treatment. Specific long-term chemotherapy is initiated upon diagnosis. In 1981, WHO study group recommended multidrug therapy (MDT) and it consists of rifampicin, dapsone and clofazimine. The widespread use of MDT dramatically reduces the disease burden. Rifampicin and dapsone for six months in case of tuberculoid type and rifampicin and dapsone along with clofazimine in case of lepromatous type is usually advocated. However, drug regimen evaluation is very difficult in certain situations. Once the infection is treated, the management is directed towards the reconstruction of the damage caused by this disease.

ACTINOMYCOSIS

Actinomyces species are classified as anaerobic, gram positive and filamentous bacteria despite their fungal and bacterial characteristics. Actinomycosis is a chronic granulomatous suppurative and fibrosing disease caused by anaerobic or microaerophilic gram-positive nonacid fast, branched filamentous bacteria. They are a normal saprophytic component of oral flora, colon, and vagina and none are known to be recoverable from the environment.

Most of the species isolated from actinomycotic lesions have been identified as *A. israelii, A. viscosus, A. odontolyticus, A.naeslundii* or *A. meyeri.* These microorganisms have been identified in dental plaque, dental calculus, necrotic pulp, and tonsils.

These microorganisms were believed to be fungi at one time. However, as our knowledge of their biochemical and serologic aspects evolved, it became apparent that they were actually bacteria, their filaments frequently breaking up into bacillary and coccoid forms.

The usual pattern of this disease is one characterized chiefly by the formation of abscesses that tend to drain by the formation of sinus tracts. If the pus from the abscesses is examined on a clean glass slide, it shows the typical 'sulfur granules' or colonies of organisms, which appear in the suppurative material as tiny, yellow grains. Another infection that produces this type of sulfur granules is botryomycosis. Actinomycosis is classified anatomically according to the location of the lesions, and thus we recognize:

- Cervicofacial
- Abdominal
- Pulmonary forms.

It is well established that the actinomycete is a common inhabitant of the oral cavity even in the complete absence of

any clinical manifestations of specific infection. Thus, the organisms may be cultured from carious teeth, nonvital root canals, tonsillar crypts, dental plaque, calculus, gingival sulcus, and periodontal pockets.

The pathogenesis of actinomycosis is not entirely known. lt appears to be an endogenous infection and not communicable. Furthermore, it does not appear to be an opportunistic infection in a situation of depressed cell-mediated immunity. Trauma seems to play a role in some cases by initiating a portal of entry for the organisms, since they are not highly invasive. Thus the extracted socket, periodontal pocket, nonvital tooth, or mucosal abrasion may act as the portal of entry for the infection.

Epidemiology. Infection occurs throughout the lifetime with peak incidence in the middle age. Males are more commonly affected than females. Incidence has decreased presently due to improved oral hygiene and antibiotics.

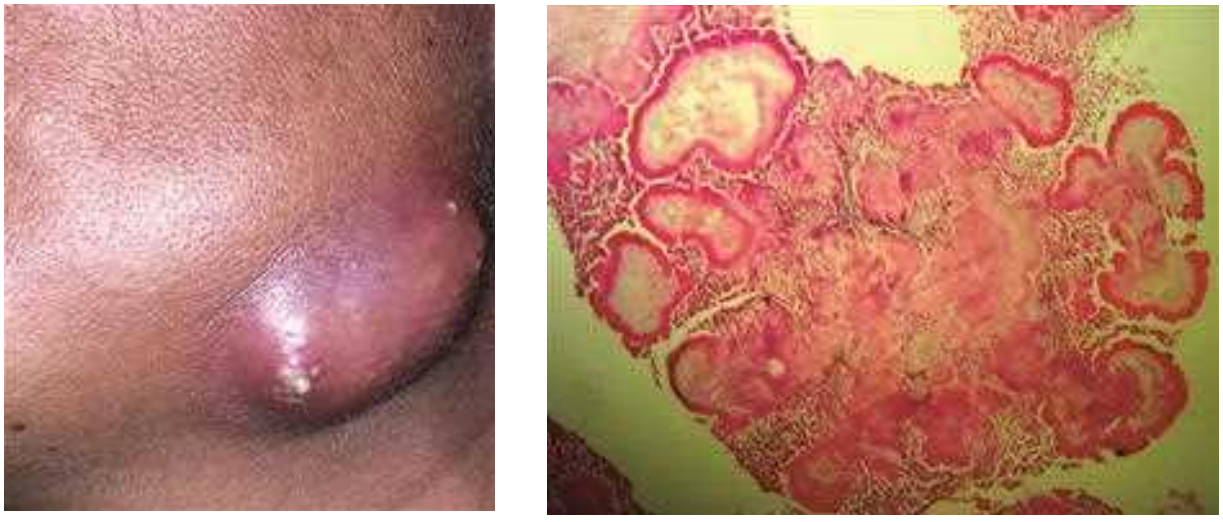
Pathogenesis. The disruption of the mucosal barrier is the main step in the invasion of bacteria. Initial acute inflammation is followed by a chronic indolent phase. Lesions usually appear as single or multiple indurations. Central fluctuance with pus containing neutrophils and sulphur granules is diagnostic of the disease. The fibrous walls are typically described as woody. It occurs in association with HIV infection, transplantation, chemotherapy, herpes, and cytomegaloviral ulcerative mucosal lesions. It is also reported in osteoradionecrosis and in patients with systemic illness.

Clinical Features. Cervicofacial actinomycosis is the most common form of this disease and is of the greatest interest to the dentist. It has been emphasized by Norman that two-thirds of all cases are of this type. Stenhouse and associates, who also emphasized the surprisingly high incidence of occurrence of *Actinomyces* in routine pathologic and bacteriologic specimens, have reported a series of 39 cases of cervicofacial and intraoral actinomycosis. The organisms may enter the tissues through the oral mucous membranes and may either remain localized in the subjacent soft tissues or spread to involve the salivary glands, tongue, very rarely gingiva, bone or even the skin of the face and neck, producing swelling and induration of the tissue. These soft tissue swellings eventually develop into one or more abscesses, which tend to discharge upon a skin surface, rarely a mucosal surface, liberating pus containing the typical 'sulfur granules' (Fig. 5-5 A). The skin overlying the abscess is purplish red, indurated and has the feel of wood or often fluctuant. It is common for the sinus through which the abscess has drained to heal, but because of the chronicity of the disease, new abscess develop and perforate the skin surface. Thus the patient, over a period of time, may show a great deal of scarring and disfigurement of the skin.

The infection of the soft tissues may extend to involve the mandible, or less commonly, the maxilla which results in actinomycotic osteomyelitis. If the bone of the maxilla is invaded, the ensuing specific osteomyelitis may eventually involve the cranium, meninges, or the brain itself. Once the infection reaches the bone, the destruction of the tissue may be extensive.

Such destructive lesions within the bone may occur or localize at the apex of one or more teeth and simulate a pulp-related infection such as a periapical granuloma or cyst. Such a case has been reported by Wesley and his colleagues, who noted 12 other similar cases in the literature.

Abdominal actinomycosis is an extremely serious form of the disease and carries a high mortality rate. In addition to generalized signs and symptoms of fever, chills, nausea and vomiting, intestinal manifestations develop, followed by symptoms of the involvement of other organs such as the liver and spleen.



A B

Figure 5-5. Cervicofacial actinomycosis.
Clinical photograph **(A)** showing multiple graining abscess and photomicrograph **(B)** showing actinomycotic colony in a smear of the pus *(Courtesy of Dr Leela Poonja, Dr G Sriram, Dr Vaishali Natu).*

Pulmonary actinomycosis produces similar findings of fever and chills accompanied by a productive cough and pleural pain. The organisms may spread beyond the lungs to involve adjacent structures.

Histologic Features. The typical lesion of actinomycosis, either in soft tissue or in bone, is essentially a granulomatous one showing central abscess formation within which may be seen the characteristic colonies of microorganisms. These colonies appear to be floating in a sea of polymorphonuclear leukocytes, often associated with multinucleated giant cells and macrophages particularly around the periphery of the lesion. The individual colony, which may appear round or lobulated, is made up of a meshwork of filaments that stains with hematoxylin, but shows eosinophilia of the peripheral club shaped ends of the filaments (Fig. 5-5 B). This peculiar appearance of the colonies, with the peripheral radiating filaments, is the basis for the often-used term 'ray fungus.' The tissue surrounding the lesion exhibits fibrosis. Methenamine silver stain can demonstrate the organisms better.

Diagnosis. It should be differentiated from osteomyelitis caused by other bacterial and fungal organisms and soft tissue infections caused by staphylococcus. The diagnosis of actinomycosis depends not only upon clinical findings in the patient and the demonstration of the organisms in the tissue section or smear, but also upon their culture. However, as Brown pointed out in his extensive review of 181 cases of actinomycosis, the organisms are difficult to culture. Of the 67 cases in which culture was attempted, the organism was isolated in only 16 instances. Various organisms isolated are A *israelii, A. naeslundii, A. odontolyticus, A. viscosus, A. meyeri, A. gerencseriae,* and *Propionibacterium propionicum.* They are established but are a less common cause of the disease. Most actinomycosis is polymicrobial. *Actinobacillus actinomycetemcomitans, Eikenella corrodens, Enterobacteriaceae* and species of *Fusobacterium*, *Bacteroides*, *Capnocytophaga*, *Staphylococcus* and *Streptococcus* are commonly isolated depending upon the site of infection.

Treatment and Prognosis. The treatment of this disease is difficult and has not been uniformly successful. Long standing fibrosis cases are treated by draining the abscess, excising the sinus tract with high doses of antibiotics. Long term high dose penicillin, tetracycline and erythromycin have been used most frequently, but the course of the disease is still often prolonged, In addition to this surgical drainage of the abscesses and excision of sinus tract is necessary to accelerate healing.

BOTRYOMYCOSIS

(Bacterial actinophytosis, actinobacillosis)

Botryomycosis is a chronic granulomatous infection which was recognized over 130 years ago when it was first found to affect horses. Since that time, approximately more than 50 cases occurring in humans have been reported in literature, and the first case involving the oral cavity was reported by Small and Kobernick. There is some confusion as to the actual causative organism in this disease, although an *Actinobacillus* has been thought to be the one involved. Nevertheless, a variety of other types of organisms have been reported which may or may not represent secondary invaders. The *Actinobacillus* is often characterized as an 'associate' organism with the *Actinomycetes,* and some workers feel that the presence of Actinobacilli is necessary for the disease process of actinomycosis. However, actinomycosis is known to occur from a 'pure culture' of *Actinomycetes.* Whether 'pure cultures' of Actinobacilli can produce botryomycosis is not known, but many workers believe that a number of common bacteria such as *Staphylococcus, Streptococcus, Escherichia, Pseudomonas* and probably many others may serve as etiologic agents of the disease.

Clinical Features. Human botryomycosis is usually a localized granulomatous infection of the skin or mucosa. It has been reported in patients with impaired immunity or with underlying systemic conditions such as diabetes mellitus, cystic fibrosis or HIV infection. It may disseminate, involving the liver, lungs or kidneys, in which case the disease is usually fatal. The significance of this disease lies in the fact that the localized infection may closely mimic actinomycosis by producing a chronic granulomatous mass with multiple ulcers and sinuses. The oral case reported by Small and Kobernick involved the tongue and presented clinically as a firm, nodular infiltration of the body and base of the tongue. However, there were no sinuses present.

Differential diagnoses for botryomycosis include mycetoma, tuberculosis, nocardiosis, cat-scratch disease, and fungal infections.

Histologic Features. The chronic granulomatous nodules are characterized by the presence of suppurative foci which contain grains or granules that are recognized as forming around microorganisms in certain cases as apparently a nonspecific reaction between agent and host, possibly related to hypersensitivity. In the ordinary H and E stained section these granules may be indistinguishable from those of actinomycosis. These grains or granules are eosinophilic and PAS negative and negative to methenamine silver. The eosinophilic, peripheral clubs formation typical of actinomycetes is usually not identifiable in this disease.

Treatment. The suggestion has been made that botryomycosis may be caused by a variety of different microorganisms of low virulence, and therefore, the pathogenesis may be related more to a modified host resistance or tissue hypersensitivity than to a specific microorganism. Therefore, treatment is nonspecific. However surgical intervention aids in cure.

TULAREMIA

(Rabbit fever)

Tularemia is a disease caused by the gram-negative, non-motile, bacillus *Francisella tularensis,* also known as *Bacterium tularensis* and *Pasteurella tularensis.* This infection is contracted through contact with infected rodents and rabbits. This exposure and subsequent infection may occur during skinning and dressing freshly killed infected animals, through ingestion of contaminated meat and water, or through the bite of an infected deer fly or tick. This disease is highly communicable from infected

mammals to human. The organisms can persist for longer period of time in mud, water and decaying animal carcasses.

Clinical Features. Based on the site of infection tularemia has six characteristic clinical syndromes namely ulceroglandular (the most common type), glandular, oropharyngeal, pneumonic, oculoglandular and typhoidal. After a variable incubation period of upto seven days, the patient usually suffers a sudden headache, nausea, vomiting, chills, and fever. A single cut or sore on the skin develops into a suppurative ulcer. The lymphatic vessels become swollen and painful and the lymph nodes remarkably enlarged. This general sequel of events is the most common course of the disease and is called ulceroglandular tularemia. The eyes also become involved, with conjunctivitis developing through localization of the disease in the conjunctivital sac, oculoglandular tularemia. Tularemic pneumonia and pleuritis are complications of the disease, which may eventuate in gangrene and lung abscesses.

The disease occurs most frequently in adults. However, as Hughes has reported, children are sometimes affected and, in such cases, the correct diagnosis may be easily overlooked.

Oral Manifestations. The oral lesions account for 3–4% of all cases and are manifested as necrotic ulcers of the oral cavity or pharynx, usually accompanied by severe pain. In some cases it has been reported that a generalized stomatitis develops rather than isolated lesions; single nodular, masses eventually developing into abscesses have also been described. Regional lymphadenitis may arise in the submaxillary and the cervical groups of nodes.

Treatment. The disease responds well to antibiotic therapy. Streptomycin is the drug of choice. This disease also responds to adequate doses of gentamicin and tetracycline. Before the availability of the newer antibiotics, the disease was considered a serious one and even today, in some persons, it may run such a fulminating course that death occurs despite all forms of therapy.

Since *F. tularensis* is easy to aerosolize, highly infective, and the number of organisms needed to infect is very less, it is considered to be a biological weapon.

MELIOIDOSIS

Melioidosis is a specific infection in man and animals, caused by the bacillus *Burkholderia pseudomallei,* an aerobic, gram-negative nonacid-fast, and rod-shaped bacilli. This disease is endemic in certain areas of the far East, including Burma, Ceylon, India, Indochina, Malaysia, Thailand and Dutch East Indies. Military operations in that part of the world by United States Armed Forces have increased the significance of this disease, and cases have now been diagnosed in American servicemen who have returned from duty in Southeast Asia.

Clinical Features. There are two recognized forms of the disease, acute and chronic. In the acute form, the patients rapidly develop a high fever, evidence of acute pulmonary infection, diarrhea, and hemoptysis. There is widespread visceral involvement as a result of hematogenous dissemination of microorganisms. Death, as a result of fulminating septicemia may occur in a few days to weeks.

The chronic form of the disease usually develops in patients who have survived the acute form. It is of granulomatous type, characterized by multiple, small, nonspecific abscesses occurring subcutaneously or in the viscera, lymph nodes or bones, which often develop draining sinus tracts. These may involve the cervicofacial area and mimic fungal infection or tuberculosis.

The most important risk factor for developing melioidosis is diabetes mellitus. Other risk factors include thalassemia and kidney disease. The mode of transmission is not from one man to another man or from contact with the affected animals or animal excretions. The causative organism is abundant in soil and stagnant water where the disease occurs. It is believed that most human infections occur through contamination of skin abrasions by the soil or water. Diagnosis is usually made by culturing the organism from any one of the clinical sample and the throat sample is most sensitive.

Treatment. Incision and drainage, accompanied by massive antibiotic therapy, have proven moderately successful in treating the disease. Tetracycline alone or in combination with chloramphenicol were considered to be drugs of choice.

TETANUS

(Lock-jaw)

Tetanus is an acute infection of the nervous system characterized by intense activity of motor neurons and results in severe muscle spasms. It is caused by the exotoxin of the anaerobic, gram-positive bacillus *Clostridium tetani* that is commensal in human and animal gastrointestinal tracts and soil. It acts at the synapse of the interneurons of inhibitory pathways and motor neurons to produce blockade of spinal inhibition. The organisms can enter the body through even the most trivial injury.

Epidemiology. Tetanus is now a comparatively rare disease in developed countries. It occurs sporadically and almost always affects nonimmunized persons, partially immunized and even, less often, fully immunized individuals. It is common in areas where the soil is cultivated, rural areas, warm climates, and during summer. It is more common in males than females. It usually occurs after acute injuries such as laceration or abrasion. It may be acquired during farming, gardening, etc. It may also occur in patients with abscesses, ulcers and gangrene. It is associated with burns, frostbite, middle ear infection, surgery, abortion, and childbirth. Neonatal tetanus is fatal with a mortality rate of 80–90%. However, in Asia, especially in China, Myanmar, Indonesia and India, the death rate due to neonatal tetanus is greatly reduced due to immunization coverage of pregnant woman with a protective dose of tetanus toxoid. Bhutan, Korea, the Maldives, Sri Lanka and Thailand have declared neonatal tetanus, elimination.

Tetanus occurs mainly in Asia due to four reasons:

- In newborns where the umbilical cord is cut with an unsterile instrument

- In children with otorrhea
- In women with unsterile handling of genital tracts
- After acute trauma.

Pathogenesis. Under the suitable anaerobic conditions with low oxidation-reduction, potential spores of the *Cl. tetani* germinate and produce a potent neurotoxin (tetanospasmin) in the wounds. Once released it binds to the peripheral motor nerve terminal, enters the axon and is transported to the nerve cell body in the brainstem and spinal cord by retrograde intraneuronal transport. The toxin migrate across the synapse to presynaptic termina, where it blocks the release of glycine and gamma-aminobutyric acid (GABA). Once the inhibitory action is diminished, the resting-fixing rate of locomotor neuron increases, producing rigidity. The length of the nerve travelled determines the time of ascent and explains why the disease manifests first in muscles supplied by the short cranial nerves.

Clinical Features. The incubation period ranges from 3 days to 4 weeks. However, it may be as short as one day or as long as months due to dormant spores in the wound. The prophylaxis against tetanus can also prolong the incubation period.

Generalized tetanus is characterized by lock-jaw or trismus due to spasm of masseter, which is the initial symptom and a dental surgeon is the first person often to be consulted.

Dysphagia, stiffness or pain in the neck, shoulder or back muscles appear concurrently. Marked rigidity interferes with the movement of chest and impairs cough and swallowing reflexes. Laryngeal spasms may lead to asphyxia. The involvement of various muscles produces rigid abdomen and stiff proximal limb muscles. Hands and feet are relatively spared and sustained contraction of facial muscles results in a grimace or sneer called as risus sardonicus. The contraction of muscles of the back produces an arched back called opisthotonus. The spasms occur repetitively or spontaneously or provoked by slight stimulation.

Local tetanus manifests as spasm of muscles near the wound and is uncommon. Cephalic tetanus characterized by trismus and facial palsy is rare one, and may occur after head injury or ear infection.

This disease, which has been reviewed in depth by Smith and Myall, is of significance to the dentist because of the acute trismus which may develop in these patients and simulate acute oral infection, trauma, temporomandibular dysfunction and even hysteria.

It should be differentiated from other inflammatory conditions of oral cavity, strychnine poisoning, drug-induced reactions, and hypocalcemic tetany.

Treatment

General measures. The aim of treatment is to remove spores at the site of the wound, prevent toxin production, neutralize unbound toxins and prevent muscular spasms. Cardiopulmonary monitoring should be maintained continuously. Sedation, airway, and nutrition should be maintained. Antibiotics should be given to eradicate vegetative organisms or source of toxins. Penicillin 10–12 million units IV for 10 days, metronidazole 1 gm every 12 hours should be administered. Clindamycin or erythromycin is an alternative for penicillin allergic patients,

Antitoxin is injected to neutralize circulating toxin and unbound toxin.

Human tetanus immunoglobulin (TIG) 3000–6000 units IM individual doses. Though the optimum dose is not known, a 500 unit dose is as effective as higher doses.

Prophylaxis. Wound debridement and booster doses of TT.

Unimmunized individuals. Anti-tetanus serum 1500 units or TIG 250 units should be given.

An active immunization schedule requires three doses triple vaccine in the first year of life with subsequent doses or booster doses of TT at school entry and at 5–10 year interval should be given.

SYPHILIS
(Lues)

Syphilis is a centuries-old infectious disease that has protean clinical features. The name was probably derived from a handsome and wealthy shepherd who was affected by the disease. It is said to have evolved from between 15,000 and 3,000 BC and transported to Asia by Portuguese sailors led by Vasco da Gama. It was an extremely common infection a few decades ago. Widespread use of antibiotics after World War II reduced the incidence of syphilis. However, within the past three decades there has been as astonishing upsurge in the incidence of the disease, much of it in teenagers. Its return is associated with the emerging HIV pandemic.

Syphilis is caused by *Treponema pallidum,* a spirochete, and is characterized by episodes of active disease interrupted by the period of latency. This gram-positivea, motile, microaerophilic spirochete is pathogenic to humans, which may be best demonstrated by the dark field microscope, since it stains poorly except by silver impregnation. In 1998, the complete genetic sequence of *T. pallidum* was reported which might help in understanding the pathogenesis of syphilis.

The route of transmission of syphilis is usually by sexual contact, although there are examples of congenital syphilis via transmission from mother to child in utero.

Epidemiological studies demonstrate that sexually transmitted diseases including syphilis, and particularly genital ulcers associated with primary syphilis, are associated with an increased risk of HIV infection.

Acquired Syphilis

The acquired form of syphilis is contracted primarily as a venereal disease, after sexual intercourse with an infected partner, although persons, such as dentists, working on infected patients in a contagious stage, have innocently acquired it in many cases. The disease, if untreated, manifests three distinctive stages throughout its course, so that it is customary to speak of primary, secondary and tertiary lesion of acquired syphilis.

In the **primary stage,** a lesion known as chancre develops at the site of inoculation approximately 3–90 days after contact with the infection. Chancre is usually solitary but may be multiple at times. It most commonly occurs on the penile in the male and on the vulva or cervix in the female. About 95% of chancres occur on the genitalia, but they are also found in other areas. In recent years, there appears to have been an increase in the occurrence of extragenital syphilis as result of an increase in altered sexual activity and increased contact among infected male homosexuals. Of particular interest to the dentist are those lesions occurring on the lips, tongue, palate, gingiva, and tonsils. The chancre has been reported developing even at the site of a fresh extraction wound. The usual primary lesion is an elevated, ulcerated nodule showing local induration and producing regional lymphadenitis. Such a lesion on the lip may have a brownish, crusted appearance (Fig. 5-6). Very rarely, it appears vascular, mimicking a pyogenic granuloma.

The intraoral chancre is an ulcerated lesion covered by a grayish-white membrane, which may be painful because of secondary infection. The chancre abounds with spirochetes, easily demonstrable by dark field examination of a smear, and is highly infectious. The *Treponema microdentium,* which is found in many nonsyphilitic people, may be confused with *T. pallidum* on dark field examination. Therefore, lesions contaminated by saliva should not be diagnosed by dark field examination of the lesion, but by dark field examination of an affected regional lymph node. An enlarged lymph node is almost always found along the lymphatic draining of the area of the chancre.

The chancre appears microscopically as a superficial ulcer showing a rather intense inflammatory infiltrate. Plasma cells are particularly numerous. The microorganisms are present in the tissue and may be demonstrated by silver stain, although the diagnosis should not be established by this means but, rather, by any one of a variety of serologic tests. Of considerable importance is the fact that not every patient with a primary lesion exhibits a positive serologic reaction despite the presence of a spirochete. The chancre heals spontaneously in three weeks to two months.

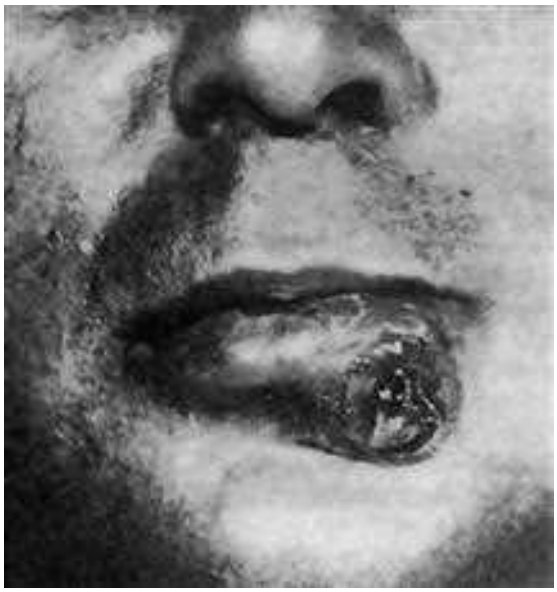
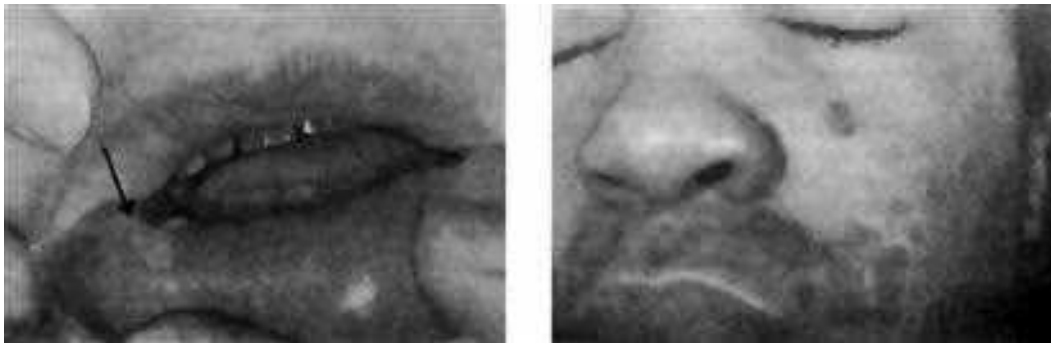


Figure 5-6. Chancre of lip.
(Courtesy of Dr Boynton H Booth).

The **secondary or metastatic stage,** usually commencing about six weeks after the primary lesion, is characterized by diffuse eruptions of the skin and mucous membranes. In contrast to the solitary lesion in the primary stage, lesions of the secondary stage are typically multiple. On the skin, the lesions often appear as macules or papules which are painless. The oral lesions, called 'mucous patches,' are usually multiple, painless, grayish-white plaques overlying an ulcerated surface (Fig. 5-7). They occur most frequently on the tongue, gingiva, or buccal mucosa. They are often ovoid or irregular in shape and are surrounded by an erythematous zone. Mucous patches are also highly infectious, since they contain vast numbers of microorganisms. In the secondary stage the serologic reaction is always positive. The lesions of the secondary stage undergo spontaneous remission within a few weeks, but exacerbations may continue to occur for months or several years.



A B

Figure 5-7. Secondary syphilis.
(A) Mucous patch of lip in secondary syphilis. **(B)** Annular, circinate lesions of skin in secondary syphilis *(Courtesy of Dr Edward V Zegarelli)*.

Secondary syphilis can be present as an explosive and widespread form known as **lues maligna**, characterized by fever, headache, and muscle pain followed by necrotic ulcerations involving the face and the scalp. This form is reported in patients with a compromised immune system, particularly acquired immune deficiency syndrome.

After second-stage patients are free from lesions and symptoms, they enter the latent stage which may last for 1–30 years till the next stage, tertiary syphilis, develops. Patients demonstrate reactive serological test for syphilis.

Tertiary syphilis, also called late syphilis, does not usually appear for several years and involves chiefly the cardiovascular system, the central nervous system, and certain other tissues and organs. Late syphilis is noninfectious. Classic lesion of the tertiary syphilis is gumma. It is the result of hypersensitivity reaction between the host and the treponemes or their breakdown products. Gumma occurs most frequently in the skin and mucous membranes, liver, testes, and bone. It consists of a focal, granulomatous inflammatory process with central necrosis. The lesion may vary in size from a millimeter or less to several centimeters in diameter.

The intraoral gumma most commonly involves the tongue and palate. In either situation the lesion appears as a firm nodular mass in the tissue, which may subsequently ulcerate, to form a deep painless ulcer. Lesions of the palate cause perforation by sloughing of the necrotic mass of tissue. (Fig. 5-8). Such an occurrence frequently follows vigorous antibiotic therapy, a Herxheimer reaction.

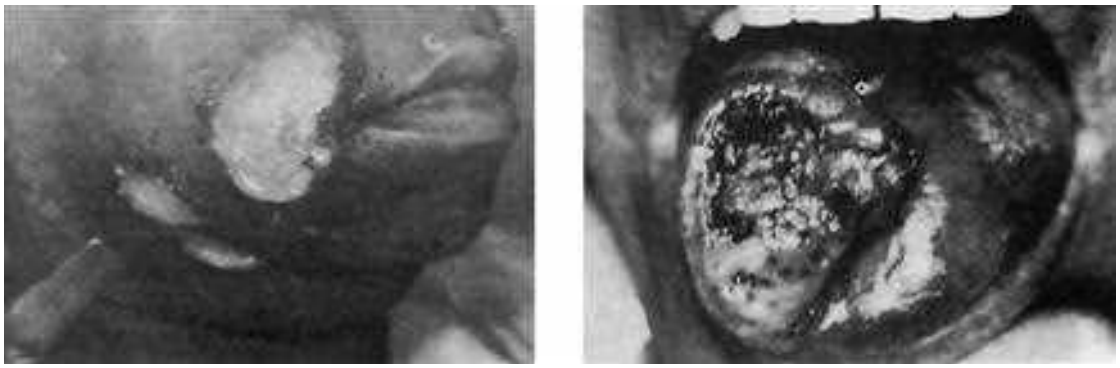
Meyer and Shklar have reported oral manifestations in 81 cases of acquired syphilis, and have stressed that tertiary lesions are far more common than lesions in either primary or secondary syphilis. However this ratio is probably changing. Atrophic or interstitial glossitis is the most characteristic and important lesion of syphilis and is due to endarteritis obliterans.

In syphilitic glossitis, the surface of the tongue gets broken up by fissures due to atrophy and fibrosis of tongue musculature; and hyperkeratosis frequently follows. Syphilitic glossitis is found almost exclusively in males. The predilection for syphilitic glossitis to undergo carcinomatous transformation has been recognized for many years. The incidence of such malignant transformation has been as high as 30% in various reported series. However, in the series of Meyer and Shklar, the development of epidermoid carcinoma in luetic glossitis occurred in only 19% of the cases. In a separate study, the same authors reported that only 7.5% of the patients in a series of 210 cases of carcinoma of the tongue had a past history of syphilis. The prominent apparent decrease in the relationship between syphilis and lingual carcinoma was suggested to be related to the early and intensive treatment of the disease with antibiotics since 1940.

Congenital (Prenatal) Syphilis

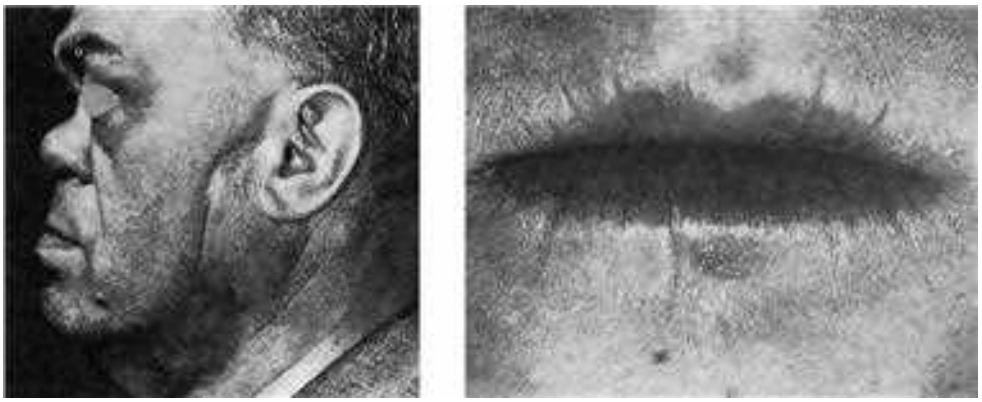
Congenital syphilis is transmitted to the offspring only by an infected mother and is not inherited. Though congenital syphilis is totally preventable, it still continues to be a major problem in many countries. It is recognized that if treatment with antibiotics begins in infected pregnant women before their fourth month of pregnancy, approximately 95% of the offspring of these mothers will be free of the disease. It is to be noted that not all infected pregnant women deliver children with congenital syphilis. One-third of pregnancies result in abortion or stillbirth; one-third deliver normal children and the rest deliver children with congenital syphilis. Persons with congenital syphilis manifest a great variety of lesions, including frontal bossae (found in 87% of a series of 271 patients with congenital syphilis reported by Fiumaraand Lessell), short maxilla (in 84%), high palatal arch (in 76%). saddle nose(in 73%), mulberry molars (in 70%); Higoumenakis sign or irregular thickening of the sternoclavicular portion of the clavicle (in 39%), relative protuberance of mandible (in 26%), rhagades (in 7%), and saber shin (in 4%) (Fig. 5-9). Reportedly pathognomonic of the disease is the occurrence of Hutchinson's triad: hypoplasia of the incisor and molar teeth, eighth nerve deafness, and interstitial keratitis (q.v.).

In the above reported series, 75% of the persons with congenital syphilis had one or more of the components of



A B

Figure 5-8. Tertiary syphilis.
(A) Gumma of skin. **(B)** Gumma of tongue *(Courtesy of Dr Charles A Waldron).*



A B

Figure 5-9. Congenital syphilis.
Saddle nose **(A)** and rhagades or radiating fissures **(B)** of congenital syphilis *(Courtesy of Dr Wilbur C Moorman and Dr Robert J Gorlin)*.

Hutchinson's triad. It is unusual; however, for all features of this triad to occur simultaneously in the same person.

Diagnosis and Treatment. Wassermann test and Hinton test (based on flocculation) were considered to be effective tests for the diagnosis of syphilis, but the disadvantage is false positive results. The diagnosis can be made by examining the exudates of the active lesion under a dark field microscope for spirochaetes. Care should be taken to eliminate salivary contamination since false positive results are possible due the presence of *T. microdentium, T. macrodentium,* and *mucosum.* Specific and highly sensitive serological tests are fluorescent treponemal antibody absorption and *T. pallidum.* hemagglutination assays.

Penicillin is the drug of choice. Erythromycin or tetracycline is used if the patient is allergic to penicillin. Surgical correction of the facial defects gives good esthetic results.

GONORRHEA

Gonorrhea is primarily a venereal disease affecting the male and female genitourinary tract and is transmitted by sexual intercourse. It is an infection of epithelium and commonly manifests as cervicitis, urethritis, prostatitis, and conjunctivitis. It is caused by *Neisseria gonorrhoeae* a gram-negative, nonmotile, nonspore forming organism that grows in pairs *(diplococci).* The common age group affected is 15–29 years with about half in the adolescent age.

It is a significant cause of morbidity in developing countries and may play a role in the transmission of HIV. In India gonorrhea is more widely prevalent than syphilis and 80% of infected women are reported to be asymptomatic carriers. It predominantly affects young persons.

The incidence of gonorrhea has increased in developing countries, but the exact incidence is difficult to ascertain because of limited surveillance and variable diagnostic criteria. It is transmitted from males to females and vice versa. Oropharyngeal gonorrhea occurs in 20% of women who practice fellatio with infected partners. The incubation period is one to five days.

Clinical Features. Infection in males results in acute urethritis, dysuria and urethral discharge of a purulent nature. Some patients may have mucoid discharge. It may lead to epididymitis, chronic prostatitis, balanitis and posterior urethritis.

In females, it manifests as cervicitis with candidal or trichomonal vaginitis. Mostly they are symptomatic. Carrier symptoms include vaginal discharge, discomfort, and dysuria. It may affect the rectum, oropharynx, and the eye.

Oral Manifestations. Extragenital gonorrheal infection of oral cavity is being seen with increasing frequency, especially among but not confined to homosexuals, and occurs as a result of oral-genital contact or inoculation through infected hands. Transmission by fomites is rare. Schmidt and coworkers have reviewed the literature on gonococcal stomatitis and have pointed out the clinical similarity between the oral lesions of this disease and the oral lesions of erythema multiforme, erosive or bullous lichen planus, and herpetic stomatitis. Chue has also reviewed this disease, describing the various oral lesions in detail. The lips may develop acute painful ulceration, limiting motion; the gingiva may become erythe-matous, with or without necrosis; and the tongue may present red, dry ulcerations or become glazed and swollen with painful erosions, with similar lesions on the buccal mucosa and palate.

Gonococcal pharyngitis and tonsillitis are also well recognized lesions. These appear as vesicles or ulcers with a gray or white pseudomembrane. Oral lesions are commonly accompanied by fever and regional lymphadenopathy. Finally, gonococcal parotitis, presumably a result of an ascending infection from the duct to the gland, has been reported on numerous occasions.

Complications. Epididymitis, salpingitis, pelvic inflammatory disease, and bartholinitis are the usual copmlications. Gonococcal bacteremia leads to dermatitis and arthritis. Joint

involvement leads to arthritis or arthralgia with effusion. Patients with gonorrhea are at risk for additional sexually transmitted diseases, most commonly *Chlamydia trachomatis.*

Diagnosis. Rapid diagnosis is done by Gram staining of urethral discharge. Samples can be collected with Dacron or Rayon swabs. Special media used for gonococcus are Thayer-Martin media or Stuart or Armies media.

Treatment. Antibiotics and other preventive measures should be followed.

GRANULOMA INGUINALE

(Granuloma venereum, donovanosis)

Granuloma inguinale was first recognized in India by McLeod in 1882. This disease is a progressive, chronic, infectious, granulomatous disease caused by microorganisms, probably bacilli, formerly designated as Donovania granulomatis and popularly called Donovan bodies, but now carrying the name **Calymmatobacterium granulomatis**. Their taxonomic status is uncertain. It is considered to be a venereal disease, but is only mildly contagious. Care should be exercised not to confuse granuloma inguinale with lymphogranuloma venereum, a venereal disease that is caused by strains of *Chlamydia trachomatis,* once designated as viruses but now morphologically classified as bacteria. The oral cavity is not notably involved in this latter disease.

Clinical Features. The disease is most prevalent in the tropical zones, but is found in the southern portion of the United States. It chiefly affects adult blacks of either gender, but may occur in any race. The primary lesions of granuloma inguinale appear on the external genitalia, anus, and in the inguinal region. They are manifested as papules or nodules, which ulcerate to form clean, granular lesions with rolled margins and which show a tendency for peripheral enlargement. Occasionally, verrucous, necrotic, or cicatricial lesions have been reported. Satellite lesions often arise through lymphatic extension. Inguinal ulceration is commonly secondary to the genital lesions and arises initially as a fluctuant swelling known as a pseudobubo.

Extragenital lesions also may occur on the oral mucous membranes, usually through autoinoculation rather than as a primary infection, as well as in the pharynx, esophagus, and larynx. Finally, metastatic spread to bones and soft subcutaneous tissues has been, reported. Two separate investigators have reported an incidence of extragenital lesions of granuloma inguinale to be 6% and 1.5%, respectively.

Oral Manifestations. Oral lesions appear to be the most common extragenital form of granuloma inguinale. Ferro and Richter, who described additional cases, have reviewed the reported cases. The lesions of the oral cavity are usually secondary to active genital lesions and appear in a variable period of time after the primary lesion, frequently months to several years later. The definitive diagnosis rests upon the demonstration of Donovan bodies in tissue from the lesions. Lesions may occur in any oral location such as the lips, buccal mucosa, or palate, or they may diffusely involve the mucosal surfaces. The varied clinical appearance of the lesions is the basis for their classification into one of three types: ulcerative, exuberant, and cicatricial. Thus there may be painful ulcerated lesions, sometimes bleeding, suggestive but not pathognomonic of the disease. Or, in other instances, the lesions may appear as proliferative granular masses, with an intact epithelial covering. The mucous membrane generally may be inflamed and edematous. Cicatrization is one of the most characteristic of the oral manifestations of granuloma inguinale. Fibrous scar formation may become extensive, and if present in areas such as the cheek or lip, may also limit mouth opening as to necessitate surgical relief.

Histologic Features. The microscopic pattern of the various forms of granuloma inguinale is one of granulation tissue with infiltration of polymorphonuclear leukocytes and plasma cells. There is usually a marked overlying pseudoepitheliomatous hyperplasia. Pathognomonic of the disease is the presence of large mononuclear phagocytes, each containing intracytoplasmic cysts within which are found the Donovan bodies. These bodies are tiny, elongated, basophilic and argyrophilic rods and are present in profuse numbers within the macrophages. Differential diagnoses of oral lesions include all granulomatous lesions of the oral cavity. Where genital lesions are also present, other sexually transmitted disease must be considered in differential diagnosis.

Treatment. Tetracycline, chloramphenicol, streptomycin garamycin, and cotrimoxazole are effective in the treatment of this disease. Complete healing usually occurs within two to three weeks. It has been noted that, after treatment, improvement of the genital lesions is usually accompanied by improvement of the extragenital oral lesion; conversely, exacerbation of genital lesions usually results in worsening of the oral condition.

RHINOSCLEROMA

(Scleroma)

Rhinoscleroma is a chronic, slowly progressive, localized infectious, granulomatous disease caused by the bacillus *Klebsiella rhinoscleromatis* (Klebsiella type 3), a gram-negative non-motile bacillus. This etiologic agent has been discussed in detail by Hoffman. This disease has worldwide distribution and is endemic in countries such as China, India, Indonesia, Africa, South and Central America, and in central parts of Eastern Europe. The mode of transmission is through infected nasal exudate.

The granulomatous, nodular lesions that occur in rhinoscleroma are found chiefly in the upper respiratory tract, often originating in the nose, but involvement of the lacrimal glands, orbit, skin, paranasal sinuses, and intracranial invasion have also been described. The proliferative nasal masses may produce the configuration known as the 'Hebra nose,' which is typical of this disease.

Oral lesions appearing as proliferative granulomas are also known to occur. In addition, impairment of the sensation of taste, anesthesia of the soft palate and enlargement of the uvula and upper lip are described. Three cases of rhinoscleroma

seen in a maxillofacial practice in Nigeria have been discussed by Edwards and associates, who have included an extensive bibliography of the disease.

Treatment of this disease consists of administration of tetracycline or ciprofloxacin. If left untreated the outcome will be fatal.

NOMA

(Cancrum oris, gangrenous stomatitis)

Noma, which means to devour (a spreading sore), is a rapidly spreading mutilating, gangrenous stomatitis that occurs usually in debilitated or nutritionally deficient persons associated with high morbidity and mortality. It is seen chiefly in children but is also found in adults under certain conditions, such as those existing among the malnourished internees of the Belsen concentration camp reported by Dawson after World War II. Today, the disease is rare in North America and Western Europe. Most cases occur in Africa, Southeast Asia and South America. For example, one of the last reports of an extensive series was that of Enwonwu, who described 69 cases of noma in 'miserably malnourished' Nigerian children between the ages of two and seven years. He also documented occurrence of necrotizing ulcerative gingivitis (NUG) in 27% of Nigerian children hospitalized for treatment of protein-calorie malnutrition.

Predisposing factors play an important role in the development of this condition, since it occurs chiefly in persons who are undernourished or debilitated from infections such as diphtheria, dysentery, measles, pneumonia, scarlet fever, syphilis, tuberculosis, and blood dyscrasias, including anemia. Thus noma may be considered a secondary complication of systemic disease rather than a primary disease.

Noma appears to originate as a specific infection by Vincent's organisms, an acute necrotizing gingivostomatitis, which is soon complicated by secondary invasion of many other microbial forms, including streptococci, staphylococci, and diphtheria bacilli.

Selye reported the production of a noma-like condition in rats as a result of simultaneous administration of cortisone and clipping of the mandibular incisors, forcing the animals to chew with their gingiva and thus to cause excessive mechanical injury to the mucosa. This condition usually began around the gingiva and progressed to destroy the floor of the mouth and the lower lip. The increase in susceptibility of the rat tissues to injury, induced by the cortisone, could be eliminated by the simultaneous administration of pituitary growth hormone (somatotrophic hormone, or STH). On the basis of his experimental findings, Selye suggested that noma may not necessarily be due to a specific pathogenic agent, but may be due to a 'pathogenic situation' resulting from faulty adaptation to a nonspecific injury or stress.

Clinical Features. Noma usually begins as a small ulcer of the gingival mucosa which rapidly spreads and involves the surrounding tissues of the jaws, lips, and cheeks by gangrenous necrosis (Fig. 5-10). The initial site is commonly an area of stagnation around a fixed bridge or crown. The overlying skin

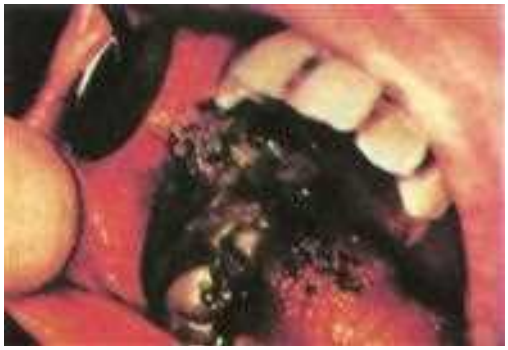


Figure 5-10. Noma.

becomes inflamed, edematous and finally necrotic, with the result that a line of demarcation develops between healthy and dead tissue, and large masses of the tissue may slough out, leaving the jaw exposed. The commencement of gangrene is denoted by the appearance of blackening of the skin. It is reported that the subcutaneous fat pad and buccal fat pad undergo necrosis in advance of the other adjoining tissues.

The odor arising from the gangrenous tissues is extremely foul. The palate and occasionally the tongue may become involved in this process, but this is not common. Patients have a high temperature during the course of the disease, suffer secondary infection and may die from toxemia or pneumonia.

Treatment and Prognosis. The mortality rate of noma approximated 75% before the availability of antibiotics. Although the disease is still serious, the prognosis is considerably better if antibiotics are administered before the patient reaches the final stages. Immediate treatment of any existing malnutrition further improves the probability of saving the patient.

CAT-SCRATCH DISEASE

(Cat-scratch fever, benign lymphoreticulosis, benign nonbacterial regional lymphadenitis)

Cat-scratch disease was first reported by Debre and his coworkers in 1950. Once it was thought to be a viral infection and was even called nonbacterial regional lymphadenitis. Though common in the USA and Britain, it is relatively rare in the Indian subcontinent. The causative organism is *Bartonella henselae,* a gram-negative bacillus demonstrable with silver stain.

Clinical Features. This disease, occurring at any age, but predominantly in children and young adults, is thought to arise after a traumatic break in the skin due to the scratch or bite of the household cat. On rare occasions, dogs and monkeys have served as the vector. Actually, there is a definite history of scratches in only 55–60% of patients, according to Rickles and Bernier, although 90% of patients with the disease had recent contact with cats. The primary lesion is often a papule, pustule or vesicle that develops at the site of the injury. Within one to three weeks, a regional lymphadenitis without lymphangitis develops. The cat apparently serves only as a carrier of the disease, since the animal is not ill and does not respond to the intradermal antigen test.

The lymphadenopathy is usually the cause for the patients seeking professional advice. In a series of 115 patients with clinical cat-scratch disease reported by Margileth, 57% had lymphadenopathy involving the extremities, and 43%, the head and neck. The nodes are painful and may be several centimeters in diameter. The overlying skin may be inflamed. This lymphadenopathy may persist for one to six months and may be accompanied in the early stages of the disease by a low-grade fever, headache, chills, nausea, malaise, or even abdominal pain. Other manifestations occasionally seen include a nonpruritic macular or maculopapular rash, parotid swelling, conjunctivitis, and grand mal seizures. Another unusual manifestation of the disease, reported by Carithers, is the oculoglandular syndrome of Parinaud. This consists of a localized granuloma of the eye and preauricular lymphadenopathy. The lymph nodes gradually become soft and fluctuant, owing to necrosis and suppuration. Pus has been reported in numerous studies to be bacteriologically sterile. Occasionally, an abscessed node will perforate the skin and drain.

If the preauricular, submaxillary, or cervical chain of nodes are involved, the dentist may be consulted to rule out dental disease as an etiologic factor. Cat-scratch disease may also resemble more serious infectious granulomatous diseases such as tuberculosis or tularemia, lymphogranuloma venereum, infectious mononucleosis, or Hodgkin's disease and lymphosarcoma.

Diagnosis is usually established by a positive intradermal skin test of antigen from a patient with proved cat-scratch disease. This test is not invariably positive, however. Indirect immunofluorescent antibody assay is used for detecting antibodies to *Bartonella henselae.* The alternate one is finding IgM antibodies to the organism by ELISA.

Histologic Features. Early in the course of the disease the involved lymph nodes manifest reticuloendothelial hyperplasia; later, destruction of lymph node architecture with focal granulomas, suppuration, and necrosis develops with capsular thickening. Epithelioid cells and multinucleated giant cells are occasionally seen. The microscopic appearance is not particularly pathognomonic, but is certainly suggestive. Warthin-Starry silver staining demonstrates the causative organisms taken in areas free from significant necrosis. Brown-Hopps Gram staining method may also be used to highlight the bacilli.

Prognosis. The prognosis is good, since the disease is self-limiting and regresses within a period of weeks or months. Incision and drainage of the involved node may be necessary. Antibiotic therapy is ineffective.

PYOGENIC GRANULOMA

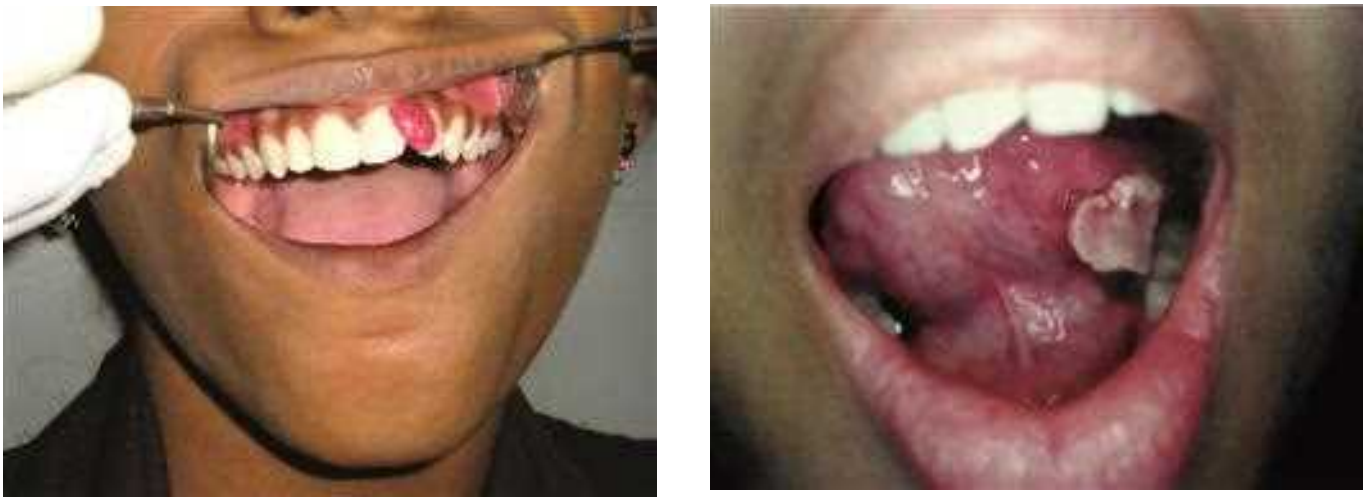
(Granuloma pyogenicum)

It is a distinctive clinical entity originating as a response of the tissues to a nonspecific infection. It is a tumor like growth that is considered as an exaggerated, conditioned response to minor trauma. The term pyogenic granuloma was applied based on an identical lesion on the skin, thought to be caused by pyogenic organisms. However, this is no longer accepted. It is of particular significance because of its common intraoral occurrence and because of its alarming clinical course sometimes.

Etiology. Pyogenic granuloma was originally believed to be a botryomycotic infection, an infection in horses thought to be transmissible to man. Subsequent work suggested that the lesion was due to infection by either staphylococci or streptococci, partially because it was shown that the microorganisms could produce colonies with fungus like characteristics. It is now generally agreed; however, that the pyogenic granuloma arises as a result of some minor trauma to the tissues, which provides a pathway for the invasion of nonspecific types of microorganisms. The tissues respond in a characteristic manner to these organisms of low virulence by the overzealous proliferation of a vascular type of connective tissue. Some investigators think that penetration of microorganisms into the tissues does not occur or is negligible, since microorganisms can seldom be demonstrated deep in the lesion with appropriate bacterial staining techniques. The surface of the pyogenic granuloma, especially in areas of ulceration, abounds with typical colonies of saprophytic organisms.

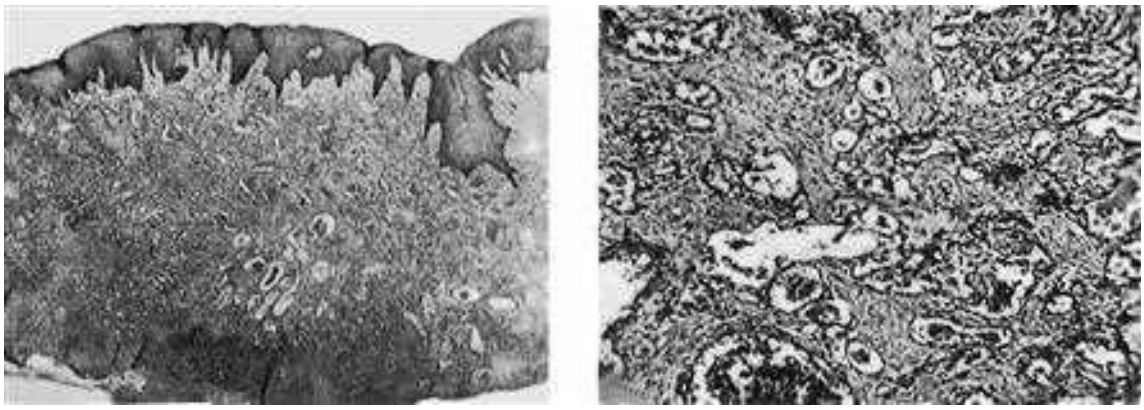
This tissue response reiterates the well-known biologic principle that any irritant applied to living tissue may act either as a stimulus or as a destructive agent, or as both. In adult tissues, the relative quiescence of the cells may be due either to an active restraint of growth or to a passive absence of stimulus for growth. Tissue culture studies of adult cells have shown that there is no active restraint of growth. It may then be assumed that tissues of embryos and young animals contain stimuli for the proliferation of cells. The sulfhydryl radical is probably one of the most essential stimulating agents. Burrows believed that all cells give off a stimulating substance. If many cells are present in a small volume of tissue and there is a relative reduction of blood flow through the area, as in inflammation, the concentration of this stimulating substance will be high and growth will be stimulated. As differentiation and maturation are attained, the cells become widely separated; the concentration of the substance falls, and little growth occurs. In the type of inflammation which results in the formation of pyogenic granuloma, the destruction of the fixed tissue cells is slight, but the stimulus to proliferation of the vascular endothelium persists and exerts its influence over a long period of time.

Clinical Features. The pyogenic granuloma of the oral cavity arises most frequently on the gingiva accounting around 75% of all cases. It may also occur on the lips, tongue and buccal mucosa, and occasionally on other areas. The lesion is usually an elevated, pedunculated or sessile vascular mass with a smooth, lobulated, or even a warty surface, which commonly is ulcerated and shows a tendency for hemorrhage either spontaneously or upon slight trauma (Fig. 5-11). The lesions are more common in the facial aspect than the lingual or palatal aspects of gingiva and can occur involving both sides including interdental papilla. It may be single or occurs at more than one site, unilateral or bilateral especially when it involves gingiva. Sometimes there is exudation of purulent material, but this is not a characteristic feature despite the suggestive



A B

Figure 5-11. Pyogenic granuloma.
Gingiva **(A)** and tongue **(B)**.



A B

Figure 5-12. Pyogenic granuloma.
(A) Low-power photomicrograph of pyogenic granuloma covered on the surface by epithelium and on the other by a fibrinous exudate; the vascularity of the lesion is obvious. **(B)** High-power photomicrograph of A demonstrates the numerous endothelium-lined blood channels and fibroblasts.

name of this lesion. It is deep red or red purple, depending upon its vascularity, painless, and rather soft in consistency. Some lesions have a brown cast if hemorrhage has occurred into the tissue.

The pyogenic granuloma may develop rapidly, reach full size and then remain static for an indefinite period. The lesion is more common in the maxillary anterior region than the posterior region. The lesions in different cases may vary considerably in size, ranging from a few millimeters to a centimeter or more in diameter. In an excellent study of the pyogenic granuloma, in which he reported 289 cases, Kerr stated that the age group incidence was not significant, cases having been seen in both very young infants and elderly persons with no apparent predilection for any one age group. Nor were any significant differences in occurrence found between the genders. However, in a series of 835 cases discussed by Angelopoulos, he noted that about 60% of the lesions occurred in persons between 11 and 40 years of age, that over 70% involved females. The reason for female predilection is because of vascular effects of female hormones.

An **intravenous pyogenic granuloma** occurring on the neck and upper extremities has been reported by Cooper and his associates in a series of 18 patients between 15 and 66 years of age. These lesions, which appear to represent a different entity from that known as intravascular papillary endothelial hyperplasia (q.v.), have not been reported in the oral cavity.

Histologic Features. The histologic appearance of the pyogenic granuloma is similar to that of granulation tissue except that it is exuberant and is usually well localized (Fig. 5-12). The overlying epithelium, if present, is generally thin and atrophic, but may be hyperplastic. If the lesion is ulcerated, it shows a fibrinous exudate of varying thickness

over the surface. The most startling features are the occurrence of vast numbers of endothelium-lined vascular spaces and the extreme proliferation of fibroblasts and budding endothelial cells. In addition, there is usually a moderately intense infiltration of polymorphonuclear leukocytes, lymphocytes, and plasma cells, but this finding will vary, depending upon the presence or absence of ulceration. The connective tissue stroma is typically delicate, although frequently fasciculi of collagen fibers are noted coursing through the tissue mass. If the lesion is not surgically excised, there is gradual obliteration of many capillaries, and it assumes a more fibrous appearance. This maturation of the connective tissue elements is construed as evidence of healing of the lesion. Both clinically and microscopically, an old lesion may resemble a fibroepithelial polyp or even a typical fibroma, and it is likely that many so-called intraoral fibromas are healed pyogenic granulomas.

Pregnancy tumor is histologically identical to pyogenic granuloma of the gingiva frequently occurring during pregnancy and often has been called the pregnancy tumor. This is a well-defined lesion, which appears about the third month of pregnancy or sometimes later, gradually increases in size and, after delivery, may or may not regress (Fig. 5-13). If surgically removed during pregnancy, it frequently recurs. It is now believed by most workers that the pregnancy tumor is simply a pyogenic granuloma which occurs as a result of local minor trauma or irritation and in which the tissue reaction is probably intensified by the endocrine alteration occurring during pregnancy. There appears to be no justification for retaining the term pregnancy tumor, since lesions of an identical clinical and histologic nature are seen in men as well as in non-pregnant women.

Treatment and Prognosis. Pyogenic granulomas are treated by surgical excision. The lesion occasionally recurs because it is not encapsulated, and the surgeon may have difficulty in determining its limits and excising it adequately. Some recurred lesions may represent examples of a second episode of irritation with reinfection of tissue.

When excising a pyogenic granuloma of the gingiva, extreme care should always be taken to scale the adjacent tooth and make certain that it is free of calculus, since the calculus may act as the irritation leading to recurrence of the lesion. Careful microscopic examination of excised pyogenic granulomas will almost invariably reveal fragments of calculus on the inner surface of the lesion which was adjacent to the tooth.

PYOSTOMATITIS VEGETANS

Pyostomatitis vegetans is an uncommon inflammatory disease of the oral cavity originally described by McCarthy in 1949. The name was suggested because of the clinical similarity between the oral lesions of this disease and the skin lesions in a dermatologic disease known as 'pyodermatite végetanté'. The disease has been described in even greater detail by McCarthy and Shklar, who pointed out that the oral lesions are one part of a syndrome in which the patients also manifest concomitantly ulcerative colitis or other gastrointestinal disturbances. In fact, the history of colitis or a gastrointestinal disturbance often points to the diagnosis of the oral lesions. Regional enteritis or regional ileitis, also known as Crohn's disease, is a granulomatous inflammation of the intestine of unknown etiology which is also recognized as one form of gastrointestinal disturbance that may be associated with pyostomatitis vegetans. This has been discussed by Cataldo and his associates who illustrated a case in which the oral lesions ultimately led to the diagnosis of the intestinal disease. A few patients with liver disease also have oral manifestations related to pyostomatitis vegetans.

Oral Manifestations. The oral lesions consist of large numbers of broad based papillary projections, tiny abscesses or vegetations developing in areas of intense erythema (Fig. 5-14). These lesions may occur in any area of the oral cavity, although tongue involvement appears to be uncommon. The oral lesions may precede or occur concurrently with systemic disease. These many small projections are red or pink in color, but careful examination may show tiny pustules beneath the epithelium, which liberate purulent material when ruptured. These leave areas of ulceration, which may coalesce, into large areas of necrosis known as snail track ulcerations. The protean oral manifestations of 24 cases of Crohn's disease have been

Figure 5-13. Pyogenic granuloma occurring in women during the later months of pregnancy.

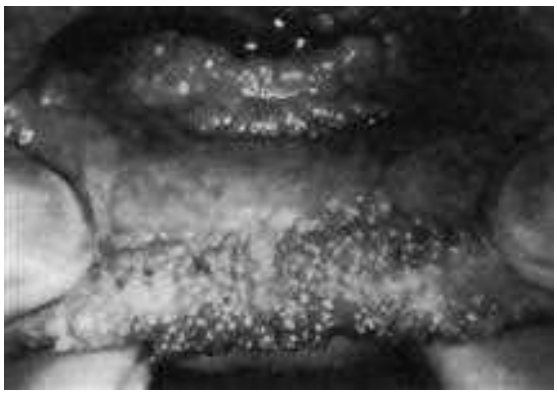


Figure 5-14. Pyostomatitis vegetans.
(Courtesy of Dr Nathaniel H Rowe).

reviewed in detail by Bernstein and McDonald. They noted that the most frequently affected area was the buccal mucosa which presented a 'cobblestone' appearance, while the vestibular lesions appeared as folds and ulcers, the lips were diffusely swollen and indurated, gingival and alveolar mucosal lesions were granular, and erythematous swellings, and palatal lesions appeared as multiple aphthous ulcers.

Histologic Features. The papillary projections generally show hyperplastic stratified squamous epithelium with an underlying loose connective tissue which is generally densely infiltrated by large numbers of plasma cells, lymphocytes, and occasional polymorphonuclear leukocytes, sometimes with a preponderance of eosinophils. Tiny areas of focal necrosis and microabscess formation, either intraepithelial or subepithelial, are common features of the lesions. In some instances, focal areas of degeneration and necrosis of the overlying epithelium are present.

Laboratory Findings. Bacteriologic studies are generally nonspecific, since only organisms of the normal oral microbial flora can be cultured from smears of the lesions.

Treatment. The treatment of pyostomatitis vegetans is not specific, since the oral lesions are usually refractory to antibiotic therapy. It has been found that the oral lesions tend to regress when the intestinal disturbance is brought under control. However, exacerbations of the gastrointestinal disease frequently result in exacerbation of the oral lesions as well.

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CHAPTER 6

Viral Infections of the Oral Cavity

■ B SIVAPATHASUNDHARAM, N GURURAJ AND K RANGANATHAN

CHAPTER OUTLINE

The Latin word *virus* means venom or poison. Viruses are ultramicroscopic, metabolically inert, infections organism. They live and multiply in the living cells. Viruses are almost infinite in distribution, affecting not only plants and animals, including man, but also insects and even bacteria. The size of viruses has been measured by various techniques and ranges between 10 millimicrons or less to more than 200 millimicrons. Virus consists of a central core of DNA or RNA (but never both) surrounded by a capsid made up of proteins or an ensheathed outer envelope made of glycoproteins and lipids derived from the host cell membranes. It has been suggested that virally infected cells produce the nucleic acid characteristics of the virus and that, therefore, the susceptibility of cells to viral infection may depend upon the availability of suitable nucleic acid within the cell to sustain the virus.

Viruses have long been known to cause certain infectious diseases, and many of them produce a long-lasting immunity against reinfection by the same virus. In addition, there are many neoplasms in animals that have been transmitted by cell free extracts of the tumor to other animals, establishing a viral etiology. More recent proof of the viral origin of certain animal leukemias has given impetus of the search for specific viruses in the cause of human cancer and the possibility of immunization against this disease.

The mechanism of viral replication (adsorption, penetration, uncoating, synthesis, maturation and release) in the susceptible host cell is unique to the different group of viruses, and influences the pathogenesis, diagnosis, management and clinical manifestations. The sequelae of viral infection of the host cell could be

Acute infection	:	Usually due to lysis of the cell, example: polio virus
Latent infection	:	With periodic activation, example: herpes virus
Persistent infection	:	Persistent for many years, example: HIV, hepatitis B
Transformation	:	Transformation into malignant cells, example: certain subtypes of HPV and retroviruses

The classification of viral diseases is difficult because of the size of viruses and their incompletely understood metabolic systems. However, their classification based on the biologic, chemical and physical properties of the animal viruses, separating them into groups according to the type of nucleic acid, and the size, shape and substructure of the particle, has been undertaken by the International Committee

on Nomenclature of Viruses of the International Association of Microbiological Societies. This classification, with examples of human diseases in the various groups, is shown in Table 6-1.

Table 6-1: Classification of major virus groups and virus diseases

RNA viruses
- (a) Orthomyxovirus
  - Influenza
- (b) Paramyxovirus
  - (i) Measles (rubeola)
  - (ii) Mumps
- (c) Rhabdovirus
  - (i) Rabies
  - (ii) Hemorrhagic fever
- (d) Arenavirus
  - (i) Lymphocytic choriomeningitis
  - (ii) Lassa fever
- (e) Calicivirus
- (f) Coronavirus
  - (i) Upper respiratory infection
- (g) Bunyavirus
- (h) Picornavirus
  - (i) Poliomyelitis
  - (ii) Coxsackie diseases
  - (iii) Common cold
  - (iv) Foot-and-mouth disease
  - (v) Encephalomyocarditis
- (i) Reovirus
- (j) Togavirus
  - (i) Rubella
  - (ii) Yellow fever
  - (iii) St. Louis encephalitis
- (k) Retrovirus (RNA tumor virus)

DNA viruses
- (a) Herpesvirus
  - (i) Herpes simplex virus 1
    Gingivostomatitis, keratoconjuctivitis, genital and skin lesions
  - (ii) Herpes simplex virus 2
    Genital and skin lesions, keratoconjuctivitis, neonatal infections, meningitis
  - (iii) Varicella zoster virus
    Varicella (Chicken pox)
  - (iv) Cytomegalovirus
    Cytomegalic inclusion disease
  - (v) Epstein-Barr virus
    Infectious mononucleosis, hepatitis, encephalitis
  - (vi) Human herpes virus 6
    Otitis media, encephalitis
  - (vii) Human herpes virus 7
    Roseola infantum
  - (viii) Human herpes virus 8
    Infectious mononucleosis, febrile exanthema
  - (ix) Simian herpes virus
    Mucocutaneous lesions, encephalitis
- (b) Poxvirus
  - (i) Smallpox
  - (ii) Molluscum contagiosum
- (c) Adenovirus
  - (i) Pharyngoconjunctival fever
  - (ii) Epidemic keratoconjunctivitis
- (d) Parvovirus
- (e) Iridovirus
- (f) Papovavirus
  - (i) Human warts or papillomas
  - (ii) Tumorigenic viruses in animals

Modified after JR McGhee, SM Michalek, and GH Cassell: Dental Microbiology. Philadelphia, Harper and Row, 1982.

Diagnostic confirmation of viral infection by laboratory investigations is slow and difficult. Thus, most viral infections are diagnosed by their clinical presentation.

HERPES SIMPLEX

(Acute herpetic gingivostomatitis, herpes labialis, fever blisters, cold sores)

Herpes simplex, an acute infectious disease, is probably the most common viral disease affecting man, with the exception of viral respiratory infections. The tissues preferentially involved by the herpes simplex virus (HSV), often referred to as herpes virus hominis, are derived from the ectoderm and consist principally of the skin, mucous membranes, eyes, and the central nervous system. HSV is composed of double stranded DNA, protein capsid, tegument and lipid envelope, which contains glycoproteins derived from the nuclear membrane of host cells. There are two immunologically different types of HSV: type 1 and type 2. They differ antigenically and biologically, but share 50% of the nucleotide sequence. Many types of specific regions exist in both HSV 1 and 2 and are responsible for host immunity. These subtypes can be distinguished serologically or by restriction endonuclease analysis of the DNA. A state of latency and reactivation is common in many viral infections, especially the herpes group. The incubation period is 1–26 days and can occur throughout the year. Transmission is mainly through close contact, kissing, sharing of glasses, cutlery or crockery, etc.

Pathogenesis. The primary HSV infection is usually acquired through direct contact with affected area or through secretions. The virus once attached to the cells at inoculation site through specific receptors; it replicates too many virions to the maximum number and discharges to neighboring cells. Subsequently it affects adjacent cells, spreads to distant sensory nerve endings and autonomic axons, further to adjacent related ganglia, and remains latent there. The lymph node is involved through viral proteins by mobile dendritic cells and begins its primary immune response. The reason for the wide anatomical distribution and multiple crops may be due to descending spread of virions back to periphery from various neuronal site. Initial or primary infection is asymptomatic and occurs commonly in childhood or infancy. This disease manifests as characteristic vesicles containing desquamated cells, multinucleated giant cells, and free viruses with edema fluid. Though both subtypes produce orofacial and genital lesions, which are clinically indistinguishable, HSV-1 predominantly affects the face, lips, the oral cavity, and upper body skin; and HSV-2 usually affects the genitals and skin of the lower half of the body. Primary infection resolves and the virus can no longer be recovered from ganglia but viral DNA can be found in the ganglion cells. Both humoral and cell mediated immunity is responsible for the clinical manifestation, latency, and recurrence of the disease. Immune-compromised individuals, especially with impaired cellular immunity, are more prone for dissemination and recurrence of the primary disease.

An in-depth summary of the structure, composition, growth cycle, and cytopathogenic effects of HSV-1 has been published by Hicks and Terezhalmy. Gruter was among the first to offer evidence that the herpes simplex infection was caused by an infectious agent and that the fluid of vesicles from patients with herpes simplex would produce keratitis when inoculated on scarified rabbit cornea. Subsequently, the virus has been found to multiply well on the chorioallantoic membrane of the chick embryo. Andrews and Carmichael, in 1930, found that neutralizing antibodies against the herpes simplex virus were present in the circulating blood of most normal adults and persisted throughout life, but that recurrent herpetic lesions frequently developed in these persons.

These and other studies have finally led to the established principle that two types of infection with the herpes simplex virus occur. The first is a **primary infection** in a person who does not have circulating antibodies, and the second is a **recurrent infection** in persons who have such antibodies. It is impossible to differentiate clinically between the lesions of a primary and a recurrent attack, although the primary infection is accompanied more frequently by severe systemic manifestations and is occasionally fatal. It has been shown; however, that most adults have circulating antibodies in the blood, but have never exhibited a severe primary illness. Thus, it is reasoned, subclinical primary infections must be common. The relation between the primary and secondary forms of the herpes simplex infection is shown in Figure 6-1.

Herpes genitalis, caused by HSV-2, is a relatively common disease of the uterine cervix, vagina, vulva, and penis. The incidence of this form of the infection has increased precipitously in the United States within the past decade, and in fact, is now often termed the 'new epidemic venereal disease,' since it is transmitted through sexual contact. This virus differs immunologically from type 1 herpes virus, which is responsible for most cases of herpetic infection of the oral cavity. The type 2 virus of genital herpes is somewhat more virulent than type 1, and significantly, has been associated repeatedly with carcinoma of the uterine cervix, thus suggesting a possible cause and effect relationship. However, because of changing sexual practices, there has been rather widespread translocation in the usual habitats of type 1 and type 2 HSV. Thus, it is not unusual today to find HSV-2 on the lips or oral mucous membranes and HSV-1 on the genitalia.

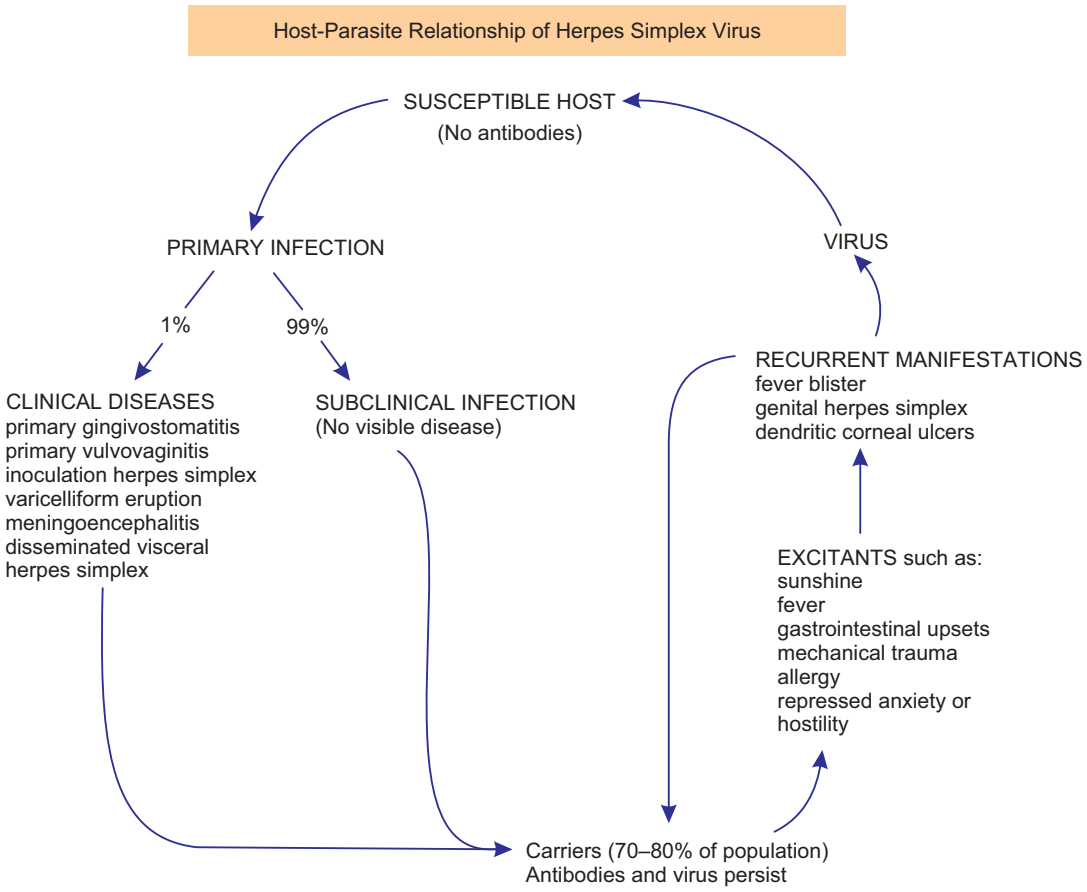


Figure 6-1. Relationship of primary and recurrent herpes simplex.
(Courtesy of Dr Harvey Blank. From H. Blank and G. Rake: Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. Boston, Little, Brown and Company, 1955).

Herpetic meningoencephalitis is a serious form of this infection, characterized by sudden fever and symptoms of increased intracranial pressure. Paralysis of various muscle groups occurs, while convulsions and even death may ensue. It is difficult to differentiate clinically between meningoencephalitis caused by the herpes virus and that produced by other viruses.

Herpetic conjunctivitis, or keratoconjunctivitis, is a rather common disease and is characterized by swelling and congestion of the palpebral conjunctiva, although keratitis and corneal ulceration also may occur. Herpetic vesicles of the eyelids are typical, but these eye lesions usually heal rapidly.

Herpetic eczema (Kaposi's varicelliform eruption) is an epidermal form of the herpetic infection superimposed upon a pre-existing eczema (possibly an example of anachoresis) and is characterized by diffuse vesicular lesions of the skin, usually of an extremely serious nature. In addition to this atopic dermatitis, the herpetic infection may also be superimposed on severe seborrheic dermatitis, impetigo, scabies, Darier's disease, and pemphigus vulgaris or foliaceus. It is most frequently due to the primary herpetic attack and may be fatal. The patients, usually children, exhibit a high fever, coincident with the typical umbilicated vesicles as well as other systemic manifestations.

Disseminated herpes simplex of the newborn is a relatively uncommon disease in which the newborn baby acquires the infection during passage through the birth canal of a mother who is suffering from herpetic vulvovaginitis. However, occasional cases of transplacental infection by the virus have been reported. These infants usually manifest the disease by the fourth to seventh day of life, exhibit a wide variety of signs and symptoms of the disease and with few exceptions, usually die on the 9th to 12th day of life. Surviving infants frequently show residual neurological involvement.

Herpetic whitlow occurs in fingers due to autoinoculation.

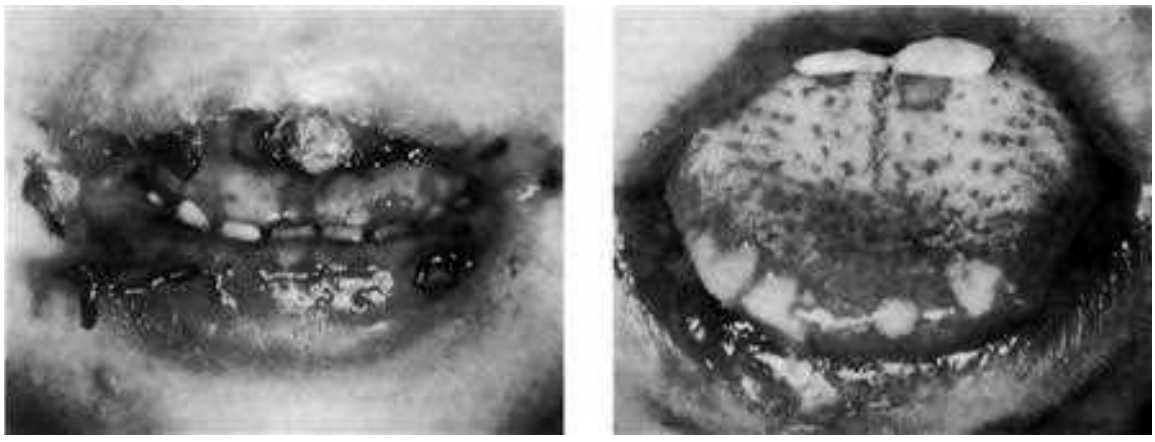
Herpes gladiatorum occurs in wrestlers.

Primary Herpetic Stomatitis

Dodd and her coworkers reported that the herpes simplex virus could be isolated from patients suffering from a gingivostomatitis with a particular clinical configuration. Burnet and Williams reported similar findings, and in addition, demonstrated that infants with this disease developed circulating antibodies during the convalescent period.

Clinical Features. Herpetic stomatitis is a common oral disease transmitted by droplet spread or contact with the lesions. It affects children and young adults. However, it has been suggested by Sheridan and Herrmann that the primary form of the disease is probably more common in older adults than was once thought. It rarely occurs before the age of six months, apparently because of the presence of circulating antibodies in the infant derived from the mother. The disease occurring in children is frequently the primary attack and is characterized by the development of fever, irritability, headache, pain upon swallowing, and regional lymphadenopathy. Within a few days, the mouth becomes painful and the gingiva which is intensely inflamed appears erythematous and edematous. The lips, tongue, buccal mucosa, palate, pharynx, and tonsils may also be involved. Shortly, yellowish, fluid-filled vesicles develop. These vesicles rupture and form shallow, ragged, extremely painful ulcers covered by a gray membrane and surrounded by an erythematous halo (Fig. 6-2). It is important to recognize that the gingival inflammation precedes the formation of the ulcers by several days. The ulcers vary considerably in size, ranging from very tiny lesions to lesions measuring several millimeters or even a centimeter in diameter. They heal spontaneously within 7–14 days and leave no scar.

Utilizing culture techniques, August and Nordlund found that the HSV-1 could be isolated from facial, labial, and oral herpetic lesions for a mean duration of three-and-a-half days, with a range of 2–6 days, after the onset of the lesions, while



A B

Figure 6-2. Primary herpetic gingivostomatitis.
The children in both cases exhibited severe involvement of the lips and oral cavity *(Courtesy of Dr Warren B Davis and Dr John R Mink).*

HSV-2 could be isolated from genital lesions for a mean duration of five-and-a-half days, with a range of 2–14 days, after onset. They also noted that viral persistence in lesions did not seem to differ between mild primary infection and recurrent infection. In addition, Turner and his colleagues have shown that HSV could survive for two to four hours on environmental surfaces such as cloth and plastic as well as on the skin of the hands contaminated by direct contact with labial or oral lesions.

It is now well established that the HSV does not remain latent at the site of the original infection in the skin or oral mucosa. Instead, the virus reaches nerve ganglia supplying the affected areas, presumably along nerve pathways, and remains latent there until reactivated. The usual ganglia involved are the trigeminal for HSV-1 and the lumbosacral for HSV-2. Viral DNA can be demonstrated in these ganglia. Unfortunately, this incorporation of viral DNA into host DNA ensures a lifelong infection beyond the reach of antibody, cell mediated immune responses or chemotherapy.

Mode of Transmission. The fact that the herpes virus may be recovered from the saliva of patients during the course of the disease leads to the assumption that transmission may occur by droplet infection, although some workers believe that direct contact is necessary. There is no animal reservoir for this virus. It has been reported in one series of patients that a history of contact with affected persons was present in nearly 50% of the cases. After such contact, the incubation period appears to range from 2–20 days, with an average of six days before development of lesions. There also have been occasional epidemics of herpetic stomatitis, such as that reported by Hale and his associates in an orphanage nursery. In addition, it has been noted that primary herpetic eruptions are commonly associated with pneumonia, meningitis, and common cold.

Histologic Features. The herpetic vesicle is an intraepithelial blister filled with fluid. The infected cells are swollen and have pale eosinophilic cytoplasm and large vesicular nuclei, described as 'ballooning degeneration,' while others characteristically contain intranuclear inclusions known as Lipschütz bodies. These are eosinophilic, ovoid, homogeneous structures within the nucleus, which tend to displace the nucleolus and nuclear chromatin peripherally. The displacement of chromatin often produces a peri-inclusion halo. Cytoplasm of the infected cells forms giant cells. The subjacent connective tissue is usually infiltrated by inflammatory cells. When the vesicle ruptures, the surface of the tissue is covered by exudates made up of fibrin, polymorphonuclear leukocytes, and degenerated cells. The lesions heal by peripheral epithelial proliferation.

Diagnosis. It can be diagnosed both clinically and by laboratory procedures. Scrapings obtained from the base of the lesions are stained with Wright's, and Giemsa stain. Pap stain demonstrates balloon cells, multinucleated giant cells and intranuclear inclusions. Though cytological procedures give a quick result but it will not differentiate between HSV and varicella zoster virus (VZV). More than that, identification of giant cells requires experience.

HSV can be demonstrated in the laboratory by isolation of virus in tissue culture or by DNA in the scrapings from lesions. The most sensitive and accurate method for diagnosing these lesions is PCR technique.

Treatment. Antiviral drugs have significant impact on the course of the disease, if it is diagnosed early. Antibiotic therapy helps in the prevention of secondary infection. Nonsteroidal anti-inflammatory drugs and topical anesthetic gel may relieve the discomfort considerably.

Latency

It is a state in viral infection in which the viral genome is present in non-replicating stage in an infected cell, but can become active intermittently. Establishment of latency is contributed by host factors like neurons, IgG, CD8+ cytotoxic T-lymphocytes, and cytokines and viral factors include downregulation of α gene expression and DNA replication. Latent stage is maintained by viral genes expressed primarily during latency. Expression of these latency-associated genes may function to keep the viral genome from being digested by cellular ribozymes or being found out by the immune system.

Recurrent or Secondary Herpetic Labialis and Stomatitis

Recurrent herpetic stomatitis is usually seen in adult patients and manifests itself clinically as an attenuated form of the primary disease. It has been reported by Nahmias and Roizman that between 80 and 100% of adults in the lower socioeconomic levels have HSV-1 and/or HSV-2 circulating antibodies, whereas only 30–50% of adults in the higher socioeconomic levels, including medical, dental, and nursing personnel, have such antibodies. Those without antibodies are at higher risk of contact and infection, especially the latter groups because of the nature of their occupation. Also, as pointed out by Rowe and his coworkers, recurrent lesions of the fingers or hands (herpetic whitlow) and eyes may be encountered in these professional groups more frequently than in the general population.

The recurrence is related to reactivation of infection and various theories namely (i) ganglionic trigger theory due to nerve section, surgery, or fever (ii) skin trigger theory due to UV light or trauma and (iii) emotional theory due to stress, have been put forward for reactivation. The recurrent form of the disease is often associated with other factors like fatigue, menstruation, pregnancy, upper respiratory tract infection, allergy, or gastrointestinal disturbances. The mechanism through which these various precipitating factors elicit an outbreak of lesions is unknown. The viruses, once introduced into the body, appear to reside dormantly within the regional ganglia, and when reactivation is triggered, spread along the nerves to sites on the oral mucosa and skin where they destroy the epithelial cells and induce the typical inflammatory response with the characteristic lesions of recurrent infection.

Figure 6-3. Recurrent herpetic vesicle of the lip.
(Courtesy of Dr Ajayprakash P and Dr Susma P, Kamineni Institute of Dental Sciences and Hospitals, Narketpally, Andhra Pradesh).

Clinical Features. Recurrent herpes simplex infection may occur at widely varying intervals, from nearly every month in some patients to only about once a year or even less in others. The lesions may develop either at the site of primary inoculation or in the adjacent area supplied by the involved ganglion. It may develop on the lips (recurrent herpes labialis, Fig. 6-3) or intraorally (Fig. 6-4). In either location, the lesions are frequently preceded by a burning or tingling sensation and a feeling of tautness, swelling or slight soreness at the location in which the vesicles subsequently develop. These vesicles are generally small (1 mm or less in diameter), tend to occur in localized clusters, and may coalesce to form somewhat larger lesions. These gray or white vesicles rupture quickly, leaving a small red ulceration, sometimes with a slight erythematous halo. On the lips, these ruptured vesicles become covered by a brownish crust. The degree of pain present is quite variable.

It has been emphasized by Weathers and Griffin that the recurrent intraoral herpetic lesions almost invariably develop on the oral mucosa that is tightly bound to periosteum. Seldom do they occur on mobile mucosa, in contrast to the recurrent aphthous stomatitis (q.v.) which almost invariably occurs only on mobile mucosa. Thus, the most common sites for the recurrent intraoral herpetic lesions are the hard palate and attached gingiva or alveolar ridge. Interestingly, herpes labialis is seldom seen concurrently with intraoral lesions.

The lesions gradually heal within 7–10 days and leave no scar.

Histologic Features. A number of investigators, beginning with Blank and his associates, have shown that the Papanicolaou smear, using fresh scrapings from the base of a vesicle, is a reliable technique for the diagnosis of active herpes simplex infection if herpes zoster/varicella infection is ruled out, since no other conditions produce a similar cytopathic effect. 'Ballooning degeneration,' chromatin margination and typical Lipschütz bodies as described earlier are all seen in smears from these lesions, as well as characteristic multinucleated giant cells originally observed by Tzanck (Fig. 6-5). Nowakovsky and her coworkers have thoroughly reviewed

Figure 6-4. Recurrent intraoral herpes simplex infection.

the manifestations of viral infections in exfoliated cells. The histologic findings in biopsy specimens from the recurrent lesions are identical to those described under the primary form of the disease.

Laboratory Findings. Isolation of the herpes simplex virus can be accomplished in tissue culture, particularly in the early stages of the recurrent infection. According to Tokumaru, the virus is easily isolated when there is a low production of γ-A globulin, but there is a rapid clearing of the virus, often within one day, after a rebound production of γ-A globulin. Similarly, smears would be positive for only a short time after the virus has cleared because of the rapid degeneration of the affected cells.

Current diagnostic methods for herpes viral diagnosis have been reviewed by Burns. These have included:

- Viral isolation and identification in various systems, including eggs, and mice, as well as cell culture technique.
- Immunofluorescent staining of smears, impressions, or cryostat sections with fluorescein-labeled HSV protein or antibody protein.
- Immunoperoxidase technique, which is reportedly far more sensitive than the immunofluorescence technique, is similar in basic principle but does not require fluorescence microscopy.
- Serologic assays such as the complement fixation assay, radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA).

Treatment. Until recently, little could be provided in the way of actual therapy except for symptomatic relief, although many drugs have been tested over the years.

Several specific antiviral chemotherapeutic agents are presently available for use under certain conditions and with certain forms of HSV infection. The most prominent of these are: (1) acyclovir (9– [2– hydroxyethoxymethyl] guanine); (2) vidarabine (adenine arabinoside); and (3) idoxuridine (5–iodo-2'-deoxyuridine). However, these must only be used according to prescribed indications and do not represent curative drugs for this disease.

Differential Diagnosis. A consideration of differential diagnosis is of great importance, since numerous diseases may bear some resemblance to herpes simplex. Thus, some

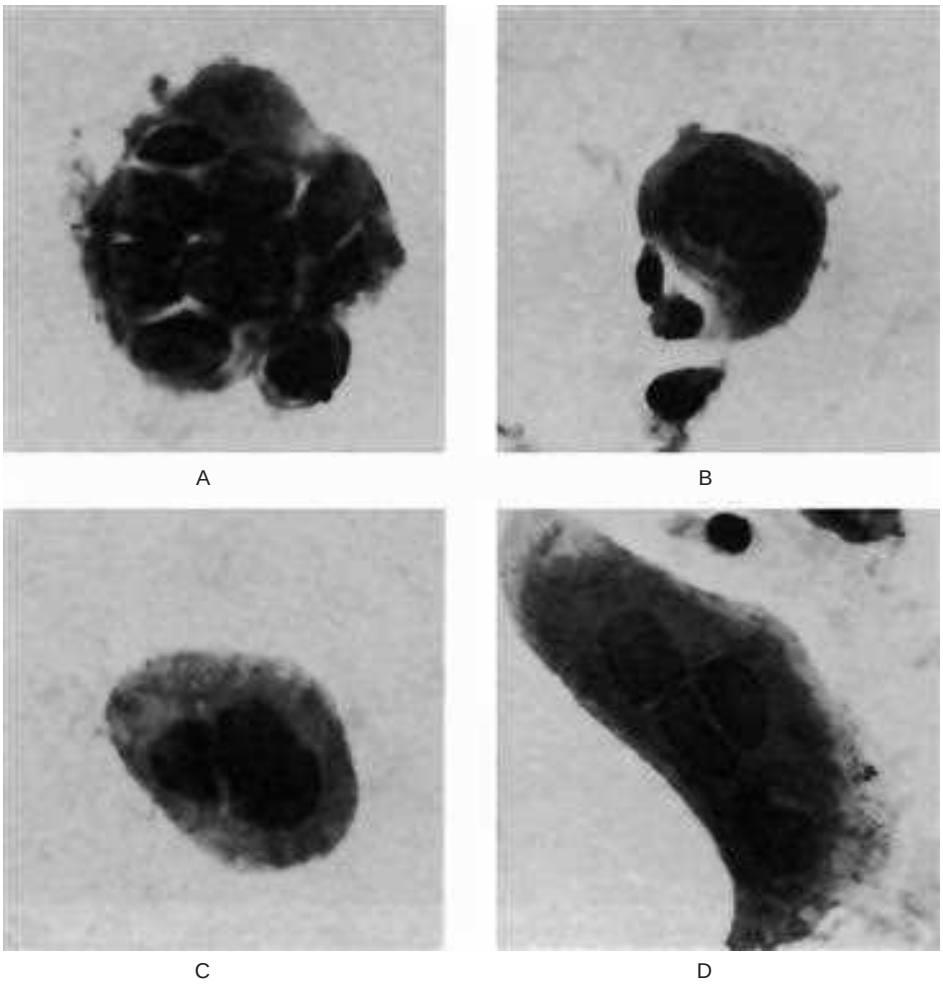


Figure 6-5. Recurrent intraoral herpes simplex infection.
Cytologic smear of lesions shows typical alterations in epithelial cells infected by herpes simplex virus.

difficulty may be encountered in distinguishing herpes simplex particularly from the recurrent aphthous stomatitis (q.v.). Other conditions to be considered are herpes zoster, impetigo, erythema multiforme, and related diseases, smallpox, pemphigus, epidermolysis bullosa, food or drug allergies, and chemical burns.

HERPANGINA

(Aphthous pharyngitis, vesicular pharyngitis)

Herpangina is a specific viral infection, which was described by Zahorsky in 1920 and later named by him. Studies by Huebner and coworkers proved that Coxsackie group A viruses are the cause of the disease, with types 1 through 6, 8, 10, 16, and 2 , as well as other enteroviruses, being isolated at various times. Infection occurs through ingestion, direct contact, or through droplet spread and multiple cases in a single household are common.

Clinical Features. The incubation period is probably 2–10 days. It is most commonly seen in young children; older children and adults are only occasionally affected. Herpangina is chiefly a summer disease, and many children may actually harbor the virus at this time without exhibiting clinical manifestations of the disease.

The clinical manifestations of herpangina are comparatively mild and of short duration. It begins with sore throat, cough, rhinorrhea, low-grade fever, headache, sometimes vomiting, prostration, and abdominal pain. The patients soon exhibit small vesicles which rupture to form crops of ulcers, each showing a gray base and an inflamed periphery on the anterior faucial pillars and sometimes on the hard and soft palates, posterior pharyngeal wall, buccal mucosa; and tongue (Fig. 6-6). Vesicles preceding the ulcers are small and of short duration, and are frequently overlooked by the examiner. The ulcers do not tend to be extremely painful, although dysphagia may occur. The systemic symptoms resolve within few days. Ulcers generally heal within 7–10 days.

Children have been affected several times in one season by infection with different strains of the Coxsackie virus. A permanent immunity to the infecting strain usually develops rapidly, and most adults have neutralizing antibodies against numerous strains.

Laboratory Findings. The Coxsackie virus can be isolated in suckling mice or hamsters by inoculation of scrapings

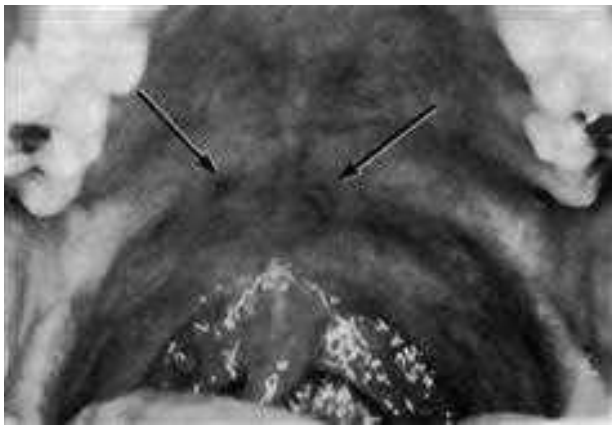


Figure 6-6. Herpangina.
Small ulcers are shown on the soft palate and fauces.

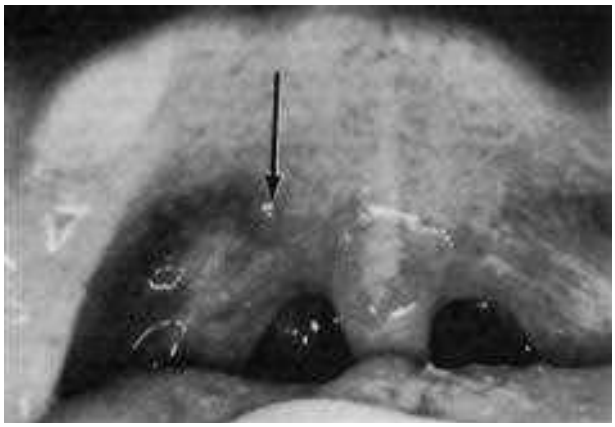


Figure 6-7. Acute lymphonodular pharyngitis.
Small papules are present on the soft palate and fauces.

from the throat lesions or stool specimens of nearly all patients who manifest clinical signs and symptoms of the disease or who have had contact with infected patients. Although there are distinct immunologic differences between various strains of herpangina virus, animal inoculation of any type produces the same manifestations—destruction of skeletal muscles followed by death. Even after the disappearance of clinical manifestations of the disease in the human patient, the virus may still be isolated from him/her for one to two months.

Treatment. No treatment is necessary, since the disease appears to be self-limiting and presents few complications. Those reported have consisted of acute parotitis, meningitis, hemolytic anemia, and hemorrhagic diathesis.

ACUTE LYMPHONODULAR PHARYNGITIS

Acute lymphonodular pharyngitis is an acute febrile disease, first reported by Steigman and coworkers in 1962. It is caused by a strain of Coxsackie virus A10. The first recognized outbreak of the disease occurred in the vicinity of Louisville and Fort Knox, Kentucky, during the fall of 1960. Since then it has been recognized as occurring with a wide distribution. Delay in recognition of the disease as an entity may have occurred because of the marked resemblance between this and herpangina.

Clinical Features. The disease affects predominantly children and young adults, although older adults are also occasionally involved. The chief complaints consist of sore throat, an elevation of temperature varying from 100°–105° F, mild headache, and anorexia. Typically, the patients do not manifest rhinorrhea, cough, tracheitis, gingivostomatitis, skin eruptions, arthralgia, otitis media, or lymphadenopathy.

The symptomatic course varies from 4–14 days and the local oral lesions resolve within 6–10 days, although a residual ring of fading erythema may sometimes be seen for several days. The estimated incubation period of the disease is 2–10 days.

Oral Manifestations. The lesions, characteristic of the disease, are raised, discrete, whitish or yellowish to dark pink solid papules or nodules, surrounded by a narrow zone of erythema (Fig. 6-7). The lesions are not vesicular and do not ulcerate. The lesions characteristically appear on the uvula, soft palate, anterior pillars, and posterior oropharynx.

Laboratory Findings. Primary isolation of Coxsackie A10 virus can be established in suckling mice by inoculation of throat swab or fecal material. Serologic evidence of infection by this virus is also positive.

Histologic Features. The papules or nodules consist of hyperplastic lymphoid aggregates. In some cases the overlying epithelium show inclusion of bodies which in some instances are intranuclear but in others, cytoplasmic.

Treatment. No specific treatment is necessary as the disease is self-limiting. It has been found that antibiotic therapy is of no benefit.

HAND, FOOT AND MOUTH DISEASE

Hand, foot and mouth disease is an epidemic infection, first reported by Robinson and coworkers in 1958. It is caused by the enterovirus Coxsackie A16 and has been reported to be caused less frequently by types A5 and A6, and occasionally even by B2, B5 or enterovirus 71. This first recognized outbreak of the disease occurred in Toronto, Canada, but since then it has appeared in many parts of the United States, as well as in many other countries around the world. Despite the similarity in names, it bears no relationship to foot-and-mouth (hoof-and-mouth) disease, another viral disease with an animal vector.

Clinical Features. The disease is primarily one affecting young children, the majority of cases occurring between the ages of six months and five years. It is characterized by the appearance of maculopapular, exanthematous, and vesicular lesions of the skin, particularly involving the hands, feet, legs, arms, and occasionally the buttocks. The patients commonly manifest anorexia, low-grade fever, coryza and sometimes lymphadenopathy, diarrhea, nausea, and vomiting.

Oral Manifestations. A sore mouth and refusal to eat is one of the most common findings in the disease. This is due to the small, multiple vesicular, and ulcerative oral lesions that are more numerous than seen in herpangina. In the series of cases reported by Adler and his associates, sore mouth was the principal symptom in 90% of the patients, and oral lesions were present in 100% of the patients. The most common sites for the oral lesions were the hard palate, tongue, and buccal mucosa, with a much smaller percentage of patients showing involvement of the lips, gingiva and pharynx, including the tonsils. The tongue may also become red and edematous.

Laboratory Findings. Intracytoplasmic viral inclusions can sometimes be demonstrated in vesicular scrapings of the lesions. It has been found that these inclusions are indistinguishable from those found in vaccinia. In addition, viral isolates may usually be obtained from rectal or throat swabs from vesicular fluid itself. Finally, there is generally a remarkable rise in acute or convalescent serum antibody titer to Coxsackie A16. In a few patients there is concomitant rise in herpes simplex virus antibody titer, but this is probably a fortuitous occurrence. Nevertheless, the clinical findings of hand, foot and mouth disease and of herpes simplex infection may be remarkably similar so that the two may be separated only with appropriate laboratory viral tests.

Treatment. No specific treatment is necessary since the disease is self-limiting and generally regresses within one to two weeks.

Differential Diagnosis. There is an obvious similarity in the clinical appearance of the oral lesions of hand, foot and mouth disease and a variety of other conditions which may be encountered. In an excellent review of this disease, McKinney has listed several such conditions to be considered in the differential diagnosis, including herpetic gingivostomatitis, herpangina, erythema multiforme, recurrent aphthous ulcers, and animal foot-and-mouth disease.

FOOT-AND-MOUTH DISEASE

(Aphthous fever, hoof-and-mouth disease, epizootic stomatitis)

Foot-and-mouth disease is a viral infection, which only rarely affects man, but does affect dogs and sheep as well as cattle. Transmission of the disease occurs through contact with infected animals; in human beings this is usually through the use of milk from affected animals or through the handling of tissues from these animals. An excellent review of foot-and-mouth disease in human beings was published by Roset. This disease should not be confused in nomenclature with hand, foot and mouth disease, a Coxsackie virus infection previously discussed.

Clinical Features. When it is transmitted to the human, foot-and-mouth disease manifests itself clinically by fever, nausea, vomiting, malaise, and the appearance of ulcerative lesions of the oral mucosa and pharynx. Development of vesicles on the skin also occurs in some cases. These vesicular lesions appear most commonly on the palms and soles.

Oral Manifestations. The lesions of the oral mucosa may occur at any site, although the lips, tongue, palate, and oropharynx appear to be those chiefly affected. These lesions begin as small vesicles, which rapidly rupture, but heal usually within two weeks.

MEASLES

(Rubeola, red spots, morbilli)

Measles is an acute, contagious, dermatropic and endemic viral infection, primarily affecting children and occurring many times in epidemic form. It is caused by paramyxovirus belonging to the family paramyxoviridae, which is a RNA virus. Outbreaks are often cyclic in their appearance and are seen commonly at two- or three-year intervals. Spread of the disease occurs by direct contact with an affected person or by droplet infection, the portal of entry being the respiratory tract.

Epidemiology. Measles has a worldwide distribution but incidence is more in developing countries. In Asia, incidence was reduced after the introduction of a vaccine schedule, but resurgence of measles may be due to failure to immunize infants and young children, and failure of vaccination or waning immunity. The mortality rate is high among children and adults. It varies from 1–10% in developing countries. It is contagious from first or second day even before the onset of serious illness or appearance of rash. It is transmitted mainly through respiratory secretions and also through direct contact of droplets. The incubation period is generally from 8–12 days. It is mainly transmitted in large families, crowded homes and slums. It is a self-limiting disease in healthy immune competent children, but morbidity and mortality is high in malnourished and immunocompromised individuals.

Pathogenesis. Upon invasion of respiratory epithelium it reaches reticuloendothelial system through blood stream and thereby infect skin, respiratory tract, and other organs. The invasion of T lymphocytes and increased levels of suppressive cytokines leads to transient suppression of cellular immunity. Monocyte is mainly infected. Symptoms show mainly due to the infection of the entire respiratory epithelia and the secondary infection with bacteria. Viremia develops, but specific antibodies are not developed before the onset of rash. Cellular immunity plays a major role in host defense against measles.

Clinical Features. There are three stages in measles namely pre-eruptive stage or prodromal stage, eruptive stage and post-eruptive stage. Incubation period of 8–10 days, is characterized by the onset of fever, malaise, cough, conjunctivitis, photophobia, lacrimation, and eruptive lesions of the skin and oral mucosa. Skin eruptions usually begin on the face, in the hair line and behind the ears, and spread to the neck, chest, back, and the extremities. These appear as tiny red macules or papules which enlarge and coalesce to form blotchy, discolored, irregular lesions which blanch upon pressure and gradually fade away in four to five days with a fine desquamation.

Oral Manifestations. The oral lesions are prodromal, frequently occurring two to three days before the cutaneous rash,

and are pathognomonic of this disease. These intraoral lesions are called Koplik's spots and have been reported to occur in as high as 97% of all patients with measles. The Koplik's spots are white papules resembling table salt like crystals with red base which appear usually on the buccal mucosa opposite to first and second molar teeth. Immune reaction to the virus in the endothelial cells of dermal capillaries plays a role in the development of spots. The spots disappear after the onset of rash. In actual practice, they are seldom seen unless the affected child has had a known contact with measles and the dentist or parent watches carefully, since the child is often well at the time they appear. These characteristic spots are small, irregularly shaped flecks which appear as bluish, white specks surrounded by a bright red margin. These macular lesions increase in number rapidly and coalesce to form small patches. Palatal and pharyngeal petechiae as well as generalized inflammation, congestion, swelling, and focal ulceration of the gingiva, palate and throat may also occur.

Histopathological features show pathognomonic multinucleated giant cells called Warthin–Finkeldey giant cells.

Complications. Measles is a disease which lowers the general body resistance, and for this reason, often leads to complications. These may include diarrhea, bronchial pneumonia, encephalitis, otitis media, and occasionally, noma. In addition, it has been recognized that measles has an immunosuppressive effect through impairment of cell-mediated immunity. Thus, while it may result in a delay in wound healing, it may also cause induction of remission of leukemia and Hodgkin's disease. The disease is rarely fatal except in the case of secondary complications.

Control Measures. Measles vaccines are available as single or in combination (MMR). In Asian countries, especially in India, the Edmonton–Zagreb (E-Z strain) 5 ml of vaccine is given subcutaneously. Studies have suggested the age for vaccination as nine months. A second dose should be given in the form of MMR at 15–18 months for adequate immunity.

RUBELLA

(German measles)

Rubella or the German measles should not be confused with rubeola. In rubella, Koplik's spots do not occur, and the oral mucous membranes are not usually inflamed, although the tonsils may be somewhat swollen and congested and red macules may appear on the palate. Complications following this disease are rare except when the disease occurs in women during the first trimester of pregnancy. In such cases, the offspring has a high incidence of congenital defects such as blindness, deafness, and cardiovascular abnormalities, if miscarriage does not occur.

Occasionally reports in the literature have suggested that rubella affecting women during the first trimester of pregnancy can cause a number of developmental defects, including enamel hypoplasia, a high caries incidence, and delayed eruption of deciduous teeth. However, a study by Grahnen provided some evidence that maternal rubella did not give rise to any clinically detectable defects in either the deciduous or permanent dentition of the offspring.

SMALLPOX

(Variola)

Smallpox is an acute viral disease which, before the discovery of vaccination by Jenner, was epidemic in nature and accounted for literally millions of deaths. For example, in Europe alone at the end of the 18th century, it is estimated that at least 400,000 people died of the disease each year.

The World Health Assembly in 1958 requested the Director General of WHO to study the implications of a global smallpox eradication program, and in 1967, such a program was initiated. During 1967, 131,000 cases of smallpox were reported, although 10–15 million cases are estimated to have occurred in 33 countries with the endemic disease and 14 other countries reporting importations.

On December 9, 1979, the WHO Global Commission for the Certification of Smallpox eradication declared:

- Smallpox eradication has been achieved throughout the world.
- There is no evidence that smallpox will return as an endemic disease.

This was officially endorsed by the World Health Assembly Meeting in Geneva on May 8, 1980, when, in Resolution 33.3, it 'declares solemnly that the world and all its people have won freedom from smallpox ... an unprecedented achievement in the history of public health ...'.

The last known patient in the world with 'wild' or natural smallpox was a hospital cook in Somalia who developed the rash on October 26, 1977. Two other cases did occur in Birmingham, England, in 1978 as a result of a laboratory accident, but there have been no further cases, even though six laboratories throughout the world are known to be maintaining this virus.

Thus, there has been official international acceptance of the fact that, for the first time in history, a disease has been totally eliminated from this planet, an effort to which all future generations should pay tribute. The long eradication campaign is a fascinating documentation of public health officials carrying out a complex program with great technical, financial, and administrative problems. Some of this information has been published by Breman and Arita and provides a fascinating insight into many aspects of this disease.

A discussion of the clinical and oral manifestations of smallpox is still maintained here in as much as all members of the United States overseas military forces still receive smallpox vaccinations, one complication of which is the development of the disease itself. Such vaccinations are still used because of the possibility of germ warfare, since controlled stocks of live virus are still maintained in certain countries.

Clinical Features. Smallpox, after an incubation period of 7–10 days, manifests itself clinically by the occurrence of a high fever, nausea, vomiting, chills, and headache. The patient is extremely ill and may become comatose during this period.

The skin lesions begin as small macules and papules which first appear on the face, but rapidly spread to cover much of the body surface. Within a few days the papules develop into vesicles which themselves eventually become pustular. The pustules are small, elevated, and yellowish green with an inflamed border. They are secondarily infected and occasionally become hemorrhagic, a most serious portent. Desquamation marks the beginning of the healing phase of the disease. Severe pitting or pocking of the skin as a result of pustule formation is a common complication of smallpox.

Oral Manifestations. Ulceration of the oral mucosa and pharynx is rather common, and similar involvement of other mucous membranes such as the trachea, esophagus, and vagina also occurs. Multiple vesicles appear much like the cutaneous lesion but, instead of proceeding to the development of pustules, they rupture and form ulcers of a nonspecific nature. In some cases the tongue is swollen and painful, making swallowing difficult.

Complications. Complications are related to the secondary infection which often occurs. Thus the formation of abscesses and the development of septicemia sometimes occur, as well as respiratory infection, erysipelas and infections of the eye and ear.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a disease caused by a virus of the pox group. The lesions, which only occur on the skin or mucosal surfaces, are often considered tumor like in nature because of the typical localized epithelial proliferation caused by the virus.

Clinical Features. The infection is more common in children and young adults and manifests itself as single, or more frequently, multiple discrete elevated nodules, usually occurring on the arms and legs, trunk and face, particularly the eyelids. However, it is now recognized that the disease can be sexually transmitted, and lesions of the genitalia and pubo-abdominal area also occur with some frequency.

These lesions are hemispheric in shape, usually about 5 mm in diameter with a central umbilication which may be keratinized, and are normal or slightly red in color. The disease appears to be spread by autoinoculation, by direct contact with an infected individual or by fomites with a reported incubation period of 14–50 days. Lack of inflammation and necrosis differentiates these proliferative lesions from other poxvirus lesions. Lesions can occur anywhere in the body, other than palm and soles, and may be associated with eczematous rash. HIV-infected individuals are more prone to these lesions. Linear distribution of these lesions suggests that autoinoculation of virus occurs due to scratching. Lesions in HIV-infected patients are atypical in manifestations. Lesions are multiple and grow to a large size resembling carcinomas. The virus replicates in the stratum spinosum and forms inclusion bodies which are characteristic, and pathognomonic of poxvirus infection called Cowdry type A inclusion bodies. Most of the lesions heal spontaneously in about 30–60 days and the infection may rarely persist for more than two or three years.

Oral Manifestations. Mucous membrane involvement, particularly the oral cavity, is not common. Cases have been reported; however, such as that of Barsh. Oral lesions, which occur most frequently on the lips, tongue and buccal mucosa, are similar to those on the skin.

Histologic Features. The lesion is quite characteristic, showing thickening and down growth of the epithelium with the formation of large eosinophilic intracytoplasmic inclusion bodies known as Henderson-Paterson inclusions or simply molluscum bodies, measuring approximately 25 μ in diameter. These bodies characteristically accumulate in the crater formed by the distinctive central umbilication of the dome-shaped lesion.

Diagnosis. Smears are prepared from lesions scraping or its contents and stained with pap stain, Giemsa or Gram stain, to demonstrate molluscum bodies.

Treatment. The lesions of molluscum contagiosum have been treated by surgical excision or by topical application of a wide variety of drugs such as podophyllin or cantharidin. There is some evidence that immunosuppressive drugs may evoke eruption of lesions.

CONDYLOMA ACUMINATUM

(Verruca acuminata, venereal wart)

Condyloma acuminatum is an infectious disease caused by a virus which belongs to the same group of human papillomaviruses (HPV) as those associated with common and plantar warts, flat warts, cervical flat warts, pityriasis-like lesions in patients with epidermodysplasia verruciformis and juvenile laryngeal papillomas.

Etiology. Human papillomaviruses are DNA virus that belongs to the family *Papovaviridae*. More than 50 serotypes of HPV are recognized and they are species specific and have not been propagated in tissue culture or in experimental animals. However HPV type 1, 6, 11, 16, 40, and 83 have been produced in human tissues implanted in immunodeficient mice. Condyloma acuminatum is caused by HPV type 6, a11, a30, b42, 43, 45, 46b 51, b54, 55, and 70.

The virus of anal, genital, and presumably oral condyloma acuminatum is HPV-6.

Epidemiology. It is one of the most common sexually transmitted diseases in the world. Incidence among children and adults is high, but low in early childhood. It reaches its peak between 12–16 years of age and then declines sharply to the age of 20 or more. Transmission is mainly by close contact with infected persons, autoinoculation, and orogenital sexual practice.

Pathogenesis. Once inoculated in the epithelium, the virus replicates and is transcribed in the basal cells. Virions are assembled in the cytoplasm and released along with the desquamated cells. This process is associated with the proliferation of all layers except basal cells and produces acanthosis,

hyperparakeratosis and hyperorthokeratosis. Koilocytes are large vacuolization of cells in and below the granular layer with basophilic inclusion bodies composed of viral particles and eosinophilic inclusions.

Clinical Features. This transmissible and autoinoculable viral disease presents as soft pink nodules which proliferate and coalesce rapidly to form diffuse papillomatous clusters of varying size. They occur most frequently on the anogenital skin or other warm, moist intertriginous areas.

Oral Manifestations. Oral lesions of condyloma acuminatum have been reported by Knapp and Uohara, as well as by Doyle and his associates and by Swan and his colleagues. These lesions have appeared as small, multiple, white or pink nodules which enlarge, proliferate and coalesce, or as papillomatous, bulbous masses scattered over or diffusely involving the tongue, especially the dorsum, buccal mucosa, palate, gingiva, or alveolar ridge.

Histologic Features. The papillomatous projections making up the verrucoid lesion generally show a parakeratotic surface with marked underlying acanthosis. Vacuolated cells in the spinous layer are common, as are numerous mitotic figures. In some instances, the epithelial changes are sufficiently disturbing to be mistaken for carcinoma. The supporting connective tissue is usually edematous, with dilated capillaries and a chronic inflammatory cell infiltrate. A case of oral condyloma acuminatum has been studied with both the light microscope and electron microscope by Shafer and his associates, who found intranuclear viral inclusions in the lesional epithelial cells.

Treatment. Surgical excision is usually used to eradicate the lesions, although topical podophyllin has also been used.

CHICKENPOX
(Varicella)

Chickenpox is an acute, ubiquitous, extremely contagious disease usually occurring in children, and is characterized by an exanthematous vesicular rash. It is most common in the winter and spring months.

Etiology. Varicella zoster virus is a DNA virus, which causes two distinct lesions known as chickenpox, a primary lesion and a reactivated lesion known as herpes zoster. The incubation period is approximately two weeks. It has been stated by Sabin that the virus causing this disease is one of the most contagious and sooner or later infects everyone in the world. It rather closely resembles smallpox, but is far less severe. The virus is the same as that which causes herpes zoster, and the lesions of the two diseases have many features in common. The relationship between these two diseases is discussed under herpes zoster. The mode of transmission is by airborne droplets or direct contact with infected lesions, with the probable portal of entry being the respiratory tract.

Clinical Features. The disease is characterized by the prodromal occurrence of headache, nasopharyngitis, and anorexia, followed by maculopapular or vesicular eruptions (dew drops) of the skin and low-grade fever. These eruptions usually begin on the trunk and spread to involve the face and extremities. They occur in successive crops so that many vesicles in different stages of formation or resorption may be found. The lesions of the skin eventually rupture, form a superficial crust and heal by desquamation. A charecterstic feature in all the stages of the disease is occurrence of the papules, vesicles and crusts are seen at a time in same area. The disease runs its clinical course in a week to 10 days, seldom leaving any after effects. Occasionally, secondary infection of the vesicles results in the formation of pustules, which may leave small pitting scars upon healing.

Oral Manifestations. Small blister-like lesions occasionally involve the oral mucosa, chiefly the buccal mucosa, tongue, gingiva, and palate, as well as the mucosa of the pharynx (Fig. 6-8). The mucosal lesions, initially slightly raised vesicles with a surrounding erythema, rupture soon after formation and form small eroded ulcers with a red margin, closely resembling aphthous lesions. These lesions are not particularly painful. Typical cases have been reported by Badger.

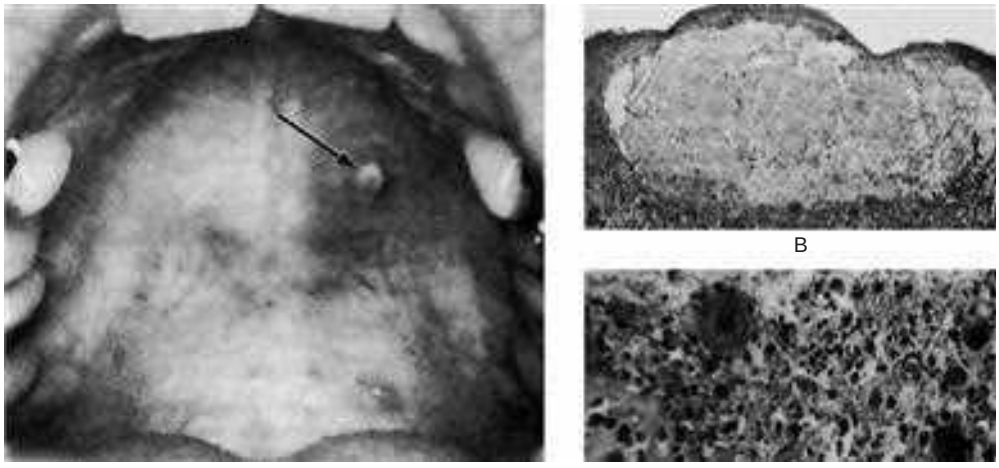


Figure 6-8. Chickenpox.
A single intraoral vesicle formed in association with the typical skin lesions **(A)**. A vesicular lesion **(B)** showing typical viral inclusion bodies **(C)** *(A, Courtesy of Dr Stephen F Dachi).*

Complications. Secondary infection is common and caused by *Streptococcus* or *Staphylococcus*. CNS involvement leads to encephalitis, transverse myelitis, Guillain-Barre syndrome, and Reye's syndrome. Other complications include pneumonia, myocarditis, nephritis, arthritis, and bleeding diatheses. Renal and hepatic involvement can also occur. Perinatal infections are fatal.

HERPES ZOSTER

(Shingles, zona)

Herpes zoster is an acute infectious viral disease of an extremely painful and incapacitating nature which is characterized by inflammation of dorsal root ganglia, or extra-medullary cranial nerve ganglia, associated with vesicular eruptions of the skin or mucous membranes in areas supplied by the affected sensory nerves. The virus causing this disease is the same as that of varicella, or chickenpox (the V-Z virus), and occasionally the two diseases are clinically nearly indistinguishable. Similar eosinophilic intranuclear inclusion bodies, indicative of viral infection, occur in both diseases. It is now believed that herpes zoster is caused by reactivation of the latent V-Z virus which had been acquired during a previous attack of chickenpox. In essence, a primary infection by the V-Z virus results clinically in chickenpox, while a recurrent infection results clinically in herpes zoster. The fact that herpes zoster is sporadic in occurrence whereas varicella is seasonal further supports the belief that herpes zoster is not a result of a primary exogenous infection.

Clinical Features. The disease is most common in adult life and affects males and females with equal frequency. Although rare, it does occur in children. In 576 cases of herpes zoster in patients of all ages, 31(5.4%) were in children under 15 years of age, according to Rogers and Tindall, but in this age group the disease has a very benign clinical course.

Initially, the adult patient exhibits fever, a general malaise, and pain and tenderness along the course of the involved sensory nerves, usually unilaterally. Often the trunk is affected. Within a few days the patient has a linear papular or vesicular eruption of the skin or mucosa supplied by the affected nerves. It is typically unilateral and dermatomic in distribution. After rupture of the vesicles, healing commences, although secondary infection may intervene and slow the process considerably. Occasionally, herpes zoster may resemble the lesions of herpes simplex, but the two diseases can be separated since the zoster virus cannot be transmitted to animals, e.g. the rabbit cornea, as can the simplex virus.

The triggering factors initiating the onset of an attack of herpes zoster are varied and may include trauma, development of malignancy or tumor involvement of dorsal root ganglia, local X-ray radiation or immunosuppressive therapy. It is a common infection in immunocompromised patients and those with certain malignancies, including Hodgkin's disease and the malignant lymphomas, and can be life-threatening if the viscera become involved. However, many attacks begin for no apparent reason, and these have often been attributed to a decrease in host resistance due to age.

Oral Manifestations. Herpes zoster may involve the face by infection of the trigeminal nerve (Fig. 6-9). This usually consists of unilateral involvement of skin areas supplied by either the ophthalmic, maxillary or mandibular nerves. Lesions of the oral mucosa are fairly common, and extremely painful vesicles may be found on the buccal mucosa, tongue, uvula, pharynx, and larynx (Fig. 6-10). These generally rupture to leave areas of erosion. One of the characteristic clinical features of the disease involving the face or oral cavity is the unilaterality of the lesions. Typically, when large, the lesions will extend up to the midline and stop abruptly.

A special form of zoster infection of the geniculate ganglion, with the involvement of the external ear and oral mucosa, has been termed Hunt's syndrome (James Ramsay Hunt's syndrome). The clinical manifestations include facial paralysis as well as pain of the external auditory meatus and pinna of the ear. In addition, vesicular eruptions occur in the oral cavity and oropharynx with hoarseness, tinnitus, vertigo and occasional other disturbances.

Diagnosis. Herpes zoster can frequently be recognized by the characteristic distribution of the lesions, although there may be a similarity to the lesions of herpes simplex infection. Skin lesions and oral lesions in particular may be easily identified as viral diseases by cytologic smears and the finding of characteristic multinucleated giant cells (Tzanck test) and intranuclear inclusions. However, this does not differentiate between herpes zoster and herpes simplex. This can only be done by fluorescent antibody staining techniques, viral culture or serologic diagnosis.

Treatment. The newer antiviral drugs are now under intensive clinical testing for potential effectiveness in treatment of herpes zoster. The preliminary results appear very promising.

MUMPS

(Epidemic parotitis)

Mumps is an acute contagious viral infection characterized chiefly by unilateral or bilateral swelling of the salivary glands, usually the parotid. The submaxillary and sublingual glands are occasionally involved, but seldom without parotid involvement also. Other than salivary glands, it may also involve nerves meninges, pancreas and gonads. Although it is usually a disease of childhood, mumps may also affect adults, and in such cases there is a greater tendency for complications to develop. Mumps has an incubation period of two to three weeks.

Epidemiology. The incubation period varies from 14–18 days with the extreme of one to four weeks. Mumps is transmitted through the respiratory route. It can be isolated from the saliva of the infected patients either seven days before the onset of parotitis or nine days after its onset. Most cases were unrecognized because of the absence of parotid swelling. As the disease is contagious before the onset of parotitis,

Figure 6-9. Herpes zoster involving face and oral mucosa.

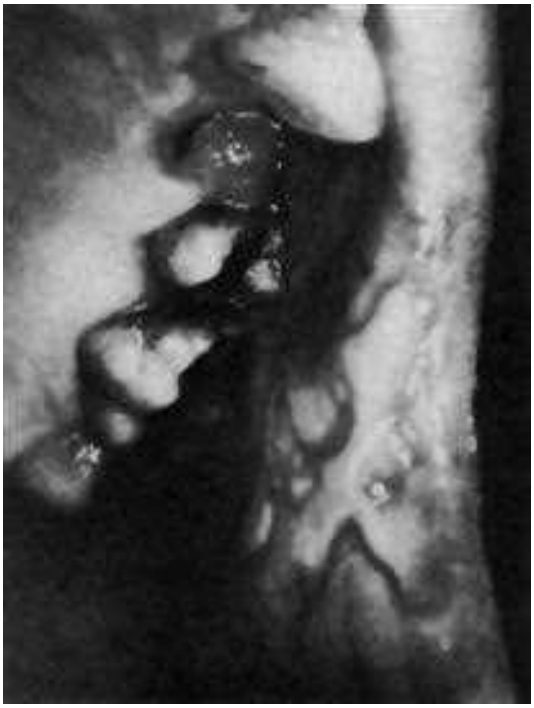


Figure 6-10. Herpes zoster involving the buccal mucosa.

isolation of patient is not possible to prevent the infection. Once infected, patients develop a lifelong immunity against the disease but recurrence is also reported.

Pathogenesis. Once transmitted through droplet nuclei or saliva or fomites, it starts replicating in the respiratory epithelium. It spreads to local lymph nodes and subsequently develops viremia. The affected area shows perivascular and interstitial mononuclear cell infiltrates with edema. Necrosis of acinar and epithelial duct cells are seen in salivary glands and in the germinal epithelium of seminiferous tubules.

Clinical Features. The disease is usually preceded by the onset of headache, chills, moderate fever, vomiting, and pain below the ear. These symptoms are followed by a firm, somewhat rubbery or elastic swelling of the salivary glands, frequently elevating the ear, which usually lasts about one week. This salivary gland involvement produces pain upon mastication. Bilateral parotid involvement occurs in about 70% of the cases. Pain and tenderness may be severe during the rapid phase of parotid enlargement and swelling reaches its maximum in about three days; it remains at its peak for two to three days and then gradually subsides. The submandibular gland may also involve separately or in conjunction with the parotid gland. The involvement of the sublingual gland is

rare. Presternal edema may be present in a few cases due to pressure on the lymphatics in the neck. It is also reported that the papilla of the opening of the parotid duct on the buccal mucosa is often puffy and reddened.

Differential Diagnosis. It should be differentiated from other parotid swelling caused by influenza, parainfluenza 1 and 3, Coxsackie, HIV, and cytomegalovirus, Sjögren's syndrome, pleomorphic adenoma, etc.

Diagnosis. Virus can be isolated from saliva and throat swabs two days before or seven days after the onset of parotitis and from CSF. It can also be confirmed by the complement fixation test, hemagglutination inhibition or ELISA. Serum amylase is elevated in both parotitis and pancreatitis.

Complications. Other organs of the body may be affected as a complication of the disease. These include the testes, ovaries, pancreas, mammary glands, and occasionally the prostate, epididymis, and heart. When mumps involves the adult male, orchitis is a great danger and ensues in approximately 20% of cases. This orchitis is usually unilateral, but occasionally complete sterility results. The involvement of the pancreas producing an acute pancreatitis often causes an elevation in serum lipase. Serum amylase is also elevated but this is regardless of pancreatic involvement. Meningoencephalitis, deafness, and mastoiditis are also occasional complications. Rare complications like nerve deafness, facial paralysis, cerebral ataxia, and encephalitis have also been reported. When occurs in the first trimester of pregnancy it results in abortion.

The disease, though discomforting and often producing an acutely distressing condition, is seldom fatal.

> The availability of live attenuated mumps virus vaccine, first licensed in 1968, has resulted in a marked decline in the incidence of the disease, with a corresponding decrease in cases of meningitis and encephalitis. Unfortunately, the vaccine is not protective to individuals already exposed to the virus and who are in the incubation state of the disease.

Prognosis. An overall prognosis is good in uncomplicated cases. Death occurs due to CNS or cardiac involvement.

Treatment. Treatment is conservative; maintaining hydration and alimentation. Prevention is by means of vaccination.

NONSPECIFIC 'MUMPS'

There are several 'nonspecific' conditions characterized by enlargement of one or more of the major salivary glands that are not related etiologically to epidemic parotitis, or true mumps, but yet may produce considerable difficulty in diagnosis and differential separation from true mumps of viral origin. Banks has summarized a variety of these in his classification (Table 6-2) and discussion of parotid swellings. Although not all of these are of specific microbial origin, some of the more common conditions which have clinical and occasional microscopic resemblance to epidemic parotitis, or mumps. These include: (1) chronic nonspecific sialadenitis, (2) acute postoperative parotitis ('surgical mumps', retrograde sialadenitis), (3) nutritional 'mumps', (4) chemical 'mumps', and (5) miscellaneous.

Table 6-2: Classification of parotid swellings

1. Developmental
   - (a) Polycystic disease of the parotid gland
   - (b) Adenomatoid hyperplasia
   - (c) Lymphoepithelial cysts
2. Infectious and inflammatory
   - (a) Bacterial
     - (i) Acute suppurative parotitis
     - (ii) Recurrent subacute parotitis
     - (iii) Chronic nonspecific parotitis
     - (iv) Chronic specific parotitis
       1. Tuberculosis
       2. Actinomycosis
   - (b) Viral
     - (i) Mumps
     - (ii) Cytomegalic sialadenitis
     - (iii) HIV associated salivary gland disease
     - (iv) EBV infection
     - (v) Coxsackie A
     - (vi) Echo virus infection
     - (vii) Parainfluenza type 1, 3 infections
3. Obstructive and traumatic lesions
   - (a) Retention cysts (salivary duct cyst)
   - (b) Sialolithiasis
   - (c) Congenital atresia
4. Allergic and immunologic disorders
   - (a) Allergic sialadenitis
   - (b) Sjögren's syndrome
   - (c) Sarcoidosis
   - (d) Uveoparotid fever
5. Metabolic and hormonal disorders (sialosis or sialadenosis)
   - (a) Hormonal
     - (i) Diabetes mellitus
     - (ii) Catecholamine excess
     - (iii) Acromegaly
   - (b) Mulnutrition
   - (c) Drug induced
   - (d) Dysenzymatic
     - (i) Alcoholic cirrhosis
     - (ii) Pancretogenic sialadenosis
     - (iii) Nephrogenic sialadenosis
     - (iv) Obesity
6. Ageing
   - (a) Oncocytosis
7. Neoplastic
   - (a) Benign tumors
   - (b) Malignant tumors
8. Miscellaneous
   - (a) Pneumoparotitis

Chronic Nonspecific Sialadenitis

Nonspecific chronic sialadenitis is an insidious inflammatory disease of the major salivary glands characterized by intermittent swelling of the glands which may lead to the development of clinically obvious fibrous masses. It is most common in adults, particularly males. A similar, and perhaps related, condition

has been reported by Katzen and du Plessis under the term 'recurrent parotitis' in children. They observed that the disease usually subsided spontaneously at puberty although David and O'Connell reported that it may extend into adult life. Brook has published an excellent review of this recurrent suppurative parotitis in children.

The most frequent cause of chronic sialadenitis is the occurrence of salivary duct calculi (q.v.) with subsequent pyogenic bacterial infection. However, any condition which may result in salivary duct occlusion, such as tumors, foreign bodies or scar formation may result in this form of the disease.

If the etiologic factor is removed, there is generally subsidence of the clinical manifestations of the disease. If untreated, the salivary gland may be replaced by fibrous tissue, which may be tumor like in its extent.

Acute Postoperative Parotitis

This condition has a long and interesting history that has been reviewed by Schwartz and coworkers. It is believed to be the result of a retrograde infection (one reaching the parotid gland by microorganisms ascending the parotid duct) in debilitated patients suffering from dehydration, suppression of salivary secretion, vomiting and/or mouth-breathing, after a surgical procedure. Thus it is felt that xerostomia, or dry mouth, is one of the most important factors, since the stagnation of salivary flow would allow the ascension of microorganisms through the duct into the gland.

The microorganisms involved are usually *Staphylococcus aureus, Staphylococcus pyogenes, Streptococcus viridans* and pneumococci.

The majority of patients involved are adults, of middle age or older. Bilateral parotid gland involvement is common and the clinical signs and symptoms generally occur between the second and 20th postoperative days. Any type of surgical procedure may be followed by the appearance of this condition, not just a local procedure in the area of the salivary glands, although the exact mechanism is not known.

The onset of the disease is rapid and is frequently accompanied by severe pain and rapid swelling of the parotid gland. The overlying skin may be reddened, and the associated edema may involve the cheek, periorbital area, and neck. Trismus is present, as is a low-grade fever with headache, malaise, and leukocytosis. A purulent discharge may be expressed from the parotid duct by digital pressure along the duct toward its orifice. Treatment of this condition is generally the administration of antibiotics.

Nutritional 'Mumps'

Numerous investigators have reported a chronic, asymptomatic, bilateral enlargement of the parotid and/or submandibular glands occurring endemically in populations suffering from malnutrition. The dietary factors specifically involved have not been identified, but the lesions occur most frequently in patients with multiple signs of nutritional deficiency such as hypoproteinemia, anemia, angular cheilosis, pellagroid pigmentation of the hands and face, and general underweight. A relation to either vitamin A or C deficiency has not been demonstrated.

The condition is progressive one, but relatively slow to develop. It appears to be somewhat more common in young and middle-aged adults.

Histologic studies indicate that salivary gland involvement is essentially noninflammatory. The enlargement of the salivary glands in the acute phase of the condition is due to hypertrophy of the individual acinar cells, but in the chronic phase, to a replacement of normal gland parenchyma with fat. There is apparently little interference with normal salivary gland function.

A clinically identical form of parotid swelling has been reported by Borsanyi and Blanchard in a series of patients suffering from Laennec's hepatic cirrhosis with a history of chronic alcoholism. This form of salivary gland disease is undoubtedly only one manifestation of the 'nutritional mumps' discussed by Sandstead and his group.

Chemical 'Mumps'

Bilateral swelling of the salivary glands occasionally accompanies the administration of either inorganic or organic iodine, and this has frequently been referred to as 'iodine mumps.' This condition has been reviewed by Carter, who pointed out that this probably represents an iodine idiosyncrasy reaction. A similar form of salivary gland swelling has been reported by Albright and his coworkers to follow administration of triiodothyronine in the treatment of myxedema. These findings are of special interest in view of the long series of studies of Shafer and Muhler that have conclusively shown a close relation between the thyroid and salivary glands.

Another example of chemically induced experimental salivary gland swelling has been that following administration of isoproterenol to rats, reported by Selye and his group. In their studies the salivary glands increased approximately five times their normal size within 17 days after the initiation of drug administration. In this case the glandular enlargement is due to a true hypertrophy of acinar cells.

Miscellaneous Factors. There are numerous other situations in which salivary gland swelling may occur, and many of these have been discussed by Pearson and are described in more detail in other sections of this text. For example, salivary gland swelling is common in Sjögren's syndrome, Mikulicz's disease or benign lymphoepithelial lesion, salivary duct calculus, and allergic phenomena. In addition, swelling of the salivary glands was reported by Dobreff in 1936 to follow hypofunction of pancreatic islets and by Racine in 1939 to occur as a premenstrual phenomenon.

Fibrocystic disease (mucoviscidosis) of the pancreas is a hereditary defect of the secretory mechanism of most of the exocrine glands in the body, including the salivary glands. Bilateral enlargement of the submaxillary glands has been reported by Barbero and Sibinga in 92% of a group of 106

children with fibrocystic disease as contrasted to similar enlargement in only 2% of a group of 300 normal children. At necropsy, these submaxillary glands from patients with fibrocystic disease were two to three times heavier than normal. These investigations suggested that cystic fibrosis is an important cause of chronic submaxillary gland enlargement in the pediatric age group.

Sarcoidosis has been reported by Greenberg and his associates to have caused enlargement of the parotid gland in 6% of a series of 388 patients with this disease. The enlargement was bilateral in 83% of the cases, and unilateral in 17%.

Nevertheless, as in nearly every nonspecific condition of such an etiologically diverse nature, there is always an idiopathic group in which even careful evaluation of clinical, microscopic, and laboratory findings fail to reveal the cause of the disease, and such is the case in noninfectious 'mumps,' a certain percentage of these cases cannot be explained.

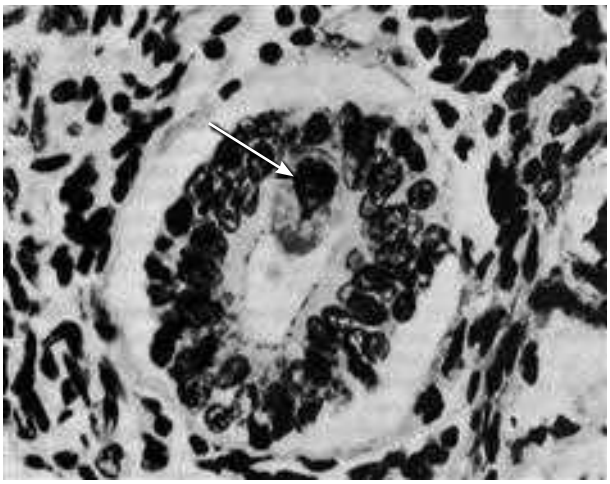


Figure 6-11. Cytomegalic inclusion disease.
The arrow points to the typical inclusion body in the parotid ductal epithelium *(Courtesy of Dr Charles A Waldron).*

CYTOMEGALIC INCLUSION DISEASE

(Salivary gland virus disease)

Salivary gland inclusion disease is a viral infection of interest since routine postmortem examinations have revealed that a considerable proportion of infants who die exhibit this disease, regardless of the cause of their death. Although it is frequently an inapparent infection, it is a cause of fetal encephalitis and may produce irreversible damage to the central nervous system. Smith and Vellios reported that in the majority of cases, the patients are less than two years of age although the disease has been reported in a few adults. Some cases, reviewed by Amromin, have occurred widely disseminated in adults. There are no particular signs or symptoms of this disease, although some infants have been reported to have manifested hepatosplenomegaly, hemolytic anemia, and a hemorrhagic tendency. It may be an incidental autopsy finding in patients who have died of blood dyscrasias, liver damage, pertussis, purpura, and other diseases. Transplacental infection may occur even without visible evidence of infection in the mother. In fact, approximately 50% of women in the childbearing group are seropositive for complement fixing antibodies to this virus, while approximately 4% of pregnant women excrete the virus in the urine. Occasional infants without an established diagnosis of generalized cytomegalic inclusion disease survive, although there may be some retardation of mental and motor development. In a review of cytomegalovirus as a major cause of birth defects, Marx has stated that it is the most common viral cause of mental retardation, surpassing even rubella virus.

Intranuclear and cytoplasmic inclusions in the cells of the salivary glands are a constant feature, while similar inclusions frequently occur in the kidneys, liver, pancreas, lungs, adrenals, intestine, brain, and occasionally other organs. The diagnosis is frequently established in living infants by examination of urinary sediment and the demonstration of the inclusion bodies here. These inclusions have a distinctive morphologic appearance and are pathognomonic of the disease (Fig. 6-11).

There is evidence to suggest that disturbances of cellular metabolism such as those occurring in certain vitamin deficiencies may predispose to the viral infection or may possibly activate an existing subclinical infection. The widespread distribution of the virus is apparent from the fact that over 80% of adults possess serum antibody against the virus. It is also now recognized, as reported by Cangir and Sullivan, that dissemination of the latent disease may occur in leukemia patients receiving antimetabolite therapy and in organ transplantation patients or others receiving immunosuppressant drugs and subject to opportunistic infection.

Other interesting manifestations of this virus include:

- Cytomegalovirus mononucleosis, which may be very difficult to distinguish from infectious mononucleosis, since the clinical characteristics of the two may be nearly identical.
- Its association with Kaposi's sarcoma in the acquired cellular immunodeficiency syndrome (q.v.).

POLIOMYELITIS

(Infantile paralysis)

Poliomyelitis, at one time, was a very serious viral disease which has been almost totally eliminated, particularly the paralyzing form, as a result of the widespread use of the Salk and Sabin vaccines. Prior to this, poliomyelitis was of some significance in dentistry because of scattered reports which suggested that the exposed dental pulp might act as a portal of entry into the body for the virus. This no longer appears to be of any clinical significance.

CHIKUNGUNYA

Chikungunya fever is a mosquito borne illness of humans caused by chikugunya virus. It belongs to Arboviruses (arthropod-borne viruses), which are viruses of vertebrates biologically transmitted by hematophagous insect vectors. They are world wide in distribution but are more numerous in tropical regions. In India, over 40 arboviruses have been detected, of which more than 10 are known to produce human disease. Chikungunya is believed to have originated in Africa and was subsequently introduced in Asia where it is transmitted from human to human mainly by *Aedes aegypti* and, to a lesser extent by *Ae. albopictus* through an urban transmission cycle.

After inoculation, primary viral multiplication occurs in lymphoid and myeloid cells. The virus then spreads to the targeted organs and immune system starts functioning at this stage leading to the activation of both humoral and cellular immunity. This response of the body leads to the clinical features of the disease.

Clinical Features. Patients become symptomatic after the incubation period of 4–7 days. The infection is of acute onset with variable clinical features. This disease is characterized by the clinical triad of 'fever, rashes and arthralgia'. Chikungunya is a Makonde word meaning 'the one which bends up' referring to the posture of the affected patient acquired due to excruciating pain in the joints.

Severe headache, chills and rigors, nausea and vomiting may present along with fever. The fever may disappear to return in one or two days giving it the name of 'saddle back fever. The occurrence of polyarthralgia along with myalgia, is a typical feature of the illness. The joint pain is frightening in severity, completely immobilizing many patients. The joint becomes very painful to touch. Different joints of the same patient may be involved at different times.

Oral Manifestations. The maculopapular rashes and gingival hemorrhages are uncommon signs although more frequent in children. But in India and other Asian countries cases with gingival bleeding were reported. Rashes occur mainly on trunks or extensor surface of the limbs and are itching in nature.

The probable diagnosis of chikungunya fever can be made on the basis of presence of the virus in community, and a clinical triad of fever, rashes and arthralgia.

Diagnosis. The virus produces neutralizing and hemagglutination inhibiting (HI) antibodies and that helps in making serological diagnosis. Reverse transcriptase polymerase chain reaction (RT-PCR) is confirmatory for the identification of chikungunya virus. IgM capture ELISA is the most sensitive serologic assay, and is necessary to distinguish the disease from dengue.

Treatment and Prognosis. The disease is considered to be self-limiting and benign in nature. The available literature does not report mortality due to this virus. There is no specific antiviral therapy available for chikungunya and treatment is mostly, supportive one. Symptoms may be treated with analgesics and antipyretics.

ORAL MANIFESTATIONS OF HIV INFECTION

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) and is characterized by immunosuppression, which leads to a spectrum of clinical manifestations that include opportunistic infections, secondary neoplasms, and neurologic manifestations. Two genetically distinct populations of viruses known to cause AIDS are HIV-1 and HIV-2. HIV- 1 is the most common type responsible for AIDS in central Africa and the rest of the world, and HIV-2 in west Africa and India.

EPIDEMIOLOGY

Estimates at the end of 2007 indicate that there are 33 million people living wih HIV infection, 2.7 million have new infection and 2.0 million have succumbed to the disease. 96% of the infected are in low and middle income countries. The demographic features of the spread of HIV in Asia is somewhat different from that in other parts of the world, as the infection was first seen in intravenous drug users (IDUs) in Thailand and Burma in contrast to groups indulging in high-risk sexual behavior in the western countries. Globally, South and South-east Asian countries follow South Africa in terms of the total number of people living with the disease (UNAIDS).

India

The evidence of HIV infection was first documented in Chennai in southern India in 1986. The heterosexual route is the predominant mode of transmission, followed by intravenous drug use. India's prevalence estimates are based on sentinel surveillance conducted at public sites, according to the National AIDS Control Organization (NACO). Nationwide, an annual HIV sentinel surveillance was first organized in 1994, at 55 sentinel sites, which grew to 1134 HIV sentinel sites across the country, in 2007. Coverage and outreach of the HIV sentinel sites has been improving each year (Table 6-3).

The Annual Round of HIV Sentinel Surveillance, 2003, was conducted in 455 sentinel sites in all Indian states and union territories. These included: 271 sites at antenatal clinics (as proxy for the general population), 166 sites in clinics for sexually transmitted diseases, 13 sites among injecting drug users, three sites for men having sex with men and two sites for commercial sex workers. In 2004, the number of sentinel sites increased to 1134. Data from NACO indicate that India stands third in the number of people living with HIV/AIDS, with 23.9 million people living with the infection and a prevalence of 0.31 percent in the adult population.

Table 6-3: Coverage and outreach of the HIV sentinel sites

Year	2000	2001	2002	2003	2007
No. of sites	232	320	384	455	1134

HUMAN IMMUNODEFICIENCY VIRUS

The human immunodeficiency virus is a nononcogenic human retrovirus that belongs to the lentivirus group type III. The virion is an icosahedral structure that contains numerous external spikes formed by two major envelope proteins, the external gp120 and the transmembrane gp41. The core protein p17 is found outside the viral nucleoid and forms the matrix of the virion. The HIV glycoprotein antireceptors (GP-41 and GP-120) make a snug attachment of their specific receptors on a human cell membrane. These receptors are CD4, which are typically found on T4 lymphocytes and other white blood cells. A coreceptor called CCR-5 (fusin) permits docking with the host cell and fusion with the cell membrane leading to the formation of syncytia.

Mode of HIV Transmission. Sexual transmission is the predominant mode of infection worldwide, accounting for more than 75% of all cases of HIV transmission. It is also transmitted through infected body fluids such as blood and blood products, and breast milk. HIV has been demonstrated in oral fluids, but their infectivity appears to be reduced. So, saliva is not a significant route of transmission of HIV infection. Infection can be transmitted vertically from mother to the child.

Pathogenesis of HIV Infection. The two major targets of HIV infections are the immune system and the central nervous system. A characteristic feature of AIDS is the profound immunosuppression of cell mediated immunity. After gaining entry into the host, either through exposure to blood, body fluids, or sexual activity, the first step in virus infection involves binding of the virion to the surface of a target cell. This is mediated by binding of the envelope gp120 to the CD4 surface protein found on most helper T cells. After binding, the virus becomes internalized into the host cell where it becomes uncoated. The viral RNA is then reverse transcribed into linear double-stranded viral DNA in the cytoplasm of infected cells by the reverse transcriptase and then transported to the nucleus, where it is first 'circularized' and then integrated into the host cell. The integrated viral DNA is transcribed into full length RNA by the host cell. These RNA transcripts can either be packaged within virus particles, to serve as the genome of progeny virus, or they can serve as mRNA for the synthesis of viral gene products.

HIV first infects macrophages where it multiplies and is shed, infecting lymphocytes and other cells that possess the CD4 receptor site. The most significant of these are the T4 (helper) cells that coordinate the immune responses to most infections. Following the infection, the virus often enters a dormant stage lasting for 2–15 years.

When HIV is transmitted, fusion with CD4 cells occurs rapidly, and within a few days the virus migrates to regional lymph nodes, and then enters the circulation. This results in widespread dissemination to the brain and the lymphatic system, causing the 'primary HIV infection' or the 'seroconversion syndrome.'

The most common signs and symptoms of acute infection include fever, fatigue, maculopapular rash, headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, aseptic meningitis, retrorbital pain, weight loss, depression, gastrointestinal distress, night sweats, and oral or genital ulcers. The acute illness may last from a few days to more than 10 weeks, but the duration is usually less than 13 days. The severity and the duration of the illness may have prognostic implication; severe and prolonged symptoms are correlated with rapid disease progression.

After infection, there is a rapid rise in plasma viremia, often to levels in excess of 1 million viral RNA molecules per milliliter. After the initial rise in plasma viremia, there is a marked reduction from the peak viremia to a steady-state level of viral replication. The decrease in the viral load during acute HIV-1 infection is probably due to virus specific immune responses that limit viral replication. There is also a correlation between cytotoxic T-lymphocyte responses to the envelope protein and the reduction in plasma viral RNA. In addition, soluble factors produced by CD8 cells inhibit HIV-1 replication in the early stages of acute infection and may thus contribute to the reduction of the viral load.

Within 6–12 weeks, antibodies to HIV are detectable in the blood, and enzyme linked immunosorbent assay (ELISA) and Western blot testing can document seroconversion. At this time, patients are confirmed as HIV positive. The time between viral infection and seroconversion is referred to as the 'window period.' During this period, HIV is present in body fluids and can be transmitted, but the HIV serology may be nonreactive. The disease subsequently progresses to 'asymptomatic chronic infection with or without persistent generalized lymphadenopathy' (PGL). PGL consists of lymphadenopathy for a duration of more than three months and involves two or more extrainguinal sites. Though the immune function is normal during this phase, viral replication occurs at a rapid rate resulting in the destruction of the CD4 cells. At this time, the lymphatic tissue serves as the major reservoir for HIV, the follicular dendritic cells filter and trap free virus and infected CD4 cells, and the viral burden in peripheral blood mononuclear cells is relatively low. With progressive disease, the lymph node architecture is disrupted, and more HIV is released. As more viruses are generated and released, more CD4 cells are destroyed, leading to decreased immune function and disease progression.

Clinical Features. The clinical features of HIV infection, therefore, range from asymptomatic infection to severe clinical illness and AIDS. The time for the onset of symptoms varies from five to six months to few years, and may be influenced by the source of HIV infection, patient's age, gender, drug habits, immunogenetics, and other factors. In 1993, the Centers for Disease Control (CDC) revised their classification system proposed in 1986 and expanded the surveillance case definition for AIDS among adolescents and adult.

Patients generally remain asymptomatic until their CD4 cell count falls below 500 cells/mm^3, at which time the patient enters the 'symptomatic HIV infection' previously known

Table 6-4: 1993 revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults

CD4+T-cell categories	Clinical categories		
	(A) Asymptomatic acute (primary) HIV or PGL	(B) Symptomatic not (A) or (C)	(C) AIDS-indicator conditions
≥500/mm^3	A1	B1	C1
200–499/mm^3	A2	B2	C2
<200/mm^3 (AIDS indicator T-cell count)	A3	B3	C3

Source: http://hivinsite.ucsf.edu

as the 'AIDS related complex' and more recently referred to as 'Stage B,' according to the 1993 CDC classification, which is characterized by the development of opportunistic infections. As HIV continues to replicate, the CD4 cell count dramatically decreases. AIDS is diagnosed when the CD4 cell count falls below 200 cells/mm^3 or when one of the AIDS defining illnesses is documented (Table 6-4). Eventually, the immune function ceases, resulting in advanced HIV infection, characterized by a CD4 cell count <50 cells/mm^3, overwhelming opportunistic infections, and death. Without antiretroviral therapy, the progression of HIV from transmission to death is approximately 10–12 years.

Oral Lesions in HIV Infection. Oral lesions are often clearly visible and several can be diagnosed accurately on clinical features alone. In those cases where HIV status is unknown and where HIV testing is difficult, certain oral lesions provide a strong indication of the presence of HIV infection. Oral lesions that are associated with this disease are important, as they not only affect the quality of life of the patient but also are useful markers of disease progression and immunosuppression. They are strongly associated with immunosuppression, as measured by CD4 cell counts, and are modestly associated with a high viral burden. Thus oropharyngeal lesions feature in all classifications (CDC 1986, CDC 1993) (Table 6-5), staging, and prognosis. Oral lesions have also been advocated and are used as entry criteria and end points for prophylaxis therapy and vaccine trials.

In 1995, European Commission (EC) Clearinghouse on oral problems related to HIV infection and the WHO Collaborating Center on oral manifestations of the immunodeficiency virus released the following classification:

- Presumptive criteria: Relate to the initial clinical appearance of the lesion.
- Definitive criteria: They are the result of special investigations for absolute diagnosis.

These two added criteria give the diagnostic criteria of the oral manifestations of HIV infection.

Oral Candidiasis

Oral candidiasis is the most common intraoral opportunistic fungal infection strongly associated with HIV infection. It has been reported that oral/esophageal candidiasis, in HIV-infected patients, may herald the development of full-blown AIDS within two years.

Table 6-5: Revised classification of HIV infection (1993)

Group 1:	Lesions strongly associated with HIV infection Candidiasis Erythematous Pseudomembranous Hairy leukoplakia Kaposi's sarcoma Non-Hodgkin's lymphoma Periodontal disease Linear gingival erythema Necrotizing ulcerative gingivitis Necrotizing ulcerative periodontitis
Group 2:	Lesions less commonly associated with HIV infection Bacterial infections *Mycobacterium avium–intercellulare* *Mycobacterium tuberculosis* Melanotic hyperpigmentation Necrotizing ulcerative stomatitis
Group 3:	Lesions seen in HIV infection Bacterial infections *Actinomyces israelii* *Escherichia coli* *Klebsiella pneumoniae* Cat-scratch disease Drug reactions (ulcerative, erythema multiforme, Lichenoid reaction, toxic epidermolysis) Epithelioid (bacillary) angiomatosis Fungal infections other than candidiasis *Cryptococcus neoformans* *Geotrichum candidum* *Histoplasma capsulatum* Mucormycosis (zygomycosis) *Aspergillus flavus* Neurologic disturbances Facial palsy Trigeminal neuralgia Recurrent aphthous stomatitis (RAS) Viral infections CMV Molluscum contagiosum

The four clinical patterns seen are:

Pseudomembranous Candidiasis. This clinically appears as white to yellowish white plaques which can be easily scraped off, exposing red areas. The lesions are usually extensive, involving more than one site in the oral cavity. It may also extend to involve the oropharynx and esophagus.

Erythematous Candidiasis. This is clinically seen as red lesions, which are commonly located on the dorsum of the tongue, palate, and buccal mucosa. Tongue lesions are also referred to as central papillary atrophy.

Hyperplastic Candidiasis (Fig. 6-12). These lesions are characterized by white plaques which cannot be removed by scraping. Diagnosis can be confirmed by biopsy, which demonstrates the fungal hyphae in the keratinized layers of the epithelium. This lesion can be differentiated from other oral

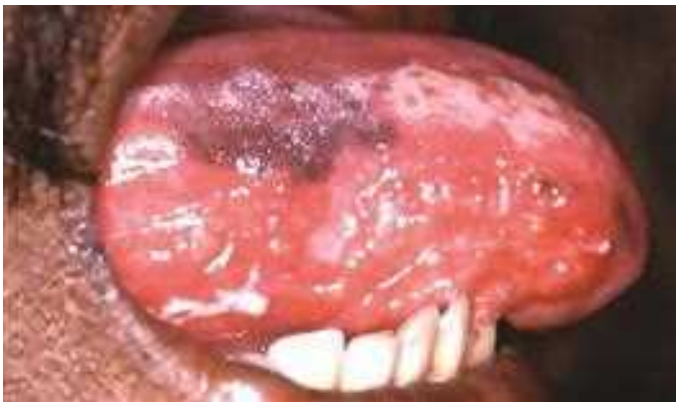


Figure 6-12. Hyperplastic candidiasis involving the tongue.

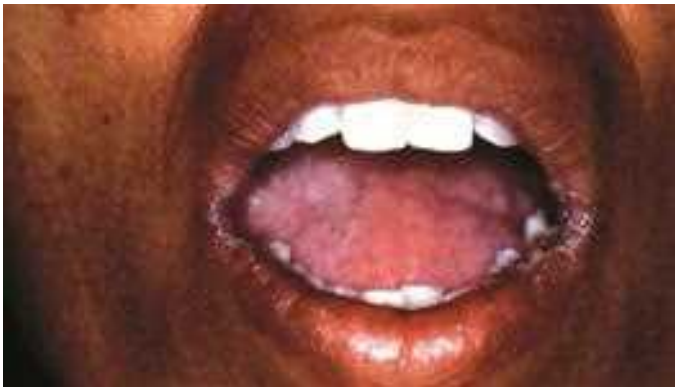


Figure 6-13. Angular cheilitis.

white lesions as these respond to topical or systemic antifungal therapy mixed infection of *Candidia albicans* and Staphylococcus or candida alone.

Angular Cheilitis (Fig. 6-13). Erythema and/or fissuring and/or scaling of the angles of the mouth clinically characterize this lesion. Microbiologically, the lesion can be due to mixed infection of *Candida albicans* and *Staphylococcus aureus* or Staphylococcus or Candida alone.

Diagnosis. Candidiasis is diagnosed by its clinical appearance, PAS staining for candidal hyphae, of biopsied tissue or smears from lesion, or culturing the organism on Sabouraud's agar.

Candidiasis can be effectively treated by topical application of antifungal agents nystatin or clotrimazole. The systemic antifungals used are fluconazole or itraconazole. Though the systemic azoles produce longer disease free intervals, they are more frequently associated with drug interactions and drug resistance.

Periodontal Lesions

Periodontitis in HIV-positive patients is influenced by age, smoking, viral load, and microorganisms such as *Fusobacterium nucleatum, Prevotella intermedia, and Actinobacillus actinomycetemcomitans.*

HIV-associated periodontal lesions as listed by EC-Clearinghouse (1993) include:

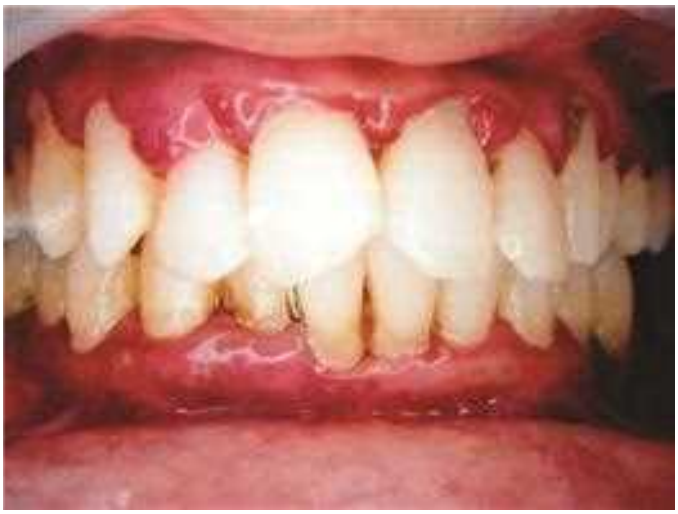


Figure 6-14. Linear gingival erythema.
(Courtesy of Dr R Saravanakumar, Meenakshi Ammal Dental College, Chennai).

- **Linear gingival erythema (LGE)** is a non-plaque induced gingivitis exhibiting a distinct erythematous band of the marginal gingiva with either diffuse or punctuate erythema of the attached gingiva (Fig. 6-14).
- **Necrotizing periodontal diseases** are subclassified as necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP) and necrotizing stomatitis (NS). NUG involves destruction of one or more interdental papillae and is limited to the marginal gingiva. NUP extends beyond the papillae and marginal gingiva causing the loss of the periodontal attachment, and possibly exposing the bone. When the necrosis extends beyond the periodontium into the mucosa and osseous tissue, it results in NS. These three conditions are different stages of the same disease. The only distinction appears to be their severity.
- **Chronic periodontitis** has also been reported with an increased rate of attachment loss or exacerbated periodontitis.

NUG, NUP and NS appear to have the same pathogens as the corresponding diseases in HIV noninfected populations. HIV-related periodontitis seems to be a multifactorial, multimicrobial disease with no single organism being responsible. The disease may be initiated by conventional periodontal pathogens but the progression and tissue destruction depends upon many factors. The most important factors are the overwhelming host response and an increase in secretion of potentially destructive inflammatory mediators. This condition may also allow other opportunistic microorganisms including viruses to become established and cause further destruction.

The progression of the periodontal disease and tissue destruction in the presence of the HIV infection is dependent upon the presence of typical and atypical subgingival microorganisms including viruses, their byproducts and the local inflammatory host response.

HERPES SIMPLEX VIRUS INFECTION

Herpes (Fig. 6-15) labialis is clinically seen as vesicles on the lip and adjacent facial skin which rapidly break down to produce shallow ulcers. Intraoral lesions on the gingiva are referred to as acute herpetic gingivostomatitis. Lesions may extend to involve the palate, pharynx, and tonsils. The lesions present as numerous pinhead sized vesicles, which collapse to form small ulcers exhibiting a red base covered with yellow fibrin. The persistence of active sites of HSV infection for more than one month in a patient with HIV infection is one of the accepted definitions of AIDS. These lesions can be treated by the administration of oral acyclovir.

Herpes Zoster

Herpes zoster virus infection is a recurrent viral infection seen in HIV-infected patients and presents a clinical course, which is more severe in morbidity than that encountered in immunocompetent patients. In AIDS patients herpes zoster begins as a unilateral cluster of vesicles and ulcers in a classical dermatome distribution but subsequently extends beyond the dermatomal boundary and heals by scarring. Oral acyclovir is the drug of choice in the treatment of herpes zoster.

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) was first reported by Greenspan and coworkers in 1984 on the lateral margin of the tongue among young homosexual males. The term hairy leukoplakia was given because of the corrugated surface of the epithelium. Initially this lesion was observed exclusively in male homosexuals. Further reports indicated their prevalence among other risk groups for AIDS (IDUs, transfusion recipients, hemophiliacs) and in certain immunocompromised HIV seronegative patients.

The association of these lesions with Epstein-Barr virus (EBV) has been demonstrated by immunohistochemistry, electron microscopy and *in situ* hybridization. It has been hypothesized that basal epithelial cells of the lateral margin of the tongue normally harbor latent EBV and significant diminution of Langerhans cells by HIV, in the affected site, permits reactivation of EBV with subsequent epithelial hyperplasia. It must be noted that EBV is associated with several forms of lymphoma in HIV-positive patients.

Oral candidiasis and OHL are predictive indicators for subsequent development of AIDS in HIV-seropositive patients. OHL is included under the Group I category of the EC-Clearinghouse revised classification of oral lesions associated with the HIV infection.

Clinical Features. OHL frequently appears bilaterally on the lateral borders of the tongue as painless, faint white vertical streaks or thickened and furrowed areas with a shaggy keratotic surface with vertical striations imparting a corrugated appearance. The floor of the mouth, the buccal mucosa, the tonsillar region, the soft palate, and the posterior portion of pharynx are the other areas involved less frequently.

Histologic Features. Lesion shows features of epithelial hyperplasia with acanthosis and hyperkeratosis, which produce surface corrugations. A remarkable feature of the acanthotic epithelium is the presence of varying numbers of lightly stained, swollen, balloon cells in the upper prickle cell layer. Superficial epithelial cells show dense aggregates of nuclear chromatin material marginated along the nuclear membrane known as nuclear beading. Ultrastructural studies reveal heterochromatin distribution along the inner aspect of nuclear envelope and ground-glass nucleoplasm with an even distribution of EBV particles throughout. Occasional, minor atypical changes including basal cell hyperchromatism and increased number of mitoses are seen. The presence of candidal hyphae in the overlying superficial epithelial cell layers is not an uncommon finding. EBV can be demonstrated by *in situ* hybridization, PCR, or immunohistochemistry.

Management. OHL is usually asymptomatic, but occasional slight soreness, discomfort, and unsightly appearance of the lesion warrant treatment. Since many OHL cases reveal candida, topical antifungal agents like nystatin, and clotrimazole, and systemic agents like ketoconazole and fluconazole are employed. Antiviral agents like acyclovir, desciclovir and ganciclovir, result in clinical improvement. However, discontinuation of therapy results in recurrence of the lesion, if immunosuppression persists.

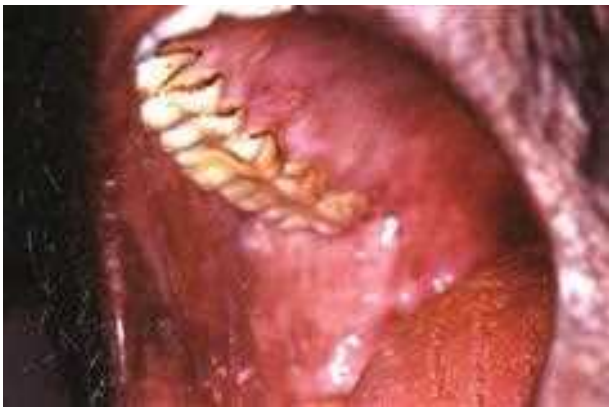


Figure 6-15. Herpetic ulcer of the palate.

Kaposi's Sarcoma

Kaposi's sarcoma is a multifocal neoplasm of vascular endothelial origin. Human herpes virus type 8 is involved in the pathogenesis of Kaposi's sarcoma. Commonly affected sites include palate, gingiva, tongue, and oropharynx or the skin. The clinical appearance of oral Kaposi's sarcoma can be macular, nodular, or raised and ulcerated, the color of which can range from red to purple. Early lesions tend to be flat, red and asymptomatic, with the color becoming darker as the lesion ages. As lesions progress, they can interfere with the normal functions of the oral cavity and become symptomatic secondary to trauma or infection. Bacillary angiomatosis often mimics Kaposi's sarcoma, but diagnosis can be made from a biopsy from the lesion, examined with the Warthin-Starry

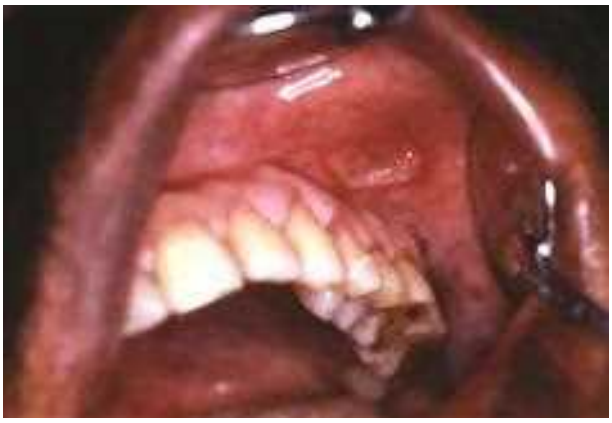


Figure 6-16. Aphthous ulcer in HIV-infected patient.

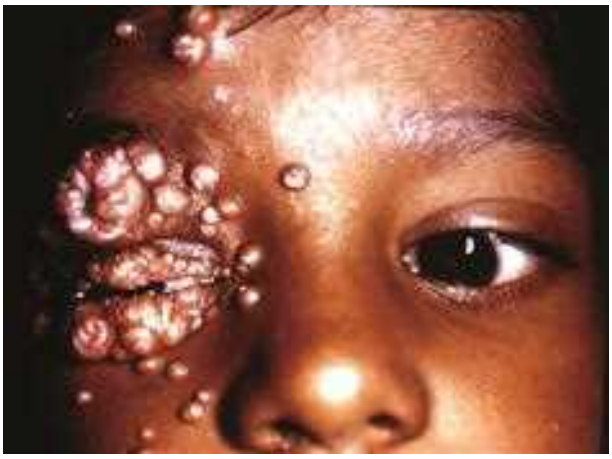


Figure 6-17. Shiny dome-shaped papules of molluscum contagiosum.

stain. Treatment features intralesional vinblastine or surgical removal. Systemic chemotherapy is indicated for widespread or disseminated form.

Aphthous Ulcers

Aphthous ulcers (Fig. 6-16) present as recurrent, round, shallow, painful ulcers of variable size and duration that are typically found on nonkeratinized oral mucosa. Oral ulcers in HIV-infected patients are large and more extensive. They usually measure more than 2 cm in diameter with regular borders. Aphthous ulcers respond to topical steroids. Though systemic corticosteroids have proved to be beneficial in immunocompetent patients, they are avoided in HIV-infected patients to prevent further immune depression. Chlorhexidine and tetracycline rinses have been reported to be useful in treating herpetiform aphthae.

Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma has been reported in HIV/AIDS patients with the same frequency as in the general population, associated with same risk factors but at a younger age. Impaired immunosurveillance, and an increased chance of human papilloma virus infection are a few suggested causes. The treatment consists of surgical resection, chemotherapy and/or radiotherapy.

Molluscum Contagiosum

Molluscum contagiosum (Fig. 6-17) is an infection of the skin, caused by a pox virus. It presents as shiny, white, and hemispherical skin-colored dome-shaped papules that often demonstrate a central depressed crater. In patients with AIDS, numerous lesions may be present which have no tendency to undergo spontaneous resolution and some grow to a large size. Histopathologically, the epithelium exhibits many large intracytoplasmic inclusions known as molluscum bodies. Cryotherapy is recommended for large and disfiguring lesions.

Thrombocytopenic Purpura

Thrombocytopenic purpura (TP) is a hematologic disorder characterized by a decreased number of circulating blood platelets (less than 150,000 platelets/mm^3 of blood). The reduction may be due to reduced production, increased destruction and sequestration subsequent to splenomegaly. Thrombocytopenic purpura in HIV diseases is characterized by reduced production of platelets due to drugs, malnutrition, immunological alterations, microbial invasion, or due to the course of HIV disease. Oral TP is characterized by pinpoint petechiae following minor trauma and even mastication. Spontaneous gingival hemorrhage is not uncommon. Platelet transfusions and/or corticosteroid therapy may be beneficial, provided the cause is removed.

HIV-associated Salivary Gland Disease

HIV-associated salivary gland disease (HIV SGD) is a heterogeneous group of signs and symptoms that vary from person to person and as the HIV infection progresses in the same individual. About 5% of HIV patients exhibit this condition. The main clinical sign noted in children and in earlier stages of the disease is parotid enlargement, which is bilateral and associated with cervical lymphadenopathy. As HIV progresses, salivary glands are infiltrated with CD8 lymphocytes leading to diffuse infiltrative lymphocytosis syndrome, resulting in salivary gland enlargement, in a few cases. This group of patients is at risk of B cell lymphoma. At the other end of the spectrum of HIV-associated salivary gland disease, qualitative and quantitative xerostomia (reduced salivary secretion) is experienced by most HIV-positive patients. The causes of xerostomia include drugs (antiretrovirals, antifungals, chemotherapeutics, antihistaminics, mood-altering drugs, multivitamins), oral diseases (candidiasis) or as a part of the progression of the HIV disease. The symptoms include dryness of the mouth, predisposition to fungal diseases, dental caries, and infections.

Non-Hodgkin's Lymphoma

In 1984, non-Hodgkin's lymphoma was described in 90 homosexual men with AIDS. Since 1985, aggressive B cell lymphoma has been classified as an AIDS-defining illness and is the second most common cancer associated with HIV. HIV patients are 60 times at risk of non-Hodgkin's lymphoma than the general population and around 3% of HIV-infected people develop lymphomas. A relationship between Epstein-Barr virus infection and non-Hodgkin's lymphoma has been suggested. This lesion tends to present as a large, painful, ulcerated mass on the palate or gingival tissues. Biopsy is necessary for a definitive diagnosis, often with a confirmatory immunohistochemical panel of markers. The treatment of non-Hodgkin's lymphoma is often a combination of chemotherapy and radiation.

Hyperpigmentation

In HIV-infected patients, hyperpigmentation (Fig. 6-18) of the oral mucosa, the skin and nails has been reported. Oral hyperpigmentation may occur suddenly in HIV-infected individuals and has been attributed to several medications including ketoconazole and zidovudine taken by AIDS patients. Adrenocortical destruction has been reported from several infections associated with HIV disease. Hyperpigmentation in HIV-infected individuals may also be due to a direct result of the HIV infection. Diagnosis is made by the clinical appearance of a recent onset, and brown to brownish-black intraoral focal or diffuse macules.

Oral lesions and Highly Active Anti-retroviral Therapy (HAART)

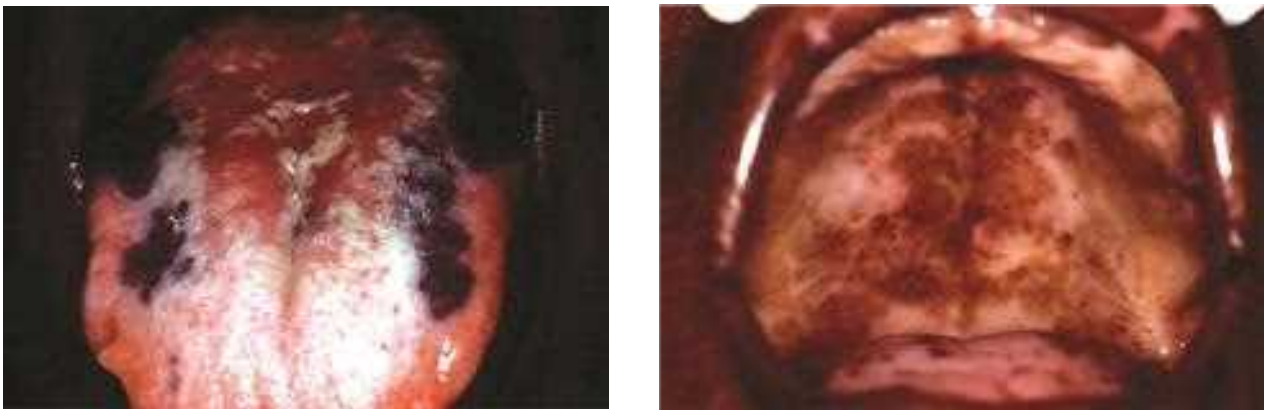
With the introduction of HAART therapy there has been a decrease in the opportunistic infections associated with HIV infection. HAART therapy has been associated with a decrease in the occurrence of oral candidiasis, oral hairy leukoplakia and Kaposi's sarcoma. Interestingly, there have been reports of increase in the occurrence of human papilloma virus (HPV) infection, attributed to the functionally incomplete reconstitution of the immune system.

Human papilloma viruses are small double-stranded DNA viruses, which infect stratified epithelium, of both skin and mucosa. More than 100 types of HPV viruses have been identified, around 60 of which are known to infect the head and neck region. The viruses can cause papillomas or warts and premalignant and malignant lesions of the epithelium.

DIAGNOSIS OF HIV

Virus-based Tests

1. **Viral Culture**. It directly detects the virus and hence is highly specific. It is positive, even during the window period and during the terminal phase when the viral load is high and when the ELISA may be negative. With the availability of PCR, HIV culture is not done routinely any more.
2. **PCR**. Polymerase chain reaction (PCR) has revolutionized the diagnosis and treatment of HIV infection. Two types of PCR are available: PCR for DNA of provirus present in the infected host cells and PCR for HIV RNA from plasma, which detect the free virus present in plasma. PCR can detect as low as 20 copies/ml of plasma and is highly sensitive and specific test. It is very useful for early diagnosis of HIV infection in newborn. Results of PCR are available in 24–48 hours unlike viral culture that takes 2–4 weeks. Quantitative PCR can be done to define the viral load in copies per ml of plasma. This is useful before starting therapy and monitoring response and relapse following antiretroviral drugs. The limitations of PCR are its cost and the need for sophisticated laboratory equipment.
3. **P24 Antigen Detection**. It is detectable during the window period and the late phase of infections when the virus is replicating fast. It is often not detectable at other times as viral replication is low. Hence this test is not sensitive enough to be of use for routine diagnosis. It is useful in blood banks where the P24 antigen, along with ELISA, can shorten the window period of diagnosis to less than two weeks.



A B

Figure 6-18. Hyperpigmentation of tongue (A) and palate (B).

Anti-HIV Antibody Tests

1. **Enzyme Linked Immunosorbent Assay (ELISA)/ Immunofluorescence.** ELISA is the more popular and widely done test. ELISA tests have nearly 99% sensitivity and specificity, especially on repeated testing. These tests are also much cheaper than PCR and culture, and can be done at any center. In the West, it is mandatory to do a Western blot, if the ELISA is positive, before confirming a person as HIV-positive. In India and according to WHO, it is not necessary to do a Western blot if the ELISA is positive. Instead, one should confirm it by repeating one or two more ELISA tests, using different kits on repeated blood samples. So, if two or preferably three ELISA tests are positive, a person is confirmed as HIV infected. One will have to wait 18 months to diagnose HIV infection in a newborn if one uses only ELISA. Hence ELISA cannot help in early diagnosis of HIV infection in the newborn. Similarly, ELISA is negative during the window period, that is, 6–12 weeks following HIV exposure, and sometimes during the last phase of HIV infection due to severe immunodeficiency leading to severe hypogammaglobulinemia. PCR is useful in such cases. Being cheap and easy to do, ELISA is the mainstay of HIV diagnosis in older children and adults in developing countries.
2. **Western Blot Analysis**. This detects specific antibodies and shows them as separate bands on gels. Hence it is more specific than ELISA. It is interpreted as positive if at least two of three bands, i.e. p24, gp41, gp120/160 bands, are positive. If none are positive, it is labeled as negative. If only one band is positive, it is labeled as indeterminate. When the test is indeterminate, one needs to repeat both ELISA and Western blot once or twice after 4–6 weeks until it becomes definitely positive or negative. Like ELISA, Western blot is also negative during the window period, and sometimes in the late phase of HIV infection. It cannot be relied upon for early diagnosis of HIV in newborns, as it detects maternal antibodies for as long as 18 months.

Immunological Tests and Surrogate Markers

CD4+T cell count, CD4+T cell % and CD4/CD8 ratio are tests done to determine immune status. A gradual decline in CD4+T cell count suggests disease progression. CD4+T cell % is more constant whereas absolute CD4 is age dependent. It helps to prognosticate, monitor disease progression and to determine response and relapse following antiretroviral drug therapy.

Salivary Tests

The fluids obtained from the oral cavity are saliva and gingival crevicular fluid. The immunoglobulin content of oral fluids is similar to that of blood, but their levels are lower. However, the use of an HIV IgG antibody capture assay (GAC ELISA), designed specifically for testing oral fluids, has produced encouraging results. A number of studies, including several in developing countries, report that the sensitivity and specificity of these optimized tests lie in the range of 95–100% and 98–100%, respectively.

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CHAPTER 7

Mycotic Infections of the Oral Cavity

■ B SIVAPATHASUNDHARAM AND N GURURAJ

CHAPTER OUTLINE

Mycology, the study of fungal infections, has gained remarkable impetus in the past few decades, owing at least in part to the fact that fungal diseases are far more common than was previously suspected. Many erroneous conceptions of this branch of microbiology existed until only recently, but careful scientific investigation of various aspects of mycology, such as epidemiology, pathogenesis, immunology, diagnosis and treatment, has done much to eliminate the confusion. Furthermore, excellent monographs and reviews on certain fungal diseases, such as those on blastomycosis by Witorsch and Utz and by Sarosi and Davies; on coccidioidomycosis by Fiese and by Stevens; on cryptococcosis by Littman and Zimmerman; on histoplasmosis by Sweany and by Goodwin and his colleagues; and on mucormycosis (phycomycosis) by Lehner, have been valuable contributions to our understanding of these conditions.

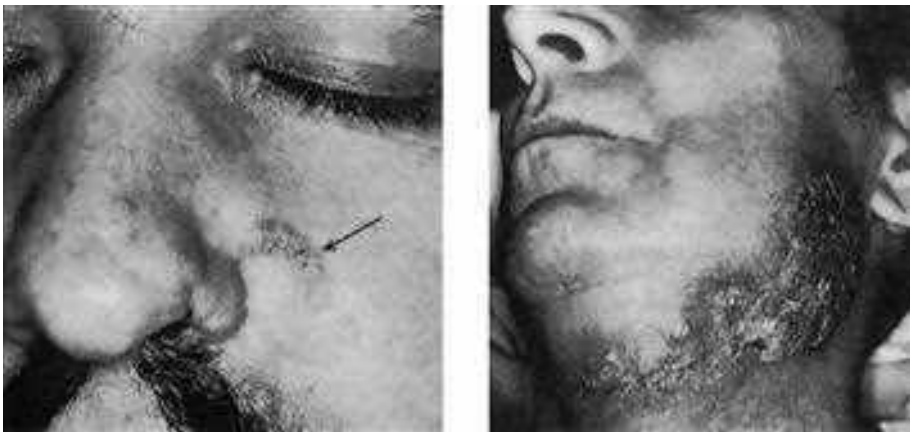
NORTH AMERICAN BLASTOMYCOSIS

(Gilchrist's disease)

North American blastomycosis is a mycotic infection caused by *Blastomyces dermatitidis* and may occur either in a cutaneous form or in a systemic form involving bones, liver, lungs, subcutaneous tissues, and other organs. Experimental transmission to animals is only haphazardly successful and cannot be used as an aid in diagnosis, although spontaneous infection in dogs is quite common. The source of the infection in human beings is unknown, although affected persons commonly work or spend a great deal of time outdoors. It is becoming an important medical problem, particularly in central United States as has been pointed out by Furcolow and his associates.

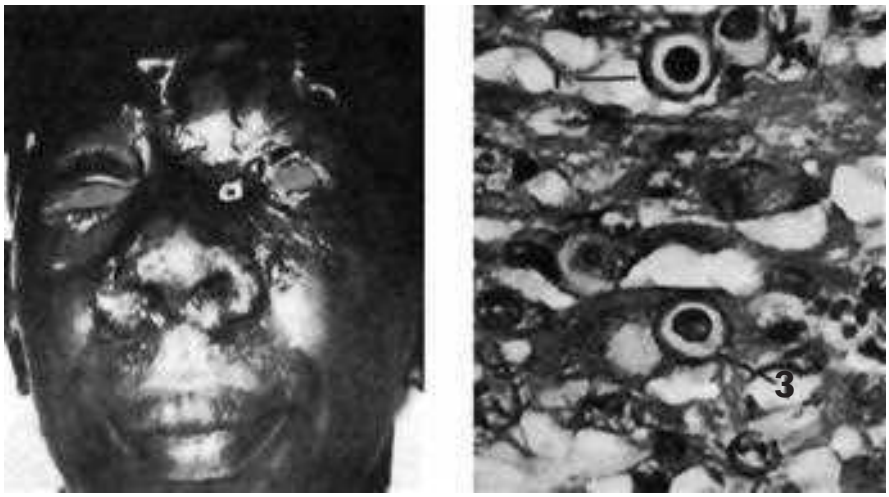
Clinical Features. North American blastomycosis is far more common in men than in women and typically occurs in middle age. Skin lesions usually begin as small red papules which gradually increase in size and form tiny miliary abscesses or pustules which may ulcerate to discharge the pus through a tiny sinus. Crateriform lesions are typical and these often exhibit indurated and elevated borders (Figs. 7-1, 7-2). The infection commonly spreads through the subcutaneous tissues and becomes disseminated through the blood stream. The systemic disease is characterized by fever, sudden weight loss, and in cases of lung involvement, a productive cough associated with other symptoms typical of pulmonary tuberculosis.

Oral Manifestations. Lesions of the oral cavity have been reported occurring in blastomycosis and may resemble those of actinomycosis, although abscess formation is not usually as prominent. Tiny ulcers may be the chief feature. The oral infection may be either the primary lesion or secondary to lesions elsewhere in the body. In an extensive discussion of this disease, Witorsch and Utz have reported that 25% of their group of patients had oral or nasal mucosal lesions. Bell and his coworkers have also pointed out that the oral lesions, which may be the first apparent manifestation of the disease, are probably more common than has been thought. In two



A B

Figure 7-1. North American blastomycosis.
(A) Early lesion. **(B)**, Advanced lesion *(Courtesy of Dr Stephen F Dachi).*



A B

Figure 7-2. North American blastomycosis.
(A) Advanced North American blastomycosis of the face. **(B)** Photomicrograph of granulomatous lesion of blastomycosis, showing typical yeast like organisms with doubly refractile capsule (1) *(A, Courtesy of Dr Wilbur C Moorman).*

cases reported by Page and his associates, the oral lesions bore enough resemblance to epidermoid carcinoma to warrant it as a consideration in the differential diagnosis.

Histologic Features. The microscopic features of North American blastomycosis are similar to those of other chronic granulomatous infections. The inflamed connective tissue shows occasional giant cells and macrophages and the typical round organisms, often budding, which appear to have a doubly refractile capsule (Fig. 7-2). The organisms, usually measuring between 5μ and 15μ in diameter, are common within giant cells. Microabscesses are frequently found. If the lesions are not ulcerated, overlying pseudoepitheliomatous hyperplasia may be prominent.

SOUTH AMERICAN BLASTOMYCOSIS
(Lutz's disease, Paracoccidioidomycosis)

South American blastomycosis is related to the North American form of the disease and is caused by infection with *Blastomyces (Paracoccidioides) brasiliensis*. The systemic lesions are similar to those of North American blastomycosis.

Oral Manifestations. Bogliolo reported that the organisms may enter the body through the periodontal tissues and subsequently reach the regional lymph nodes, producing a severe lymphadenopathy. He has demonstrated the organisms in both the periodontal membrane and in a periapical granuloma and has cultivated them from these sites. The microorganisms

also have been shown to penetrate the tissues and establish infection after extraction of teeth, producing papillary lesions of the oral mucosa. Widespread oral ulceration is also a common finding.

The chief difference between North American and South American blastomycosis is in the size of the causative organisms. The fungus in the South American form of the disease varies between approximately 10μ and 60μ in diameter, being considerably larger than that of the North American disease.

HISTOPLASMOSIS

(Darling's disease)

Histoplasmosis is a generalized fungal infection caused by the organism *Histoplasma capsulatum*. It is widespread in its distribution and endemic in the Mississippi Valley and Northeastern United States, where up to 75% of the population have had a primary but subclinical infection. It is usually acquired by inhalation of dust containing spores of the fungus, the contamination probably occurring from excreta of birds such as pigeons, starlings, and blackbirds. It is classified clinically into acute primary pulmonary, chronic pulmonary and disseminated forms. In the disseminated forms, the infection spreads to extra pulmonary sites including oral cavity.

Oral lesions are present in a high percentage of cases. Reports of 73 cases have been reviewed by Weed and Parkhill, which found that 33% of the cases had oral lesions as part of the presenting complaint.

Clinical Features. The disease is characterized by a chronic low-grade fever, productive cough, splenomegaly, hepatomegaly and lymphadenopathy, since the organisms have a special predilection for the reticuloendothelial system and chiefly involve the spleen, liver, lymph nodes, and bone marrow. Anemia and leukopenia may also be present. The infection by this organism may be extremely mild, manifesting only local lesions such as subcutaneous nodules or suppurative arthritis, and may produce no more serious effects than a positive histoplasmin skin reaction or calcified pulmonary nodules similar to those seen in tuberculosis. Histoplasmosis often terminates fatally; however, particularly the generalized form.

Oral Manifestations. The oral lesions of histoplasmosis have been reviewed by Levy and by Stiff. They appear as nodular, ulcerative or vegetative lesions on the buccal mucosa, gingiva, tongue, palate, or lips (Fig. 7-3). The ulcerated areas are usually covered by a nonspecific gray membrane which is indurated with raised and rolled out borders resembling carcinoma. The organisms may be demonstrated in tissue sections in many, but not all cases. Thus it is wise in suspected cases to preserve a piece of tissue at the time of biopsy for microbiologic examination. The organism may be readily isolated by inoculating the emulsified tissue onto blood agar containing penicillin and streptomycin. Occasionally cases have been mistaken for carcinoma or even Vincent's infection, while the lymphadenopathy has suggested Hodgkin's disease.

Histologic Features. Histoplasmosis appears basically to be a granulomatous infection which affects chiefly the reticuloendothelial system. Thus the organisms are found in large numbers in phagocytic cells and appear as tiny intracellular structures measuring little more than 1μ in diameter (Fig. 7-3).

Treatment. Pulmonary histoplasmosis usually, resolves spontaneously, while severe forms of the disease are usually treated by amphotericin B.

COCCIDIOIDOMYCOSIS

(Valley fever, San Joaquin valley fever)

Coccidioidomycosis is now recognized as a relatively common fungal disease and endemic chiefly in the Southwestern portion of the United States, Arizona, California, Nevada, New Mexico, Texas, and Utah. It is also known to occur in Mexico, Central and South America, and occasionally Europe. In those areas where the disease is endemic, the vast majority of the population has at one time or another been infected by the organism, but usually this has been a subclinical infection. The disease appears to be transmitted to man and animals by inhalation of dust contaminated by the spores of the causative organism, *Coccidioides immitis*. This organism develops from an arthrospore into a nonbudding spherule, measuring between 10μ and 80μ in diameter, which is packed with endospores measuring approximately 5μ in diameter. When the spherules rupture, the endospores which are set free then develop into full-size spherules

Clinical Features. There are two basic forms of the disease: primary nondisseminated and progressive disseminated coccidioidomycosis. In primary coccidioidomycosis, patients generally develop manifestations suggestive of a respiratory disease such as cough, pleural pain, headache, and anorexia. In addition, about 20% of the patients develop skin lesions, either erythema nodosum or erythema multiforme. This form of the disease is self-limiting and runs its course within 10-14 days. In a small percentage of cases, pulmonary cavitation, calcified nodules or pulmonary fibrosis may remain.

In the **disseminated** form of the disease that occurs in only about 1% of the cases, there is a mortality rate of approximately 50%. The disease usually runs a rapid course and the dissemination extends from the lung to various viscera, bones, joints, skin, and to the central nervous system where meningitis is the most frequent cause of death. The dissemination to bone results in osteomyelitis in 10–50% of cases.

Oral Manifestations. Lesions of the head and neck, including the oral cavity, occur with some frequency as has been pointed out by Frauenfelder and Schwartz. The lesions of the oral mucosa and skin are proliferative granulomatous and ulcerated lesions that are nonspecific in their clinical appearance. These lesions tend to heal by hyalinization and scar. Marked chronicity is often a feature of these lesions. Lytic lesions of the jaws may also occur and such a case has been reported by Igo and his associates.

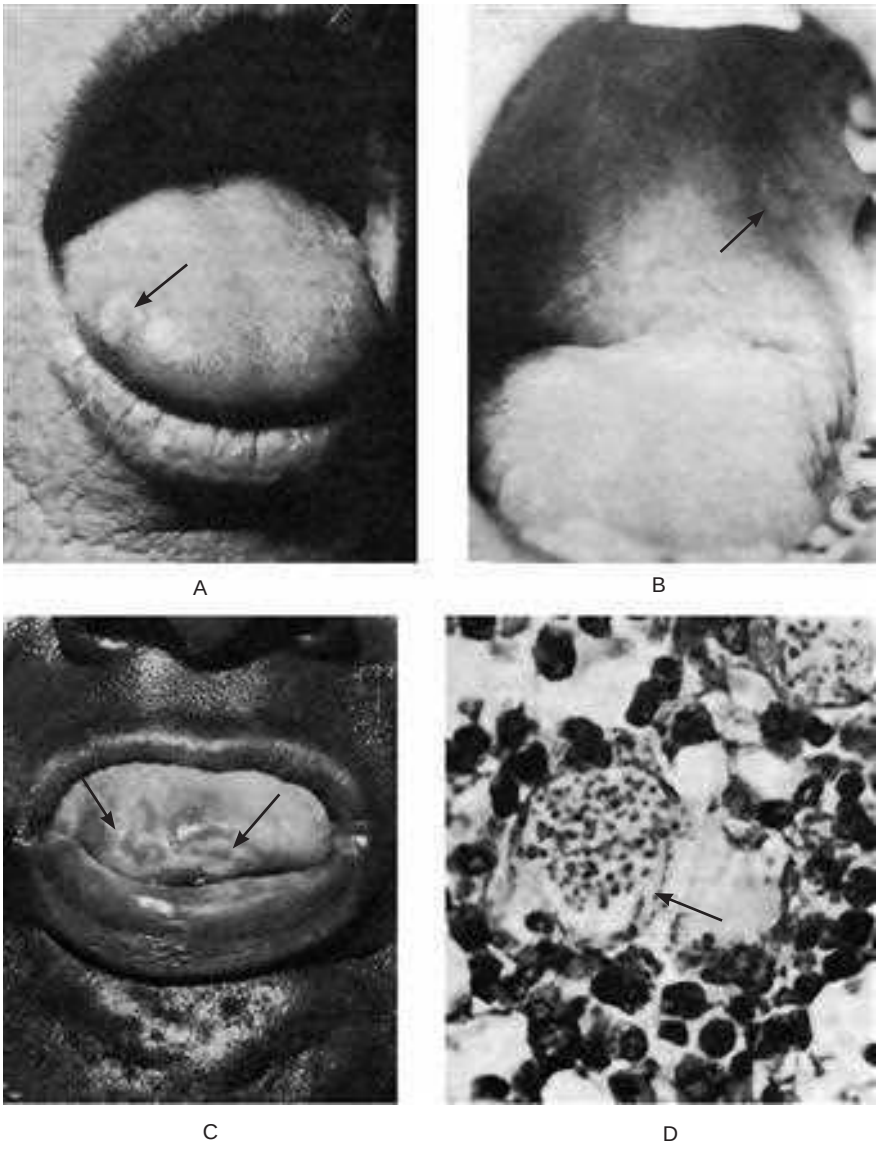


Figure 7-3. Histoplasmosis.
Lesions involving tongue **(A, C)** and palate **(B)**. The photomicrograph **(D)** of the bone marrow biopsy shows *Histoplasma capsulatum* within macrophages (*A and B, Courtesy of WJ Bruins Slot: Arch Dermatol, 76: 4, 1957, and C, of Dr Charles Newman).*

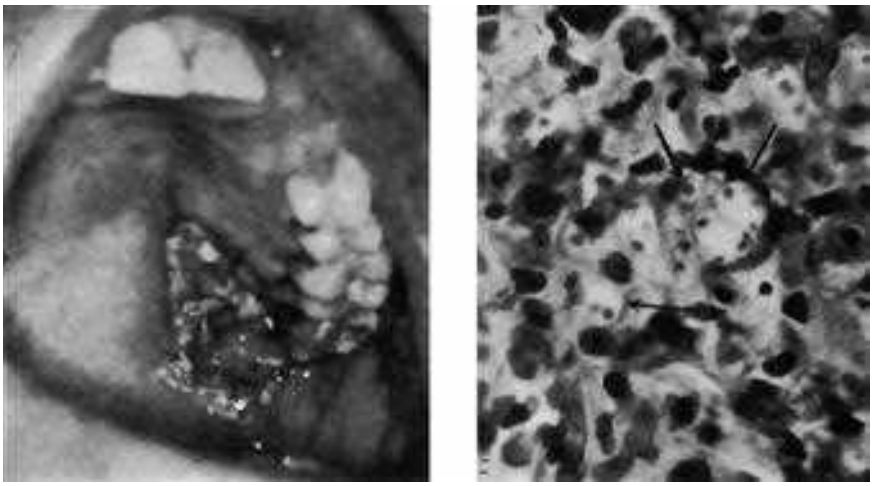
Histologic Features. The tissue reaction in coccidioidomycosis is similar to that of many specific infectious granulomas. Large mononuclear cells, lymphocytes and plasma cells predominate, although epithelioid cells are not usually seen. Foci of coagulation necrosis are often found in the center of the small granulomas, and multinucleated giant cells are scattered throughout the lesion. The organisms themselves are often found within the cytoplasm of the giant cells as well as lying free in the tissue. In tissue sections, the organisms will be found to vary greatly in size and generally show no budding. The endospores within the large spherules can usually be identified without difficulty.

Treatment. Amphotericin B has been found to provide effective chemotherapeutic control of the disease.

CRYPTOCOCCOSIS

(Torulosis, European blastomycosis)

Cryptococcosis is a chronic fungal infection caused by *Cryptococcus neoformans (Torula histolytica)* and *Cryptococcus bacillispora*, and may present widespread lesions in the skin, oral mucosa, subcutaneous tissues, lungs, joints, and particularly the meninges. The organisms are widespread and frequently found on the skin of healthy persons; for this reason, the exact mechanism of infection is not known. The organisms appear to be harbored by pigeons, but the actual infection of the human probably results from inhalation of airborne microorganisms. Since it is often an opportunistic infection, the disease has increased in incidence as immunosuppression has become more prevalent.



A B

Figure 7-4. Cryptococcosis.
The large ulcer of the palatal mucosa **(A)** contained the typical organisms **(B)**, and these were subsequently cultured *(Courtesy of Dr Charles W Newman. From CW Newman and D Rosenbaum: Oral cryptococcus. J Periodontol, 33: 266, 1962).*

Clinical Features. The first evidence of infection by these organisms is the presence of skin lesions from which blood stream dissemination to other parts of the body frequently occurs. Nevertheless, some authorities consider the respiratory tract colonization or visceral lesions to be the primary site, the skin lesions occurring secondarily. The skin lesions appear as multiple brown papules which ultimately ulcerate; the clinical picture is not specific. Most studies indicate a slight predilection for occurrence in middle-aged males.

The lesions of the lungs produce symptoms of a nonspecific pneumonitis, while the meningeal lesions produce a variety of neurologic signs and symptoms generally associated with increased intracranial pressure.

Cryptococcosis has been repeatedly reported in patients already suffering from some form of malignant lymphoma, evidence of the opportunistic nature of the disease.

Oral Manifestations. Occasional cases of oral cryptococcosis, almost invariably occurring in patients with other visceral or cutaneous lesions have been reported. One of these reports was that of Newman and Rosenbaum, in which the oral lesions were the first evidence of the infection. Interestingly, their patient was also suffering from chronic lymphatic leukemia.

The oral lesions appear as simply nonspecific single or multiple ulcers, which in a patient known to have leukemia, may be mistaken for the widespread ulceration often seen in leukemic patients as a result of their inability to react to a mild, nonspecific bacterial infection (Fig. 7-4A).

Histologic Features. The causative organism is a gram-positive, budding, yeast-like cell with an extremely thick, gelatinous capsule. The *Cryptococcus* measures 5–20μ in diameter, and in tissue sections, appears as a small organism with a large clear halo, sometimes described as 'tissue microcyst' (Fig. 7-4B). The capsule is colored intensely with the periodic acid-Schiff (PAS) stain, and the organisms may be cultured on Sabouraud's glucose agar.

The tissue reaction is essentially a granulomatous one of the tuberculoid type, but focal necrosis is often absent and epithelioid cell proliferation is minimal. Multinucleated giant cells are common as the organisms with their characteristic halos are found singly or in groups scattered throughout the granuloma.

Treatment and Prognosis. The use of amphotericin B has been found to give excellent results. The ultimate prognosis of the patient is variable; however, and especially dependent upon the sites of involvement.

CANDIDIASIS
(Candidosis, moniliasis, thrush)

Candidiasis is caused by a yeast-like fungus, *Candida (Monilia) albicans.* Although other species, such as *C. tropicalis, C. parapsilosis, C. stellatoidea, and C. krusei. C. guilliermondii, C. dubliniensis,* and *C. glabrata* may also be involved.

Candida exists in three forms namely, pseudohyphae, yeast, and chlamydospore forms. It reproduces by asexual budding and forms pseudohyphae. These species grow rapidly at 25–37°C. In general, *candida* species differ from one another but can be identified by the formation of pseudohyphae or by biochemical test.

It has been shown repeatedly that this microorganism is a relatively common inhabitant of the oral cavity, gastrointestinal tract, and vagina of clinically normal persons. When the favorable condition develops, the organism transforms into pathogenic form, that is yeast form transformed into hyphae. Thus it appears that the mere presence of the fungus is not sufficient to produce the disease. There must be actual penetration of the tissues, although such invasion is usually superficial and occurs only under certain circumstances. This disease is said to be the most opportunistic infection in the world. Its occurrence has increased remarkably since the prevalent use of antibiotics, which destroy the normally inhibitory bacterial flora and immunosuppressive drugs, particularly corticosteroids

Predisposing factors

- Acute and chronic diseases like tuberculosis, diabetes mellitus, and anemia
- Myxedema, hypoparathyroidism, and Addison's disease
- Immunodeficiency like AIDS
- Nutritional deficiency like Fe, vitamin A and vitamin B_6 deficiencies, etc.
- Prolonged hospitalization for chronic illness and debilitating diseases
- Prolonged use of antibiotics, corticosteroids, and cytotoxic drugs
- Radiation therapy
- Use of intravenous tubes, catheters, heart valves and poorly maintained dentures, heavy smoking
- Old age, infancy, and pregnancy
- Xerostomia. The protective antifungal proteins present in the saliva like histatins and calprotectin are absent in patients with xerostomia

Immunopathogenesis of Candidiasis. Many specific and nonspecific factors have a role in the development of candidiasis. Various anticandidal factors and antiadherence factors also play a major role in its development. Salivary IgA affects the adherence of *Candida* to mucosal cells. T cells and neutrophils also play a role in preventing and clearing the infection. Other factors of less significant role are complement, transferrin, lactoferrin, vitamins A, C, and serum antibody.

and cytotoxic drugs. This is the chief cause of this disease in patients with leukemia, lymphoma or other tumors. In addition to affecting the oral cavity, monilial infection frequently involves the skin as well as the gastrointestinal tract, vaginal tract, urinary tract, and lungs. Vaginal colonization appears to be increased by diabetes, pregnancy, and oral contraceptive agents. The incidence of oral candidiasis has increased after the advent of human immunodeficiency virus. It is reported that more than 90% of the HIV infected individuals develop oral candidiasis during some part of their disease (Ellepola ANB and Samaranayake LP, 2000). Oral candidiasis, usually remains a localized disease, but on occasion it may show extension to the pharynx or even to the lungs, often with a fatal outcome.

Clinical Features. It has a variety of clinical manifestations, making the diagnosis sometimes difficult. Candidal infection may range from mild superficial mucosal involvement to severe, fatal disseminated form seen in immunocompromised individuals. The classification proposed by Samaranayake in 1991 and modified by Axéll et al, in 1997 divides candidiasis into two major categories namely: (1) primary oral candidiasis (infection exclusively confined to oral and perioral tissues), and (2) secondary oral candidiasis (oral lesions as a manifestation of systemic mucocutaneous candidiasis).

Oral Manifestations. Oral lesions in different forms of candidiasis may have a different appearance and must be discussed separately (Table 7-1).

Table 7-1: Classification of oral candidiasis [as proposed by Samaranayake (1991) and modified by Axell et al (1997)]

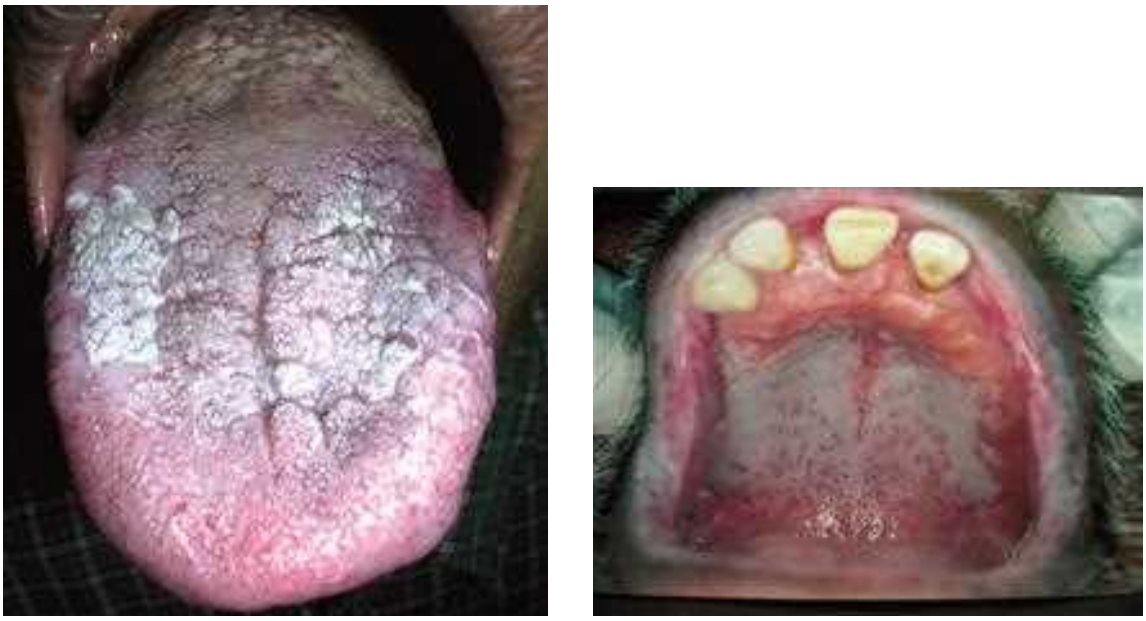
Primary oral candidiasis	Secondary oral candidiasis
Acute forms Pseudomembranous Erythematous	Oral manifestations of systemic mucocutaneous candidiasis as a result of diseases such as a thymic aplasia and candidiasis endocrinopathy syndrome
Chronic forms Hyperplastic Nodular Plaque like Erythematous Pseudomembranous	
Candida-associated lesions Denture stomatitis Angular cheilitis Median rhomboid glossitis	
Keratinized primary lesions superinfected with Candida Leukoplakia Lichen planus Lupus erythematosus	

Pseudomembranous Candidiasis

It is also known as thrush and is one of the most common forms of the candidiasis. It may occur at any age, but is especially prone to occur in the debilitated or the chronically ill patients or in infants. Occurrence of this lesion in a healthy individual indicates the presence of immune suppression especially HIV infection. It also occurs in patients receiving systemic corticosteroid therapy. The oral lesions are characterized by the appearance of soft, white, slightly elevated plaques most frequently occurring on the buccal mucosa and tongue, but also seen on the palate, gingiva, and floor of the mouth (Figs. 7-5, 7-6 A). The plaques, which have often been described grossly as resembling milk curds, consist chiefly of tangled masses of fungal hyphae with intermingled desquamated epithelium, keratin, fibrin, necrotic debris, leukocytes, and bacteria. The white plaque can usually be wiped away with a gauze, leaving either a relatively normal appearing mucosa or an erythematous area. In severe cases, the entire oral cavity may be involved. Concomitant involvement of oral cavity and esophagus is common in HIV patients.

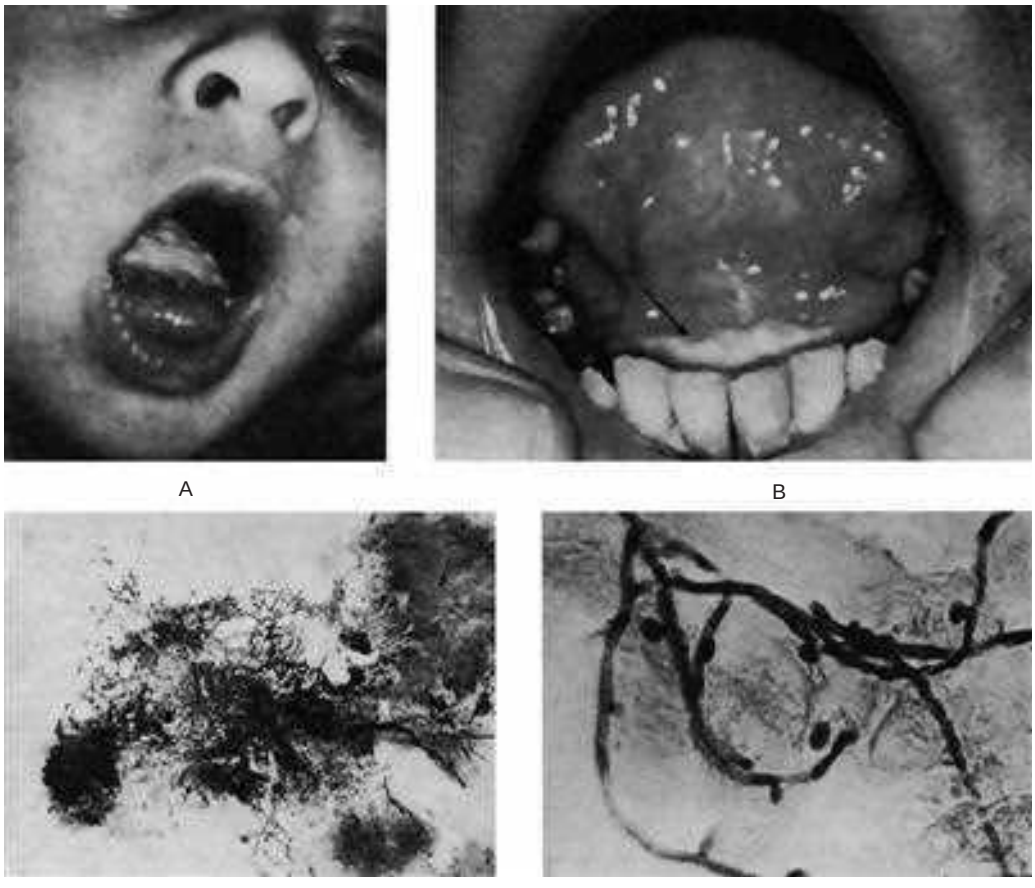
Erythematous Candidiasis

Also known as **antibiotic sore mouth,** includes central papillary atrophy of the tongue and **cheilocandidiasis**. It usually occurs as a sequela to a course of broad spectrum antibiotics, corticosteroids or any disease which suppresses the immune system, more commonly HIV disease. The lesions in this form of the disease appear red or erythematous rather than white, thus resembling the pseudomembranous type in which the white membrane has been wiped off. The redness is due to increased vascularity. It is distinguished from erythroplakia by its diffuse border wherein erythroplakia the borders are sharp and well demarcated. It too may occur at any site. It is the only



A B

Figure 7-5. Oral Candidiasis.
(Courtesy of Dr Leela Poonja, Dr G Sriram, Dr Vaishali Natu, Nair Hospital Dental College, Mumbai).



A B C D

Figure 7-6. Oral candidiasis.
(A) Acute pseudomembranous type in an infant. **(B)** Chronic hyperplastic type in floor of mouth in adult. **(C, D)** Thread-like *Candida albicans* organisms having budding yeast cells are scattered along the pseudohyphae *(C and D, Courtesy of Dr Grant Van Huysen: Oral Surg, 9: 970, 1956).*

variety of oral candidiasis, which is consistently painful. Central papillary atrophy of the tongue is an asymptomatic, symmetric erythematous lesion of the dorsal aspect in the posterior region. The erythematous appearance occurs due to the loss of filiform papillae. A strong relationship exists between this lesion and chronic smoking and *C. albicans*.

Chronic Hyperplastic Candidiasis
(Candidal leukoplakia)

This is often spoken of as the 'leukoplakia' type of candidiasis. The oral lesions consist of firm, white persistent plaques, usually on the lips, tongue, and cheeks and appear similar to leukoplakia (Fig. 7-6B). These lesions may be homogeneous or speckled (nodular) and persists for periods of years. In this regard, Roed-Petersen and his associates have reported a high incidence of *Candida* organisms present in the lesions of a series of 226 patients with true leukoplakia. In addition, they found a definite relationship between the presence of the organisms and the occurrence of cytologic epithelial atypia in the biopsied lesions of leukoplakia. Cawson and Binnie have presented data which indicate a definite relationship between chronic candidiasis and oral epidermoid carcinoma, basing this relationship on the finding that chronic candidiasis itself is a cause of leukoplakia and thus must be regarded as having possible premalignant potential. These lesions resolve completely following antifungal therapy.

Some cases of chronic hyperplastic candidiasis are associated with iron and folate deficiency and defective cell mediated immunity. There are few keratotic lesions which may be superimposed by candidal infection. These include leukoplakia, lichen planus and lupus erythematosus. They may appear similar to chronic hyperplastic candidiasis clinically but may not regress with antifungal treatment as does the chronic hyperplastic candidiasis.

CANDIDA-ASSOCIATED LESIONS

Denture Stomatitis
(Chronic atrophic candidiasis)

Denture stomatitis is now considered to be synonymous with the condition better known as **denture sore mouth**, a diffuse erythema and edema of the denture-bearing area, often occurring with angular cheilitis. Usually asymptomatic except for the soreness and the presenting complaint may be angular stomatitis. Mandibular mucosa is rarely affected. There is no apparent age limit and some studies show women are affected more frequently than men.

Denture-related candidiasis may be the most common form of the oral disease. For example, in a study reported by Holbrook and Rodgers, they found that in nearly two-thirds of a group of 100 patients with candidiasis, dentures were the one 'disorder' or situation predisposing or traceable to the development of the infection.

Other lesions under this category namely angular stomatitis and median rhomboid glossitis are discussed elsewhere.

SECONDARY ORAL CANDIDIASIS

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is a group of different forms of the infection, some of which may have multiple features in common; although they can usually be separated as entities. Oral manifestations occur in numerous forms of candidiasis and these have been categorized most conveniently by Lehner, whose slightly modified classification is shown in Table 7-1, and includes the various forms of chronic mucocutaneous candidiasis. In general, chronic mucocutaneous candidiasis is characterized by chronic candidal involvement of the skin, scalp, nails, and mucous membranes. As a group, the patients exhibit varying abnormalities in their immune system — impaired cell-mediated immunity, isolated IgA deficiency, and reduced serum candidacidal activity — and they are usually resistant to the common forms of treatment. Chronic familial mucocutaneous candidiasis is an inherited disorder, probably an autosomal recessive characteristic, which occurs early in life, usually before the age of five years and has an equal gender distribution. Oral lesions occur in these children.

Chronic Localized Mucocutaneous Candidiasis

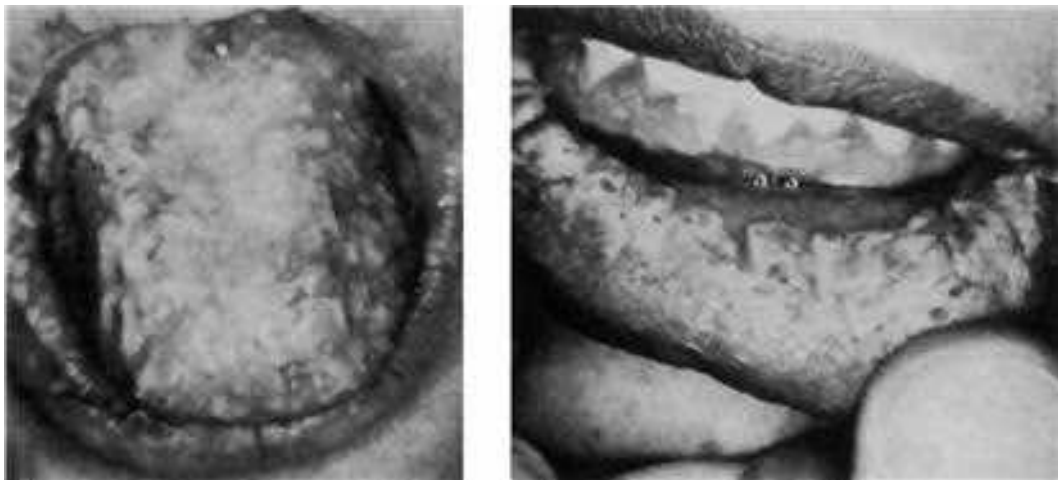
Chronic localized mucocutaneous candidiasis is a severe form of the disease also occurring early in life, but there is no genetic transmission. There is widespread skin involvement and granulomatous and horny masses on the face and scalp. There is an increased incidence of other fungal and bacterial infections. The mouth is the common primary site for the typical white plaques, and nail involvement is usually present.

Candidiasis Endocrinopathy Syndrome

Candidiasis endocrinopathy syndrome is also a genetically transmitted condition characterized by *Candida* infection of the skin, scalp, nails, and mucous membranes, classically the oral cavity, in association with either hypoadrenalism (Addison's disease), hypoparathyroidism, hypothyroidism, ovarian insufficiency or diabetes mellitus. It is recognized that the endocrine manifestations, which may be multiple, may not appear clinically for several years after the appearance of the thrush in the children. The oral findings in the autoimmune polyendocrinopathy-candidiasis syndrome, including the common finding of enamel hypoplasia have been discussed by Myllarniemi and Perheentupa.

Chronic Diffuse Mucocutaneous Candidiasis

Chronic diffuse mucocutaneous candidiasis is the least common form of the disease and appears to be of late onset, since all patients reported by Lehner were over 55 years of age. They exhibit extensive raised crusty sheets involving the limbs, groin, face, scalp and shoulders as well as mouth and nails. There is no familial history and usually the patients have no other abnormality.



A B

Figure 7-7. Oral candidiasis in chronic localized mucocutaneous type (A), and in candidiasis endocrinopathy syndrome (diabetes) type (B).

Id Reaction. It is a hypersensitivity reaction to candidal antigen, which manifests as vesicular and papular rash on the skin of patients with chronic candidiasis.

Chronic mucocutaneous candidiasis presents oral lesions in all forms of the disease. In general, their clinical appearance is similar to the lesions described in chronic hyperplastic candidiasis and occur in the same intraoral locations (Fig. 7-7).

Histologic Features. Fragments of the plaque material may be smeared on a microscopic slide, macerated with 20% potassium hydroxide and examined for the typical hyphae (Fig. 7-6C, D). In addition, the organisms may be cultured in a variety of media, including blood agar, cornmeal agar and Sabouraud's broth, to aid in establishing the diagnosis.

Histologic sections of a biopsy from a lesion of oral candidiasis show the presence of the yeast cells and hyphae or mycelia in the superficial and deeper layers of involved epithelium (Fig. 7-8B). These are more easily visualized if the sections are stained with PAS or methenamine silver, since the organisms are positive in both instances. Chlamydospores are seldom seen on oral smears or histologic sections.

Treatment. The development of new specific antifungal agents such as nystatin has been beneficial in the treatment of candidiasis. Suspensions of nystatin, held in contact with the oral lesions, have been successfully used in even chronic and severe cases of the disease. The use of tablets of the fungicide, prepared specifically for the treatment of intestinal thrush, are of little value in managing oral lesions, since the drug must make intimate contact with the organisms in order to be effective. Other drugs of value are clotrimazole, amphotericin B, and miconazole.

It has been found that occasional cases of candidiasis have remained refractory to treatment by nystatin. These have frequently been associated with one of the endocrinopathies just described in connection with immunologic abnormalities.

GEOTRICHOSIS

Geotrichosis is a fungal disease similar to candidiasis in its clinical features, but caused by organisms of the Geotrichum species.

Clinical Features. The most common lesions are those of the lungs and oral mucosa, although cutaneous and intestinal tract lesions occur on occasion. The lung involvement produces symptoms of pneumonitis or bronchitis but the organisms can be detected in the sputum.

Oral Manifestations. The oral lesions are identical to those of candidiasis or thrush, being a white, velvety, patch-like covering of the oral mucosa, isolated or diffuse in distribution. The differentiation is made only by microscopic examination and/or culture of the organisms.

The development of the disease also parallels that of candidiasis, being seen frequently in debilitated persons or as a secondary type of infection.

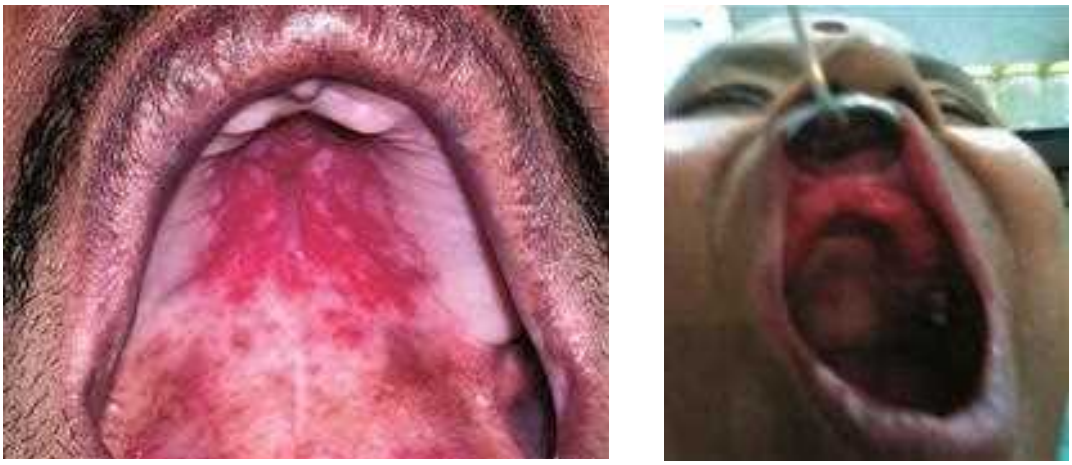
Histologic Features. The organisms are small, rectangular-shaped spores measuring approximately 4 by 8μ, often with rounded ends. The tissue reaction is a nonspecific, acute inflammatory one.

Treatment. Treatment is nonspecific, and there are insufficient data on the effects on geotrichosis of drugs used in treating candidiasis.

PHYCOMYCOSIS

(Mucormycosis, zygomycosis)

Phycomycosis is a fungal infection caused by the order mucorales. Zygomycosis refers to the infection caused by both the order of fungus *Mucorales* and *Entomophthorales*. It is worldwide in distribution and the organisms normally occur in soil, manure,



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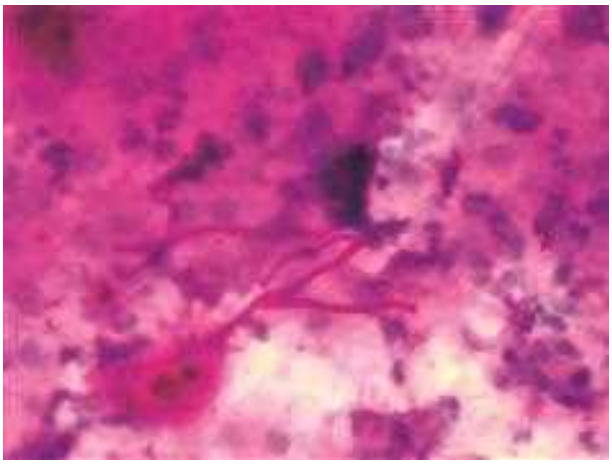


C

Figure 7-8. (A and B) Chronic atrophic candidiasis in denture wearing patients. (C) Candidal hyphae are seen in a background of epithelial cells (PAS stain) *(Courtesy of Dr Ravindra Shetty, Dr G Sriram, Dr Vaishali Natu, Department of Oral Pathology, Nair Dental College, Mumbai, and Dr N Gururaj, Department of Oral Pathology, CSI Dental College, Madurai)*

fruits, and in decaying matter. These organisms are present in the nasal passages and oral cavities of normal persons.

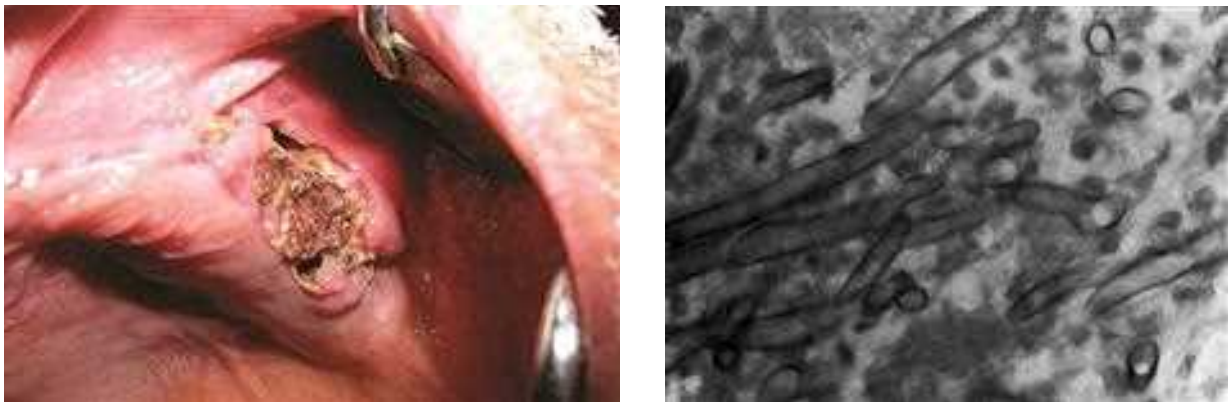
A thorough review of this disease was published by Hutter, and by Lehner, and the craniofacial or rhinocerebral form discussed by Green and his coworkers as well as Landau and Newcomer, Taylor and his associates. This is an opportunistic infection associated with debilitation and is becoming more frequently recognized as a secondary occurrence in cancer patients, especially those with any of the malignant lymphomas and in patients having renal failure, organ transplant, AIDS, and cirrhosis. It is also especially common in patients with diabetes mellitus, especially those with diabetic ketoacidosis; fully 75% of the patients with the rhinocerebral form of mucormycosis have the ketoacidosis. As might be expected, immunosuppressed patients are prone to develop this infection as well as patients with burns or open wounds. Cases have also been reported after administration of steroids and chemotherapeutic antimetabolites.

This disease may actually be caused by numerous Phycomycetes organisms of the Eumycetes (true fungi) class characterized by lack of septation (coenocytic). The three most important types causing infection in man are *Rhizopus*, *Mucor* and *Absidia*.

Clinical Features. Two main types of phycomycosis infection occur in human beings: (1) superficial and (2) visceral, although it is sometimes also classified as localized and disseminated. The superficial infection includes involvement of the external ear, the fingernails, and the skin. The visceral forms of phycomycosis are of three main types: (a) pulmonary, (b) gastrointestinal, and (c) rhinocerebral. Although all forms of phycomycosis are important, the rhinocerebral is of greatest interest to the dental profession, and only this variety will be discussed here.

Infections of the head by these organisms are characterized by the classical syndrome of uncontrolled diabetes, cellulitis, ophthalmoplegia and meningoencephalitis. The infection apparently enters the tissues through the nasal mucosa and extends to the paranasal sinuses, pharynx, palate, orbit, and brain.

One early clinical manifestation of the disease is the appearance of a reddish-black nasal turbinate and septum with



A B

Figure 7-9 (A,B). Mucormycosis involving the maxillary antrum.
(Courtesy to Dr Neelakandan RS, Department of Oral and Maxillofacial Surgery, Meenakshi Ammal Dental College, Chennai).

a nasal discharge. The necrosis may extend to the paranasal sinuses and orbital cavity, with the development of sinus tracts and sloughing of tissue.

Cases of phycomycosis involving the maxillary sinus may present clinically as a mass in the maxilla, resembling carcinoma of the antrum, and radiographs may support the latter diagnosis (Fig. 7-9A). Typical cases have been reported by Green and his associates, by Berger and his coworkers, and by Cruickshank and his colleagues. Surgical exploration; however, will reveal only masses of necrotic tissue in which the organisms can be demonstrated histologically. This involvement may occur at any age, cases having been reported in infants as well as adults.

Histologic Features. The tissue involved by this infection shows a variable amount of necrosis, some of which may be related to infarction brought about by thrombi consisting of the organisms. This fungus has an apparent predilection for blood vessels; it is able to penetrate their walls and thereby produce thrombosis.

The organisms appear as large, nonseptate hyphae with branching at obtuse angles (Fig. 7-9B). Round or ovoid sporangia are also frequently seen in the tissue section. The organisms can be cultured. Hisopathologically mucormycosis should be differentiated from aspergillosis in which the former has an acute angulating branched hyphae of smaller width and latter has septate branched hyphae. A special stain like Grocott's silver methenamine stain may use to confirm the diagnosis

The majority of reported cases of phycomycosis have been diagnosed only at the time of autopsy. In recent years; however, numerous cases of even fulminating head and neck infection by this organism have been diagnosed, treated, and cured. The current survival rate for rhinocerebral disease in patients with no systemic disease is about 75%; with diabetes, about 60%; and with other underlying diseases, about 20%. Pulmonary disease is almost uniformly fatal.

Treatment and Prognosis. Treatment of the disease consists of control of the predisposing factors such as diabetes, surgical excision if the lesion is localized, and administration of amphotericin B, since it is the only drug with proven efficacy.

SPOROTRICHOSIS

Sporotrichosis is a fungal infection caused by *Sporotrichum schenckii* in which the portal of entry is not entirely understood. It has been reported to occur after:

- Exposure to a wide variety of animals, both domestic and wild.
- Accidental injury from the thorns of some plants or bushes.
- Accidental laboratory or clinical inoculation of hospital workers.

Clinical Features. The most common lesions of sporotrichosis involve the skin, subcutaneous tissues and oral, nasal and pharyngeal mucosa, although disseminated visceral involvement occasionally occurs. The skin lesions, often described as sporotrichotic 'chancres,' appear at the site of inoculation as firm, red to purple nodules, which soon ulcerate. Neighboring nodules with regional lymphadenopathy generally develop soon, and both these subcutaneous nodules and involved lymph nodes may also ulcerate and drain.

Oral Manifestations. Nonspecific ulceration of the oral, nasal and pharyngeal mucosa also occurs in this disease, usually associated with regional lymphadenopathy. The lesions are described as healing by soft, pliable scars even though the organisms may still be present in the tissues.

Histologic Features. The fungus is a small, ovoid branching organism with septate hyphae, showing budding forms. It is only 3–5μ in diameter and because of the small size, is seldom recognized in the routine tissue sections. However it can be cultured on Sabouraud's medium.

The tissue reaction is a granulomatous one with epithelioid cells, multinucleated giant cells of the Langhans type and lymphocytes, often surrounding a central area of purulent or caseous necrosis. Polymorphonuclear leukocytes are prominent in some cases. Asteroid bodies radiate formations around the fungal spores in tissues are commonly found in this disease as reported by Lurie. Pseudoepitheliomatous hyperplasia of

the overlying epithelium of skin or mucosal lesions is also almost invariably present.

Treatment and Prognosis. There is no specific treatment for the disease, most antibiotics being ineffective, but the prognosis is generally good, although chronic repetitive remissions and relapses are common. The chronic pulmonary form of the disease is often fatal.

RHINOSPORIDIOSIS

Rhinosporidiosis is a chronic granulomatous disease caused by a fungus called *Rhinosporidium seeberi*, which affects chiefly the oropharynx and nasopharynx as well as the larynx, skin, eyes, and genital mucosa. The mode of infection is not known. This infection is common in India and Sri Lanka.

Clinical Features. Nasal mucosa is the most common site involved. Lesions appear as small verrucae or warts, which ultimately become pedunculated. Genital lesions resemble condylomas.

Oral Manifestations. The oronasopharyngeal lesions are often accompanied by a mucoid discharge and appear as soft red polypoid growths of a tumor like nature, which spread to the pharynx and larynx. The lesions are vascular and bleed readily. Though any intraoral site may be involved, soft palate appears to be the most frequent site. The oral lesions have been reviewed by Ramanathan and his coworkers. In addition, an unusual case involving the parotid duct has been reported by Topazian.

Histologic Features. The organisms appear as sporangia containing large numbers of round or ovoid endospores, each approximately 5–7μ in diameter. In either smear preparations or tissue sections, these sporangia are characteristic in appearance. The surrounding tissue reaction itself is a nonspecific one consisting of a vascular granulation tissue with focal abscess formation and occasional multinucleated giant cells. Both acute and chronic inflammatory cells are present in variable number (Fig. 7-10).

Treatment. Surgical removal of the growths is recommended as treatment of choice.

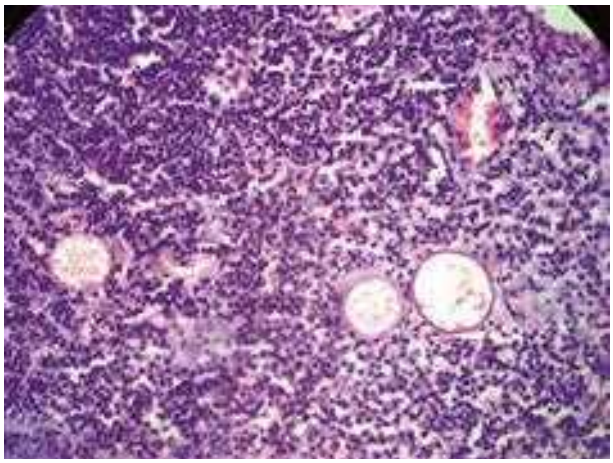


Fig. 7-10. Rhinosporidiosis.
Vascular granulation tissue with sporangia containing endospores *(Courtesy of Dr G Sriram, Meenakshi Ammal Dental College, Chennai).*

Parasitic Infections

There is a considerable variety of protozoal and helminthic parasitic diseases which occasionally manifest oral involvement. The protozoa are unicellular animals which are usually divided into two subphyla: the Plasmodroma—protozoa which move by means of pseudopodia or flagella—and the *Ciliophora*—protozoa which move by means of cilia.

Of the more common protozoal diseases, it is recognized that the following may involve oral structures in some fashion: trypanosomiasis (**Chagas' disease**), leishmaniasis, trichomoniasis and toxoplasmosis.

Helminthic Diseases

The helminths are multicellular parasitic worms, often referred to as metazoa, and are generally divided into two phyla, the Nemathelminthes or roundworms and the Platyhelminthes or flatworms. Of the nemathelminthes, those belonging to the class Nematoda (roundworms) are of medical importance, while of the platyhelminthes, those belonging to the Cestoda class (tapeworms) and the Trematoda class (flukes) are important.

These diseases may also involve oral structures with perhaps an even greater frequency than the protozoal diseases. Of the more common helminthic diseases, the following may manifest oral involvement: cysticercosis, trichinosis (trichiniasis), schistosomiasis (bilharziasis), echinococcus disease (hydatid disease), ascariasis, strongyloidiasis, and myiasis.

The entire field of parasitology is becoming increasingly important since some parasitic infections, once restricted to certain parts of the world are becoming worldwide in their distribution as a result of travel and military entanglements in countries which are parasite reservoirs. Nevertheless, the relative infrequency with which parasitic oral problems are encountered precludes a discussion of the individual diseases here.

CYSTICERCOSIS

Cysticercosis is an infestation caused by Cysticercus. Cysticercus (Gr. Kystis: bladder + kerkos: tail) is a larval form of certain Taenia species. Among various species, the larval form of tape worm, the **Taenia solium** i.e. **Cysticercus cellulosae** (a larval form of T. solium) infests human beings who serve as either definitive or as intermediate hosts of the adult tapeworm.

Consumption of inadequately cooked pork is the primary cause since pigs serve as intermediate hosts. The other causes include consumption of fecally contaminated vegetables, food or water, as well as self-contamination by reflux from the intestine into the stomach or by contaminated hands.

Intraorally, cysticercosis commonly involves lips, cheeks, and tongue. Cysticercosis involving the masseter muscle has been reported by B Dilip Kumar, Bindi Dave, and SM Meghana. Most cases present as a solitary or multiple, painless, well circumscribed, fluctuant swellings, and often mimic mucoceles.

Fig. 7-11. Cysticercosis.
(Courtesy of Dr Ranganathan K, Saraswathi TR, Umaram N. Know this field, J Oral Maxillo Pathol, 8:86, 2004).

Microscopically, cysticercosis appears as a fibrous capsule surrounding a Cysticercus (Fig. 7-11). The bladder wall of larva appears as lightly eosinophilic wavy membrane with multiple tiny ovoid nuclei in the fibrillary stroma beneath. The host reaction to a viable cyst is often minimal. When a cyst dies spontaneously or following chemotherapy, there is usually more inflammation. Local eosinophilia, granulation tissue, and a granulomatous reaction follow. The dead parasite disintegrates and often gets calcified within a residual fibrous scar.

ORAL MYIASIS

Oral Myiasis (Gr. Myia: fly) is defined as a condition in which the soft tissue of different parts of the oral cavity are invaded by the parasitic larvae of flies (Moshref, Ansari and Loftfi, 2008). These larvae commonly known as **maggots**, are of two winged flies, the Diptera. Myiasis occurs mainly in the tropics and is associated with poor personal hygiene. Usually the female fly infests ova in open wounds, dead tissue, or in the natural body cavities, such as ear, nostrils, and oral cavity. The flies lay over 500 eggs directly on diseased tissue. These eggs hatch and the larvae get their nourishment from the soft tissue.

Oral myasis is relatively a rare condition but cases have been reported in gingiva, palate, and extracted wounds. Antunes AA et al (2011) presented a series of 10 cases of oral and maxillofacial myasis and reviewd the literature.

The usual presenting symptoms are painful growth with ulceration and itching due to crawling movement of the larvae (Fig. 7-12). The treatment is aimed at removal of larvae from the affected area and flushing the area with normal saline or antiseptics.

Fig. 7-12. Oral myiasis.
Ulceration with presence of maggots *(Courtesy of Dr Bhaskaran M, Jagan Kumar B, Amritha Geevarghese. Cutaneous myiasis of face, J Oral Maxillo Pathol, 11: 70–72, 2007).*

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CHAPTER 8

Diseases of the Periodontium

■ B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

Diseases of periodontium comprise of a group of heterogeneous disorders, and majority of them are caused by bacteria. Periodontal diseases have been known since antiquity. Skulls of some ancient cave dwellers show evidence of chronic periodontal disease, while an acute form now known as acute necrotizing ulcerative gingivitis, or 'Vincent's infection,' was reported as early as 400 BC in soldiers in the Greek army of Xenophon. Man suffers to a greater extent from periodontal disturbances than lower animals.

Though there are many distinct types, chronic diseases of the periodontal tissues exist, chronic plaque associated gingivitis and periodontitis are most common. Inflammation confined only to the marginal gingiva is known as gingivitis. Once it extends to involve the connective tissue attachment and alveolar bone loss, it is called periodontitis. Chronic periodontitis causes more teeth loss than any other disease for adults does. Classification of the various periodontal diseases is difficult, because in nearly every case the condition begins as a minor localized disturbance, which unless adequately treated, may gradually progress until the alveolar bone is resorbed and the tooth is exfoliated. Also, a variety of local irritating factors and underlying systemic situations may alter the progress of the disease. The various resulting pathologic conditions are generally similar regardless of the etiologic factors involved. In other words, the reaction to injury that occurs in the gingiva and the supporting tissues of the teeth is usually a chronic inflammatory response. Histologic studies of the periodontium seldom indicate the type of irritant causing the disease or suggest a specific method of therapy.

THE HEALTHY PERIODONTIUM

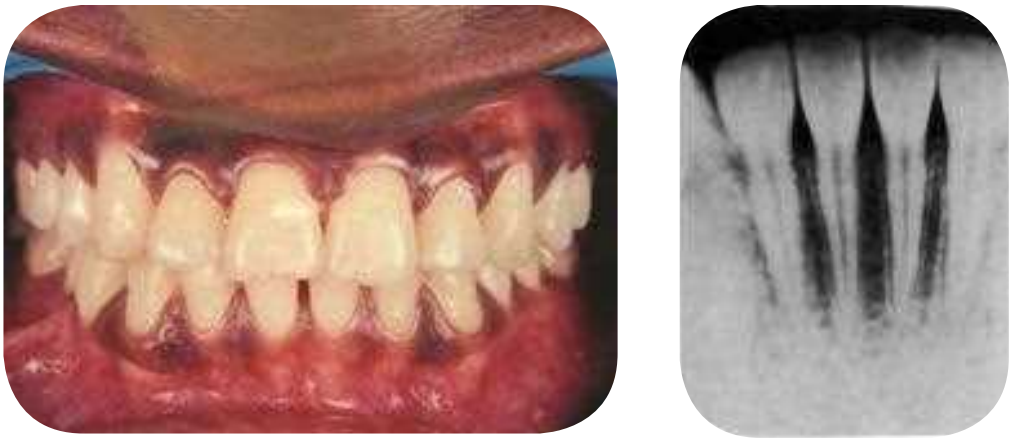
The periodontium (peri—around, odonto—tooth) or 'the attachment apparatus' includes the following tissues: (1) the gingiva, (2) the periodontal ligament, (3) the root cementum, (4) the alveolar bone. Its main function is to attach the tooth to jaw bone and to maintain the integrity of the masticatory system.

GINGIVA

A healthy gingiva is a part of the masticatory mucosa covering the alveolar process and surrounds the cervical portion of the tooth by snugly fitting into each interproximal space between the teeth (Fig. 8-1A).

Gingiva is anatomically differentiated into two parts; the free gingiva and the attached gingiva. The color of the gingiva is coral pink and it has a stippled 'orange peel' surface. In children, the gingiva is not stippled and appears redder and more delicate. The attached gingiva and the central portion of the interdental papillae are stippled but not the marginal gingiva. Stippling is a form of adaptive specialization or reinforcement for the function. So, reduction or loss of stippling is a common sign of gingival disease. Microscopically gingival epithelium is stratified squamous and parakeratinized except in the gingival sulcus and interdental area where it is nonkeratinized.

In the coronal direction, the gingiva terminates in the free gingival margin with a scalloped outline. In the apical direction it is separated from the loose, darker red alveolar mucosa, by a border termed as mucogingival junction or mucogingival line.



A B

Figure 8-1. Healthy gingiva (A) and healthy alveolar bone (B) in the young adult.

The free gingiva extends apically from the gingival margin to the free gingival groove at the level of the cementoenamel junction (CEJ). The free gingival margin is rounded and is located approximately 1.5–2 mm coronal to the CEJ. It comprises buccal or labial and lingual or palatal aspects and the interdental gingiva. The interdental gingiva also called as interdental papillae has a shape in conformity with the outline of the proximal interdental contact surfaces, as a concavity or a small depression called 'col', (a term used by mountaineers to describe a depression between two peaks) which is covered by non-keratinized epithelium. The col lies between the buccal and lingual papillae and is covered with a vestigial structure consisting of the epithelial remnants of the enamel organs of the two adjacent teeth.

Fish believes that a clinically healthy col is gradually replaced by stratified squamous epithelium unless interrupted by inflammation. According to him, a clinically healthy col covered with enamel epithelium is found only in adolescents or very young adults. If the col becomes inflamed or irritated from aggressive scaling at an early age, it might develop an infrabony pocket, since the col is a vulnerable area of the periodontium.

The attached gingiva is firmly attached to the underlying alveolar bone to form a tough mucoperiosteum and to the cementum by the connective fibers and extends apically to the mucogingival junction.

Differences between the oral epithelium, sulcular epithelium and the junctional epithelium

- Junctional epithelium cell size is relative to the tissue volume, larger than in the oral epithelium
- Intercellular spaces of the junctional epithelium are, relative to the tissue volume, comparatively wider than in the oral epithelium
- The number of desmosomes is more in the oral epithelium than in the junctional epithelium

The epithelium of the free gingiva is microscopically differentiated as oral epithelium, facing the oral cavity, sulcular epithelium, which faces the tooth, and the junctional epithelium between the gingiva and the tooth.

The most coronal portion of the attachment apparatus is called the 'epithelial attachment' or 'epithelial cuff.' This is a band of modified stratified squamous epithelium (normally about 0.2 mm. in vertical dimension) wrapped around the neck of the erupted tooth in the adult. This epithelium is continuous with the epithelium lining the gingival crevice (crevicular epithelium). The attached epithelium, like all other surface epithelium throughout the body, is continuously replaced by multiplication of the basal cells to compensate for the desquamation of the surface cells. This epithelium has relatively high turnover rate. Whether this band is organically attached to the tooth or not is controversial, but the nature of its attachment does not seem to be as important as the fact that the epithelium is present at the site where the tooth extrudes into the oral cavity and that when healthy it forms an effective seal, protecting the underlying connective tissues. The epithelium in this area, whether attached firmly or lightly, is an external cover for the oral cavity, which is resistant to the invasion of irritants and bacteria into the underlying connective tissues. It is a continuous, living, protective device around the neck of the tooth.

Lamina Propria

The connective tissue (lamina propria) components of the gingiva consist of collagen fibers (60%), fibroblasts (5%), vessels and nerves (35%). They are embedded in amorphous ground substances. Cells of the connective tissue include fibroblasts, mast cells, macrophages and the inflammatory cells.

The connective tissue fibers produced by the fibroblast are collagen fibers, reticulin fibers, oxytalan fibers and the elastic fibers. The collagen fibers of the gingiva are oriented in bundles and run in specific direction. Accordingly they are divided into the following groups:

1. **Circular fibers,** these fiber bundles are contained in the free gingiva and encircle the tooth in a cuff or ring-like fashion.

Gingival fluid (sulcular fluid)

Gingival fluid is present at the gingival sulcus in minute amounts. It is not considered as secretion. It is a fluid that exudates and increases during inflammation. Gingival crevicular fluid is a complex mixture of substances derived from serum, leukocytes, cells of the tissues of periodontium, and microbial flora inhabiting the marginal gingiva or the sulcus (pocket). It also contains significant amounts of antibodies, cytokines, enzymes, and tissue degradation products. The amount of gingival fluid is less in healthy sulcus. Gingival fluid helps to cleanse material from the sulcus, and the presence of plasma proteins may improve adhesion of the epithelium to the tooth, thereby maintaining the structure of junctional epithelium. By its antimicrobial property it defends the periodontium.

Defense mechanisms of gingiva

Nature of the gingival epithelium (i.e. the degree of keratinization, permeability, etc.), presence of leukocytes, salivary components, and gingival crevicular fluid guard the periodontal tissues against the various microbial threats.

Gingival crevicular fluid exhibits both cell mediated and humoral immune responses in healthy and diseased periodontal state by having cytokines. Interferon-α in gingival crevicular fluid inhibits the bone resorption activity of interleukin-1β in periodontal diseases.

Leukocytes, predominantly polymorphonuclear leukoctyes (PMN) are present in the healthy gingival sulci. Apart from PMN a smaller amount of B lymphocytes, T lymphocytes, and mononuclear phagocytes are also present. They have phagocytic and killing property and prevent the extension of plaque and bacterial toxins into the gingival sulcus.

Saliva contains antibodies, enzymes, other antibacterial substances, and leukocytes, which protect the oral tissues by its cleansing, buffering, and antibacterial property. It exerts influence on initiation, progression, and maturation of bacterial plaque.

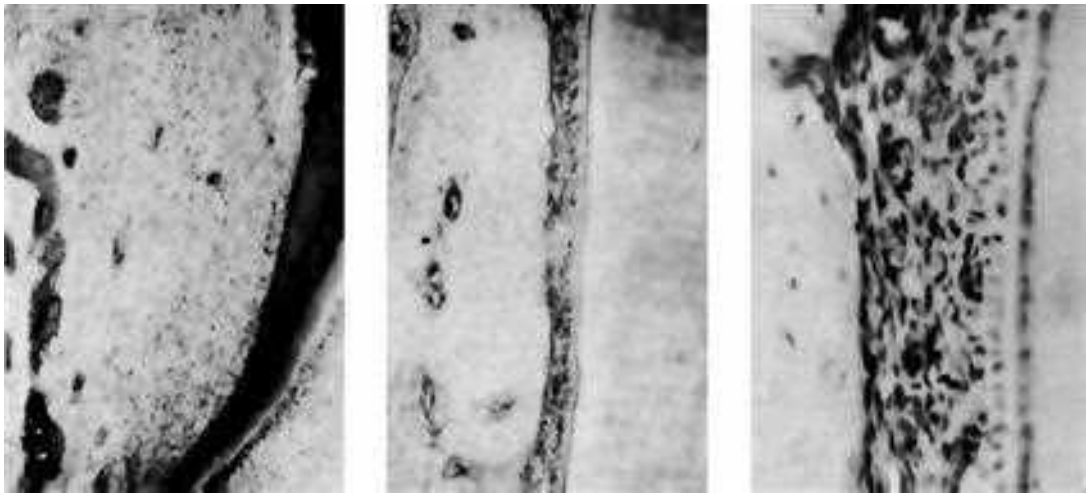
2. **Dentogingival fibers** are embedded in the cementum and project in a fan-like configuration into the free gingival tissue.
3. **Dentoperiosteal fibers** are also embedded in the cementum as dentogingival fibers, but run apically and terminate at the periosteum of the alveolar crest.
4. **Alveologingival fibers** extend from the crest of the alveolar bone to the lamina propria of the gingiva.
5. **Transseptal fibers,** these fibers run straight across the interdental septum and are seen embedded in the cementum of the adjacent teeth.

Periodontal Ligament

The periodontal ligament is a soft, richly vascular, dense fibrous connective tissue and is attached to the cementum on one end and alveoloar bone on the other end and occupies the space between the root cementum and the alveolar bone proper. The embedded portion of the periodontal ligament fibers is known as Sharpey's fibers and the diameters of these fibers are smaller in the cementum than in the alveolar bone proper.

Periodontal ligament is made up of collagen fibers, oxytalan fibers, fibroblasts, amorphous ground substance, and interstitial tissue. Cells of the periodontal ligament include cementoblasts, osteoblasts, osteoclasts and epithelial remnants of Malassez (Figs. 8-2, 8-3). The shape of the periodontal ligament space is of an hourglass-like which is narrowest at the mid-root level. And width of the periodontal ligament ranges from 0.2 to 0.4mm.The mobility of the tooth is largely determined by the width, height and quality of the periodontal ligament.

The principal fibers of the periodontal ligament are collagenous bundles, with a wavy course in longitudinal



A B C

Figure 8-2. Normal immature periodontium.
The unoriented periodontal fibers of a developing tooth are illustrated in **(A)**. The periodontal ligament of an unerupted tooth is shown under low magnification in **(B)** and high magnification in **(C)**.

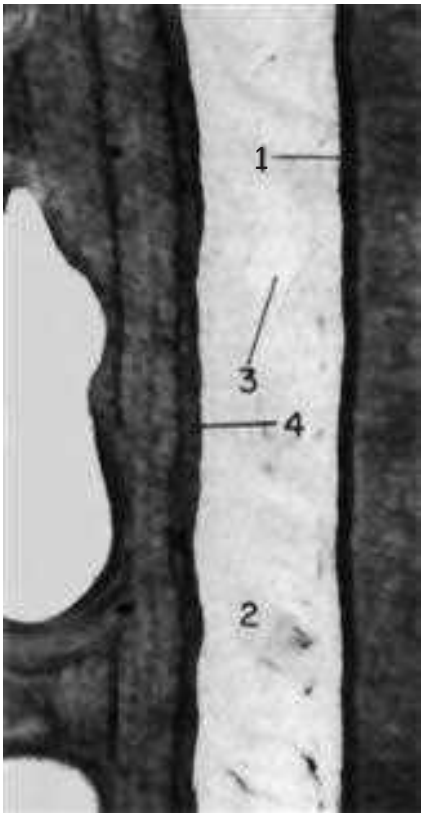


Figure 8-3. Normal mature periodontium.
Note the thin layer of cementum (1), the periodontal fibers (2), the large and empty capillaries (3), and alveolar bone (4).

sections. The principal fibers of the periodontal ligament are broadly grouped into:

1. **Alveolar crest group.** This group of fibres radiate from the crest of the alveolar process and attach to the cervical part of the cementum
2. **Horizontal group.** This group of fibers run at right angles to the long axis of the tooth from cementum to the alveolar bone.
3. **Oblique group.** These are the largest group of fibers extending from the cementum in the coronal direction obliquely to the bone.
4. **Apical group.** Apical fibers run from the cementum to the bone in an irregular manner at the apical portion of the tooth socket.
5. **Interradicular group.** This group of fibers which extend from the interradicular cementum of multi-rooted teeth to the crest of the interradicular bone.

The principal fibers of the periodontal ligament always develop conjunction with the eruption of the teeth.

The collagen fibers hold the tooth in position, suspend it in the alveolus, and transform occlusal pressures to tensile forces on the alveolar bone. Although these fibers are not elastic fibers, they are wavy in arrangement, and straighten under occlusal pressure. Sicher has stated that although fiber bundles extend from cementum to bone, the individual fibers do not. The fibers from the cementum and the bone are connected by an intermediate group of interlacing fibers in the middle of the periodontal ligament. The periodontal ligament also contains elastic fibres, associated with the blood vessels and the oxytalan fibers.

Oxytalan fibers are so named because they are acid-resistant, in contrast to collagen fibers and may be related to elastic fibers. An increase in the number of large oxytalan fibers in the transseptal region of periodontal ligaments supporting teeth, which serve as abutments for fixed bridges, suggests that they may be stress related. A concentration of these fibers is also observed to be inferior to the epithelial attachment, irrespective of its location on the tooth. Although oxytalan fibers may persist for a short time after the collagen fibers have been destroyed in periodontal disease, they ultimately disappear as well, and there is no evidence that they deter the progress of a periodontal lesion.

The functions of the periodontal ligament are the tooth anchorage, fibrous tissue development and maintenance, calcified tissue development and maintenance, nutritive and metabolite transport, and innervation.

The tooth is suspended in its position by the unique attachment (gomphosis) formed by strong connective fibers. Thus the functional arrangement is such that physiologic force from any direction will result in tension in the fiber groups and not compression on the bone or fiber groups.

The cells of the periodontal ligament are the fibroblast, osteoblast, cementoblasts, osteoclasts, nerve fibers, and the epithelial cells. The clusters of the epithelial cells are called as the epithelial cell rests of Malassez, a remnant of the Hertwig's epithelial root sheath.

The epithelial rests are found in all people, but apparently their total number decreases with age. They vary in size from small resting types of larger proliferative masses of epithelial cells. Some are calcified and persist as cementicles. The majority of epithelial rests are located in the cervical area of the teeth at all ages except during the first and second decades, at which time the greatest number is found in the apical area. Reeve and Wentz have suggested that the greater persistence of epithelial rests in the cervical area may be correlated with and influenced by the constant inflammatory reaction present in the area of the gingival sulcus.

Root Cementum

Cementum is a mineralized tissue covering the root surfaces of the tooth. It does not contain blood or lymph vessels or nerves. The different forms of cementum are the cellular, acellular, and afibrillar cementum. The functions of the cementum are to attach the fibers of the periodontal ligament to the root and to repair of the damaged root surface. Cementum of erupted and unerupted teeth undergoes resorption and repair (Fig.8-4). Cementum resorption may be idiopathic or may be caused by local conditions such as occlusal trauma, orthodontic tooth movement, pressure from cysts and tumours, teeth without antagonists, embedded teeth, replanted and transplanted teeth, and tooth with periapical and periodontal diseases. Systemic conditions such as hypothyroidism, calcium deficiency, and

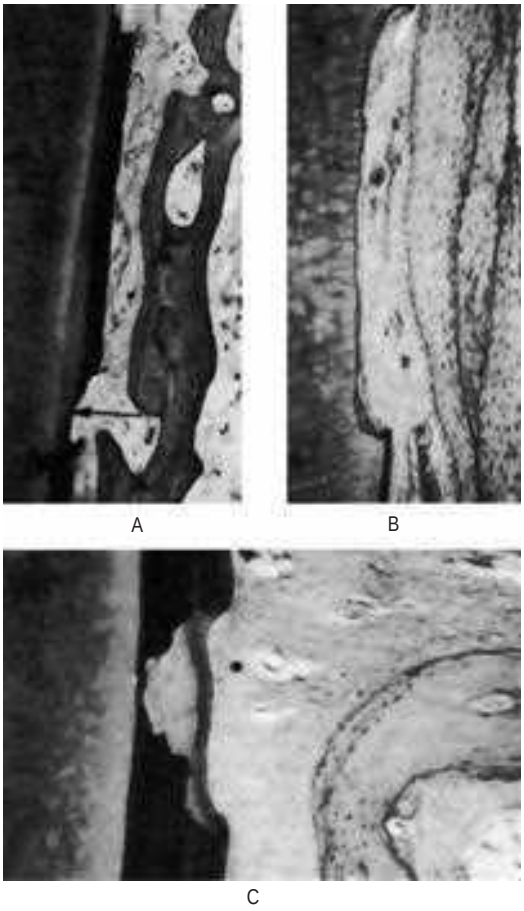


Figure 8-4. Resorption of cementum.
(A and B), Focal microscopic resorption of cementum is common. **(C)** Repair of an area of resorption is evident.

Paget's disease may predispose or induce cemental resorption. Bimstein E and coworkers have examined cemental surface under light microscope and found that teeth from children with leukocyte adhesion deficiency, Down's syndrome, and aggressive periodontitis have narrower cementum areas and concluded that these cemental anomalies may facilitate the establishment and progress of periodontitis in children. In another study by Bimstein and coworkers on histologic characteristics of root surfaces of primary teeth from children with prepubertal periodontitis revealed bacteria inside dentin tubules or covering cementum, a cuticle, or resorbed dentin; normal, wider than normal, or hypoplastic cementum; resorption lacunae with various depths; aplastic root resorption; alternate resorption and repair; and active repair.

Alveolar Bone

Alveolar process is the part of the maxilla and the mandible containing the sockets, which protects and supports the tooth. The main function is to distribute and resorb forces generated by mastication. Radiographs show that the alveolar bone has a definite cribriform plate with uniform trabeculae and it extends to a definite point between the teeth (Fig. 8-1B)

Isolated areas in which the root is denuded of bone and the root surface is covered by periosteum and overlying gingiva are termed as fenestrations. In fenestrations the marginal bone is intact. When such denuded areas extend through the marginal bone the defect is termed as dehiscence.

The layer of bone into which the principal fibers of the periodontal ligament are inserted is termed as 'Bundle bone'. Alveolar bone is constantly renewed as a response to functional demands. Thus the periodontium is a site of continuous readaptation due to its function. The rate of this replacement is unknown, but is probably variable and related, in part at least to the physical forces applied to the periodontal ligament.

DEPOSITS ON TEETH

The organic coverings of tooth enamel are divided into two types: (1) anatomic structures, and (2) acquired pellicle. The anatomic covering, formed during the developmental and eruptive stages, is known as Nasmyth's membrane or enamel cuticle, and remnants of this membrane persist throughout the life of the tooth.

Pellicle

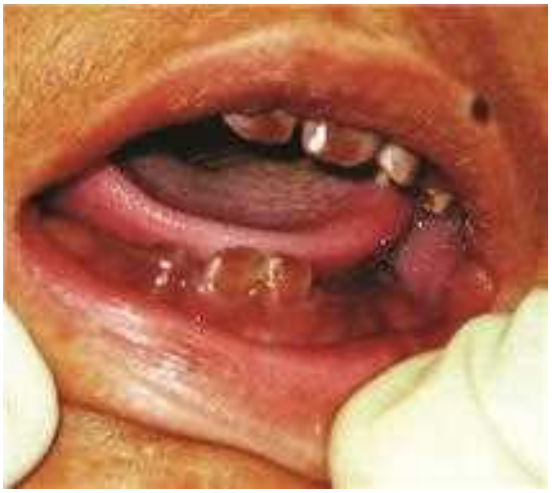
The acquired pellicle is a thin deposit, which may form shortly after eruption on the exposed surface of teeth. It is usually invisible and is probably of no pathologic significance. It is reformed within minutes of polishing. It is fully formed in 30 minutes and reaches its mature thickness of 0.1–0.8 microns within 24 hours. It is free of bacteria and completely covers the tooth surface.

The pellicle has been thoroughly investigated by Meckle, by Leach and Saxton, and by Sonju and Rolla, utilizing electron microscopy, electron histochemistry, optical histochemistry, and chemistry. They found that the brownish stained, smooth, structureless deposits, in contradistinction to plaque, did not stain with basic fuchsin. The brown pigment forms due to the presence of tannins in the pellicle. The pellicle frequently penetrates into the enamel, especially on the proximal surfaces of the teeth. The histochemistry and the electron histochemistry indicated that pellicles are of salivary origin. The histochemistry of the pellicle was found to be practically identical with that of dried salivary films on glass. In addition, similar structures were formed *in vitro* by incubating enamel in saliva. The acquired pellicles were composed of mucoproteins or glycoproteins similar to those found in saliva and contained some lipid material. Primary amino acid groups and 1:2 glycol groups were also demonstrated by both electron histochemistry and chemical analysis. Bacterial enzymatic degradation of salivary glycoproteins did not take place, either because the material was rapidly deposited before bacterial enzyme action could occur or because the stereo-chemical structure of the glycoproteins enabled them to resist enzymatic degradation. A persistent extraneous calcification was always observed in pellicle from the lingual surfaces of lower anterior teeth, but was of such small magnitude that it could not be resolved by light microscopy.

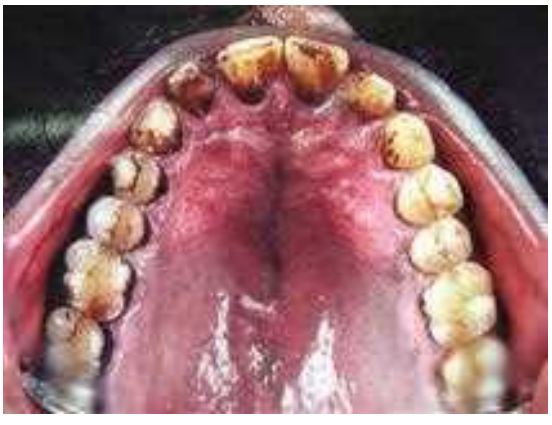
Dental Stains

Pigmented deposits on the tooth surface are called dental stains or extrinsic stains. The oral cavity is subjected to many types of exogenous and endogenous substances that stain teeth. And since the oral flora in many cases contains chromogenic microorganisms, stained deposits are common on the teeth. The stains that are incorporated into tooth structure are known as intrinsic stains and are seen in porphyria, erythroblastosis fetalis and tetracycline therapy (Fig. 8-5A).

Stain from Smoking. As a result of the collection of tobacco tars and resins, a yellowish-brown to black deposit forms on the tooth surfaces of persons who smoke often (Fig. 8-5B). This stain varying from a light brown, powdery deposit in the person who smokes an occasional cigarette to a dense black tarry deposit in heavy smokers. The deposit is harmless to the teeth, although it should be removed because of its objectionable appearance and may act as a nidus for calculus or have a mild, irritating effect on the gingiva. If the dentin is exposed, as in older patients by attrition, the staining may be severe.



A



B

Figure 8-5. (A) Intrinsic stain in congenital erythropoietic porphyria (erythrodontia). (B) Tobacco stain.
(Courtesy to Dr. Rashmi Santosh Kumar, Kamineni Institute of Dental Sciences, Narketpalli, Andhra Pradesh).

Brown Stain. This is a thin, brown, delicate pellicle-like structure that occurs on the teeth and is thought to be composed of salivary mucin. Its occurrence on those surfaces of teeth that are closely adjacent to the orifices of the salivary gland ducts tends to confirm its relation to saliva.

A delicate pigmented dental plaque, called the mesenteric line by some, was described by Pickerill to be a plaque of brown or black dots that coalesce to form a thin, dark line on the enamel at the cervical margin of the tooth. Pickerill, F Bibby and Shourie noted that the presence of this line is often associated with a relative freedom from dental caries.

Black Stain. A thin, black deposit that forms in some patients, both children and adults, on the teeth, is usually in a narrow line or band, just above the free gingiva. It is not associated with smoking. This black stain may be caused by chromogenic microorganisms, although none has been identified or cultured from adult stains. The black stain on primary teeth is associated with a low incidence of dental caries. Slots in 1974 demonstrated that the microflora of black stain was dominated by *Actinomyces* species and showed that they could produce black pigment in culture.

Green Stain. In some persons, mostly children, there is usually a heavy gray-green stain especially prominent on the gingival third of the maxillary anterior teeth. This stain appears to be soft or 'furry' and is difficult to remove, suggesting its association with the enamel cuticle. Sometimes a green stain covers a decalcified area of the enamel. No chromogenic microorganism, which could cause this green stain, has been identified, although it has been assumed that such an organism is the cause. It has also been suggested that coloration of remnants of Nasmyth's membrane, possibly by blood pigments, may be responsible for the stain.

Orange Stain. Occasionally, a light, thin deposit of a material of brick red or orange color is seen on teeth. The cause of this stain is not known, but it is also believed to be due to pigment-producing microorganisms. This stain can be easily removed, is of no apparent significance and may or may not recur.

CALCULUS

In some children and most adults, varying amounts of a hard, stone-like concretion form on the surfaces of teeth or prosthetic appliances (Figs. 8-6, 8-7, 8-8). These deposits are called 'calculus', 'odontolithiasis', or 'tartar.' Calculus is mineralised dental plaque.

Mandel considers calculus formation to be a triphasic process, consisting of cuticle or pellicle deposition, bacterial colonization and plaque maturation, and mineralization, although all three steps may not always be essential. Frank and Brendel have indicated that bacteria can be attached directly to enamel without a cuticular intermediary. Theilade and his coworkers have shown that calcareous deposits can occur in germ-free animals. Nevertheless, the usual process in man is probably a triphasic one.

Calculus is deposited as a soft, rather 'greasy' material, which gradually hardens by deposition of mineral salts in the

Figure 8-6. Supragingival calculus on lingual surface of lower anterior teeth.

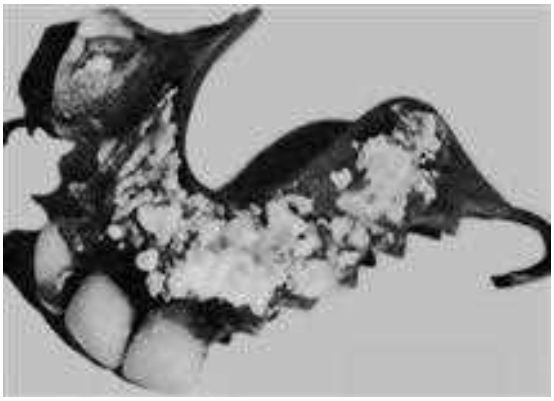
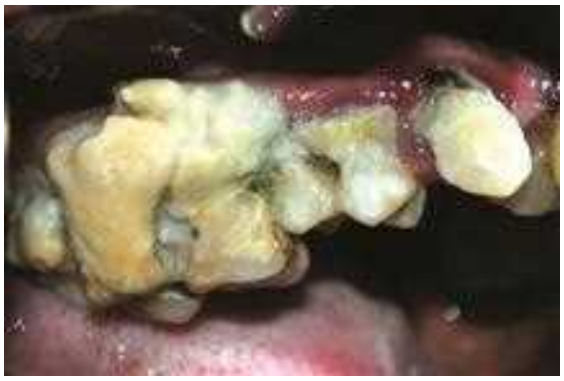


Figure 8-7. Calculus deposited on ill-fitting removable partial denture.

A



B

Figure 8-8. (A, B) Calculus.

organic interstices, until it becomes hard. It varies in color, from yellow to dark brown or black, depending upon the amount of stain present on or within the deposit.

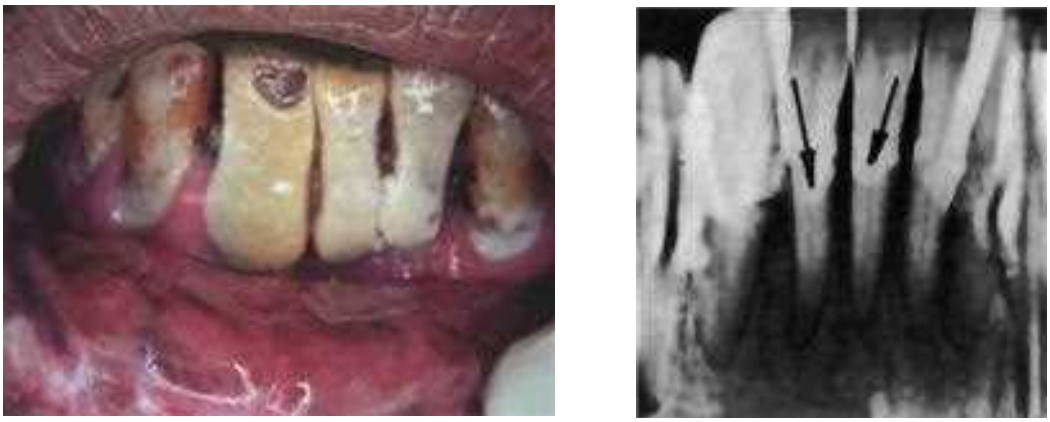
Distribution of Calculus. Calculus is classified or divided into two general types according to its location. Deposits above the gingiva on the exposed coronal surfaces of the teeth are spoken of as **supragingival calculus,** while those covered by the free gingiva are **called subgingival calculus**. The subgingival calculus is generally much harder, denser, less extensive, flatter, more brittle, and darker in color while the supragingival calculus is white or whitish yellow in color and hard with clay-like consistency. Supragingival calculus can be easily detached from the tooth. Many investigators believe that both types of calculus result from a deposit of inorganic substances into bacterial plaque from saliva and that their physical difference is dependent only upon their environment. Many deposits include both types of calculus; one shading into the other, so any actual division is indistinguishable. Others believe that saliva does not penetrate the gingival crevice and that the source of the inorganic salts in calculus is the blood or tissue fluid from the gingival tissues.

The greatest accumulations of calculus, both supragingival and subgingival, occur on those surfaces of the teeth that are closest to the orifices of the major salivary gland ducts. Thus the lingual surfaces of the mandibular anterior teeth opposite the submandibular and sublingual gland openings and the buccal surfaces of the maxillary molars opposite the parotid duct opening are the common sites of deposition of calculus (Fig. 8-9). It may be localized in its distribution or generalized over many tooth surfaces.

Incidence of Calculus Deposition. Careful clinical observations have indicated that calculus is deposited at irregular intervals throughout life. Patients will sometimes demonstrate a rapid deposition for a short time and then no deposition of calculus for days or weeks.

Although there have been few epidemiological studies on the incidence of calculus, several indices to evaluate the quantity of calculus have been developed. The Simplified Calculus Index of Greene and Vermillion and the Probe Method of Calculus Assessment of Volpe and his coworkers were developed to measure the quantity of calculus formed in long-term longitudinal studies, whereas the Calculus Surface Index of Ennever and his coworkers was developed for short-term clinical trials of calculus inhibitory agents. In fact, the WHO proposed in 1978 that since plaque and gingivitis were so closely correlated, it was unnecessary to assess plaque (and presumably calculus) in population studies and field trials.

However, Marshall-Day reported that in a study of persons 13–60 years old, the 19–22-year age group showed an increase in calculus deposition over the younger age group and that there was a further sharp increase in the 31–34-year age group. The incidence of calculus reached a peak of 91% of persons studied in the 56–59-year age group. Of the entire group, 71% of men and 62% of women manifested calculus formation. 26% exhibited supragingival calculus only, with no significant difference between men and women. Persons



A B

Figure 8-9. Calculus an one side of the lower arch. This patient was not using this side due to the presence of a painful tooth in the upper arch.
(A) Massive amount of calculus in a patient who had not had a prophylaxis for many years. **(B)** Radiographic appearance of teeth with a heavy calculus deposit.

with subgingival calculus alone were comparatively few, the incidence being 7% for men and 8% for women. The greater proportion of subjects studied exhibited both types of calculus after 30 years of age. Third National Health and Nutrition Examination Survey revealed that 91.8% of the subjects had detectable calculus and 55.1% had subgingival calculus based on their survey involving 9689 adults in the United States.

Composition of Calculus. Calculus is composed of approximately 75% calcium phosphate, 15–25% water and organic material and the rest calcium carbonate and magnesium phosphate with traces of potassium, sodium, iron, and other elements. When deposits of calculus are washed and analyzed, their basic structure and composition are about the same, regardless of their location. Chemical analyses of calculus varies widely, depending upon the age of the calculus studied, the amount of food debris, and bacterial elements present, and so forth. Calculus consists primarily of calcium phosphate arranged in a hydroxyapatite crystal lattice structure similar to that of bones, enamel, and dentin. The similarity of chemical analyses and physical characteristics of dentin, enamel, cementum, bone, and calculus indicates that removal of calculus from the enamel, cementum or dentin must be done with care, or the dental tissues, especially the cementum, might be damaged.

The organic stroma of the calculus in which the mineral salts are deposited consists of protein polysaccharide complexes, a tangled meshwork of microorganisms, especially gram-positive filamentous types, desquamated epithelial cells and other debris, and white blood cells. Gram-negative filaments and cocci are also present in varying numbers. Mucin has been identified in calculus, as expected from its universal presence in saliva. Mandel and Levy demonstrated a carbohydrate fraction, probably in combination with a protein, and lipid in calculus. Salivary proteins make 5.9–8.2% of the organic component. The composition of subgingival calculus slightly differs from the supragingival calculus. Though the hydroxyapatite content is similar in both types, the magnesium content is more and brushite and octacalcium phosphate is less in subgingival calculus with absence of salivary proteins.

Attachment of Calculus. The manner of attachment of calculus to the tooth surface is an interesting problem, since it is well known that calculus can be scaled from the teeth very easily in some people, but with great difficulty in others. This suggests that calculus has more than one mode of attachment. Acquired pellicle formation has already been discussed. It is important to reiterate McDougall's findings that all plaques on enamel include an acquired cuticle or pellicle. Zander also investigated calculus attachment and observed four types of attachment of the organic calculus matrix to the tooth surface: (1) attachment to the secondary dental cuticle, (2) attachment to microscopic irregularities in the surface of the cementum corresponding to the previous location of Sharpey's fibers, (3) attachment by penetration of microorganisms of the calculus matrix into the cementum, and (4) attachment into areas of cementum resorption. He also found that one piece of calculus seldom got attached by a single mode, but rather by a combination of modes. Calculus embedded deeply into the cementum may appear morphologically similar to cementum and has been referred to as **calculocementum.**

Bacterial Colonization and Plaque Maturation. Many theories have been formulated to explain calculus deposition, but none of them are completely acceptable. No one knows exactly why calculus forms in some persons and not in others, or in the same person at some times but not others.

Numerous studies indicate that the early plaque is composed of a preponderance of coccal microbial forms. As the plaque ages, fusobacteria and filamentous organisms increase in number and, by the second or third week of plaque formation, about half of the organisms in the plaque become filamentous. Gram-positive cocci and rods make up the remainder of the plaque population. The population dynamics of plaque development indicates a progressive decline in aerobic organisms with a concomitant increase in anaerobic organisms.

There is increasing evidence that the various diseases included under the term 'chronic periodontal disease' are in fact different diseases and are associated with distinct microbial organisms. Reports from the laboratories of Socransky and his colleagues, Slots and of Kornman and Loesche and others indicate that there is certain specificity to the combination of bacteria in this subgingival plaque in periodontal diseases like chronic gingivitis, acute necrotizing gingivitis, and juvenile periodontitis. The evidence for microbial specificity of individual periodontal diseases was well presented in a review by Loe in 1981.

There are several reports of microbial differences between clinical forms of periodontal disease. Studies by Tanner and his colleagues showed that the predominant cultivable organisms from periodontitis lesions varied among patients. Their studies were early attempts to distinguish 'pathogens' associated with different clinical features of destructive periodontal disease. Studies of the plaque in various forms of periodontal disease indicate that there are indeed differences not only in clinical and microbial features but also in host responses to microbial complexes. For example, it is possible that *Peptococcus asaccharolyticus* and *Actinobacillus actinomycetemcomitans* play significant etiologic roles in distinctly different destructive forms of periodontal disease.

Plaque Mineralization. The soft dental plaque that is hardened by the precipitation of mineral salts usually starts between the 1st and 14th day of plaque formation. The investigations of Mandel and Levy, as well as Wasserman and his associates, on early developing calculus utilizing histochemical as well as histologic techniques have added to the knowledge of calculus formation. They studied calculus formation by placing contoured strips around lower anterior teeth in patients known to form calculus rapidly. It was noted that the calcifying areas were frequently laminated by alternating dark and light staining bands that produced a concentric ring-like appearance similar to that of pulp stones and urinary calculi. This lamination had been noted by Black in human calculus 70 years earlier.

That bacteria may not be essential for calculus formation was demonstrated by the finding that calcareous deposits developed on the teeth of germ-free animals. Such calcified deposits may be laboratory curiosities and may or may not have relevance to human calculus formation. In any event, the human bacterial plaque does mineralize, but there is no evidence that viable microorganisms are essential for the process.

The major mineral present in calculus is a carbonate apatite similar to that formed in bones and teeth. It is not known why some dental plaques mineralize and others do not. The bulk of the calculus mass consists of mineralized bacteria, and the earliest visible mineral deposition is usually associated with them. Certain microorganisms, such as *Corynebacterium matruchotii* and some strains of *Streptococcus mutans*, can be isolated from plaque, which forms an apatite intracellularly when cultured in a medium rich in calcium phosphate. In addition, dead microbial cells induce apatite formation when suspended in metastable calcium phosphate solutions. This finding suggested to Ennever and his coworkers that some component of the cell functions as a catalyst for apatite nucleation. They isolated such a catalyst from microbial cells and characterized it as a proteolipid, nonpolar protein-acidic phospholipid complex. Bacterial cells do not calcify if the proteolipid has been completely removed. The dental calculus matrix also contains proteolipid, which is essential for its remineralization *in vitro* after it has been decalcified. It is chemically similar to microbial proteolipid. Thus it appeared that proteolipid derived from plaque microbial membranes provided the catalyst for calculus formation. Isolated proteolipid and synthetically prepared analogs have been used to determine the mechanisms of calcification. An essential feature of the mechanism is the initial calcium binding by acidic phospholipids of the complex. The binding is followed by dehydration, which forms a microenvironment in which apatite nuclei are stabilized long enough for crystal growth.

Importance of Calculus. Calculus is always covered with the unmineralized plaque. This unmineralized plaque is the chief irritant and the underlying calculus acts as a significant contributing factor. Calculus is uniformly associated with periodontal diseases. Since it is adherent to the tooth surface, it moves with the tooth during its functions. Subsequently, injuries can occur to the adjacent or overlying gingival tissues that do not move in unison with the teeth. Also, when pressure is placed on the gingiva during mastication, the underlying calculus could irritate the gingival tissues. Thus calculus causes an inflammatory reaction in the gingiva with its overlying mat of microorganisms (Fig. 8-10). Occasionally, supragingival calculus collect in prodigious amounts with little more pathosis present than a superficial inflammation; possibly due to high tissue resistance. Removal of calculus results in rapid clinical improvement.

Prevention of formation of calculus is dependent primarily upon removal by the patient of the fresh, uncalcified deposits with toothbrush and dental floss.

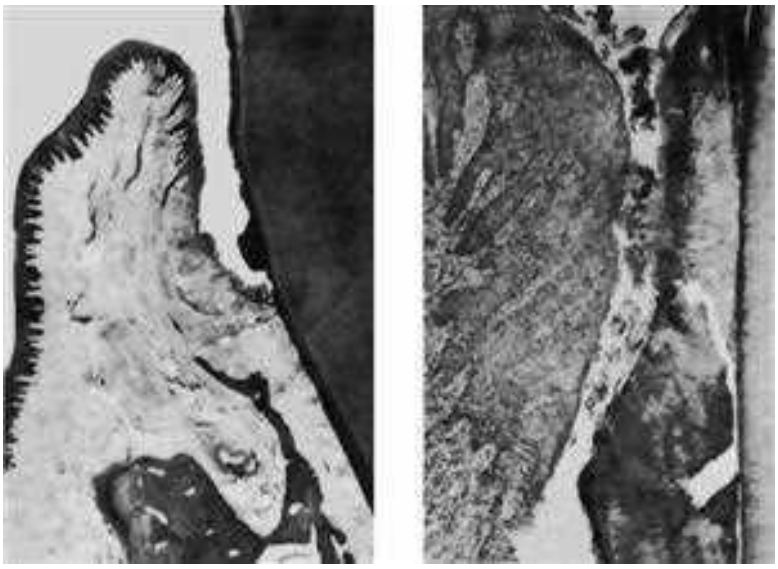
Halitosis

(Oral malodor, fetor oris, fetor ex ore)

Halitosis an unpleasant or foul odor exhaled while breathing or talking. It is one of the most common reasons for seeking dental aid. It is present in all mouth for some time (transient) and some mouth for all time (persistent). Transient halitosis occurs in fasting, eating certain foods such as garlic, onions, fish and the like, obesity, smoking, and alcohol consumption. Because the mouth is dry and inactive during the night, the odor is usually worse upon awakening (morning breath).

Causes of halitosis may be local or extraoral. Among local causes tongue and gingival sulcus are the major sources of oral malodor, which also include retention of food debris on and between the teeth, unclean prostheses and diseased states like chronic periodontitis, dental caries, abscesses, and dry socket.

Extraoral causes of halitosis include respiratory tract infections, hepatic disorders and excretion through breath of



A B

Figure 8-10. Calculus.
The gingival tissues opposite the rough deposits of calculus show inflammation and alterations in the epithelium *(B, Courtesy of Dr JP Weinmann, GW Burnett and Williams and Wilkins Company).*

metabolites. The later includes the sweet odor of diabetes, alcoholic breath, and uremic breath of kidney diseases.

Proteins retained in the mouth are broken down by the anaerobic bacteria into amino acids which in turn is further broken down to produce volatile sulfur compounds namely hydrogen sulfide and methyl mercaptan, which are foul smelling.

The methods of detecting or diagnosing halitosis are organoleptic measurement, sulfide monitoring and gas chromatography.

In some patients no halitosis may be present in spite of their complaint of oral malodor. These non-genuine halitosis patients are either pseudo-halitosis patients or halitophobic. Causes include chemosensory dysfunction like taste or olfactory dysfunction or psychosomatic factor.

CLASSIFICATION OF PERIODONTAL DISEASE

Many classifications of periodontal disease have been proposed. The classification presented here (Table 8-1) is the most accepted and was presented and discussed at the International Workshop for the classification of the periodontal diseases organized by the American Academy of Periodontology in 1999.

GINGIVAL DISEASES

Gingival diseases are broadly classified into dental plaque induced and nonplaque induced. Plaque induced gingival diseases comprise of two categories namely those caused by local factors and those affected by local factors modified by the specific systemic factors of the host.

Table 8-1: Classification of periodontal disease

Gingival diseases Plaque induced gingival disease Nonplaque induced gingival lesions
Chronic periodontitis Localized Generalized
Aggressive periodontitis Localized Generalized
Periodontitis as a manifestation of systemic disease
Necrotizing periodontal disease Necrotizing ulcerative gingivitis (NUG) Necrotizing ulcerative periodontitis (NUP)
Abscesses of periodontium Gingival abscess Periodontal abscess Pericoronal abscess
Periodontitis associated with endodontic lesions Endodotic – periodontal lesion Periodontal – endodontic lesion Combined lesion
Developmental or acquired deformities and conditions Localized tooth related factors that predispose to plaque induced gingival diseases or periodontitis Mucogingival deformities and conditions around teeth Mucogingival deformities and conditions on edentulous ridges
Occlusal trauma

Plaque induced gingival disease is the most common form of gingival disease. This may occur on a periodontium with no attachment loss or on a periodontium with a previous

attachment loss that is stable and not progressing. Plaque induced gingival disease is the result of the interaction of plaque bacteria and defense cells of the host.

This bacteria and host interaction is modified by local and systemic factors. The factors that have been most commonly cited are as follows:

Local factors
1. Microorganisms
2. Calculus
3. Food impaction
4. Faulty or irritating restorations or appliances
5. Mouth breathing
6. Tooth malposition

Systemic factors
1. Nutritional deficiencies
2. Drug action
3. Endocrine changes associated with puberty, pregnancy, menstrual cycle, and diabetes mellitus
4. Allergy
5. Heredity
6. Psychic phenomena
7. Specific granulomatous infections
8. Neutrophil dysfunction
9. Immunopathies

Microorganisms. One must recognize the omnipresence of the many varieties of oral microorganisms that grow as biofilm or plaque, for the most part, on the nonself-cleansing areas of the teeth, particularly below the cervical convexity of the crown and in the cervical areas. Smears of the material taken from the normal gingival sulcus, the gingival sulcus in a case of marginal periodontitis or from the gingival pocket in advanced periodontal disease reveal myriad microorganisms of many different types. Prominent among these will be cocci, various types of bacilli, fusiform organisms, spirochetes, and in advanced periodontitis, amoebas and trichomonads. The normal oral flora is so vast; however, and is made up of so many varieties of microorganisms that it has never been possible to prove conclusively that any one type of microorganism is of greater importance than others as far as periodontal diseases are concerned. The plaque associated with gingivitis and early periodontitis is complex and heterogeneous. However, Slots and coworkers in 1978 demonstrated that in the early stages of gingivitis the *Actinomyces* group of organisms is the dominant genus in the supragingival plaque.

Plaque and plaque-derived endotoxins may act as irritants or antigens in both nonspecific acute inflammatory responses and immune mechanisms of defense. One of the prime functions of the immune response is to activate the inflammatory system. Both the nonspecific acute inflammatory reaction and the immune response are homeostatic mechanisms, each of which usually succeeds in restoring and maintaining homeostasis. The growing weight of evidence suggests that the breakdown in host resistance dental plaque is a result of tissue injury brought about by the immune reaction. When both nonspecific and immunologically mediated inflammatory lesions of the gingiva occur, the lesion is no longer a self-limiting and protective reaction becomes progressively tissue destructive. There are many destructive enzymes released by polymorphonuclear leukocytes (PMNs) and numerous tissue destructive lymphokines and lymphotoxins elaborated by B- or T lymphocytes. Thus, collagenase liberated by both PMNs and lymphocytes, other lysosomal enzyme secretions, lysosomal acid hydrolases (of macrophages), lymphotoxin-mediated cytotoxins, and osteoclast-activating factor (OAF) are all tissue destructive substances released as part of the inflammatory reaction to injury. The subject of host-parasite interactions in gingivitis and periodontitis was reviewed by MacPhee and Cowley in 1981.

Specific microorganisms sometimes cause an inflammatory reaction of the gingiva, although the clinical appearance may be entirely nonspecific. For example, a monilial or a tuberculous infection may affect the gingiva. The herpes simplex virus and the fusospirochetal organisms of necrotizing ulcerative gingivitis may also infect the gingiva. Furthermore, both streptococcal and staphylococcal gingivitis have been described as being due specifically to these organisms. Definite proof of a cause-and-effect relation here is difficult and questionable.

Calculus. Calculus, whether in a supragingival or a subgingival position, causes irritation of the contracting gingival tissue. This irritation is probably caused by the byproducts of the microorganisms, although the mechanical friction resulting from the hard, rough surface of the calculus may also play a role.

Food Impaction and General Oral Neglect. The impaction of food and the accumulation of debris on the teeth because of oral neglect result in gingivitis, through irritation of the gingiva by toxins of microorganisms growing in this medium. The degradation of food debris may also prove irritating to the gingival tissues.

Faulty or Irritating Restorations or Appliances. Faulty restorations may act as irritants to gingival tissues and thereby induce gingivitis. Overhanging margins of proximal restorations may directly irritate the gingiva and in addition allow the collection of food debris and organisms that further injure these tissues. Improperly contoured restorations may also produce gingival irritation by causing food packing or abnormal excursions of food against the gingiva during mastication. Prosthetic or orthodontic appliances impinging on the gingival tissues produce gingivitis as a result of the pressure and of the trapping of food and microorganisms.

Mouth Breathing. Drying of the oral mucous membrane due to mouth breathing, excessive environmental heat, or excessive smoking causes gingival irritation, with accompanying inflammation or sometimes hyperplasia.

Tooth Malposition. Teeth which have erupted or which have been moved out of physiologic occlusion, where they are repeatedly subjected to abnormal forces during mastication, are apparently very susceptible to the development of periodontal

disease. For example, a lower incisor may be 'bucked' out of alignment in the second or third decade of life and suddenly, in its new position, receive much of the occlusal stress of one or two upper anterior teeth. Calculus may be deposited on the lingual surface of such a tooth; the bacteria present attack the tissue around this tooth. As a result the gingival tissues may become inflamed and may recede. Teeth in labial positions have less osseous coverage over their radicular surface and hence are more susceptible to trauma from toothbrushing and other local irritations. Abnormally high frenal attachments also contribute to gingival recession.

Chemical or Drug Application. Many drugs are potentially capable of inducing gingivitis, particularly an acute case of gingivitis, owing to a direct local or systemic irritating action. For example, phenol, silver nitrate, volatile oils, or aspirin, if applied to the gingiva, will provoke an inflammatory reaction. Others, such as dilantin sodium, produce gingival changes when administered systemically. These have been discussed specifically in the Chapter 12 on Physical and Chemical Injuries of the Oral Cavity.

An unusual type of gingivostomatitis termed 'plasma cell gingivitis' (q.v.) first appeared in the United States about 1968. Although a number of etiologic factors such as hypersensitivity, allergy, endocrine disease, specific infection, etc. were proposed, it remained for Kerr and his associates in1971 to identify the most probable causative agent. They found that the disease represented an allergic reaction to some component of chewing gum. When the patients eliminated the use of chewing gum, the tissues returned to normal. The clinical features of the disease were so characteristic that it could be readily recognized as a specific entity, probably with a common etiology.

Nutritional Disturbances. Nutritional imbalance is frequently manifested in changes in the gingiva and deeper underlying periodontium. The effects of nutritional deficiencies on these structures as well as on the oral cavity as a whole have been considered in detail in Chapter 15 on Oral Aspects of Metabolic Disease. It is sufficient to point out that adequate intake, absorption and utilization of the various vitamins, minerals and other foodstuffs are essential to the maintenance of a normal periodontium.

Pregnancy. Many investigators have reported that the gingiva undergoes certain changes during pregnancy which have been termed 'pregnancy gingivitis' (Table 8-2). Among studies of relatively large numbers of pregnant patients, the following may be cited as representative.

The clinical appearance of the gingiva in the pregnant woman varies from an unchanged to a smooth, shiny, deeply reddened marginal gingiva with frequent focal enlargement, and intense hyperemia of the interdental papilla. Occasionally, a single tumor like mass will develop, the 'pregnancy tumor,' which is histologically identical with the pyogenic granuloma (q.v.). Pregnancy induces a hypersensitive response to a mild injury which otherwise would have been innocuous. This gingivitis, clinically nonspecific in appearance, may occur near the end of the first trimester and may regress or even completely disappear at the termination of the pregnancy.

Table 8-2: Incidence of pregnancy gingivitis

Looby (1946): 475 women	(In percentage)
Slight gingivitis	40
Hypertrophic gingivitis	10
Pregnancy tumor	2
Ziskin and Nesse (1946): 416 women	(In percentage)
Pregnancy gingivitis	37.9
Hypertrophic gingivitis	7.0
Raspberry-red gingiva	40.0
Combination	1.8
Maier and Orban (1949): 530 women	(In percentage)
No pathosis	44.6
Mild inflammation	35.9
Moderate inflammation	17.5
Severe inflammation	1.5
Pregnancy tumor	0.5

Diabetes Mellitus. This has been repeatedly reported in association with severe periodontal disease, especially in younger people. It has not been proved that diabetes is a specific cause of severe periodontal disease, since many patients with diabetes have normal periodontal structures. However, in uncontrolled diabetes, many metabolic processes are affected, including those which make up resistance to infection or trauma. For example, a diabetic may suffer from persistent chronic ulcers of the skin of the legs, presumably because resistance is lowered and any minor irritation such as trauma or bacterial infection of the skin will result in injury greater than that in a normal person. Also, the effectiveness of the healing process is decreased, possibly as a result of a disturbance in cellular carbohydrate metabolism. Therefore, considering the periodontium located in the oral cavity with its many factors predisposing to disease, including calculus, bacteria, and trauma, it is not surprising that this structure appears to breakdown more readily in persons with uncontrolled diabetes than in normal people. Controlled experimental animal studies have been performed repeatedly in which the animals were made deficient in insulin production and yet no consistent special periodontal pathosis resulted. Perhaps the local factors were insufficient to overcome the inborn vitality of the periodontium in such cases.

It has been reported by Russell that nearly 40% of a group of 37 diabetics exhibited gingival angiopathy in the form of PAS-positive, diastase-resistant thickening of vessel walls, hyalinization of vessel walls and sometimes luminal obliteration. Similar changes were also found in the periodontal ligament vessels of patients with diabetes mellitus.

Other Endocrine Dysfunctions. Gingivitis is reported to occur with some frequency in puberty as the so-called puberty gingivitis. The gingiva appears hyperemic and edematous. The fact that many adolescents are chronic mouth-breathers as a result of lymphoid hyperplasia of the tonsils and adenoids has suggested that the endocrine basis is relatively unimportant,

while the local irritant (drying of the mucosa because of the mouth breathing) being the actual cause of the condition. Gingivitis associated with menstruation has been reported by many. In addition, a nonspecific gingivitis with gingival bleeding, vicarious menstruation may occur sometimes. This phenomenon is rare.

Psychiatric disturbances appear to have a definite influence upon the severity of periodontal disease. Belting and Gupta reported that the severity of periodontal disease was significantly greater in psychiatric patients than in a controlled group of patients. Significant differences in severity were noted even when such variable factors as amounts of calculus, brushing frequency and bruxism were held constant in the two groups. The severity of periodontal disease increased significantly as the degree of anxiety increased. It was also noted that the severity of periodontal disease decreased significantly in both normal and psychiatric groups as the educational level of the patient increased.

Incidence. Numerous studies have been devoted to ascertaining the incidence or prevalence of gingival disease. It is generally accepted that periodontal disease is worldwide in distribution and that there is no age group (except in very young infants) in which it does not occur. Although all races are affected, there is some difference in incidence between different races and different countries.

Marshall-Day and his associates studied the incidence of periodontal disease in a group of 1,279 persons ranging in age from 13–65 years residing in the Boston, Massachusetts. Their investigations revealed that the incidence of gingivitis was extremely high even in the early age groups, ranging from 80% at age 13–15, to 95% at age 60. An interestingly significant reduction in incidence of gingival disease to 62% occurred in the late teens and early 20s. It was suggested that this reduction was associated with the end of puberty and/or social factors, where the adolescents placed a greater emphasis on oral hygiene and esthetics than they had previously. In 10 of the 13 different age groups, men were affected more frequently than women; the overall average being 88% for males and 80% for females.

Clinical Features. Acute gingivitis is painful uncommon lesion with sudden onset and shorter duration. Specific forms of acute gingivitis will be discussed separately, and the present considerations will be limited to the most common form of gingival disease, the chronic gingivitis.

In gingivitis the inflammation is limited only to the gingiva without underlying attachment loss. It may be localized or generalized. Beginning of periodontitis is marked by the spreading of inflammatory process from the gingiva to the underlying periodontal tissues. Although all forms of periodontitis are preceded with gingivitis, it is not necessarily progress to periodontitis all the time.

Gingivitis sometimes involves only the marginal gingiva, known as marginal gingivitis or interdental papilla, papillary gingivitis. When hyperemia and swelling of the marginal gingiva are confined to a localized area of the gingiva, the affected area sometimes assumes a crescent shape and has been termed a

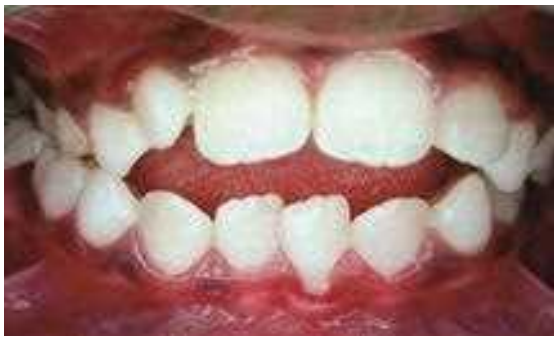


Figure 8-11. Traumatic crescent.
The recession and inflamed gingival tissue of the mandibular left central incisor resulted from local irritation and trauma.

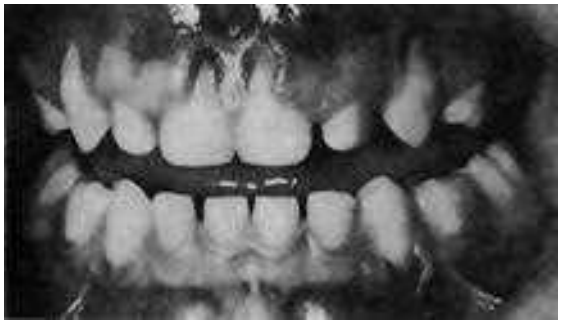


Figure 8-12. Traumatic gingival recession.
Gingival recession in a five-year-old girl caused by injury while sucking her finger. Stripping of the gingiva by a fingernail is a common manifestation of a habit that often has a psychogenic background *(Courtesy of Dr Thompson M Lewis: J Periodontol, 33: 353, 1962).*

'traumatic crescent' (Figs. 8-11, 8-12). Diffuse gingivitis affects marginal gingiva, attached gingiva and interdental papilla. The earliest manifestations of chronic gingivitis consist in slight alterations in the color of the free or marginal gingiva from a light to a deeper hue of pink, progressing to red or reddish blue as the hyperemia and inflammatory infiltrate become more intense. Bleeding from the gingival sulcus following even mild irritation such as tooth brushing or probing is also an early feature of gingivitis. Edema, which invariably accompanies the inflammatory response and is an integral part of this as it causes a slight swelling of the gingiva and loss of stippling (Fig. 8-13). Inflammatory swelling of the interdental papillae often produces a somewhat bulbous appearance of these structures. This increase in the size of the gingiva favors the collection of more debris with increased bacterial accumulations, which in turn induce more gingival irritation, thus bringing about a continuing cycle. When there is marked enlargement due to edema and fibrosis as a result of chronic inflammation, the process is called chronic hyperplastic gingivitis.

Suppuration of the gingiva, manifested by the ability to express pus from the gingival sulcus by pressure, may occur in advanced chronic gingivitis.

Radiographic Features. Chronic gingivitis, in which the inflammation is limited strictly to the gingiva, does not manifest

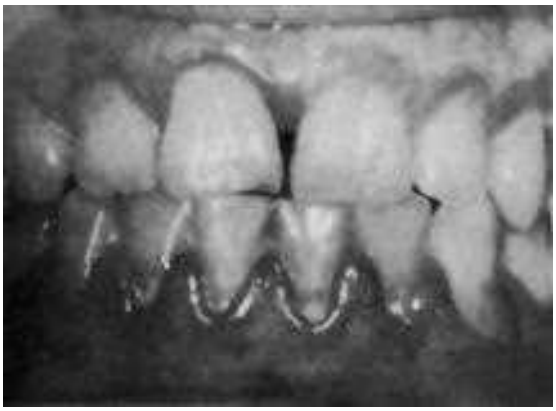


Figure 8-13. Gingivitis.
The inflammation of the gingiva results in swelling with reduction and eventual loss of normal stippling.

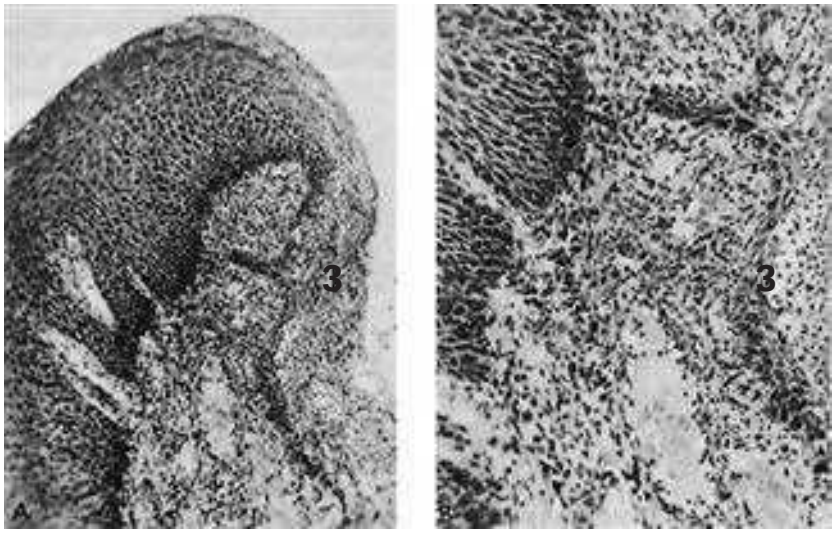
changes in the underlying bone. When bony changes become evident, the condition is termed 'periodontitis'.

Histologic Features. The gingiva in chronic gingivitis reveals infiltration of the connective tissue by varying numbers of lymphocytes, monocytes, and plasma cells. Polymorphonuclear leukocytes are occasionally noted, particularly beneath the crevicular epithelium. The crevicular epithelium is usually nonkeratinized and irregular. It is infiltrated by inflammatory cells and is frequently ulcerated (Fig. 8-14). The capillaries of the connective tissue are usually engorged and sometimes increase in number. Hyperemia, edema, and hemorrhage may be present. The underlying periodontal ligament, except perhaps for those fibers of the free gingival group, is not involved, nor is the crest of the alveolar bone disturbed. The junction of the epithelial attachment to the tooth represents a weak point in the epithelial barrier to the oral environment, and at this point a collection of polymorphonuclear leukocytes and lymphocytes are always found (Fig. 8-15).

Dewar, and Turesky and his associates studied the glycogen content of the granular and spinous layers of the epithelium and found that it increases as the intensity of the underlying inflammation increases. Mast cells containing granules of sulfonated mucopolysaccharide are increased in the inflamed gingiva, but the significance of this finding is not clear. The alkaline phosphatase activity increases somewhat in the inflamed gingiva, since it is present in the inflammatory and endothelial cells, and these are obviously present in larger numbers in chronic gingivitis. No remarkable differences were found in nucleic acid distribution between normal and inflamed gingiva, although the concentration of ribonucleic acid (RNA) was always lower in all cells of the crevicular epithelium and in the marginal epithelium where leukocytic infiltration had occurred.

Histochemical studies of acid phosphatase in normal and inflamed human gingiva have shown that this enzyme is located almost exclusively in the epithelium. There is a greater reaction in the superficial layers (with the exception of the stratum corneum, which is acid phosphatase-free) and a gradual diminution toward the basal cell layer. The reaction is absent or very weak in the epithelial lining of the gingival sulci and periodontal pockets and in the epithelial attachment.

Treatment and Prognosis. Most cases of chronic gingivitis are due to local irritation. If the irritants are removed at this stage, the inflammation with its attendant swelling due to hyperemia, edema, and leukocytic infiltration will disappear within a matter of hours or a few days, leaving



A B

Figure 8-14. Gingivitis.
The gingiva is infiltrated by large number of lymphocytes, plasma cells and polymorphonuclear leukocytes. The crevicular epithelium (1) is invaded by these inflammatory cells and is degenerating (**(A)** Low-power, and **(B)**, high-power photomicrographs).

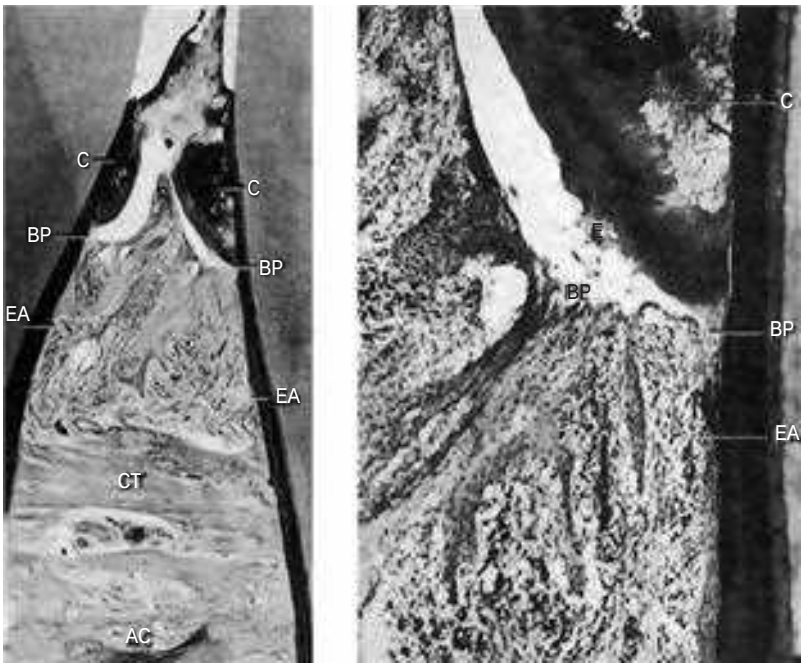


Figure 8-15. Gingivitis.
(A) A photomicrograph of the tissue from interproximal space between two bicuspids. AC marks alveolar crest; CT, transseptal fibers; P, interdental papilla; BP, bottom of pockets; C, calculus: EA, epithelial attachment. Photomicrograph on the right **(B)** shows higher magnification of the bottom of the pocket BP with the calculus C *in situ*. In this case the calculus fills almost the entire pocket. PE, The pocket epithelium, which is broken in some areas; E, the epithelium which is clinging to the calculus; EA, the epithelial attachment alongside the tooth. Note the severe inflammatory reaction in the connective tissue and the elongated rete pegs resulting from this inflammation *(Courtesy of Dr B Orban and J Periodontol)*.

no permanent damage. The fact that recovery usually follows the removal of irritants emphasizes the need for careful early treatment followed by proper brushing of teeth and frequent prophylaxis. Mechanical removal of plaque can be aided by chemical plaque control measures such as using mouthwashes containing chlorhexidine, listerine or triclosan. If there is poor response to good local therapy, a search should be made for systemic factors, which might be complicating the case.

As in all infections, the immune response plays an important role in delineating the signs and symptoms of the process. Obviously, factors governing leukocyte migration and chemotactic activity influence the host response. If the bacterial plaque does not evoke a positive chemotactic response in the polymorphonuclear leukocytic cells, there will be few, if any, signs of inflammation. On the other hand, if the patient's leukocytes are unable to respond to the 'call of the plaque', either because of a genetic defect or for some other reason, infection and tissue destruction may occur without the inflammatory reaction.

Nonplaque induced gingival diseases may have different etiology and have characteristic clinical presentation. These groups of gingival diseases include specific bacterial, viral, and fungal infections, gingival manifestations of certain dermatoses.

Necrotizing Gingivostomatitis

Necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and necrotizing stomatitis are together termed necrotizing gingivostomatitis and they share many clinical and etiological characteristics. The spectrum of necrotizing gingivostomatitis ranges from necrotizing gingivitis to cancrum oris. Predisposing factors may include emotional stress, immunosuppression, HIV infection, smoking, malnutrition, and pre-existing gingivitis. The diagnosis of necrotizing gingivostomatitis becomes more important in recent years since it serves as a marker for immune deterioration in HIV-seropositive patients. Necrotizing periodontitis shares many of the clinical and etiologic characteristics of necrotizing ulcerative gingivitis in patients with no known systemic disease or immune dysfunction, except that patients with necrotizing periodontitis demonstrate attachment loss.

Necrotizing Ulcerative Gingivitis

(Vincent's infection, trench mouth, acute ulceromembranous gingivitis, phagedenic gingivitis, fusospirochetal gingivitis, acute ulcerative gingivitis)

Necrotizing ulcerative gingivitis is a specific type of gingivitis with characteristic signs and symptoms. The disease manifests both acute and recurrent (subacute) phases; a chronic stage also has been described, but most investigators believe that treating

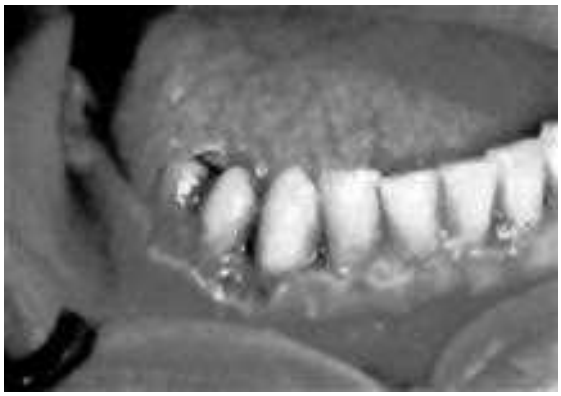


Figure 8-16. Necrotizing ulcerative gingivitis.
A typically heavy, necrotic membrane covers the gingival tissues of the anterior teeth in this severe case *(Courtesy of Dr Merrill Wheatcroft)*.

chronic necrotizing gingivitis as a separate entity cannot be justified, since it is neither clinically nor histologically specific. This inflammatory condition involves primarily the free gingival margin, the crest of the gingiva, and the interdental papillae (Fig. 8-16). On rare occasions the lesions spread to the soft palate and tonsillar areas, and in such instances the term **Vincent's angina** has been applied. Pain, interdental ulceration, and gingival bleeding are considered to be the diagnostic triad.

Necrotizing ulcerative gingivitis can cause destruction of the supporting tissues of the tooth and is termed as necrotizing ulcerative periodontitis, when bone loss occurs.

Epidemiology. Necrotizing ulcerative gingivitis frequently occurs in an epidemic pattern, sweeping through groups of persons in close contact, especially those living under similar conditions. This was especially apparent during World War I, when the Allied troops suffered severely from the disease. It was here that the term 'trench mouth' originated, since the disease was especially prevalent among the troops in the trenches. Similar sporadic outbreaks also occurred during World War II. Though this condition is relatively uncommon in developed countries nowadays, there has been a global increase associated with HIV infection.

The pattern of the spread of this disease, in many instances, indicated that it was a contagious infection, but this theory is not accepted now. Its occurrence in groups of persons can be explained on the basis of similar predisposing conditions among the members of the group, which may cause gingivitis to develop in each, even though there is no actual contact between them. Necrotizing ulcerative gingivitis may occur at any age, but is reportedly more common among young and middle-aged adults. In developing countries, it is seen almost exclusively in children, related to poverty and malnutrition. Pindborg et al, have reported 232 cases out of 10,000 patients examined in south India, of which 68% were children under 10 years. Malberger diagnosed 50 cases, all in children between one and six years of age among 7,650 patients who attended in an oral surgery clinic in West Africa.

Etiology. It is an endogenous, polymicrobial infection causing destructive inflammation due to the coexistence of several predisposing factors. Most investigators believe that necrotizing ulcerative gingivitis is caused by a *fusiform bacillus* and *Borrelia vincentii*—a spirochete. These organisms may be present in small numbers in the healthy gingival flora. Both microorganisms dominate in this 'fusospirochetal' disease, although other spirochetes, fusiforms, and filamentous organisms are also found. It is likely that a number of factors disturb the host-parasite relationship, facilitating overgrowth of the organisms of the fusospirochaetal complex. Chung et al, found that significant increase in IgG and IgM antibody titers to spirochetes and increased IgG titers to *Bacteroides melaninogenicus* in acute necrotizing ulcerative gingivitis through indirect immunofluorescence and Elisa. Some workers also include vibrio and coccal forms as important agents in the etiology of this disease. The fact that these two microorganisms, the fusiform bacillus and *Borrelia vincentii*, are found in moderate numbers in other oral diseases, including acute herpetic gingivostomatitis, as well as in many apparently healthy mouths, suggests that predisposing factors are essential to the development of the necrotizing ulcerative gingivitis. This is apparent in view of the fact that the disease has never been produced experimentally, in either human beings or animals, simply by oral inoculation of material from lesions in patients with the disease. Fusospirochetal abscesses can be produced in the animals by the subcutaneous injection of gingival exudate, or as reported by Hampp and Mergenhagen, by subcutaneous injection of pure cultures of either *Borrelia vincentii* or *Borrelia buccale*. Rosebury suggested that the subcutaneous tissues are readily susceptible to infection by these microorganisms but that the gingival tissues are relatively resistant because previous contact of the oral tissues with the bacteria had resulted in a local immunity. Some experimental studies showed that *B. intermedius* was responsible for the signs and symptoms of the disease. MacDonald et al, concluded that *Bacteroides melaninogenicus*, a motile gram negative anaerobic bacillus, was the true causative agent of necrotizing ulcerative gingivitis.

Predisposing Factors. Psychological stress plays an important role in the development of necrotizing ulcerative gingivitis, since there is an increased frequency of the disease in people in the military services. Other predisposing factors include immunosuppression, smoking, upper respiratory tract infection, local trauma, poor nutritional status, and poor oral hygiene.

HIV-positive persons suffer from a severe form of necrotizing ulcerative gingivitis as the immune function deteriorates and this progresses to HIV associated periodontitis.

Decreased resistance to infection is one of the most important predisposing factors in the development of necrotizing ulcerative gingivitis. This was apparent during World War I, when the Allied troops living under poor sanitary conditions in the trenches and subsisting on inadequate diets, acquired gingivitis in almost epidemic proportions, suggesting

a contagious disease. According to Schluger, similar outbreaks occurred during and after World War II among soldiers in the field, when poor food, poor oral hygiene and fatigue prevailed.

Stones has reported that the incidence of necrotizing ulcerative gingivitis in Liverpool Dental Hospital (England) shows a significant seasonal variation, the highest incidence occurring between October and February, when respiratory infections and exanthemas are at their peak, and the lowest incidence occurring in July and August. Experimentally, Swenson and Muhler produced fusospirochetal infection in dogs after the administration of Scillaren-B—a mixture of glucosides which lowers tissue-resistance by inducing leukopenia.

Numerous investigators have reported that fusospirochetal infection may be produced more readily in animals deficient in various vitamins. Necrotizing lesions of the oral cavity have been produced in animals deficient in vitamin C and B complex, but it still remains to be proved that the lesions are due to fusospirochetal organisms. In some instances a relation between vitamin deficiency and necrotizing ulcerative gingivitis in humans has been suggested, but the data is conflicting, especially in view of the general inability to alter the course of the disease by administration of vitamins.

Clinical Features. The disease is characterized by the development of painful, hyperemic gingiva and sharply punched-out crater like erosions of the interdental papillae of sudden onset (Fig. 8-16). The ulcerated remnants of the papillae and the free gingiva bleed when touched and generally become covered by a grayish green, necrotic pseudomembrane (Fig. 8-17). The ulceration tends to spread and may eventually involve all gingival margins. It begins rather commonly at a single isolated focus, with a rapid onset. A fetid odor ultimately develops that is extremely unpleasant.

The patient almost always complains of an inability to eat because of the severe gingival pain and the tendency for gingival bleeding. The pain is that of a superficial 'pressure.' The patient usually suffers from headache, malaise, and a low-grade fever. Excessive salivation with the presence of a metallic taste to the saliva is often noted, and regional lymphadenopathy is usually present.

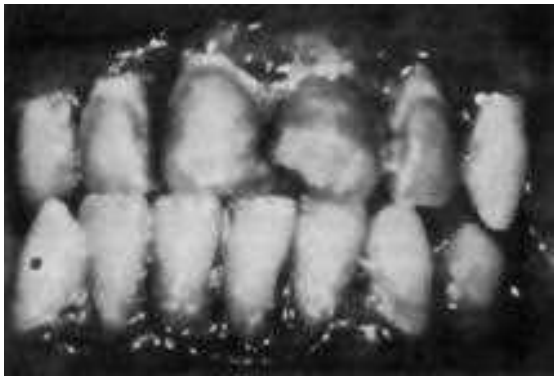


Figure 8-17. Advanced necrotizing ulcerative gingivitis.
Note the presence of a gray necrotic membrane and destruction of the interproximal tissues, particularly in the mandibular anterior region.

In advanced and more serious cases, there may be generalized or systemic manifestations, which may include leukocytosis, gastrointestinal disturbances, and tachycardia. After the necrotizing ulcerative gingivitis is cured, the crests of the interdental papillae, which have been destroyed leaving a hollowed-out area, constitute an area which retains debris and microorganisms and can serve as an 'incubation zone.' Such areas, along with gingival flaps of erupting third molars, are ideal locations for organisms to persist, and in many cases, the recurrence of necrotizing ulcerative gingivitis will begin here.

Bacteriologic Examination. Smears of material from the gingiva in cases of necrotizing ulcerative gingivitis show vast numbers of fusiform bacilli (genus *Fusobacterium* or *Fusiformis*) and an oral spirochete (*Borrelia vincentii*), various other spirochetes, filamentous organisms, vibrios, cocci, desquamated epithelial cells and varying numbers of polymorphonuclear leukocytes (Figs. 8-18, 8-19). The relative numbers of microorganisms present vary with the stage of the disease, secondary invaders being more prominent in the later phases as well as in the subacute form of necrotizing ulcerative gingivitis.

The fusiform bacillus associated with necrotizing ulcerative gingivitis is an elongated rod with tapered ends measuring 5–14 microns in length and 0.5–1.0 microns in diameter. This nonmotile organism is weakly gram-positive, occurs singly or in clusters and can be cultured under anaerobic conditions.

Borrelia vincentii is a gram-negative spirochete with three to six long, loose spirals. It measures approximately 10–15 microns in length, is actively motile and can be cultured anaerobically, although with some difficulty.

The diagnosis of necrotizing ulcerative gingivitis based upon a smear of gingival material is hazardous because of the

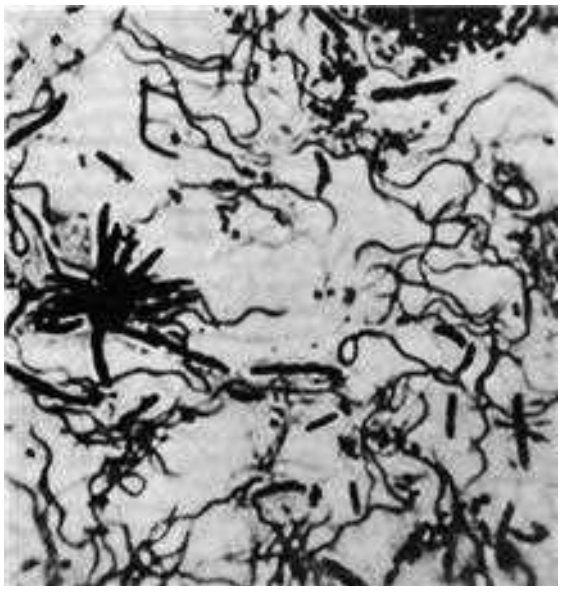
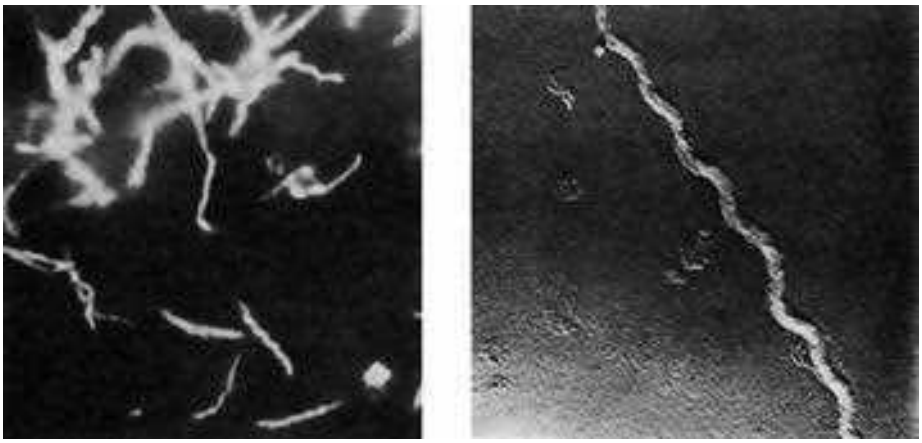


Figure 8-18. Necrotizing ulcerative gingivitis.
Photomicrograph of a smear from gingival exudate. Note the many spirochetes, fusiform bacteria, and other microorganisms.



A B

Figure 8-19. Oral spirochetes.
(A) Darkfield examination. **(B)** Electron photomicrograph, x 11,000 original magnification *(Courtesy of Dr E Hampp)*.

nonspecific findings. Although the presence of the disease can often be confirmed when vast numbers of the spirochete and fusiform bacteria are found in the smear, fewer numbers are often seen in smears from 'normal mouths,' cases of acute herpetic gingivostomatitis, simple pericoronitis, marginal gingivitis and chronic gingivitis. Although the bacterial smear may be of value as an aid in diagnosis of atypical cases of necrotizing ulcerative gingivitis, the final diagnosis is a clinical one.

Histologic Features. Microscopic examination of the gingiva in this disease reveals an acute gingivitis with extensive necrosis. The surface epithelium is ulcerated and replaced by a thick fibrinous exudate, or pseudomembrane, containing many polymorphonuclear leukocytes and microorganisms. Even in nonulcerated areas, a common feature noted by most investigators is the general lack of keratinization of the gingival tissues. The connective tissue is infiltrated by dense numbers of polymorphonuclear leukocytes and shows an intense hyperemia. The microscopic picture is an entirely nonspecific one.

There is not a complete consensus among investigators as to the penetration of the gingival tissues by the microorganisms associated with this disease. Vast numbers of both spirochetes and fusiform bacilli are found on the surface of the living tissue in and beneath the necrotic pseudomembrane. Both forms have also been reported as invading viable tissues to variable depths below the surface. It has been suggested that the presence of microorganisms in the tissues is due to surgical artifact. Schaffer, failed to find bacteria penetrating vital tissues under light microscopy. Listgarten, on the other hand, utilizing electron microscopic techniques, was able to identify spirochetes between viable epithelial cells (Fig. 8-20).

Treatment and Prognosis. The treatment of necrotizing ulcerative gingivitis is extremely varied, depending upon

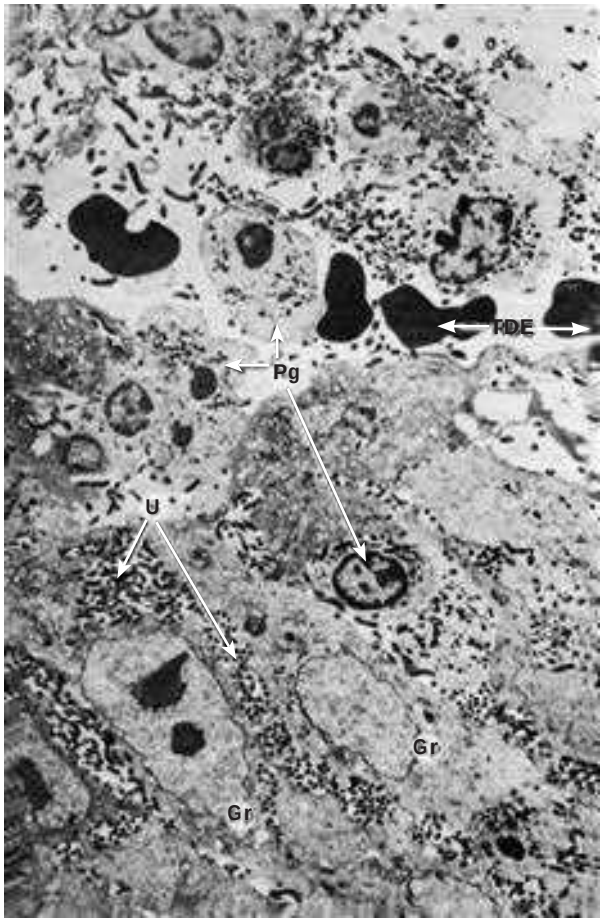


Figure 8-20. Necrotizing ulcerative gingivitis.
Electron microscope photomicrograph illustrates the epithelium adjacent to ulcerated lesion. Neutrophils (Ne), red blood cells (RBC), microorganisms and cellular debris cover the epithelium. Dense masses of large and medium spirochetes (S) and some neutrophils (Ne) distend the space between the epithelial cells (Ep). Original magnification, x 3500 *(Courtesy of Dr Max A Listgarten: J Periodontol, 36: 328, 1965).*

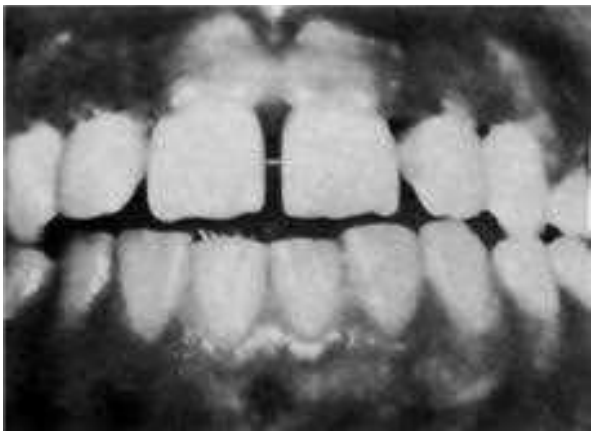


Figure 8-21. Necrotizing ulcerative gingivitis after initial treatment.
Note the persisting gray necrotic membrane on the free margin of the gingival tissue between the maxillary right central and lateral incisors. Note also the cupped-out gingival papillae between the maxillary anterior teeth that might become an incubation zone. Treatment must be continued until such areas are recontoured.

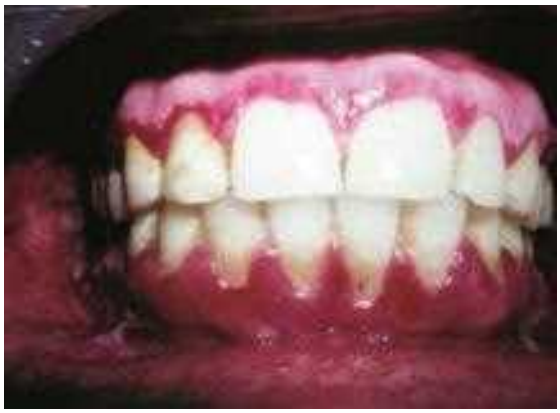
the individual dentist's experience with the disease. Some prefer to treat this condition conservatively, instituting only superficial cleansing of the oral cavity in the early acute stage of the disease with chlorhexidine, diluted hydrogen peroxide or warm saltwater. This is followed by thorough scaling and polishing. Topical anesthetics may be required to reduce the pain during this procedure. In many such cases, prompt regression of the disease results even without medication. Other dentists prefer the use of antibiotics coupled with local treatment.

The usual case of necrotizing ulcerative gingivitis begins to subside in 48 hours with adequate treatment. Sometimes there may be considerable destruction of tissue, involving the interdental papillae and marginal gingiva, and leading to punched-out appearance of the interproximal gingiva and the apparent gingival recession even after the regression of the disease (Fig. 8-21). Recontouring of gingival papillae is usually required; this can be accomplished by proper use of round toothpicks or by gingivoplasty. Treatment cannot be considered complete until the gingival tissue contours almost normal.

Necrotizing ulcerative gingivitis recurs with considerable frequency in patients who have already been treated. Occasional serious sequelae such as gangrenous stomatitis or noma, septicemia and toxemia, and even death have also been reported following this disease.

Desquamative Gingivitis

Desquamative gingivitis is not a disease entity but a clinical term used for many years to describe a unique condition of the gingiva characterized by intense redness and desquamation of the surface epithelium (Fig. 8-22). At one time, this was thought to be a specific degenerative disease of the gingival tissues, although of unknown etiology, and was sometimes also called 'gingivosis'. However, the term 'gingivosis' was first used by Schour and Massler in 1947 to describe a probably



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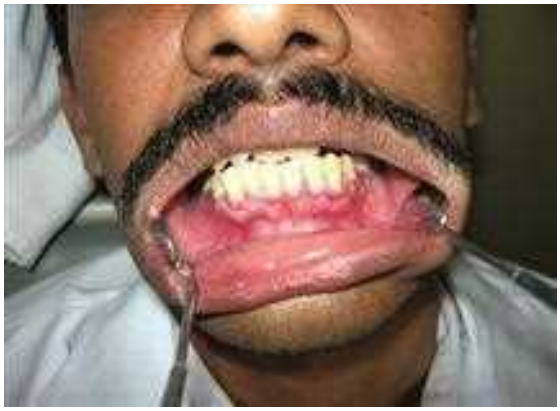


B

Figure 8-22. Chronic desquamative gingivitis.
(Courtesy of (A), Dr Saravanakumar R, Department of Periodontics, Meenakshi Ammal Dental College, Chennai and (B), Dr Surapaneni Sunilkumar, Department of Periodontics, Meenakshi Ammal Dental College, Chennai).

unrelated disease of the gingiva which they found in a group of malnourished Italian children.

McCarthy and his colleagues studied 40 cases of desquamative gingivitis and concluded in 1960 that it was not a specific disease entity but rather a clinical manifestation of several diseases and thus had several etiologies. The term 'desquamative gingivitis' is now used by most workers as a descriptive term for the oral manifestations of any one of a variety of diseases which, once identified, may permit a rational therapeutic approach of value for patient management.

Etiology. McCarthy and his colleagues proposed a classification of desquamative gingivitis based on etiology. They suggested the causative factors to be:

- Certain dermatoses
- Hormonal influences
- Abnormal responses to irritation
- Chronic infections
- Idiopathic.

Subsequent studies such as those of Nisengard and Neiders and of Rogers and his associates have shown that the dermatoses are numerically the most important of the causative factors.

For example, in the study of Nisengard and Neiders, 67 of the 100 patients exhibited immunofluorescent findings suggestive of or diagnostic of a dermatosis.

The most important dermatoses presenting oral findings categorized as a desquamative gingivitis are:

- Cicatricial pemphigoid (benign mucous membrane pemphigoid)
- Pemphigus
- Lichen planus.

Other diseases such as pemphigus vulgaris, epidermolysis bullosa, systemic lupus erythematosus, and linear IgA disease may also have gingival involvement, presenting as desquamative gingivitis. These individual diseases along with their identification by immunofluorescence will be considered with other diseases of the skin in Chapter 19.

Gingival Abscess

Gingival abscess is an acute, localized, and painful lesion of sudden onset. It is caused by sudden forceful penetration of any foreign objects such as a bristle of a toothbrush or an apple core, which carry bacteria deep into the gingival tissue.

Clinical Features. It is usually limited to the marginal gingiva. Initially it appears as reddish swelling with a smooth and shiny surface. Within hours, it becomes fluctuant and exhibits pointing and through which pus discharges.

Histologic Features. Connective tissue shows vascular engorgement, edema and formation of abscess cavity surrounded by a diffused collection of polymorphonuclear leukocytes. The overlying epithelium exhibits secondary changes in the form of intra- and inter-cellular edema, microabscess formation, and sometimes ulceration.

Treatment. Spontaneous rupture is common. The invading foreign material, if any, will be usually expelled along with the pus.

Pericoronitis

Periocoronitis is an inflammatory lesion occurring around the impacted or partially erupted tooth. Incomplete eruption of the tooth provides a large stagnation area for food debris under the gingival flap. This becomes infected easily and results in inflammation of the pericoronal flap. It exhibits chronic inflammation for a long period. If the debris and bacteria are deeply entrapped, an abscess may form which is called a pericoronal abscess. It is a mixed infection and various bacteria of the dental plaque (particularly anaerobes) play a significant role in the development of pericoronitis.

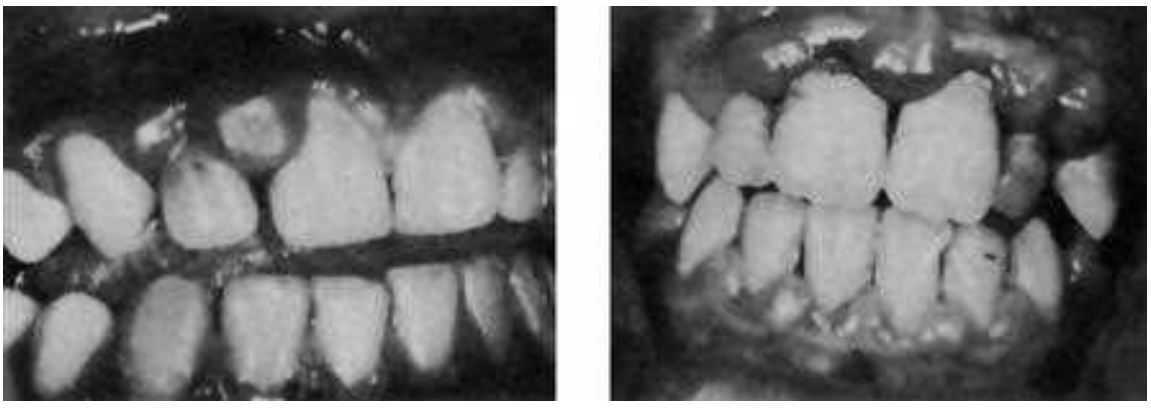
Clinical Features. Mandibular third molar is the commonly involved tooth. Pain and swelling of the pericoronal tissue around the affected tooth, difficulty in chewing, and difficulty in opening the mouth are the usual complaints. Patient may be mildly ill with fever, malaise, and regional lymphadenopathy.

Histologic Features. The epithelium of the pericoronal flap shows hyperplasia, intercellular edema, and leukocytic infiltration. The underlying connective tissue exhibits increased vascularity, dense diffused infiltration with lymphocytes, and plasma cells along with varying number of polymorphonuclear leukocytes.

Management. Entrapped food debris must be removed. When the upper tooth is involved, it should be grounded or extracted if it is malposed. Radiograph helps in assessing the position of the involved tooth. If impacted, the tooth must be removed. And if it is in a favorable position, surgical removal of the pericoronal flap is advocated after acute symptoms subside. The administration of antibiotics helps to relieve the symptoms and prevents the spread of infection to the adjacent tissue spaces.

Gingival Enlargement

The gingival tissues in the healthy adult completely, though barely, fill the interproximal spaces between teeth, beginning near the contact area and extending apically and laterally in a smooth curve. However, there is frequently an increase in the size of the gingiva so that soft tissue overfills the interproximal spaces, balloons out over the teeth and protrudes into the oral cavity. The enlargement of the gingiva may be localized to one papilla or may involve several or all of the gingival papillae throughout the mouth (Fig. 8-23). The enlargement



A B

Figure 8-23. Gingival enlargement.
Focal enlargement involving only two papilla **(A)**, and diffuse enlargement of papillae **(B)**.

is usually more prominent on the labial and buccal surfaces, although it does occasionally develop in the lingual gingiva. It does not involve the vestibular mucosa.

The term 'gingival hyperplasia' was used for a long time for a gross increase in size of gingival tissues, which may result from a number of different conditions. Gingival enlargements are not to be confused with overgrowths of bone, or exostoses, noted occasionally on the alveolar bone, usually at some distance from the gingiva.

Gingival enlargements can be classified based on etiologic factors and pathologic changes as follows:

1. Inflammatory gingival enlargement
2. Drug induced gingival enlargement
3. Enlargement associated with systemic factors
   a. Conditioned enlargement
   b. Enlargements due to systemic diseases
4. Idiopathic gingival enlargement
5. Neoplastic enlargement
6. False enlargement.

Inflammatory enlargement of the gingiva usually results from prolonged chronic inflammation of the gingival tissue. In most cases, the enlargement results because of local irritations such as poor oral hygiene, accumulation of dental calculus or mouth breathing, and represents a variation in host tissue response to dental plaque accumulation.

In inflammatory enlargement, the gingivae are soft, edematous, hyperemic or erythematosus and sensitive to touch. They can bleed easily, and present a glossy, nonstippled surface. Usually gingival enlargements are secondary to other types of enlargements. In such cases, dual etiologic factors should be kept in mind during management (Fig. 8-24). Clinical examination often reveals the nature of the local irritation that causes the enlargement, but the histologic picture is usually nonspecific, showing merely inflammation of the gingiva. The local irritation results in hyperemia, edema and lymphocytic infiltration. Many times the irritation results also in a proliferation of the fibrous connective tissue of the gingiva. The proliferation may be increased by some predisposing systemic factors.

Figure 8-24. Inflammatory gingival enlargement due to local collection of plaque.
(Courtesy of Dr Ajayprakash, Department of Oral Pathology, Kamineni Institute of Dental Sciences, Andhra Pradesh).

Drug-induced Gingival Enlargement. It is now well established that gingival enlargement sometimes occurs as a result of the use of the anticonvulsants, immune suppressants, and calcium channel blockers.

Diphenylhydantoin (dilantin sodium) was the first reported anticonvulsant to produce gingival enlargement. Other hydantoins known to induce gingival enlargement are ethotoin and mephenytoin. Other anticonvulsants such as valproic acid, methsuximide, and succinimides also produce gingival enlargement.

Dilantin sodium induces gingival enlargements in 3–84.5% of the patients receiving the drug. Phenytoin stimulates proliferation of fibroblast-like cell in tissue culture and also decreases the collagen degradation. It occurs most commonly in younger individuals, especially shortly after the institution of dilantin sodium therapy.

Cyclosporine, a potent immunosuppressive agent, has also been reported to produce gingival enlargement in 30% of the patients receiving the drug.

Calcium channel blockers such as nifedipine, nitrendipine, and verapamil also induce gingival enlagement. Nifedipine, the commonly used drug in cardiovascular conditions, induces gingival enlargement in 20% of the cases.

Drug-induced gingival enlargement begins painlessly, involving one or two interdental papillae, which present an increased stippling and ultimately a roughened or pebbled surface with lobulations. The gingival tissues are dense, resilient, and insensitive; they show little or no tendency to bleed (Fig. 8-25).

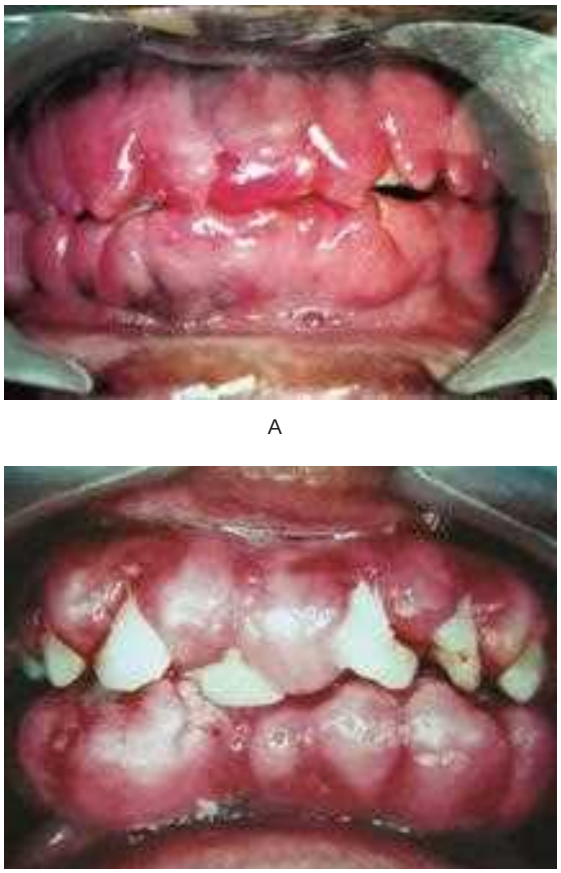
The bulk of the enlargement is due primarily to proliferation of the fibrous connective tissue with numerous fibroblasts. There is a possibility of superimposed chronic inflammation. The enlargement generally presents no difficulties, although it is esthetically objectionable. It may be so severe as to interfere with everyday functions, and for this reason it may be surgically excised. Unfortunately, its recurrence is common. It has been found that careful oral hygiene will result in slower development of the enlargement, and slower recurrence after surgical excision. Some regression of the enlargement may result if the use of the drug is discontinued. Cyclosporine-induced enlargements are more vascularized and have more amounts of plasma cells and extracellular substance.

There is no strict line of demarcation between hyperplasia of connective tissue and benign neoplasia of fibroblasts; indeed, there are several conditions which resemble fibromas but which should not be so designated. Keloid is one such condition, and fibrous enlargement of the gingiva is another.

ENLARGEMENT ASSOCIATED WITH SYSTEMIC FACTORS

CONDITIONED ENLARGEMENT

Conditioned enlargements are caused by the systemic condition of the patient, which exaggerates the usual gingival response to dental plaque. However, bacterial plaque is essential for the



A

B

Figure 8-25. Drug-induced gingival enlargement.
(A) Enlargement of the gingiva in an epileptic patient receiving dilantin sodium. **(B)** Gingival enlargement in a patient receiving nifedipine *(A and B, Courtesy of Dr ND Jayakumar, Saveetha Dental College, Chennai)*.

initiation of this type of enlargement. There are three types of conditioned enlargements: hormonal, nutritional, and allergic.

Hormonal Enlargement

Inflammatory gingival enlargement often occurs at puberty, both in men and women. Some investigators think that this enlargement may result from an endocrine imbalance at this particular stage of the patient's development. Others believe that it may occur, at this age, because oral care is poor, there is local irritation associated with eruption of teeth, and/or nutrition may be inadequate. Thus, the enlargement may be only indirectly associated with an endocrine disturbance.

One also notices a tendency for gingival enlargement of the inflammatory type during pregnancy. This proliferation may be due to disturbed nutrition, poor oral hygiene, or some systemic predisposition toward proliferation. Increased levels of estrogen and progesterone in pregnancy cause change in the vascular permeability, which leads to gingival edema and altered inflammatory response to dental plaque.

The so-called pregnancy gingivitis, more properly spoken of as 'gingivitis in pregnancy', is often associated with isolated gingival proliferation, sometimes so severe that it is referred to as a 'pregnancy tumor,' which is basically a pyogenic granuloma (q.v.). These proliferations resemble those seen in some nonpregnant women who have severe local irritations. Microscopic studies of these gingival lesions reveal increased vascularity, multiplication of fibroblasts, edema, and infiltration of leukocytes into the gingiva.

Nutritional Enlargement

Vitamin C Deficiency. The spongy, bleeding gums of scurvy, vitamin C deficiency (q.v.), have long been recognized as a specific entity. The enlargement of gingiva is generally included in the classic description of scurvy. This enlargement is essentially a conditioned response to bacterial plaque. The combined effect of vitamin C deficiency and inflammation produces this enlargement. Although clinical scurvy is now rare, there are a few occasional cases. Subclinical cases are probably common, since it has been reported that many patients do not include adequate vitamin C in their diets. In such cases, the gingivae become tender, swollen, and edematous. They bleed upon the slightest provocation. Gingival sulci are often filled with partially clotted blood, and the crests of the interdental papillae are red or purple. There is sometimes ulceration and necrosis of the papillae as infection becomes superimposed upon the susceptible tissues. Hemorrhages following slight trauma to other parts of the body are also noted.

Treatment includes improvement of oral hygiene and administration of vitamin C.

Allergic Enlargement

Plasma Cell Gingivitis (Atypical gingivitis, plasma cell gingivostomatitis). This distinct form of gingivitis first reported in the United States, usually arises as a hypersensitive reaction to a component of chewing gum, dentifrices, or some of the dietary components. It commonly presents as a mild marginal gingival enlargement, sometimes extending to involve the attached gingiva.

Clinical Features. This disease is more prevalent in young women. The initial symptom is soreness of the mouth, which is intensified by hot or spicy food. It starts as mild marginal gingival enlargement and extends to attached gingiva, and in severe cases, extends to buccal and vestibular mucosa. Gingiva appears swollen, erythematous, and friable with loss of stippling. The involvement of other oral tissues like the tongue and lips is common. They appear atrophic, dry, and exhibit cracks or fissures.

Histologic Features. The surface epithelium is hyperplastic, shows intracellular edema, and micro abscesses. The underlying connective tissue is densely infiltrated with chronic inflammatory cells, predominantly a polyclonal mixture of plasma cells. There is marked vascular dilatation with severe thinning of epithelium over the connective tissue pegs.

Treatment and Prognosis. Possible allergens should be identified by careful study of the patient's history and eliminated. Topical and systemic steroids give good results.

ENLARGEMENT DUE TO SYSTEMIC DISEASES

Leukemia

Gingival enlargement is often an early finding in acute monocytic, lymphocytic or myelocytic leukemia (q.v.). Leukemic enlargement may be diffused or marginal, localized or generalized. Gingiva appears shiny, bluish red, soft, edematous, easily compressible, tender, and frequently ulcerated. They show no signs of stippling (Fig. 8- 26). The gingivae are usually inflamed, owing to local infection, and occasionally a necrotizing ulcerative gingivitis develops.

Histologic study of this type of gingival enlargement shows that the gingival tissues are packed with immature leukocytes, the specific type depending on the nature of the leukemia. These abnormal white blood cells are unable to perform their defensive function and cannot control the infection at the gingival margin. Capillaries are engorged, and the connective tissue is edematous.

Granulomatous Diseases

Some local and systemic granulomatous diseases may involve the gingiva and present as gingival enlargement. Common diseases in which gingiva is involved are Crohn's disease, sarcoidosis (q.v.), Wegner's granulomatosis (q.v.), and foreign body gingivitis. The latter is caused by the introduction of foreign materials into the sulcular epithelium.

Regional Enteritis
(Crohn's Disease)

Regional enteritis is a slowly progressive disease of unknown etiology. Some of the features suggest an unusual reaction to an extrinsic agent, possibly of infective origin. Atypical mycobacteria have been implicated in some cases. It occurs in persons of all ages, involves both genders equally and is characterized by granulomatous, superficial ulcerations of the intestinal tract with frequent fistulas developing onto body surfaces or viscera, or between intestinal loops. This disease has been reported as having oral manifestations or oral extensions, and 24 such cases have been reviewed by Bernstein and McDonald. The most commonly involved areas are the buccal mucosa, where the lesions present a cobblestone appearance; the vestibule, where linear and hyperplastic folds, which may mimic denture-induced hyperplasia; the lips, which appear diffusely swollen and indurated; the gingiva and alveolar mucosa, which exhibit a granular erythematous swelling; and the palate, where multiple ulcers occur. Glossitis may be seen secondary to malabsorption of vitamin B_{12}. The oral lesions may either precede or follow the appearance of the intestinal lesions, and like those lesions, commonly show periods of quiescence alternating with exacerbations of the process. The microscopic findings of the oral lesions are those of a chronic granulomatous disease, reminiscent of sarcoid.

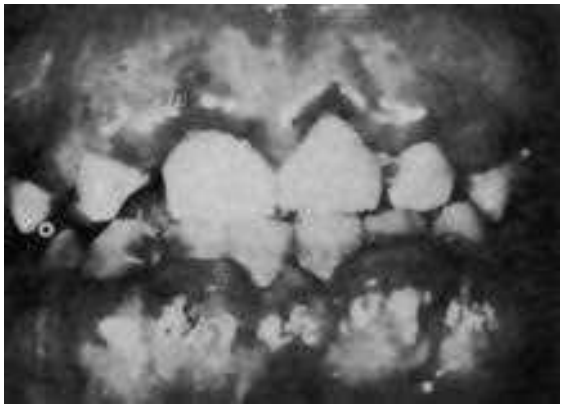


Figure 8-26. Gingival enlargement due to acute monocytic leukemia.

Microscopically, it consists of fibrosis and a focal dense collection of lymphocytes and plasma cells. Lymph vessels appear dilated. The presence of noncaseating granulomas which are typically small, consisting of macrophages, epithelioid cells, and occasional giant cells are seen. Typical cases have also been reported by Bottomley and his associates and by Eisenbud and his colleagues.

Management. Oral lesions resolve when intestinal Crohn's disease is controlled. The use of oral sulfasalazine or intralesional injection of corticosteroid gives good results.

Idiopathic Gingival Enlargement

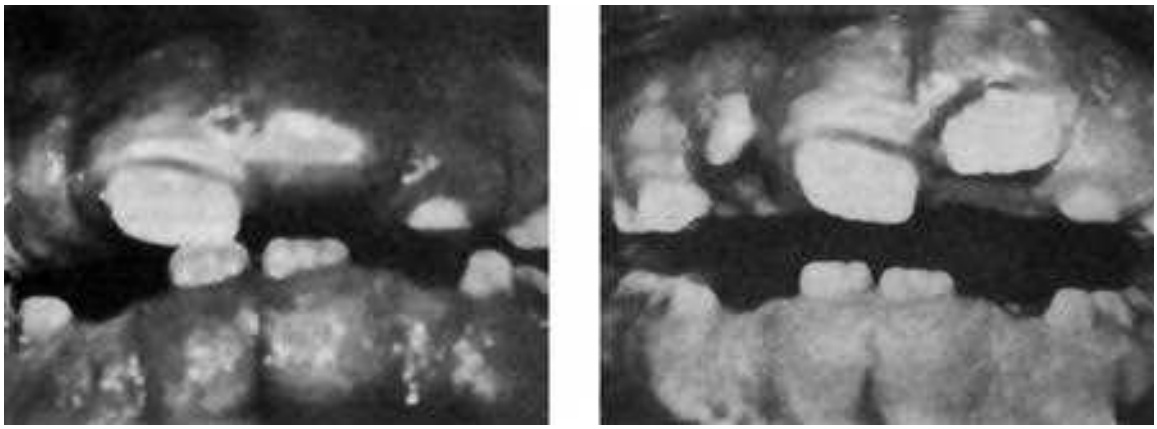
There have been a few cases where the patient's gingival tissues are so diffusely enlarged that the teeth are completely covered. If the enlargement is present before tooth eruption, the dense fibrous tissue may even interfere with or prevent eruption (Fig. 8-27). Other names for this condition are 'fibromatosis' (q.v.), 'fibromatosis gingivae,' 'elephantiasis gingivae,' and 'congenital macrogingiva'. The cause of this developmental enlargement of gingival tissue is not known. It is probably hereditary, being transmitted as an autosomal dominant trait in some instances, since reports have been made of several cases occurring in the same family.

A typical case of idiopathic gingival enlargement presents large masses of firm, dense, resilient, insensitive growth that covers the alveolar ridges and extends over the teeth. It is normal in color, and the patient complains only of the deformity. Often the gingivae are so enlarged that the lips protrude, and the fibrous mat of tissue upon which the patient chews may be 25 mm wide and as much as 15 mm thick.

This enlargement may be detected at an early age and in a few cases even at birth. Teeth do not erupt normally because of the dense fibrous tissue.

Histologic sections of tissue from idiopathic fibrous gingival enlargement show hyperplastic epithelium with elongation of rete ridges and mild hyperkeratosis. The underlying stroma is made up almost entirely of dense bundles of mature fibrous tissue with few young fibroblasts present. Occasionally, some chronic inflammation caused by local irritation may also be present.

Surgical removal of the excess fibrous tissue is the only feasible treatment. The condition may recur afterwards.



A B

Figure 8-27. Fibromatosis gingivae.
Idiopathic fibrous hyperplasia **(A)** before and **(B)** after an incision had been made to allow eruption of the maxillary central incisor. Eventually these teeth assumed a relatively normal position.

Neoplastic enlargements are due to benign and malignant neoplasms involving the gingiva, discussed in Chapter 2 on Benign and Malignant Tumors of the Oral Cavity.

False enlargements occur due to underlying dental or osseous anomalies and are not an abnormality of the gingiva as such.

PERIODONTITIS

Periodontitis is defined as 'an inflammatory disease of the supporting tissues of the tooth caused by specific microorganisms or group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both'. It is classified as chronic, aggressive, and as a manifestation of systemic diseases. The so-called acute periodontitis that results from acute trauma is now termed as occlusal trauma.

Chronic Periodontitis

(Periodontoclasia, pyorrhea, pyorrhea alveolaris, Schmutz pyorrhea)

Chronic periodontitis is the most common form of periodontal disease and is associated with local irritation. This begins as a marginal gingivitis, which usually progresses, if untreated or improperly treated, to chronic periodontitis. This type of periodontitis, sometimes referred to as marginal periodontitis, is most common in the adult, although it is found occasionally in children, especially when oral hygiene is lacking, or in certain cases of malocclusion.

The amount of tissue destruction is consistent with local factors. In the adult, periodontal disease of this type accounts for more than 90% of the cases of periodontal disturbances and is responsible for greater tooth mortality than dental caries. In general, the treatment of this form of periodontal disease, as of all others, is dependent upon the removal of etiologic factors, both local and systemic, the maintenance of good oral hygiene, and the establishment of a stable, harmonious articulation free from traumatic interferences.

Etiology. Gingivitis may precede and develops into a more severe periodontitis, which involves not only the gingiva, but also alveolar bone, cementum, and periodontal ligament. Etiologic factors, in general, are the same as for gingivitis, but are usually more severe or of longer duration.

Local factors such as microbial plaque, calculus, food impactions, and irritating margins of fillings appear to be most important in the development of this common form of periodontal disease. No abnormalities of the immune system seem to appear. Chronic periodontitis is predominantly associated with *Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Porphromonas gingivalis,* and *Prevotella intermedia.* The microflora in advanced periodontitis is characterized by the presence of large numbers of asaccharolytic microorganisms, including *Fusobacterium nucleatum, Bacteroides melaninogenicus, Eikenella corrodens, Bacteroides corrodens,* and *Bacteroides capillosus.* Slots (1977) found that these organisms constituted up to 75% of the isolates from periodontitis pockets.

Incidence. The incidence of periodontal disease is difficult to determine, and figures vary according to the criteria used by the individual investigators. This wide variation in the reported prevalence of periodontal disease is doubtless due to lack of uniformity in methods of assessment used, and of course, to inherent differences in the populations examined.

According to a study by Marshall-Day, chronic periodontal disease occurs rarely before 18 years of age, but increases in incidence so rapidly that after 45 years of age almost all subjects show evidence of localized or generalized bone loss. The incidence of bone loss in men is slightly higher than in women, and of pocket formation increased constantly with age, reaching a peak of 94% at ages 52–55 years. Abnormal tooth mobility was rarely encountered before 25 years of age, but increased sharply from 25% at ages 35–39 to 49% at ages 40–48, with a steady rise to 79% at age 60. Localized or generalized

clinically demonstrable suppuration occurred spontaneously or under digital pressure in almost 40% of subjects at age 40 and approximately 50% in the older age groups. There was also a rapid rise in tooth loss after 35 years of age, so that by 60 years of age, 60% of the teeth had been lost and 26% of patients were completely edentulous.

Immunologic Features. There is considerable evidence indicating that plaque-induced effector mechanisms play a major role in the pathogenesis of inflammatory periodontal disease. Both the cellular and humoral immunologic pathways have been implicated in the destruction of periodontal tissues. Correlations of varying magnitudes have been demonstrated between the clinical severity of periodontal disease and plaque antigen-induced peripheral blood lymphocyte blastogenesis by Ivanyi and Lehner (1971), by Horton and coworkers (1972), and by Mackler and associates (1974). The clinical severities of periodontal disease have also been correlated with salivary IgA concentrations by Orstavik and Brandtzaeg (1975). Robertson and his coworkers (1980) studied the periodontal status of patients with primary immunodeficiencies and compared them with age-matched and plaque-matched individuals. Since most patients with immunodeficiency diseases have a short life span, most of the patients examined were younger than 15 years of age. There were; however, two patients, one 45 years old and the other 16 years old, with IgA deficiency, although low to undetectable levels of IgA were noted in all of the immunodeficient patients studied.

Without exception, immunodeficient patients demonstrated less gingival inflammation than immunocompetent subjects matched in age and plaque index. These results are in accord with studies by Tollefsen and colleagues and by Kardachi and Newcomb of patients receiving immunosuppressant drugs. The diminished levels of gingival inflammation in immunodeficient patients can be explained if there was a qualitative difference in the oral microflora or if there was impairment in the host's ability to react to plaque. Brown and coworkers found very few differences in the microbial composition of dental plaque between the two patient groups reported on by Robertson and his colleagues (1980). However, significantly higher plaque levels of catalase-negative diphtheroids and *Candida sp*. were found in immunodeficient patients, whereas control groups had higher concentrations of *Fusobacterium sp*. They concluded that immunoglobulins have minimal influence on the microbial composition of dental plaque. Therefore, if dental plaque is present and the reaction to it is absent or minimal, there would be lesser chances of periodontal disease. On the other hand, if the immunologic effector mechanisms are responsible for the signs or symptoms of periodontal disease, there would be inflammation and tissue destruction only in patients who are able to mount an immunologic response to the presence of dental plaque. Mackler and his coworkers reported in 1978 that the earlier mild gingivitis lesions contained predominantly thymus (T)-derived lymphocytes, whereas the more advanced lesions contained large numbers of B-lymphocytes and plasma cells. Thus, patients with humoral (B-lymphocyte) immunodeficiencies would be expected to have some gingival inflammation, since many such patients manifest normal T-cell mediated responses. In fact, some of the IgA-deficient patients in Robertson's study did show mild gingivitis, but it was less severe than in the age and plaque-matched controls.

Evidence that the immune response is capable of destroying all periodontal tissues in experimental animals was provided by Levy and his colleagues (1976). When complete (CFA) and incomplete (IFA) Freund's adjuvant was injected into the periodontium of CFA-sensitized marmosets, capuchins, and rhesus monkeys, all animals developed a proliferative granulomatous reaction to the injection site. However, only in CFA-injected animals was there marked destructive periodontitis with considerable bone destruction. The injection of IFA into the periodontium of the same animals resulted in the formation of nondestructive proliferative granulation tissue.

It seems obvious then that the immune response, while often protective, can also be a highly destructive reaction to injury. Page and Schroeder have summarized the histopathology and immunopathology of periodontitis.

There are contradicting reports regarding the genetic polymorphism for cytokines as potential markers for periodontitis. Lopez NJ and coworkers reported positive association of interleukin-1 polymorphism with periodontitis based on a study involving 330 patients with periodontitis and 101 healthy controls. While Sumer AP et al found association of interleukin-10 gene polymorphism and generalized chronic periodontitis, in their study involving 75 Turkish patients with generalized chronic periodontitis and 73 healthy controls.

Cystatin C is a potent inhibitor of lysosomal proteinases and probably one of the most important extracellular inhibitors of cysteine proteases. According to a study done by Sharma A et al (2012), the mean cystatin C concentration in gingival crevicular fluid and serum was highest in periodontitis group and lowest in periodontally healthy group with intermediate concentration in gingivitis group and after periodontal therapy group. With this finding they suggested that cystatin C increases with disease progression to prevent further periodontal degeneration and decreases after treatment due to bone metabolic homeostasis.

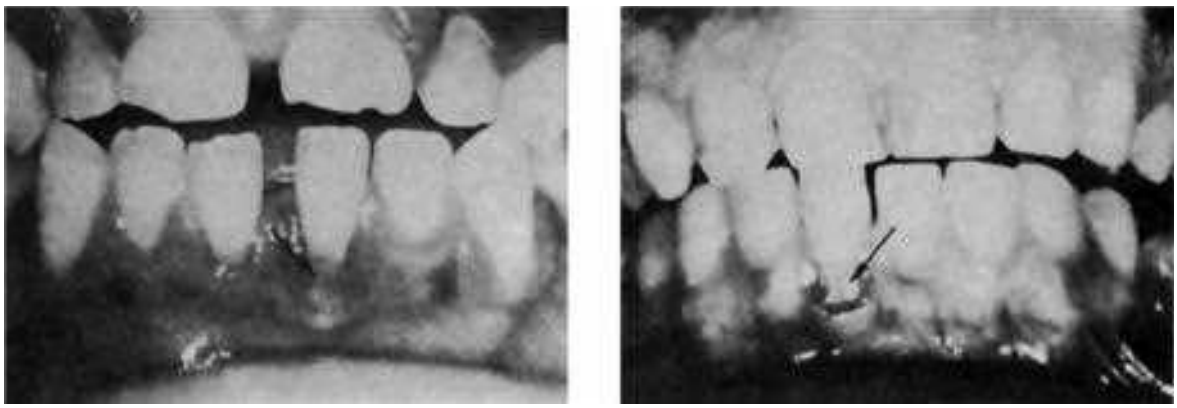
Clinical Features. Periodontitis usually begins as a simple marginal gingivitis, as a reaction to plaque or calculus. An early, and perhaps the first, pathologic finding is a tiny ulceration of the crevicular epithelium. Unless the irritants are removed, more plaque and calculus are deposited with the passage of time, and the marginal gingivitis becomes more severe. The gingiva becomes more inflamed and swollen, and with irritation, the crevicular epithelium suffers ulceration more frequently. It proliferates as a result of the inflammation so that at this stage there is a tendency for the epithelial attachment to extend or 'migrate' apically on the tooth. As it does so, it gets easily detached at its coronal portion. Through this process and because of the increased swelling of the marginal gingiva, the gingival crevice gradually becomes deeper and is classified as an early periodontal pocket (Fig. 8-28). The presence of periodontal pockets measuring more than 3–4 mm indicates the destruction of periodontal ligament and alveolar bone resorption.

Figure 8-28. Developing periodontal pocket.
C labels a firmly attached deposit of subgingival calculus. The arrow indicates a break in the integrity of the epithelial lining of the pathologic pocket. Note the chronic inflammatory reaction in the soft tissue and the scarcity of gingival fibers *(Courtesy of Dr JP Weinmann and Dr GW Burnett, and Williams and Wilkins Company).*

Clinically, the presence of calculus may be detected at this stage. Subgingival calculus may be more readily visualized if the free marginal gingivae are blown-back from the tooth by compressed air. Besides the mild visible swelling and hyperemia of the gingivae there is also a tendency for them to bleed readily; minute 'spontaneous' hemorrhages will often appear if the gingivae are simply rubbed by the examiner in the region of the interdental papillae. An unpleasant, almost foul type of halitosis is also present.

As periodontitis becomes more severe, the teeth become mobile and give off a rather dull sound and hurt when tapped with a metal instrument. Suppurative material and other debris occasionally may be expressed from the pathologic pocket adjacent to a tooth by slight pressure on the gingiva. Compressed air and instrument exploration will reveal that the tissue detachment may be severe. The embrasures may be open because the interdental papillae are deficient. The normal festooning is not apparent, and the gingivae appear 'boggy' because of hyperemia and edema; no stippling is detected, and the gingival tissues are smooth, shiny, and perhaps redder or bluer than normal. The patient may have no subjective symptoms or may complain of a bad taste, bleeding gums, and hypersensitivity of the necks of the teeth due to exposure of cementum as the soft tissues recede. In other words, the patient has a severe chronic gingivitis and an involvement of the deeper portions of the periodontium. This is the stage of severe periodontitis.

Gingival recession is a common phenomenon, particularly in later years in life. In such cases the gingival tissues recede toward the apex, exposing the cementum, sometimes to an alarming degree. Since the cementum is softer than enamel, it is often worn away by a toothbrush and an abrasive dentifrice. Gingival recession can occur more rapidly if there has been rapid alveolar bone loss, due to any cause, since gingival tissue in health will maintain uniform relations with alveolar bone crest. Gingival recession often begins as a thin break in the free gingiva adjacent to the center of a tooth. This is called a Stillman's cleft (Fig. 8-29).



A B

Figure 8-29. Gingival recession (Stillman's cleft).
The recession on the lower anterior teeth is due to poor oral hygiene and an abnormal amount of local irritation **(A and B)**.

Abnormal frequency and direction of tooth brushing, occlusal forces, or a high muscle attachment will sometimes lead to gingival recession. Gingival recession is preceded by alveolar bone loss, but bone loss is not necessarily accompanied by an equal amount of recession.

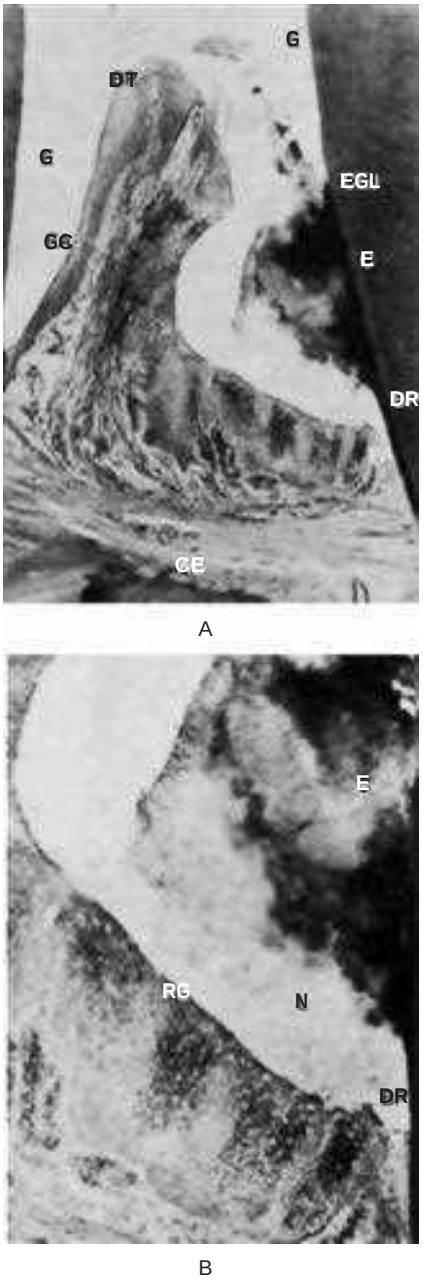


Figure 8-30. Periodontitis, early.
Photomicrographs of the interproximal space between a second and third molar. The bottom of the pocket on the third molar is on the enamel (BP_1), whereas it is on the cementum (BP) of the second molar. E, Enamel is lost in decalcification; EA, epithelial attachment; CEJ, cementoenamel junction; C, deposit of calculus; AC, alveolar crest showing resorption. The illustration on the right is a higher magnification of the bottom of the pocket, showing calculus (C) separated from the epithelium (PE), and leukocytes (L), which have migrated from the connective tissue *(Courtesy of Dr B Orban and J Periodontol)*.

Histologic Features. In marginal gingivitis, which is just beginning to undergo transition into early periodontitis, the enlarged free marginal gingiva is densely infiltrated with lymphocytes and plasma cells. The apical border of the inflamed area approaches the crest of the alveolar bone and the crestal fibers of the periodontal ligament (Figs. 8-30, 8-31). The crevicular epithelium shows various degrees of proliferation, and often, tiny ulcerations. One of the early microscopic signs of the encroachment of the inflammatory process on the periodontium is the appearance of the osteoclasts on the surface of the bone crest. They soon appear to lie in the little bays of bone resorption known as Howship's lacunae. The underlying tissues of the periodontium show no changes at this stage. The pathologic process involves the alveolar bone

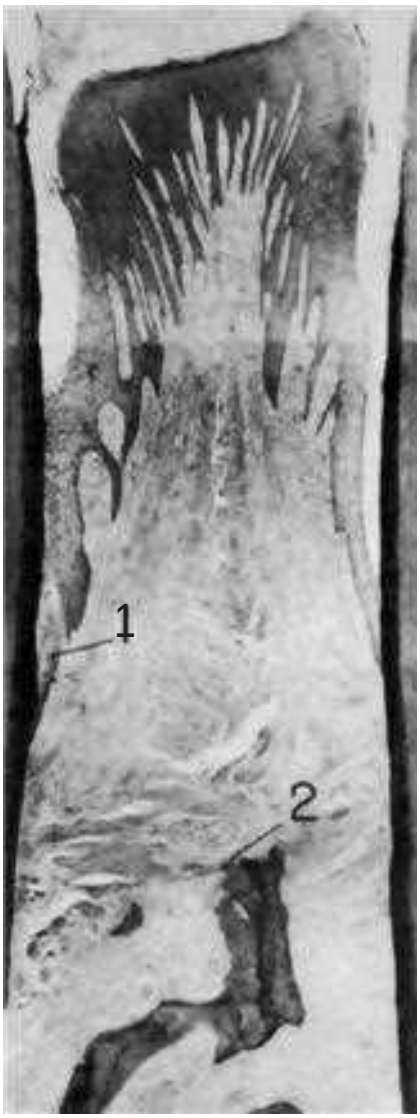


Figure 8-31. Periodontitis, early.
Composite photomicrograph of case of gingivitis gradually progressing toward a periodontitis. Note that the epithelium (1) is proliferating along the cementum and that the resorption of the alveolar bone has begun (2). *(Courtesy of Dr JP Weinmann and Dr GW Burnett, and Williams and Wilkins Company).*

prior to involvement of the periodontal ligament.

The next stage of the progress of the disease is a continuation of the factors just described:

- More plaque is deposited in an apical direction on the tooth
- More irritation of the free gingiva occurs
- The epithelial attachment proliferates apically down onto the cementum of the tooth and shows more ulceration
- The alveolar crest of bone is resorbed further apically
- Principal periodontal ligament fibers become disorganized and detached from the tooth
- A periodontal pocket exists between the free gingiva and the tooth, to depths from 2 mm down, until finally the apex of the tooth is approached.

The deep pocket that exists between the calculus and plaque-covered tooth surface and the epithelial lining of the gingival tissues forms a protective trap for multiplying microorganisms and for leukocytic cellular exudate from the inflamed soft tissue of the pocket wall. The vicious cycle of irritant collection, inflammation and detachment continues, along with periodontal bone resorption in an apical direction (Fig. 8-32).

Classification of Periodontal Pockets. In a normal healthy periodontium, the gingival tissues fit snugly around the teeth, and the gingival crevice approximates zero. In the presence of inflammation; however, the gingival tissues increase in bulk, causing an increase in the depth of the pocket around the teeth. If the pathologic changes are limited to the gingiva, this is called a gingival pocket or pseudopocket. If; however, the base of the pocket has invaded further into the periodontium, it is called a periodontal pocket. The base of the periodontal pocket is on the root of the tooth, and the epithelial attachment is on cementum. Although periodontal disease usually progresses apically and advances at the expense of the horizontal loss of the crest of the alveolar bone, sometimes the depth of the pocket extends apically to the crest of the alveolar bone. Such a pocket, which has bone on its lateral wall, is called an infra-bony pocket, and is the exception rather than the rule, since usually the bottom of the pathologic pocket is level with or coronal to the alveolar crest of bone (supra-bony pocket, Fig. 8-33). The infra-bony pocket may result from food impaction and is frequently found along the tooth that has shifted considerably out of its usual position or has

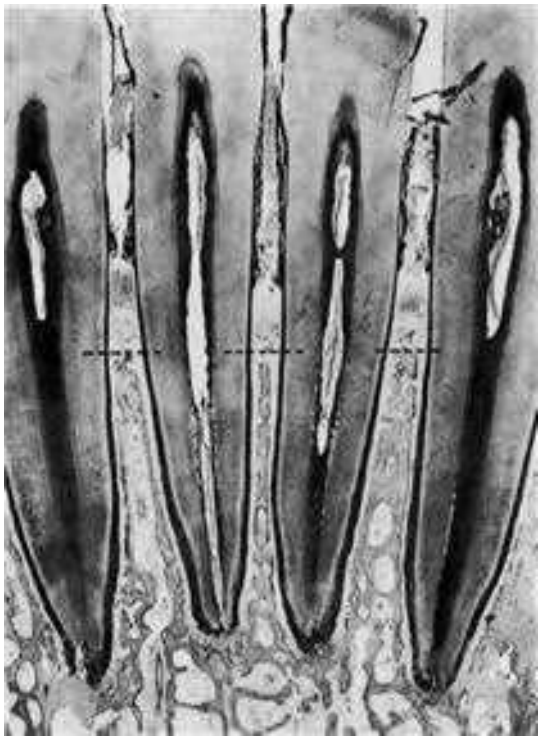
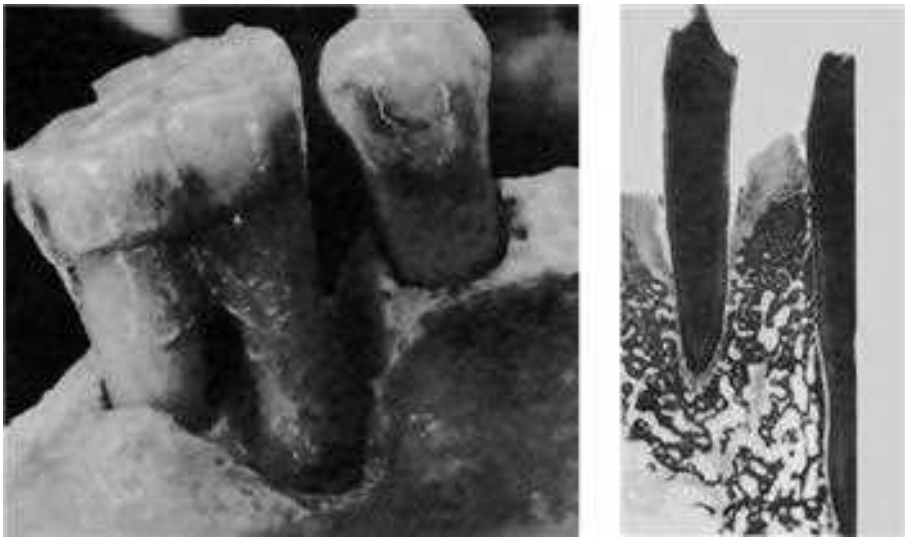


Figure 8-32. Periodontitis.
Note the collection of debris interproximally and the horizontal bone loss *(Courtesy of Dr JP Weinmann)*.



A B

Figure 8-33. Infra-bony pocket.
(A) Typical infra-bony pocket of the mandibular molar region. **(B)** Photomicrograph of a similar pocket *(A, Courtesy of Dr John Pritchard: J Periodontol, 28: 202, 1957).*

been subjected to severe occlusal trauma. Infra-bony pockets are classified according to their shape (narrow or broad) and the number of bony walls. According to Goldman and Cohen in a complete discussion of this condition, three-wall infra-bony pockets are commonly observed in the interdental areas where one finds an intact proximal wall as well as buccal and lingual walls of the alveolar process. Two-wall infra-bony pockets may be seen in the interdental areas, with the buccal and lingual walls intact, but the proximal wall destroyed. A 'curtain' of soft tissue remains where the osseous wall has been destroyed. Infra-bony pockets with one osseous wall are occasionally seen in the interdental area.

The type of periodontal pocket present can be determined by careful clinical examination and study of good radiographs. Consideration of the topography and type of infra-bony pocket is important in planning the treatment of periodontal disease. The most favorable type of pocket for reattachment to occur is, of course, the one with three osseous walls. A 'slating fill-in' of bone can occur in a pocket with two bony walls; but when only one wall is present, chances for the formation of additional height of alveolar bone are poor.

Radiographic Features. The earliest change in the periodontal bone is a blunting of the alveolar crest due to the beginning of bone resorption (Fig. 8-34). A straight line can be drawn along the edge of alveolar bone at almost any stage of the disease and the bone loss is said to be horizontal. There is a tendency for cupping out of the interdental alveolar bone. The periodontal ligament space retains its usual thickness, and generally no changes are noted except the superficial bone changes that actually may become extensive (Fig. 8-35). It is of interest that radiographic evidence of alveolar bone changes has been reported in about 12% of cases in which pocket formation does not exist clinically.

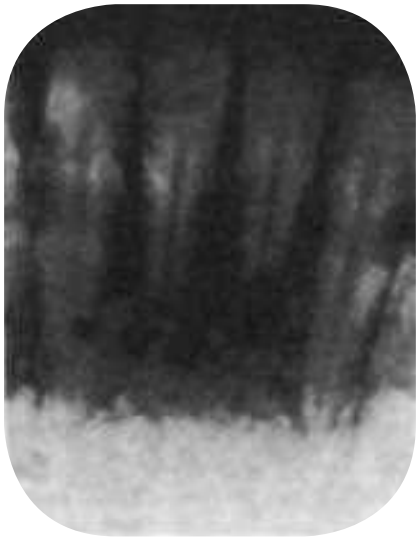
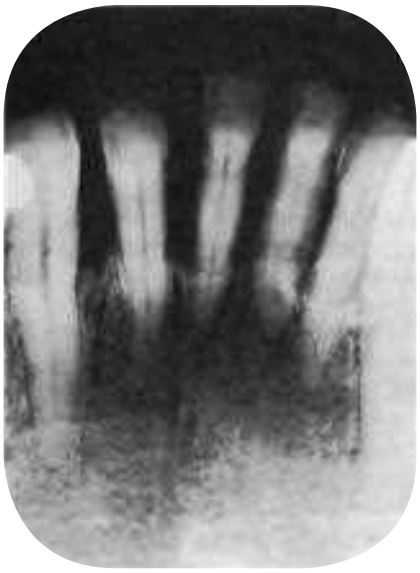


Figure 8-34. Periodontitis, early.
Note the blunting of the alveolar crest and loss of alveolar bone in the radiograph *(Courtesy of Dr R Gottsagen)*.



A

B

Figure 8-35. (A) Periodontitis, advanced. (B) Severe form of chronic periodontitis.

Treatment and Prognosis. By careful complete periodontal treatment, the teeth involved by periodontal disease can be saved if the bone loss has not been too extreme, if irritants are removed by scaling and curettage and if pockets are eliminated by gingival recession or by surgical removal of the gingiva (gingivectomy), if osseous deformities are eliminated and the tooth-supporting tissues are recontoured to a normal physiologic architecture, if occlusal forces are balanced, and systemic factors are corrected.

Clinicians for many years have demonstrated that after the successful treatment of periodontitis, pathologic pockets are shallower, even though no tissue was removed. Obviously this loss of pocket depth can be caused either by gingival recession or by reattachment of periodontal ligament to the tooth surface next to the pocket. Actually, both recession and reattachment may occur in the same case. There is usually a shrinkage or recession of the gingival tissues as inflammation and its associated edema and hyperemia is diminished, for as the gingival tissues return to a state of health the normal relation of gingiva to alveolar bone is gradually re-established just above the bone level. The distance from the crest of the

gingiva to the base of the pocket is diminished by the reduction in the size of the gingiva.

The second possible explanation for the shallower pocket after therapy is reattachment. Reattachment may be defined as a re-establishment of fibrous connection of the tooth to the alveolar bone and gingiva by periodontal fibers in an area of cementum which is adjacent to a pathologic pocket. A typical epithelial attachment is described as reforming. The cellular elements that would make reattachment possible are all present in the periodontium; resorption of the bone and rebuilding of new bone with reattachment of new periodontal ligament fibers go on constantly.

Considering this problem from a purely theoretic point of view, if reattachment is to occur, it is necessary that connective tissues remain in contact with the tooth for an appreciable, but as yet undetermined, period of time. Since the cementum lining the pocket is necrotic, cementoclasts must resorb the cementum to a level at which it is viable. Next, cementoblasts must develop to deposit a new layer of cementum which traps ends of connective tissue fibers. Finally, new alveolar bone must be built opposite the newly attached periodontal fibers in response to the stimulus of the periodontal ligament.

Reattachment will not occur as long as inflammation persists in the tissues next to the tooth. Factors interfering with reattachment include the following:

Crevicular epithelium. For reattachment to occur, this epithelium must be curetted away. Since cementum can be deposited only by connective tissue, the presence of epithelium interferes with the reattachment. The fresh bleeding connective tissue surface will form a blood clot in contact with the tooth, which can organize and contribute to reattachment. In certain cases, particularly those with infra-bony pockets, the blood clot is easily protected and healing occurs more easily.

Mobility. During the period of reorganization the tooth must be at least relatively immobile, since motion tends to disturb the healing process and allow any remaining crevicular epithelium to proliferate and reline the pathologic pocket.

Inflammation itself apparently interferes with reattachment, perhaps because cementoblasts cannot develop in areas of inflammation.

Necrotic cementum is also a barrier to reattachment, since new cementum apparently will not be deposited upon cementum that has been in contact with oral fluids and suppuration for an appreciable time.

Other, as yet unknown, factors are also involved. Connective tissue can lie adjacent to cementum for months without being lined by epithelium or establishing a reattachment of the periodontal ligament to tooth.

Provided the condition is not too advanced and therapy is adequate, periodontitis can be arrested, and teeth can be maintained to function almost indefinitely. The inflammatory process gradually subsides; gingival tissues return to normal size, color and contour; the teeth become less mobile, and suppuration and bleeding stops. The depth of the gingival crevice approaches zero, owing to tissue shrinkage or gingivectomy; stippling returns and the case appears normal, even though the gingival tissues and alveolar crest are apical to their original position. In other words, a new steady state is reached, different from the original but compatible with the maintenance of good oral health.

Aggressive Periodontitis

Aggressive periodontitis is a rapidly progressing type of periodontitis that occurs in patients who do not have large accumulations of plaque and calculus. This may be either localized or generalized; replacing the terms localized and generalized juvenile periodontitis and rapidly progressive periodontitis. It has a familial tendency suggesting a genetic predisposition.

This disease appears to be the result of a defect in the immune response rather than plaque and calculus deposition. The disease is specific. Microflora associated with this disease are *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis. P. gingivalis,* and *Bacteriodes forsythus* frequently are detected in the plaque that is present. Other species related are *Capnocytophaga sputigena, Mycoplasma* subspecies and *Spirochetes.*

Several investigators have shown that patients with aggressive periodontitis display functional defects of polymorphonuclear leukocyte, monocytes, or both, but without any systemic manifestations. Because of this, their defensive ability against some of the periodontal pathogens is defective. The bactericidal activity against *Actinobacillus actinomycetemcomitans* is particularly faulty in localized form.

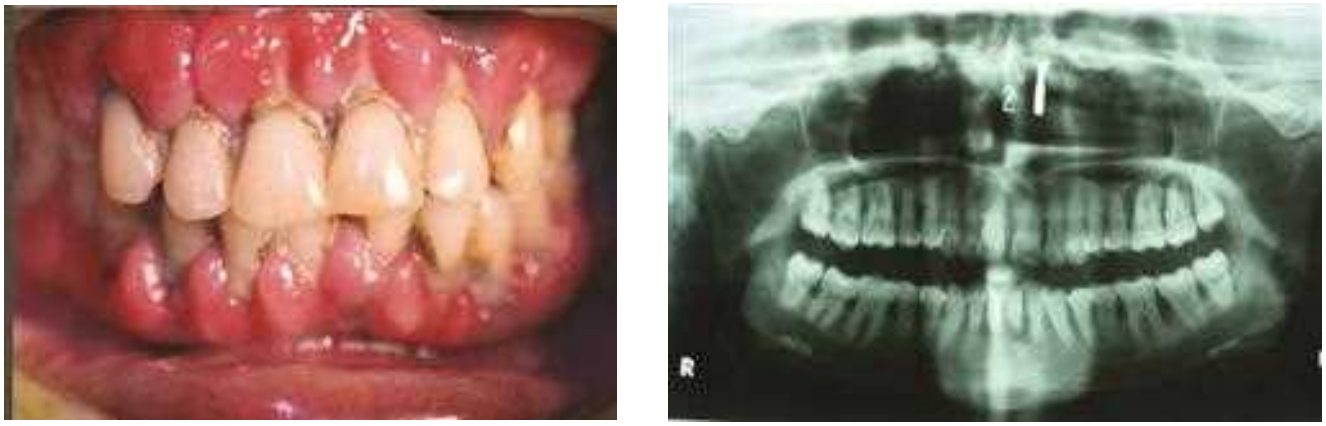
Clinical Features

Localized form. This usually occurs around puberty and has a strong familial tendency. It is localized to the first molars and incisors; there is attachment loss in at least two permanent teeth, one of which is the first molar. A striking feature is the absence of clinical inflammation with minimal local factors despite the presence of a deep periodontal pocket. The rate of alveolar bone loss is considerably higher than in chronic periodontitis. The disease is associated primarily with *A. actinomycetemcomitans*.

Generalized form. This form usually affects patients under 30 years of age. It involves at least three teeth other than the first molar and incisor, and exhibits poor serum antibody response to infecting agents. Many cases represent the localized form which becomes generalized with time. The marked distinction between this and the localized form is the presence of large accumulation of plaque, calculus, and gingival inflammation (Fig. 8-36A). The organism associated with the generalized form is more complex and closely resembles chronic periodontitis.

A definitive diagnosis can be made based on family history, clinical, radiographical, microbiological, and histological examination with leukocyte function tests.

Papillon-Lefèvre syndrome is an autosomal recessive disorder that is characterized by cutaneous and oral manifestations. The characteristic skin lesions consist of keratotic lesions of palmar and plantar surfaces. The oral lesions are characterized by aggressive periodontitis leading to severe



A B

Figure 8-36. Generalized aggressive periodontitis.
The presence of a large amount of plaque, calculus and gingival infection, **(A)**. Loss of bone support involving more than three teeth other than first molars and incisors, **(B)** *(Courtesy of Dr KL Vandhana, Department of Periodontics, College of Dental Sciences, Davanagere).*

destruction of the alveolar bone involving both the deciduous and permanent dentitions. Due to rapid bone loss, mobility and pathological migration occurs, which results in loss of the entire dentition at a much younger age.

Radiographic Features. In the localized form, vertical loss of alveolar bone is seen around the first molar and incisor at around the age of puberty in otherwise healthy patients. An arc-shaped alveolar bone loss extends from the distal surface of the second premolar to the mesial surface of the second molar, and there is widening of the periodontal ligament space (Fig. 8-36B). This 'vertical' pocket formation, with the bone loss often more extensive on one tooth than on an adjacent tooth, differs from the 'horizontal' type of bone loss seen in chronic periodontitis. In chronic periodontitis, many teeth are involved in about the same degree, so that the bone loss appears to be 'horizontal.' In the generalized form, bone loss may range from the involvement of one or two teeth to a maximum number of teeth (Fig. 8-36B).

Histologic Features. These closely resemble the features of chronic periodontitis (Fig. 8.37).

Management. Antibiotics should be administered in combination with mechanical removal of plaque and inflamed periodontal tissues. Periodontal surgery should be performed with prophylactic antibiotic cover and postoperative usage of chlorhexidine mouthrinse. Periodic follow-up is necessary since there is possibility of reinfection.

Figure 8-37. Aggressive periodontitis.
Photomicrograph of an early case. One finds normal width of the periodontal membrane on the distal surface of the tooth on the left and degenerative connective tissue replacing the periodontal ligament on the mesial surface of the tooth on the right. Note also the alveolar bone loss and the lack of inflammation *(Courtesy of Dr B Orban and J Periodontol).*

Necrotizing Ulcerative Periodontitis

Necrotizing ulcerative periodontitis occurs in younger patients than those with chronic periodontitis. This, along with necrotizing ulcerative gingivitis, is grouped as necrotizing periodontal diseases. These diseases may be accompanied by fever, malaise, and lymphadenopathy. Necrotizing ulcerative gingivitis is discussed under gingival diseases since it does not always present with attachment loss. Necrotizing ulcerative periodontitis shows attachment and bone loss and may be associated with immune suppression or malnutrition. Recent reviews of the etiologic and clinical characteristics suggest that necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis represent the same disease with a different degree of clinical manifestations. Immune dysfunction plays a major role and may predispose patients to develop necrotizing ulcerative gingivitis

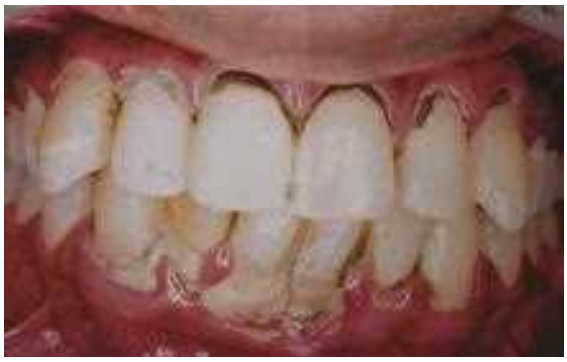


Figure 8-38. Necrotizing ulcer periodontitis in an HIV-positive patient.
(Courtesy of Dr R Saravanakumar, Department of Periodontics, Meenakshi Ammal Dental College, Chennai).

and necrotizing ulcerative periodontitis, especially when associated with an infection of microorganisms such as *Treponema* and *Selenomonas species, Fusobacterium nucleatum, Prevotella intermedia,* and *Porphyromonas gingivalis*.

Necrotizing ulcerative periodontitis may be observed in HIV-positive patients (Fig. 8-38). The CD4+ cell count is below 200 cells/mm in more than 90% of the HIV-infected patients with necrotizing ulcerative periodontitis. In HIV-positive patients, it causes ulceration and necrosis of gingiva with pain and spontaneous bleeding. The exposed underlying bone then undergoes rapid destruction.

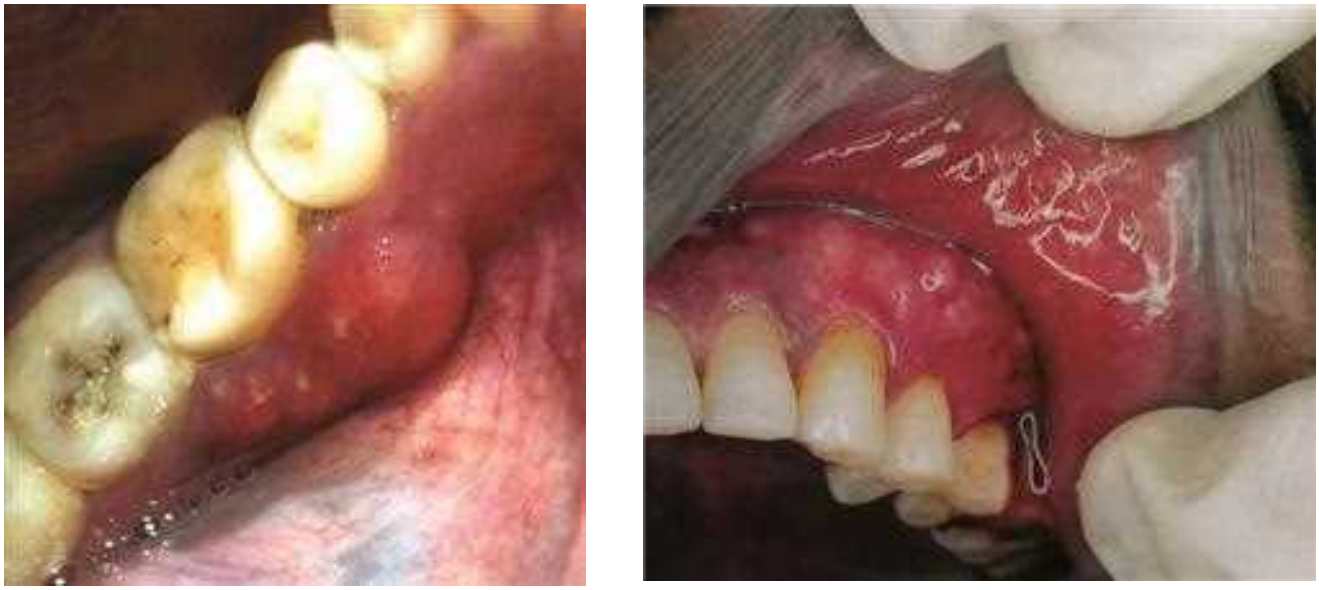
Management and Prognosis. If the underlying immunosuppression and malnutrition is corrected, it usually responds to oral hygiene and antibiotics. Roughly 72.9% of the HIV-infected patients have the cumulative probability of death in 24 months from the time of the diagnosis of necrotizing ulcerative periodontitis.

Lateral Periodontal Abscess
(Lateral abscess)

The lateral periodontal abscess is related directly to a pre-existing periodontal pocket. Precipitating factors include subgingival flora, host resistance, or both. When such a pocket reaches sufficient depth, around 5–8 mm, the soft tissues around the neck of the tooth approximate the tooth so tightly that the orifice of the pocket is occluded. Bacteria multiply in the depth of the pocket and cause enough irritation to form an acute abscess with exudation of pus into this area. A foreign body, particularly food debris, may also lead to abscess formation. This may result in enough swelling to destroy the cortical plate of bone, if it still exists, allow the abscess to balloon the overlying tissues, forming a 'gum boil', or parulis (Fig. 8-39).

Clinical Features. It usually occurs in adults and is rare in children. The most common cause of periodontal abscess is foreign bodies. The acute periodontal abscess will cause the afflicted tooth to be tender to percussion. Pain, foul taste, mobility of the involved tooth, tenderness over the corresponding gingiva, and lymphadenopathy are the other symptoms.

The occurrence of periodontal abscesses of both lateral and periapical types was reported by Dinsdale and Holt in a group of 34 children treated with cortisone for rheumatic fever. The abscesses appeared within two weeks after therapy had been discontinued. The cortisone apparently actuated pre-existing periodontal lesions, but the abscesses were unusual in that pain



A B

Figure 8-39. Periodontal abscess.
(Courtesy of Dr Joshua Sheih,Emmanuel Dental Clinic, Chennai).

was very mild or even absent, and there was no local swelling or cellulitis. Lymph node involvement was also rare. In some cases the only clinical manifestation of the abscess was the release of pus from the neck of a loose deciduous tooth upon pressure. It was noted that the erythrocyte sedimentation rate, which is seldom elevated in normal children with a periodontal abscess, was usually elevated in cortisone treated children with rheumatic fever with a periodontal abscess.

Histologic Features. Microscopically, the abscess resembles an abscess elsewhere. It consists of a central cavity filled with pus walled off on one side by the root of the tooth and on the other by connective tissue; because it is likely that in most instances that the epithelial lining of the crevice would have been destroyed by the inflammatory process.

Treatment of a periodontal abscess is similar to that of an abscess elsewhere. A direct incision, perpendicular to the long axis of the involved tooth, releases pus. If the abscess does not drain spontaneously through the gingival crevice, and if it is not treated, a fistula may develop to release the pus spontaneously onto the mucosal surface (Fig. 8-39B). Careful insertion of a dull probe into the pocket along the tooth will usually induce drainage, and the acute symptoms will subside. The abscess will recur; however, unless the cause is removed and the depth of the pocket is reduced. Cases in which normal tissue contours cannot be developed and maintained, extraction of the tooth is advised after the acute symptoms have subsided.

PERI-IMPLANTITIS

Inflammation of the soft tissues surrounding the osseo integrated implant in function and progressive bone loss is termed as peri-implantitis. It is a multifactorial process. Clinical studies have documented that peri-implantitis may lead to implant failure and loss. Implant failure is usually associated with high degree of plaque accumulation. Bacterial plaque and smoking are the risk factors resulting in implant failure.

Microbial plaque is the major factor which causes inflammation in soft tissue around dental implants. Bacterial infection and biomechanical factors in relation to extra load on implants are the main cause for crestal bone loss around the implants. Gram-negative anaerobic rods, spirochetes and fusiform bacteria are found in higher proportions at peri-implant sites as compared with healthy sites.

Contributory factors include the status of the peri-implant tissue, implant design, degree of roughness, the poor alignment of implant components, external morphology and excessive mechanical load, and oral hygiene.

The response of the gingiva and the peri-implant mucosa to early and more long standing periods of plaque formation has been analyzed. In a study by Berglundh et al (1992), similar amount and composition of the developing plaque that accumulate on the tooth surface were noted around implant segments. Leonhardt et al, in subsequent studies, concluded that the microbial colonization on titanium implant followed the same pattern as that on teeth. Similar observations were made by Pontoriero et al (1994), who concluded that in a given individual, the only soft tissue response to plaque in the mucosa at the site of implant placement is similar to that seen in gingiva around the teeth. With increasing duration of plaque build up, it was noted that the lesions in the peri-implant mucosa expanded more and progressed further apically than gingiva. The composition of the lesion in the two tissues also differed with respect to their content of fibroblasts. The lesion in peri-implant mucosa was found to have a much smaller number of fibroblast than the corresponding compartment in gingiva.

It was also noted that, in the gingival lesion, the amount of tissue destruction that occur during a breakdown phase was more or less compensated by tissue build up which occurred during a subsequent phase of repair. However, in lesion within the peri-implant mucosa, the tissue break down which occurred was not fully recovered by the reparative phase. The small number of fibroblasts present in this lesion may have been unable to produce enough collagen and matrix during the reparative phase. It was concluded that peri-implant mucosa seems less effective than gingiva in encapsulating plaque-associated lesion.

The key bacterial virulence factor for destruction of periodontal tissue is endotoxin, a ubiquitous component of the cell walls of all gram-negative bacteria. Endotoxin-activated macrophages produce proteases that can degrade collagen and proteoglycans, ultimately producing degradation of extracellular matrix. Furthermore, activated macrophages produce the cytokines, interleukin-1 (IL-1) and prostaglandin E2 (PGE2).

The PGE2 produced by endotoxin-activated macrophages and IL-1-activated fibroblasts has as it target, the osteoclast. PGE2 activates osteoclasts, leading to resorption of alveolar bone and results in loss of support. This completes the circuits leading to destruction of soft and hard periodontal tissue.

Clinical Features. Symptoms of peri-implantitis relate to infectious/inflammatory nature of the lesion. Implants showing the signs and symptoms of infectious failure but not yet mobile may be called 'ailing'. An ailing implant displays progressive bone loss and pocketing, but no clinical mobility. A failing implant displays feature similar to the ailing implant, but is refractory to therapy and continues to become worse. The term **ailing** suggests a somewhat more favorable prognosis than the term **failing**. A failed implant is one that is fractured, has been totally refractory to all methods of treatment, or demonstrates clinical mobility or circumferential peri- implant radiolucency.

All failing implants are characterized by mobility and peri-implant radiolucency. Implants failing as a result of infection are additionally characterized by pain, bleeding on probing, suppuration, increased probing depth, high gingival and plaque indices, attachment loss, and granulomatous tissue on removal. Implants failing for traumatic reasons (surgical trauma, faulty design of prostheses, or overloading) may be painful, but otherwise lack the additional characteristics associated with infectious failure

Few cases present with the proliferation of gingival tissues in and around peri-implant area or inflammation of surrounding soft tissue as redness are called **Peri-implant mucositis**. Various indices like plaque index, gingival index, bleeding index, probing pocket depth, and probing attachment level are used frequently to evaluate the health of soft tissues around implants.

Intra-oral periapical radiographs are used to determine the peri-implant bone status. Radiographically there is vertical destruction of crestal bone.

Histologic Features. Large number of polymorphonuclear leukocytes are noted in the peri-implant lesion. In comparison with the periodontitis, these lesions lack an epithelial lining between lesion and biofilm. These lesions are poorly encapsulated, extend into the marginal bone tissue, and if allowed to progress may lead to the loss of implant. Peri-implantitis is associated with opportunistic periodontal pathogens such as *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Bacteroides forsythus, Prevotella intermedia, Peptostreptococcus micros and Fusobacterium nucleatum.* Proliferation of these opportunistic pathogens results in an inflammatory response and may lead to peri-implant infection. This emphasizes the importance of establishment of healthy periodontal condition prior to placement of implant, and the importance of a regular maintenance program thereafter.

Management. Combination of systemic antibiotic administration with meticulous removal of biofilm from the contaminated implant surface is effective in management of peri-implantitis. Local therapies which include mechanical brushing of the surface, use of air powder abrasives, application of chemicals like citric acid, chlorhexidine and delmopinol are effective in cleaning the titanium surface to allow soft tissue healing and bone fill.

The goal of therapy is suppression of opportunistic pathogens associated with infection, and establishment of a local environment and microflora compatible with health.

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CHAPTER 9

Dental Caries

■ B SIVAPATHASUNDHARAM AND AR RAGHU

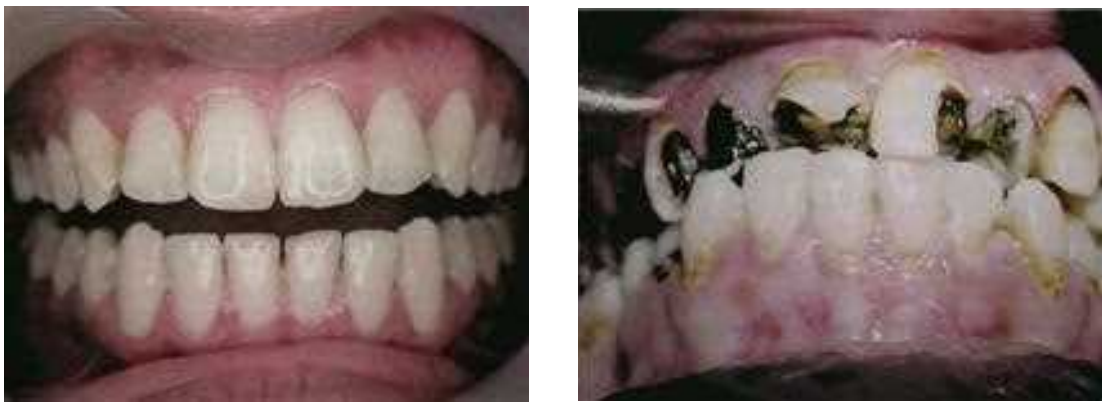
CHAPTER OUTLINE

Dental caries is an irreversible microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitations. The word caries is derived from the Latin word meaning 'rot' or 'decay'. It is a complex and dynamic process where a multitude of factors initiate and influence the progression of disease. Although effective methods are known for prevention and management of dental caries, it is a major health problem with manifestations persisting throughout life despite treatment. It is seen in all geographic areas in the world and affects persons of both genders in all races, all socioeconomic strata, and every age group. Some stay 'caries-free' for unknown reasons (Fig. 9-1). Despite extensive studies for more than a century, many aspects of etiology are still obscure, and efforts at prevention have been partially successful.

EPIDEMIOLOGY OF DENTAL CARIES

Caries in Prehistoric Man

Dental caries is probably a disease of modern civilization. Anthropologic studies of von Lenhossek revealed that the dolichocephalic skulls of men from preneolithic periods (12,000 BC) did not exhibit dental caries, but brachycephalic skulls of the neolithic period (12,000–3000 BC) contained carious teeth. Apparently the carious lesions were found at or just below the contact areas and an increased frequency of caries at the cementoenamel junction was noted.



A B

Figure 9-1. The caries-resistant and caries-susceptible mouth.
(Courtesy of A, Dr S Rohini, Chennai and B, Dr N Bhargavi, Department of Conservative Dentistry, Meenakshi Ammal Dental College, Chennai).

Caries Incidence in Modern Societies

By about the 17th century, there was a significant increase in the total caries experience and a smaller increase in the number of carious lesions involving the interproximal contact areas of teeth, characteristic of the pattern and occurrence of caries in modern population.

Extensive studies on the incidence of dental caries from various geographic areas have illustrated the apparent influence of civilization on dental disease. Mellanby in 1934 reviewed the literature on caries in existing primitive races and noted that the incidence was invariably less than that in modern man suggesting isolated populations that have not acquired the dietary habits of modern, industrialized man retain a relative freedom from dental caries. Native population living in the North West territories of Canada, Alaska and Greenland who consumed native food, had a lower evidence of carious lesion (0.1%) compared to those living at trading posts (13%). A comparable effect of diet upon caries was demonstrated by Mellanby in studies on natives of Southern Rhodesia. The determinants of the carious process are essentially local and limited to the oral cavity. Although there may be a certain degree of racial resistance to dental caries, dietary factor appears to be more significant, especially since caries incidence is increased by contact with 'civilized' food.

Comprehensive Assessment of Dental Caries Prevalence in Modern-day Population

While dental caries is all pervading in highly industrialized societies, the caries experience varies greatly among countries and even within a country. The difference in caries rates noted in different parts of the world are extreme from rates fewer than one decayed, missing and filled (DMF) tooth per person at all ages up to 39 years in Ethiopia (Littleton, 1963) to 60 times greater in Alaska-Aleuts (Russel et al, 1961). Findings from the Interdepartmental Committee on Nutrition for National Defence (ICNND) and WHO studies (Barmes, 1981) indicate that caries prevalence follows definite regional patterns. It is generally lowest (0.5–1.7 DMF) in Asian and African countries and highest (12–18 DMF) in America and other Western countries. Consistently, low to moderate caries rates were found in populations of the Indo-Chinese peninsula, Malaysia, central and southern Thailand, Burma, South Vietnam, mainland China, Taiwan, India and New Guinea.

Generally, highly industrialized countries have the highest caries indices with decayed, missing, and filled teeth (DMFT) of approximately 4.5. However, within this large group of countries a very high caries pattern of over 5.6 DMFT occurs in New Zealand, Australia, Brazil, and Argentina.

DMF AND def INDEX

The most commonly employed method to measure the extent of previous damage to permanent dentition is by a measure known as the DMF index. The designation DMF (T) is used to denote decayed, missing, and filled teeth; DMF(S) denotes decayed, missing and filled surfaces in permanent teeth and therefore takes into account the number of surfaces attacked on each tooth. A similar index def (t) or def (s) index is used for primary dentition. The DMF/def index can be used to quantify both caries prevalence and caries incidence in a given population. It is an arithmetic index of the cumulative caries attack in a population.

A commonly used modified form of this test is the caries increment, which refers to the number of new carious lesions occurring in a specified time interval, either for an individual or averaged over a population. The assessment of the caries increment involves at least two examinations—one at the beginning and one at the end of the period in question. In children, primary teeth may be lost due to natural exfoliation and, for the purpose of the def index, it is essential that the examiner designates as missing only those teeth that are lost due to caries.

Factors Affecting Caries Prevalence

Race. Some studies show remarkable differences in the caries experience between races. American blacks and whites, living in the same geographic areas under similar conditions, offer an excellent opportunity for comparison. Investigations indicate that the blacks have fewer carious lesions than the whites. Most studies concerning other races have been relatively unsatisfactory because of complicating factors such as differences in diet or exposure to fluoride, which tend to mask any differences due to racial background. Nevertheless, there is some evidence to indicate that blacks, Chinese, and East Indians have considerably less caries than American Whites. The English have a higher caries incidence than Italians, Russians, and Chinese.

Age. Carious lesions that result in cavitation are irreversible and therefore, cumulative with age. There is a strong correlation between age and DMF indices. Several studies have shown that by the age of 6 years, about 20% of children have experienced dental caries in their dentition and a DMFT of 0.5 can be expected. By the age of 12 years, 90% of children would have experienced a DMFT of approximately 5.5. The decayed, missing and filled surface (DMFS) accelerates at a greater rate than the DMFT beyond the age of eight years. By the age 12, an average DMFS of 7.5 is seen in most populations. In general, other reports of caries prevalence among children in various parts of the world show rates that seem to be comparable to those cited here. Another common element is that children from families in lower socioeconomic groups consistently have greater caries prevalence than their peers from families at a higher socioeconomic level.

Gender. Studies indicate that the total caries experience in permanent teeth is greater in females than in males of the same age. This is attributable largely to the fact that the teeth of girls erupt at an earlier age. This time difference is particularly significant during the formative years because teeth have been shown to be maximally susceptible to dental

caries immediately after eruption since, the chemical structure of teeth in the immediate post eruptive stage is suboptimal in terms of caries resistance. As teeth are exposed to saliva and constituents in the diet, the outer layers of the tooth take up additional minerals from the oral environment in a process known as posteruptive maturation. This maturation process confers a greater resistance to dental caries on the tooth.

Familial. Siblings of individuals with high caries susceptibility are also generally caries active, whereas siblings of caries immune individuals generally exhibit low caries rates. Children of parents with a low caries experience also tend to have low caries; the converse is true for children whose parents have a high caries rate (Garn et al, 1976). Studies of the dental caries experience in monozygotic and dizygotic twins indicate that concordance for carious sites in monozygotic twins is much higher than in dizygotic twin pairs.

Current Trends in Caries Incidence

Significant data have been presented since the National Caries Program, USA in 1979–80 to substantiate numerous observations that there has been marked improvement in dental health as measured by prevalence of dental caries, especially in children and young adults, throughout the 'civilized Western world'. Especially impressive was the increase in the percentage of children classified as caries-free in their permanent dentition. These changes had occurred in the absence of both fluoridation and organized preventive programs. This decrease in caries prevalence is also seen in England, Denmark, Ireland, the Netherlands, New Zealand, Norway, Scotland, and Sweden. A substantial decrease in the prevalence of dental caries has been reported from less developed countries. The cause for this widespread decline in the prevalence of dental caries is multifactorial. In some instances, communal water fluoridation has been present in the areas studied and in other cases organized preventive dentistry programs were available.

However, the time period involved in most of these studies coincides with the introduction and increased utilization of fluoride dentifrices and dietary fluoride supplements, as well as an increased awareness of the importance of oral health. The very limited studies available give no evidence that there is any change; for example, in the pervasiveness of *Streptococcus mutans* or any changes in dominant serotypes. Emphasis on improved physical health through food, exercise, and decreased carbohydrate consumption all may be the factors that have led to this decline.

ETIOLOGY OF DENTAL CARIES

The etiology of dental caries is generally agreed to be a complex problem complicated by many indirect factors that obscure the direct cause or causes. There is no universally accepted opinion for the etiology of dental caries. Numerous references on dental caries, including early theories attempting to explain its etiology, have been found in recorded history of ancient people. However, many theories have evolved through years of investigation and observation; the acidogenic theory of Miller (Miller's chemico-parasitic theory), the proteolytic theory and the proteolysis chelation theory, are among those which have stood the test of time.

THE EARLY THEORIES

The Legend of Worms. The earliest reference to tooth decay is probably from the ancient Sumerian text known as the 'Legend of Worms' from about 5,000 BC. The idea that caries is caused by worms was possibly prevalent for a long time as evident from the writings of Homer who made a reference to worms as the cause of toothache.

Endogenous Theories. Keeping with the humoral theory of Greek physicians, dental caries was thought to be produced by internal action of acids and corroding humors. Along with this, the early Greek physicians such as Hippocrates, Celsus, and Galen, proposed the vital theory of tooth decay, which postulated that tooth decay originated, like a bone gangrene, from within the tooth itself.

Chemical Theory. Parmly in 1820s observed that dental decay affected externally, not internally, as had been thought previously. It was proposed that an unidentified 'chymal agent' was responsible for caries. This was further supported by Robertson in 1835 who proposed that dental decay was caused by acid formed by fermentation of food particles around the teeth.

Parasitic Theory. The first to relate microorganisms to caries on a causative basis as early as 1843 was Erdl who described filamentous organisms in the membrane removed from teeth. Shortly thereafter, Ficnus in 1847, a German physician in Dresden, attributed dental caries to 'denticolae' the generic term he proposed for decay related microorganisms. Leber and Rottenstein, two German physicians, disseminated the idea that dental caries commenced as a chemical process but that living microorganisms continued the disintegration in both enamel and dentin. In addition to these observations, Clark (1871, 1879), Tomes (1873) and Magitot (1878) concurred that bacteria were essential to caries, although they suggested an exogenous source of the acids. In 1880, Underwood and Miller presented a septic theory with the hypothesis that acid capable of causing decalcification was produced by bacteria feeding on the organic fibrils of dentin. They reported sections of decayed dentin having micrococci as well as oval and rod shaped forms.

MILLER'S CHEMICO-PARASITIC THEORY OR THE ACIDOGENIC THEORY

The chemico-parasitic theory is a blend of the above mentioned two theories. Willoughby D Miller, an American who was working at the University of Berlin, is probably the best known of the early investigators on dental caries. He published extensively on the results of his studies, beginning in 1882, which culminated in the hypothesis, "Dental decay is a chemico-parasitic process consisting of two stages, the

decalcification of enamel, which results in its total destruction and the decalcification of dentin as a preliminary stage, followed by dissolution of the softened residue. In case of enamel; however, the second stage is practically wanting, the decalcification of enamel signifying its total destruction". The acid, which affects this primary decalcification, is derived from the fermentation of starches and sugar lodged in the retaining centers of the teeth. Miller found that bread, meat and sugar incubated *in vitro* with saliva at body temperature, produced enough acid within 48 hours to decalcify sound dentin. Subsequently, he isolated numerous microorganisms from the oral cavity, many of which were acidogenic and some were proteolytic. Since a number of these bacterial forms were capable of forming lactic acid, Miller believed that caries was not caused by any single organism, but rather by a variety of microorganisms. He assigned an essential role to three factors in the caries process: the oral microorganisms in acid production and proteolysis; the carbohydrate substrate; and the acid which causes dissolution of tooth minerals. Miller's chemico-parasitic theory is the backbone of current knowledge and understanding of the etiology of dental caries.

However, Miller's chemico-parasitic theory could not explain the predilection of specific sites on a tooth to dental caries and the initiation of smooth surfaces. Also, why some populations are caries-free and the phenomenon of arrested caries. The concept of dental plaque adhering to teeth and serving to localize bacterial enzymatic activity was proposed later in 1897 by Williams. This theory has been accepted by majority of investigators in a form essentially unchanged since its inception. The bulk of scientific evidence does implicate carbohydrates, oral microorganisms and acids, and for this reason, these deserve further consideration.

Miller's chemico-parasitic theory or acidogenic theory

Theory: Caries is caused by acids produced by microorganisms of the mouth

Dental decay is a chemico-parasitic process consisting of two stages:

- Decalcification of enamel and dentin (preliminary stage)
- Dissolution of the softened residue (subsequent stage)

Acids resulting in primary decalcification are produced by the fermentation of starches and sugar from the retaining centers of teeth.

Role of Carbohydrates

Reference has been made previously to the finding that members of isolated primitive societies who had a relatively low caries index manifested a remarkable increase in caries incidence after exposure to refined diets. The presence of readily fermentable carbohydrates has been thought to be responsible for their loss of caries resistance.

The early studies of Miller showed that when teeth were incubated in mixtures of saliva and bread or sugar, decalcification occurred. There was no effect on the teeth when meat or fat was used in place of the carbohydrate. Both cane sugar and cooked starches produced acid, but little acid was formed when raw starches were substituted. Volker and Pinkerton reported the production of similar quantities of acid from mixtures of either sucrose or starch incubated with saliva with no difference in acid production between raw and refined sugarcane. The etiology of dental caries involves interplay between oral bacteria, local carbohydrates and the tooth surface that may be shown as follows: Bacteria + sugars + teeth → organic acids → caries.

The cariogenic carbohydrates are dietary in origin, since uncontaminated human saliva contains only negligible amounts regardless of the blood sugar level. Salivary carbohydrates are bound to proteins and other compounds, and are not readily available for microbial degradation. The cariogenicity of a dietary carbohydrate varies with the frequency of ingestion, physical form, chemical composition, route of administration and presence of other food constituents. Sticky, solid carbohydrates, soft retentive foods those that are cleared slowly, monosaccharides and disaccharides are more caries-producing. Plaque organisms produce little acid from the sugar alcohols, sorbitol, and mannitol. Glucose or sucrose fed entirely by stomach tube or intravenously, does not contribute to decay as they are unavailable for microbial breakdown. Meals high in fat, protein or salt reduce the oral retentiveness of carbohydrates.

Role of Microorganisms

Miller demonstrated the presence of microorganisms within the tubules of decayed teeth. These were mainly cocci and leptothrix, as he called them, and laid the foundation for the role of acids elaborated by bacteria in caries production. In 1900, Goadby isolated a gram-positive bacillus from carious dentin and termed it *B. necrodentalis*. These, he concluded, played a role in decalcification of both enamel and dentin. Later he changed his views, stating that certain streptococci were the active cause of caries. Later in 1922, McIntosh, James and Lazarus-Barlow were concerned with microorganisms capable of lowering the pH to the degree that the enamel was softened. From carious dentin they isolated bacteria which they called *Bacillus acidophilus odontolyticus*. Around the same time, Clarke in Great Britain isolated a streptococcus from teeth that was found to be in the early stages of the disease. In 1924, he described a new streptococcus species, *S. mutans*, which was almost always isolated from carious lesions in the teeth of British patients. Although the work was confirmed three years later by McLean, scientific interest in *S. mutans* lay dormant until its rediscovery in the mid 1960s.

Many of the earlier workers focused attention on *L. acidophilus* because it was found with such frequency in caries-susceptible persons that it came to be regarded as of etiologic importance. In 1925, Bunting and Palmerlee reported the bacillary forms in every initial lesion of caries similar to those described by McIntosh and they termed them *B. acidophilus*. Bunting stated in 1928, so definite is

this correlation between *B. acidophilus* and dental caries that, in the opinion of this group, the presence or absence of *B. acidophilus* in the mouth constitutes a definite criterion of the activity of dental caries that is more accurate than any clinical estimation could be. Furthermore, it was noted that there was a spontaneous cessation of caries coincident with the disappearance of *B. acidophilus* from the mouth, either from prophylactic, therapeutic or dietetic control.

Bunting, Nickerson and Hard carried out extensive studies on *B. acidophilus* and reported that it was almost universally absent in the mouths of caries-immune persons, but was usually present in the mouths of caries-susceptible persons. Similar findings were reported in 1927 by Jay and Voorhees, who also found that the presence of *L. acidophilus* in persons without active caries was often a presage of the development of cavities some months later. Jay reported the isolation of 12 strains of *Leptothrix* in 1927, but doubted their importance in the carious process even though they produced acid from carbohydrates.

Between this period and the 1940s, numerous studies were carried out in attempts to confirm or deny the existence of a microorganism responsible for dental caries. Harrison observed streptococci to predominate on the surfaces of non-carious rat molars, about half of the strains being acidogenic. On the other hand, in rats with carious lesions, the surface flora consisted primarily of lactobacilli. Microorganisms isolated from the deeper carious cavities were mainly acidogenic streptococci and he thus concluded that there was an apparent relationship of lactobacilli with initial caries and of streptococci with more advanced lesions of dentin. Florestano, in 1942, cultured organisms from the saliva of carious and noncarious persons and studied their acidogenic potential. Aciduric streptococci and staphylococci were isolated from both the groups. Their acid production and presence in large numbers suggested a role in dental caries equal to that of lactobacilli. Bacteriologic studies in recent years have helped clarify the role of various organisms in the etiology of dental caries. Considerable emphasis has been placed on the various diet-bacterial interactions, which are involved in lesion development on different tooth surfaces. Specific microorganisms as well as combinations of microorganisms, including *Lactobacillus, S. mutans, Actinomyces* species and others, have been studied. Although there may be disagreement as to specifics, there is little doubt that bacteria are indispensable to the production of caries. One or more organisms are implicated in the initiation of caries, while other distinctly different organisms may influence the progression of the disease. Also, there is good evidence that different diet–bacterial interactions are involved in root surface and coronal caries, and they may represent two different diseases from the ecological and microbiological point of view.

In 1960, Keyes demonstrated that under certain laboratory conditions, dental caries in hamsters and rats could be considered an infectious and transmissible disease and therefore subject to those biologic principles which govern any infectious process. Fitzgerald and Keyes showed that even in a so-called caries-inactive strain of hamster, oral inoculation of certain pure cultures of streptococci isolated from hamster caries would induce the typical picture of active dental caries. The caries-inactive strain of hamster was found to have a noncariogenic microflora. These findings have led to interesting speculation about the importance of streptococci in the etiology of dental caries.

Microbial Flora and Dental Caries

It is uniformly agreed that caries cannot occur without microorganisms. Several organisms have been found capable of inducing carious lesions when used as monocontaminants in gnotobiotic (germ-free) rats. These include the mutans group of streptococci, a *Streptococcus salivarius* strain, *Streptococcus mitior, Streptococcus milleri, Streptococcus oralis, Streptococcus sanguis* (different strains), *Peptostreptococcus intermedius*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Actinomyces viscosus* and *Actinomyces naeslundii*. In addition, in the same animal system, some streptococcis and lactobacilli such as *Lactobacillus fermentum* and *Streptococcus lactis*, were not able to induce caries, suggesting that not all organisms are cariogenic, at the same time caries will not occur even in the complete absence of microorganisms. Different organisms display certain selectivity for the tooth surface they localize and attack (Table 9-1).

A wide variety of organisms are able to initiate pit and fissure caries as they colonize in these retentive areas. A limited number of organisms have proved to colonize smooth surfaces and *S. mutans* is very significant in this respect. Some of the organisms involved in root caries are different from those in other smooth surface lesions because the initial lesion involves the cementum or dentin and not enamel. Bacteriological sampling of plaque covering caries of the root surfaces has yielded predominantly *Actinomyces viscosus*. However, other studies have found no difference in the prevalence of *A. viscosus* on carious versus intact root surface. Strains of *Nocardia* and *S. sanguis*, besides causing enamel caries may, at times, also cause root caries. While in the deep dentinal caries, the predominant organism is *Lactobacillus*, the exact extent to which these organisms participate in human disease is yet to be explored.

Studies in humans are largely based on the mathematical relationship between various streptococci, lactobacilli and dental

Table 9-1: Localization of carious microflora in animal models and its significance to humans

Type of caries	Microorganism	Human
Pit and fissure	*S. mutans* *S. sanguis* Lactobacillus species Actinomyces species	Very significant Uncertain Very significant By chance
Smooth surface	*S. mutans* *S. salivarius*	Very significant By chance
Root surface	*A. viscosus* *A. naeslundii* *S. mutans* *S. sanguis*	Very significant Very significant Significant By chance
Deep dentinal caries	Lactobacilli species *A. naeslundii* Other filamentous rods	Very significant Very significant Very significant

caries. Available data strongly suggest an active involvement of *S. mutans* in caries initiation. Strains of *S. mutans* isolated from humans have proved to be cariogenic in animal studies and *S. mutans* can almost always be found in plaques over incipient lesions involving pits and fissures or smooth tooth surfaces. Not all studies support a unique or sole relationship between *S. mutans* and the initiation of caries in humans. The characteristics and properties of some known potentially cariogenic plaque microorganisms are discussed.

Lactobacilli. Lactobacilli are gram-positive, nonspore forming rods that grow best under microaerophilic conditions. The isolation of lactobacilli has been made possible by the use of a selective agar medium (Rogosa) which suppresses the growth of most other organisms by its low pH. The genus *Lactobacillus* includes many species and represents about 1% of oral flora. Among the homofermentative isolates, *L. casei* and *L. acidophilus* are the most common, while hetero fermentative members mostly include, *L. fermentum* and *L. brevis*. The idea that lactobacilli are important in the carious process was owing to the fact that they are both acidogenic as well as aciduric and could therefore multiply in the low pH of plaque and carious lesions. Lactobacilli as a universal etiologic agent in dental caries is; however, questioned because the amount of acid formed by lactobacilli present in plaque is insignificant in comparison to that produced by other acidogenic oral organisms. The occurrence of lactobacilli in carious lesions and their increased numbers in plaque and saliva does not necessarily establish their causative role although they could be secondary invaders. This possibility is supported by the observations that lactobacilli are not detectable in plaques covering white spot lesions on smooth surfaces and their predominant sites are in deep fissures and in deep dentinal lesions, favoring their retention.

Oral Actinomyces. These are gram-positive, filamentous organisms that include *A. naeslundii* and *A. viscosus* which are facultative anaerobes and *A. israelii* and *A. odontolyticus* which are strict anaerobes. Actinomyces and Rothia species are found in human dental plaque in significant numbers and they have been isolated in high proportions from decayed root surfaces of human teeth. *A. viscosus* are acidogenic bacteria which, in addition to having intracellular polysaccharide stores, also form extracellular levans and heteropolysaccharides consisting of hexosamine and hexose. It is the predominant flora of plaque overlying root lesions, but its role in initiating these lesions is difficult to assess because *A. viscosus* is also found on sound root surfaces.

Veillonella. This is one of the gram-negative cocci commonly found in plaque. Interest in this group relates to its possible anticariogenicity. These organisms lack key enzymes involved in glycolysis and the hexose monophosphate shunt, and therefore do not utilize sugars as an energy source. Veillonella utilizes lactic acid by converting it to propionic and other weak acids. By this reaction, the stronger lactic acid with a pKa of 3.08 is converted to a less dissociated acid of pKa in the range of 4.7. It has also been observed that the veillonella strains increase in number in dental plaque after lactic acid producing organisms have first colonized. A positive correlation between veillonella and caries activity has been reported by some but contradicted by others.

Oral Streptococci. Of all the oral bacteria, streptococci have been studied most comprehensively. The most important species found in the oral cavity include: *S. mutans, S. sanguis, S. mitior, S. salivarius*, and *S. milleri.*

S. mutans. A Streptococcus that prevailed in many human carious lesions and first isolated in 1924 by Clarke was termed *Streptococcus mutans*. These bacteria are catalase negative, gram-positive cocci forming short to medium chains. On mitis salivarius agar, they grow as highly convex colonies. Unlike other oral streptococci, most strains of *S.mutans* can be selectively cultured in mitis salivarius agar containing 20% sucrose and 0.2% units/ml of bacitracin. Characteristically, *S. mutans* synthesizes insoluble polysaccharides from sucrose. It is homofermentative and is more aciduric than other oral streptococci.

Cariogenic strains of *S. mutans* contain a lysogenic bacteriophage which has not been isolated from non-cariogenic strains. Non-cariogenic strains are unable to adhere to glass and have decreased ability to form insoluble polysaccharides. In the oral cavity, *S. mutans* does not colonize the mouths of infants prior to the eruption of teeth. Likewise, it disappears from the mouth following the extraction of all teeth. Infants most likely become infected from their parents or from other individuals with whom they have frequent contact since these organisms are not found free living in nature and have only been isolated from humans and certain animals.

S. mutans forms a homogeneous group based on several phenotypic characteristics. However, based on nucleic acid base content and hybridization, *S. mutans* has been divided into five genotypes as *S. mutans*, *S. rattus*, *S. sobrinus*, *S. cricetus*, and *S. ferus*. Among, these, *S. mutans* and *S. sobrinus* are most commonly found in human plaque. *S. mutans* strains have also been divided into eight serotypes designated 'a' through 'h'. The specific antigen for each serotype represents cell-wall constituents which have been isolated and chemically characterized as polysaccharides. Theoretical possibilities exist for inhibiting glucosyltransferase of several serotypes by an antiserum against purified glucose transferase of one single serotype.

Metabolism of *S. mutans*. The most important substrate for the involvement of *S. mutans* in the caries process is the disaccharide sucrose. Different pathways by which *S. mutans* may dissimilate sucrose, are by conversion of sucrose to adhesive extracellular carbohydrate polymers by cell bound and extracellular enzymes. The transport of sucrose into the cell interior is accompanied by direct phosphorylation for energy utilization through the glycolytic pathway, leading to lactic acid production and degradation of sucrose to free glucose and fructose by invertase. The intermediary metabolites from sucrose enter the glycolytic cycle or may be utilized in intracellular polymer synthesis in order to provide a reservoir for energy.

Most of the sucrose metabolized by *S. mutans* is utilized for its energy requirements and results in the production of lactic acid. Sucrose, which does not enter the cell, may be used for the extracellular synthesis of carbohydrate polymers. The ability of *S. mutans* to form adhesive plaques could explain its specific dependence on sucrose rather than other dietary carbohydrates.

It must be emphasized that *S. mutans* polymerizes the glucose and the fructose moieties of sucrose to synthesize glucans and fructans, which are two types of extracellular polymers. The enzymes responsible for the synthesis of extracellular glucans and fructans are called **glucosyl-** and **fructosyltransferases**, respectively. Synthesis of glucans from sucrose has been considered for several years to be the essential glue in *S. mutans* attachment to enamel and subsequent plaque formation. Two of the homopolymers of glucans are dextran and mutan. Mutan is an important constituent of fibrillar plaque matrix and is less soluble and more resistant to enzymatic attack than dextran.

Besides functioning as a resistant structural matrix, insoluble extracellular polysaccharides can act as a diffusion barrier. The transport of metabolites and salivary buffers into the plaque and the diffusion of acid out of the plaque may be affected by glucan. Besides producing glucan, certain oral bacteria can degrade this polymer and utilize it as a carbon source.

Fructans, on the other hand, unlike the mutan homopolymer of glucan, are generally soluble and can be degraded by plaque bacteria, thus serving as a reservoir of fermentable sugars for oral bacteria. A group of fructans produced by bacteria or created by breaking down other kinds of plant fructans are called levan beta 2, 6. Levans are both more soluble and more readily catabolized than glucans. Since levan hydrolysis is rapid, it may function as a short-term reservoir for the sustenance of bacterial anaerobic glycolysis in times of relative unavailability of dietary carbohydrate. Current opinion holds that this plaque component plays only a small role in the cariogenic potential of plaque because of the rapidity of its hydrolysis and the fact that it is purportedly not sticky.

Electron microscopic observation of the plaque formed by *S. mutans* reveals two types of extracellular products: a globular component, representing the water soluble, and a fibrillar component, the water insoluble glucan.

Lipoteichoic acid is another extracellular polymer that is found in cultures of *S. mutans*. These highly negatively charged compounds might contribute to the adhesiveness of bacteria. In addition to this, *S. mutans* strains have an ability to store intracellular glycogen amylopectin type polysaccharide, which provides a reservoir of substrate and enables prolonged periods of increased metabolic activity. Intracellular glycogen and extracellular polysaccharides serve as substrate reservoirs, which the organism may utilize for energy production, as the exogenous supplies of readily metabolized carbohydrate are depleted. In this fashion, both types of polysaccharides may play a role in the survival of organisms and in their potential to prolong acid production via glycolysis well beyond meal time.

It is known that sucrose-adapted *S. mutans* strains possess significant levels of invertase activity, and this enzyme is known to hydrolyze sucrose intracellularly to free glucose and fructose. Invertase is activated by inorganic phosphate and since phosphate accumulation is coupled with acid production, it is probable that one of the several mechanisms by which sucrose degradation is regulated in *S. mutans* is the activation of invertase by inorganic phosphate.

***S. sanguis*.** This is consistently present in plaque obtained from both carious and noncarious sites. Caries from this strain occurs primarily in occlusal fissures and is significantly less extensive than *S. mutans*, as it has low cariogenicity in experimental animals. This α-hemolytic Streptococcus species was originally isolated from patients with subacute bacterial endocarditis. The serology of *S. sanguis* is complex but they are easily identifiable on sucrose-containing media as small, firm colonies and form extracellular polysaccharides in sucrose broth.

***S. salivarius*.** This species is found in tongue, throat and in saliva but not in high numbers in dental plaque. It adheres well to epithelial surfaces but not to hard tissues and produces copious amounts of the water-soluble polymer of fructose called levan. Even though some strains of this organism have been shown to produce caries in experimental animals, their role in human dental caries is of minimal significance.

***S. mitior*.** This is one of the most commonly isolated bacteria in the oral cavity. It produces soft, round and black-brown colonies on mitis salivarius agar. Along with *S. sanguis* it forms the most predominant organisms in dental plaque. However, its significance in human caries is assumed to be very minor.

Based on these observations from earlier studies, it is certain that bacteria, principally the gram-positive cocci and gram-positive pleomorphic rods, are essential for the development of caries. There is also a significant variation in the microbial flora associated with pit and fissure caries, smooth surface caries, root caries and deep dentinal caries. Since several factors may influence the formation, composition and metabolism of dental plaque, human dental caries may also be considered to be a diverse microbiologic disease. In the past, the total plaque was viewed as a pathogenic structure which had to be eliminated or reduced if caries was to be prevented. The present available data indicates that the qualitative nature of the flora in plaque determines the metabolism and the potential for caries production. This view is termed the **Specific Plaque Hypothesis** (Loesche, 1982), and according to this hypothesis, most but not necessarily all carious lesions are due to specific bacterial species. This concept suggests that cariogenesis is a specific bacterial infection and methods implemented for its elimination are more than just reduction of total plaque.

Role of Acids

The exact mechanism of carbohydrate degradation to form acids in the oral cavity by bacterial action is not known. It probably occurs through enzymatic breakdown of the sugar, and the acids formed are chiefly lactic acid, although others such as butyric acid are also formed. Since acid production is dependent upon a series of enzyme systems, methods of

decreasing this acid formation by interference with certain enzymes could be an effective strategy to decrease caries.

The presence of acids in the oral cavity is of less significance than the localization of acids upon the tooth surface. This suggests a mechanism for holding acids, at a given point, for relatively long periods. Dental plaque fulfils this function. Acid production from carbohydrates have been extensively studied in human plaque. Generally, monosaccharides and disaccharides result in the greatest fall in plaque pH. On the other hand, acid formation is slower upon application of cooked starch. This is possibly because of the slower diffusion of larger starch molecules and acid production that occurs from the comparatively low concentration of maltose released from starch. Fermentation or glycolysis are ways of anaerobic catabolism of carbohydrates, which predominates in plaque and leads to acid production. The end products of glycolysis have the same empirical formulas as the starting substrate in that one molecule of glucose breaks into two molecules of lactic acid.

Organisms such as streptococci and lactobacilli ferment sugars, which produce 90% or more lactic acid as the end product; such bacteria are called homofermentative. Heterofermentatives produce a mixture of metabolites including other organic acids such as propionic, butyric, succinic, and ethanol using divergent metabolic pathways. For example, pyruvic acid, an intermediate metabolite in glycolysis, may be rendered to lactic acid by the enzyme lactic acid dehydrogenase or split into formic acid and acetyl coA by the enzyme pyruvate formate lyase. The acetyl coA is then converted into acetate and ethanol. The proportion of lactic acid or other organic acids formed by plaque may be markedly affected by growth conditions and by the bacterial types present. For example acid accumulation by *S. mutans* is substantially greater than by *S. sanguis* or *S. mitis* and *Actinomyces* are homolactic in anaerobic conditions but in the presence of carbon dioxide the fermentation is heterolactic with formate, acetate, lactate and succinate as their products.

Role of the Dental Plaque

Dental plaque (microbial plaque or bacterial plaque) is a structure of vital significance demonstrated for the first time in histologic preparations by Williams in 1897. It has been recognized for many years as a contributory factor to at least the initiation of the carious lesion.

Although Miller emphasized the role of foods and the acids produced by their bacterial degradation, he thought that the plaque protected enamel against attack by a carious process. In contrast, GV Black in 1899 regarded plaque to be important in the caries process and described it as "The gelatinous plaque of the caries fungus is a thin, transparent film that usually escapes observation, and which is revealed only by careful search. Neither it is the thick mass of material alba so frequently found upon the teeth, nor is the whitish gummy material known as sordes, which is often prominent in fevers and often present in the mouth in smaller quantities in the absence of fever."

Plaque is the soft, nonmineralized, bacterial deposit which forms on teeth and dental prostheses that are not adequately cleaned. It characteristically forms on tooth surfaces which are not constantly cleansed, and appears as a tenacious, thin film, which may accumulate to a perceptible degree in 24–48 hours. A characteristic of plaque is that it resists removal by physiologic and oral cleansing forces such as saliva and tongue movement but is removable by toothbrushing. An important component of the dental plaque is acquired pellicle, which forms just prior to or concomitantly with bacterial colonization and may facilitate plaque formation. The pellicle is a glycoprotein that is derived from the saliva and is adsorbed on tooth surfaces. It is not dependent on bacteria but may serve as a nutrient for plaque microorganisms.

Dental plaque, or microcosm, as denoted by Arnim, is variable in both chemical and physical composition. It consists of salivary components such as mucin, desquamated epithelial cells and microorganisms. Plaque is composed of about 80% water and 20% solids. These are rich in bacteria with studies showing approximately 2×10^{11} bacteria per gram. Bacterial and salivary proteins comprise about one half of the dry weight of plaque. Plaque also contains carbohydrates and lipids, which account for approximately 25% of the plaque's dry weight. Most of the carbohydrates in the matrix consist of polymers, glucans, fructans, and heterosaccharides synthesized by the bacteria. Some of these polymers are thought to play a role in bacterial attachment and cohesion, and others are more important as a reservoir of fermentable substrates metabolized by bacteria when other more readily utilized carbohydrates in plaque become depleted.

Inorganic components of plaque account for approximately 5–10% of the dry weight of plaque. The concentration of calcium and phosphate in dental plaque is several magnitudes higher than in saliva. This is thought to be due, in part, to the infiltration of salivary proteins containing these constituents in the bound form. These probably include statherin, the salivary protein which, by adsorbing onto early crystal nuclei and preventing crystal growth, maintains super saturation of the fluid phase of plaque with apatite. In addition, bacteria may accumulate polyphosphates, which bind to calcium. Most of the calcium found in plaque is non-ionic and solubilisation occurs as pH drops. Dental calculus (q.v.) is plaque in which mineralization has involved both the plaque matrix and the microorganisms. However, the free surface of calculus usually harbors living bacteria.

There is a general agreement that enamel caries begins beneath the dental plaque. The presence of a plaque; however, does not necessarily mean that a carious lesion will develop at that point. Variations in caries formation have been attributed to the nature of the plaque itself, to the saliva or to the tooth. Extensive study of the bacterial flora of the dental plaque has indicated a heterogeneous nature of the structure. Most workers have stressed the presence of filamentous microorganisms, which grow in long interlacing threads and have the property of adhering to smooth enamel surfaces. Smaller bacilli and cocci then become entrapped in this reticular meshwork.

Aciduric and acidogenic streptococci and lactobacilli are particularly numerous in this setup. Occasionally, strains of the filamentous organisms are actively acidogenic through carbohydrate fermentation, but this does not appear to be a general feature of this group.

Bibby (1940) studied the characteristics of different strains of filamentous organisms isolated from dental plaques and noted their ability to adhere to smooth surfaces. Blayney and his associates (1942) pointed out that the time required for the development of definite cavitation representing early caries in an intact enamel surface was several months. Hemmens and his coworkers (1946) believed that dental plaque was the most likely starting point for investigations aimed at understanding the earliest stage of enamel caries. They examined numerous plaques from areas of children's teeth which became carious during the course of investigation. Aciduric streptococci were the organisms most commonly isolated from plaques during the period of caries activity, being present in varying numbers in 86% of the plaques. α-streptococci were isolated from slightly over 50% of the plaques from carious surfaces and from 75% of those from noncarious surfaces. The greatest incidence of occurrence of lactobacilli in plaque was 57%, but these organisms increased in incidence during that period in which the carious lesions were developing.

Most investigations of the microbiology of the dental plaque have concluded that three basic groups of microorganisms predominate: streptococci, actinomyces and veillonellae. The major strains of streptococci present in plaque are *S.mutans, S. sanguis, S. mitior, S. milleri* and *S. salivarius* (uncommonly). Major actinomyces strains include *A. viscosus, A. naeslundii, A. israelii*, and *Rothia dentocariosa*. The veillonellae group are the anaerobic gram-negative cocci organisms, chiefly *V. parvula and V. alcalescens.* Of all these, *Streptococcus mutans* is considered to be the chief etiologic agent in human dental caries today.

Plaques are classified as supra or subgingival, according to the anatomical area in which they form. Supragingival plaques play an essential role in the pathogenesis of dental caries while marginal and subgingival plaques are responsible for the initiation of periodontal diseases.The amount of plaque can be assessed directly by clinical examination (Fig. 9-2). Often dye solutions, referred to as disclosing agents, are used to stain plaques for visual scoring. Although carious lesions will not develop without plaque, it should be emphasized that plaques can often be relatively innocuous, have buffering capacity and protecting the teeth from exposure to acids present in many foods. However, when plaques contain appreciable proportions of highly acidogenic bacteria such as *S. mutans* and are exposed to readily fermentable dietary sucrose, they produce sufficient concentrations of acids to demineralise the enamel.

Mechanism of Plaque Formation. It is now known that the formation of dental plaque requires two types of specific bacterial adherent interactions. Firstly, bacteria attach selectively to the acquired pellicle, and secondly, bacteria accumulate via specific adhesive and cohesive interactions involving components of the plaque matrix and direct bacterial cell contact.

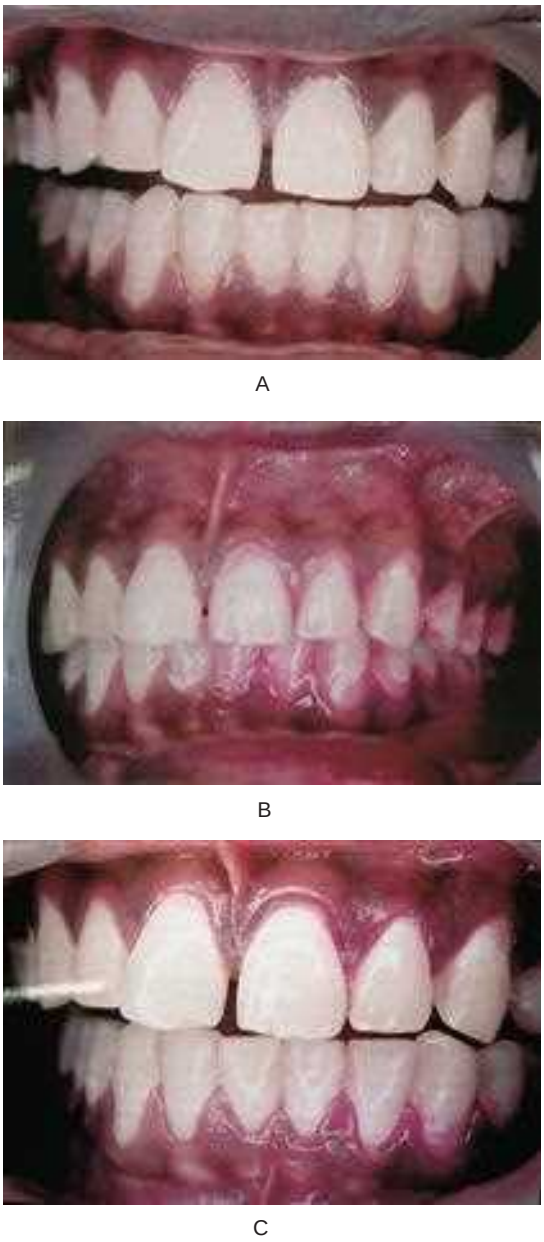


Figure 9-2. Dental plaque.
(A) The appearance of the teeth in all quadrants is similar, although the teeth on one side were not brushed for three days. **(B)** The dental plaque on the unbrushed teeth becomes obvious after the application of a disclosing solution. **(C)** Brushing the teeth and reapplying disclosing solution reveals that the plaque, if in an accessible area, is readily removed by brushing *(Courtesy of Dr L Natarajan and Dr Duliganti Santosh Reddy, Meenakshi Ammal Dental College, Chennai).*

The pellicle appears as three distinct components. The subsurface component, below the surface of enamel having a dendritic configuration, the 1μm thick surface component closely associated with the surface of the tooth, and a suprasurface portion of 10 μm thickness which has a scalloped appearance. These amorphous organic films on the enamel surface may influence caries formation and bacterial adhesion. The acquired pellicle, like most proteinaceous adsorbed layers, is a membrane that may impart semipermeable properties to the enamel surface.

The role of the salivary pellicle in modifying plaque formation has been extensively studied because bacteria attached to salivary proteins adsorbed to the enamel rather than to the inorganic tooth surface. Some organisms such as *S. salivarius*, which are prominent on the dorsum of tongue and in saliva, do not adsorb well to teeth. Other organisms such as *S. sanguis* and *A. viscosus*, which are not as numerous in saliva, adsorb avidly to the pellicle and are prominent in developing new plaque. The important point is that organisms are not passively entrapped but rather selectively attached because of specific interactions involving their cell surface constituents and the macromolecules of salivary pellicle.

Bacterial Adherence. Almost all bacteria and all natural surfaces, including teeth have a net negative charge. In the first phase of loose association, the organisms are thought to be attracted on to the surface by van der Waals forces. Firm contact does not occur because of the repulsive effects of the negative electrostatic charges. The second phase of attachment results in firmer bonding and appears to involve polymeric substances on the surface of the bacterium which links the organisms to the target surface.The polymeric material may bind to the surface by the formation of hydrogen, hydrophobic, ionic or other types of bonds.

The adsorption of proteins and other materials to hydroxyapatite occurs via electrostatic attractions involving calcium and phosphate groups on the mineral surface. It may be that initial adsorption of bacteria such as *S. mutans* to the pellicle also involves electrostatic interactions. It has been postulated that cell wall teichoic acids, which contribute to the net negative charge possessed by bacteria, may form bridges with calcium ions onto the enamel or pellicle.

Bacteria appear to possess surface components that have recognition potential, which bind to specific receptors on the pellicle and other host tissues. These surface components are referred to as adhesins. Some adhesins bind to saccharide receptors. Protein adhesins, which bind to specific sugars, are called 'lectins'. Other adhesins, which contain hydrophobic moieties, may interact with hydrophobic residues in specific receptor. Adhesins, therefore, permit bacterial cells to recognize and adhere to complex macromolecules.

Bacterial Accumulation. Both bacterially-derived polymers and salivary components appear to play important roles in this process. Early studies demonstrated that *S. mutans* accumulated on the teeth of rats or hamsters fed on diets rich in sucrose but not glucose. It was subsequently found that *S. mutans* synthesized extracellular glucans and fructans from sucrose but not from other common carbohydrates and that this polymer synthesis enabled the organism to accumulate in large masses. Most tooth-associated streptococci, actinomyces and neisseria can produce extracellular polymer glucan. More recently, several studies have suggested that *S. mutans* can adsorb on to hydroxyapatite without the synthesis of extracellular polymers and certain *S. mutans* serotypes can form plaque in the absence of sucrose. However, such plaques are less tenacious to enamel than are plaques formed by *S.mutans* in the presence of sucrose. More research is needed to further elucidate its role in plaque build-up and retention.

Role of pH of Dental Plaque. It was once thought that dental plaque, which is permeable to carbohydrates with the possible exception of starch, acted to hold the carbohydrates at a restricted site for a relatively long time. Stephan (1940) showed that this concept was incorrect and that carbohydrates permeating the plaque were degraded rapidly. He used an antimony microelectrode capable of measuring the pH in a dental plaque *in situ*. The pH of plaques in different persons varied, but averaged about 7.1 in caries-free persons and about 5.5 in persons with extreme caries activity.

Investigation of actual proximal cavities, opened mechanically, showed that the lowest pH varied from 4.6 to 4.1. Stephan also studied the pH in dental plaques after rinsing of the mouth with a 10% glucose or sucrose solution. Within two to five minutes after the rinse, the pH in the plaque dropped to between pH 4.5 and 5.0 and gradually returned to the initial pH level within one to two hours (Fig. 9-3). Further studies indicated differences in reductions in pH between caries free and caries-active subjects. The plaque pH in the caries-free group did not fall below 5.0 after the glucose rinse, while the pH in the caries active group dropped below 5.0 units after the glucose rinse in over half the cases.

A drop in local pH below 5.5 causes demineralization of tooth surfaces. At a critical pH of 5.5, the tooth minerals act as buffers and they loose calcium and phosphate ions into the plaque. This type of buffering activity initially would help in maintaining the

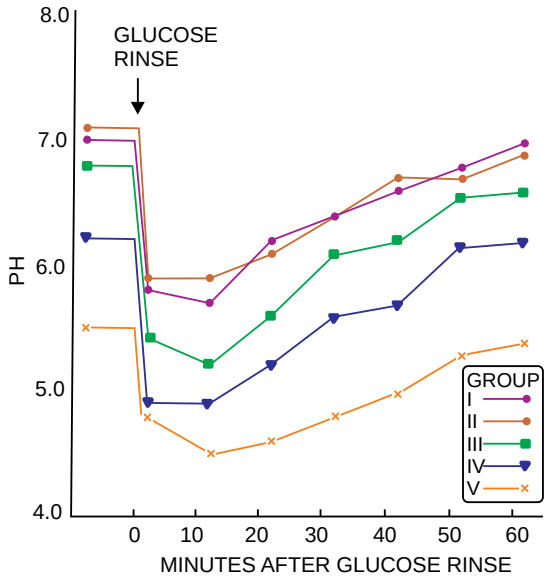


Figure 9-3. The pH curves of plaques on labial surfaces of maxillary anterior teeth in different caries activity groups.
Group I was caries-free; group II had caries previously, but was caries-inactive during the period of study; group III had slight caries activity; group IV had moderate caries activity; group V had extreme caries activity *(Courtesy of Dr Robert M Stephan: J Dent Res, 23: 257, 1944).*

local pH at about 5.5. However, when the local pH falls below 5.0 , subsurface demineralization is inevitable. This results in the formation of incipient caries, where the surface is intact but demineralization starts below the surface, a process known as subsurface demineralization. When the pH is lowered further it leads to the surface demineralization of enamel.

Factors Determining the Rate of Plaque Acid Production. The maxillary anterior teeth exhibited a greater pH drop in the plaque than the mandibular anterior teeth, indicating that the saliva influences plaque acid production.Brushing the teeth before the test carbohydrate rinse gave unsatisfactory plaque pH curves because of removal of plaque material.

Stralfors (1948) found a correlation between the lowest level to which the plaque pH dropped after the carbohydrate rinse and the lactobacillus count, utilizing this count as a test of caries activity. It was shown that persons with a higher pH have a lower lactobacillus count, and presumably, lower caries activity. Stralfors also reported that the plaque had greater buffering capacity than saliva owing to the presence of bicarbonates and proteins. Vratsanos and his colleagues studied plaque acidogenesis in caries-susceptible and caries-resistant patients and found that plaque pH in caries susceptible persons was lower (6.1 ± 0.3) than in caries resistant persons (7.3 ± 0.4) and that total plaque acid production was also significantly lower in the caries-resistant group.

Some studies have investigated substances capable of inhibiting the reduction in plaque pH after exposure to carbohydrate. Stephan and Miller (1943) applied several synthetic detergents and found at least partial inhibition of the pH drop. One drawback is the penetration of the plaque by inhibitory substances. In thin plaques, the inhibition is greater than in thick plaques. Application of urea was also found to be effective by Stephan, apparently because of hydrolysis by bacterial urease, with the subsequent formation of ammonium carbonate.

Role of Dextranase in Dental Plaque Reduction. An important discovery in dental caries was the recognition that certain cariogenic and highly acidogenic strains of streptococci, especially *S. mutans*, have the ability to metabolize dietary sucrose and synthesize glucan by utilizing cell surface and extracellular glucosyltransferase. This enzyme is considered to be of special importance in the establishment of *S. mutans* in the dental plaque. This appears to occur through glucan on the *S. mutans* cell surface acting as the primary binding site for the enzyme. This reaction then evokes new glucan synthesis from exogenous sucrose with subsequent adherence on to the enamel surface. This glucan is an insoluble, sticky or slimy gel, relatively inert, and resistant to bacterial hydrolytic enzymes, which causes plaque to adhere tenaciously to tooth surfaces. It also appears to act as a barrier against the diffusion of salivary buffers, which ordinarily would neutralize the acids formed in the plaque. Certain cariogenic bacteria are capable of storing intracellular polysaccharides, which may act as a reserve source of carbohydrate for fermentation and maintenance of acid production in the plaque during periods when the diet of the individual is sugar-free.

Both Bowen and Fitzgerald and his associates in 1968 studied dextranase, an enzyme produced by *Penicillium funiculosum* which hydrolyzes dextran (glucan) and found that it minimizes plaque formation and prevents smooth surface caries in experimental animals.

It is now agreed that the accumulation of dental plaque, even on a clean tooth surface, can result in dental caries in an individual susceptible to the disease and consuming a diet conducive to the disease. Parenthetically, it may be pointed out that plaque-forming streptococci, isolated from the gingival crevice, have been found to be morphologically and serologically similar to known cariogenic strains, thus suggesting a similar etiologic origin for both dental caries and periodontal disease.

THE PROTEOLYTIC THEORY

Although the evidence for the so-called acidogenic theory of dental caries is considerable, it is not wholly accepted as conclusive because much is circumstantial in nature. The proteolytic theory is an alternative explanation in which it has been proposed that the organic or protein elements are the initial pathways of invasion by microorganisms. As a proof of principle, it has been established that enamel contains approximately 0.56% by weight of organic matter.

Certain enamel structures are made up of organic material, such as enamel lamellae and enamel rod sheaths. Enamel lamellae might be important in the progress of dental caries, since they could serve as a pathway for microorganisms through the enamel. Baumgartner (1911) and Fleischmann (1914, 1921) demonstrated that microorganisms could invade the enamel lamellae, and stated that acids produced by these bacteria were capable of destroying the inorganic portion of the enamel.

Gottlieb (1944) and Gottlieb, Diamond and Applebaum (1946) postulated that caries is essentially a proteolytic process: the microorganisms invade the organic pathways and destroy them in their advance. They did admit that acid formation accompanied the proteolysis— Gottlieb held that yellow pigmentation was characteristic of caries and that this was due to pigment production by proteolytic organisms. A similar pigmentation has also been produced by exposing extracted caries-free teeth to pure cultures of lactobacilli in a synthetic medium containing glucose. If no glucose was present, no pigmentation occurred.

Frisbie, Nuckolls and Saunders (1944, 1947) described a microscopic phase of caries in which microorganisms could be demonstrated beneath an apparently intact enamel surface. In some cases, a bacterial plaque was found in position on the overlying enamel surface. Definite early white or brown carious lesions in the enamel exhibited similar but more advanced changes in the enamel matrix. These early lesions extended laterally beneath the intact surface, thus explaining the phenomenon, described by Thewlis, Darling and others,

of a radiopaque layer overlying early carious lesions. Fosdick and Hutchinson (1965) ascribed the radiopaque layer to a maturation process in the tooth surface following exposure to the oral environment, which renders the pathways of diffusion at or near the surface less reactive to acids. Under these circumstances, acids have to penetrate to a considerable depth before meeting acid-soluble apatite crystals. Minor variations in the organic and inorganic structures of the tooth are therefore important in determining the pattern and progression rate of early caries.

Caries of the dentin was demonstrated by Frisbie and Nuckolls (1945, 1947) to be similar to that occurring in enamel. These investigators also pointed out that there might be some softening of dentin even though the overlying enamel appeared hard and intact. They assumed that acid would be neutralized before penetrating the full thickness of the enamel and therefore could not cause decalcification of less acid soluble dentin.

Pincus (1948, 1949) proposed that Nasmyth's membrane and other enamel proteins are mucoproteins, which yield sulfuric acid upon hydrolysis. Lending support to this theory has been the isolation from the oral cavity of gram-negative bacilli capable of producing the enzyme sulfatase. This enzyme releases the combined sulfuric acid from the mucoprotein, but minimally unless the protein is first hydrolyzed to free the polysaccharide component. The liberated acid then dissolves the enamel, combining with the calcium to form calcium sulfate. Interestingly, this compound has been found in carious enamel but not in sound enamel. Sognnaes and Wislocki (1949, 1950) demonstrated the presence of an acid mucopolysaccharide in the interprismatic organic matter of mature enamel, but pointed out that sulfatase had not been demonstrated at the site of a carious lesion. Furthermore, no enzyme systems capable of attacking keratin have been demonstrated in the oral cavity, although other enzymes such as collagenase, hyaluronidase, phosphatase and mucinase, capable of attacking less resistant proteins, have been found.

Manley and Hardwick (1951) attempted to reconcile these two theories concerning the etiology of dental caries. They pointed out that, while the acidogenic and proteolytic mechanisms may be separate and distinct, they need not be so. Many bacteria produce acid from an appropriate carbohydrate substrate; some bacteria capable of producing acid from carbohydrate may even degrade protein in the absence of carbohydrate. On this basis, it has been proposed that there may be two types of carious lesions. In one type, microorganisms invade enamel lamellae, attack the enamel and involve the dentin before there is clinical evidence of caries. In the other, no enamel lamellae are present, and there is alteration of the enamel prior to invasion by microorganisms. This alteration is produced through decalcification of the enamel by acids formed by bacteria in a dental plaque overlying the enamel. The early lesions produced are those typically described as 'chalky' enamel.

Summary of Miller's experiment

An essential role to three factors:

- Oral microorganisms
- Carbohydrate substrate
- Acid

Questions unanswered by Miller:

- Predilection of specific sites on a tooth
- Initiation of smooth surface caries
- Why some populations are caries free?
- Phenomenon of arrested caries

Although the proteolysis of the organic matrix of dentin may eventually occur after demineralization, there is no satisfactory evidence to support the claim that the initial attack on enamel is proteolytic. In fact, gnotobiotic studies show that caries can occur in the absence of proteolytic organisms. The part played by proteolysis in the initiation of dental caries is likely to be of no significance, but its role in the progression of the more advanced carious lesions cannot be ruled out.

THE PROTEOLYSIS-CHELATION THEORY

This theory proposed by Schatz et al (1955) implies a simultaneous microbial degradation of the organic components (hence, proteolysis) and the dissolution of the minerals of the tooth by the process known as chelation. However, this proposal deals with theoretical discussions of the dental disease and the chemical aspects of chelation, with little direct evidence for proteolysis chelation as a mechanism in the caries process.

Chelation is a process involving the complexing of a metallic ion to a complex substance through a coordinate covalent bond which results in a highly stable, poorly dissociated or weakly ionized compound (chelas: claw). Chelation is independent of pH of the medium, so that removal of such metallic ions as calcium from even a biological calcium-phosphorus system may occur at a neutral or even alkaline pH. Numerous naturally occurring biological chelating agents exist, the most common of these being citrate. Amino acids are also known to act as chelators, as well as hydroxy and ketoesters of the Meyerhoff-Embden system of glycolysis; phosphorylated and nonphosphorylated compounds in the hexose monophosphate shunt; polyphosphates including those involved in phosphorylation; carboxylates of the Krebs tricarboxylic acid cycle; certain antibiotics and fermentation products; some proteins, carbohydrates, lipids, nucleic acids and certain enzymes; amines, amidases and certain vitamins; and oxalates, tartrates, salicylate, polyhydric alcohols and even dicumarol.

The proteolysis-chelation theory considers dental caries to be a bacterial destruction of teeth where the initial attack is essentially on the organic components of enamel. The breakdown products of this organic matter have chelating properties and thereby dissolve the minerals in enamel. This results in the formation of substances which may form soluble chelates with the mineralized component of the

tooth and thereby decalcify the enamel at a neutral or even alkaline pH. Enamel also contains other organic components besides amelogenin and non amelogenin proteins, such as mucopolysaccharides, lipids and citrates, which may be susceptible to bacterial attack and act as chelators. The proteolysis-chelation theory resolves the argument as to whether the initial attack of dental caries is on the organic or inorganic portion of enamel by stating that both may be attacked simultaneously.

However, several reconciliations have to be made if the proteolysis-chelation theory is to be accepted.These include the observation of:

- Increased caries incidence with increased sugar consumption.
- Increased lactobacillus count with high caries activity.
- Decreased caries incidence following topical or systemic administration of fluoride.

Increased caries incidence concomitant with increased carbohydrate consumption might occur through the action of the carbohydrate in stimulating or increasing proteolysis; producing conditions under which enamel proteins are less stable; and complexing calcium.

Increased caries incidence accompanying increased lactobacillus counts might be explained by the microorganisms being the result of the caries process, rather than its cause. Thus Schatz has suggested that:

- Proteolysis may provide ammonia which prevents a pH drop that would tend to inhibit growth of the lactobacilli.
- The release of calcium from hydroxyapatite by chelation might encourage the growth of lactobacilli, since calcium has been reported to produce this effect.
- Calcium exerts a vitamin-sparing action on some lactobacilli.

The proteolytic theory

- ***Theory:*** Organic or protein elements of a tooth are the initial pathway of invasion by microorganisms
- Enamel lamellae are pathways for organisms in the progress of dental caries
- ***Gottlieb and Gottlieb, Diamond and Applebaum:*** "Caries is essentially a proteolytic process: the microorganisms invade the organic pathways and destroy them in their advance. Acid formation accompanied proteolysis"
- ***Drawbacks:*** No satisfactory evidence to support the claim that the initial attack on enamel is proteolytic
- Gnotobiotic studies: Caries can occur in the absence of proteolytic organisms
- ***Conclusion:*** Proteolysis in the initiation of dental caries is likely to be of no significance, but its role in the progression of the more advanced carious lesions cannot be ruled out

Reduced caries incidence concomitant with administration of fluoride might occur through the formation of fluorapatite, which strengthens the linkages between the organic and inorganic phases of the enamel, thereby preventing or reducing their complexing.

Although Schatz's theory is unique and reconciles some of the unexplained facts of the dental caries process, there is insufficient scientific data to permit sound evaluation. Jenkins and Dawes carried out studies to discover whether chelation plays a role in the etiology of caries. They concluded that saliva and plaque do not contain substances in sufficient concentrations to chelate calcium in detectable amounts from enamel. However, although chelation is unlikely to be involved in the initiation of the lesions, it may play a minor role in the established lesion when the plaque pH level returns to neutrality.

The proteolysis-chelation theory

Theory: Simultaneous microbial degradation of the organic components and the dissolution of the minerals of the tooth by the process known as chelation (Schatz et al, 1955)

Chelation: A process involving the complexing of a metallic ion to a substance through a covalent bond which results in a highly stable, poorly dissociated or weakly ionized compound (chelas: claw)

Effects of chelation

- Independent of pH of the medium
- Removal of metallic ions such as calcium from a biologic calcium-phosphorus system may occur at a neutral or even alkaline pH

The proteolysis-chelation theory resolves the argument as to whether the initial attack of dental caries is on the organic or inorganic portion of enamel by stating that both may be attacked simultaneously

Several animal studies, such as those of Zipkin and of Larson and her associates, showed that the incorporation of a chelating agent, ethylenediamine tetraacetic acid (EDTA), into the cariogenic diet resulted in an increase in the severity of dental caries as well as a difference in the distribution pattern of the lesions. Although such evidence does not lend great strength to the proteolysis-chelation theory, at least it does not contradict it.

THE SUCROSE-CHELATION THEORY

Egglers-Lura (1967) proposed that sucrose itself, and not the acid derived from it, can cause dissolution of enamel by forming an ionized calcium saccharate. They postulated that calcium saccharates and calcium complexing intermediaries require inorganic phosphate, which is subsequently removed from the enamel by phosphorylating enzymes. However, reinvestigation by other workers failed to confirm this but showed that soluble complex can be formed, even at alkaline pH values, between sucrose and calcium oxide and calcium hydroxide, although not with calcium phosphate.

CURRENT CONCEPTS OF CARIES ETIOLOGY

Dental caries is a multifactorial disease with interplay of three primary factors: the host, the microbial flora, and the substrate

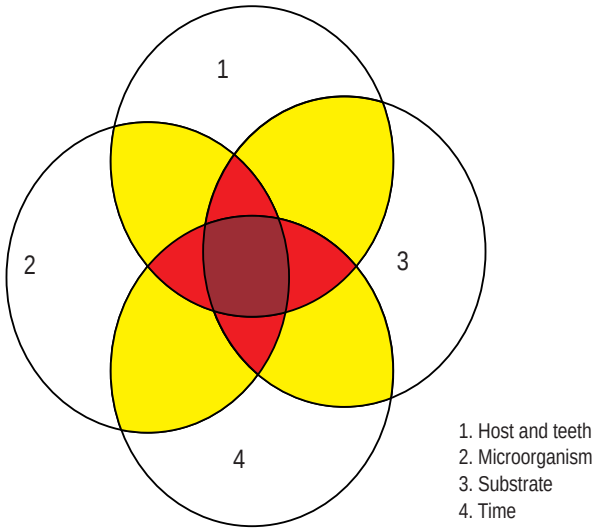


Figure 9-4. Contributing factors in dental caries.

with time, as an inevitable fourth factor. In other words, caries requires a susceptible host, a cariogenic flora and a suitable substrate that must be present for a sufficient length of time (Fig. 9-4).Conversely, caries prevention is based upon attempts to increase the resistance of the host, lower the number of microorganisms in contact with the tooth and modify the substrate by selecting noncariogenic foodstuffs and reduce the time that the substrate is in the mouth.

The mere presence of microorganisms and a suitable substrate at a given point on a tooth surface is insufficient to establish a carious lesion in all individuals. Variations in caries incidence are due to the presence of a number of indirect or contributing factors.

A workshop on dental caries mechanisms and control techniques was held at the University of Michigan in 1947. This group listed a number of indirect factors that might influence the etiology of caries (Table 9-2).

Table 9-2: Factors that influence in caries etiology

Host factors	Components
Tooth	1. Composition 2. Morphologic characteristics 3. Position
Saliva	1. Composition a) Inorganic b) Organic 2. pH 3. Quantity 4. Viscosity 5. Antibacterial factors
Diet	1. Physical factors a) Quality of diet 2. Local factors a) Carbohydrate content b) Vitamin content c) Fluorine content
Systemic conditions	

TOOTH FACTOR

The tooth factor or a susceptible tooth is the most important feature in caries etiology. The structure and composition of teeth undoubtedly influences the initiation and progression of a carious lesion. Studies on the chemical composition of enamel indicate that the surface enamel is more resistant to caries than subsurface enamel. Significant differences in fluoride content of sound and carious teeth have been reported. The enamel of sound teeth contain 0.0111 ± 0.0020% fluoride, while that of carious teeth contain 0.0069 ± 0.0011% fluoride. Microradiographs of the initial carious lesions also indicate a marked decalcification of the subsurface enamel while the surface is relatively intact.

The surface is lower in carbon dioxide, dissolves at a slower rate in acids, contains less water and has more inorganic material than subsurface enamel. These factors apparently contribute to caries resistance and are partly responsible for the slower disintegration of surface enamel than of the underlying enamel in initial carious lesions. Also, the concentration of phosphate and potassium in enamel remains relatively constant after the completion of mineralization of the tissue, suggesting that chemical changes on the enamel surface involve primarily the surface of apatite crystals and the inner lattice structure is less affected. Changes in enamel, such as a decrease in density and permeability and an increase in nitrogen and fluoride content, occur with age. These alterations are part of the posteruptive 'maturation' process whereby teeth become more resistant to caries with time.

Morphologic Characteristics of Tooth

The only morphologic feature which conceivably might predispose to the development of caries is the presence of deep, narrow occlusal fissures or buccal or lingual pits. Such fissures tend to trap food, bacteria and debris, and since defects are especially common in the base of fissures, caries may develop rapidly in these areas. Conversely, as attrition advances, the inclined planes become flattened, providing less opportunity for entrapment of food in the fissures, and the predisposition towards caries diminishes.

Certain surfaces of teeth are more prone to decay, whereas other surfaces rarely show decay. For example, in mandibular first molars, the likelihood of decay, in descending order, is occlusal, buccal, mesial, distal and lingual, whereas in maxillary first molars the order is occlusal, mesial, lingual, buccal and distal. On maxillary lateral incisors, the lingual surface is more susceptible to caries than the labial surface due to the frequent presence of a pit at this site. The most susceptible permanent teeth are the mandibular first molars, closely followed by the maxillary first molars and the mandibular and maxillary second molars. The mandibular incisors and canines are least likely to develop lesions.

All available evidence indicates that alteration of the tooth structure by disturbances in formation or in calcification is of only secondary importance in dental caries. The rate of caries progression may be influenced, but caries initiation is affected only to a very little extent.

Position

The position of the teeth seems to be an important factor in the etiology of dental caries. Teeth which are malaligned, out of position, rotated, or otherwise not normally situated may be difficult to cleanse and tend to favor the accumulation of food and debris. This, in susceptible persons, would be sufficient to cause caries in a tooth, which under normal circumstances of proper alignment, would conceivably not develop caries.

SALIVA FACTOR

The fact that the teeth are in constant contact with, and bathed by saliva would suggest that they could profoundly influence the dental caries process (Table 9-3). The complex nature of saliva and variation in its composition are the challenges involved in establishing those factors which may directly influence dental health (Table 9-4).

The composition of saliva varies between persons and exhibits no constant relation to composition of the blood. There have been many studies on the elementary composition of saliva and its approximate percentage under various circumstances, as well as the correlation with dental caries incidence.

Calcium and Phosphate Concentrations in Saliva. The inorganic phase of enamel consists of crystalline hydroxyapatite essentially in the form of calcium and phosphate complexes of various compositions. These complexes usually dissociate as the pH drops and result in free active concentration of ions. The solubility equilibrium exists when a chemical compound in the solid state is in chemical equilibrium with a solution of that compound. This is an example of dynamic equilibrium in that some individual molecules migrate between the solid and solution phases such that the rates of dissolution and precipitation are equal to one another. At equilibrium, the saliva as a solution is saturated and the ion activity product (IAP) is same as the solubility product (K_{sp}). If IAP = K_{SP}, then saturation index (SI) is zero, which means that the mineral is in equilibrium with solution. Under normal circumstances saliva is supersaturated with respect to enamel apatite, which not only prevents enamel from dissolving but even tends to precipitate apatite, in the surface enamel of carious lesions. If IAP is less than K_{sp}, then SI is negative, the saliva is unsaturated and the teeth would solubilize. If IAP is more than K_{sp} then SI is positive and saliva is supersaturated and mineral precipitates. Thus, calcium and phosphate in saliva forms an important natural defense mechanism against dissolution of teeth.

Table 9-3: Salivary constituents and factors studied in relation to caries

Inorganic constituents	Organic constituents	Enzymes, solids, and physical factors
Positive ions	Carbohydrates	Enzymes
Calcium	Glucose	Carbohydrases
Hydrogen		Amylase
pH	Lipids	Maltase
Buffering power	Cholesterol	Proteases
Neutralizing power	Lecithin	Trypsin
Salivary factor		Oxidases
Titratable alkalinity	Nitrogen	Catalase
Magnesium	Nonprotein	Oxidase
Potassium	Ammonia	Total solids
Negative ions	Nitrites	
Carbon dioxide	Urea	Physical factors
Carbonate	Amino acids	Conductivity
Chloride	Protein	Freezing point
Fluoride	Globulin	Osmotic pressure
Phosphate	Mucin	Specific gravity
Thiocyanate	Total protein	Surface tension
Ash peroxide	Miscellaneous	Viscosity
	Peroxide	

Modified from F Krasnow: Biochemical analysis of saliva in relation to caries. Dent Cosmos, 78: 301, 1936.

Table 9-4: Salivary enzymes

Enzymes	Sources		
	Glands	Microorganisms	Leukocytes
Carbohydrases			
Amylase	O	O	O
Maltase	O	X	X
Invertase	O	X	O
β-glucuronidase	X	X	X
β-D-galactosidase	O	X	X
β-D-glucosidase	O	X	O
Lysozyme	X	O	X
Hyaluronidase	O	X	O
Mucinase	O	X	O
Esterases			
Acid phosphatase	X	X	X
Alkaline phosphatase	X	X	X
Hexose diphosphatase	O	X	O
Aliesterase	X	X	X
Lipase	X	X	X
Acetylcholinesterase	X	O	X
Pseudocholinesterase	X	X	X
Chondrosulfatase	O	X	O
Arylsulfatase	O	X	O
Transferring enzymes			
Catalase	O	X	O
Peroxidase	X	O	X
Phenyloxidase	O	X	O
Succinic dehydrogenase	X	X	X
Hexokinase	O	X	X
Proteolytic enzymes			
Proteinase	O	X	X
Peptidase	O	X	X
Urease	O	X	O
Other enzymes			
Carbonic anhydrase	X	O	O
Pyrophosphatase	O	X	O
Aldolase	X	X	X

From H H Chauncey: Salivary enzymes. J Am Dent Assoc, 63: 360, 1961. Copyright by the American Dental Association. Reprinted with permission.

The phosphate concentration in saliva tends to fall as the flow rate of saliva increases, whilst the calcium concentration falls initially but then rises at higher flow rates. This is due to the associated increase in pH at high flow rates. The pH affects the IAP in two ways. Firstly, the fraction of total phosphate present as PO_4^{3-} ions (as opposed to HPO_4^{2-} or $H_2P_4^-$ or H_3PO^4) increases markedly with pH. Secondly, the hydroxyl ion concentration also increases with pH.

The concentrations of inorganic calcium and phosphorus show considerable variation, depending upon the rate of salivary flow. Currently no consistent relationship has been established between dental caries prevalence and the calcium and phosphorus content of saliva.

There are numerous other inorganic components such as sodium, magnesium, potassium, carbonate, chloride, and fluoride present in the saliva. With the exception of fluoride, these substances have not been thoroughly investigated. Thiocyanate has also been isolated from saliva, and at one time, was thought to inhibit the growth of microorganisms associated with dental caries. It is now conceded that thiocyanate probably has no effect either on the bacterial flora or on dental caries.

The organic constituents of saliva as a group have also been subjected to little more than a cursory examination.

The ammonia and urea content of saliva has been studied by many workers. Turkheim in 1925 noted that the saliva of caries immune persons exhibited greater ammonia content than saliva from persons with caries. Grove and Grove (1934) confirmed this finding and reported that the ammonia of saliva from caries susceptible individuals was about 0–8 mg/100 ml, where as the same in caries-immune individuals was about 4.0–10 mg/100 ml. It was suggested that a high ammonia concentration retarded plaque formation and neutralized acid, at least to some extent. However, White and Bunting, Youngberg and Karshan, among others, found no relation between salivary ammonia and dental caries. The average concentration of urea in saliva which is about 20 mg/100 ml in resting saliva and 13 mg/100 ml of stimulated saliva may be hydrolyzed to ammonium carbonate by urease, thus increasing the neutralizing power of the saliva. The amino acids of saliva have also been suggested as a source of ammonia nitrogen, although Kirch and coworkers could find no correlation between the amounts of amino acids in saliva and caries activity.

The presence of a secreted carbohydrate in the saliva has been argued by various workers. Young, in 1941, reported the presence of a reducing substance in saliva, which he assumed to be glucose. This substance ranged from 11.3–28.1 mg/100 ml in resting saliva and from 14–30 mg/100 ml in stimulated saliva. It was concluded that saliva is not rich in glucose. A number of different enzymes have been isolated from saliva. As shown in Table 9-4, these enzymes are derived from both intrinsic and extrinsic sources..

The most prominent and important oral enzyme is amylase, or ptyalin, a substance responsible for the degradation of starches. Parotid saliva is always higher in amylase content than saliva from the other glands. The relation between amylase activity and dental caries has been studied by numerous investigators with conflicting results.

pH of Saliva

The pH of saliva has been studied intensively because of the apparent relation of acidic pH of saliva to dental caries. However, inconsistent and conflicting data may arise from failure to collect the saliva under oil, thus reducing loss of carbon dioxide which would cause elevation of the pH.

The pH at which any particular saliva ceases to be saturated with calcium and phosphate is referred to as the 'critical pH'; below this value, the inorganic material of the tooth may dissolve. Critical pH varies according to the calcium and phosphate concentration, but it is usually about 5.5. With increasing concentration of hydrogen ions in the plaque, more phosphate ions will leave the solid apatite phase.

Buffer Capacity of Saliva

The buffer capacity of the saliva, which may account for some of the observed differences between salivary pH and caries incidence is not necessarily reflected by the pH of the saliva. Karshan and his associates (1931) pointed out that titratable alkalinity is a better indicator of buffer capacity than the pH, but found that saliva from caries immune and caries susceptible persons exhibited essentially the same titratable alkalinity. White and Bunting in 1936 studied the carbon dioxide capacity of resting and stimulated saliva in caries free and caries susceptible children. Although the values for stimulated saliva were much higher than those for resting saliva, no remarkable differences were noted in the mean values. However, Karshan (1936) noted a significant difference in the mean value of carbon dioxide capacity of stimulated saliva between caries free group and caries active group, which was between 31.1 ml/100 ml of saliva and 19.5 ml/100 ml of saliva respectively. Sellman (1949) studied the buffer capacity of saliva and its relation to dental caries and found that the total amount of acid needed to reduce the salivary pH to a given pH level (6, 5, 4 and 3) was always greater for saliva from caries-resistant persons. Sullivan and Storvick (1950) also reported a significant inverse correlation between the DMF teeth and the buffer capacity of saliva.

The acid production, significant in the caries process, occurs at a localized site on the tooth. This site, particularly in the early stages of caries is protected by the dental plaque, which appears to act as an osmotic membrane preventing free exchange of ions. Thus, even though buffer ions are present in the saliva, they may not be totally available at specific sites. The entire problem of the buffering capacity of saliva and its relation to dental caries requires further investigation.

In saliva, the chief buffer systems are bicarbonate carbonic acid (HCO_3^-/H_2CO_3, pk1=6.1) and phosphate (HPO_4^- or $H_2PO_4^-$, pK2 = 6.8). pK marks the point on the curve where the pH changes the least. Variations in bicarbonate concentration are the chief determinants of salivary pH. Saliva is poorly buffered with a pH as low as 5.3 as seen in unstimulated saliva where the bicarbonate concentration is low, whereas the salivary bicarbonate concentration may reach as high as 60 mM at high flow rates and this type of saliva is well buffered with a pH as high as 7.8.

By virtue of the volatile nature of CO_2 gas, the breakdown of bicarbonate by acids leads to the eventual escape of CO_2. The loss of CO_2, in effect, removes the acid element of the bicarbonate carbonic acid system and reduces the change in the ratio of bicarbonate to carbonic acid. Most of the CO_2 in saliva is in the form of bicarbonate, carbonate and dissolved CO_2. When saliva is exposed to atmospheric air in the mouth or in a beaker, there is a loss of dissolved CO_2 and an increase in pH, which may reach higher than 9. Further loss of CO_2 occurs due to the presence of carbonic anhydrase in saliva. The rapid loss of CO_2 from freshly secreted saliva and the rise of pH may be sufficient to cause the solubility product for hydroxyapatite to be exceeded leading to precipitation of this compound, as well as other calcium phosphate salts. These properties of saliva may be the reason why calculus formation is greatest in the area approximating the orifices of the parotid and submandibular salivary gland ducts.

The buffering capacity of saliva is a very significant property that affects the dental caries process. The bicarbonate in saliva is able to diffuse into the dental plaque to neutralize the acid formed from carbohydrate by the microorganisms. The higher the flow rate, the greater will be its buffering capacity. Dialysis of saliva, which removes both bicarbonate and phosphate but not protein, results in total loss of salivary buffering capacity. This indicates that salivary proteins can be disregarded as buffers in saliva. Further evidence of the importance of saliva as a buffer was demonstrated when the pH of carious lesions and of dental plaque was studied. Within active carious lesions, a pH gradient exists. The deep advancing edges of such lesions were more acidic than the shallower layers, which had a pH similar to that of saliva. In enlarged and exposed cavities that are emptied of their contents, the carious layerwas shallower and the pH closer to neutrality, probably because of better access to saliva.

Quantity of Saliva

The quantity of saliva secreted in a given period of time may, theoretically at least, influence caries incidence. This is especially evident in cases of salivary gland aplasia and xerostomia in which salivary flow may be entirely lacking, typically resulting in rampant dental caries. It has been found that the range of variation of resting saliva among different persons is greater than the range of stimulated saliva. Furthermore, when persons from a slow flowing group and from a fast-flowing group are stimulated, the flow of activated saliva from the two groups exhibits little difference, thus masking the natural difference. It seems probable that the rate of salivary flow is simply one additional factor which helps contribute to caries susceptibility or caries resistance. Mild increases or decreases in flow may be of little significance; However, total or near-total reduction in salivary flow adversely affects dental caries in an obvious manner.

Reduced salivary flow or hyposalivation is a consequence of pathological conditions or the use of antisialagogues. Under normal conditions, salivary flow is almost entirely under parasympathetic neural control. Drugs such as atropine, which affect the cholinergic parasympathetic nerves, produce decreased salivation. Hyposalivation also occurs in patients who are dehydrated due to conditions such as fever or prolonged diarrhea. Hyposalivation is also associated with diabetes, anemia, hypovitaminosis A or B, uremia and dehydrating disease of old age. Many of the common drugs administered to old people for a variety of health problems can result in xerostomia. A restriction in salivary flow leads to exacerbation of dental caries, as the removal of bacteria and food debris from the mouth are two important functions of saliva with respect to caries. Despite the continuous flow of saliva, dental plaque can accumulate at a rapid rate of (10–20 mg/day) in the absence of oral hygiene procedures but the rate of plaque accumulation appears to be even more rapid in patients with xerostomia (Llory et al, 1972).

Viscosity of Saliva

The viscosity of saliva accounting for differences in caries activity between different persons, appears to have an empiric foundation rather than a scientific basis, as judged by the paucity of pertinent experimental studies reported in scientific literature. Miller thought that salivary viscosity was not of great importance in the caries process since numerous cases could be found in which saliva was extremely viscous and the patients were free of caries. The reverse has also been shown where patients with an abundant, thin, watery saliva often exhibit rampant caries. The viscosity of the saliva is largely due to the mucin content, derived from the submandibular, sublingual and minor salivary glands, but the significance of this substance in relation to dental caries is not entirely clear.

Antibacterial Properties of Saliva

The antibacterial properties of saliva have been investigated by numerous workers in an attempt to explain the wide variation in caries incidence among different persons. Clough in 1934 tested 41 different salivas for their effect on the growth of *L. acidophilus*, utilizing 'wells' in seeded culture plates. The caries experience of the patients from whom the saliva was taken with the degree of bacterial inhibition could not be correlated. van Kesteren and associates found that the saliva probably contains at least two antibacterial substances, one of which resembled lysozyme, the other being distinctly different. Using *L. acidophilus* as the test organism, Hill in 1939 found that saliva from caries free person had a greater inhibiting effect than saliva from caries active persons.

A bacteriolytic factor in the saliva of caries immune persons, which was absent in saliva from caries susceptible ones, was reported by Green. This factor was active against lactobacilli and streptococci, and appeared to exert its lytic effect on cells commencing the process of division. Further studies indicated that the factor was a protein associated with the globulin fraction of saliva. Since it resembled some antibacterial factors in serum, it was apparently different from other reported salivary antibacterial substances.

Lysozyme (N-acetylmuramide glycanohydrolase). A hydrolytic enzyme in saliva cleaves the β-1-4 linkage between N-acetylglucosamine and N-acetylmuramic acid, which constitute the repeating disaccharide unit of the cell wall peptidoglycan. In the presence of sodium lauryl sulfate, a detergent, lysozyme can lyse many cariogenic and noncariogenic streptococci and it has been found that the lysozyme activity is significantly greater in a group of caries free preschool children than in a caries susceptible group.

Salivary peroxidase system. The salivary glands secrete salivary peroxidase and thiocyanate (SCN^-), which acts on hydrogen peroxide generated by certain bacteria. This oxidoreductase system catalyzes the oxidation of the thiocyanate ion to hypothiocyanate ion ($OSCN^-$). The product $OSCN^-$ reacts readily with sulfhydril compounds of low molecular weight and thereby inactivates many bacterial enzymes of the glycolytic pathway and inhibit their growth.

This antibacterial system is known to be inhibitory towards *L. acidophilus* and *S. cremoris*, by preventing cells from accumulating lysine and glutamic acid, which are essential for growth. Further investigation is necessary to determine whether this enzyme can control cariogenic bacteria *in vivo*. The significance of antibacterial factors in saliva has been questioned by many workers, including Bibby (1956) who pointed out that regardless of the quality of the saliva, including the relative presence or absence of inhibitory principles, saliva always appears to contain bacteria capable of producing caries if carbohydrates are present.

Immunoglobulins. The predominant immunoglobulin class in saliva is secretory IgA or sIgA. Salivary IgA differs from serum IgA, Secretory IgA is a product of two different cell types where plasma cells synthesize polymeric IgA containing J chain of about 1.5 kD and glandular cells synthesize a glycoprotein secretory component (SC) of 7 kD. While the secretory component is attached entirely to one of the 2 IgA molecules, the J chain is attached to both. SC is a receptor for the polymeric immunoglobulin A containing J chain; the IgA binds to SC below the tight junction of glandular epithelial cells and is then transported across to the luminal surface. The presence of SC makes sIgA resistant to proteolytic enzymes. Purified salivary IgA and IgG fractions have been found with agglutinating activity against oral isolates of α-hemolytic streptococci. The existence of plasma cells located in salivary glands is of great interest because of the potential for producing a local response to an antigen. It is known that ingestion of inactivated *S. mutans* cells by germ free rats elicits salivary antibody formation as does the consumption of large numbers of S. mutans cells by human subjects (McGhee et al, 1978). The concentration of salivary IgA is approximately 4 mg/100 ml in stimulated submandibular and parotid saliva. However, its concentration is considerably higher in the secretions of minor salivary glands and reaches levels of about 30 mg/100 ml. Animal experiments suggest that both systemically and locally produced antibodies may operate to protect against caries. The latter involves the local immune mechanism via the saliva and the other involves gingival crevicular fluid, which is derived from plasma (Lehner, 1978).

The Diet Factor

The role of the diet and nutritional factors deserves special consideration because of the often observed differences in caries incidence of various populations who subsist on dissimilar diets. Although many clinical studies have been carried out in an attempt to study certain components of the diet with regard to caries, a number of variable factors have usually clouded the results. The use of experimental animals which are susceptible to destruction of the teeth similar to human dental caries has greatly aided the study of dietary considerations in dental caries (Fig. 9-5).

Physical Form

The physical nature of the diet has been suggested as one factor responsible for the difference in the caries experience between primitive and modern man. The diet of the primitive man consisted generally of raw unrefined foods containing a great deal of roughage, which cleanses the teeth of adherent debris during the usual masticatory excursions. In addition, the presence of soil and sand in incompletely cleaned vegetables in the primitive diet induced severe attrition of both occlusal and proximal surfaces of the teeth. This resulted in flattening of the occlusal and proximal surfaces causing a reduction in the probability of decay. In the modern diet, soft refined foods tend to cling tenaciously to the teeth and are not removed because of the general lack of roughage. Augmenting this collection of debris on the teeth is the reduction of mastication due to the softness of the diet. The detrimental effect of this decreased function on the periodontal apparatus should be obvious.

It has been demonstrated that mastication of food dramatically reduces the number of cultivable oral microorganisms. Since those areas of teeth that are exposed to the excursions of

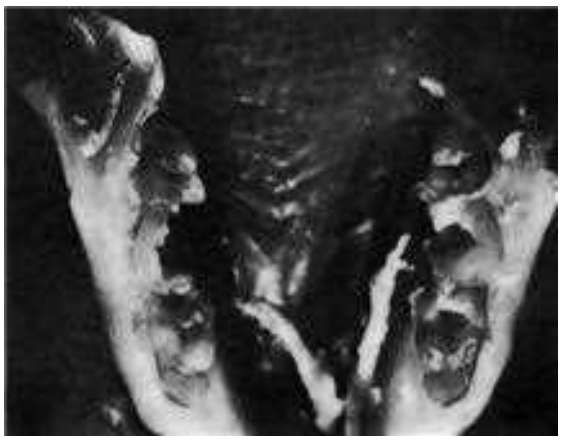


Figure 9-5. Dental caries in the albino rat.
Occlusal caries has led to severe destruction of several molars *(Courtesy of Dr Joseph C Muhler).*

food are usually immune to caries, mechanical cleansing by detergent foods may have some value in caries control. Clinical studies have not confirmed that physical parameters are as important as the frequency of eating in determining cariogenicity of foods. The carbohydrate content of the diet has been almost universally accepted as one of the most important factors in the dental caries process and one of the few factors, which may be consciously altered as a preventive measure.

Epidemiological studies have shown that the incidence of dental caries differs immensely among population groups. Although part of the variance can be due to genetic factors, the diets of different ethnic groups probably account for the major differences. The prevalence of caries among native populations was very low and native diet did not contain any sucrose other than small amounts found in fruits and vegetables. As their diets changed to include products containing sugar, their prevalence increased.

Becks and his associates (1944) studied the effect of carbohydrate restriction on the *L. acidophilus* index and the caries experience in a group of 1,250 persons with rampant caries and in 265 caries free persons. Replacement of refined dietary carbohydrate with meat, eggs, vegetables, milk and milk products resulted in an 82% reduction in the lactobacillus index and in clinical evidence of extensive arrest of caries. The observation was made that some persons consumed large amounts of carbohydrate without acquiring caries, while others had rampant caries even though consuming very little carbohydrate. These workers were prompted to suggest that, in addition to excessive amounts of refined carbohydrates, other factors undoubtedly have a bearing on the disease.

Institutional studies were carried out in a mental institution at the Vipeholm Hospital near Lund, Sweden, more popularly known as the Vipeholm study. The institutional diet was nutritious but contained little sugar with no provision for between meal snacks. The dental caries rates in the inmates were relatively low. The experimental design divided the inmates into seven groups; sugar was introduced either at mealtime in bread and solution or between meals in caramels, toffee and chocolates. The conclusions from the study were that an increase in carbohydrate definitely increased the caries activity. The risk of sugar increasing caries activity was greatest when the sugar was consumed between meals and in a form that tends to be retained on the surfaces of the teeth.The increase in caries activity drastically reduced upon withdrawal of the sugar-rich foods.

Most importantly, the clearance time of the sugar correlated closely with caries activity. The Vipeholm study clearly showed that the physical form of carbohydrates, clearance time of sugars and the frequency of intake were more important in cariogenicity than the total amount of sugar ingested. Another large-scale and important experiment on caries in human subjects was carried out inTurku, Finland with the aim of comparing the cariogenicity of sucrose, fructose and xylitol. The basis of the experiment was that xylitol is a sweet substance not metabolized by plaque organisms. In addition to data indicating that xylitol would be an acceptable metabolite in humans, there was a dramatic reduction in the incidence of dental caries after two years of xylitol consumption. Fructose was as cariogenic as sucrose in the first 12 months but became less so at the end of 24 months.

In spite of the overwhelming evidence relating carbohydrate intake to dental caries, enough exceptions have been noted. In India among certain segments of the population there may be a high carbohydrate intake, but a very low caries incidence. A complicating factor has been the difficulty in obtaining data from human feeding studies under experimental conditions.

Carbohydrate Intolerance and Dental Caries

An intolerance to disaccharide or monosaccharide occurs because of a deficiency of a specific enzyme involved in the metabolism of the sugar is described as **hereditary fructose intolerance syndrome**. Hereditary fructose intolerance syndrome first described by Froesch in 1959 is an inborn error of fructose metabolism transmitted by an autosomal recessive gene. It is caused by remarkably reduced levels of hepatic fructose-1-phosphate aldolase, which splits fructose-1-phosphate into two to three carbon fragments to be further metabolized by the Embden-Meyerhof (EM) pathway. Persons affected with this metabolic disorder learns to avoid any food containing fructose because the ingestion of these foods causes symptoms of nausea, vomiting, malaise, tremor, excessive sweating and even coma due to fructosemia. Most of these symptoms can be attributable to secondary hypoglucosemia resulting from a block in glycogenolysis. However, they eat glucose, galactose, lactose and starch containing foods such as milk, dairy products, rice and noodles. Although there have been only a limited number of cases reported in the literature, the dental caries prevalence of these subjects have generally known to be extremely low. Caries, when found, is restricted to pits and fissures and is usually not found in smooth enamel surfaces.

Assessment of Cariogenic Potential of Diet. A number of different approaches have been used in attempting to develop reliable methods for measuring the caries inducing potential of individual foods. These include *in vitro* models of caries such as adhesiveness of foods, enamel demineralization, production of titratable acids, monitoring of plaque pH changes *in vivo* and *in vitro,* and animal testing to measure cariogenicity of individual foods fed to rodents under standardized conditions.

Many animal studies have been carried out in attempting to clarify some of the perplexing problems of dental caries. Some of these have dealt with the cariogenic effect of different carbohydrates, and it has been found that not all sugars have the same cariogenicity. The animal data must be interpreted with caution due to the entirely different ecologic system in the human mouth compared to experimental animal mouths.

However, some general conclusions may be drawn from the data in which experimental animals fed by stomach tube did not develop caries despite the prevalence of cariogenic microorganisms. The relationship between the sucrose content

of the food or of the total diet and the resulting caries may not necessarily be linear but it is direct. Other animal studies have shown that the concentration of sucrose in the diet strongly influences the incidence of smooth surface and fissure caries. On a sound scientific basis, it is difficult to draw definite conclusions about the relation between dental caries and refined carbohydrates. Nevertheless, the bulk of available evidence indicates that a positive relationship exists, even though many other factors are also important.

Cariogenicity of Sucrose and other Carbohydrates

The principal carbohydrates available in human diets are starches, sucrose and some lactose, with less glucose, fructose or maltose. From a clinical standpoint the significant comparison is between starch and sucrose or between the two sucroses, as they have been labeled the primary culprit in the pathogenesis of dental caries. In many foods, such as cakes and pastries, sucrose coexists in a mixture with cooked starch. The key role of sucrose as a dietary substrate in the caries process on smooth surfaces can be explained on a biochemical basis. Dental plaque is a prerequisite for the development of smooth surface caries. The presence of extracellular polysaccharides, namely glucan and levan, has been clearly demonstrated in dental plaque. The glucans, particularly the water insoluble fraction, can serve as structural component of the plaque matrix and effect in gluing certain bacteria to the teeth.

The soluble levans and some of the soluble glucans are degradable by the plaque flora and may function as transient reserves of fermentable carbohydrates thereby prolonging the duration of acid production. These polysaccharides are synthesized by enzymes, which for most part are extracellular or bound to the cell surface and show a high specificity for sucrose as a substrate. Polysaccharide is built up by extrusion from the enzyme. The enzymes involved in the synthesis, glucosyl and fructosyl transferases, have been isolated and purified from *S. sanguis* and *S. mutans*.

These enzymes are highly specific for sucrose and will not utilize sugars such as fructose, glucose, maltose, or lactose. They have a large pH optimum of 5.2–7.0 coinciding with the pH range of dental plaque. As long as sucrose is present in plaque, the glucosyl transferase enzymes will continue to utilize it to form plaque matrix material and fructose. The latter can be readily fermented by the plaque flora to form organic acids. The glucosyl transferase (GTF) of the mutans group has received considerable attention and several isozymes have been isolated. There are two types of these enzymes:

- Those that synthesize a soluble glucan with predominantly 1,6-α-D-glucose sequences (GTF-S).
- Those that synthesize an insoluble, essentially linear 1,3-α-D-glucan (GTF-I).

By cooperative action of these enzymes, a sticky water insoluble polysaccharide is synthesized from sucrose that is a major factor in the accumulation of mutans group of streptococci on smooth surfaces of teeth. Starches are probably prevented from direct entry into plaque because of limited diffusion of such large molecules.

The first step in the catabolism of sugars is their transport into the cytoplasm of the microorganism. Sugars are transported either by a carrier mediated active transport (permease) system or group translocation (phosphotransferase system, PTS). Active transport releases sugar unmodified into the cytoplasm, whereas the sugar gets chemically modified to a phosphate ester before it appears inside the cell by group translocation. The uptake of sugars by oral streptococci (*S. mutans, S. sanguis, and S. salivarius*) involves a phosphoenol pyruvate dependent phosphotransferase system. Sucrose is utilized directly by *S. mutans* mostly via PTS, than via prior hydrolysis to glucose and fructose by invertase. The intracellular product, sucrose 6-phosphate is then cleaved by a sucrose 6-phosphate hydrolase, yielding glucose 6-phosphate and fructose. The sucrose 6-phosphate hydrolase has dual specificity for sucrose 6-phosphate and sucrose. Sugar phosphates are subsequently integrated into the catabolic pathways, which in the case of the oral streptococci is predominantly the EM pathway.

Maltose, lactose, fructose and glucose can be used by the oral flora for the synthesis of bacterial cell walls, capsular and intracellular polysaccharides and organic acids. The bulk of glucosyl and fructosyl moieties of sucrose are fermented to organic acid products. Sucrose is unique in that it can also serve in the formation of insoluble extracellular polysaccharides and thereby enhance plaque formation and microbial aggregation on the tooth surface. Of considerable ecological significance are some of the properties of these extracellular glucans, which are high molecular weight polymers of glucose. Many are sticky and insoluble, which makes them more resistant to oral bacterial degradation. Glucans cause clumping of specific strains of oral bacteria and can be adsorbed onto hydroxyapatite. Although the adherence of *S. mutans* to smooth surfaces is greatly increased by the production of glucans in the presence of sucrose, these organisms can attach to surfaces in the absence of sucrose, but at much lower levels.

Other Dietary Components of Dental Caries

Lipids. The medium chain fatty acids and their salts have antibacterial properties at low pH. The mechanism of action is not well defined. They serve as anionic surfactants and uncouple substrate transport and oxidative phosphorylation from electron transport in bacteria. Changes in cell permeability may be involved. Potassium nonanoate has been studied because, when added to a cariogenic diet fed to rats, it produced a significant reduction in the caries score. Human studies with a daily mouthwash containing nonanoate have demonstrated a change in the plaque flora, including a reduction in the proportion of acidogenic organisms. The potential of lipids as anticariogenic food additives requires further exploration.

Vitamin. The vitamin content of the diet has been reported by many workers to have a significant effect on dental caries incidence. Vitamin A deficiency has definite effects on developing teeth in animals and presumably in human beings as well, although only a few reports on dental disturbances in vitamin A deficiency in humans are available in literature. Vitamin D has probably been investigated with greater

thoroughness in relation to dental caries than any other vitamin. There is general agreement on the necessity of vitamin D for the normal development of the teeth. Malformation, particularly enamel hypoplasia, has been described in the deficiency state by many workers. The relation of rickets to dental caries is not well defined, however. The only possible way in which infantile rickets could influence dental caries incidence is through an alteration in tooth structure, which makes the teeth more susceptible to caries. Pertinent clinical studies are not in agreement and many of the earlier studies are particularly confusing because of inaccurate reporting of data. Subsequent studies on the permanent teeth showed no differences in the caries incidence between the rachitic and control groups.

The effect of vitamin D supplement on the dental caries experience has also been studied to determine whether this might be of significant benefit. The evidence indicates that vitamin D supplements may reduce dental caries increment, particularly in children who may not be receiving adequate vitamin D. Ingestion of vitamin D in excess of adequate metabolic requirements has only a questionable effect on the caries experience. Although the effect of vitamin D on the dental caries experience is uncertain, its effect on forming dental structures cannot be overemphasized.

Vitamin K has been tested as a possible anticaries agent by virtue of its enzyme-inhibiting activity in the carbohydrate degradation cycle. There are no known effects of vitamin K deficiency on dental caries incidence.

Dreizen and his coworkers (1947) studied the effect of vitamin B deficiency diseases on dental caries in children. The malnourished children presented a remarkably lower caries increment than the group of well-nourished children. The data suggest that vitamin B complex deficiency may exert a caries-protective influence on the tooth, since several of the B vitamins are essential growth factors for the oral acidogenic flora and also serve as components of the coenzymes involved in glycolysis. Vitamin B_6 (pyridoxine) has been proposed as an anticaries agent on the hypothetical ground that it selectively alters the oral flora by promoting the growth of non-cariogenic organisms, which suppress the cariogenic forms (Strean, 1957). Slight to significant reduction in the caries increment of children and pregnant women have been reported following the use of pyridoxine-containing lozenges after each meal.

Vitamin C deficiency is well recognized for producing severe changes in the periodontal tissues and pulps of the teeth. A few studies have also been carried out to determine whether scurvy might be related to dental caries incidence or whether ascorbic acid supplements might prevent dental caries. The available scientific evidence indicates that there is no relation between scurvy and increased caries incidence in the human being. Furthermore, there is no evidence to indicate that vitamin C supplements would in any way protect against dental caries.

The calcium and phosphorus dietary intake has been popularly related to the dental caries experience, although the scientific evidence for this correlation is lacking. Disturbance in calcium and phosphorus metabolism during the period of tooth formation may result in severe enamel hypoplasia and defects of the dentin. But a calcium disturbance occurring after tooth formation has been completed, results in no changes in tooth substance itself. Albright and his associates in 1934 studied 16 cases of human hyperparathyroidism and noted that even though there was severe loss of calcium from the bone, the teeth remained intact.

The literature is replete with studies which show that phosphates are effective cariostatic agents when added to the cariogenic diets of laboratory rodents (Nizel and Harris, 1964). Their effectiveness depends on the anions and cations with which they are combined and on the foodstuffs with which they are fed. The caries reduction in rodents given supplemental phosphates involves a mechanism, which operates after the teeth have erupted. The results of clinical tests of phosphate additives for the purpose of controlling human caries have been equivocal. Available evidence indicates that there is no relation between dietary calcium and phosphorus and dental caries experience.

The fluoride content of the diet and of specific foodstuffs, in particular, has been investigated by numerous workers. Varying amounts of fluoride are found in many plant substances, depending to some extent upon the fluoride content of the soil in which they were grown. In general, the leaves of plants contain more fluoride than the stems, and the skin of fruit contains more than the pulp. There has been little attempt made to study the dietary fluoride in relation to dental caries as has been done for the fluoride content of drinking water. Some workers believe that dietary fluoride is relatively unimportant compared to fluoride in the drinking water because of its metabolic unavailability.

The effect of two additional trace minerals, selenium and vanadium, present in drinking water and food in certain localities, has been investigated for possible effects on dental caries by Tank and Storvick. Their studies indicate that dental caries rates were significantly higher in permanent teeth of persons residing in seleniferous areas than in nonseleniferous areas, but that a decrease in dental caries rates of permanent teeth was observed with increasing vanadium concentrations. The significance of these findings has not been clarified.

Systemic Factors

There are certain factors, dissociated from the local environment or at least not intimately associated with it, which have been related to dental caries incidence and which may be conveniently discussed under this general heading.

Heredity

Heredity has been linked with the dental caries incidence in scientific literature for many years. In 1899, GV Black wrote, "When the family remains in one locality, the children living under the conditions similar to those of the parents in their childhood, the susceptibility to caries will be very similar in the great majority of cases. This will hold good even to the particular teeth and localities first attacked, the order of

occurrence of cavities, and the particular age at which they occur."

This racial tendency for high caries or low caries incidence, in some instances at least, appears to follow hereditary patterns. The fact that local factors may easily alter this tendency (e.g. exposure to a highly refined diet inducing high caries experience) would indicate that heredity does not exert a strong influence in determining individual caries susceptibility. That it is a factor, however, cannot be denied since even in the experimental conditions, definite caries-susceptible and caries immune strains of rats and hamsters have been developed. Some of the earlier studies aimed primarily at confirming this heredity–caries relationship were carried out on different races living in the same geographic areas. Unfortunately, in any such study, there are uncontrollable factors which cannot be compensated. Dietary habits, food likes and dislikes, cooking habits and even toilet habits such as toothbrushing frequency and methods are often passed down from generation to generation, parents to offspring, may ultimately confound the pure effects of heredity.

One of the most significant studies is that reported by Klein in 1946 on the results of examination of 5,400 persons in 1,150 families of Japanese ancestry. In this study, the DMF was established for each individual, and 30% of the fathers with the lowest DMF rate were designated arbitrarily as 'low DMF'. The 30% with the highest DMF were designated as 'high DMF', while the middle 40% were classified as 'middle DMF'. The same groupings were used for the mothers and for the sons and daughters of these parents. It was found that a 'high DMF' father and 'high DMF' mother produced offsprings with a 'high DMF' rate. On the other hand, if the father and mother were both 'low DMF', the children also were in a 'low DMF' group. The differences between these two extremes became more pronounced with increasing age. However, the results were so consistent that it was difficult to exclude the view that dental caries in children involved strong familial vectors, probably with a genetic basis and perhaps sex-linked (Fig. 9-6).

There is still no indisputable evidence that heredity *per se* has a definite relation to dental caries incidence. The possibility exists that if there is any such relation, it may be mediated through inheritance of tooth form or structure, which predisposes to caries immunity or susceptibility. The problem is of such complexity that more intensive investigation is necessary before any positive conclusions can be drawn.

Pregnancy and Lactation

Studies relating to lactation and caries incidence are too few to contribute any significant data for clarifying this problem. Evidence suggests that there is no correlation between the dental caries experience and pregnancy *per se* or between caries and the number of pregnancies. It should also be remembered

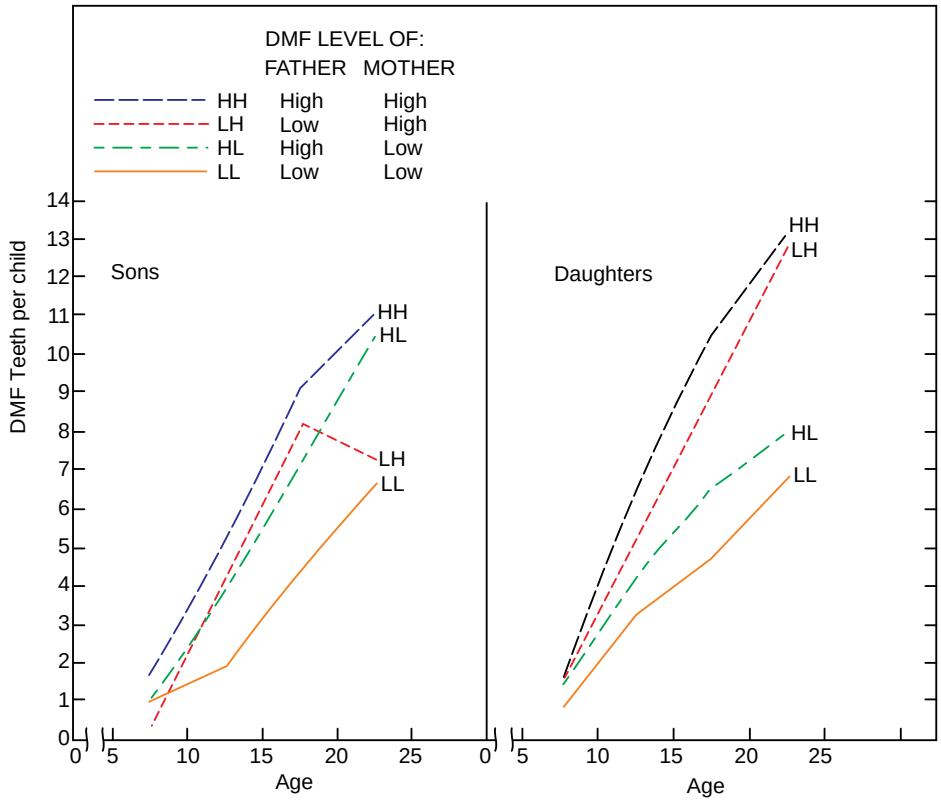


Figure 9-6. Heredity and dental caries.
The relation between DMF levels of sons and daughters and DMF levels of fathers and mothers, by age of offspring, is illustrated (From H Klein: The family and dental disease. IV: dental disease [DMF] experience in parents and offspring. J Am Dent Assoc, 33: 735, 1946).

that there is no mechanism for the physiologic withdrawal of calcium from teeth so that a developing fetus cannot calcify at the expense of the mother's teeth.

Deakins (1943) and Deakins and Looby (1943) studied the specific gravity of dentin as an indication of its mineral content and found that there were no significant differences in dentin samples from carious teeth of pregnant and nonpregnant women. They concluded that there was no calcium withdrawal from sound dentin during pregnancy.

It is a fairly common clinical observation that a woman, during the later stages of pregnancy or shortly after delivery, will manifest a significant increase in caries activity. In nearly all cases, thorough questioning will reveal that the woman has neglected her ordinary oral care because of the pressure of other duties attendant to the birth of the baby. Thus the increased caries incidence, though indirectly due to pregnancy, may actually be a local problem of neglect.

CLINICAL ASPECTS OF DENTAL CARIES

Clinical Classification of Caries

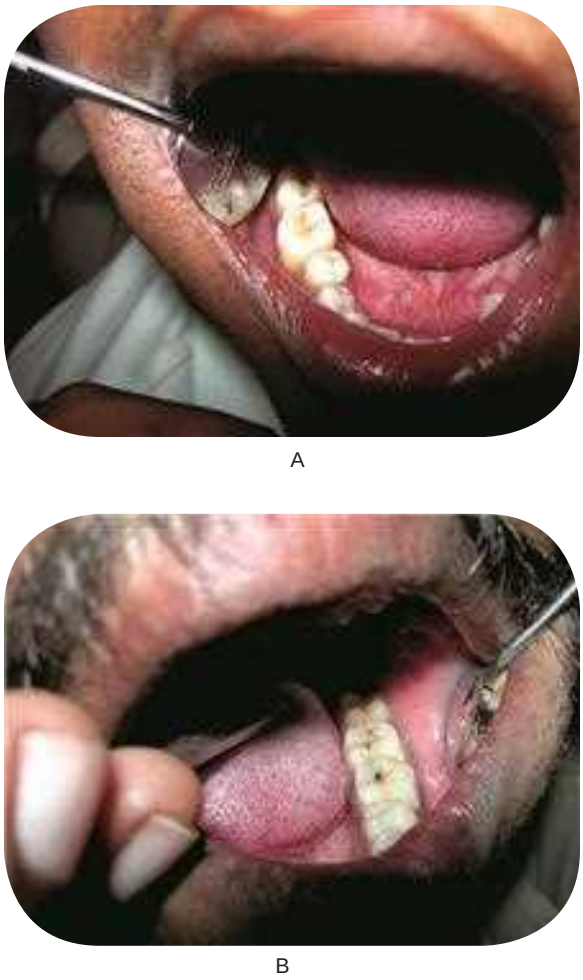
There is no universally accepted classification of dental caries. It may be classified according to three basic factors depending on morphology, dynamics and chronology.

According to the morphology or anatomical site of the lesion on an individual tooth, caries is classified as: (1) pit or fissure caries (Fig. 9-7 A, B), and (2) smooth surface caries.

Depending on the rate of carious progression, the process is classified as: (1) acute dental caries, and (2) chronic dental caries. It can also be a primary (virgin) caries, attacking previously intact surface (Fig. 9-8), or a secondary (recurrent) caries–occurring around the margins of a restoration (Fig. 9-9). It can also be classified as infancy (soother or nursing bottle caries) and adolescent caries based on chronology.

Pit and Fissure Caries. The commonest and simplest classification of dental caries is based on relative susceptibility of surfaces of teeth. Pit and fissure caries of the primary type develops on the occlusal surface of molars and premolars, buccal and lingual surface of the molars and the palatal surface of the maxillary incisors. Pits and fissures with high steep walls and narrow bases are those most prone to develop caries due to their mechanical characteristics, which result in poor self-cleansing features. These deep pits or fissures are sometimes considered developmental faults, particularly since the enamel in the extreme depth is often very thin or even occasionally absent. Deep and narrow pits and fissures favor the retention of food debris along with microorganisms, and caries may result from fermentation of this food and the formation of acid.

Pits and fissures affected by early caries may appear brown or black and will feel slightly soft and 'catch' a fine explorer point. The enamel directly bordering the pit or fissure may appear opaque bluish white as it becomes undermined. This undermining occurs through lateral spread of the caries at the dentinoenamel junction, and it may be a rapid process if the enamel in the base of the pit or fissure is thin.



A

B

Figure 9-7. A and B, Pit and fissure caries.

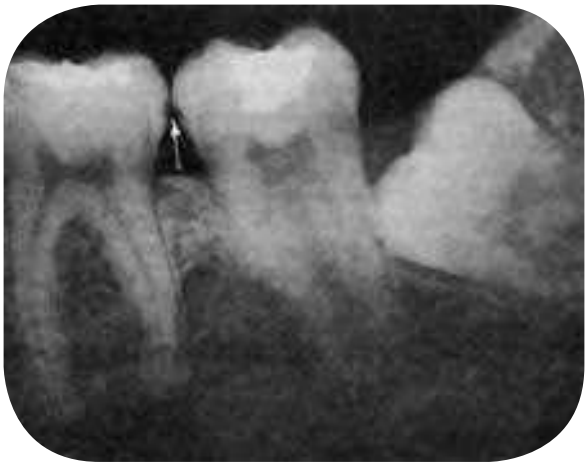
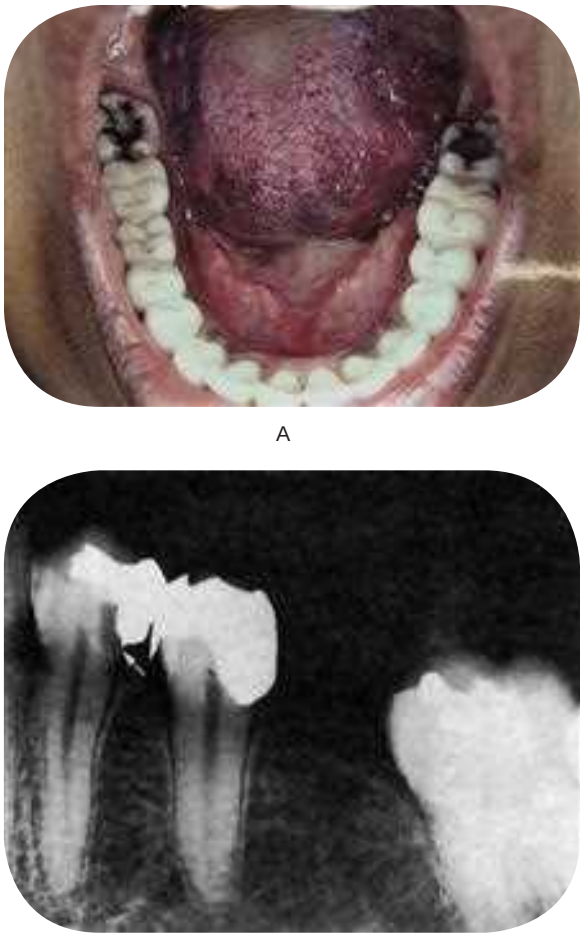


Figure 9-8. Primary caries of interproximal surfaces.

The lateral spread of caries at the junction as well as penetration into the dentin along the dentinal tubules may be extensive without fracturing away the overhanging enamel. Thus, there may be a large carious lesion with only a tiny point of opening. This undermined enamel may suddenly give way



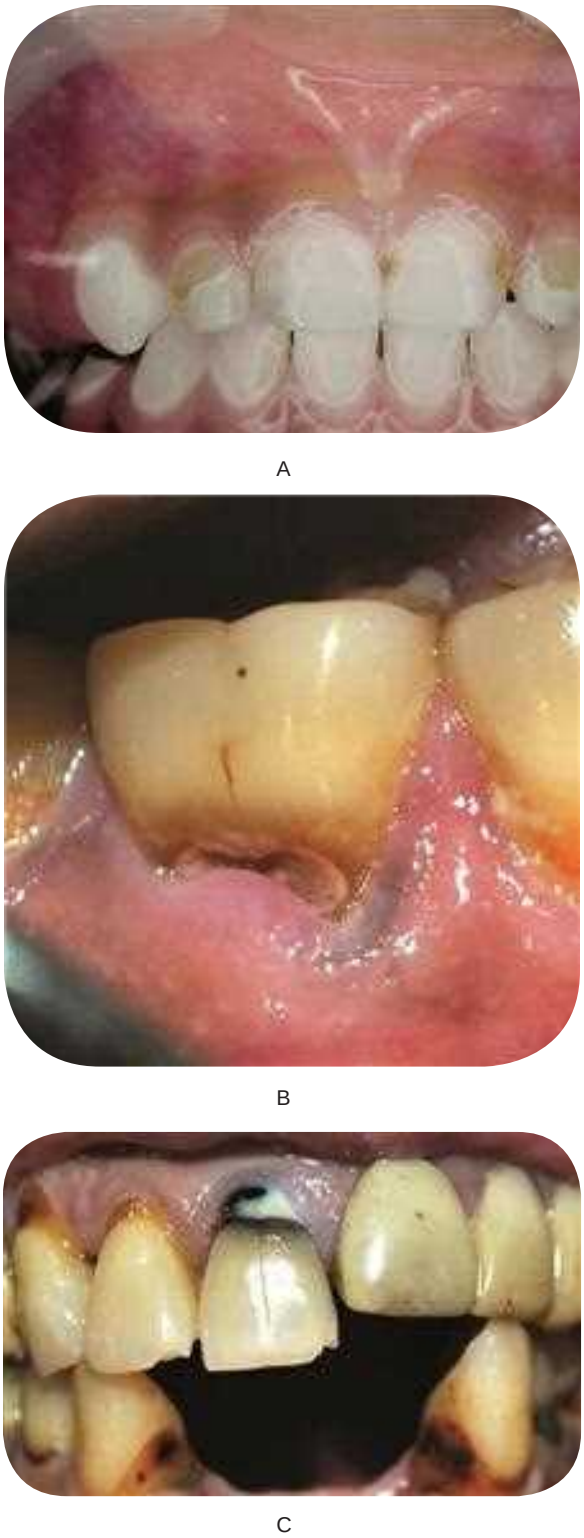
A

B

Figure 9-9. (A) Recurrent caries beneath a faulty restoration. (B) Secondary caries around the margins of restoration.
(A, Courtesy of Dr V Gopikrishna, Department of Conservative Dentistry, Meenakshi Ammal Dental College, Chennai).

under the stress of mastication, or the dentist may suddenly open into a large cavity when excavating the pit or fissure. This phenomenon was the origin of the mistaken idea of 'internal caries', the view that a tooth may decay from inside outward. Needless to say, a point of penetration is always present. It should not be inferred that all pit and fissure caries begin with a narrow penetration point and develop a large cavitation with overhanging enamel. In many cases, the lesion begins as an open cavity and becomes progressively larger. In this type of caries the progress of the disease is usually much slower and pulp involvement is often delayed.

Smooth Surface Caries. Smooth surface caries (Fig. 9-10A) of the primary type is caries that develops on the proximal surfaces of the teeth or on the gingival third of the buccal and lingual surfaces. Seldom does caries occur on other areas of the teeth, except in cases of malposed or malformed teeth, because of the self-cleansing properties of these areas. Unlike pit or fissure caries, which is not dependent on the development of a definite, grossly recognizable plaque for the initiation of caries, smooth surface caries is generally preceded by the formation of a microbial plaque. This ensures the retention of



A

B

C

Figure 9-10. (A) Smooth surface caries. (B) Cervical Caries. (C) Root Caries.
(Courtesy of A, Dr MS Muthu, Dr Sarath Asokan, Department of Pedodontics, Meenakshi Ammal Dental College, Chennai, Dr Joshua Sheih,Emmanuel Dental Clinic, Chennai and B, C, Dr Joshua Sheih,Emmanuel Dental Clinic, Chennai).

carbohydrate and microorganisms on the tooth surface in an area not habitually cleansed and subsequent formation of acid to initiate the caries process.

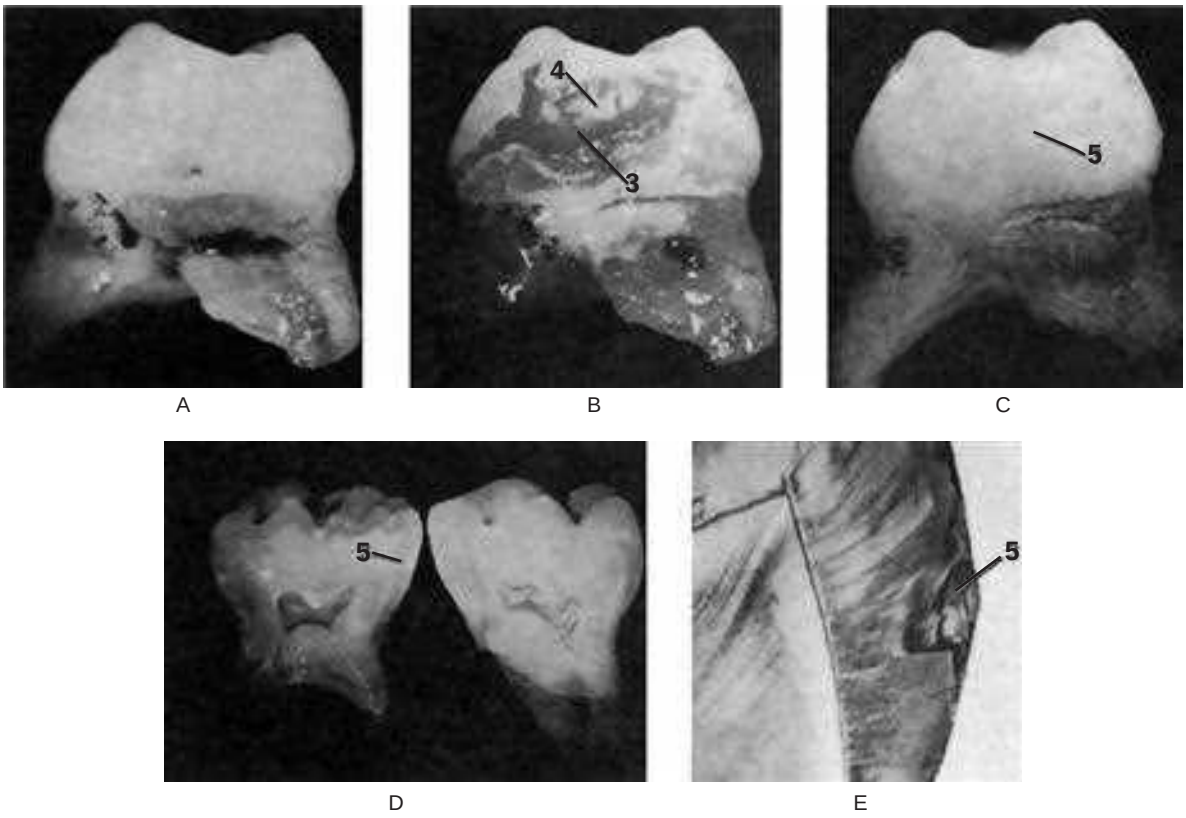


Figure 9-11. Smooth surface caries.
The bacterial plaque is difficult to see **(A)** unless stained by a disclosing solution **(B)**. The plaque (1) is disclosed by aqueous basic fuchsin. Note the absence of the plaque at the contact point (2). **(C)** The plaque is mechanically removed, revealing the chalky white spot of early enamel caries (3). **(D)** The tooth is split to show the extent of the carious lesion (3). **(E)** Photomicrograph of a ground section through the carious lesion (3).

Proximal caries usually begins just below the contact point and appears in the early stage as a faint white opacity of the enamel without apparent loss of continuity of the enamel surface (Fig. 9-11). In some cases it appears as a yellow or brown pigmented area, but in either event is usually rather well demarcated. The early white chalky spot becomes slightly roughened owing to superficial decalcification of the enamel.

As the caries penetrates the enamel, the enamel surrounding the lesion assumes a bluish-white appearance similar to that seen sometimes around carious pits or fissures. This is particularly apparent as lateral spread of caries occurs at the dentinoenamel junction. The more rapid type of caries usually produces a small area of penetration; the slower forms an open and shallow cavity. It is not uncommon for proximal caries to extend both buccally and lingually, but seldom does the cavity encroach upon areas accessible to excursion of food or to the toothbrush.

Linear Enamel Caries. An atypical form of dental caries that has been observed in the primary dentition of children in Latin American and Asian countries. The lesions predominate on the labial surface of the anterior maxillary teeth in the region of the neonatal line, which results from metabolic disturbances such as hypocalcemia or trauma at birth. A variant of the linear enamel form of caries in the primary teeth of children in the far East has been named odontoclasia. The morphological aspects of this type of caries are atypical and results in gross destruction of the labial surfaces of incisor teeth.

Cervical Caries. This type of caries occurs on buccal, lingual or labial surfaces and usually extends from the area opposite the gingival crest occlusally to the convexity of the tooth surface marking the self-cleansing portion of this surface. It extends laterally towards the proximal surfaces, and on occassion, extends beneath the free margin of the gingiva (Fig. 9-10B). Thus, the typical cervical carious lesion is a crescent-shaped cavity beginning, as a slightly roughened chalky area which gradually becomes excavated. Cervical caries is almost always an open cavity and does not present the narrow point of penetration seen commonly in pit or fissure caries and proximal caries. Cervical caries occurs on any tooth without predilection and is directly related to lack of oral hygiene. Of all forms of dental caries on different areas of the tooth, there is least excuse for cervical caries, since it can be prevented in nearly every instance by proper oral hygiene practice.

Root Caries. Root caries is defined by Hazen and his colleagues as "a soft, progressive lesion that is found anywhere on the root surface that has lost connective tissue attachment and is exposed to the oral environment". This type of caries is predominantly found in dentitions of the older age groups with significant gingival recession and exposed root surfaces (Fig. 9-10C). At one time, it was also referred to as 'caries of cementum'. Root

caries initiates on mineralized cementum and dentin surfaces which have greater organic component than enamel tissue. Root surface caries in contemporary populations occurs most frequently on the buccal and lingual surfaces of roots.

There are few published studies on the prevalence of root caries. However, it is generally recognized that the longer lifespan of persons today, with the retention of teeth into the later decades of life, has increased the number of people in the population exhibiting gingival recession with clinical exposure of cemental surfaces and, thereby, probably increasing the prevalence of root caries. Enamel may become secondarily involved if it is undermined during the progression of the lesion. Dental plaque and microbial invasion are an essential part of the cause and progression of this lesion. However, there is some evidence that the microorganisms involved in root caries are different from those involved in coronal caries, being filamentous rather than coccal.

Microorganisms appear to invade the cementum either along Sharpey's fibers or between bundles of fibers, in a manner comparable to invasion along dentinal tubules. Since cementum is formed in concentric layers and presents a lamellated appearance, the microorganisms tend to spread laterally between the various layers. Irregular mineralization on this cemental surface may often be seen at the same time, probably representing the beginning of calculus formation. After decalcification of the cementum, destruction of the remaining matrix occurs similar to the process in dentin, with ultimate softening and destruction of this tissue. As the caries process continues, there is invasion of microorganisms into underlying dentinal tubules, subsequent matrix destruction and finally pulpal involvement.

Most investigators have felt that once caries involves the dentin, the process is identical with coronal dentinal caries. However, it has been pointed out that since there are more dentinal tubules per unit area in the crown than in the root of the tooth, one may expect differences in the rate of caries progression and the amount of dentinal sclerosis present. The intraoral distribution patterns for root caries revealed that the teeth most frequently affected were the mandibular molars, the mandibular premolars, and the maxillary canines in descending order. The mandibular incisors were the least frequently affected teeth. It was also noted that the interproximal surfaces were affected most frequently in the maxillary arch, while the buccal surfaces were attacked most frequently in the mandibular arch.

The effect of fluoride on root caries was studied by Stamm and Banting, and the authors concluded that the lifelong consumption of fluoridated water is capable of significantly reducing the prevalence of root surface caries, which may itself be a growing dental public health problem in the adult population.

Classification Based on Severity and Rate of Progression

Acute Dental Caries. Acute dental caries is that form of caries which runs a rapid clinical course and results in early pulp involvement by the carious process. It occurs most frequently in children and young adults, presumably because the dentinal tubules are open and show no sclerosis. The process is usually so rapid that there is little time for the deposition of reparative dentin.

The initial entrance of the carious lesion remains small, while the rapid spread of the process at the dentinoenamel junction and diffuse involvement of the dentin produce a large internal excavation. It has been suggested that saliva does not easily penetrate the small opening to the carious lesion so that, as acids are formed, there is little opportunity for buffering or neutralization. In acute caries the dentin is usually stained light yellow rather than the darker brown of chronic caries (Fig. 9-12). Pain is more apt to be a feature of acute caries than of chronic caries, but this is not an invariable finding.

Rampant Caries. A condition which is characterized by sudden, rapid and almost uncontrollable destruction of teeth, affecting surfaces of teeth that are relatively caries free. These include the proximal and cervical surfaces of the mandibular incisors which are normally relatively caries free. A caries increment of 10 or more new carious lesions over a period of about one year is characteristic of rampant caries. Rampant caries (Fig. 9-13) is most often observed in the primary dentition of young children and the permanent dentition of teenagers. Dietary factors affecting oral substrate and oral flora and physiological factors affecting saliva are often significant in the development of rampant caries.

Nursing Bottle Caries. Is also called nursing caries, baby bottle syndrome, and bottle mouth syndrome. This is an unfortunate form of rampant caries affecting the deciduous dentition. It has been variously attributed to prolonged use of:

- A nursing bottle containing milk or milk formula, fruit juice or sweetened water
- Breastfeeding
- Sugar or honey-sweetened pacifiers.

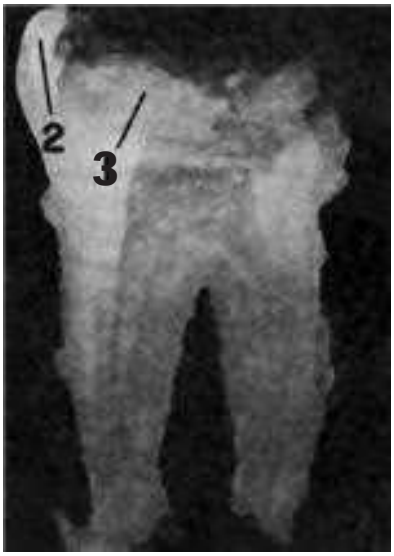


Figure 9-12. Acute dental caries.
There is accumulation of soft, necrotic dentin (1) and undermined enamel (2).

Figure 9-13. Rampant caries.
(Courtesy of Dr Sarath Asokan, Meenakshi Ammal Dental College, Chennai).

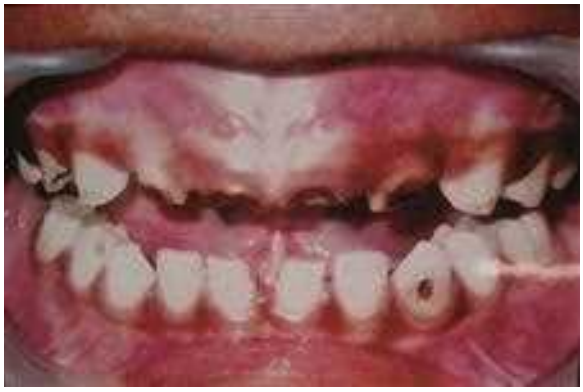


Figure 9-14. Nursing bottle caries.
Destruction of maxillary incisors.

Almost invariably, there is habitual use of one of the above after one year of age, usually as an aid for sleeping at night or at naptime.

The disease presents clinically as widespread carious destruction of deciduous teeth, most commonly the four maxillary incisors, followed by the first molars and then the cuspids if the habit is prolonged. It has been emphasized that it is the absence of caries in the mandibular incisors which distinguishes this disease from ordinary rampant caries (Fig. 9-14). The carious process in affected teeth may be so severe that only root stumps remain.

When milk or other forms of carbohydrate are cleared rapidly from the mouth, they are not highly cariogenic. However, if they pool in the mouth when the baby falls asleep, the repetitious act soon leads to severe caries. The mandibular incisors usually escape because they are covered and protected by the tongue. It is essential that parents be made aware of this condition.

Adolescent Caries. There are two chronological periods when acute, rapidly progressing caries is commonly observed. Acute exacerbations in caries rates are usually seen at 4–8 years of age and at 11–18 years of age. The acute caries attack in the latter period is usually characterized as adolescent caries. These are usually seen in teeth and surfaces that are relatively immune to caries, with a relatively small opening in enamel and with extensive undermining of enamel. Because of rapid progression of lesion there is little time for the formation of reparative dentin. It is important to detect cases of rampant caries in the adolescent at an early stage so that preventive procedures may be rigorously applied.

Chronic Dental Caries. Chronic dental caries is that form which progresses slowly and tends to involve the pulp much later than acute caries. It is most common in adults. The entrance to the lesion is almost invariably larger. Because of this there is not only less food retention, but also greater access of saliva. The slow progress of the lesion allows sufficient time for both sclerosis of the dentinal tubules and deposition of reparative dentin in response to adverse irritation. The carious dentin is often stained dark brown.

Although there is considerable surface destruction of tooth substance, the cavity is generally a shallow one with a minimum softening of dentin. There is little undermining of enamel and only moderate lateral spread of caries at the dentinoenamel junction. Pain is not a common feature of chronic caries because of the protection afforded to the pulp by secondary dentin.

Recurrent Caries. Recurrent caries is that type which occurs in the immediate vicinity of a restoration. It is usually due to inadequate extension of the original restoration, which favors retention of debris, or to poor adaptation of the filling material to the cavity, which produces a 'leaky margin'. In either event, the renewed caries follows the same general pattern as primary caries. It has been thought that recurrent caries occurs beneath restorations where the carious dentin has not removed before inserting the filling.

Arrested Caries. Arrested caries has been described as caries which becomes static and does not show any tendency for further progression. The deciduous and permanent dentitions are both affected by this condition. It occurs almost exclusively in caries of occlusal surfaces and is characterized by a large open cavity in which there is lack of food retention and in which the superficially softened and decalcified dentin is gradually burnished until it takes on a brown stained, polished appearance and is hard. This has been referred to as 'eburnation of dentin' (Fig. 9-15). Sclerosis of dentinal tubules and secondary dentin formation commonly occur in cases of arrested caries.

Another form of arrested caries is that sometimes seen on the proximal surfaces of teeth in cases in which the adjacent approximating tooth has been extracted, revealing a brown stained area at or just below the contact point of the retained tooth. This represents very early caries which, in many cases, is arrested following the extraction because of the formation of a self-cleansing area.

Caries arrest following the topical application of stannous fluoride solution has been reported by Muhler in as high as 22–25% of tooth surfaces originally diagnosed as carious. When areas that had been considered incipient carious lesions, demineralized areas, etchings or frank carious lesions were

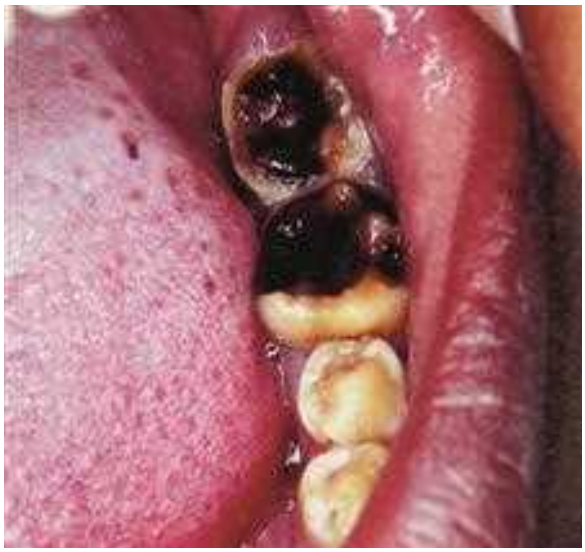


Figure 9-15. Arrested caries.
The dentin is dark brown, hard and shiny. The enamel is not appreciably undermined *(Courtesy of Dr Spencer Lilly, Meenakshi Ammal Dental College, Chennai).*

treated with the stannous fluoride solution, teeth appeared to be apparently sound, but manifested certain typical acquired characteristics:

- The presence of brown pigmentation
- The change from a soft to a hard texture
- The change from a chalky whiteness to light brown
- No increase in the size of the lesion
- No further progress of the lesion as long as the pigmentation remained.

Muhler stated that smaller the size of the lesion at the time of the initial application of stannous fluoride, greater the chance of caries arrest.

Radiation Caries. The development of rampant caries in patients undergoing radiation therapy in the head and neck region is referred to as radiation caries. It differs from the other types of caries by involving the cusp tips, incisal edges and the cervical areas. Rate of progression is faster when compared to the former. It starts as a diffuse area of demineralization encircling the entire crown of the tooth at the cervical portion and proceeds further to result in amputation of the crown at the gingival margin.

It is widely accepted that xerostomia is one of the complications of radiation to the head and neck region due to the involvement of salivary glands by the radiation. Besides the reduced salivary secretion there is change in the properties of saliva, which include increased viscosity, low pH. Multiple doses of radiation also weaken the dentinoenamel junction.

Frank et al, 1965 and Baden, 1970 described three forms of dental defects following irradiation namely,

1. A characteristic caries like lesion usually completely encircle the neck of the tooth. Amputations of the crowns may occur due to this type of lesion. Sometimes extension to labial, buccal, or lingual surfaces is also observed.
2. Brown to black discoloration of the crown. The occlusal surface of posterior teeth and incisal edges of anterior teeth wear away.
3. A spot depression which spreads from incisal or occlusal edges on the labial or buccal and lingual surfaces.

In time, the enamel is destroyed with partial disintegration of dentin leaving the crown reduced to an irregularly shaped discolored stump projecting over gingiva.

The effect of X-rays upon the cellular elements in human saliva in experiments on healthy male adults was studied by Watanabe and he showed an increased threshold of leukopedesis of mature leukocytes into saliva. The duration of this increased leukopedesis was dependent upon the amount of radiation.

Experiments of Selvaraj and Sbarra showed the role of the host in dental caries development. Lesser hydrogen peroxide production and impaired bactericidal activity was obtained in phagocytizing neutrophil leukocytes isolated from irradiated animals was noted by them. The association of irradiation caries with increased migration of neutrophil leukocytes into the oral cavity and increased excretion of lysosomal enzymes into the oral environment should be considered in dental caries development research as quoted by Janez John Gabrovsek.

Enamel Caries Remineralization

This process, also described under the terms 'caries reversibility' and 'consolidation' of the early enamel carious lesion, has received increased attention in recent years, chiefly due to recognition of its more common occurrence than formerly believed.

Clinical classification of caries

According to the anatomical site
- Pit or fissure caries
- Smooth surface caries

According to the rate of caries progression
- Acute dental caries
- Chronic dental caries

According to the nature of attack
- Primary (virgin) caries
- Secondary (recurrent) caries

Based on chronology
- Infancy caries (rampant caries)
- Adolescent caries

A natural biologia remineralizing process exists in the mouth which is responsible for the maintenance of tooth surfaces by precipitation of mineral salts from saliva. It is further suggested that the fluoride ion plays a role in stimulating the remineralization process by increasing the rate of deposition of calcium phosphate and enhancing the degree of remineralization achieved, and by becoming incorporated itself into the mineral, produces a remineralized enamel with a reduced acid solubility. Clinical evidence for the remineralization phenomenon occurring *in vivo* is well documented. It is also well established that this can only take place if cavitation has not occurred.

Caries Susceptibility of Jaw Quadrants, Individual Teeth and Tooth Surfaces

Caries Susceptibility of Jaw Quadrants. This has been shown by numerous investigators to exhibit a bilateral distribution between the right and left quadrants of both maxillary and mandibular arches. Although unilateral caries is found in some persons, it occurs with random distribution. In a relatively large sample of the population, the right and left sides of the mouth are involved with equal frequency. This horizontal relation is closer than either a vertical or a diagonal one. It was reported by Scott in 1944, for example, that bilateral caries was found in over 95% of a group of 300 persons whose dental radiographs were studied.

There is general acceptance of the numerous reports that the maxillary arch is more frequently involved by caries than the mandibular arch. This appears to hold true despite the extremely high incidence of carious mandibular first molars, since this is compensated for by the general immunity of mandibular anterior teeth. The reason for this difference between the arches in caries susceptibility is not well documented. It may relate to gravity and the fact that saliva with its buffering action would tend to drain from the upper teeth and collect around the lower. It is of interest that in the laboratory rat, mandibular caries far surpasses maxillary caries.

Caries Susceptibility of Individual Teeth. This has been studied by numerous investigators, and it has been found that, there is a definite order of caries attack for the different teeth of both the deciduous and the permanent dentitions.

Klein and Palmer in 1941 studied the problem of individual tooth susceptibility, pointing out that the teeth farthest back in the mouth are most frequently carious and that these are the teeth with the pits, fissures and broadest contact points.

The posteruptive tooth age is also an important factor, but probably minor compared to other factors such as tooth morphology, structure and position in the mouth as concluded by Healey and Cheyne.

Caries Susceptibility of Individual Tooth Surfaces. This has been found to exhibit considerable variation depending upon the morphology, location and posteruptive age.

HISTOPATHOLOGY OF DENTAL CARIES

The study of morphological and biochemical events of dental caries is challenging because of technical problems involved in the preparation of hard tissue for examination. The morphological changes associated with caries have been studied extensively. The principal manner in which caries of the enamel has been studied is through the use of ground sections of teeth that are usually between 60 μm and 100 μm in thickness. Since the carious process is one involving demineralization, the decalcification usually results in complete loss of enamel unless special methods are used. This has materially impeded the investigation of dental caries at the microscopic level. Microradiography of carious lesions offers the distinct advantage in that the photodensity of the image on the film is directly related to the amount of mineral. Microdensitometric tracings of this image permit quantitative measurement of the degree of demineralization. The application of transmission and scanning electron microscopy to the study of dental caries has added greatly to our understanding of this disease, as has utilization of other techniques, including histochemical studies, and the use of radioactive isotopes.

For ease of understanding, the histopathology of dental caries will be considered under the general headings of caries of enamel, of dentin, and of cementum.

Caries of the Enamel

Most of the histological description of enamel caries is in relation to early lesions. The carious process varies slightly depending on the occurrence of the lesion either on smooth surfaces or in pits and fissures. Accordingly, the caries of enamel is discussed under these headings.

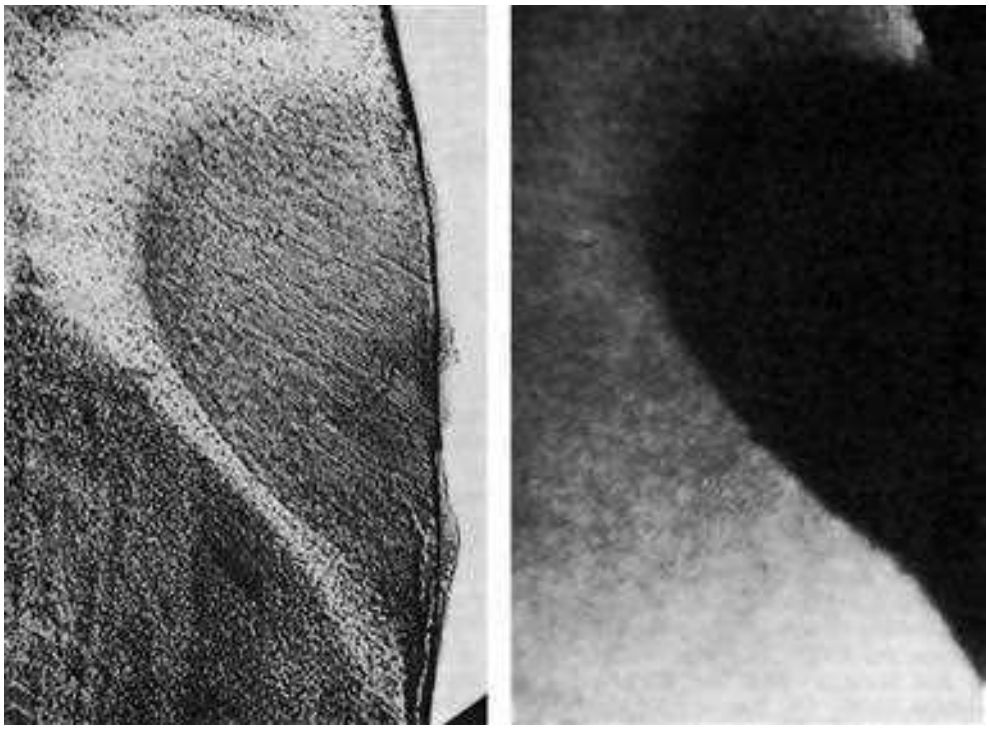
Smooth Surface Caries. The earliest macroscopic evidence of incipient caries on the smooth surface is the appearance of an area of decalcification beneath the dental plaque, which resembles a smooth chalky white area (Figs. 9-11, 9-16). It is best observed on an extracted tooth, usually at the cervical margin of the interdental facet referred to as white spot. The enamel surface overlying the white spot is hard and shiny and cannot be distinguished from the surface of adjacent sound enamel using a sharp explorer point. Intact surface lesions may also appear brownish when they are described as brown spots. This largely depends on the degree of exogenous material adsorbed by the porous region.

Study of early lesions by the transmission electron microscope, particularly by Scott and his associates, has revealed that the first change is usually a loss of the interprismatic or interrod substance of the enamel with increased prominence of the rods. In some instances, the initial change seems to consist of roughening of the ends of the enamel rods, suggesting that the prism may be more susceptible to early attack (Fig. 9-17). Another change in early enamel caries is the accentuation of the incremental lines of Retzius (Fig. 9-18). This conspicuous appearance of the calcification lines is an optical phenomenon due to loss of minerals, which causes the organic structures to appear more prominent. There may also be accentuation of perikymata which are the external manifestation of striae of Retzius.

Methods used to study dental caries

- Ground sections, especially using polarized light microscopy
- Microradiography
- SEM and TEM
- Histochemistry and radioisotopes

As this process advances and involves deeper layers of enamel, it will be noted that smooth surface caries, particularly of proximal surface has a distinctive shape. It forms a triangular or cone-shaped lesion with the apex toward the junction and



A B

Figure 9-16. Early enamel caries.
A photomicrograph through a chalky area of enamel **(A)** shows a demonstrable change without actual cavitation. The Grenz-ray picture **(B)** shows loss of mineral in this area *(Courtesy of Dr Edmund Applebaum)*.

Figure 9-17. Early enamel caries.
Electron photomicrograph of demineralized enamel showing microorganisms apparently localized within prisms in early stage of caries. The specimen was cut from a tooth slice and demineralized for 18 hours in 5% trichloroacetic acid. Original magnification: X 7500 *(Courtesy of Dr David B Scott; From DB Scott and JT Albright: Oral Surg, 7: 64, 1954).*

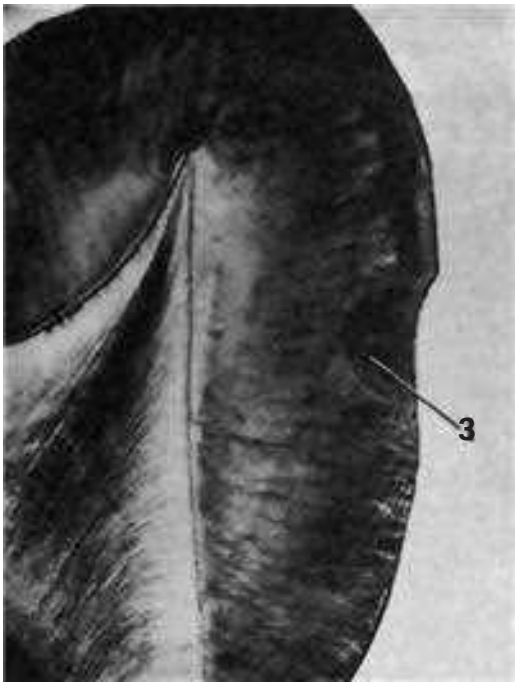


Figure 9-18. Early enamel caries.
Accentuation of striae of Retzius (1) as it crosses the carious lesion is illustrated.

the base toward the surface of tooth (Fig. 9-19). There is an eventual loss of continuity of the enamel surface, and the surface feels rough to the point of an explorer (Fig. 9-20).

Pit and Fissure Caries. The carious process in pits and fissures does not differ in nature from smooth surface caries except for its anatomical and histological variations.

Figure 9-19. Advanced enamel caries with early involvement of dentin.
The typical pyramidal shape of the proximal enamel lesion is apparent.

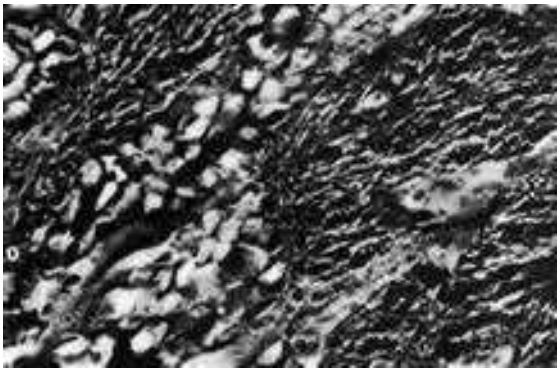


Figure 9-20. Advanced enamel caries.
Electron photomicrograph of demineralized enamel showing the presence of matrix fibrils in advanced stage of caries. A tooth slice was demineralized for 11 days in 5% formic acid, and the specimen was cut from the demineralized enamel. Original magnification: X 10,000 *(Courtesy of Dr David B Scott; from DB Scott and JT Albright: Oral Surg, 7: 64, 1954).*

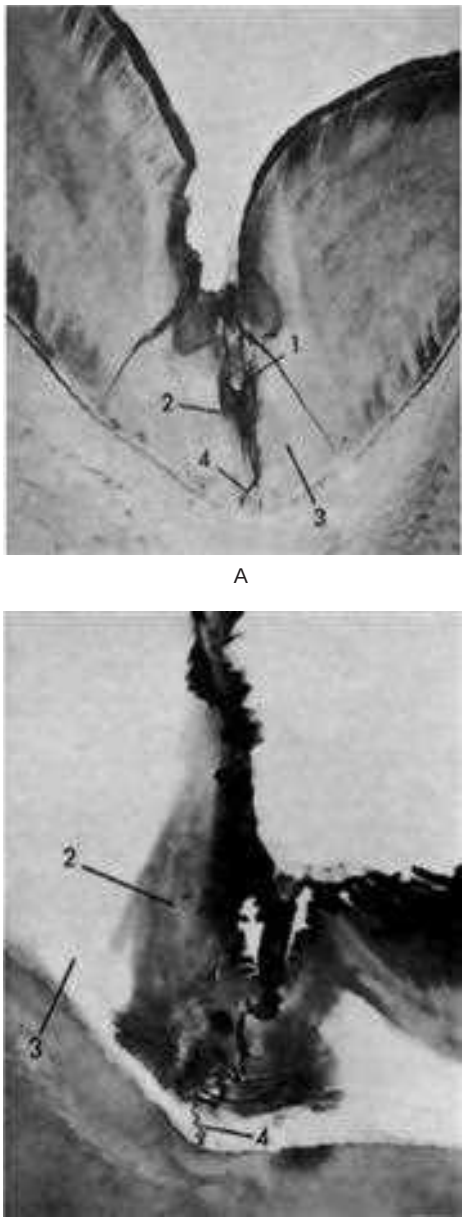


Figure 9-21. Fissure caries of enamel.
Ground section of tooth **(A)** shows the bacterial plaque (1), carious enamel (2) and noncarious enamel (3). The decalcified section **(B)** illustrates that the carious enamel (2) is not lost during preparation of the section as is noncarious enamel (3). Enamel lamella is shown at (4).

The occlusal fissures are deep invaginations of enamel that have been described as broad or narrow funnels, constricted hour glasses, multiple invaginations with inverted Y-shaped divisions and irregularly shaped (Fig. 9-21). The carious lesion starts along the fissure walls rather than at the base and visual changes such as chalkiness or yellow, brown or black discoloration may be seen. If the enamel in the bottom of the pit or fissure is thin, early dentin involvement frequently occurs. When caries occurs in a pit and fissure, it follows the direction of the enamel rods and characteristically forms a triangular or cone-shaped lesion with its apex at the outer surface and base toward the dentinoenamel junction (Fig. 9-22). It should be noted that the general shape of the lesion here is just the opposite of that occurring on smooth surface. Because of this, greater number of dentinal tubules are involved when the lesion reaches the dentinoenamel junction. Pit and fissure caries, usually produce greater cavitations than smooth surface caries.

The carious lesion is more prone to be stained with a brown pigment in pits and fissures. In newly erupted teeth, a brown stain is indicative of underlying decay, while in teeth of older individuals it may be due to arrested lesions. Occasionally, enamel lamellae are found at the base of pits and fissures and their role in caries initiation has been dealt with (Fig. 9-23). Histochemical staining of early lesions of enamel has shown them to be more permeable to methyl green and to contain free calcium ions detected with Alizarin red. Normal enamel

Figure 9-22. Fissure caries of enamel.
The lesion is pyramidal in shape and generally follows the direction of the enamel rods. Note the depth of the actual fissure (1).

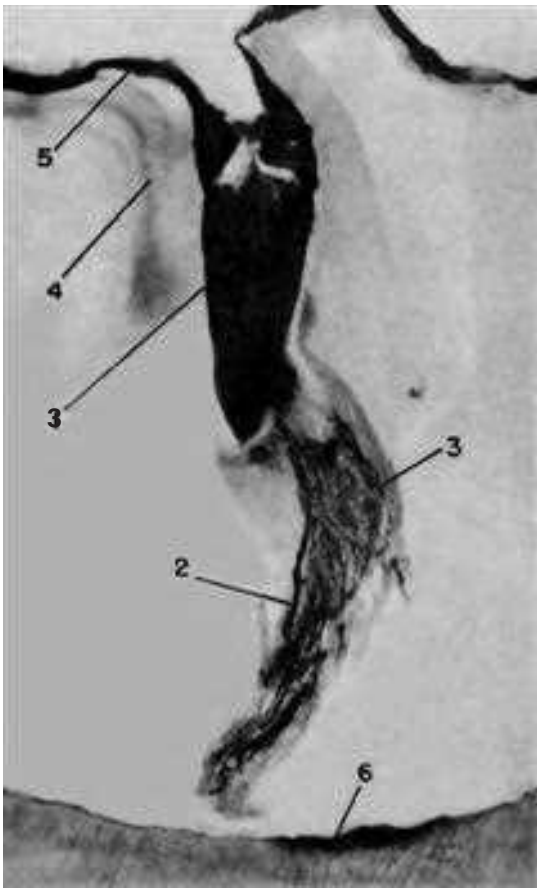


Figure 9-23. Fissure caries.
Decalcified section of a tooth demonstrating a bacterial plaque (1), enamel lamella (2), carious enamel (3), accentuated striae of Retzius (4), enamel cuticle (5) and early caries of dentin (6). *(Courtesy of Dr Edmund Applebaum)*.

remains uncolored by these dyes. Some lesions also react with PAS reagent in demineralized zones probably due to ingress of exogenous organic material rather than the release of endogenous mucoprotein in the enamel (Sullivan, 1954).

The histological features of the initial carious lesion in enamel have been described by a number of workers. Evidences support the concept that in early stages caries causes minimal damage to the outer smooth surface but considerable demineralization below the surface. The initial lesion has been divided into different zones based upon its histological appearance when longitudinal ground sections are examined with the light microscope. Four zones are clearly distinguishable, starting from the inner advancing front of the lesion. These are the: (1) translucent zone (2) dark zone (3) body of the lesion and (4) surface layer.

Zone 1. The translucent zone. This lies at the advancing front of the enamel lesion and is the first recognizable zone of alteration from normal enamel. It is not always present as only about half of the lesions demonstrate a translucent zone at their advancing front. It is observable when a longitudinal ground section is examined in a clearing agent having a refractive index identical to that of enamel. Quinoline is suitable since its refractive index is identical to that of the enamel (RI 1.62). When ground section is examined in transmitted light after imbibition with quinoline, the translucent zone appears structureless. The spaces or pores created in the tissue at this stage of enamel caries are located at prism boundaries and other junctional sites. Therefore, when the pores are filled with a medium having the same refractive index as enamel, normal structural markings are no longer visible. By means of polarized light it has been shown that this zone is slightly more porous than sound enamel, having a pore volume of 1% compared with 0.1% in sound enamel. The fluoride content of translucent zone enamel has shown to be increased relative to adjacent sound enamel beside preferential removal of magnesium and carbonate rich mineral without any evidence of protein loss.

Zone 2. The dark zone. This lies adjacent and superficial to the translucent zone. It has been referred to as the 'positive zone', because it is usually present. This zone is formed as a result of demineralization and appears dark brown in ground sections examined by transmitted light after imbibition with quinoline. Polarized light studies show that the dark zone has a pore volume of 2–4%. When examined with the polarizing microscope after imbibition with quinoline, the dark zone shows positive birefringence in contrast to the negative birefringence of sound enamel. These effects have been shown to be due to the presence of very small pores in the zone besides the relative large pores that are present in the first stage, the translucent zone (Fig 9-24). Therefore, when a ground section is examined in a mounting medium such as quinoline, the relatively large molecules of the medium are unable to penetrate the micro pore system of the dark zone. Since the micro pores remain filled with air or vapor, light is scattered on passing through the zone, causing brown discoloration of the dark zone. In a similar manner, the presence of a medium or low refractive index within the micro pore system is responsible for the reversal of birefringence when examined in polarized light. If a ground section is examined in an

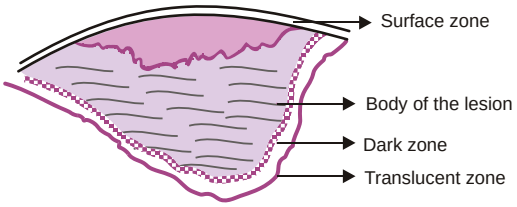


Figure 9-24. Histological zones of enamel caries

aqueous medium having a small molecule which penetrates the micro pores, the dark zone is no longer seen. The above work led to the conclusion that the formation of a micro pore system must be regarded as a result of demineralization. The increased level of demineralization in the dark zone of carious lesion has been confirmed with microradiography as the region of visible radiolucency often extends into it. It has been reported by some that the appearance of the dark zone was due to remineralization occurring at the advancing front of the lesion.

Zone 3. The body of lesion. This zone lies between the relatively unaffected surface layer and the dark zone. It is the area of greatest demineralization. In polarized light, the zone shows a pore volume of 5% in spaces near the periphery, to 25% in the center of the intact lesion. When a longitudinal ground section is examined in quinoline with transmitted light, the body of the lesion appears relatively translucent compared with sound enamel. However, the striae of Retzius within this region are well marked and therefore appear enhanced in contrast to the translucency of the area. When the section is examined with polarized light after imbibition with water, the body of the lesion shows as a region of positive birefringence in contrast to sound enamel. Microradiographs confirm the reduced mineral content of this zone and a reduction of 24% mineral per unit volume is noted compared with sound enamel and also a corresponding increase in unbound water and organic content due to the ingress of bacteria and saliva.

Zone 4. The surface zone. When examining an initial carious lesion with the polarizing microscope, the surface zone is an important feature. The quantitative studies of the surface zone indicate a partial demineralization of about 1–4% along with a pore volume of less than 5% of spaces. After imbibing with a medium like water, although the porous subsurface zone is seen to be positively birefringent, the surface zone retains a negative birefringence. This relatively unaffected surface zone is also identifiable on microradiographs as it is sharply demarcated from the underlying radiolucent regions of the lesion. Thus, the surface zone, when examined by the polarizing microscope has been defined as the zone of negative birefringence, superficial to the positively birefringent body of the lesion seen when the section is examined in water. It is important to realize that all the four histological zones of the initial enamel lesion cannot be seen when examined in a single medium.

The surface zone remains intact and also well mineralized because it is a site where calcium and phosphate ions, released by subsurface dissolution, become re-precipitated. This process is referred to as remineralization. The high fluoride concentration of enamel surface would favor remineralization.

Figure 9-25. Microorganisms in an enamel lamella or 'defect' isolated by acid-flotation from clinically noncarious enamel.
Original magnification: X 13,000 *(Courtesy of Dr David B Scott; from DB Scott and JT Albright: Oral Surg, 7: 64, 1954).*

The surface zone is thus maintained at a relatively low level of demineralization through lesion formation and progression. Eventually, the surface zone is demineralized, usually at the stage when the lesion has penetrated some way into the dentin.

Scott and Wyckoff reported that there is no direct relation between the occurrence of enamel lamellae and smooth surface caries on the basis of electron microscopic studies. They have pointed out that in those cases in which lamellae appear to be associated with caries, the association is only by chance (Fig. 9-25).

Ultrastructural Changes in Enamel Caries

Ultrastructural techniques in caries research have proved to be demanding because of difficulties involved in the preparation of ultra thin sections from enamel. The first alteration found in enamel is the scattered destruction of individual apatite crystals, both within the enamel prisms and at their boundaries. Studies attempting to describe features of carious enamel by transmission electron microscope reveal that progressive dissolution of crystals results in broadening of the intercrystalline spaces when seen in transverse sections. However, obvious spacing and damage to crystals were not detectable unless the sections came from areas having a pore volume of 10–25 %, which was identifiable only in the body of the enamel carious lesion. High resolution electron microscope shows that carious dissolution starts in the center of one end of the crystal and develops anisotropically along the lattice C-axis. Since dislocations or linear lattice defects are evident in biological or synthetic apatite, dissolution extends across accounting for greater demineralization. As the number of dissolved crystals increases, the densely calcified tissue becomes progressively more porous. In addition to crystal damage in the carious process, a different crystal form has been found at prism border in carious enamel.

A B

Figure 9-26. Early caries of dentin.
There is lateral spread of caries at the dentinoenamel junction.

These crystals at the prism boundary are larger, isodiametric and electron dense than elsewhere, their average size being greater than the crystals in sound enamel. These larger crystals are thought to be the result of remineralization of crystals that have resisted dissolution. Eventually, with diffuse destruction of the apatite crystals, numerous bacteria can be observed invading the enamel lesion.

Caries of the Dentin

Caries in enamel is clearly a dynamic process, but this tissue is devoid of cells and is therefore incapable of reacting in a vital manner; whereas dentin, being a part of the dentin pulp complex is able to mount a reparative response. Caries of the dentin begins with the natural spread of the disease process along the dentinoenamel junction and the rapid involvement of great numbers of dentinal tubules, each of which acts as a potential pathway leading to the dental pulp along which the microorganisms may travel at a variable rate of speed, depending upon a number of factors (Fig. 9-26). In some instances, carious invasion appears to occur through an enamel lamella so that little, if any, visible alteration in the enamel occurs. Thus, when lateral spread at the dentinoenamel junction takes place with the involvement of underlying dentin, a cavity of considerable size may form with only slight clinically evident changes in the overlying enamel.

Early Dentinal Changes. The initial penetration of the dentin by caries may result in alterations in the dentin previously described as dentinal sclerosis. This dentinal sclerosis is a reaction of vital dentinal tubules and a vital pulp in which there is calcification of the dentinal tubules that tends to seal them off against further penetration by microorganisms. The formation of sclerotic dentin is minimal in rapidly advancing caries and is most prominent in slow chronic caries. By reflected light the sclerotic dentin appears dark.

Zones of enamel caries

Translucent zone (TZ)
- First recognizable zone of alteration
- Advancing front of the lesion
- Half the lesions demonstrate TZ, not always present
- Seen in long GS in clearing (quinoline – RI – 1.62)
- TZ appears structureless
- Pore volume — 1% (compared to 0.1% of sound enamel)

Dark zone
- Lies adjacent and superficial to the translucent zone
- Positive zone
- Shows positive birefringence (in contrast to sound enamel)
- Pore volume of 2–4% (polarized light)
- Presence of small pores; large molecules of quinoline are unable to penetrate
- Micropore system — gets filled with air and become dark
- Medium like water may penetrate

Body of the lesion
- Between unaffected surface and dark zone
- Area of greatest demineralization
- Pore volume — 5% in periphery and 25% in center
- Quinoline imbibition — body appears transparent
- Water imbibition — positive birefringence compared to sound enamel
- Striae of Retzius — prominent

Surface zone
- Quantitative studies — partial demineralization of 1–10%
- Pore volume — less than 5% of the spaces
- Negative birefringence — water imbibitions
- Positive birefringence — porous subsurface

All the four zones of enamel caries cannot be seen with same immersion medium.

The appearance of fatty degeneration of odontoblast process, with the deposition of fat globules, precedes even the early sclerotic dentinal changes. The use of the term 'fatty degeneration' has been questioned since it is not a degenerative process. Two types of lipid staining have been seen, one of which is more superficial and probably of bacterial origin. The other type may be due to unmasking of lipids present in the intratubular dentin by demineralization. This can be demonstrated only by the application to fresh dentin of special stains such as Sudan red, which selectively stains fat. The significance of this phenomenon is not known, although it has been suggested that fat contributes to the impermeability of the dentinal tubules. Fatty degeneration may be a predisposing factor favoring sclerosis of the tubules.

Except in unusual cases of arrested caries, continued destruction of dentin inevitably occurs despite attempts at walling off one part of the tooth. The rate at which the carious destruction progresses, tends to be slower in older adults than in young because of the generalized dentinal sclerosis that occurs as a part of the aging process. Close examination of the dentin behind a zone of sclerosis formed in response to caries will reveal decalcification of the dentin, which appears to occur slightly in advance of the bacterial invasion of the tubules. In the earliest stages of caries, when only a few tubules are involved, microorganisms may be found penetrating these tubules before there is any clinical evidence of the carious process (Figs. 9-27, 9-28). These have been termed **pioneer bacteria.**

The initial decalcification of dentin involves the walls of the tubules, allowing them to distend slightly as they become packed with masses of microorganisms (Fig. 9-29). Study of individual tubules will usually show almost pure forms of bacteria in each one. Thus one tubule may be filled with

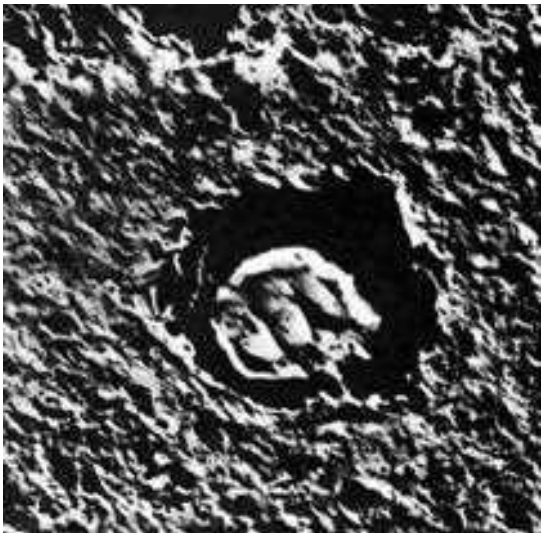


Figure 9-27. Caries of the dentin.
Electron photomicrograph of demineralized carious dentin showing bacteria in a dentinal fiber. Specimen cut from tooth slice and demineralized 3 days in 5% trichloroacetic acid. Original magnification: X 16,500 *(Courtesy of Dr David B Scott; from DB Scott and JT Albright: Oral Surg, 7: 64, 1954).*

Figure 9-28. Caries of the dentin.
Electron photomicrograph of demineralized carious dentin showing bacteria in a dentinal tubule. Specimen cut from tooth slice and demineralized 3 days in 10% acid. Original magnification: X 10,000 *(Courtesy of Dr David B Scott; from DB Scott and JT Albright: Oral Surg, 7: 64, 1954).*

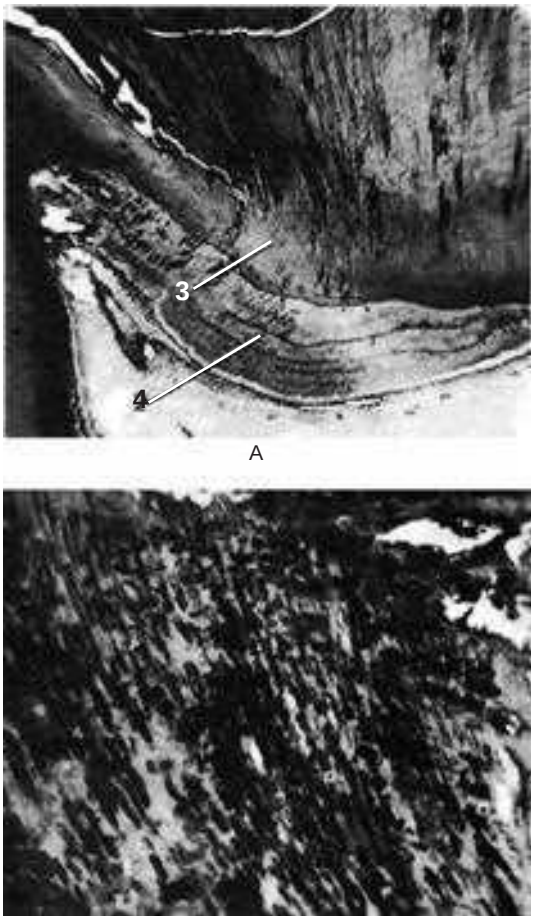


Figure 9-29. Caries of dentin.
The low-power photomicrograph **(A)** shows involvement of both primary (1) and secondary dentin (2) by the carious process. In the high-power photomicrograph **(B)** the dentinal tubules are seen packed with microorganisms.

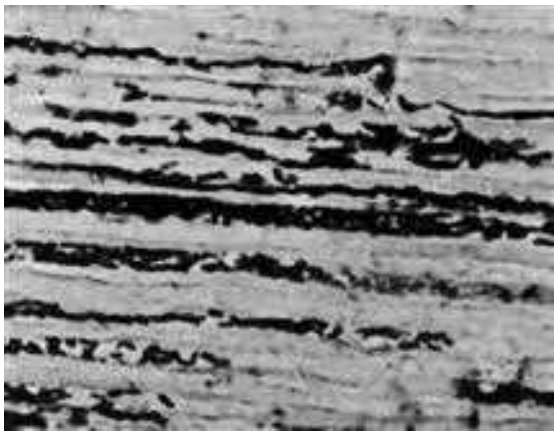


Figure 9-30. Microorganisms in individual dentinal tubules (Gram stain).

coccal forms, while the adjacent tubules may contain only bacilli or thread forms (Fig. 9-30).

It is evident that the microorganisms, as they penetrate farther and farther into the dentin, become more and more separated from the carbohydrate substrate upon which the bacteria depend. The high protein content of dentin would favor the growth of those microorganisms which have the ability to utilize this protein in their metabolism. Thus, proteolytic organisms would appear to predominate in deeper caries of the dentin, while acidogenic forms are more prominent in early caries.

The observation that the morphological type of the bacteria in deep carious dentin is different from that of the bacteria in initial caries substantiates the hypothesis that initiation and progression of dental caries are two distinct processes and must be differentiated. The evidence indicates that the organisms responsible for the initiation of caries are subsequently replaced by others as the environmental conditions occasioned by the advancing carious lesion are altered. Nevertheless, many microorganisms do have both acidogenic and proteolytic properties.

Advanced Dentinal Changes. The decalcification of the walls of individual tubules leads to their confluence, although the general structure of the organic matrix is maintained for some time.

A thickening and swelling of the sheath of Neumann may sometimes be noted at irregular intervals along the course of involved dentinal tubules, in addition to an increase in the diameter of dentinal tubules due to the packing of tubules by microorganisms (Fig. 9-31). Tiny 'liquefaction foci', described by Miller, are formed by focal coalescence and breakdown of a few dentinal tubules (Fig. 9-32). This 'focus' is an ovoid area of destruction, parallel to the course of the tubules and filled with necrotic debris which tends to increase in size by expansion. This produces compression and distortion of adjacent dentinal tubules so that their course is bent around the 'liquefaction focus'. In areas of interglobular dentin, decalcification and confluence of tubules occur rapidly. The presence of considerable amounts of interglobular dentin accounts for the rapid spread of caries in so-called malacotic or soft teeth.

It has been pointed out that acidogenic organisms are apparently responsible for the initial decalcification of dentin occurring in the caries process, but that another mechanism must be necessary for the ultimate destruction of the remaining organic matrix. The most logical explanation is that this matrix

Early dentinal caries

Fatty degeneration of odontoblast process

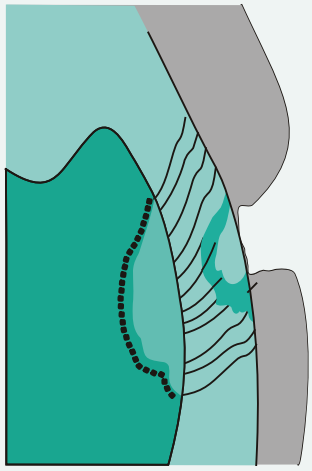
- Disposition of fat globules—precedes early sclerotic changes
- Special stains—Sudan red
- Significance
  - Fat contributes to impermeability
  - Predisposing factor for dental sclerosis

Sclerotic dentin

- Reaction of vital pulp—calcification of dentinal tubules (DT)
- Seals off DT from further penetration of microorganisms
- Minimal in rapidly advancing caries
- Prominent in slow caries
- Sclerotic dentin—appear white in transmitted light

Decalcification of dentinal tubules

- Above dentinal sclerosis → zone of decalcification
- Occurs in advance of bacterial invasion of DT
- Pioneer bacteria
- The initial decalcification → only the walls of DT
- Study of tubules → pure form of microorganisms



Zone of microbial invasion

- Proteolytic organisms—predominant in deeper layers
- Acidogenic microorganisms—more in early caries
- Supporting the hypothesis that initiation and progression are two distinct processes and must be differentiated

Figure 9-31. Caries of dentin.
Electron photomicrograph of demineralized carious dentin shows packing by bacteria of dentinal tubules cut in cross-section. Original magnification: X 10,000 *(Courtesy of Dr David B Scott)*.

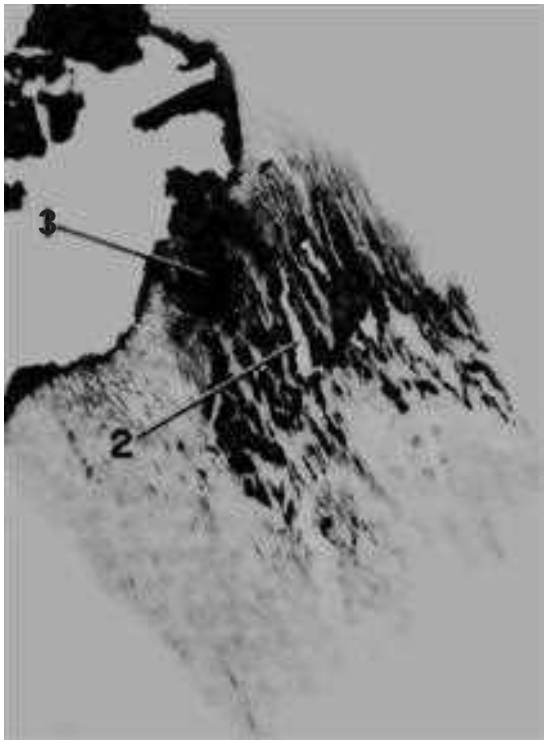


Figure 9-32. Caries of dentin.
The tubules contain microorganisms. There are liquefaction necrosis (1) and clefts (2) in the carious dentin (periodic acid-Schiff stain).

is destroyed by the action of proteolytic enzymes produced by microorganisms deep in the cavity. This enzymatic digestion is of maximal activity only when the organic matrix is decalcified; there is little effect on the intact dentin.

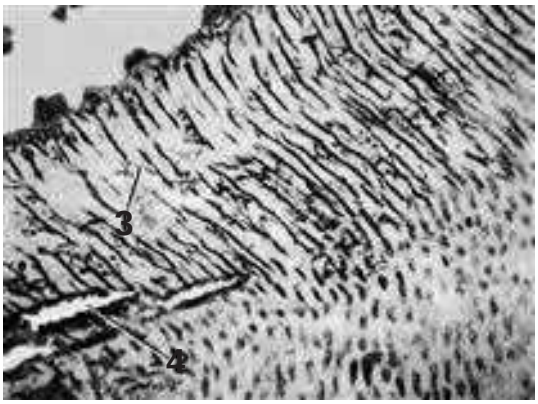


Figure 9-33. Caries of dentin.
Lateral branches of the dentinal tubules (1) are filled with microorganisms. Note the typical transverse clefts (2).

The destruction of dentin through a process of decalcification followed by proteolysis occurs at numerous focal areas, which eventually coalesce to form a necrotic mass of dentin of leathery consistency. Clefts are rather common in this softened dentin, although they are rare in chronic caries, since the formation of a great deal of softened necrotic dentin is unusual. These clefts extend at right angles to the dentinal tubules and appear to be due to extension of the carious process along the lateral branches of the tubules or along the matrix fibers which run in this direction (Fig. 9-33). These clefts parallel the incremental lines of the dentin, which are due to alternating resting periods during the calcification of the dentin. The clefts account for the manner in which carious dentin can often be excavated by peeling away thin layers with hand instruments.

As the carious lesion progresses, various zones of carious dentin may be distinguished which grossly tend to assume the shape of a triangle with the apex toward the pulp and the base toward the enamel. Beginning pulpally at the advancing edge of the lesion adjacent to the normal dentin, these zones are as follows:

Zone 1: Zone of fatty degeneration of odontoblast process
Zone 2: Zone of dentinal sclerosis characterized by deposition of calcium salts in dentinal tubules
Zone 3: Zone of decalcification of dentin, a narrow zone, preceding bacterial invasion
Zone 4: Zone of bacterial invasion of decalcified but intact dentin
Zone 5: Zone of decomposed dentin

Secondary Dentin Involvement. The carious involvement of secondary dentin does not differ remarkably from the involvement of primary dentin, except that it is usually somewhat slower because the dentinal tubules are fewer in number and more irregular in their course, thus delaying the penetration of the invading microorganisms. Sooner or later; however, the involvement of pulp results with ensuing inflammation and necrosis. Occasionally, caries will spread laterally at the junction of the primary and secondary dentin and produce a separation of the two layers.

Advanced dentinal caries

- Decalcification of the walls of DT→ confluence
- Thickening of sheath of Neumann → along its course
- Increase in the diameter of DT → microorganisms
- Focal coalescence of adjacent tubules and ovoid area of destruction → Liquefaction foci
- Acidogenic organisms—initial decalcification
- Proteolytic organisms—matrix destruction
- Multiple areas of destruction
- Necrotic mass of dentin (leathery consistency)
- Formation of transverse clefts
- Extend at right angles to DT and parallel contour lines
- Peeling away of carious dentin

DIAGNOSIS OF DENTAL CARIES

Radiographic Diagnosis

The radiograph is a necessary adjunct to a complete oral examination by the dentist. Although many carious lesions are accessible and visible for easy diagnosis, there is a great percentage of lesions, chiefly interproximal in location, which are not found by the routine examination with mouth mirror and explorer. It has been pointed out previously that the use of radiograph may reveal 50% more cavities than may be found by visual examination alone.

The interproximal carious lesion is most easily recognized on the radiograph and appears in early lesions as a small, triangular radiolucent area of enamel, and later of the dentin, occurring approximately at the contact point (Fig. 9-34). Though radiograph is of little value in the diagnosis of occlusal cavities, because of the irregularity of the surface and the superimposition of cusps, it plays a significant role in assessing the proximity to the pulp chamber (Fig. 9-35). The radiograph is similarly unsuited for use in the detection of small cavities in buccal or lingual pits or at the cervical margin.

Alternative methods for early detection of dental caries have been emphasized to understand the nature of the carious process. Among the newer technologies that are being explored, a few of interest are discussed in brief.

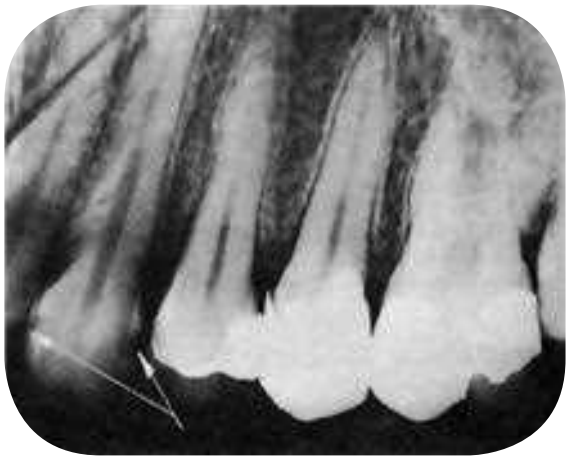


Figure 9-34. Interproximal caries.

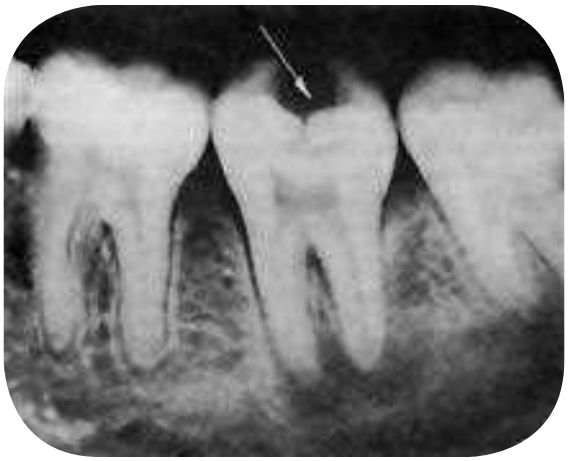


Figure 9-35. Occlusal caries (with periapical involvement).

Infrared Laser Fluorescence

Infrared laser fluorescence instrument was developed for the detection and quantification of dental caries of occlusal and smooth surfaces. It uses a laser light source and a fiberoptic cable that transmits the light to a handheld probe with a fiberoptic eye at the tip. The light is absorbed and induces infrared fluorescence which is collected at the probe tip and transmitted through ascending fibers, and processed and presented on a display window as an integer between 0 and 99. Increased fluorescence reflects carious tooth substance particularly for numerical value higher than about 20. The material responsible for fluorescence is under investigation but appears to be bacterial metabolites, particularly porphyrins.

Digital Imaging Fiberoptic Transillumination

Conventional clinical caries examination routinely use transillumination to identify lesions located on interproximal surfaces of anterior teeth. Recently, fiberoptic transillumination has become available for clinical use. It provides an intense light beam that is transmitted through a fiberoptic cable to a specially designed probe to permit the use of transillumination on the proximal surfaces of posterior teeth.

Digital imaging fiberoptic transillumination is a further advancement of this technology in which the visually observed images are captured using a digital charged coupled device camera and sent to a computer for analysis, using dedicated algorithm.

Quantitative Light Fluorescence

Quantitative light fluorescence (QLF) is a dental diagnostic tool for quantitative assessment of dental caries lesions, dental plaque, bacterial activity, calculus, staining, and tooth whitening. QLF uses the principle of fluorescence to detect dental caries. With QLF, real-time fluorescent images are

captured into the computer and stored in an image database. Optional quantitative analysis tools enable the user to quantify parameters like mineral loss, lesion depth, lesion size, stain size and severity with high precision and repeatability. The QLF method is based on the autofluorescence of teeth. When teeth are illuminated with high intensity blue light, they will start to emit light in the green part of the spectrum. The contrast between demineralized enamel and sound enamel increases almost by a factor of 10. The digital image processing system calculates the size and severity of the lesion.

METHODS OF CARIES CONTROL

The control of dental caries presents one of the greatest challenges that must be dealt with by the dental professionals. It is not sufficient that we try to perfect techniques to repair damage to the dental apparatus once it has occurred. It has been a general failing of the healing profession that the treatment of disease has been overemphasized and prevention minimized. Research in dentistry for a better understanding of the carious process has not been lacking and there have been definite accomplishments in the field of caries control. Methods are at hand for producing a substantial reduction in dental caries experience, provided that the patient are properly educated. The most promising methods of caries control will be discussed in this section, along with the experimental evidence upon which their use has been predicted. These suggested methods of control may be classified into three general types:

1. Chemical measures
2. Nutritional measures
3. Mechanical measures.

CHEMICAL MEASURES OF CARIES CONTROL

A vast number of chemical substances have been proposed to control dental caries. The use of some of these have been both emperial and based on experimental evidence. These include substances which:

- Alter the tooth surface or tooth structure
- Interfere with carbohydrate degradation through enzymatic alterations
- Interfere with bacterial growth and metabolism.

In the light of our present knowledge, each of these may theoretically be of benefit in controlling caries. The final proof, however, depends on thorough clinical trials.

Substances which Alter the Tooth Surface or Tooth Structure

Of the chemical substances falling within this category, fluorine appears to be the most promising and hence has been most widely tested. The exposure of the teeth to fluoride through professional application of fluoride solutions, gels, foams and varnishes plus exposure from dentifrices and other fluoride preparations used at home is beneficial in preventing dental caries.

Fluorine. The association of fluorine and dental caries dates back to GV Black and Frederick S McKay, who recognized that the teeth with severe degree of mottling have greater immunity to dental caries than normal teeth. Fluorine as a member of halogen family, because of its electronegative properties makes it extremely reactive. In mineralized tissues such as bones and teeth, it occurs as the apatite salt of fluoridated hydroxyapatite. Fluorine has been administered principally in two ways: through the communal water supply and by topical application.

Fluoridation of Water Supplies. The studies of Dean and other members of the United States Public Health Service were instrumental in establishing an inverse relation between the fluorine content of the communal water supply and the dental caries experience. These studies have been carried out in numerous cities throughout the United States and have generally indicated that persons residing for their entire lives in an area where significant amount of fluorine are naturally present in the drinking water exhibited less caries than persons born and raised in fluoride-free areas. If persons are born in a fluoride area, but are removed from exposure to fluoride containing water at variable times after birth, their caries experience increases proportionately.

Many clinical studies have reported that a reduction in the caries experience is not necessarily dependent upon the presence of mottled enamel. Hodge and Smith clearly showed the relation between the fluoride content of water, the index of dental fluorosis and the DMF rate based upon public health data. This data demonstrates the optimum ppm levels of fluoride in drinking water which may produce maximal amount of protection against caries with minimal hazard of fluorosis. These workers have pointed out that a two-fold factor of safety exists between the protective level of 1 ppm of fluoride and the level necessary to produce significant clinical fluorosis.

However, the optimal concentration depends on the annual average maximum daily air temperature in the community (temperature influences the amount of water ingested). In temperate zones of North America, where the annual average maximum daily air temperature ranges between 14.7°C and 17.7°C, the optimal level of fluoride is 1 ppm.

In Africa and Asia, the optimal level is not known and may differ, requiring increased water consumption. The natural occurrence of fluoride in the drinking water and the attendant reduced caries incidence suggested that the artificial addition of fluoride to the communal water supply might result in a similar reduction in caries. In addition, it has been indicated that the fluoride content of caries free teeth is higher than carious teeth.

One of the first experimental clinical studies of artificial fluoridation was that carried out in two cities in New York, Kingston and Newburgh. The water supply of Kingston was low in fluoride (less than 0.15 ppm); so Kingston served as the control city. Sufficient fluoride was added to the water of Newburgh to raise the level to 1.0–1.2 ppm. The results of caries examinations completed eight to nine years after

the initiation of fluoridation in Newburgh were reported by Ast and his coworkers, which indicated that the DMF rate among Newburgh children was 60% lower than that among Kingston children. The DMF rate of the first permanent molars in the Newburgh children was only about 50% of that among Kingston children. There was not a single missing first permanent molar in Newburgh children even though approximately 7% of the first permanent molars were missing in the 9- and 10- year-old children residing in Kingston. Newburgh children in the 6- to 9-year-old age range exhibited over three times as many caries free deciduous teeth as the Kingston group.

Since central water supplies are not available to large segments of the world's population, considerable research related to the effect of school water fluoridation on dental caries has been conducted using even higher concentrations of fluoride. Currently recommended level for school water fluoridation is 4–5 times the optimum amount recommended for community water fluoridation in the same geographic area. In Asia, the only Malaysian state that fluoridated its water supplies was Johore. A vast reduction in the caries experience was noted following this. In Singapore, fluoridation of the water supply began in 1956 and by 1970, two million people were receiving fluoridated water.

Good reviews on the subject of fluoridation and caries prevention have been published by Ericsson (1977) and Fejerskov and coworkers in 1981. Careful studies of chronic toxicity by many workers have failed to reveal the slightest detrimental effect caused by fluoridation of the water supply. Opponents of water fluoridation have questioned its safety, yet careful comparison of communities with optimal versus those with suboptimal levels of fluoride in the water supplies reveals no significant differences in the frequency of birth defects or mortality statistics. Blood cell counts, hemoglobin level and urine analyses have always been within normal limits, and there has been no evidence of alterations in development of bones. It must be concluded that fluoridation of water is not only an absolutely safe procedure, but also a highly beneficial one because of its caries protective action.

Mechanism of Action of Ingested Fluoride The mechanism of action of fluoride in the drinking water has been discussed by many workers, and several theories have been proposed. Since fluoride inhibits enzymes by inactivating the coenzyme portion of the enolase system, and specifically by inhibiting the conversion of 2-phosphoglyceric acid to (enol) phosphopyruvic acid, it has been thought to protect against caries by preventing carbohydrate degradation. But the level of fluoride taken in is so low, the dilution factor by saliva is so great and the oral clearance is so rapid that this mechanism is generally dismissed as insignificant.

The *L. acidophilus* counts of the saliva of patients in cities with varying amounts of fluoride in the drinking water received considerable attention by the United States Public Health Service workers in earlier studies. The scientific consensus based upon these studies is that the *L. acidophilus* counts are more closely associated with caries activity than with the fluoride content of the water supply. Thus, the mechanism of action of fluoride does not appear to be through inhibition of microorganisms.

The most widely accepted theory on the mechanism of action of ingested fluoride is that of alteration of the structure of the developing tooth through systemic absorption of the element. Such a mechanism would explain the clinical observation of greater caries protection of children residing in fluoride areas during tooth formation as compared to the caries experience of children moving into such an area after tooth crown formation has been completed. The exact means whereby fluoride would alter the tooth structure to resist caries has not been completely established, but it is probably through the incorporation of fluorine into the crystal lattice structure of enamel, with the formation of a fluorapatite producing less acid soluble enamel.

Fluoride Supplements. Where communal water fluoridation is not feasible, fluoride tablets, drops, or lozenges have been proven definitely to be effective cariostatic agents, provided such supplements are taken on a daily basis from birth to about 14 years. The cariostatic effects of fluoride supplements have ranged from less then 10% to more than 80%, depending on how soon after birth, supplementation starts, the degree of fulfilment and the dosage. The correct dosage in prescribing fluoride supplements depends on two factors: the age of the child and the existing fluoride concentration in the water supply (Table 9-5). Failure to determine the fluoride concentration in the water source can result in overdosage and consequent dental fluorosis. For young infants, drops are more convenient and can be added to foods such as cereals or beverages such as milk formula or juices. For older children, whose primary teeth have erupted, fluoride tablets or lozenges are indicated as these provide both systemic benefits when swallowed and topical benefits as they are swished around the mouth. The concentration of total fluoride in human milk is about 0.05 ppm and cow's milk about 0.1 ppm. Nevertheless, in most cases there is no need to supplement breast fed children who reside in optimally fluoridated areas.

Topical Application of Fluoride. The second manner in which fluoride is used for the prevention of dental caries is by topical or local application to the teeth. The first suggestion that such a technique might be effective was explained in the work of Volker and his associates when they reported that the exposure of powdered enamel to solutions of sodium fluoride resulted in a reduction in the solubility of enamel.

Table 9-5: Supplemental fluoride dosage schedule (mg/d) according to fluoride concentration of drinking water

Age	Concentration of fluoride in drinking water (ppm)		
	Less than 0.30	0.3–0.7	Greater than 0.7
	Supplemental fluoride requirement		
Birth to 2 years	0.25	0	0
2–3 years	0.50	0.25	0
3–16 years	1.00	0.25	0

Subsequent work indicated that the enamel adsorbed fluoride onto its surface. Although the exact mechanism is not known, it appears that there is formation of either a calcium fluoride or a calcium fluorapatite.

Numerous laboratory studies have been carried out to improve the means of decreasing enamel solubility. Thus various fluoride compounds have been tested at varying pH levels. Although early studies dealt with sodium fluoride, it was subsequently found that potassium, ammonium and even lead fluoride were effective in reducing enamel solubility. Muhler and van Huysen found that tin fluoride was an even more effective fluoride compound.

Professionally applied topical fluoride preparations usually contain 2% sodium fluoride, 8% stannous fluoride, or 1.23% acidulated phosphate fluoride.

It was only natural that some attempt would be made to decrease the solubility of 'whole' enamel *in vivo* by exposing it to a relatively concentrated fluoride solution, thereby adsorbing some of the material onto the surface. This, theoretically, should result in a greater resistance of the tooth to acid decalcification. A great many clinical studies have been carried out and the majority has conclusively demonstrated the benefit of topical application of fluoride.

Sodium Fluoride. Neutral sodium fluoride was the first to be used in early clinical trials tested in the 1940s and were shown to reduce caries by about 30% . This technique first proposed by Knutson et al, involved the cleaning of the teeth with pumice paste followed by a four-minute topical application of 2% sodium fluoride solution at pH 7. The initial topical application was then followed by three similar applications at weekly intervals, except that no prophylaxis was carried out at these subsequent visits. The treatment series was recommended at ages 3, 7, 10 and 13 years. The disadvantage of this technique was that the patient had to make four visits to the dentist within a relatively short time. However, sodium fluoride as a topical agent had many advantages in that it is chemically stable, has an acceptable taste, nonirritating to gingiva and does not discolor the teeth.

Stannous Fluoride (SnF_2). The first clinical trial of SnF2 was conducted by Howell et al, in 1955. The procedure again involved coronal polishing and application of stannous fluoride for four minutes semiannually. The advantages of using SnF_2 were rapid penetration of tin fluoride and formation of a highly insoluble tin-fluorophosphate complex on enamel surfaces. The disadvantages of aqueous SnF_2 far outweighed advantages in that it is unstable and should be prepared fresh for every treatment, its naturally low pH make it astringent, it produces discoloration of the teeth particularly in hypocalcified areas, and the solution has a metallic taste.

In order to overcome some of the disadvantages of a freshly prepared 8.5–10% solution of SnF_2, stannous fluoride gel containing 0.4% SnF_2 in methylcellulose and glycerin base was developed. This was flavored with cinnamon or grape and remained stable for 15 months. However, for fluoride ion to be released, the gel should be diluted with water following its application to the teeth. This material was found to be effective in postradiation cancer patients and for reducing decalcification around bands in orthodontic patients.

To allow topical fluoride to react with the enamel for more time and thereby increase its uptake, fluoride varnishes have been developed. Some of these are Duraphat which contains 2.26% fluoride in an alcoholic suspension and fluor protector which contains 0.7% fluoride in a polyurethane varnish.

Many problems had to be investigated in the early studies, such as the number of applications necessary to derive maximal benefit in caries reduction, the appropriate interval between applications and the optimal concentration of fluoride solution. Reported studies indicate that the topical application of sodium fluoride to the teeth of children has a significant favorable effect in reducing the dental caries incidence.

A great many clinical studies on the effectiveness of topical application of stannous fluoride in reducing the incidence of dental caries have been reported. For example, Muhler treated the teeth of a group of 232 children, 6–17 years of age, with a single topical application of 8% solution of stannous fluoride; 228 children of a similar age were treated with distilled water and served as controls. All children in this study had resided for their entire lifetime in an area in which fluoride had been added to the communal water supply, and thus the experiment tested an additional beneficial anticariogenic effect of topical fluoride under optimal communal fluoride conditions. At the end of 12 months, Muhler found a 35% reduction of DMF teeth in the stannous fluoride treated group, thus indicating an extension of benefit of fluoride therapy in children already benefiting from communal water fluoridation.

Many other studies testing the clinical anticariogenic effectiveness of topical stannous fluoride solution have been reported in the literature, and the results are generally uniform in their findings of benefit of this compound.

By far the most useful fluoride therapy is the application of acidulated phosphate fluoride (APF) in the form of a solution or gel. The use of these agents provides a 25–40% reduction in caries. APF agent has to be applied for four minutes usually in a disposable tray applicator. APF agents have a pH of approximately 3 and contain 1.23% fluoride and 0.1 M orthophosphoric acid. The low pH favors more rapid fluoride uptake by enamel and the presence of the orthophosphate prevents enamel dissolution by the common ion effect. The application of these solutions or gels is often preceded by a coronal polishing. This removes exogenous stains and plaque but does not affect the cariostatic potential of topical fluoride gel.

Two studies by Muhler and his associates (1965), using a stannous fluoride-phosphate system, found exceptional reductions in caries incidence, and it appeared that this modality is more effective than either stannous fluoride alone or the acidulated sodium fluoride phosphate mixture.

Another method for the topical application of fluoride to prevent dental caries, suggested by Bibby and his associates, is that it could be used in a prophylactic paste. There are numerous studies; however, in which stannous fluoride has been incorporated in a prophylactic paste with either a lava pumice or silex base. In general, it has been reported that

stannous fluoride in a prophylactic paste provides caries reductions of between 30 and 40% in both children and adults, in the presence or absence of fluoride in the communal water supply. Also tested was a stannous fluoride-zirconium silicate paste used as a patient-applied treatment procedure.

One of the most effective means of caries reduction involves the daily self-application of 0.5% fluoride gel (5000 ppm F), about 40% of the concentration used for professional office applications in custom fitted trays for five minutes. This form of self-therapy is best suited for high caries risk patients who are sufficiently motivated to conform to the daily regimen. It is appropriate for those school going children and patients who have received therapeutic radiation in the head and neck region. Self-application by brushing with 0.4% stannous fluoride gel (1000 ppm F) has been used as an alternative to the custom-fitted tray method.

The mechanism by which fluoride works also depends on the conditions of its use. For example, at the high fluoride concentrations (12,000–22,600 ppm F) used for topical therapy, there is at least a temporary effect on bacterial metabolism, inhibiting glycolysis and suppressing *S. mutans*. At lower concentrations, such as systemic fluoride provided by water fluoridation or supplements of topical fluoride from dentifrices and mouth rinses, there is an uptake of fluoride by hydroxyapatite, rendering it less soluble and improving its crystallinity.

Fluoride Dentifrices. This is another method of applying fluoride. The first fluoride containing dentifrice reported to decrease in the incidence of caries as compared with the similar use of a nonfluoride dentifrice, contained stannous fluoride (0.4%) together with calcium pyrophosphate that had been heat treated to increase its compatibility with fluoride.

Sodium monofluorophosphate (MFP) has been used as a therapeutic agent in dentifrices. In the USA, MFP at 0.76% or 1,000 ppm is the most commonly used therapeutic ingredient in commercial toothpastes. Similarly, sodium fluoride was tested in toothpastes with acrylic particles or hydrated silica used as an abrasive. Because of its significant cariostatic benefits, several commercial products use sodium fluoride as the active therapeutic ingredient. A sodium fluoride formulation of 1,100 ppm with silica abrasive was found more effective than the stannous fluoride-calcium pyrophosphate dentifrice because of greater availability of fluoride. However, the degree of effectiveness varies with different dentifrice formulations.

It is generally recognized that the most effective mass reduction in dental caries is afforded by communal fluoridation. This procedure is unavailable; however, in many communities and rural areas. Therefore, it is possible that the use of more than one of the other effective anticariogenic agents may produce cumulative effects. The use of 'multiple principles of preventive dentistry' is highly effective.

Fluoride Mouthwashes or Rinses. There has been extensive clinical trial of mouthwashes or rinses containing fluoride used either as a mouthwash to flush the oral cavity, or in a few instances, by application with a toothbrush in efforts to prevent dental caries. For geographic areas where it is impossible to fluoridate the water supplies because of the lack of a central water system, alternative measures should be considered in the form of school-based fluoride mouthrinse program. One of the most important outcomes of early trials with neutral sodium fluoride, acidulated phosphate fluoride and stannous fluoride rinses was the recognition that supervised fluoride rinse programs could reduce caries by 20–50%. NaF was recommended for school-based use over others because it was easy to prepare and had an acceptable taste.

Rinsing is a simple and inexpensive method of utilizing fluoride to inhibit dental caries. This has been proven so unequivocally that the Council on Dental Therapeutics of the American Dental Association has recognized neutral sodium fluoride and acidulated phosphate fluoride rinses as effective caries preventive agents (1975) as well as stannous fluoride rinse (1980). Since rinsing can be performed as an individual caries-preventive measure at home or as a school-based group preventive program, the dentist must be familiar with the different techniques involved, because they vary considerably with the different circumstances and objectives.

One of the earliest large-scale successful clinical trials was reported by Torell and Ericsson in 1965. They undertook a two-year study to evaluate the caries reducing effects of various methods of local application of fluorides. Of six experimental groups, each containing approximately 200 children, 10 years of age, several groups developed significantly less caries compared with control groups.

The vast majority of succeeding studies were aimed not at continuously proving the value of fluoride mouthrinses as a caries-preventive agent, but rather at defining the best technical methods to use in achieving the desired result. Thus, many different fluoride concentrations were tested, ranging from 0.01% to 0.66% NaF, and many rinsing frequencies tried, ranging from twice a day to three or four times a year. These studies are too numerous to review individually, but they have basically given rise to the two chief techniques used nowdays:

- The low potency/high frequency technique, usually recommended for home use.
- The high potency/low frequency technique, usually recommended for school based programs.

The extreme importance of fluoride rinsing as a caries inhibiting technique mandates periodic thorough review and update of these procedures by all practicing dentists.

Bis-biguanides

Chlorhexidine and alexidine have received the most attention as potential anticaries agents, since they have been shown to be effective antiplaque agents. It has been shown by *in vitro* studies that chlorhexidine is adsorbed onto tooth surfaces and salivary mucins, and then released very slowly in an active form.

The effect of chlorhexidine on the growth of human dental plaque has been studied by Harrap in persons using a chlorhexidine gluconate dentifrice. He found highly significant reductions in plaque growth that were related to the concentrations of the drug. In contrast, Johansen and

his colleagues could find no effect on the plaque index as a result of the use of chlorhexidine dentifrice by a group of dental students, although possible favorable effects on caries were noted. Unfortunately, chlorhexidine has a bitter taste, produces a brownish discoloration of hard and soft tissues and may produce a painful desquamation of mucosa.

Silver Nitrate

Silver nitrate impregnation of teeth was used clinically for many years to prevent or arrest dental caries. The earlier workers believed that the silver 'plugged' the enamel, either the organic invasion pathways such as the enamel lamellae or the inorganic pathways, combining with the soluble inorganic portion of enamel to form a less soluble combination. Klein and Knutson investigated the effect of ammoniacal silver nitrate on the caries experience in a group of 700 children, ranging in age from 5–12 years and found no significant differences in the caries attack rate between treated and untreated teeth. Carious lesions present at the time of silver nitrate treatment had extended to approximately the same degree in both treated and control teeth. This study was in contrast to one of Younger, who applied silver nitrate precipitated with calcium chloride to the teeth of 25 children, 5–12 years of age, and reported a reduced caries incidence. In a later study, Younger reported a similar reduction in caries in a group of children who were 8–13 years of age.

Zinc Chloride and Potassium Ferrocyanide

Gottlieb, in accordance with his theories of the importance of the protein matrix of the enamel in the dental caries process, proposed that the use of a solution of zinc chloride and potassium ferrocyanide would effectively impregnate the enamel and seal off caries invasion pathway.

Ast and his associates tested the effect of these substances in a group of children 12–15 years of age. The teeth on one side of the mouth were impregnated, while those on the opposite side served as controls. After one year, no significant differences were noted between the two sides in the number of new carious surfaces. A similar result was obtained from a study by Pelton on a group of 100 children ranging from 8–14 yeas of age and a study of Anderson and Knutson on 299 children ranging in age from 7–15 years in whom the total new decayed or filled surfaces after approximately one year were essentially the same for treated and untreated teeth.

The available evidence indicates that the use of substances to impregnate the enamel and thus block organic pathways of caries is of little clinical value.

Substances which Interfere with Carbohydrate Degradation through Enzymatic Alterations

There are many substances known to have the ability to interfere with enzyme systems responsible for carbohydrate degradation and the subsequent formation of acid. If such an inhibitor is to be effective in the clinical prevention of dental caries, it must reach the susceptible areas of the mouth in sufficient concentration at the time at which the sugar undergoes breakdown.

Vitamin K. Synthetic vitamin K (2-methyl-1, 4-naphthoquinone) was suggested by Fosdick and his coworkers to be of potential value in the prevention of caries on the basis of certain studies *in vitro*. In these studies, the vitamin K was found to prevent acid formation in incubated mixtures of glucose and saliva. Many of the quinones have been found to have a similar action, but none has been superior to synthetic vitamin K.

The clinical effectiveness of this vitamin K was tested by Burrill and his associates. A group of students received a chewing gum containing the synthetic vitamin K and sodium bisulfite, and were instructed to chew this gum for at least 10 minutes after eating any food. The control group received the same chewing gum without the vitamin K. The occurrence of new cavities was determined at 12- and 18 month intervals, at which time it was found that the incidence of new carious lesions was decreased by 48% and 42% respectively, for the two intervals in the experimental group. Thus there is evidence to indicate that the naphthoquinones may be of value in preventing caries.

Sarcoside. A method for screening potential anticariogenic compounds was suggested by Fosdick and his coworkers in 1953, based on the ability of some compounds to penetrate the dental plaque and prevent pH fall below a level of 5.5 after a carbohydrate rinse. They tested several hundred compounds and noted that two of these were promising enzyme inhibitors or 'antienzymes': sodium N-lauroyl sarcosinate and sodium dehydroacetate.

Brudevold and Little continued investigation of this sarcoside in patients who brushed their teeth with solutions of the material and then measured the fall in pH of plaque material from proximal surfaces after a sugar rinse. The effectiveness of a toothpaste containing sodium lauroyl sarcoside and dehydroacetic acid was also studied. All tests were negative, and it was concluded that the sarcoside did not reduce acid production in subsurface material of bulky plaque.

The effect of sodium lauroyl and palmitoyl sarcosinate in reducing the solubility of powdered enamel was studied by Volker and his associates. The palmitoyl compound was found to be better than the lauroyl, and in concentrations of 0.01% to 1.0%, was found to be as effective as sodium fluoride in reducing enamel solubility in the presence of acids.

Substances which Interfere with Bacterial Growth and Metabolism

An alternative method for preventing enzymatic degradation of carbohydrates to acids is the prevention of, or at least interference with, bacterial growth and metabolism. There are, of course, great numbers of bactericidal or bacteriostatic agents, but the number of these which are compatible with the oral mucous membranes and with continued good health are small.

Urea and Ammonium Compounds. Urea and ammonium compounds have been tested extensively for use in the oral cavity as anticariogenic agents. The urea in particular was found useful after the preliminary report of Wach and his associates that a quinine-urea solution prevented acid formation in tests *in vitro* on carbohydrate-saliva mixtures. They also noted that the oral bacteria count was decreased after the use of a quinine-urea mouthwash and that the salivary pH generally increased to a value over 8 and remained high for approximately an hour.

Stephan continued the study of urea and found that a 40–50% solution of urea applied to dental plaques for several minutes prevented the typical pH fall following a carbohydrate rinse for periods up to 24 hours. The evidence indicates that urea, upon degradation by urease, releases ammonia, which acts to neutralize acids formed through carbohydrate digestion and interferes with bacterial growth.

Kesel and his associates reported that dibasic ammonium phosphate in both mouthwash and dentifrice caused a reduction in oral Lactobacillus counts. Studies *in vitro* indicated that the combination of 5% dibasic ammonium phosphate and 3% urea was even more effective as a bacteriostatic agent and in preventing acid formation than either substance alone.

Other workers, such as Jenkins and Wright have indicated that the ammonium ion plays no specific role in inhibiting growth of acidogenic microorganisms. The ammonium ion has failed to inhibit the growth of lactobacilli in the studies of Kirchheimer and Douglas, while the work of Ludwick and Fosdick showed no relation between the ammonia content of oral cavity and caries immunity.

Cohen and Donzanti reported the results of a study on a group of 169 children using a dentifrice containing 13% urea and 3% diammonium phosphate and 137 children using a similar dentifrice without these two ingredients. Brushing was supervised in the schools twice daily. At the end of one year the mean number of new carious teeth was 1.01 in the control group, but only 0.78 in the experimental group, and a 23% reduction in caries incidence. By the end of the second year, the number of new carious teeth in the control group was 2.27 and in the experimental group 1.70, and a reduction of 25% in caries incidence.

Hawes and Bibby reported the results of a study on 372 children between the ages of 7 and 13 who brushed their teeth for a period of one year under supervision with a dentifrice containing 12% urea (carbamide) and urease. Bacteriologic studies showed that the *Lactobacillus* counts of the children using the therapeutic dentifrice were not affected to any greater extent than those of the children using the cosmetic dentifrice. The 177 children in the control group exhibited an average increase of 9.01 total tooth surfaces decayed and filled, while the test group, composed of 196 children, presented an average of 9.33 surfaces decayed and filled during the test period. The difference between the two groups was approximately 4% and indicated that the urea dentifrice failed to produce any significant reduction in occurrence of new caries under the conditions of this study.

Although there are some studies to indicate that ammoniated dentifrices are capable of producing some reduction in dental caries incidence, the magnitude of this reduction, particularly in persons whose toothbrushing habits are not controlled or supervised, is not so great as to justify recommending them for widespread use as an anticariogenic agent.

Chlorophyll, the green pigment of plants, has been proposed as an anticariogenic agent on the basis of a number of *in vitro* and animal studies. Shafer and Hein reported that a watersoluble form of chlorophyll, sodium copper chlorophyllin, was capable of preventing or reducing the pH fall in carbohydrate- saliva mixtures *in vitro.* The same workers found that the incidence of experimental caries in hamsters was reduced when a chlorophyllin solution was substituted for the drinking water of these animals, but that the *Lactobacillus* counts were not affected. Other workers, such as Griffiths and Rapp and Nevin and Bibby, have reported that chlorophyll is bacteriostatic with respect to many oral microorganisms, including lactobacilli, streptococci and micrococci.

There have been no clinical studies reported testing the effect of water-soluble chlorophyll on dental caries experience. A number of short-term clinical studies have suggested that this compound may be of some use in reducing mouth odors and allaying gingivitis. Results however have been inconclusive.

Nitrofurans are derivatives of furfural, which itself is derived from pentoses. They have been found to exert a bacteriostatic and bactericidal action on many gram-positive and gram-negative organisms, and on this basis, have been tested by Dreizen and his associates for their ability to inhibit acid production. A number of different nitrofuran compounds were utilized in this study, and it was reported that, even in low concentrations, acid production in saliva from caries active persons was prevented in nearly all cases.

Hufstader and his associates tested the effect of furacin (2-nitro-5-furaldehyde semicarbazone) incorporated in chewing gum on the oral *Lactobacillus* counts of a group of students. During the 10-day test period during which only a sugar coated gum was chewed, the *Lactobacillus* counts were definitely increased in the majority of patients. Chewing gum containing furacin did not reduce the oral *Lactobacillus* count.

The effectiveness of furadroxyl (5-nitro-2- furaldehyde-2-hydroxyethyl semicarbazone) in preventing dental caries was tested clinically by Dreizen and Spies through use of the compound incorporated in a chewing gum. Although the number of patients in each group was relatively small, the data indicated that the nitrofuran compound significantly reduced the dental caries experience and that this substance may have potential use as an anticariogenic agent.

Penicillin has been tested as an anticariogenic compound because of its antibiotic property, which is the ability of the product of an organism to inhibit the normal biologic processes of other organisms. The effects of oral *Lactobacillus* counts of a dentifrice containing 1,000 units of penicillin per gram were studied by Hill in a group of 10 students. A remarkable reduction from an average of 72,000 colony count to an average of 300 was found after the use of dentifrice for five weeks. After discontinuing the use of dentifrice, the count stayed low for three months and then returned to the same high level. The reduction in colonies were noted with the resumption

of penicillin dentifrice, but was considerably slower. A second study was carried out by Hill on a group of orphanage children, and though full cooperation was doubtful, there was some tendency for reduction in *Lactobacillus* counts in the group who brushed their teeth with a penicillin dentifrice. White and her associates reported that small amounts of penicillin did not greatly alter the balance of the normal oral flora, although larger doses resulted in an increase of gram-negative organisms of the genera Aerobacter and Escherichia, apparently owing to their replacing that part of the flora destroyed by the penicillin.

The effect of prolonged use of a penicillin dentifrice was studied by Fitzgerald and his associates. Their results indicated that after the use of dentifrice for eight months or longer, there were no changes in the *Lactobacillus* counts attributable to the penicillin. However, there was no increase in numbers of penicillin-fast lactobacilli.

Studies of Zander and Bibby indicated that penicillin effectively interfered with the production of acid in carbohydrate- saliva mixtures even in quantities as low as 10 units in 5 ml of the total solution. These investigators also reported the effect of brushing the teeth of hamsters with a penicillin dentifrice. Brushing with a penicillin toothpaste resulted in a remarkable reduction in caries. McClure and Hewitt reported complete inhibition of caries in rats by administering penicillin to the experimental animals in the food and drinking water.

A clinical study was designed by Hill and Kniesner revealed no significant differences in new carious surfaces between control and experimental groups even though there was a reduction in *Lactobacillus* counts in the experimental group. Such a finding only emphasizes the difficulty in attempting to relate caries susceptibility or caries activity with the *Lactobacillus* count.

The results appear to indicate that penicillin is not a particularly effective anticariogenic agent. The wisdom of using this material for such a purpose has been further questioned by many because of the possibility of development of penicillin-resistant pathogenic microorganisms and sensitization.

Other Antibiotics. A variety of other antibiotics have been tested, in both experimental animal and clinical trials, for potential use as anticaries agents. These, along with other chemotherapeutic agents, have been reviewed by Johnson and Rozanis with special reference to plaque control. These investigators also pointed out that some of the problems in using these drugs in humans include the possible induction of resistant strains of microorganisms, the possibility of allergic reactions, the occurrence of side effects such as nausea and diarrhea, and the expense of long-term use. They also characterized the 'ideal' antibiotic for use as an anticaries agent as being one which has a very narrow spectrum directed toward plaque-forming microorganisms, is not in general use against systemic diseases, is neither toxic nor allergenic and is retained in the tissue in an active state for a prolonged period with a predilection for the oral cavity.

Erythromycin was tested by Lobene and his associates, who reported a 35% decrease in plaque formation after a seven-day test period of rinsing and then swallowing the agent four times a day. This effect was lost rapidly when the drug was withdrawn in three of four patients, and in addition, all developed diarrhea as a side effect.

Kanamycin has been evaluated by Loesche and his associates for its effects on dental plaque in a small low-caries group when the antibiotic was applied topically for a few weeks and for one year. While there was some improvement in gingivitis scores, plaque scores were not changed despite some physicochemical changes in the plaque.

Spiramycin was noted by Keyes and his colleagues to be the most effective of nine antibacterial agents tested in hamsters for controlling dental plaque, caries and periodontal lesions. However, the clinical trials have been somewhat conflicting as to the beneficial effects of the drug on dental plaque. It would appear that any benefits derived are considerably less than highly significant.

Tetracycline was reported by Löe and his coworkers to decrease plaque scores when used as 0.5% mouthwash three times a day for five days in place of mechanical oral hygiene. However, there is little additional information available concerning its potential use as an anticaries agent.

Tyrothricin was reported by Shiere to be responsible for a 35% reduction in the incidence of new decayed and filled permanent tooth surfaces in children 7–14 years of age after one year and for a 26% reduction in the incidence of such surfaces after two years during a controlled clinical trial of brushing with a 0.05% tyrothricin toothpaste.

Vancomycin has been reported by DePaola and his associates to temporarily suppress *S. mutans* when applied to the teeth of children as a 15% gel on five successive days. The microorganisms generally could not be detected on teeth for one week following the cessation of treatment. A similar diminution in *S. mutans* was found following testing with a 1% vancomycin paste. DePaola and his colleagues also conducted a one-year clinical trial on the effect of topically applied vancomycin on dental caries increment. They found a statistically significant reduction in dental caries experience in fissures but not on smooth surfaces in the experimental groups. Furthermore, they found that caries reduction was significant in newly erupting teeth but not in teeth already present in the mouth at the initiation of the study. Thus, this antibiotic also does not appear to satisfy sufficient criteria for universal use as an anticaries agent.

Plaque Control Agents (Table 9-6)

Caries Vaccine. Interest in a vaccine for dental caries protection dates back to a period when the lactobacilli were thought to be of paramount importance in the initiation of dental caries. By means of immunization with a homologous *Lactobacillus* vaccine, in 1944 Williams was partially successful in reducing the number of lactobacilli in human saliva. The recognition of the important role that *S. mutans* plays in the initiation of caries has led to a reawakening of interest in the vaccine approach, as evidenced by the numerous experimental attempts to control caries immunologically

Table 9-6: Plaque control agents

Antiseptic agents	1. Positively charged organic molecules: *Quaternary ammonium compounds* a. Cetylpyridinium chloride b. Pyrimidines: Hexidine c. Bis-bisguanides, chlorhexidine, alexidine 2. Noncharged phenolic agents: Listerine, triclosan, phenol and thymol. 3. Oxygenating agents: Peroxides and perborates 4. Bispyridines: Octenidine 5. Halogens: Iodine, Iodophors and fluorine 6. Heavy metal salts: Silver, mercury, zinc, copper, and tin
Antibiotics	Niddamycin, kanamycin sulfate, tetracycline hydrochloride, and vancomycin hydrochloride
Enzymes	Mucinases, pancreatin, fungal enzymes and proteases
Plaque modifying agents	Urea peroxide
Sugar substitutes	Xylitol and mannitol
Plaque attachment interference agents	Sodium polyvinylphosphonic acid and perfluoroalkyl

in laboratory animals such as the rat and monkey. Although results have always been encouraging, development of a caries vaccine is considered a highly desirable goal because of the potentially important public health implications. Considering the properties of *S. mutans*, which are associated with its cariogenicity, an antibody (immunologic) approach to caries control could theoretically be accomplished by a number of mechanisms, including:

- Interfering with adherence, colonization and dissemination of the organisms in the oral cavity.
- Reducing its 'stickiness' by altering its polysaccharide metabolism.
- Altering the ability of the microorganism to produce acid.

Although recent studies have shown that an antibody can reach the oral environment via saliva or gingival crevicular fluid, much more research will be necessary before a caries vaccine becomes available to the general public. Many important unanswered questions remain about the effectiveness of mode and route of immunogen administration, dosages and schedules of immunization, types of immunogen and adjuvants, possible adverse reactions and crossreactivity of immunogens, and effectiveness in monitoring the immune response to immunization procedures.

NUTRITIONAL MEASURES FOR CARIES CONTROL

The importance of diet, particularly sucrose containing foods and beverages in cariogenesis, is well known. On an individual basis, the dentist, dental hygienist and/ or dietitian consultant can provide information on safe foods and drinks. But the ultimate responsibility for diet modification lies on the individual. Voluntary dietary restriction may suit some patients and certainly reduce caries as evidenced by persons who have hereditary fructose intolerance. The function of the dental office personnel in diet modification is one of counseling, providing information, motivation and encouragement. The diet used in caries prevention is essentially a healthy, adequate, balanced diet and resembles a normal diet except for the exclusion of a few food components and eating practices.

Microbiological examination provides an objective method for assessment of the patient's cooperation. Changes in dietary habits are reflected within a couple of weeks in corresponding reductions in the numbers of oral lactobacilli and *Streptococcus mutans*. Follow-up visits are advised so that the patient's diet can be rechecked and further modifications adopted if necessary.

The control of dental caries through nutritional or dietary means is impossible to achieve on the basis of a mass prevention program and, for this reason, is relatively unimportant in public health and preventive dentistry in contrast to fluoridation of water supplies. Accordingly, caries control by dietary modification on a public health scale requires the help and cooperation of the food industry if it has to have any serious impact. Strict statutory definitions cover claims that products are 'anticavity', 'noncariogenic', and 'less cariogenic'. It is important, however, for the dentist in private practice to understand the significance of controlling caries in individual patients by dietary measures. In many persons, particularly those suffering from rampant caries, every means at the disposal of the dentist must be utilized to preserve the dentition.

The chief nutritional measure advocated for the control of dental caries is restriction of refined carbohydrate intake. Only the most cooperative patient will adhere rigidly to the type of diet designed to reduce sugar consumption drastically. For this reason, clinical studies on large groups of patients for the purpose of ascertaining the extent of caries reduction that would occur with restriction of sugar consumption are difficult to carry out. This count frequently has been used to study sugar restriction because of the apparent relation between the oral *Lactobacillus* count and carbohydrate intake. This does not necessarily imply that a causative relation exists between the *Lactobacillus* and dental caries activity.

One of the best known studies dealing with the effect of dietary carbohydrate restriction on dental caries incidence is that of Becks and his coworkers. This project was designed to investigate the association of dental caries and the *L. acidophilus* indices in patients with rampant caries and in caries free persons, as well as the effect of carbohydrate reduction on the *Lactobacillus* count and on subsequent caries experience in a group of patients with rampant caries.

A close correlation between caries activity and the *Lactobacillus* index was found in this study.

Phosphated Diets. The results of clinical tests of dietary phosphate additions for the sole purpose of controlling human dental caries are as yet inconclusive. Stralfors mixed 2% dibasic calcium phosphate into the bread, flour, and sugar used in a school lunch program in Sweden and obtained a significant reduction in caries incidence in the maxillary incisors over a two-year period. Ship and Mickelsen found no meaningful reduction in the caries attack rate of children

consuming a diet in which flour used in the preparation of bakery products was supplemented with 2% calcium acid phosphate for three years. The cariostatic superiority of sodium dihydrogen phosphate over calcium acid phosphate was attributed to the greater systemic action of the sodium salt as demonstrated by radiophosphorus uptake studies on sound and carious enamel. The possibility that dicalcium phosphate may be caries inhibitory in the human, if permitted to remain in the oral cavity long enough, has lately been demonstrated by Finn and Jamison, who had children chew a sugar containing gum supplemented with 225 mg dicalcium phosphate per stick for 20 minutes five times daily. After 30 months on this regimen, there was a significant reduction in caries increment compared to that of a group using an unphosphated sugar gum.

In Australia, Harris and Beveridge obtained a 30% reduction in caries in 1,400 children restricted to a diet in which calcium sucrose phosphate was added to the carbohydrate component at levels ranging from 0.2–1.0%. They hypothesized that the calcium sucrose phosphate penetrates the surface crystalline layers of enamel, tightening the attachment between crystals. This reinforcing action protects enamel from disintegration by acids.

Despite the apparent importance of caries control through nutritional measures, there is a remarkable dearth of controlled studies by which one may judge the value of such procedures. This attests to the difficulties which would be involved in imposing such measures on large groups of patients.

MECHANICAL MEASURES FOR CARIES CONTROL

The control of dental caries by mechanical measures refers to procedures specifically designed for and aimed at removal of plaque from tooth surfaces. Although the saying "A clean tooth does not decay" is not based upon sound scientific evidence, it seems reasonable that a tooth surface free from the accumulation of microorganisms and carbohydrate substances could not become carious.

There are numerous means of cleansing the tooth mechanically, and these were reviewed and classified by Hine in a discussion of caries control measures as:

- Oral prophylaxis by the dentist
- Toothbrushing
- Mouth rinsing
- Use of dental floss or toothpicks
- Incorporation of detergent foods in the diet.

He further pointed out that although most investigators have stressed the importance of maintaining oral hygiene in preventing dental caries, no evidence was cited to support these statements. Experienced clinicians know that filthy teeth do not always decay and that, conversely, 'clean' teeth often become carious. Although progress has been made in identifying the pathogens which play a role in dental caries, the primary method in preventing dental diseases remain mechanical removal of plaque and promotion of the remineralization of the tooth surface.

Oral Prophylaxis. In the control of periodontal disease, the value of routine scaling and polishing of the teeth at periodic intervals of three or six months cannot be denied. Yet since dental plaque formation occurs within a matter of hours to a day or two after complete removal of the structure, there is probably little value, if any, in prophylaxis for the control of dental caries. Hine pointed out that the careful polishing of roughened tooth surfaces and the correction of faulty restorations is probably of more importance than the mechanical cleansing of the tooth by prophylaxis. These procedures might conceivably reduce the retention of food debris and decrease the formation of bacterial plaques, thereby reducing the development of new carious lesions. Many studies have demonstrated that, in dental caries, the pathogenicity of plaque is related to the numbers of *S. mutans* and related species present. In contrast, the plaques associated with gingival inflammation are characterized by a predominance of gram-negative flora rather than the predominantly grampositive flora found in health. This transition seems to coincide with inflammatory changes that occur at the gingival margins. Plaque control efforts should be directed towards two goals: limiting the numbers of *S. mutans* in dental plaques for the prevention of caries by mechanical elimination of supragingival plaque and limitation of dietary sucrose and secondly, maintaining the predominantly gram-positive flora associated with gingival health by mechanical removal of plaque from the subgingival area on a regular basis.

Toothbrushing. This is the most widely accepted technique for plaque removal on teeth. The value of toothbrushing in the control of dental caries has been argued by many authorities. It cannot be denied that there are some individuals who have never used a toothbrush and yet are free of caries. These persons are certainly exceptional and may prove that the inherent caries resistance of the individual may be of greater importance than local factors. On the other hand, there are many persons who conscientiously brush their teeth at least twice a day and yet suffer from a serious amount of dental caries. Since most persons delay brushing their teeth after meals for varying periods of time and since, acid production in the dental plaques occurs within a matter of minutes after the ingestion of carbohydrate, as Stephan has shown, a high caries incidence despite persistent toothbrushing is at least understandable.

Another factor in the explanation of the failure of toothbrushing to prevent dental caries lies in the difficulty of reaching all exposed surfaces of teeth upon which plaques may form with the brush. In considerable number of patients, brushing does not reach all areas of the teeth. Indeed, it is ironic that most patients spend the greatest amount of time brushing buccal, labial and lingual surfaces, which are not so prone to decay as the more inaccessible interproximals and the deep fissures of occlusal surfaces into which toothbrush bristles will not reach (Fig. 9-36).

The extent to which plaque is removed is related to the duration of brushing. A minimum time of five minutes daily has been recommended for brushing or flossing or using

Figure 9-36. Toothbrushing.
A ground section of a tooth shows the relative size of an occlusal fissure compared with a single bristle from a standard toothbrush to illustrate the difficulty which may be encountered in attempting to cleanse the depth of these fissures.

other interproximal cleansing aids. The thoroughness of toothbrushing is usually measured by plaque or oral hygiene scores. However, no consistent relationship is demonstrable since the two indices gauge items that occur considerably over different time intervals.

As an alternative to measuring the efficacy of plaque removal, some investigators have studied the diligence of toothbrushing, using questionnaires about brushing frequency. For example, it has been reported that children who brush twice or more per day had significantly less caries than children who brushed only once a day or less. Since a majority of children use fluoride-containing dentifrice, these results may be due to increased contact with a topical fluoride agent rather than to mechanical cleansing of tooth surface.

A number of studies have indicated that toothbrushing will reduce the number of bacteria in the oral cavity; but in view of the countless millions of microorganisms remaining in the oral cavity, the significance of removing a certain but undoubtedly small percentage is probably negligible. There are several studies on the effect of toothbrushing on the incidence of experimental dental caries in animals. In a study testing the effect of a penicillin dentifrice on caries in hamsters, Zander and Bibby found that simply brushing the teeth of animals with controlled nonmedicated toothpaste resulted in a 69% reduction in caries as compared to a group in which the teeth were not brushed. Subsequent studies in other animals have demonstrated similar results.

Although toothbrushing would seem to be important, not all clinical studies completely support this idea.

Mouthrinsing. The use of a mouthwash for the benefit of its action in loosening food debris from the teeth has been suggested to be of value as a caries control measure. There is no scientific evidence to confirm this suggestion, and mouthwashes would appear to be of only limited value except for the fluoride mouthwashes previously discussed.

Dextranase, an agent which is sought to disperse dental plaque by hydrolyzing the streptococcal polysaccharides *in vitro*, has been used in mouthrinses. This has been tested in clinical trials by using various durations and frequencies of rinsing, ranging from one minute, four times per day to five minutes, seven times per day. Rinsing with these enzyme solutions does not prevent the development of plaque, although the proportion of *S. mutans* in plaque was seen to be reduced. The use of dextranase as a caries control agent represents an attractive concept of disease control in which the therapeutic agent is directed at a specific metabolic product of the causative organism rather than at the organism itself.

Dental Floss. Dental flossing has been shown to be effective in removing plaque from an area gingival to the contact areas on proximal surfaces of teeth, an area impossible to reach with the toothbrush. There is general agreement that flossing is necessary if interproximal gingival health is to be maintained, but opinions differ as to the value of flossing in preventing dental caries. The research findings regarding control or prevention of dental caries by flossing are contradictory. Most studies involved children, and thus digital aptitude in manipulating the dental floss is an important variable. Fluoridated dental floss successfully reduced interproximal colonization by *S. mutans* as shown by the studies of Gillings.

Oral Irrigators. The custom of flushing the mouth for therapeutic purposes dates from antiquity. However, the use of flushing devices was first reported in the early 1900s. Most of these reports with regards to treating the dental infection by flushing are concerned with the beneficial effects of oral irrigation on gingival infections. No reports have referred to the effect of irrigation on the control of dental caries.

Detergent Foods. Some workers have related the high caries incidence among modern civilized races to the unrestrained use of soft, sticky, and refined foods, which tend to adhere to the teeth. It has been stated that fibrous foods in the diets prevent lodging of food in pits and fissures of teeth, and in addition, act as a detergents.

A number of studies have indicated that the act of eating removes a relatively large number of microorganisms from the oral cavity. Crowley and Rickert reported that after eating, there was a reduction of as high as 78% of bacteria that could be recovered from the mouth. It is only reasonable to state that hard, fibrous food would be more beneficial in mechanically cleansing the oral cavity than soft, and sticky food. It also appears acceptable that the adherence of soft foods to the teeth would predispose to the development of more caries than would be found in a mouth kept relatively clean by a fibrous diet. Yet, despite recommendations that the eating of fibrous foods, either as a part of the diet or simply after meals, is beneficial as a caries control measure, there is no scientific evidence based upon controlled studies in human beings to indicate that this is true.

Chewing Gum. It has been suggested that the chewing of gum would tend to prevent dental caries by its mechanical cleansing action. But most chewing gums contain a considerable amount of carbohydrate, and this might actually increase caries susceptibility.

Xylitol, a pentose alcohol found naturally in variety of fruits and vegetable, and obtained commercially from birch trees, coconut shells and cottonseed hulls, has been proposed as a possible sugar substitute. Several studies have provided dietary xylitol in the form of xylitol sweetened chewing gum as an add-on without attempting to restrict sucrose intake. Short-term chewing of xylitol gum (two packages per day for four weeks) significantly reduced salivary levels and plaque proportions of *S. mutans*, whereas sorbitol or fructose sweetened gum had no such effect. Xylitol, due to its organoleptic properties, stimulates salivation thereby increasing plaque pH and thus promotes remineralization. It is thus used as a sweetener in noncariogenic confectionary and less frequently in dietetic foods.

Chewing gum has been utilized as a vehicle for delivery of fluoride (Fluomin, 0.25 mg F). Peak fluoride concentrations were in the range of 15–25 ppm in the first five minutes after the ingestion of a 0.25 mg preparation. However, the fluoride concentration decreased rapidly by about 30 minutes reaching a level of 1 ppm. However, with regular follow-up, the use of chewing gum may indeed have a perceptible cariostatic effect.

Pit and Fissure Sealants. Pits and fissures of occlusal surfaces are among the most difficult areas on teeth to keep clean and from which to remove plaque. Because of this, it was suggested many years ago that prophylactic odontotomy, the preparation of cavities in these areas and their restoration by some material such as amalgam had to be carried out before extensive decay developed. In this way, these caries susceptible pit and fissure areas would be made less susceptible to subsequent caries. The use of polymers as fissure sealants, and to a lesser extent, as coatings owes its origin to Gore, who in 1939 had used solutions of cellulose nitrate inorganic solvents to fill the surface enamel which was made porous by the action of acids in the saliva. The sealant is not necessarily required to fill the entire depth of the fissure, but it must extend along its entire length, bonding firmly at the fissure entry. Although some bacteria sealed within fissures may remain viable for extended periods of time, they do not produce sufficient acid to initiate caries if deprived of a continuous external source of fermentable carbohydrate.

A major breakthrough in the efforts to produce an effective sealant occurred when Buonocore reported greatly improved retention of an acrylic filling material to an enamel surface that had been etched with a 50% phosphoric acid solution. The etchant, referred to as a conditioning agent, removes surface layers and a part of the enamel surface to about 5–10 μm and thereby produces surface irregularity into which the resin materials penetrate and polymerize. The pit and fissure sealants, generally used in conjunction with an acid pretreatment to enhance their retention, contain either cyanoacrylate, polyurethane or the adduct of bisphenol A and glycidyl methacrylate (BIS-GMA) as major components. BIS-GMA, an epoxy resin is currently the resin component of most composite resin materials. Others include Duraphat a varnish preparation containing sodium fluoride. The advantage of this material is that it sets on the moist tooth surface as a thin film and functions as an extended fluoride application than as a true sealant.

Glass-ionomer cement, has an impressive cariostatic effect because of its high fluoride content, has been used as a fissure sealant.

Cueto and Buonocore (1967) reported that a cyanoacrylate sealant, applied every six months, resulted in an 86% reduction in caries after one year. Ripa and Cole, utilizing the same type of sealant, reported that 85 first permanent molars had 84.3% less occlusal caries than an equal number of controls after one year. Buonocore tested 60 patients using bisphenol A-glycidyl methacrylate containing benzoin methyl ether, making the curing process sensitive to ultraviolet light. He reported that there was a caries reduction of 100% after one year, and 99% after two years in the permanent molars. In the tested deciduous teeth, he reported an 87% protection.

Thus, the evidences accrued indicate that pit and fissure sealants are an additional aid in the prevention of one form of dental caries. Boudreau and Jerge (1976) concluded that sealants were effective in preventing occlusal decay, although they re-emphasized what most investigators had suggested that occlusal sealants should be but one component of a multiple approach to a preventive dentistry program.

CARIES ACTIVITY TESTS

Clinical examination of carious lesions with a probe and mirror, coupled with radiographs, neither predicts caries activity nor a patient's susceptibility to dental caries. A reliable laboratory test for measuring caries activity offers a valuable adjunct for patient motivation in a caries prevention program. Caries activity refers to the increment of active lesions (new or recurrent lesions) over a slated period of time. Caries susceptibility refers to the inherent tendency of the host and target tissue, the tooth, to be afflicted by the caries process. This is the susceptibility of a tooth to a caries producing environment. A caries activity test measures the degrees to which the local environmental challenge (e.g. dietary effect on microbial growth and metabolism) favors the probability of carious lesions. A caries activity test establishes the need for personalized preventive measures provides an index of the success of therapeutic procedures and monitors the effectiveness of education program.

Several biochemical and microbiological tests, which are suitable for use in a dental office, have been developed as indices of caries activity, keeping in mind that bacterial flora, the local substrate for bacteria in the oral cavity and the host may all interact in determining the caries activity. The interpretations of these laboratory tests are; however more reliable with a good clinical assessment.

Lactobacillus Colony Test

The oldest and the most widely used microbiological method for assessing the caries activity is the *Lactobacillus* colony count. This method, measures the number of aciduric bacteria in a patient's saliva by counting the number of colonies which appear on tomato peptone agar plates, a selective medium with pH 5.0, after inoculation of the patient's saliva and incubation. An improved selective media with an acidic pH having high amounts of acetate, salts and lower surface tension that is highly selective for growth of *Lactobacillus* is the Rogosa's medium. The colonies grown on media upon incubation reflect the number of aciduric flora in the patient's saliva. The lactobacilli count is interpreted as shown in Table 9-7.

Quantitating lactobacilli in paraffin stimulated saliva can give variable counts, thus limiting the usefulness of caries activity. However, by repeated salivary sampling, the lactobacilli count may be an important measure of caries activity and is used as a reference test for new caries activity tests.

Colorimetric Snyder Test. This test developed by Snyder in 1951 is based on the rate of acid produced when a sample of stimulated saliva is inoculated into a glucose and agar containing medium of pH 4.7–5.0. The medium has bromocresol green as a color indicator, which changes from blue-green at pH 4.7–5.0 to yellow at pH 4.0, indirectly checking the presence of acidogenic and aciduric microorganisms. The acid produced by the oral acidogenic flora is detected by the changes in pH indicator, and is compared to an uninoculated control tube after 24, 48 and 72 hours of incubation. Snyder's test is charted for interpretation as follows (Table 9-8). The Snyder test is simple and correlates well with *Lactobacillus* colony count. Neither the Snyder test nor the *Lactobacillus* colony count can predict the extent of expectancy of caries with any reliability for one individual, but are of value in assessing the oral environmental cariogenic challenge.

Swab Test

The principle involving the swab test is essentially the same as Snyder test, where the aciduric and acidogenic elements of the oral flora are measured after appropriate incubation periods by employing a color indicator in the test medium and recording the pH directly. The test involves sampling the oral flora by swabbing the buccal surfaces of teeth with a cotton applicator, which is subsequently incubated in the medium.

The pH following a 48-hour incubation is read on a pH meter or the color change is read by use of color comparator. A pH of 4.1 and below denotes marked caries activity; 4.2–4.4 is considered active; 4.5–4.6 is considered slightly active; and a pH of 4.6 and above is considered as caries inactive.

Table 9-7: Results and interpretation of lactobacilli count in relation to caries activity

No. of lactobacilli per ml of saliva	Caries activity
0–1000	Little or none
1000–5000	Slight
5000–10,000	Moderate
> 10,000	Marked

Table 9-8: Observations in Snyder's test

Time in hours	24	48	72
Color	Yellow	Yellow	Yellow
Caries activity	Marked	Definite	Limited
Color	Green	Green	Green
Caries activity	Continue test	Continue test	Inactive

Salivary *S. mutans* Level Test

The problem with regard to *S. mutans* caries activity test is that it accounts for less than 1% of the total flora of plaque and their numbers are extremely variable even from the same site. As *S. mutans* harbor at specific sites, the salivary *S. mutans* count does not ascertain its location on teeth or assess its degree of infection at a given site. It is also understandably difficult to distinguish a carrier state from a cariogenic infection based on *S. mutans* numbers alone. However a clinician could use these counts as an add-on in caries management.

The number of *S. mutans* forming units per unit volume of saliva is the fundamental basis of this test. Plaque samples from distinct sites such as pits and fissures or from a proximal area are, however, more appropriate for detecting and quantitating *S. mutans* that have colonized on teeth. Saliva, on the other hand, provides a workable alternative as it may not be practical to sample a large number of dental sites for evaluation. The test involves incubation of the sample obtained using tongue blades or a wooden spatula on Mitis Salivarius Agar (MSA), a selective streptococcal medium with increased concentration of sucrose (20%) and 0.2U bacitracin per ml to suppress the growth of most non *S. mutans* colonies. Agar plates are incubated at 37° C for 48 hours 95% N2- 5% CO_2.

Levels of *S. mutans* greater than 10^5 are indicative of an acceptable cariogenic challenge because colonization does not occur until the level of *S. mutans* reaches 4.5×10^4/ml for smooth surface and 10^3/ml of occlusal fissures. Several clinical studies have corroborated the finding that the percentage of *S. mutans* in saliva increases significantly as a function of the DMFS score. There is thus substantial evidence for associating high *S. mutans* counts with caries activity.

S. mutans Dip-slide Method

This test classifies salivary samples according to estimates of *S. mutans* colonies growing on modified MSA. In this method, the stimulated saliva is collected for five minutes and is poured over the agar coated slide, totally wetting the surface and the excess allowed to drain off. After the slides are dry, the bacitracin disks are placed in the middle of the inoculated agar, about 1 cm from each other. The slide is then incubated in a tube containing a CO_2 tablet for 48 hours. A zone of inhibition 10–20 mm in diameter is formed around each bacitracin disk. If present, *S. mutans* appears as small blue colonies growing within the zone of inhibition. The colony

density is compared with a model chart and classified as 0 (negligible), 1 (less than 100,000), 2 (100,000–1000,000) 3 (more than 1000,000) *S. mutans* CFU/ml of saliva.

Buffer Capacity Test

This test evaluates the quantity of acid required to lower the pH of saliva through an arbitrary pH interval or, in other words, the amount of acid or base necessary to bring color indicators to their end point. Importantly, buffer capacity could be quantitated either using a pH meter or color indicators. This test relates the buffering capacity of saliva and caries activity. Patients with increased proneness to carious lesions have a lower buffering capacity in their saliva than saliva of those who are relatively free.

Enamel Solubility Test

The Fosdick calcium dissolution test measures a milligram of powdered enamel dissolved in four hours by acid formed when the patient's saliva is mixed with glucose and powdered enamel. Even though the correlation is reportedly good from limited studies, the test is not simple and requires trained personnel and the cost involved is high. A test similar to the Fosdick calcium dissolution is available where the pH achieved at the end after four hours is measured instead of the amount of calcium dissolved. This caries susceptibility test is not suited for office procedures.

Salivary Reductase Test

The salivary reductase test is yet another caries susceptibility assay to measure the rate at which the indicator molecule diazoresorcinol, changes from blue to red to colorless or whitish on reduction by the mixed salivary flora. The activity of the reductase enzyme present in salivary bacteria is measured by this test. No incubation procedures are required and the caries conduciveness reading is taken in 15 minutes (Table 9-9). Some investigators have concluded that this test does not give accurate results and may not be of diagnostic value, while others have proposed that this test is rather a measure of oral hygiene status of individual. However, caries free adults exhibit low or negative scores on the reductase test.

Table 9-9: Interpretation of salivary reductase test

Color	Time	Score	Caries activity
Blue	15 min	1	Nonconducive
Orchid	15 min	2	Slightly conducive
Red	15 min	3	Moderately conducive
Red	Immediately	4	Highly conducive
Pink/ white	Immediately	5	Extremely conducive

Caries activity tests

- Caries activity test — measures the degree to which the local environmental challenge favors the probability of carious lesions
- Caries activity → increment of active lesions (new or recurrent lesions) over a slated period of time
- Caries susceptibility → inherent tendency of the host, the target tissue, i.e the tooth to be afflicted by the caries

None of the above caries activity tests are comprehensive or reliable indicators of expected caries activity. This is not surprising as caries activity tests measure a single parameter such as acids produced or colony counts of a bacterial species. Dental caries being a multifactorial disease far outweighs the caries predictive tests which do not include factors involved in caries resistance such as fluoride exposure, maturation of enamel, or immune protection. The combined use of several selected tests is the best predictor of expected caries activity. The caries activity test thus provides indirect evidence that an aciduric and acidogenic flora is associated with the development of dental caries. The management of patients with increased caries proneness becomes less complicated by the effective use of caries activity tests which offer measurable parameters and accordingly institute a novel therapeutic approach.

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CHAPTER 10

Diseases of the Pulp and Periapical Tissues

■ B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

DISEASES OF DENTAL PULP

The dental pulp is a delicate connective tissue liberally interspersed with tiny blood vessels, lymphatics, nerves, and undifferentiated connective tissue cells. Like other connective tissues throughout the body, it reacts to bacterial infection or to other stimuli by an inflammatory response known as pulpitis, which is the most common cause of odontalgia or toothache. Certain anatomic features of this specialized connective tissue; however, tend to alter the nature and the course of this response. The enclosure of the pulp tissue within the rigid calcified walls of the dentin precludes the excessive swelling of tissue that occurs in the hyperemic phases of inflammation in other tissues. The fact that the blood vessels supplying the pulp tissue must enter the tooth through the tiny apical foramina precludes the development of an extensive collateral blood supply to the inflamed part.

The diseases of the dental pulp to be considered in this section are those occurring chiefly as sequelae of dental caries. Those reactions following various physical and chemical injuries are discussed in Chapter 12 on Physical and Chemical Injuries of the Oral Cavity. The sequential conditions are almost exclusively inflammatory and do not differ basically from inflammation elsewhere in the body.

Etiologic Factors

Most cases of pulpitis are primarily a result of dental caries in which bacteria or their products invade the dentin and pulp tissue. Dental caries is usually obvious unless it extends under the edge of a restoration. Brannstrom and Lind, among others, have reported that changes in the pulp may occur even with very early dental caries represented by demineralization limited to the enamel alone, appearing as white spots without actual cavitations.

> Bacteria circulating in the blood stream tend to settle out or accumulate at sites of pulpal inflammation, such as that which might follow some chemical or mechanical injury to the pulp and is known as 'anachoretic pulpitis'. Anachoresis is a phenomenon by which blood borne bacteria, dyes, pigments, metallic substances, foreign proteins, and other materials are attracted to the site of inflammation. One probable cause of this phenomenon is increased capillary permeability in the particular area. Anachoretic pulpitis probably occurs in a clinically insignificant number compared with the number of cases occurring as a result of dental caries.

Occasionally, there is bacterial invasion in the absence of caries, as in cases of tooth fracture due to trauma or cracked tooth syndrome that expose the dental pulp to the oral environment. In cracked tooth syndrome, a tooth, usually a restored premolar may split under masticatory stress. These cracks are often minute and invisible clinically, and they allow the bacteria to enter into the pulp. Bacterial invasion may also occur as a result of a bacteremia and septicemia. Pulpitis may rarely follow chronic periodontal disease wherein the microorganisms enter through the accessory canals of the exposed root surface especially through lateral canals in furcation areas of molars.

The significance of microorganisms in the etiology of pulpitis has been confirmed by Kakehashi and his associates, who produced surgical pulp exposures in germ-free rats. It was found that no devitalized pulps or periapical infections

developed even when gross food impactions existed. By contrast, conventional animals rapidly developed complete pulpal necrosis.

Pulpitis may also arise as a result of chemical irritation of the pulp caused by erosion or use of acidic restorative materials. This may occur not only in an exposed pulp to which some irritating medicament is applied but also in intact pulps beneath deep or moderately deep cavities into which some irritating filling material is inserted. This is undoubtedly a result of penetration of the irritating substances into the pulp via the dentinal tubules. In many instances; however, the pulp may respond to the irritation either by dentinal sclerosis or by forming reparative dentin rather than progressing to pulpitis.

Severe thermal change in a tooth may also produce pulpitis. Polishing procedures, tooth restored with exothermic restorative materials, or large metallic restorations, particularly, in which there is inadequate insulation between the restoration and the pulp are more prone to pulpal inflammation.

A condition clinically simulating pulpitis by the occurrence of toothache was reported during World War II in flying personnel and has been called aerodontalgia. This has also been described in aircrew flying at high altitudes, astronauts, submarine crews, and in deep sea divers. This pain has been attributed to the formation of nitrogen bubbles in the pulp tissue or vessels. It is relatively uncommon and is associated particularly with recently filled teeth. The work of Orban and Ritchey suggests that the pain in decompression does not usually occur in normal pulps. Interestingly, aerodontalgia reportedly may be delayed for hours or even days after decompression or ascent to high altitudes. Some cases of pain localized to the dental area and resembling aerodontalgia have been reported to represent aerosinusitis and not to be related to the teeth.

Heat produced by over-rapid tooth preparation or without sufficient coolant may also cause pulpal irritation. Heat and more particularly, cold are transmitted to the pulp, often producing pain, and if the stimulus is prolonged and severe, leading to actual pulpitis. Mild thermal changes are most apt to stimulate only the formation of reparative dentin, and this is a relatively common phenomenon.

When two dissimilar metallic restorations are present, the saliva acts as an electrolyte and there will be formation of a galvanic current. This may be transmitted to the pulp through metallic restoration and may thus initiate pulpitis.

It is apparent that pulpitis may be caused by a variety of circumstances and the nature of the etiologic agent or agents can usually be found through study of the clinical or microscopic features of the condition or both.

CLASSIFICATION OF PULPITIS

Pulpitis has been classified in a variety of ways, the simplest being a division into acute and chronic pulpitis. Furthermore, some investigators classify both **acute** and **chronic pulpitis** in several different ways. There may be a **partial pulpitis** or a **subtotal pulpitis**, depending upon the extent of involvement of the pulp. If the inflammatory process is confined to a portion of the pulp, usually a portion of the coronal pulp such as a pulp horn, the condition has been called **partial** or **focal pulpitis**. If most of the pulp is diseased, the term **total** or **generalized pulpitis** has been used. But this is of marginal clinical significance.

Another classification of both acute and chronic pulpitis is based upon the presence or absence of a direct communication between the dental pulp and the oral environment, usually through a large carious lesion. The term **open pulpitis** (pulpitis aperta) has been used to describe those cases of pulpitis in which the pulp obviously communicates with the oral cavity, whereas the cases in which no such communication exists are described as **closed pulpitis** (pulpitis clausa). In both the clinical and the histologic features of open and closed pulpitis, differences do exist that are referable to the presence or absence of drainage, which in turn determine the degree of pain present. The basic process is the same in each case, but the classification has been used as an aid in understanding the variations in clinical features that occur in different cases.

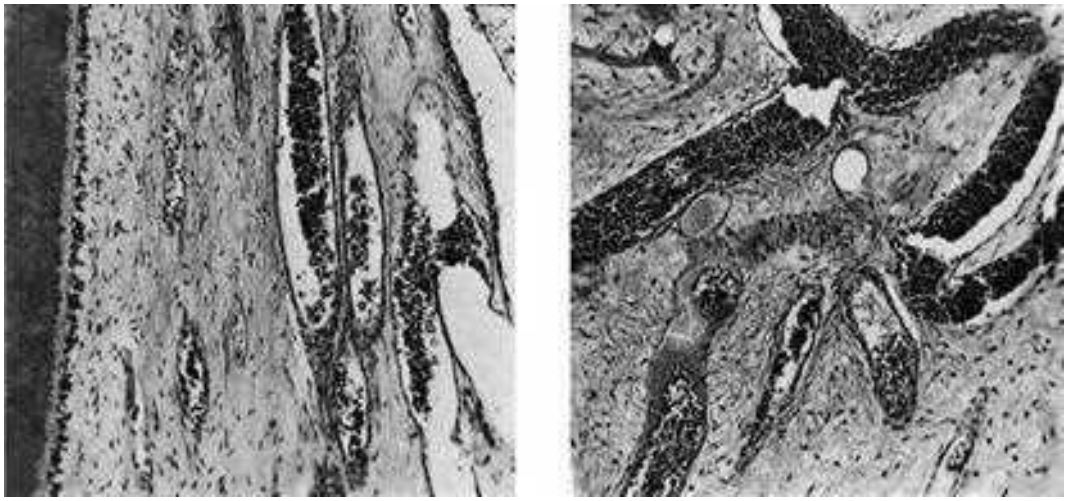
In this section, pulpitis will be discussed under the two chief types of the disease: **acute** and **chronic**. In addition, attention will be drawn to those differences in clinical and histologic features that are dependent upon the extent of the inflammation and upon whether drainage can occur.

Focal Reversible Pulpitis

One of the earliest forms of pulpitis is the condition known as **focal reversible pulpitis**. At one time, this was often referred to as **pulp hyperemia**. However, it is known that vascular dilatation can occur artefactually from the 'pumping' action during tooth extraction as well as pathologically as a result of dentinal and pulpal irritation. Therefore, this early mild transient pulpitis, localized chiefly to the pulpal ends of irritated dentinal tubules, is now known as focal reversible pulpitis.

Clinical Features. A tooth with focal pulpitis is sensitive to thermal changes, particularly to cold. The application of ice or cold fluids to the tooth results in pain, but this disappears upon removal of the thermal stimuli or restoration of the normal temperature. It will be found also that such a tooth responds to stimulation by the electric pulp tester at a lower level of current, indicating a lower pain threshold (or a greater sensitivity) than that of adjacent normal teeth. Teeth in which this condition exists usually show deep carious lesions, large metallic restorations (particularly without adequate insulation), or restorations with defective margins.

Histologic Features. Focal pulpitis is characterized microscopically by dilatation of the pulp vessels (Fig. 10-1). Edema fluid may collect because of damage to the capillary walls, allowing actual extravasation of red blood cells or some diapedesis of white blood cells. Slowing of the blood flow and hemoconcentration due to transudation of fluid from the vessels conceivably could cause thrombosis. The belief has prevailed also that



A B

Figure 10-1. Focal reversible pulpitis.
The photomicrographs show vasodilatation but no extravasation of red or white blood cells.

self-strangulation of the pulp may occur as a result of increased arterial pressure occluding the vein at the apical foramen. Boling and Robinson argued that this belief is incorrect because the pulp may have several afferent and efferent vessels and several foramina, making self-strangulation unlikely.

Supporting this, in clinical practice, when a necrosed pulp chamber is opened, there may be vital tissue in the root canal of some teeth proving that total necrosis does not always occur. Reparative dentin may be noted in the adjacent dentinal wall.

Treatment and Prognosis. Focal pulpitis is generally regarded as a reversible condition, provided the irritant is removed before the pulp is severely damaged. Thus, a carious lesion should be excavated and restored or a defective filling replaced as soon as it is discovered. If the primary cause is not corrected, extensive pulpitis eventually results, with subsequent 'death' of the pulp.

Acute Pulpitis

Extensive acute inflammation of the dental pulp is a frequent immediate sequela of focal reversible pulpitis, although it may also occur as an acute exacerbation of a chronic inflammatory process. Significant differences in both the clinical and microscopic features are found between acute and chronic pulpitis.

Clinical Features. Acute pulpitis usually occurs in a tooth with a large carious lesion or restoration, commonly a defective one around which there has been 'recurrent caries'. Even in its early stages when the inflammatory reaction involves only a portion of the pulp, usually in the area just beneath the carious lesion, relatively severe pain is elicited by thermal changes, particularly when taking ice or cold drinks. Characteristically, this pain persists even after the thermal stimulus has disappeared or been removed. However, a clinicopathologic study by Mitchell and Tarplee provided evidence that evaluation of the type or degree of pulpitis is present by sensitivity to either heat or cold is fallacious, since in their study most patients with any type of pulpitis exhibited increased sensitivity to both heat and cold. This has been confirmed by Seltzer and his associates, who have also shown that the severity of the pain is only partially related to the severity of the inflammatory response.

Other factors include establishment of drainage, the patient's previous experiences, emotions, and so forth.

> The pulpal pain is poorly localized and may be felt in any of the teeth of the upper or lower jaw of the affected side, since the pulp of the individual tooth is not represented precisely on the sensory cortex.

As a greater proportion of the pulp becomes involved with intrapulpal abscess formation, the pain may become even more severe and is often described as lancinating or throbbing type. The pain generally lasts for 10–15 minutes but may be more or less continuous, and its intensity may be increased when the patient lies down. The application of heat may cause an acute exacerbation of pain. The tooth reacts to the electric pulp vitality tester at a lower level of current than adjacent normal teeth, indicating increased sensitivity of the pulp. When necrosis of the pulp tissue occurs, this sensitivity is lost.

Severe pain is more likely to be present when the entrance to the diseased pulp is not wide open. The pulpal pain is not only caused by the pressure built-up due to lack of escape of inflammatory exudates but also by the pain producing substances released by the inflammatory reaction. Caviedes-Bucheli J and coworkers have demonstrated that, the receptors for substance P, a neurotransmitter in the pain fiber system, increases during inflammation of pulp. Soon there is rapid spread of inflammation throughout the pulp with pain and necrosis. Until this inflammation or necrosis extends beyond root apex, the tooth is not particularly sensitive to percussion. When a large open cavity is present, there is no opportunity for

a build-up of pressure. Thus the inflammatory process does not tend to spread rapidly throughout the pulp. In such a case the pain experienced by the patient is a dull, throbbing ache, but the tooth is still sensitive to thermal changes. Mobility and sensitivity to percussion are usually absent.

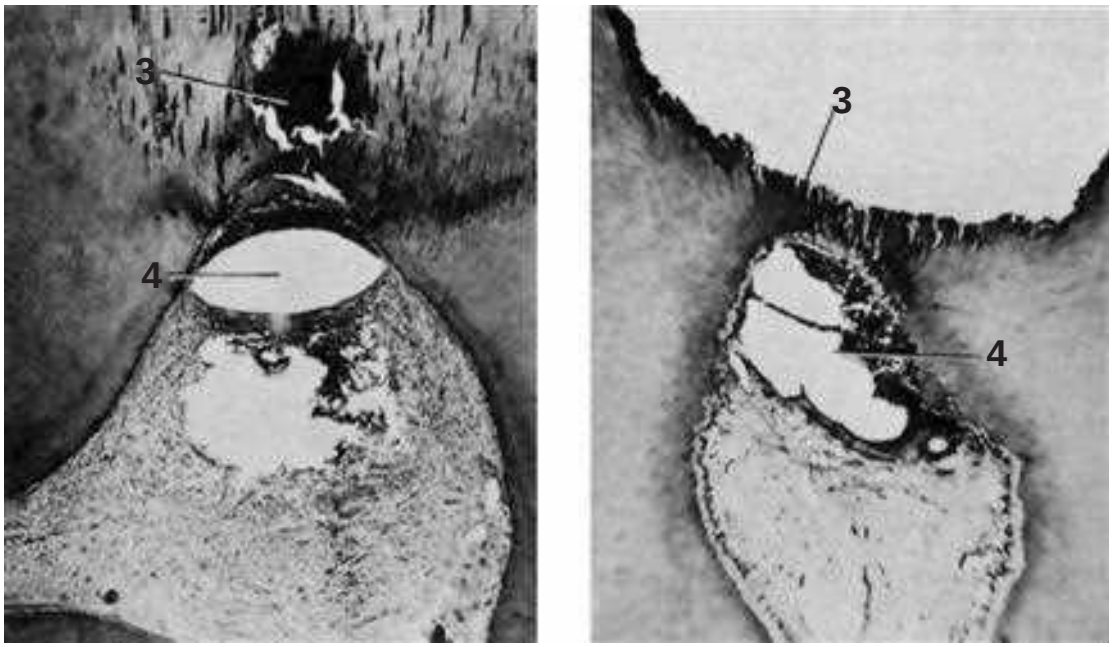
The patient with a severe acute pulpitis is extremely uncomfortable and at least mildly ill. He/she is usually apprehensive and desirous of immediate attention from the dentist.

Histologic Features

Early acute pulpitis is characterized by the continued vascular dilatation seen in focal reversible pulpitis, accompanied by the accumulation of edema fluid in the connective tissue surrounding the tiny blood vessels. The pavementing of polymorphonuclear leukocytes becomes apparent along the walls of these vascular channels, and these leukocytes rapidly migrate through the endothelium-lined structures in increasing numbers. CD 44 is an adhesion molecule present in leukocytes, epithelial cells, endothelial cells, and smooth muscle cells. It has an important role in migration of leukocytes from the blood vessels to the area of inflammation. Pisterna GV and Siragusa M have demonstrated that CD 44 expression is higher during initiation and maintenance phase of pulp inflammation. As great collections of white blood are found in the inflamed region, especially beneath an area of carious penetration the odontoblasts in this area have usually been destroyed.

Early in the course of the disease, the polymorphonuclear leukocytes are confined to a localized area, and the remainder of the pulp tissue appears relatively normal. The rise in pressure in the pulp associated with an inflammatory exudate causes local collapse of the venous part of the circulation. This leads to local tissue hypoxia and anoxia, which in turn may lead to localized destruction and the formation of a small abscess, known as a pulp abscess, which contains pus arising from breakdown of leukocytes and bacteria as well as from digestion of tissue (Figs. 10-2, 10-3). This necrotic zone contains polymorphonuclear leukocytes and histiocytes. Abscess formation is most likely to occur when the entrance to the pulp is a tiny one and there is lack of drainage. The chemical mediators released from the necrotic tissue lead to further inflammation and edema. Hepatocyte growth factor (HGF), a multifunctional cytokine mediates epithelial mesenchymal interaction, and is involved in the development and regeneration of various tissues including teeth. Ohnishi T et al, have reported the presence of HGF during acute inflammation of the pulp. Interleukin-8 level in the exudate of the acute pulpitis is higher than that in chronic pulpitis as shown by Guo X et al.

Eventually, in some cases in only a few days, the acute inflammatory process spreads to involve most of the pulp so that neutrophilic leukocytes fill the pulp. The entire odontoblastic layer degenerates. If the pulp is closed to the outside, there is considerable pressure formed, and the entire pulp tissue undergoes rather rapid disintegration. Numerous small abscesses may form, and eventually the entire pulp undergoes liquefaction and necrosis. This is sometimes referred to as acute suppurative pulpitis (Fig. 10-4).



A B

Figure 10-2. Acute pulpitis with pulp abscess formation.
There is diffuse inflammation of the pulp chamber in A beneath the carious lesion (1) with the formation of a circumscribed focus of suppuration, a pulp abscess (2). In B, the carious lesion (1) has evoked only a focal inflammation of the pulp with abscess formation (2).

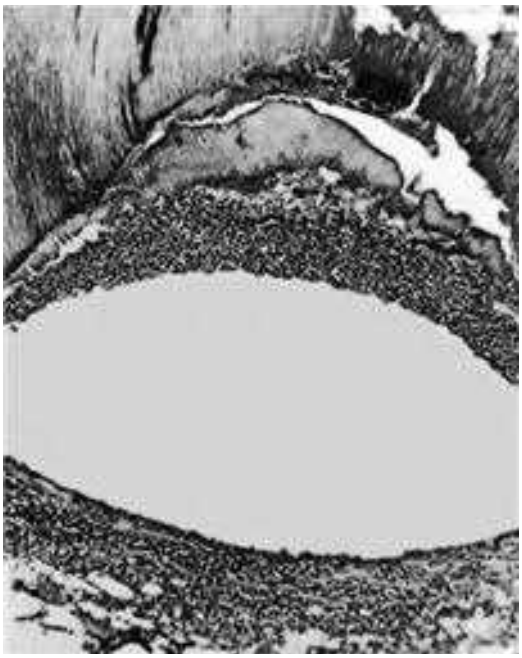


Figure 10-3. Pulp abscess.
The high-power photomicrograph of Figure 10-2 A, shows the void caused by the loss of the suppurative contents of the abscess and the limiting band of leukocytes.

Figure 10-4. Acute pulpitis.
The entire pulp is involved (total pulpitis), and a focal area of suppuration is present.

The pulp, especially in the later stages of pulpitis following carious invasion, contains large numbers of bacteria. These microorganisms are usually a mixed population and consist essentially of those found normally in the oral cavity.

Treatment and Prognosis. There is no successful treatment of an acute pulpitis involving most of the pulp that is capable of preserving the pulp. Once this degree of pulpitis occurs, the damage is irreparable. Occasionally, acute pulpitis—especially with an open cavity—may become quiescent and enter a chronic state. This is unusual; however, and appears to occur most frequently in persons who have a high tissue resistance or in cases of infection with microorganisms of low virulence. In very early cases of acute pulpitis involving only a limited area of tissue, there is some evidence to indicate that pulpotomy (removal of the coronal pulp) and placing a bland material that favors calcification, such as calcium hydroxide, over the entrance to the root canals may result in survival of the tooth. This technique is also used in cases of mechanical pulp exposures without obvious infection (Fig. 10-5). Teeth involved with acute pulpitis may be treated by filling the root canals with an inert material, provided the pulp chamber and root canals can be sterilized.

Chronic Pulpitis

Chronic pulpitis may arise on occasion through quiescence of a previous acute pulpitis, but more frequently it occurs as the chronic type of disease from the onset. As in most chronic inflammatory conditions, the signs and symptoms are considerably milder than those in the acute form of the disease. A special form of chronic pulpitis known as **chronic hyperplastic pulpitis** has characteristic features and will be described separately.

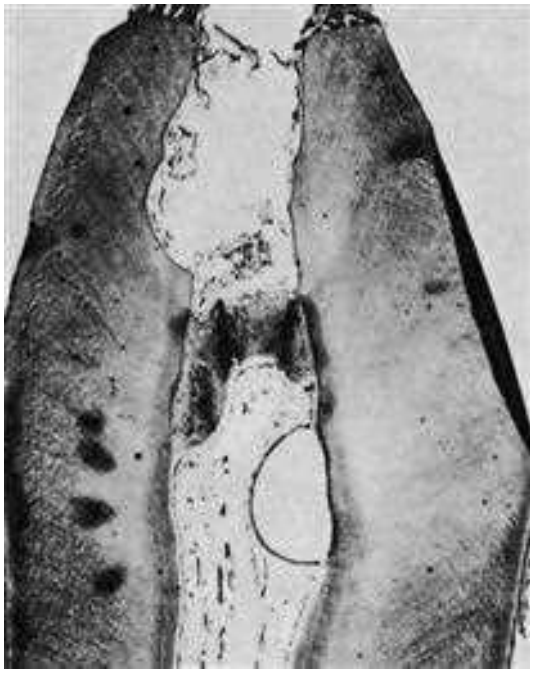


Figure 10-5. Healing of a pulp exposure by a dentinal bridge.
Calcium hydroxide placed over the mechanically exposed pulp stimulated the production of a dentinal bridge over the pulp. The circumscribed space in the pulp is an artifact and not a pulp abscess.

Clinical Features. Pain is not a prominent feature of chronic pulpitis, although sometimes the patient complains of a mild, dull ache, which is more often intermittent than continuous. The reaction to thermal change is dramatically reduced in comparison to that in acute pulpitis. Because of the degeneration of nerve tissue in the affected pulp, the threshold for stimulation by the electric pulp vitality tester is often increased. The general features of chronic pulpitis are not distinctive, and serious involvement of the pulp may be present in the absence of significant symptoms. Even in cases of chronic pulpitis with wide-open carious lesions and with exposure of the pulp to the oral environment, there is relatively little pain. The exposed pulp tissue may be manipulated by a small instrument, but though bleeding may occur, pain is often absent. As Selzer and his associates have emphasized, pulps may become totally necrotic without pain.

Histologic Features. Chronic pulpitis is characterized by infiltration of the pulp tissue by varying numbers of mononuclear cells, chiefly lymphocytes and plasma cells (Fig. 10-6) and more vigorous connective tissue reaction. Bacterial products may act as antigens and the dendritic cells of the pulp capture the antigens, migrate to lymph nodes and present them to lymphocytes. These activated T cells then leave the lymph nodes and reach the pulp. Capillaries are usually prominent; fibroblastic activity is evident; and collagen fibers are seen, often gathered in bundles. There is sometimes an attempt by the pulp to ward off the infection through deposition of collagen fibers around the inflamed area. The tissue reaction may resemble the formation of granulation tissue. When this occurs on the surface of the pulp tissue in a wide-open exposure, the term ulcerative pulpitis is applied. With bacterial stains, microorganisms may be found in the pulp tissue, especially in the area of a carious exposure. In some cases, the pulpal reaction vacillates between an acute and a chronic phase. This holds true not only for diffuse inflammation but also for that form of pulp disease characterized by pulp abscess formation. Thus a pulp abscess may become quiescent and be surrounded by a fibrous connective tissue wall, which is known as the pyogenic membrane.

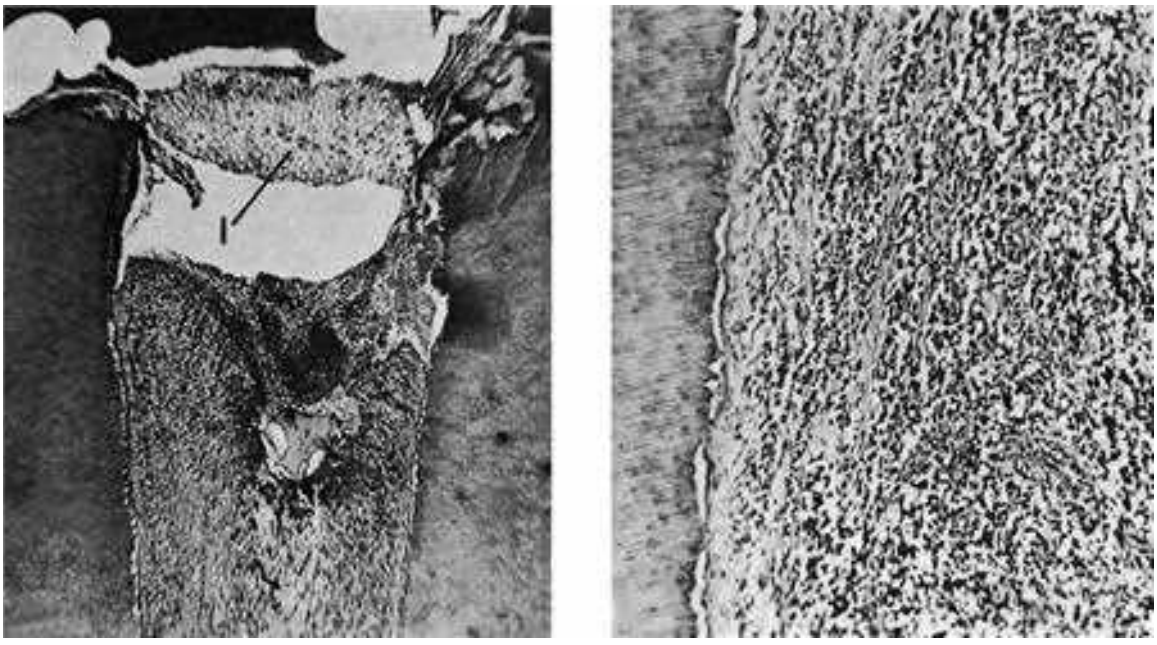
In nearly all cases, the pulp is eventually involved in its entirety by the chronic inflammatory process, although this may take a long time to present few clinical symptoms.

Treatment and Prognosis. The treatment of chronic pulpitis does not differ dramatically from that of acute pulpitis. The integrity of the pulp tissue is lost sooner or later, necessitating either root canal therapy or extraction of the tooth.

Chronic Hyperplastic Pulpitis
(Pulp polyp)

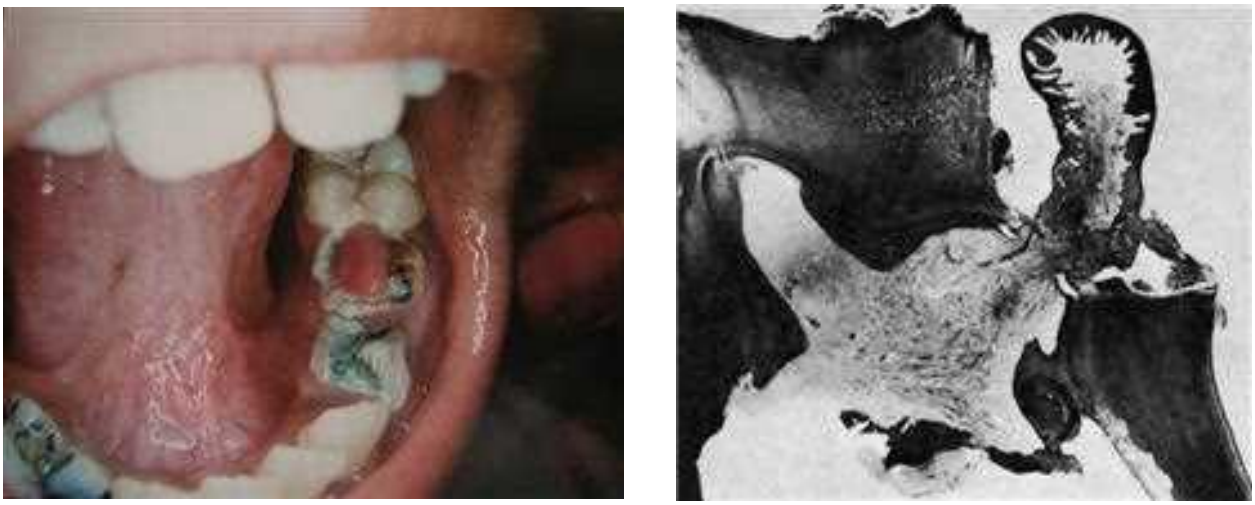
Chronic hyperplastic pulpitis is a unique form of pulpitis wherein the inflamed pulp, instead of perishing by continued suppuration, reacts by excessive and exuberant proliferation. It occurs either as a chronic lesion from the onset or as a chronic stage of a previously acute pulpitis.

Clinical Features. Chronic hyperplastic pulpitis occurs almost exclusively in children and young adults who possess a high degree of tissue resistance and reactivity, and readily respond to proliferative lesions. It involves teeth with large, open carious lesions. A pulp so affected appears as a pinkish-



A B

Figure 10-6. Chronic pulpitis.
(A) The pulp of this tooth shows diffuse involvement by chronic inflammatory cells. The entrance to the pulp chamber is wide open (open pulpitis), but contains food debris (1). **(B)** In the high-power photomicrograph there is seen diffuse infiltration of lymphocytes and plasma cells with fibrosis and loss of the odontoblastic layer.



A B

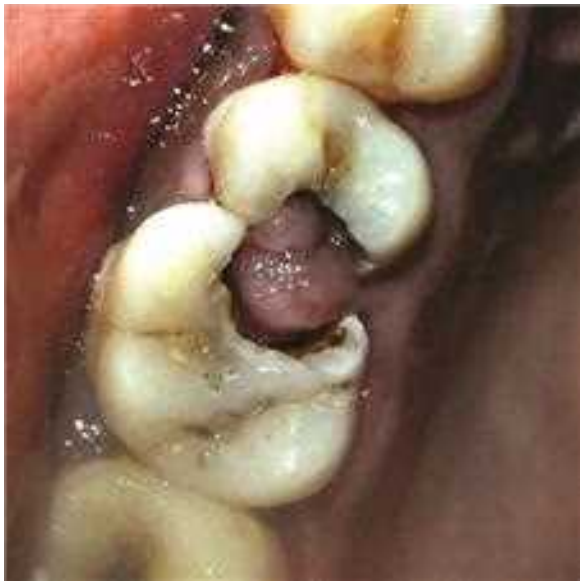
Figure 10-7. Chronic hyperplastic pulpitis.
(A) There is a mass of tissue protruding from the pulp chamber into the carious lesion. **(B)** In the photomicrograph this is seen to be continuous with the pulp and covered by stratified squamous epithelium *(A, Courtesy of Dr S Karthigakannan, Department of Oral Medicine, Sree Moogambica Dental College, Tamil Nadu)*.

red globule of tissue protruding from the pulp chamber and not only fills the caries defect but also extends beyond (Fig. 10-7). Because the hyperplastic tissue contains few nerves, it is relatively insensitive to manipulation. However, Southam and Hodson have found that sometimes innervation of polyps may be quite rich and have stated that the number of nerve fibers in pulp polyps cannot be presumed to be directly related to the sensory acuity found on clinical examination. They have even noted innervation of the epithelium in epithelialized polyps in some instances. The lesion may or may not bleed readily, depending upon the degree of vascularity of the tissue and epithelialization.

On occasion the gingival tissue adjacent to a broken carious tooth may proliferate into the carious lesion and superficially resemble an example of hyperplastic pulpitis. In such cases the distinction can be made by careful examination of the tissue mass to determine whether the connection is with pulp or gingiva (Fig. 10-8).

The teeth most commonly involved by this phenomenon are the deciduous molars and the first permanent molars. These have an excellent blood supply because of the large root opening, and this coupled with the high tissue resistance and reactivity in young persons, accounts for the unusual proliferative property of the pulp tissue.

Histologic Features. The hyperplastic tissue is basically granulation tissue made up of delicate connective tissue fibers interspersed with variable numbers of small capillaries (Fig. 10-7). Inflammatory cell infiltration, chiefly lymphocytes and plasma cells, sometimes admixed with polymorphonuclear leukocytes, is common. In some instances fibroblast and endothelial cells proliferation is prominent.



Proliferation of interdental gingiva resembling clinically a pulp polyp, *(Courtesy of Dr Joshua Sheih,Emmanuel Dental Clinic, Chennai).*

This granulation tissue commonly becomes epithelialized and the origin of these epithelial cells is a matter of controversy. The epithelium is stratified squamous in type and closely resembles the oral mucosa, even to the extent of developing well formed rete ridges. The grafted epithelial cells are thought to be normally desquamated cells carried to the surface of the pulp by the saliva. Most desquamated epithelial cells in the saliva are degenerated superficial squames, which have lost their dividing capacity. For the polyp to become epithelialized, the cells should have the capacity to divide and differentiate into stratified squamous

epithelium. So, such cells must come from the region of the basal cell layer and might be released from trauma or from the gingival sulcus. In some instances, the buccal mucosa may rub against the hyperplastic tissue mass, and epithelial cells become transplanted directly. Southam and Hodson have reported that polyps from deciduous teeth were epithelialized far more frequently (82% of 56 polyps) than those of permanent teeth (44% of 77 polyps). It should be appreciated that the tissue reaction here is an inflammatory hyperplasia and does not differ from inflammatory hyperplasia occurring elsewhere in the oral cavity as well as in other parts of the body. In time, organization of the tissue leads to decreased vascularity and increased fibrosis. M Sattari, AK Haghighi, and HD Tamijani showed that presence and concentration of IgE, histamine and IL-4 were higher in pulp polyps than in normal pulps, and suggested that type I hypersensitivity reaction being involved in pulp polyp's pathogenesis.

Gangrenous necrosis of pulp

Untreated pulpitis, either acute or chronic, will ultimately result in complete necrosis of the pulp tissue. Since this is generally associated with bacterial infection, the term **pulp gangrene** has sometimes been applied to this condition, gangrene being defined as necrosis of tissue with superimposed bacterial infection. This gangrenous necrosis of the pulp is associated with a foul odor when such infected pulps are opened for endodontic treatment.

Pulp gangrene should not be considered a specific form of pulp disease but simply the most complete end result of pulpitis in which there is total necrosis of tissue. Necrosis of pulp has been reported in sickle cell anemia where there is blockage of pulp microcirculation by sickle erythrocytes. A type of gangrene known as **dry gangrene** sometimes occurs when the pulp dies for some unexplained reason. The nonvital pulp maintains its general histologic characteristics, being nonpurulent. This condition may be due to some traumatic injury or infarct.

Treatment and Prognosis. Chronic hyperplastic pulpitis may persist as such for many months or several days. The condition is not reversible and may be treated by extraction of the tooth or by pulp extirpation.

DISEASES OF PERIAPICAL TISSUES

Once infection has become established in the dental pulp, spread of the process can be in only one direction—through the root canals and into the periapical region. Here a number of different tissue reactions may occur, depending upon a variety of circumstances.

It is important to realize that these periapical lesions do not represent individual and distinct entities, but rather that there is a subtle transformation from one type of lesion into another type in most cases. Furthermore, it should be appreciated that a certain degree of reversibility is possible in some lesions. The interrelations between the types of periapical infection must be clearly understood, and the schematic diagram shown in Figure 10-9 will aid in clarification of this.

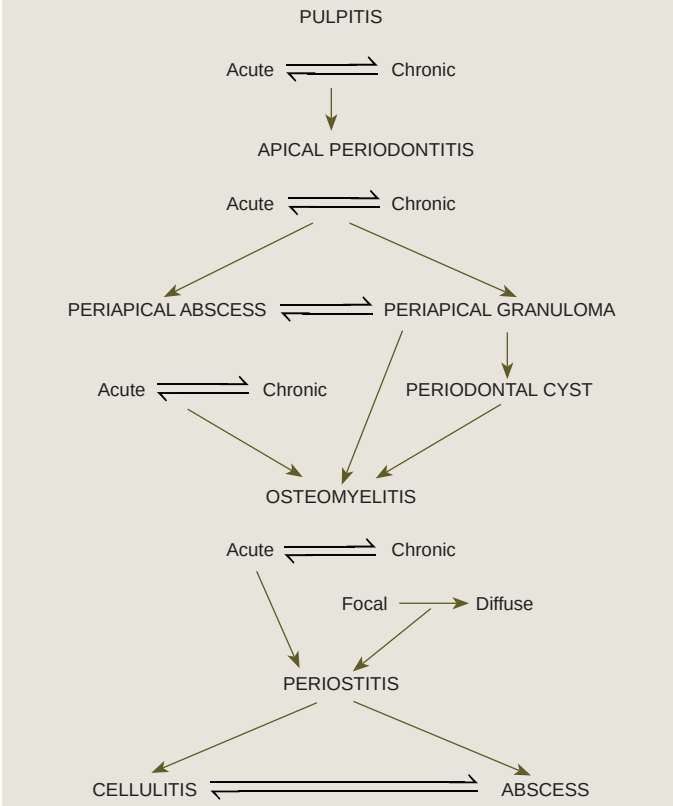


Figure 10-9. Interrelationships of periapical infection.

Apical Periodontitis

Apical periodontitis is the inflammation of the periodontal ligament around the root apex. Though the inflammatory process here is similar to that occurring elsewhere, there may be resorption of the periapical bone and sometimes the root apex. This process may be acute or chronic depending upon the virulence of the microorganisms involved, the type and severity of the physical or chemical irritants, and host resistance. The common causes of apical periodontitis include spread of infection following pulp necrosis, occlusal trauma from a high restoration or biting suddenly on a hard object, inadvertent endodontic procedures such as over instrumentation, pushing the infected material into the apical portion or chemical irritation from root canal medicaments.

Acute Apical Periodontitis

Patients suffering from acute apical periodontitis usually give the history of previous pulpitis. Thermal change does not induce pain as in pulpitis. Due to the collection of inflammatory edema in the periodontal ligament, the tooth is slightly elevated in its socket and causes tenderness while

biting or even to mere touch. The external pressure on the tooth forces the edema fluid against already sensitized nerve endings and results in severe pain. Radiographic appearance is essentially normal at this stage except for a slight widening of periodontal ligament space.

Histologic Features. The periodontal ligament shows signs of inflammation characterized by vascular dilatation and infiltration with polymorphonuclear leukocytes. Initially, these changes are localized around the root apex, as this area is richly vascular. The inflammation is transient if it is caused by acute trauma. If the irritant is not removed, it progresses with resorption of the surrounding bone. Abscess formation may occur if it is associated with bacterial infection and is known as acute periapical abscess or alveolar abscess.

Treatment and Prognosis. If the inflammation is caused by occlusal trauma, it should be relieved by selective occlusal grinding. If the periapical periodontitis occurs due to the spread of pulpal infection, the tooth should be extracted or endodontic treatment be initiated to drain the exudate.

Chronic Apical Periodontitis
(Periapical granuloma)

Chronic apical periodontitis, also known as periapical granuloma, is a low-grade infection and one of the most common of all sequelae of pulpitis or acute periapical periodontitis. If the acute process is left untreated, it is incompletely resolved and becomes chronic. The acute inflammatory process is an exudative response whereas the chronic one is proliferative. Periapical granuloma is essentially a localized mass of chronic granulation tissue formed in response to the infection (Fig. 10-10). But the use of this term is not totally accurate since it does not shows true granulomatous inflammation microscopically.

It should be pointed out here that the spread of pulp infection is usually, but not always, in a periapical direction. The presence of lateral or accessory root canals opening on the lateral surface of the root at any level is a well-recognized anatomic deviation along which the infection may spread. This would give rise to a 'lateral' granuloma or related inflammatory lesion.

Clinical Features. The involved tooth is usually nonvital and may be slightly tender to percussion, and percussion may produce a dull sound instead of a normal metallic sound because of the presence of granulation tissue around the root apex. Patients may complain of mild pain on biting or chewing on solid food. In some cases, the tooth feels slightly elongated in its socket and may actually be so. The sensitivity is due to hyperemia, edema, and inflammation of the apical periodontal ligament. The early or even the fully developed chronic periapical granuloma seldom presents any more severe clinical features than those just described.

Actually, many cases are entirely asymptomatic. There is usually no perforation of overlying bone and oral mucosa with the formation of a fistulous tract unless the lesion undergoes an acute exacerbation.

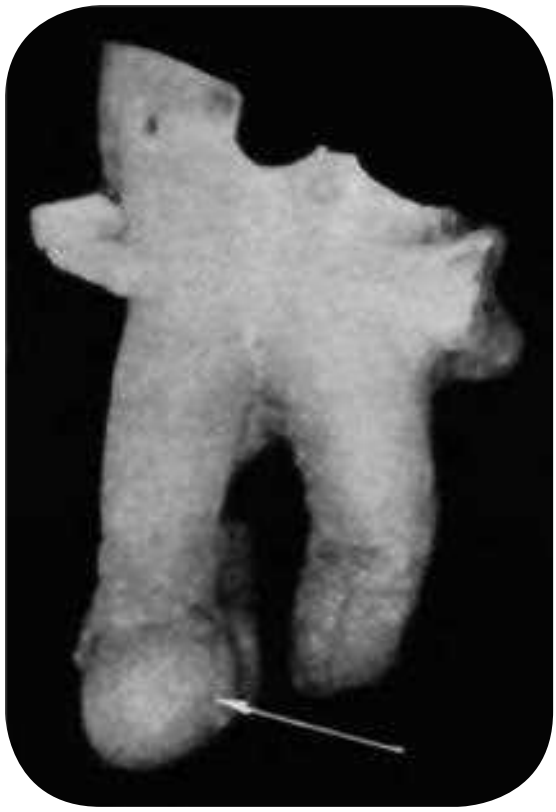


Figure 10-10. Periapical granuloma.
The granuloma often remains attached to the root when the tooth is extracted.

Radiographic Features. The earliest periapical change in the periodontal ligament appears as a thickening of the ligament at the root apex (Fig. 10-11). As proliferation of granulation tissue and concomitant resorption of bone continues, the periapical granuloma appears as a radiolucent area of variable size seemingly attached to the root apex (Fig. 10-12). In some cases, this radiolucency is a well-circumscribed, definitely demarcated from the surrounding bone. In these instances a

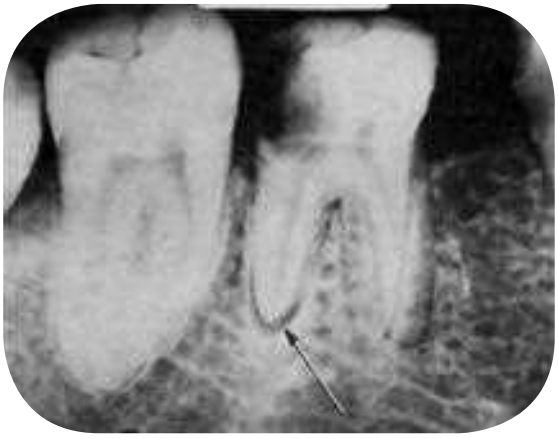
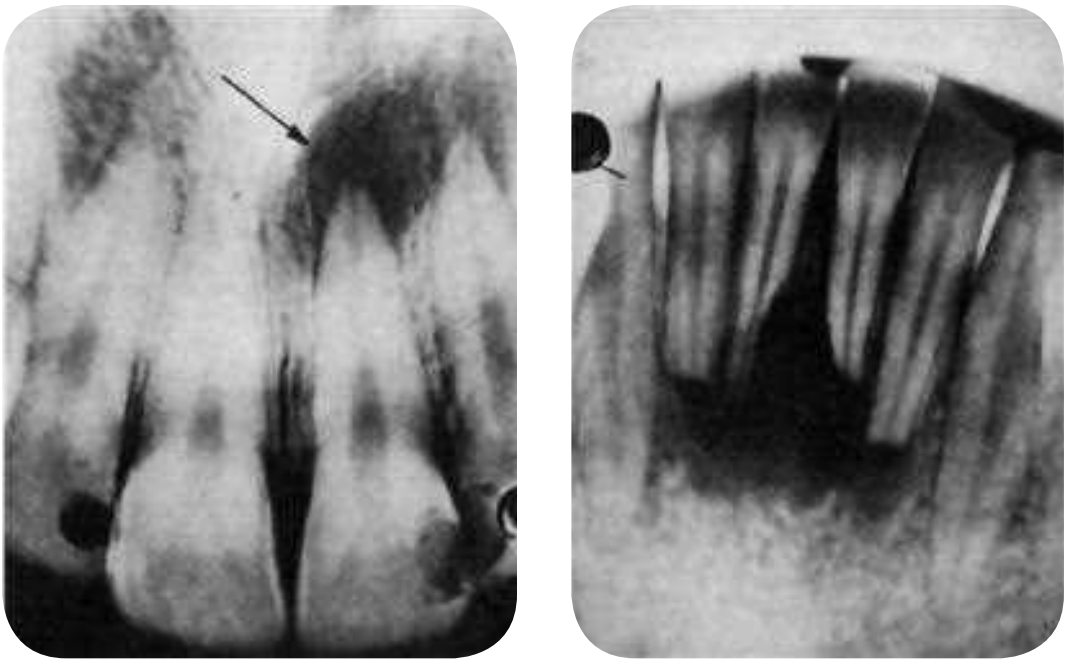


Figure 10-11. Early apical periodontitis.
There is radiographic evidence of thickening of the apical periodontal membrane as a result of the large carious lesion involving the dental pulp.



A B

Figure 10-12. Periapical granuloma.
The periapical radiolucencies signify destruction of bone and replacement by granulation tissue. The maxillary central incisor **(A)** has a carious lesion of the distal surface that involves the pulp. The mandibular incisors **(B)** have sustained traumatic injury with loss of pulp vitality and subsequent formation of diffuse periapical granulomata.

thin radiopaque line representing a zone of sclerotic bone may sometimes be seen outlining the lesion. This indicates that the periapical lesion is a slowly progressive and long standing one that has probably not undergone an acute exacerbation.

The periphery of granulomas in other instances appears on the radiograph as a diffuse blending of the radiolucent area with the surrounding bone. This difference in radiographic appearance is due to the difference in cellular activity around the margins of the lesion and cannot be used to distinguish between different forms of periapical disease. Although the diffuse radiolucency might suggest a more acute phase of disease or a more rapidly expanding lesion, this is not necessarily the case. In addition, some degree of root resorption is occasionally observed.

Histologic Features. The periapical granuloma that arises as a chronic process from the onset and does not pass through an acute phase begins as a hyperemia and edema of the periodontal ligament with infiltration of chronic inflammatory cells. The inflammation and locally increased vascularity of the tissue are associated with resorption of the supporting bone adjacent to this area. Occasionally, microscopic or even macroscopic resorption of the root apex occurs, but this is not usually an early finding. As the bone is resorbed, there is proliferation of both fibroblasts and endothelial cells and the formation of more tiny vascular channels as well as numerous delicate connective tissue fibrils (Figs. 10-13, 10-14). The new capillaries are usually lined by swollen endothelial cells. It is a relatively homogeneous lesion

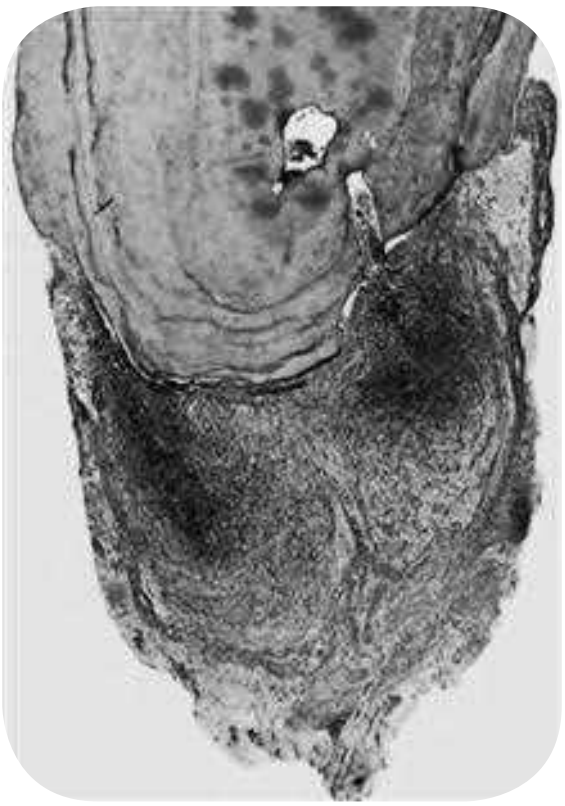


Figure 10-13. Periapical granuloma.
The mass attached to the root is composed of granulation tissue.

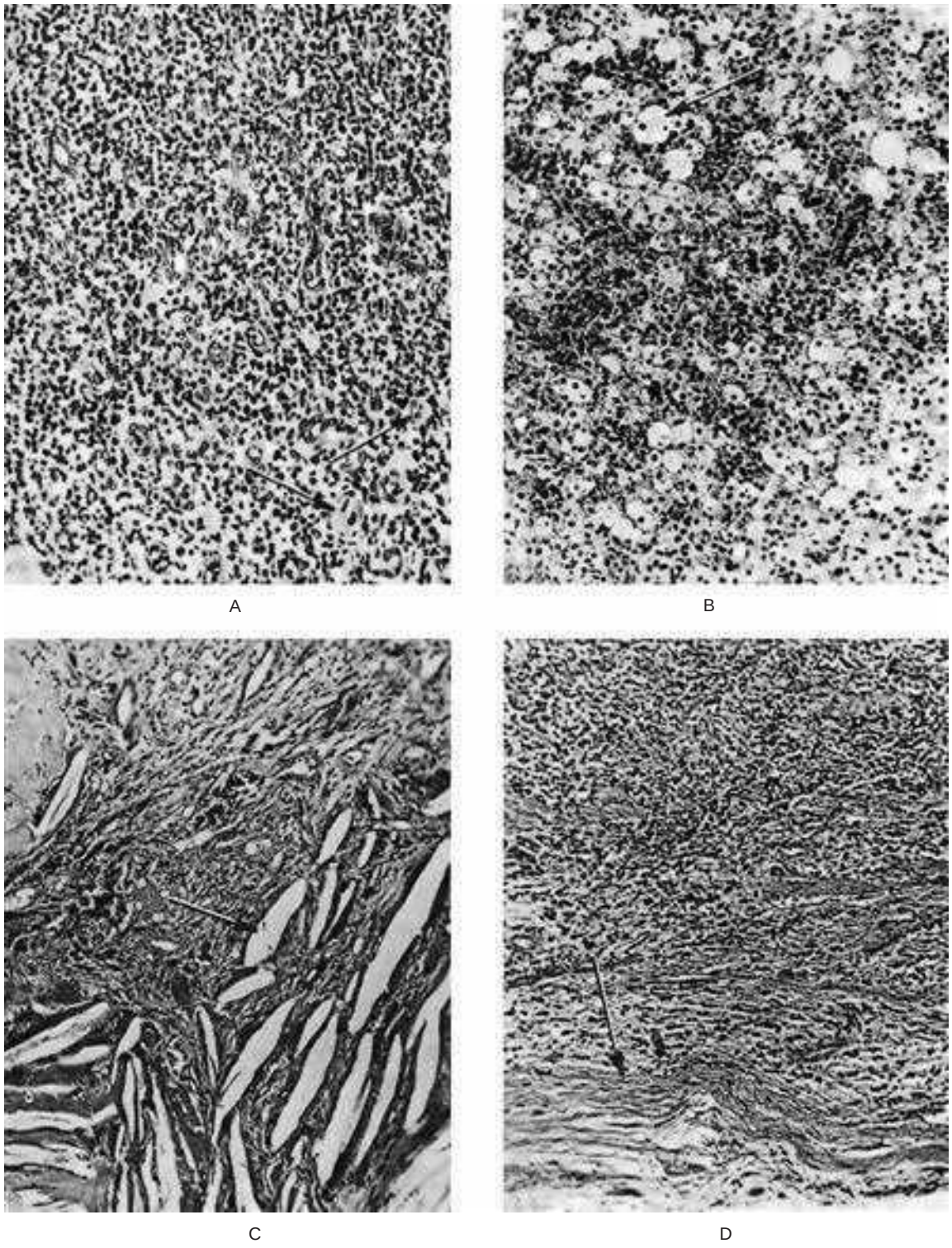


Figure 10-14. Periapical granuloma.
The photomicrographs represent various histologic features, although all such features need not be present in a single granuloma. The typical periapical granuloma shows the delicate fibrillar stroma with intense lymphocytic and plasma cell infiltration and sometimes polymorphonuclear leukocytes as well as many small capillaries **(A)**, collections of macrophages that are often filled with lipoid material **(B)**, and cholesterol slits in the tissue **(C)**. The typical granuloma is usually surrounded by a connective tissue 'capsule' **(D)**.

composed predominantly of macrophages, lymphocytes, and plasma cells, and less frequently with mast cells and eosinophils, thus qualifying as an immune-type granuloma. As Athanassiades and Spears, and Page and his associates have pointed out, immune granulomas have more lymphocytes and plasma cells than non-immune granulomas, which are relatively pure collections of macrophages and giant cells with only a rare plasma cell.

The vast majority of the small lymphocytes (81%) was not associated with immunoglobulin production and was designated non-B lymphocytes. 19% of the lymphocytes contained immunoglobulins, of which the majority (74%) produced IgG. IgA was found in 20% of the lymphocytes, while IgE and IgM were found in 4% and 2%, respectively. Many of the plasma cells contained Russell bodies, some of which were subsequently extruded and could be found extracellularly. The non-B lymphocytes are probably the T cells of the cellular arm of the immune system, thus making the lesion an expression of delayed type hypersensitivity. There is ample evidence to indicate that T cell activity could account for much of the bone and tooth resorption through the production of osteoclast activating factor (OAF). Since T cells also produce various cytotoxic lymphokines, collagenase and other enzymes, and destructive lymphokines, they may be responsible for much of the destructive potential of the periapical lesion. On the other hand, the presence of antibody-producing lymphocytes and plasma cells in periapical granulomas is very important because antibodies are known to be modulators of disease activity. In addition, their specificity may provide clues to the antigens and thus to the causes of periapical granulomas and cysts.

Macrophages and other mononuclear phagocytes are the hallmarks of granulomatous inflammation, a specific form of chronic inflammation.

In periapical granuloma substantial amount of dendritic cells are present. As per the study by Kaneko T et al, these dendritic cells are associated with local defense reactions as stronger antigen presenting than macrophages.

Compared with granulomatous inflammation, banal chronic inflammation lacks organization. Rather it is a diffuse heterogeneous collection of cells, usually dominated by mononuclear cells other than macrophages, as Adams has noted. The cause of differentiation from solid to cystic periapical lesions cannot be deduced from alterations in the inflammatory cell populations of granulomas and cysts. There were no differences in inflammatory cell composition, immunoglobulin production, or immunoglobulin distribution between granulomas and cysts.

In some granulomas, large numbers of phagocytes will ingest lipid material and become collected in groups, forming sheets of so-called foam cells (Fig. 10-14B). Abundant mast cells may also be found. Deposits of cholesterol as well as hemosiderin are often present and both are probably derived from the breakdown of extravasated red blood cells. Cholesterol crystals appear microscopically as clear needlelike spaces or clefts owing to the dissolving of the contained cholesterol by the agents used in the preparation of the tissues for histologic examination (Fig. 10-14C) and are almost invariably associated with multinucleated giant cells of the foreign body type.

Connective tissue activity is usually most prominent on the periphery of the granuloma, and the bundles of collagen become condensed there, apparently as a result of the slow expansion of the soft-tissue mass, to form a continuous capsule separating the granulation tissue from the bone (Fig. 10-14D).

Another important feature noted in the chronic periapical granuloma is the presence of epithelium.

Epithelium of periapical granuloma may also originate from:

- Respiratory epithelium of the maxillary sinus in cases in which the periapical lesion perforated the sinus wall
- Oral epithelium growing in through a fistulous tract
- Oral epithelium proliferating apically from a periodontal pocket, or bifurcation or trifurcation involvement by periodontal disease also with apical proliferation.

In early periapical granulomas, the epithelium is confined to the immediate vicinity of the periodontal ligament. In course of time, the epithelium undergoes proliferation by the inflammatory stimuli, in an attempt to wall off the irritant coming out through the apical foramen, which becomes extensive, and presents as sheets of stratified squamous epithelial cells as well as anastomosing cords (Fig. 10-15). It is this epithelium that gives rise to the apical periodontal cyst, and a sharp dividing line between granuloma and cyst cannot always be drawn because of the tendency for degeneration of individual epithelial cells that could be considered precystic (Fig. 10-16).

That epithelium is uniformly present in all periapical granuloma has been substantiated by numerous workers. Its demonstration is dependent, in many cases, upon serial section of the tissue specimens, but this procedure will reveal its presence. Thus every periapical granuloma may potentially form a periodontal cyst if it is left undisturbed and if the inflammatory reaction persists to stimulate the epithelium.

One additional interesting finding in occasional periapical granulomas is a condition described by Dunlap and Barker as **giant-cell hyaline angiopathy**. This consists of inflammatory cell infiltration, collections of foreign body type giant cells, and the presence of ringlike structures known as Rushton bodies, composed of an eosinophilic material resembling hyalinized collagen. There may also be seen as fragments of foreign material, sometimes resembling vegetable matter such as legumes, which suggested the use of the term 'pulse granuloma' for this lesion by King and by Mincer and his coworkers. Dunlap and Barker believed that the earliest change was an acute vasculitis with subsequent thickening and hyalinization of vessel walls. This tissue finding is not confined to periapical granulomas but has also been reported in granulomas in edentulous jaws, in a nasopalatine duct cyst, and in chronic periostitis.

This has been studied by both electron microscopy and immunoperoxidase procedure by Chen and his colleagues, who concluded that the hyaline bodies are probably endogenous in origin. The true nature of this lesion still remains uncertain but is of little apparent clinical significance.

Microbiologic Features. Bacteria were found not only in the periapical abscesses but also in granulomas and cysts. One of the factors that has made this a difficult area of investigation is the inability of the dentist to extract a tooth without microbial contamination of the periapical area or the granuloma.

The majority of studies have been based upon bacteriologic cultures taken after extraction of the tooth. Pre-extraction

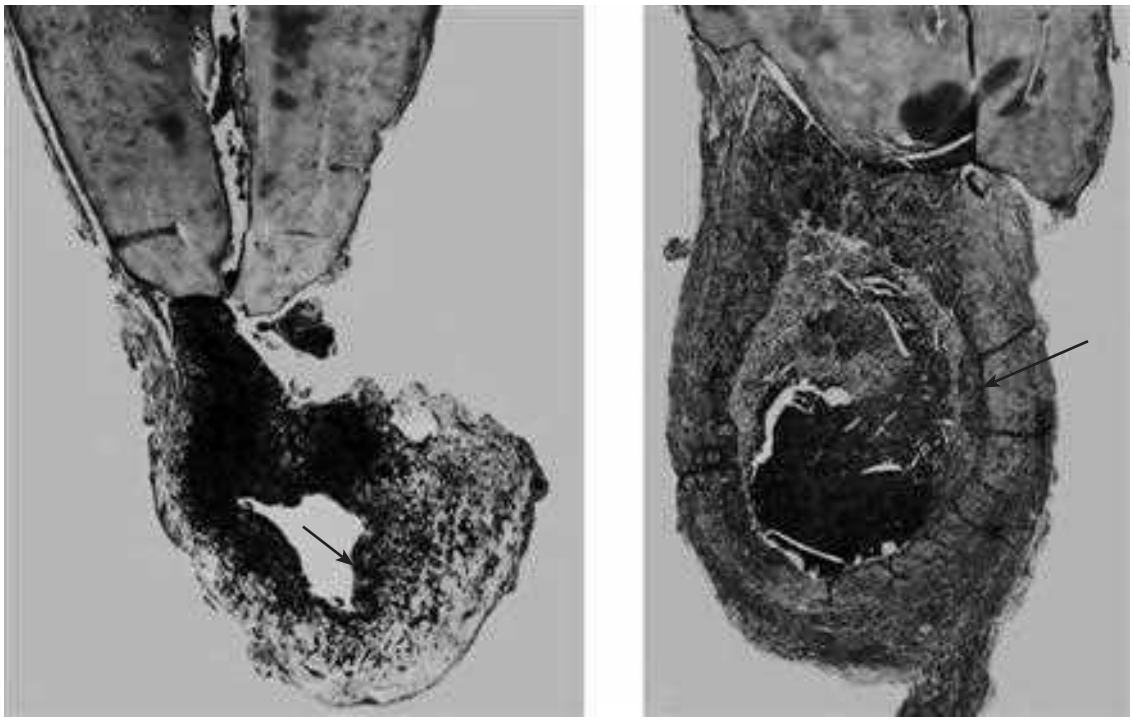


Figure 10-15. Epithelial proliferation in a periapical granuloma attached to the tooth root.
Arrow indicates sheets of proliferating epithelial cells, derived from the epithelial cell rests of Malassez.

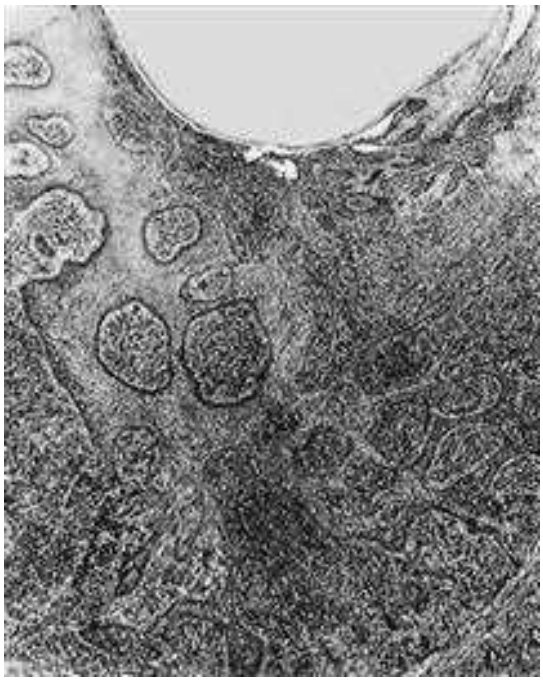


Figure 10-16. Precystic epithelial proliferation in a periapical granuloma.
A lumen has just formed and may be considered the beginning of an apical periodontal cyst.

cultures have been made in a few instances through the root canal or the alveolar plate, and these have been relatively free of actual contamination. The microorganisms that have been isolated by such techniques, e.g. in the studies of Burket, were those generally found in the oral cavity, such as *Streptococcus viridans*, *Streptococcus hemolyticus*, nonhemolytic streptococci, *Staphylococcus aureus, Staphylococcus albus, Escherichia coli,* and pneumococci. Seldom can microorganisms actually be demonstrated histologically in the periapical granuloma.

Some investigators have even suggested that the dental granuloma is usually a sterile lesion. However, the body of evidence now forming indicates that many of these lesions may indeed be infected before and after endodontic treatment. Iwu et al, in a study showed 88% or 14 of 16 periapical granulomas were bacteria positive when they were homogenized and cultured. Mixed infections are the rule, as the organisms present being generally found in the mouth. It has not been possible to associate particular types of microorganisms with specific periapical lesions, based upon either clinical or histologic evaluation.

Sebati M and Slots J claimed on their study on 34 periapical lesions, that most teeth with necrosed pulp and periapical lesions harbored human cytomegalovirus and Epstein-Barr virus in periapical granulomatous tissue, and these viruses along with the endodontopathic bacteria may play an important role in etiopathogenesis of aggressive type of periapical pathosis in human.

Slots J and coworkers in their study involving 25 symptomatic and 19 nonsymptomatic periapical lesions found human cytomegalovirus (HCMV) in 100% of symptomatic and 37% of non-symptomatic periapical lesions and Epstein-Barr virus (EBV) only in lesions infected with HCMV. They

concluded that periapical pathosis may be caused by HCMV and EBV by induction of cytokine and lymphokine induction from inflammatory or connective tissue cells or by impairing the local host defenses which increase the virulence of resident bacterial pathogens.

Treatment and Prognosis. The treatment of the periapical granuloma consists in extraction of the involved teeth, or under certain conditions, root canal therapy with or without subsequent apicoectomy. If left untreated, the periapical granuloma may ultimately undergo transformation into an apical periodontal cyst.

Apical Periodontal Cyst

(Radicular cyst, periapical cyst, root end cyst)

The apical periodontal cyst is the most common odontogenic cyst encountered in a dental clinic. It is the usual but not inevitable sequela of the periapical granuloma originating as a result of bacterial infection and necrosis of the dental pulp, nearly always following carious involvement of the tooth.

It is a true cyst, since the lesion consists of a pathologic cavity that is lined by epithelium and is often fluid-filled (Fig. 10-15). The epithelial lining is derived from the epithelial rests of Malassez, which proliferate as a result of the inflammatory stimulus in a pre-existing granuloma. As pointed out in the section on the periapical granuloma, the epithelium may be derived in some cases from:

- Respiratory epithelium of the maxillary sinus when the periapical lesion communicates with the sinus wall
- Oral epithelium from a fistulous tract
- Oral epithelium proliferating apically from a periodontal pocket.

Pathogenesis. This type of periodontal cyst exhibits a lumen that almost invariably lined by stratified squamous epithelium, while the wall is made up of condensed connective tissue. Although the stimulus for the proliferation of epithelium in the periodontal cyst is recognized to be the inflammation in the periapical granuloma, the reason that all such granulomas do not eventually develop into cysts is not known. This is particularly puzzling, since rests of Malassez are universally present in the periodontal ligament areas of all teeth. It might be that if all periapical granulomas persisted for a sufficiently long time, they would eventuate in cysts.

The actual mode of development of the apical periodontal cyst is an interesting phenomenon. The initial reaction leading to cyst formation is a proliferation of the epithelial rests in the periapical area involved by the granuloma. This epithelial proliferation is induced by the keratinocyte growth factor elaborated by the stromal cells of the periodontal ligament, or inflammatory stimulus. Gao et al, speculated that activated T cells in the periapical granulomas produce lymphokines that may act on the rest of Malassez causing proliferation and altered differentiation leading to cyst formation. This epithelial proliferation follows an irregular pattern of growth and occasionally presents a frightening picture because of the pseudo-invasiveness and inflammatory altered appearance

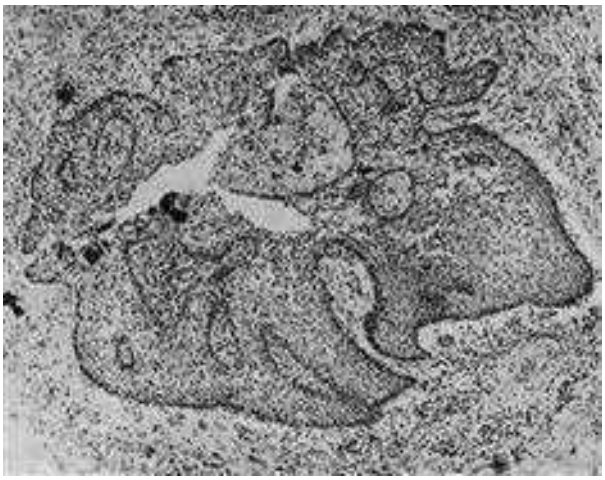


Figure 10-17. Precystic epithelial proliferation in a periapical granuloma. A lumen has just formed and may be considered the beginning of an apical periodontal cyst.

of the cells (Fig. 10-16). As this proliferation continues, the epithelial mass increases in size by division of the cells on the periphery, corresponding to the basal layer of the surface epithelium, and the cells in the central portion of the mass become separated further and further from their source of nutrition, the capillaries and tissue fluid of the connective tissue. As these central cells fail to obtain sufficient nutrients, they eventually degenerate, become necrotic, and liquefy (Fig. 10-17). This creates an epithelium-lined cavity filled with fluid, the apical periodontal cyst.

It is conceivable also that a cyst may form through proliferation of epithelium to line a preexisting cavity formed through focal necrosis and degeneration of connective tissue in a periapical granuloma. But the finding of epithelium or epithelial proliferation near an area of necrosis is not common, so that the formation of a cyst in this manner is presumably unlikely.

Once begun, the cyst increases its size by various mechanisms, namely osmosis, local fibrinolysis, and continued epithelial proliferation.

Clinical Features. The majority of cases of apical periodontal cysts are asymptomatic and present no clinical evidence of their presence. They are commonly seen between the ages of 20 and 60 years, but the involvement of deciduous dentition is not uncommon. The most commonly involved teeth are maxillary anteriors. The associated tooth is non-vital or shows deep carious lesion or a restoration which is seldom painful or even sensitive to percussion. This type of cyst is only infrequently of such a size that it destroys much bone, and even more rarely does it produce expansion of the cortical plates. The apical periodontal cyst is a lesion that represents a chronic inflammatory process and develops only over a prolonged period of time. In some cases, such a cyst of long standing may undergo an acute exacerbation of the inflammatory process and develop rapidly into an abscess that may then proceed to a cellulitis or form a draining fistula. The cause of

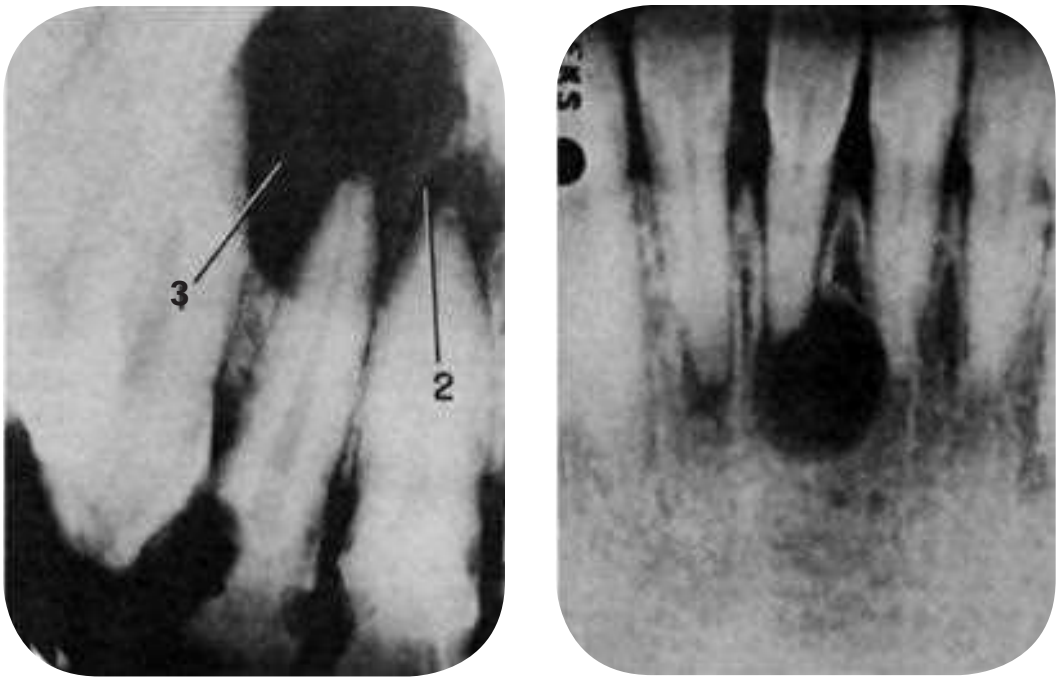


Figure 10-18. Apical periodontal cyst.
(A) This cyst (1) developed in a pre-existing periapical granuloma such as that involving the apex of the maxillary central incisor (2). The two conditions cannot be differentiated by the radiograph—only histologically. **(B)** This cyst developed after traumatic injury to the mandibular incisors with loss of pulp vitality. There is mild apical root resorption associated with the development of the periapical lesion.

such a sudden flare up is not known, but it may be a result of loss of local or generalized tissue resistance.

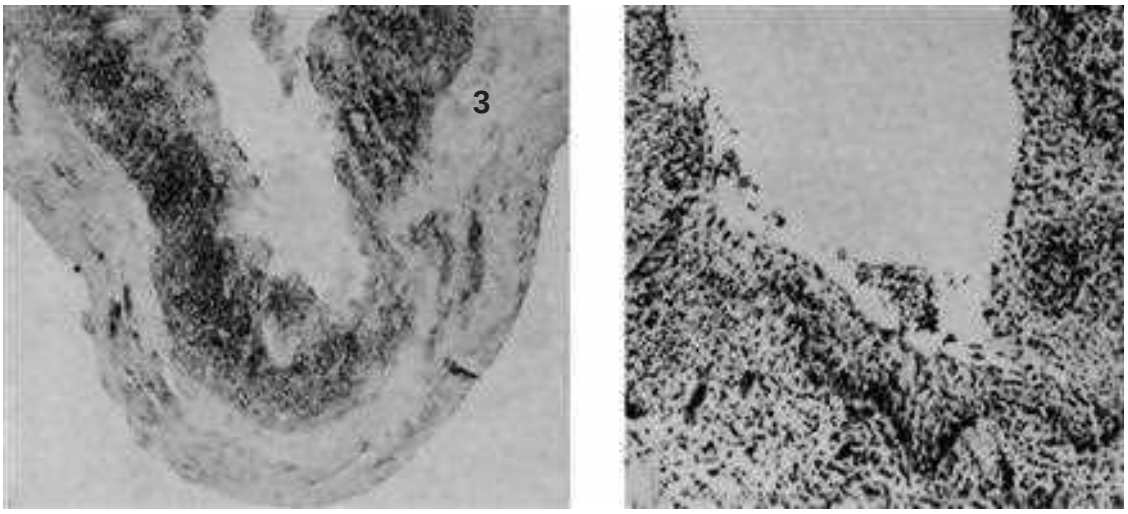
Radiographic Features. The Radiographic appearance of the apical periodontal cyst is identical in most cases with that of the periapical granuloma. Since the lesion is a chronic progressive one, developing in a pre-existing granuloma, the cyst may be of greater size than the granuloma by virtue of its longer duration, but this is not invariably the case (Fig. 10-18). Priebe and his coworkers showed that it is impossible to distinguish between a periapical granuloma and a cyst by radiographic means alone. These workers reported that the oral surgeon and radiologist were able to diagnose correctly only 13% of a group of 55 cases of periodontal cysts by means of radiographs alone. Of the group of 46 periapical granulomas and abscesses, 59% were correctly diagnosed. The actual diagnoses were established by histologic examination of the tissue after its removal. Occasionally the apical periodontal cyst exhibits a thin, radiopaque line around the periphery of the radiolucent area, and this indicates a reaction of the bone to the slowly expanding mass. The granuloma also presents such a phenomenon in many instances. Carillo C et al, based on their study on 70 cases concluded that neither the radiographic size nor the presence of radiopaque lamina helps in the typing of periapical lesion. Simon JH et al, claim cone beam computed tomography may provide a more accurate diagnosis than biopsy in differentiating cyst from granuloma based on their study on 17 cases.

Priebe and his associates indicated the fallacy of attempting to distinguish between the granuloma and the cyst, although such a distinction may have important endodontic implications. Thus periapical radiolucent areas will fill in with bone, apparently healing, after root canal therapy of some teeth. In other instances, even after clinically identical treatment, healing does not take place. The latter cases may represent examples of periodontal cysts, which would, of course, heal slowly if at all after endodontic therapy.

Histologic Features. The apical periodontal cyst is histologically identical with the periapical granuloma, from which it is actually derived, except for the presence of the epithelium-lined lumen. The epithelium lining the apical periodontal cyst is usually stratified squamous in type (Fig. 10-19). The only exception to this is in those rare cases of periapical lesions of maxillary teeth that involve the maxillary sinus. In occasional instances the cyst may then be lined with a pseudostratified ciliated columnar or respiratory type of epithelium. The usual squamous epithelium seldom exhibits keratin formation. This lining epithelium varies remarkably in thickness. In newly formed cysts the epithelial thickness is uneven and often shows hyperplasia while in established cysts it is of regular appearance and of fairly even thickness. It may be only a few cells thick, or exceedingly thick with a great deal of proliferation into the adjacent connective tissue. Actual rete ridge formation sometimes occurs. The epithelial lining many times is discontinuous, frequently missing over areas of

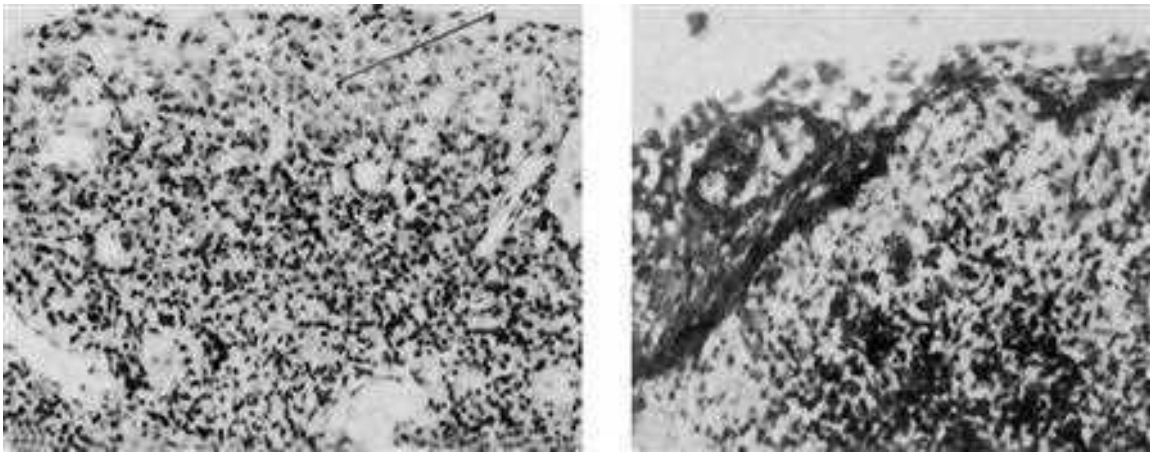
intense inflammation. Despite the presence of long-standing inflammation, alterations in individual epithelial cells, such as dyskeratosis, are uncommon (Fig. 10-20). Shear has reported that there is no apparent relationship between the degree of inflammation present, either in the connective tissue wall or within the epithelium itself, and the thickness of the epithelial lining of the cyst.

In rare instances, carcinoma has been reported to develop from the lining epithelium of odontogenic cysts, including the apical periodontal cyst. These have been reviewed by Gardner. An interesting and peculiar structure, originally described by Rushton and subsequently reported by Molyneux, Medak and Weinmann, and Shear, is the hyaline body or Rushton body, often found in great numbers in the epithelium of apical periodontal or residual cysts. These hyaline bodies are tiny linear or arc-shaped bodies, generally associated with the lining epithelium, that appear amorphous in structure, eosinophilic in reaction, and brittle in nature, since they evidence fracture in some cases (Fig. 10-21). Their frequency of occurrence in cyst linings ranges between 2.6 and 9.5% of cysts, according to a review by Allison. They appear to have no clinical or diagnostic significance and their origin is unknown, but they may represent some type of epithelial product. However, Sedano and Gorlin have reported a marked morphologic and histochemical similarity between these bodies and red blood cells, suggesting that they arise from thrombus formation in small capillaries, being formed chiefly from these red blood cells—a rouleau phenomenon. Nevertheless, even by electron microscopic study of these hyaline bodies, Allison was unable to shed any further light on their etiology. The connective tissue that makes up the wall of the apical periodontal cyst is composed of parallel bundles of collagen fibers that



A B

Figure 10-19. Apical periodontal cyst.
The epithelium lining the cavity is relatively thin and distorted by the inflammation but is recognizable as stratified squamous type.



A B

Figure 10-20. Apical periodontal cyst.
The epithelium (1) sometimes shows considerable reaction to the underlying inflammation.

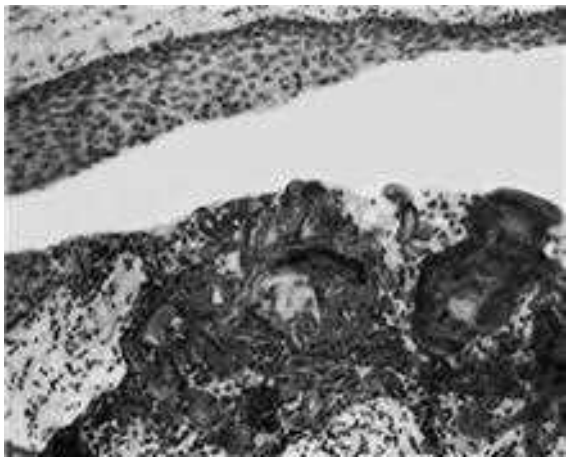


Figure 10-21. Apical periodontal cyst with numerous hyaline (Rushton) bodies.

often appear compressed. Variable numbers of fibroblasts and small blood vessels are also present. A characteristic feature is the almost universal occurrence of an inflammatory infiltrate in the connective tissue immediately adjacent to the epithelium. This infiltrate varies in its composition but is generally made up of lymphocytes and plasma cells, with some admixed polymorphonuclear leukocytes, depending partially upon the intensity of the infection. In some lesions, dystrophic calcifications and collections of cholesterol slits with associated multinucleated giant cells are found in the wall of the lesion. This mass of cholesterol frequently erodes through the lining epithelium and is extruded into the cyst lumen. The source of this cholesterol is not known, although there are numerous theories as reviewed by Shear. It appears that local tissue damage is a prerequisite for the cholesterol accumulation. In other instances, collections of lipid-filled macrophages or even macrophages containing hemosiderin are present. The contents of the cyst lumen vary from watery, straw-colored, blood tinged fluid to semisolid materials, with a low concentration of protein that stains palely eosinophilic. Occasionally, the lumen may contain a great deal of cholesterol which imparts a shimmering effect; in rare instances, limited amounts of keratin are present. Blood is a rare finding except when associated with the surgical procedure involved in removing the cyst. Whitten has reported that cytologic smears on aspirated material from cysts and cystlike lesions of the jaws, including the apical periodontal cyst, frequently permit a provisional diagnosis of the nature of the lesion.

Treatment and Prognosis. The treatment of this type of cyst is similar to that of the periapical granuloma. The involved tooth may be removed and the periapical tissue carefully curetted. Under some conditions root canal therapy may be carried out with apicoectomy of the cystic lesion. The cyst does not recur if surgical removal is thorough. As per the study by Carillo C et al, if the size of the periapical lesion is larger the prognosis is worst, particularly the periapical cyst.

Residual cyst

Residual cyst is another type of inflammatory odontogenic cyst that occurs in the edentulous alveolar ridge. It may occur due to extraction of the tooth, leaving the periapical pathology untreated or incomplete removal of periapical granuloma or periapical cyst.

Radiographically, it appears as round to ovoid radiolucency in the alveolar ridge. Occasionally lumen shows radiopacity indicative of dystrophic calcification. A thorough history and clinical examination is a must to rule out other primary odontogenic and nonodontogenic cysts, tumors, and metastatic lesions. In time, the cyst may get infected and discharge purulent material through a sinus opening.

Treatment and Prognosis. The cyst should be curetted thoroughly and the lining should be subjected to histopathological examination. Usually this cyst does not recur if the inflammatory foci near the cyst are eliminated.

If untreated, the apical periodontal cyst slowly increases in size at the expense of the surrounding bone. The bone undergoes resorption, but seldom is there a remarkable compensating expansion of the cortical plates, as is frequently seen in the case of the dentigerous cyst. Epidermoid carcinoma may develop from the lining epithelium rarely.

Periapical Abscess

(Dentoalveolar abscess, alveolar abscess)

Periapical abscess is an acute or chronic suppurative process of the dental periapical region. It may develop either from acute periapical periodontitis or more commonly from a periapical granuloma. Acute exacerbation of a chronic periapical lesion is known as *Phoenix abscess*. It usually arises as a result of infection following carious involvement of the tooth and pulp infection, but it also does occur after traumatic injury to the teeth, resulting in necrosis of the pulp, and in cases of irritation of the periapical tissues either by mechanical manipulation or by the application of chemicals in endodontic procedures. It is a mixed infection with the culture of pus yielding to a wide range of different bacterial species.

Clinical Features. The acute periapical abscess presents the features of an acute inflammation of the apical periodontium. The initial stages produce tenderness of the tooth, which is often relieved by application of pressure. In time, the tooth is extremely painful and is slightly extruded from its socket. As long as this abscess is confined to the immediate periapical region, there are seldom severe systemic manifestations, although regional lymphadenitis and fever may be present. However, rapid extension to adjacent bone marrow spaces frequently occurs, producing an actual osteomyelitis, but this is sometimes still considered clinically to be a dentoalveolar abscess. In such cases the clinical features may be severe and serious with swelling of the tissues. The chronic periapical abscess generally presents no clinical features, since it is essentially a mild,

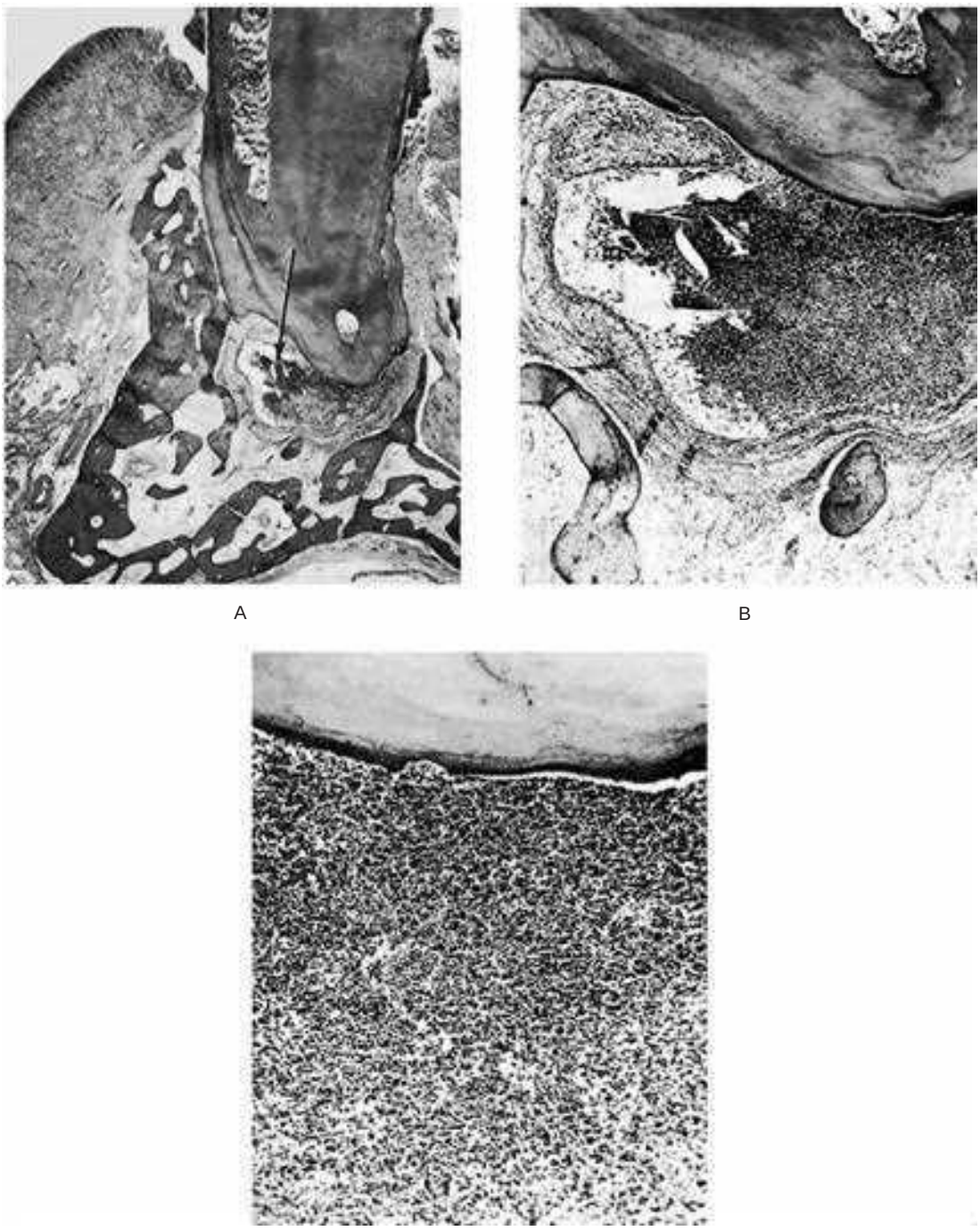


Figure 10-22. Chronic periapical abscess.
The periapical destruction of bone in **(A)** is shown in the high-power photomicrograph **(B)** to be caused by a circumscribed area of suppuration. This area of suppuration **(C)** consists entirely of inflammatory cells in various stages of disintegration.

well-circumscribed area of suppuration that shows little tendency to spread from the local area (Fig. 10-22).

Radiographic Features. The acute periapical abscess is such a rapidly progressive lesion that, except for slight thickening of the periodontal ligament space, there is usually no radiographic evidence of its presence. The chronic abscess, developing in a periapical granuloma, presents the radiolucent area at the apex of the tooth described previously or the radiolucency may be ill-defined.

Histologic Features. The area of suppuration is composed chiefly of a central area of disintegrating polymorphonuclear leukocytes surrounded by viable leukocytes, occasional lymphocytes, cellular debris, necrotic materials and bacterial colonies. There is dilatation of the blood vessels in the periodontal

ligament and adjacent marrow spaces of the bone. These marrow spaces also show an inflammatory cell infiltrate. The tissue around the area of suppuration contains a serous exudate.

Treatment and Prognosis. The principle of treatment of the periapical abscess is the same as for any abscess, drainage must be established. This can be accomplished by either opening the pulp chamber or extracting the tooth. Under some circumstances, the tooth may be retained and root canal therapy is carried out if the lesion can be sterilized.

If the periapical abscess is not treated, it may lead to serious complications through the spread of the infection. These include osteomyelitis, cellulitis, and bacteremia and the ultimate formation of the fistulous tract opening on the skin or oral mucosa. Cavernous sinus thrombosis has also been reported.

OSTEOMYELITIS

Osteomyelitis is defined as the inflammation of bone and its marrow contents. Changes in the calcified tissue are secondary to inflammation of the soft tissue component of the bone. Though the pathologic changes of periapical abscess can even be considered as osteomyelitis as there is involvement of bone, the term 'osteomyelitis' is reserved for infections which spread through the bone to a larger extent. The dividing line between osteomyelitis and a localized abscess involving the bone is; however, still unclear. Though osteomyelitis commonly occurs as a complication of dental sepsis, it is also seen in various other situations. Despite antibiotics, it is still not uncommon in developing countries.

Predisposing factors include fractures due to trauma and road traffic accidents; gunshot wounds, radiation damage, Paget's disease, and osteopetrosis. Systemic conditions like malnutrition, acute leukemia, uncontrolled diabetes mellitus, sickle cell anemia, and chronic alcoholism may also predispose to osteomyelitis. The disease may be acute, subacute, or chronic and presents a different clinical course, depending upon its nature.

Lukošiūnas A, et al, have analyzed the factors associated with the development of osteomyelitis during the treatment of mandibular fractures. They found that the immunity dysfunction, caries-affected teeth at the fracture line, mobile fractured bones, bone fixation after more than a week following trauma, insufficient bone reposition, and bone fixation after 3–7 days following trauma were the factors associated with the development of osteomyelitis.

Acute Suppurative Osteomyelitis

Acute suppurative osteomyelitis of the jaw is a serious sequela of periapical infection that often results in a diffuse spread of infection throughout the medullary spaces, with subsequent necrosis of a variable amount of bone. Clinical features of this form of osteomyelitis, which arises from a dental infection, are the same as those present after infection due to a fracture of the jaw, a gunshot wound, or even hematogenous spread. For this reason, the disease and its clinical aspects will be considered a single entity.

Dental infection is the most frequent cause of acute osteomyelitis of the jaws. It may be a rather well-localized infection of one involving a great volume of bone. A periapical infection (usually an abscess), if it is a particularly virulent one and not walled off, may spread spontaneously throughout the bone. In other instances, a chronic periapical infection such as a granuloma, or even a cyst that is walled off, may undergo an acute exacerbation, especially if the area is traumatized or surgically disturbed without establishing and maintaining drainage.

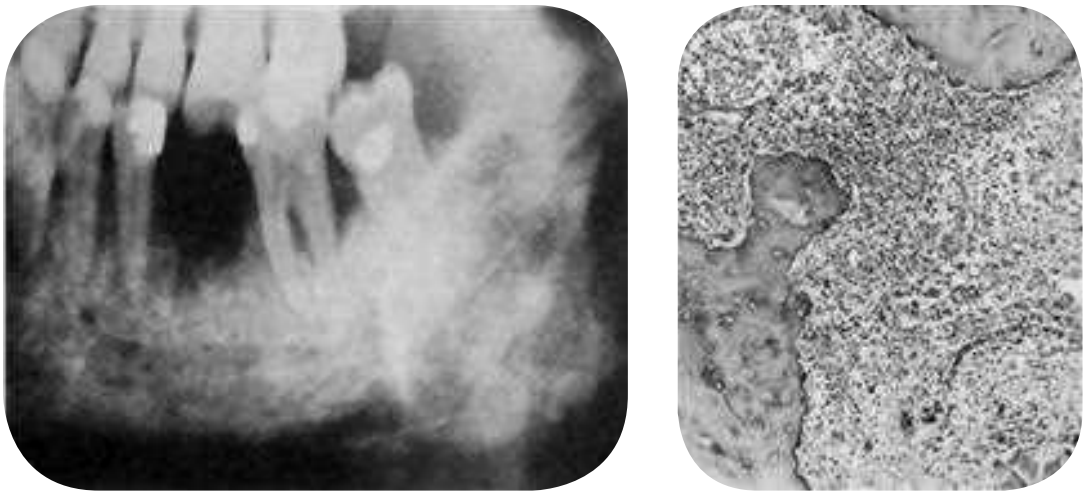
It is usually a polymicrobial infection. Different types of organisms may be cultured from these lesions; the most common are *Staphylococcus aureus* and *Staphylococcus albus,* and various streptococci. Anaerobes such as *Bacteroides, Porphyromonas* or *Prevotella* species also predominate. Cases of specific infectious osteomyelitis in tuberculosis, syphilis, actinomycosis, and so forth, are considered in the discussions of these diseases.

Clinical Features. Acute or subacute suppurative osteomyelitis may involve either the maxilla or the mandible. In the maxilla the disease usually remains fairly well localized to the area of initial infection. In the mandible, bone involvement tends to be more diffuse and widespread. The disease may occur at any age. A particular form of acute osteomyelitis, referred to as neonatal maxillitis in infants and young children, is a well recognized entity that is fortunately becoming extremely uncommon nowadays because of antibiotic drugs. In some instances, this osteomyelitis of infants is of hematogenous origin, but at other times it seems to be a result of local oral infection following some minor injury or abrasion. Infants so affected are seriously ill and may not survive the disease. In some cases, the source of the infecting organism cannot be discovered. A series of 24 such cases of maxillary osteomyelitis in infants was reported by Cavanagh, while Norgaard and Pindborg reviewed the literature and discussed the dental implications of this disease.

The adult afflicted with acute suppurative osteomyelitis usually has severe pain, trismus, and paresthesia of the lips in case of mandibular involvement and manifests an elevation of temperature with regional lymphadenopathy. The white blood cell count is frequently elevated. The teeth in the area of involvement are loose and sore so that eating is difficult, if not impossible. Pus may exude from the gingival margin. Until periostitis develops, there is no swelling or reddening of the skin or mucosa.

Radiographic Features. Acute osteomyelitis progresses rapidly and demonstrates little radiographic evidence of its presence until the disease has developed for at least one to two weeks. At this time diffuse lytic changes in the bone begin to appear. Individual trabeculae become fuzzy and indistinct, and radiolucent areas begin to appear (Fig. 10-23A).

Histologic Features. The medullary spaces are filled with inflammatory exudates (Fig. 10-23B). The inflammatory cells are chiefly polymorphonuclear leukocytes, but may show occasional lymphocytes and plasma cells. The osteoblasts bordering the bony trabeculae are generally destroyed, and depending upon the duration of the process, the trabeculae may lose their viability and begin to undergo slow resorption.



A B

Figure 10-23. Acute osteomyelitis.
The diffuse destruction of bone is evident on the radiograph in a case of acute osteomyelitis of several weeks' duration. Note the raggedness of the inferior border of the mandible in **(A)**. The inflammatory process in **(B)** shows both a polymorphonuclear leukocyte, a lymphocyte and plasma cell response. There is also irregular resorption of bone.

Pathology. The infection causes acute inflammation of the marrow tissue and the resultant inflammatory exudate spreads through the marrow spaces. This causes compression of blood vessels in the bone, leads to thrombosis and obstruction of blood flow, resulting in necrosis of the bone. Liquefaction of the necrotic tissue, dead and dying inflammatory cells, and bacteria form the pus, and this may fill the marrow spaces. This suppurative reaction extends through the cortical bone to involve the periosteum causing lifting of the periosteum, which further leads to compromise in the blood supply to the underlying bone resulting in further necrosis. By osteoclastic activity, the necrosed bone, known as sequestrum, is separated from the surrounding vital bone and exfoliates through the sinus.

Treatment and Prognosis. General principles of management includes debridement, drainage, and antimicrobial therapy. When the intensity of the disease becomes attenuated, either spontaneously or under treatment, the sequestrum begins to separate from the living bone. If the sequestrum is small, it gradually exfoliates through the mucosa. If large, surgical removal may be necessary, since its removal by normal processes of bone resorption would be extremely slow. Sometimes an involucrum forms when the sequestrum becomes surrounded by new living bone. Unless proper treatment is instituted, acute suppurative osteomyelitis may proceed to the development of periostitis, soft-tissue abscess, or cellulitis (Fig. 10-24). Pathologic fracture occasionally occurs because of weakening of the jaw by the destructive process.

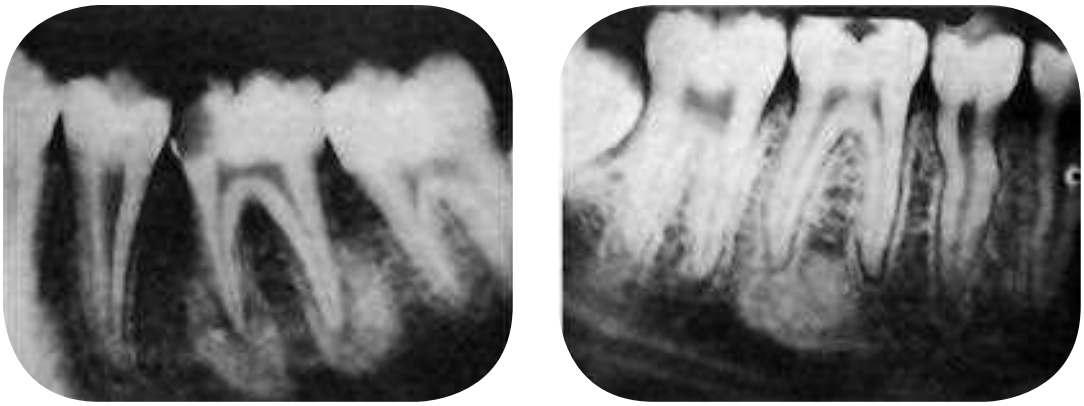
Figure 10-24. Palatal abscess following periapical infection of maxillary second bicuspid.

Chronic Suppurative Osteomyelitis

Chronic suppurative osteomyelitis may develop in inadequately treated acute osteomyelitis or may arise from a dental infection without a preceding acute stage. Rarely may it occur as a complication of irradiation. Clinical features are similar to those of acute osteomyelitis except that all signs and symptoms are milder. The pain is less severe; the temperature is still elevated, but only mildly; and the leukocytosis is only slightly greater than normal. Teeth may not be loose or sore, so that mastication is at least possible even though the jaw may not be perfectly comfortable.

Acute exacerbations of the chronic stage may occur periodically, and these present all features of acute suppurative osteomyelitis. The suppuration may perforate the bone and overlying skin or mucosa to form a fistulous tract and empty on the surface. This form of the disease should be treated on the same principles as its acute counterpart.

As per Hudson(1991), treatment of both acute and chronic forms of the disease is successful if surgically supported with



A B

Figure 10-25. Chronic focal sclerosing osteomyelitis.
The apical sclerosis involves both roots of the first molar in **(A)**. Only the distal root of the first molar is involved in **(B)**, while the mesial root shows thickening of the apical periodontal membrane. Note the large carious lesions in the teeth associated with this focal sclerosing osteomyelitis.

sustained bacteriocidal antibiotic therapy, especially in the face of potentially refractory virulent microorganisms and compromised regional vascular penetrance. He further stated that hyperbaric oxygen therapy also may be included in the more refractory forms of osteomyelitis of the jaws to enhance the local and regional immune response of the jaws as well as to produce microvascular neoangiogenesis for reperfusion support. With resolution of infection, hard and soft tissue reconstruction may be necessary to augment the reparative process.

Chronic Focal Sclerosing Osteomyelitis
(Condensing osteitis)

Chronic focal sclerosing osteomyelitis is an unusual reaction of the bone to infection: a reaction to mild bacterial infection entering the bone through a carious tooth in persons who have a high degree of tissue resistance and tissue reactivity. In such instances, the tissues react to the infection by proliferation rather than destruction, since the infection acts as a stimulus rather than an irritant.

Clinical Features. This form of osteomyelitis arises most commonly in children and young adults and rarely in older individuals. The tooth most commonly involved is the mandibular first molar, which presents a large carious lesion. There may be no signs or symptoms of the disease other than mild pain associated with an infected pulp.

Radiographic Features. The periapical radiograph demonstrates the pathognomonic, well-circumscribed radiopaque mass of sclerotic bone surrounding and extending below the apex of one or both roots (Fig. 10-25). The entire root outline is nearly always visible, with an intact lamina dura. Periodontal ligament space is widened and this is an important feature in distinguishing it from the benign cementoblastoma (q.v.) that may closely resemble it radiographically. The border of this lesion, abutting the normal bone, may be smooth and distinct or appears to blend into the surrounding bone in contrast to focal cemento-osseus dysplasia, which has radiolucent border. In either case, the radiopacity stands out in distinct contrast to the trabeculation of the normal bone.

Histologic Features. Histologic examination reveals only a dense mass of bony trabeculae with little interstitial marrow tissue (Fig. 10-26). The osteocytic lacunae appear empty. The bony trabeculae exhibit many reversal and resting lines giving pagetoid appearance. If interstitial soft tissue is present, it is generally fibrotic and infiltrated only by small numbers of lymphocytes. Osteoblastic activity may have completely subsided at the time of microscopic study.

Condensing osteitis should be differentiated from idiopathic *osteosclerosis*, which is generally accepted as developmental intraosseous anatomic variation and characterized by the occurrence of asymptomatic, round, elliptical, or irregular radiopaque mass, in the bicuspid, molar region of the mandible.

Treatment and Prognosis. The tooth with which this specific lesion is associated may be treated endodontically or extracted,

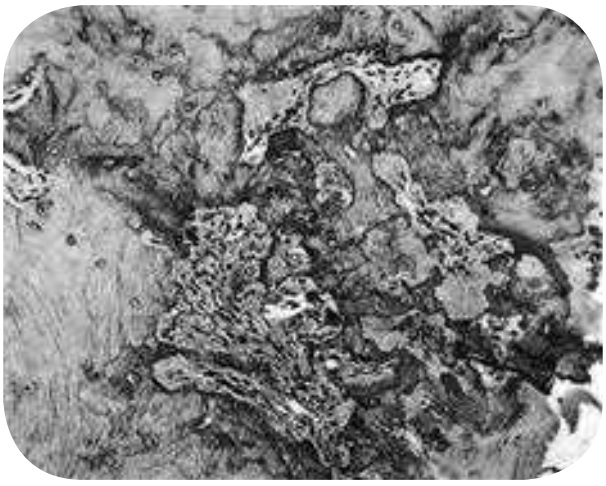


Figure 10-26. Chronic focal sclerosing osteomyelitis.
The lesion consists of dense, irregular bone with some intermingled fibrous tissue.

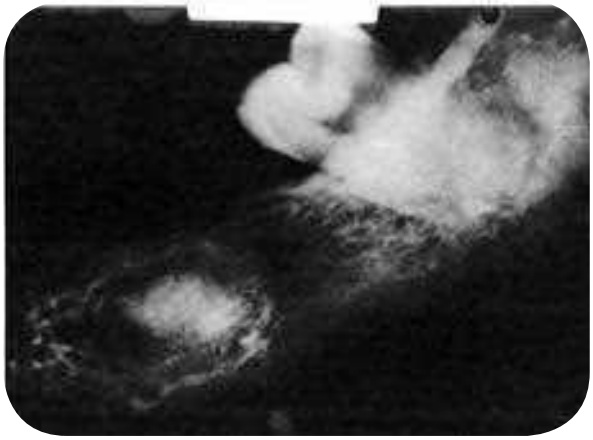


Figure 10-27. Residual chronic focal sclerosing osteomyelitis (bone scar).

since the pulp is infected and the infection has spread past the immediate periapical area. The sclerotic bone constituting the osteomyelitis is not attached to the tooth and remains after the tooth is removed. This dense area of bone is sometimes not remodeled but in many cases may be recognized on the radiograph even years later and is referred to as bone scar (Fig. 10-27). For example, Boyne has reported 38 cases of such focal osteosclerotic areas in a review of 927 full-mouth radiographs of male patients between the ages of 22 and 56 years, an incidence of 4%. This incidence is somewhat higher than previously supposed. Since the condition is actually an indication that the body has been able to deal effectively with the infection, surgical removal of the sclerotic lesions is not indicated unless symptomatic.

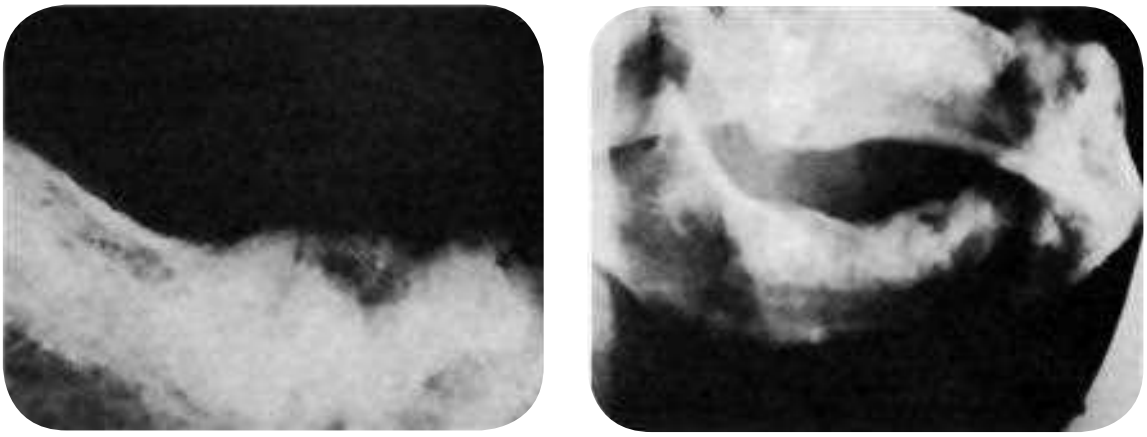
Chronic Diffuse Sclerosing Osteomyelitis

Chronic diffuse sclerosing osteomyelitis is a condition analogous to the focal form of the disease and also apparently represents a proliferative reaction of the bone to a low-grade infection. In many of these cases, the portal of entry for the infection is not through a carious lesion with subsequent pulp infection, as in chronic focal sclerosing osteomyelitis but rather through diffuse periodontal disease. The basic nature of this condition has been discussed by Shafer and by Bell.

Clinical Features. The diffuse type of sclerosing osteomyelitis, in contrast with the focal type, may occur at any age, but is most common in older persons, especially in edentulous mandibular jaws or edentulous areas and does not exhibit any gender predominance. Often the disease is of such an insidious nature that it presents no clinical indications of its presence. On occasion there is an acute exacerbation of the dormant chronic infection and this results in vague pain, unpleasant taste, and mild suppuration, many times with the spontaneous formation of a fistula opening onto the mucosal surface to establish drainage.

Radiographic Features. The radiographic appearance of chronic diffuse sclerosing osteomyelitis is, as the name suggests, that of a diffuse patchy, sclerosis of bone often described as 'cotton-wool' appearance (Fig. 10-28). This radiopaque lesion may be extensive and is sometimes bilateral. In occasional cases, there is bilateral involvement of both the maxilla and the mandible in the same patient. Because of the diffuse nature of the disease, the border between the sclerosis and the normal bone is often indistinct. The pattern may actually mimic Paget's disease of bone or cemento-osseous dysplasia.

Histologic Features. Microscopic study of tissue taken from the lesion shows dense, irregular trabeculae of bone, some of which are bordered by an active layer of osteoblasts (Fig. 10-29). Focal areas of osteoclastic activity are sometimes seen. The bone in some lesions shows a pronounced 'mosaic' pattern, indicative of repeated periods of resorption followed by repair. The soft tissue between the individual trabeculae is fibrous and shows proliferating fibroblasts and occasional small capillaries as well as small focal collections of lymphocytes and plasma cells. Polymorphonuclear leukocytes may be present, particularly



A B

Figure 10-28. Chronic diffuse sclerosing osteomyelitis.
The periapical radiograph **(A)** shows osteosclerosis in a diffuse pattern. The extent of this sclerosis is seen on the lateral jaw film **(B)**.

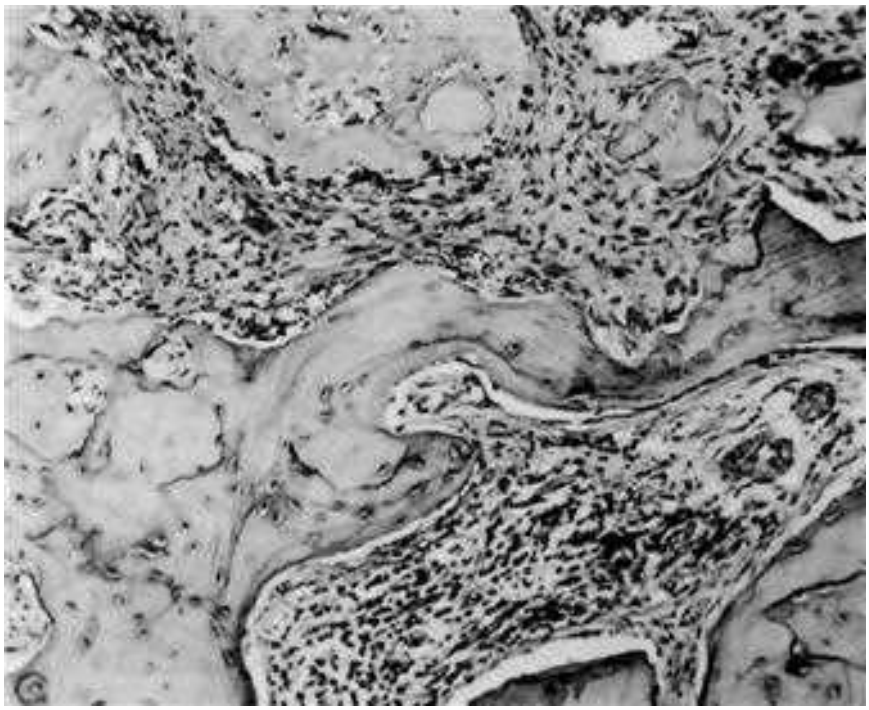


Figure 10-29. Chronic diffuse sclerosing osteomyelitis.
The reactive nature of the lesion is evident from the presence of both formation and destruction of bone. A mild inflammatory cell infiltration is present in the fibrous stroma.

if the lesion is undergoing an acute phase. In some lesions, the inflammatory component is completely 'burned out', leaving only sclerotic bone and fibrosis, but this does not contravene a diagnosis of chronic sclerosing osteomyelitis.

Treatment and Prognosis. The treatment of chronic diffuse sclerosing osteomyelitis is a difficult problem. Resolution of the adjacent foci of chronic infection often leads to improvement of this lesion. The lesion is usually too extensive to be removed surgically, yet it frequently undergoes acute exacerbations. The most reasonable approach to this disease is a conservative one. Acute episodes are treated with antibiotics. Although the lesion may be slowly progressive, it is not particularly dangerous, since it is not destructive and seldom produces any complications. If a tooth is present in one of these sclerotic areas and must be extracted, the probability of infection and protracted healing must be recognized. Sclerotic bone is hypovascular and responds poorly to any bacterial infection. Bell has recommended tooth extraction only as a last resort, utilizing a surgical approach with removal of liberal amounts of bone to facilitate extraction and increase bleeding. Sclerosed bone may remain as such in some patients even after the resolution of the lesion and may be remodeled in others.

Sclerotic Cemental Masses

A series of 38 cases of lesions of the jaws with striking similarities to those lesions described as chronic diffuse sclerosing osteomyelitis has been reported by Waldron and his coworkers under the term 'sclerotic cemental masses of the jaws'.

Clinical Features. Just as in chronic diffuse sclerosing osteomyelitis, the majority of cases reported by Waldron and his associates occurred in older black females, who often presented with multiple, symmetric lesions that sometimes produced pain, drainage, or localized expansion. The radiographic appearance was also similar to that of diffuse sclerosis.

Histologic Features. The only significant difference between the two diseases, described in one case as sclerosing osteomyelitis and in the other as sclerotic cemental masses, was in the microscopic appearance of the radiopaque lesional tissue. In sclerosing osteomyelitis, the tissue was essentially sclerotic bone, while in the cemental masses, the tissue usually was interpreted as cementum. In some instances, this cementum was in the form of large solid masses with smooth, lobulated margins, often with a globular accretion pattern. In other cases, variable amounts of bone were admixed. The remarkable similarities between the two diseases suggest very strongly that these represent two closely related facets of the same basic disease process. Supporting this concept, in addition to the clinical and radiographic similarities, is the fact that lesions are commonly seen that exhibit the microscopic features of both diseases in the same lesional tissue: sclerotic bone and sclerotic cementum. For this reason, it appears more appropriate to understand the nature of the reaction of the tissues to injury rather than to adhere to rigid standards of nomenclature.

Florid osseous dysplasia

Florid osseous dysplasia is another disease that appears very closely related to both chronic diffuse sclerosing osteomyelitis and sclerotic cemental masses and was described by Melrose and his associates under the term 'florid osseous dysplasia'.

The clinical and radiographic features, as well as the microscopic findings, are virtually identical with those described under the former two diseases. However, Melrose and his coworkers did describe one additional feature that had not been reported previously: the simultaneous occurrence of simple bone cysts in approximately 40% of their series of 34 cases of florid osseous dysplasia.

The suggested cause for the occurrence of these cysts is obstruction of the normal interstitial fluid by the fibro-osseous proliferation. It appears that the term 'florid osseous dysplasia' has been used to imply rather broad parameters of an 'exuberant variant of osseous dysplasia, defined by Robinson to be an abnormal reaction of bone to irritation or stimulation,' according to Melrose and his associates, and includes chronic diffuse sclerosing osteomyelitis and sclerotic cemental masses.

Chronic Osteomyelitis with Proliferative Periostitis

(Garrè's chronic nonsuppurative sclerosing osteitis, periostitis ossificans)

This is a distinctive type of chronic osteomyelitis in which there is focal gross thickening of the periosteum, with peripheral reactive bone formation resulting from mild irritation or infection. It is essentially a periosteal osteosclerosis analogous to the endosteal sclerosis of chronic focal and diffuse sclerosing osteomyelitis. The synonym 'Garrè's osteomyelitis' for this lesion is unfortunate as Garrè, in his original publication, neither described the periostitis nor the classical onion skin appearance in the radiograph produced by the cortical duplication.

Clinical Features. This sclerosing osteomyelitis occurs almost entirely in young persons before the age of 25 years and most frequently involves the anterior surface of the tibia. The lesion in this location has been recognized for many years by orthopedic surgeons and pathologists. It was generally overlooked as a distinctive entity affecting the jaws also until the report of Pell and his associates. Since there is probably greater opportunity for infection to enter the bone of the maxilla and the mandible than any other bone of the body, because of the peculiar anatomic arrangement of the teeth situated in and protruding from the bone, it is surprising that the disease has not been described more frequently as a dental complication. The condition in the jaws occurs almost exclusively in the mandible in children and young adults, and most cases occur in the bicuspid and molar region. The maxilla is seldom affected, and the reason for this is not clear.

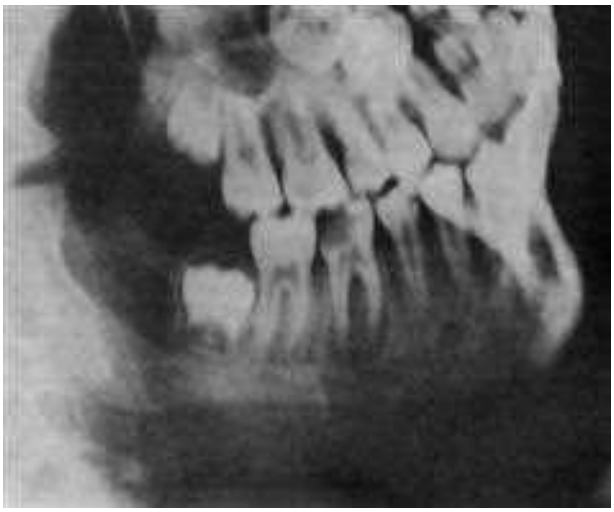


Figure 10-30. Chronic osteomyelitis with proliferative periostitis.
There are caries and periapical involvement of the mandibular first molar, but the periosteal reaction is not evident on the lateral jaw radiograph.

The patient usually complains of a toothache or pain in the jaw and a bony hard swelling on the outer surface of the jaw. This mass is usually of several weeks duration. Occasionally, this reactive periostitis may develop not as a result of a central dental infection of the jaw that perforates outward but as a result of an overlying soft-tissue infection or cellulitis that subsequently involves the deeper periosteum. A most unusual case of the condition occurring simultaneously in four quadrants of the jaws in an 11-year-old child has been reported by Eisenbud and his coworkers.

Radiographic Features. Intraoral radiographs will often reveal a carious tooth opposite the hard bony mass (Fig. 10-30). An occlusal radiograph shows a focal overgrowth of bone on the outer surface of the cortex, which may be described as duplication of the cortical layer of bone (Fig. 10-31). This mass of bone is smooth and rather well calcified and may itself show a thin but definite cortical layer.

Histologic Features. This supracortical but subperiosteal mass is composed of much reactive new bone and osteoid tissue, with osteoblasts bordering many of the trabeculae. These trabeculae often are oriented perpendicular to the cortex, with the trabeculae arranged parallel to each other or in a retiform pattern. The connective tissue between the bony trabeculae is rather fibrous and shows a diffuse or patchy sprinkling of lymphocytes and plasma cells (Fig. 10-31D). The periosteal reaction is a result of the infection from the carious tooth perforating the cortical plate and becoming attenuated, stimulating the periosteum rather than producing the usual suppurative periostitis.

Treatment and Prognosis. Chronic osteomyelitis with a proliferative periostitis is treated endodontically or removal of the carious infected tooth, with no surgical intervention

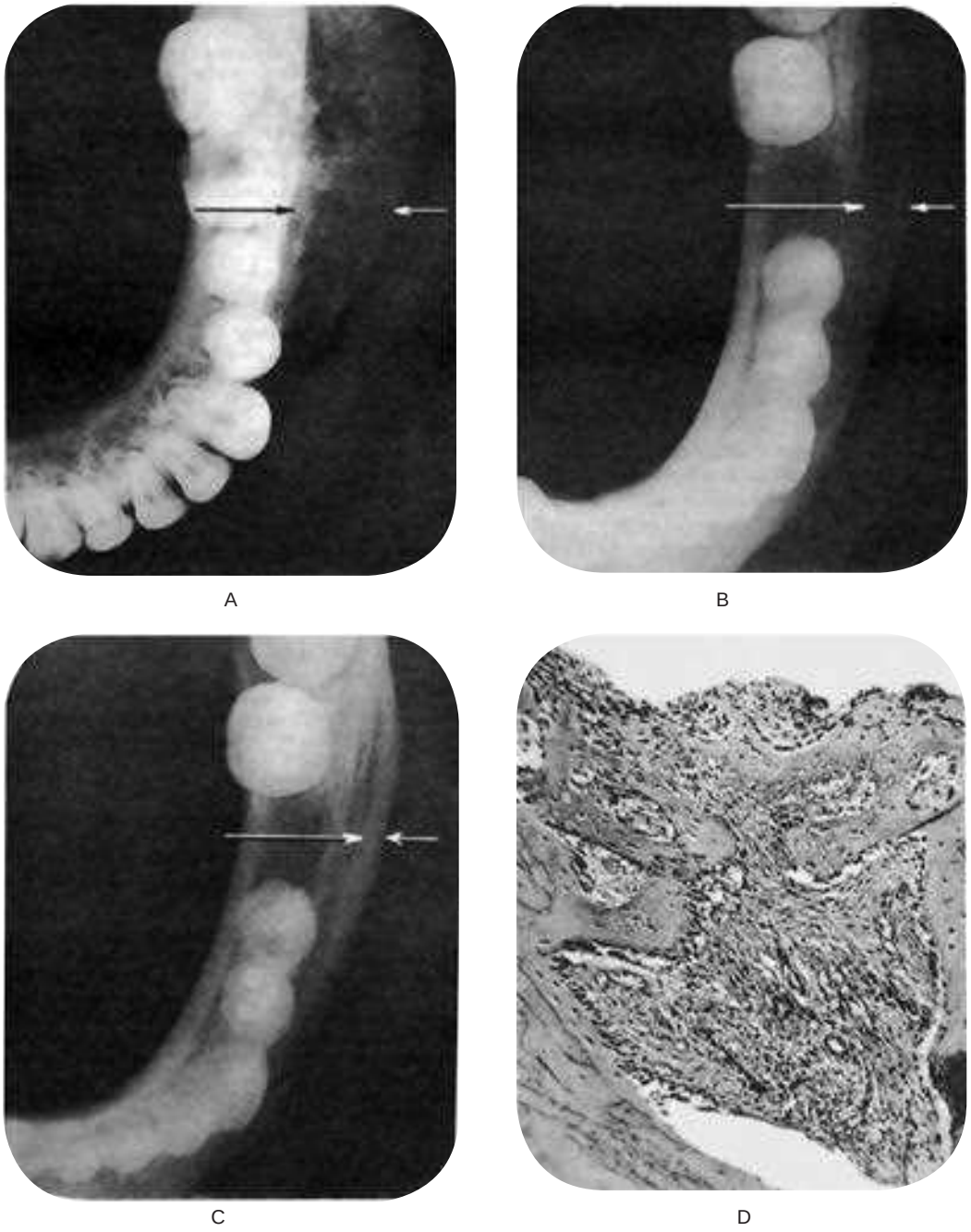


Figure 10-31. Chronic osteomyelitis with proliferative periostitis.
The intense periosteal reaction is seen on the occlusal film **(A)**. The second occlusal film **(B)** was taken three months after extraction of the first molar, while the third film **(C)** was taken one year after the extraction and demonstrates the remarkable remodeling that occurred without other treatment. The photomicrograph **(D)** shows reactive new periosteal bone formed in response to the mild chronic inflammation present.

for the periosteal lesion except for biopsy to confirm the diagnosis. Pell and his coworkers reported that after extraction of the involved tooth, gradual remodeling of the jaws occurs, restoring the original facial symmetry (Fig. 10-31C).

Periosteal new bone formation or neoperiostosis may occur in a variety of other conditions, and care must be taken to exclude them from the diagnosis. These include infantile cortical hyperostosis (Caffey's disease), hypervitaminosis A, syphilis, leukemia, Ewing's sarcoma, metastatic neuroblastoma, and even a fracture callus. This differential diagnosis has been discussed by Eversole and his associates in their review of this disease.

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CHAPTER 11

Spread of Oral Infection

■ B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

Oral cavity consists of more than 500 bacterial taxa, several fungal species, few protozoal genera and many viruses as normal residents. Occurrence of infectious disease is determined by the interaction of the host, the organism and the environment. In a healthy state, there is a balance existing among these three factors. When the balance is lost disease occurs.

Odontogenic infection is one of the most common infections in humans. An oral infection can originate in the dental pulp and extend through the root canals of the tooth into the periapical tissues or it may originate in the superficial periodontal tissues and subsequently disperse through the spongy bone. Later it may perforate the outer cortical bone and spread in various tissue spaces or discharge onto a free mucous membrane or skin surface. It may become localized or extend diffusely. The spread of the disease depends upon a variety of factors and circumstances that may alter its course at any point. It is definitely dangerous if the infection escapes from the confines of the bone of the maxilla or the mandible.

The routes by which the infection can spread are: the lymphatic system, the blood stream or directly through the tissues. Factors affecting the ability of the infection to spread depend on the type and virulence of the organism, general health of the patient, the anatomical site of the initial infection, which decides the drainage of pus, and the effectiveness of the patient's immune mechanism.

To a large extent, certain anatomic features determine the actual direction that the infection may take (Fig. 11-1).

It is usually easy to determine whether an infection is present or not, based on local and systemic factors. Local changes include pain, swelling, restriction of movement, surface erythema, and pus formation. Systemic factors include toxic

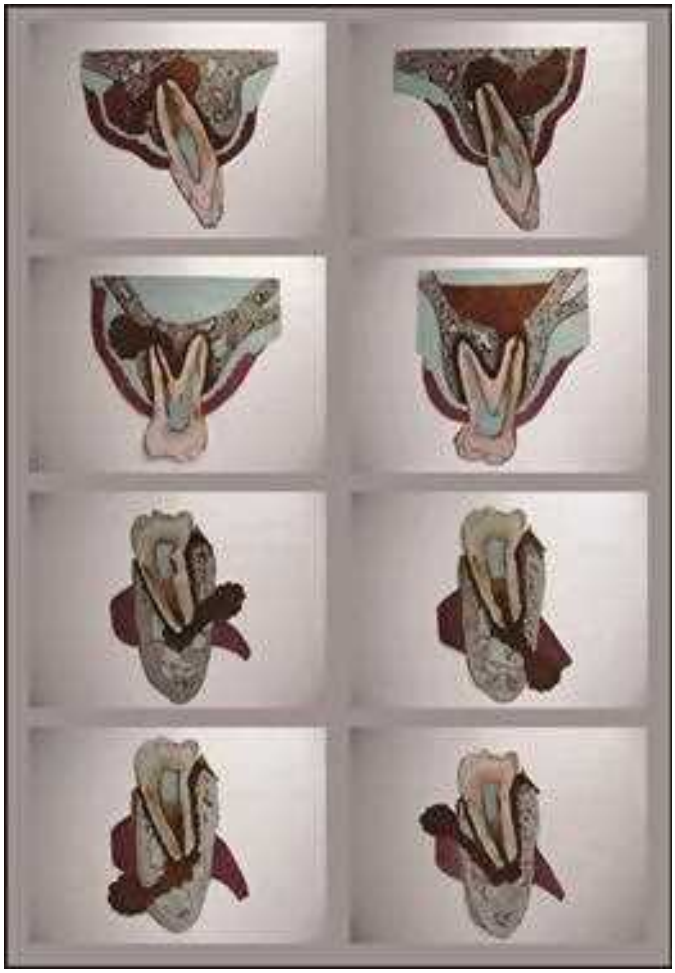

Figure 11-1. Possible paths of spread of infection from acute periapical abscess.

appearance, fever, lymphadenopathy, malaise, and increased white blood cell count.

Cellulitis
(Phlegmon)

Cellulitis is a diffuse inflammation of soft tissues which is not circumscribed or confined to one area, but which, in contrary to the abscess, tends to spread through tissue spaces and along fascial planes. This type of reaction occurs as a result of infection by microorganisms that produce significant amounts of streptokinase, hyaluronidase (the spreading factor of Duran-Reynolds) and fibrinolysins, which act to breakdown or dissolve hyaluronic acid, the universal intercellular cement substance, and fibrin. Streptococci are particularly potent producers of hyaluronidase and are therefore a common causative organism in cases of cellulitis. Streptococci in their growth phase consume local oxygen and metabolize nutrients to produce an acidic environment, which is conducive to the subsequent growth of anaerobic microbes. The anaerobes such as *Prevotella* and *Porphyromonas* species destroy collagen.

Cellulitis of the face and neck most commonly results from dental infection, either as sequela of an apical abscess or osteomyelitis, or following periodontal infection. The pericoronal infection or **pericoronitis** (q.v.) occurring around erupting or partially impacted third molars and resulting in cellulitis and trismus is an especially common clinical condition. Sometimes cellulitis of the face or neck will occur as a result of infection following a tooth extraction, injection, either with an infected needle or through an infected area, or following jaw fracture.

Injectable soft tissue fillers are used in plastic and reconstructive surgery, dermatology and cosmetic salons for facial augumentation and rejuvenation. Hyaluronic acid is normally used as fillers. Schütz P et al, have reported 22 cases of acute facial inflammation following infected facial tissue fillers. Of the 22 patients, three were diagnosed with facial cellulitis, four with periorbital abscess and 15 with a buccal space abscess.

Clinical Features. The patient with cellulitis of the face or neck originating from a dental infection is usually moderately ill and has elevated temperature and leukocytosis. One feels painful swelling of the soft tissues involved that are firm and brawny. Much of the swelling is due to inflammatory edema. (Fig. 11-2). If the superficial tissue spaces are involved, the skin is inflamed, has an orange peel appearance and is even purplish sometimes. In the case of inflammatory spread of infection along deeper planes of cleavage, the overlying skin may be of normal color. In addition, regional lymphadenitis is usually present.

Infections arising in the maxilla perforate the outer cortical layer of bone above the buccinator attachment and cause swelling, initially of the upper half of the face. The diffuse spread; however, soon involves the entire facial area. Extension towards the eye is a potentially serious complication because of the cavernous sinus thrombosis through the veins of the inner canthus of the eye. When infection in the mandible perforates the outer cortical plate below the buccinator attachment, there is a diffuse swelling of the lower half of the face, which then sees a superior as well as cervical spread. Spread to the cervical tissue can cause respiratory discomfort.

Figure 11-2. Cellulitis of the face.
(Courtesy of Dr RS Nealakandan, Meenakshi Ammal Dental College, Chennai).

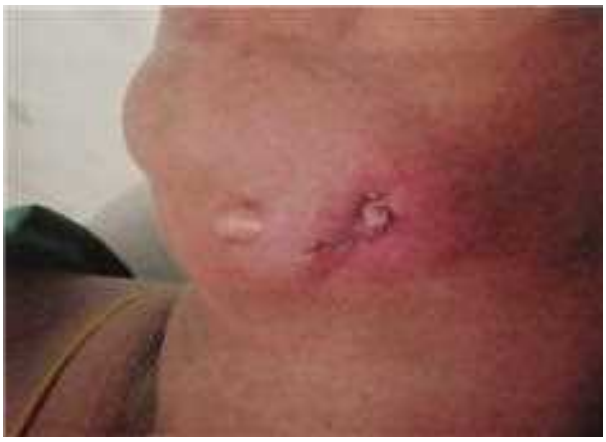

Figure 11-3. Fistulous tract from dental infection opening on skin.
(Courtesy of Dr RS Nealakandan, Meenakshi Ammal Dental College, Chennai).

As the typical facial cellulitis persists, the infection frequently tends to become localized, and a facial abscess may form. When this happens, the suppurative material present seeks to 'point' or discharge upon a free surface (Fig. 11-3). If early treatment is instituted, a resolution usually occurs without drainage through a break in the skin.

Histologic Features. A microscopic section through an area of cellulitis shows only a diffuse exudation of polymorphonuclear leukocytes and occasional lymphocytes, with considerable serous fluid and fibrin, causing separation of connective tissue or muscle fibers (Fig. 11-4). Cellulitis presents only a nonspecific picture of diffuse acute inflammation.

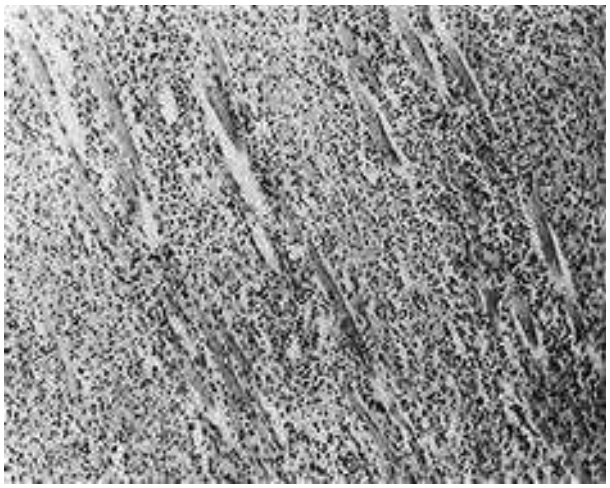

Figure 11-4. Cellulitis.
An acute inflammatory exudate separates the muscle fibers.

Treatment and Prognosis. Cellulitis is treated by the administration of antibiotics including antianaerobics and also the removal of the cause of the infection. To avoid the further spread of infection or solidification of abscess, the patients should be advised not to massage the affected area with any medication. Although this condition is extremely serious, the resolution is usually prompt with adequate treatment, and untoward sequelae are uncommon.

INFECTIONS OF SPECIFIC TISSUE SPACES

Tissue spaces, or fascial spaces are potential spaces situated between planes of fascia that form natural pathways along which infection may spread producing a cellulitis, or within which infection may become localized with actual abscess formation. Knowledge of these fascial spaces, their boundaries, contents and relation to other structures is a necessity for the dentist because of the propensity for their involvement by spread of dental infection.

Shapiro defined the fascial space as potential tissue space, since none are actually spaces until pus has been formed. These potential spaces are compartments that contain structures such as salivary glands, fat or lymph nodes. Normally, these structures are surrounded by loose connective tissues, which can be easily stripped back by finger pressure, either during surgery in the patient, or by dissection in the cadaver to produce a cavity. In 1930 Grodinsky and Holyoke hypothesized that infections spread by hydrostatic pressure, with the flow of infected fluids guided by the resistance of certain tissue such as the fasciae, muscle, and bone.

Drainage by perforation of a bony plate occurs along lines of least resistance, so that, perforation of a thin cortex occurs before that of a thick cortex. The attachment of muscles may determine the route that an infection will take, channeling the infection into certain tissue spaces. The distribution and the interrelations of the many potential tissue spaces in the facial and cervical regions must be appreciated to understand the ease with which infection may spread throughout this area and even into distant areas.

Spaces can be classified broadly into primary and secondary spaces. Primary spaces are directly related to teeth and secondary spaces are not directly related to teeth.

Important spaces in maxillofacial region are

In relation to the lower jaw	*In relation to the upper jaw*
1. Submental space	1. Within the lip
2. Submandibular space fossa	2. Within the canine
3. Sublingual space	3. Palatal subperiosteal interval
4. Buccal space	4. Buccal space
5. Submasseteric interval	5. Maxillary antrum
6. Parotid space	6. Infratemporal space
7. Pterygomandibular space	7. Subtemporalis muscle interval
8. Pharyngeal space	
9. Peritonsillar space	

SPREAD OF INFECTION FROM MAXILLARY TEETH

From the **maxillary central** and **lateral incisor** the infection spreads to form labial, palatal abscess or vestibular abscess. Sometimes abscesses may form within the lip, which depends upon whether the pus penetrates above or below the muscle attachment.

Infections of the **canine** tooth may result in labial or vestibular abscess if the site of penetration of pus is below the muscle attachment. They form a canine space abscess if the site of penetration of the pus exists above the levator muscle of the upper lip.

Infected **premolars** form abscesses mostly on the buccal or palatal side, and in a long rooted tooth form canine space abscess.

Infections from **molars** form buccal or palatal abscess, if the site of penetration is below the buccinator muscle attachment and a buccal space abscess if the site of penetration of pus is above the muscle attachment.

SPREAD OF INFECTION FROM MANDIBULAR TEETH

From the **mandibular incisor**, the infection spreads to form a labial abscess if the pus penetrates above the muscle attachment, and forms a submental space abscess if it is below the muscle attachment.

Since all the muscle attachments are well below the mandibular **canine root apex**, the site of the penetration of the pus is above the muscle attachment, and forms only a labial or vestibular abscess.

Premolars may form vestibular abscesses, and lingual perforation may form sublingual abscesses.

If the pus from the **first molar** penetrates above the buccinator attachment, it forms a vestibular abscess on the buccal side, and below the muscle attachment results in a buccal space abscess. A sublingual abscess may be formed if the pus penetrates through the lingual side.

In **second molars** there are four possibilities, namely a vestibular or buccal space abscess if the pus penetrates through the buccal side and sublingual or a submandibular abscess if it penetrates through the lingual side. Infections from the **third molars** form submandibular or pterygomandibular or submasseteric abscesses.

Secondary sites of spread are the parotid space, temporal, infratemporal, and pharyngeal spaces.

MANIFESTATIONS OF VARIOUS SPACE INFECTIONS

The **canine space** is the region between the anterior surface of the maxilla and the overlying levator muscles of the upper lip. Infection of this space manifests as swelling with obliteration of the nasolabial fold and sometimes pus may drain through the inner canthus of the eye.

The **buccal space** is bounded medially by the buccinator muscle and its covering buccopharyngeal fascia; laterally by the skin and subcutaneous tissues; anteriorly by the posterior border of the zygomaticus major muscle above; the depressor anguli oris muscle below; and posteriorly by the anterior edge of the masseter muscle. Superiorly, the space is bounded by the zygomatic arch (Fig. 11.5A), and inferiorly by the lower border of the mandible.

Clinically, the buccal space infection is dome shaped, and periorbital edema develops due to impaired venous and lymphatic drainage. Swelling begins at the lower border of the mandible and extends upward to the level of the zygomatic arch. Trismus is usually not present.

Infratemporal Space

Boundaries. The infratemporal space is bounded anteriorly by the maxillary tuberosity; posteriorly by the lateral pterygoid muscle, the condyle and temporal muscle; laterally by the tendon of the temporal muscle and the coronoid process; and medially by the lateral pterygoid plate and inferior belly of the lateral pterygoid muscle. The infratemporal space contains the pterygoid plexus, the internal maxillary artery, the mandibular nerve, mylohyoid nerve, lingual nerve, buccinator nerve and chorda tympani nerves, and the external pterygoid muscle.

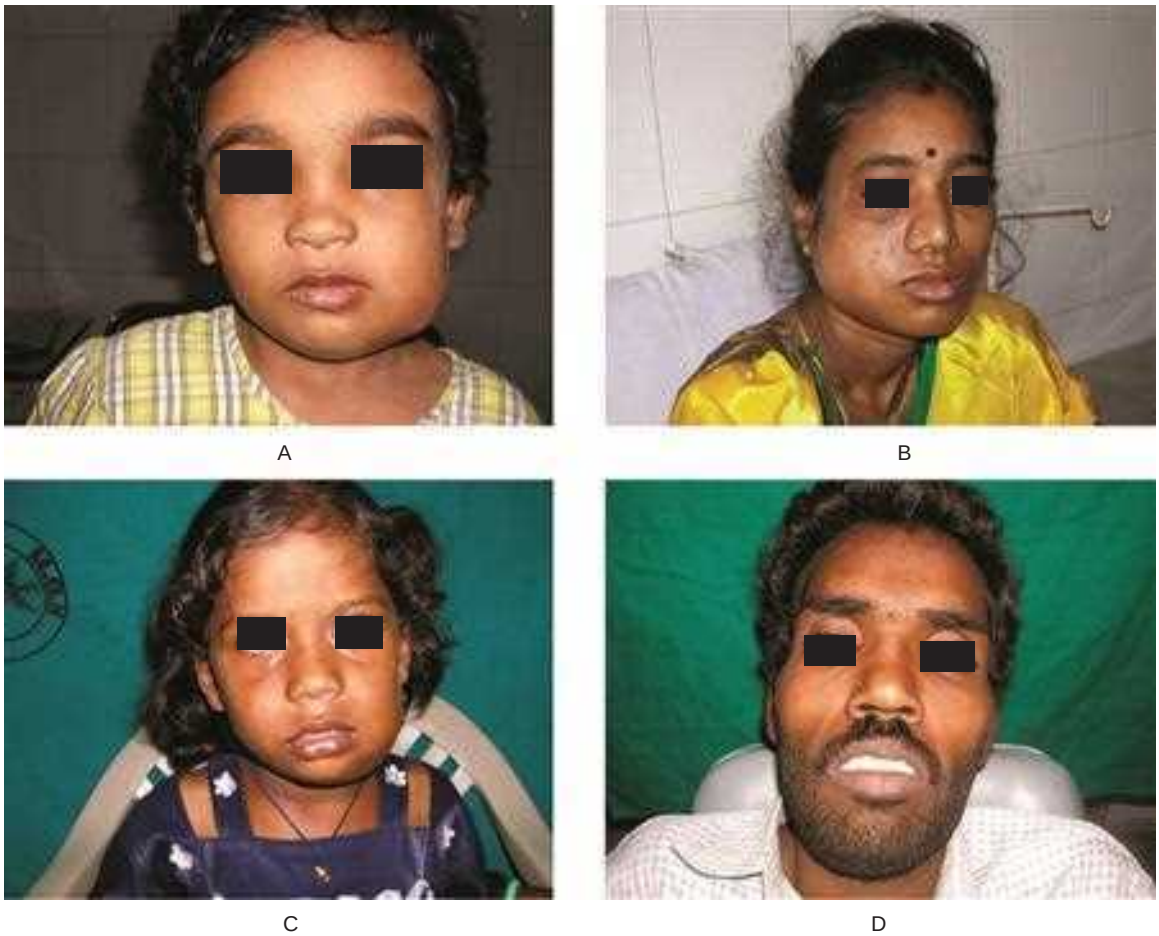

Figure 11-5. Infections involving spaces.
(A) Buccal space. **(B)** Submasseteric space. **(C)** Submandibular space. **(D)** Submental space *(Courtesy of Dr RS Nealakandan, Meenakshi Ammal Dental College, Chennai).*

Clinical Features. Infection in this space is often difficult to diagnose. Clinically an infratemporal abscess usually produces swelling extraorally over the region of the sigmoid notch and intraorally in the tuberosity region. The entire cheek may also be swollen if the buccal space is involved. The patient may exhibit trismus and sometimes swelling of the eyelids, especially if the postzygomatic fossa is involved. The involvement of the pharynx may cause dysphagia and severe pain or a feeling of pressure in the area of the infection.

Pterygomandibular Space

Boundaries. The inferior portion of the infratemporal space is called the pterygomandibular space and it lies between the internal pterygoid muscle and the ramus of the mandible. The **postzygomatic** space extending anteromedially from the infratemporal space and is considered a part of it.

Clinical Features. Infection in the pterygomandibular space may arise through extension from a pericoronitis of a mandibular third molar and has occurred in cases of injection of local anesthetic solution into this space. Severe trismus results from infection in this location, and extreme radiating pain is common. There is no evidence of clinical facial swelling, although swelling of the lateral posterior portion of the soft palate may occur. Injection of the maxillary tuberosity with an infected needle or solution has also caused infection of the infratemporal fossa. The pterygomandibular space abscess must be distinguished from the peritonsillar abscess. In the latter there is no dental involvement and less trismus.

Lateral Pharyngeal Space Boundaries

The lateral pharyngeal space, one of the parapharyngeal spaces, is bounded anteriorly by the buccopharyngeal aponeurosis, the parotid gland and the pterygoid muscles, posteriorly by the prevertebral fascia, laterally by the carotid sheath and medially by the lateral wall of the pharynx (Fig. 11-6).

Clinical Features. The source of the infection is usually a third molar, sometimes a second molar, particularly by way of infection in the submandibular space or by direct extension from the tooth.

Infection of this space with abscess formation may impinge on the pharynx, causing difficulty in swallowing and even in breathing. The pain also may be referred to the ear. Trismus is usually present. An anesthetic may be required to confirm the diagnosis. The tonsillar pillars and tonsil are displaced medially, and so is the uvula. This infection must be differentiated from a peritonsillar abscess. In the latter condition trismus is less severe or absent, and the tonsil, instead of being normal, is enlarged and inflamed.

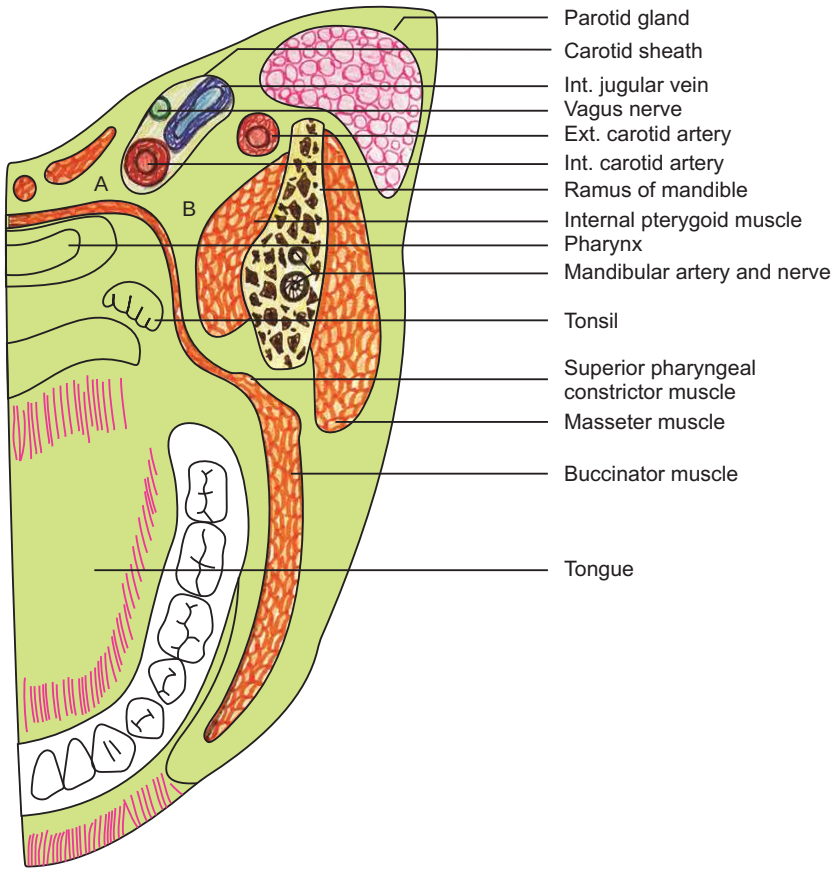

Figure 11-6. Horizontal section through the head at the level of the mandibular occlusal plane.
The parapharyngeal spaces are indicated: **(A)** retropharyngeal space, **(B)** lateral pharyngeal space.

Lateral pharyngeal space infections have the potential to spread upward through various foramina at the base of the skull and cause cavernous sinus thrombosis, meningitis, and brain abscess. They can also spread posteriorly into the retropharyngeal space or invade the carotid sheath. The lateral pharyngeal space communicates with the mediastinum by the prevertebral fascia, so that the infection may reach this area by direct extension.

Retropharyngeal Space

Boundaries. The retropharyngeal space is bounded anteriorly by the wall of the pharynx, posteriorly by the prevertebral fascia, and laterally by the lateral pharyngeal space and carotid sheath.

Clinical Features. Infection here may result from medial extension of infection in the lateral pharyngeal space, and an abscess may form, displacing or pressing the buccopharyngeal fascia forward and impinging on the pharynx.

Patients with a retropharyngeal space infection will have pain, dysphagia, dyspnea, and nuchal rigidity. Bulging of the posterior pharyngeal wall is seen, which is often more prominent on one side because of adherence of the median raphe of the prevertebral fascia.

Downward extension of a retropharyngeal space infection will result in mediastinitis. In addition to the possibility of mediastinitis, it may cause thrombosis of the internal jugular vein and erosion of the internal carotid artery, resulting in fatal hemorrhage.

Since the prevertebral fascia extends inferiorly to the posterior mediastinum, it is possible for the infection in this retropharyngeal space to spread down to the mediastinum. Radiographs of lateral soft tissue can be helpful in establishing a diagnosis by permitting visualization of the widened retropharyngeal space. A computed tomography can also be used.

Parotid Space

Boundaries. The parotid space contains the parotid gland and all associated structures, including the facial nerve, the auriculotemporal nerve, the posterior facial vein, and the external carotid, internal maxillary, and superficial temporal arteries.

Clinical Features. Infection in the parotid space reaches the gland from the lateral pharyngeal space or by retrograde extension along the parotid duct, typically points medially or inferiorly and opens into the neck or oral cavity. Primary infections of the parotid space break into the lateral pharyngeal space readily because the fascia is thin over the deep portion of the parotid space. Spreading of the infection superiorly to the temporal fossa may also occur. A parotid space infection can be distinguished from a submasseteric space infection since there is lack of trismus, the elevatsion of the lobule of the ear, and the possible escape of pus from the parotid duct when the gland is milked.

SPACE OF BODY OF MANDIBLE

The space of the body of the mandible is enclosed by a layer of fascia derived from the outer layer of the deep cervical fascia, which attaches to the inferior border of the mandible and then splits to enclose the body of the mandible. Superiorly, it becomes continuous with the alveolar mucoperiosteum and muscles of facial expression, which have their attachment on the mandible. The space contains the mandible, anterior to the ramus as well as the covering periosteum, fascia, muscle attachments, blood vessels, nerves, teeth, and periodontal structures. Shapiro pointed out that infections in this space may be dental, periodontal or vascular in origin, or may arise from fractures or by direct extension from infection in the masticator or lateral pharyngeal spaces.

Infections originating from incisors, cuspid or bicuspid teeth can involve the space of the body of the mandible; there is an induration or fluctuation of the labial sulcus if the outer cortical plate is involved. The infection is restricted to the floor of the mouth when the inner cortical plate is involved.

An infection originating from the molar teeth and involving the outer cortical plate results in a swelling in the oral vestibule if the infection perforates the bone above the external oblique line and the buccinator attachment. If perforation is below this line, the infection may point on the skin and lingual spread from infected bicuspid or molar teeth is into the floor of the mouth, when perforation of the bone is above the level of attachment of the mylohyoid muscle. The infection extends into the submandibular space or medially and posteriorly into the lateral pharyngeal space below the mylohyoid.

Submasseteric Space

Boundaries. The submasseteric space is situated between the masseter muscle and the lateral surface of the mandibular ramus. The masseter attaches to the ramus at three sites: the deep part on the lateral surface of the coronoid process, the middle part in a linear pattern on the lateral surface of the ramus extending upward and backward, and the superficial part close to the angle of the mandible. The submasseteric space is a narrow space that parallels the middle attachment by extending upward and backward between the middle and deep attachments. The posterior boundary of this space is the parotid gland, and anteriorly it adjoins the retromolar fossa (Fig. 11-7).

Clinical Features. Infection of this space usually occurs from a mandibular third molar, the infection passing through the retromolar fossa and into the submasseteric space. The patient may suffer from severe trismus and pain, and there may be facial swelling (Fig. 11.5B). The patient is often seriously ill.

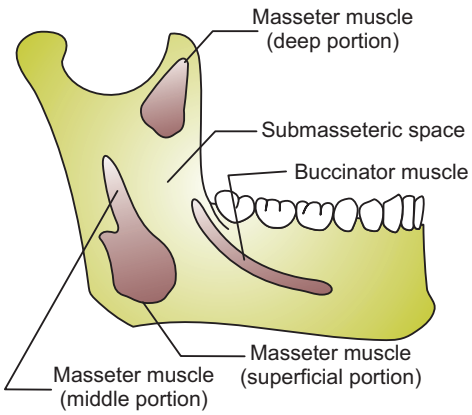

Figure 11-7. Lateral surface of the mandible showing the location of the submasseteric space.
Redrawn from GM Bransby-Zachary: The submasseteric space. Br Dent J, 84: 10, 1948.

SUBMANDIBULAR OR INFRAMANDIBULAR SPACES

There are three chief spaces in the submandibular region: the submandibular, sublingual, and submental spaces. Each is in anatomic continuity with the other as well as with its mate of the opposite side, and infection may spread contralaterally by extension, anterior to the hyoglossus muscle (Fig. 11-8).

Submandibular Space

Boundaries. The submandibular space is located medial to the mandible and below the posterior portion of the mylohyoid muscle. It is bordered medially by the hyoglossus and digastric muscles and laterally by superficial fascia and skin. This space encloses the submandibular salivary gland and lymph nodes.

Clinical Features. Infection of the submandibular space usually originates from the mandibular molars and produces a swelling near the angle of the jaw. This space abscess is triangular, begins at the lower border of the mandible, and extend to the level of the hyoid bone (Fig. 11.5C). It is one of the most commonly involved of all facial and cervical tissue spaces. Because of their anatomic proximity, the submandibular gland and nodes are also involved, resulting in sialadenitis and lymphadenitis. The infection spreads locally to involve the other submandibular spaces and may also extend to the lateral pharyngeal space, carotid space, cranial fossa or even the mediastinum. Involvement of the pharynx and larynx may even necessitate tracheotomy.

Sublingual Space

Boundaries. The sublingual space is bound superiorly by the mucosa of the floor of the mouth, inferiorly by the mylohyoid muscle, anteriorly and laterally by the body of the mandible, medially by the median raphe of the tongue and posteriorly by the hyoid bone. This space is situated above the submandibular space, and an infection here involves the tongue sometimes.

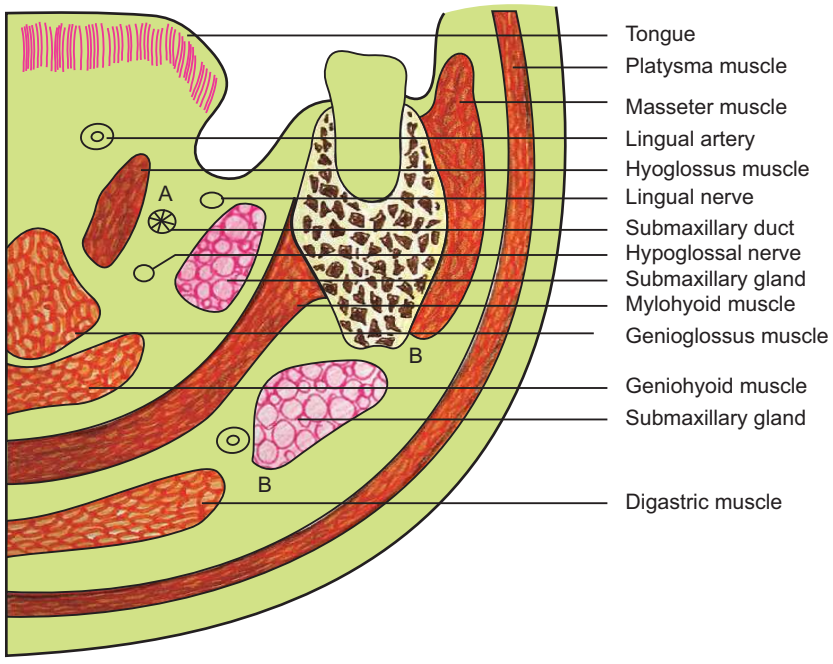

Figure 11-8. Frontal section through the head in the molar region.
The sublingual space **(A)** and the submaxillary space **(B)** are illustrated.

Clinical Features. The infection may arise directly by perforating the lingual cortical plate above the mylohyoid attachment or by extension from other spaces, primarily the submandibular space. Infection in the sublingual space produces an obvious swelling in the floor of the mouth and may cause both dyspnea and dysphagia. Extension of the infection takes the same path as the infection of the submandibular space.

Submental Space

Boundaries. The submental space extends from the anterior border of the submandibular space to the midline and is limited in depth by the mylohyoid muscle.

Clinical Features. Infection in this area presents as an anterior swelling in the submental area (Fig. 11.5D). This may cause dyspnea and dysphagia. The spread of the infection is similar to that in the submandibular and sublingual spaces.

LUDWIG'S ANGINA

Ludwig's angina named after the German physician Wilhelm Friedrich von Ludwig, is an acute, potentially life threatening, toxic cellulitis, beginning usually in the submandibular space and secondarily involving the sublingual and submental spaces as well. The disease is not usually considered to be true Ludwig's angina unless all submandibular spaces are involved. It is most commonly a disease of dental origin. Dental infections account for 80% of cases of Ludwig's angina. The chief source of infection is involvement of a mandibular molar, either periapical or periodontal. It may also result from submandibular gland sialadenitis, oral soft tissue lacerations, intaoral and perioral piercing, a penetrating injury of the floor of the mouth, such as a gunshot or stab wound, or from osteomyelitis in a compound jaw fracture. However, this has become rare since the advent of antibiotics.

The second and third molars are the teeth most commonly cited as the source of infection. The study of Tschiassny showed that of 30 teeth involved in 24 cases of Ludwig's angina, 20% were first molars, 40% were second molars, and 40% were third molars. The explanation for this phenomenon lies in the fact that when an infection perforates bone to establish drainage, it seeks the path of least resistance. Since the outer cortical plate of the mandible is thick in the molar region, the lingual plate is the one most frequently perforated. According to the studies of Tschiassny, initial infection of the submandibular space, particularly in cases of the second and third molars, is due to the fact that the apices of these teeth are situated below the mylohyoid ridge in 65% of cases. He also noted that because the apices of the roots of the first molar are above this ridge in about 60% of the cases, infection of the sublingual space is most common in cases of infection of this tooth.

Clinical Features. The patient with Ludwig's angina manifests a rapidly developing board-like swelling of the floor of the mouth and consequent elevation of the tongue. The swelling is firm, painful and diffuse, showing no evidence of localization and paucity of pus. There is difficulty in eating and swallowing as well as in breathing. Patients usually have a high fever, rapid pulse and fast respiration. A moderate leukocytosis is also found.

As the disease continues, the swelling involves the neck, and edema of the glottis may occur. This carries the serious risk of death by suffocation. Next, the infection may spread to the parapharyngeal spaces, to the carotid sheath or to the pterygopalatine fossa. Cavernous sinus thrombosis with subsequent meningitis may be sequela to this type of spread of the infection.

Laboratory Findings. Most cases of Ludwig's angina are mixed infection, but streptococci are almost invariably present. Fusiform bacilli and spiral forms, various staphylococci, diphtheroids and many other microorganisms have been cultured on different occasions. *Prevotella melaninogenicus, Prevotella oralis,* and *Prevotella corrodens* have also been isolated from patients with Ludwig's angina.

There are no apparent specific organisms associated with the etiology of this disease. It appears to be a nonspecific mixed infection.

Treatment and Prognosis. Management consists of early recognition of incipient cases, maintenance of airway, intense and prolonged antibiotic therapy, extraction of the affected tooth, and surgical drainage. Before the advent of antibiotics, the disease carried an exceedingly high mortality rate, primarily due to asphyxiation and severe sepsis. Most studies reported a death rate of 40–50%. Antibiotics have greatly reduced the occurrence of cases of Ludwig's angina, and the seriousness of the cases that do arise is attenuated by the antibiotic therapy. The edema of the glottis, which may develop rapidly, often necessitates emergency tracheotomy to prevent suffocation.

Intracranial complications of dental infection

A variety of intracranial complications may occur as a direct result of dental infection or dental extraction. Haymaker reviewed a series of 28 fatal infections occurring after tooth extraction, noting that the infection process proceeded along fascial planes to the base of the skull and then, traversing the skull by one or more routes, spreading to the intracranial cavity despite combative measures. The specific complications included:

	No of cases
Subdural empyema	1
Suppurative encephalitis and ependymitis	1
Transverse myelitis	1
Subdural empyema and brain abscess	2
Leptomeningitis	2
Leptomeningitis and brain abscess	2
Brain abscess	8
Sinus thrombosis	11

The majority of these cases occurred after extraction of maxillary teeth. Interestingly, only 8 of the 28 cases occurred in patients whose mouths were classified as being in poor hygienic condition. Furthermore, in 19 of the 28 cases the dental extraction involved only a single tooth.

Cavernous Sinus Thrombosis or Thrombophlebitis

Cavernous sinuses are bilateral venous channels for the content of middle cranial fossa, particularly the pituitary gland. Areas drained by cavernous sinus include the orbit, paranasal sinuses, anterior mouth, and middle portion of the face. Cavernous sinus thrombophlebitis is a serious condition consisting in the formation of a thrombus in the cavernous sinus or its communicating branches. Infections of the head, face, and intraoral structures above the maxilla are particularly prone to produce this disease. There are many routes by which the infection may reach the cavernous sinus. The facial and angular veins carry infection from the face and lip, while dental infection is carried by way of the pterygoid plexus. Gram-positive organisms(specifically *S. aureus*) are usually the pathogens in this setting. It has been emphasized by Mazzeo that infection spreading by the facial or external route is very rapid with a short fulminating course because of the large, open system of veins leading directly to the cavernous sinus. In contrast, infection spreading through the pterygoid or internal route reaches the cavernous sinus only through many small, twisting passages and has a much slower course, often with a lack of obvious symptoms early in the disease.

Clinical Features. The patient with cavernous sinus thrombophlebitis is extremely ill and manifests the characteristic features of exophthalmos with edema of the eyelids as well as chemosis. Paralysis of the external ocular muscles is reported, along with impairment of vision and sometimes photophobia and lacrimation. There are also headaches, nausea and vomiting, pain, chills and fever. Orbital cellulitis and cavernous sinus thrombosis can have similar signs and symptoms, and differentiation between them sometimes is impossible on clinical basis alone. Neuroimaging with CT, MRI or magnetic resonance angiography may help distinguish these entities.

Treatment and Prognosis. A combination of intravenous antibiotics, anticoagulants, and surgery is the optimal treatment for cavernous sinus thrombosis.The primary site of infection may require early drainage, especially when acute sinusitis is the cause of infection. The disease was once almost invariably fatal, death occurs as a result of brain abscess or meningitis. The use of antibiotics has decreased this mortality, but the condition is still serious, with a mortality rate of up to 30%.

MAXILLARY SINUSITIS

Maxillary sinusitis, an acute or chronic inflammation of the maxillary sinus, is often due to direct extension of dental infection, but originates also from infectious diseases due to bacteria, fungus, or virus such as the common cold, influenza and the exanthematous diseases; from local spread of infection in the adjoining frontal or paranasal sinuses; or from traumatic injury of the sinuses with a superimposed infection. The common organisms include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis* in children, gram-negative bacilli, anerobic organisms, rhinovirus and parainfluenza viruses, etc. The occurrence of maxillary sinusitis as a result of the extension of dental infection known as odontogenic sinusitis, is dependent, to a great extent, upon the relation and proximity of the second premolar, the first and second molar teeth to the sinus. When sinusitis is secondary to dental infection, the microorganisms associated with the sinusitis are the same as those associated with the dental infection. Apart from periapical infection, foreign bodies, tumors, and granulomatous lesions of the nasomaxillary complex may also produce maxillary sinusitis.

Acute Maxillary Sinusitis

Acute sinusitis may result from an acute periapical abscess or acute exacerbation of a chronic inflammatory periapical lesion, which involves the sinus through direct extension. In some cases a latent chronic sinusitis may be awakened by extraction of a maxillary bicuspid or molar and perforation of the sinus. Usually, the organisms involved in acute sinusitis are *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. Anerobic organisms are isolated during acute infections at times.

Clinical Features. Patients with acute maxillary sinusitis suffer from moderate to severe pain with swelling overlying the sinus or may have headache. Pressing over the maxilla increases the pain. Often, the painful sensation is one of pressure. Pain may be referred to various areas, including the cheek, posterior teeth, and ear. Sometimes patient may feel numbness in maxillary molars and premolars. Sinus pain increases when the patient bends over or is supine. The patient may complain of a discharge of pus into the nose and often a fetid breath. Fever and malaise are usually present. The diagnosis of acute maxillary sinusitis from clinical manifestations alone is quite difficult.

Diagnosis. Clinical signs and symptoms, transillumination with strong flashlight in darkroom, sinus view radiograph, nasal and sinus endoscopy, and computed tomography are some aids that can be used in diagnosis.

Histologic Features. The lining of the maxillary sinus may show a typical acute inflammatory infiltrate with edema of the connective tissue and often hemorrhage. A squamous metaplasia of the specialized ciliated columnar epithelium occurs sometimes.

Treatment and Prognosis. The prime objective of treatment is the removal of the infecting locus. This is particularly efficacious if the infection is of dental origin. Because of the infection present, antibiotics should also be administered.

Chronic Maxillary Sinusitis

Chronic sinusitis refers to sinusitis of more than three months duration and may develop as the acute lesion subsides or may represent a chronic lesion from the onset. Common predisposing factors are recent upper respiratory viral infections or allergic sinusitis. In cases of acute or chronic maxillary sinusitis, the possibility of phycomycosis infection (q.v.) must always be considered, especially in diabetic patients. In chronic sinusitis, the organisms are anaerobes and streptococcus, bacteroides, or veillonella are the most commonly involved.

Clinical Features. Clinical symptoms of chronic sinusitis may be generally lacking, and the condition may be discovered only during routine examination. Sometimes headache, fever, vague facial pain or upper toothache is present, or there is a stuffy sensation on the affected side of the face. There may be a mild discharge of pus into the nose and a fetid breath. Children may have persistent cough, fever, and purulent rhinorrhea. In chronic sinusitis, rarely will there be dystrophic calcification termed antrolith, which may be detected radiographically.

Radiographic Features. Sinusitis can be seen on the radiograph as a clouding of the sinus due to the hyperplastic tissue or fluid present. Films of both sinuses should be compared before a diagnosis is attempted. CT scan may reveal thickening of the mucosa.

Histologic Features. The mucosa lining the maxillary sinus may show remarkable thickening and the development of numerous sinus 'polyps'. These polyps are simply hyperplastic granulation tissue with lymphocytic and sometimes plasma cell infiltration. This tissue, which is usually covered by ciliated columnar epithelium, tends to fill the sinus and obliterate it. In some instances there is no remarkable proliferation of granulation tissue; rather, there is only a mild lymphocytic infiltration of the lining tissue with squamous metaplasia of the epithelium.

Treatment and Prognosis. The treatment for chronic maxillary sinusitis consists in removal of the cause of the disease. The prognosis is considered good if the disease is due to dental infection, since it can be eliminated. Infection from other sites may be difficult to eradicate.

FOCAL INFECTION

A focal infection is a localized or general infection caused by the dissemination of microorganisms or toxic products from a focus of infection. Focus of infection refers to a circumscribed area of tissue, which is infected with exogenous pathogenic microorganisms and is usually located near a mucous or cutaneous surface. This should be carefully distinguished from **focal infection**.

The theory of focal infection played a dominating role in medicine for many years and has been a subject of controversy. About a century ago, William Hunter first synthesized the notion that oral microorganisms and their products were involved in a range of systemic diseases not always of obvious infectious origin, such as arthritis. Oral foci of infection have been related to general health since the very inception of the theory of focal infection early in the 20th century. This theory, originating during the infancy of microbiology as a science, was based chiefly upon clinical observation with little foundation in scientifically determined fact. As early as 1940, Reimann and Havens criticized the theory of focal infection with their findings. The enthusiastic acceptance of this concept by the medical and dental professions soon after its promulgation has gradually waned. But it is still of sufficient importance to warrant detailed consideration here because of its recent resurrection.

MECHANISM OF FOCAL INFECTION

There are two generally accepted mechanisms in the possible production of focal infection. In one instance there may be a metastasis of microorganisms from an infected focus by either hematogenous or lymphogenous spread. Secondly, toxins or toxic products may be carried through the blood stream or lymphatic channels from a focus to a distant site where they may incite a hypersensitive reaction in the tissues.

The spread of microorganisms through vascular or lymphatic channels is a recognized phenomenon, as is their localization in tissues. Thus certain organisms have a predilection for isolating themselves in specific sites in the body. This localization preference is probably an environmental phenomenon rather than an inherent or developed feature of the microorganisms.

The production of toxins by microorganisms and their dissemination by vascular channels are also recognized occurrences. One of the most dramatic examples is in scarlet fever, the remarkable cutaneous features of the disease being due to the erythrogenic toxin liberated by the infecting streptococci.

Rheumatic fever is an example of an important disease, which probably develops as a result of an altered reactivity or hypersensitization of the tissues to hemolytic streptococci. A high concentration of antibodies to antigens of the group of hemolytic streptococci is found in many patients with rheumatic fever. But the fact that microorganisms cannot be cultured from the blood or from any of the tissues involved in the disease indicates that this is not a direct bacterial infection.

ORAL FOCI OF INFECTION

A variety of situations exist in the oral cavity which are at least theoretical sources of infection and which may set up distant metastases. These include:

- Infected periapical lesions such as the periapical granuloma, cysts, or abscesses
- Teeth with infected root canals
- Periodontal disease with special reference to tooth extraction or manipulation.

Bacteremia has been found to be closely related to the severity or degree of periodontal disease present after manipulation of the gingiva or more commonly, after tooth extraction. As early as 1932, Richards had demonstrated that simple massage of inflamed gingiva resulted in a transitory bacteremia in 3–17 patients. Okell and Elliott reported that a transitory bacteremia developed in 75% of a group of 40 patients who had severe periodontal disease after tooth extraction, but only in 34% of 38 patients with 'no noticeable pyorrhea'. The organism usually recovered was *Streptococcus viridans*. In 110 cases of periodontal disease in this same study, 11% of patients showed a bacteremia at the time of examination, regardless of the operative procedure. But no positive blood cultures were found in a group of 68 patients who had no obvious gingival disease.

The 'rocking' of teeth in their sockets by forceps before extraction has been shown by Elliott to favor bacteremia in patients who have periodontal disease. Thus 86% of patients with severe periodontal disease had positive blood cultures under the foregoing conditions, while only 25% of patients with no demonstrable gingival disease showed a bacteremia. Fish and MacLean have shown that the 'pumping' action occurring during dental extraction may force microorganisms from the gingival crevice into the capillaries of the gingiva as well as into the pulp of the tooth. In their study, two teeth were extracted after cauterization of the periodontal pockets, and two others were extracted without bacteriologic precautions. Organisms were readily cultured from the pulp and periodontal tissues of the untreated teeth, but not from those with cauterized pockets. Burket and Burn utilized a tracer microorganism, *Serratia marcescens*, to demonstrate the forcing of microorganisms into the blood stream by 'rocking' the teeth during extraction. This microorganism was cultured from the blood of 60% of 37 patients who had a suspension of the bacteria painted on the gingival margin before extraction.

Lazansky, Robinson, and Rodofsky studied the occurrence of bacteremia in 221 operations in the oral cavity involving 125 patients. Transient streptococcal bacteremias were found in 22 cases, or 10% of the operations. A positive blood culture was found in 16 cases, or 17% of a group of 92 multiple extractions, but only once in 56 single extractions. It is of considerable interest that a positive blood culture was found in five cases of a group of 72 patients receiving simple periodontal scalings.

Even oral prophylaxis may be followed by bacteremia, as was demonstrated by De Leo and his associates in a group of 39 children between 7 and 12 years of age. Of these patients, 5% were found to have a preprophylaxis bacteremia, but 28% had a postprophylaxis bacteremia. On the basis of these findings, they concluded that it was mandatory that, prior to dental prophylaxis, antibiotic premedication be employed for those children diagnosed as having rheumatic or congenital heart disease, because of the possible serious consequences of bacterial endocarditis.

Many studies dealing with tooth extraction or manipulation and bacteremia have been reported, some of which are summarized in Table 11-1. The evidence overwhelmingly

Table 11-1: Summary of results of studies on bacteremia following oral procedures

Type of operation	Investigator	No. of cases	No. of postoperative cultures considered positive by investigator	No. of postoperative cultures considered positive for pathogenic microorganisms*
Single extractions	Okell et al	10	1	1
	Burket et al	182	44	19
	Glaser et al (control group)	16	10	10
Total		208	55	30 (14%)
Multiple extractions only	Okell et al	128	83	83
	Bender et al (control group)	30	25	25
	Glaser et al (control group)	24	17	17
Total		182	125	125 (69%)
One or more extractions	Marseille	100	42	42
	Northrop et al (control group)	99	16	16
	Hopkins	108	18	18
	Hirsh et al (control group)	65	22	19
	Rhoads et al (control group)	68	24	24
Total		440	122	119 (27%)
All extractions		830	302	274 (33%)
Rocking; chewing; gingival massage	Elliott	41	23	23
	Richards	17	3	3
	Round et al	10	2	2
	Murray et al	336	185	0
Total		404	214	28 (7%)
Irritation of dental foci		1232	515	302 (25%)

From L Robinson, FW Kraus, JP Lazansky, RE Wheeler, S Gordon, and V Johnson: Bacteremias of dental origin. I: a review of the literature. Oral Surg, 3: 519, 1950.

**Included here are pure or mixed cultures containing streptococci, Staphylococcus aureus, pneumococci, actinomyces. Excluded are cultures not containing any of the mentioned, but showing growth of Staph. albus, Diphtheroids, unspecific diplococci, sarcinae, gram-negative cocci and rods, and fusiform bacilli.*

indicates that the extraction of teeth, and sometimes even more minor oral procedures, may produce a transient bacteremia. This bacteremia seldom persists for over 30 minutes in the majority of patients.

SIGNIFICANCE OF ORAL FOCI OF INFECTION

There have been a vast number of reports, based chiefly on clinical evidence alone, purporting to show that oral foci of infection either cause or aggravate a great many systemic diseases. The diseases most frequently mentioned are:

- Arthritis, chiefly of the rheumatoid and rheumatic fever type
- Valvular heart disease, particularly subacute bacterial endocarditis
- Gastrointestinal diseases
- Ocular diseases
- Skin diseases
- Renal diseases.

Arthritis of the rheumatoid type is a disease of unknown etiology, but probably represents only one manifestation of a generalized systemic disease. It bears close resemblance to many features of rheumatic fever, and though microorganisms cannot be cultured from the joints, the patients frequently have a high antibody titer to group A hemolytic streptococci. This suggests a tissue hypersensitivity reaction as the cause for the basic inflammatory reactions.

It was only logical that dental infection would be implicated because of the occurrence of streptococcal infection in the mouth. The Ninth Rheumatism Review (Hench) emphasized several points in favor of the septic foci theory of the etiology of rheumatoid arthritis. These include the following:

1. Streptococcal infections of the throat, tonsils, or nasal sinuses may precede the initial or recurrent attacks.
2. Removal of a septic focus show dramatic improvement sometimes.
3. The pathologic and anatomic features of lymphoid tissue in tonsillar infection, sinus infection, and root abscesses suggest that toxic products can be absorbed into the circulation.
4. A temporary bacteremia may occur immediately after tonsillectomy or tooth extraction or after vigorous massage of the gums.

The following points; however, are against this theory:

1. Often no infectious focus can be found.
2. No dramatic results are produced when a focus has been extirpated.
3. Many persons who are in good health or are suffering from a disease other than rheumatoid arthritis may have septic foci in the same situations and of the same magnitude as patients who are suffering from rheumatoid arthritis.
4. Sulfonamides, antibiotics, and vaccines fail to produce beneficial effects.

The failure of removal of oral foci to result in improvement of rheumatoid arthritis has proved the wisdom of the advice of Freyberg, who stated that two conditions should govern the management of foci of infection:

- Just like when a patient without rheumatic disease should have abscessed teeth or infected tonsils removed, so should the patient with rheumatoid arthritis.
- By removal of such infected tissues, the patient's general health might be improved, and thereby his/her ability to combat the arthritis might be indirectly facilitated.

He stressed that the patient should be warned that removal of such foci might not be of direct value as treatment for his/her arthritic disease.

Subacute bacterial endocarditis (or infective endocarditis) can without doubt be related to oral infection, since:

- There is a close similarity in most instances between the etiologic agent of the disease and the microorganisms in the oral cavity, in the dental pulp, and in periapical lesions.
- Symptoms of subacute bacterial endocarditis have been observed in some instances shortly after extraction of teeth.
- Transient bacteremia frequently follows tooth extraction.

This disease is generally recognized as being due to the accretion of bacterial vegetation on heart valves that are predisposed to the development of the condition, usually by rheumatic fever or congenital heart disease. Although streptococci of the viridans type once caused the majority of the subacute cases of bacterial endocarditis, the advent of the antibiotics has resulted in the drug-resistant microorganisms assuming a more important role.

Numerous studies have already been cited indicating that tooth extraction is often followed by a streptococcal bacteremia of the type usually associated with subacute bacterial endocarditis. In addition, many reports have indicated that the appearance of this form of endocarditis is sometimes preceded by tooth extraction. Elliott, for example, reported that 13 of 56 patients, or 23%, gave a history of recent dental operations preceding the occurrence of infective endocarditis. Geiger noted that beginning of subacute bacterial endocarditis among 50 patients was specifically related to tooth extraction in 12 cases. Bay reported that in a series of 26 cases of subacute bacterial endocarditis, six patients had had dental extraction, while Barnfield reported six of 92 cases to be associated with tooth extraction. In a series of 250 cases reported by Kelson and White, the predisposing cause in one of each four cases of bacterial endocarditis was found to be some dental procedure, usually tooth extraction.

The majority of cases of subacute bacterial endocarditis reported in the literature as following tooth extraction have occurred within a few weeks to a few months after the dental procedure. Premedication of patients with various antibiotics is usually prescribed to prevent the transient bacteremias that follow dental manipulations, and this prophylactic measure is considered to be an absolute necessity in patients who have

a past history of rheumatic fever or other evidence of known valvular damage. In contrast, BL Strom, and his associates noted in their study of patients with endocarditis who either did or did not have dental treatment at a reasonable interval before the onset of the disease concluded that there was no relationship between dental treatment and bacterial endocarditis (although the study did demonstrate a strong relation between cardiac valve pathology and endocarditis). Studies by van der Meer JT, Thompson J and associates (1992) and B Hoen, F Lacassin, and associates (1995) have also supported a very low risk rate for endocarditis with dental treatment. The most recent American Heart Association guidelines for the prevention of endocarditis clearly state that the vast majority of endocarditis due to oral organisms is not related to dental treatment procedures.

Gastrointestinal diseases have been periodically related to oral foci of infection. Gastric and duodenal ulcers have reportedly been produced experimentally by the injection of streptococci. Some workers have proposed that the constant swallowing of microorganisms might lead to a variety of gastrointestinal diseases. In most instances; however, the low pH of the gastric secretions is an adequate defense against such infection.

The lack of either clinical or experimental evidence of a relation between oral foci of infection and gastrointestinal diseases suggests that such a relation is highly questionable.

Ocular diseases have often been attributed in the ophthalmologic literature to primary foci of infection such as those associated with the teeth, tonsils, sinuses, genitourinary tract, and so forth. Guyton and Woods carried out a study on 562 patients hospitalized with iritis, cyclitis, choroiditis, and generalized uveitis. Definite evidence of foci of infection as the etiologic factor was found in 31, or 5.5% of the patients, and presumptive evidence of the same etiologic factor in 116, or 20.6% of the patients. But when this group of patients was compared with a control group of 517 persons without uveitis, the percentages of foci of infection were almost identical. This would indicate that the role of foci of infection in this situation is questionable at the very least.

Woods evaluated the role of foci of infection in ocular disease, and as pointed out by Easlick, listed the factors supporting the hypothesis as follows:

1. Many ocular diseases occur in which no systemic cause other than the presence of remote foci of infection can be demonstrated.
2. Numerous instances of prompt and dramatic healing of ocular diseases are reported to have followed the removal of these foci.
3. Sudden transient exacerbations occasionally are observed after the removal of teeth or tonsils and often are accepted as an indication of a relationship.
4. Some reports indicate the presence of blood stream infection in the early stages of ocular disease.
5. Iritis may be produced in animal experiments by the intravenous injection of microorganisms, especially streptococci.
6. Very little evidence is to support that some microorganisms may have a special predilection for ocular tissue.

There are objections to these points; however, and they may be listed as follows:

1. Many, otherwise healthy people, can be found to have focal infection, but no ocular disease.
2. Spontaneous cures frequently occur if nothing is done.
3. The exacerbations following surgery may also be explained as simple examples of the Shwartzman phenomenon, the flaring of an inflammatory focus through absorption of nonspecific protein, or on the basis of allergic shock to specifically sensitized tissue.
4. Positive blood cultures and cultures of the aqueous humor are rare in cases of acute iritis, and few secondary infections of the uveal tract follow the common transient streptococcal or staphylococcal bacteremia in patients.
5. Although lesions do occur in the eyes of laboratory animals after intravenous injection of microorganisms, they also occur with equal frequency in other organs, and the eye lesions are usually purulent, which occasionally simulates the clinical lesions of the iris and uveal tract.
6. Scientific proof that ocular disease of unclear etiology may be caused by bacteria from remote foci of infection appears to be missing, and the acceptance of the conclusion must be based largely on faith; however, there exists a strong possibility (on research, not clinical basis) that sensitization to secondary metastatic products from a focus may be related to ocular disease.

Studies with ACTH and cortisone in ocular disease suggest that, in many such cases, the ophthalmologist may be dealing with an abnormal metabolism rather than with a reaction to a focus of infection. Scientific evidence establishing dental foci of infection as the etiologic agent in ophthalmic disease is scanty. If such a relationship does exist, the most probable mechanism is sensitization.

Skin diseases have been suggested by some dermatologists to be related to foci of infection in occasional instances. Fox and Shields discussed dermatologic lesions and stated that the 10 most common skin diseases are: (1) acne, (2) seborrhea dermatitis, (3) tinea (fungus infection of the scalp, body, groin, hands, feet, nails), (4) eczema (eczematous dermatitis, nummular eczema, infectious eczematoid dermatitis, and atopic dermatitis), (5) dermatitis venenata (eczematous contact type dermatitis, occupational dermatitis), (6) impetigo, (7) scabies, (8) urticaria, (9) psoriasis, and (10) pityriasis rosea. Of these diseases, only some forms of eczema and possibly urticaria can conceivably be related to oral foci of infection.

A few other dermatoses have been related to focus of infection, although there is little scientific proof of this association. These diseases include erythema multiforme, pustular dermatitis, lupus erythematosus, lichen planus, and pustular acrodermatitis. If such a relationship does exist, the mechanism is probably sensitization rather than metastatic spread of microorganisms.

Renal diseases of certain types are sometimes attributed to foci of infection. The type of microorganism most commonly involved in urinary infections is *Escherichia coli,* although other staphylococci and streptococci also may be cultured. Of the

streptococci, *Streptococcus hemolyticus* seems to be the most common. This Streptococcus is an uncommon inhabitant of dental root canals or periapical and gingival areas. Since the microorganisms commonly involved in oral infection are only infrequently involved in renal infections, it appears that there is little relation between the two and that oral foci of infection play a small role even when the possibility of superimposition on a damaged urinary tract exists.

The present evidence for the relationship of oral microorganisms and systemic disease particularly that involving the coronary arteries, is very limited. Occurrence of metastatic infections from the mouth to distant bodily sites is also not very common.

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SECTION III

Injuries and Repair

SECTION OUTLINE

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CHAPTER 12

Physical and Chemical Injuries of the Oral Cavity

■ B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

Injuries of the oral cavity may be caused by physical or chemical causes. Physical injuries may be iatrogenic, self-inflicted, traumatic, or occupational. The most important iatrogenic cause is the repair of tooth affected by dental caries or other developmental defects and restoration of missing tooth. Iatrogenic cause also includes *X* radiation and laser radiation. Self-induced or factitious injuries are due to overzealous oral hygiene practices, caused by psychotic or neurotic condition, or habitual. Traumatic causes include a fall, fight, road traffic accidents, and sports injuries.

Although chemical injuries are caused by environmental elements such as toxic levels of chemicals in the water, air, or consumables, the restorative and endodontic materials used in the routine dental practice play an important role.

INJURIES OF TEETH ASSOCIATED WITH TOOTH PREPARATION

The teeth, particularly the dentin and pulp, may be injured not only by dental caries, but also from those procedures necessary for the repair of lesions involving dental hard tissues. Preparation of the teeth for receiving the restorations include cutting, grinding, and etching with acids etc. These physical and chemical methods of tooth preparation as well as the various medicaments and filling materials which are inserted into the prepared tooth, have their own effects.

EFFECT OF TOOTH PREPARATION

The effect upon the dental pulp of restorative procedure alone is difficult to assess except in the sound tooth, since the carious lesion itself produces demonstrable changes in both the dentin and the pulp. Even when a sound tooth is prepared for experimental purpose, care must be taken in observing the effects to separate those which are due solely to the tooth preparation from those which are due to the restorative materials applied.

Tooth preparation is usually done by rotary instruments such as tungsten carbide burs and diamond burs of different sizes and shapes. Lasers and air abrasion are also used alternatively. Pulpal responses to these various procedures depend on the heat generated by friction, cutting of odontoblastic processes and drying of dentinal tubules, thickness of remaining dentin, vibration, removal of minerals and exposure of the organic matrix of dentin, and formation of smear layer.

REACTION TO ROTARY INSTRUMENTATION

Stainless steel burs revolving at low speed were used in the past for cavity and crown preparation. As the hardness of the enamel is high, these burs could not abrade instead they cut or chip away the tooth material. Also a considerable amount of pressure is applied during the procedure, which results in excessive heat production and evaporation of the contents of

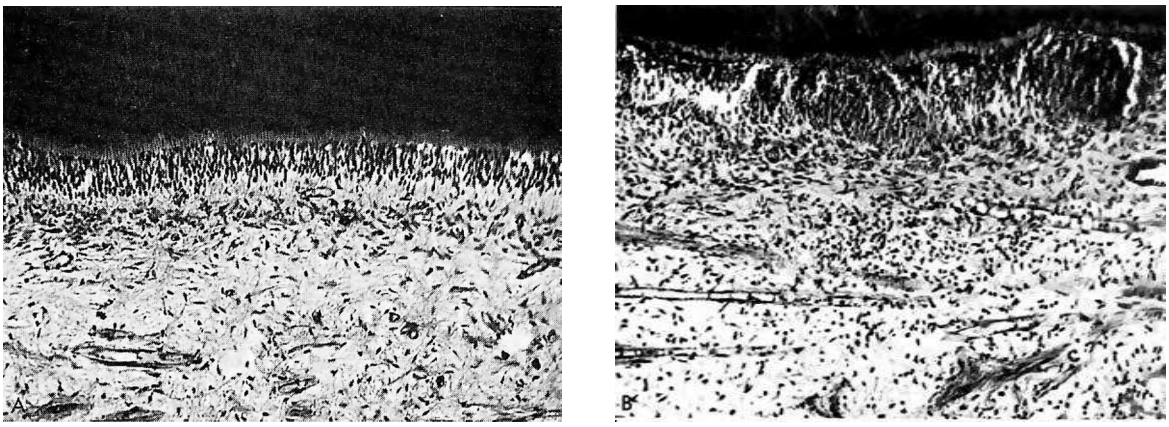


Figure 12-1. Effect on dental pulp of cavity preparation by steel bur.
Cavities were prepared in human teeth and filled with gutta-percha. A section of pulp from an intact normal tooth is shown in **(A)**, while the injured area in the pulp six days after cavity preparation is seen in **(B)** *(Courtesy of Drs David F Mitchell and Jensen JH. J Am Dent Assoc, 55:57, 1957).*

the dentinal tubules. High speed rotary instrumentation with tungsten carbide and diamond burs has replaced the steel burs in recent years. Nevertheless stainless steel burs are used in procedures involving bone.

The reaction of the dental pulp to cutting of dentin with a dental bur has been studied by Fish in both dogs and monkeys. When dentin is injured, there is stasis of the contents of the dentinal tubules, which lose their fluid communication with the pulp because of the formation of secondary dentin. Involved dentinal tubules are occluded by the deposition of calcium which separates these sclerosed dentinal tubules physiologically from the rest of the tooth.

The cavities prepared by Fish in the teeth of dogs or monkeys were cut with steel burs which were kept wet to prevent the complication of heat-induced damage to the pulp. In some cases the cavities were then filled with copper oxyphosphate cement and in other instances they were left open and exposed to the oral fluids. The animals were sacrificed after varying periods of time, and sections of the filled teeth were prepared for microscopic study. Three general reactions to cavity preparation were noted: (1) the production of secondary dentin, (2) changes in the odontoblasts associated with injured tubules, and (3) general changes in the pulp. Fish carefully pointed out that the reaction of the tooth with the formation of a calcified barrier and secondary dentin production is always strictly confined to the pulp surface of the injured dentinal tubules. There is never overlap of uninjured tubules, and for this reason the changes may be regarded as a specific reaction to injury of the dentinal tubules.

The pulp reaction to superficial injury of the dentin varies in degree of severity, depending partially upon the depth of the prepared cavity and partially upon the elapsed time between cutting the cavity and extraction of the tooth for study. In mild reactions the odontoblasts become distorted and reduced in number. Small vacuoles may appear between them, probably lymph exudate. Capillaries in the damaged area may be prominent. In more severe injuries, there may be complete disorganization of and hemorrhage in the odontoblastic layer (Fig. 12-1). The bulk of the pulp tissue away from the cut tubules may exhibit little or no reaction.

In more serious injuries there is a greater infiltration of the injured locus by polymorphonuclear leukocytes, which gradually become replaced by lymphocytes. The majority of the severe pulp injuries are probably associated with irritation brought about by the open cavities, with the sudden exposure of large numbers of open dentinal tubules to oral fluids and bacteria.

Even after such severe injuries the majority of damaged pulps undergo spontaneous healing or at least enter a quiescent phase and produce no signs or symptoms of persisting damage (Fig. 12-2). The factors responsible for this phenomenon, especially from the clinical aspect, are unknown.

It appears that dentin has a heat-dissipating action which reduces the temperature rise within the pulp to only a fraction of the actual temperature applied to the tooth.

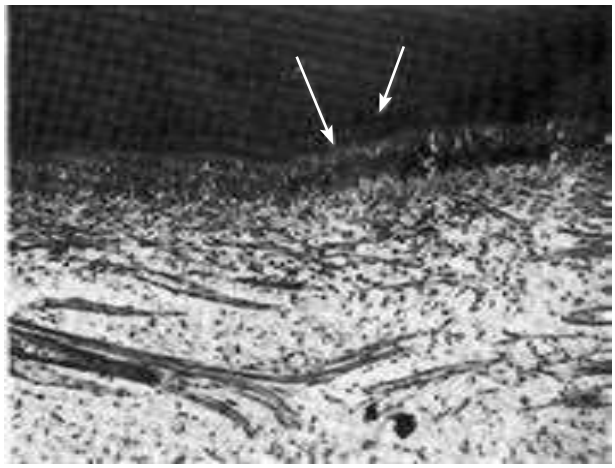


Figure 12-2. Effect of cavity preparation by steel bur on dental pulp.
A calciotraumatic line (1) and reparative dentin (2) are found beneath the cavity nine weeks after preparation *(Courtesy of Drs David F Mitchell, JH Jensen. J Am Dent Assoc, 55: 57, 1957).*

This is due to the low thermal conductivity of dentin, which acts as an effective insulating medium. Nevertheless the application of heat to a dental pulp already injured from a carious lesion of the dentin, but not an actual pulp exposure, may be sufficient to affect adversely the repair or healing of the pulp even though an apparently successful restoration is given to the tooth.

The preparation of tooth under the constant application of water to cool the cutting instrument and tooth will prevent many of the serious consequences due to heat, and this procedure is strongly recommended.

High-Speed Instrumentation. The development of high-speed dental engines and hand-pieces necessitated investigation of the possible effects which their use might have on pulp tissue, and numerous reports of such studies have been published.

Bernier and Knapp reported a study on high-speed instrumentation utilizing various speeds up to 100,000 rpm. They found evidence of mild pulpal damage, but, in addition, observed a new type of lesion which they termed the 'rebound response'. This consisted variously in: (1) an alteration in ground substance, (2) edema, (3) fibrosis, (4) odontoblastic disruption, and (5) reduced predentin formation in a region directly across the pulp opposite the cavity site or at a distant pulpal site, and thought to be caused by waves of energy transmitted to the pulp focused into a certain region by the pulpal walls. The significance of this phenomenon is still not clear.

Swerdlow and Stanley in their study involving 450 human teeth found that speeds over 50,000 rpm with coolants were less injurious to the pulp than lower speeds. They concluded that the combination of high speed, controlled temperature, and light load produced minimal pathologic pulpal alteration. When heavy loads were used, even coolants did not minimize inflammatory responses. Extending this investigation to 13 operative techniques, Diamond and his coworkers found that the 300,000 rpm air-water spray—No. 35 carbide bur technique—provided all the cutting efficiency of a high-speed instrument without producing extended or burn lesions and caused the highest incidence of reparative dentin formation, a favorable protective reaction. A speed of 250,000 rpm with water coolant was reported by Nygaard-Ostby to produce even less pulpal reaction than the conventional (6,000 rpm) machine without water-spray. Caviedes-Bucheli and coworkers in their study found that substance P expression is increased in tooth where cavity preparation is done and concluded that it may have an important clinical significance in terms of inflammation and pain experience.

The practicability of use of accelerated hand-piece speeds has been accurately summarized by Stanley and Swerdlow, who stated: 'In principle, high speed techniques approach the ideal but at the same time these methods can be easily abused. . . properly used, ultraspeed is an extremely safe and efficient method of reducing tooth structure'.

Effect of Air Abrasive Technique. In the air abrasive technique, aluminum oxide sprayed under pressure is used as an abrasive for the cavity preparation and surface treatment. The main drawback of this procedure is, it does not allow the operators' stereognostic ability to control the depth of cutting. However Ferrazzano et al, based on their study in 60 mandibular third molar concluded that the macroscopic size and shape of cavities is connected to working distance, while working time is important to determine the depth of preparation. Also the abrasive dust is a potential health hazard to the operator and the patient. Nowadays it is used only to clean the pit and fissures prior to the application of sealants.

Effect of Ultrasonic Technique. The use of ultrasonic equipment for cutting cavities in teeth has been advocated because it involves less heat, noise, and vibration in contrast to rotary instruments. Essentially, the technique consists in the conversion of electrical energy into mechanical energy in the form of vibration of a tiny cutting tip, approximately 29,000 vibrations *per se*cond with an amplitude of about 0.0014 inch. Aluminum oxide abrasive in a liquid carrier is washed across this tip, and the vibration of the particles in turn results in a rapid reduction of tooth substance.

The effects of this technique, as used in cavity preparation, on the tooth and dental pulp have been evaluated by a number of investigators whose results are in essential agreement. Zach and Brown, Healey and his coworkers, and Lefkowitz among others have found that there are no remarkable differences in the reaction of the dental pulp to the preparation of cavities by the steel bur, the diamond stone or the ultrasonic instrument. This again emphasizes that only the dentinal injury itself is important, not how this injury is produced.

Mitchell and Jensen, studying the effect of steel bur and ultrasonic cavity preparation on the human tooth, also reported that no differences could be observed in the reaction of the pulp to these two techniques. Mild hyperemia, hemorrhage and a slight neutrophilic and lymphocytic infiltration of the pulp tissue immediately below the cut dentinal tubules were noted during the 6–12 day period following cavity preparation by either means. After several weeks the late reaction consisted in slight, irregular secondary dentin deposition and the formation of a 'calciotraumatic' line, a hematoxyphilic line between the regular dentin and the postoperative dentin apparently representing a disturbance in dentin formation at the time of the operative procedure.

Lasers. Laser is an acronym for Light Amplification by Stimulated Emission of Radiation. It is an electro-optical device which, upon stimulation, can convert jumbles of light waves into an intense, concentrated, uniform, narrow beam of monochromatic light with an energy source of great intensity and exceptional flexibility. The radiation may be continuous or modulated, or the emission may occur in short pulses. This high-intensity radiation can be focused on an extremely small area, approximately 1 micron in diameter, because of the small angle of divergence and coherency of the beam. Light photons of characteristic wavelengths are produced, amplified, and filtered to produce the laser beam. Carbon dioxide and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers are most commonly used. The main problem with laser cutting of hard dental tissues is the generation of heat and forbidden tactile control.

Lasers are used in dental practice to coalesce pits and fissures to eliminate retention sites for bacteria, to desensitize the exposed root surfaces, to make the hard tissue surfaces rough to promote bonding as an alternative to acid etching, to vaporize the carious tissue, to vaporize the organic tissues in the root canal in endodontic procedures, cavity preparation, restoration removal, treatment of dentinal sensitivity, caries prevention and bleaching.

Effects on Teeth. The effects of laser on teeth were first reported by Stern and Sognnaes, who found that exposure of intact enamel, caused a glass like fusion of the enamel, whereas dentin exposed to laser exhibited a definitive charred crater. Chalky spots, craters, or small holes in enamel may also be produced under other conditions. Scanning electron microscopic analysis showed the effects of laser on dentin vary from no effects to disruption of the smeared layer to actual melting and recrystallization of the dentin, depending on power level, duration of exposure, and color of the dentin. Although it has been shown that selective deep destruction of carious tooth substance can be accomplished, the practicality of its use in removing carious lesions is still questionable. Laser irradiation alters the dentin structure and produces surface layers that give the appearance of being more enamel-like. The laser-modified surface may be more resistant to demineralization; hence, many investigators are proposing continued development of the laser for caries prevention.

Open dentin surface exposed to laser results in melting and closure of the orifices of the dentin and this property is used to treat dentin hypersensitivity.

Bleaching of stained teeth has also been accomplished by lasing.

Effects on Pulp. The pulps of teeth in animals subjected to laser radiation have been described by Taylor and his associates as showing severe pathologic changes, including hemorrhagic necrosis with acute and chronic inflammatory cell infiltration. The odontoblastic layer also underwent coagulation necrosis, although the severity of the response varied with the amount of radiation.

EFFECT OF HEAT

The reaction of the dental pulp to heat is an important clinical problem because of the extraordinary amount of heat that may be generated by the revolving cutting and grinding instruments used in tooth preparation. Actually, temperatures over 700° F have been recorded on the cutting surfaces of stones and burs under abusive conditions.

Thermal change may be influenced by: (1) the size, shape, and composition of the bur or stone, (2) the speed of the bur or stone, (3) the amount and direction of pressure applied, (4) the amount of moisture in the field of operation, (5) the length of time that the bur or stone is in contact with the tooth, and (6) the type of tissue being cut, enamel or dentin. Of further significance is the heat generated during the setting of various restorative materials, particularly the direct resins. In *in vitro* experiments, Wolcott and his associates showed that the temperature at the dentin-resin junction may reach 212° F, and they recorded a temperature of 133° F in the pulp chamber.

Smear layer

Smear layer is an amorphous micro layer deposited on the prepared tooth surfaces and consists of inorganic enamel and dentin debris, organic pulp materials, dentinal fluid, bacteria, and saliva. The thickness of smear layer may vary from 1μm to 5μm. Its morphology, composition, and biological behavior still remain controversial. Smear layer has the protective effect by forming a physical barrier, which reduces the permeability of dentin and prevents the exit of dentinal fluid. On the other hand it also acts as a barrier against the microoraganisms, which already penetrated before the treatment, may flow back and express their pathogenicity. Many investigators advocate the removal of smear layer as it interferes with the bonding between the restorative material and the tooth structure in restorative treatment and affects the action of irrigants and disinfectants and penetration and adhesion of sealers in endodontic treatment.

EFFECT OF RESTORATIVE MATERIALS

The dentist has at his/her disposal a great many materials prepared commercially to restore the original contour of the tooth attacked by dental caries and other lesions of the tooth including trauma. The dentist must be familiar with the advantages and disadvantages of each material from the point of view of its physical and chemical properties and its ability to fulfil the purpose for which it is intended. In addition, he must be acquainted with the biologic effects of the restorative materials on the tooth, especially on the dental pulp.

A great many experimental studies have been carried out to investigate the effects of the different restorative materials on the dental pulp, and today such testing is routine before new restorative materials are released by ethical manufacturers for use by dentists. It should be obvious that a restorative material applied to a prepared tooth is in contact with more than just a mass of inert calcified material. The dentinal tubules, containing odontoblastic processes which have been freshly cut, form a series of passage ways leading directly to the pulp through which a fluid or soluble material may reach the pulp tissue. If this material is irritating, it may lead to serious injury. For this reason a comparison of the effects of the various common restorative materials is important.

Remaining dentin thickness

It is generally agreed that if the cavity depth is shallow, with 2.0 mm or more of primary dentin remaining between the floor of the cavity preparation and the dental pulp, dentin probably provides its own insulation against traumatic, thermal or restorative material irritation. However, if the remaining thickness of primary dentin is less than 2.0 mm, it is necessary that a cement base of one type or another be utilized.

Zinc Oxide and Eugenol. It is used routinely as a temporary filling material or root canal sealer. Eugenol of this cement fixes cells, depresses the cell respiration, and reduces the neural transmission *in vitro*. There is almost universal agreement that zinc oxide and eugenol is the least injurious of all filling materials to the dental pulp. Not only is there no irritation produced by this substance, but actually it exerts a palliative and sedative effect on the mildly damaged pulp, since it inhibits synthesis of prostaglandins and leukotrienes. It seems to be such a bland substance that it may lack even the necessary irritating properties requisite to the stimulation of secondary dentin formation. In view of these findings, zinc oxide and eugenol is the material of choice for use over injured pulps or as a base in deep cavity preparations.

Zinc Phosphate (Oxyphosphate) Cement. This particular cement is widely used in dentistry both as a protective base in deep cavities before the insertion of the restoration and also in cementing cast inlays, crowns, and other similar restorations. The majority of investigators have reported significant deleterious effects on the pulp when the material is placed in cavities, the actual injurious agent supposedly being the phosphoric acid.

Gurley and Van Huysen prepared cavities in teeth of young dogs and filled them with zinc phosphate cement. After approximately 1½ months they found hyperemia and inflammatory cell infiltration of the pulp with disarrangement of the odontoblastic layer. Secondary dentin had formed under the shallower cavities. The more severe pulpal reactions occurred under the deeper cavities.

Studies on human teeth, such as those by Manley, by Shroff, and by Kramer and McLean, show that hyperemia or hemorrhage with inflammatory cell infiltration of the pulp accompanied by reduction in the size and number of the odontoblasts occurs after placement of this cement in prepared cavities.

The studies generally indicate that zinc oxyphosphate cement is an irritant when placed in the base of a deep cavity, particularly in bulk, although the human pulp may be able to localize this reaction in most instances. When this cement is used in shallow cavities, it is relatively innocuous and reportedly serves a useful function in the stimulation of secondary dentin formation.

Polycarboxylate or polyacrylate cements have properties comparable to those of the phosphate cements, but have a low degree of pulpal irritation similar to that of the zinc oxide-eugenol cements.

Silver Amalgam

Silver amalgam is used as a filling material in dentistry. It is an innocuous material, particularly in shallow cavities. Beneath deep cavities filled with amalgam, Manley found a decrease in the number of odontoblasts, as well as mild inflammatory cell infiltration of the pulp. The complication of thermal shock transmitted by deep amalgam restorations is difficult to evaluate, but is a source of potential damage.

In contrast, Swerdlow and Stanley studied the pulpal responses in 73 intact human teeth with cavities prepared at speed of 20,000–300,000 rpm and filled with either amalgam or zinc oxide and eugenol. They reported that the amalgam increased the intensity of mild pulpal response to cavity preparation and that this appeared to be due, in part at least, to the mechanical aspects of amalgam condensation. Brännström studied the effect of amalgam restorations on pulp tissue, and concluded that any damage to the pulp was due to leakage around the restoration, not to the filling material itself. Dark colored metallic components of the silver alloy turn the dentin dark gray and tooth may appear discolored.

Amalgam restorations when in contact with gingiva cause inflammation because of corrosion products and dental plaque.

Relationship between oral lichenoid reactions and silver amalgam fillings is a matter of controversy. A number of studies have been published with respect to amalgam filling and lichenoid reactions. A Dunsche and coworkers suggest the removal of amalgam fillings in all patients with symptomatic oral lichenoid reactions associated with amalgam fillings if no cutaneous lichen planus is present.

Glass-ionomer

Glass-ionomer cement is considered as biocompatible and is widely used as filling and lining material and as a luting agent. It consists of fluoroaluminosilicate glass powder and polycarboxylic acid. Glass-ionomers are water-based, and the set materials are composed of an inorganic-organic complex with high molecular weight. In contrast to other cements, glass-ionomer has the advantages of chemically bonding to mineralized tissues and release of fluorides.

Glass-ionomer cement bonds to the dentin by chemical and mechanical means. The chemical bonding is based on the exchange of ions between carboxylic groups of the substrate and calcium ions derived from partially dissolved apatite crystallites. The mechanical interlocking is based on the demineralization of exposed dentin by polycarboxylic acid treatment. Collagen fibers can be exposed and an intermediate layer can be formed between glass-ionomer material and undemineralized dentin.

Biocompatibility of glass-ionomer cement is due to the weak nature of polyacrylic acid. Histologically there is minimal or absence of inflammation in pulp after a month. Pulpal pain may be present for a short period after the filling of cervical cavities, and is due to the increased dentin permeability after acid etching.

Self-polymerizing Acrylic Resin. Self-curing resins were extensively used as restorative materials, particularly in anterior teeth. There is evidence to indicate, however, that these resins may cause serious damage to the dental pulp. Still, not all investigations are in complete agreement.

Conventional Composite Resins. These are restorative materials developed chiefly because methyl methacrylate or unfilled acrylic resins have restrictive characteristics such as low hardness and strength, a high coefficient of thermal expansion and a lack of adhesion to tooth structure. The resin matrix is a compromise between epoxy and methacrylate resins. This resin is combined with a filler of dispersed particles of varying types in relatively high concentration. While most

conventional composite resins are chemically activated, some are now marketed whose cure is based on light activation.

The biologic properties of the composite resins show the same irritational characteristics as the unfilled acrylic resins. For this reason, the same measures should be taken to protect the pulp from possible injury, especially when the cavity preparation is deep. A calcium hydroxide base is preferable to a zinc oxide and eugenol base because of the possible interaction of eugenol and resin.

Microfilled Composite Resins. These are a newer group of resins which contain the same resin matrix as the conventional composite resins but differ in that the size of the filler is much smaller than in the conventional resin. The biologic properties of the microfilled resins, including their irritational effects on the pulp, are comparable to those of the conventional composite resins. Thus, some pulpal protection is necessary under deep cavities.

Acid etching

Resin based restorative materials are mechanically bonded to the tooth structure by creating micropores, a procedure known as acid etching. This process demineralizes hard tissues and exposes the organic matrix. Phosphoric acid is the most commonly used etchant in clinical practice.

In contrast to the scanty organic matrix of enamel which is lost during the demineralization and subsequent washing, the components of dentin are demineralized selectively. Peritubular dentin demineralizes quicker than does the intertubular matrix. Demineralization of dentin widens the tubules, makes them funnel shaped towards the surface. It exposes the collagen in the wall of the tubules and also uncovers the openings of a large number of lateral branches. The exposed collagen forms an interwoven mesh of fibers in which the resin infiltrates. This collagen mesh infiltrated by resin is referred to as the hybrid layer. After polymerization, the resin-impregnated collagen, together with the resin in the dentinal tubules and their branches, constitutes the adhesion between the dentin and the resin. If the hybrid layer becomes too dry, the collagen mesh will collapse and penetration of resin will be impaired. Adequate moisture content of the surface is a must to prevent collapse of the collagen mesh for an optimal bonding between the resin and the hybrid layer.

The many experimental studies cited would indicate superficially that the majority of restorative materials used in dentistry today are dangerous because of the serious effects on the dental pulp which they often induce. It is true that many of these materials are potentially injurious. Nevertheless, literally millions of restorations with these substances are placed each year, and clinical experience has shown that, unless actual pulp exposure has occurred, the death rate of dental pulps directly attributable to the restorative material is extremely low. Even the occurrence of clinical symptoms of pulp injury is uncommon. Although this seems contradictory to experimental evidence, it should be appreciated that most cavities prepared by the dentist in which these materials are inserted are to repair a destructive carious lesion. The presence of this carious lesion, in contrast to the experimental cavities prepared in sound human and animal teeth, has usually induced the deposition of secondary dentin and has caused a certain amount of dentinal sclerosis, and these reactions offer considerable protection to the pulp. It is on this basis that the dentist is justified in continuing to use these filling materials. There is a need, however, for continued study of this general problem.

Effect of Cement Bases, Cavity Liners, Varnishes and Primers

A variety of materials commonly used in dental practice are inserted in a cavity preparation between the tooth and the restoration for the following purposes:

- To serve as a bacteriostatic agent.
- To provide thermal insulation, particularly under metallic restorations.
- To provide electrical insulation under metallic restorations .
- To prevent discoloration of tooth structure adjacent to certain types of restorative materials.
- To prevent the penetration of deleterious constituents of restorative materials into the dentin and pulp.
- To improve the marginal seal of certain restorative materials by preventing microleakage and the ingress of saliva and debris along the tooth-restoration interface.

These materials are generally classified as cement bases, cavity liners, cavity varnishes and cavity primers, and they are important because of their possible effects on the dental pulp.

Cement Bases. A cement base is a layer of cement commonly used beneath the dental restoration either to encourage recovery of the injured pulp or to protect the pulp against the injuries. Intermediary base materials that are commonly used under permanent restorations include zinc phosphate cement, zinc oxide-eugenol cement, and calcium hydroxide cement. Ideally, a cement base should be biologically compatible with the dental pulp and such is the case with zinc oxide-eugenol and calcium hydroxide. However, zinc phosphate cement, when placed against dentin, acts as an irritant to the dental pulp because of the acid content which varies between pH 3.5 and 6.6, as discussed previously.

Cavity Liners. Cavity liners are aqueous or volatile organic liquid suspensions or dispersions of zinc oxide or calcium hydroxide that can be applied in a relatively thin film to the surface of a cavity. They may also be solutions of resins in an organic solvent to which has been added calcium hydroxide or zinc oxide, or aqueous suspensions of calcium hydroxide in methylcellulose. The cavity liner provides the beneficial effects of zinc oxide and calcium hydroxide as thin films in shallow cavities and, in addition, neutralizes the free acid of zinc phosphate and silicate cements. The cavity liners themselves have no effect on dental pulp and, in fact, actually

form a chemical barrier to provide reliable protection for the pulp under certain deep restorations.

Stanley has compared the protective effect of reparative dentin with cavity liners and bases, and generally concluded that: (1) pulpal tissue beneath preoperatively formed reparative dentin is safe from most subsequent procedures; (2) cavity liners and/or bases, should be employed since the completeness of the reparative dentin barrier cannot be ascertained; (3) the unrestored tooth being utilized as an abutment lacks reparative dentin and is more subject to the damaging effects of chemical agents because of patent dentinal tubules; (4) although 2 mm of primary dentin between the floor of the cavity preparation and the dental pulp is usually a sufficient protective barrier, the condensation of amalgam or gold foil, as well as the chemical irritation of cements and self-curing resins, may render this thickness of protection insufficient; (5) age changes in the tooth, with the production of reparative dentin in the involved area, are of no recognizable benefit regarding pulp protection; (6) high-speed, water-cooled cutting techniques produce an average incidence of reparative dentin formation of under 20%; even less reparative dentin formation is produced if more than 1 mm of primary dentin remains beneath the cavity preparation; (7) if reparative dentin does not form within the first 50 days following a restorative procedure, then there will be none; (8) nearly 20 postoperative days are required for new odontoblasts to differentiate and produce reparative dentin, and it has been shown that an average of 100 productive days of matrix formation is required to produce a reparative dentin barrier of 0.15 mm; (9) final cementation of restorations need not be delayed in allowing time for reparative dentin to form, since the use of cavity-lining materials is a reasonable substitute; and (10) cavity varnish and calcium hydroxide lining materials appear capable of protecting pulp if used appropriately.

Cavity Varnishes. Cavity varnishes are solutions of one or more resins from natural gums, synthetic resins, and rosin in organic solvents. It is generally agreed that varnishes may be of aid in reducing postoperative sensitivity, but their film thickness is insufficient to provide thermal insulation. This film also acts as a semipermeable membrane so that certain types of ions penetrate it, while others do not. It has been found also that varnishes are effective in reducing the microleakage of fluids around the margins of restorations.

While cavity varnishes themselves appear to have no significant effect upon a dental pulp, neither do they have a sedative effect. Therefore, in deep restorations, it may be advisable to utilize calcium hydroxide or zinc oxide-eugenol cements first, and then apply the varnish over this base.

Effect of Cavity-sterilizing Agents

Cavity-sterilizing agents are frequently used as a final step in routine cavity preparation and also in an attempt to sterilize discolored, infected dentin in the base of deep carious lesions when this dentin cannot be completely removed without risk of pulp exposure. It has been suggested that cavity sterilization is unnecessary, since microorganisms persisting in the dentinal tubules after a restoration has been placed do not flourish but, rather die or exist in an inactive state. Furthermore, should the dentin be carious so near the pulp that exposure is feared were it all to be removed, the pulp tissue by this time would almost certainly have become infected, and attempts at sterilization would be worthless.

Mineral trioxide aggregate (MTA)

Mineral trioxide aggregate (MTA) is a moisture friendly biocompatible material composed of refined Portland cement and bismuth oxide. Portland cement is a mixture of dicalcium silicate, tricalcium silicate, tricalcium aluminate gypsum, and tetracalcium aluminoferrate. MTA has wide endodontic applications, which include pulp-capping, pulpotomy dressing, root-end filling, perforation repair, and apexification. The effect of white mineral trioxide aggregate on dental pulp was investigated by Moghaddame-Jafari and coworkers on mouse MDPC-23 odontoblast-like cells and OD-21 undifferentiated pulp cells. They found that there was no induction of apoptosis and increased DNA synthesis. In another *in vitro* study where exposed pulps were covered with MTA or calcium hydroxide, histological evaluation demonstrated less inflammation, hyperemia and necrosis, a thicker dentinal bridge, and more frequent odontoblast layer formation with MTA than with calcium hydroxide. There are many reports available comparing the effect of calcium hydroxide and MTA on pulp-capping procedures and pulpotomy dressing and most of them claim MTA is superior over calcium hydroxide. Although the overall results in human studies involving MTA is promising further extensive, long-term studies are needed to find out its adverse reactions if any.

PHYSICAL INJURIES OF THE TEETH

Bruxism

('Night-grinding', bruxomania)

Bruxism is the habitual grinding or clenching of the teeth, either during sleep or as an unconscious habit during waking hours. This term is generally applied both to the clenching habit, during which pressure is exerted on the teeth and periodontium by the actual grinding or clamping of the teeth, and also to the repeated tapping of the teeth. Bruxism is one of the most common sleep disorders. The incidence of bruxism has been variously reported as between 5 and 20%.

Etiology. In a review of the subject by Nadler and Meklas, the causes of bruxism have been described as: (1) local, (2) systemic, (3) psychologic, and (4) occupational.

Local factors are generally associated with some form of mild occlusal disturbance which produces mild discomfort, and chronic, even though unrecognized, tension. It has been suggested that in many cases bruxism becomes a firm habit as a result of an unconscious attempt by the patient to establish a greater number of teeth in contact or to counteract a local

irritating situation. In children the habit is frequently associated with the transition from the deciduous to the permanent dentition and may result from an unconscious attempt to place the individual tooth planes so that the musculature will be at rest.

Systemic factors have been proposed as etiologically significant, but the role of most of these is difficult to assess. Gastrointestinal disturbances, subclinical nutritional deficiencies, and allergy or endocrine disturbances have all been reported as causative factors. A hereditary background has been described in some cases.

Psychologic factors are believed by some investigators to be the most common cause of bruxism. High levels of anxiety, stress, and emotional tension may be expressed through a number of nervous habits, one of which may be bruxism. Thus, when a person suffers from fear, rage, rejection, or a variety of other emotions which he/she is unable to express, these become hidden in the subconscious but are expressed periodically by numerous means. It has been observed that bruxism is common in mental institutions. Bruxism is a manifestation of nervous tension in children also and may be related to chronic biting or chewing of toys. Polysomnographic studies suggested that sleep bruxism episodes are part of sleep arousal response. The sleep arousal response is nothing but sudden change in the depth of sleep. Besides the sleep bruxism appears to be a disturbance in the dopaminergic system.

Occupations of certain types favor the development of this habit. Athletes engaged in physical activities often develop bruxism, although the exact reason for this is uncertain. Occupations, in which the work must be unusually precise, such as that of the watchmaker, are prone to cause bruxism. **Voluntary bruxism** is also recognized in those persons who habitually chew gum, tobacco, or objects such as toothpicks or pencils. Although voluntary, this too is a nervous reaction and may lead eventually to involuntary or subconscious bruxism.

Clinical Features. The person who engages in bruxism performs the typical grinding or clenching motions during sleep or subconsciously when awake. These may be associated with a grinding or grating noise. The symptomatic effects of this habit have been reviewed by Glaros and Rao, who have divided them into six major categories: (1) effects on the dentition, (2) effects on the periodontium, (3) effects on the masticatory muscles, (4) effects on the temporomandibular joint, (5) head pain, and (6) psychologic and behavioral effects.

When the habit is firmly established, severe wearing or attrition of the teeth may occur, not only occlusal wear, but also interproximal wear which produces sensitivity. On both surfaces actual facets may be worn in the teeth. As the bruxism continues, there may be loss of integrity of the periodontal structures, resulting in loosening or drifting of teeth or even gingival recession with alveolar bone loss. Temporomandibular joint disturbances are also reported to occur as a result of the traumatic injury of continuous tooth impact without normal periods of rest. Hypertrophy of the masticatory muscles, particularly the masseter muscle, may interfere with maintenance of the rest position, cause trismus, and alter occlusion and the opening and closing pattern of the jaws.

Finally, while it has been suggested that bruxism may give rise to facial pain and headache as well as psychologic and behavioral effects, these are very difficult manifestations to evaluate and correlate.

Treatment and Prognosis. If the underlying cause of the bruxism is an emotional one, the nervous factor must be corrected if the disease is to be cured. Removable splints to be worn at night may be constructed to immobilize the jaws or to guide the movement so that periodontal damage is minimal. Recently Botulinum toxin (Botox) has been very successful in treating the grinding and clenching of bruxism. Botox when injected into the masseter muscle, weakens the muscle enough to stop the grinding and clenching, but not so much as to interfere with chewing or facial expressions. RC DiFrancesco and coworkers suggest that there is a positive correlation between sleep-disordered breathing and bruxism and stated that there was an important improvement of bruxism after adenotonsillectomy based on their study of 69 children. If the disease is left untreated, severe periodontal and/or temporomandibular disturbances may result.

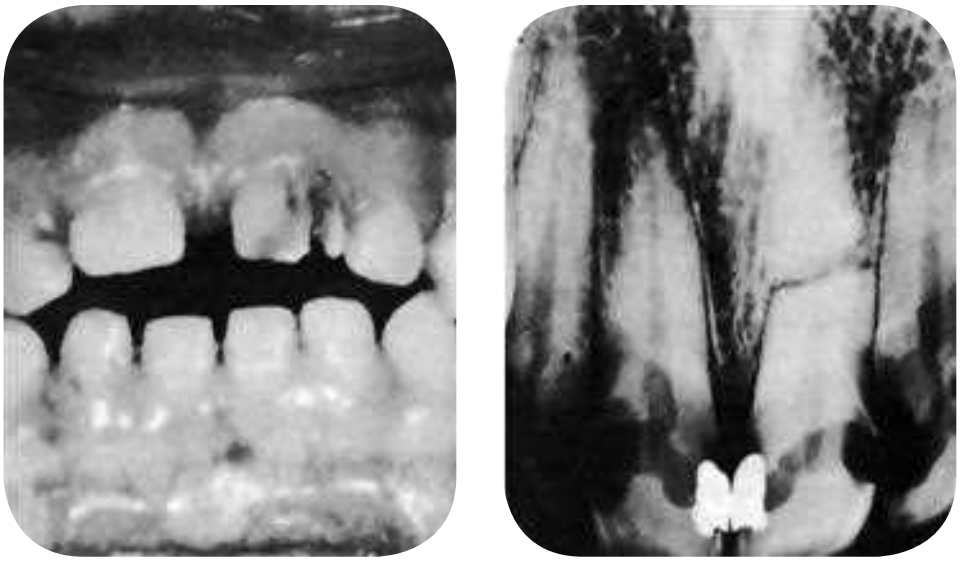
Fractures of Teeth

Tooth fracture is a common injury which may arise in a variety of situations, the most frequent of which is sudden severe trauma. This is usually a fall, a blow, an automobile accident or any of a large number of incidents in which children especially are frequently involved. Some cases of fracture occur when a tooth is weakened as by a large restoration, leaving thin walls or unsupported cusps which give way under the stress of mastication. A similar weakening and subsequent fracture occurs also in cases of internal resorption of teeth. Teeth which have had root canal therapy are often described as being somewhat brittle and susceptible to fracture.

Clinical Features. Although fracture of teeth may occur at any age, children are especially prone to sustain this type of injury. The prevalence of tooth fracture is difficult to assess or evaluate, particularly since minor chipping of teeth is common. As might be expected, boys are more frequently involved than girls. There is a definite predilection for involvement of maxillary teeth, with between 75 and 90% of fractures occurring there (Fig. 12-3).

There are several classifications of fractured teeth, the simplest being only whether or not the fracture line involves the pulp. A more detailed classification is that of Ellis, who divides all traumatized anterior teeth (for these constitute the vast majority of such injuries) into nine classes:

Class 1: Simple fracture of the crown, involving little or no dentin.
Class 2: Extensive fracture of the crown, involving considerable dentin but not the dental pulp.
Class 3: Extensive fracture of the crown, involving considerable dentin and exposing the dental pulp.
Class 4: The traumatized tooth becomes nonvital, with or without loss of crown structure.



A B

Figure 12-3. Fractured teeth after traumatic injury.
(A) Fracture of crown with pulp exposure. **(B)** Root fracture.

Class 5: Teeth lost as a result of trauma.
Class 6: Fracture of the root, with or without loss of crown structure.
Class 7: Displacement of a tooth, without fracture of crown or root.
Class 8: Fracture of the crown *en masse* and its replacement.
Class 9: Traumatic injuries to deciduous teeth.

The clinical manifestation as well as the treatment and prognosis of the fractured tooth depend chiefly upon whether the dental pulp is pierced by the fracture and whether the crown or the root of the tooth is involved. If there is crown fracture without pulp involvement, vitality of the tooth is usually maintained, although there may be mild pulp hyperemia even when the overlying dentin is relatively thick. If the dentin over the pulp is exceedingly thin, bacteria may penetrate the dentinal tubules, infect the pulp and produce pulpitis, leading to death of the pulp. When vitality is maintained, usually a layer of secondary dentin is deposited over the involved dentinal tubules. The tooth may be sore and slightly loose because of the traumatic injury, but severe pain is usually absent.

A fractured tooth crown which exposes the pulp is a more serious problem, but pulp exposure does not necessarily imply that death of the pulp will occur. In some cases the exposure can be capped by calcium hydroxide, and a dentinal bridge will form as a part of the healing reaction. Pulpotomy or pulpectomy may often be necessary; however, since the pulp becomes infected almost immediately after the injury.

Root fractures are somewhat uncommon in young children, since their tooth roots are not completely formed and the teeth have some resilience in their sockets. It occurs in patients between the ages of 10 and 20 years and most are traumatic in origin. Root fractures involve mostly the middle third of the root and are horizontal. When fracture does occur, the tooth is loose and sore and there may be displacement of the coronal portion of the tooth. Most of the time tooth becomes nonvital after fracture. Some teeth may be repaired by forming a layer of reparative dentin along the pulp wall and cementum on the outer surface, or form granulation tissue between the fractured segments. Few may remain vital with resorption of the sharp edges of the fractured fragments.

In certain situations where the injury is sufficient to cause root fracture, fragments of cementum may be severed from dentin and is called cemental tear.

Histologic Features. Healing in such cases may be of several types. The most satisfactory form of healing is the union of the two fragments by calcified tissue, and this is analogous to the healing of a bony fracture. The clot between the root fragments is organized, and this connective tissue is subsequently the site of new cementum or bone formation. There is nearly always some resorption of the ends of the fragments, but these resorption lacunae ultimately are repaired. If the apposition between the two fragments is not close, the union is by connective tissue alone. It appears likely that the repair process can be organized from connective tissue cells in both the pulp and the periodontal ligament.

Cracked Tooth Syndrome

Cracked tooth syndrome (CTS) is characterized by sharp pain on chewing without any obvious reason, which is actually caused by a 'hidden' crack of the tooth. These are incomplete fractures that are too small to be seen on radiographs. The typical symptom is sharp fleeting pain when releasing biting pressure on an object. This is because when biting down, the segments are usually moving apart and thereby reduce the

pressure in the nerves of the pulp. When the bite is released, the 'segments' snap back together sharply increasing the pressure causing pain. The pain is often inconsistent, and frequently hard to reproduce. Causes of CTS include attrition, bruxism, trauma, accidental bitting on a hard object, presence of large restoration, and improper endodontic treatment. The American Association of Endodontists have classified five specific variations of cracked teeth; craze line, fractured cusp, cracked tooth, split tooth, and vertical root fracture.

Treatment and Prognosis. The site, direction, and size of the crack or fracture dictates the choice of the treatment. It ranges from stabilization with a stainless steel band or crown to endodontic treatment and restoration. If untreated, CTS can lead to severe pain, possible pulpal necrosis and periapical abscess. Unfortunately, management of CTS is not always successful. In some cases, such as in vertical root fractures (split root) in single rooted teeth, the only treatment option is tooth extraction.

Abrasion

Wearing away of tooth substance due to mechanical means is known as abrasion. The most common cause is the faulty brushing techniques. Habits such as opening the hairpin constantly using anterior teeth, holding bobby pins, and holding pipe also produce a characteristic form of abrasion. This is described in Chapter 13 on Regressive Alterations of the Teeth.

Abuse of the teeth such as opening of beer or other bottles using teeth causes chipping away of enamel in incisors, canine and premolars.

Injuries to the Supporting Structures of the Tooth

Concussion is produced by injury which is not strong enough to cause serious, visible damage to the tooth and the periodontal structures. On clinical examination tooth may not be mobile or displaced from its original position. Crown appears normal and patient may not feel any difference in occlusion. Pulp gives normal response to vitality test. But the characteristic feature is the increased sensitivity of the tooth to percussion from any direction.

Treatment consists of selective grinding of the tooth to eliminate occlusal forces.

Subluxation refers to abnormal loosening of tooth without displacement due to sudden trauma. Tooth is mobile on palpation and sensitive to percussion and occlusal forces. Rupture of the periodontal tissue is usually evident by bleeding at the gingival marginal crevice. In time tooth becomes nonvital due to severance of apical blood supply.

Avulsion is dislocation of the tooth from its socket due to traumatic injury. It can be partial or total. Partial avulsion includes intrusion, extrusion, or facial, lingual or palatal, or lateral displacement.

Avulsion is usually accompanied by fracture of the alveolar bone. Partial avulsion is managed by reposition of the tooth and stabilization with splints. Completely avulsed tooth can be replanted in its socket. The prognosis of the replantation will be good if the extraoral time is minimal and the avulsed tooth is kept in a suitable medium during transportation. Nevertheless many of the replanted teeth undergo ankylosis to the alveolar bone.

Tooth Ankylosis

Fusion between the tooth and bone, termed ankylosis is an uncommon phenomenon in the deciduous dentition and even more rare in permanent teeth. The condition of deciduous tooth ankylosis (submerged tooth) has been described in Chapter 1 on Developmental Disturbances of Oral and Paraoral Structures.

Ankylosis ensues when partial root resorption is followed by repair with either cementum or bone that unites the tooth root with the alveolar bone. It must not be inferred that root resorption invariably leads to ankylosis. Actually, it is an uncommon sequela, and the cause for this sporadic happening is unknown. Ankylosis does occur rather frequently after a traumatic injury to a tooth, particularly occlusal trauma, but it is also seen as a result of periapical inflammation subsequent to pulp infection. Periapical inflammation is a well-recognized cause of root resorption. Ankylosis sometimes also follows root canal therapy if the apical periodontal ligament is irritated or seriously damaged. Resorption and ankylosis is more common in replanted teeth.

Clinical Features. Ankylosis of the permanent tooth seldom manifests clinical symptoms unless there is a concomitant pulp infection which may be the underlying cause. If there is an extensive area of the root surface involved, the tooth may give a dull, muffled sound on percussion rather than the normal sharp sound. The fact that this condition exists may become apparent only at the time of extraction of the tooth, when considerable difficulty will be encountered, sometimes necessitating surgical removal.

Radiographic Features. If the area of ankylosis is of sufficient size, it may be visible on the radiograph. There is loss of the normal thin radiolucent line surrounding the root that represents the periodontal ligament, with a mild sclerosis of the bone and apparent blending of the bone with the tooth root.

Histologic Features. Microscopic examination reveals an area of root resorption which has been repaired by a calcified material, bone or cementum, which is continuous with the alveolar bone. The periodontal ligament is completely obliterated in the area of the ankylosis (Fig. 12-4).

Treatment and Prognosis. There is no treatment for ankylosis. Ankylosed teeth have a good prognosis and, unless removed for some other reason, should serve well indefinitely.

Figure 12-4. Tooth ankylosis.
Resorption of a portion of root with repair unites the root and alveolar bone.

PHYSICAL INJURIES OF THE BONE

The most common physical injury involving the bone is fracture.

Fractures of Jaws

Fractures of the craniofacial complex occur commonly due to automobile, industrial, and sports accidents, and fights. Fracture can occur more easily in bones, which are already weakened by certain developmental and systemic disorders. Fracture may be simple, greenstick, compound, or comminuted. In simple fracture, the bone is broken completely; the overlying structures are intact and are not exposed to exterior. Greenstick fracture common in children is characterized by break of bone in one side and bend on the other side. In compound fractures external wound is associated with the break and is common in road traffic accidents. Bone is crushed or splintered in comminuted fractures and may or may not be exposed to the exterior.

Mandible is more prone for fractures, since chin is a prominent feature of the face. Fractures of the jaw are more common in males.

Fractures of the Maxilla

Maxillary fractures are more serious, than the mandibular fractures. Causes include road traffic accidents, blow, fall, and industrial accidents. Direction, force, and the location of the impact determine the extent of fracture.

Classification

Le Fort I or horizontal fracture, also known as floating fracture is characterized by separation of body of the maxilla from the base of the skull, below the level of zygomatic process.

Le Fort II or pyramidal fracture is characterized by vertical fractures through the facial aspects of the maxilla and extend upward to the nasal and ethmoid bones and usually extends through the maxillary sinus.

Le Fort III or transverse fracture is a high level fracture that extends across the orbits through the base of the nose and ethmoid region to the zygomatic arch. Bony orbit is fractured and the lateral rim is separated at the zygomaticofrontal suture. Zygomatic arch is fractured.

Displacement, anterior open bite, swollen face, reddish eye due to subconjunctival hemorrhage, and nasal hemorrhage are the common features. If the skull is involved, history of unconsciousness, cerebrospinal fluid rhinorrhea, cranial nerve involvement are characteristic.

Fractures of the Mandible

Most common causes of mandibular fractures are road traffic accidents and physical violence. Fractures of the mandible most commonly involve angle of the mandible, which is followed by condyle, molar region, mental region, and symphysis. Displacement of the mandible depends on the direction of the line of fracture, muscle pull, and the direction of force.

Clinical Features. Pain during movement, occlusal derangement, abnormal mobility, gingival lacerations, crepitus on movement, trismus, loss of sensation of the involved side, and ecchymosis are common features of mandibular fracture.

Treatment. Like other fracture management jaw fractures are also treated by reduction and immobilization. Complications include nonunion, malunion, and fibrous union.

Traumatic Cyst

(Solitary bone cyst, hemorrhagic cyst, extravasation cyst, unicameral bone cyst, simple bone cyst, idiopathic bone cavity)

The traumatic cyst is a pseudo cyst (lacks an epithelial lining) and an uncommon lesion comprises about 1% of all jaw cysts. It occurs in other bones of the skeleton as well.

Etiology. The etiology of the solitary bone cyst is unknown, although a number of theories have been proposed and at least one, the trauma—hemorrhage theory has been rather widely accepted. Howe and also Sieverink have carried out extensive reviews of the literature and pointed out the wide acceptance of the theory of origin from intramedullary hemorrhage following traumatic injury. Hemorrhage occurring within the medullary spaces of bone after trauma heals in most cases by organization of the clot and eventual formation of connective tissue and new bone. According to the traumatic theory, the clot breaks down and leaves an empty cavity within the bone. Steady expansion of the lesion occurs secondary to altered or obstructed lymphatic or venous drainage. This expansion tends to cease when the cyst-like lesion reaches the cortical layer of bone, so that expansion of the involved bone is not a common finding in the solitary bone cyst.

It is not at all unusual; however, for the patient to be unable to recall any traumatic injury to the jaw. This may indicate that an injury so mild that the patient would not be aware of

it or remember it, is sufficient to cause this lesion to develop. In the series reported by Howe, only slightly over 50% of the patients gave a history of trauma, the time lag between injury and discovery of the lesion varying from one month to 20 years.

Other theories of origin, reviewed by Whinery, have included:

- Cystic degeneration of primary bone tumors.
- A result of faulty calcium metabolism such as that induced by parathyroid disease.
- Ischemic necrosis of fatty marrow.
- The end result of a low-grade chronic infection.
- A result of osteoclasis resulting from a disturbed circulation caused by trauma creating an unequal balance of osteoclasis and repair of bone.

Clinical Features. The traumatic cyst occurs most frequently in young persons, the median age being 18 years in a series of 45 cases reviewed and reported by Gardner and Stoller. According to Howe, over 75% of cases occur in the second decade of life. There is no definite sex predilection although many series have shown the males being affected more commonly than females. Although it has been stated that the posterior portion of the mandible is more commonly involved than the anterior, numerous cases have been reported in the incisor region, since in the young person this area contains hemopoietic marrow. The maxilla has been known to develop the solitary bone cyst, but only on extremely rare occasions. In some cases enlargement of the mandible has been observed, but often the lesion is discovered during routine radiographic examination of the patient. In the majority of cases the pulps of the teeth in the involved area are vital, and this is important to ascertain, because the vital teeth should not be sacrificed. The presenting complaint may be swelling or rarely pain.

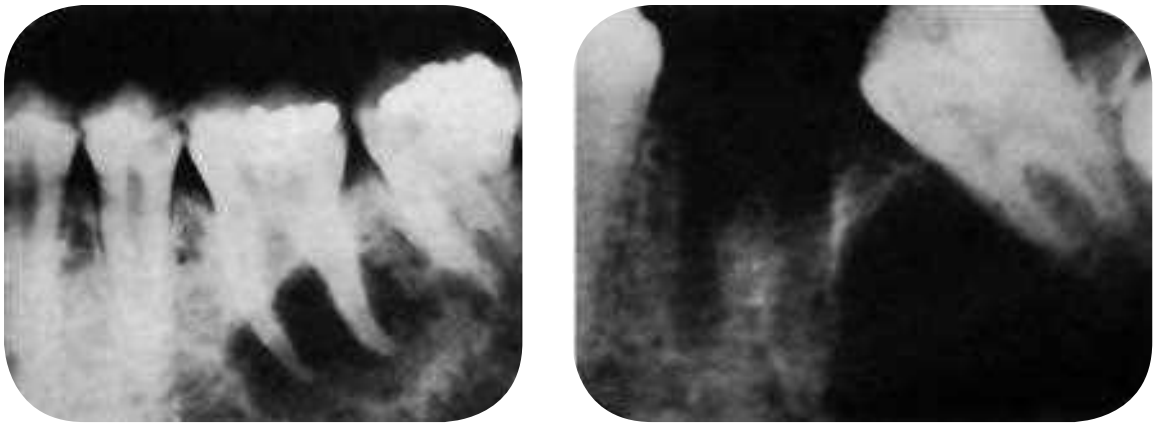
When the cavity is opened surgically, it is found to contain either a small amount of sero-sanguinous fluid, shreds of necrotic blood clot, fragments of fibrous connective tissue, or nothing. The dentist is frequently astonished to open into an empty space in bone and find that it has no clinically demonstrable membrane. It was reported by Toller in one case that the hydrostatic intracystic pressure was exceptionally low and comparable with capillary pressure, quite unlike that in other cysts of the jaw.

Radiographic Features. Radiographic examination usually reveals a rather smoothly outlined radiolucent area of variable size, sometimes with a thin sclerotic border, depending upon the duration of the lesion. Some traumatic cysts may measure only a centimeter in diameter (Fig. 12-5), whereas others may be so large that they involve most of the molar area of the body of the mandible as well as part of the ramus. When the radiolucency appears to involve the roots of the teeth, the cavity may have a lobulated or scalloped appearance extending between the roots of these teeth (Fig. 12-6). Seldom is there any displacement of teeth and, in many cases, the lamina dura appears intact. Rodrigues and Estrela reported a case of traumatic bone cyst in upper premolar-molar region, mimicking a large periapical lesion.

Care must be taken to differentiate the small solitary traumatic cyst occurring in the molar area and appearing as a round or ovoid radiolucent area associated with vital teeth from the lingual salivary gland depression of the mandible (q.v.) which has a similar radiographic appearance. However, the latter lesion is usually located below the mandibular canal, whereas the traumatic cyst usually lies above it.

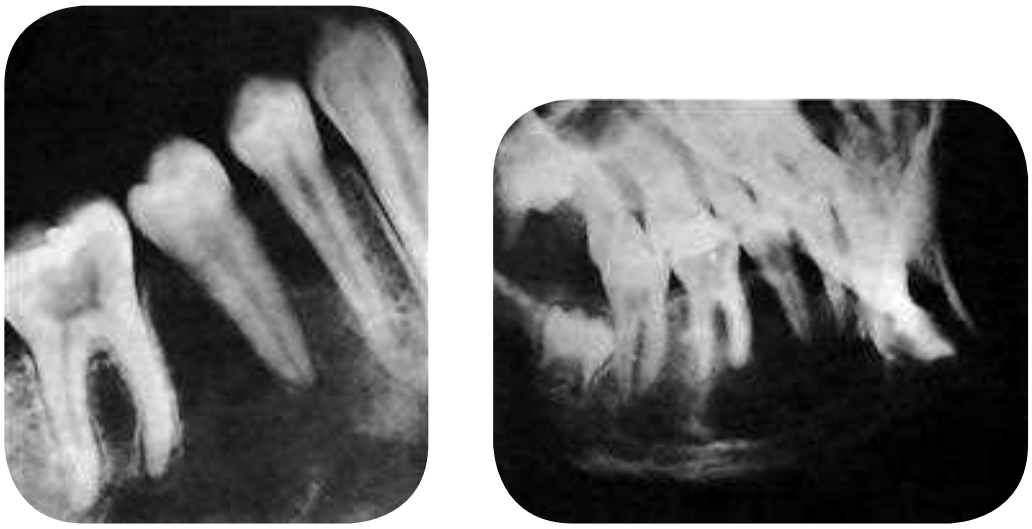
Histologic Features. Histologic examination of the solitary bone cyst may reveal a thin connective tissue membrane lining the cavity, but no other significant features. Sometimes no such membrane is demonstrable. Waldron had the opportunity to study a solitary bone cyst *in toto* in a resected mandible. His case exhibited a thin connective tissue membrane and, in addition, an extensive osteophytic reaction on the outer surface of the cortical plate (Fig. 12-7). There may be presence of few red blood cells, blood pigments, or giant cells adhering to the bone surface.

Treatment and Prognosis. Since the definitive diagnosis of the solitary bone cyst cannot be established without surgical



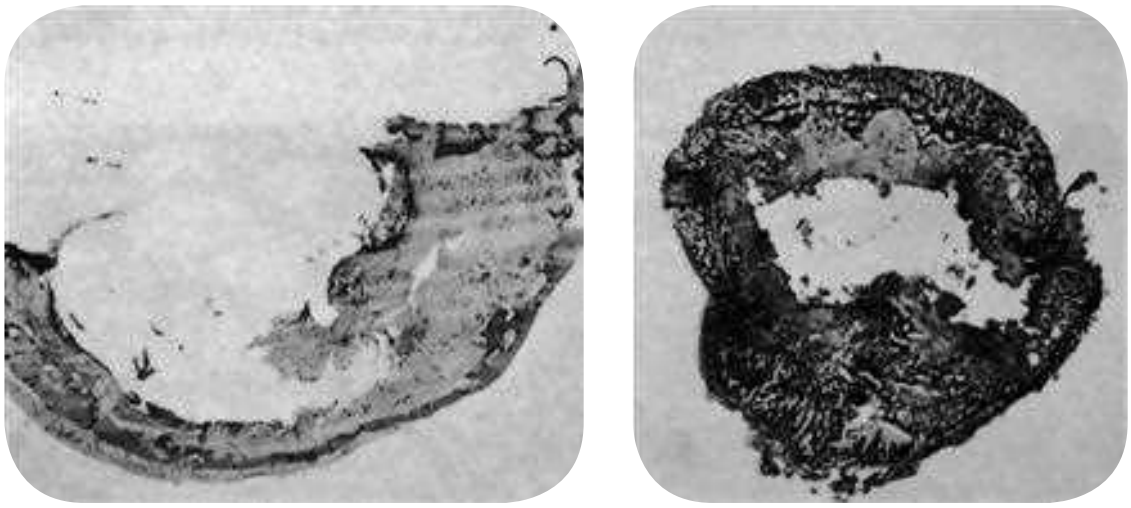
A B

Figure 12-5. Traumatic bone cyst.
The radiolucent area in both cases was entirely empty and devoid of any lining. The molar teeth were vital.



A B

Figure 12-6. Traumatic bone cyst.
This large empty space in bone extended between the roots of the teeth. Periapical film **(A)** and lateral jaw film **(B)**.



A B

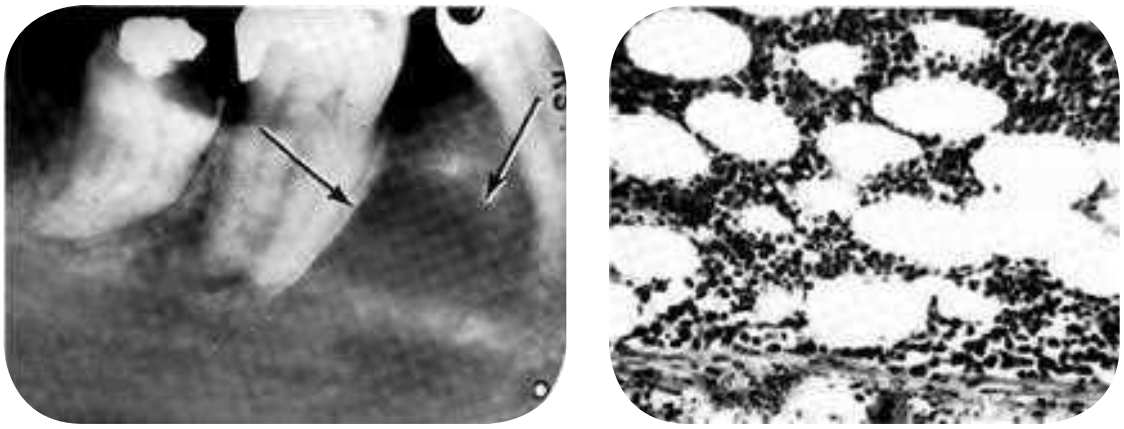
Figure 12-7. Traumatic bone cyst.
Traumatic cyst of mandible **(A)** and fibula **(B)**. Only a thin shell of the cortical plates of the jaw remains with limited peripheral osteophyte reaction. The fibula shows a similar empty central cavity and thinning of the cortex, although osteophyte reaction is pronounced *(A, Courtesy of Dr Charles A Waldron and B, of Dr William C Sprague).*

exploration, the dentist usually opens into the cavity, attempts to enucleate a lining and, in the course of manipulation, re-establishes bleeding into the lesion. If the cavity is then closed, it has been found that healing and filling of the space by bone occur in most cases in 6–12 months. Seldom is a second surgical procedure necessary. If the space is a large one, bone chips have been used to aid in filling the defect with good results.

The extreme rarity of these lesions in older patients would suggest that not only may they be self-limiting, but at least some are capable of complete and spontaneous remission.

Focal Osteoporotic Bone-marrow Defect of the Jaw

The focal osteoporotic bone-marrow defect of the jaw is an uncommon lesion producing a focal radiolucency away from normal hematopoietic marrow. Hematopoietic marrow occurs normally in the jaws at the angle of the mandible, the maxillary tuberosity and occasionally other areas. It is well recognized that bone marrow may be stimulated in response to unusual demands for increased blood cell production and that this hyperplastic marrow may extend between adjacent trabeculae of bone, producing radiographically obvious osteoporosis and even thinning of the cortex. Other views regarding its pathogenesis include abnormal healing following tooth



A B

Figure 12-8 Focal osteoporotic bone-marrow defect of the jaw.
The obvious radiolucency in **(A)** was filled with normal hematopoietic bone marrow **(B)**.

extraction since these lesions are most common in extracted sites, and persistence of remnants of fetal marrow.

Clinical Features. In the three reported series of cases, approximately 75% of the focal osteoporotic bone-marrow defects of the jaws occurred in women, and they involved the mandible in approximately 85% of the cases. In nearly every instance the lesions were asymptomatic and discovered only during routine radiographic examination.

Radiographic Features. This lesion, which has a predilection for the mandibular molar area, generally appears as a radiolucency of variable size, a few millimeters to a centimeter or more, with a poorly defined periphery indicative of lack of reactivity of adjacent hone (Fig. 12-8A).

Histologic Features. The tissue removed from these defects consists of either normal red marrow, fatty marrow or a combination of the two (Fig. 12-8B). Megakaryocytes and small lymphoid aggregates may be present. The trabeculae of bone usually present in the sections are long, thin, irregular, and devoid of an osteoblastic layer.

Treatment. The radiographic appearance of these lesions is not sufficiently characteristic to permit diagnosis with certainty, and for this reason they must be investigated surgically to rule out osteomyelitis, traumatic bone cyst, and other odontogenic tumors. Once the diagnosis has been established, no additional treatment is necessary.

Surgical Ciliated Cyst of Maxilla
(Sinus mucocele)

The surgical ciliated cyst of the maxilla was originally reported by Gregory and Shafer. This cyst develops either after surgical entry into the maxillary sinus, usually a Caldwell-Luc operation or due to the obstruction of ostium. Basically, it is an implantation type of cyst in which epithelium of the maxillary sinus becomes entrapped along the line of surgical entry into the sinus and subsequently proliferates to form a true cystic cavity, anatomically separated from the sinus.

Clinical Features. The majority of patients with this type of lesion are middle-aged or older and present with a complaint of a nonspecific, poorly localized pain, tenderness, or discomfort in the maxilla. Extraoral or intraoral swelling is also frequently evident. Careful questioning of the patient usually reveals a history of some type of surgical procedure involving the maxilla and maxillary sinus, frequently 10–20 years previously. When content of the mucocele is infected, the lesion is called mucopyocele. Interestingly, it has been emphasized by Ohba and his associates among others that this lesion is more common in Japan than in America or Europe, possibly because of the higher incidence of maxillary sinusitis in Japan. Yamamoto and Takagi in their study involving 60 cases reported that postoperative maxillary cyst accounted for 19.5% of all oral cystic lesions.

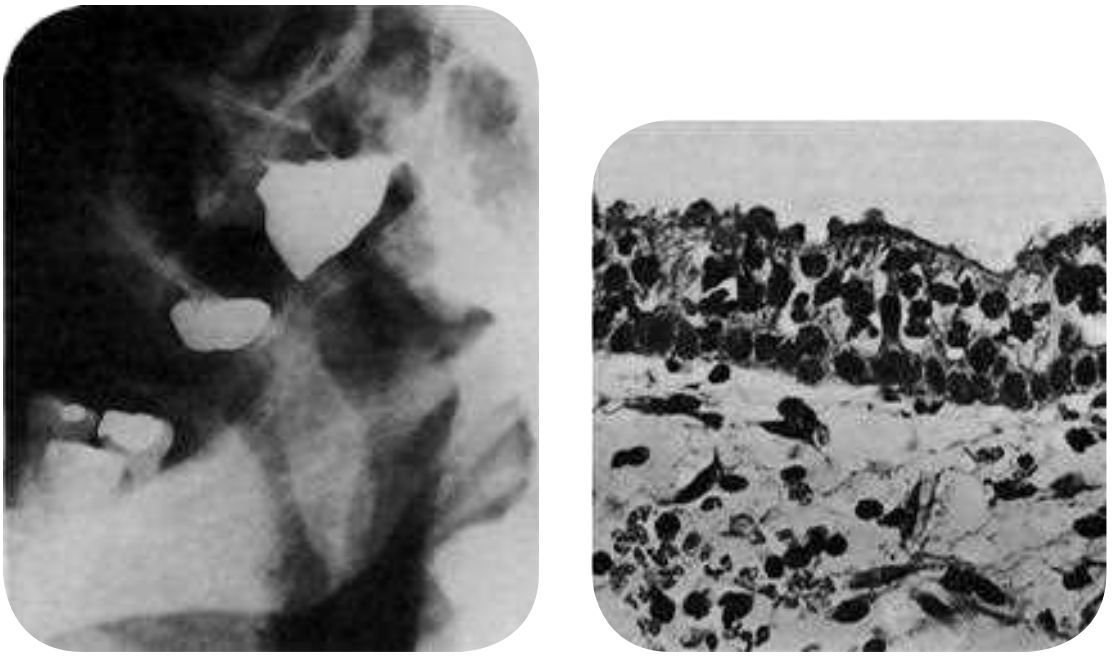
Radiographic Features Radiographic examination shows a well-defined unilocular radiolucent area closely related to the maxillary sinus, often appearing to encroach upon the sinus but anatomically separate from it, as may be demonstrated by injection of the sinus with a radiopaque material. A filling defect of the cyst can then be seen (Fig. 12-9A).

Histologic Features. The surgical cyst is lined by pseudostratified ciliated columnar epithelium identical with that of the maxillary sinus (Fig. 12-9B). If infection or inflammation is present, squamous metaplasia may be found. The wall of the cyst is composed of fibrous connective tissue with or without inflammatory cell infiltration.

Treatment. The treatment of this lesion consists in enucleation of the cyst. It does not tend to recur.

Effects of Orthodontic Tooth Movement

The science of orthodontics is based upon the ability of teeth to be moved through bone, without their subsequent extrusion or loss, by the application of pressure or tension



A B

Figure 12-9. Surgical ciliated cyst of the maxilla.
The two anatomically separated cavities, the maxillary sinus and surgical cyst, were injected with radiopaque material **(A)**. The cyst lining was respiratory in type **(B)**.

under appropriate and controlled circumstances. Although the exact biologic mechanism responsible for this phenomenon is unknown, it is generally agreed that bone under pressure responds by resorbing, whereas the application of tension results in deposition of new bone. The periodontal ligament transfers the pressure or tension applied through orthodontic appliances.

Sandstedt applied force to the maxillary incisors of a dog, moving them lingually by means of a labial arch wire, and described the histologic findings of bone resorption, with numerous associated osteoclasts, on the pressure side of the teeth and formation of new bone on the tension side. He noted no tooth resorption, although necrosis or at least hyalinization of the periodontal ligament was found in the areas of pressure.

Tipping Movement. The exact movements which a tooth will undergo and the exact position it will assume after the application of orthodontic force will depend upon the degree and direction of the force and the position of the fulcrum around which the force acts. The general statement can be made, however, that pressure upon a tooth results in the resorption of bone in the direction of the application of force and compensatory new bone formation on the opposite side of the tooth, the tension side (Fig. 12-10).

The initial reaction on the pressure side is a compression of the periodontal ligament which, if excessive and prolonged, may result in ischemia with hyalinization and/or actual necrosis of tissue (Fig. 12-11B). On the opposite side under excessive force there may be actual tearing of the periodontal fibers and small capillaries with hemorrhage into the area. With reasonable forces, the periodontal ligament on the tension side of the tooth demonstrates stretching and widening of the periodontal space. Within a matter of hours or at the most a few days, large numbers of osteoclasts make their appearance along the surface of the bone under pressure, and resorption begins. This continues until the force of the pressure has been entirely dissipated.

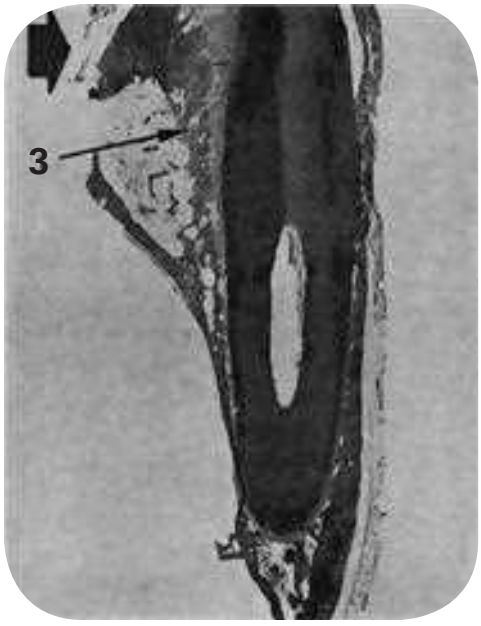


Figure 12-10. Tipping tooth movement.
Force was applied to this dog's tooth in the direction of the arrow, and even at this magnification, widening of the periodontal ligament space (1) is noted.

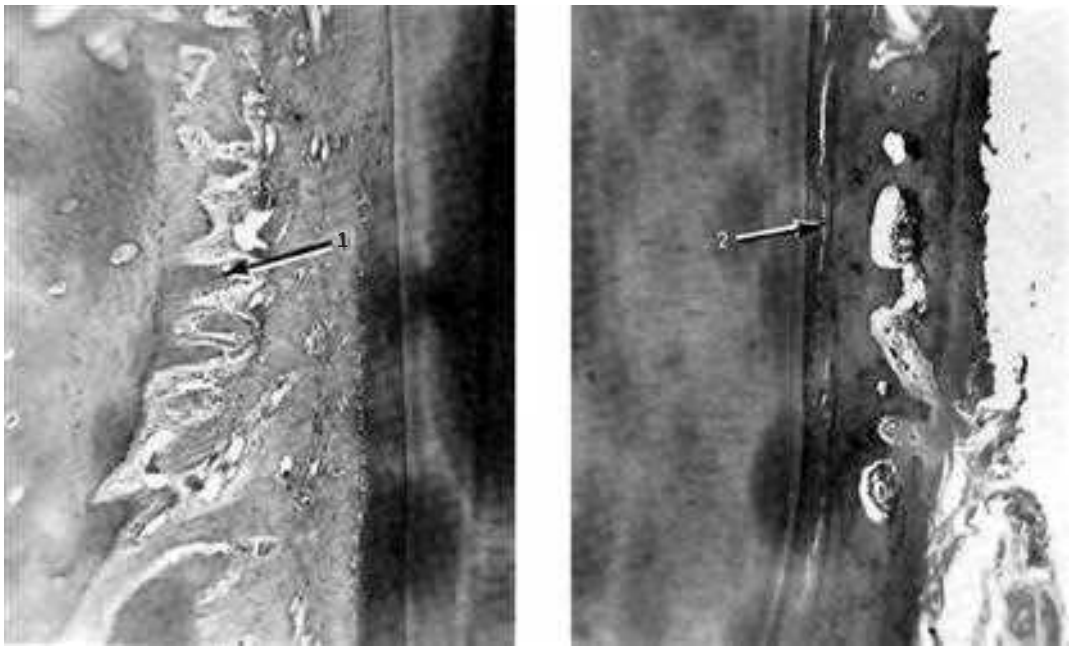


Figure 12-11. Tipping tooth movement.
There is widening of the periodontal ligament with formation of new spicules of bone (1) on the tension side of the tooth **(A)** and compression of the periodontal ligament (2) on the pressure side **(B)**.

New trabeculae of bone on the tension side become evident early and appear as thin, elongated spicules arranged parallel to the periodontal fibers and confluent with them at their bony attachment (Fig. 12-11A). These spicules show evident osteoblastic activity along the sides and the end adjacent to the tooth, but usually there is intense osteoclastic activity at the ends of the spicules away from the tooth. As stabilization occurs, the alveolar bone gradually assumes its compact pattern that existed before movement occurred.

A secondary but most important occurrence is the deposition of new spicules of bone on the outer surface of the labial plate in instances of pressure in the labial direction. This serves to maintain the thickness of the already thin labial plate and prevent its perforation by the tooth. It is not entirely certain why resorption of even compact bone occurs before resorption of cementum and the tooth root. It is known that resorption of calcified tissues is favored by increased local vascularity, and the hypothesis has been advanced in explanation that the bone of the alveolus is in a more vascular environment than the cementum when orthodontic pressure is applied, particularly since ischemia of the periodontal ligament adjacent to the cementum is the usual situation.

It is generally recognized that the teeth of young persons respond much more rapidly and with less applied force to orthodontic movements than do the teeth of older adults. Although differences do exist in the chemical constitution of bone at varying ages, the difference in orthodontic response is probably due to variation in general tissue reactivity and local vascularity. Although bone retains the ability to undergo resorption throughout life, the degree of the stimulus needed to evoke this response shows dramatic differences between the various age groups.

Extrusive Movement. Extrusion of a tooth by an orthodontic appliance is similar to normal tooth eruption. The tissue changes induced by this form of movement consist apposition of new bone spicules at the alveolar crest and at the fundus of the alveolus arranged in a direction parallel to the direction of force. The direction of the spicules then is parallel to the long axis of the tooth and tends to increase the height of the alveolar crest. The normal width of the apical periodontal ligament is maintained by the new bony spicules here formed in the same direction. The relation between the tooth and the alveolus tends to remain constant.

Intrusive or Depressive Movement. The application of orthodontic force in such a manner as to cause depression of a tooth results in tissue changes that are the opposite of those found during extrusion, or elongation. In tooth depression, resorption of bone occurs at the apical area and around the alveolar margin. New bone formation is actually minimal.

Tissue Reactions during Retention Period. Discontinuance of the active phase of orthodontic force signals the beginning of alterations in the bone characteristic of the retention period. During this period there is gradual reformation of the normal dense pattern of the alveolar bone by apposition of bone around the bony spicules until they meet, fuse, and gradually remodel. The studies of Oppenbeim indicated that this reformation is slower around teeth held in position dur-

ing the retention period by a retaining appliance as compared to teeth which remained free during this time. In any event, the final remodeling and the attainment of absolute bone-tooth equilibrium following orthodontic movements involve an extremely slow process, and a breakdown in this process is probably one of the most important contributing factors in cases of orthodontic failure due to relapse during the retention period.

Effect of Deciduous Tooth Movement upon Permanent Tooth Germs. Breitner and Tischler based on their study in young monkeys found that when a deciduous tooth was moved, the associated permanent tooth germ followed this movement.

Whenever a deciduous tooth was moved away from a tooth germ, the permanent tooth germ quickly followed. If a deciduous tooth was moved toward a permanent tooth germ, this germ moved in the same direction as the deciduous tooth.

These studies offered suggestive evidence that the form of the permanent dental arch may be modified by altering the deciduous arch through orthodontic treatment of the deciduous dentition.

PHYSICAL INJURIES OF SOFT TISSUES

Linea Alba

Linea Alba is a white line seen on the buccal mucosa extending from the commissures posteriorly at the level of the occlusal plane (Fig. 12-12). It is caused by the physical irritation and pressure exerted by the posterior teeth. It is usually bilateral and is more pronounced in persons who have clenching habit or bruxism. Histologically hyperkeratosis and intracellular edema of the epithelium is seen.

Toothbrush Trauma

This injury occurs to the gingiva and is produced by the toothbrush. It appears as white, reddish, or ulcerative lesions or linear superficial erosions, involving marginal and attached gingiva of maxillary canine and premolar region. They may be mistaken for vesiculobullous or infectious lesions if the history is not elicited properly. Severe form of toothbrush injury is characterized by clefting of the gingival margin and gingival recession. In more severe form there will be notching of the tooth and loss of alveolar bone. Presenting complaints are pain and burning sensation.

Figure 12-12. Linea alba.
(Courtesy Dr G Sriram, Department of Oral Pathology, Meenakshi Ammal Dental College, Chennai).

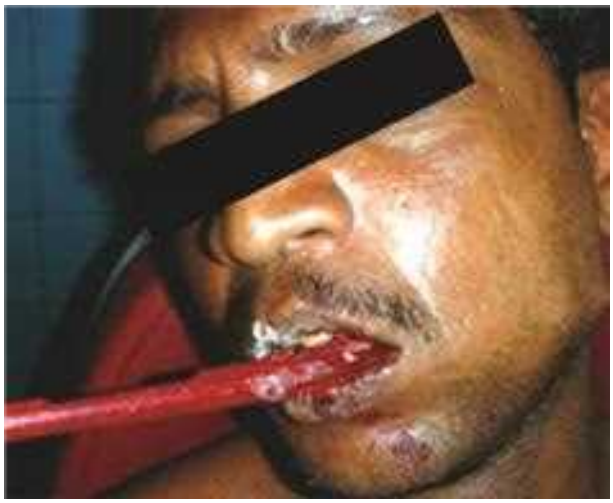


Figure 12-13. Penetrated injury caused by tooth brush.
(Courtesy to Dr B Saravanan, Tamilnadu Government Dental College, Chennai and Dr Devaki Saravanan, Meenakshi Ammal Dental College, Chennai).

The above mentioned injury is caused by faulty brushing technique or rabid practice of cleanliness. But B Saravanan reported a case of penetrated injury of the buccal mucosa caused by toothbrush in middle-aged man due to a freak accident and reviewed literature with respect to such similar injuries (Fig. 12-13).

Tooth pick injury is another form of factitial injury occurs as a result of overzealous oral hygiene practice. In contrast to toothbrush injury this involves the interdental gingiva.

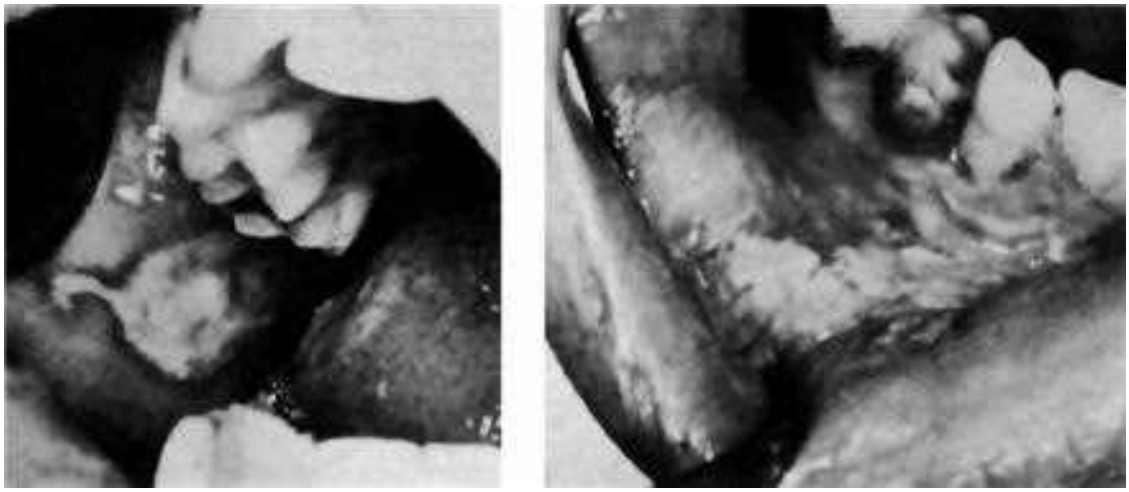
Histologic Features. Microscopically there is focal ulceration with formation of granulation tissue with diffuse chronic inflammatory cell infiltration. Epithelium shows hyerkeratosis and acanthosis adjacent to the ulcers.

Treatment consists of medications to relieve the symptoms and teaching proper brushing technique.

Traumatic Ulcer
(Decubitus ulcer)

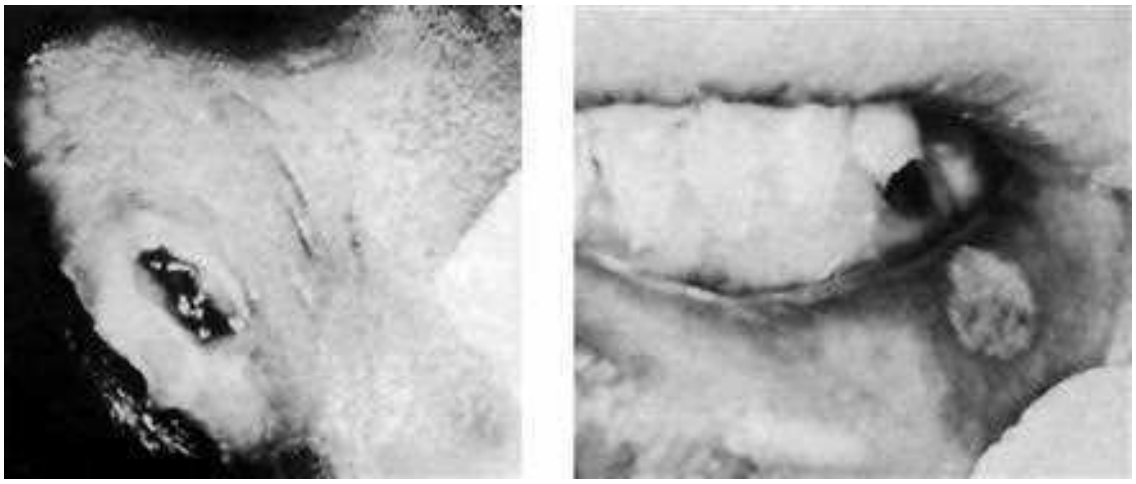
The traumatic ulcer of the oral mucous membranes is a lesion that is caused by some form of trauma. This may be an injury such as biting the mucosa, denture irritation, toothbrush injury, exposure of the mucous membrane to a sharp tooth or carious lesion, or it may be injury to the mucosa by some other external irritant.

The 'cotton roll injury', an iatrogenic injury, is a common reaction when the dry cotton roll placed by the dentist is roughly removed and the mucosa adhering to it is torn



A B

Figure 12-14. Iatrogenic injuries.
The lesion on the buccal mucosa **(A)** is a burn produced by a hand-piece used injudiciously by a dentist. The lesion in the mucobuccal fold **(B)** represents macerated mucosa torn by a cotton roll which had dried and adhered to the surface and was removed carelessly by a dentist *(A, Courtesy of Dr Stephen F Dachi).*



A B

Figure 12-15. Traumatic ulcer.
The ulcer of the tongue **(A)** occurred during an epileptic seizure as a result of the patient's biting himself. The ulcer of the lip **(B)** resulted from injury of the lip by rubbing against the large gingival carious lesion on the cuspid. The ulcer healed promptly after restoration of the carious lesion. *(A, Courtesy of Dr Stephen F Dachi).*

(Fig. 12-14). The traumatic ulcer often occurs in such sites as the lateral border of the tongue, usually after injury in which the patient severely bites the tongue (Figs. 12-15, 12-16). These ulcers are also seen, however, on the buccal mucosa, on the lips, and occasionally on the palate. Although in most instances of injury to the oral mucous membrane, healing is rapid and uneventful, occasional injuries persist for a long time without healing. This is particularly true in case of the traumatic ulcer of the tongue, which may bear considerable clinical resemblance to carcinoma and which sometimes is repeatedly biopsied in an attempt to establish a diagnosis of neoplasm. It is interesting; however, that many times the traumatic ulcer which has persisted for a matter of weeks or even months without healing will heal promptly after a minor surgical procedure such as an incisional biopsy.

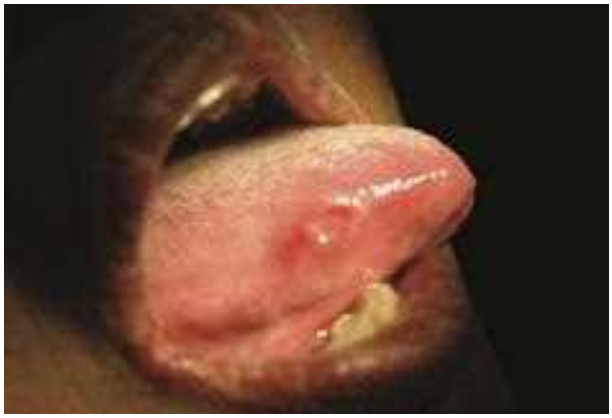


Figure 12-16. Traumatic ulcer of the tongue.

Traumatic Ulcerative Granuloma with Stromal Eosinophilia

(Eosinophilic ulceration, traumatic granuloma)

The term traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) was suggested by Elzay in 1993 to delineate the eosinophilic ulcerations from more aggressive lesions, such as the eosinophilic granuloma of histiocytosis X. TUGSE is a reactive, benign, asymptomatic, self-limiting lesion of the oral mucosa. Cinically it may mimic squamous cell carcinoma at times. Its etiology remains obscure and may be associated with trauma. Although trauma might have an etiologic role, the pathogenesis of eosinophilic ulcer of the oral mucosa is probably T cell mediated as suggested by el-Mofty et al, who reported 38 cases of TUGSE. Trauma may be due to malposed teeth, or a partial denture. In infants the erupting teeth sometimes causes sublingual ulcerations and is referred to as Riga-Fede disease.

Riga-Fede disease occurs in infants between one week and one year of life. Lesions are usually observed on the anteroventral surface of the tongue, caused by contact with the erupting mandibular incisors. These associated teeth are usually natal or neonatal teeth.

Atypical eosinophilic ulcerations (atypical histiocytic granuloma) a rare lesion and exhibits sequential ulceration, necrosis, and self-regression. They are not associated with trauma and are believed to represent the oral counterpart of a T-cell cutaneous lymphoproliferative disorder.

Clinical Features. Eosinophilic ulcerations may occur at any age with a significant male predilection. Though common in anteroventral and dorsal surfaces of the tongue, these lesions may also be observed in other sites such as gingiva, palate, and mucobuccal fold. The ulcerations usually persist weeks to months and resemble traumatic ulcers. The center of the lesion is covered by a removable yellow fibropurulent membrane with erythematous borders.

Histologic Features. Eosinophilic ulcerations are similar to simple traumatic ulcerations in histologic pattern and are characterized by a dense and deeply infiltrative lymphoproliferation, showing epitheliotropism and massive eosinophilia. Presence of sheets of lymphocytes and histiocytes along with hyperplasia of the vascular connective tissue causes elevation of the surface ulceration.

Ulceration resulting from trauma permits the ingress of microorganisms, toxins, and foreign proteins into the connective tissue. These substances, in predisposed persons induce a severe inflammatory response resulting from an exaggerated mast cell-eosinophil reaction similar to that noticed in the pathogenesis of bronchial asthma. Degranulation of the mast cells leads to release of eosinophil chemotactic factor of anaphylaxis.

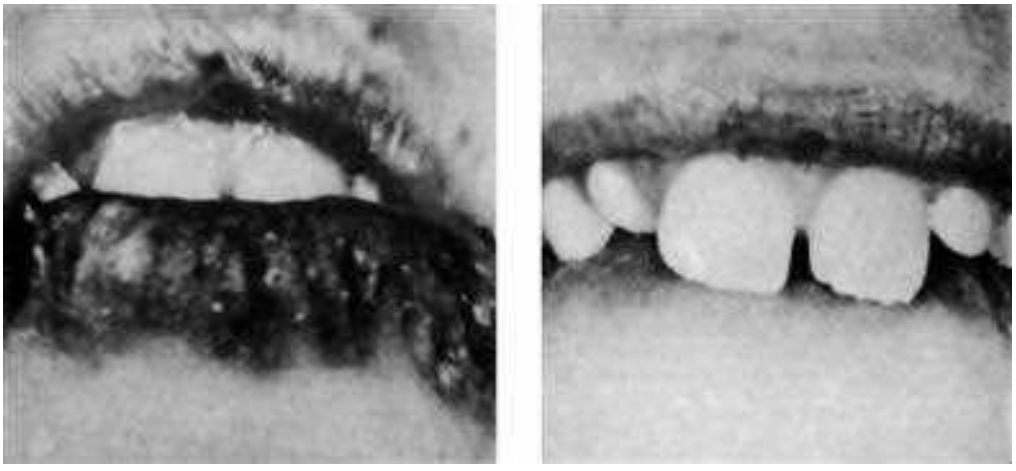
Treatment and Prognosis. Treatment of eosinophilic ulcerations is similar to simple traumatic ulcerations. Even large eosinophilic ulcerations heal rapidly after a biopsy. Though extraction of the involved teeth solves the problem in Riga-Fede disease, the teeth should be retained if they are stable.

Factitial Injuries

Factitial injuries are self-induced injuries. These may be habitual, accidental, or may have psychogenic background. As such, these overlap with a number of physical and chemical injuries to be discussed in this section.

Lip-biting and Cheek-biting

Also referred as **morsicatio labiorum and morsicatio buccarum** these injuries are habitual or psychogenic. It involves holding, biting, and tearing of the epithelium of the lip, buccal mucosa, or tongue, chewing of the cheek or stripping of the epithelium using fingers or creating negative pressure by sucking the lips and cheeks (Fig. 12-17). Most commonly seen in patients who are under psychologic stress.



A B

Figure 12-17. Factitial injury
Severe maceration of the lip had occurred as a result of a biting habit *(Courtesy of Dr Ralph E McDonald).*

Intra and perioral piercing

Body piercing is the act of puncturing or cutting a part of the human body, creating an opening in which jewelry may be worn. This may be the reflection of cultural, religious, and spiritual practice. Ear and nose piercing is followed for centuries in many Asian countries. Modern body piercing is associated with fashion and sexual expression. Eyebrow, ear, ala of the nose, lip, tongue, nipple, navel, and genitals are the areas of piercing and are decorated with an ornament for fashion (Fig. 12-18A–C). Whereas tongue and cheek may be pierced for religious purpose, complications associated with piercing include bleeding, hematoma formation, infection, intolerance to the metal jewelry, aspiration of the jewelry, embedded jewelry, and hypertrophic scar and keloid formation.

Apart from edema, hemorrhage and infection the complications of orofacial piercing include mucosal or gingival trauma, chipped or fractured teeth, increased salivary flow, calculus build-up, gingival recession, localized periodontal destruction, and interference with speech, mastication and swallowing. Perkins and coworkers have reported a case of Ludwig's angina, secondary to tongue piercing. Kapferer et al, in their study involving 50 subjects with lower lip stud, concluded that prevalence of gingival recessions is associated with labial piercing, and the position of the intraoral disk and time since piercing is associated with a greater prevalence of gingival recession.

In most of the occasions piercing is done by non-medical individuals who do not have adequate knowledge about sterilization and disinfection. Catherine HY Yu and coworkers reported a case of prosthetic valve endocarditis caused by a *Gemella* species in a patient with a pierced tongue, and reviewed 18 additional cases of local and systemic bacterial infections associated with tongue piercing.

With the increased prevalence of intra- and perioral piercing, dentists should be prepared to address issues, such as potential damage to the teeth and gingiva, and risk of oral infection that could arise as a result of piercing. Patients should be educated regarding the sequela and the potential dangers of oral piercing.

Gingiva may also be involved by factitial injury. This habitual gingival injury is inflicted by the patient using fingernails in which the patient presses the attached gingiva with his/her nails or force the free gingival margin apically.

Clinical Features. The lesions are usually bilateral and seen along the occlusal line and also on the vestibular surface of the lips. The mucosa appears white and shredded, with areas of redness. Ulceration is common. This condition is more prevalent in females. Factitial gingival injury is characterized by vertical clefting in the free gingiva, exposure of the root, and gingival ulcers.

Histologic Features. There will be extensive areas of hyperkeratosis with keratin projections representing the ragged areas. Chronic inflammatory cell infiltration is seen in the areas of ulceration.

Treatment. Counseling and psychotherapy are the treatment of choice. However an acrylic shield will help to prevent the access of the teeth to lips and cheeks.

Denture Injuries

The oral mucosa is subject to a variety of injuries as a result of the wearing of artificial dentures. These may he manifested specifically as: (1) traumatic ulcer, (2) generalized inflammation, (3) inflammatory hyperplasia, (4) papillary hyperplasia of palate, and (5) denture base (acrylic or vulcanite) intolerance or allergy.

Traumatic Ulcer

(Sore spots)

The traumatic ulcer caused by denture irritation is the same type of ulcer that may be produced by a variety of other physical injuries.

Clinical Features. The denture ulcer, one or more, commonly develops within a day or two after the insertion of a new denture. This may be a result of overextension of the flanges, sequestration of spicules of bone under the denture or a roughened or 'high' spot on the fitting surface of the denture.

These ulcers are small, painful, irregularly shaped lesions usually covered by a delicate gray necrotic membrane and surrounded by an inflammatory halo. If treatment is not instituted, there sometimes may be beginning of proliferation of tissue around the periphery of the lesion on an inflammatory basis.

Histologic Features. The traumatic ulcer is a nonspecific ulcer and microscopically shows loss of continuity of surface epithelium with a fibrinous exudate covering the exposed connective tissue (Fig. 12-19). The epithelium bordering the ulcer usually demonstrates proliferative activity. There is infiltration of polymorphonuclear leukocytes in the connective tissue, particularly beneath the area of ulceration, although in chronic lesions these may be replaced by lymphocytes and plasma cells. Capillary dilatation and proliferation may also be evident. Fibroblastic activity is sometimes prominent, and macrophages may be present in moderate numbers.

The treatment for the traumatic denture ulcer consists in correction of the underlying cause: relief of the flange, removal of a tiny sequestrum, or relief of high spots. When this is accomplished, the ulcer usually heals promptly.

Generalized Inflammation

(Denture sore mouth, denture stomatitis)

The 'denture sore mouth' is an uncommon condition occurring in patients who may or may not have a new set of dentures. The condition is not due to a true allergy, since patch

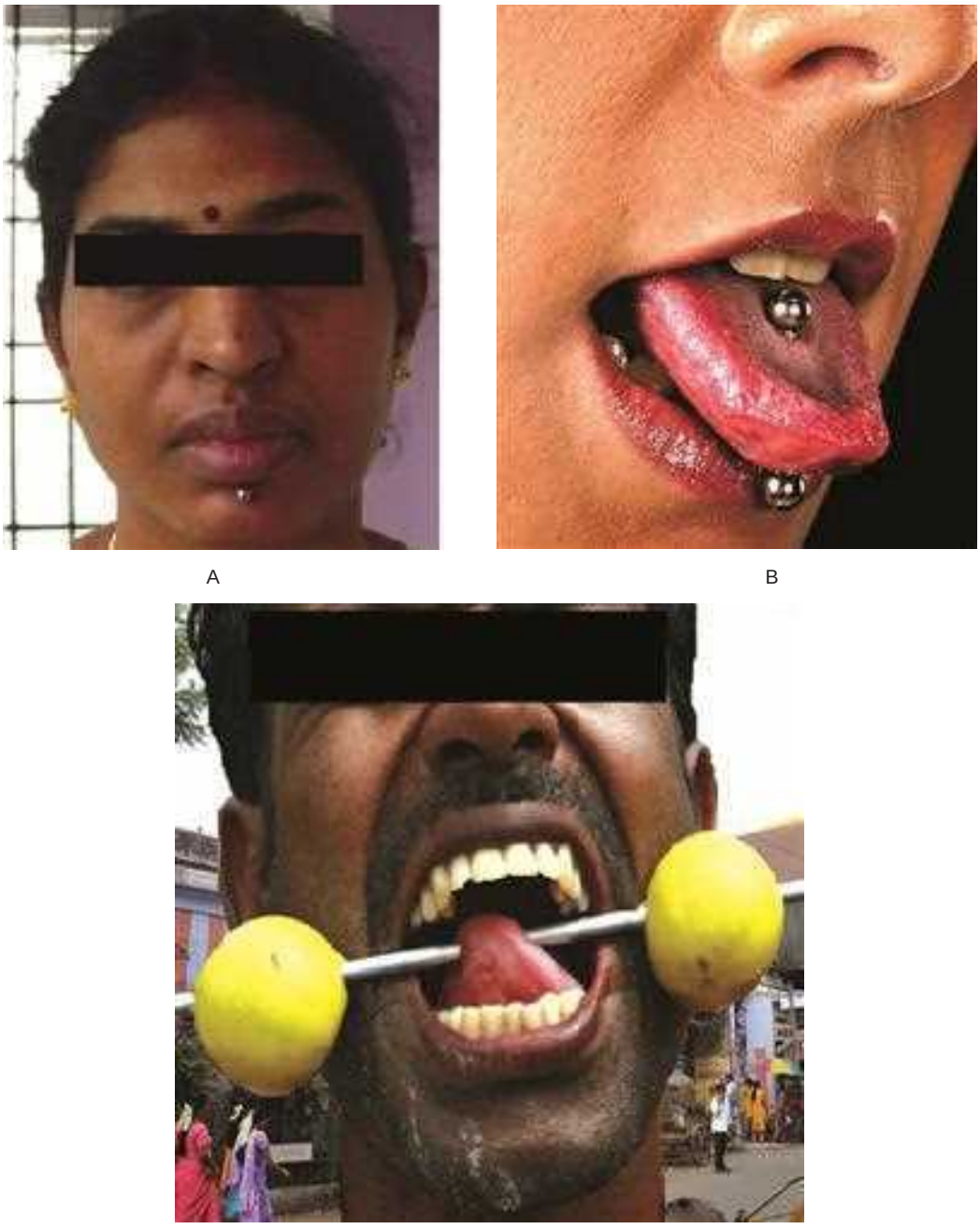


Figure 12-18. Lip piercing (A) and tongue piercing (B and C).
(Courtesy of Dr Rohini S, Chennai, India).

testing with the denture material gives negative results. Some cases appear to be due to an infection with *Candida albicans,* although the typical white patches of thrush (q.v.) do not usually develop, according to Calm and Bartels. Lehner has classified the condition as chronic atrophic candidiasis. Newton has suggested that denture sore mouth may be related to the 'sweat retention syndrome' in which keratin plug formation of the sweat glands or accessory salivary glands forces sweat or saliva into the adjacent tissues with subsequent inflammation. This concept has not been accepted widely, however Budtz-Jørgensen and Bertram demonstrated that yeast like fungi of *C. albicans* type could be cultivated from 90% of patients with denture stomatitis, but from only 40% of patients with dentures but without stomatitis. They also showed that poor denture cleanliness was associated with severe inflammation.

Renner and his associates emphasized that this condition is a multifaceted disease entity in which parasitism by *C. albicans* may be an extremely important factor often in association with other major contributions from denture trauma and continual denture wearing, poor oral hygiene habits and possibly dietary and systemic alterations.

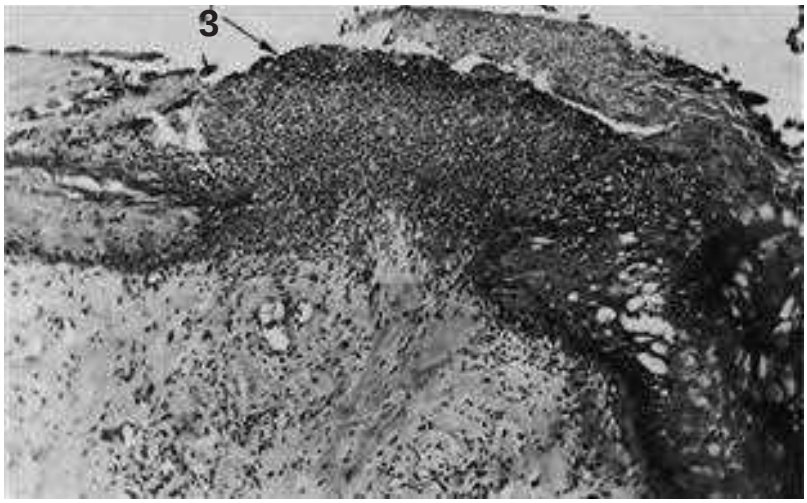


Figure 12-19. Traumatic ulcer.
The area of the ulceration is covered by a fibrinous exudate (1).

Clinical Features. The mucosa beneath the denture becomes extremely red, swollen, smooth or granular and painful. Multiple pinpoint foci of hyperemia, usually involving the maxilla, frequently occur. A severe burning sensation is common. The redness of the mucosa is rather sharply outlined and restricted to the tissue actually in contact with the denture.

Treatment of this condition may not be successful. However, Budtz-Jørgensen and Bertram have reported significant therapeutic effects on denture stomatitis by antifungal therapy. Nystatin tablets 500,000 units, were allowed to dissolve in the mouth three times a day for 14 days. Bergendal and Isacsson reported similar results by treating denture stomatitis with nystatin powder placed on the fitting surface of the denture three times a day for 14 days. In addition, when the dentures fit poorly, construction of new appliances and instruction on hygienic care of the dentures aid in correcting the situation. If new dentures are not constructed, the old dentures must be sterilized daily by soaking in a nystatin solution overnight during the treatment period. Rebasing dentures with soft-tissue conditioners is also reported of benefit in addition to nystatin.

Inflammatory (Fibrous) Hyperplasia

(Denture injury tumor, euplis fissuratum, redundant tissue)

One of the most common tissue reactions to a chronically ill-fitting denture is the occurrence of hyperplasia of tissue along the denture borders. Such hyperplasia of oral mucosa is not restricted to this location but occurs in many areas where chronic irritation of any type exists, such as on the gingiva, buccal mucosa, and angle of the month.

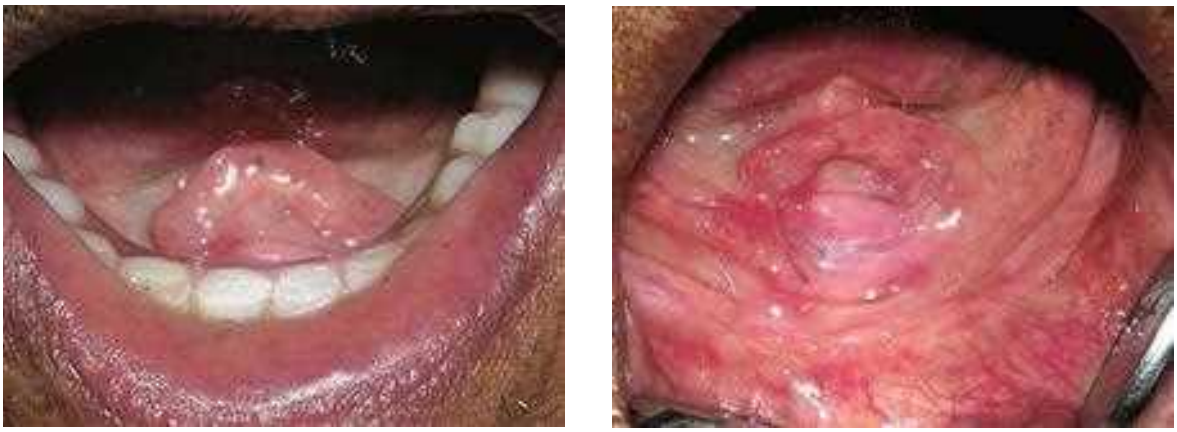
Clinical Features. Inflammatory fibrous hyperplasia as a result of denture injury is characterized by the development of elongated rolls of tissue in the mucolabial or mucobuccal fold area into which the denture flange conveniently fits (Figs. 12-20, 12-21). This proliferation of tissue is usually slow in developing and probably is as much a result of the resorption of the alveolar ridge as of the trauma of the loose dentures.

This excess fold of tissue is not usually highly inflamed clinically, although there may be irritation or even ulceration in the base of the fold into which the denture flange fits. The lesion is firm to palpation.

Histologic Features. The hyperplastic mass of tissue is composed of an excessive bulk of fibrous connective tissue covered by a layer of stratified squamous epithelium which may be of normal thickness or show acanthosis (Fig. 12-21). Pseudoepitheliomatous hyperplasia is often found. Hyperkeratosis is frequently present. The connective tissue is composed chiefly of coarse bundles of collagen fibers with few fibroblasts or blood vessels unless there is an active inflammatory reaction present. Such a reaction is frequently seen, however, in the base of the fissure adjoining the denture flange, especially if the tissue is superficially ulcerated.

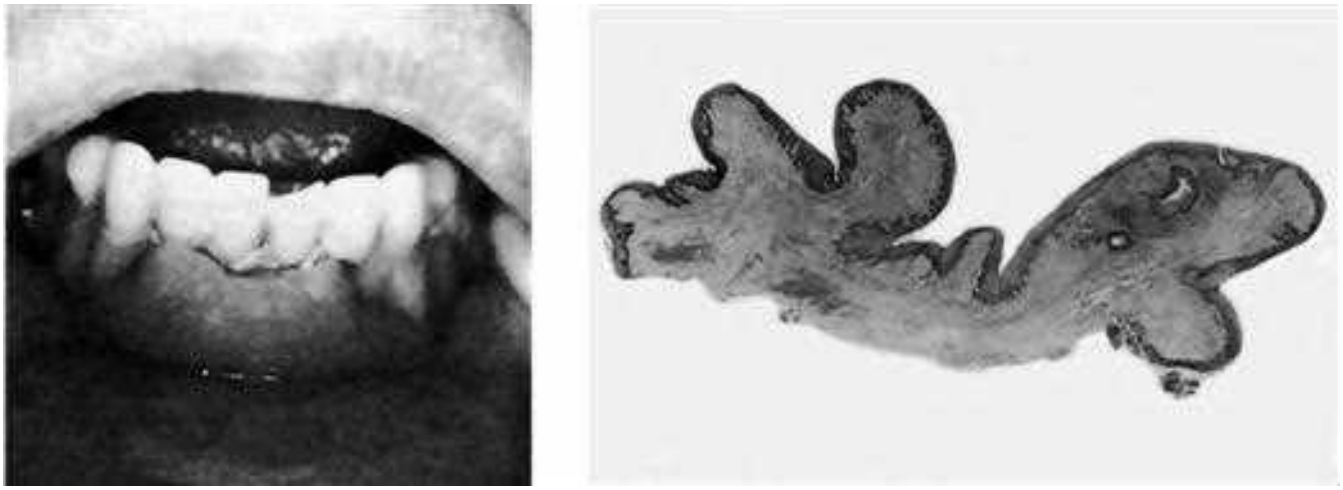
One additional histologic finding often seen in the surface epithelium of inflammatory fibrous hyperplasia is **mucopolysaccharide keratin dystrophy**, also referred to as 'plasma pooling', first described by Toto. Its occurrence is not confined to inflammatory hyperplasia but may also be found in oral epithelium under a wide variety of other conditions, especially those involving irritated epithelium. This mucopolysaccharide keratin dystrophy consists histologically of homogeneous, eosinophilic pools of material in the superficial spinous layer of epithelium, where it appears to have replaced individual cells. Its significance is not known.

Treatment and Prognosis. Inflammatory fibrous hyperplasia should he surgically excised, and either new dentures constructed or the old dentures rebased to provide adequate retention. If the denture is replaced or repaired, the lesion should not recur. Complete regression, even after construction of new dentures, will not occur, although subsidence of the inflammatory reaction may produce some clinical improvement of the condition.



A B

Figure 12-20. Inflammatory hyperplasia.
The redundant tissue forming at the border of the poorly fitting denture *(Courtesy of Drs Poonja LS, G Sriram, and Vaishali Natu, Nair Hospital Dental College, Mumbai)*.



A B

Figure 12-21. Inflammatory hyperplasia.
Some cases of redundant tissue exhibit extremely large rolls of fibrous tissue around the denture *(B, Courtesy of Dr Grant Van Huysen)*.

Inflammatory Papillary Hyperplasia
(Palatal papillomatosis)

Papillary hyperplasia is an unusual condition involving the mucosa of the palate. It is of unknown etiology but may be considered a form of inflammatory hyperplasia associated in most instances with ill-fitting dentures, which permit frictional irritation and a poor state of oral hygiene. Often there is associated chronic hyperplastic candidiasis, which may be a contributing factor. Since many persons who have what might be described as poor-fitting dentures never acquire papillomatosis; however, there must be some as yet unidentified predisposing factors present in those persons who develop the lesion.

Clinical Features. Papillary hyperplasia occurs predominantly in edentulous patients with dentures, but is seen on rare occasions in patients with a full complement of teeth and no prosthetic appliance. In a series of 5,892 dental patients, Guernsey reported an incidence of 2.9% in denture wearers but only 0.2% in nondenture wearers. However, Bhaskar and his associates have stated that approximately 20% of all patients who wear dentures 24 hours a day show papillary hyperplasia, while among all denture wearers, the prevalence is 10%. Ettinger, studying the etiology and incidence of papillary hyperplasia, reported a similar occurrence of 97 affected patients, or 13.9%, in a series of 700 denture wearers. He concluded that constant wearing of the denture was one of the most important factors associated with the condition. When an appliance is present, the site of the lesion corresponds to the denture base, sometimes only to the relief chamber. It may arise at any age in the adult and has no definite sex predilection.

The lesion presents itself as numerous, closely arranged, red, edematous papillary projections, often involving nearly all of the hard palate and imparting to it a warty appearance.

A B

Figure 12-22. Papillary hyperplasia of palate in dentulous and edentulous patients.
The many small projections are confined to the palatal area and may be free of inflammation *(Courtesy of Dr Sujatha G, Department of Oral Pathology, and Dr Srinivasa Prasad T, Department of Oral and Maxillofacial Surgery, Meenakshi Ammal Dental College, Chennai).*

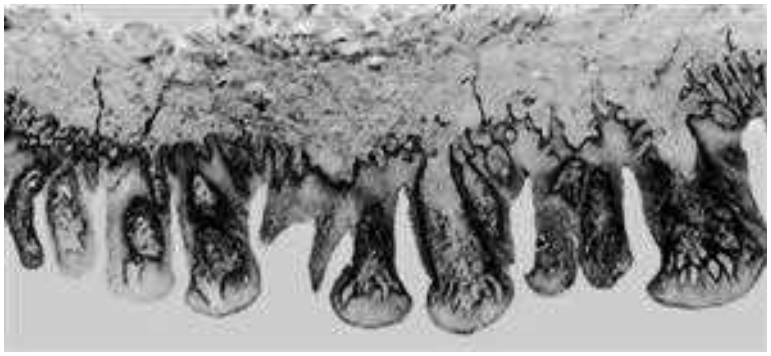


Figure 12-23. Photomicrograph of papillary hyperplasia of palate.
The lesion is composed of numerous small papillary projections.

The lesions may extend onto the alveolar mucosa, and mandibular alveolar mucosa involvement occasionally occurs. The individual papillae are seldom over a millimeter or two in diameter. The tissue exhibits varying degrees of inflammation, but ulceration is rare (Fig. 12-22).

Histologic Features. The microscopic section of papillomatosis shows numerous, small vertical projections each composed of parakeratotic or sometimes orthokeratotic stratified squamous epithelium and a central core of connective tissue (Fig. 12-23). Pseudoepitheliomatous hyperplasia, in varying degrees, is seen in the vast majority of cases; this is sometimes so severe as to be interpreted by the inexperienced pathologists as epidermoid carcinoma. However, most authorities now agree that true epithelial dysplasia and malignant transformation do not occur in palatal papillomatosis. Relatively severe inflammatory cell infiltration is nearly always present in the connective tissue, as is chronic sialadenitis in the accessory palatal glands. In the latter instance, metaplastic changes in acinar and ductal epithelium may mimic neoplastic transformation.

Treatment and Prognosis. There is no well recognized and accepted course of therapy for this condition. Discontinuing the use of the ill-fitting dentures or construction of new dentures without surgical removal of the excess tissue will generally result in regression of the edema and inflammation, but the papillary hyperplasia persists. Preferably, surgical excision of the lesion prior to new denture construction will return the mouth to a normal state. The use of a tissue conditioner to rebase an old denture often results in some improvement of the lesion, but seldom complete regression unless it is in an early stage.

Denture Base Intolerance or Allergy

Plasticizers of the soft liners are cytotoxic and affect many cellular metabolic reactions *in vitro*. Studies in animal exhibited significant epithelial changes. A true allergy to denture base material is extremely rare. Occasional cases have been reported, and studies have suggested that these were due to sensitivity to the monomer, both regular and self-curing types.

Mucous Retention Phenomenon
(Mucocele, mucous retention cyst)

The mucous retention phenomenon, which is generally conceded to be of traumatic origin, is a lesion involving salivary glands and their ducts.

Etiology and Pathogenesis. The mucous retention phenomenon is a common lesion. Many authorities formerly believed that this type of lesion resulted from obstruction of the duct of a minor or accessory salivary gland, but experimental investigations on mice by Bhaskar and his associates and on rats by Standish and Shafer failed to produce the mucous retention phenomenon by ligation of the submaxillary and sublingual gland ducts. The studies of Bhaskar and coworkers have shown instead that if the salivary duct was severed so that a continuous pooling of saliva occurred in the tissues, a well-demarcated cavity developed which was histologically identical with the natural mucocele.

These investigations appear to indicate that traumatic severance of a salivary duct, such as that produced by biting the lips or cheek or pinching the lip by extraction forceps, precedes the development of the retention phenomenon. It is also possible that a chronic partial obstruction of a salivary duct, in contrast to the acute total obstruction experimentally produced by ligation in mice and rats, may be of etiologic importance. Such a partial obstruction could result from a small piece of intraductal calculus or even from contraction of developing scar connective tissue around a duct after a traumatic injury. Occasional cases of calculus in the ducts of accessory salivary glands, or sialolithiasis (q.v.), have been reported, but are rather uncommon. Thus, mucoceles often have been classified as: (1) an extravasation mucocele, or (2) a retention mucocele (or true retention cyst). The extravasation type is far more common than the retention type.

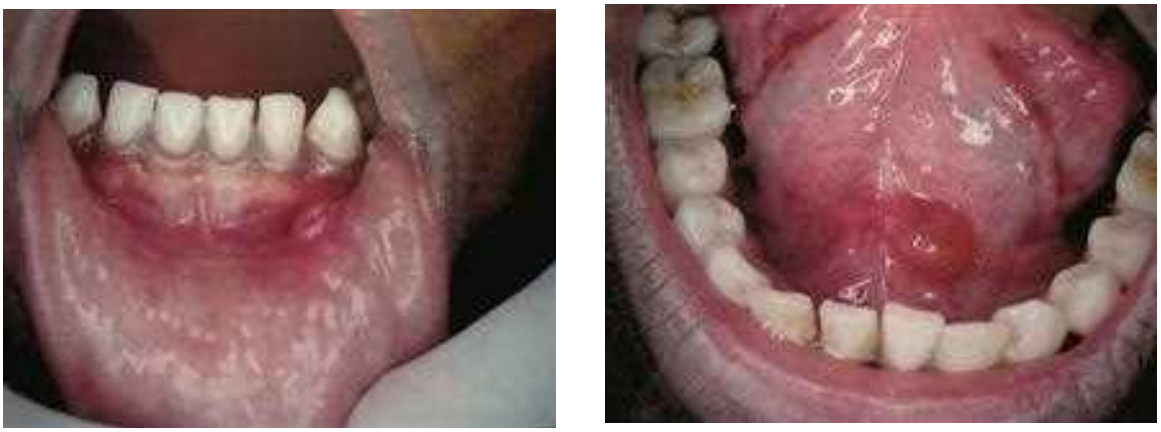
Clinical Features. The retention phenomenon involving accessory salivary gland structures occurs most frequently on the lower lip, but may also occur on the palate, cheek, tongue (involving the glands of Blandin-Nuhn), and floor of the mouth. In the series of cases reported by Standish and Shafer, nearly 45% of the 97 mucoceles occurred on the lower lip. No cases were found in their series on the upper lip. In addition, there was no predilection for any age group, the lesions being rather equally divided among all decades of life, from lesions present at birth to the ninth decade. An equal distribution in occurrence between males and females was also noted in their study. In a study of 125 cases of mucocele, Robinson and Hjørting-Hansen reported similar findings except for the age predilection. They found that nearly 65% of their cases occurred within the first three decades of life. Ramanathan and his coworkers, in their series of 250 cases of mucoceles, found that nearly 85% occurred in the same time span.

Clinically, the lesion may lie fairly deep in the tissue or be exceptionally superficial and depending upon the location, will present a variable clinical appearance (Fig. 12-24). The superficial lesion appears as a raised, circumscribed vesicle, several millimeters to a centimeter or more in diameter, with a bluish, translucent cast. The deeper lesion is manifested also as a swelling but because of the thickness of the overlying tissue, the color and surface appearance are those of normal mucosa.

It is interesting and significant that the mucous retention phenomenon is restricted almost entirely to the lower lip, seldom found on the upper lip, while accessory salivary gland neoplasms of the lips are almost universally found on the upper lip and only rarely on the lower lip. This could imply that trauma plays no role in the development of salivary gland tumors in this location.

The mucous retention phenomenon often arises within a few days, reaches a certain size and may persist as such for months unless treated. If the contents of the cyst are liberated, they usually are found to consist of a thick, mucinous material. Some lesions regress and enlarge periodically and may disappear after traumatic injury which results in their evacuation. They almost invariably recur, however.

Histologic Features. The majority of mucoceles, being of the extravasation type, consist of a circumscribed cavity in the connective tissue and submucosa, producing an obvious elevation of the mucosa with thinning of the epithelium as though it were stretched (Fig. 12-25). The cavity itself is not lined by epithelium and is, therefore, not a true cyst.



A B

Figure 12-24. Retention cyst.
The typical lesion appears as a small vesicle on the lip **(A)** and floor of the mouth **(B)**. *(Courtesy of Dr Spencer Lilly D, Meenakshi Ammal Dental College, Chennai).*

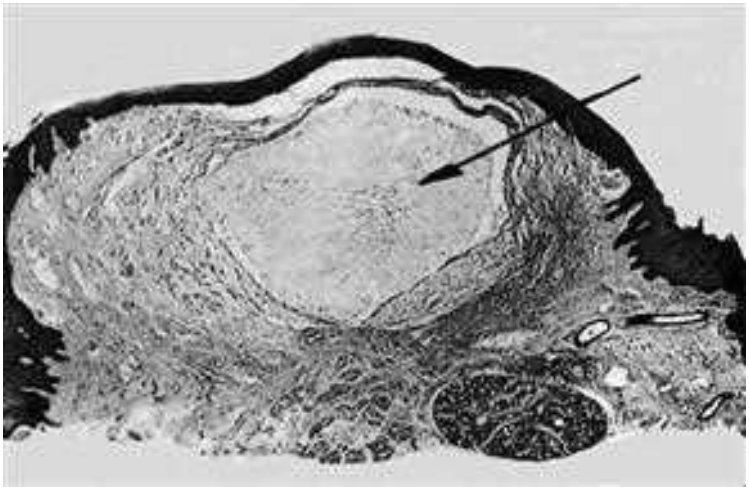


Figure 12-25. Mucous retention phenomenon.
The photomicrograph shows the circumscribed lesion containing mucoid material.

Instead, its wall is made up of a lining of compressed fibrous connective tissue and fibroblasts. Sometimes these cells may be mistaken for flattened epithelial cells. Not uncommonly the connective tissue wall is essentially granulation tissue, but in any event it usually shows infiltration by abundant numbers of polymorphonuclear leukocytes, lymphocytes, and plasma cells. The lumen of the cyst like cavity is filled with an eosinophilic coagulum containing variable numbers of cells, chiefly leukocytes and mononuclear phagocytes.

Occasional mucoceles demonstrate an intact, flattened epithelial lining. It is probable that this simply represents the portion of the excretory duct bordering the line of severance, if severance is actually the manner in which these lesions develop. The flattened epithelial lining has been referred to as epithelium of the 'feeder duct'. In other instances, the epithelium-lined mucocele represents a lesion of the retention type.

The salivary gland, acini which lie adjacent to the area of the mucocele and are associated with the involved duct often show alterations. These may consist of interstitial inflammation or sialadenitis, dilatation of intralobular and interlobular ducts with collection of mucus, and breakdown of individual acinar mucous cells resulting in the formation of tiny areas of pooled mucus.

Treatment and Prognosis. Treatment of the mucous retention phenomenon is excision. If the lesion is simply incised, its contents will be evacuated, but it will be rapidly filled again as soon as the incision heals. There is occasional recurrence after excision, but this possibility is less likely if the associated salivary gland acini are removed also.

Ranula

The ranula is a form of mucocele but larger, which specifically occurs in the floor of the mouth in association with the ducts of the submaxillary or sublingual gland. The etiology and pathogenesis appear to be essentially the same as for the mucous retention phenomenon involving accessory glands, although some workers believe that it may arise through duct blockage or through the development of a ductal aneurysm.

Clinical Features. This lesion, which is rare compared to the usual mucocele, develops as a slowly enlarging painless mass on one side of the floor of the mouth (Fig. 12-26).The tongue may be elevated and when it is large it may hide the salivary gland. Since the lesion is usually a deep-seated one, the overlying mucosa is normal in appearance. If the lesion is superficial, the mucosa may have a translucent bluish color. A rare, plunging, suprahyoid type which has herniated through the mylohyoid muscle is also described. A thorough review of the literature on the plunging or cervical ranula has been reported by van den Akker and his associates, who also described four typical cases.

Histologic Features. The microscopic appearance is similar to that of the smaller mucocele except that a definite epithelial lining is sometimes present. Because of this finding, most investigators consider the ranula to be a true retention cyst, probably occurring as a partial blockade phenomenon, although a salivary duct stone is often not demonstrable.

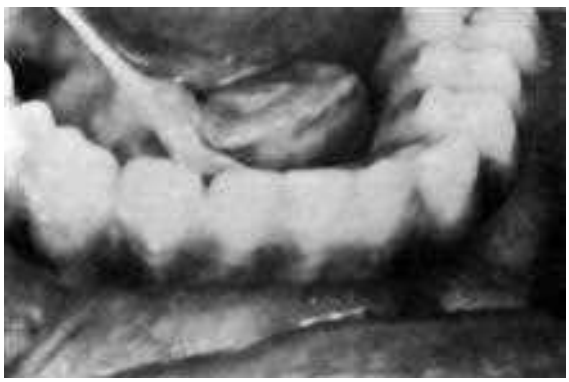


Figure 12-26. Ranula.
This form of retention cyst manifests itself as a mass in the floor of the mouth.

Treatment and Prognosis. The treatment is either marsupialization or more often excision of the entire sublingual gland. Occasionally the lesion recurs if the entire sublingual gland or other gland causing them is not excised with the lesion.

Retention Cyst of Maxillary Sinus

(Secretory cyst of maxillary antrum, mucocele of maxillary sinus, mucosal cyst of maxillary sinus)

The retention cyst of the maxillary sinus is an uncommon variant of the mucous retention phenomenon most frequently encountered as an incidental finding in dental radiographs. It should be recognized; however because of the possibility of confusing it with a variety of other lesions occurring in the same location.

This lesion appears to represent a retention phenomenon of the mucous glands associated with the lining of the maxillary sinus. The cause of development of the cyst-like lesion is unknown, although traumatic injury associated with tooth extraction may be of etiologic significance. In some cases; however, the lesion develops in dentulous areas with no history of a surgical procedure. Other suggested causative factors include sinusitis, allergy and sinus infection, but these are without firm support.

Clinical Features. Most retention cysts of the maxillary sinus are completely asymptomatic and are discovered only during routine radiographic examination of the jaws. Occasionally, discomfort in the cheek or maxilla may be present. Pain and soreness of the face and teeth and numbness of the upper lip were described by Wright in about 10% of his series of 78 cases. Buccal expansion of the maxillary antrum has also been reported. There is no clear-cut age or sex predilection for occurrence of the lesion. Additional series of cases have been reported by Casamassimo and Lilly (73 cases in 4,546 patients, or 1.6%), Myall and his coworkers (73 cases in 1,469 patients, or 5.1%), and Halstead (45 cases in 2,325 patients, or 1.9%).

Radiographic Features. In the dental periapical radiograph, the lesion appears as a well-defined, homogeneous, dome-shaped or hemispheric radiopacity, varying in size from a tiny lesion to one completely filling the antrum, arising from the floor of the antrum and superimposed on it (Fig. 12-27). This radiopacity appears as a soft tissue mass rather than a calcified area, so that medial and lateral landmarks can generally be visualized through the lesion. In some instances the lesion appears more radiolucent than radiopaque. In the various reported series, between 10 and 20% of the cases have occurred bilaterally.

Histologic Features. Some of these retention cysts are analogous to the mucous retention phenomenon in as much as they consist of the accumulation of fluid within connective tissue spaces and have no definite lining. This type has sometimes been referred to as a **non-secretory** cyst. In other instances the lesion may be lined by a respiratory type of epithelium, and this has sometimes been described as the **secretory** type of antral cyst. In either case inflammatory cell infiltration in the connective tissue wall of the specimen is common.

Treatment. The majority of these cysts either persist unchanged or disappear spontaneously within a relatively

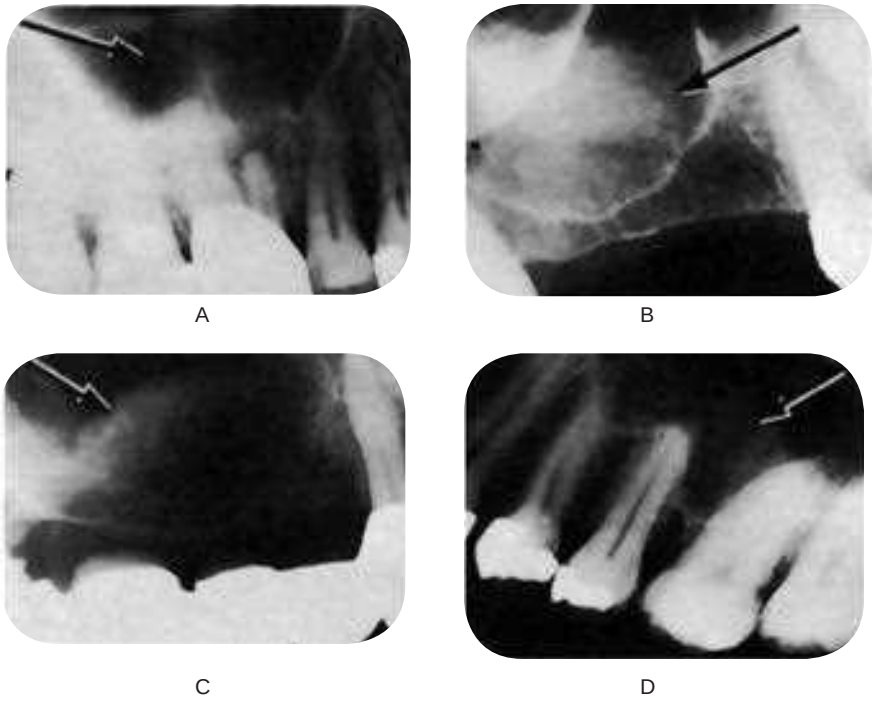


Figure 12-27. Antral pseudocyst.
Four examples of this soft-tissue opacity in association with the maxillary sinus are shown.

short period, and for this reason it has been suggested that no treatment is necessary.

Differential Diagnosis. Care must he taken to differentiate this lesion from apical periodontal cysts of teeth in close association with the maxillary sinus, from fibro-osteomas of this area, and especially from the surgical ciliated cyst of the maxilla. Although etiologically different from the last lesion, the antral mucocele may be related to it pathogenetically.

Sialolithiasis

(Salivary duct stone, salivary duct calculus)

A stone in the salivary ducts or glands is called sialolithiasis. They are formed by deposition of calcium salts around a central nidus which may consist of altered salivary mucins, desquamated epithelial cells, bacteria, foreign bodies, or products of bacterial decomposition. It is the most common cause of salivary gland obstruction. The etiology is unclear and it can be complete or partial and may show recurrence.

Clinical Features. Many patients with sialolithiasis involving a duct of a major salivary gland complain of moderately severe pain, particularly just before, during and after meals, owing to psychic stimulation of salivary flow, associated with swelling of the salivary gland. The occlusion of the duct prevents the free flow of saliva, and this stagnation or accumulation of saliva under pressure produces the pain and swelling. In some instances this swelling is diffused and simulates a cellulitis. Occasionally the stone presents no remarkable symptoms, and the only evidence may be a firm mass palpable in the duct or gland. In some cases large numbers of individual small stones may be found occluding the duct system.

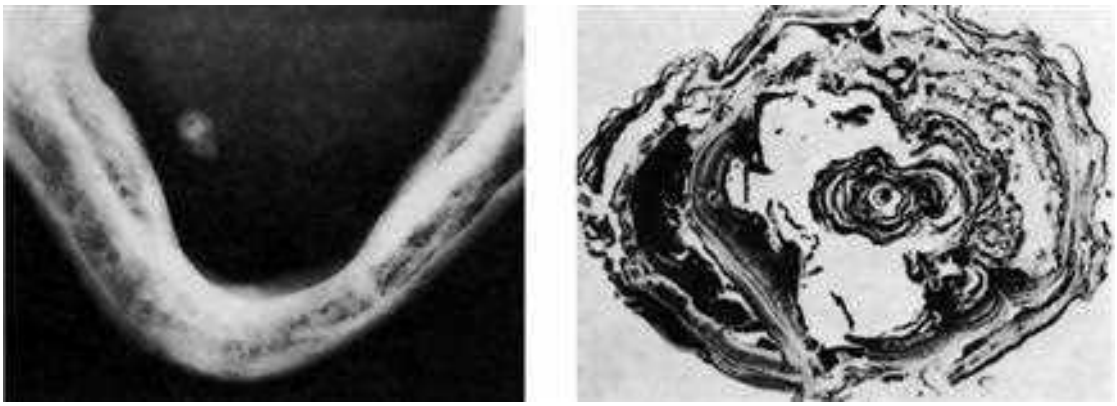
Stones, particularly in the more peripheral portion of the duct, may often be palpated if they are of sufficient size. They may also be demonstrated on the dental radiograph when appropriately located, particularly by the use of sialography (Fig. 12-28A). However 20% of the parotid and 40% of the submandibular stones are not radiopaque. Sialography is the retrograde injection of a radiopaque material into the duct system of a salivary gland and the study of its distribution by radiographs.

Sialolithiasis may occur at any age, but is most common in middle-aged adults. Wakely reported that the occurrence of sialolithiasis in a large group of cases shows the following distribution: submandibular gland and duct, 64%; parotid gland and duct, 20%; and sublingual gland and duct, 16%. In a series of 180 cases reported by Levy and his associates, the gland distribution was 80%, 19%, and 1%, respectively. The common involvement of the submandibular gland and duct is thought to be due to the tenacity of the submandibular saliva, which, because of its high mucin content, adheres to any foreign particle. The submandibular duct is also long and irregular in its course.

Sialolithiasis involving ducts of the minor or intraoral accessory salivary glands sometimes is also seen. The majority of these sialoliths are found in the upper lip, with only slightly fewer in the buccal mucosa, together accounting for nearly 90% of all cases. Occasional cases are reported in the buccal sulcus, lower lip, palate, and tongue. They usually present as solitary, firm, freely movable, small masses or nodules, and may or may not be symptomatic.

Chemical and Physical Features. The sialolith may be round, ovoid, or elongated. It may measure just a few millimeters or 2 cm or more in diameter. The involved duct may contain a single stone or many stones. The surface of the calculi is rough, which may cause the duct lining to undergo squamous metaplasia. They are usually yellow and occasionally white or yellowish-brown in colour. It consists mainly of calcium phosphates and smaller amounts of calcium carbonates, organic materials, and water. Submandibular stones tend to be larger than those of the parotid or other minor glands.

Histologic Features. Microscopically the calcified mass exhibits concentric laminations (Fig 12-28B) around a central nidus of amorphous debris. The lamellated structure of the calculi is the result of successive deposition of inorganic and organic material. Periductal inflammation is also seen. The ductal obstruction frequently is associated with an acute or chronic sialadenitis of the feeding gland.



A B

Figure 12-28. Sialolithiasis.
(A) A piece of calculus in the submandibular gland duct is shown in the occlusal radiograph. **(B)** The laminated structure of the stone is obvious in the photomicrograph.

Treatment and Prognosis. Small calculi may sometimes be removed by manipulation or increasing the salivation by sucking a lemon, leading to expulsion of the stone. An intravenous antibiotic is given for bacterial infection due to persistent obstruction of the duct. The larger stones almost always require surgical removal. If they are present near or in the substance of the gland itself, particularly if multiple, surgical extirpation of the gland may be necessary. Piezoelectric shock wave lithotropsy may be an alternative to surgical removal. The solitary sialolith does not usually recur, although occasional cases have presented chronic multiple recurrences.

Maxillary Antrolithiasis
(Antral rhinolith)

Maxillary antrolithiasis is a relatively rare condition which is defined as a complete or partial calcific encrustation of an antral foreign body, either endogenous or exogenous, which serves as a nidus. An endogenous nidus may consist of a dental structure such as a root tip or may simply be a fragment of soft tissue, bone, blood, or mucus. Exogenous nidi are uncommon, but may consist of such materials as snuff paper.

Clinical Features. The antrolith may occur at any age in either sex. There may be a complete absence of symptoms, although some cases are marked by pain, sinusitis, nasal obstruction, and/or foul discharge, and epistaxis. Some cases, according to Blaschke and Brady, are discovered accidentally during radiographic examination in which an opaque mass is evident in the sinus. At times Aspergillus species served as a central fungus nidus associated with long-standing sinusitis, and poor sinus drainage resulting in the formation of a sinus stone.

Treatment. The antrolith should be surgically removed.

Rhinolithiasis

Rhinoliths are calcareous concretions occurring in the nasal cavity. This uncommon lesion is formed by calcification of intranasal endogenous or exogenous foreign material. Although nasal foreign bodies are more frequently seen in children, they have been reported in patients of all ages. Rhinolith may be present for years and frequently gives rise to odorous discharge, symptoms of nasal obstruction, sinusitis, epiphora, as well as pain and epistaxis. At least one case of an antrorhinolith, a 'stone' partially in the nasal passage and partially in the antrum, has also been reported. Pinto et al, reported a case of rhinolith in a 54-year-old woman causing palatal perforation.

Radiation Injuries

The general term 'radiation' is applied to two different forms of energy: (1) that derived from electromagnetic radiation, and (2) that derived from particle radiation. Electromagnetic radiation consists of a continuous spectrum of varying wavelengths ranging from long electrical and radiowaves down through infra-red, visible light, ultraviolet light, X-rays and gamma rays. Particle radiation is generated through spontaneous decay of various natural and artificial radioactive materials; Particles may also be generated by accelerating deuterons, electrons, and so forth, in devices such as the cyclotron and betatron.

Certain natural radioactive elements such as radium and thorium give off radiant energy spontaneously in their decay process. A portion of this is electromagnetic or gamma (γ) rays, but most of the radiation consists of alpha (α) and beta (β) particles. Alpha particles, which are helium nuclei in rapid motion, have little ability to penetrate tissues and thus give up their energy in a very short distance. Beta particles, which are negatively charged electrons in rapid motion, have a greater penetrating power than alpha particles, but lose their energy in a few millimeters of tissue. Alpha and beta particles actually have little use in medical therapy and are important chiefly as hazards. Radioactive isotopes of most of the known elements have been prepared. The half-life of these isotopes ranges from a fraction of a second to centuries. The majority of the isotopes produce only beta radiation, although some produce alpha particles and gamma rays. In recent years many of these radioactive isotopes have found use in medicine as tracer substances, therapeutic agents and diagnostic agents, as well as in many areas of research.

These different types of radiant energy or radiation are sometimes spoken of as 'ionizing radiation'. This term refers to rays which carry enough energy to produce ionization in materials which absorb them, including living tissues.

Radiation injuries are caused by ionizing effects of energized particles on cells. In the process of radiation therapy, which is commonly used in the treatment of head and neck malignancies, normal tissues in and around the field of radiation is also damaged to certain extent.

General Effects of Radiation on Tissue

The exact means by which radiation exerts its effect on cells and tissues is unknown. Most investigators believe that it is related to the mechanism of ionization, localized injuries being produced in single cells. The cellular injury has been postulated to be due to a number of possible factors. These include:

- Toxic effect of protein breakdown products
- Inactivation of enzyme systems
- Coagulation or flocculation of protoplasmic colloids
- Denaturation of nucleoproteins.

There is great variation in the radio-sensitivity of different types of living cells despite the fact that it is possible to kill any living thing with sufficiently large doses of radiation (Table 12-1). In general, embryonic, immature or poorly differentiated cells are more easily injured than differentiated cells of the same type. Once these cells are injured, however, they usually show greater recovery properties, although there are many exceptions to this rule. Significantly, all cells show increased vulnerability to radiation injury at the time of mitotic division. Furthermore, if cells are irradiated during the resting phase, mitosis is delayed or inhibited.

Table 12-1. Radiosensitivity of normal cells and tissues

1. **Radiosensitive** (2500 r or less kills or seriously injures many cells)
Lymphocytes and lymphoblasts
Bone marrow (myeloblastic and erythroblastic cells)
Epithelium of intestine and stomach
Germ cells (ovary and testis)
2. **Radioresponsive** (2500–5000 r kills or seriously injures many cells)
Epithelium of skin and skin appendages
Endothelium of blood vessels
Salivary glands
Bone and cartilage (growing)
Conjunctiva, cornea, and lens of eye
Collagen and elastic tissue (fibroblasts themselves are resistant)
3. **Rardioresistant** (over 5000 r necessary to kill or injure many cells)
Kidney
Liver
Thyroid
Pancreas
Pituitary
Adrenal and parathyroid glands
Mature bone and cartilage
Muscle
Brain and other nervous tissue

Latent tissue injury is one of the most unusual phenomena related to X-ray or gamma radiation and refers to residual tissue damage after the initial radiation reaction has subsided. Although frequently no residual injury can be detected by ordinary means, the tissues will retain for years an increased susceptibility to injury if again radiated. Furthermore, repeated exposure to small doses of radiation, no one of which is sufficient to evoke a perceptible reaction, may in the aggregate produce serious latent damage. Thus the biologic effects of radiation are cumulative, but show incomplete summation.

Effects of Radiation on Oral and Paraoral Tissues. Radiation effects are dependent upon a great number of factors such as the source of the radiation, the total amount of radiation administered, the period of time over which the radiation was administered (fractionation), the type of filtration used and the total area of tissue irradiated. The changes to be described here are those frequently seen after delivery of local therapeutic doses of X-ray radiation in the treatment of neoplasms about the head and neck. They are in no way related to the use of the diagnostic X-ray machine. No attempt will be made to describe the effect of total body radiation, such as those occurring after detonation of the various nuclear bombs, because of the lack of significant clinical application of such information.

However, adult patients with acute leukemia in relapse, whose disease has become refractory to all known chemotherapeutic drugs, may receive bone marrow transplantation following total body radiation in an attempt to prolong their lives. The oral changes in 35 patients following 850–950 rads of total body X-ray radiation were detailed by Dreizen and his associates in 1979. Almost every patient exhibited bilateral parotitis, partial xerostomia, and oral mucositis following total body radiation. The parotitis resembled mumps that resolved spontaneously in 24–48 hours. Saliva production during the first week after radiation was noticeably reduced in amount and was thicker, ropier, and more mucoid than usual. The mucositis, which lasted two to three weeks, began as swelling, soreness, and whitening of the oral mucosa. Within 48–72 hours, the lips, tongue, and/or entire oral cavity showed an intense reddening of the oral mucosa. Pain and denudation accompanied the mucositis. After two or three weeks there was a whitening of the oral mucosa, which has been attributed to impaired mitotic activity and prolonged retention of the superficial epithelial cells, leading to an abnormally high degree of keratinization. Palliation of the transient radiation mucositis was achieved with warm salt water or sodium bicarbonate mouthrinses.

Evidence is accumulating that cobalt-60 radiation therapy, as contrasted with conventional orthovoltage radiation, may have significant skin- and bone-sparing qualities. Thus, this technique may reduce the incidence of radiation complications so frequently seen in the past.

Effects on Skin. The effects of heavy therapeutic doses of X-ray radiation on the skin are well documented, although variable among patients. Erythema is the earliest visible reaction and begins within a few days after irradiation. The original erythema fades quickly, only to reappear within two to four weeks. The secondary erythema fades slowly; often leaving the skin permanently pigmented a light tan shade. After heavy irradiation the secondary erythema may be accompanied by edema with desquamation of epithelial cells resulting in denudation of the surface. Re-epithelialization occurs in 10–14 days. These early effects are caused by direct injury of the radiated cells and tissues, while the later effects are brought about chiefly by changes in the vascular bed and in the intercellular material.

Alterations in the sebaceous gland activity, evidenced by a reduction in secretion with dryness of the skin, may occur within a week after the beginning of irradiation. The hair follicles are also sensitive to this type of radiation, and epilation, either temporary or permanent, may be produced. The sweat glands are similarly disturbed so that their absence of secretion contributes to the dryness and scaling of the skin.

Eventually the epithelium becomes thin and atrophic, and the superficial blood vessels become telangiectatic or occluded. The telangiectasia may persist for months or even years as evidence of the effect of X-rays. Other evidence of vascular damage includes thickening of the intima and, in some cases, thrombosis. Some veins and arteries show subintimal fibrosis with thickening of the wall at the expense of the lumen. Endophlebitis and phlebosclerosis may be particularly evident.

Effects on Oral Mucosa. The changes occurring in the oral mucosa after X-ray radiation are essentially the same as those in the skin and are related to the dose and the duration of therapy. The erythema may develop at a somewhat lower dose of X-ray, and the mucositis which occurs after therapeutic radiation is evoked somewhat earlier than the analogous dermatitis (Fig. 12-29).

Dreizen and his coworkers studied the effects of radiotherapy for oral cancer on the oral mucosa. They found that the mucosa

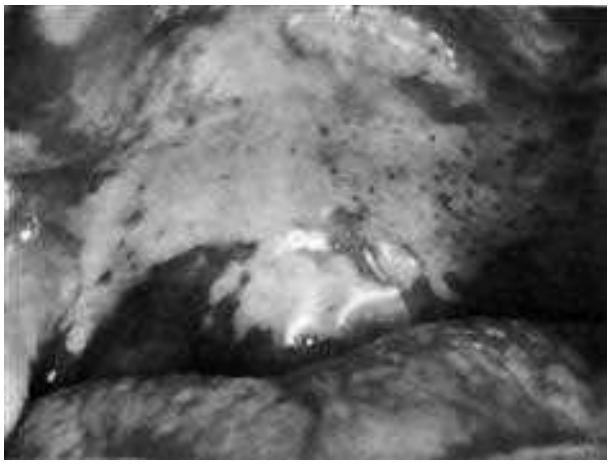


Figure 12-29. Radiation mucositis of palate.
The seven-day postradiation reaction consisted of a yellowish-white necrotic exudate, which disappeared within an additional 14 days.

in the path of radiation first appeared hyperemic and edematous. As treatment continued, the mucosa became denuded, ulcerated, and covered with a fibrinous exudate. Great discomfort, which was intensified by contact with coarse or highly seasoned foods, was commonly present. The mucositis persisted throughout radiotherapy and for several weeks thereafter. Unless secondary infection occurred, spontaneous remission followed termination of the radiation therapy. In many patients, a lidocaine mouthrinse before mealtimes was necessary to produce topical anesthesia so that eating was possible. When pain and dysphasia could not be controlled with local anesthetics and analgesics, nasogastric tube feeding was necessary.

Patients undergoing radiotherapy for oral cancer also quickly lost their sense of taste, probably because of damage to the microvilli and outer surface of the taste cells. The effect was usually transitory, and taste acuity was restored within 60–120 days after completion of the radiotherapy.

Effects on Salivary Glands. Xerostomia, or dryness of the mouth, is one of the earliest and most universal of complaints of patients receiving therapeutic radiation about the head and neck. Alterations in the salivary glands, characterized by diminution or even complete loss of secretion, may occur within a week or two after the beginning of radiation. It is interesting that the morphologic changes do not particularly mirror the physiologic changes which occur. There is some obvious damage of the acinar cells, chiefly a decrease in the number of secretory granules present, with congestion, edema, and inflammatory cell infiltration of the interstitial connective tissue. There are no remarkable changes in the ducts of the salivary glands.

One interesting feature of acute post radiation sialadenitis is the elevation of serum and urinary amylase, the source of this amylase being the salivary glands. This is one of the few biochemical changes that occur early and consistently following irradiation. Kashima and his associates have discussed this finding, as well as other clinical and histopathologic features of post radiation sialadenitis, concluding that direct exposure of the salivary glands is necessary to provoke this change and that the serum amylase response is related to the dose of irradiation.

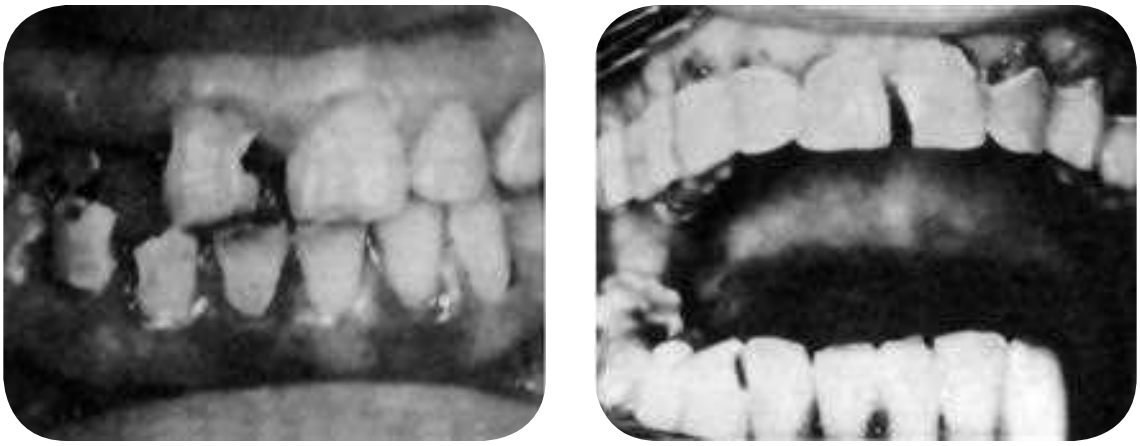
The loss of secretion may be a permanent sequelae of the radiation, or there may be a gradual return of salivation, usually only after many months.

Effects on Teeth. Erupted teeth are often affected in patients who have received X-ray radiation about the head and neck, but the damage may not appear for several years after the radiation. The most common manifestation of the injury is a peculiar destruction of tooth substance, resembling dental caries and sometimes called 'radiation caries', which often begins at the cervical area of the teeth. The lesion resembles a demineralization more than it does true caries because of its pattern or the manner in which it sweeps across the tooth, sometimes causing amputation of the tooth crown at its neck. Teeth often seem brittle, and pieces of the enamel may fracture away from the tooth (Fig. 12-30).

The primary cause of the condition lies in alterations of the saliva induced by either direct or indirect radiation of the salivary glands. Although physical and chemical changes in the saliva following salivary gland irradiation have been postulated, there is no evidence for such changes other than the direct observation that the saliva often becomes somewhat thicker and more tenacious after irradiation. The xerostomia of varying degrees certainly favors the collection of debris on the teeth and ensuing caries. Radiation induced xerostomia in humans produced pronounced shifts in the oral microbial population, with cariogenic microorganisms gaining prominence at the expense of noncariogenic ones. These changes occurred prior to the onset of clinical caries and were irrespective of the use of a topical fluoride gel as a caries preventive measure.

Close cooperation between the radiotherapist, the dentist, and the patient is essential in promoting oral care for these patients. As Dreizen and his associates pointed out, xerostomia also deprives the teeth of an important natural defense against dental decay. There is a sharp decrease in the total daily output of caries-protective salivary electrolytes and immunoproteins. Patients with xerostomia change their eating habits to include frequent, nondetergent, and high carbohydrate meals. The microbial, chemical, immunologic, and dietary changes produce an enormous increase in the caries challenge.

Regardless of the patient's previous caries history, the development of xerostomia is inevitably followed by rampant dental decay unless stringent protective steps are taken. Cariogenesis is so greatly accelerated that frank lesions may appear within three months after radiotherapy. However, the ravages of dental decay in the radiated patient can be almost completely prevented with one daily application of a 1% sodium fluoride gel containing a red, plaque-disclosing dye. This protocol was developed by Daly and Drane in 1972. The gel is applied for at least five minutes by means of custom fabricated flexible plastic carriers. When the carriers are removed and the gel is rinsed off, the plaque is stained red and can be removed by brushing and flossing. To be maximally effective, the program must be instituted at the beginning of radiotherapy and continued every day. Such



A B

Figure 12-30. Radiation caries.
(A) The salivary glands on the side showing the caries were radiated during the course of treatment of an intraoral neoplasm; the radiation produced a xerostomia on that side and the ultimate caries. **(B)** The typical destruction of tooth substance at the cervical margins of the teeth is well illustrated. *(B, Courtesy of Dr Charles A Waldron).*

a regimen can also arrest caries caused by xerostomia in previously unprotected patients. Because of the ever-present risk of caries in xerostomic patients, only diligent, lifelong cooperation will assure prevention.

Developing teeth are also particularly sensitive to X-ray radiation. Leist and Smith demonstrated that irradiation of developing teeth in rats resulted in a disorganization of the odontoblasts and the formation of atypical dentin. Ameloblasts appear to be considerably more resistant to radiation than odontoblasts, although Burstone demonstrated in mice that, after sufficient radiation there was cessation of ameloblastic histogenesis and metaplasia of ameloblasts to a less differentiated type of cell. Similar interference with tooth formation in rats has been reported by English and his coworkers.

Radiation of developing teeth in human beings sometimes occurs, and if it is at a sufficiently young age, manifestations of the injury may be obvious. Such radiation is usually administered for the treatment of a tumor about the head and neck, frequently a hemangioma. Depending upon the age of the patient at the time of the irradiation, there may be complete cessation of odontogenesis resulting in anodontia in the involved area or simply a stunting of the teeth (Fig. 12-31) have been cited by Carl and Wood.

Effects on Bone. Bone itself is relatively resistant to X-ray radiation, although osteoblasts are sensitive. If the radiation has been sufficiently intense, the normal balance between bone formation and bone resorption is disturbed; general bone vitality is decreased, and localized osteoporosis may result.

The greatest clinical significance of bone which has been irradiated lies in the inability of this bone to react in the normal fashion to infection. This is related, at least in part, to the damage of the vascular bed with subsequent disturbance of the typical inflammatory response. There is little actual danger to the patient except in a situation in which infection may enter the bone with little difficulty and spread widely. This may occur in the maxilla and mandible.

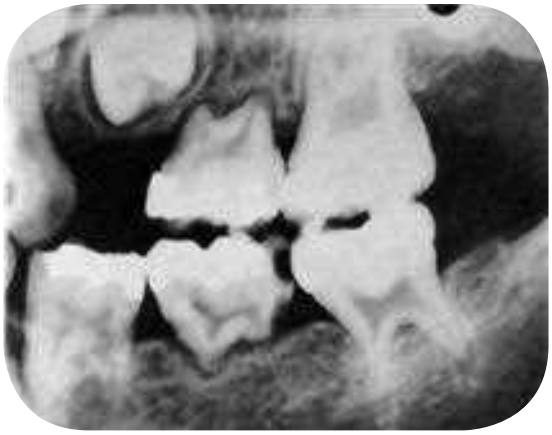


Figure 12-31. Radiation damage to teeth.
There is stunting of the roots of the teeth due to X-ray radiation of the dental area during the time of tooth formation *(Courtesy of Dr John Mink).*

An experimental study of the effects of radiation on extraction wound healing in rats has been reported by Stein and coworkers. They found that when radiation shortly followed tooth extraction, there was retardation of surface closure of the wound, leaving an open pathway for tissue infection. The healing response was poor and slow. As the interval between tooth extraction and radiation was increased, impairment of healing decreased. In general, the longer the interval between tooth extraction and initiation of radiation, the less possibility is there of healing complications.

Osteoradionecrosis

This pathologic process sometimes follows heavy radiation of bone. It is an acute form of osteomyelitis caused by damage to the intraosseous blood vessels and is characterized by a chronic, painful infection, and necrosis accompanied by late sequestration and sometimes permanent deformity.

Histologically, there is destruction of osteocytes, absence of osteoblasts, and lack of new bone or osteoid formation. The walls of the regional blood vessels are thickened by fibrous connective tissue. They are also the seat of endarteritis and periarteritis. The loose connective tissue which usually replaces the bone marrow is infiltrated by lymphocytes, plasma cells, and macrophages. The devitalized bone may undergo sequestration, although there is no clear line of demarcation between vital and nonvital bone. The necrotic process may extend throughout the radiated bone. Although the exact pathogenesis is not completely understood, it is generally agreed that there are three factors involved: radiation, trauma, and infection.

The mandible is affected by osteoradionecrosis far more frequently than the maxilla. The cause for this is unknown, but may be related to the difference in blood supply between the two bones. After the infection has gained entry to the bone, following traumatic injury, extraction, pulp infection, or even severe periodontitis, there is a relatively diffuse spread of the process. There is minimal localization of the infection, and there may be necrosis of a considerable amount of bone, periosteum, and overlying mucosa (Fig. 12-32). Sequestration eventually occurs, but this may be delayed for many months or several years, during which time the patient usually suffers intense pain. The occurrence of osteoradionecrosis is unpredictable, and it may arise even without gross infection or trauma.

Because patients that ultimately developed osteoradionecrosis of the jaws seemed to have many characteristics in common, Daly and Drane were able to formulate a bone necrosis profile. The more factors present, the greater the chance of necrosis. Factors leading to osteoradionecrosis were listed as: (1) irradiation of an area of previous surgery before adequate healing had taken place, (2) irradiation of lesions in close proximity to bone, (3) a high dose of irradiation with or without proper fractionation, (4) use of a combination of external radiation and intraoral implants, (5) poor oral hygiene and continued use of irritants, (6) poor patient cooperation in managing irradiated tissues or fulfilling home care programs, (7) surgery in the irradiated area, (8) indiscriminate use of prosthetic appliances following radiation therapy, (9) failure to prevent trauma to irradiated bony areas, and (10) presence of numerous physical and nutritional problems prior to therapy. Patients are most vulnerable to osteoradionecrosis of the jaws in the two years following radiotherapy.

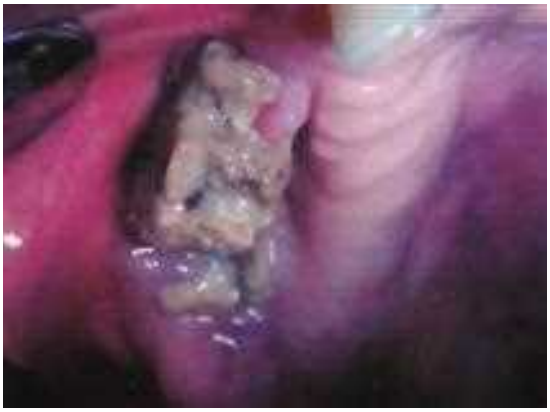


Figure 12-32. Osteoradionecrosis.
This lesion followed heavy X-ray irradiation for epidermoid carcinoma in this area *(Courtesy of Dr Anitha Balan, Department of Oral Medicine and Radiology, Government Dental College, Thiruvananthapuram).*

Laser Radiation

Applications of lasers to biology and medicine began shortly after 1960, while the laser effects on tissues and materials related to dentistry began shortly thereafter. Effects of laser on tooth and pulp were discussed already.

Effect on Soft Tissue. When directed at soft tissue, laser radiation has the ability to produce nonspecific ulceration of the epithelium with acute purulent inflammation. This finding was reported by Taylor and his associates when laser radiation was directed at the tongue of experimental animals.

Electrical Burns

Electrical burns of the oral cavity are seen with an unpleasant frequency in children. This unfortunate injury has been discussed in detail by Gormley and his associates, who also reported 22 cases. They invariably result from an accident in which the child chews on an electrical cord, breaks the insulation and contacts the bare wire or sucks on the socket end of an extension cord.

The resulting burn of the lips, and sometimes of the gingiva and tongue, usually causes destruction and necrosis of a considerable amount of tissue (Fig. 12-33). Developing tooth germs or buds are often destroyed in the accident with permanent cosmetic disfigurement. This type of wound heals relatively slowly.

Cervicofacial Emphysema

Emphysema is a swelling due to the presence of gas or air in the interstices of the connective tissue. There have been numerous cases of emphysema reported involving the cervicofacial and even mediastinal areas following a variety of dental and oral procedures—e.g. tooth extraction; blowing of compressed air into a root canal during endodontic treatment, or into a periodontal pocket; blowing of air from a high- speed air-rotor machine following middle-face fractures; or spontaneously as a result of the patient's breathing actions following some type of surgical procedure, with a break in the tissue permitting air to enter connective tissue spaces.

An analogous problem termed **pneumoparotid** can arise due to entrapment of air in the parotid duct, leading to enlargement of parotid gland caused by air insufflation. This can be occupational (such as in wind instrument players), self-induced, or accidental. Although the Stenson's duct is protected by contraction of the buccinator muscle and

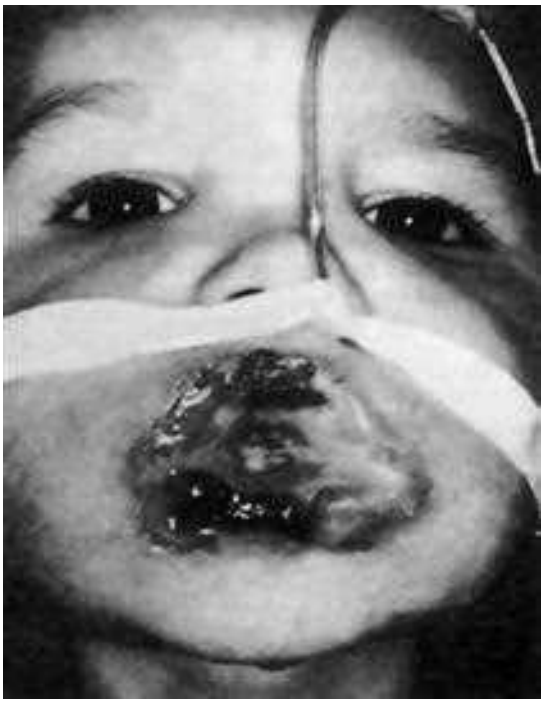


Figure 12-33. Electrical burn.
This severe burn resulted when the child bit an electrical cord carrying a current.

Figure 12-34. Cervicofacial emphysema.
The swelling of the facial soft tissues occurred within a few hours following a dental extraction.

numerous redundant mucosal folds, air enters the parotid ductal system due to dramatic increases in intraoral pressures.

Clinical Features. The emphysema manifests itself as a unilateral swelling of the tissues of the face and/or neck which occurs very rapidly and is generally somewhat painful, particularly during the first few days (Fig. 12-34). Not infrequently, the patient will complain of a 'bubbling' sensation when palpating this tissue and of difficulty in breathing. The facial enlargement is often confused with an angioedema, but it can be differentiated by identifying crepitus within the swelling. Spread into the mediastinum results in dysphagia, or dyspnea. In mediastinal involvement crepitus synchronous with the heartbeat (Hamman's crunch) is heard on cardiac auscultation.

Pneumoparotid appears as a unilateral enlargement of the parotid with demonstration of crepitus on palpation. Frothy air-filled saliva is produced by the parotid duct rather than the clear, water-like secretion.

Treatment and Prognosis. Unfortunately, venous air embolism is an unusual but often fatal complication of this condition. For example, Longenecker has reported that, of six cases of venous air embolism occurring during head and neck surgery, five terminated fatally. If the entrance of air into the venous circulation can be recognized promptly, resuscitation may prevent death. A second complicating factor is the possibility of bacterial infection in the emphysematous connective tissue, microorganisms being carried into the tissues with the air. In such instances, broad-spectrum antibiotic coverage is recommended. Aside from this, there is no particular treatment indicated and the condition will generally resolve within a week.

The treatment for pneumoparotid consists mainly of altering the inciting event to prevent air from entering the parotid duct. Acute symptoms can be treated with antibiotics, hydration, massages, sialagogues, and compresses.

Anesthetic Necrosis

At times, administration of a local anesthetic agent can cause ulceration and necrosis at the site of injection. This necrosis is thought to result from localized ischemia, although the exact cause is unknown. The possible causes include epinephrine content in local anesthetic solution, administration of excess solution in tissue firmly bound to bone, or subperiosteal injection.

Anesthetic necrosis usually appears several days after the procedure and most commonly appears on the hard palate as a well-circumscribed area of ulceration.

Treatment is not needed unless the ulcer fails to heal.

Human Bite
(Morsus humanus)

The human bite is a potentially serious injury which may occur in a variety of situations including quarrels, children's play, child abuse, mental derangements, and sexual assaults or related activities. While the bite may involve any part of the body, the extremities are most frequently involved and, according to a series of approximately 900 cases of human bite injuries reported by Boyce in 1942, about 8% involved the head and neck region. Laskin and Donohue have reported 14 cases, all involving the lips, while Freeman et al, investigated 778 bitemarks and reported that females were bitten more often than males, males were bitten on the arm more than

females, and females were bitten on the breast more often than males. Saiju and Georgescu have reported a rare case of human bite on the eyebrow.

There is great potential for serious infections as well as for marked disfigurement from the human bite. The infections are usually of mixed types of microorganisms and can be difficult to treat, especially since patients frequently delay seeking treatment for several days after the incident because of the embarrassing circumstances involved. There is a major risk of transmission of diseases such as syphilis, hepatitis, and HIV infection through biting.

The human bite also has assumed a very important role in forensic medicine and forensic dentistry, especially in murder, rape, or assault cases in which legal identification of the guilty party has been made through a set of characteristic tooth imprints in bite marks on a breast, neck, or other involved area.

Oral Trauma Related to Sexual Practices

Changes in sexual activities and increasing sexual liberalism in recent years have contributed to the recognition of intraoral lesions that have become relatively common and of diagnostic importance.

The lesion consists of palatal erythema, petechiae, and ecchymoses following fellatio, or oral intercourse, apparently as a result of the physical trauma to the area and/or the negative pressure occurring at the site from irrumation. There are usually multiple lesions, which are most often found at the junction of the hard and soft palate. They heal without treatment within seven to ten days. Typical examples have been reported by Schlesinger and his associates and by Giansanti and his coworkers. Horizontal ulceration of the lingual frenum arises from the act of cunnilingus and they also heal within a week without treatment.

The differential diagnosis is extremely important, since identical lesions at the same site may occur also in infectious mononucleosis, thrombocytopenic purpura or a variety of similar dyscrasias including leukemia in which a secondary thrombocytopenia may exist, and diseases of capillary fragility, among others.

Chemical Injuries of Oral Cavity

The oral cavity frequently manifests a serious reaction to a wide variety of drugs and chemicals, although the mechanism of this reaction may be dissimilar in different cases. In some instances the tissue reaction is that of a local response to a severe irritant or even a caustic used injudiciously. In other cases the drug or chemical is administered systemically, but manifests an oral reaction of a particular type. One of the most common reactions to drugs or chemicals is the allergic phenomenon, the two main types that are of dental interest being: (1) drug allergy, or stomatitis medicamentosa, and (2) contact stomatitis, or stomatitis venenata. Angioneurotic edema is still another allergic phenomenon which will be considered separately.

Nonallergic Reaction to Drugs and Chemicals used Locally

The materials used locally which induce a nonallergic reaction are chiefly irritants or caustics, many of which are used by the dentist in various therapeutic or technical procedures. Some of these substances also constitute occupational hazards, but these will be considered separately.

Aspirin (Acetylsalicylic Acid). Aspirin tablets are used mistakenly by many people as a local obtundent, especially for the relief of toothache. It is also available in a powder form. Although effective if used systemically, they are particularly harmful to the oral mucosa if applied locally. The usual mode of local use is to place the tablet against the offending tooth, allowing the cheek or lip to hold it in position, and to let it dissolve slowly. Within a few minutes a burning sensation of the mucosa will be noted, and the surface becomes blanched or whitened in appearance (Fig. 12-35). The caustic action of the drug causes separation and sloughing of the epithelium and frequently bleeding, especially if the area is traumatized. The healing of the painful 'aspirin burn' usually takes a week or more.

Endodontic Materials. Soft tissue damage resulting in deep spread of inflammation and necrosis may occur due to the usage of some endodontic materials or their injection into the hard tissue. For instance paraformaldehyde is used to devitalize the inflamed pulp. This caustic agent may leak from the pulp chamber into the surrounding tissues and causes necrosis of the gingiva and bone.

Sodium hypochlorite and hydrogen peroxide produces similar damage when injected beyond the apex.

Sodium hypochlorite (NaOCl) is commonly used as root canal irrigant. Due to its efficacy against pathogenic organisms and pulp digestion it is considered to be the medicament of choice. It is found to be sporicidal and virucidal and shows far greater tissue dissolving effects

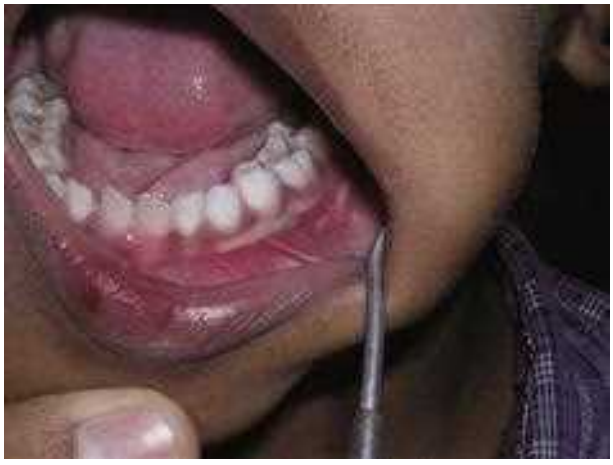


Figure 12-35. Aspirin reaction.
Blanching and sloughing of the epithelium after the local application of an aspirin tablet *(Courtesy of Dr Poonja LS, Dr G Sriram, Dr Vaishali Natu, Nair Hospital Dental College, Mumbai).*

on necrotic than on vital tissues as well as the organic components of the smear layer. Although considered safe, it may cause severe tissue damage if come in contact with the tissues or extruded beyond the apex. On contact with vital tissue, it causes hemolysis, ulceration, facial nerve weakness, and necrosis, inhibits neutrophil migration, and damages endothelial cells and fibroblasts. Inadvertent injection of NaOCl solution into periapical tissues leads to emphysema, caused by oxygen liberation into the tissues, permanent facial and trigeminal nerve weakness and allergic reactions. Bowden, Ethunandan, and Brennan have reported a case of life-threatening airway obstruction secondary to hypochlorite extrusion during root canal treatment.

Gutta-percha is a biologically inert latex material used to obturate, or fill the empty space inside the root of a tooth during endodontic treatment. It is used along with zinc oxide eugenol to attain apical seal. Gutta-percha points extruded past. The apices result in infective periapical periodontitis caused by the transport of bacteria beyond the apex and an incomplete cleansing and foreign body reactions.

Hydrogen peroxide is used commonly in varying concentrations in many branches of dentistry. It is a caustic agent. Upon contact it burn tissues and release toxic free radicals, perhydroxyl anion, or both. It should be handled with care in high concentrations, since it is thermodynamically unstable and may explode if not refrigerated or stored in a dark container.

30–35% hydrogen peroxide (superoxal) is used along with heat (thermocatalytic) for bleaching. This thermocatalytic process damages the tooth by causing irritation to the cementum and periodontal ligament leading to cervical root resorption.

Sodium perborate has been widely used as a mouthwash, bleaching agent, and in dentifrices because of its supposed therapeutic effect on gingival disease. Clinical studies reveal, however, that the compound may produce an erythema of the oral mucosa which may even progress to sloughing of the tissues. In some instances the inflammation was aggravated, and edema and ulceration of mucosa frequently occurred. The lesions healed spontaneously with cessation of treatment.

Carbamide peroxide is used as a component in bleaching preparation. These preparations were reported to be associated with varying degrees of damage to the teeth and the surrounding structures if not used cautiously.

Phenol is widely used in dentistry as a cavity sterilizing agent as well as a cauterizing agent in various procedures. It is extremely caustic and if used carelessly may produce severe painful burns of the oral mucosa and skin which heal slowly (Fig. 12-36).

Silver nitrate is also used extensively in dentistry as a cavity sterilizing agent, topically as a caries-preventive agent and as a chemical cautery. Injudicious or overzealous use may produce painful burns of the oral mucous membranes.

Trichloroacetic acid used as a cauterizing agent, particularly to cauterize gingival tissue when preparing a proximal or gingival cavity, placing a band or taking an impression of a cavity. Because of its extremely caustic nature, this acid may cause serious injury to the mucosa or skin if it is used carelessly.

Figure 12-36. Phenol burn.
Injudicious handling of phenol resulted in severe burns of the lips.

Volatile oils such as oil of cloves, oil of wintergreen, and eucalyptus oil are used in dentistry and can produce mild burns of the mucous membranes.

Miscellaneous Drugs and Chemicals

The various drugs and chemicals listed above constitute only an infinitesimal number of those substances which are of potential danger if used injudiciously in the oral cavity and are included for exemplary purposes only. Any strong acid, alkali, germicidal agent, strong counter-irritant, or even certain plant and animal irritants (Figs. 12-37, 12-38) may produce injury.

Fig. 12-37 Pyrozone burn of the face.

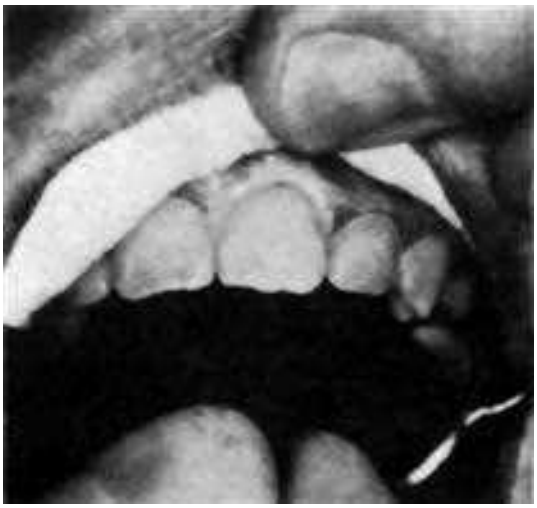


Figure 12-38. Chloral hydrate 'burns' of the gingiva.

NONALLERGIC REACTIONS TO DRUGS AND CHEMICALS USED SYSTEMICALLY

The systemic administration of various drugs and chemicals frequently evokes an oral reaction which is not on the basis of an allergy or sensitivity. This reaction is often a part of a generalized epidermal reaction, but other times it occurs as a specific phenomenon apparently due to the anatomic peculiarities of the oral cavity.

Arsenic in both organic and inorganic forms is sometimes used therapeutically and may produce symptoms of either acute or chronic poisoning. Many cases of arsenic poisoning occur as an occupational hazard because of the wide use of this metal in industry.

Oral Manifestations. These include intense inflammation of oral mucous membranes, and severe gingivitis. The tissues may be painful. Local contact with arsenic trioxide often produces ulceration. Systemic arsenic poisoning also produces excessive salivation.

Bisphosphonate a potent antiresorptive agent, used in the management of benign and malignant diseases involving excessive bone resorption, such as bone lesions of multiple myeloma and metastatic bone diseases. They act by blocking the dissolution of hydroxyapatite, inhibiting differentiation of bone marrow precursors into osteoclasts, and inhibiting the osteoclast function. It causes osteonecrosis in many patients. The incidence of bisphosphonate associated osteonecrosis has been increased recently, and most of the cases involve nitrogen-containing bisphosphonates, mainly pamidronate and zolendronate. Osteonecrosis of the jaw probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling. According to some authors, the predilection for this location may be attributed to the fact that the jaws are the only bone structures submitted to continuous trauma and masticatory stress with exposure to the environment and to oral microorganisms. Dental extractions have been identified as a predisposing factor for osteonecrosis in many cases; but cases of 'spontaneous' exposures and necrosis of the alveolar bone have also been reported.

Hellstein et al, reported 28 suspected cases of osteonecrosis of the jaw and discussed the nomenclature, the clinical and radiographic findings, as well as the main modalities of therapy and prevention. They suggested the term bisphosphonate osteochemonecrosis or bis-phossy jaw, since the features of bisphosphonate-associated osteonecrosis are similar to those found in phossy jaw, the historical occupational osteonecrosis of the jaw caused by exposure to white phosphorus during the manufacture of matches.

Treatment and Prognosis. There is no effective treatment for this condition. Most of the lesions have not responded well to surgical intervention, antibiotic therapy, hyperbaric oxygen therapy, or to the topical use of mouthrinses. Current conservative approach is sequential removal of sequestrum. Removal of the bone sequestrum with minimal epithelial manipulation with topical and systemic antibiotics seem to be the treatment modality of choice.

Bismuth was formerly used widely in the treatment of syphilis, but it has been replaced in recent years by the antibiotics. The use of this metal is still common in treating certain dermatologic disorders as well as various other diseases, so that oral signs are still sometimes seen.

Oral Manifestations. Bismuth pigmentation of the oral mucosa, particularly of the gingiva and buccal mucosa, is the most common oral feature of bismuth therapy and is reported to occur in a high proportion of patients receiving preparations containing the metal.

The pigmentation appears as a 'bismuth line', a thin blue-black line in the marginal gingiva which is sometimes confined to the gingival papilla (Fig. 12-39). There may also be the same type of pigmentation of the buccal mucosa, the lips, the ventral surface of the tongue, or in any localized area of inflammation such as around partially erupted third molars or around the periphery of an ulcer as an anachoretic phenomenon (Fig. 12-40).

This pigment represents precipitated granules of bismuth sulfide produced by the action of hydrogen sulfide on the bismuth compound in the tissues. The hydrogen sulfide is formed through bacterial degradation of organic material or food debris and is most common in sites of food retention. The bismuth line occurs in the majority of patients receiving prolonged bismuth treatment and is more frequent in unclean mouths. Patients receiving this metal also complain occasionally of a burning sensation of the mucosa and a metallic taste in the mouth.

Histologic Features. The granules of the sulfide are seen in the tissue section as small, irregular black collections of pigment, sometimes perivascular in location, but other times diffuse without apparent arrangement (Fig. 12-41). The material may be present in endothelial cells or in mononuclear phagocytes in the tissue, but it usually is in the intercellular tissue. It provokes no foreign body response and may be present even in the absence of inflammation.

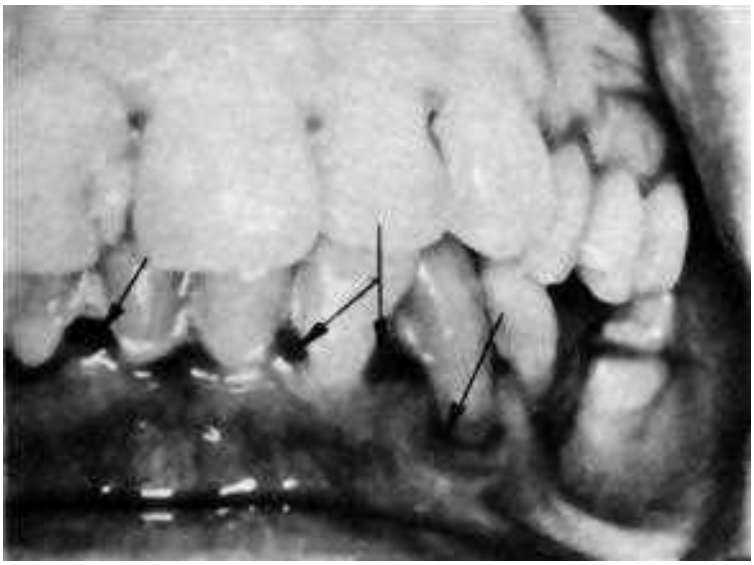


Figure 12-39. Bismuth pigmentation.
The gingiva shows the black line caused by the deposition of bismuth salts.

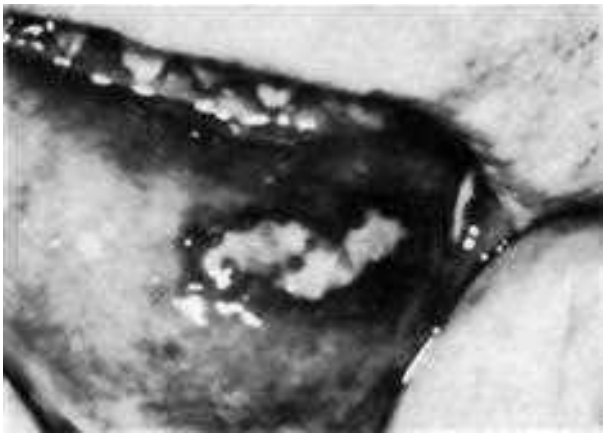


Figure 12-40. Bismuth pigmentation.
Deposition of bismuth around the periphery of this ulcer has produced a black 'halo' effect. Gingival pigmentation is also present.

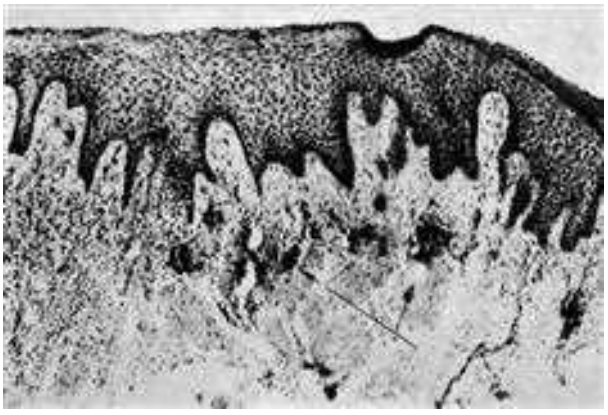


Figure 12-41. Bismuth pigmentation.
Collections of black amorphous material, the bismuth salts, are seen in the photomicrograph of a section through the gingiva.

Treatment and Prognosis. There is no specific treatment for the bismuth line. Once it is established, although it reportedly can be bleached by concentrated hydrogen peroxide. Its prevention by scrupulous oral hygiene during therapy is recommended. The prognosis of the condition is good. If untreated, the line will gradually disappear over a long period of time if use of the bismuth compound is discontinued.

Dilantin Sodium

Dilantin sodium (sodium diphenylhydantoinate) is an anticonvulsant drug, extensively used in the control of epileptic seizures. An unfortunate side effect of its use is fibrous hyperplasia of the gingiva. Most clinicians expect this hyperplasia to occur in less than half the cases, but if good oral hygiene is maintained, the incidence may be less than 10%. Why proliferation of fibrous tissue occurs in one case and not in another is not known, nor is it understood why dilantin stimulates overgrowth of gingival fibrous tissue, Nuki and Cooper have shown experimentally in cats that in the presence of local irritants in the form of orthodontic bands on the teeth and in the absence of brushing to remove plaque and debris, inflammation was produced and gingival enlargement occurred after diphenlhydantoin administration. However, when no bands were present and the teeth were brushed so that there was no irritation, the administration of the drug produced no gingival enlargement. In addition, studies of Shafer and his associates have shown stimulation of wound healing in experimental animals treated with dilantin, presumably as a result of stimulation of fibroblastic proliferation and increased collagen synthesis. In other studies Shafer has also shown remarkable stimulation of growth of human gingival fibroblasts in a tissue culture system after exposure to dilantin. Interestingly, this drug appeared to be cell-specific in his studies, since there was no similar stimulation of other types of cells.

Figure 12-42. Dilantin induced hyperplasia of gingiva, demonstrating remarkable gingival enlargement.
(Courtesy of Dr Jayakumar ND, Saveetha Dental College, Chennai).

Oral Manifestations. Gingival hyperplasia may begin as early as two weeks after dilantin therapy has been instituted, although usually it takes two to three months. The first change noted is a painless increase in the size of the gingiva, starting with the enlargement of one or two interdental papillae. The surface of the gingiva shows an increased stippling and finally a cauliflower, warty, or pebbled surface. As enlargement increases, the gingival tissue becomes lobulated, and clefts remain between each enlarged gingiva in many cases (Fig. 12-42). Palpation reveals that the tissue is dense, resilient and insensitive. It shows little tendency to bleed.

The hyperplasia of oral mucosa is almost entirely confined to the gingival tissues surrounding the teeth. In cases in which a patient is dentulous, but has a few edentulous areas, the gingival tissues around the teeth may show extreme hyperplasia, while the edentulous regions are generally normal in appearance. On rare occasions hyperplasia may occur in localities apart from the gingiva, such as the palate in patients wearing a prosthetic appliance, a probable source of chronic irritation (Fig. 12-43).

Histologic Features. Microscopic study of the gingival tissue reveals a suggestive but not pathognomonic appearance. The stratified squamous epithelium covering the tissue is thick and has a thin keratinized layer. The rete ridges are extremely long and thin, sometimes called 'test-tube' pegs, with considerable confluence, but mitotic figures are seldom seen. The bulk of the tissue is made up of large bundles of collagen fibers interspersed with fibroblasts and fibrocytes (Fig. 12-44). Vascularity is not a prominent feature of the lesion. If chronic inflammation is superimposed on this hyperplasia, plasma cells and leukocytes will be found.

Treatment and Prognosis. No treatment is necessary until the enlargement becomes esthetically objectionable. If the hyperplasia interferes with function, surgical excision is recommended, but the hyperplasia will often recur. Discontinuing use of the drug will result in a gradual diminution of the bulk of the gingiva. Most patients, however, prefer to continue use of the drug and suffer with the hyperplasia rather than resort to some other, less effective drug for the prevention of the epileptic seizures.

Cyclosporine

Cyclosporine is a selective immunosuppressant (suppress helper T cells), used primarily in organ transplant patients to overcome transplant rejection. It causes generalized gingival

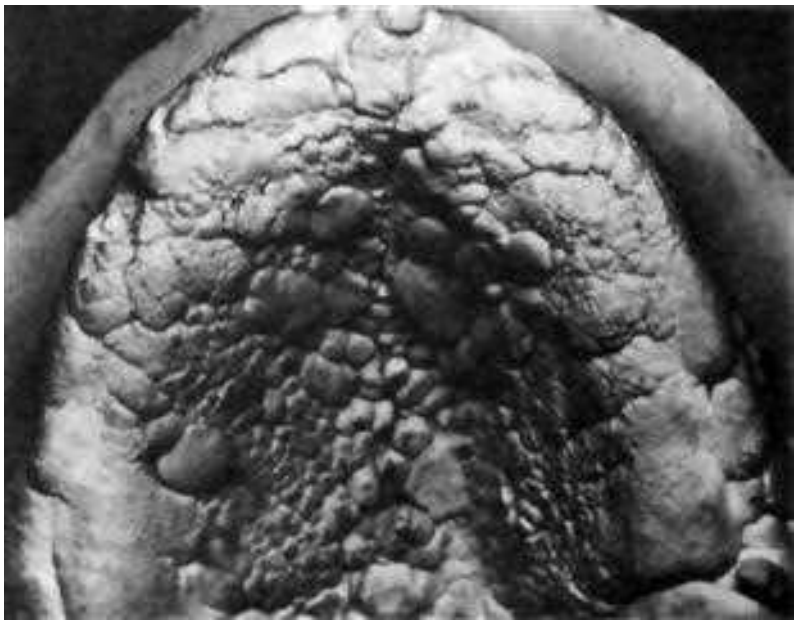


Figure 12-43. Dilantin related gingival enlargement in an edentulous patient, an uncommon situation.
In this case the denture probably acted as a contributing irritating factor. *(Courtesy of Dr Frank R Shroff and Dr B Dallas).*

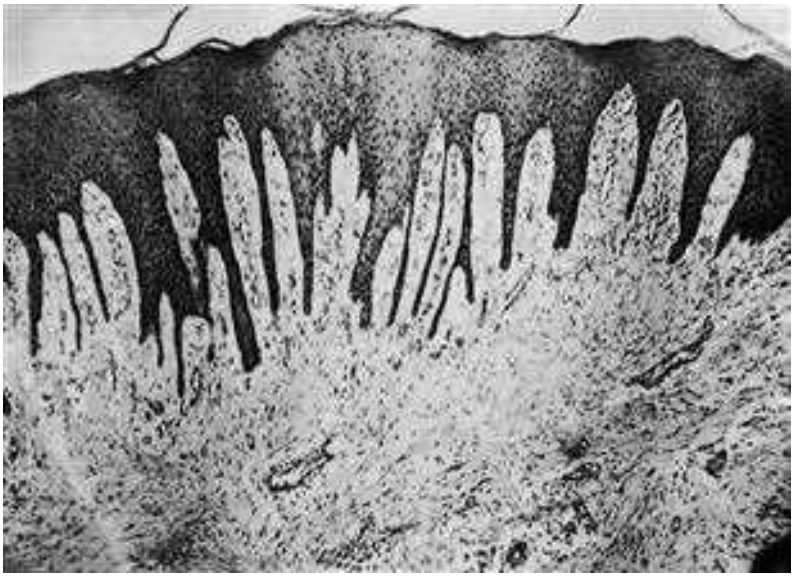


Figure 12-44. Dilantin induced gingival hyperplasia.

hyperplasia and perioral hyperesthesia. The mechanism for this phenomenon is not known.

Clinical Features. Not seen in all patients receiving cyclosporine. Appearance of gingival overgrowth is similar to that induced by dilantin. Presence of local factors aggravates the extent of the lesion.

Nifedipine

Nifedipine is a calcium channel blocker used in cardiovascular disorders. Calcium channel blockers interfere with the production of collagenase, through altered calcium influx into fibroblasts and collagen keeps accumulating without any degradation. Gingival enlargement begins after 1 to 3 months of taking these drugs. Gingiva is firm, nodular, and the clinical appearance is similar to that seen in dilantin and cyclosporine induced gingival hyperplasia.

Lead

Lead poisoning (plumbism) occurs chiefly as an occupational hazard today, but occasionally occurs because of some other accidental exposure of either an acute or chronic nature. In adults the chief means of poisoning is through inhalation of lead vapor or dust. In infants most cases result from ingestion by the child while chewing on wood painted with lead-containing paint. Many other unusual sources of lead may also result in poisoning. It appears that there have been increasing environmental levels of lead in recent years and that much of the increase is related to industry.

Clinical Features. Lead intoxication is manifested by serious gastrointestinal disturbances which include nausea, vomiting, colic, and constipation. A peripheral neuritis also develops which may produce the characteristic wrist-drop or foot-drop. Encephalitis may also occur. Blood changes are those of a hypochromic anemia with basophilic stippling of the red blood cells. Skeletal changes due to deposition of lead in growing bone occur in children and are demonstrable on the radiograph.

Oral Manifestations. The formation of a 'lead line' similar to the 'bismuth line' occurs in lead poisoning. This gray or bluish black line of sulfide pigmentation occurs in the gingiva, but is somewhat more diffuse than that of bismuth. It is also found occasionally in other areas of the oral cavity. Ulcerative stomatitis is an additional reported finding.

Excessive salivation and a metallic taste are also common complaints in this condition, as is swelling of the salivary glands. It is reported by Altshuller and his associates that lead is deposited in the deciduous teeth of children suffering from lead poisoning, and that those teeth may serve as an index of the body burden of lead.

Treatment and Prognosis. Treatment of the oral lesions is secondary to systemic treatment, and the prognosis depends upon the systemic condition of the patient.

Mercury

Mercury poisoning may be acute or chronic, but the systemic reactions in the acute form are so serious that the oral features need not be considered. Chronic mercurialism occurs after prolonged contact with mercurial compounds in a variety of situations, including therapeutic use of these compounds and as an occupational hazard. Intoxication from repeated exposure to mercury is still reported secondary to liquid mercury spills.

Clinical Features. Chronic mercurialism is characterized by gastric disturbances, diarrhea, excitability, insomnia, headache, and mental depression. The patients frequently have fine tremors of the fingers and limbs as well as of the lips and tongue. In addition, a desquamative dermatitis occurs in some

persons. Nephritis is common in acute mercurial poisoning, but does not occur in severe form in the chronic type.

Oral Manifestations. The oral cavity suffers seriously in mercurialism and evidences numerous characteristic but not necessarily pathognomonic signs and symptoms. There is a remarkably increased flow of saliva (ptyalism), and a metallic taste in the mouth due to excretion of mercury in the saliva. The salivary glands may be swollen, and the tongue is also sometimes enlarged and painful. Hyperemia and swelling of the gingiva are occasionally seen.

Ulcerations on the gingiva, palate, and tongue are common. In severe cases pigmentation of the gingiva similar to the bismuth and lead lines may occur as a result of deposition of the dark sulfide compound. Loosening of the teeth, even leading to exfoliation, has been reported.

A toxic reaction from absorption of mercury in dental amalgam has heen reported on a number of occasions. Frykholm, after a thorough review of the literature and numerous studies on the absorption and excretion of mercury, concluded that the amount of estimated exposure to mercury from dental amalgam is not sufficient to cause mercury poisoning in the conventional sense. Nevertheless this exposure may suffice to bring about allergic manifestations in patients sensitive to the mercury, as in the case reported by Fernström and his associates.

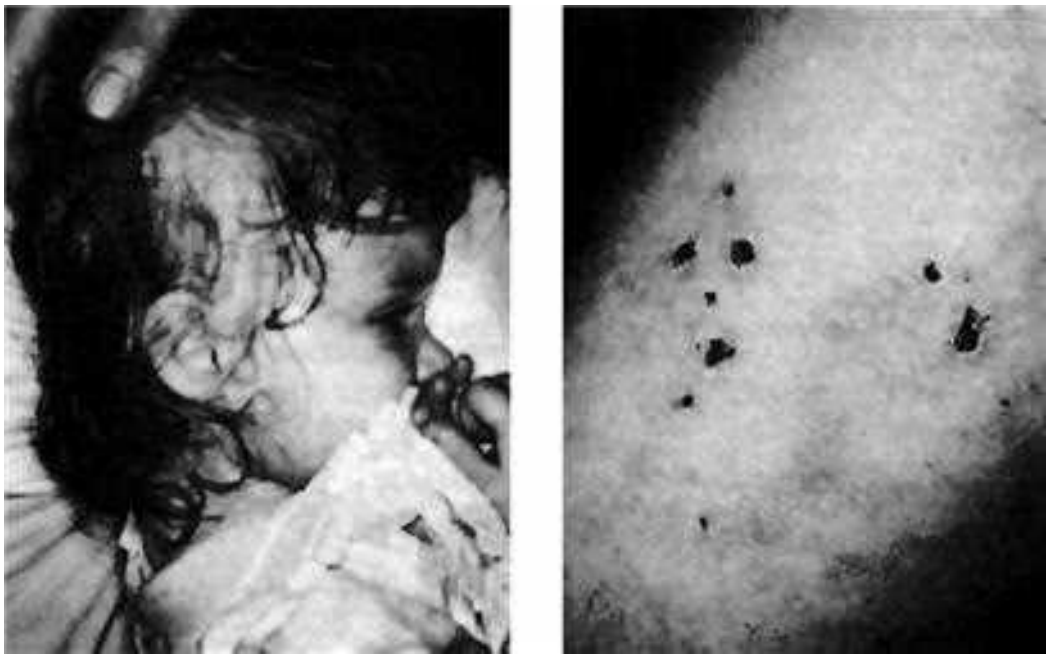
Treatment and Prognosis. The treatment of the oral lesions in chronic mercurialism is supportive only and is secondary to the treatment of the poisoning itself. The prognosis is usually good, although severe periodontal destruction and loss of teeth may occur.

Acrodynia
(Pink disease, Swift's disease)

Acrodynia is an uncommon disease of unknown etiology, with striking cutaneous manifestations. Warkany and Hubbard established the cause of the disease as a mercurial toxicity reaction, either an actual mercury poisoning or, more likely, an idiosyncrasy to the metal. The source of the mercury is usually a teething powder, ammoniated mercury ointment, calomel lotion or bichloride of mercury disinfectant.

Clinical Features. Acrodynia occurs most frequently in young infants before the age of two years, although children are occasionally affected up to the age of five or six years. The skin, particularly of the hands, feet, nose, ears, and cheeks, becomes red or pink and has a cold, clammy feeling. The appearance has been described as resembling raw beef. The skin over the affected areas peels frequently during the course of the disease. The patients also have a maculopapular rash which is extremely pruritic. Severe sweating is an almost constant feature of acrodynia. Other features are a state of extreme irritability, photophobia with lacrimation, muscular weakness, tachycardia, hypertension, insomnia, gastrointestinal upset, and stomatitis. The children will frequently tear their hair out in patches (Fig. 12-45).

The excretion of mercury from the body appears to be a variable phenomenon. For this reason the recovery of unusual amounts of mercury from the urine is not always possible.



A B

Figure 12-45. Acrodynia.
The child shows patchy loss of hair and numerous lesions of the skin, which are scabbed from the scratching due to the severe pruritus. Premature exfoliation of numerous deciduous teeth had also occurred *(Courtesy of Dr Nathaniel Rowe)*.

Oral Manifestations. Patients with acrodynia exhibit profuse salivation and often much 'dribbling.' The gingiva becomes extremely sensitive or painful and may exhibit ulcerations. Bruxism is a common finding and loosening and premature shedding of teeth often occurs; many times the child will extract loose teeth with his/her fingers. Mastication is difficult because of the pain.

Treatment and Prognosis. It is crucial to identify and remove the source of mercury. Immediate chelation therapy is the standard of care for a patient showing symptoms of severe mercury poisoning. The administration of dimercaprol, D-pencillamine, or DMSA, 2,3-dimercapto-1-propanesulfonic acid has proved successful in most cases unless the disease is of long duration. Some of the toxic effects of mercury are in some cases partially or wholly reversible. However, heavy or prolonged exposure can do irreversible damage, particularly in fetuses, infants, and young children.

Silver
(Argyria, argyrosis)

Chronic exposure to silver compounds may occur as an occupational hazard or as the result of therapeutic use of silver compounds such as silver arsphenamine or silver nitrate. It results in a permanent pigmentation of the skin and mucous membranes. Appearance of a slate-blue silver line along the gingival margins arising due to the deposition of metallic silver and silver sulfide pigments is one of the earliest signs of argyria. The pigmentation of the oral mucous membrane is diffusely dispersed throughout the oral cavity. The sclera and the nails are also pigmented. There are usually no other signs or symptoms, either local or systemic, associated with argyria.

Amalgam tattoo of oral mucous membrane is a relatively common finding in dental practice, generally occurring in one of four ways, according to Buchner and Hansen: (1) from condensation in gingiva during amalgam restorative work, (2) from particles entering mucosa lacerated by revolving instruments during removal of old amalgam restorations, (3) from broken pieces introduced into a socket or beneath periosteum during tooth extraction, or (4) from particles entering a surgical wound during root canal treatment with a retrograde amalgam filling.

Clinical Features. Amalgam tattoo appears as macules, or rarely, as slightly raised black, blue, or gray lesion. The most common locations for amalgam tattoos were gingiva, buccal mucosa, and alveolar mucosa. This tattoo has frequently been mistaken for a melanin-pigmented lesion, and in some cases biopsy is necessary to differentiate if the amalgam fragments are too small or diffuse to be visible on the dental radiograph. When the amalgam fragments are embedded within bone, they may be mistaken for a variety of other foreign bodies (Fig. 12-46).

Histologic Features. Microscopically, the dental amalgam fragments frequently show no tissue reaction to their presence, even no inflammatory response (Fig. 12-47). However, in 38% of the cases there was a chronic inflammatory response, usually manifesting as a foreign body granuloma with either foreign body giant cells or Langhans giant cells. In 17% of the cases there was a macrophagic reaction of some type, with or without a chronic inflammatory cell response.

The amalgam fragments appear as black or olive-brown granules or even as macroscopic pieces of material which can be seen plainly in the paraffin-embedded specimen as silver-gray flecks in the tissue. These granules are prominently arranged in a linear fashion along collagen fibers and around blood vessels. In addition, they are found around nerve sheaths and striated muscle fibers and along the basement membrane of mucosal epithelium.

Harrison and his associates have studied these tattoos by electron microscope and electron probe analysis and found that the original mercury-silver-tin amalgam undergoes eventual corrosion, leaving chiefly silver in the extracellular sites.

Tetracycline

Discoloration of either deciduous or permanent teeth may occur as a result of tetracycline deposition during prophylactic or therapeutic regimens instituted either in the pregnant female or postpartum in the infant. Tetracycline and its homologues have a selective affinity for deposition in bone and tooth substance, possibly through the formation of a complex with calcium ions in the surface of the microcrystals of hydroxyapatite.

The severity of the staining by tetracycline is determined by the stage of tooth development at the time of drug administration. Since tetracycline does cross the placental barrier, it may involve those deciduous teeth developing antepartum, although the discoloration itself depends upon the dosage, the length of time over which administration occurred, and the form of the tetracycline. Moffitt and his coworkers have emphasized that the critical period for tetracycline-induced discoloration in the deciduous dentition (the period of mineralization of the first millimeter of dentin nearest the dentinoenamel junction) is four months *in utero* to three months postpartum for maxillary and mandibular incisors and five months *in utero* to nine months postpartum for maxillary and mandibular canines. The period for permanent maxillary and mandibular incisors and canines is three to five months postpartum to about seven years of age. The age at which tetracycline administration occurred can easily be pinpointed by reference to a chart on the chronology of odontogenesis.

According to Grossman and his associates, the use of oxytetracycline, or possibly doxycycline, may diminish tooth discoloration if tetracycline therapy is indicated in the pregnant female or during the first six to seven years of life. After this age, the probability of discoloration need not be considered since the cosmetically important anterior teeth have completed their formation.

Significant discoloration of the teeth is also produced by minocycline hydrochloride, a semisynthetic derivative of tetracycline. Binding of minocycline to certain types of collagenous tissues like dentin, dental pulp, bone, and dermis,

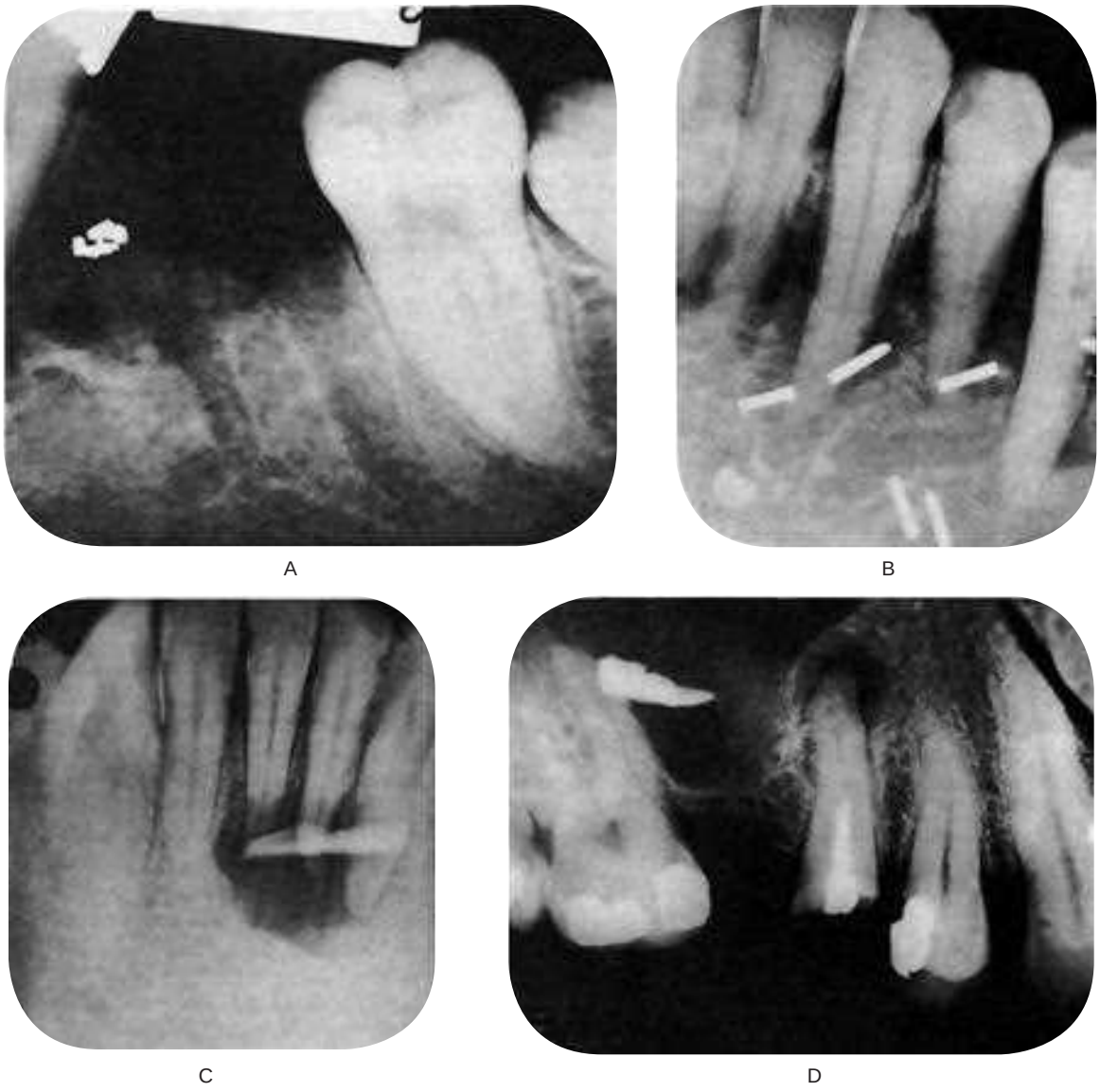


Figure 12-46. Amalgam in bone.
Dental amalgam in the bone **(A)** is compared to other foreign bodies seen occasionally such as radon seeds for radiation of a tumor **(B)**, embedded glass after an automobile accident **(C)**, and a bomb-shell fragment **(D)**. *(B, Courtesy of Dr Henry M, Swenson C, Dr G Thaddeos Gregory, Dr Raymond Price).*

results in oxidation and produces the discoloration. The stained pulp is seen through the overlying translucent dentin and enamel.

Clinical Features. The teeth affected by tetracycline appear to have a yellowish or brownish-gray discoloration which is most pronounced at the time of eruption of the teeth. This discoloration gradually becomes more brownish after exposure to light. Oxytetracycline and tetracycline give a yellowish color, whereas chlortetracycline tends to cause a brownish-gray color. Tetracycline itself fluoresces under ultraviolet light and, accordingly, the teeth involved by its discoloration also fluoresce a bright yellow under ultraviolet light. However, in time this fluorescence gradually diminishes. It has been shown by Wallman and Hilton and by Zussman that the dentin is more heavily stained than the enamel.

Minocycline hydrochloride causes discoloration of the skin, nails, conjunctiva, bone, and teeth. Palate or anterior alveolar mucosa has a distinctive blue-gray appearance due to the black bone showing through the thin, translucent mucosa. The incisal edge of the fully erupted teeth reveal a blue-gray discoloration, with the middle one third being maximally involved and the exposed roots of the erupted teeth reveal dark green discoloration. The roots of developing teeth show a dark black color.

Cancer Chemotherapeutic Agents

A chemically very diverse group of drugs and agents has come into recent use for the treatment of certain malignant neoplasms. Their chief function is the destruction of malignant cells. Most of these cytotoxic agents exert their effect preferentially against

Figure 12-47. Amalgam tattoo.
The black deposits of amalgam exhibit no surrounding tissue reaction.

cells in mitosis. Unfortunately, in addition to neoplastic cells, which undergo rapid division, certain normal cells including the cells of the oral and gastrointestinal mucosa, bone marrow, and skin also exhibit a similar degree of mitotic activity and are especially prone to manifest the toxic and damaging effects of the antineoplastic agents. Newer and experimental approaches like hematopoietic stem cell transplant (especially in treating myeloma, lymphoma, and leukemia) and isolated infusion of chemotherapy (to treat neoplasms in the liver and lung) are in use.

Clinical Features. Cancer chemotherapeutic agents are grouped into: (1) alkylating agents, (2) antimetabolites, (3) antitumor antibiotics, (4) plant alkaloids, (5) nitrosoureas, (6) enzymes, (7) hormonally active agents, and (8) miscellaneous compounds.

Because the major effect of these materials on cells and tissues is similar, regardless of each agent's specific mechanisms of action, there are a few general manifestations of the group as a whole that can be emphasized. These are: (1) alopecia, due to arrest of mitosis of the rapidly germinating hair roots, (2) stomatitis, which may take a variety of forms, and (3) radiation recall or radiation sensitization, a reactivation of radiation reaction within the field of radiation following administration of certain of the antineoplastic agents.

Oral Manifestations. The most common oral reaction is mucosal erosion and ulceration, frequently diffuse and multiple, often related to the neutropenia produced by the drug but occasionally occurring in its absence. This may occur anywhere in the mouth but is most likely to be seen on the lips, tongue, and buccal mucosa. Hemorrhage is also a common manifestation resulting from the thromboeytopenia secondary to the drug therapy. These reactions do not occur following use of all cancer chemotherapeutic agents but are especially common with the alkylating, antimetabolite, and antitumor antibiotic groups.

Another oral finding in patients undergoing this type of therapy is the presence of any one of a variety of specific or nonspecific infections (commonly herpes simplex infection, candida infection, or infection by staphylococcal or streptococcal organisms), especially since many of these patients are also immunosuppressed. Finally, hyperpigmentation of oral mucosa has been reported occasionally, especially in patients receiving alkylating agents and antitumor antibiotics.

Treatment. There is no specific treatment for the oral lesions which, although severe, must be considered of only secondary importance to the patient's major problem.

OCCUPATIONAL INJURIES OF THE ORAL CAVITY

Occupational injuries of the oral cavity occur as a result of work or occupational activity. In recent years, industrial health programs have recognized the necessity of maintaining oral health and have stressed the need for special safety measures to prevent injuries to the oral and paraoral structures.
The inherent dangers in many occupations have been recognized and preventive measures have been taken to avoid injuries. Such remarkable advances have been made in the application of organic chemicals in industrial techniques that health officers, including the dentist, must constantly be alert against new hazards. Examples of occupational injuries are listed in Table 12-1.

The examination of the oral cavity in the study of occupational disease is of generally accepted importance, since local effects are recorded both in the teeth themselves and in the soft tissues. Dentin and enamel damage is usually

Table 12-2: Oral manifestations of occupational disease according to the etiologic agent*

Etiologic agent			Occupation	Possible oral manifestations
Physical states	Principal action	Specific factor		
Solid	Physical	Instruments for prehension	Cobblers, carpenters, glass bowers, musicians (wind instruments), seamstresses	Localized abrasion
	Chemical	Tar	Fishermen, asphalt and coal tar workers, pavers, pitch roofers, wood preservers	Stomatitis, carcinoma of lip and mucosa
Dust	Physical	Inorganic copper, iron, nickel, chromium, coal, etc.	Bronzers, cement workers, electrotypers, grinders (metal), miners, stone cutters	Staining of teeth, pigmentation of gingiva, generalized abrasions, calculus, gingivostomatitis, hemorrhage
		Organic bone, celluloid, sawdust, flour, tobacco	Bone, celluloid, flour, sawmill, textile, and tobaccoworkers	Staining of teeth, pigmentation of gingiva, generalized abrasion, calculus, gingivo-stomatitis, hemorrhage
	Chemical	Inorganic Arsenic	Chemical workers, electroplaters, metal refiners, rubber mixers lead smelters, insecticide makers	Necrosis of bone
		Bismuth	Bismuth handlers, dusting powder makers	Blue pigmentation of gingiva, oral mucosa, gingivostomatitis
		Chromium	Aniline compound, chrome, photographic and steel workers, blue printers, rubber mixers	Necrosis of bone, ulceration of oral tissue
		Fluorine	Cryolite workers	Osteosclerosis
		Lead	Electrotypers, insecticide and storage battery makers, lead refiners printers, rubber compounders	Blue-black pigmentation of gingiva, gingivostomatitis
		Mercury	Bronzers (gun barrels), battery and paint makers, dentists, detonators, explosives and mercury salts workers	Gingivostomatitis, osteomyelitis, pytalism
		Phosphorus (white, yellow)	Brass founders, match factory, phosphor bronze workers, fertilizer and fireworks makers	Gingivostomatitis, ulceration of oral tissues, osteomyelitis
		Organic sugar	Refiners, bakers, candy makers	Caries
Liquid		Hot food (coffee, tea, soup)	Tasters	Stomatitis, leukoplakia
	Physical	Aniline	Aniline, coal tar, explosives workers, painters, tannery workers, vulcanizers	Blue coloration of lips and gingiva
		Benzene	Coke oven and lacquer workers, dry cleaners, vulcanizers, smokeless powder makers	Hemorrhage from gingiva, stomatitis, blue coloration of lips
	Chemical	Cresol	Coal tar, rubber, tar, distillery and surgical dressing workers, disinfectant markers	Stomatitis
		Wine and liquor atmosphere	Tasters	Anesthesia and paresthesia of tongue
		Increased pressure	Divers, caisson workers	Bleeding from gingiva
		Decreased pressure	Aviators	Bleeding from gingiva
Gas	Physical	Acids: H_2SO_4, HNO_3, HCl, HF	Acid and cartridge dippers, petroleum refiners, explosives and gun cotton workers, galvanizers	Bleeding, stomatitis, decalcification of enamel and dentin
		Amyl acetate	Alcohol, distillery, explosives, shellac, smokeless powder and shoe factory workers	Stomatitis
		Acrolein	Bone grinders, lard, soap, linoleum markers, varnish boilers	Stomatitis
		SO_2, NH_3, BR, Cl_2	Acetylene, dye, photographic film, phosgene markers, sugar refiners, refrigerating plant, disinfectant, laundry workers	Stomatitis
	Chemical	CO, CO_2	Miners, smelters, gasoline motor workers	Coloration of lips (cherry red, blue)
Ray	Physico-chemical	Radium, X-ray	Technicians, watch dial painters, research men	Gingivitis, periodontitis, osteomyelitis and necrosis, xerostomia, osteosclerosis
		Actinic	Sailors, fishermen	Carcinoma of lip

**From I Schour and BG Sarnat: Oral manifestations of occupational origin. J Am Med Assoc, 120: 1197 1942. (Courtesy of Dr Isaac Schour).*

permanent and is an indicator of past occupation. Saliva and blood stream transmit the systemic effects to the oral cavity. Prevention of these diseases must be the primary goal of our public health authorities, although early recognition and treatment of oral occupational diseases are important.

OCCLUSAL TRAUMA

Occlusal forces can cause changes in the alveolar bone and periodontal connective tissue both in the presence and in the absence of periodontitis. Occlusion and local irritants are two

factors in the etiology and pathogenesis of periodontal disease. Occlusal trauma and periodontal inflammation may act as co-destructive agents in periodontal disease. Excessive occlusal forces result in typical changes in periodontal tissues. These may be acute or chronic. Acute trauma occurs when biting on a hard food substance or a high point of a restoration. This causes acute inflammation of the periodontal ligament and results in pain, sensitivity to percussion, and slight mobility. If left untreated, it progresses to necrosis.

An acute traumatic force sufficient to produce traumatic injury to the periodontium also results in rather specific changes in the tooth attachment apparatus. For example, a force, which tips a tooth sharply to the buccal side, results in a crushing of the periodontal ligament fibers and perhaps that of the alveolar crest bone. The blood vessels in the involved area become thrombosed, and edema and extravasation of blood occur. On the opposite side of the tooth, there is often a tearing of the periodontal ligament, and sometimes cementum or bone is torn loose. Since the tooth rotates around a fulcrum point slightly apical to the midroot, the same changes may occur near the apex on the opposite side. These changes result in tenderness of the tooth for a few days, but if the forces are not grossly excessive, eventually the damaged alveolar crest bone will be resorbed. New periodontal fibers, cementum, and bone develop, and after a few weeks the tissues will return to normal, with the periodontal ligament space wider or the tooth reoriented in a new position.

When excessive forces occur in different and alternating directions, as may happen in cases of cusp interference, destruction of the supporting bone may occur around the entire periphery of the root, resulting in widening of the periodontal ligament space. This in turn, by interfering with mastication, favors collection of debris on teeth and predisposes to further periodontal disease.

Chronic occlusal trauma is relatively more common than acute forms. The most common cause is faulty occlusion. Physiological tooth wear, drifting, parafunctional habits like bruxism, clenching, and improper orthodontic tooth movement are the causes for chronic trauma.

In chronic trauma, the periodontal ligament gradually becomes denser, and the periodontal space widens. The alveolar bone also becomes denser and the teeth will show obvious 'wear patterns', with definite facets on the crowns of teeth.

Results of various types of trauma on the periodontium have been studied experimentally in laboratory animals. For example, Wentz and his colleagues subjected the premolar teeth of rhesus monkeys to excessive occlusal stresses, which tended to move the teeth buccally upon closure and lingually when the mouth was opened. Histologic studies after three days showed compression and pressure necrosis of the periodontal ligament, thrombosis of blood vessels, and the beginning of bone resorption at the buccal alveolar margin and lingual apical area (Figs. 12-48, 12-49A). Even though the excessive force was of three days duration, both areas

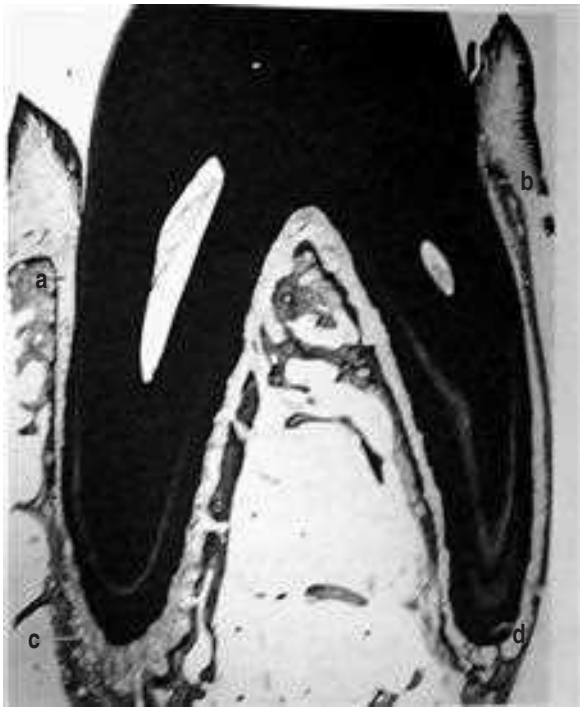
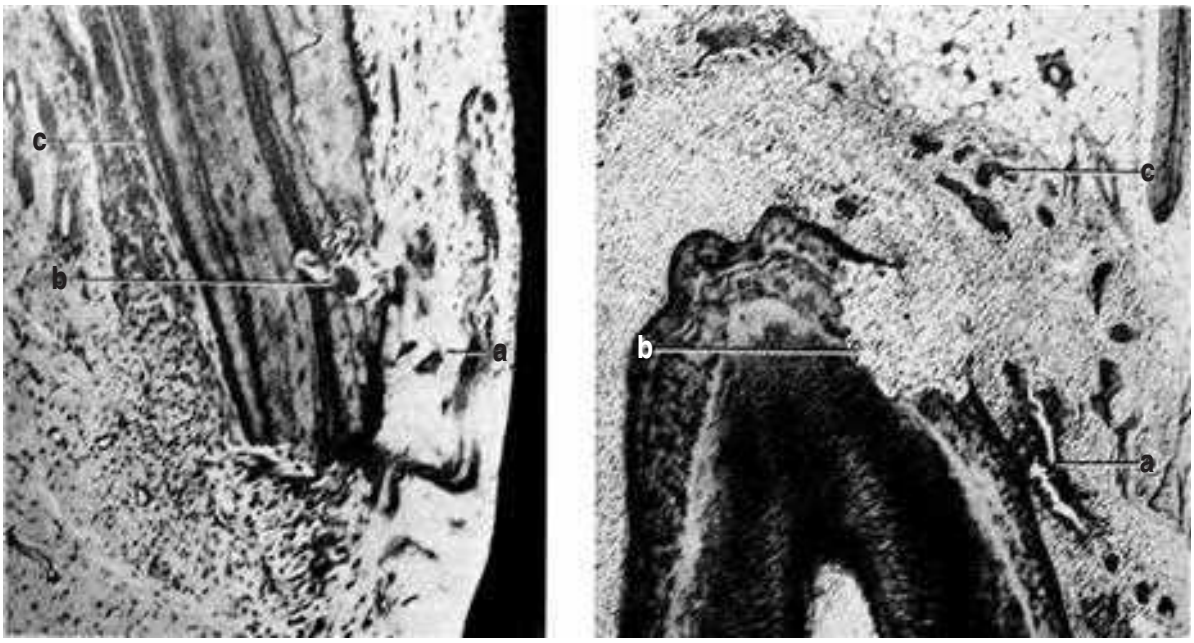


Figure 12-48. Periodontal traumatism.
A buccolingual section through the premolar of a rhesus monkey after excessive occlusal stresses had been applied for three days. Buccal alveolar margin (a), lingual alveolar margin (b), apex of mesiobuccal root (c), and apical area of lingual root (d). Note pressure necrosis at (a) and resorption of bone at (d). *(Courtesy of Dr Frank M Wentz: J Periodontol, 29: 117, 1958).*



A B

Figure 12-49. Periodontal traumatism.
A, Reaction of tissues after three days; high magnification of the pressure area (a) in Figure 12-48. Area of necrosis in the periodontal ligament (a), resorption of bone (b), and deposition of new bone (c). B, Reaction of tissues after 14 days; extensive necrosis near palatal root (a). Resorption has eliminated the area of compression (b, c). *(Courtesy of Dr Frank M Wentz: J Periodontol, 29: 117, 1958).*

showed undermining resorption of alveolar bone, while on the opposite sides of the root there was evidence of new bone formation on the endosteal surface of the alveolar bone. The characteristic cellular picture of inflammation was not present. After 14 days, the premolars used in the experiment were very loose. Histologic study revealed more extensive necrosis, undermining resorption of the bone and the adjoining root, and new bone formation on the opposite side of the root (Fig. 12-49B). After three, and later six months, involved teeth were still loose, but the traumatic tissue changes were no longer present. The periodontal ligament was lengthened, however, and the periodontal space was much wider (average 0.65 mm as compared to 0.19 mm in the control). New bone formation was noted on the buccal periosteal surface of the alveolar process. At no time was gingivitis or periodontitis noted. This experiment illustrates the extent of damage to the periodontium that can occur from excessive occlusal stresses. If the damage is not enough to cause exfoliation of the tooth, the periodontium is gradually adapted to withstand the added stress.

Management. In those cases in which the trauma is not immediately self-corrective, it is imperative that correction of the occlusal relation, elimination of cuspal interference, and fixation or splinting of loose teeth be carried out to prevent further damage.

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CHAPTER 13

Regressive Alterations of the Teeth

■ R RAJENDRAN

CHAPTER OUTLINE

Regressive changes in the dental tissues include a variety of alterations that are not necessarily related either etiologically or pathogenetically. Some of the changes to be considered here are associated with the general aging process of the individual. Others arise as a result of injury to the tissues. Still other regressive changes of teeth occur with such frequency that there is some doubt whether they should actually be considered pathologic. None of the lesions discussed here can be regarded as developmental abnormalities or as inflammatory lesions. They are brought together in this chapter because they do represent what must be considered lesions of a retrograde nature.

ATTRITION, ABRASION AND EROSION

Mechanical wear and tear of tooth substance is a consequence of both physiological and pathological means and therefore different adaptive strategies have evolved to tackle this situation. A disease state arises when this delicate balance goes awry resulting in early dissolution and loss of tooth substance with subsequent involvement of pulpal and periapical tissues. It is currently acknowledged that there are several mechanisms that contribute to tooth wear. These include abrasion resulting from the friction of exogenous material forced over tooth surfaces (e.g. masticating food) or the use of teeth as 'tools', erosion resulting from the chemical dissolution of tooth surfaces (e.g. effects of acid from various sources or from a highly acidic diet), and attrition from tooth-to-tooth contact (e.g. night grinding). These mechanisms most often occur together, each acting at different intensity and duration in a continuously changing salivary medium, producing immensely variable patterns and degrees of wear.

Attrition

Attrition may be defined as the physiologic wearing away of a tooth as a result of tooth-to-tooth contact, as in mastication. This occurs only on the occlusal, incisal, and proximal surfaces of teeth, not on other surfaces unless a very unusual occlusal relation or malocclusion exists. **This phenomenon is physiologic rather than pathologic**, and it is associated with the aging process. The older a person becomes, the more attrition is exhibited.

Attrition commences at the time contact or occlusion occurs between adjacent or opposing teeth. It may be seen in the deciduous dentition as well as in the permanent, but severe attrition is seldom seen in primary teeth because they are not retained normally for any great period of time. Occasionally; however, children may suffer from either dentinogenesis imperfecta or amelogenesis imperfecta, and in both diseases pronounced attrition may result from ordinary masticatory stresses.

The first clinical manifestation of attrition may be the appearance of a small polished facet on a cusp tip or ridge or a slight flattening of an incisal edge. Because of the slight mobility of the teeth in their sockets, a manifestation of the resiliency of the periodontal ligament, similar facets occur at the contact points on the proximal surfaces of the teeth. As the person becomes older and the wear continues, there is gradual reduction in cusp height and consequent flattening of the occlusal inclined planes. According to Robinson and his associates, there is also shortening of the length of the

dental arch due to reduction in the mesiodistal diameters of the teeth through proximal attrition.

Only minor variation in the hardness of tooth enamel exists between individuals; nevertheless considerable variation in the degree of attrition is observed clinically. Men usually exhibit more severe attrition than women of comparable age, probably as a result of the greater masticatory force of men. Variation also may be a result of differences in the coarseness of the diet or of habits such as chewing tobacco or bruxism either of which would predispose to more rapid attrition. Certain occupations, in which the person is exposed to an atmosphere of abrasive dust and cannot avoid getting the material into his/her mouth, also are important in the etiology of severe attrition.

Advanced attrition, in which the enamel has been completely worn away in one or more areas, sometimes results in an extrinsic yellow or brown staining of the exposed dentin from food or tobacco (Figs. 13-1, 13-2). Provided there is no premature loss of the teeth, attrition may progress to the point of complete loss of cuspal interdigitation. In some cases the teeth may be worn down nearly to the gingiva, but this extreme degree is unusual even in elderly persons.

The exposure of dentinal tubules and the subsequent irritation of odontoblastic processes result in formation of secondary dentin (q.v.) pulpal to the primary dentin, and this serves as an aid to protect the pulp from further injury. The rate of secondary dentin deposition is usually sufficient to preclude the possibility of pulp exposure through attrition alone. Sometimes, as the teeth wear down by attrition, little tendrils of pulp horn remain and are exposed to the oral cavity. These can be seen only when the tooth is examined carefully under a magnifying lens.

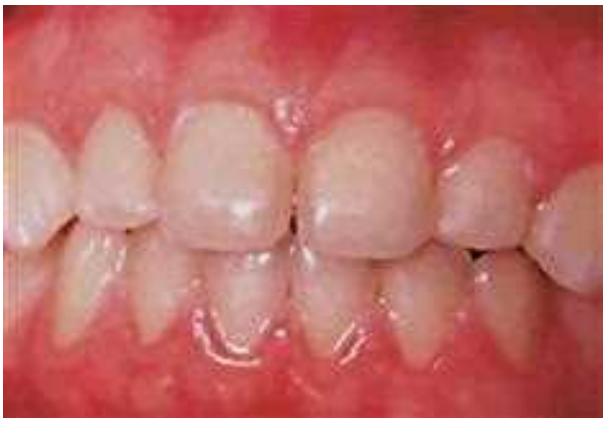


Figure 13-1. Advanced attrition.
This 14-year-old female exhibits total loss of surface characteristics and polished appearance of enamel on her maxillary incisors. The enamel layer was also very thin.

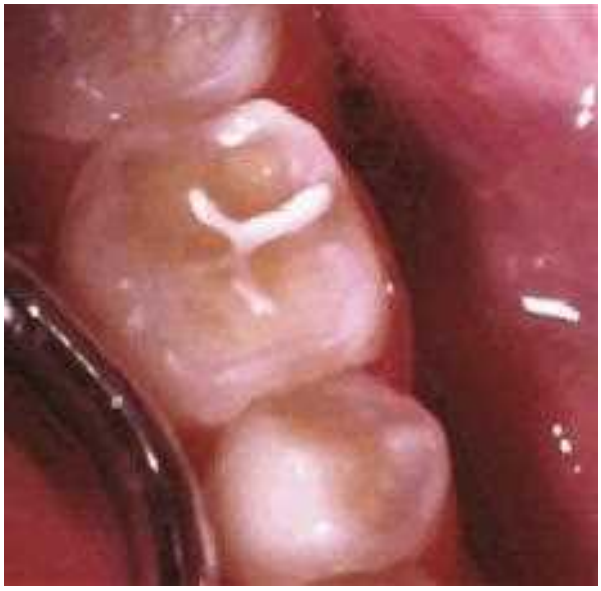


Figure 13-2. Advanced attrition.
The fissure sealant in this 14-year-old boy stands 'raised' from surrounding eroded occlusal enamel.

Abrasion

Abrasion is the pathologic wearing away of tooth substance through some abnormal mechanical process. Abrasion usually occurs on the exposed root surfaces of teeth, but under certain circumstances it may be seen elsewhere, such as on incisal or proximal surfaces.

Robinson stated that the most common cause of abrasion of root surfaces is the use of an abrasive dentifrice. Although modern dentifrices are not sufficiently abrasive to damage intact enamel severely, they can cause remarkable wear of cementum and dentin if the toothbrush carrying the dentifrice is injudiciously used, particularly in a horizontal rather than vertical direction. In such cases abrasion caused by a dentifrice manifests itself usually as a V-shaped or wedge-shaped ditch on the root side of the cementoenamel junction in teeth with some gingival recession (Fig. 13-3). The angle formed in the depth of the lesion, as well as that at the enamel edge, is a rather sharp one, and the exposed dentin appears highly polished. It has been shown by Kitchin and by Ervin and Bucher that some degree of tooth root exposure is a common clinical finding, and a 66% incidence of abrasion among 1,252 patients

Figure 13-3. Toothbrush abrasion.
Severe gingival notching of the teeth as a result of improper toothbrushing habits is clearly seen.

examined was reported by Ervin and Bucher. The fact that abrasion was more common on the left side of the mouth in right-handed people, and vice versa, suggested that improper toothbrushing caused abrasion. The results of a study by the American Dental Association on the comparative abrasiveness of a number of popular dentifrices are shown in Table 13-1 and indicate the wide variation among the commercial products.

Other less common forms of abrasion may be related to habit or to the occupation of the patient. The habitual opening of bobby pins with the teeth may result in a notching of the incisal edge of one maxillary central incisor (Fig. 13-4). Similar notching may be noted in carpenters, shoemakers, or tailors who hold nails, tacks, or pins between their teeth. Habitual pipe smokers may develop notching of the teeth that conforms to the shape of the pipe stem (Fig. 13-5). The improper use of dental floss and toothpicks may produce lesions on the proximal exposed root surface, which also should be considered a form of abrasion.

It is apparent that though the etiology of abrasion can be varied, the pathogenesis under these different conditions is essentially identical. The loss of tooth substance that occurs by one means or another is certainly pathologic but should present no problem in diagnosis.

Table 13-1: Abrasiveness of dentifrices

Product	Manufacturer index	Abrasivity
T-Lak	Laboratories Cazé	20 (20–21)⁺ (Lowest)
Thermodent	Chas. Pfizer & Co.	24 (23–24)
Listerine	Warner-Lambert Pharm. Co.	26 (22–30)
Pepsodent*	Lever Brothers Co.	26 (23–29)
Amm-i-dent	Block Drug Co.	33 (31–34)
Colgate with MFP	Colgate-Palmolive Co.	51 (46–56)
Ultra-Brite	Colgate-Palmolive Co.	64 (52–82)
Macleans,* Spearmint	Beecham Inc.	66 (66)
Macleans,* regular	Beecham Inc.	70 (68–72)
Pearl Drops	Cameo Chemicals	72 (65–83)
Crest, mint*	Procter & Gamble Co.	81 (71–90)
Close-up	Lever Brothers Co.	87 (70–101)
Macleans, Spearmint	Beecham Inc.	93 (85–99)
Macleans, regular	Beecham Inc.	93 (74–103)
Crest, regular*	Procter & Gamble Co.	95 (77–110)
Gleem	Procter & Gamble Co.	106 (88–136)
Phillips	Sterling Drug Inc.	114 (111–116)
Vote	Bristol-Myers Co.	134 (112–162)
Sensodyne	Block Drug Co., Inc.	157 (151–168)
Iodent No. 2	Iodent Co.	174 (172–176)
Smokers toothpaste	Walgreen Lab., Inc.	202 (198–205) (Highest)

Modified from American Dental Association Report of the Council on Dental Therapeutics: Abrasivity of current dentifrices. J Am Dent Assoc, 81:1177, 1970. Copyright by the American Dental Association. Reprinted by permission.

**New formulation.*

⁺Average and range.

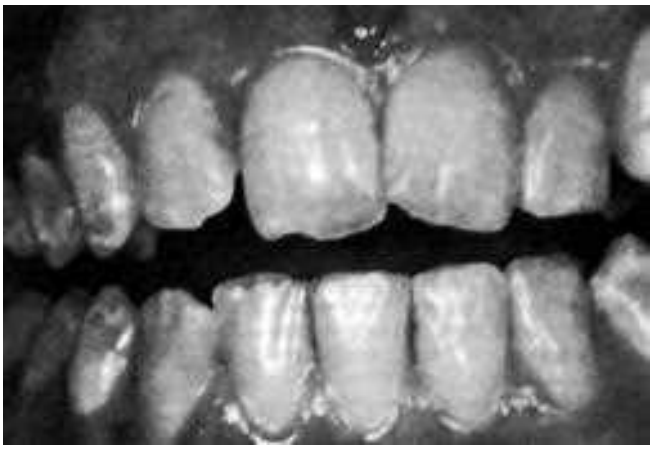


Figure 13-4. Abrasion of maxillary central incisor caused by habitual opening of bobby pins with tooth.

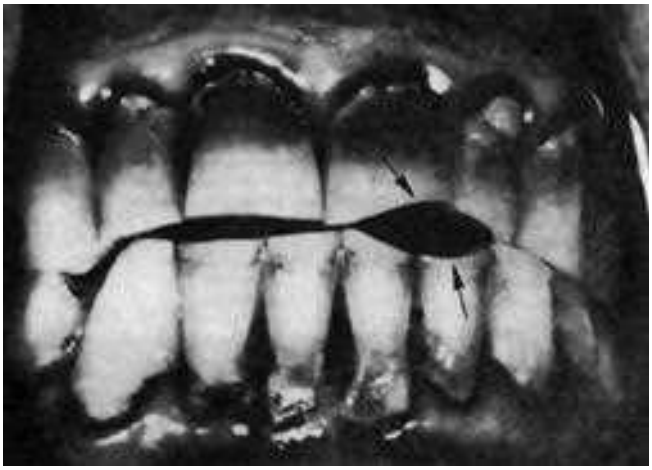


Figure 13-5. Abrasion of teeth caused by pipestem.

The exposure of dentinal tubules and the consequent irritation of the odontoblastic processes stimulate the formation of secondary dentin similar to that seen in cases of attrition. Unless the form of abrasion is an extremely severe and rapidly progressive one, the rate of secondary dentin formation is usually sufficient to protect the tooth against pulp exposure.

Erosion

Dental erosion is defined as irreversible loss of dental hard tissue by a chemical process that does not involve bacteria. Dissolution of mineralized tooth structure occurs upon contact with acids that are introduced into the oral cavity from intrinsic (e.g. gastroesophageal reflux, vomiting) or extrinsic sources (e.g. acidic beverages, citrus fruits). This form of tooth surface loss is part of a larger picture of toothwear, which also consists of attrition, abrasion, and possibly, abfraction. Table 13-2 lists the definitions of each of these forms of tooth surface loss or tooth wear.

Table 13-2: Definitions of tooth surface loss

Term	Definition	Clinical appearance
Erosion	Progressive loss of hard dental tissue by chemical processes not involving bacterial action	• Broad concavities within smooth surface enamel • Cupping of occlusal surfaces (incisal grooving) with dentin exposure • Increased incisal translucency • Wear on nonoccluding surfaces • 'Raised' amalgam restorations • Clean, non-tarnished appearance of amalgams • Loss of surface characteristics of enamel in young children • Preservation of enamel 'cuff' in gingival crevice is common • Hypersensitivity • Pulp exposure in deciduous teeth
Attrition	Loss by wear of surface of tooth or restoration caused by tooth to tooth contact during mastication or parafunction	• Matching wear on occluding surfaces • Shiny facets on amalgam contacts • Enamel and dentin wear at the same rate • Possible fracture of cusps or restorations
Abrasion	Loss by wear of dental tissue caused by abrasion by foreign substance (e.g. toothbrush, dentifrice)	• Usually located at cervical areas of teeth • Lesions are more wide than deep • Premolars and cuspids are commonly affected
Abfraction	Loss of tooth surface at the cervical areas of teeth caused by tensile and compressive forces during tooth flexure (studies needed to prove this hypothetical phenomenon)	• Affects buccal/labial cervical areas of teeth • Deep, narrow V-shaped notch • Commonly affects single teeth with excursive interferences or eccentric occlusal loads

Milosevic A. Toothwear: etiology and presentation. Dent Update 25: 6–11, 1998.

Causes

Extrinsic causes. Erosion of tooth substance is mainly due to contact with acidic media either by way of foodstuff or by iatrogenic exposure. There could be either extrinsic or intrinsic sources of acid that could cause this mode of tooth substance loss. Examples of extrinsic acids (source outside the body) are acidic beverages, foods, medications or environmental acids. The most common of these are dietary acids. It can be seen that most fruits and fruit juices have a very low pH (high acidity). Carbonated drinks and sports drinks are also very acidic. Several studies have found that the frequency of consumption of acidic drinks was significantly higher in patients with erosion than without. This finding is of concern, particularly since children and adolescents are the primary consumers of these drinks. With consumption of acidic drinks identified as a risk factor in erosion, this amount of soft drink consumption will likely lead to an increase in prevalence of erosion. The erosive potential of beverages does not depend on pH alone. Other components of beverages, such as calcium, phosphates, and fluoride may lessen erosive potential. Also, factors such as frequency and method of intake of acidic beverages as well as the toothbrushing frequency after intake may influence susceptibility to erosion.

Therefore, the role(s) of confounders like oral hygiene status, complicate the role of acids *per se* which necessitates further investigation to clarify the relationship between acidic beverage intake and dental erosion.

Medications that are acidic in nature can also cause erosion via direct contact with the teeth when the medication is chewed or held in the mouth prior to swallowing. Numerous case reports exist describing extensive erosion secondary to chewing vitamin C preparations or hydrochloric acid supplements. Less common sources of extrinsic erosive acids are related to occupational and recreational exposure. Chromic, hydrochloric, sulfuric and nitric acids have been identified as erosion-causing acid vapors. They are released into the work environment during industrial electrolytic processes. However current work safety standards make this type of erosion very rare. Dental erosion has been reported in swimmers who work out regularly in pools with excessive acidity as well as individuals who are occupational wine-tasters.

Intrinsic causes. Intrinsic causes (acid source inside the body), for erosion are gastric acids regurgitated into the esophagus and mouth. Gastric acids, with pH levels that can be less than 1, reach the oral cavity and come in contact with the teeth in conditions such as gastroesophageal reflux and excessive vomiting related to eating disorders. The association of gastroesophageal reflux disease (GERD) with dental erosion has been established in a number of studies in adults (Figs. 13-6, 13-7). GERD is a common condition, estimated to affect 7% of the adult population on a daily basis and 36% at least one time a month. In this condition gastric contents pass involuntarily into the esophagus and can escape up into the mouth. This is caused by increased abdominal pressure, inappropriate relaxation of the lower esophageal sphincter or increased acid production by the stomach. However, GERD can also be 'silent' with the patient unaware of his or her condition until dental changes elicit assessment for the condition.

Chronic, excessive vomiting has long been recognized as causing erosion of the teeth. The patient with an eating disorder such as anorexia nervosa or bulimia is the classic example. The problem was first reported by Hellstrom and Hurst in 1977. Many reports and reviews have been published

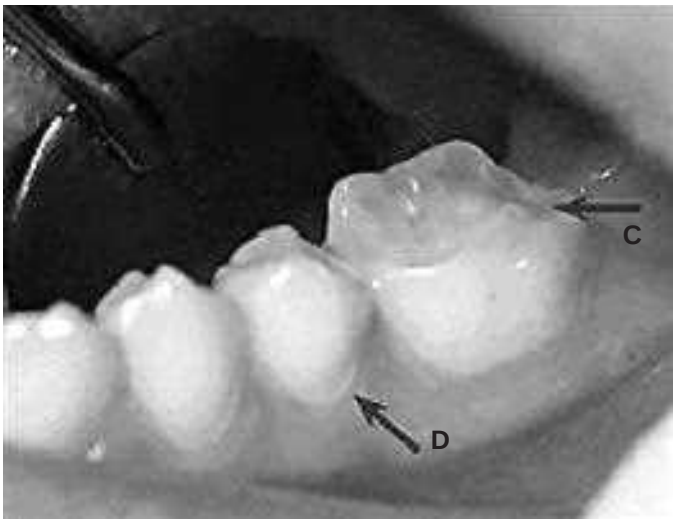


Figure 13-6. Gastroesophageal reflux disease (GERD) was discovered in this 19-year-old boy who exhibited early generalized erosion (arrow A).
Note the preservation of the enamel at the gingival crevice (arrow B).

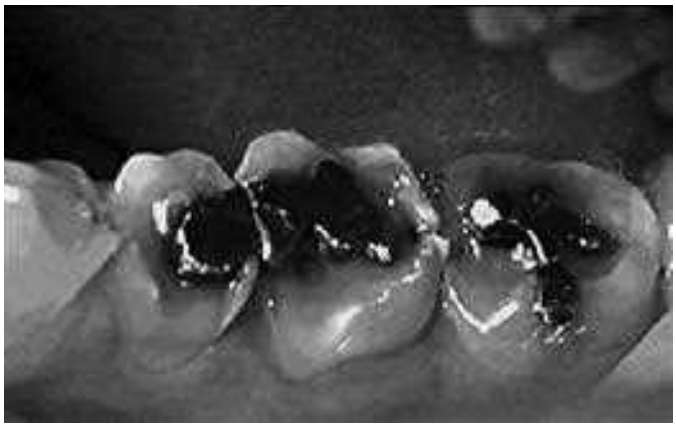


Figure 13-7. This 33-year-old male with GERD had severe asymptomatic erosion.
Note the amalgams 'rising' above the adjacent eroded occlusal surfaces.

on the topic since that time. Although erosion caused by vomiting typically affects the palatal surfaces of the maxillary teeth, it is also common for individuals with eating disorders to consume large amounts of acidic beverages and fresh fruits (Tables 13-3, 13-4). This results in another source of acid exposure, primarily affecting the labial surfaces of the teeth. In addition, treatment for bulimia may include use of antidepressants or other psychoactive medications that may cause salivary hypofunction. Therefore, the cause of erosion cannot be reliably determined from its location.

Table 13-3: Acidity of common foods and beverages

	pH range		pH range
Fruits			
Apples	2.9–3.5	Lemons, limes/juice	1.8–2.4
Apricots	3.5–4.0	Oranges/juice	2.8–4.0
Grapes	3.3–4.5	Pineapple/juice	3.3–4.1
Peaches	3.1–4.2	Blueberries	3.2–3.6
Pears	3.4–4.7	Cherries	3.2–4.7
Plums	2.8–4.6	Strawberries	3.0–4.2
Grapefruit	3.0–3.5	Raspberries	2.9–3.7
Beverages			
Cider	2.9–3.3	Grapefruit/juice	2.9–3.4
Coffee	2.4–3.3	7 Up	3.5
Tea (black)	4.2	Pepsi	2.7
Beers	4.0–5.0	Coke	2.7
Wines	2.3–3.8	Root beer	3.0
Ginger ale	2.0–4.0	Orange crush	2.0–4.0
Condiments			
Mayonnaise	3.8–4.0	Cranberry sauce	2.3
Vinegar	2.4–3.4	Sauerkraut	3.1–3.7
A-1* Sauce	3.4	Relish	3.0
Mustard	3.6	Ketchup	3.7
Italian salad dressing	3.3	Sour cream	4.4
Other			
Yogurt	3.8–4.2	Tomatoes	3.7–4.7
Pickles	2.5–3.0	Vegetables/fermented	3.9–5.1
Rhubarb	2.9–3.3	Fruit jam/jellies	3.0–4.0

Clark DC, Woo G, Silver JG, et al. The influence of frequent ingestion of acids in the diet on treatment for dentin sensitivity. J Can Dent Assoc, 56: 1101–1103, 1990.

Table 13-4: Risk factors for dental erosion

- Citrus fruits intake (more than twice daily)
- Soft drinks consumed (4–6 or more per week)
- Eating disorder (weekly or more often)
- Bruxism habit
- Whole saliva unstimulated flow rate (£0.1 ml/min)
- Sports drinks intake (weekly or more often)
- Apple vinegar intake (weekly or more often)
- Vomiting
- Excessive attrition
- Symptoms or history of gastroesophageal reflux disease

Jarvinen VK, Rytomaa II, and Heinonen OP. Risk factors in dental erosion. J Dent Res 70: 942–947, 1991.

Erosion associated with alcoholism is caused by frequent vomiting. Other causes of vomiting that may cause erosion include gastrointestinal disorders such as peptic ulcers or gastritis, pregnancy, drug side effects, diabetes or nervous system disorders.

Saliva as a modifying factor. The fluctuations in pH of saliva is mainly kept in balance by the buffering capacity of saliva. This property is largely due to the bicarbonate content of the saliva which is in turn dependent on the salivary flow rate. Bicarbonate concentration also regulates salivary pH. Therefore, there is a relationship between salivary pH, buffering capacity and flow rate, with pH and buffer capacity increasing as flow rate increases. Normally, when an acid enters the mouth, whether from an intrinsic or extrinsic source, salivary flow rate increases, along with pH and buffer capacity. Within minutes, the acid is neutralized and cleared from the oral cavity and the pH returns to normal. Patients with erosion were found to have lower salivary buffer capacity when compared with controls in several studies. In other studies, low whole salivary flow rates in patients with erosion were determined to be the major difference. Therefore, salivary function is an important factor in the etiology of erosion. Since many common medications and diseases can lower salivary flow rate (xerostomia), both whole and stimulated, it is important to assess salivary characteristics when evaluating a patient with erosion.

Management of Erosion

Treatment of etiology. Identification of the etiology is important as a first step in management of erosion. If excessive dietary intake of acidic foods or beverages is discovered, patient education and counseling are important. If the patient has symptoms of GERD, then he/she should be referred to a medical doctor for complete evaluation and institution of therapy if indicated. A patient with salivary hypofunction may benefit with the use of sugarless chewing gum or mints to increase residual salivary flow. The use of oral pilocarpine (Salagen) may be beneficial in patients with dry mouth caused by Sjögren's syndrome or post-therapeutic head and neck radiation. A patient suspected of an eating disorder should be referred to a medical doctor for evaluation.

In some cases, an etiologic agent is not identifiable. In other cases, the etiologic agent may be difficult to control, such as the problem of alcoholism. However, regardless of the cause, it is important to follow preventive measures to prevent the progress of erosion. There are several preventive measures that can be taken to control tooth erosion. These are listed in Table 13-5. Patient education is of paramount importance. Much of erosion prevention depends on the compliance of the patient with dietary modification, use of topical fluorides, use of occlusal splint, etc.

Table 13-5: Protocol for the prevention of progression of erosion

1. Diminish the frequency and severity of the acid challenge
   - Decrease amount and frequency of acidic foods or drinks
   - Acidic drinks should be drunk quickly rather than sipped. The use of a straw would reduce the erosive potential of soft drinks
   - If undiagnosed or poorly controlled gastroesophageal reflux is suspected, refer to a physician
   - In the case of bulimia, a physician or psychologist referral is appropriate
   - A patient with alcoholism should be assisted in seeking treatment in rehabilitation programs
2. Enhance the defense mechanisms of the body (increase salivary flow and pellicle formation)
   - Saliva provides buffering capacity that resists acid attacks. This buffering capacity increases with salivary flow rate
   - Saliva is also supersaturated with calcium and phosphorus, which inhibits demineralization of tooth structure
   - Stimulation of salivary flow by use of a sugarless lozenge, candy or gum is recommended
3. Enhance acid resistance, remineralization and rehardening of the tooth surfaces
   - Have the patient use daily topical fluoride at home
   - Apply fluoride in the office 2–4 times a year. A fluoride varnish is recommended
4. Improve chemical protection
   - Neutralize acids in the mouth by dissolving sugarfree antacid tablets 5 times a day, particularly after an intrinsic or extrinsic acid challenge
   - Dietary components such as hard cheese (provides calcium and phosphate) can be held in the mouth after acidic challenge (e.g. hold cheese in mouth for a few minutes after eating a fruit salad)
5. Decrease abrasive forces
   - Use soft toothbrushes and dentifrices low in abrasiveness in a gentle manner
   - Do not brush teeth immediately after an acidic challenge to the mouth, as the teeth will abrade easily
   - Rinsing with water is better than brushing immediately after a acidic challenge
6. Provide mechanical protection
   - Consider application of composites and direct bonding where appropriate to protect exposed dentin
   - Construction of an occlusal guard is recommended if a bruxism habit is present
7. Monitor stability
   - Use casts or photos to document toothwear status
   - Regular recall examinations should be done to review diet, oral hygiene methods, compliance with medications, topical fluoride and splint usage

Adapted from: Beatrice K Gandara, Edmond L Truelove. The Journal of Contemporary Dental Practice, Volume 1, No. 1, Fall Issue, 1999.

ABFRACTION

Abfraction is currently described as a mode of tooth loss which has clinical and circumstantial evidence. Till recently this type of tooth loss which is mainly confined to the gingival third of the clinical crown was thought to be the result of toothbrush abrasion. It is proposed that with each bite, occlusal forces cause the teeth to flex though little. Constant flexing causes enamel to break from the crown, usually on the buccal surface. The physiological basis of this type of tooth substance loss held that, while not providing a complete explanation, does offer a significant clue to the real cause of this troubling phenomenon. Grippo, in 1991, coined the term **abfraction** to describe the pathologic loss of both enamel and dentin caused by biomechanical loading forces (Fig. 13-8). He stated that the forces could be static, such as those produced by swallowing and clenching; or cyclic, as in those generated during chewing action. The abfractive lesions were caused by flexure and ultimate material fatigue of susceptible teeth at locations away from the point of loading. The breakdown was dependent on the magnitude, duration, direction, frequency, and location of the forces.

DENTINAL SCLEROSIS

(Transparent Dentin)

Sclerosis of primary dentin is a regressive alteration in tooth substance that is characterized by calcification of the dentinal tubules. It occurs not only as a result of injury to the dentin by caries or abrasion but also as a manifestation of the normal aging process. For many years it has been known that if a ground section of a tooth with a very shallow carious lesion of the dentin is examined by transmitted light, a translucent zone can be seen in the dentin underlying the cavity (Fig. 13-9). This was readily recognized as being due to a difference between the refractive indices of the sclerotic or calcified dentinal tubules and the adjacent normal tubules. Both Beust and Fish showed that dyes do not penetrate those dentinal tubules that are sclerotic as a result either of age or of a slowly progressive type of dental caries.

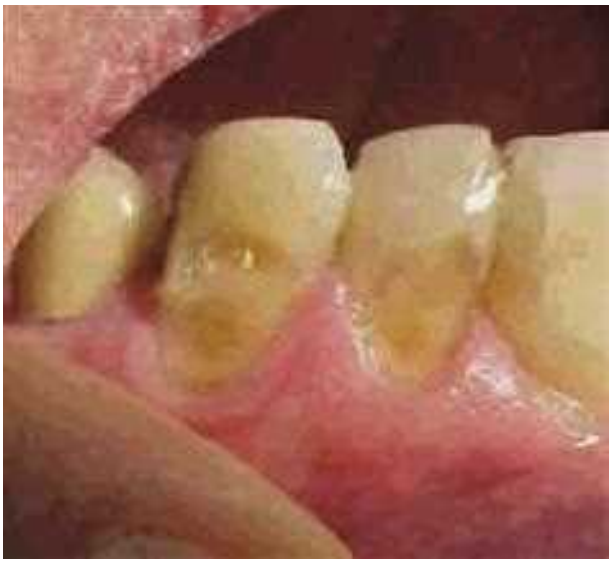


Figure 13-8. Abfraction.

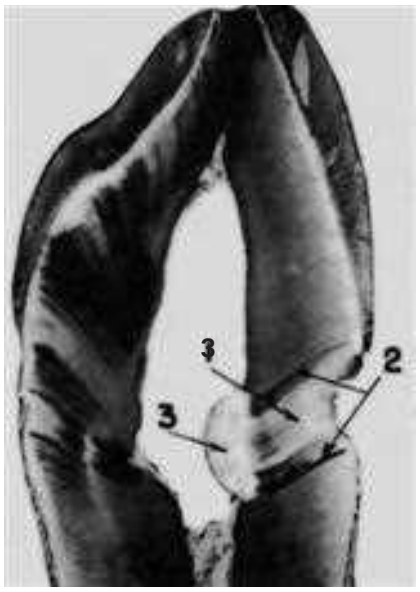


Figure 13-9. Dentinal sclerosis.
Sclerosed dentin (1) beneath a cervical cavity bounded on either side by 'dead tracts' (2) and below by secondary dentin (3).

The exact mechanism of dentinal sclerosis or the deposition of calcium salts in the tubules is not understood, although the most likely source of the calcium salts is the fluid or 'dental lymph' within the tubules. The increased mineralization of the tooth decreases the conductivity of the odontoblastic processes. In addition, the sclerosis slows an advancing carious process.

Sclerotic dentin under a carious lesion was shown by Hodge and McKay to be actually harder than adjacent normal dentin. Subsequently, Van Huysen, Hodge, and Warren confirmed the fact that sclerotic dentin is more highly calcified than normal dentin by employing a unique adaptation of the X-ray absorption technique in which ground slabs of teeth were photographed by X-rays and the degree of radiopacity in areas of normal and sclerotic dentin was measured.

DEAD TRACTS

'Dead tracts' in dentin are seen in ground sections of teeth and are manifested as a black zone by transmitted light but as a white zone by reflected light (Fig. 13-9). This optical phenomenon is due to differences in the refractive indices of the affected tubules and normal tubules. The nature of the change in the affected tubules is not known, although these tubules are not calcified and are permeable to the penetration of dyes.

SECONDARY DENTIN

Secondary dentin is dentin that is formed and deposited in response to a normal or slightly abnormal stimulus, after the complete formation of the tooth.

There is a considerable variation in the composition of primary and secondary dentin. The dentinal tubules that make up dentin are generally irregular in secondary dentin and deposits contain less calcium, phosphorus, and collagenous matrix per unit volume than the primary dentin. Secondary dentin is less mineralized and contains 6–10% less mineral than primary dentin.

There are generally two types of secondary dentin, produced as a result of different stimuli. The two types of secondary dentin are physiological secondary dentin and reparative secondary dentin.

Physiological Secondary Dentin

This type of dentin is a regular, uniform layer of dentin around the pulp chamber that is laid down throughout the life of the tooth as a result of physiological factors generally thought to be age and tooth eruption. This type of secondary dentin is produced more slowly than primary dentin.

Reparative Secondary Dentin

Reparative secondary dentin is the dentin that forms around the pulp chamber as a result of irritation or attrition, which is a form of tooth wear. Attrition is due to tooth-to-tooth contact, which results from occlusal function, such as bruxism, and can cause loss of tooth structure. This gradual traumatic process stimulates the development of natural protective measures, such as secondary dentin.

Clinical Features

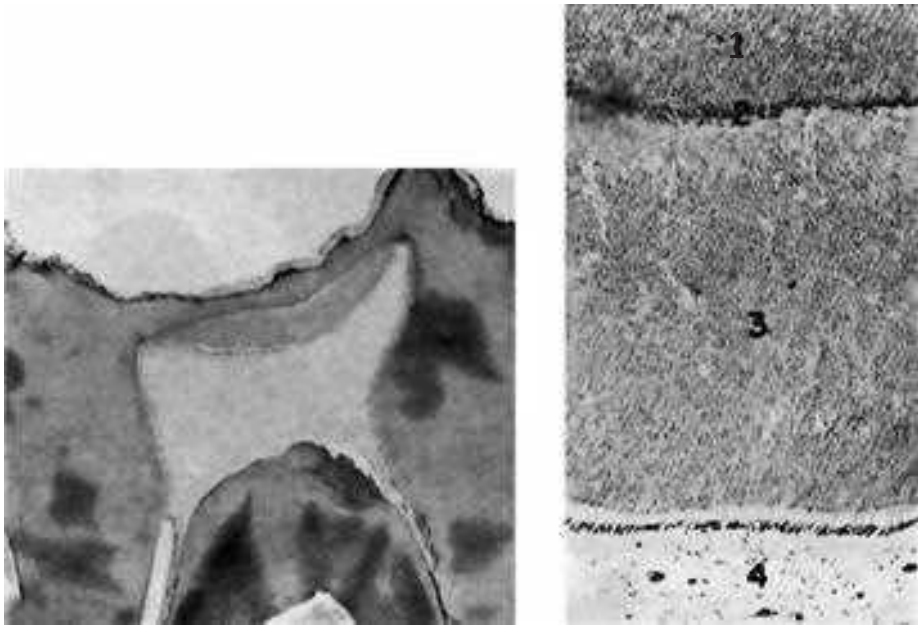
There are no significant clinical features that may be used to determine when teeth have formed secondary dentin, although there is an evident decrease in tooth sensitivity when secondary dentin formation is extensive, as it is in elderly persons. This type of dentin forms an additional insulating layer of calcified tissue between the pulp and the particular pathologic process that initiated the dentinal response. Thus the eventual pulp involvement is usually delayed. Although secondary dentin occurs in all teeth, including those of the deciduous dentition, a study by Bevelander and Benzer indicated that the anterior teeth exhibit a higher incidence of secondary dentin formation than the molar teeth.

Radiographic Features. Secondary dentin often may be visualized on the dental radiograph if it occurs in an area that is not overshadowed by other calcified tissue, either bone or tooth substance. Such secondary dentin formation may be noted particularly in the pulp horn areas as well as on the proximal walls of teeth with proximal caries.

The decrease in size of the pulp chamber and root canals that occurs with advancing age as a result of secondary dentin formation is obvious radiographically.

Histologic Features. Physiologic secondary dentin is usually similar in appearance to primary dentin, but in decalcified stained sections it often exhibits a different tinctorial reaction and may be rather well demarcated from the primary dentin by a deeply staining 'resting line'. This type of secondary dentin exhibits somewhat fewer tubules, although their course is not especially irregular.

Adventitious secondary dentin arising in response to irritation is usually irregular in nature, being composed of few tubules that may be tortuous in appearance (Fig. 13-10). In some instances tubules are inconspicuous if not completely absent. Occasionally, this secondary dentin is formed at a rapid rate and odontoblasts may become entrapped, producing a superficial resemblance to bone. Such calcified tissue has been termed **osteodentin**.



A B

Figure 13-10. Secondary dentin.
Secondary dentin beneath carious lesion, **(A)**. Normal dentin (1), resting line (2), secondary dentin (3), and pulp (4) are shown in higher magnification, **(B)**.

Stanley and his associates have studied the rate of reparative dentin formation in human teeth following cavity preparation under a variety of clinical conditions. They found that reparative dentin formation was insignificant in the first postoperative month. Between one and one-and-a-half months, new dentin formation reached a maximum rate of approximately 3.5µ per day. After this period, new dentin formation rapidly decreased.

RETICULAR ATROPHY OF PULP

Reticular atrophy of the pulp and more discrete vacuolization of the pulpal tissue and cells have often been described as degenerative or regressive changes of pulp, particularly when they occur as an age change in elderly persons. It has been stated that teeth so affected are clinically symptomless and respond normally to vitality tests. Histologically, reticular atrophy has been described as being characterized by the presence of large vacuolated spaces in the pulp, with a reduction in the number of cellular elements. Accompanying these changes are degeneration and disappearance of the odontoblasts.

It is most interesting and significant that alterations in the pulp tissue identical with those described above can be produced by improper fixation of the tooth and pulp after extraction preparatory to histologic sectioning. Most investigators now believe that this condition is purely an artifact brought about by autolysis of the pulp tissue and does not occur *in vivo*.

PULP CALCIFICATION

Various forms of calcification within the pulps of teeth are found with such frequency that it may be questioned whether their presence represents a pathologic state or merely an occurrence within the range of normal biologic variation. These calcifications may be located in any portion of the pulp tissue, although certain types are more common in the pulp chamber and others in the root canal.

A number of studies have been carried out to determine the actual incidence of pulp calcification, and the results of these investigations are in essential agreement. For example, Willman reported that of a series of 164 teeth picked at random and examined histologically, 143 (or 87%) exhibited calcification in the pulp. Interestingly, only 15% of the areas of calcification were large enough to be seen on the dental radiograph. These findings confirm the investigations of Hill, who reported calcifications in 66% of all teeth examined in young persons between the ages of 10 and 20 years and in 90% of all teeth examined in persons between the ages of 50 and 70 years. There is no apparent difference in the frequency of occurrence either between the genders or among the various teeth in the dental arch.

The two chief morphologic forms of pulp calcifications are discrete pulp stones (denticles, pulp nodules) and diffuse calcification. Pulp stones have been classified as either true or false stones, depending upon their microscopic structure.

True denticles are made up of localized masses of calcified tissue that resemble dentin because of their tubular structure. Actually, these nodules bear greater resemblance to secondary dentin than to primary dentin, since the tubules are irregular and few in number. They are considerably more common in the pulp chamber than in the root canal.

True denticles may be subdivided further according to whether or not they are attached to the wall of the pulp chamber. Denticles lying entirely within the pulp tissue and not attached to the dentinal walls are called 'free denticles', while those that are continuous with dentinal walls are referred to as 'attached denticles'. The latter type of calcification is somewhat more common than the former. It should be remembered that though a denticle may appear free in the one plane of section in which it is visualized, it may be attached in another plane. Thus, without serial section on an entire tooth pulp, one cannot state with any degree of assurance that a given denticle is free and not attached.

False denticles are composed of localized masses of calcified material, and unlike true denticles, do not exhibit dentinal tubules. Instead, the nodule appears to be made up of concentric layers or lamellae deposited around a central nidus (Fig. 13-11). The exact nature of this nidus is unknown, although Johnson and Bevelander believe that it is composed of cells, as yet unidentified, around which is laid down a layer of reticular fibers that subsequently calcify.

The false denticle also may be classified as free or attached. As the concentric deposition of calcified material continues, it approximates and finally is in apposition with the dentinal wall. Here it may eventually become surrounded by secondary dentin, and it is then referred to as an 'interstitial denticle'. False denticles, which occur more commonly in the pulp chamber than in the root canal, are generally somewhat larger than true denticles. They may fill nearly the entire pulp chamber, while true denticles are seldom larger than a fraction of a millimeter in diameter.

Johnson and Bevelander concluded from their studies that a differentiation between 'true' and 'false' denticles should not be drawn, since all denticles originally show no tubules even though they subsequently may become surrounded by tissue containing dentinal tubules.

Diffuse calcification is most commonly seen in the root canals of teeth and resembles the calcification seen in other tissues of the body following degeneration. This type of calcification is frequently termed 'calcific degeneration'. Its usual pattern is in amorphous, unorganized linear strands or columns paralleling the blood vessels and nerves of the pulp.

Etiology. The etiology of the various types of pulp calcification is unknown. Although the incidence appears to increase with the age of the persons, there is no definite association with pulpal irritation or inflammation such as that arising from caries or trauma. Since pulp calcifications have been described in unerupted teeth, it is doubtful whether pulpal

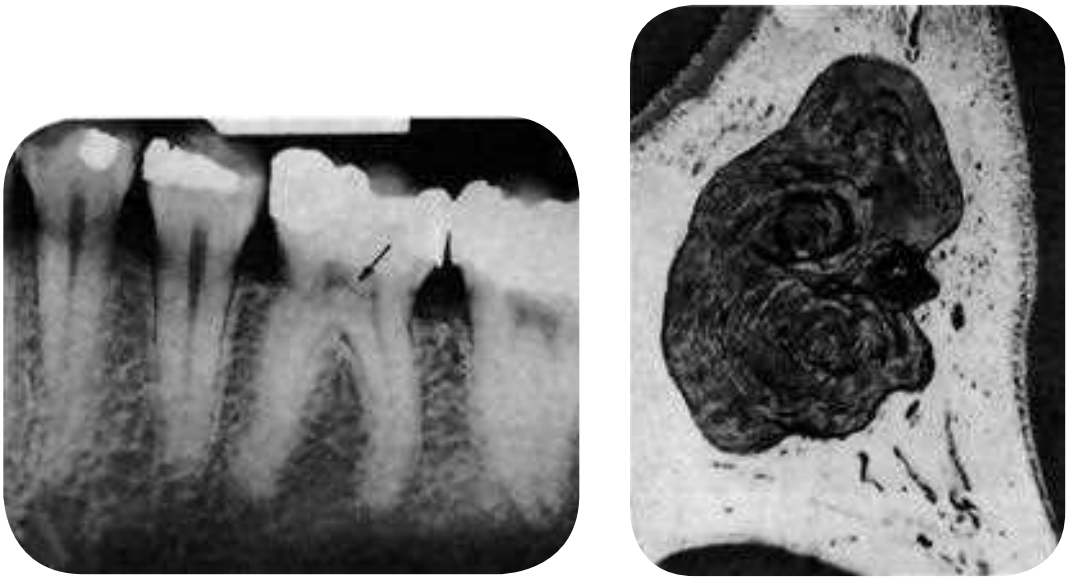
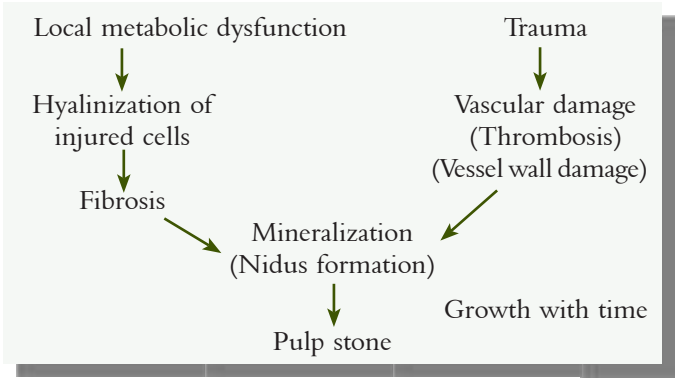


Figure 13-11. Denticle in pulp chamber. Radiograph (A) and histologic section (B).

disease such as inflammation is of any significance. Stafne and Szabo attempted to correlate pulp nodules with various local or systemic diseases including cholelithiasis, renal lithiasis, arteriosclerosis, gout, acromegaly, osteitis deformans, hypercementosis, and torus palatinus or mandibularis. Their data indicate that no clear-cut relation exists between any of these conditions and pulp calcification.

Kretschmer and Seybold reported that an extremely high percentage of pulp stones yield a pure growth of streptococci upon culture. On this basis it has been suggested that microorganisms are the cause of pulp calcifications. Since the pulps of the affected teeth were reportedly normal, aside from the calcification, and since it is well recognized that bacteria may be forced into the pulp tissue at the time of tooth extraction, it is most unlikely that bacteria are of any significance in the development of these pulp nodules.

More recently, Sundell and his associates have attempted to determine whether the degree of pulp response elicited by cutting procedures and restorative materials was capable of increasing the incidence of pulp stone nidi and pulp stones. They found no significant correlation between pulp stones or nidi and the age or gender of the patient, the thickness of remaining dentin beneath the cavity preparation, the preparation time, or the traumatic potential of the operative procedure. In addition, these workers have proposed the following schematic diagram incorporating several hypotheses from the literature, and concomitantly, including the mechanism of thrombosis or vascular wall injury or both, leading to pulpstone formation.



Clinical Significance. The clinical significance of pulp calcification is not completely understood. It has been reported upon numerous occasions that pulp stones are a cause of pain, varying from mild pulpal neuralgia to severe, excruciating pain resembling that of tic douloureux. The consensus is that though denticles may seem to impinge on nerves of the pulp, they probably do not. Most investigators now believe that seldom, if ever, are pulp stones the cause of dental pain. Therefore, the extraction of teeth with radiographically demonstrable pulp stones in the hope of relieving dental pain or vague facial neuralgia cannot be defended. Neither can the view that the presence of pulp stones indicates pulpal infection be condoned. In the light of our present knowledge, pulp calcification is a purely coincidental finding without clinical significance. Difficulty may be encountered in extirpating the pulp during root canal therapy if calcifications are present (Fig. 13-12).

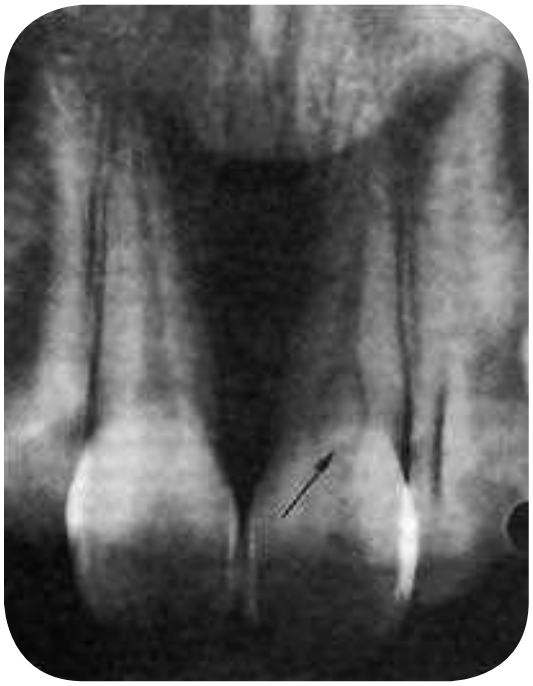


Figure 13-12. Large denticle occluding entrance to root canal.

RESORPTION OF TEETH

Resorption of teeth occurs in many circumstances other than the normal process associated with the shedding of deciduous teeth. The roots of permanent teeth may undergo resorption in response to a variety of stimuli; moreover, it is recognized that root resorption in permanent teeth occurs to a slight degree even under apparently normal conditions. Since resorption of a tooth may begin either on the external surface (arising as a result of a tissue reaction in the periodontal or pericoronal tissue) or inside the tooth (from a pulpal tissue reaction), the general terms 'external resorption' and 'internal resorption' are used to distinguish between the two types. The chief causes or situations in which resorption may occur are as follows:

External resorption
- Periapical inflammation
- Reimplantation of teeth
- Tumors and cysts
- Excessive mechanical or occlusal forces
- Impaction of teeth
- Idiopathic

Internal resorption
- Idiopathic

EXTERNAL RESORPTION

Resorption Associated with Periapical Inflammation

Resorption of calcified dental tissues occurs in the same fashion as that of bone, and in most instances, the presence of osteoclasts is an outstanding feature in areas of active resorption. It should be pointed out; however, that there is considerable evidence indicating that osteoclasts may not be essential for the resorption of calcified tissues.

A periapical granuloma (q.v.) arising as a result of pulpal infection or trauma occasionally causes subsequent resorption of the root apex if the inflammatory lesion persists for a sufficient period of time (Fig. 13-13). Most teeth involved by a periapical granuloma; however, do not exhibit any significant degree of resorption. The reason for the occasional occurrence is not known. It is generally agreed that bone resorption occurs more readily in highly vascular areas than in relatively avascular areas, and since the periapical granuloma is quite vascular, it is surprising that resorption of the root is not more frequently seen. That bone is more readily resorbed than dental tissue is borne out by the fact that bone is always destroyed when a periapical granuloma develops, whereas resorption of the tooth root without loss of bone seldom occurs except at a microscopic level.

In those cases of periapical granuloma in which root resorption does occur, it is usually obvious on the dental radiograph. It appears as a slight raggedness or blunting of the root apex in the early stages, proceeding to a severe loss of tooth substance. In a tooth that has had the root canal treated and filled, but around which periapical inflammation persists, resorption of the root may occur and ultimately leave only the root canal filling projecting out of the shortened root. The radiographic picture of this phenomenon presents an unusual appearance and superficially resembles overfilling of the root canal.

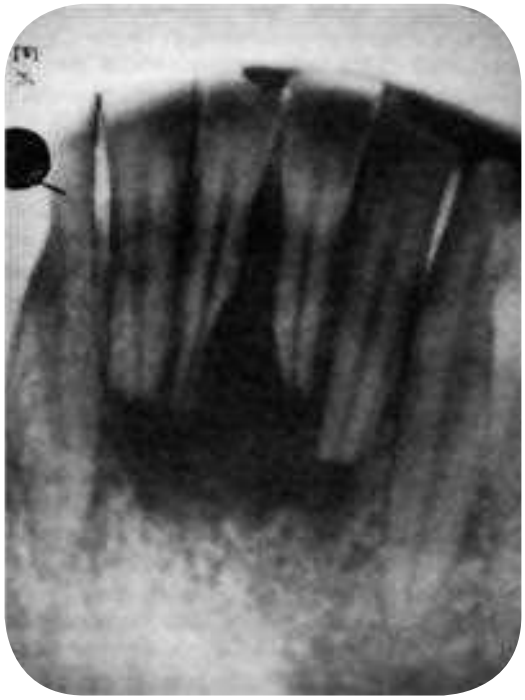


Figure 13-13. Root resorption.
Diffuse periapical granuloma resulting from death of pulp caused by traumatic injury has resulted in resorption of roots.

Reimplanted Teeth

The reimplantation, or transplantation, of teeth (q.v.) almost invariably results in severe resorption of the root. The tooth substance, regardless of whether the root canal has been filled or not, must be considered nonvital tissue, except in the case of transplanted developing teeth when the vascular supply to the tooth may be reestablished and its vitality maintained. Thus the implanted tooth is analogous to a bone graft which acts only as a temporary scaffold and is ultimately resorbed and replaced. The tooth root is resorbed and replaced by bone, producing an ankylosis. If the tooth root does not become completely resorbed, the ensuing ankylosis may result in a functional tooth. Many reimplanted teeth; however, exhibit complete resorption of the root and are exfoliated.

Tumors and Cysts

The resorption of roots brought about by tumors is similar to that seen in teeth involved by cysts (Fig. 13-14). In many instances resorption by tumors or cysts appears to be essentially a pressure phenomenon. This is to be expected, since the phenomenon of resorption of bone under pressure is well recognized and actually forms the basis of orthodontic practice.

Both benign and malignant tumors may cause root resorption, although benign lesions are more likely to produce displacement than actual destruction of the tooth. In most cases connective tissue is present between the tumor and the tooth, and it is from this tissue that cells develop, chiefly osteoclasts, which appear responsible for the root resorption. This is particularly true of epithelial tumors that invade the jaws. Occasionally tumors are seen in which, histologically, the neoplastic cells are found adjacent to and within the ragged resorption lacunae on the root surface.

Figure 13-14. Resorption of the root apex associated with an ameloblastoma.

Cysts cause root resorption in a manner similar to resorption caused by benign tumors, that is, chiefly by pressure, although displacement of the tooth is more common than resorption. An apical periodontal cyst arising as a result of pulp infection may exert such pressure on the apex of the involved or adjacent tooth that the intervening connective tissue is stimulated, osteoclasts form, and resorption begins. This reaction may occur with any type of cyst that progressively expands, but it is more common with the periodontal cyst than with the dentigerous, primordial, or fissural cysts.

Excessive Mechanical or Occlusal Forces

The usual form of excessive mechanical force with which root resorption may be associated is that applied during orthodontic treatment. It has been recognized for many years, at least since the work of Ketcham, that patients who have undergone orthodontic treatment frequently exhibit multiple areas of root resorption irrespective of the manner of treatment, i.e. the type of appliance or the duration and degree of force exerted. In some patients this resorption is mild and involves only a few teeth; in others there may be loss of over 50% of the root length of most of the teeth.

The cause for this extreme variation under apparently similar clinical conditions is unknown. Becks reported that systemic disturbances, the chief among these being hypothyroidism, may predispose to root resorption, particularly in the patient who is receiving orthodontic treatment. The influence of the systemic factor remains to be confirmed, however.

It is fortunate that bone undergoes resorption far more readily than cementum when force is exerted upon the tooth by orthodontic appliances or by occlusal trauma. This pressure upon the supporting bone invariably results in destruction, primarily of bone. Small lacunae often appear on the surface of the cementum and ultimately extend into the dentin, indicating early tooth resorption. Probably most cases of this minor type of resorption are soon repaired by the deposition of bone or cementum in these ragged lacunae, particularly if the occlusal force or orthodontic pressure is relieved.

Some investigators have questioned the clinical significance of root resorption secondary to mechanical or occlusal forces since, regardless of the severity or degree of the resorption, seldom is a tooth ever exfoliated. There may be destruction of the apical two thirds of the root of a tooth with no evidence of looseness or other signs of impending difficulties.

Impacted Teeth. Teeth that are completely impacted or embedded in bone occasionally will undergo resorption of the crown or of both crown and root. Stafne and Austin pointed out that although this resorption most commonly begins on the crown of the tooth, destruction of all the enamel epithelium is not a prerequisite for the onset of resorption. In some cases only a limited amount of epithelium appears to be destroyed,

Table 13-6: Distribution of embedded teeth exhibiting radiographic evidence of resorption

	Central incisor	Lateral incisor	Cuspid	Second bicuspid	Third molar	Total	
						No.	Percentage
Maxilla	4	1	106	2	64	177	78
Mandible	1	0	17	7	24	49	22

EC Stafne and LT Austin: Resorption of embedded teeth. J Am Dent Assoc, 32: 1003, 1945.

allowing the connective tissue to come in contact with the crown and thus initiating the resorptive process. Stafne and Austin reported that teeth that are completely embedded are those most apt to undergo resorption. In a study of 226 embedded teeth in which resorption occurred, they found that 78% of the teeth were in the maxillary arch and that 60% of these maxillary teeth were cuspids (Table 13-6). This finding is unusual and significant because, although maxillary and mandibular third molars far outnumber maxillary cuspids in incidence of impaction, the cuspids undergo resorption more frequently than the third molars. The reason for this is unknown. Impacted supernumerary teeth, particularly mesiodens, also are prone to undergo resorption.

The radiographic picture presented by these teeth is an unusual one, particularly when the resorption occurs on the tooth crown. The irregular destruction frequently has suggested that the impacted or embedded tooth is involved by caries, an obvious impossibility (Fig. 13-15).

Impacted teeth also may cause resorption of the roots of adjacent teeth without being resorbed themselves. This is particularly common in the case of a horizontally or mesioangularly impacted mandibular third molar impinging on the roots of the second molar. There is always connective tissue interposed between the second and third molars, and the pressure of the third molar appears to activate the resorptive cells, thus setting the stage for tooth destruction.

Idiopathic Resorption

Many investigators have reported that the roots of permanent teeth may undergo a certain amount of resorption in apparently normal adults without any obvious cause (Fig. 13-16A). The term 'idiopathic root resorption' has been applied to this phenomenon. The actual incidence of this form of resorption was not appreciated until the study of Massler and Perreault, in which it was found that of 301 young (18–25 years old) male and female patients, all exhibited some degree of root resorption in four or more teeth, as judged by radiographic examination alone. Furthermore, it was reported that 82% of the teeth in the men and 91% of the teeth in the women showed some evidence of resorption. In less than 3% of the cases was there any indication as to the cause of this condition. The teeth most commonly involved by root resorption were the maxillary bicuspids, while the mandibular incisors and molars exhibited the least resorption.

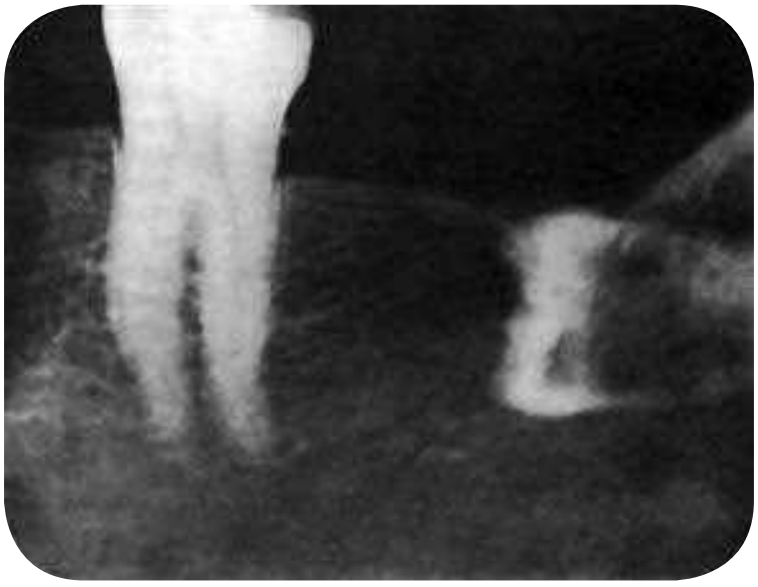


Figure 13-15. Resorption of impacted tooth.
(Courtesy of Dr Paul and Dr Emmett Jurgens).

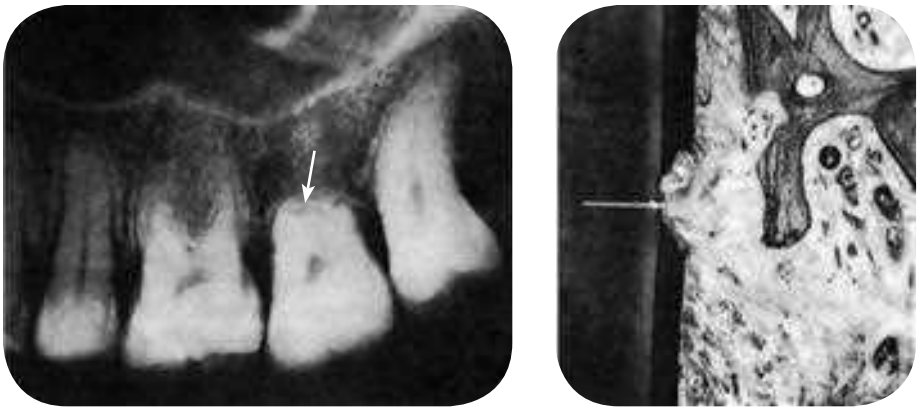


Figure 13-16. Root resorption.
(A) Severe idiopathic root resorption of maxillary second molar. **(B)** Mild root resorption, visible only microscopically.

Table 13-7: Teeth involved in idiopathic resorption

Teeth involved	Maxilla		Mandible	
	No.	Percentage	No.	Percentage
Central incisor	45	22.5	44	22.0
Lateral incisor	15	7.5	11	5.0
Cuspid	18	9.0	14	7.0
Premolar	10	5.0	25	12.5
Molar	0	0	18	9.0
Total	88	44.0	112	56.0

Massler and Perreault pointed out; however, that this finding is in contradistinction to nearly all other reported studies, including those of Becks and of Stafne and Slocumb (Table 13-7), in which the maxillary and mandibular central incisors were shown to be most frequently involved.

It appears that root resorption is far more common than was formerly believed. The majority of cases of idiopathic resorption are mild (Fig. 13-16B). According to the data of Massler and Perreault, over 75% of the teeth exhibiting resorption showed loss of less than 4 mm of the root apex. Although the etiology remains unknown, several possibilities present themselves. The resorption may be related to one or more systemic disorders, the most obvious being some form of endocrine disturbance (Figs. 13-17–13-20). A genetic characteristic governing the resorption potential of bone and tooth substance has been demonstrated in animals and is conceivable in human beings. Finally, the possibility that root resorption, with subsequent repair, is no more pathologic than an analogous resorption and repair of bone must be considered.

A rare form of multiple idiopathic root resorption may occur that involves all or nearly all of the teeth. The resorption may begin at the cementoenamel junction or nearer to the root apex. This disease has been discussed by Kerr and his associates, who pointed out that these patients are medically normal and have no past history such as orthodontic treatment or radiation that might explain the phenomenon.

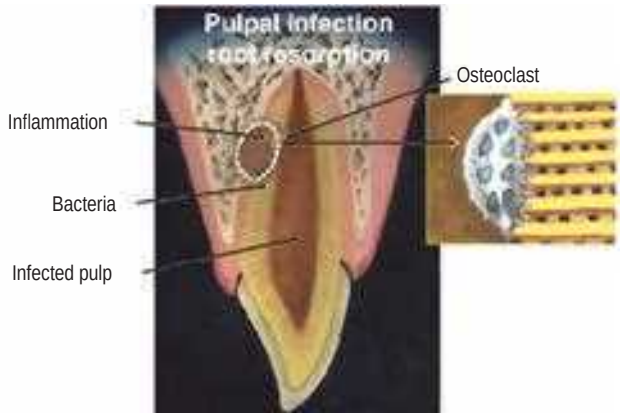


Figure 13-17. Graphical illustration of pulpal infection root resorption.
Root canal and dentinal tubules are necrotic and infected, and inflammatory response with osteoclastic activity is taking place in the dentin and the bone. Enlargement of osteoclast attached to dentin on the right demonstrates the stimulation factor of bacteria in the dentinal tubules.

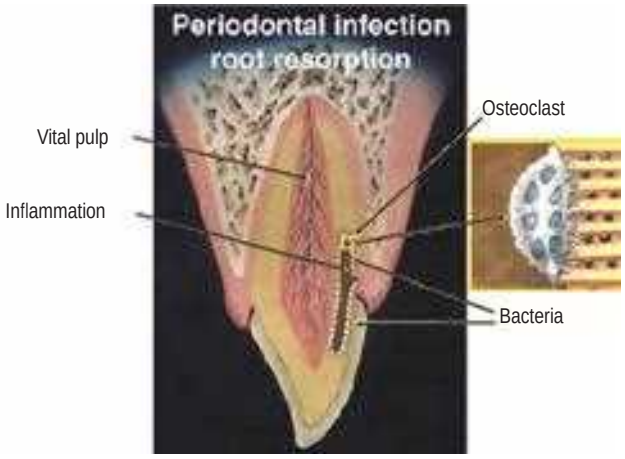


Figure 13-18. Graphical illustration of periodontal infection root resorption.
Pulp is vital and healthy, but the dentinal tubules adjacent to coronal cemental trauma are infected and inflammatory response with osteoclastic activity is taking place in dentin. Enlargement of osteoclast attached to dentin on the right demonstrates the stimulation factor of bacteria in the dentinal tubules. The bacteria originate from the periodontal tissues and not from the pulp space.

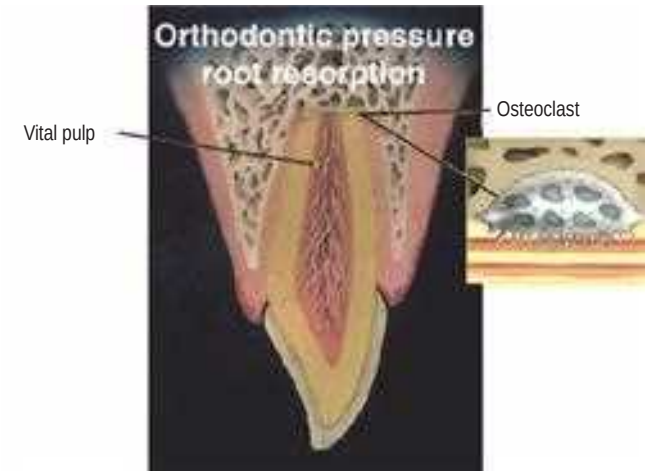


Figure 13-19. Graphical illustration of orthodontic pressure root resorption.
Pulp is vital and stimulation to the osteoclastic activity in the apex is related to extensive pressure during orthodontic treatment. Enlargement of an osteoclast attached to the dentin on the right demonstrates intact dentinal tubules with no bacteria.

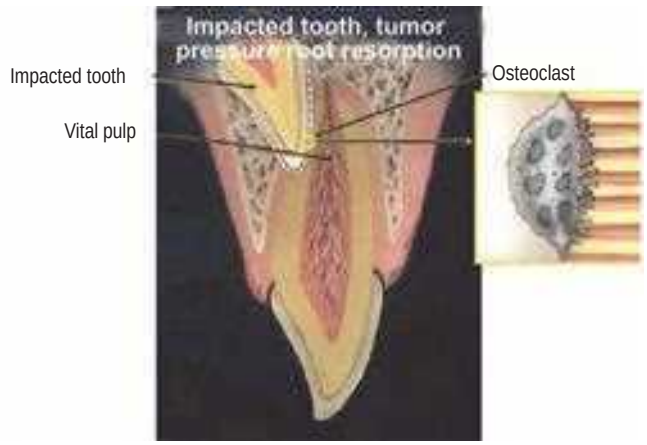


Figure 13-20. Graphical illustration of impacted tooth or tumor pressure root resorption.
Pulp is vital and stimulation to the osteoclastic activity is related to extensive pressure by the impacted tooth. Enlargement of an osteoclast attached to the dentin on the right demonstrates intact dentinal tubules with no bacteria.

INTERNAL RESORPTION

(Chronic perforating hyperplasia of pulp, internal granuloma, odontoclastoma, pink tooth of Mummery)

Internal resorption is an unusual form of tooth resorption that begins centrally within the tooth, apparently initiated, in most cases, by a peculiar inflammatory hyperplasia of the pulp. The cause of the pulpal inflammation and subsequent resorption of tooth substance is unknown, although an obvious carious exposure and accompanying pulp infection are sometimes present. It is even possible that true internal resorption does not exist but rather is a result of resorption of the tooth and invasion of the pulp by granulation tissue arising in the periodontium. An excellent discussion of the problem of idiopathic tooth resorption, both external and internal, has been published by Sullivan and Jolly, while Sweet has presented a historic review of the internal resorption of teeth, beginning with the first description of the problem by Bell in 1830.

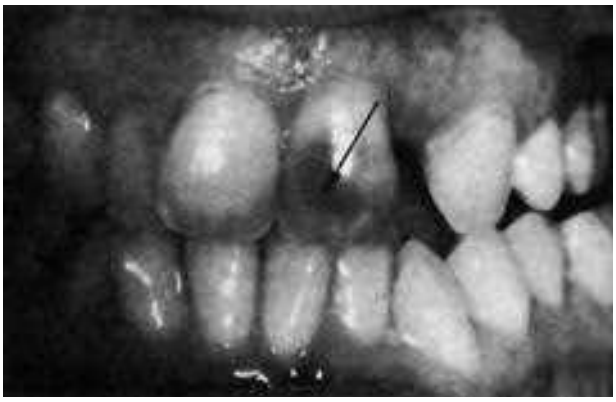


Figure 13-21. Internal resorption of maxillary central incisor.
The dark shadow represents pulp tissue visible through the tooth substance.

Clinical Features. Most cases of internal resorption present no early clinical symptoms. The first evidence of the lesion may be the appearance of a pink-hued area on the crown of the tooth, which represents the hyperplastic, vascular pulp tissue filling the resorbed area and showing through the remaining overlying tooth substance (Fig. 13-21). In the event that the resorption begins in the root, there are no significant clinical findings.

It is unusual for more than one tooth in any given patient to be affected by internal resorption, although cases of multiple tooth involvement have been recorded. There appears to be no specific predilection for occurrence in one jaw rather than the other, although no large enough series of cases has been reported to justify drawing any significant conclusions. The individual tooth involved may be any tooth, and examples of internal resorption in incisors, cuspids, bicuspids and molars have all been reported at one time or another.

Radiographic Features. Radiographic examination may provide the first revelation of pulpal disease when the patient appears for a routine check-up. The involved tooth exhibits a round or ovoid radiolucent area in the central portion of the tooth, associated with the pulp but not with the external surface of the tooth unless the condition is of such duration that perforation has occurred (Fig. 13-22). Complete perforation is not an uncommon finding if the tooth is left untreated.

Histologic Features. Microscopic examination of a tooth with internal resorption shows a variable degree of resorption of the inner or pulpal surface of the dentin and proliferation of the pulp tissue filling the defect. The resorption is of an irregular lacunar variety showing occasional osteoclasts or 'odontoclasts', hence the term 'odontoclastoma'. The pulp tissue usually exhibits a chronic inflammatory reaction but little else to explain the cause for this unusual condition (Figs. 13-23, 13-24).

Sometimes the tooth exhibits alternating periods of resorption and repair, as manifested by irregular lacuna-like

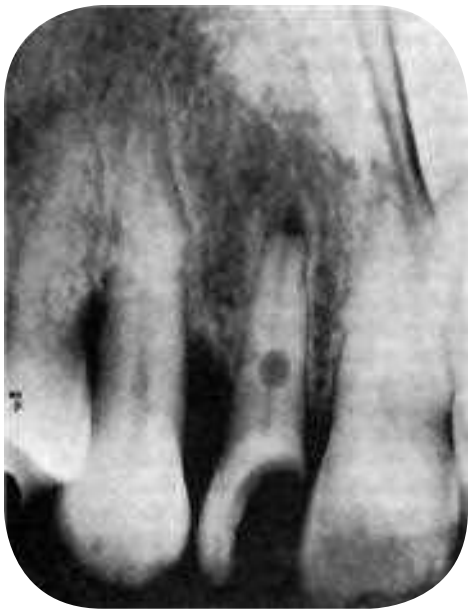


Figure 13-22. Internal resorption.

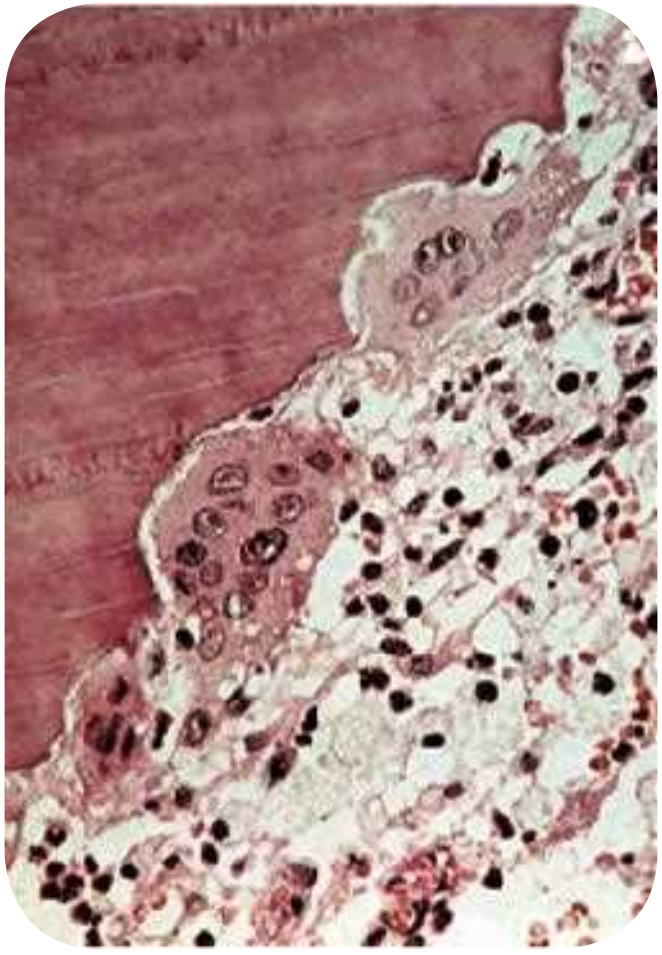


Figure 13-23. Internal resorption.
This section demonstrates the scalloped effect produced by the multinucleated odontoclasts as they resorb the dentinal surface.

Figure 13-24. Internal resorption.

areas in the dentin that are partially or completely filled in with irregular dentin or osteodentin, which itself is undergoing resorption. As the resorptive process advances, the dentin may be completely resorbed in a narrow segment. The enamel is also resorbed if the lesion is situated in the coronal portion of the tooth. If the lesion is in the root of the tooth, perforation of the dentin and cementum may occur, which, if left untreated, may eventually result in complete separation of the apical portion from the remainder of the tooth. When the root surface is perforated, it is impossible to determine whether the lesion began 'externally' or 'internally'.

Treatment and Prognosis. If the condition is discovered before perforation of the crown or root has occurred, root canal therapy may be carried out with the expectation of a fairly high degree of success. Once perforation has occurred, the tooth must usually be extracted.

There are a few cases known in which spontaneous regression of the internal resorption occurred, with the lesion either remaining but showing no further progress or with actual repair by deposition of calcified tissue. The cause of the abrupt cessation of tissue destruction is as obscure as the cause of its initiation.

HYPERCEMENTOSIS

(Cementum Hyperplasia)

Hypercementosis is a non-neoplastic condition in which excessive cementum is deposited in continuation with the normal radicular cementum. Apart from the idiopathic nature of hypercementosis, this condition is associated with several local and systemic factors.

Hypercementosis may be regarded as a regressive change of teeth characterized by the deposition of excessive amounts of secondary cementum on root surfaces. This most commonly involves nearly the entire root area, although in some instances the cementum formation is focal, usually occurring only at the apex of a tooth.

Etiology. A variety of circumstances may favor the deposition of excessive amounts of cementum. These include:

- Accelerated elongation of a tooth
- Inflammation about a tooth
- Tooth repair
- Osteitis deformans, or Paget's disease of bone.

In addition, hypercementosis of unknown etiology may occur either in a generalized form, involving all the teeth, or in a localized form, involving one tooth. Tooth function does not appear to favor the increased deposition of cementum on root surfaces. Actually, studies have indicated that the thickness of cementum is increased in nonfunctioning teeth, including embedded or impacted teeth. The stimulus in these instances is unknown.

Acceleration in the elongation of a tooth owing to loss of an antagonist is accompanied by hyperplasia of the cementum, apparently as a result of the inherent tendency to maintain the normal width of the periodontal ligament. This hypercementosis is most prominent at the apex of the root, although deposition of secondary cementum usually involves the entire root, tapering off in thickness toward the cervical portion of the tooth.

Inflammation at the apex of a tooth root, usually occurring as a result of pulpal infection, sometimes stimulates excessive deposition of cementum. This does not occur at the apex of the root directly adjacent to the area of inflammation, since the cementoblasts and their direct precursors in this area have been lost as a result of the inflammatory process. Instead, the cementum is laid down on the root surface at some distance above the apex, apparently being induced by the inflammatory reaction that, at some distance from its center, acts as a stimulus to cementoblasts. At the apex of the involved root itself it is not uncommon for actual resorption of cementum and dentin to occur. Thoma and Goldman pointed out that the periapical inflammation tends to cause some increase in eruption of the tooth, and this also favors the deposition of cementum in attempting to maintain the width of the periodontal ligament.

Tooth repair does not occasion the deposition of remarkable amounts of secondary cementum. Nevertheless, the cementum that is formed is often laid down with such rapidity that a mild form of hypercementosis is simulated. On occasion, occlusal trauma results in mild root resorption. Such resorption is repaired by secondary cementum. Root fracture is also repaired on occasion by deposition of cementum between the root fragments as well as on their periphery. Finally, cemental tears, detachment of strips of cementum from the root due to trauma, are repaired by cementum growing into and filling the defects and eventually uniting with the torn cementum.

Osteitis deformans or Paget's disease of bone (q.v.) is a generalized skeletal disease characterized by deposition of excessive amounts of secondary cementum on the roots of the teeth and by the apparent disappearance of the lamina dura of the teeth, as well as by other features related to the bone itself. Although the bone changes are the most prominent features of the disease, generalized hypercementosis should always suggest the possibility of the presence of osteitis deformans.

Spike formation of cementum is an uncommon condition characterized by the occurrence of small spikes or outgrowths of cementum on the root surface. These cemental spikes appear in some cases of excessive occlusal trauma, probably as a result of deposition of irregular cementum in focal groups of fibers of the periodontal ligament. The exact mechanism of spike formation is unknown, and its significance is obscure.

Clinical Features. Hypercementosis produces no significant clinical signs or symptoms indicative of its presence. There is no increase or decrease in tooth sensitivity, no sensitivity to percussion unless periapical inflammation is present, and no visible changes in gross appearance *in situ*. When the tooth with hypercementosis is extracted, the root or roots appear larger in diameter than normal and present rounded apices.

Radiographic Features. On the periapical radiograph most cases of hypercementosis, at least of any significant degree, are distinguished by the thickening and apparent blunting of the roots. The roots lose their typical 'sharpened' or 'spiked' appearance and exhibit rounding of the apex (Fig. 13-25). It is generally impossible to differentiate the root dentin

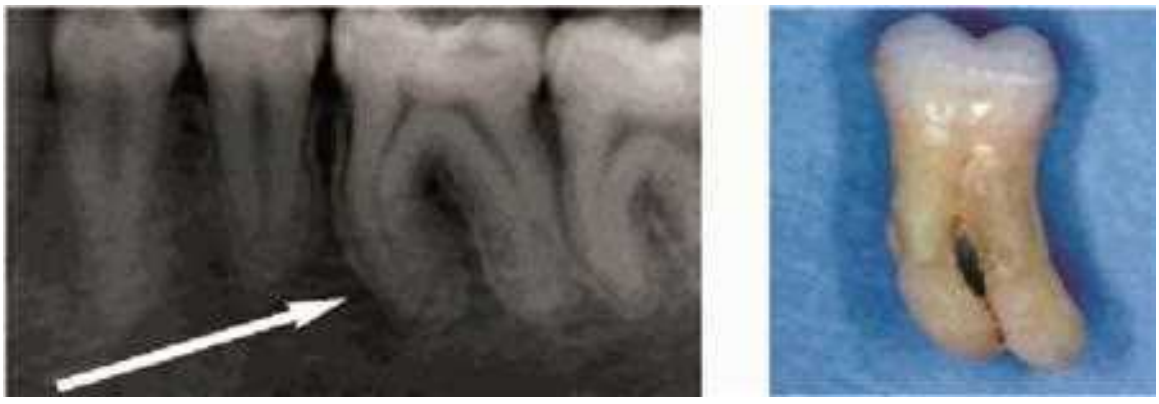


Figure 13-25. Hypercementosis.
(Courtesy of Dr Charles Dunlap, 2004).

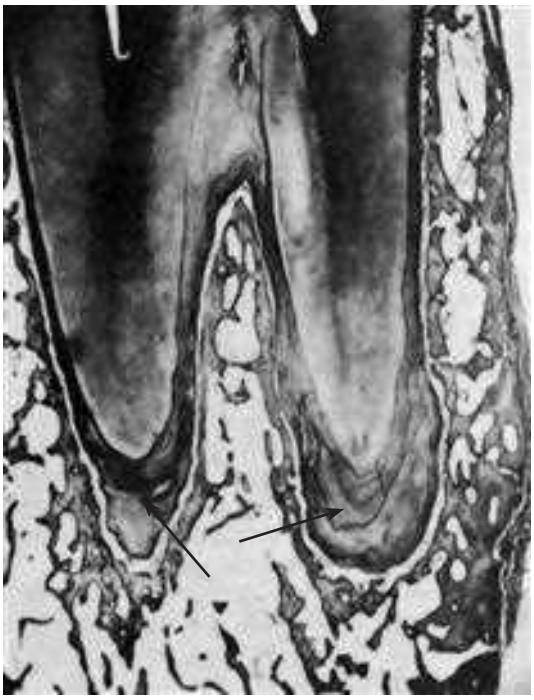


Figure 13-26. Hypercementosis.

from the primary or secondary cementum radiographically; therefore the diagnosis of hypercementosis is established by the shape or outline of the root rather than by any differences in radiodensity of the tooth structure.

Histologic Features. The microscopic appearance of hypercementosis is a characteristic one in which an excessive amount of secondary or cellular cementum is found deposited directly over the typically thin layer of primary acellular cementum (Fig. 13-26). The area involved may be the entire root or only a portion, typically the apical region. The secondary cementum has been termed 'osteocementum' because of its cellular nature and its resemblance to bone. This cementum typically is arranged in concentric layers around the root and frequently shows numerous resting lines, indicated by deeply staining hematoxyphilic lines parallel to the root surface.

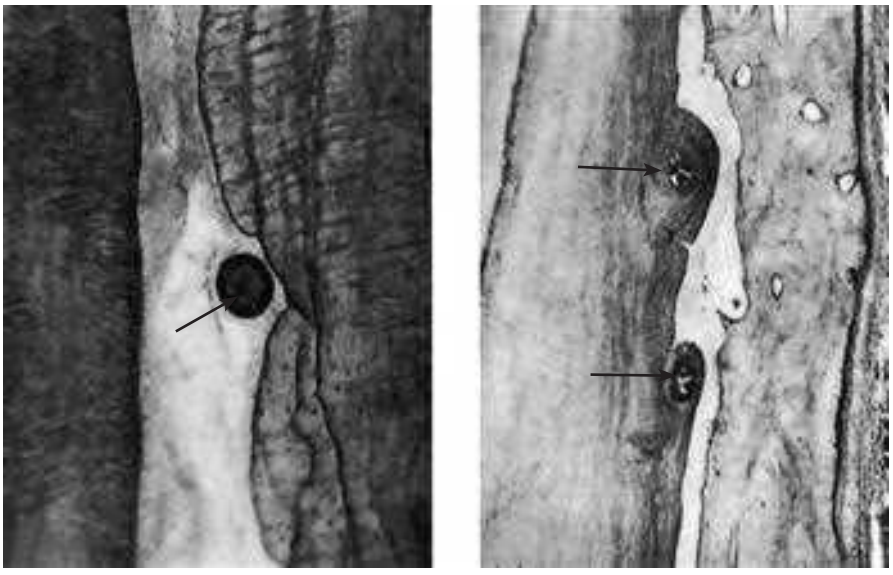
Treatment and Prognosis. No treatment is indicated for teeth exhibiting hypercementosis, since the condition in itself is innocuous. In those cases in which the overproduction of cementum is due to inflammation of pulpal origin, treatment of the primary condition is obviously necessary. The extraction of teeth because of hypercementosis is contraindicated, since the prognosis of such teeth is excellent in the absence of concomitant infection.

CEMENTICLES

Cementicles are small foci of calcified tissue, not necessarily true cementum, which lie free in the periodontal ligament of the lateral and apical root areas. The exact cause for their formation is unknown, but it is generally agreed that in most instances they represent areas of dystrophic calcification and thus are an example of a regressive or degenerative change.

It is recognized that actually a variety of calcified bodies may occur in the periodontal ligament, not all of which have the morphologic characteristics of cementum. Nevertheless, they have all been commonly known as cementicles. These various types of calcifications have been reviewed by Moskow.

The most common manner in which cementicles develop is by calcification of nests of epithelial cells, i.e. epithelial rests, in the periodontal ligament as a result of degenerative change. These bodies enlarge by further deposition of calcium salts in the adjacent surrounding connective tissue (Fig. 13-27A). The continued peripheral calcification of the



A B

Figure 13-27. Cementicles.
(A) Free cementicle. **(B)** Attached cementicle.

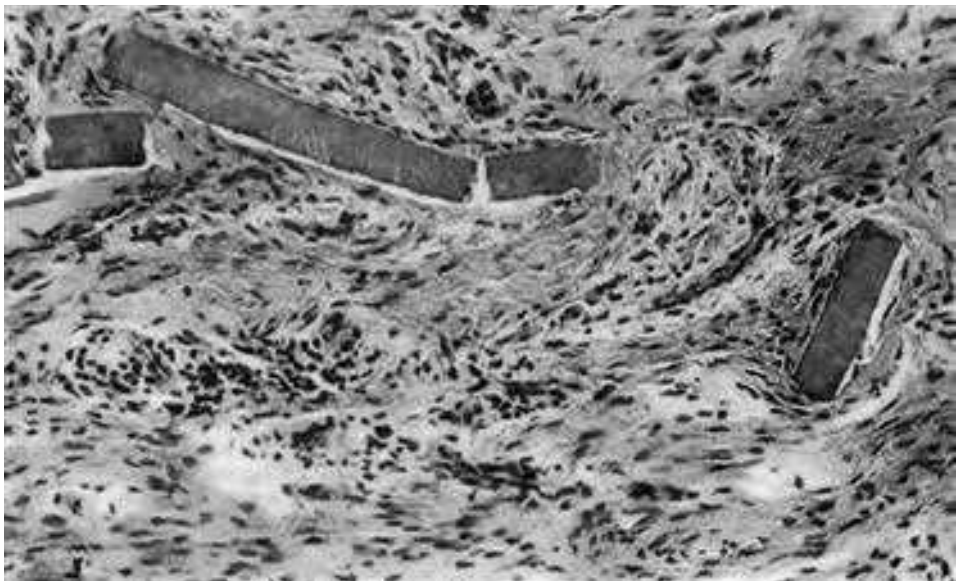


Figure 13-28. Cemental tears.
Small strips of primary cementum lying free in the periodontal membrane after traumatic injury.

connective tissue may result in the eventual union of the cementicle with, and even inclusion in, root cementum or alveolar bone. The pattern of calcification often gives the appearance of a circular lamellated structure. When only partially embedded in the root cementum, the cementicle may impart a roughened globular outline to the root surface (Fig. 13-27B).

Cementicles may arise from focal calcification of connective tissue between Sharpey's bundles with no apparent central nidus. This calcification occurs as small round or ovoid globules of calcium salts.

Small spicules of cementum torn from the root surface—i.e. cemental tears—or fragments of bone detached from the alveolar plate, if lying free in the periodontal ligament may resemble cementicles, particularly after they have undergone some remodeling through resorption and subsequent repair (Figs. 13-28, 13-29).

Finally, cementicles appear to arise through calcification of thrombosed capillaries in the periodontal ligament, and as Mikola and Bauer pointed out in their excellent discussion of the formation of cementicles, are analogous to phleboliths that can occur elsewhere in the body. Although all cementicles are composed of calcified material, they are too small to be seen on the intraoral radiograph, seldom being larger than 0.2–0.3 mm in diameter. Clusters of cementicles may form, and at the apices of teeth these have sometimes been regarded as a cementoma (q.v.), particularly as the clusters unite through interstitial deposition of bone or cementum.

Cementicles are of no clinical significance and, as far as can be determined, are not detrimental to tooth function.

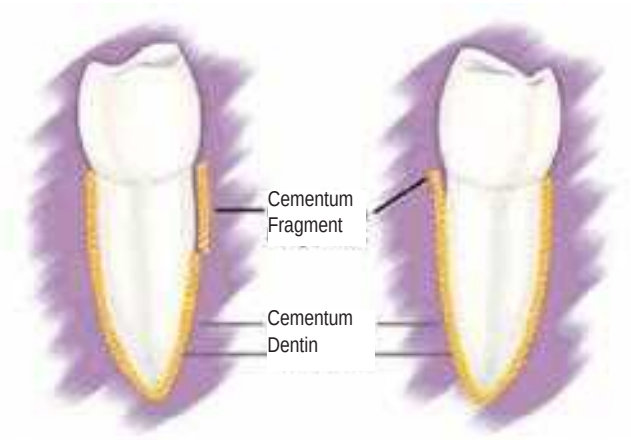


Figure 13-29. Complete and partial cemental tears.
(Courtesy of Barbara J Marquam. The Journal of Contemporary Dental Practice, Volume 4, No. 3, August 15, 2003).

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CHAPTER 14

Healing of Oral Wounds

■ B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

The word healing refers to replacement of damaged tissue by living tissue to restore function. Healing of wounds is one of the most interesting phenomenon which characterizes a living organism. Some insects, amphibians and crustaceans possess the remarkable ability to replace lost parts. The ability of damaged tissue to repair itself is a response of life itself. It is said that an unhealed wound will eventually result in the death of an organism. Therefore, wound healing must be considered as one of the primary survival mechanisms from birth onwards. It should be clearly understood that the healing of a wound is not an isolated, solitary phenomenon but actually a very complex series of biological events.

Healing is a process not an incident. It consists of wound contraction ascribed at least in part to myofibroblasts, (altered fibroblasts with characteristics of smooth muscle cells ultrastructurally). This contraction causes reduction in the size of the wound in the first few weeks and replacement of lost tissue, brought about by division and migration of neighboring cells. Replacement of the lost tissue by granulation tissue is known as 'repair' which results in scarring, and replacement by similar type tissue is known as 'regeneration'.

Healing of tissue is generally considered to be a phase of the inflammatory reaction, since it cannot be separated from the preceding vascular and cellular phenomena occurring in response to an injury. Where the edges of the wound are approximated, the healing process is fast and is known as healing by first intention or primary healing. When there is tissue loss, and wound edges cannot be apposed, the wound contracts to reduce the size, granulation tissue fills the wound and epithelialization occurs across the wound surface. This is called healing by secondary intention. Granulation tissue is characteristically bright pink in appearance and is composed chiefly of proliferating capillaries and fibroblasts.

Various growth factors and cytokines play a significant role in healing. The epidermal growth factor, produced by the epithelium around the damaged area, helps in the regeneration of the epithelial tissue. Macrophages liberate fibroblast growth factor, which mediates fibroblast activity along with transforming growth factor-α. Endothelial growth factor triggers the formation of new blood vessels.

Healing of all tissues after injury has an essentially identical pattern, but may be modified considerably, depending upon numerous intrinsic and extrinsic factors.

Oral wounds are common, some sustained accidentally (e.g. jaw fractures), some inflicted by the dentist for a specific purpose (e.g. extraction wounds, biopsy wounds, etc.) and others caused by disease process (e.g. various oral ulcers). The unusual anatomic situation of the oral cavity—the teeth protruding from the bone, the constant inflammation present in the gingival tissues, the presence of countless microorganisms in a warm, moist medium of saliva — all contribute to modify the healing reaction of the various wounds.

FACTORS AFFECTING HEALING OF ORAL WOUNDS

A number of factors influence the healing process of wounds in the oral cavity. Although interference with the normal healing phenomena is not a common occurrence, the dentist must recognize the possible causes.

Location of Wound. The particular location of a wound is important, as it may modify the rate of healing. Wounds in an area with a good vascular bed heal considerably more rapidly than wounds in an area which is relatively avascular.

Immobilization. Immobilization of the wound is also important in the healing reaction. If the wound is in an area subjected to constant movement so that formation of the new connective tissue is continuously disrupted (e.g. in the corner of the mouth), it will result in delayed healing. Immobilization is particularly important in the healing of bone fractures, for without it bony union may be delayed or even completely inhibited, resulting in fibrous union.

Physical Factors

Severe trauma to tissue is an obvious deterrent to rapid wound healing. Under certain situations, however, mild traumatic injury may actually favor the healing process. For example, it is well recognized that a second wound inflicted in the site of a healing initial wound, heals more rapidly than the initial or single wound.

Local temperature in the area of a wound influences the rate of healing, probably by its effect on local circulation and cell multiplication. Thus, in an environment of hyperthermia, wound healing is accelerated while in hypothermia healing is delayed.

The effect of **X-ray radiation** on the healing of wounds has been extensively studied, and the data indicates that generally low doses of radiation tend to stimulate healing, while large focal doses of radiation or total body radiation tend to suppress healing.

Circulatory Factors. Anemia has been reported to delay wound healing, although not all studies have confirmed this observation. Similarly, dehydration has been found to affect the healing wound adversely.

Nutritional Factors. It has been shown that delay in healing of wounds may occur in a person who is deficient in any of the vast variety of essential foods.

Protein is one of the most important substances, which may influence the speed of wound healing. Numerous clinical studies have indicated that poorly nourished patients with low protein intake resulting in a protein deficiency, manifested by a hypoproteinemia, exhibit a delay in the appearance of new fibroblasts as well as a decreased rate of multiplication of fibroblasts in wounds. Conversely, it has been shown that feeding high protein diets to animals will increase the rate of fibroblastic proliferation and cause wounds to heal more rapidly. The exact manner in which protein influences the wound is not known, although there is considerable evidence that this effect is related to dietary compounds containing free sulfhydryl groups. Of all the essential amino acids, only methionine furnishes such a group, and studies have shown that administration of methionine to hypoproteinemic animals restores the rate of wound healing to a normal level.

Vitamins are another group of nutritional factors related to wound healing. One of these, which has been known for many years to influence the rate of wound healing, is vitamin C or ascorbic acid. It acts through regulation of collagen formation and formation of normal intercellular ground substance of the connective tissue. It appears that, in scurvy or ascorbic acid deficiency, this inhibitory effect on wound healing is specifically related to interference with the production of mucopolysaccharides, which make up the cement substance. Microscopically, it is recognized that fibroblastic proliferation in a wound of a scorbutic animal continues longer than in control animals. This is interpreted to mean that there is prolonged need for formation of connective tissue, and this is borne out by the fact that scorbutic animals exhibit a decreased tensile strength of the healing wounds.

There have been no extensive studies on the possible role of vitamins A and D in wound healing, but the available reports indicate that a vitamin A deficiency retards healing and that vitamins A and D, as in cod liver oil, may be factors in promoting tissue repair. The available studies indicate that riboflavin and pyridoxine deficiencies result in delayed healing process.

Age of Patient. Wounds in younger persons heal considerably more rapidly than in elderly persons, and the rate of healing appears to be in inverse proportion to the age of the patient. The cause for this is unknown, but probably relates to the general reduction in the rate of tissue metabolism as the person ages, which itself may be a manifestation of decreased circulatory efficiency. Also at the molecular level, slowing of protein synthesis and formation of structurally altered protein, affects healing.

Infection. Wounds which are completely protected from bacterial infection heal considerably more slowly than wounds which are exposed to bacteria or other mild physical irritation. Furthermore, Lattes and his coworkers showed that bacterial infection of wounds suppressed the cortisone-inhibitory effect on fibroplasias in the experimental animal. Some studies on germ free animals with experimental wounds, primarily incised and closed, have shown a reduction in tensile strength, as compared to control animals, thus indicating that the germ free state is a deterrent to wound healing.

It is obvious, however, that severe bacterial infection slows the healing of wounds. In view of the vast bacterial flora of the oral cavity, one might question whether all wounds of the oral cavity are not heavily infected. Since the antibody titer of a person against his/her own microorganisms is usually extremely high, there is seldom cause to worry about infection from autoinoculation. Occasionally, however, the resistance of the tissue is decreased, either locally or on a systemic basis, and an oral wound becomes massively infected and heals slowly, if at all.

Hormonal Factors

Adrenocorticotropic hormone (ACTH) and cortisone are substances that have been repeatedly shown to interfere with the healing of wounds. Not long after ACTH and cortisone were first used clinically, it was noted that wounds

in recipients of these compounds exhibited delayed healing. Since this observation, a number of careful experimental studies were carried out in which it was shown that, in patients receiving ACTH or cortisone, the growth of granulation tissue was inhibited, apparently because of inhibition of proliferation of new fibroblasts and new endothelial sprouts and because of a depression of the inflammatory reaction. There is apparently not an actual suppression of mesenchymal activity, but rather a delay in the mesenchymal reaction. An experimental study by Shafer on the healing of extraction wounds in rats receiving cortisone showed that the healing of such wounds was delayed. This would suggest that patients under long time steroid therapy or with Cushing's syndrome, should be carefully evaluated by the dentist before he or she carries out oral surgical procedures.

Numerous investigators have also studied the effects of administration of pituitary growth hormone and thyroid hormone (thyroxin) and concluded that these had no significant role in wound healing. The opposite situations, obtained by surgical ablation of the pituitary gland and thyroid gland, have also been reported as having no significant effects on wound repair. There is one interesting experimental study in the literature, which shows that wound healing was delayed during pregnancy, but this has not been confirmed clinically.

Diabetes mellitus (insulin deficiency) is one of the most widely recognized diseases in which there is significant, clinically evident retardation in repair of wounds after surgical procedures, including tooth extraction. Wounds in diabetic patients are notoriously slow to heal and frequently show complications in the repair process. The exact mechanism of this phenomenon is not known, but is probably related to disturbance in carbohydrate metabolism at the cellular level in the local area of the wound. Because of this recognized relation of insulin deficiency to wound healing, a number of investigators have studied the effect of administration of insulin to normal animals (hyperinsulinism), but the reports are indecisive on its influence on wound healing. Nevertheless tissue culture studies have almost invariably shown stimulation of fibroblastic proliferation when insulin was added to the growth medium.

Miscellaneous Factors

Other factors include enzymes, such as trypsin, streptokinase, alkaline phosphatase, and coenzyme adenosine 5-monophosphate, growth-promoting factors such as cartilage and mucopolysaccharide, N-acetyl-D-glucosamine, tissue extracts and pantothenyl alcohol, hydroxyproline, hydrogen ion concentration, electrolyte balance, therapeutic agents such as dilantin sodium, sulfonamides and antibiotics, anticancerous drugs which inhibit cell cycle or kill the cells involved in active proliferation, immunosuppressive drugs, anticoagulants such as heparin and dicumarol, emollients, sclerosing agents, metals, particularly trace elements such as zinc, copper, and deuterium oxide, antigen-antibody reactions, and lathyrism.

The effects of suture materials on healing of skin wounds also have been studied by many investigators. A large comparative study in dogs was reported by Van Winkle and his coworkers, who concluded that, there were no differences in healing among wounds closed with different suture materials up to a postoperative period of about one month. However, on a more long-term basis, they found that wounds sutured with nonabsorbable sutures were weaker than those sutured with absorbable ones and that, in general, there was a lower incidence of wound infection with monofilament sutures than with multifilament sutures. However, in some findings these investigators noted that, when compared with other similar studies, there were species differences, and they cautioned against direct application of such observations to a human patient.

Use of tissue adhesives such as butyl and isobutyl cyanoacrylate have been studied by many investigators. These may serve as an alternative for sutures in wound closure and are widely utilized in surgical procedures involving numerous organs. These adhesives, have also been applied to a variety of surgical procedures of the oral cavity.

Their chief attributes are:

- Their ability to act as a surface tissue adhesive in the presence of moisture.
- Their hemostatic and bacteriostatic effects.

Bhaskar and Frisch have reviewed the use of cyanoacrylate adhesives in dentistry, concluding that butyl cyanoacrylate is not only well tolerated by tissues and permits uncomplicated healing but also generally hastens the healing process. It has been successfully tested as a surface dressing after gingivectomy, on mucoperiosteal flaps, biopsy sites, extraction wounds, aphthous ulcers, leukemic ulcerations, pulp capping, and in the grafting of mucosal tissues from one region of the mouth to another.

It may be concluded that the repair of damaged tissue is a vital dynamic process, which may be influenced by a multitude of exogenous and endogenous factors. That alteration in this process does not occur more frequently than it does is proof of the inherent resistance of the living organism to those factors, which could interfere with perpetuation of life. In certain instances this resistance is diminished, and pathologic alterations in the repair phenomenon occur. The factors that may be responsible for this unfortunate occurrence must be recognized and understood so that proper measures may be taken to correct the problem.

COMPLICATIONS OF WOUND HEALING

Infection. Wounds may provide a portal of entry to microorganisms. Infections of the wound delay the healing process. It is a common phenomenon in maxillofacial trauma cases. Most of the times, the oral wounds heal without this complication, but at times the underlying systemic conditions such as diabetes mellitus, immunosuppressive state, etc. make the individual prone to infections.

Keloid and Hypertrophic Scar Formation. Keloids are overgrown scar tissues with no tendency for resolution. They

occur in wounds, which heal without any complications. The common sites of occurrence include chest, back and shoulders.

Hypertrophic scars occur in wounds where healing is delayed. These hypertrophic scars are more cellular and vascular. The remodeling phase in these scars is prolonged; and the imbalance between collagen production and disintegration leads to excess of collagen in these scars. Clinically they appear red, raised, itchy, and tender. They become pale and flat as they mature. Spontaneous resolution may occur in time and this distinguishes them from keloid.

Keloids and hypertrophic scars are not seen in the wounds of the oral cavity. In the oral cavity, the wound remodeling rate is so high that even a normal scar is not seen most of the times.

Pigmentary Changes. These are common in healing of wounds on the skin and may appear as hypopigmented or hyperpigmented areas. Though hypopigmented scars are not common in the oral cavity, some lesions leave hyperpigmentations while healing (e.g. lichen planus, lichenoid reactions, etc.).

Cicatrization. Cicatrization refers to late reduction in the size of the scar in contrast to immediate wound contraction. It is a complication due to burns of the skin.

Implantation Cysts. Epithelial cells may slide or get entrapped in the wound and later may proliferate to form implantation cysts.

Healing after Pulpal Diseases. Inflammation of the pulp does not always result in pulpal necrosis. Resolution occurs in a considerable number of cases. Healing of pulp is the common outcome of pulpal inflammation in clinical conditions. But nevertheless, it depends on the degree of infection, inflammation, amount of the pulpal tissue involved, and the age of the patient. If the carious cavities are thoroughly cleaned and restored with suitable materials, the abscesses heal by reparative dentin formation. Pulpal inflammation might even resolve, in teeth with carious lesions remaining, with the formation of sclerotic dentin, which reduces the permeability to bacteria and bacterial products. In some cases, the healing occurs by localized fibrosis.

Healing after Periapical Diseases. Healing of periapical lesions may result in the formation of new bone or fibrosis in the involved area. In periapical lesions treated surgically, there is an outgrowth of fibroblasts and capillaries from the surrounding healthy connective tissue. Slowly this granulation tissue fills the entire defect. Osteoblasts appear in the granulation tissue towards the deeper portion adjacent to the healthy bone, and the granulation tissue is gradually replaced by bone in the course of time.

BIOPSY AND HEALING OF BIOPSY WOUND

Biopsy is the removal of tissue from the living organism for the purposes of microscopic examination and diagnosis. Although the diagnosis of many lesions can be made clinically by the dentist with experience, such a diagnosis is generally a provisional one, contingent upon the final report on the tissue specimen by the pathologist. Biopsy not only helps in the diagnosis but also serves as a treatment option for smaller lesions by excising *in toto*, though few lesions do not present a specific microscopic appearance. Nevertheless, the biopsy procedure helps in the treatment plan. Although the microscope in the hands of a qualified pathologist is an irreplaceable diagnostic tool, its limitations must always be kept in mind. Fortunately, with the rapid advancement occurring in scientific techniques adaptable to microscopic diagnosis, such as histochemical techniques, fluorescent microscopy, microradiography, histoautoradiography, transmission and scanning electron microscopy, and so forth, this sphere of diagnostic limitation is gradually shrinking.

Types of Biopsy

Total excision of a small lesion for microscopic study is called **excisional biopsy**. The pathologist will usually be able to tell the operator whether the lesion was removed in entirety by observing the appearance of the tissue along the line of excision. Excisional biopsy is preferred, if the size of the lesion is such that it may be removed along with a margin of normal tissue and the wound can be closed primarily.

Some lesions are too large to excise initially without having established a diagnosis, or are of such a nature that excision would be inadvisable. In such instances, a small piece is removed for examination. This is termed an **incisional** or **diagnostic biopsy** (Fig. 14-1). It is most useful in dealing with large lesions, in which the operator suspects may be treated by some means other than surgery once the diagnosis is made, or lesions in which the diagnosis will determine whether the treatment should be conservative or radical.

The biopsy should include surrounding normal tissue with adequate depth of underlying connective tissue.

There are several methods by which material may be obtained from a lesion for microscopic study:

- Surgical excision by scalpel
- Surgical removal by cautery or a high-frequency cutting knife
- Laser
- Removal by biopsy forceps or biopsy punch
- Aspiration through a large bore needle
- The exfoliative cytology technique (q.v.) whereby the surface of a lesion is scraped and smeared on a microscope slide and studied by the pathologist after suitable staining.

Needle biopsy has little value in the diagnosis of oral lesions. The scalpel is the instrument of choice, since it cleanly removes the tissue and does not dehydrate it as cautery or the high-frequency cutting knife may. This latter instrument is of great value, however, in dealing with vascular lesions, where it controls bleeding at the biopsy site.

Biopsy Technique

Biopsy technique is a simple procedure and may be carried out by any dentist as a routine clinical procedure if certain

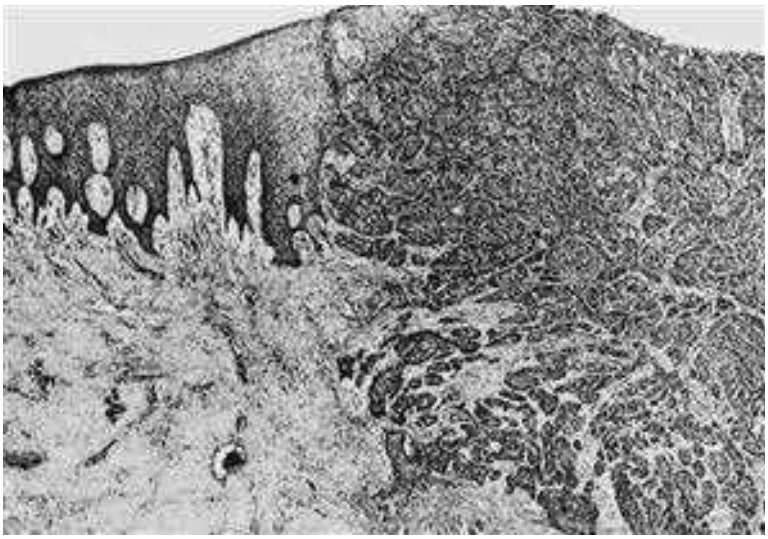


Figure 14-1. Epidermoid carcinoma, diagnostic biopsy.
An adequate border of normal mucosa was obtained with the biopsy of the neoplastic mass, and no attempt was made initially to excise the lesion completely.

precautions are taken and certain rules are followed. The advantages of a biopsy so far outweigh its disadvantages or potential dangers that the biopsy is seldom, if ever, contraindicated in case of a lesion in which the diagnosis has not been established. To ensure obtaining a proper specimen for the pathologist, the following points must be considered:

1. Do not paint the surface of the area to be biopsied with iodine or a highly colored antiseptic.
2. If using infiltration anesthesia, do not inject anesthetic solution directly into the lesion. Inject around the periphery of the lesion instead.
3. Use a sharp scalpel to avoid tearing tissue.
4. Remove a border of normal tissue with the specimen if at all possible.
5. Use care not to mutilate the specimen when holding it with forceps.
6. Fix the tissue immediately upon removal in 10% formalin or 70% alcohol. If the specimen is thin, place it upon a piece of glazed paper and drop into fixative to prevent curling of tissue.

Biopsy Report

The report of a biopsy is usually returned to the operator by the pathologist within a few days unless some special procedures, such as decalcification of tooth, bone or other calcified substance or application of special stains, are necessary.

A negative biopsy report or a histopathological diagnosis not in conformity with the expected diagnosis should never be considered final. It means only that there are no features to suggest the expected diagnosis in that **particular piece** of tissue, which was removed at that **particular time**. A repeat biopsy should always be performed when there is any doubt about the adequacy or representative nature of the original specimen.

Healing of Biopsy Wound

The healing of a biopsy wound of the oral cavity is identical with the healing of a similar wound in any other part of the body and thus may be classified as either primary healing or secondary healing. The nature of the healing process depends upon whether the edges of the wound can be brought into apposition, often by suturing, or whether the lesion must fill in gradually with granulation tissue.

Primary Healing. Primary healing, healing by primary intention or healing by first intention is healing that occurs after the excision of a piece of tissue with the close apposition of the edges of the wound by sutures. This is the form of healing one might expect after the excision of a lesion in an area of the oral cavity where the pliability of the tissues is such that the wound may be drawn together and sutured.

When the edges of the wound are brought into contact and held in place by sutures, the blood clots, and in a matter of hours numerous leukocytes are mobilized to that area. Connective tissue cells in the immediate vicinity undergo transformation into fibroblasts, which in turn undergo mitotic division, and the new fibroblasts begin to migrate into and across the line of incision. In time, these cells form thin, delicate collagen fibrils, which intertwine and coalesce in a general direction parallel to the surface of the wound. At the same time, endothelial cells of the capillaries begin to proliferate, and small capillary buds grow out and across the wound. These buds eventually form new capillaries, which fill with blood, and a rich network of young capillaries and capillary loops are formed.

When there is a close apposition of the edges of the wound, the surface epithelium proliferates rapidly across the line of incision and re-establishes the integrity of the surface. The delicate connective tissue fibrils eventually coalesce into denser bundles and usually contract, so that in time all that is left

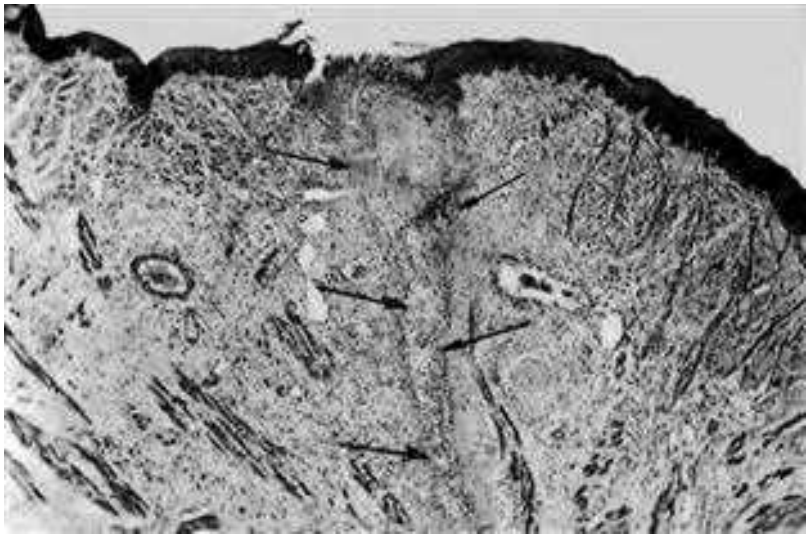


Figure 14-2. Primary healing of a wound.
The thin linear incision shows re-establishment of continuity of the tissue only after 48 hours.

to indicate the biopsy area is a small linear scar which may be depressed below the surface. Because there is no defect which must be filled with new tissue, this type of wound heals rapidly (Fig. 14-2).

Secondary Healing. Secondary healing, healing by second intention, healing by granulation or healing of an open wound occurs when there is loss of tissue and the edges of the wound cannot be approximated. Healing of this type is often spoken of as a process in which the wound 'granulates in' since the material, which fills the defect during the healing process, is called granulation tissue. This type of wound is a result of biopsy of a lesion in an area of the oral cavity in which the tissues are not pliable and in which the edges cannot be approximated. For example, removal of a lesion of the palate or a large lesion of the alveolar ridge is usually followed by healing by second intention, since the edges of the wound cannot be coapted.

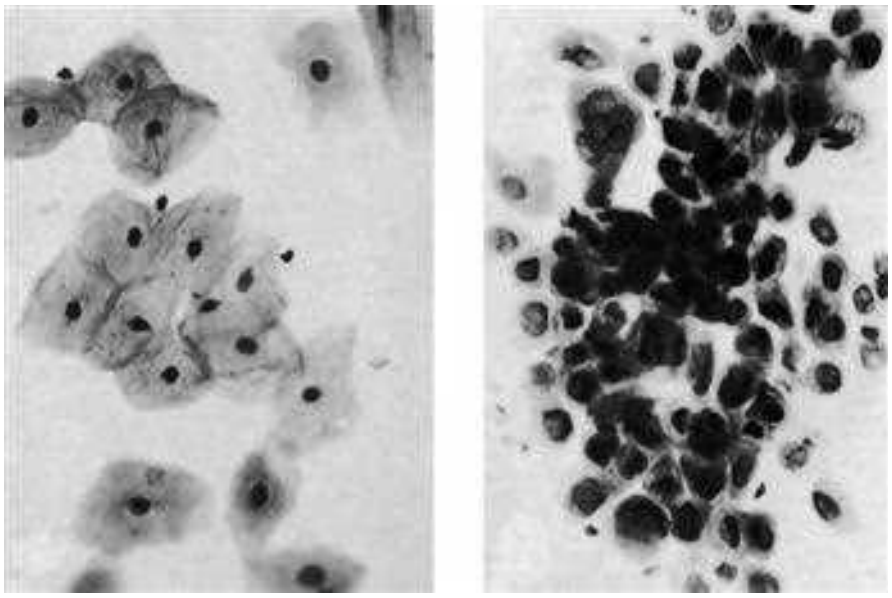
After the removal of the lesion, the blood fills the defect, clots and the repair process begins. It is basically identical with healing by primary intention except that the fibroblasts and capillaries have a greater distance to migrate; more granulation tissue must form, and of necessity the healing is slower. Cellular proliferation begins around the periphery of the wound, and the fibroblasts and endothelial cells grow into the clot along fibrin strands. In addition, polymorphonuclear leukocytes, and later, lymphocytes, and mononuclear phagocytes migrate into the granulation tissue from the adjacent vessels and tissues. Large numbers of leukocytes also accumulate on the surface of the wound. As the granulation tissue matures, it becomes more fibrous through condensation of collagen bundles, and the surface of the granulation tissue becomes epithelialized. As in primary healing, the collagen fibrils coalesce and the lesion becomes somewhat less vascular, and eventually the only evidence of the wound may be a small depressed area of the mucosa.

EXFOLIATIVE CYTOLOGY

Exfoliative cytology is the study of cells which exfoliate or abrade from the body surfaces. The rationale for exfoliative cytology lies in epithelial physiology. Normal epithelium undergoes exfoliation of its superficial cells due to physiological turnover. The cells of the deeper layers are adherent to each other normally. When the epithelium becomes seat of any pathological condition, the cells may lose their cohesiveness, and cells in the deeper layer may shed along with the superficial cells. These exfoliated cells as well as cells which are scrapped off by means of specific instruments, can be studied quantitatively or qualitatively. Considerable interest has developed in the use of exfoliative oral cytology for the diagnosis of oral mucosal lesions (Fig. 14-3). Application of cytodiagnosis as a routine procedure in the detection of cervical cancer was introduced by George N Papanicolau in 1941. Its application in oral cancer has been known for a long time. In a review of the historic background of oral cytology, von Hamm cited numerous series of cases of patients with oral cancer in which the diagnostic accuracy of cytologic smears was compared with that of the surgical biopsy and was found to be almost identical. He concluded that:

- Cytology is not a substitute but an adjunct to the surgical biopsy.
- It is a quick, simple, painless and bloodless procedure.
- It helps as a check against false-negative biopsies.
- It is especially helpful in follow-up detection of recurrent carcinoma in previously treated cases.
- It is valuable for screening lesions whose gross appearance is such that biopsy is not warranted.

Obviously, the use of the cytologic smear is predicated upon the proper preparation of the smear by the clinician and sufficient experience in its evaluation by the cytologist.



A B

Figure 14-3. Oral mucosa, cytologic smears.
Normal epithelial cells are shown **(A)**, contrasted with malignant cells from a patient with epidermoid carcinoma **(B)**.

The preferred technique is a relatively simple one. It consists essentially of cleansing the surface of the oral lesion of debris and mucin, and then vigorously scraping the entire surface of the lesion several times with a metal cement spatula, a moistened tongue blade or a cytobrush. The collected material is then quickly spread evenly over a microscopic slide and fixed immediately before the smear dries. The fixative may be either, a commercial preparation such as Spray-cyte, 95% alcohol, or equal parts of alcohol and ether. After the slide is flooded with the fixative, it should be allowed to air-dry for 30 minutes. Slides are never flame fixed as bacteriologic smears. It is essential that the procedure be repeated and a second smear be prepared for submission to the cytologist. In preparing the duplicate slide, a separate scraping should be utilized. Two smears are always submitted from each lesion, since additional staining techniques are frequently employed.

The cytologic smear will usually be reported by the cytologist as falling into one of five classes:

Class I (Normal): Indicates that only normal cells were observed
Class II (Atypical): Indicates the presence of minor atypia but no evidence of malignant changes
Class III (Indeterminate): This is an inbetween cytology that separates cancer from noncancer diagnosis. The cells display wider atypia that may be suggestive of cancer, but they are not clear-cut and may represent precancerous lesions or carcinoma *in situ*. Biopsy is recommended
Class IV (Suggestive of cancer): A few cells with malignant characteristics or many cells with borderline characteristics. Biopsy is mandatory
Class V (Positive for cancer): Cells that are obviously malignant. Biopsy is mandatory

Though exfoliative cytological study has a significant role in cancer diagnosis, it has its own limitations. The presence or extent of invasion cannot be assessed. It should be remembered that the majority of benign lesions that occur in the oral cavity do not lend themselves to cytologic smear. For example, lesions which have a normal appearance and an intact surface, such as a fibroma, should be excised and never smeared. In addition, most authorities agree that leukoplakia does not lend itself to cytologic diagnosis because of the scarcity of viable surface cells in the smears taken from such lesions. Finally, it should be remembered that a negative cytology report does not rule out cancer and that a repeat smear or biopsy is indicated in all clinically suspicious lesions.

It has been recognized that the exfoliative oral cytologic smear is also of value in the diagnosis of diseases other than carcinoma, particularly diseases which are characterized by the presence of certain specific cells. Thus, cytologic smears have been useful in the diagnosis of lesions of herpes simplex infection, herpes zoster, pemphigus vulgaris, benign familial pemphigus, keratosis follicularis, hereditary benign intraepithelial dyskeratosis, white sponge nevus, and pernicious and sickle cell anemia. Apart from the diagnosis of oral mucosal lesions, it has widespread research applications. Many quantitative and qualitative studies have been done in tobacco users, patients with premalignant and malignant lesions, and iron deficiency. N Gururaj, B Sivapathasundharam, and N Sumathy have estimated the antioxidant level using the oral exfoliated cells. Cells retrieved from household objects, such as a toothbrush, for identification of a person or determination of gender find useful application in forensic odontology.

HEALING OF GINGIVECTOMY WOUND

The elimination of the periodontal pocket by gingivectomy has become a routine clinical procedure principally because of the excellent results which are generally attained. Gingivoplasty, similar to gingivectomy, is surgical reshaping of gingiva to produce physiologic gingival contours. Numerous techniques are in use for the removal of the tissue, and different types of postoperative packing material are applied to control bleeding, maintain tissue position, relieve pain, and keep the fresh wounds free of debris. Despite these variations, the general features of the healing process are similar.

Orban and Archer studied the wound healing following gingivectomy without the application of a surgical packing or dressing, while Bernier and Kaplan carried out a similar investigation, but using zinc oxide-eugenol packing.

An interesting finding of acceleration of gingival wound healing in nonepileptic patients receiving dilantin sodium was reported by Shapiro. He pointed out, however, that this accelerated healing may not be important in gingivectomy in which recession of tissue is the primary objective. Gültekin et al, have shown that the local application of taurine-hydrated collagen membrane on human gingival wounds demonstrated the histologic evidence of rapid re-epithelialization with taurine. Taurine is an essential amino acid known to have osmoregulatory, antioxidative, antiapoptotic, anti-inflammatory, and antilipid activities.

Eearly Healing Phase

Healing of the gingivectomy wound takes place rapidly regardless of whether a postoperative pack is used. There is some evidence, however, that healing may be slightly facilitated by the dressing.

Two days after the gingivectomy the surface of the tissue is covered by a grayish blood clot, and beneath the clot there is histologic evidence of delicate connective tissue proliferation. Even at this early stage there is also considerable activity of the epithelial cells bordering the wound, preparing for beginning of actual epithelialization. Four days after the operation, the deeper portion of the blood clot demonstrates considerable organization, while the more superficial portion exhibits dense number of polymorphonuclear leukocytes entrapped in the fibrinous meshwork. There is proliferation of young capillaries and fibroblasts into the base of the blood clot. Infiltration of polymorphonuclear leukocytes in the deeper connective tissue is present in varying degrees. The epithelium has extended over a portion of the wound below the necrotic surface layer of the clot, but above the proliferating and organizing connective tissue.

Late Healing Phase

Continuation of the healing process is manifested by a condensation of the young connective tissue with nearly complete organization of the clot after 8 to 10 days. Clinically, at this period, the wound has a red, granular appearance and bleeds readily. Epithelialization is usually complete within 10 to 14 days after gingivectomy. The epithelium remains thin, however, and begins to mature and form rete pegs only after the two weeks interval. At this time, the inflammatory cells would have largely disappeared, except for those in the subepithelial zone.

Healing of the interproximal tissue appears to lag behind that adjacent to the labial or buccal surfaces. This may be partly because the epithelium which covers the interproximal tissue must grow in from the labial and lingual areas, a relatively great distance.

The surface epithelium grows downward along the surface of the cementum within a month after gingivectomy. This is a rather shallow proliferation which, nevertheless, is in close physical apposition to the tooth.

Healing of the gingivectomy wound is basically similar to the healing of wounds elsewhere in the body, but is somewhat modified by the special anatomy of the involved region. The chronic inflammation present in the diseased gingiva does not adversely affect the healing process and may actually provide some stimulus for healing. Though the tissue changes in healing of gingivectomy wounds are the same in all individuals, the time required for complete healing varies considerably, depending upon the local condition and the systemic status of the individual.

HEALING OF EXTRACTION WOUND

A thorough understanding of the phenomenon of healing of extraction wounds is imperative for the dentist, since vast numbers of teeth are extracted because of pulp and periapical infection as well as various forms of periodontal disease, and there is an ever-present possibility of complications in the healing process.

A number of careful scientific studies have been carried out, both on the experimental animal and in human, dealing with undisturbed as well as complicated extraction wound healing. The healing of an extraction wound does not differ from the healing of other wounds of the body except that it is modified by the peculiar anatomic situation, which exists after the removal of a tooth. The healing process to be described here is a composite of the various studies reported in the literature, and while minor variations in the time sequence have been described, the uncomplicated healing of an extraction wound in the human may be expected to parallel to what will be described later. Normal human biologic variation precludes the establishment of a day-to-day timetable for such healing wounds; the healing process can only be described as an 'average' sequence of events.

Immediate Reaction Following Extraction

After the removal of a tooth, the blood which fills the socket coagulates, red blood cells being entrapped in the fibrin meshwork, and the ends of the torn blood vessels in the periodontal ligament become sealed off. The hours after tooth extraction are critical, for if the blood clot is

dislodged, healing may be greatly delayed and may be extremely painful.

Within the first 24 to 48 hours after extraction, a variety of phenomena occur which consist principally of alterations in the vascular bed. There are vasodilatation and engorgement of the blood vessels in the remnants of the periodontal ligament and the mobilization of leukocytes to the immediate area around the clot. The surface of the blood clot is covered by a thick layer of fibrin, but at this early period visible evidence of reactivity on the part of the body in the form of a layering of leukocytes here is not particularly prominent. The clot itself shows areas of contraction. It is important to recognize that the collapse of the unsupported gingival tissue into the opening of a fresh extraction wound is of great aid in maintaining the clot in position.

First Week Wound

Within the first week after tooth extraction, proliferation of fibroblasts from connective tissue cells in the remnants of the periodontal ligament is evident, and these fibroblasts have begun to grow into the clot around the entire periphery (Figs. 14-4, 14-5). This clot forms an actual scaffold upon which cells associated with the healing process may migrate.

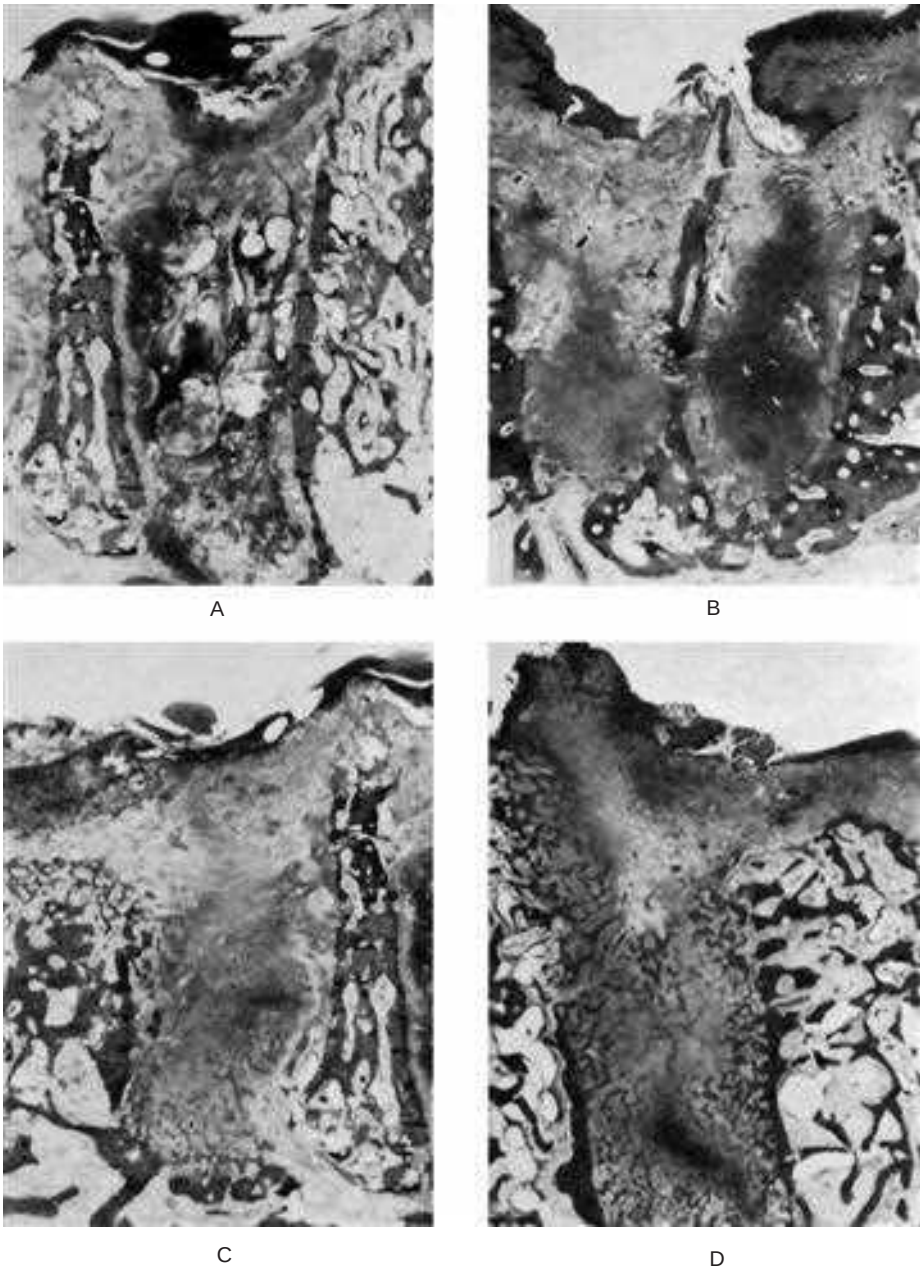


Figure 14-4. Healing of extraction wounds.
The four-day postextraction wound **(A)**, 7-day postextraction wound **(B)**, 14-day postextraction wound **(C)**, and 21-day postextraction wound **(D)** in the dog illustrate the progressive nature of the healing process. Extraction wounds in dogs heal at a more rapid rate than those in humans.

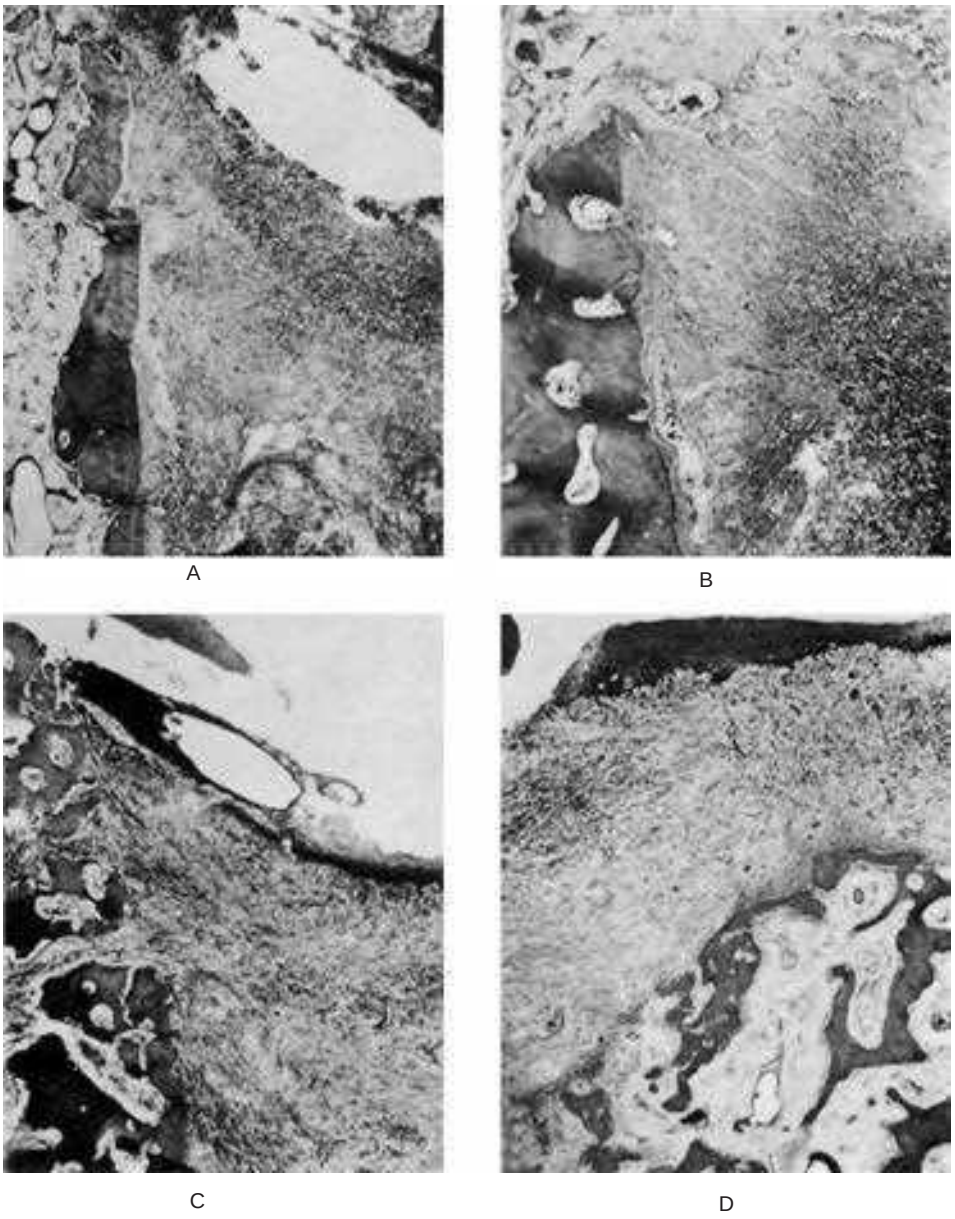


Figure 14-5. Healing of extraction wounds.
The four-day postextraction wound **(A)**, 7-day postextraction wound **(B)**, 14-day postextraction wound **(C)**, and 21-day postextraction wound **(D)** in the dog under high magnification illustrate the progressive changes in the alveolar crest, periodontal ligament and superficial portion of the wound.

It is only a temporary structure, however, and is gradually replaced by granulation tissue. The epithelium at the periphery of the wound exhibits evidence of proliferation in the form of mild mitotic activity even at this time. The crest of the alveolar bone which makes up the margin or neck of the socket exhibits the beginning of osteoclastic activity. Endothelial cell proliferation signaling the beginning of capillary ingrowth may be seen in the periodontal ligament area.

During this period, the blood clot begins to undergo organization by the ingrowth around the periphery of fibroblasts and occasional small capillaries from the residual periodontal ligament. Remnants of this periodontal ligament are still visible, but as yet there is no evidence of significant new osteoid formation, although in some cases it may have just commenced. An extremely thick layer of leukocytes forms over the surface of the clot, and the edge of the wound continues to exhibit epithelial proliferation.

Second Week Wound

During the second week after extraction of the tooth, the blood clot becomes organized by fibroblasts growing into the clot on the fibrinous meshwork (Figs. 14-4, 14-5). At this stage, new delicate capillaries penetrate to the center of

the clot. The remnants of the periodontal ligament gradually undergo degeneration and are no longer recognizable as such. Instead, the wall of the bony socket now appears lightly frayed. In some instances, trabeculae of osteoid can be seen extending outward from the wall of the alveolus. Epithelial proliferation over the surface of the wound is extensive, although the wound is usually not covered, particularly in the case of large posterior teeth. In smaller sockets, epithelialization may be complete. The margin of the alveolar socket exhibits prominent osteoclastic resorption. Fragments of necrotic bone, which may have been fractured from the rim of the socket during the extraction, are seen in the process of resorption of sequestration.

Third Week Wound

As the healing process continues into the third week, the original clot appears almost completely organized by maturing granulation tissue (Figs. 14-4, 14-5). Very young trabeculae of osteoid or uncalcified bone form around the entire periphery of the wound from the socket wall. This early bone is formed by osteoblasts derived from pluripotential cells of the original periodontal ligament which assumes an osteogenic function. The original cortical bone of the alveolar socket undergoes remodeling so that it no longer consists of such a dense layer. The crest of the alveolar bone is rounded off by osteoclastic resorption. By this time the surface of the wound may have become completely epithelialized.

Fourth Week Wound

During the fourth week after the extraction, the wound begins the final stage of healing, in which there is continued deposition and remodeling resorption of the bone filling the alveolar socket (Figs. 14-4, 14-5). However, this maturative remodeling will continue for several more weeks. Much of this early bone is poorly calcified, as is evident from its general radiolucency on the radiograph. Radiographic evidence of bone formation does not become prominent until the sixth or eighth week after tooth extraction. There is still radiographic evidence of differences in the new bone of the alveolar socket and the adjacent bone for as long as four to six months after extraction in some cases (Fig. 14-6). Because the crest of alveolar bone undergoes a considerable amount of osteoclastic resorption during the healing process and because the bone filling the socket does not extend above the alveolar crest, it is obvious that the crest of the healed socket is below that of the adjacent teeth. Surgical removal of teeth, during which the outer plate of bone is removed, nearly always results in loss of bone from the crest and buccal aspects, producing in turn a smaller alveolar ridge than that after simple forceps removal of teeth. This may be of considerable significance in construction of dentures.

COMPLICATIONS IN HEALING OF EXTRACTION WOUNDS

Dry Socket

(Alveolitis sicca dolorosa, alveolalgia, postoperative osteitis, localized acute alveolar osteomyelitis, alveolar osteitis)

The most common and painful complication in the healing of extraction wounds is alveolar osteitis, commonly known as dry socket. It is basically a focal osteomyelitis in which the blood clot has disintegrated or been lost, with the production of a foul odor and severe pain of the throbbing type, but no suppuration. The condition derives its name from the fact that after the clot is lost the socket has a dry appearance because of the exposed bone. This condition is more common in women and tobacco users, and is most frequently associated with difficult or traumatic extractions and thus most commonly follows removal of an impacted mandibular third molar. In a series of 138 'dry sockets' among 6,403 teeth extracted in human patients, Krogh reported that 95% were in lower bicuspid and molar sockets, and this is confirmed by most other large series of cases. The reported frequency of occurrence of 'dry socket' in most series is between 1 and 3.2% of all extractions. Sometimes the 'dry socket' is a sequel to normal extraction of an erupted tooth resulting from a dislodgement or a disintegeration of the clot and the subsequent infection of the exposed bone. This complication usually arises within the first few days after extraction, but has been known to occur even a week or longer after extraction. It has been reported by Macgregor that teeth, which fracture during extraction more frequently develop 'dry socket' than teeth removed *in toto*. He also noted that there does not appear to be any significant relationship between the general health of an individual and the occurrence of 'dry socket'. Nevertheless, it is an expected complication in Paget's disease and in patients who have undergone radiotherapy, wherein there is ischemia of the bone caused by endarteritis. Alveolar osteitis is also common in patients taking oral contraceptives since the estrogen component of oral contraceptives enhances the fibrinolytic activity.

Destruction of the clot is caused by the action of proteolytic enzymes produced by the bacteria or local fibrinolytic activity. Activators of fibrinolysins are liberated from the alveolar bone and other oral tissues when the alveolar bone is traumatized. Fibrinolytic activity is currently thought to be responsible for premature clot loss and severe pain in dry socket. Clot lysis occurs by two mechanisms: plasminogen dependent pathway as proposed by Birn, and plasminogen independent pathways. Plasminogen is hepatically synthesized and released into the circulation. It transforms into plasmin, which in turn acts on the fibrinogen and fibrin, causing clot dissolution. Anaerobic microorganisms may also play a significant role in the development of this condition.

Dry socket is observed commonly in patients of 40 to 45 years old, and the incidence in all extracted sockets is 1 to 4%. Mandible is affected more commonly than maxilla.

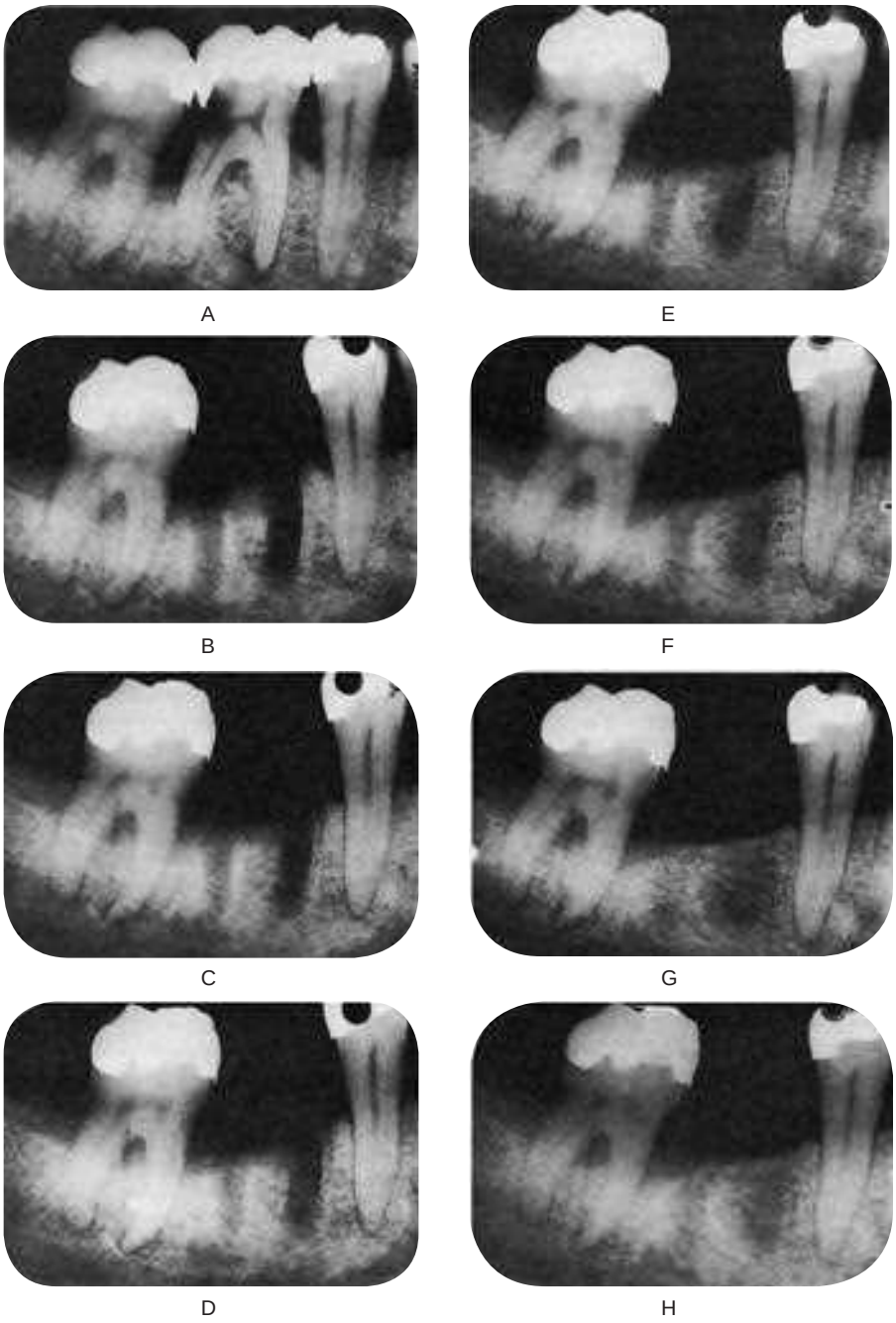


Figure 14-6. Healing of extraction wounds.
The radiographic features of the healing wound are shown serially: **(A)** tooth just before extraction; (B) after two weeks; **(C)** after one month; **(D)** after two months; **(E)** after four months; **(F)** after six months; **(G)** after eight months; **(H)** after 14 months.

Cardoso CL et al, have recently reviewd the pathophysiology, etiology, prevention, and treatment of dry socket. The 'dry socket' is what usually starts by the second or third postoperative day and lasts for 7 to 10 days and is extremely painful. The pain may radiate to the ear and neck. Sometimes, the dry socket may be associated with low-grade fever and ipsilateral lymphadenopathy. The socket may contain decomposed food debris which gives the foul smell and taste. The exposed bone is necrotic, and sequestration of fragments is common.

Prevention and Management. The healing of such infected wounds is extremely slow, and little can be done for the patient other than to relieve the subjective symptoms.

Some investigators have suggested that complications in the healing of extraction wound sockets can considerably be eliminated or at least decreased in incidence and degree of severity by the insertion of one agent or another in the tooth socket at the time of extraction. Some agents, that have been used, have been thought to hasten formation of the blood

clot, to protect the socket against bacterial infection and to promote healing. A variety of agents used in both experimental studies on animals and in clinical studies on human beings have generally been antibacterial substances such as certain of the sulfonamides or the antibiotics.

Versnel reported that a sulfanilamide-sulfathiazole cone placed in the fresh tooth socket of a dog remained as a well-tolerated foreign material. But this agent retarded blood clot formation and even caused some breakdown of the clot. Furthermore, it caused a remarkable delay in epithelialization of the surface of the wound. Oxidized cellulose inserted into a socket for its hemostatic properties produced retardation of healing similar to that of the combined sulfonamides.

Sulfathiazole was evaluated by use in human impacted third molar extraction wounds by Olech, who reported that though it was a clinical impression that the sulfonamide promoted healing and lessened the incidence of postoperative complications, this could not be supported by statistical analysis.

Davis and his associates also found a 38% reduction in the frequency of complicated healing after the use of sulfanilamide and sulfathiazole cones, while Rud reported a reduction in postoperative pain after removal of impacted lower third molars following use of sulfanilamide and sulfathiazole cones.

Olech also tested the effect of the insertion of penicillin into the sockets of human patients, but came to the same general conclusion that healing was not significantly promoted and that postoperative complications were not decreased. On this basis he concluded that the local implantation of these chemotherapeutic agents into sockets of impacted teeth was not justified. Similar studies of Versnel, using penicillin in dog extraction wounds, confirmed the fact that this antibiotic did not promote healing.

A clinical study of the healing of human extraction wounds implanted with pure crystalline penicillin G tablets was reported by Holland and Tam. They found that there were no observable clinical differences during the postoperative period between the experimental group and a control group whose sockets were implanted locally with a lactose placebo tablet.

The local implantation of Aureomycin in extraction wound sockets of human mandibular bicuspid and molar teeth was studied by Verbic. In these cases it was found that the antibiotic resulted in a significant reduction in the incidence of decomposition of blood clots in addition to a decreased incidence of postoperative pain and swelling after one week. There was no evidence of a foreign body reaction or a toxicity reaction.

Quinley reported a reduction in the incidence of 'dry sockets' to 0.78% with the use of tetracycline hydrochloride tablets placed in the extraction sockets, while Stickel and Clark reported a 50% decrease in the incidence of 'dry sockets' when the tetracycline hydrochloride was administered systemically. In the study of Quinley, the local use of antibiotics occasionally resulted in a foreign body reaction. **Myospherulosis** is a complication of healing of an extraction wound or soft tissue wound into which was placed antibiotic ointment with a petrolatum base. This treatment results in the formation of clear space within the area of healing and the presence of altered erythrocytes which assume the appearance of solitary or clusters of spherules that have been mistaken for large microorganisms. This condition has been reviewed by Dunlap and Barker.

Hansen has reported encouraging results in the use of trypsin in cases of 'dry socket' to relieve pain and promote healing. Trypsin itself is not bacteriostatic by digesting necrotic tissue and debris, but it appears to restrain bacterial growth. However, Gustafson and Wallenius have found that the use of trypsin statistically decreased the duration of pain by only about two days, but that there were no significant differences in the frequency of 'dry socket' between trypsin applied locally and placebos. In addition, they noted a high percentage of side effects as the result of use of trypsin, which include erosions of the tongue, lips and buccal mucosa and burning sensations of the mouth.

Debrisan or dextranomer is a highly hydrophilic dextran polymer manufactured in the form of dry spherical beads. These dextranomer beads are sprinkled over the socket and covered with Orabase gel containing benzocaine, showed a significant faster pain relief which is attributed to its absorbent action which removes local kinins, exudates, bacteria and toxins which are responsible for causing pain by irritating the free nerve endings.

Lilly and his associates studied the use of a phenolated antiseptic mouthrinse prior to extraction of mandibular third molars and reported a decrease in the incidence of 'dry sockets' following such oral lavage as compared to the incidence in a group of patients not treated in this fashion.

Probably the oldest and most widely used method of treatment for 'dry socket' is simply palliative medication and permitting nature to heal the wound. There are many palliative medicaments that have been used, such as iodoform gauze with a variety of incorporated dressing materials, zinc oxide and eugenol, and a large number of commercial compounds.

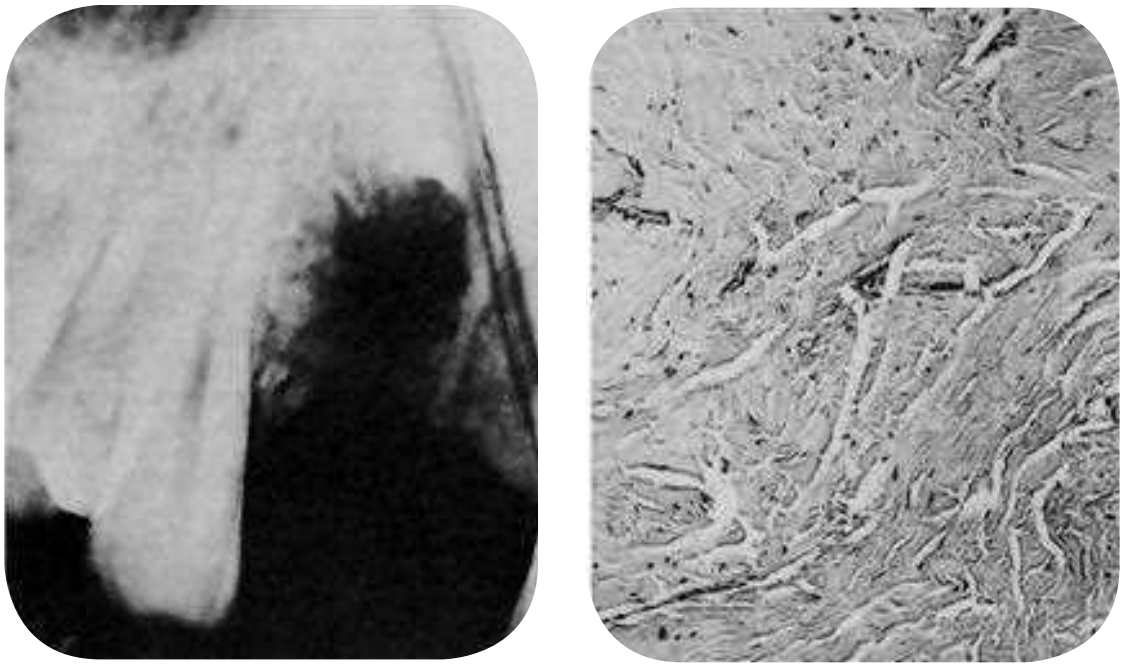
The various studies dealing with the prevention of extraction wound healing complications indicate that the routine use of agents inserted into the sockets is of questionable value. There may be some benefit derived in cases of difficult extractions, but since the actual incidence of complications even in these cases is low, chemotherapeutic adjuncts cannot be routinely recommended.

The aim of the treatment is to keep the extracted socket clean and protect the exposed bone. The socket is irrigated with mild warm antiseptic and then filled with obtundant dressing. The commonly used socket dressings are zinc oxide-eugenol and iodoform gauze. The dressing is changed every day. Most of the patients become free from symptoms after one or two dressings.

Probably the most important single factor in the prevention of extraction complications is gentleness in handling living tissues. One should strive to produce as little trauma as possible, consistent with the successful completion of the operation.

Fibrous Healing of Extraction Wound

Fibrous healing of an extraction wound is an uncommon complication, usually following a difficult, complicated or



A B

Figure 14-7. Fibrous healing of extraction wound.

surgical extraction of a tooth. It occurs most frequently when the tooth extraction is accompanied by loss of both the lingual and labial or buccal cortical plates and the periosteum.

The exact mechanism of development of this condition is not known, but is apparently related to the necessity of the labial and lingual periosteum for normal healing. The lesion is generally asymptomatic and is discovered only during radiographic examination.

Radiographic Features. The lesion appears as a rather well-circumscribed radiolucent area in the site of a previous extraction wound and may be mistaken for residual infection, e.g. a residual cyst or granuloma (Fig. 14-7A). There is no certain way of differentiating fibrous healing from residual infection without surgical exploration. At the time of surgery, simply a dense mass of fibrous connective tissue or scar tissue is found.

Histologic Features. The area of fibrous healing consists of dense bundles of collagen fibers with only occasional fibrocytes and few blood vessels (Fig. 14-7B). The lesion is essentially fibrous scar tissue with little or no evidence of ossification. Inflammatory cell infiltration is minimal or absent.

Treatment and Prognosis. Excision of the lesion for the purpose of establishing a diagnosis will sometimes result in normal healing and subsequent bony repair of the fibrous defect.

HEALING OF FRACTURE

Fractures of the jaws are common injuries, and may range from minor alveolar process fracture to destructive injuries of the maxillofacial region. Although it would seem that the sequence of events is a well-understood and thoroughly described phenomenon, there are surprisingly many controversial points about the general features of bone repair.

Immediate Effects of Fracture

When fracture of a bone occurs, the Haversian vessels of the bone are torn at the fracture site, as are the vessels of the periosteum and the marrow cavity that happen to cross the fracture line. The resulting tissue damage evokes acute inflammation in the soft tissue adjacent to the fracture line, especially in the periosteal region, marrow spaces, and the Haversian canals. Because of the disruption of vessels, there is considerable extravasation of blood in this general area, but at the same time there is loss of circulation and lack of local blood supply. Circulation actually stops as proximal to the fracture site as there is an anastomosis of undamaged vessels.

The Haversian canals of bone contain only a single vessel. When the flow of blood in this vessel is interrupted by tearing at the fracture site, the bone cells or osteocytes of the Haversian system supplied by this vessel die. The dead bone extends away from the fracture area to the site of the anastomosing circulation, and the distance may measure several millimeters or more. Because of the overlapping pattern of the blood supply to bone, seldom can a definite line of demarcation between living bone and dead bone be discerned. Concomitant with the disruption of the blood supply, there is death of the bone marrow adjacent to the fracture line. The tearing of the blood vessels in the periosteum also contributes to the local death of bone, since branches of the periosteal vessels supply the Haversian vessels.

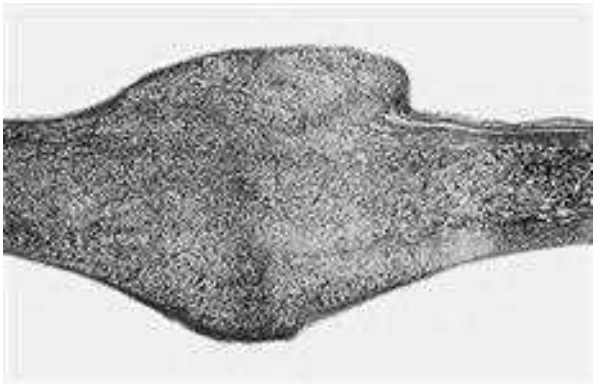


Figure 14-8. Healing of fracture.
The external callus is particularly prominent.

Figure 14-9. Healing fracture of a long bone.
The external callus above the fracture line (1) is composed of new bone (2), cartilage (3), and vascular connective tissue (4).

The blood clot which forms was once thought to play an important role in healing of the fracture through the replacement by granulation tissue and its subsequent replacement by bone. Most authorities now feel that the role of the blood clot in the healing process is only a passive one and that the newly forming bone, the callus, forms outside the granulation tissue replacement. Actually, the presence of the clot is not necessary for invasion of osteogenic cells, although frank necrosis of the clot may cause some retardation in the healing process.

Callus Formation. Callus is a Latin word means 'over growth of hard skin'. Callus unites the fractured ends of bone, and it is composed of varying amounts of fibrous tissue, cartilage and bone. The external callus consists of the new tissue which forms around the outside of the two fragments of bone (Fig. 14-8). The internal callus is the new tissue arising from the marrow cavity.

The periosteum is an important structure in callus formation and ultimate healing of the fracture, and for this reason its preservation is essential. The cells of the periosteum immediately adjacent to the periosteum torn at the fracture line usually die. Peripheral to this area, however, may be found a flurry of cellular activity within a matter of hours after the injury. The outer or fibrous layer of periosteum is relatively inert and is actually lifted away from the surface of bone by the proliferation of cells in the osteogenic or inner layer of the periosteum. These cells assume the features of osteoblasts, and within a few days after the fracture, begin formation of a small amount of new bone at some distance from the fracture. The continued proliferation of these osteogenic cells forms a collar of callus around or over the surface of the fracture.

The new bone which begins to form in the external callus usually consists of irregular trabaculae often laid down at right angles to the surface. This differentiation of cells into osteoblasts and subsequent formation of bone occur in the deepest part of the callus collar. Away from the fracture line in the rapidly growing area of the collar, varying numbers of cells of the osteogenic layer differentiate into chondroblasts rather than osteoblasts, and actually form cartilage. This cartilage fuses with the bone, although there is no sharp line of demarcation. The fact that the cells of the osteogenic layer may differentiate into chondroblasts rather than osteoblasts indicates their pluripotentiality and emphasizes that, in bones preformed in cartilage, the periosteum was once a perichondrium (Fig. 14-9).

The amount of cartilage formed in a callus may vary remarkably in different cases, and is determined by several factors. One factor of importance is the vascularity of the local environment. In a well-vascularized area the tendency is to form bone, but in a poorly vascularized environment cartilage develops. It will be noted that in the callus, bone forms adjacent to the blood vessels, while the cartilage forms from cells, which have proliferated so rapidly that the blood vessels have not kept pace with and are outdistanced. The speed of healing, then, is another factor determining how much cartilage forms. In slow healing, cartilage formation is minimal. Finally, movement of the fragments is often associated with formation of considerable amounts of cartilage. In completely immobilized fractures little cartilage is laid down.

As callus formation progresses, the cartilage cells begin to mature, and the cartilage begins to calcify in a fashion similar to normal endochondral bone formation. This calcification is prominently adjacent to blood vessels developing in the immediate vicinity. The calcified cartilage is gradually resorbed and replaced by bone.

The internal callus forms from the endosteum of the Haversian canals and undifferentiated cells of the bone marrow. Shortly after the fracture occurs, the endosteum begins to proliferate and within a week or two begins formation of new bone and cartilage. The new bone formed at the end of each fragment gradually unites and establishes continuity of the bone.

Remodeling of the Callus. The external and internal calluses, which unite the two fragments of bone, must be remodeled because there is always an abundance of new bone produced to strengthen the healing site. In addition, the new bone is frequently joined with fragments of the original dead bone. These fragments are slowly resorbed and replaced by a mature type of bone, which follows normal stress patterns. The external callus should also be remodeled so that in time the excess bone is removed. Ultimately, the bone in a fracture site is nearly indistinguishable from that existing before the fracture was sustained.

COMPLICATIONS OF FRACTURE HEALING

Delayed union and nonunion of the fragments of bone are occasional complications of the fracture healing process. These result when the calluses of osteogenic tissue over each of the two fragments fail to meet and fuse or when endosteal formation of bone is inadequate. The causes of nonunion are not always clear, although, in general, it may be said that anything which delays growth and fusion of the collars is a factor. Local infection and the presence of foreign bodies may also result in delayed healing. Nonunion is relatively common in elderly persons, in whom it is apparently related to a lack of osteogenic potential of cells, and in patients with systemic debility, diabetes mellitus, and systemic infection.

Fibrous union is another complication of fracture healing, which arises usually as a result of lack of immobilization of the damaged bone. The fractured ends of fragments are united by fibrous tissue, and there is failure of ossification. In certain circumstances this may produce a pseudoarthrosis.

Lack of calcification of newly formed bone in the callus may occur, but only in unusual circumstances of dietary deficiency or mineral imbalance which is seldom seen clinically. This may be produced in the experimental animal. Key and Odell reported that the opposite situation—an excess of minerals in the diet of normal rats— failed to accelerate the healing of experimental fractures of the femur.

Distraction Osteogenesis
(Osteodistraction, callus distraction)

Distraction osteogenesis is a surgical procedure to lengthen the long bones or to correct skeletal deformity. This involves creation of a fracture by corticotomy. The fractured segments are gradually moved apart during distraction phase, allowing new bone to fill the gap. When the desired length is achieved the bone is allowed to heal, and this stage is known as consolidation phase. This procedure not only lengthens the bone but also increases the soft tissue volume. In maxillofacial region distraction osteogenesis is used to correct craniofacial deformities.

Preservation of medullary blood supply, periosteum, and stability of the fixator are important factors which determine the success of bone distraction. Fractured segments should be moved slowly and gradually, as rapid distraction results in fibrous union.

REPLANTATION AND TRANSPLANTATION OF TEETH

Both replantation and transplantation of teeth have been recognized clinical procedures for many years. Because of the generally poor success of these particular techniques, they gradually fell out of use. In recent years, however, there has been a remarkable revival of interest in replantation and transplantation of teeth, due in part to the availability of antibiotics which readily control infection and in part to a greater knowledge of tissue reactions.

The literature now contains a large number of replanted teeth, autogenous transplanted teeth and homogeneous transplanted teeth, in humans. An exceedingly thorough review of this topic, including all of these reported cases, has been published by Natiella and his associates.

Replantation refers to the insertion of a vital or nonvital tooth into the same alveolar socket from which it was removed or otherwise lost. This procedure finds its greatest use after traumatic injuries resulting in avulsion or other accidental loss of a tooth. Avulsion, a severe form of tooth injury is characterized by total displacement of tooth from the alveolar socket with severance of neurovascular bundle leading to loss of pulp vitality. However, it has been used in other unique situations as well. For example, unerupted teeth with dentigerous cysts have been replanted after removal of the cyst.

Many investigators believe that a tooth may be replanted without root canal therapy if root formation has not been completed and the apex is open. In some cases, the pulp tissue will undergo necrosis within a short period. In other instances, there is apparently revascularization and reinnervation, with the establishment of vital pulp responses. The majority of investigators believe that mature teeth with complete root formation must have the root canals filled before replantation or else pulp necrosis will result. In atleast some of these cases, if the root canal is not filled, there is gradual obliteration of the pulp chamber and canal by bone like material.

There has been some question of whether the preservation of the periodontal ligament on the root surface is of importance in the successful retention of a replanted tooth. Most investigations reveal that preservation of the periodontal ligament is an important factor in successful replantation. Partially formed teeth often have the ability to complete root formation as well as to re-establish a normal periodontal ligament space. Mature teeth may also develop a reasonably normal periodontal ligament, although the more common finding is varying degrees of resorption of cementum and dentin followed by subsequent replacement by bone resulting in a certain degree of ankylosis. There is some evidence to indicate that injury to the periodontal ligament or alterations in the cementum are important factors favoring root resorption and subsequent ankylosis. It also has been suggested by some investigators that whenever the extraoral period for the tooth exceeds 60 minutes, the chance for successful replantation with repair is significantly reduced, particularly if the storage of the tooth is in a dry rather than moist environment. When a tooth is avulsed it is very important to reduce the extraoral

time, in order to keep the periodontal cells in a viable state for a successful replantation. It is not always possible to replant the tooth immediately after avulsion. In such situations, a transport medium or storage medium is used to preserve the viability of periodontal ligament cells. Commonly used storage media are milk, saliva, saline, Hank's balanced salt solution (HBSS), propolis and Viaspan. Recently V Gopikrishna and coworkers have demonstrated that coconut water maintains the viability of periodontal ligament cells better than 50% propolis, HBSS and milk. There are a number of other factors which have also been considered of importance in determining whether a replanted tooth will be retained. For example, many investigators have stressed the necessity of handling the tooth to be replanted with great care so that there is no stripping or tearing of periodontal ligament fibers or of cementum. The matter of sterilization of the tooth has been argued, some investigators cautioning against sterilization but others recommending one of a large variety of sterilizing solutions in which the tooth should be placed for varying periods of time. Finally, fixation of the replanted tooth has also been the source of some disagreement. Some investigators believe that no splinting should be done, while others have used a variety of appliances including stainless steel wires, acrylic splints, orthodontic banding, arch wires with wire ligatures and even surgical cement with gauze, with recommendations that these splints remain in place for a few days to several months. There is still no general agreement on many of these fine details.

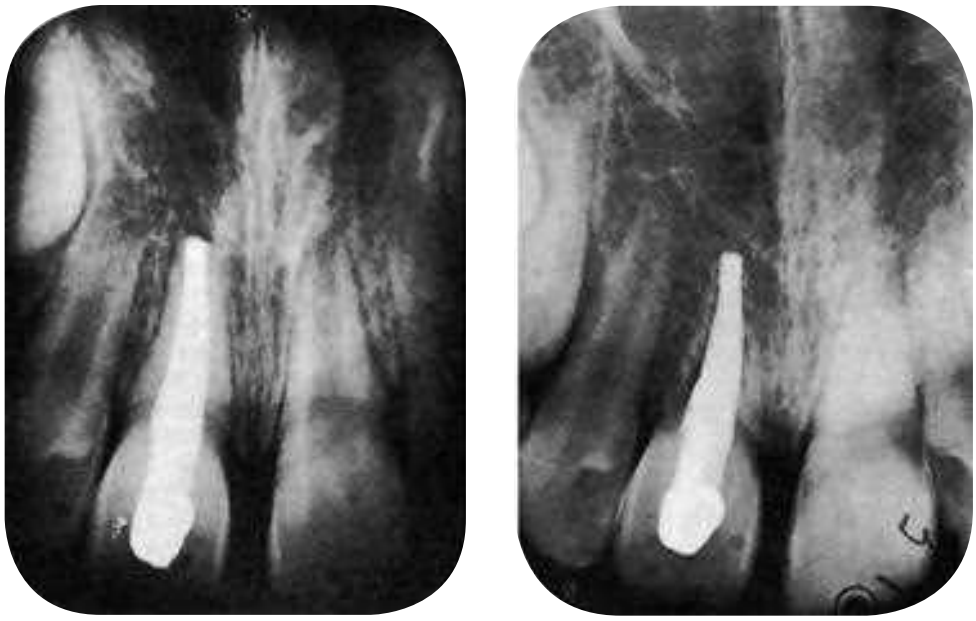
Healing after Replantation

Following replantation, clot forms between the root surface and ruptured periodontal ligament. Proliferation of fibroblasts and endothelial cells occurs in the periodontal ligament remnants on the alveolar bone side. The reconnecting of periodontal ligament is evidenced by the extension of collagen fibers from the cementum to the alveolar bone. The epithelium is reattached to the tooth at the end of the first week. Complete regeneration of the periodontal ligament takes place within two to four weeks. In the course of time, a number of replanted teeth result in root resorption or ankylosis.

Superficial resorption of the root surface is repaired by new cementum deposition. However, root resorption is totally unpredictable in its degree and the time of onset. In some cases, root resorption may begin within a matter of weeks to a few months after replantation, while in other cases, gross resorption may take as long as 10 years. It appears likely that the roots of many replanted teeth are constantly being resorbed, but the rate at which this occurs varies remarkably between different cases. If the process is extremely slow that it takes place over a period of years, the operative procedure may be considered a clinical success. If root resorption is rapid, the tooth will be quickly exfoliated. Many cases are considered successful clinical results if the tooth is maintained beyond the period of two years (Fig. 14-10).

Unfortunately, there are many unknown factors which influence root resorption and ultimately determine the prognosis of a replanted tooth. In some cases, even after the most meticulous root canal therapy and sterilization, the tooth is either quickly resorbed or quickly exfoliated.

Ankylosis is the result of the fusion of alveolar bone and cementum of the tooth. Increased extraoral time or extensive damage to the periodontal ligament fibers result in ankylosis. Progenitor cells with osteogenic potential from the adjacent bone marrow migrate to the root surface and lay down the bone in direct contact with the root creating ankylosis.



A B

Figure 14-10. Replanted tooth.
(A) Tooth immediately after replantation. **(B)** Tooth several months later, showing root resorption *(Courtesy of Dr Samuel S Patterson).*

Transplantation of Teeth

The transplantation of teeth finds its greatest use in the replacement of teeth damaged beyond repair by caries. Autotransplants (transplantation of the tooth in the same individual) are more successful than allotransplants (transplantation from one person to another of same species). Allotransplant rejection of the tooth is similar to the homograft rejection of tissue elsewhere in the body and is mediated by the cells of the reticuloendothelial system.

Generally, it is the mandibular first molar, which is replaced by a developing third molar.

The criteria of a satisfactory transplantation, as listed by Agnew and Fong, are that the transplant:

- Has become organically integrated with its new environment of discernible periapical or lateral lesions.
- Is capable of effective masticatory function.
- Shares adequately in the maintenance of physiologic maxillomandibular and muscular relations.
- Displays clinically and radiographically such status of gingiva, periodontal ligament and bone (lamina dura and supporting bone) and such measure of the root length and overall stability as seems compatible with indefinite maintenance.
- Is esthetically acceptable.

These same investigators carried out on monkeys, a critical experimental study dealing with histologic observation of developing teeth transplanted into prepared sockets of freshly extracted teeth. Their report indicated that no generalized pulpal necrosis necessarily occurs after the transplantation. Actually, the pulp becomes revascularized, and there is continued growth of the root dentin, although the shape of the root may be distorted. A functional, viable, highly cellular periodontal ligament develops, the tooth reattaches in the bony socket, and the gingival epithelium and epithelial attachment closely resemble those of normal teeth. The normal color and luster of the tooth are usually maintained. These findings appear similar to those few histologic studies reported in humans.

Most failures of autogenous transplants have been teeth that simply dropped out, have to be extracted or underwent severe resorption of the roots. Interestingly, these transplanted teeth may become carious, just as normal teeth do, and may even develop pulpitis and periapical infection.

Homologous transplants of preserved frozen teeth have also been successfully carried out. The establishment of 'tooth banks' has even been proposed to simplify the procedure. There are several techniques available for the preservation of teeth, and these have been discussed by Pafford. They include:

1. Regular freezing
2. Freeze-drying, or lyophilization
3. Vitrification
4. Chemical coagulation, as by thimerosal (Merthiolate).

Teeth may apparently be used even after storage for months. Teeth that have been preserved frozen and have been transplanted may be retained by the patient in some cases indefinitely. The gingival tissues heal promptly, and reattachment occurs within a few weeks, although readaptation of bone may take several months. The dentin of the transplanted tooth may be maintained in its normal state. Revascularization of the pulp is necessary if the tooth is to be retained indefinitely. New cementum may be laid down on the root surface after transplantation, and there is reformation of the connective tissue fibers of the periodontal ligament. Unsuccessful transplants are usually lost because of root resorption or local infection.

It must be recognized that replantation and transplantation of teeth are sufficiently established as procedures that can be utilized in the routine dental practice. Care must be exercised in selecting the proper cases and in following certain principles of treatment, but favorable long-term results should be expected as the rule rather than exception.

IMPLANTS

Implants are any foreign material fixed or inserted into the body tissue. Today there is widespread application for implant procedures ranging from single tooth replacement to total jaw reconstruction.

Oral implants also serve as support for overdentures, fixed prosthesis, and serve as orthodontic anchorage. Implant supported prosthesis has many advantages over the removable soft tissue borne restorations, such as regained proprioception, stability, retention, and reduced size of the prosthesis. Active research is going on for more than half a century in all aspects of oral implants.

Oral implants are of three types, namely endodontic, endosseous, and subperiosteal. Endodontic implants are inserted into the bone through the root canal to stabilize the tooth. Endosseous implants form a core over which tooth or denture may be reconstructed.

The subperiosteal implant is placing a metal framework contoured to the alveolar ridge, beneath the periosteum. Such implants, used in severely resorbed alveolar ridges where denture construction has been a problem, are not in use currently due to soft tissue problems and fracture of the metal framework.

The blade vent type of endosseous implants refers to the placing of a metal strip having holes, into the jawbone, and this design is in clinical practice for over 25 years.

Osseointegrated Implant

This was developed by Branemark and his coworkers in the early 1960s. Osseointegration, as defined by Branemark, is a direct structural and functional connection between ordered living bone and the surface of a load carrying implant. Osseointegration was not an accepted phenomenon at that time. Branemark performed animal experiments and demonstrated that direct bone anchorage was possible and subsequently he has documented this in the first clinical report, which he published a few years later. Osseointegrated implants, however, are used widely now. Factors that determine the outcome of the implant treatment depend upon the biocompatibility of

the implants, status of the host tissue, surgical technique, and the loading condition.

Many biocompatible materials are used as implants. These include titanium, titanium alloys, and ceramics. Currently, interest is centered on zirconia ceramics. The successful use of zirconia in orthopedics led to a demand for dental zirconium-based implant systems. Because of its excellent biomechanical characteristics, biocompatibility, tooth-like color, and low plaque affinity, zirconia has the potential to become a substitute for titanium as dental implant material.

Surface modifications (grit blasting and/or acid etching, machining, plasma-spraying) of implants are done to achieve better osseointegration. Studies have shown that, when the surface of the implants is rough, the healing is faster and it integrates well with the bone.

After the implant insertion, a period of 10 to12 weeks of healing is required. During healing, compact and cancellous bone forms around the implant together with a variable amount of fibrous marrow. Implants do not have direct contact with the bone. A certain amount of bone marrow and soft tissue are interposed between the bone and implants. The implant and the mucosal interface serve similar functions as the dentogingival junction. The connective tissue of the mucosa forms intimate contact with the implant. The collagen fibers of the connective tissue run parallel to the long axis of the implant, and the epithelium is attached to the implant by means of basal lamina and hemidesmosomes.

Pathologic changes of tissues around the implant are referred to as periimplant disease. Inflammatory changes confined to the soft tissues of the implant are called periimplant mucositis. Progressive bone loss around the implant along with inflammation of the soft tissue is known as peri-implantitis.

Periimplantitis develops at the coronal portion of the implant while the more apical portion of the implant maintains an osseointegrated status. The implant is not mobile until the bone loss progresses to involve the entire implant surface.

Complications and Management. Loss of osseointegration can occur due to bone loss. The cause of periimplant crestal bone loss can be due to bacterial or biomechanical factors, or both. Other factors such as traumatic surgical techniques, smoking, implant exposure at the time of placement due to inadequate amount of host bone, and compromised host response can act as cofactors in the development of periimplant disease.

In cases of severe bone loss extending up to the apical half of the implant or where the implant exhibits mobility, the removal of the implant is advisable. Nonsurgical management of periimplant disease includes local removal of plaque by subgingival irrigation of periimplant pockets with 0.12% chlorhexidine and systemic antimicrobial therapy.

When excessive occlusal load is considered as a factor for periimplant bone loss, restoring the occlusal equilibrium will arrest the progression of the periimplant tissue breakdown.

Stem Cell Therapy

Treating certain diseases using stem cells is not at all new, particularly in the management of bone and blood cancers. As a result of advances in cell and molecular biology techniques, the stem cell research and its application in clinical practice has gained much importance recently. Owing to the recognition that stem cell therapy has the potential to improve the life of patients with conditions ranging from Alzheimer's disease to cardiac ischemia and regenerative medicine, like bone or tooth loss, stem cell research has grown exponentially.

Stem cells are the cells of multicellular organisms, that can divide and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. There are three broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocysts, adult stem cells also known as somatic stem cells, found in various tissues and induced pluripotential cells, which are produced through transcriptional reprogramming of somatic cells, such as fibroblasts, which can be converted into induced pluripotential cells that resemble embryonic stem cells.

In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. Depends on the cell signals or environmental stimuli stem cells may differentiate into cells derived from any of the three primary germ layers: ectoderm, endoderm, and mesoderm, a powerful advantage for regenerative therapies.

James Alexander Thomson, a developmental biologist derived the first human embryonic stem cell (hESC) line in 1998.

Embryonic stem cells are derived from the embryo and are grown in the laboratory, by cell culture technique. Unlike somatic or 'adult' stem cells, hESCs proliferate indefinitely. Stem cells that have proliferated in cell culture for a prolonged period of time without differentiating, are pluripotent**,** and are referred to as an embryonic stem cell line. They remain undifferentiated in appropriate laboratory conditions. They can be manipulated to differentiate into specific cell type, for example muscle cells, nerve cell etc, and is known as directed differentiation. Reports are available involving the application of hESCs for spinal cord injury, age-related macular degeneration, cardiovascular diseases, and diabetes. However hESCs considered as problematic because of the following factors namely, formation of teratomas, potential immunologic cellular rejection and ethical issues.

Somatic (adult) stem cells are relatively rare, undifferentiated cell found in many organs and differentiated tissues with a limited capacity for both self-renewal and differentiation. The primary function of somatic stem cells in a living organism is to replenish dying cells and repair the damaged tissue in which they reside. Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They are thought to reside in a specific area of each tissue known as 'stem cell niche'.

Types of somatic stem cells include hematopoietic, mesenchymal, neural, epithelial and skin stem cells.

Hematopoietic stem cells give rise to all the types of blood cells and macrophages. Mesenchymal stem cells give rise to osteocytes, chondrocytes, adipocytes, and other kinds of

connective tissue cells. Neural stem cells in the brain give rise to neurons and two categories of non-neuronal cells—astrocytes and oligodendrocytes. Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells. Skin stem cells are seen in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes and hair follicle.

Somatic stem cell therapy has wide variety of clinical application. The stem cells whether embryonic or somatic when injected into a particular part of the body, differentiate into a specific cell type, integrate into that site, replacing damaged tissue, and thus help improved function.

Induced pluripotent stem cells are produced by converting the adult somatic stem cell into embryonic stem cell-like state by genetic reprogramming.

Stem Cells of Dental Tissues

Guido Giordano et al, have recently reviewed the stem cells from oral niches. As per their review currently, niches have been identified in the dental pulp of permanent teeth (dental pulp stem cells—DPSCs) in naturally exfoliated deciduous teeth (stem cells from human exfoliated decicuous teeth—SHED), in the periodontal ligament (periodontal ligament stem cells—PDLSC), in the apical papilla (stem cells from apical papilla), in the dental follicle (dental follicular PCs), and in the periosteum of the maxillary tuberosity (oral periostium stem cells). They concluded that cells with the best results in terms of potentiality and proliferative capacity, and differentiation seem to be the stem cells from human exfoliated decicuous teeth. Mesenchymal stem cells obtained from periodontal ligament and dental pulp have similar morphological and phenotypical features of the bone marrow derived mesenchymal stem cells. Adult dental stem cells can differentiate into many dental components, such as dentin, periodontal ligament, cement and dental pulp tissue, but not into enamel. Seo and coworkers, based on their study on stem cells of the periodontal ligament (PDL) suggested that PDL contains stem cells that have the potential to generate cementum/PDL-like tissue *in vivo* and transplantation of these cells might help in reconstruction of tissues destroyed by periodontal diseases.

As Honda MJ and coworkers rightly said, "with the advancement of stem cell biology and tissue engineering, regenerating the whole tooth has become a realistic and attractive option to replace a lost or damaged tooth, and therefore has strongly attracted attention in the field of dental research".

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SECTION IV

Disturbances of the Metabolism and Immunologic Diseases

SECTION OUTLINE

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CHAPTER 15

Oral Aspects of Metabolic Diseases

■ B SIVAPATHASUNDHARAM AND R RAJENDRAN

CHAPTER OUTLINE

Loeb described individual man as a 'mosaic of many tissues and organs', each one functioning and **metabolizing** in its own peculiar way. Each tissue or organ has properties not restricted to it, but common to all parts of the organisms, and it is these common properties which bind the tissues and organs well together into a unit.

Health is largely determined by man's reaction to his environment, both social and physical, but different individuals behave differently in the same environment and under apparently identical conditions. On this basis we recognize the variations of the substratum upon which environmental factors act. Individual variations in response to the internal and external environment are dependent upon constitution. Each response represents a complex interplay between the genetic and environmental factors acting on the individual.

Certain characteristics of an organism are fixed in the germ cells and give rise to definite metabolic, structural, and functional conditions in the individual. These inherited features represent the core of his constitution, the unchangeable part of it. In actual life; however, it is often difficult to separate this core from effects produced by the environment.

It might be well to visualize man—the organism—as a universe: a universe of cells living together within a restricted framework. Some of the individuals (the cells) of this universe form rather tightly knit communities (the organs) which perform highly specialized tasks. Each individual within the community responds to his inner as well as his outer environment, and each is influenced by his neighbor. The outer environment in this instance is fluid—mostly water. Each individual cell influences the tissue fluid in some manner by removing and/or adding metabolic products. Each cell or organ system reacts to its changing environment within the limits of its inherent capabilities. If an analogy is drawn between the cells as an individual within the organisms and the organisms as an individual within the cosmos, the complexity of the interrelations becomes apparent, even though the nature of the interrelations is nebulous.

Duncan defined metabolism as "the sum total of tissue activity as considered in terms of physicochemical changes associated with and regulated by the availability, utilization, and disposal of protein, fat, carbohydrate, vitamins, minerals, water, and the influences which the endocrines exert on these processes". Alterations from these normal metabolic processes constitute the **disturbances of metabolism**. One recognizes immediately that this definition embodies a concept of cellular change as influenced not only by intrinsic factors, but also by such extrinsic factors as food supply, temperature, altitude, society; in other words, by environment.

The volume of literature pertaining to metabolism is rapidly surpassing the ability of investigators to keep pace with it. Obviously it is impossible to provide an in-depth look at any particular area. Excellent references, many recent and some classic, are available. These include Wolbach and Bessey (1942), Schour and Massler (1943 and 1945), Follis (1948 and 1958), Bodansky and Bodansky (1952), Bourne and Kidder (1953), Duncan (1959), Comar and Bronner (1960), Gÿorgy and Pearson (1967), Sebrell and Harris (1967), Greenberg (1967, 1968, 1969, 1970), Vogel (1971), Hokin (1972), Prasad (1976), Underwood (1977), Stanbury, Wyngaarden, and Fredrickson (1978), Alfin-Slater and Kritchevsky (1979), Goodhart and Shills (1980) and Bondy and Rosenberg (1980).

DISTURBANCES IN MINERAL METABOLISM

Although hormones are the primary regulators of metabolism, they are ineffective without minerals and vitamins. Minerals are inorganic elements that are essential for life and provide both the structural and regulatory functions of the body. It is observed that there are at least 29 different elements in our body constituting about 4% of the body weight, concentrated mostly in the skeleton. The elements considered essential for normal growth and development of mammals are calcium, phosphorus, magnesium, potassium, sodium, chlorine, iodine, copper, iron, zinc, manganese, cobalt, chromium, selenium, and fluoride.

Minerals that are present in relatively high amounts in the body are referred to as macrominerals and those that are less than 0.005% of the body weight are called the microminerals. Macrominerals or principal elements are nutritionally important minerals whose daily requirement is more than 100 mg. These include sodium, potassium, chloride, calcium, phosphorus, magnesium and sulfur. The microminerals or trace elements are those found in tissues in minute amounts but are found to be essential to life. Their requirement is less than 100 mg/day and these include chromium, copper, cobalt, iron, iodine, manganese, selenium, fluorine, and zinc. The other trace elements that are possibly essential include cadmium, nickel, silicon, tin, and vanadium.

Inorganic and organic combinations of these elements are active in many physiologic processes. They constitute the basic structure of bone and teeth; help maintain the osmotic relations of the body fluids; regulate the acid-base equilibrium of the tissues; form part of hormones; are an integral part of some enzymes; serve as activators of certain enzymatic reactions; and they are an essential part of the oxygen-carrying pigments. Mertz's definition of 'essential' has been widely accepted. He stated that an element is considered essential when a deficient intake consistently results in suboptimal physiologic function that can be prevented or reversed by supplementation with physiologic levels of the element.

It is interesting that in many physiologic processes one mineral element may be substituted for another. For example, strontium or lead may replace calcium in the inorganic structure of bone. Rubidium may replace potassium in a potassium-deficient diet with the result that, even though the animals maintained on the diet die, the characteristic myocardial necrosis found in potassium deficiency will not occur. A thorough understanding of the normal processes of mineral metabolism and the effects of abnormal mineral metabolism is essential in pointing the way to the solution of many of the problems related to calcification of the teeth and jaws that constantly arise during the practice of dentistry.

MINERALS

Although the literature concerned with calcium, phosphorus, and magnesium is voluminous, we still do not have a clear picture of the role of these elements in nutrition. The exact relation of magnesium to calcium and phosphorus metabolism is not known. For convenience, we shall discuss each element separately, trying to combine or integrate our knowledge whenever possible.

Calcium

Calcium is the fifth most abundant element in the body, and in crystalline form, with phosphorus, in a proteinaceous matrix, forms the major structural support of the body (bones). The total calcium in the body is 100–170 gm, about 99% of which is found in bones existing as carbonate or phosphate of calcium while about 0.5% is present in soft tissue and 0.1% in extracellular fluid. The normal serum calcium level is about 9–11 mg/dl. The calcium in plasma is of three types: ionized calcium, protein bound calcium, and complexed calcium. About 40% of the total calcium is in ionized form, which is also physiologically active form of calcium. The level of the blood calcium is largely controlled by the action of the parathyroid glands, which are stimulated by low serum calcium levels and inhibited by high serum calcium levels.

Requirements and Absorption. The Food and Nutrition Board of the National Academy of Sciences, National Research Council, recommends a daily dietary calcium intake of 360 mg for newborn infants and 800 mg for children and adults. Adolescents and pregnant and lactating women are advised to increase their daily dietary calcium intake by 50% to 1,200 mg. Calcium is taken in diet principally as calcium phosphate, carbonate, and tartrate. Unlike sodium and potassium that are readily absorbed, the absorption of calcium in man is an inefficient process. Only about one-third of the daily dietary intake of calcium is absorbed under normal conditions. About 40% of average daily dietary intake of calcium is absorbed from the gut, mainly from the duodenum and first half of jejunum against an electrical and concentration gradient.

Absorption. In well-balanced diets, the ratio of calcium to phosphorus is of little significance, but in less balanced diets, this ratio assumes considerable importance. Phytic acid, which is found in cereals, forms an insoluble calcium phytate with ingested calcium and renders it nonavailable. Since this substance constitutes over 50% of the phosphate of cereals and is hydrolyzed only to the extent of 30–60% in the alimentary tract, the phosphate-calcium ratio is thus upset, interfering with the normal absorption of calcium. Vitamin D increases absorption of calcium from the intestine. Under normal metabolic conditions for fat splitting and fat absorption, the ingestion of fat has been found to aid calcium absorption, but in conditions in which there is excessive fat excretion, such as in sprue or idiopathic steatorrhea, calcium is lost in the feces as calcium soaps.

Citrates, that may lower the pH of the intestinal tract, form calcium citrate which is relatively soluble. The addition of citrates to a rachitogenic diet seems to render the diet nonrachitogenic and also aid calcification. It has therefore been suggested that the lowering of the intestinal pH aids absorption of calcium and that the calcium citrate ion, though relatively soluble, aids the deposition of calcium in bones by raising the

pH of the calcifying tissue or of the fluids surrounding the calcifying tissue. High protein diets have also been shown to increase calcium absorption, probably through the formation of soluble calcium compounds with the amino acids produced by the digestion of the protein.

Oxalic acid interferes with calcium absorption by forming an insoluble calcium oxalate. For example, spinach contains sufficient oxalic acid to render all its calcium nonavailable, with some oxalic acid to spare for other calcium which might be present in the diet. The presence of hypochlorhydria or achlorhydria also exerts an adverse influence upon calcium and phosphate absorption, since normal secretion of hydrochloric acid by the stomach is necessary for optimal absorption of calcium and phosphate.

Lactose or milk sugar increases calcium absorption in rats, presumably by increasing intestinal acidity. In humans, lactose increases the retention of calcium without materially affecting absorption.

Many factors affect the utilization of absorbed calcium and phosphorus. Obviously, conditions which produce profound disturbance of any vital metabolism may have an indirect influence upon the metabolism of these minerals. Those factors; however, which appear to have a well-defined effect on calcium and phosphorus metabolism, are the parathyroid hormone, vitamin D, thyroid, calcitonin, and the steroid hormones.

Excretion. Calcium is excreted in both the feces and the urine, with 80% of the total amount being excreted in the feces. Fecal calcium consists not only of unabsorbed calcium, but also of calcium which has been absorbed and re-excreted. Although the small intestine is the predominant site in which the calcium is re-excreted, all segments of the intestinal tract probably excrete some calcium. Unless there is excessive perspiration, the dermal losses do not exceed 50 mg/dl. The normal daily urinary calcium excretion in adults is less than 250 mg for women and 300 mg for men. The calcium in the urine is excreted mainly as calcium chloride and calcium phosphate. The renal threshold for calcium is approximately 7 mg/dl of serum calcium. The urinary excretion of calcium is increased by increased plasma calcium, deprivation of phosphate, excessive vitamin D, increased urinary excretion of sodium, immobilization, corticosteroid administration, increased dietary calcium, metabolic acidosis, hyperthyroidism, and idiopathic; whereas urinary excretion of calcium is decreased by decreased ultrafiltrable plasma calcium, decreased glomerular filtration rate, parathyroid hormone, decreased dietary calcium, increased dietary phosphate, increased calcium utilization as in growth, pregnancy, and lactation.

Function. Calcium plays a large role in the formation of bones and teeth, in the maintenance of skeletal structure, tooth structure, normal membrane permeability, normal heart rhythm and other neuromuscular excitability, in the coagulation of blood, muscle contraction, and as a secondary or tertiary messenger in hormone action. Variations of serum calcium ion concentration from the limited optimal range of 9–11 mg/dl have profound effects. A low concentration of calcium ions (about 8 mg/dl) produces hyperirritability and tetany with characteristic carpopedal spasm and at times laryngospasm and convulsions, while high concentration produces depressed nerve conductivity and muscle rigor.

Hypocalcemia is said to exist when serum calcium is less than 8.5 mg/dl. The commonest cause of hypocalcemia is hypoalbuminemia, closely followed by renal failure. The other common cause of hypocalcemia is surgically induced hypoparathyroidism. Hypercalcemia occurs when serum calcium levels exceed 11.0 mg/dl and the most common cause is primary hyperparathyroidism, malignancy, and endocrine causes such as acute adrenal insufficiency and renal failure.

Experimental calcium deficiency in rats leads to a derangement of blood coagulation and of the integrity of the capillaries. Internal hemorrhages and generalized paralysis of the young born of calcium-deficient females are common. In addition, stomach ulcers have been described in rats, and lens opacities (cataracts) have been described in rabbits deficient in calcium. Hyperplasia and hypertrophy of the parathyroid glands of rats maintained on calcium-deficient diets have also been observed. In adult animals maintained on low calcium diets, sterility and reduction in lactation are frequently found. There are no descriptions of the teeth of animals maintained on a low calcium diet.

Osteoporosis and Calcium Deficiency. The etiology of osteoporosis was once thought to be a lack of adequate bone matrix. But evidences indicate that it may be due to a long-term negative calcium balance. Skeletal mass in old age is proportional to skeletal mass at maturity, indicating that infant and childhood calcium intake may play a major role in the occurrence and severity of the disease in later years. Based on these findings, the treatment of osteoporosis has changed over the years. Androgen and estrogen therapies have been replaced by increased calcium intake and strontium and sodium fluoride ingestion. The role of strontium and fluoride in bone metabolism is not fully known, but they do act to sustain bone mass in elderly osteoporotic patients. Long-term metabolic balance studies indicate that in a majority of osteoporotic patients, calcium balance can be achieved with a high calcium intake. The importance of calcium, strontium, and sodium fluoride in the prevention and treatment of senile osteoporosis have been found encouraging.

Phosphorus

Total body phosphorus is approximately 500–800 gm, of which 85–90% is in the skeleton, leaving approximately 100 gm in soft tissues. There are multiple pools of phosphorus having different turnover rates; bones and teeth have the lowest rates. A major portion of phosphorus is incorporated into organic phosphorus compounds (phospholipids of cell membranes, nucleic acids, etc). The normal inorganic phosphate level of blood in adults ranges from 2–4 mg/dl, while in children its range is from 3–5 mg/dl. These blood levels are maintained by a balance of various factors, such as parathyroid hormone, phosphatase activity, and vitamin D. Phosphorus is; however, not as finely regulated as plasma calcium but is under some hormonal control via PTH and renal production of 1,25 $(OH)_2D_3$.

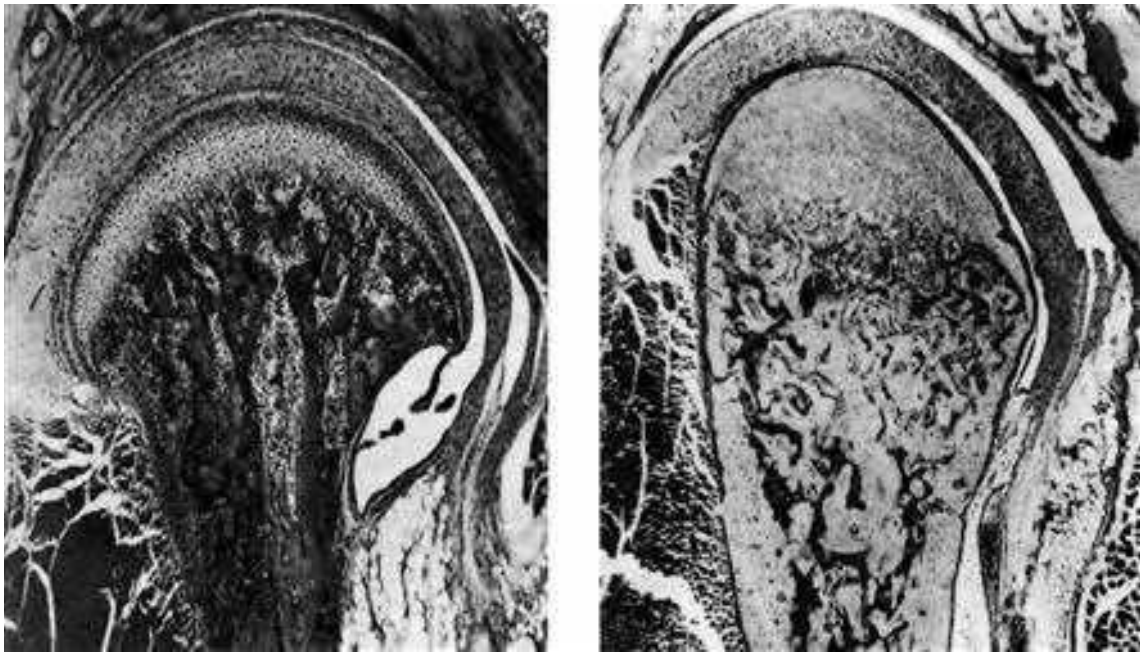
Requirements and Absorption. The suggested daily dietary intake of phosphorus ranges from 240 mg for infants to 800 mg for adults. As with calcium, adolescents, pregnant and lactating women are advised to increase their daily dietary phosphorus intake by 50% to 1,200 mg. 90% of daily dietary phosphate is absorbed. Absorption of phosphorus takes place in the small intestine in the form of soluble inorganic phosphate. Approximately 70% of food phosphorus is absorbed in the form of orthophosphate after intestinal phosphatase releases the food-bound phosphorus during the digestive process. An excess of calcium, iron, or aluminum may interfere with the absorption of phosphorus because of a tendency to form insoluble phosphates in the intestinal tract.

Excretion. Regulation of calcium and phosphorus is under the similar control mechanisms by kidney with respect to parathormone and vitamin D. Excretion of phosphorus occurs primarily in the urine. Phosphate uptake is sodium dependent, about 85% of filtered PO_4 is reabsorbed by the proximal tubules. Phosphate reabsorption is increased when dietary intake is reduced by a parathormone-dependent mechanism. Almost two-thirds of the total phosphorus excreted is found in the urine as phosphates of various cations. Fecal phosphorus, which is usually composed of unabsorbed as well as re-excreted phosphate, is usually excreted as calcium phosphate.

Function. Although most of the body phosphorus is intimately associated with calcium in the metabolism of bones and teeth, a much higher proportion of phosphorus than of calcium is concerned in other vital processes. Phosphates form an intermediate stage in the metabolism of fats and carbohydrates by their function in phosphorylation. They are used in building the more permanent organic phosphates, including some catalysts, essential to the structure and function of cells. Phosphates are utilized in the formation of phosphoproteins, such as milk casein, and in the formation of the nerve phosphatides and the nucleoproteins of cells. They provide the energy-rich bonds in such compounds as adenosine triphosphate, which is important in muscle contraction, and they form part of such coenzymes as pyridoxal phosphate, which is necessary in decarboxylation and transamination of certain amino acids, such as tyrosine, tryptophan and arginine.

When young rats are placed on a low phosphorus diet, there is some retardation in growth. The only specific gross or microscopic alterations are found in the skeletal system, where severe rickets is present (Fig. 15-1). This finding appears after the rats have been on the experimental phosphorus-deficient diet for only one week.

Phosphate depletion in man is nonexistent under most dietary regimens. Long-term antacid use; however, will render phosphate unabsorbable. Lotz and coworkers have described such a condition, which is characterized by weakness, malaise, anorexia, and bone pain. Increased calciuria results in a negative calcium balance with bone demineralization. Rickets and osteomalacia are important dietary deficiency disorders of calcium, phosphorus, or vitamin D. The other causes of hypophosphatemia may be due to decreased intake (starvation, malabsorption, or vomiting) or increased cell uptake as in high dietary carbohydrate, liver disease, or increased excretion due to diuretics, hypomagnesemia, and increased parathormone.



A B

Figure 15-1. Phosphorus deficient diet.
(A) Sagittal section of mandibular joint of a normal rat 70 days of age. **(B)** Sagittal section of mandibular joint of rat 70 days old, which received a phosphorus-deficient diet since weaning at 21 days of age *(Courtesy of Dr Herman Becks)*.

Hyperphosphatemia, on the other hand, is due to factitious hemolysis, increased intake of vitamin D, increased release from bone as in malignancy or decreased excretion.

Magnesium

Magnesium is the fourth most abundant and important cation in humans. It is extremely essential for life and is present as intracellular ion in all living cells and tissues. Magnesium appears to participate in practically every phosphorylating mechanism. In addition, this ion is necessary for the activity of certain enzymes, such as phosphatase and cocarboxylase.

Body Distribution. Although the concentration of magnesium in the intracellular fluids is not as great as the concentration of potassium, magnesium is widely distributed in the tissues of the animal body. The body of a 70 kg man contains approximately 25 mg of magnesium. Over half of this amount is found in the bones, and one quarter in the muscles. The remainder is distributed between liver, pancreas, erythrocytes, serum, and cerebrospinal fluid.

Requirements. The recommended daily dietary allowance for magnesium ranges from 50 mg for infants to 400 mg for teenage males. A daily increase of 150 mg is suggested during pregnancy and lactation. Like calcium, magnesium is ingested in inorganic and organic forms. It is also absorbed and excreted in the same manner as calcium. Absorption takes place primarily in the small bowel. Besides other factors, the size of magnesium load is important as absorption is doubled when normal dietary Mg requirement is doubled and vice versa. Since there is a common transport mechanism from intestinal tract for both Ca and Mg, decreased absorption occurs in the presence of excess Ca. The absorption is also affected in hurried bowel and damaged mucosal states. Vitamin D, parathormone, growth hormone, high protein intake, and neomycin therapy increase absorption. High calcium diets raise the requirement for magnesium.

Excretion. Almost 60% of the excreted magnesium is fecal, the rest being urinary; 0.75 mEq and 3–7 mEq of magnesium is lost daily in sweat and urine, respectively.

Hypermagnesemia is rare because of the renal capacity to excrete excess ion. The administration of magnesium-containing antacids to patients with renal insufficiency has resulted in central nervous system depression. Somjen and coworkers have also reported severe voluntary muscle paralysis with hypermagnesemia. Controlled human hypomagnesemia was studied by Shils, who noted a concurrent hypocalcemia and hypokalemia despite normal dietary calcium and phosphorus intake. Clinically the patients exhibited personality change, anorexia, nausea and vomiting, and carpopedal spasms.

High magnesium intake will produce rickets in growing animals, especially if the phosphorus and calcium intake is relatively low. The normal serum magnesium level is 1–3 mg/dl. When the level reaches 5 mg/dl, mild sedative or hypnotic effects may occur. Profound coma and even death may result when the serum level reaches 18–21 mg. A distinct but not fully understood relationship exists between magnesium, calcium, parathyroid hormone, and bone metabolism. Buckle and coworkers have shown that hypomagnesemia and hypocalcemia have identical effects on the parathyroid glands, i.e. increased parathyroid hormone production. An apparent contradiction exists in that despite elevated hormone levels, many affected individuals exhibit hypocalcemia. Studies have indicated that the parathyroid hormone produced is defective, although some investigators have described hypomagnesemic patients who were refractory to exogenous parathyroid extract, suggestive of a bone defect rather than a glandular abnormality.

Functions. Magnesium is involved as a cofactor and as an activator to a wide spectrum of enzymatic actions. It is essential for peptidases, ribonucleases, glycolytic enzymes and cocarboxlylation reactions. Magnesium exerts an effect on neuromuscular irritability similar to that of calcium ions. High levels depress nerve conduction and low levels may produce tetany (hypomagnesemic tetany). As constituent of bones and teeth, about 70% of body magnesium is present as apatites in bones, enamel, and dentin.

Deficiency. In humans, 'overt' magnesium deficiency occurs rarely. In experimental animals, magnesium deficiency leads to disturbances in the neuromuscular and vascular systems as well as to changes in the teeth, liver, and kidneys. The effects of magnesium-deficient diets on the teeth and their supporting structures have been thoroughly described by Becks and Furuta and by Klein and his associates. Diets containing only 13 ppm of magnesium caused the ameloblasts from the labial side near the apex of the growing incisor tooth in rats to show various stages of localized degeneration with subsequent formation of enamel hypoplasia. The hypoplastic areas increased in size and number with the duration of the experiment, although the changes were noted in all animals after 41 days.

The syndrome of human magnesium-deficiency tetany was first described by Vallee and his associates in 1960. The condition is virtually identical with that of hypocalcemic tetany from which it can be differentiated only by chemical means. Clinically, patients with this deficiency exhibit a semicoma; severe neuromuscular hyperirritability, including carpopedal spasm and a positive Chvostek's sign; athetoid movements; marked susceptibility to auditory, visual, and mechanical stimuli; a decreased serum magnesium; and a normal serum calcium concentration. Precipitating factors are severe dietary inadequacy of magnesium or excessive losses of this ion due to vomiting, intestinal malabsorption, and the administration of large amounts of magnesium free parenteral fluids which induce a large urine volume. The tetany appears when the serum magnesium level is depressed below 1.30 mEq per liter. Treatment by the intramuscular injection of magnesium sulfate is followed by a prompt rise in serum magnesium and a concomitant disappearance of the tetany and convulsions. Discontinuance of the therapy in the presence of precipitating factors results in a rapid reappearance of tetany.

Raised values of magnesium or hypermagnesemia have been reported in uncontrolled diabetes mellitus, adrenocortical insufficiency, hypothyroidism, advanced renal failure, and acute renal failure.

Pathologic Calcification

Pathologic calcification implies the abnormal deposition of calcium salts together with smaller amounts of iron, magnesium, and other mineral salts. Pathologic calcification is commonly classified as:

- Dystrophic calcification
- Metastatic calcification
- Calcinosis.

It is not always possible to make a clear distinction between these various forms.

Dystrophic Calcification. In the dystrophic form of calcification, calcium salts are deposited in dead or degenerating tissues. This is the most frequent type of pathologic calcification and is found in a wide variety of tissues. Areas of tuberculous necrosis, blood vessels in arteriosclerosis, scars and areas of fatty degeneration are commonly recognized as sites of dystrophic calcification by the general pathologist. This type of calcification is not dependent upon an increase in the amount of circulating blood calcium, but appears to be related to a change in the local condition of the tissues. A local alkalinity in comparison with adjacent undamaged tissues appears to be an important factor in initiating the precipitation of calcium in degenerating or nonvital tissues.

In the mouth, areas of dystrophic calcification may frequently be found in the gingiva, tongue or cheek. Such areas are also found in the benign fibromas of the mouth and adjacent structures (Fig. 15-2). One of the most common intraoral dystrophic calcifications is found in the pulp of teeth, and this has been discussed in Chapter 13 on Regressive Alterations of the Teeth. Boyle described the pulp calcifications as calcific degeneration of the pulp tissue. They are usually found in the teeth of older persons, although they also may be seen in young people. They may occur in the wall of blood vessels or in the perineural connective tissue of the pulp, or they may be rather diffusely scattered both in the pulp chamber and in the root canal. They appear as fine fibrillar calcifications which may coalesce to form large masses of calcific material.

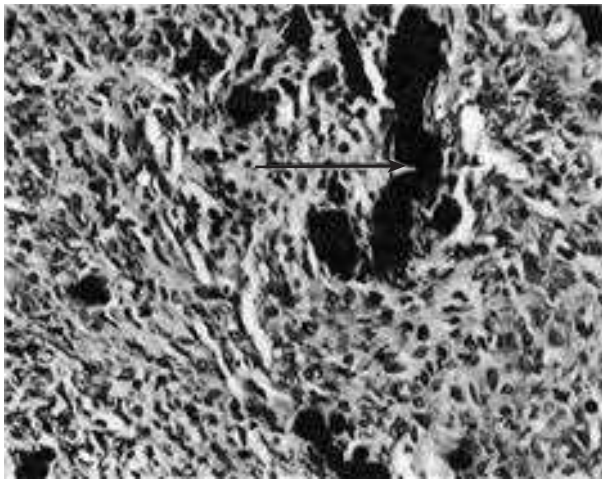


Figure 15-2. Focal calcification is illustrated in the photomicrograph of a fibroma of the gingiva.

Hill classified calcific degenerations of the pulp into two types. The first, a nodular type, is a result of calcification of hyalinized connective tissue. Such calcification is usually perivascular or perineural and is often associated with increased fibrosis. The calcium deposits are most frequently found in the coronal portion of the pulp chamber and increase in size by accretion and deposition of calcium along the collagenous fibrils. The second type of calcification of the pulp is that found in and around necrotic cells and corpora amylacea. It occurs in a multicentric manner and is most frequently found in the radicular portion of the pulp canal. This type of calcification always shows a nidus in the center and increases in size by concrescence which is obvious on histologic examination.

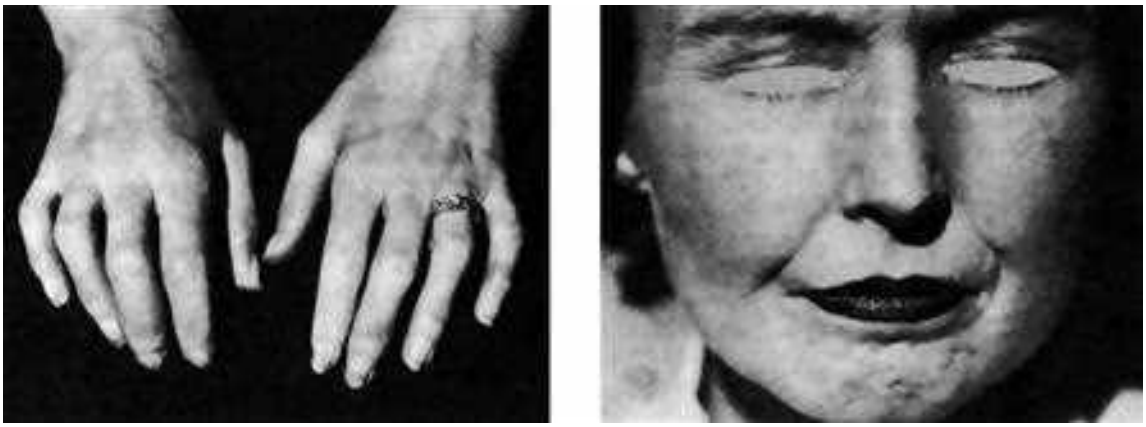
Many of the deposits of calcareous material are found in degenerative processes of the pulp as well as in pulps which are the seat of inflammatory processes. In these cases the calcifications probably have the same relation to body health as calcifications within arterial walls in arteriosclerosis. This type of calcification probably does not cause pulpal inflammation, and there is no justification for considering it a source of dental infection. The other types of pulp stones or pulp nodules (denticles) are discussed in Chapter 13 on Regressive Alterations of the Teeth.

Metastatic Calcification. In metastatic calcification, calcium salts are precipitated in previously undamaged tissues. This precipitation is due to an excess of blood calcium and occurs particularly in such diseases as hyperparathyroidism, which depletes the bone calcium and causes a high level of blood calcium. Metastatic calcifications also occur in hypervitaminosis D. In this type of calcification, the deposits of calcium occur mainly in the kidneys, lungs, gastric mucosa, and media of blood vessels. Since any degenerating or necrotic tissue will also be calcified when there is an increase in blood calcium levels, the differentiation between metastatic calcification and dystrophic calcification becomes extremely difficult.

Calcinosis. Calcinosis is the presence of calcifications in or under the skin. There are two forms of calcinosis: calcinosis circumscripta, which, as the name suggests, is a circumscribed form, and calcinosis universalis, which is a generalized form. Calcinosis universalis is often associated with scleroderma and sometimes dermatomyositis. These different forms of calcinosis have been discussed by Johnson (Fig. 15-3).

Sodium

The sodium found in the body is mainly associated with chloride and as NaCl and $NaHCO_3$. The sodium ion content of the normal (70 kg) adult male ranges from 83–97 gm. Over one-third of this amount is in the skeleton, of which 65–75% is unexchangeable. Most of the remaining sodium is extracellular and accounts for 90% of the basic ions of both extracellular fluid and plasma. Enamel ash contains about 0.3%. The question of whether the sodium of the dental tissues is associated with the inorganic or organic fractions or with small quantities of tissue fluid present in the teeth remains unanswered.



A B

Figure 15-3. Calcinosis universalis of the hands (A) and face (B).
(Courtesy of Dr Robert J Gorlin).

Requirements and Excretion. The minimal requirement of salt is thought to be about 0.5 gm. The lower limit of salt intake is not really known. The estimate of 0.5 gm was reached based on the salt intake of breastfed infants. Breast milk contains 0.4 gm NaCl per liter. Interestingly, cow's milk contains 1.7 gm NaCl per liter. The maximal intake without accumulating edema fluid is 35–40 gm per day. In the United States, the average dietary intake of sodium is 10–15 gm per day. The normal blood level is 160 mg/dl of whole blood, or 340 mg/dl of plasma (147.8 mEq/liter of plasma).

Under conditions of profuse sweating, 1 gm of salt should be ingested for each liter of water in excess of 4 liters. Sweat may contain 2–3 gm of salt per liter in hot environments if the person has not been acclimatized; after acclimatization, 0.5 gm of salt per liter is found.

The kidney is the principal organ for the excretion of water and salt. Abnormal losses of either sodium or chloride must be balanced by the kidney. When the diet is low in salt, or when there is profuse sweating, practically no sodium or chloride is found in the urine. The regulatory mechanism controlling the reabsorption of sodium and chloride by the renal tubules is controlled in part by the adrenal glands. An inadequate intake or excessive loss of sodium stimulates the adrenal cortex to secrete aldosterone, a steroid hormone which acts directly on the renal tubules to increase reabsorption and to conserve sodium. The adrenal glands also control, to a smaller degree, the salt content of sweat.

Function. Sodium ions play an important role in the maintenance of the acid-base equilibrium as well as of osmotic pressure, which depends largely on total base. In fact, the bulk of basic metabolic energy expenditure is concerned exclusively with the maintenance of proper intracellular sodium concentration, i.e. the sodium pump. When tissues are depleted of potassium, sodium may substitute for it, regulating the contraction of the heart. Sodium also helps in maintaining the neuromuscular excitability, viscosity of blood, and fluid balance.

Deoxycorticosterone, cortisone, and hydrocortisone act to increase the tubular reabsorption of glomerular filtrate of sodium and to decrease tubular reabsorption of filtrate potassium. It should be realized, therefore, that care must be taken in using these drugs to avoid edema resulting from excess sodium retention. Potassium loss must also be anticipated and provided for by increased potassium ingestion. For every 24 hours approximately 25,000 mmol of sodium are filtered by the kidneys. However, due to tubular reabsorption, less than 1% of this sodium appears in the urine. Two types of clinical conditions exist in sodium metabolism—hypernatremia and hyponatremia. Specific conditions where hypernatremia occurs are simple dehydration, diabetes insipidus, excess sodium intake, and steroid therapy. Hyponatremia occurs as a result of diuretic medication, excessive sweating, kidney diseases, congestive heart failure, and in cases of increased gastrointestinal loss as in case of diarrhea.

Many of the features of Addison's disease are referable to salt depletion. In this disease extracellular water and sodium are rapidly excreted by the kidneys, resulting in a fall of plasma sodium concentration and an increase in the serum potassium level. Water migrates intercellularly, and the result is a deprivation of both sodium and water. Studies with radioactive sodium (Na^{22}) have shown that the sodium of bone, which constitutes about 30% of the body sodium, is located on the surface of the apatite crystal lattice.

Deficiency. Sodium deficiency in man probably never occurs in an uncomplicated form, but it may be present as a sodium and chloride deficiency. When diets very low in salt are used for long periods of time, gradual weakness, excessive fatigue, lassitude, apathy, anorexia, a sense of exhaustion, nausea, muscle cramps, and peripheral vascular collapse may ensue.

Potassium

Potassium is the major intracellular cation. It is widely distributed in the body fluid (whole blood and plasma) and tissues such as nerve, muscle as well as in cells. Most of the potassium of the body is intracellular. It is the predominant base in the cells. Radioactive potassium (K^{42}) studies have

indicated that there is a constant exchange of potassium between its intracellular and extracellular phases, although it is clear from the studies of Peters and Van Slyke that potassium is prevented from diffusing freely out of cells by a membrane or by some other restraining factor or factors in the cellular or extracellular fluids.

Requirements and Excretion. An average amount of 4 gm of potassium is present in the diet. The requirement for potassium is greatest during periods of rapid growth. As soon as potassium is absorbed, it enters the cells. About 90% of the excreted potassium is eliminated in the urine. The amount of potassium excretion increases, where there is an excessive dietary intake of sodium. The average normal human body contains 3.6 moles of potassium. Urinary excretion is influenced by aldosterone, which controls the active tubular secretion of potassium. The normal blood plasma level is about 4 mEq/liter of plasma. Potassium is also excreted in the gastrointestinal tract, saliva, and gastric, bile, pancreatic, and intestinal juices.

Function. The major functions of potassium and sodium are carried out in coordination with each other and are common. It influences the muscular activity, is involved in the acid-base balance, has a role in cardiac function, and is involved in neuromuscular irritability and the nerve conduction process.

Deficiency. Primary dietary deficiency of potassium has not been observed, but depletion secondary to some pathologic condition has been encountered. It may occur in gastrointestinal disorders, in which there may be a loss of potassium through diarrhea and vomiting. It may also occur in general malnutritional states. It develops as a result of the administration of diuretics or ion-exchange resins. Excessive doses of cortisone or hydrocortisone may result in potassium depletion, and potassium deficiency is common in diabetic acidosis during insulin therapy.

Death in potassium deficiency may result from cardiac or respiratory failure or from paralytic ileus. The signs of potassium deficiency are primarily those of decreased muscular irritability, muscular weakness, reduced or absent reflexes, mental confusion, paralysis, disturbances in conductivity and contractility of heart muscle, and alterations in the gastrointestinal tract.

Hyperkalemia. Hyperkalemia, which may result from extensive tissue breakdown, adrenal insufficiency, advanced dehydration or administration of excessive amounts of potassium, will produce such signs and symptoms as mental confusion, numbness and tingling of the extremities, pallor, cold skin, weakness, disturbances in cardiac rhythm, and peripheral collapse, as noted by Darrow. Clinically, most cases of hyperkalemia are due to kidney failure with decreased excretion of potassium or due to the sudden release of potassium from the intracellular compartment which may happen in a variety of diseases. The effects of potassium deficiency or of excess potassium on the oral structures *per se* have not been reported.

Chlorine

The metabolism of chlorine, together with that of sodium and potassium, is closely related to the water balance and the acid-base equilibrium of the body. The average intake is about 6–9 gm per day. Chlorine is taken in diet as sodium chloride. The absorption of chlorine takes place in small intestines. The mechanism of chloride uptake is unclear, but it appears to depend on an exchange process with the bicarbonate, whilst the accompanying sodium exchange for a hydrogen ion. Quantitatively, chlorine and sodium are the most important mineral constituents of the extracellular fluids. Chlorine is excreted primarily through the kidney. It is one of the so-called threshold substances which are reabsorbed into the circulation after passing through the glomeruli to maintain normal body fluid concentrations. The normal blood plasma concentration of chlorine is 550–650 mg/dl as sodium chloride. Chlorine is important in the production of HCl in the gastric juice and is also important in chloride shift.

Chloride activates salivary amylase. Little else is known of the function of chlorine in the animal organism. Rats placed on synthetic diet low in chlorides failed to grow normally. The only histologic lesions reported were in the kidney. The role of chloride *per se* in sodium deficiency in man is not clear. Large quantities of chloride ions may be lost in pyloric obstruction with gastric tetany, leading to signs of hyperexcitability and convulsions. These may be prevented by the administration of chloride ions. No oral manifestations of chloride deficiency have been reported.

TRACE ELEMENTS

A large number of elements have been shown to occur in a wide range of animal tissues and fluids in such minute quantities that they are usually described as 'traces.' Demonstration of a physiologic role for many of these elements has lagged far behind their mere detection in the living organism. It has been shown that both barium and strontium are essential for growth and especially for calcification of the bones and teeth of rats and guinea pigs. Mertz has reported silicon, vanadium, nickel, and arsenic to be essential in various animal species. However, no imbalances in humans have been reported.

Iodine

Iodine in small amounts is widely distributed in living matter. Sea foods are the best natural source and useful amounts may be present in vegetables and milk. The food color erythrosine is very rich in iodine. Normal whole blood contains an average of 8–12 μg/dl (range, 3–30 μg); protein-bound iodine varies from 3–8 μg/dl. The level of protein-bound iodine is increased during pregnancy and in hyperthyroidism and decreased in hypothyroidism. Iodine is essential for the formation of thyroid hormone. No other function for iodine in the nutrition of higher animals is known.

Iodine deficiency in man results in goiter. Iodine deficiency in experimental animals does not lead to colloid goiter. On the other hand, addition of iodine to the salt or water supply

of endemic goiter areas has been successful in acting as a prophylactic in colloid goiter. About one-third of the total body iodine is found in the thyroid. The precise mechanism of conversion of thyroid-concentrated iodine to colloid is unclear. However, thyroxin formation is intimately related to tyrosine metabolism.

The effects of the thyroid gland on oral structures will be considered in the section dealing with the endocrine glands. The ovaries also contain a high concentration of iodine.

Copper

Iron and copper have been inextricably involved in the development of all forms of life since the earth's atmosphere dramatically changed from a reducing to an oxidizing environment. Copper deficiency in experimental animals leads to anemia. Adult humans contain 100–150 mg of copper, out of which approximately 65 mg is found in muscles, 23 mg in bones, and 18 mg in liver. Fetal liver contains approximately 10 times more copper than adult liver.

Requirement and Absorption. Copper requirements for infants and children are 0.05 mg/kg body weight per day, whereas adult requirement is approximately 2.5 mg/day. Ordinary diets consumed daily contain about 2.5–5.0 mg of copper. Acute copper deficiency in human beings has not been demonstrated.

The value of copper supplements, with and without iron, in the treatment of anemias of infancy and childhood and of secondary anemias of adults has been extensively studied. Copper is necessary for normal erythropoiesis as well as for iron absorption. Copper deficiency produces microcytic hypochromic anemia, due to impairment of erythropoiesis and decrease in erythrocyte survival time, which cannot be corrected by administration of iron. Iron absorption is mediated by ceruloplasmin, which acts as a ferroxidase. Other metalloenzymes which require copper are cytochrome c oxidase, superoxide dismutase, tyrosinase, and lysyl oxidase. Human copper deficiency diseases of importance are hepatolenticular degeneration (Wilson's disease) and Menkes' syndrome (steely- or kinky-hair syndrome).

Iron

Iron is one of the most essential trace elements in the body. In spite of the fact that iron is the fourth most abundant element in the earth's crust, iron deficiency is one of the most important prevalent nutritional deficiencies in India. The total iron content in a human of 70 kg body weight varies approximately from 2.3–3.8 gm. The average iron content of adult males is about 3.8 gm and of females about 2.3 gm. There are two broad categories that are used to describe iron in the body. They are essential (or functional) iron and storage iron. Essential iron is involved in the normal metabolism of cells whereas storage iron is present in two major compounds—ferritin and hemosiderin.

Requirement and Absorption. The requirement of iron varies according to age, gender, weight, and state of health. An adult male requires approximately 10 mg/day and adult female 20 mg/day. Pregnancy and lactation demand more: pregnant women require 10 mg/day and lactating mothers 25–30 mg/day. Children require 10–15 mg/day. Iron is absorbed in the upper portion of the duodenum, either as ferrous or as ferric salts, depending on the species studied. Absorption depends on the amount of the element that the organism has stored. If the tissues are depleted, iron is absorbed rapidly; if sufficient quantities are present, absorption is slight. Since little excretion of iron takes place either by the alimentary canal or by the kidneys, this element has been called a 'one-way substance'. Normally, the loss of iron from the body of a man is limited to 1 mg/day.

Few studies have been reported on the histopathologic changes occurring in the tissues of human beings or experimental animals with iron deficiency anemias. Iron deficiency in the human being, particularly in women and children, however, is more common than has been realized. Changes in the resulting anemia include formation of an esophageal web in the Plummer-Vinson syndrome, spooning of the nails (koilonychia), normoblastic arrest in the bone marrow and microcytosis, anisocytosis, and hypochromia of the erythrocytes in the peripheral blood. Sore tongue, similar to that found in nicotinic acid and riboflavin deficiencies, has been described in the iron deficiency anemias. These anemias respond well to iron therapy. It is imperative to determine iron levels in all patients with anemias, since there are disorders such as thalassemias that may be present and misdiagnosed as iron deficiency.

Iron overload can occur in a number of conditions. Idiopathic hemochromatosis results in excessive iron absorption and is characterized by micronodular cirrhosis with marked brown pigmentation, diabetes mellitus, and skin pigmentation called **'Bronze diabetes'.** Hemoglobinopathies such as sideroblastic anemia and thalassemia can also cause iron overload. **Bantu siderosis,** a form of iron overload resulting from ingestion of home made beer fermented in iron pots, has been extensively described.

Zinc

The role of zinc as an essential nutrient is known for more than 100 years. Zinc is obtained from liver, milk and dairy products, eggs, unmilled cereals, legumes, pulses, oil seeds, and leafy vegetables. An average man has about 1.4–2.3 gm of zinc in the body. The zinc is distributed in highest concentration in skin and prostate where it is about 70–80 mg/100 gm followed by bone and teeth where zinc concentration varies between 10–15 mg/100 gm. The concentration of zinc in enamel and dentin is about 0.02%, which is higher than in many other hard tissues of the body. Bone, nails, and hair have a slightly lower concentrations.

Only a small percentage of dietary zinc is absorbed from duodenum and ileum. A low molecular weight zinc binding factor secreted by the pancreas, forms complex with zinc and helps in its absorption. High amounts of dietary calcium and phosphates interfere with zinc absorption. In a normal healthy

adult, approximately 9.0 mg of zinc is excreted through feces and urine and only about 0.5 mg retained in the body. Adult men and women require about 15–20 mg as the recommended daily dose is about 0.3 mg/kg body weight.

Among many functions of zinc, the most important is its role in enzyme action as it forms an integral part of several enzymes in the body. Important zinc containing enzymes are superoxide dismutase, carbonic anhydrase, and leucine aminopeptidase. Zn^{++} has been claimed to stimulate the release of vitamin A from the liver into the blood and thus increases its plasma level and its utilization in rhodopsin synthesis. Protamine zinc insulin and globin zinc insulin contain Zn^{++} for its functioning. Zinc content of pancreas also has been found to diminish in diabetes mellitus. Zinc is also necessary for the healing of wounds as zinc has been found to accumulate in granulation tissues and zinc deficiency delays wound healing.

In 1961, Prasad and his associates reported a symptom complex of dwarfism and hypogonadism in male Iranians which stemmed from a deficiency of zinc in the diet. This deficiency was thought to occur from zinc binding with phytates present in bread. Subsequent studies in Egypt by Prasad and his coworkers confirmed this impression. The zinc-deficient subjects appeared much younger than their stated age, lacked facial, axillary and pubic hair, had atrophic testes and small external genitalia and were retarded in bone age. The zinc content of the plasma, red blood cells and hair was consistently lower than in normal ethnically identical controls. Radioisotope studies demonstrated a significantly increased plasma zinc turnover and a decreased excretion of Zn^{65} in the urine and stools of the dwarfs, indicative of zinc retention and conservation. A low plasma level of alkaline phosphatase, a zinc-containing enzyme, was also found in these patients.

Acrodermatitis enteropathica, a specific multiorgan disorder resulting from zinc deficiency, has been described. It is an autosomal recessive disorder in which the primary defect is in zinc absorption. Its symptoms include diarrhea and a wide range of mucocutaneous problems including vesicles, eczematoid and hyperkeratotic plaques, alopecia, stomatitis, and glossitis. In leukemias, zinc content is almost reduced to 10% of the normal amount. Zinc in leukocytes probably has immunologic function. Serum zinc levels are decreased in cirrhosis of liver and lower plasma levels of zinc has been noted in acute viral hepatitis which returns to normal level with recovery. Zinc deficiency in humans results in a number of disorders involving taste, keratogenesis, bone growth, wound healing, and reproduction.

Manganese

Manganese is an essential oligo element widely distributed in the crust of the earth. The total amount of manganese distributed in our body is in the range of 10–18 mg and is found in highest concentration in the kidney and liver. Manganese is obtained in diet principally from cereals, vegetables, fruits, nuts and tea. Blood manganese is usually about 4–20 μg/100 ml. They are mainly in RBCs in combination with several porphyrins and are transported in the plasma in combination with a β_1 globulin called transmanganin.

Manganese acts as a 'cofactor' or as an activator of many enzymes like arginase, isocitrate dehydrogenase (ICD), lipoprotein lipase, cholinesterase, and many others. Manganese may be associated with mitochondrial respiratory chain enzymes and act as a cofactor of all hydrolases and decarboxylases. Manganese has also been shown to have a role in animal reproduction and plays a part in the synthesis of mucopolysaccharides in the cartilaginous matrices of long bones. Deficiencies in animals produce alterations of bones, ataxia, and infertility.

Manganese excess in primates produces damage to the extrapyramidal system, with depletion of dopamine and serotonin in the caudate nucleus. In man, there is a transient period of psychosis followed by irreversible Parkinsonism. Increased susceptibility to manganese poisoning has been reported in anemic adults and in newborn and premature children, which appears to be due to increased intestinal absorption of manganese.

Cobalt

Cobalt is an important constituent and an integral part of vitamin B_{12}. The main source of cobalt is from animal origin and the normal diet contains about 5–8 μg of cobalt. This is more than the recommended daily allowance of 1–3 μg of vitamin B_{12} containing about 0.0045–0.09 μg of cobalt. It has a principal role in the formation of cobamide enzyme (adenosyl coenzyme) and is also required to maintain normal bone marrow function and maturation of RBCs.

A deficiency of cobalt results in decreased vitamin B_{12} supply resulting in nutritional macrocytic anemia. Excessive availability of cobalt results in polycythemia. The polycythemic effect is a result of inhibition of certain respiratory enzymes namely cytochrome oxidase, and succinate dehydrogenase leading to relative anoxia. The element does not seem to have a storage depot in the animal organism. Vitamin B_{12} contains about 4.5% cobalt. If this is the only cobalt required by man, the amount must be infinitesimal, since 1–2 μg of vitamin B_{12} by injection each day will adequately treat pernicious anemia.

Chromium

The nutritional importance of trace quantities of Cr^{3+} for mammals has been conclusively established since this element was first identified as necessary dietary ingredient for normal glucose metabolism in rats in 1959 by Shwartz and Mertz. The level of chromium in normal healthy adult is 6–20 μg/100 ml. Significant amounts of chromium is obtained in the diet by cooking foods in stainless steel utensil. Mertz has suggested that chromium may facilitate insulin binding to cell membranes via a 'chromium bridge'. This appears to be accomplished by the participation of Cr^{3+} in a ternary complex with insulin and insulin receptor sites that expedites the initial attachment of insulin to these sites. Inorganic Cr^{3+} is poorly

absorbed and has only limited biological activity compared with naturally occurring organic chromium complex that has been termed the glucose tolerance factor (GTF). While it may potentiate insulin action, chromium is not thought to be a hypoglycemic agent *per se.*

Chromium deficiency has been described in cases of malnutrition and total parenteral alimentation. The total body content of chromium is less than 6 mg. It appears to have a role in carbohydrate and lipid metabolism. Results of supplementation studies using physiological quantities of Cr^{3+} indicate that chromium depletion is one etiologic factor that has to be considered in a variety of disorders of carbohydrate metabolism, ranging from infants suffering from protein calorie malnutrition to elderly people with impaired glucose intolerance. Chromium metabolism appears to be significantly disturbed in diabetes mellitus, and may be one etiologic factor in some gestational and maturity onset diabetes mellitus.

Selenium

The importance of trace element selenium was first reported when it was described to prevent liver cell necrosis. Current evidence suggests selenium to be an essential trace element for all species including humans. Biological forms of selenium occur as selenium analogs of selenium containing amino acids namely **selenomethionine, selenocysteine, and selenocystine**, at a mean concentration of less than 0.2 μg/gm. It is found in higher concentrations in the liver, nails, and kidneys. Major source of selenium for food is the plant material; and selenium is absorbed mainly from the duodenum, particularly in the form of methionine analog. The total body selenium has been estimated to be approximately 4–10 mg. Selenium levels in the blood and tissues are very much influenced by dietary selenium. Selenium concentration in the blood is about 0.22 μg/ml. In selenium deficient areas of China, blood levels may be as low as 0.009 μg/ml in selenium concentration.

The metabolic role of selenium is played by the prosthetic group of selenium enzyme **glutathione peroxidase** which is present in cytoplasm and mitochondria. This results in the reduction of hydroperoxide, thus functioning as part of the multicomponent antioxidant defense system within the cell. It is supplementary to vitamin E and acts as the primary antioxidant by scavenging reactive oxygen species and free radical intermediates of polyunsaturated lipid peroxidation. Selenium has a sparing effect on vitamin E and reduces the vitamin E requirement; conversely vitamin E appears to reduce the selenium requirements by preventing loss of selenium from the body or by maintaining it in an active form. Rotruck and coworkers have reported that glutathione peroxidase is a selenoenzyme that is responsible for eliminating potentially harmful peroxides and free radicals. Burk and coworkers have described selenium deficiency in humans with protein energy malnutrition.

Specific features of selenium deficiency include liver cell necrosis, exudative diathesis, pancreatic degeneration, muscular dystrophies, and myopathies. Numerous reports of selenium toxicity in humans are also available. Clinical manifestations include chronic dermatitis, loss of hair, brittle nails, and an early indication of selenium toxicity is a garlicky breath caused by exhalation of **dimethyl selenide**. The likely cause is occupational exposure in electronics, glass, and paint industries.

Fluoride

Fluoride is one of the most interesting trace elements and man's intake of fluoride comes from the food and water ingested every day. Tea, salmon, sardine, and mackerel are among other sources of fluoride in addition to it being derived from water. Fluoride is essential in human nutrition and one part of fluorine in one million parts of drinking water (1 ppm) seems to serve the daily requirement of fluorine in human adults and children. Several studies from India indicate that many foods from the continent contain appreciably higher concentrations of fluoride than are found in western foods. For example, samples of rice contained 0.4–14 ppm fluoride, table salt contained 0.88–17.6 ppm fluoride, and various spices contained 0.9–14.4 ppm fluoride.

If 1 ppm of fluoride is added to the drinking water, about 1–2 mg of fluoride will be added to the diet daily. Daily dietary fluoride should not exceed 3 mg as it is a toxic element. Balance studies in man have shown that when the quantities of fluoride ingested do not exceed 4–5 mg daily, little is retained by the body. This finding indicates the safety of the preventive dentistry programs based on the addition of fluoride to drinking water in concentrations of approximately 1 ppm. Dietary fluorides are absorbed by diffusion from the intestine and approximately 20 μg of fluoride is present in blood mostly in the ionized form. Fluorides are mainly excreted in urine. One must remember; however, that the rates of absorption and excretion as well as the rate of retention are related to the nature of the diet; e.g. intake of calcium above certain minimal levels will reduce the absorption of dietary fluoride.

Reports of the effect on animals of diets low in fluoride have been conflicting. With the exception of McClendon's work, there have been no published findings which indicate that fluoride is essential to animal growth, development, and reproduction. McClendon, using hydroponic techniques for preparing fluoride free foods, showed that a few rats raised on such foods evidenced severe caries that they were unable to eat and eventually starved. It is a well known fact that fluorine is present in the human tooth in trace quantities and helps in tooth development and hardening of surface enamel, thereby resisting acid dissolution. Cariostatic effects of fluorine are due to its entry into the apatite salts of dental enamel. Fluorine is also present in human bones in trace amounts. Catalytic amounts of fluorine are required for the conversion of the phosphates of calcium to apatite salts of bones and teeth, which is the basis of the role of fluorine in teeth and bone development.

The effects of fluoride as a prophylactic in dental caries are reviewed in Chapter 9 on Dental Caries. We should mention here; however, some of the work done on toxic fluorosis. Although fluoride normally accumulates slowly in bones as the person ages, it accumulates rapidly if ingested in abnormally high quantities.

Excess of fluoride in drinking water or diet is harmful and is considered to be the main cause of the crippling disease known as fluorosis. Chronic fluoride intoxication, such as that described in cryolite workers in Denmark, is characterized by widespread calcification of tendons and muscle sheaths, by extensive arthritic changes in the spine, producing rigidity, and by osteosclerosis of the bones. These workers probably inhaled 20–80 mg F/daily for 10–20 years. The afflicted individuals could not perform simple daily tasks. Hypermineralization due to osteofluorosis has been identified in workmen employed in various industries with fluoride exposure and also in residents of India associated with excessive fluoride concentrations in the drinking water. The progressive development of crippling fluorosis initially results in the osteosclerosis of pelvic vertebra, later in other bones, and finally in all bones with ligamentous calcification and exostoses. The mechanism of osteofluorosis is not well understood; but fluoride in certain doses stimulates osteoblasts and alters osteoclastic and osteoblastic activity differentially.

Due to increased fluoride levels, collagen synthesis is found to be adversely affected due to reduced proline uptake. The formation of deficient collagen fibers with abnormal biochemical sites provides an impulsion for pathological calcification which occurs during fluoride intoxication.

DISTURBANCES IN PROTEIN METABOLISM

Proteins are complex biologic compounds of high molecular weight containing nitrogen, hydrogen, oxygen, carbon, and small amounts of sulfur. As the third principal group of organic compounds, they are much more complex in structure and have a larger range of functions than carbohydrates or lipids. All living tissues, whether plant or animal, contain proteins. The fundamental difference between protein metabolism of plants and that of animals is the ability of plants to synthesize proteins from the nitrogen and sulfur of soil and from the carbon, oxygen, and hydrogen of air. Animals must ingest, breakdown, absorb, and rearrange dietary proteins to form tissue proteins. The chemical process of digestion, which is essentially hydrolytic, is common to all heterotrophic organisms. Substances of high molecular weight—proteins, nucleic acids, and carbohydrates are hydrolyzed to yield smaller molecules which are absorbed and assimilated. A normal adult has about 12–18% protein. Nitrogen balance studies are used to determine the lowest protein intake that will support homeostasis.

Protein Requirements

The accepted figure of 1 gm of protein for each kilogram of body weight is designed to give a factor of safety to cover individual differences in requirement. Protein is required in increased quantity in the last half of pregnancy and during lactation, and in even greater amounts in infancy, childhood, and adolescence. Proteins constitute the most important group of foodstuffs. In addition to contributing to cells and intercellular materials, proteins and their constituent amino acids are of importance in the formation of hormones, enzymes, plasma proteins, antibodies, and numerous other physiologically active substances.

Complete proteins contain sufficient amounts of the essential amino acids for normal metabolic reactions and these are usually found in foods of animal origin. Incomplete proteins are those that have insufficient quantities of one or more essential amino acids and among few are the corn protein which is low in lysine and legume protein that is low in methionine. Complementary proteins are proteins that, when ingested singly, are incomplete but, when combined, provide sufficient essential amino acids.

Comparatively little is known of the processes by which digested protein is recombined to form body proteins. Build-up of body protein is particularly active during growth, late pregnancy, and lactation. There is apparently a constant flux of tissue breakdown and tissue formation, producing a dynamic equilibrium. Proteins have an important bearing on the pre-eruptive and post-eruptive effects on teeth. They form an integral component of cells necessary for the normal development of the tooth and specifically for the formation of the matrix of hard tissues of teeth. The chemical nature of protein foods can neutralize the acids produced by oral bacteria.

Protein Energy (Calorie) Malnutrition

Protein energy malnutrition (PEM) is a spectrum of diseases with kwashiorkor whose essential feature is deficiency of protein at one end; and nutritional marasmus, which is total inanition of infant due to severe and prolonged restriction of all food at the other end. In the middle of the spectrum is marasmic kwashiorkor in which there are clinical features of both disorders. Some children adapt to prolonged energy and protein shortage by nutritional dwarfism. The most prevalent of all the varieties is mild to moderate PEM or the underweight child. PEM, in its various forms, has a higher incidence in India, south east Asia, parts of Africa, the Middle East, the Caribbean Islands, and in South and Central America.

In some developing countries, **marasmus** is of greater clinical importance than kwashiorkor. The factors which predispose to marasmus are a rapid succession of pregnancies, and early and often abrupt weaning, followed by artificial feeding of infants in inadequate amounts. The two constant features of marasmus are retarded growth and wasting of subcutaneous tissues, giving the child an aged appearance. Marasmus is usually associated with energy deficiency and occurs in many pathologic states besides simple starvation. Protein deficiency is common in prolonged febrile illness, in massive burns and large chronic ulcers, in 'stress', hyperthyroidism and other hypermetabolic states, in conditions interfering with digestion and absorption and in metabolic diseases which interfere with utilization. The other clinical findings in protein deficiency include loss of weight and of subcutaneous fat, wasting of muscles, pigment changes in the skin with hair loss, hypotension, weakness, and edema. Anemia is common. A decrease in serum proteins, hemoconcentration, and a decrease in blood volume are other frequent findings.

In **kwashiorkor**, some amino acid or protein deficiency arises typically after prolonged breastfeeding and the child is weaned on to a low protein family diet. This combined protein energy deficiency in children in many parts of the world, due to insufficient supply of amino acids, leads to inadequate protein synthesis, reduced synthesis of enzymes, and plasma proteins and impaired development of organs. The child's weight is usually well below standard for age but the deficit may be masked by edema often due to hypoalbuminemia. Impaired synthesis of digestive enzymes may be partially responsible for diarrhea which is so commonly present and which leads to loss of potassium and magnesium in the stools. The child is prone to infections due to subnormal levels of immune responsiveness.

The oral lesions, when apparent, include a bright reddening of the tongue with a loss of papillae, bilateral angular cheilosis, fissuring of the lips, and a loss of circumoral pigmentation. In addition, the mouths of kwashiorkor patients have been described by Van Wyk as being dry, dirty, caries-free, and easily traumatized, with the epithelium readily becoming detached from the underlying tissues, leaving a raw, bleeding surface. In oral cytologic smears from his patients, he described a perinuclear vacuolization or halo around the nucleus in a remarkable number of the epithelial cells present and interpreted this as a sign of epithelial atrophy.

King has pointed out that about half of the world's population lives in areas where the lack of milk, meat, poultry, fish, eggs, and so on, leads to early retardation of growth. Typically, children so retarded have edema, episodes of diarrhea, skin pigmentation, liver enlargement, alopecia, and poor resistance to infection, especially of the lungs and intestinal tract. The death rate may reach 25 times than that considered normal for the age group. Those that survive show permanent physical stunting. This stunted condition is so general that it is often mistaken for a genetic phenomenon. In some areas 50% of the children die before school age. It is significant that most of the children exhibit a normal growth rate up to weaning time.

Frandsen and his coworkers, Chawla and Glickman, Di Orio and coworkers, Navia, Aponte-Merced and Navia, Menaker and Navia, and Navia and coworkers have studied the effect of protein and protein energy deprivation on salivary glands and teeth, and their supporting structures in experimental animals. Overall growth and growth of the jaws were decreased. Eruption was delayed, and incisor and molar growth was retarded. Radicular osteocementum was decreased. The enamel of affected incisors exhibited increased acid solubility. Increased dental caries was also reported. The gingiva and periodontal membranes exhibited varying degrees of degeneration. Salivary volume was decreased as were the DNA, RNA, and protein concentrations of affected animals. The severity of these changes was dependent on the degree of protein deprivation.

Some of the genetic disorders, where dietary modifications become important include, phenylketonuria (PKU), which is an inherited enzyme defect in which individuals cannot metabolize the phenylalanine found in nearly all proteins. Patients with this condition are prescribed a diet which is protein restricted, just enough to meet growth and maintenance needs. Gout is yet another disorder of protein metabolism which is characterized by excessive uric acid production leading to the formation of urate crystals deposited in joints. The treatment often includes restriction of protein to limit purine and uric acid production.

Protein needs increase during fever, after severe injury and surgery, intestinal malabsorption, increased protein loss from the kidneys, or diminished protein synthesis by the liver. Dietary protein must be restricted when the kidneys can no longer remove nitrogenous wastes from the body or in severe liver disease when the nitrogenous by-products of protein catabolism can no longer be synthesized.

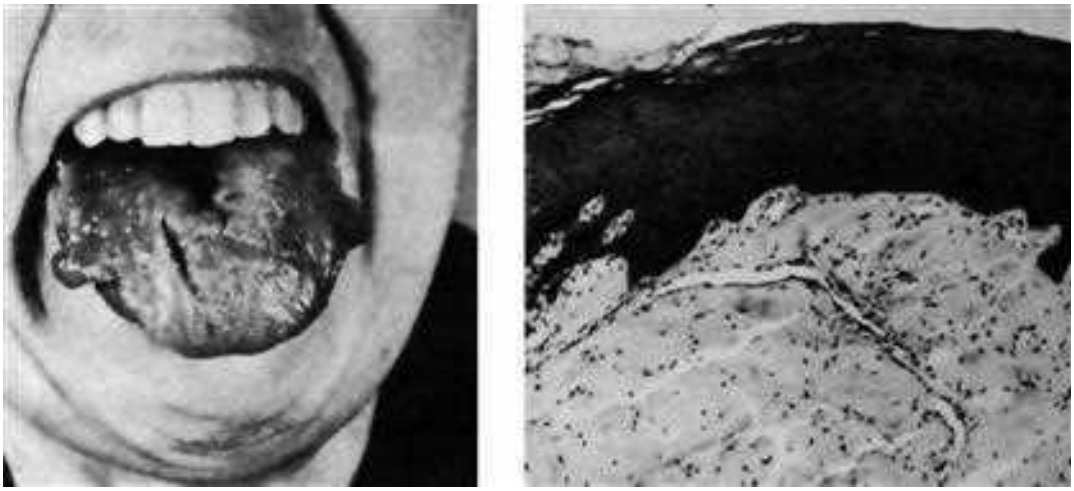
INDIVIDUAL AMINO ACIDS

The inadequacy of zinc as a sole source of protein in rat nutrition brought out the importance of the variations in amino acid content of different proteins and led to the work of Rose and his collaborators and others on the essential and nonessential amino acids. The essential amino acids are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. This list of nine essential amino acids must not be accepted as final; however, more may have to be added and some may eventually be dropped. The original concepts of 'essential' and 'nonessential' must be modified, since the determination of essentiality depends not only on the species studied, but also on the experimental criteria used (e.g. nitrogen balance, growth), the age of the animal used and the presence or absence of vitamins in the diet. For example, arginine is nonessential in the adult. However, infants are incapable of producing sufficient amounts of arginine for normal physiologic functions. Therefore arginine is considered essential in infants. It is unlikely; however, that a deficiency of a single essential amino acid occurs in humans.

Amyloidosis

An abnormal proteinaceous substance that is deposited between cells in tissues and organs of the body in a variety of clinical disorders is referred to as an amyloid. Using routine stains, it is seen as intercellular pink translucent material by light microscopy. Despite its morphologic uniformity, it is quite clear that amyloid is a complex material with at least two distinct forms: type A and type B. By electron microscopy, X-ray crystallography and infrared spectroscopy, amyloid appears to be made up largely of nonbranching fibrils with a characteristic 'β-pleated sheet confirmation', which is unique among mammalian fibrillar proteins. Two major classes of amyloid identified include **amyloid light chain** (AL), composed of immunoglobulin light chain, and **amyloid associated** (AA), made up of nonimmunoglobulin protein.

Type A (secondary) amyloid is a fibrillar protein of unknown origin that is seen in prolonged inflammatory diseases, genetic diseases, and syndromes such as familial Mediterranean fever. Type B (primary) amyloid is thought to be of immune origin



A B

Figure 15-4. Amyloidosis.
Amyloid tumors of the tongue **(A)**. The photomicrograph **(B)** illustrates a section through such a nodule *(Courtesy of Dr Boynton H Booth)*.

because of its sequence homology with the NH2 terminal end of immunoglobulin light chains. Type B amyloid is commonly seen in patients with multiple myeloma and macroglobulinemia. Clinically asymptomatic patients found to have type B amyloid serum and urine immunoglobulin abnormalities. A third type of amyloid (type C) includes amyloid of aging, localized nonspecific amyloid, and amyloid adjacent to APUD (amine precursor uptake and decarboxylase) tumors, i.e. pheochromocytoma (Fig. 15-4). A review of the association of amyloid with a variety of diseases in men and animals has been published by Rigdon. The most common diseases predisposing to amyloidosis are the collagen diseases, particularly rheumatoid arthritis, chronic infections such as tuberculosis and osteomyelitis, regional enteritis, ulcerative colitis, and certain malignant diseases, particularly multiple myeloma, Hodgkin's disease, and renal cell carcinoma. Since modern surgery and medicine have largely eliminated chronic suppurative disease, rheumatoid arthritis and myeloma are now the chief predisposing causes for amyloidosis. Excellent reviews of amyloidosis were written by Franklin and by Kyle and Bayrd.

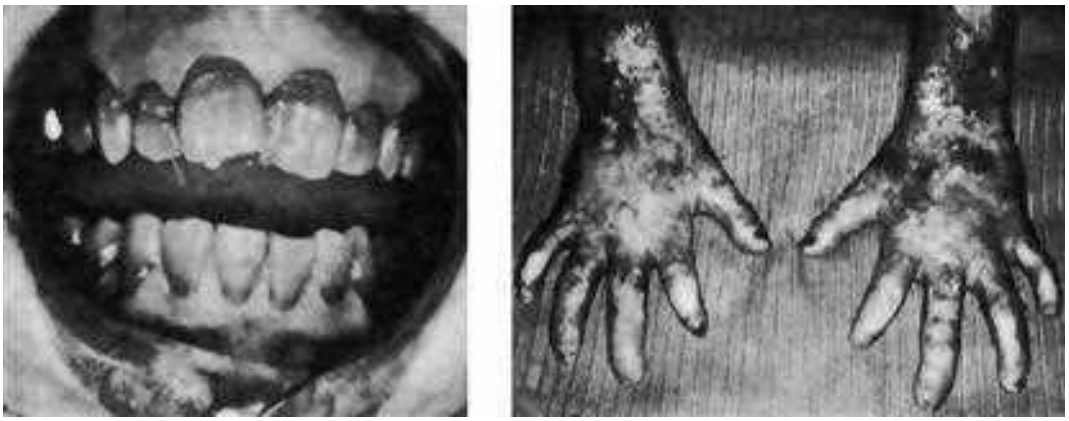
While any organ may be involved, those most commonly affected are the kidneys, heart, gastrointestinal tract, liver, and spleen. Amyloidosis is also seen with considerable frequency in the respiratory tract, skin, eye, adrenals, and nerves, and may involve bone. A primary localized cutaneous amyloidosis is also recognized. Amyloidosis itself is generally considered to be an irreversible disease.

Amyloid deposition in the tongue, resulting in macroglossia, and gingiva is also reported to be commonly seen. Because of the reported frequency of amyloid in gingival tissues, it has often been suggested that the gingival biopsy may be used conveniently for the diagnosis of amyloidosis. However, the results have been quite varied, some investigators reporting a high incidence of positive biopsies, while others have found so few positive results that the technique has been considered of little value. This subject has been reviewed by Lovett and his associates. Ulmansky, and Stanback and Peagler have discussed the oral manifestations of primary amyloidosis, and van der Waals and coworkers have reported on the significance of amyloidosis in oral surgery.

The amyloidosis may or may not be apparent on macroscopic examination. However, when the cut surface of the suspected organ is painted with iodine and sulfuric acid, a peculiar mahogany brown staining of the amyloid deposit is revealed. If large amounts of amyloid are accumulated the affected organ is frequently enlarged and the tissue appears gray with a waxy firm consistency. Histologically, the deposition always begins between the cells and eventually surround and destroy the trapped native cells. The amyloid in the microscopic sections of involved tissue appears as a hyaline, homogeneous material, often perivascular in distribution especially in the immune-associated form. It is best demonstrated by special stains such as Congo red and crystal violet or by the thioflavin-T fluorescent technique. Under polarized light the Congo red-stained amyloid shows green birefringence. This reaction is shared by all forms of amyloid and is due to the crossed β-pleated configuration of amyloid fibrils. AA and AL amyloid can be distinguished in histologic sections. AA protein loses affinity for Congo red after incubation of tissue sections with potassium permanganate, whereas AL proteins do not. In suspected cases of immunocyte associated amyloidosis, serum and urinary protein electrophoresis and immunoelectrophoresis should be performed.

Porphyria

Porphyria is a term which has been generally used to connote one of the inborn errors of porphyrin metabolism, characterized by overproduction of uroporphyrin and related substances. Not all cases of porphyria; however, represent a constitutional disturbance, since porphyria may appear as a



A B

Figure 15-5. Congenital porphyria.
The intrinsic brown pigmentation of the teeth is seen in **(A)**, while the active skin lesions as well as scarring are shown in **(B)** *(Courtesy of Dr Sidney B Finn).*

sequel to some infections or intoxications. The classification of the porphyrias remains unsettled, although the most basic classification defines two types:

- Erythropoietic porphyria, characterized by early photosensitivity, splenomegaly, and excessive abnormal porphyrin formation in developing erythrocytes. Two subclasses, uroporphyria (congenital porphyria) and protoporphyria, have been described based on their respective porphyrin precursor type.
- Hepatic porphyria, also a multisystem disorder, which has four subclasses; acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda, and hereditary coproporphyria.

Heritable enzymatic effects have been identified in uroporphyria, acute intermittent porphyria and porphyria cutanea tarda. An excellent review of the porphyrias has been published by Elder and coworkers.

Erythropoietic Uroporphyria
(Congenital porphyria)

This disease, the most important of the group, is transmitted as a nonsex-linked recessive character, both genders being equally affected. The first sign of erythropoietic porphyria is usually the excretion of red urine containing much uroporphyrin. This may be noted at birth or only during the first year of life. Photosensitivity is frequently absent in the neonatal period, but may become apparent during the first year of life as exposure to sunlight increases. A vesicular or bullous eruption appears on the face, back of the hands, and other exposed parts of the body (Fig. 15-5). The vesicles contain a serous fluid which usually exhibits red fluorescence. Ruptured vesicles heal slowly and leave depressed, pigmented scars. Occasionally the cutaneous manifestations may be relatively mild, resulting in little scarring. There is an interesting oral finding. The deciduous and permanent teeth may show a red or brownish discoloration, although this is not invariably present. Under ultraviolet light; however, the teeth always exhibit red fluorescence. Deposition of porphyrin in the developing teeth and bones is believed to be due to its physical affinity for calcium phosphate. The presence of porphyrin in the deciduous teeth indicates that the metabolic disorder may have been present during fetal life.

LYSOSOMAL STORAGE DISEASES

Lysosomal storage diseases are a heritable group of heterogeneous disorders characterized by the accumulation of undigested macromolecules intralysosomally, resulting in an increase in the size and number of these organelles, and ultimately in cellular dysfunction and clinical abnormalities. Lysosomal storage diseases are generally classified by the accumulated substrate and they include sphingolipidoses, glycoproteinoses, mucolipidoses, mucopolysaccharidoses (MPSs), and others. The concept of lysosomal storage disorders is now being extended to include deficiencies in lysosomal enzymes, noncatalytic role of lysosomal proteins, and abnormalities of lysosomal function.

The pathologic manifestations of this error in metabolism mainly depends on the nature and quantity of the accumulating material as well as the organs affected. For example, neurons which are incapable of cell division and cell turnover are particularly vulnerable to intracellular accumulations. Similarly, cells of the mononuclear phagocyte system are especially rich in lysosomes and are frequently affected by lysosomal storage disorders. Recent advances in molecular genetics have shifted the focus from conventional theories, holding gene products and genes themselves responsible for these disorders. The defective genes in most of these genetic disorders have been isolated, characterized and their specific mutations identified. At the gene level, genetic heterogeneity is complex despite similarities in phenotypes, biochemistry, and enzymology.

Over 40 lysosomal storage diseases exist.

- Glycogen storage disease type II (alpha-glucosidase)
- The mode of inheritance is autosomal recessive, and the gene encoding for acid alpha-glucosidase has been localized to chromosome arm 17q23.
- Mucopolysaccharidoses
- Mucolipidosis II (I-cell disease) and mucolipidosis III (phosphotransferase)
- Schindler disease/Kanzaki disease (alpha-*N*-acetylgalactosaminidase)
- Glycoprotein degradation
- α-mannosidosis and β-mannosidosis
- Fucosidosis
- Sialidosis
- Aspartylglycosaminuria (AGU)
- Carbohydrate-deficient glycoprotein syndrome
- Wolman and cholesterol ester storage disease (acid lipase)
- Farber disease, disseminated lipogranulomatosis (ceramidase)
- Niemann-Pick disease
- Gaucher disease types I, II, and III (beta-glucosidase)
- Krabbe disease, infantile globoid-cell leukodystrophy (galactosylceramidase)
- Fabry disease (alpha-galactosidase A)
- Multiple sulfatase deficiency (sulfatases)
- GM1 gangliosidosis and Morquio B disease (beta-galactosidase)
- GM2 gangliosidosis, Tay-Sachs and Sandhoff diseases (hexosaminidase)
- Cystinosis (cysteine transporter)
- Sialic acid storage disease (sialic acid transporter)
- Pyknodysostosis (cathepsin K)
- Metachromatic leukodystrophy (galactose-3-sulfatase)
- Galactosialidosis (neuraminidase, beta-galactosidase, protective protein)
- Neuronal ceroid lipofuscinosis, infantile (palmityl protein thioesterase)
- Neuronal ceroid lipofuscinosis, late infantile (carboxypeptidase)
- Cobalamin deficiency type F (cobalamin transporter)

DISTURBANCES IN CARBOHYDRATE METABOLISM

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) result from abnormal degradation of glycosaminoglycans such as dermatan sulfate, keratan sulfate, heparan sulfate, and chondroitin sulfate resulting in organ accumulation and eventual dysfunction. Glycosaminoglycans or mucopolysaccharides are normally a component of the cornea, cartilage, bone, connective tissue, and the reticuloendothelial system and are therefore target organs for excessive storage. The catabolic enzymes involved in the breakdown of glycosaminoglycans or mucopolysaccharides are deficient. Ten known enzyme deficiencies give rise to six distinct MPS.

The stepwise degradation of the glycosaminoglycans requires four glycosidases, five sulfatases, and one nonhydrolytic transferase. The mode of transmission is autosomal recessive except for MPS II, which is X-linked. A variety of mutations are described, and the correlation of genotype with disease severity is beginning to emerge from mutation analysis.

In general, MPS are progressive disorders, characterized by the involvement of multiple organs, including the brain, liver, spleen, heart, and blood vessels; many are associated with coarse facial features, clouding of the cornea, and mental retardation. Diagnosis can often be made by examination of urine, which reveals increased concentration of glycosaminoglycan fragments (Table 15-1).

Clinical Presentation. MPS type I includes **Hurler, Hurler-Scheie,** and **Scheie syndromes.**

MPS type I H (Hurler syndrome).

MPS type I H/S. This form is intermediate between the Hurler syndrome and Scheie syndrome.

MPS type I S (Scheie syndrome). Biochemical findings are identical to type I Hurler syndrome, but the clinical features are less severe.

Glycosaminoglycan fragments are generated by alternative pathways and are excreted in the urine. Simple enzyme assays are available for the diagnosis of MPS from fibroblast, leukocyte, or serum samples. Because heterozygous individuals are identified on the basis of enzyme activity, the diagnosis can be difficult. However, it is becoming more definitive as specific mutations are identified. Prenatal diagnosis is made by means of amniocentesis or chorionic villus biopsy.

HURLER SYNDROME

(Mucopolysaccharidosis I, MPS IH, gargoylism)

A chromosomal abnormality occurs in chromosome arm **4p16.3.**

Hurler syndrome is a disturbance of mucopolysaccharide metabolism exhibiting a variety of classic clinical features. It is characterized by an elevated mucopolysaccharide excretion level in the urine. The disease, in which there is an excessive intracellular accumulation of both chondroitin sulfate B and heparan sulfate in those tissues and organs where they are normally found, is inherited as an autosomal recessive trait.

Clinical Features. The disease usually becomes apparent within the first two years of life, progresses during early childhood and adolescence and terminates in death usually before puberty. The head appears large and the facial characteristics are quite typical, consisting of a prominent forehead, broad saddle nose and wide nostrils, hypertelorism, puffy eyelids with coarse bushy eyebrows, thick lips, large tongue, open mouth, and nasal congestion with noisy breathing. Progressive corneal clouding is a classic manifestation of the disease as is hepatosplenomegaly, resulting in a protuberant

Table 15-1: The genetic mucopolysaccharidoses*

	Designation	Clinical features	Excessive urinary		
			Genetics	MPS	Substance deficient
MPS I H	Hurler syndrome	Early clouding of cornea, grave manifestations, death usually before age 10	Homozygous for MPS I H gene	Dermatan sulfate Heparan sulfate	α-L-iduronidase (formerly called Hurler corrective factor)
MPS I S	Scheie syndrome	Stiff joints, cloudy cornea, aortic regurgitation, normal intelligence,? normal life-span	Homozygosity for MPS I S gene	Dermatan sulfate Heparan sulfate	α-L-iduronidase
MPS I H/S	Hurler-Scheie compound	Phenotype intermediate between Hurler and Scheie	Genetic compound of MPS I H and I S genes	Dermatan sulfate Heparan sulfate	α-L-iduronidase
MPS II A	Hunter syndrome, severe	No clouding of cornea, milder course than in MPS I H but death usually before age of 15 years	Hemizygous for X-linked gene	Dermatan sulfate Heparan sulfate	Hunter corrective factor
MPS II B	Hunter syndrome, mild	Survival to 30s to 50s, fair intelligence	Hemizygous for X-linked allele for mild form	Dermatan sulfate Heparan sulfate	Hunter corrective factor
MPS III A	Sanfilippo syndrome A	Identical phenotype	Homozygous for San-filippo A gene	Heparan sulfate	Heparan sulfate sulfatase
MPS III B	Sanfilippo syndrome B	Mild somatic, severe central nervous system effects	Homozygous for San-filippo B (at different locus)	Heparan sulfate	N-acetyl-α-D-glucosaminidase
MPS IV	Morquio syndrome (probably more than one allelic form)	Severe bone changes of distinctive type, cloudy cornea, aortic regurgitation	Homozygous for Morquio gene	Keratan sulfate	Unknown
MPS V	Vacant				
MPS VI A	Maroteaux-Lamy syndrome, classic form	Severe osseous and corneal change, normal intellect	Homozygous for M-L gene	Dermatan sulfate	Maroteaux-Lamy corrective factor
MPS VI B	Maroteaux-Lamy syndrome, mild form	Severe osseous and corneal change, normal intellect	Homozygous for allele at M-L locus	Dermatan sulfate	Maroteaux-Lamy corrective factor
MPS VII	β-glucuronidase deficiency (more than one allelic form?)	Hepatosplenomegaly, dysostosis multiplex, white cell inclusions, mental retardation	Homozygous for mutant gene at beta-glucuronidase locus	Dermatan sulfate	β-glucuronidase

By permission of Dr Victor A McKusick. From McKusick VA. Heritable Disorders of Connective Tissue (4th ed). CV Mosby, St Louis, 1972.

abdomen. A short neck and spinal abnormalities are typical, while flexion contractures result in the 'claw hand'. These dwarfed individuals are mentally retarded.

Oral Manifestations. The oral manifestations of the Hurler syndrome have been reviewed by Gardner. These consist of a shortening and broadening of the mandible with prominent gonions, a wide intergonial distance and a greater than normal distance around the arch from ramus to ramus accounting, at least in part, for the typical spacing of the teeth. Localized areas of bone destruction in the jaws may be found which appear to represent hyperplastic dental follicles with large pools of metachromatic material, probably mucopolysaccharide. The teeth themselves are frequently described as being small, widely spaced, and mishappen. However, many investigators have been unable to demonstrate abnormalities of the teeth, except for some delay in the time of eruption.

Gingival hyperplasia has been repeatedly described in patients with Hurler syndrome, although it is not a constant feature of the disease. In some patients the gingiva appears normal, while in others the gingiva appears enlarged as a result of local factors such as poor oral hygiene or mouth breathing. In occasional patients, the gingival tissues appear to be involved in a manner similar to fibromatosis gingivae. Finally, the tongue is also characteristically enlarged.

Histologic Features. There is excessive accumulation of intracellular mucopolysaccharide in many tissues and organs throughout the body including the liver, spleen, reticuloendothelial system, nervous system, cartilage, bone, and heart. Abnormal deposits are also found in many sites, with involved fibroblasts assuming the appearance of **clear** or **gargoyle** cells.

Gardner has reported the demonstration of these 'Hurler cells' or 'gargoyle cells' in the gingival tissues of affected patients. The Hurler cells are relatively large, with metachromatically staining cytoplasm which is either agranular or finely granular, often with crescent-shaped nuclei. These cells are not identified with hematoxylin and eosin but become evident with toluidine blue or with Alcian blue/aldehyde fuchsin stains. Some difficulty may be encountered in differentiating these from mast cells.

Laboratory Findings. There is an elevated level of mucopolysaccharides in the urine. In addition, metachromatic granules or Reilly bodies can often be demonstrated in the cytoplasm of circulating lymphocytes.

Treatment. There is no treatment for the disease.

Lipoid Proteinosis

(Hyalinosis cutis et mucosae, Urbach-Wiethe disease)

Lipoid proteinosis is a rare, autosomal recessive disorder typified by generalized thickening of skin, mucosae and certain viscera. Lipoid proteinosis was first described by a Viennese dermatologist and otorhinolaryngologist, Urbach and Wiethe, in 1929.

Clinical Features. Classical features include beaded eyelid papules and laryngeal infiltration leading to hoarseness of voice. One of the characteristic features of the disease is the inability of infants to cry at birth and the hoarseness of the voice also present from birth. These features are due to the yellowish-white plaques in the epiglottis, aryepiglottic folds, and interarytenoid region. On laryngoscopic examination, the cords are seen to be thickened and nodular. On rare occasion, dyspnea may be so severe as to necessitate stripping the nodules from the cords or laryngectomy. The exact pathogenesis of this disease is not known but has been postulated to be the result of either a lysosomal storage disorder involving multiple enzyme defects or from a disturbance in collagen synthesis, as evidenced by a decrease in the ratio of type I to type III collagen associated with a decrease in mRNA for type I procollagen. There is also an increase in mRNA for type IV procollagen resulting in underproduction of fibrous collagens and an overproduction of basement membrane collagens, which tend to deposit in the skin and various organs, which form the hallmark of the disease.

Oral Manifestations. The oral cavity is usually severely affected in this disease with much of the oral mucous membrane developing the characteristic yellowish-white papular plaques which become increasingly more prevalent and prominent from childhood into adult life. The lips become thickened and nodular while the tongue becomes thickened, enlarged, very firm on palpation, and sometimes bound to the floor of the mouth (Fig. 15-6). Recurrent painful parotitis may occur as a result of involvement of the buccal mucosa, with stenosis of the parotid duct opening. Congenital absence of teeth and severe enamel hypoplasia have also been reported. The oral manifestations of the disease have been discussed by Gorlin, Williams, Hofer, and Bergenholtz.

Other mucocutaneous changes may include thickening of the tongue and frenulum, blisters, warty skin papules, scarring, alopecia, nail dystrophy, and dental anomalies. Extracutaneous features may include epilepsy and neuropsychiatric abnormalities, sometimes in association with calcification in the temporal lobes or hippocampi.

Lipoid proteinosis occurs worldwide, but is more common in certain areas such as the Northern Cape province of South Africa. Lipoid proteinosis is mapped to **1q21** and identified the extracellular matrix protein 1 gene (*ECM1*) as the LP gene.

Histologic Features. Lipoid proteinosis is characterized by deposition of PAS-positive, diastase-resistant material at the level of the basement membrane (resulting in its thickening at the dermoepidermal junction), papillary dermis, surrounding blood vessels, and around adnexal epithelia especially sweat glands. There is widespread deposition of hyaline (glycoprotein) material and disruption/reduplication of basement membrane. Ultrastructural examination reveals concentric rings of excess basement membrane surrounding blood vessels, and irregular reduplication of lamina densa at dermoepidermal junction resulting in onion-skin appearance. Biochemically, this material is characterized by decrease in type I collagen with overproduction of type IV or basement-membrane collagen. The hyaline deposits in the biopsies examined consist of a carbohydrate-protein complex containing hyaluronic acid and probably chondroitin sulfate, plus large amounts of lipids.

Figure 15-6. Lipoid proteinosis.
(Courtesy of Dr Robert J Gorlin).

Treatment. There is no treatment for the disease.

Hereditary Fructose Intolerance

Over 25 years ago Chambers and Pratt reported an unusual case of a young woman who repeatedly became nauseated and vomited after the ingestion of fruit or cane sugar. Numerous reports have since appeared in the literature, and over two dozen families have been diagnosed as having hereditary fructose intolerance.

Clinical Features. The disease is transmitted as an autosomal recessive trait and is manifested by hypoglycemia and vomiting after the ingestion of fructose-containing foods. It results from a deficiency in fructose 1-phosphate aldolase. Affected individuals rapidly acquire an intense aversion to all sweets and fruits.

Oral Manifestations. Newbrun and coworkers reported on the dietary habits and dental health of 17 affected individuals. Subjects with hereditary fructose intolerance had a total sucrose intake of less than 5% of that of controls. Caries

scores (DMFS) were less than 10% of those of controls. This study confirms the previous observations of Cornblath and coworkers, Levin and colleagues, and Marthaler and Froesch.

DISTURBANCES IN LIPID METABOLISM

Lipid metabolism is concerned with the assimilation, utilization, replacement, and synthesis of the various fatty acids of the cell. All living cells contain fatty acids, largely in the form of esters with glycerol, cholesterol or other alcohols, or combined with phosphoric acids, nitrogenous bases or carbohydrates.

Disturbances of lipid metabolism are rare, but they do occur. These disturbances have been classified as 'lipoid storage diseases', xanthomatoses, lipid granulomas, and so on. Several disease entities have been identified on the basis of the particular lipid involved.

Gaucher's Disease

Gaucher's disease is a common lysosomal storage disease, characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system. Deficiency of a specific lysosomal hydrolase, glucocerebrosidase, which cleaves glucocerebroside to ceramide is held responsible for this disorder. Three clinical subtypes exist and are delineated by the absence or presence of neurologic involvement and its progression.

Clinical Features. Gaucher's disease has been divided into three clinical forms:

Type I: **Chronic nonneuronopathic form** often presents in childhood with hepatosplenomegaly, pancytopenia, and skeletal disease, although striking clinical variability occurs in disease severity. This is the most common variety (99%) and has a striking predilection for occurrence amongst individuals of Ashkenazi Jewish descent.

Most patients have radiographic evidence of skeletal involvement, including an **Erlenmeyer flask** deformity of the distal femur, which is an early skeletal change.

Type II: **Infantile or acute neuronopathic form** causes rapidly progressive neurovisceral involvement and results in death at infancy.

Type III: **Juvenile or Norrbottnian form (intermediate between type I and type II).** The patients are juveniles presenting with systemic involvement. Progressive central nervous system involvement usually begins in teens or twenties.

All three subtypes are inherited as **autosomal recessive** traits. When bone is involved, the bone marrow shows diffuse changes. Numerous large, foamy, slightly granular cells with small, round pyknotic nuclei, which are the Gaucher's cells, group together and replace the normal marrow structure. These skeletal manifestations have been discussed by Amstutz and Carey. Gaucher's cell accumulations are also found in the spleen, the lymph nodes, and the liver. An excellent review of both the infantile and adult forms of Gaucher's disease was published by Levin. In all three types of Gaucher's disease, sternal puncture or examination of the biopsies of the spleen or liver will reveal the typical Gaucher's cell. This is a round pale cell, measuring between 20 and 80μ in diameter, containing a small eccentric nucleus and a wrinkled or 'crumpled silk' cytoplasm.

Treatment and Prognosis. The prognosis of the malignant infantile form is very poor, the disease resulting in death usually within the first year. The less virulent form may persist until the sixth decade of life, when the patients usually die of some intercurrent infection. Brady and coworkers have reported that the administration of purified glucocerebrosidase to affected patients results in a dramatic decrease in hepatic accumulations of glucocerebroside. Although this therapeutic regime is experimental and fraught with potential side effects, it nevertheless holds promise for future treatment of the disease. Enzyme replacement therapy with recombinant enzymes for Gaucher's disease is now available, which is very effective but extremely expensive.

Niemann-Pick Disease

In 1914, German pediatrician Albert Niemann described a young child with brain and nervous system impairment. Later, in the 1920s, Luddwick Pick studied tissues after the death of such children and provided evidence of a new disorder, distinct from those storage disorders previously described. It is the least common of the genetic disturbances of lipid metabolism. It is inherited as an autosomal recessive trait. Niemann-Pick disease results from lysosomal accumulation of sphingomyelin resulting from inherited deficiency of sphingomyelinase.

Niemann-Pick disease can be classified as: **Type A** is the acute infantile; **Type B** is a less common, chronic, non-neurological form, while **Type C** is a biochemically (intracellular cholesterol esterification) and genetically distinct form of the disease. The mutant gene is localized to **18q11–12.**

Niemann-Pick disease type A is a severe infantile form with extensive neurologic involvement, marked visceral accumulation of sphingomyelin and progressive wasting resulting in early death within first three years of life. Niemann-Pick disease type B has a more variable course, with the first symptoms occurring in early childhood and many persons surviving into adulthood. In this type of patients, organomegaly is seen commonly but no nervous system involvement is noticed. Like Gaucher's disease, it is more common in Ashkenazi Jews and has pathognomonic cell, the Niemann-Pick cell. Niemann-Pick cells are foamy, lipid-laden cells distributed throughout the reticuloendothelial system. Unlike Gaucher's cells, they are positive for cholesterol and only weakly positive for alkaline phosphatase. They are most easily distinguished from Gaucher's cells by phase or electron microscopy. Epstein and coworkers have developed a procedure for detecting Niemann-Pick disease *in utero* by measuring sphingomyelinase activity in cultured amniotic cells. The clinical findings in this disease have been discussed by Gildenhorn and Amromin as well as by Knudson.

Histologic Features. Histologically, the affected cells become extremely enlarged secondary to the distention of lysosomes due to the accumulation of sphingomyelin and cholesterol. The cells show foamy cytoplasm due to numerous vacuoles which stain for fat.

Treatment. Enzyme replacement therapy in Niemann-Pick disease is currently being explored. Current treatment is symptomatic and consists mainly of antibiotic therapy for infections resulting from pulmonary involvement. Organ transplantation, e.g. the liver, has been proposed. To date the prognosis is poor, and the vast majority of patients die of the disease.

Letterer-Siwe Disease

Letterer-Siwe disease is an acute, often fulminating histiocytic disorder which invariably occurs in infants, usually before the age of three years.

Clinical Features. The initial manifestation of this disease is often a skin rash involving the trunk, scalp, and extremities. This rash may be erythematous, purpuric, or ecchymotic, sometimes with ulceration. The patients will also commonly have a persistent, low-grade spiking fever with malaise and irritability. Splenomegaly, hepatomegaly, and lymphadenopathy are early manifestations as well as nodular or diffuse involvement of visceral organs, particularly the lungs and gastrointestinal tract, later in the course of the disease. Diffuse involvement of the skeletal system also usually occurs later in the disease.

Oral Manifestations. The oral lesions may consist of ulcerative lesions, although gingival hyperplasia has also been described. Furthermore, diffuse destruction of bone of the maxilla and mandible may occur, causing loosening and premature loss of teeth. In some cases the disease has such a rapid course that significant oral involvement does not occur.

Histologic Features. The microscopic appearance of the lesions is very similar to that seen in Hand-Schüller-Christian disease where there is basically a histiocytic proliferation with or without eosinophils. However, these histiocytes do not contain significant amounts of cholesterol so that foam cells are not a feature of the disease, nor is fibrosis encountered. In some cases cytologically altered histiocytes are present in sufficient numbers to resemble a histiocytic lymphoma.

Laboratory Features. Progressive anemia is often present as well as leukopenia or thrombocytopenia.

Treatment and Prognosis. The prognosis in Letterer-Siwe disease is extremely poor. In the majority of cases, the course of the disease is rapid and terminates fatally in a short time. However, some patients show response to chemotherapy and are sometimes maintained in remission for years.

AVITAMINOSES

A vitamin is usually defined as an organic substance not made by the body, which is soluble in either fat or water and is ordinarily needed in only minute quantities to act as a cofactor in a variety of metabolic reactions. The word 'vitamin' has reference to the fact that the substance it designates is essential to life. The term, therefore, is functional and not chemically descriptive.

It is useful to consider the vitamins together, for they share certain features. They are present and active in amounts that are minute in contrast to the considerable quantities of the ordinary nutrients. They differ from other nutrients in that many of them are inactivated by heat and oxidation. Some of the vitamins occur in natural sources in a physiologically inactive form. These are called provitamins. They become active only after conversion within the animal. For example, vitamin A exists in plants as carotene, which is activated in the liver. As will be seen with vitamin D, and to a certain extent, with vitamin A, recent evidence points to a hormonal rather than a coenzyme role for certain vitamins. Because of historical convention and the lack of conclusive evidence that vitamins have a hormonal activity, these compounds will be discussed with the remainder of the vitamins.

Although the avitaminoses are as assorted group of diseases, and as unrelated to each other as the chemical constituents of the various vitamins, they too share enough common characteristics to justify their inclusion as a single group of diseases. The avitaminoses are due to the **absence** of minute amounts of biologically important materials rather than to the **presence** of minute amounts of biologically active materials (infectious agents). They cause disease not in a positive but in a negative way. The deficiency is the disease. Another characteristic of the deficiency diseases is that they may be present in varying degrees. There may be latent infection, but not a partial infection. A malignant growth is present or it may not. Deficiency diseases; however, may occur in partial form, i.e. they may occur to a mild degree and in their incipient forms the lesions and symptoms might be difficult to recognize. They may also occur in more severe forms, but they are seldom so serious as to be the immediate cause of death.

FAT-SOLUBLE VITAMINS

Vitamin A

The therapeutic usefulness of vitamin A has been known since the time of the Egyptian pharaohs. The Ebers papyrus (circa 1500 BC) recommends liver as a cure for night blindness. However, the isolation, synthesis, and recognition of the metabolic functions of vitamin A were not discovered until the 20th century. The classic works of McCollum and Davis, Drummond, and Steenbock and coworkers provided a foundation upon which more recent vitamin A research is based. Moore published an excellent treatise on vitamin A in 1957. There are over 600 carotenoids in nature and approximately 50 of these can be metabolized to vitamin A. β-carotene is the most prevalent carotenoid in the diet that has provitamin A activity. Approximately 80% of preformed vitamin A is absorbed from the diet and the absorption partially depends on adequate bile concentration.

The best known and most intensively studied role for vitamin A is that in vision. George Wald was awarded the Nobel Prize for medicine in 1967 for his discovery of the role of vitamin A in vision, and he has published an excellent review of the subject. Briefly, rhodopsin (visual purple) is formed by the union of vitamin A (11-*cis* retinal) and a protein, opsin, in the rods of the retina. When stimulated by light, the 11-*cis* retinal is isomerized to the all-*trans* retinal form and split form the protein moiety. The electrical potential generated during this process is transmitted to the brain via the optic nerve, resulting in visual sensation. In the dark, the all-*trans* form is enzymatically isomerized back to the 11-*cis* form and subsequently binds to opsin, thus completing the cycle. A continuous supply of vitamin A is therefore necessary for rod (low-light) vision, and the first manifestation of vitamin A deficiency is an impaired, low-light vision, i.e. night blindness.

Current research indicates that in addition to its role in vision and lysosomal stability, vitamin A may have a hormonal function in the regulation of epithelial differentiation. Intracellular receptors have been identified and may transport vitamin A molecules to the cell nucleus, where they interact with DNA to direct cellular differentiation.

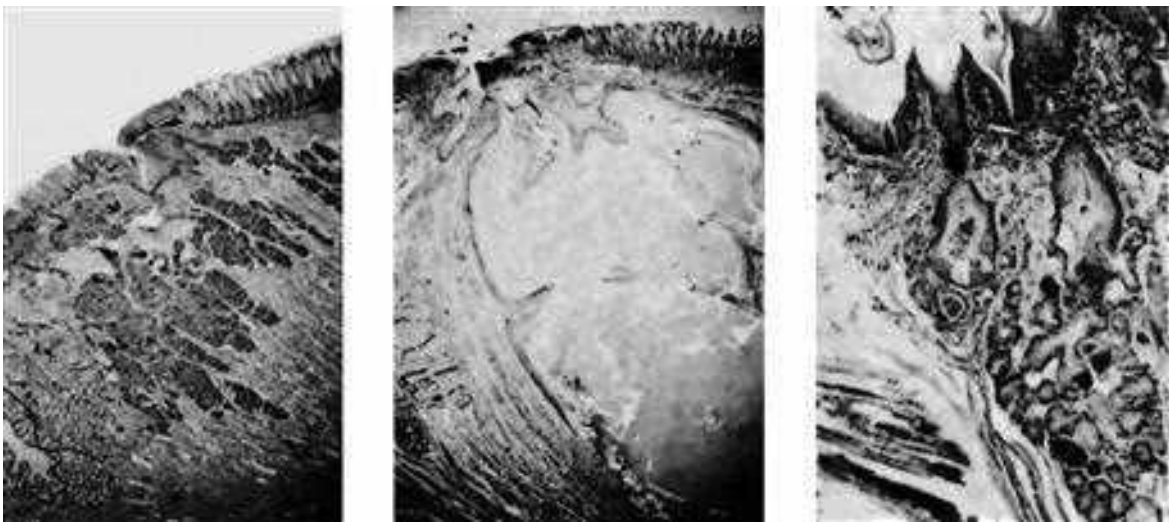
The classic work of Wolbach and Howe on the dental changes in vitamin A deficiency of the rat and guinea pig was confirmed and elaborated by Schour and his coworkers. Excellent reviews have been written by Frandsen and Jolly. Most of our knowledge of the dental effects of vitamin A deficiency is based on findings in the continuously developing and erupting incisor tooth of the rat.

It is well established that vitamin A is concerned primarily with the process of differentiation of epithelial cells. In vitamin A deficiency the epithelial cells fail to differentiate. This means that the cells in the basal layer lose their specificity and tend to form a stratified squamous epithelium with keratin production, independent of the type of cell previously formed by the basal cells. Thus one of the basic changes is a keratinizing metaplasia of epithelial cells. This occurs throughout the body, including the mucous membranes of the trachea, conjunctiva, and ureter, and the salivary and other glands (Fig. 15-7).

In the developing tooth of the rat that is deficient in vitamin A, the odontogenic epithelium fails to undergo normal histodifferentiation and morphodifferentiation, and the result is an increased rate of cell proliferation. Therefore, epithelial invasion of pulpal tissue is characteristic in vitamin A deficiency.

In young rats whose mothers are maintained on a diet deficient in vitamin A for five months preceding their birth, changes are more severe, resulting in a distortion of the shape of both the incisors and the molars. Since the enamel forming cells are disturbed, enamel matrix is arrested and/or poorly defined so that calcification is disturbed and enamel hypoplasia results. The dentin, too, is atypical in structure, lacking the normal tubular arrangement and containing cellular and vascular inclusions. Harris and Navia reported an increase in caries susceptibility of the rat molars of pups nursed by vitamin A-deficient dams, indicating a pre-eruptive role for vitamin A in tooth development. Post-eruptive vitamin A deficiency has been reported to result in higher caries scores. However, Salley and coworkers posited that this increase in caries may be due to changes in salivary gland function rather than to dental changes *per se*.

The teeth of animals on a vitamin A deficient diet contain less total ash than the teeth of normal animals. Eruption rate is retarded, and in prolonged deficiencies eruption ceases completely. The alveolar bone is retarded in its rate of formation. The gingival epithelium becomes hyperplastic and in prolonged deficiencies shows keratinization. This



A B C

Figure 15-7. Vitamin A deficiency.
Photomicrographs of the tongue of a normal rat **(A)** and of vitamin A-deficient rat **(B, C)**. There is squamous metaplasia in the mucous glands of the tongue and a large cyst filled with keratinaceous material (B).

tissue is easily invaded by bacteria that may cause periodontal disease and microabscess formation. The major and minor salivary glands undergo the typical keratinizing metaplasia. This is characteristic, of course, of all the epithelial cells in vitamin A deficiency. Most of the changes described are reversible with the feeding of vitamin A to deficient animals.

Requirements. The recommended daily dietary allowance for vitamin A ranges from 420 mcg to 800–1000 mcg of retinol equivalents (RE) for adolescent and adult females and males (1 RE = 1 mcg retinal or 6 mcg β-carotene). Pregnant and lactating females should increase their daily intake by 200 and 400 mcg RE, respectively.

Clinical Features of Vitamin A Deficiency. If the deficiency is mild, the manifestations in man are night blindness, xerophthalmia, and keratomalacia. Hyperkeratotic changes in the oral epithelium of adults have also been noted. Follicular keratotic changes have been described in naturally occurring vitamin A deficiency by Frazier and Hu and by Sweet and K'ang. Hume and Krebs, and Steffens and coworkers studied controlled vitamin A deficiency in humans and were able to produce cutaneous manifestations in only one patient.

As it progresses, keratinizing metaplasia appears in the trachea and bronchi, kidney, pelvis, conjunctiva, cornea, salivary glands, and genitourinary tract. Documented autopsy studies have been published by Wilson and DuBois and by Blackfan and Wolbach. If vitamin A deficiency were to cause changes in the human tooth bud, the deficiency state would have to occur before the sixth year of life, since by that time the crowns of all the teeth except the third molars are completely formed. The only cases of changes in human tooth buds attributable to vitamin A deficiency are those described by Boyle and by Dinnerman. Their findings were similar to those described in the rat incisor tooth in vitamin A deficiency. An excellent symposium on vitamin A deficiency and its clinical implications may be found in the Federation Proceedings for 1958.

Measurement of serum retinol (normal range: 30–65 mg/dl), tests of dark adaptation, impression cytology of conjunctiva, and measurement of body storage pools either by liver biopsy or by isotopic dilution are the various investigations for vitamin A deficiency.

Hypervitaminosis A

Cases of hypervitaminosis A in children are reported with increasing frequency. Gradual loss of hair and dryness of skin, lips, and oral mucosa are the common findings. If it persists, pigmentation, erythema, follicular keratosis, and purpura develop. The syndrome in children is characterized by anorexia, low-grade fever, hepatomegaly, sparse hair, and increased vitamin A serum levels. Radiographs of the long bones show fragmentation of the distal fibular epiphyses and pronounced periosteal thickening. Furman has reported a case of adult hypervitaminosis A.

Vitamin D

Vitamin D (1,25-dihydroxycholecalciferol) is one of a number of compounds that are grouped together as the hydroxylated cholecalciferols. Vitamin D is commonly referred to as the antirachitic vitamin, although a variety of biochemical analogs have similar activity, e.g. vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Mellanby demonstrated in 1919 that rickets could be produced experimentally and prevented by cod liver oil administration. Shortly thereafter, McCollum and coworkers distinguished the antirachitic factor from the previously discovered vitamin A in cod liver oil. Finally Steenbock reported in 1924 that antirachitic activity could be produced in food and animals by exposing them to ultraviolet radiation.

The metabolism and action of vitamin D have been widely described and will not be repeated in detail here. A schematic representation is provided in Figure 15-8. An excellent review of this subject has been published by Haussler and McCain.

Vitamin D has always been classified as a vitamin; however, it is probably best thought of as a hormone. Unlike a true vitamin, the hydroxylated cholecalciferols are not essential nutrients. Vitamin D_3 is formed from 7-dehydrocholesterol, which is an intermediate compound in the synthesis of cholesterol. 7-Dehydrocholesterol is ultimately formed from acetyl-CoA, which is never in short supply. The hydroxylated cholecalciferols have the same basic biochemical structure as the steroid hormones, and they control calcium ion concentration in a manner similar to sodium and potassium ion concentration regulation by the mineralocorticoids. Also, vitamin D is not required in many cell cultures. Finally, vitamin D exerts its

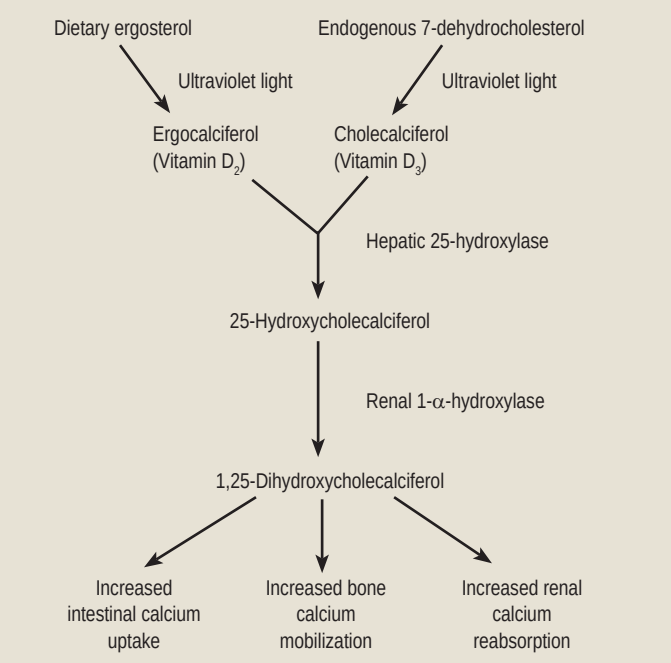


Figure 15-8. Schematic representation of the metabolism and action of vitamin D.

major influence by combining with nonhistone proteins in the nuclei of intestinal epithelial cells. This combination, in turn, exposes a portion of the genetic material for transcription of a specific protein, calcium-binding protein.

Relationship to Calcium and Phosphorus Homeostasis. A discussion of vitamin D is incomplete without mentioning its relationship to calcium and phosphorus homeostasis. In its role as an activator of calcium-binding protein, vitamin D has protean manifestations in parathyroid function, which subsequently affect calcium and phosphorus levels in the body. Hypervitaminosis D, as seen in overzealous food faddists, results in hypercalcemia with irreversible renal and vascular damage. Hypovitaminosis D, although now uncommon because of dietary fortification, can and does result in secondary hyperparathyroidism. Parathyroid hormone levels are elevated, and serum calcium levels are maintained at the expense of bone calcium. Serum phosphate levels are decreased as a result of the effect of parathyroid hormone on renal excretion of phosphate. Serum alkaline phosphatase levels are increased due to the bones' attempt at reformation. Dietary calcium forms insoluble calcium phosphates in the intestines because of its increased concentration.

Requirements. The recommended daily dietary allowance of vitamin D from infancy through puberty is 10 mcg of cholecalciferol (400 IU of vitamin D). Rickets can be prevented and growth will proceed at a normal rate with significantly less vitamin D (2–5 mcg of cholecalciferol), provided adequate amounts of calcium and phosphorus are present in the diet. Calcium uptake will be reduced slightly (25–30% compared with 35–40%) with decreased vitamin D intake. The recommended daily dietary intake tapers off to 7.5 mcg in young adulthood and should be maintained at 5 mcg after the age of 25. Pregnant and lactating females should increase their daily intake by 5 mcg.

Vitamin D-deficient Rickets

In common parlance, rickets refers to any disorder in the vitamin D-calcium-phosphorus axis which results in hypomineralized bone matrix, i.e. a failure of endochondral calcification. It should be realized that such a defect may result from a number of etiologies; thus there are a variety of forms of 'rickets'. A comprehensive review of rickets has been published by Pitt and Haussler.

Historically, vitamin D-deficient rickets developed in urban areas that were deprived of adequate sunlight. When air pollution filters out the ultraviolet portion of the spectrum, cholecalciferol formation is blocked. Infants rapidly develop the characteristic bony deformities. Identical lesions are seen in sun-rich areas where the diet is high in phytate, which binds the available dietary calcium. Social customs, e.g. the use of the *purdah,* may also result in rickets. The age of onset of the deficiency is important in the eventual morbidity, with premature infants being at highest risk. Although the incidence of rickets in Western societies has been drastically decreased because of food fortification with irradiated ergosterol, e.g. ergocalciferol in milk, Richards and coworkers have reported an incidence of radiographic changes consistent with rickets in 9% of young children in Glasgow, Scotland.

Clinical Features. Rat is the laboratory animal commonly used for the experimental investigation of rickets. The effects of rickets are reflected only in the bones and teeth of the afflicted animal. The changes in the bones are found in the epiphyseal plate, the metaphysis, and the shaft. Since the degree of change encountered depends on the rate of growth of the bones at the time of the deficiency, young animals are more seriously affected than older animals.

In young rats placed on rachitogenic diets, the first change seen is the cessation of calcification of their epiphyseal disks. Since the intercellular ground substance does not become calcified, the cartilage cells are not denied nutrition. Therefore, they do not die, and their continued growth and multiplication lead to an increase in the width of the disk. The disk thickens irregularly because some focal areas usually calcify. The osteoblasts continue to lay down osteoid around the bone and cartilage spicules in the metaphysis, as well as beneath the periosteum in the region of the metaphysis and other areas of the shaft. The changes in the ribs and long bones of children with rickets are essentially the same as those described for the rat. Since undermineralized bone is not as capable of supporting weight as normal bone, children with rickets show bowing of the legs.

Oral Manifestations. Mellanby was the first to report the effects of rickets on the teeth, which included developmental abnormalities of dentin and enamel, delayed eruption, and misalignment of the teeth in the jaws. Her later work showed that affected teeth had a higher caries index than those of controls. In human rachitic teeth there is an abnormally wide predentin zone and much interglobular dentin. Although many reports are found in the literature linking rickets with enamel hypoplasia, infantile rickets does not always result in hypoplastic enamel. The eruption rate of the deciduous and permanent teeth; however, is retarded in rickets.

Osteomalacia
(Adult rickets)

Osteomalacia is the adult equivalent of juvenile (vitamin D-deficient) rickets. Unlike juvenile rickets, only the flat bones and the diaphyses of the long bones are affected. The disease is most commonly seen in postmenopausal females with a history of low dietary calcium intake and little exposure to ultraviolet light. This disorder is endemic in certain areas of India, Japan, and China. Malabsorption is also a commonly reported etiology.

Clinical Features. Essentially there is a remodeling of bone in the absence of adequate calcium, which results in a softening and distortion of the skeleton and an increased tendency towards fracture. Pelvic deformities are commonly seen in affected multiparous females.

Oral Manifestations. Taylor and Day have reported a 50% incidence of severe periodontitis in a series of 22 Indian

women with osteomalacia. These data are questionable in view of the prevalence of endemic periodontal disease in this population group.

Radiographic Features. Radiologically there are severe asymmetric deformities of all stress-bearing bones, e.g. the pelvis, spine, and long bones of the legs. Longitudinal hairline fractures are seen in the long bones.

Histologic Features. The histologic findings in osteomalacia, like those in rickets, are nonspecific. There is an attempt at bone remodeling with inadequate calcification of bone matrix. The cortical bone is thin and osteoid borders are found on the trabeculae.

Treatment and Prognosis. The treatment (and for that matter prevention) of osteomalacia consists of dietary enrichment of vitamin D, usually in the form of milk, and the certainty of adequate dietary calcium. Hormonal therapy and fluoride administration have also been reported to be useful in the treatment of the disease. If the osteomalacia is secondary to malabsorption, the daily dietary fat intake must be severely restricted. While the mortality associated with osteomalacia is negligible, the morbidity is prominent and related to the extent of the disease at the time of initial diagnosis. Complications may arise from long bone fractures and compression of the spinal vertebrae.

Vitamin D-resistant Rickets

(Familial hypophosphatemia, refractory rickets, phosphate diabetes)

A number of isolated renal tubular defects, associated with an inability to reabsorb certain metabolites such as water, phosphate, calcium, and potassium have been recognized. Some defects in reabsorption may lead to rickets or osteomalacia. Albright and coworkers first described a case of vitamin D-resistant rickets in 1937. Shortly thereafter, Christensen described a familial pattern of occurrence. Twenty years after its initial description, Winters and colleagues and Graham and coworkers proposed that the disorder was an X-linked dominant defect in renal phosphate metabolism. A large series of cases has been investigated by Stickler and associates.

The disease is now recognized as a specific disorder characterized by:

- Hypophosphatemia and hyperphosphaturia associated with decreased renal tubular reabsorption of inorganic phosphates.
- Familial occurrence, being inherited as an X-linked dominant trait.
- Rickets or osteomalacia which does not respond to the usual doses of vitamin D.
- Normocalcemia with high-normal parathyroid hormone levels.
- Diminished intestinal calcium and phosphate absorption.
- Decreased growth with short stature.
- Normal vitamin D metabolism.
- The absence of other related abnormalities.

This definition excludes conditions such as sporadic, nonfamilial vitamin D-resistant rickets and familial vitamin D-resistant rickets associated with normal or high serum concentration of inorganic phosphate.

Clinical Features. The mildest form of this disease is a simple hypophosphatemia without clinical manifestation other than a slight decrease in the height of the patient as compared with a normophosphatemic sibling. In hypophosphatemic adults the varying degrees of deformities due to rickets in childhood constitute more serious disturbances, such as bowing of the legs, shortening of stature, continuing osteomalacia, and the presence of pseudofractures.

In children affected with this form of resistant rickets, the disease is usually first recognized when the child begins to walk. The history or X-ray examination, however, might reveal abnormalities such as skull deformities; retardation of eruption of teeth and 'sitting' deformities of the legs. Such children have usually received prophylactic doses of vitamin D but have failed to respond. Permanent deformities and short stature are often present.

Among family members with hypophosphatemia, females show considerably less bone disease than males. Few patients have the muscular weakness and atony which are so prominent and frequent in vitamin D-deficient rickets.

Oral Manifestations. Vitamin D-resistant rickets has marked effects on the teeth and supporting structures. These have been discussed in detail by many workers including Marks and his associates, Archard and Witkop, Tracy and his associates, Vasilakis and coworkers, Ainley, and Cohen and Becker.

Characteristically, there is histologic evidence of widespread formation of globular, hypocalcified dentin, with clefts and tubular defects occurring in the region of the pulp horns. In addition, these pulp horns are elongated and extend high, often reaching nearly to the dentinoenamel junction. This may even be evident on the radiograph (Fig. 15-9). Because of these defects, there is commonly invasion of the pulp by microorganisms without demonstrable destruction of the tubular matrix. Following this, there is often periapical involvement of grossly normal-appearing deciduous or permanent teeth, followed by the development of multiple gingival fistulas. In addition to abnormal cementum, the lamina dura around the teeth is also reported to be frequently absent or poorly defined on the radiograph, and the alveolar bone pattern is often abnormal.

Histologic Features. Alterations are found primarily in the cartilage plate and shaft of the long bones and are characterized by a failure of bone salts to be deposited in the cartilage matrix between the rows of hypertrophic cells, so that these cells are not invaded and destroyed by capillaries. The histologic picture is characterized by a broad zone between the multiplying cartilage cells and the shaft, the so-called rachitic metaphysis. This is composed of tongues of cartilage which extend down toward the shaft and are separated from one another by collections of capillaries. This zone contains trabeculae made up of uncalcified cartilage matrix upon which osteoid has been

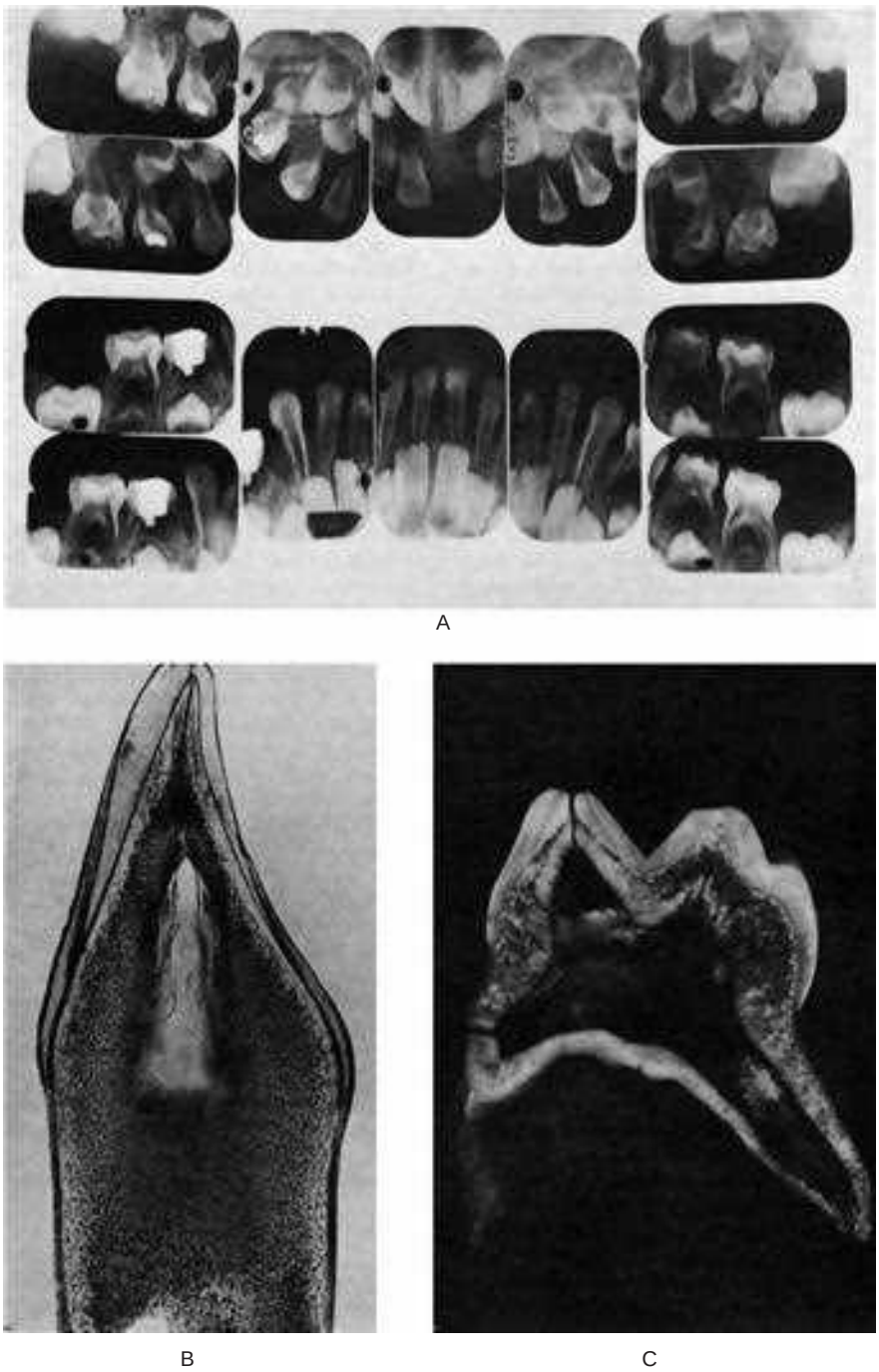


Figure 15-9. Vitamin D-resistant rickets in a boy six years of age.
The full mouth radiographs **(A)** show the wide root canals and pulp chambers. A ground section of an incisor tooth **(B)** shows the interglobular nature of the dentin. The deciduous molar **(C)** when split shows the relatively small quantity of dentin as well as the poor quality of the dentin. Note the connection between the pulp chamber and the occlusal surface of the tooth, a common finding in this disease, accounting for the frequent pulp infection and periapical involvement without the presence of a carious lesion *(Courtesy of Dr SS Arnim).*

deposited. Since osteoblastic activity is not affected, osteoid is found deposited on pre-existing bony trabeculae. The calcification is interfered with, so the osteoid does not calcify and is not remodeled.

Treatment and Prognosis. The treatment of vitamin D-resistant rickets is highly individualized. Massive doses of vitamin D frequently result in repair, but the risk of hypervitaminosis D in such cases is considerable. Success has been reported using 25-hydroxycholecalciferol in lower dosages than conventional vitamin D (10,000–25,000 IU per day of 25-hydroxycholecalciferol, as opposed to 50,000–100,000 IU per day of vitamin D). Healing of the rickets can be initiated by measures other than prescribing massive doses of vitamin D. Such methods include immobilization

and administration of large amounts of phosphate. Decreased dosages of vitamin D (15,000–50,000 IU per day) combined with supplemental oral phosphate have been used successfully.

Renal Rickets
(Renal osteodystrophy)

Painful, crippling bone disease is a common finding in patients with chronic renal disease. Renal rickets results from the inability of diseased kidneys to synthesize 1-α-hydroxylase and convert 25-hydroxycholecalciferol to the active form of vitamin D. Calcium absorption in the intestines is impaired, with a dramatic increase in fecal calcium excretion and negative calcium balance. Secondary hyperparathyroidism may lead to a superimposed osteitis fibrosis cystica.

Treatment and Prognosis. Renal osteodystrophy is refractory to physiologic doses of vitamin D. Kaye and Sagar have reported success in treating renal rickets with dihydrotachysterol, a vitamin D analog. Catto and coworkers have administered 1-α-hydroxycholecalciferol and reported good treatment success. The prognosis for the bone disease is guarded because of the inability to cure the underlying renal disease. Renal transplant patients function adequately after an initial post-transplantation hypercalcemia.

Hypophosphatasia
(Hypophosphatasemia)

Hypophosphatasia, a hereditary disease first recognized as an entity by Rathbun in 1948, is transmitted as a recessive autosomal characteristic. Since then many cases have been reported and several reviews of the disease presented. One such excellent review, that of Bruckner and his associates, stressed the dental findings in this condition as observed in a series of cases. Ritchie, Haupt and associates, Kjellmann and coworkers, Beumer and colleagues, Brittain and coworkers, and Witkop and Rao have discussed in detail the oral manifestations of hypophosphatasia.

The basic disorder is a deficiency of the enzyme alkaline phosphatase in serum or tissues and excretion of phosphoethanolamine in the urine. The severity of disease is not directly related to serum alkaline phosphatase levels. There is an interesting similarity of many aspects of this disease to the condition known as 'vitamin D-resistant rickets with familial hypophosphatemia'.

Clinical Features. On the basis of clinical manifestations and chronology of the appearance of bone disease, hypophosphatasia is divided into three clinical forms: infantile, childhood, and adult. The infantile form is manifested by severe rickets, hypercalcemia, bone abnormalities, and failure to thrive. Most of these cases are lethal. Hypophosphatasia of childhood is characterized by premature exfoliation of deciduous teeth, increased infection, growth retardation and rachitic-like deformities, including deformed extremities, costochondral junction enlargement (rachitic rosary), and failure of the calvarium to calcify. Pulmonary, gastrointestinal, and renal disorders are also present. The adult form includes spontaneous fractures, prior history of rickets and osseous radiolucencies.

Oral Manifestations. The earliest manifestation of the disease may be loosening and premature loss of deciduous teeth, chiefly the incisors. There are varying reports of gingivitis; however it does not appear to be a consistent feature of the disease.

Radiographic Features. The metaphyses of long bones have been described as showing 'spotty', 'streaky', or 'irregular ossification'. Dental radiographs generally reveal hypocalcification of teeth and the presence of large pulp chambers, as well as alveolar bone loss; however, these findings have not been consistently reported.

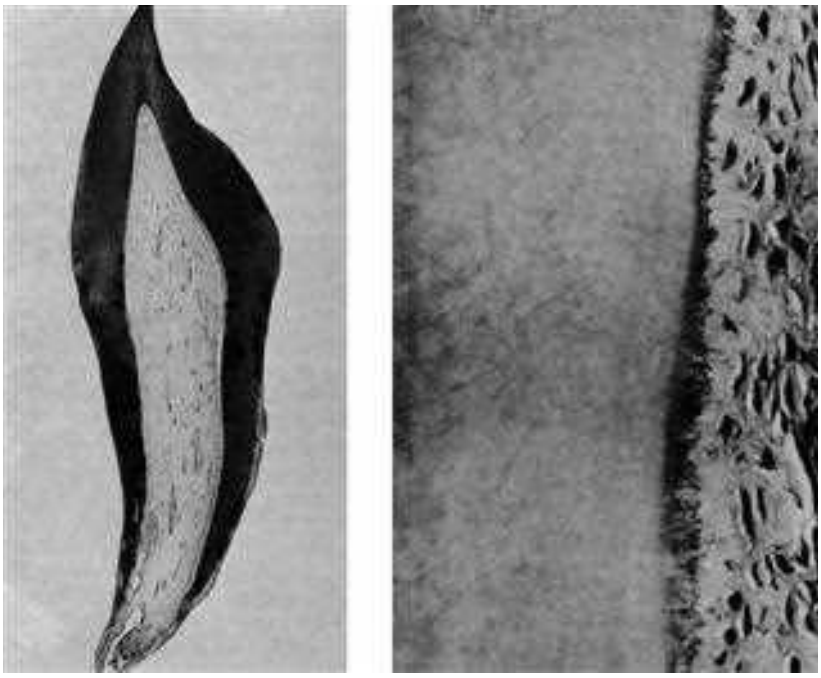
Histologic Features. The long bones characteristically exhibit an increased width of proliferating cartilage with widening of the hypertrophic cell zone, irregularity of cell columns, irregular penetration of the cartilage by marrow with persistence of numerous cartilage islands in the marrow, and formation of large amounts of osteoid which is inadequately calcified. These findings are indistinguishable from those in true rickets.

The teeth present a unique appearance characterized by the absence of cementum, presumably as a result of failure of cementogenesis, so that there is no sound functional attachment of the tooth to bone by periodontal ligament (Fig. 15-10). This lack of attachment is thought to account for the early spontaneous exfoliation of the deciduous teeth. Occasional foci of poorly formed cementum may be found on some teeth.

Treatment. Therapeutic measures are generally unsuccessful. Vitamin D in high doses has resulted in partial improvement in some cases, but this may lead to deposition of calcium in many tissues, including the kidney. Bongiovanni and coworkers have reported that administration of high oral doses of phosphate results in moderate improvement in bone calcification as judged radiologically.

Pseudohypophosphatasia

A disease resembling classic hypophosphatasia but with a normal serum alkaline phosphatase level has been reported by Scriver and Cameron. Patients afflicted by pseudohypophosphatasia exhibit osteopathy of the long bones and skull, premature loss of deciduous teeth, hypotonia, hypercalcemia, and phosphoethanolaminuria. Only the alkaline phosphatase level remains normal. This disease also appears to be hereditary. Méhes and coworkers have reported the appearance of hypophosphatasia and pseudohypophosphatasia in the same kindred. This suggests that the two diseases may represent variations of a basic metabolic effect.



A B

Figure 15-10. Hypophosphatasia.
A maxillary deciduous incisor of a patient with hypophosphatasia which was exfoliated at 15 months of age **(A)**. The tooth root showed only a poor attempt at cementogenesis indicated by the granular, basophilic material between the dentin on the left and the periodontal fibers on the right **(B)** *(Courtesy of Dr Robert J Bruckner).*

Vitamin E

Sixty years ago Evans and Bishop noted that a fat-soluble factor prevented fetal resorption in animals. This factor was named vitamin E and given the generic name of tocopherol, which means 'the alcohol which brings forth offspring'. Olcott and Emerson soon recognized the antioxidant properties of vitamin E. The main function of vitamin E is to prevent peroxidation of polyunsaturated fatty acids. Vitamin E consists of eight naturally occurring tocopherols of which alpha-tocopherol is the most active.

Vitamin E deficiency in experimental animals results in multisystem disorders, including decreased male fertility, impaired fetal-maternal vascular relationships, nutritional muscular dystrophy, and encephalomalacia, increased vascular disruption, and hemolysis. All of these disorders can be attributed in part to the increased peroxidation of unsaturated fatty acids in vitamin E-deficient animals. Irving has described a loss of pigment and atrophic, degenerative changes in the enamel organ of vitamin E-deficient rats.

Dietary vitamin E deficiency does not occur. It is seen only in severe and chronic diseases like celiac disease or after the resection of small intestine or in children with cystic fibrosis. Infants are born with low levels of vitamin E and are particularly susceptible to vitamin E deficiency, especially if they are fed diets high in polyunsaturated fatty acids. Hassan and coworkers have described this syndrome, which consists of edema, desquamating erythematous papular dermatitis, thrombocytosis, and anemia. Chronic steatorrhea, for example, as it occurs with cystic fibrosis, results in hypovitaminosis E and is manifested by muscular dystrophy-type symptoms, with elevated serum creatinine phosphokinase activity and creatinuria. This secondary vitamin E deficiency has been discussed by Nitowsky and coworkers.

Requirements. The recommended daily dietary allowance for vitamin E ranges from 3 mg of d-α-tocopherol for infants to 10 mg for adult males. Increased intake in pregnant and lactating women is suggested, especially in view of the low perinatal levels of vitamin E in the infant. The average intake of vitamin E in the United States is 15 mg per day; therefore, deficiency states are rare in the absence of underlying steatorrhea and malabsorption.

Vitamin E has gained a great deal of public and scientific attention in the past decade because of its role as a polyunsaturated fatty acid antioxidant. One of the prevailing theories of aging states that aging is, in part, a progressive accumulation of cellular damage resulting from free radicals. As an antioxidant, vitamin E may play a role in the prevention of free radical damage. This subject has been reviewed by Pryor. There are interesting but inconclusive animal studies to support this particular aging hypothesis. Unfortunately, publication of these results prompted megadose consumption of vitamin E by ill-advised members of the lay public. Based on the lack of toxic symptoms in nutrition faddists, vitamin E is thought by Farrel and Bieri to be one of the least toxic of the vitamins.

WATER-SOLUBLE VITAMINS

Vitamin K

In 1929, Dam noticed a peculiar hemorrhagic diathesis in chicks fed a fat-extracted diet. This clotting defect was not due to a deficiency of vitamin A, D, or E, which had previously been discovered. The new substance was named vitamin K or 'Koagulation vitamin'. Like other fat-soluble vitamins, vitamin K is absorbed from the gut and is transported to the liver via lymph chylomicrons.

Dam and his coworkers later provided evidence that vitamin K was intimately involved in both the extrinsic and intrinsic systems of coagulation, particularly with prothrombin (factor II) synthesis. Other investigators have since shown a role for vitamin K in the regulation of levels of factors VII, IX, and X (proconvertin, Christmas factor, and Stuart-Prower factor, respectively). Prior to Dam's discovery of vitamin K, Schofield had described a hemorrhagic disease in cattle, which had consumed spoiled clover. Campbell and coworkers later described this vitamin K antagonist and identified it as dicumarol. A coumarin analog, warfarin is commonly used as an anticoagulant in both humans and animals.

There are two natural forms vitamin K, namely vitamin K_1, also known as phylloquinone, derived from vegetable and animal sources and vitamin K_2 or menaquinone, synthesized by bacterial flora and found in hepatic tissue.

Vitamin K_3 or menadione is a chemically synthesized provitamin and is water soluble. This is converted into menaquinone by the liver. For this reason vitamin K is discussed under water-soluble vitamins.

Vitamin K is necessary for the post-transitional carboxylation of glutamic acid necessary for calcium binding to gamma carboxylated proteins such as prothrombin, factors VII, IX, X, protein C, protein S, and proteins found in the bone.

Vitamin K is found in green leafy vegetables, butter, margarine, liver, milk, and also in vegetable oils.

Primary vitamin K deficiency is rare in humans; however, newborns are particularly susceptible to vitamin K deficiency, and hypoprothrombinemia due to poor placental lipid transmission and a lack of vitamin K-synthesizing gastrointestinal flora may ensue. Secondary hypovitaminosis K may occur in adults with impaired fat absorption, which may accompany obstructive jaundice, sprue, ulcerative colitis, and surgical bowel resection. Iatrogenic deficiency of vitamin K may occur secondary to antibiotic sterilization of the gut.

The most common oral manifestation of vitamin K deficiency is gingival bleeding. Prothrombin levels below 35% will result in bleeding after toothbrushing; however, when prothrombin levels fall below 20%, spontaneous gingival hemorrhages will occur.

Requirements. The minimum daily dietary requirement of vitamin K is estimated to be between 1–2 mcg/kg, depending on the amount of gut bacterial production of the vitamin. The 'normal mixed diet' in the United States is estimated to contain 300–500 mcg of vitamin K, which is more than enough to meet minimum daily requirements.

The diagnosis of vitamin K deficiency is usually made on the basis of an elevated prothrombin time or reduced clotting factors. It is usually treated using a parenteral dose of 10 mg.

Menadione, the water-soluble form of vitamin K, has been reported to cause hemolytic anemia and hypobilirubinemia in infants when given parenterally in large doses. Toxicity from dietary vitamin K derivatives has not been reported.

Vitamin C

Vitamin C has been the object of intensive research for many years. Scurvy, which results from vitamin C deficiency, has been known since the time of the Ebers Papyrus in Egypt (1500 BC). The effect on history, through the occurrence of scurvy in military troops, is notable. British sailors in the 19th century were referred to as 'limeys' because of their consumption of citrus fruits to prevent scurvy while on long voyages. Hodges and coworkers have described the changes seen in experimental scurvy in man, and an excellent review has been written by Lloyd and Sinclair.

Svirbely and Szent-Gyorgyi isolated hexuronic acid (ascorbic acid) in 1928 and reported the results in 1932. A similar isolation procedure was reported by King and Waugh in 1932. Within two years the structure of vitamin C was determined and synthesized. Interestingly, most animals are capable of synthesizing their own vitamin C. Burns has postulated that humans, monkeys, and guinea pigs are incapable of endogenous vitamin C production owing to an inability to convert L-gulonolactone (a glucose metabolite) to L-ascorbic acid. Because of this inherent defect, guinea pigs are the animal model of choice in studying scurvy. It also aids in the promotion of nonhem iron absorption, carnitine biosynthesis, and the conversion of dopamine to norepinephrine. It is richly present in citrus fruits, green vegetables, tomatoes, and potatoes.

Vitamin C is necessary for a number of metabolic processes, including hydrogen ion transfers and maintenance of intracellular oxidation reduction potentials. It also acts as an antioxidant, facilitates iron uptake in the intestinal tract, and is involved in the formation of folinic acid (the active form of the folic acid). Standinger and associates and Goldberg have reported that ascorbic acid is critical in hydroxylation reactions which require reduced iron or copper. Its role in the hydroxylation of proline in collagen synthesis has been described by Peterkovsky and Udenfriend. Tryptophan, norepinephrine, and tyrosine metabolism all require vitamin C.

In general, the action of vitamin C appears to be to further the normal development of intercellular ground substances in bone, dentin and other connective tissues, since all signs of the deficiency of ascorbic acid are associated with disturbances in these tissues.

The dental changes in scorbutic guinea pigs are so consistent and characteristic that Hojer and Crampton devised biologic assay methods for vitamin C by grading the histologic changes in the mandibular incisor. The characteristic change in the teeth of scorbutic guinea pigs is the atrophy and disorganization of the odontoblasts, resulting early in the deficiency state

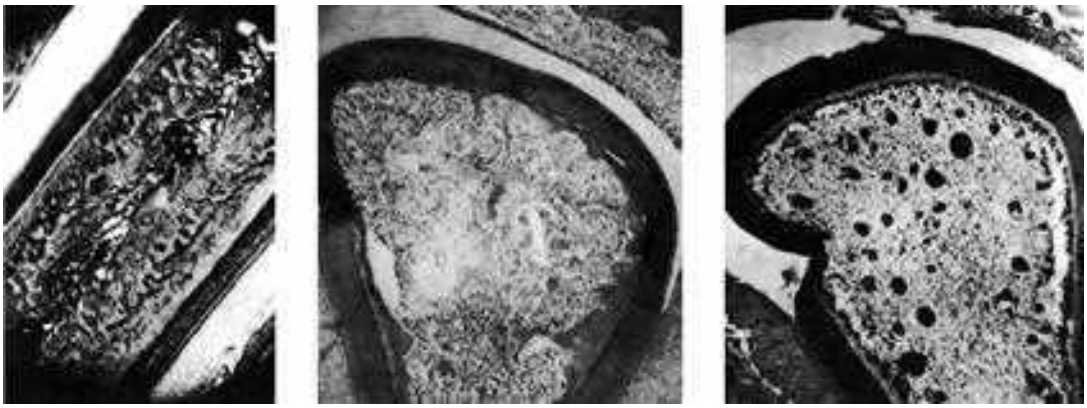


Figure 15-11. Vitamin C deficiency.
Photomicrographs of incisor teeth of guinea pigs with incomplete or early vitamin C deficiency showing the abnormal irregular dentin, **(A)** longitudinal and **(B)** cross-section. The odontoblasts eventually fail to lay down dentin **(C)**.

in the production of irregularly laid down dentin with few, irregularly arranged tubules. Eventually dentin formation ceases, and the predentin becomes hypercalcified, producing a heavy, basophilic staining line between dentin and pulp. The odontoblasts finally become indistinguishable from other pulpal cells (Fig. 15-11).

In scorbutic monkeys, hypertrophy of the gingiva covering in the entire crowns of the teeth was reported by Goldman. In some cases subperiosteal hemorrhages lifted the gingiva from the underlying bone. Focal areas of necrosis of the free margin of the gingiva also occurred. The alveolar bone showed atrophic changes, and the marrow spaces were replaced by fibroblasts growing in an edematous space.

Requirements. The recommended dietary intake for vitamin C ranges from 35 mg in infants to 60 mg in adults. Pregnant and lactating women should increase their daily intake by 20 mg and 40 mg, respectively.

Clinical Features of Scurvy. The oral effects of vitamin C deficiency in humans occur chiefly in the gingival and periodontal tissues. The interdental and marginal gingiva is bright red with a swollen, smooth, shiny surface. In fully developed scurvy the gingiva becomes boggy, ulcerates and bleeds. The color changes to a violaceous red. In infants the enlarged tissue may cover the clinical crowns of the teeth (Fig. 15-12). In almost all cases of acute or chronic scurvy the gingival ulcers show the typical organisms, and the patients have the typical foul breath of persons with fusospirochetal stomatitis. In the severe chronic cases of scurvy, hemorrhages into and swelling of the periodontal membranes occur, followed by loss of bone and loosening of the teeth, which eventually exfoliate.

Boyle studied the deciduous and permanent tooth germs of scorbutic infants and found only small cysts and minute hemorrhages in some specimens.

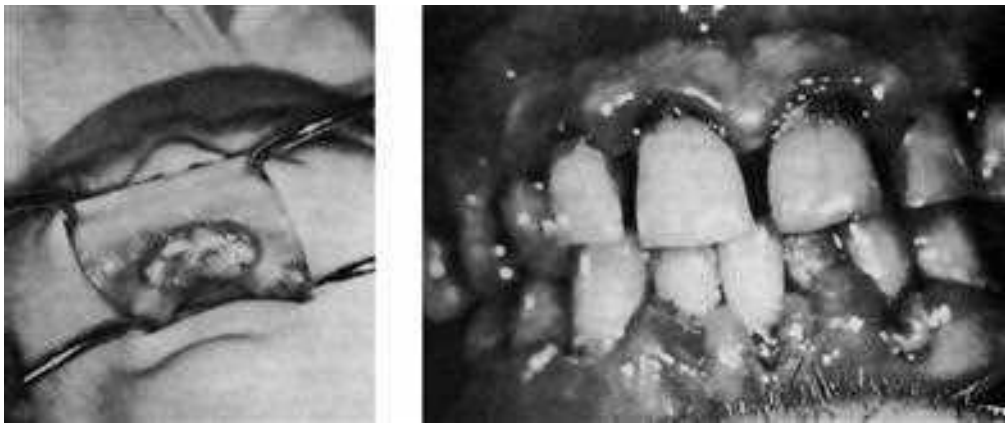


Figure 15-12. Vitamin C deficiency or scurvy in an infant (A) and an adult (B).
(A, Courtesy of Dr EV Zegarelli; B, Courtesy of Dr ER Costich).

Vitamin C is a threshold substance and is excreted primarily through the kidney. The degree of tissue saturation is the factor which determines the amount excreted. If intake has been normal, a slight increase in intake above normal will be excreted. If, on the other hand, the tissues are undersaturated through low intake or through excess metabolism of vitamin C, even high doses may be largely retained.

The role of ascorbic acid in collagen formation has been extensively studied from many aspects. It has been found that wounds produced in scorbutic guinea pigs fail to heal properly. Although there is fibroblastic proliferation in the wound area, the fibroblasts appear immature and fail to produce collagen. They do form a fluid-like material around themselves, representing an ineffectual attempt at collagen formation.

Histologic Features. The bone changes in scurvy were well reviewed by Follis in his book on the Pathology of Nutritional Disease. He pointed out that in scurvy the osteoblasts fail to form osteoid. The cartilage cells of the epiphyseal plate continue to proliferate in normal fashion, and salts are deposited in the matrix between the columns of cartilage cells. But the osteoblasts fail to lay down osteoid on the spicules of calcified cartilage matrix. In addition, the calcified matrix material is not destroyed, so that a wide zone of calcified but nonossified matrix, called the scorbutic lattice, develops in the metaphysis. The spicules are nonresistant to weight-bearing and motion stresses, and they are therefore liable to fracture. The changes which accompany the fractures lead to the characteristic lesions of the skeleton in scurvy.

As the 'lattice' increases in width, a more and more fragile zone develops, so that eventually complete fracture of the spicules occurs with separation and deformity of the cartilage-shaft junction. This fracturing of the calcified matrix material leads to the classic picture of scurvy, the so-called **Trümmer-feldzone** or region of complete disintegration. About the fractures and clefts there are pink-staining hyaline material, immature-looking fibroblasts and macrophages containing hemosiderin. The area beneath the **Trümmerfeldzone** is free of hematopoietic cells and is made up of connective tissue cells, the so-called Gerüstmark. The reason for the migration of marrow cells out of the area, leaving only connective tissue elements, is not clear. In addition, subperiosteal hemorrhages are frequent in scorbutic animals.

Symptoms of scurvy respond well within few days to few weeks to administration of vitamin C. Food rich in vitamin C may lower the incidence of certain cancers like gastric or esophageal by preventing the conversion of nitrites and secondary amines to nitrosamines.

Since vitamin C may be metabolized to oxalate, any higher doses of vitamin C supplementation could result in an increased prevalence of kidney stones.

Vitamin B Complex

Unlike the oral manifestations of vitamin A deficiency and the other vitamin deficiencies heretofore described, the oral signs of deficiencies of the B vitamins occur primarily in the oral soft tissues: the tongue, mucous membranes, gingiva, and lips. Since much of our knowledge of the avitaminoses B is derived from clinical observation, the mechanism of action, and the histologic details of the oral lesions associated with the various vitamin B deficiencies still remain to be elucidated.

At present the vitamin B group contains 11 well-characterized vitamins: thiamin, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, folic acid, vitamin B_{12}, inositol, para-aminobenzoic acid, and choline. Nearly every one of these vitamins forms part of a coenzyme essential for the metabolism of proteins, carbohydrates, or fats.

The B-complex vitamins are needed by all living cells, but with the exception of nicotinic acid and choline, animal tissues are incapable of synthesizing them. The B vitamins must therefore be absorbed from the intestinal tract either from ingested food or from the products of the intestinal flora, or from both.

Most B-complex vitamins occur in nature in bound form within the cells of vegetable or animal tissues. These cellular structures must therefore be broken down by the digestion for the liberation of the vitamin and its eventual absorption from the gut. With the possible exception of vitamin B_{12}, the vitamins of the B complex are not stored in any appreciable amount in the tissues of the body, so if the intake exceeds the requirement, the excess is excreted in the urine.

Although the functions of individual vitamins, whether fat- or water-soluble, vary greatly, vitamins tend to occur together in nature to some extent. It should be remembered, therefore, that though a lesion induced by the elimination of single vitamin from an experimental diet may occur in experimental animals and may even be induced in human subjects, lesions occurring naturally are probably associated with a deficiency of many of the essential nutrients. We are seeing only the most prominent clinical symptom and not the entire patient when we observe an angular cheilosis and assume that it is due to riboflavin deficiency. We must also remember that, though the most frequent cause of a nutritional deficiency is decreased intake of the essential nutrient, impaired absorption from the alimentary canal, failure of utilization by the tissues, inadequate storage, increased metabolism due to rapid growth, fever, pregnancy, and other factors all contribute to clinical deficiency states.

Pathologic conditions other than deficiency states may impose special demands for vitamins. Adequate nutrition is obviously important in the treatment of disease, but the diet must be governed by the nature of the disturbance. The indiscriminate use of the B vitamins is of no value in the treatment of general ill health.

Thiamin (vitamin B_1) is a colorless basic organic compound composed of a sulfated pyrimidine ring. It is readily absorbed from both the small and large intestines. It is phosphorylated mainly by the liver and to a lesser extent by the kidney. In tissues, thiamin is found as thiamin pyrophosphate (cocarboxylase), rarely as free thiamin. The main sources of thiamin are yeast, pork, legumes, whole grains, and nuts.

Thiamin pyrophosphate is required for carbohydrate and branched chain amino acid metabolism. In addition, it acts as coenzyme for transketolase reaction that mediates the conversion of hexose and pentose phosphates. It also plays a role in peripheral nerve conduction but the exact mechanism is unknown.

Clinical Features of Thiamin Deficiency. In man, thiamin deficiency leads to beriberi, which is generally insidious in onset, chronic in course and sudden death may occur. Beriberi may be of two types: wet and dry. In either form, patients may complain of pain and paresthesia. Wet beriberi manifests with cardiovascular symptoms due to impaired myocardial energy metabolism, dysautonomia, cardiomegaly, high-output cardiac failure, peripheral edema, and peripheral neuritis. In dry beriberi, same symptoms occur but for the edema.

Alcoholic patients with chronic thiamin deficiency are having CNS manifestations known as Wernicke's encephalopathy, which consists of horizontal nystagmus, ophthalmoplegia, cerebral ataxia, and mental impairment. Along with the abovementioned symptoms, if there is loss of memory and confabulatory psychosis, it is known as Wernicke-Korsakoff syndrome.

Requirements. The recommended daily dietary allowance for thiamin ranges from 0.3 mg for infants to 1.5 mg for young adults. Pregnant and lactating women should increase their daily intake by 0.4 mg and 0.5 mg, respectively.

There is no convincing evidence that thiamin exerts an influence on oral tissues. There are reported cases of oral manifestations of thiamin deficiency, but they are not supported by the experience of volunteer human subjects who lived on diets containing very low levels of thiamin for six months and showed no oral lesions.

Riboflavin

Riboflavin (vitamin B_2) is a fully dialyzable, intensely yellow water-soluble pigment which is decomposed by light. It fluoresces green under ultraviolet illumination, is readily absorbed from the intestinal tract and is phosphorylated in the walls of the intestine as well as in other tissues of the body.

Riboflavin is a constituent of two different groups of coenzymes, riboflavin 5′-phosphate (flavin mononucleotide or FMN) and flavin adenine dinucleotide (FAD). These coenzymes are essential to the oxidative enzyme systems utilizing the electron transport system. It is essential for carbohydrate, fat, and protein metabolism reflecting its role as respiratory coenzyme and electron donor.

The riboflavin deficiencies are almost always due to dietary deficiency. Its requirement is increased during pregnancy, lactation, and heavy exercise.

Requirements. The recommended daily dietary allowance for riboflavin ranges from 0.4 mg for infants to 1.7 mg for young adults. Pregnant and lactating women should increase their daily dietary intake by 0.3 mg and 0.5 mg, respectively.

Clinical Features of Riboflavin Deficiency. Riboflavin deficiency is particularly common among children who do not drink milk. In endemic areas, the incidence is greater during the spring and summer months than in other seasons.

A long period of vague, nondescript symptoms usually precedes the appearance of diagnostic lesions. The diagnostic lesions of ariboflavinosis are usually limited to the mouth and perioral regions. The oral manifestations of the disease are well recognized, since they have been experimentally produced by Sebrell and Butler in 18 healthy women placed on a riboflavin-deficient diet. Although the exact mechanism involved in the production of the oral lesion is not understood, the clinical stages have been clearly defined.

In the mild deficiency state there is a glossitis which begins with soreness of the tip and/or the lateral margins of the tongue (Fig. 15-13). The filiform papillae become atrophic, while the fungiform papillae remain normal or become engorged and mushroom shaped, giving the tongue surface a reddened, coarsely granular appearance. The lesions extend backward over the dorsum of the tongue. In severe cases the tongue may become glazed and smooth, owing to complete atrophy of all papillae. In many cases the tongue has a magenta color which can be easily distinguished from cyanosis.

Paleness of the lips, especially at the angles of the mouth, but not involving the moist areas of the buccal mucosa, is the earliest sign of the deficiency disease. The pallor, which usually continues for days, is followed by cheilosis, which is evidenced by maceration and fissuring at the angles of the mouth. The fissures may be single or multiple. Later the macerated lesions develop a dry yellow crust which can be removed without causing bleeding. The lips become unusually red and shiny because of a desquamation of the epithelium. As the disease progresses, the angular cheilosis spreads to the cheek. The fissures become deeper, bleed easily and are painful when secondarily infected with oral and/or skin microorganisms. Deep lesions leave scars on healing. The gingival tissues are not involved.

Figure 15-13. Riboflavin deficiency.
The atrophy of the filiform papillae gives the tip of the tongue a smooth, almost ulcerated appearance.

Riboflavin deficiency also affects the nasolabial folds and the alae nasi, which exhibit a scaly, greasy dermatitis. A fine scaly dermatitis may also occur on the hands, vulva, anus, and perineum. Ocular changes, consisting of corneal vascularization, photophobia, and a superficial and interstitial keratitis, have also been described. Considering that flavoproteins are widely distributed throughout the body, it is surprising that the lesions are so well localized.

In the differential diagnosis of ariboflavinosis, it is important to remember that bilateral angular cheilosis is a nonspecific lesion. Older people with greatly decreased vertical dimension, either through faulty dentures or through attrition of the natural dentition, frequently show the nonspecific angular cheilosis.

Niacin. In the living organism, ingested niacin is transformed into nicotinic acid amide, which is utilized to form coenzyme I (nicotinamide-adenine dinucleotide, or NAD) and coenzyme II (nicotinamide-adenine dinucleotide phosphate, or NADP). A deficiency of this vitamin leads to the classic symptoms of pellagra in human beings and to black tongue in dogs.

Pellagra as a widespread problem in the southeastern United States has largely disappeared. Spies and Butt formulated a working hypothesis of the pathogenesis of the disease as follows.

When the available nicotinic acid amide or compounds with similar functions are not adequate to supply the needs of the body for reasons of decreased supply, inadequate assimilation, increased demand, or increased loss, a disorder in respiratory enzyme systems occurs. As a result a state of generalized reduction in normal cellular respiration supervenes. When this biochemical lesion is severe enough, or has existed long enough, it is translated into functional disturbances in various organ systems of the body. Vasomotor instability in the skin, functional disorders of the alimentary canal, the nervous system, and the circulatory system may occur. It is probable that the most readily affected systems are those weakened by hereditary predisposition or trauma in the wear and tear of everyday life. This may explain the infinite variety of the clinical picture. Finally severe or persisting alterations in physiology lead to structural changes in various tissues which ultimately present the diagnostic lesions of pellagra.

A metabolic interrelationship between the amino acid tryptophan and nicotinic acid has been demonstrated in a number of mammalian species including man. Pyridoxal-5-phosphate is required for the conversion of tryptophan into nicotinic acid in the tissues. The accepted conversion ration (niacin equivalents) is 60 mg tryptophan to 1 mg. nicotinic acid. It is important in pentose, steroid, and fatty acid biosynthesis, glycolysis, protein metabolism and oxidation of lactate, pyruvate, and alcohol.

Clinical Features of Pellagra. The mucous membrane lesions affecting the tongue, oral cavity, and vagina are usually the earliest lesions diagnostic of the disease. Other lesions common in pellagra are the typical dermal lesions of bilaterally symmetric, sharply outlined, roughened, keratotic areas (Fig. 15-14). (The word 'pellagra' means rough skin). Mental symptoms and weight loss also occur.

In the prodromal stage of nicotinic acid deficiency, the patient may complain of loss of appetite and vague gastrointestinal symptoms. General weakness, lassitude, mental confusion, forgetfulness, and other ill-defined symptoms develop. The patient then usually complains of a burning sensation in the tongue, which becomes swollen and presses against the teeth, causing indentations. The tip and lateral margins of the tongue become red.

Figure 15-14. Pellagra.
(Courtesy of Dr Boynton H Booth).

In the acute stages of pellagra, the entire oral mucosa becomes fiery red and painful. The mouth feels as though it had been scalded. Salivation is profuse. The epithelium of the entire tongue desquamates. Tenderness, pain, redness, and ulcerations begin at the interdental gingival papillae and spread rapidly. Superimposed necrotizing ulcerative gingivostomatitis or Vincent's infection involving the gingiva, tongue, and oral mucosa is a common sequel.

Epithelial changes followed by the characteristic skin rash particularly in the areas exposed to sunlight especially in the neck region are called **Casal's necklace**. Vaginitis and esophagitis may also occur.

Requirements. The recommended daily dietary allowance for niacin ranges from 6 mg of niacin equivalents (NE) in infants to 10 mg NE in young adults. Pregnant and lactating women should increase their daily intakes by 2 mg and 5 mg NE, respectively.

Pantothenic Acid

The role of pantothenic acid in metabolic processes is not at all clear. It is a constituent of coenzyme A and is widely distributed in foods. Since no evidence of human pantothenic acid deficiency has been recorded, the human requirement for this vitamin is unknown. 5–10 mg per day is considered adequate for children and adults.

Pyridoxine

Pyridoxine (vitamin B_6) is actually a complex of three related substances: pyridoxine, pyridoxal, and pyridoxamine. Pyridoxine is the most active compound when ingested.

Pyridoxine plays an important role in protein metabolism, since pyridoxine-deficient animals placed on a high protein diet exhibit the characteristic lesions sooner and die more quickly than animals whose pyridoxine-deficient diets contain smaller amounts of protein. This vitamin has also been shown to be involved in tryptophan metabolism. If young dogs deficient in pyridoxine are fed tryptophan, both kynurenine and xanthurenine acid are excreted in the urine. If pyridoxine is fed to the animals, xanthurenic acid is not excreted, but kynurenine and kynurenic acid are found in the urine. Thus, pyridoxine apparently determines whether xanthurenic acid or kynurenic acid will be excreted after tryptophan feeding. The finding of xanthurenic acid in the urine has been suggested as a biologic test for vitamin B_6 deficiency.

Hawkins and Barsky reported that mental depression, mental confusion, albuminuria, and leukopenia occurred in normal people placed on a pyridoxine-deficient diet. The oral lesions of experimentally induced pyridoxine deficiency bear a striking resemblance to pellagrous stomatitis.

In some people with angular cheilosis, pyridoxine administration will effect a cure when riboflavin and nicotinic acid will not.

The minimum daily dietary allowance for pyridoxine is 2.0 mg for adults. Pregnant and lactating women should increase their daily intake by 2.5 mg.

Choline

Choline is an important constituent of lecithin, certain sphingomyelins, and acetylcholine. Little is known of choline requirements, since the need for choline is dependent on their sources of methyl groups in the diet, especially methionine.

Choline deficiency *per se* probably does not occur. It is possible; however, in cases in which general dietary protein is low to postulate a deficiency of choline and its precursor, methionine. Diets high in choline, methionine, and proteins are used in the treatment of fatty liver and cirrhosis, especially in chronic alcoholics; however, the results have not been promising.

No oral lesions have been ascribed to choline deficiency in man.

Biotin

It is unlikely that biotin deficiency ever develops spontaneously in man. In animals, biotin deficiency is characterized by a scaly, greasy dermatitis, and eventual alopecia. No dental changes are described in biotin-deficient animals.

Inositol

Although inositol has been shown to be necessary for growth in experimental animals, no histologic studies have been reported on animals depleted of inositol. Little is known of its role in animal or human nutrition.

Folic Acid

Various macrocytic anemias, sprue, addisonian (pernicious) anemia, and macrocytic anemia of infancy respond well to folic acid. Folic acid is essential for the growth of many animal species and is also essential in man. The primary function of folic acid is the transfer of one-carbon moieties in a number of metabolic reactions. Folic acid is also necessary for purine synthesis, the conversion of homocysteine to methionine, and the conversion of uridylate to thymidylate. The synthesis of DNA is impossible in the absence of folic acid.

Clinical Features of Folic Acid Deficiency. Folic acid deficiency in man is characterized by glossitis, diarrhea, and macrocytic anemia. The glossitis appears initially as a swelling and redness of the tip and lateral margins of the dorsum. The filiform papillae are the first to disappear, the fungiform papillae remain as prominent spots. In advanced cases, the fungiform papillae are lost and the tongue becomes slick, smooth, and either pallid or fiery red in color. These are the toxic symptoms following aminopterin therapy for leukemia. Aminopterin interferes with the conversion of folic acid to folinic acid. Administration of folic acid in aminopterin toxicity quickly alleviates the glossitis and reverses the symptoms of gastrointestinal disturbances.

The minimum daily dietary allowance for folic acid ranges from 30 mcg in infants to 400 mcg in adults. Pregnant women should double their daily intake, while nursing mothers should increase their intake by 25%.

Vitamin B_{12}. This vitamin includes a group of closely related compounds, the most common form being cyanocobalamin. It is the antipernicious anemia factor, and it has also been used in trigeminal neuralgia with some success. Massive doses, 1000 mcg daily, must be used for the treatment of trigeminal neuralgia.

The minimum daily dietary allowance for vitamin B_{12} ranged from 0.5 mcg in infants to 3.0 mcg in adults. Pregnant and lactating women should increase their intake by 30%.

DISTURBANCES IN HORMONE METABOLISM

No tissue in the mammalian body is exempt from some sort of hormonal influence, either in the course of its development and growth or in its functional activities. Yet the chemical structures of most hormonal substances are either unknown or only partially defined. Physiologic investigations of the hormones have been centered on their more specific actions, but it is becoming evident that the spheres of action of the hormones are extremely broad and reach far beyond the limits implied by the tissue of origin and its known interrelations with other organs and tissues. As Pincus points out, the expected action of ovarian estrogen as a promoter of female reproductive tract growth and of estrous behavior is accompanied by many activities outside of the reproductive sphere. Estrogens are hair-and bone-growth regulators; they are thymolytic, mitogenetic in the epidermis, enzyme-inhibitory in the adrenal cortex, phagocyte-stimulating, alkalosis-inducing, tumorigenic, antigoitrogenic, and antihyperglycemic. Similar multiplicities of action may be listed for most of the known hormones.

We can readily note that the hormones vary tremendously in chemical composition and in biologic activity. They are united only by their definition as internal secretions.

Over 50 biologically active substances circulate continuously in the blood of mammals as hormones; yet, with few exceptions, these substances are not essential for life. In the rat, for example, neither thyroidectomy, gonadectomy nor hypophysectomy is fatal. Yet, after such operations, the rates of certain processes are reduced to a minimum and cannot be speeded up if the need arises. Although animals with an inadequate hormone balance may live, their mental and physical vigor, their adaptability and drive, are gone or reduced. The mental dullness of the hypothyroid person is a good example of the influence of hormonal defect on the optimal rate of living.

Much experimental work has been done on the symptom complex production as a result of the removal of one or more endocrine glands. Studies after the injection of the active principle of one or more of the endocrine glands, either into an intact animal or into an animal from which an endocrine gland or glands had previously been removed, have added tremendously to the literature on the mode of action of the hormones. In addition, the treatment of human symptoms indicating a deficiency of a particular hormone with the hormone preparation has added much to our knowledge of endocrinology.

With the accelerating increase of literature on the physiology and biochemistry of the hormones, any attempt to review the field would be overwhelming for both the writer and the reader. We will, therefore, restrict our observations to the oral aspects of the disturbances in hormone metabolism.

PITUITARY GROUP OF HORMONES

The pituitary is considered the master gland of the body. Harvey Cushing's admirable words adequately describe its function. He stated, "Here in this well-concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence, vegetative, emotional, and reproductive".

The pituitary lies in the sella turcica of sphenoid bone beneath the middle cranial fossa. It is bounded anteriorly by the sphenoid sinus, posteriorly by the dorsum sellae, and superiorly by the diaphragma sellae. The gland is surrounded by a rich blood supply. The cavernous sinuses, which form the lateral boundary, drain pituitary hormones through the hypophyseal vein. The pituitary consists of an anterior lobe and a posterior lobe. The cells of the anterior pituitary are divided based on the staining reactions into agranular chromophobes and granular chromophils. The chromophils are further divided into acidophils and basophils.

The anterior lobe is derived from Rathke's pouch and is therefore epithelial in origin. The posterior lobe develops from the floor of the third ventricle and is composed of nervous tissue. The anterior lobe is glandular in structure and is the active part of the organ. To date, at least six hormones have been identified as coming from the anterior pituitary, namely, somatotropic, thyrotropic, adrenocorticotropic, two gonadotropic, and lactogenic hormones. In addition, the anterior lobe is said to have ketogenic, anti-insulin, diabetogenic, parathyrogenic, and pancreatotropic activity. Removal of the pituitary gland brings the entire internal secretory system into discordance because of a progressive atrophy of all the endocrine glands except, possibly, the parathyroids.

Although the physiologic activity of the posterior lobe has never been proved, extracts of this lobe have a remarkably high pharmacologic potency. Three types of activity, vasoconstrictive, oxytocic, and antidiuretic, have been reported.

Experiments in which the pituitary is removed or in which crude extracts of the gland are injected can give little information about which particular hormone is responsible for the effects observed. Precise information can be obtained only by studying the response of an animal to purified hormones. The evidence indicates that the growth hormone is mainly responsible for the effect of pituitary extracts on teeth, but that the thyrotropic hormone also plays a role. The entire spectrum of human growth hormone has been reviewed by Root.

A few workers have studied the relation of the pituitary gland to dental development, notably Schour and Van Dyke and Baume, Becks and associates. Working with rats, they found that after hypophysectomy there was a progressive retardation of eruption of the incisor tooth, which eventually ceased to erupt. The tooth attained only about two-thirds normal size and showed a distortion of form, especially at the basal end. When an extract of the anterior lobe of the pituitary was injected into the hypophysectomized rats, the eruption rate of the incisor tooth returned to normal.

Becks and his associates pointed out that the only constant pathognomonic sign of hypophysectomy in the rat was a thickening of the dentinal walls at the expense of the pulp chamber (Fig. 15-15). Baume and his associates reported that amelogenesis, and particularly the activities of the odontogenic epithelium, depended directly on the secretion of the anterior pituitary, whereas dentinogenesis and cementogenesis were able to proceed at a depressed rate without the pituitary hormones. They also pointed out some interesting interrelations. They suggested that the histologic changes in the enamel organ of the incisors of hypophysectomized rats were comparable to those of thyroidectomized animals of an equal postoperative interval. They also called attention to the similarity of the folding of the apical third of the incisor tooth of hypophysectomized animals to the changes in the teeth of magnesium-deficient animals, and they suggested that the changes in hypophysectomy may be related to salt and mineral metabolism, thus implicating the adrenal gland and its mineralocorticoids.

Collins and coworkers showed that the chronic administration of pure growth hormone to hypophysectomized animals allowed the incisors to erupt, but at only half the normal rate. The ameloblasts showed evidence of atrophy, but the dentin formed at a rate of 10μ instead of the normal 16μ per day. Baume and his associates injected thyroxin into hypophysectomized animals, either alone or with purified growth hormone. Their findings led them to the following explanation. The pituitary gland influences eruption not only with its thyrotropin, but also with its growth hormone. The effects of thyroxin on dental growth and development are quantitatively and qualitatively different from those of the

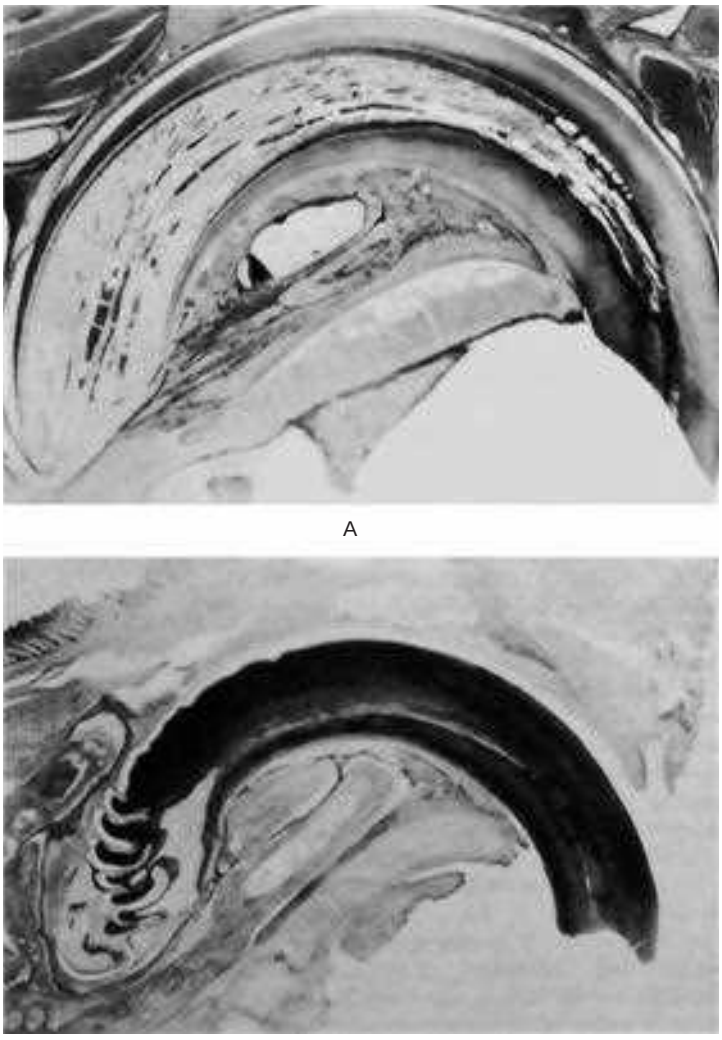


Figure 15-15. Hypophysectomy.
Photomicrographs of a maxillary incisor tooth of a normal rat **(A)** and of a hypophysectomized rat **(B)**. *(Courtesy of Dr Herman Becks).*

pituitary growth hormone. Quantitatively, thyroxin is the factor which stimulates eruptive movement and tooth size, but it has little influence on alveolar growth. Growth hormone, on the other hand, spurs dental as well as alveolar growth, but has little effect on eruption rate. It is also possible that other endocrine organs, by virtue of their effects on metabolic interrelations, also affect tooth development and eruption.

Hypopituitarism

In man, some indication of the role played by the pituitary in the development of the oral tissue can be gained from studies of hypopituitarism as well as hyperpituitarism. Hypopituitarism is caused by compression or atrophy of anterior pituitary cells or defect in the hypothalamic control of hormonal secretion. Before puberty, the hypofunctioning leads to dwarfism, which mainly manifests with features of growth hormone deficiency. After puberty, it affects other endocrine glands also. Some of the common causes of hypopituitarism, which occur after puberty, are pituitary adenoma, Simmonds' disease or hypophyseal cachexia, and Sheehan's syndrome (pituitary infarction in the postpartum woman). Hypofunction of posterior lobe leads to deficiency of vasopressin, resulting in diabetes insipidus.

Clinical Features. The typical evidences of hypopituitarism resulting in pituitary dwarfism are a diminutive but well-proportioned body, fine, silky, sparse hair on the head and other hairy regions, wrinkled atrophic skin, and often, hypogonadism. The deficiency may be congenital, or it may be due to a destructive disease of the pituitary, such as an infarct occurring before puberty. There is no distinctive pattern to the basal metabolism in this disease.

In pituitary dwarfs the eruption rate and the shedding time of the teeth are delayed, as is the growth of the body in general. The clinical crowns appear smaller than normal because, even though eruption does occur, it is not complete. The dental arch is smaller than normal and therefore cannot accommodate all the teeth, so that a malocclusion develops. The anatomic crowns of

the teeth in pituitary dwarfism are not noticeably smaller than normal, contrary to what might be expected in light of the animal experiments. There are no reports of a careful statistical study of crown size in dwarfism. The roots of the teeth are shorter than normal in dwarfism, and the supporting structures are retarded in growth. The osseous development of the maxilla is not as retarded as that of the mandible.

Hypopituitarism in the adult is usually due to an infarction of the pituitary called **Simmonds' diseases.** It is characterized by loss of weight and diminished sexual function. The basal metabolic rate is markedly lowered, and since Simmonds' disease represents a panhypopituitarism, there is a decrease in the activity of the many hormones of the pituitary gland and of those glands that are under pituitary regulation. In this disease, the skin shows atrophic alterations. Changes in the head include thin eyebrows, loss of eyelashes, sharp features, thin lips, and an immobile expression. There will be a decreased salivary flow due to hypofunctioning of salivary glands which leads to increased caries activity and periodontal disease.

Diagnosis. Radiograph and CT scan are used to diagnose structural abnormalities. Growth hormone assay may also be performed. Regular and early evaluation is required to correct skeletal and dental malocclusions. Fluoride treatment should be initiated and supplementary corticosteroids should be administered during minor oral surgical procedures.

Figure 15-16. Pituitary gigantism.
This patient was 7 feet 9 inches tall and weighed over 400 pounds *(Courtesy of Dr Rohini Sivapathasundharam, Ambattur, Chennai).*

Hyperpituitarism

An increase in the number of granules in the acidophilic cells or an adenoma of the anterior lobe of the pituitary is associated with gigantism or acromegaly. If the increase occurs before the epiphyses of the long bones are closed, gigantism results; if the increase occurs later in life, i.e. after epiphyseal closure, acromegaly develops. The clinical manifestations depend upon the type of cell involved. Somatotrophic adenoma or hyperplasia is also created with elevated levels of growth hormone. It exerts its effect by stimulating hepatocyte, chondrocytes, myoblasts, kidney, and GIT to secrete somatomedin-C, which is the primary promoter of growth.

Clinical Features. Gigantism is characterized by a general symmetric overgrowth of the body, some persons with this disturbance attaining a height of over 8 feet (Fig. 15-16). Later in life such people usually show genital underdevelopment and excessive perspiration, and they complain of headache, lassitude, fatigue, muscle and joint pains, and hot flashes. It is also characterized by the presence of broad, enlarged nose, thick and furrowed oily skin. Organomegaly and hypertension are common findings. Skeletal changes include frontal bossing and prognathic mandible. Increased glove, ring, and shoe size indicates the changes in the hands and feet. Patient may develop class III malocclusion with interdental spacing. Hypercementosis is a common finding in the intraoral radiographs.

The teeth in gigantism are proportional to the size of the jaws and the rest of the body. The roots may be longer than normal.

Acromegaly is a relatively rare disease in which there is hypersecretion by the anterior lobe, the influence being effected after ossification is complete. The following symptoms occur in acromegaly: temporal headaches, photophobia, and reduction in vision. The terminal phalanges of the hands and feet become large. The ribs also increase in size.

The lips become thick and Negroid. The tongue also becomes enlarged and shows indentations on the sides from pressure against the teeth. Microscopically, the surface epithelium and the connective tissues are hyperplastic.

The mandible, because of accelerated condylar growth, becomes large. The resulting prognathism may be extreme, giving the head a typical acromegalic appearance (Fig. 15-17). The teeth in the mandible are usually tipped to the buccal or labial side, owing to the enlargement of the tongue.

Investigations. Radiographic features suggestive of hyperpituitarism include enlarged sella turcica, enlarged paranasal sinuses, tufted terminal phalanges, and widened carpal joint spaces. Also, patients will have abnormal glucose tolerance hypertension and hyperphosphatemia.

THYROID HORMONE

The thyroid gland is situated in the middle of neck, and has two lobes connected by an isthmus. The functional unit of thyroid gland, the thyroid follicle secretes thyroxine and triiodothyronine.

Administration of the thyroid gland or its derivatives, including thyroxine, causes an increased uptake of oxygen

Figure 15-17. Acromegaly.
The patient shows the typical facies of the acromegalic *(Courtesy of Dr EV Zegarelli).*

by the body as a whole. The precise cellular and enzymatic mechanism for its effect is not known. It is probably not due to increased glycolysis. In addition to increasing oxygenation, the thyroid hormone influences a variety of other actions which affect almost every other function and tissue of the mammalian body. It therefore plays an essential role in differentiation, growth, maturation, water balance, electrolyte balance, protein storage, carbohydrate and lipid metabolism, and other physiologic functions.

Calcitonin, a hypoglycemic polypeptide secreted by the 'C' cells of the ultimobranchial elements of the thyroid gland, has gained increasing attention in recent years. It has been isolated, identified, sequenced, and more recently, synthesized. Calcitonin is responsive to hypercalcemia and acts to lower the plasma calcium level. Another of its actions is to inhibit resorption of bone mineral. Its use in human disease is still under active investigation. Excellent reviews of this hormone have been published by Foster, Hirsch and Munson and by Rasmussen and Pechet.

Hypothyroidism

A failure of thyrotropic function on the part of the pituitary gland or an atrophy or destruction of the thyroid gland *per se* leads to an inability of the thyroid to produce sufficient hormone to meet the requirements of the body. If this failure occurs in infancy, cretinism results. If it occurs in the child, juvenile myxedema occurs; if in the adult, myxedema results. Myxedema is not a rare disease. Hospital records show that 4–8 of every 10,000 admissions enter with myxedema.

Clinical Features. Congenital hypothyroidism, or cretinism, leads to mental defects, retarded somatic growth, generalized edema and other changes, depending on the severity of the deficiency of thyroid hormone. The dentofacial changes in cretinism are also related to the degree of thyroid deficiency. Usually, the base of the skull is shortened, leading to a retraction of the bridge of the nose with flaring. The face is wide and fails to develop in a longitudinal direction. The mandible is underdeveloped, and the maxilla is overdeveloped. The hair is sparse and brittle; the fingernails are brittle, and the sweat glands are atrophic.

The dental changes in juvenile hypothyroidism have been reviewed by Hinrichs, who also presented 36 cases. He indicated that the longer the time between the onset of the disease and the institution of treatment, the greater is the likelihood that the developing dentition will be affected. However, with a few exceptions, he found no striking morphologic changes in the teeth of the patients in his series.

Characteristically, the tongue is enlarged by edema fluid. It may protrude continuously, and such protrusion may lead to malocclusion. The eruption rate of the teeth is delayed, and the deciduous teeth are retained beyond the normal shedding time. Myxedema, the disease produced by thyroid deficiency in adults or children, is usually caused by atrophy of the thyroid gland of unknown etiology. The metabolic rate is lowered, although this finding should not be used as a diagnostic test for myxedema. Concentration of serum protein-bound iodine and radioactive iodine uptake or excretion studies are the diagnostic tests of value.

The myxedematous swelling is probably an extravascular, extracellular accumulation of water and protein in the tissues. The protein has a greater osmotic effect than the serum proteins, accounting for the increased blood protein concentration and decreased plasma volume which are found in myxedema.

The clinical orofacial findings in myxedematous patients are apparently limited to the soft tissues of the face and mouth. The lips, nose, eyelids, and suborbital tissues are edematous and swollen. The tongue is large and edematous, frequently interfering with speech.

Diagnosis. It is usually based on history, clinical and laboratory assessment, and hormonal assays.

Hyperthyroidism

There is apparently some debate as to whether hyperthyroidism should be considered a single disease entity or should be subdivided into several types. Boothby and Plummer described two fundamentally different types of hyperthyroidism:

- **Exophthalmic goiter,** characterized by diffuse hyperplasia of the thyroid and by eye signs.
- **Toxic adenoma,** in which hyperfunction originates in a benign tumor of the thyroid gland.

In either case, we are concerned with the manifestations of excess circulating thyroid hormone.

Most of the symptoms of hyperthyroidism are due to an increased metabolic activity of the tissues of the body. This is usually manifested as an increased basal metabolic rate. The serum protein-bound iodine concentration is elevated. The urinary iodine excretion is reduced because of the increased iodine uptake by the thyroid gland.

Clinical Features. Patient may exhibit tremor, tachycardia, sweating, weight loss, nervousness, muscle weakness, heat intolerance, and exopthalmic goiter.

Alveolar atrophy occurs in advanced cases. In children, shedding of the deciduous teeth occurs earlier than normal, and eruption of the permanent teeth is greatly accelerated.

Patients suffering from hyperthyroidism usually present a facial expression of surprise or excitement, with wide-eyed staring. Such patients are nervous and highly emotional; they have increased sensitivity to epinephrine and are usually hypertensive. Thoma warns that they make very poor dental patients.

Diagnosis. Thyroid function tests are useful to determine hyperthyroidism. Other tests include, radioactive iodine uptake, free thyroid assay, free thyroxine index, and total serum thyroxine estimation.

GONADAL HORMONES

Little is known of the relation of disturbances of metabolism of the sex hormones to oral pathology. Some evidence suggests that certain imbalances of estrogenic hormones might be reflected in the oral mucosa. In some women, gingivitis occurs periodically with abnormal or difficult menstruation. During menopause, the oral epithelium is said to become thinner than normal. In some patients a burning sensation of the tongue occurs during or after the menopause, while in other patients a 'dry feeling' of the mouth is observed with or without an actual diminution of saliva.

Shafer and Muhler demonstrated a diminution in size and in number of granular tubules in the submaxillary glands of rats after either gonadectomy or the administering of estrogenic substances. Much further work is necessary to clarify the effects of the sex hormones on the oral and dental tissues.

PARATHYROID HORMONE

Parathyroid glands are four small glands which produce and release parathormone, that maintains plasma ionized calcium level. Ionized calcium is essential for bone and tooth development, neuromuscular excitability, membrane fluidity and integrity, cell communication, cell adhesion, and blood clotting.

Two well-defined clinical entities are associated with the parathyroid glands: hyperparathyroidism, which manifests its symptoms primarily in the bones and the kidneys, and hypoparathyroid tetany.

Primary Hyperparathyroidism
(Osteitis fibrosa cystica)

Primary hyperparathyroidism is a disease in which the parathyroid glands elaborate an excessive quantity of parathyroid hormones. This increased activity is usually due to an adenoma of one or more of the four parathyroid glands, to a hyperplasia of the parathyroid tissue, or rarely, to a functional carcinoma of the parathyroid. The role of the parathyroid tumor in primary hyperparathyroidism has been discussed by Lloyd.

The bone disturbances in hyperparathyroidism vary from vague to radiographically characteristic lesions and even gross clinical evidence of bone lesions. Hypercalcemia may be manifested by poor muscle tone and decreased neuromuscular excitability.

Clinical Features. Hyperparathyroidism is a relatively rare disease which is said to be three times as common in women as in men. It usually affects people of middle age, but it may occur in childhood or in later life. In contrast to these statistics, Silverman and his coworkers, who reviewed 42 consecutive dentulous patients with hyperparathyroidism, found no correlation between gender and age and any aspect of the disease. Pathologic fracture may be the first symptom of the disease, although bone pain and joint stiffness are frequently early symptoms. In Silverman's group the most common significant early clinical finding was urinary tract stone, which occurred in 33 of the 42 patients. Occasionally the first sign of the disease may be a giant cell tumor or a 'cyst' of the jaw. The effects of the disease on bone are of special interest to dentists. Almost all patients with hyperparathyroidism have skeletal lesions, some of which may occur in the skull or jaws. The loss of phosphorus and calcium in this disturbance results in a generalized osteoporosis with abortive attempts at bone repair and new bone formation. The new bone may be resorbed, and the resorption may lead eventually to pseudocyst formation, the extent of which depends on the duration and intensity of the disease. According to Schour and Massler, malocclusion caused by a sudden drifting with definite spacing of the teeth may be one of the first signs of the disease. An extensive review and discussion of this disease was published by Teng and Nathan.

Radiographic Features. The radiographic findings in this disease are of particular importance. The bones of affected persons show a general radiolucency as compared with those of normal people. Later, sharply defined round or oval radiolucent areas develop, which may be lobulated (Fig. 15-18). If such a lobulated lesion develops in the mandible, it must be carefully differentiated from ameloblastoma, which frequently has the same appearance.

Small cystic areas may be seen in the calvarium, and large and/or small sharply defined radiolucencies may be present in the maxilla and/or mandible (Fig. 15-19). These small cystic areas must be differentiated from the lesions of multiple

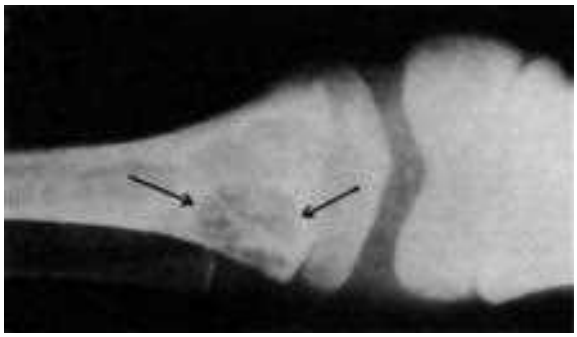


Figure 15-18. Primary hyperparathyroidism.
The circumscribed radiolucent defect in the proximal end of the tibia was accompanied by multiple lesions of other bones, including the jaws.

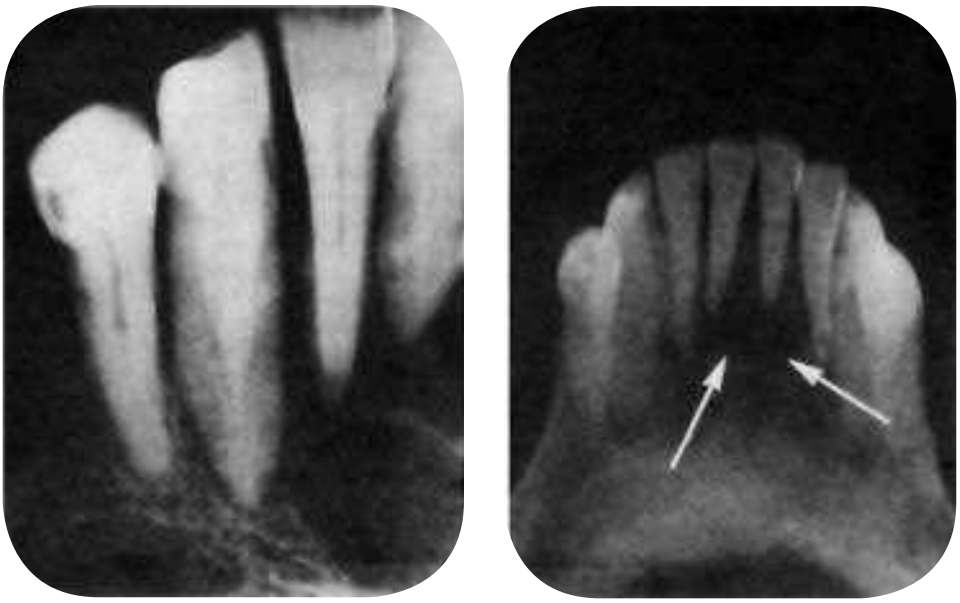


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Figure 15-19. Primary hyperparathyroidism.
The periapical radiolucencies could be mistaken for apical infection *(Courtesy of Dr Charles A Waldron).*

myeloma and eosinophilic granuloma. In the jaws, the bone radiograph in hyperparathyroidism has been described as having a 'ground-glass' appearance. The lamina dura around the teeth may be partially lost (Fig. 15-20). Twenty of Silverman's 42 patients had normal dental radiographs, and 17 showed intact lamina dura but abnormal appearing alveolar bone. None showed complete loss of lamina dura, and only five showed partial loss.

Histologic Features. Histologic findings in the bone lesions of hyperparathyroidism are not pathognomonic of the disease, but are of considerable assistance in making the diagnosis. The most characteristic change in the bone is an osteoclastic resorption of the trabeculae of the spongiosa and along the blood vessels in the Haversian system of the cortex. In the areas of resorption one also finds many plump osteoblasts lining islands of osteoid. Fibrosis, especially of the marrow spaces, is marked. The fibroblasts replace resorbed trabeculae, and in the fibrotic islands there is recent and old hemorrhage, and much hemosiderin in evidence. As the disease progresses, 'osteoclastomas' develop, characterized by masses of fibroblasts growing in a loose syncytium, among which are numerous capillaries and endothelium-lined blood spaces, red blood cells, many areas of yellow or brown hemosiderin, and innumerable multinucleated giant cells. These latter lesions are indistinguishable microscopically from the central giant cell granuloma of bone. Therefore, any patient who has a lesion diagnosed as a central giant cell lesion should be evaluated medically to rule out the possibility of hyperparathyroidism. This is most easily accomplished by a serum calcium level determination. If hyperparathyroidism is present, the serum calcium will be elevated above the normal level of 9–12 mg/dl.

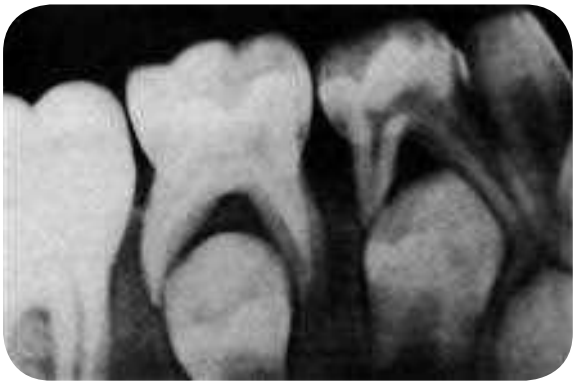


Figure 15-20. Hyperparathyroidism.
The radiograph shows absence of the lamina dura and 'ground-glass' appearance of the bone.

Diagnosis. It is confirmed by blood investigation which shows hypercalcemia, hypophosphatemia, and elevated serum parathormone level along with hypercalciuria, and hyperphosphaturia. The serum alkaline phosphates level is increased in osteolytic lesions.

Treatment and Prognosis. Excision of the parathyroid tumor will cure the patient. Careful examination of all parathyroid glands at the time of surgery should be carried out since multiple tumors occur with some frequency. Furthermore, since multiple tumors may develop over an extended period of time, patients who have had one parathyroid tumor should be followed for life.

Secondary hyperparathyroidism

Hyperparathyroidism can also occur secondary to other disorders, the most common being end-stage renal disease. Massry and coworkers reported an incidence of hyperparathyroidism in patients with chronic renal failure, ranging from 18% after one year on dialysis to 92% after more than two years. Giant cell lesions were not reported until 1963; however, by Fordham and Williams. Thirty patients undergoing chronic hemodialysis were studied by Spolnik and his associates, and 22 (73%) of these were found to have radiographic evidence of bone disease involving the jaws, including seven **brown tumors** (four in one patient) with loss of lamina dura also a prominent finding.

Hypoparathyroidism

Elimination of the parathyroid glands—by surgical removal, by destruction due to thrombosis of the blood vessels or disease of the glands, or in rare cases by congenital absence—leads to hypoparathyroidism. The disease is characterized metabolically by a decreased excretion of calcium. The blood chemistry shows a low concentration of serum calcium and a high concentration of serum phosphorus. If the calcium level of the serum falls to 7–8 mg/dl, there is increased neuromuscular excitability, which must be elicited, since it is not manifest. When the serum calcium level falls to 5–6 mg/dl, tetany and the characteristic carpopedal spasms are apparent.

Albright and Strock observed aplasia or hypoplasia of the teeth when hypoparathyroidism developed before the teeth were entirely formed. Similar changes are reported by Frensilli and his associates (Fig. 15-21).

Patients will have increased neuromuscular excitability, resulting in muscle spasms, stiffness, cramping, and tetany. Specific oral manifestations include altered tooth eruption pattern, short, blunted roots, enamel hypoplasia and dentin dysplasia, impacted teeth, and partial anodontia.

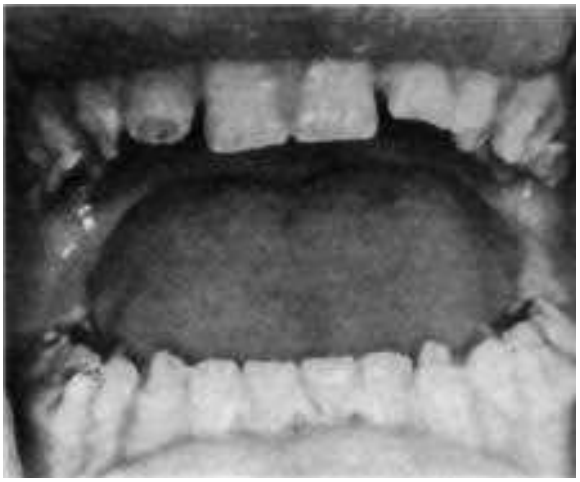


Figure 15-21. Hypoparathyroidism.
The patient, demonstrating enamel hypoplasia, suffered from hypoparathyroidism in infancy *(Courtesy of Dr EV Zegarelli)*.

Circumoral paresthesia is often one of the first symptoms of hypoparathyroidism.

Chronic candidosis, which is refractory to antifungal therapy such as nystatin, is sometimes seen in cases of idiopathic hypoparathyroidism. Such a case has been reported and discussed by Greenberg and his associates. The candidosis usually develops very early in life and precedes the hypocalcemia. The exact relationship between these two occurrences is not clear but it has been suggested that the candida infection may cause the hypoparathyroidism by inducing and 'immune response'. Enamel hypoplasia frequently accompanies this 'syndrome'.

Pseudohypoparathyroidism is a condition resembling idiopathic hypoparathyroidism in all respects, including the hypocalcemia and hyperphosphatemia, the drug-refractory candidosis and the enamel hypoplasia, except that parathyroid extract has little or no effect in correcting the hypocalcemia. This disease has been discussed by Croft and his coworkers.

ADRENAL HORMONES

Adrenal glands are small, paired endocrine glands, situated at the posterosuperior poles of the kidneys. They have an outer cortex and inner medulla, which secrete various hormones.

The adrenal cortex is divided into:

1. Zona glomerulosa, which secretes mineralocorticoids (e.g. aldosterone)
2. Zona fasciculata, which secretes glucocorticoids and cortisol
3. Zona reticularis, which secretes sex hormones.

A little over a 100 years ago (1855), Addison published his classic report on chronic adrenal cortical insufficiency, which is still called Addison's disease. Only in the last 25 years has it been recognized that the adrenal cortex, as such, plays the essential role in maintaining life. In that period; however, many substances have been isolated from the adrenal cortex, and intensive studies of the physiologic activity of adrenal cortical steroids are still being made. Much has been learned about the adrenal cortex, but much is still unknown. When the final story is written, we shall probably find that most of the metabolic interrelations in human physiology are mediated through the adrenals.

The action of the medullary portion of the adrenal gland is ascribed to epinephrine and norepinephrine. Norepinephrine may be a precursor of epinephrine, and for practical purposes one may consider an action of the hormones of the adrenal medulla to be that of epinephrine. Its effect on the various tissues of the body is similar to that of sympathetic nervous system stimulation. Increased amounts of epinephrine in the body lead to an elevated basal metabolism, mediated through its effect on the liver and on carbohydrate metabolism rather than on the thyroid gland.

The effects of epinephrine and norepinephrine on the circulatory system have been extensively studied. Epinephrine

in physiologic doses (1 mcg/kg) causes a constriction of the arterioles and capillaries of the skin, mucous membranes, and abdominal viscera, but a dilatation of the vessels of skeletal and heart muscle. The net result is a rise in blood pressure due to a sufficient vasoconstriction of the end capillaries and small arterioles of the skin and other organs. Epinephrine also relaxes the smooth muscles of the stomach, intestine, bronchioles, and wall of the urinary bladder, while it excites the muscles of the gall bladder, ureter, and sphincters of the intestine. Recent studies have shown that, under controlled conditions, epinephrine acts as an overall vasodilator drug and a powerful cardiac stimulant, while norepinephrine in comparable doses acts as an overall vasoconstrictor substance.

The formation and liberation of the adrenal cortical steroids appear to be dependent upon the action of the pituitary adrenocorticotropic hormone (ACTH). At least six adrenal cortical steroids have been identified, and several unknown factors have been observed. Those identified are corticosterone, 17-hydroxycorticosterone, 17-hydroxyprogesterone, 11-dehydrocorticosterone, 11-desoxycorticosterone, and 17-hydroxy-11-dehydrocorticosterone (cortisone). These steroids are intimately concerned with carbohydrate metabolism, mineral metabolism, protein and fat metabolism, and fluid and electrolyte balance.

So much work is being done at this time on the metabolic influences of the adrenal cortex that almost anything written now will soon be obsolete. What little we know about the cortical hormones of the adrenal gland as they relate to oral pathology is summarized.

Acute Insufficiency of the Adrenal Cortex

This is a term used to describe inadequate glucocorticosteroid or mineralocorticosteroid production. It may be acute or chronic and primary or secondary.

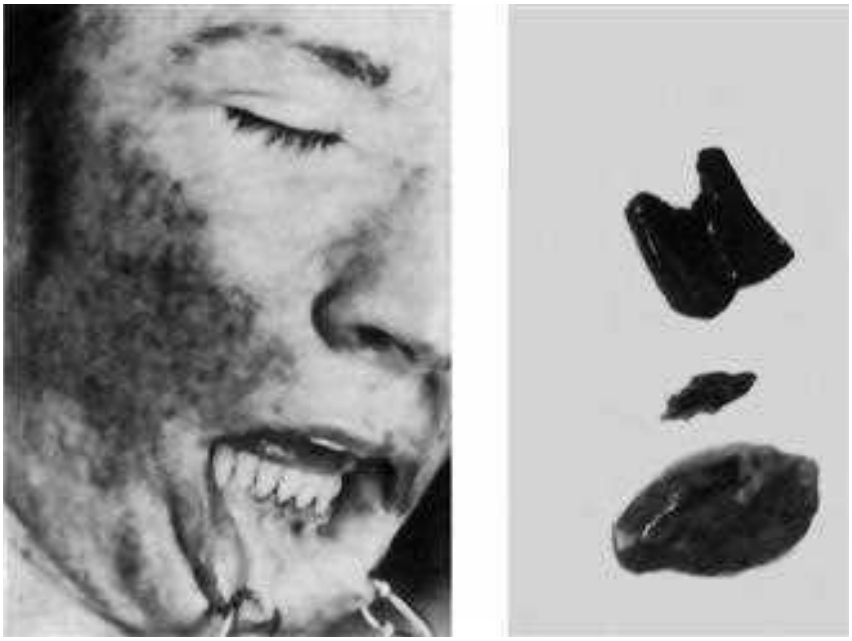
Acute adrenal cortical insufficiency is relatively rare. It usually occurs in connection with an acute septicemia and is called the **Waterhouse-Friderichsen syndrome.** This disease occurs primarily in children, but can also occur in adults. It is characterized by a rapidly fulminating septic course, a pronounced purpura and death within 48–72 hours. Meningococci, streptococci and pneumococci are the organisms most often responsible for the disease. At autopsy the conspicuous change seen is bilateral adrenal hemorrhage (Fig. 15-22). Apart from that, it can develop also in patients who take large doses of steroids for more than two weeks and abruptly stop.

The use of antibiotics and cortisone has changed the course of the disease from its usual fatal termination to recovery in some cases.

Chronic Insufficiency of the Adrenal Cortex: Addison's Disease

Modern medicine can add little to the description of the disease reported by Addison in 1855. It usually develops following the autoimmune destruction of adrenal glands and frequently occurs in conjunction with other autoimmune disorders.

Clinical Features. Early manifestations include lethargy, fatigue, and muscular weakness that may persist for months.



A B

Figure 15-22. Waterhouse-Friderichsen syndrome.
There are petechial hemorrhages and purpura in the skin and oral mucosa, **(A)**. The adrenal glands are hemorrhagic, **(B)**.

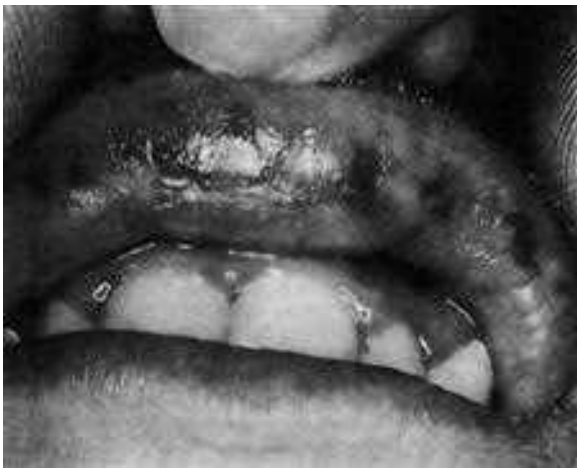


Figure 15-23. Addison's disease.
There is pigmentation of the lips and oral mucosa *(Courtesy of Dr Stephen F Dachi).*

The patient feels tired after minimal exertion but feels well on walking. Feeble heart action, general debility, vomiting, diarrhea, and severe anemia are also seen. Females develop irregular menstruation and loss of body hair.

Hypoglycemia, dehydration, hypertension, elevated serum potassium, and postural dizziness develop following low blood levels of cortisol.

Due to an increased level of ACTH in the blood, the secretion of melanocyte stimulating hormone increases, which induces the deposition of melanin in the skin and mucous membrane (Fig. 15-23). This pattern is nonspecific and may consist of multiple focal dark spots or generalized diffuse streaks of hyperpigmentation which may be macular, flat, brown, and variable in shape. In the oral mucosa, a pale brown to deep chocolate pigmentation spreading over the buccal mucosa from the angles of the mouth and/or developing on the gingiva, tongue and lips, may be the first evidence of the disease.

Diagnosis. The diagnosis of Addison's disease is based on the clinical signs as well as on characteristic changes in the blood sodium and chloride levels. Biopsy of the oral lesions shows acanthosis with silver-positive granules in the cells of the stratum germinativum. Low diurnal plasma cortisol and ACTH levels, along with an elevated level of blood urea nitrogen confirms the diagnosis.

Hyperfunction of Adrenal Gland

Adrenogenital Syndrome. A condition known as the adrenogenital syndrome results when hyperplasia or tumors of the adrenal cortex occur. Depending on the age of onset and the gender of the person affected, the clinical signs are pseudohermaphroditism, sexual precocity and virilism in women or feminization in men. If the disease begins early, premature eruption of the teeth may occur.

Cushing's syndrome. This syndrome is a result of hormonal excess resulting from any of the following:

- Hyperplastic adrenal cortices without any other clinically evident endocrine lesion.
- Adrenal cortical adenoma or carcinoma.
- Ectopically located adrenal-like tumor, for example, of an ovary.
- ACTH-secreting tumor of the anterior pituitary associated with adrenal cortical hyperplasia.
- Nonpituitary carcinoma, for example, of a lung or the pancreas, with secretion of an ACTH-like material that induces adrenal cortical hyperplasia.

When the syndrome is associated with spontaneous bilateral adrenal hyperplasia, it is referred to as Cushing's disease. In adults, it is recognized that Cushing's disease represents approximately 75% of the cases of Cushing's syndrome. While Cushing's disease is uncommon in children, McArthur and his associates have reported a series of 13 cases in patients under the age of 15 years. The pathogenesis of this disease has been reviewed by Hunder.

It is characterized by a rapidly acquired adiposity about the upper portion of the body, mooning of the face, a tendency to become round-shouldered and develop a **buffalo hump** at the base of the neck, alteration in hair distribution, a dusky plethoric appearance with formation of purple striae, muscular weakness, vascular hypertension, glycosuria not controlled by insulin, and albuminuria.

The oral pathologist's primary concern with this peculiar disease state lies in the bone changes. In children there may be osteoporosis and premature cessation of epiphyseal growth, while in adults there is a severe osteoporosis.

The mechanisms for the bone changes is not well understood. Apparently, 11-desoxycorticosterone is relatively unimportant in the pathogenesis of Cushing's syndrome. Albright's explanation for the pathogenesis of the disease is based on the S-F-N (sugar-fat-nitrogen) hormone group of steroids in which the 'N' hormone is considered an anabolic one, stimulating osteogenesis and causing closure of the epiphysis, and the 'S' hormone is considered an antianabolic one. The mechanism of osteoporosis is then explained on the basis of an excess of 'S' hormone, leading to a retardation of osteoblastic activity and reduction in matrix formation.

We appreciate the fact that a number of complex interrelations are concerned in the normal and abnormal control of bone growth and maturation. Considerable interest is now centering on these interrelations and on the precise metabolic or endocrine pathways by which particular hormones influence skeletal growth. Little definite evidence on these topics exists as yet, but some information is available on the effects of cortisone on bone growth. For example, Follis showed that cortisone injections in rats produced retardation and arrest of and interference with resorption of bone. In other species, only retardation of bone growth was found.

Fraser and Fainstat demonstrated that in certain strains of mice the injection of cortisone into pregnant females produced a high percentage of cleft palates in the offspring. This effect was not due primarily to the inhibition of growth, since cleft palate was produced even when the cortisone was administered after the palate had already closed. Doig and Coltman reported several cases of cleft palate in children born of mothers who conceived while receiving injections of cortisone or who received injections of cortisone during the first three months of pregnancy. Obviously, more work is needed in this field before definite conclusions can be drawn.

Stress and the 'Adaptation Syndrome'

The extensive studies of Hans Selye have done much to stimulate thinking and research in the area of 'stress' and the adrenal gland. He formulated a theory of response to prolonged stress as a part of the individual's adaptive mechanism which may lead to clinical signs and symptoms called the **general adaptation syndrome.** This theory is a controversial one, and much research is being done to clarify the points of controversy.

Any wasting disease produces atrophy of the adrenal cortex and loss of adrenal lipid. The mechanism for this finding is not known. Selye states that the adrenal changes are due to prolonged stress, with the mobilization of lipids and ultimate exhaustion atrophy of the cortical cells. Apparently, the hormones of the adrenal cortex are necessary for cellular enzymes to catalyze the energy-producing processes of cells. All 'stressor' agents, such as cold, heat and trauma, increase the metabolic demands of the organism and stimulate adrenocortical function through stimulation of the pituitary to secrete ACTH. If the stress is continued, the pituitary and the adrenal cortex produce excessive amounts of hormones to increase resistance. Eventually pathologic changes occur in those tissues which respond to the hormonal stimulation, and the diseases of adaptation (hypertension, periarteritis nodosa, and others) results.

Since there is a considerable amount of evidence against Selye's theory, and since the entire field of adrenal mechanisms in pathologic processes is in a state of flux, only a brief resume of Selye's theory will be presented. The reader is directed to Selye's original papers (1946, 1948) and to the excellent critical review by Sayers (1950) for a more comprehensive coverage of the subject.

Selye states that the 'stressed' person passes through a succession of stages. The first is the **'alarm reaction',** which consists of a shock phase and then a countershock phase. The next is the **'adaptation stage',** in which his resistance to the original stressor is greater, but his resistance to other stressor agents is lowered. If the stressor is continued, he eventually enters a stage of exhaustion and dies. If the stressor is removed, he enters a stage of convalescence and recovers. Figure 15-24 shows diagrammatically the control of adrenocortical activity.

Many people are receiving large doses of cortisone for the treatment of various diseases. We must remember that cortisone interferes with the formation of granulation tissue, proliferation of fibroblasts, and production of ground substance. Since these tissues and cellular products are essential to wound healing, it is important to recognize that surgery is hazardous in hyperadrenocorticism.

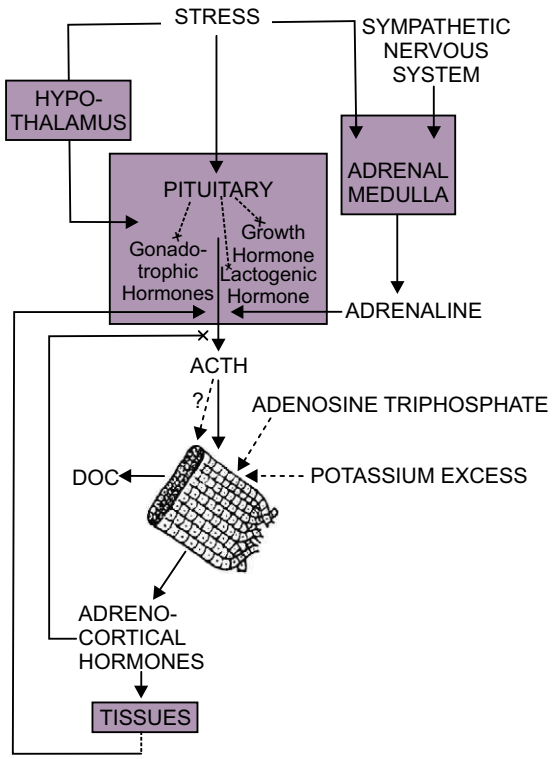


Figure 15-24. The control of adrenocortical activity.
Stress may act on the pituitary or through the hypothalamus to stimulate the secretion of ACTH at the expense of other pituitary hormones. ACTH stimulates the zona fasciculata and zona reticularis, though possibly not the zona glomerulosa, which may secrete DOC independently. The level of adrenocortical hormones in the blood controls the rate of production of ACTH. Rapid utilization of cortical hormones by the tissues lowers the blood level of cortical hormones and thus stimulates ACTH production. Adrenaline (epinephrine) may also stimulate ACTH production, and adenosine triphosphate or potassium excess may stimulate the adrenal cortex (From PMF Bishop: Cameron's Recent Advances in Endocrinology, 7th ed. London. J & A Churchill, Ltd, 1954).

PANCREATIC HORMONE: INSULIN

Diabetes Mellitus

Diabetes is a biochemical lesion, and though no complete correlation exists between the occurrence of the disease and histologically demonstrable changes in the pancreas, the role of insulin in the control of the disease and historical considerations make it legitimate to discuss diabetes in the section on the pancreas. Because recent investigations have shown that other endocrine organs play a role in its production, many writers consider diabetes mellitus more generally a disease of metabolism.

Diabetes is a disorder of carbohydrate metabolism characterized by hyperglycemia and glycosuria, reflecting a distortion in the equilibrium between utilization of glucose by

the tissues, liberation of glucose by the liver and production-liberation of pancreatic, anterior pituitary and adrenocortical hormones. This metabolic disorder lowers tissue resistance to infection.

It is a disorder caused by relative or absolute lack of insulin, and in the later stages of disease it provides multiple systemic complications. Recent evidences indicate that it is a multifactorial disease with genetic predisposition and destruction of the islet of Langerhans cells.

It is classified into two types:

- Insulin dependant diabetes mellitus (IDDM) **(Juvenile onset or type I or brittle or ketosis prone or labile diabetes).** It occurs as a result of immunologically mediated destruction of pancreatic beta cells.
- Non-insulin dependant diabetes mellitus (NIDDM) **(Adult onset or type II or maturity onset diabetes)**.

Insulin dependant diabetes mellitus is the less common form of diabetes, characterised by onset before age 20, with a thin body build, extreme thirst, hunger, constant urination, and weight loss. As there is no insulin secreted in these patients, daily injections of insulin are required to control the blood glucose level and also to prevent ketoacidosis. There is a positive family history for the disease with a weaker genetic tendency than type II diabetes mellitus.

Clinical Features. Patients manifest with glycosuria, polyuria, polydipsia, weakness, and weight loss. Abnormal and accelerated metabolism of amino acids and fats results in ketoacidosis.

The complications are microangiopathy and macroangiopathy which include atherosclerosis, retinopathy, neuropathy, renal failure, autonomic insufficiency, and susceptibility to infections.

Oral Manifestations. The oral manifestations are mainly due to inflammation and infection because of the abnormal neutrophil function, microangiopathy, and altered oral flora. Most of the patients present with a dry mouth, persistent gingivitis, multiple carious lesions, periodontal disease, and candidiasis.

Diabetic patients show an increased tendency towards delayed wound healing and dry socket formation.

Because of the lowered tissue resistance, patients with untreated or inadequately controlled diabetes sometimes exhibit a fulminating periodontitis with periodontal abscess formation and inflamed, painful and even hemorrhagic gingival papillae. Bernick and coworkers studied a series of 50 diabetic children and found that gingivitis was increased; however, the rate of caries formation was not related to the duration of the disease. Lin and colleagues noted a significant thickening of the basement membranes of gingival vessels and proposed that gingival biopsies may be useful as an adjunct in the diagnosis of diabetes. Because of excessive fluid loss, diabetic patients commonly complain of dry mouth. Even minor oral surgery is contraindicated in uncontrolled diabetic patients. Vascular changes in the dental pulp, gingiva, and periodontal ligament have been reported in diabetic patients by Russell.

Controlled diabetic patients should undergo dental operations only after consultation with the physician who is treating the patient. There are no oral manifestations of controlled diabetes mellitus.

Diagnosis. It is mainly based on clinical signs and symptoms. Blood sugar estimation and the glucose tolerance test are useful as confirmatory tests for diabetes.

Treatment. It is based on diet, oral hypoglycemic drugs, and insulin therapy.

Progeria
(Hutchinson-Gilford syndrome)

Progeria is a very rare disease originally described by Hutchinson in 1886. It is of unknown etiology and is characterized by dwarfism and premature senility. It is thought to be transmitted as an autosomal recessive trait. The term itself means prematurely old. Progeria has been discussed in an article by DeBusk.

Clinical Features. Affected infants appear normal at birth, but the typical clinical features become manifested within the first few years. The patients all have an amazing resemblance to each other, exhibiting alopecia, pigmented areas of the trunk, atrophic skin, prominent veins, and loss of subcutaneous fat. The individuals have a high-pitched, squeaky voice, a beak-like nose, and a hypoplastic mandible. Coxa valga is also a constant feature, as is severe atherosclerosis. Exophthalmos may be present, as may muscular atrophy and joint deformities. The intelligence of individuals with this disease is generally either normal or above normal. Even at a very early age, the patient resembles a wizened little old person.

Oral Manifestations. The oral findings in progeria have been described by Gardner and Majka. These basically consist of the accelerated formation of irregular secondary dentin, apparently a manifestation of the premature aging process. Delayed eruption of teeth has also been reported by Wesley and colleagues.

Treatment and Prognosis. There is no treatment for this disease, and no patient with progeria has been reported living beyond the age of 27 years.

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CHAPTER 16

Allergic and Immunologic Diseases of the Oral Cavity

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CHAPTER OUTLINE

'Allergy' is a broad term used generally to encompass the hypersensitive state acquired by exposure to a specific material, and the altered capacity of the living organism to react upon re-exposure to it. Nearly all cases of allergy depend upon the combination of an antigen, usually but not always a protein or a polysaccharide, with an antibody produced by the host, almost invariably as a result of previous exposure to the antigen.

There are two general types of allergic reactions; and a great diversity of appearance of the various phenomena exists in each group. One type of reaction, the so-called immediate reaction, is that associated with antibodies circulating in the serum of the allergic person and includes anaphylaxis, hay fever and asthma, serum sickness, angioedema, and the wheal-and-erythema skin reaction. The second category of reaction, or delayed reaction, is generally not associated with circulating antibodies since the causative agents are not strictly antigens. They attain antigenic properties by combining with the tissues of the individual. In contrast to the immediate reaction, which develops as soon as the substance is absorbed, the delayed reaction is not manifested clinically for several hours after exposure. Reactions of the latter type include drug allergies, allergies of certain infections, and contact reactions to a vast variety of materials.

Recurrent Aphthous Stomatitis

(Aphthous ulcers, aphthae, canker sores)

Recurrent aphthous stomatitis (RAS) is an unfortunately common disease characterized by the development of painful, recurring solitary or multiple ulcerations of the oral mucosa. Because of the similarity between this disease and herpes simplex infection, with respect to precipitating factors, certain aspects of the clinical appearance of lesions, duration of lesions, recurrence and general failure of response to any form of therapy, the two diseases have been generally confused. A series of intense investigations over the past few years have conclusively established the fact that there is no etiologic relationship between recurrent aphthous stomatitis and herpes simplex infection.

Etiology. Numerous possible etiologic factors have been suggested in the interesting history of recurrent aphthous stomatitis and these have been adequately reviewed by Ship and his group, and in a workshop on aphthous stomatitis and Behçet's syndrome at the National Institutes of Health in September 1977, co-chaired by Graykowski and Hooks. However, in the light of present knowledge, it is obvious that there has been considerable confusion in the past between etiologic factors and precipitating factors.

Bacterial Infection. The work of Barile, of Graykowski and of Stanley very strongly implicated a pleomorphic, transitional L-form of an α-hemolytic Streptococcus, *Streptococcus sanguis*, as the causative agent of the disease. This organism has been consistently isolated from the lesions of patients with typical aphthous ulcers, and microorganisms morphologically consistent with the L-form Streptococcus have been found histologically in the vast majority of aphthous lesions. Once

again, it should be emphasized that the herpes simplex virus cannot be isolated from these aphthous ulcers.

The administration of this pleomorphic Streptococcus to guinea pigs and rabbits has produced lesions of the skin and the oral mucosa, which appear clinically and histologically similar to aphthous ulcers in humans. Finally, the work of Graykowski and his associates has shown that patients with recurrent aphthous ulcers, when tested with a Streptococcus vaccine, give a positive delayed type of hypersensitive skin reaction in contrast to patients with no history of aphthae, who give a less frequent and less severe response. Thus, there is some evidence of this disease being an immunologic hypersensitivity reaction to an L-form Streptococcus. It has been suggested that there is a T cell-mediated response to *Streptococcus sanguis* that produces cross-reaction between streptococcal heat shock protein and oral mucosa, leads to mucosal damage.

Genetic History. There is a positive family history and occurrence of RAS is associated with HLA- B51. Further, these individuals with positive family history develop the ulcers at an early stage of their life.

Immunologic Abnormalities. As an alternative etiologic factor, Lehner has proposed that the recurrent aphthous ulcer is the result of an autoimmune response of the oral epithelium. Utilizing a fluorescent antibody technique, he has shown both IgG and IgM binding by epithelial cells of the spinous layer of oral mucosa in patients suffering from recurrent aphthous ulcers, while the same cells in healthy control patients or patients with nonspecific ulcers show no such binding.

Normal levels of antinuclear factors and complement levels within normal limits in patients with this disease have been reported by Addy and Dolby and by Lehner. This has led Cohen to suggest that recurrent aphthous stomatitis is not an autoimmune disease arising from a central immunologic fault but rather represents a local immune response against an antigenically altered mucosa. He theorizes, in this context, that the disease is the result of diffusion of bacterial toxins, food, and other substances acting as allergens or haptens, which initiate an immune response. The same substances, he pointed out, could also react with epithelial cell surface antigens to produce a change, resulting in an adverse inflammatory response.

Donatsky has found elevated gamma globulin levels against Streptococcus 2A and M5 by immunofluorescent studies in the serum of patients with recurrent aphthous stomatitis. The detected antibodies in these patients were able to bind serum complement. These investigations have led Antoon and Miller to conclude that the immune system appears actively involved in reaction to bacterial and autoimmune antigens and speculate that L-form streptococci might infect epithelium of the salivary ducts, stimulate formation of antibodies, fix complement and cause cytolysis. They believed that the disease might be further complicated by an autoimmune reaction to released antigens from epithelial tissues.

Thus, patients with recurrent aphthous stomatitis appear to have an altered immune response, which is directed against both the nonpathogenic oral flora and the host oral tissue.

Iron, Vitamin B_{12} or Folic Acid Deficiency. There has been some evidence that nutritional deficiencies might be of significance in the etiology of recurrent aphthous stomatitis. For example, a study has been reported by Wray and his colleagues in which a series of 330 patients with recurrent aphthae were screened for deficiencies of iron, folic acid, and vitamin B_{12}. A total of 47 deficient patients, or 14.2%, was found: 23 patients were deficient in iron, seven in folic acid, six in vitamin B_{12} and 11 had combined deficiencies. 39 of these patients were treated with the appropriate replacement therapy, and it was found that 23 had a complete remission of their ulcers, 11 were improved and three were not responded. While the results indicate that a small percentage of patients with recurrent aphthae do have certain nutritional deficiencies, the investigators pointed out that the prompt response to replacement therapy suggested a direct action on oral mucosa, but that it might be reasonably postulated that the presence of a deficiency allows the expression of an unrelated underlying tendency to ulceration and that the deficiency itself does not play a primary role. The failure of response in some patients also might indicate either that the deficiency was coincidental or that the therapy was inadequate. In any event, the role of nutritional deficiencies in the etiology of this disease does not appear to be a major one.

Precipitating Factors. A variety of situations have been repeatedly identified immediately preceding the outbreak of aphthous ulcers in relatively large numbers of patients and are discussed below.

Trauma. Local trauma has been found to be the precipitating factor in nearly 75% of cases in a series reported by Graykowski and his coworkers. The traumatic incidents included self-inflicted bites, oral surgical procedures, toothbrushing, dental procedures, needle injections, and dental trauma.

Endocrine Conditions. It has been recognized for many years that a time relationship exists between the occurrence of the menstrual period and the development of aphthous ulcers. Most series show that the incidence of aphthae is greatest during the premenstrual period. Dolby has similarly shown that ulceration is maximal in the postovulation period and has related this to the blood level of progesterone.
It has also been reported that women may have remission of their aphthous lesions during pregnancy but show eruptions following parturition, sometimes very rapidly. On rare occasions, the onset of the disease has been associated with menarche and menopause.

Psychic Factors. The role of psychic factors in certain oral diseases is well recognized. In cases of aphthous ulcers, acute psychologic problems appear many times to have precipitated attacks of the disease, although this is a difficult factor to analyze.

Allergic Factors. Many patients with recurrent aphthous ulcers have a history of asthma, hay fever, or food or drug allergies. This may be a purely fortuitous finding because of the high incidence of allergies in the general population. However, the outbreak of aphthae following the use of certain foods or drugs in the same patients has been reported so frequently that allergy must be considered a precipitating factor.

It is interesting to note that there is negative correlation between aphthous ulcers and smoking. As per Atkin PA and coworkers who measured the nicotine metabolite present in the blood of smokers, the incidence of recurrent aphthous ulcers is significantly lower in smokers.

Systemic diseases. Apthous ulceration occurs in various systemic diseases like Behçet's syndrome, cyclic neutropenia, magic syndrome (major aphthous and generalised inflamed cartilage), PFAPA syndrome (periodic fever, aphthae, pharyngitis,and cervical adenitis) and HIV infection.

The aphthous ulcers occur in patients with systemic illness like Crohn's disease, ulcerative colitis, and gluten sensitive enteropathy but it reflects the basic hematinic deficiencies.

Classification. Recurrent aphthous stomatitis has been classified by many investigators into four chief varieties based upon the clinical manifestations:

- **Recurrent aphthous minor,** which is the most common form of the disease and the one referred to by the lay public as the 'canker' sore.
- **Recurrent aphthous major**, which is now believed to be simply a more severe form of recurrent aphthous minor but which was thought at one time to represent a separate disease entity known as periadenitis mucosa necrotica recurrens (Mikulicz's scarring aphthae or Sutton's disease).
- **Recurrent herpetiform ulcerations**, which consist of clusters of ulcers resembling herpetic lesions but lacking evidence of the presence of viruses in patients with a low incidence of antibody to oral mucosa.
- Recurrent ulcers associated with **Behçet's syndrome,** will be considered separately.

Clinical Features. Recurrent aphthous minor occurs somewhat more frequently in women than in men, and the majority of patients report the onset of the disease between the ages of 10 and 30 years. However, it may commence much earlier in life or not begin until much later. Unfortunately, the disease typically persists with recurring attacks over a period of many years. It is believed that nearly 20% of the general population is affected by this disease at one time or another. It is interesting to note that approximately 55% of a large group of professional school students studied by Ship and his associates gave a positive history of recurrent aphthous ulcers. It is also of interest that a rather remarkable familial tendency for occurrence of the disease has been noted by many workers. For example, in the series of Graykowski and coworkers, over 80% of the affected patients had an additional member or members of their families with a history of aphthae.

The frequency of outbreaks of the aphthae varies remarkably between patients. Some persons will have only one or two attacks a year, while others will have one or two attacks a month, and almost every month for prolonged periods, sometimes years. Occasional patients have continual, repeated outbreaks and are never free of lesions for extended intervals.

The onset of the disease may occur with a variety of manifestations, which are not invariably present in all cases. These include the occurrence of one or more small nodules; burning sensation, erythema, generalized edema of the oral cavity, especially the tongue; paresthesia; malaise; low-grade fever; localized lymphadenopathy; and vesicle-like lesions containing mucus.

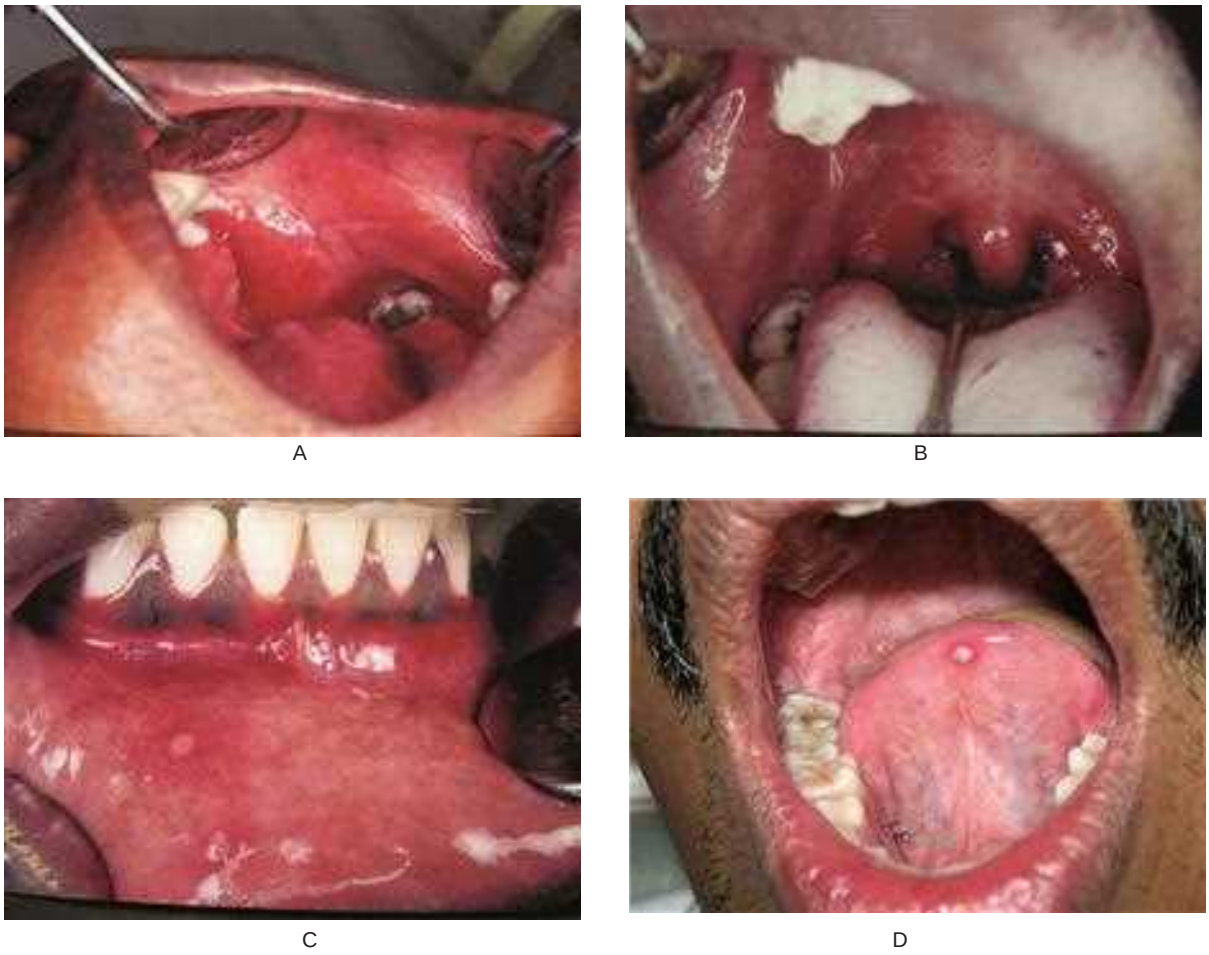
The aphthous ulcer begins as a single or multiple superficial erosions covered by a gray membrane (Fig. 16-1). It generally has a necrotic center with clearly defined raised margins surrounded by an erythematous halo. The lesion is typically very painful so that it commonly interferes with eating and speech for several days. At one time it was thought that the aphthous ulcer begins with the formation of a vesicle, as does the lesion of herpes simplex infection. The majority of the evidence now indicates that this is not the case—vesicle formation does not appear to be a stage in the development of the usual aphthous ulcer.

The number of lesions present in any one patient during a single outbreak may vary from one to over 100. However, according to Graykowski and his associates, over 90% of patients have six lesions or less during a single outbreak. They vary in size from 2 to 3 mm to over 10 mm in diameter. The most common sites of occurrence are the buccal and labial mucosa, buccal and lingual sulci, tongue, soft palate, pharynx, gingiva, and all locations of labile mucosa not bound to periosteum. This is in direct contrast to the sites of predilection of recurrent intraoral herpes simplex infection. The ulcers themselves generally persist for 7 to 14 days and then heal gradually with little or no evidence of scarring.

Recurrent aphthous major is characterized by the occurrence of large painful ulcers, usually 1 to 10 in number, on the lips, cheeks, tongue, soft palate, and fauces and cause severe pain and dysphagia (Fig. 16-2). Their incidence is more in patients with HIV infection. These ulcers occur at frequent intervals, and many patients with this disease are seldom free from the presence of at least one ulcer. Usually these lesions occur after puberty and persist up to 20 years or more. Unlike the typical ulcers of recurrent aphthous minor, these lesions may exceed one cm in diameter and persist for up to six weeks and leave a scar upon healing. Not uncommonly, the ulcers recur in waves over a long period of time, so that eventually the oral mucosa may show a great deal of scarring. Patients with these severe major aphthae also occasionally show similar lesions on vagina or penis, rectum, and larynx, with associated rheumatoid arthritis or conjunctivitis.

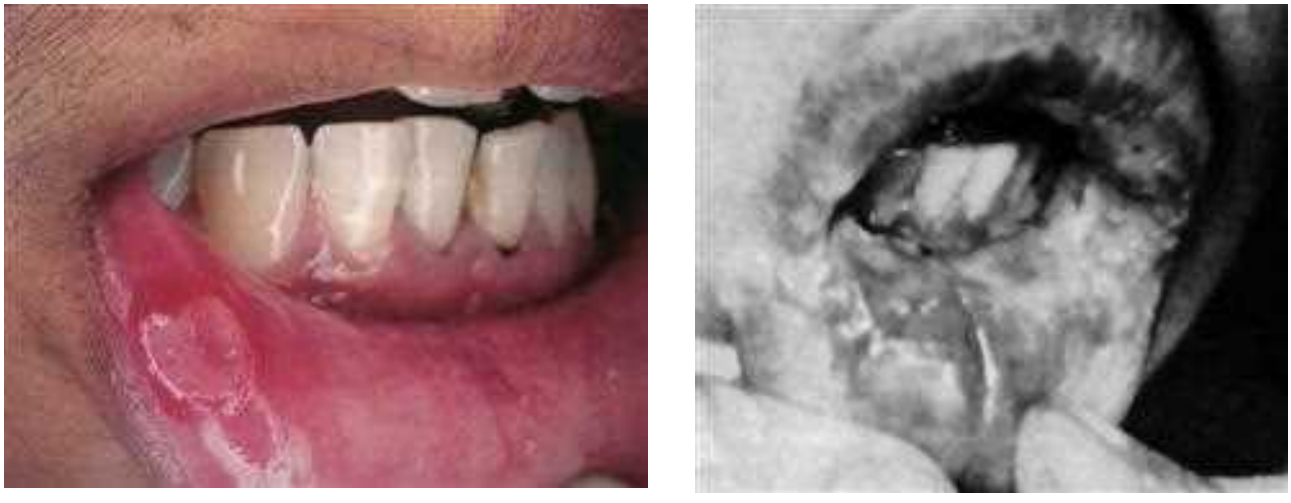
According to the review of this disease by Hjørting-Hansen and Siemssen, there is no predilection for occurrence in any particular age group, although females are affected more frequently than males.

Recurrent herpetiform ulcers are characterized by crops of multiple small, shallow ulcers, often up to 100 in number, which may occur at any site in the oral cavity. They were first described by Cooke in 1960, while Lehner as well as Brooke and Sapp have expanded our knowledge of this condition. Cooke pointed out the clinical similarities of this disease to the lesions of herpes simplex and that the corresponding histologic changes were not similar, since these lesions resemble the recurrent aphthous ulcer rather than a viral lesion. These



A B C D

Figure 16-1. Recurrent aphthous ulcers, minor.



A B

Figure 16-2. Recurrent aphthous ulcers, major.
Deep crateriform ulcer **(A)** and scars **(B)**. *(B, Courtesy of Dr TH Century).*

lesions have female predisposition with later age of onset and are not associated with herpes virus.

The characteristic clinical features of this uncommon condition were listed by Brooke and Sapp as follows:

- Numerous small lesions may be found on any intraoral mucosal surface.
- Lesions begin as small pinhead-sized erosions that gradually enlarge and coalesce.
- Lesions are more painful than would be suspected by their size.
- Lesions are present almost continuously for one to three years, with relatively short remissions.
- Patients receive immediate but temporary relief from symptoms with a 2% tetracycline mouthwash.

While these clinical features are very reminiscent of herpes simplex infection, Brooke and Sapp pointed out that laboratory tests show:

- The herpes simplex virus cannot be cultured from the lesions or demonstrated by electron microscopy, although Sapp and Brooke have demonstrated non-viral intranuclear bodies in adjacent epithelial cells.
- Cytologic smears fail to reveal the typical multinucleated epithelial giant cells found in herpetic lesions.
- The microscopic findings are nearly identical with those described for the recurrent aphthous ulcer.
- Immunofluorescent and serologic techniques are negative for antibodies to herpes virus as well as to oral epithelium.

Although the exact nature of this disease is unknown, including its etiology and pathogenesis, it is considered appropriate by most investigators to include it as a variant of recurrent aphthous stomatitis and await further clarification.

Histologic Features. The minor aphthous ulcer of the oral mucous membrane exhibits a fibrinopurulent membrane covering the ulcerated area. Occasional superficial colonies of microorganisms may be present in this membrane. An intense inflammatory cell infiltration is present in the connective tissue beneath the ulcer, with considerable necrosis of tissue near the surface of the lesion, neutrophils predominating immediately below the ulcer but lymphocytes prevailing adjacent to this. Granulation tissue may be noted near the base of the lesion. Epithelial proliferation is present at the margins of the lesion, similar to that found in any nonspecific ulcer. Accessory salivary gland tissue, commonly present in areas of aphthae, will typically exhibit focal periductal and perialveolar fibrosis, ductal ectasia and mild chronic inflammation. These features may be present in even clinically normal mucosa of the aphthous patient. It has also been found that the aphthous ulcer itself, at least in some cases, begins immediately above the excretory duct of one of these minor glands where there is disruption of this ductal epithelium. The tissue involvement is generally superficial.

Lehner has shown that the histologic findings by light microscopy of the severe oral ulcers in recurrent aphthous major are identical with those described under the recurrent aphthous minor. Electron microscopic studies have confirmed this similarity.

The microscopic picture is nonspecific, and without a careful clinical history and description, does not permit the specific diagnosis of the disease.

Wood and his associates have described characteristic changes in the nuclei of epithelial cells taken by cytologic smears from around recurrent aphthous ulcers. These have been referred to as Anitschkow cells and consist of cells with elongated nuclei containing a linear bar of chromatin with radiating processes of chromatin extending towards the nuclear membrane (Fig. 16-3). They are quite abundant in patients with recurrent aphthous stomatitis but are not pathognomonic of the disease, since they are also found in patients with sickle cell disease, megaloblastic anemias, and iron-deficiency anemias, in children receiving chemotherapy for cancer, and even in normal people. Their ultrastructure has been described by Haley and his associates, who found that the nuclear chromatin was made up of pleomorphic masses forming an irregular band along the long axis of the nucleus rather than being randomly dispersed.

Differential Diagnosis. Recurrent aphthous stomatitis is usually diagnosed by history, clinical findings and exclusion of other diseases. Lesions which may be mistaken for recurrent aphthous stomatitis include herpetic stomatitis, herpangina, erythema multiforme, erosive lichen planus, pemphigus and pemphigoid.

Treatment. There is no specific treatment for recurrent aphthous ulcers although, over the years, many drugs have been advocated. Graykowski and his coworkers found that a tetracycline mouthwash (250 mg per 5 ml), used four times daily for 5 to 7 days, produced a good response in nearly 70% of the

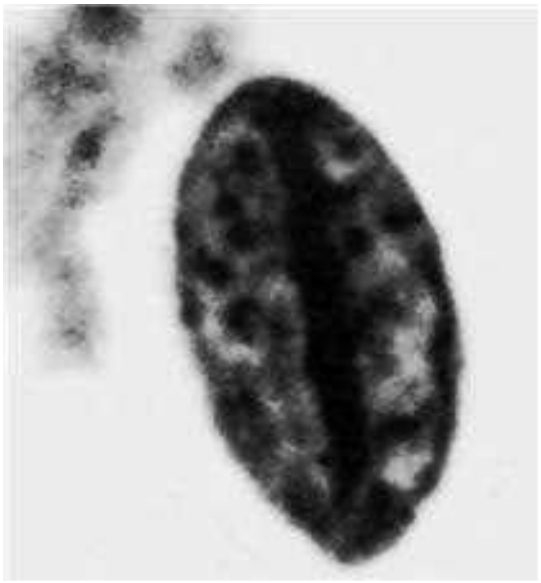


Figure 16-3. Recurrent aphthous stomatitis.
The typical Anitschkow cell in a cytologic smear from the margin of an aphthous ulcer.

patients tested, by relieving the pain, reducing the size of the lesions, and reducing the healing time. A steroid ointment, 1.5% cortisone acetate, applied locally, and hydrocortisone acetate-antibiotic lozenges also showed some effectiveness but not as great as the tetracycline. Chemical cautery reduced pain but had no other beneficial effects. No significant improvement was found with the use of antihistaminics, gamma globulin, multiple smallpox vaccinations or a *Lactobacillus acidophilus-L. bulgaricus* preparation, all of which have variously been reported to be effective.

There has also been extensive clinical trial of levamisole, an anthelmintic drug, which has also been found to potentiate the immune response in a variety of ways. The results of a number of these studies in treating recurrent aphthous stomatitis have been reported, some showing a reduction in the duration of symptoms, some showing a decrease in the duration of lesions, some showing a diminished frequency of lesions, but others conclude that the drug had no significant effect on severity or incidence of lesions.

An excellent summary of the many drugs and chemicals which have been used to treat recurrent aphthous stomatitis over the years has been prepared by Antoon and Miller and is shown in Table 16.1. Unfortunately, despite many forms of therapy, there is no known cure for the disease.

Behçet's Syndrome

Behçet's syndrome is a multisystemic, chronic disorder, characterized by oral and genital aphthous ulcers, arthritis, and cutaneous lesions, ocular, gastrointestinal and neurological manifestations. It was described by the Greek ophthalmologist Benedict Adamantiades in 1931, but it was in 1937 when the Turkish dermatologist Hulusi Behçet made an extensive study and analyzed it as a triad composed of recurrent aphthous oral ulcers, genital ulcers, and hypopyon uveitis. Behçet's disease is characterized by exacerbations and remissions. It has a distinct geographical distribution and is common among the Mediterranean and East Asia, where it is a major cause of morbidity. The next highest incidence of the disease is in Turkey, Japan, UK, and USA. Behçet's disease is usually present in adulthood and is uncommon in children. In Eastern Mediterranean populations, the disease is more common in men, who also experience more severe disease. In Asian populations; however, the sex ratio is reversed. Familial disease is uncommon in Caucasians, but a positive family history is observed in non-Caucasian patients, and the possibility of a sibling risk ratio has been reported in a Turkish study.

Table 16-1: Treatment modalities for recurrent aphthous stomatitis

Immune enhancement
Levamisole
Vaccine
Immunosuppression, inflammatory suppression
Prednisone
Triamcinolone acetonide
Betamethasone-17-benzoate
Antihistamine
Antibiotics (Tetracycline?)
Suspension, topical
Chloramphenicol
Broad-spectrum antibiotics
Antiseptic
Silver nitrate
Coagulating agent, negatol
Gentian violet
Diet supplementation (Lactobacillus?)
Vitamin B_{12}, folic acid
Iron
Zinc sulfate
Symptomatic treatment
Xylocaine/lidocaine
Silver nitrate
Benadryl, topical
Camphor-phenol

From JW Antoon, RL Miller: Aphthous ulcers—a review of the literature on etiology, pathogenesis, diagnosis, and treatment. J Am Dent Assoc, 101: 803, 1980.

The etiology of Behçet's disease remains obscure but various reports suggested that an infectious trigger with inflammatory mediators and immune deregulation is the causative factor in a genetically succepted host**.** It is well evidenced in the literature that Behçet's syndrome is associated with the allele HLA-B*51 (chromosome 6p21), which is relatively common in many ethnic groups. Organophosphates, organochlorides, heavy metal intoxication, and allergens are environmental factors that may trigger initiation or exacerbation of Behçet's disease. *Streptococcus sanguis* and *S. oralis* can be found in the oral microbiota of Behçet's syndrome patients and other agents include the hepatitis virus, parvovirus B19; some bacteria, including mycobacteria, *Borrelia burgdorferi*, *Escherichia coli*, *Saccharomyces cerevisiae* fungus may be elevated with the occurrence of this disease.

Clinical Features. Behçet's syndrome is characterized by exacerbations and remissions. The duration of attacks ranges between few days to few weeks. Attacks usually end to complete remissions but sequelae can also be left behind. This syndrome is more common in young adults between the ages of 25 and 40 and is 5 to 10 times more common in males.

It is characterized chiefly by oral and genital ulcerations, ocular lesions, and skin lesions. The first manifestation of the disease is usually the appearance of oral and/or genital lesions. The oral lesions are painful and very similar clinically and histologically to that of recurrent aphthous ulcers. They occur in crops at any intraoral site and consist of ulcers ranging in size from several millimeters to a centimeter or more in diameter. These ulcers have an erythematous border and are covered by a gray or yellow exudate. The genital ulcers are small and located on the scrotum, root of the penis or labia majora. The most common sites of oral ulcers are lips, buccal mucosa, tongue, gingiva, palate, tonsils, uvula, and pharynx. It must be emphasized that oral ulcers of Behçet's Syndrome are usually indistinguishable from ordinary recurrent oral ulcers except in multiplicity and involvement of unusual locations (soft palate and oropharynx). Cutaneous lesions include papulopustular lesions (acneiform) or pseudofolliculitis, erythema nodosum,

superficial thrombophlebitis, cutaneous ulcers and nodules, cellulitis type lesions, Sweet's syndrome, gangrenous pyoderma, other rarer lesions,which occur in addition.

The ocular lesions, beginning as photophobia and irritation, may range in severity from a simple conjunctivitis to uveitis and finally hypopyon. The ocular involvement may lead to blindness. It is more common and severe in men. Inflammation of the eyes is usually episodic and resolves after a few weeks but recurrent attacks eventually cause sequela of blindness. The skin lesions are generally small pustules or papules on the trunk or limbs and around the genitalia. In addition to the various forms of pyoderma, both erythema nodosum and erythema multiforme have been reported to occur. Arthralgia, thrombophlebitis, and CNS involvement, as well as cardiac or pulmonary involvement are occasional complications of the disease.

Histologic Features. The intraoral ulcers are entirely nonspecific, and according to Lehner, are remarkably similar to recurrent aphthous ulcers. Endothelial proliferation is reported in the lesions of Behçet's disease but not in the recurrent aphthous ulcer. Vasculitis also appears to be an essential lesion in Behçet's disease.

Laboratory Findings. These patients frequently manifest a hypergammaglobulinemia, leukocytosis with eosinophilia, and elevated ESR. Other findings are variable. There is no diagnostic test for Behçet's disease. ESR, C-reactive protein (CRP), C9 and/or C3, C4 complements may be elevated during the active phases of disease. Immunoglobulins (IgM and IgG) may be elevated and immune complex are also found in serum of some patients. Platelet rosette formation around neutrophils can be seen in acute attacks of disease and disappears after recovery. This phenomenon is relatively specific but nonsensitive.

Treatment and Prognosis. There is no specific treatment for the disease other than symptomatic or supportive measures. While Behçet's disease may undergo spontaneous remission after a variable period of months to years, it may progress to serious complications and even result in death.

While the oral ulcerations in recurrent aphthous stomatitis and in Behçet's syndrome appear clinically indistinguishable, the two diseases can be separated easily. In recurrent aphthous stomatitis, the oral ulcers are the only manifestation of disease. In Behçet's syndrome, at least two of the classic triad of the disease must be present: recurrent oral ulcers, recurrent genital ulcers, and ocular inflammation.

Reiter's Syndrome

Reiter's syndrome is associated with urethritis, balanitis, conjunctivitis, and mucocutaneous lesions. It is a disease of unknown etiology, although there is evidence of an infectious origin. It is one of the most common complications of nonspecific urethritis and, in fact, clinically mimicks gonorrhea, although the urethral discharge is negative for *Neisseria*. Pleuropneumonia-like organisms (PPLO) have been implicated and, a Bedsonia group virus has also been isolated from patients with the disease. Mycoplasmal and chlamydial species have also been suspected. There is an excellent review of the disease by Weinberger and associates. Currently it is considered to be an immunodysregulated condition. Recent evidence also suggests that this disease may be triggered by infectious agents in genetically susceptible patients. HLA-B27 is considered to be a disease susceptibility factor in Reiter's syndrome. This disease is also seen frequently in HIV positive patients.

Clinical Features. Reiter's syndrome is more prevalent in young adult men, usually between 20 and 30 years of age. The male to female ratio is 9:1. There is a typical tetrad of manifestations: nongonococcal urethritis, arthritis, conjunctivitis, and mucocutaneous lesions. In any given case, however, the full tetrad is often not present.

Urethritis may be the first sign. The urethral discharge is usually associated with itching and burning sensation. The arthritis is often bilaterally symmetrical and usually polyarticular. Conjunctivitis is often so mild as to be overlooked. The skin lesions are similar to those seen in keratoderma blennorrhagica and consist of red or yellow keratotic macules or papules which eventually desquamate. A possible relationship between Reiter's syndrome and psoriasis has been discussed by Perry and Mayne.

Oral Manifestations. Oral lesions occur in reported series of cases in less than 5 to about 50% of patients with the disease. The lesions, described by Pindborg and associates, appear as painless, red, slightly elevated areas, sometimes granular or even vesicular, with a white circinate border on the buccal mucosa, lips, and gingiva. They may be mistaken for recurrent aphthous ulcers. The palatal lesions appear as small, bright red purpuric spots which darken and coalesce, while the lesions on the tongue closely resemble 'geographic' tongue. Clinically, similar lesions occur on the glans penis, producing a circinate balanitis.

Histologic Features. The microscopic findings are not diagnostic. They consist of parakeratosis, acanthosis and polymorphonuclear leukocyte infiltration of epithelium, sometimes with microabscess formation similar to psoriasis. The connective tissue shows a lymphocyte and plasma cell infiltrate.

Laboratory Findings. The patients usually have a mild leukocytosis, an elevated sedimentation rate, and pyuria.

Treatment and Prognosis. The disease may undergo spontaneous remission but has been treated by antibiotics and corticosteroids.

Sarcoidosis

(Boeck's sarcoid, Besnier-Boeck-Schaumann disease)

Sarcoidosis is described as a multisystem granulomatous disease of unknown origin characterized by the formation of uniform,

discrete, compact, non-caseating epithelioid granulomas. It is more common in blacks than in whites.

Though many investigators have regarded this disease, of unknown etiology, both infective and noninfective agents have been implicated. Currently the infectious etiology is more favored with focus on *Mycobacterium* and *Propionibacterium*. It is interesting to note that there was a belief that sarcoidosis is in some way related to tuberculosis. The factors which stood against were inability to culture the bacteria from the pathological tissues and difficulty in identifying them in stained sections. D Gupta et al, in their excellent meta-analysis involving 31 published studies concluded that, there is an association between sarcoidosis and mycobacteria. Di Alberti et al, have demonstrated human herpes virus 8 in sarcoid tissue from lung, skin, lymph nodes, and oral tissues.

Sarcoidosis most commonly affects young adults and presents most frequently with hilar lymphadenopathy, pulmonary infiltration, and skin and eye lesions. Thus, lesions of sarcoid are most common in the lungs, skin, lymph nodes, salivary glands, spleen, and bones, but may be found to involve practically any site, including the mouth. The disease is characterized by a depression of delayed-type hypersensitivity suggesting an impaired cell-mediated immunity, and raised or abnormal serum immunoglobulins suggesting lymphoproliferation. There are numerous contributing background factors even though the precipitating cause of the disease is unknown. Prolonged antigenemia, circulating immune complexes, and serum inhibitors all contribute to the granulomatous disorder, according to James and his colleagues. Other evidences suggest that granulomatous inflammation is due to improper degradation of antigenic material. Many studies suggest that interferon gamma (IFN-γ) and cytokines such as TNF-α, IL-12 and IL-18 play an important role in the formation of granulomatous lesions.

Clinical Features. Sarcoidosis is so insidious a disease that the clinical signs and symptoms frequently are not severe enough to cause alarm. While it is most commonly seen in young and middle-aged adults, it may occur later in life and is considerably more prevalent in blacks. Mild malaise and cough may be the chief features, although involvement of a specific organ may occur and be evidenced by dysfunction of that organ.

Cutaneous lesions, which are present in approximately 25–35% of all patients with sarcoidosis, may be the only distinct manifestation of the disease. These appear as multiple, raised red patches that occur in groups, grow slowly, and do not tend to ulcerate or crust. Erythema nodosum occurs in about 15% of the patients. Involvement of lymph nodes or salivary glands is manifested only by nodular enlargement, while hepatomegaly and splenomegaly may occur, owing to the presence of the disease in the liver and spleen.

Oral Manifestations. Since there are no series of cases of sarcoidosis of the oral cavity and jaws reported in the literature, but only scattered case reports, it is difficult to describe typical lesions. There are a number of reports in the literature of oral biopsies of clinically normal tissue in patients with proven sarcoidosis that revealed lesions, which were microscopically consistent with the disease. For example, Cahn and his associates found sarcoid granulomas in 38% of such a series of 23 patients known to have the disease; Nessan and Jacoway found similar granulomas in the labial glands of 58% of a group of 75 patients with the disease. Lesions on the lips that have been reported were manifested clinically as small, papular nodules or plaques, or resembled herpetic lesions or 'fever blisters'. On the palate and buccal mucosa, the lesions have been described as bleb-like, containing a clear yellowish fluid, or as solid nodules. It also appears that sarcoid may produce diffuse destruction of the bone.

Histologic Features. Sarcoid lesions closely resemble proliferative noncaseating nodules of tuberculosis, and the differential diagnosis is frequently difficult to establish. However, no acid-fast organisms can be demonstrated in tissue sections of sarcoidosis. Nests of epithelioid cells, with multinucleated giant cells, are one of the chief microscopic features of the fibrous granulomatous nodules. These granulomas also contain T and B cells, as well as various immunoglobulins that can be identified by appropriate immunofluorescence. Caseation and necrosis do not occur, although the granuloma ultimately transforms into a solid, amorphous, eosinophilic, and hyaline mass as it ages.

In spite of the microscopic similarity of tuberculosis and sarcoidosis, it should be pointed out that the tuberculin reaction is positive in no higher a percentage of the patients with sarcoid than in the general population. Moreover, there is a low incidence of complement-fixing antibodies against tuberculosis in these patients, and when present at all, this antibody titer is usually low.

An intracutaneous test for the diagnosis of sarcoidosis, the Kveim-Siltzbach test, has been devised, utilizing a suspension of human known sarcoidal tissue as the test agent. A study by Siltzbach on 311 patients with sarcoidosis has indicated a high degree of specificity of the test with few false-positive reactions. Thus, the Kveim-Siltzbach test may be an important aid in the early and accurate diagnosis of the disease.

Uveoparotid Fever
(Uveoparotitis, Heerfordt's syndrome)

Uveoparotid fever is considered by most investigators to be a form of sarcoidosis in which characteristically there is firm, painless, usually bilateral enlargement of the parotid glands, accompanied by inflammation of the uveal tracts of the eye and cranial nerve involvement. The submandibular and sublingual glands may be similarly involved, and even the lacrimal glands may be swollen, all features suggestive of Mikulicz's disease or Sjögren's syndrome. A chronic, low-grade fever is often present, and the patient may complain of lassitude, malaise and vague gastrointestinal disturbances or even nausea, and vomiting. Xerostomia is common. A patchy erythema of the skin has also been reported to be present early in the course of the disease. Enlargement of the cervical lymph nodes is seen in some cases.

The most common eye lesion in uveoparotitis, and often the earliest symptom, is uveitis, but conjunctivitis, keratitis, and corneal herpes among others have also been reported. Although the uveitis may begin unilaterally, it eventually becomes bilateral, and in most cases, results in some permanent visual impairment. The most common nerve involvement is unilateral or bilateral seventh nerve paralysis, which is said to occur in one-third to one-half of all cases.

The signs and symptoms of this syndrome usually disappear in time, although some swelling of the parotid glands and visual disturbance may persist.

Midline Lethal Granuloma

(Malignant granuloma, lethal granuloma, midline lethal granulomatous ulceration)

The lethal granuloma is a most unusual condition, resembling a serious infection, which has been best described as an idiopathic progressive destruction of the nose, paranasal sinuses, palate, face, and pharynx. The person afflicted characteristically appears to exhibit complete lack of resistance to the insidious progress of the disease.

It is recognized that many different specific diseases may have the same clinical manifestations as originally described for the midline lethal granuloma. These diseases have been listed by Tsokos and her colleagues, and are shown in Table 16-2. Some of these are infectious diseases, while others are neoplastic, and unquestionably, many of the early reports of midline lethal granuloma were in fact what are now recognized as polymorphic reticulosis or midline malignant reticulosis or even a conventional malignant lymphoma of the nose. Nevertheless, when all diseases in these first two categories are eliminated, there still remains a third group of lesions characterized by nonspecific acute and chronic inflammation without any evidence of the presence of causative microorganisms or malignancy. The two diseases in this category are Wegener's granulomatosis and the true midline lethal granuloma or 'idiopathic midline destructive disease', as termed by Tsokos and her coworkers. At one time, these two latter diseases were thought to be closely related. However, since Wegener's granulomatosis is a systemic disease and the lethal granuloma a purely localized one, they have been clearly separated and Wegener's disease will be discussed in another section. In a discussion of this subject in 1949, Williams presented the view that the lethal granuloma is due to a dysfunction of the immune mechanisms normally responsible for granuloma formation. In essence, a vascular 'allergy' occurs, either the Arthus phenomenon or periarteritis nodosa depending on whether capillaries or arterioles are affected, and the hyperimmune tissues become necrotic because of obstruction of the blood supply. It is usually theorized that it represents a response to an unidentified antigen. No etiologic association has been made with prior allergic rhinitis, chronic sinusitis or known infection.

Table 16-2: Diseases which may appear clinically as midline lethal granuloma

- I. Infectious diseases
  - A. Bacterial
    1. Brucellosis
    2. Rhinoscleroma
    3. Leprosy
    4. Actinomycosis
    5. Tuberculosis
    6. Syphilis
  - B. Fungal
    1. Histoplasmosis
    2. Candidiasis
    3. Coccidioidomycosis
    4. Blastomycosis
    5. Rhinosporidiosis
    6. Phycomycosis
  - C. Parasitic
    1. Leishmaniasis
    2. Myiasis
- II. Neoplastic diseases
  1. Squamous cell carcinoma
  2. Rhabdomyosarcoma
  3. Polymorphic reticulosis/lymphomatoid granulomatosis (T cell lymphoma)
  4. Conventional lymphoma
- III. Inflammatory diseases of unknown etiology
  1. Wegener's granulomatosis
  2. Idiopathic midline destructive disease

Modified from M Tsokos, AS Fauci, J Costa. Idiopathic midline destructive disease (IMDD). Am J Clin Pathol, 77: 162, 1982.

Clinical Features. The peculiar granulomatous lesion may begin as a superficial ulceration of the palate or nasal septum, often preceded by a feeling of stuffiness in the nose. It may bear a close clinical resemblance to carcinoma. This prodromal stage may persist for a month or two to several years. Eventually the ulceration spreads from the palate to the inside of the nose and thence to the outside. The palatal, nasal, and malar bones may become involved, undergoes necrosis, and eventually sequestrate. Destruction becomes the prominent feature of the disease, and loss of the entire palate is not uncommon. The patient may exhibit purulent discharge from the eyes and nose; perforating sinus tracts may develop, and much of the soft tissue of the face finally may slough away, leaving a direct opening into the nasopharynx and oral cavity. The patient ultimately dies of exhaustion or of hemorrhage if a large blood vessel becomes eroded.

Histologic Features. Microscopic examination of the affected tissue reveals extensive necrosis with infiltration of some inflammatory cells and the formation of occasional new capillaries.

The diagnosis of the disease is typically one of exclusion. The evaluation should include imaging studies (to delineate the extent of disease) as well as repeated biopsy (with sampling of lesional tissue for application of sophisticated tests including immunohistochemical studies, flow cytometry, or molecular studies.

Treatment. While the disease is usually fatal, corticosteroid therapy has proven beneficial in some cases, particularly when coupled with antibiotics for secondary infection. However, some authorities believe that the disease is best treated by high-dose radiation therapy.

Wegener's Granulomatosis

Wegener's granulomatosis is a disease of unknown etiology, which basically involves the vascular, renal, and respiratory systems. It does have certain features in common with the midline lethal granuloma but is considered to represent a separate disease entity. It involves the nose, paranasal air sinuses, lower respiratory tract, gut, joints, nervous system, and kidneys. Involvement of the kidney is the common cause of death.

Some investigators believe that this disease is caused by an abnormal immune reaction secondary to a nonspecific infection or a hypersensitivity reaction to an unknown antigen. The recent view regarding the inflammation in Wegener's granulomatosis is due to the formation of anti-neutrophil cytoplasmic antibody formation. Organs involved in Wegener's granuloma exhibit inflammation with granuloma formation against a nonspecific inflammatory background. A possible hereditary predisposition has been mentioned in some cases. The disease has been discussed in detail by Kornblut and his associates and by DeRemee and his coworkers, who proposed a unifying concept between midline lethal granuloma and Wegener's granulomatosis.

Clinical Features. Wegener's granulomatosis may occur at any age, from infants to the very elderly, although the majority of cases are in the fourth and fifth decades of life. There is a sight predilection for occurrence in males. It is best described as a multisystem disease, which is usually first characterized clinically by the development of rhinitis, sinusitis, and otitis or ocular symptoms. The patient soon develops a cough and hemoptysis as well as fever and joint pain. Hemorrhagic or vesicular skin lesions are also commonly present. Granulomatous lesions of the lungs are found on the chest radiograph, while the glomerulonephritis, which develops ultimately, leads to uremia and terminal renal failure. In nervous system, sensory neuropathy may be an occasional finding.

Oral Manifestations. Involvement of the oral cavity occurs with considerable frequency in Wegener's granulomatosis. However, only rarely is the oral lesions manifest first. In reported cases, involvement of the gingiva has been the most common and characteristic manifestation, and is termed as strawberry gingivitis. Brooke, in reviewing reported cases with oral lesions of this nature, has pointed out that the gingival lesions may be ulcerations, friable granular lesions, or simply enlargements of the gingiva. The inflammatory process starts in the interdental papilla and spreads rapidly to the periodontal structure and leads to bone loss and tooth mobility, Israelson and his associates have reported a case characterized by hyperplastic gingivitis in which this was the patient's main complaint. However, as Cawson has pointed out, other lesions may occur such as ulceration of the palate by extension of the disease from the nose, where destruction of the nasal septum may develop; also occurring are small ulcerations resembling aphthae, diffuse ulcerative stomatitis, spontaneous exfoliation of teeth, and failure of tooth sockets to heal following extraction.

Laboratory Findings. Laboratory findings include anemia, leukocytosis, elevated sedimentation rate, and hyperglobulinemia. Because of kidney involvement, hematuria is common as well as the finding of albumin, casts, and leukocytes in the urine. Circulating immune complexes have been demonstrated in some patients, but this is not a consistent finding.

Histologic Findings. Wegener's granulomatosis presents a pattern of mixed inflammation centered around the blood vessels. The lesions in the upper respiratory tract and lungs consist of giant cell necrotizing granulomatous lesions showing vasculitis. Oral biopsy specimens show pseudoepitheliomatous hyperplasia and subepithelial abscesses. The gingival and other lesions show a nonspecific granulomatous process with scattered giant cells.

Treatment. The majority of cases of Wegener's granulomatosis formerly terminated fatally. The mean survival rate of untreated patients is five years. However, cytotoxic agents, especially cyclophosphamide, and prednisone have provided a good prognosis for these patients, with many known long-term remissions.

Chronic Granulomatous Disease

Chronic granulomatous disease, first described as a specific entity in 1957, is an uncommon hereditary disease with an X-linked mode of transmission, although there appears to be a variant, transmitted as an autosomal recessive characteristic. Thus, the majority of patients are males, although affected females have been reported. The disease is generally found in infants and children but is also seen in young adults. One variant of this disease is known as familial lipochrome histiocytosis.

The condition is characterized by severe recurrent infections as a result of a defect of intracellular leukocyte enzymatic function with a decreased oxidative metabolism in which there is failure to destroy certain catalase-positive microorganisms, including staphylococci, enteric bacilli (Klebsiella, Aerobacter, *E. coli*, *S. marcescens*, *Pseudomonas*, *Proteus*, and *Salmonella*) and certain fungi (*Candida*, *Aspergillus*, and *Nocardia*). Other microorganisms such as streptococci and pneumococci are readily destroyed by the leukocytes. The chemotactic and phagocytic functions of the leukocytes are generally unimpaired.

Clinical Features. The disease is characterized by widespread infection from infancy, usually affecting lymph nodes, lung, liver, spleen, bone, and skin, the latter commencing with eczematous lesions about the face, leading to tissue necrosis and granuloma formation. Abscesses, septicemia, pneumonia, pericarditis, meningitis, and osteomyelitis are but examples of the various forms, which the disease may take.

Oral Manifestations. Oral lesions have been reported in a number of cases of chronic granulomatous disease and have been discussed by Wysocki and Brooke. The lesions have consisted chiefly of a diffuse stomatitis with or without solitary or multiple ulcerations. One patient with over a dozen oral ulcers of the buccal mucosa has been reported by Wolf and Ebel. In several patients, benign migratory glossitis has

also been present but its relationship to the disease, if any, is not clear. In addition, Scully has reported enamel hypoplasia of permanent teeth in three cases, probably a result of the severe early infection.

Histologic Features. Microscopic examination of ulcerated lesions of the oral mucosa have been described as consisting of small granulomas with mononuclear histiocytes and multinucleated giant cells. Central necrosis with polymorphonuclear leukocytes may also be present.

Diagnosis. The diagnosis is established by neutrophil function tests—the impairment of *in vitro* microbicidal activity and failure of reduction of nitroblue tetrazolium (NBT) test.

Treatment. Treatment is solely vigorous treatment of the infection.

Angioedema

(Angioneurotic edema, Quincke's edema, giant urticaria)

Angioedema is a diffuse edematous swelling of the skin, mucosa, and submucosal connective tissues. It results in death occasionally when the gastrointestinal or respiratory tract is involved.

Pathogenesis. Quincke, describing this disorder as early as in 1882, related the changes observed to an alteration in vascular permeability. Considering the fact that many angioedema patients present with psychological problems, it has also been erroneously referred to as 'angioneurotic edema' in the past.

The commonly observed causes of angioedema are as follows:

- ***Allergic angioedema (due to mast cell degranulation)***: Mast cell degranulation, which leads to histamine release and the typical clinical manifestations, is seen commonly in IgE-mediated hypersensitivity reactions caused by drugs, foods, plants, dust, and inhalants. It is also observed in contact allergic reactions to foods, cosmetics, topical medications, and even dental rubber dams. Interestingly, mast cell degranulation can result even from physical stimuli such as heat, cold, physical exercise, emotional stress, and solar exposure.
- ***Associated with use of angiotensin-converting enzyme (ACE) inhibitors***: This pattern of angioedema is not mediated by IgE and is related to the use of ACE inhibitors, commonly used in the treatment of hypertension. These drugs cause angioedema by increasing the levels of bradykinin. It is a peptide with potent vasodilating action, causes rapid accumulation of fluid in the interstitium. This form of angioedema usually arises within hours of initial use of the drug.
- ***Activation of the complement pathway***:
  - Hereditary form: Two rare autosomal dominant hereditary forms are seen. Type I, comprising 85% of the cases, is caused by a quantitative reduction in the inhibitor that prevents the transformation of C1 to C1 esterase. Without adequate levels of this inhibitor (C1-INH), C1 esterase cleaves C4 and C2 and results in angioedema. Type 2 exhibits normal levels of C1-INH, but the inhibitor is nonfunctional.
  - Acquired form: Seen in association with certain type of lymphoproliferative diseases in patients who develop specific antibodies. The lymphoid proliferation increases the consumption of C1-INH, and the autoantibodies prevent the binding of C1-INH to C1.
- Due to the presence of high levels of antigen-antibody complexes (e.g. in lupus erythematosus, bacterial, or viral infections).
- In patients with grossly elevated peripheral blood eosinophil counts.

Clinical Features. Angioedema manifests as a soft, nontender, diffuse edematous swelling of relatively rapid onset, which may be solitary or multiple, most commonly involving the face around the lips, chin, eyes, lips, tongue, pharynx, and larynx (Fig. 16-4). Sometimes the hands, arms, legs, genitals, and buttocks are involved. Involvement of the skin and mucous membrane can cause enlargements that can measure upto several centimeters in diameter. The eyes may be swollen and shut and the lips extremely puffy. The symptoms appear rapidly, sometimes being present when the patient awakens in the morning. A feeling of tenseness or an itching or prickly sensation sometimes precedes the urticarial swelling. The skin may be of normal color or slightly pink. Perioral and periorbital edema are characteristic of allergic edema. Intraoral edema is typical of allergic edema and edema related to ACE inhibitors.

The enlargement usually resolves within 24–72 hours, although some cases persist for several days. The frequency of the attacks cannot be predicted; sometimes they appear daily, other times at intervals of months or even years. The disease affects both genders about equally, but is infrequent in children. Some cases seem to originate at puberty.

The hereditary forms of angioedema may be more dangerous because of involvement of respiratory and gastrointestinal systems. In these forms, most affected patients become symptomatic during the second decade of life and then follow a variable frequency of recurrences, most of the attacks occurring

Figure 16-4. Angioedema.
The patient exhibits diffuse swelling of the cheeks and lips *(Courtesy of Dr Anitha Balan, Department of Oral Medicine, Government Dental College, Thiruvananthapuram).*

without any apparent reason. Involvement of the upper airway can be life threatening. Hoarseness of voice and difficulty in breathing are important signs. Gastrointestinal symptoms include continuous pain, vomiting, and rarely watery diarrhea.

Treatment and Prognosis. When the etiologic agent, such as food, can be discovered, its elimination from the diet will prevent recurrent attacks. The causative agent can seldom be detected, however. Once developed, the edema can be treated by antihistaminic drugs with usually prompt relief. If the attack is not controlled or if laryngeal involvement is present, intramuscular epinephrine should be administered. If epinephrine does not stop the attack, intravenous corticosteroids and antihistamines should be given. Cases of angioedema related to ACE inhibitors are not IgE-mediated and may not respond to antihistamines and corticosteroids.

The disease is annoying, but in itself is seldom dangerous unless edema of the glottis or respiratory tract occurs. In such instances tracheotomy may be necessary.

Those cases related to C1-INH deficiency do not respond to antihistamines, corticosteroids, or adrenergic drugs. Intubation and tracheostomy may be necessary in such cases. C1-INH concentrate and esterase-inhibiting drugs are the treatment of choice for acute attacks. In such hereditary and acquired forms of abnormal C1-INH activity, minor trauma such as a dental procedure can precipitate an attack. Because such attacks of hereditary angioedema are potentially life threatening, prevention is paramount. Patients should avoid violent physical activity and trauma. Prophylaxis is recommended for patients with more than three attacks per year. Androgens such as danazol or stanozol induce hepatic synthesis of C1-INH and are hence used for both hereditary and acquired forms (lymphoproliferative type) of angioedema. However, the autoimmune acquired type is prevented best by corticosteroids.

Newer drugs like ecallantide, a kallikrein inhibitor, a recombinant C1-INH, and icabant, a bradykinin-B2 receptor antagonist are proved to be beneficial in kinin-induced angioedema.

Drug Allergy

(Drug idiosyncrasy, drug sensitivity, stomatitis or dermatitis medicamentosa)

Drug allergy includes a variety of sensitivity reactions following exposure to any one of a great many drugs and chemicals but is not related to any pharmacologic activity or toxicity of these materials. Practically every known drug has been recognized at one time or another as capable of producing an allergic reaction in a sensitive person. Certain drugs; however, have a far greater tendency to produce reactions than others. Furthermore, some patients have a greater susceptibility to drugs and manifest reactions more readily than others. This is particularly true in patients who have other allergic diseases, such as asthma or hay fever.

It is impossible to list even a small portion of the drugs, which have been known to produce an allergic reaction, because of their overwhelming numbers. However, the most common drugs associated with specific allergic oral mucosal reactions are mentioned in the discussion later.

Pathogenesis. One of the following several mechanisms may be involved in drug allergy:

- IgE mediated reactions may occur when the drug reacts with IgE antibody bound to mast cells, with subsequent release of chemical mediators.
- An antibody binds to the drug that is already attached to a cell surface. The pathologic changes that ensue depend on the target cell involved.
- The antigen circulates for extended periods, allowing sensitization of the patient's immune system and the production of a new antibody. Subsequent binding of antigen and antibody results in circulating complexes that may be deposited in various sites, producing conditions like dermatitis. Disease caused by this mechanism is also referred to as serum sickness.
- In nonimmunologic drug reactions, drugs directly affect the mast cells, causing release of chemical mediators. These reactions are thus not dependent on antibody production.

Clinical Features. The various allergic reactions to systemic administration of a drug are seldom anaphylactic in suddenness of appearance, but instead occur several hours to several days or longer after the beginning of the drug administration. Occasionally an immediate severe reaction occurs. The common allergic reactions to systemic administration of a drug include skin lesions, arthralgia, fever, lymphadenopathy, and rarely agranulocytosis (q.v.). The allergic reaction of the skin is called dermatitis medicamentosa. The skin lesions may be of erythematous type, as in erythema multiforme (q.v.), urticarial in nature, manifest as exfoliative dermatitis, or as fixed drug eruptions. Commonly drugs such as aspirin, barbiturates, chloramphenicol, tetracycline, penicillin, streptomycin, and sulfonamides are implicated in allergic drug reactions.

Oral Manifestations. An allergic reaction of the mucosa to the systemic administration of a drug is called stomatitis medicamentosa. Such reactions in oral mucosa, considerably less common than the analogous cutaneous reactions, present in various patterns, almost as much as the number of drugs causing these changes.

Common reactions produced in the oral cavity are stomatitis, ulceration and necrosis, hemorrhage, gingival hyperplasia, pigmentation, altered salivary function, and altered taste sensation (Fig. 16-5).

The most common type of allergic reaction of oral mucosa is erythema multiforme (q.v.), characterized by multiple ulcerations of the tongue, palate, buccal mucosa, and gingiva, with associated pain and discomfort. The other common patterns of oral mucosal disease are anaphylactic stomatitis, intraoral fixed drug eruptions, lichenoid drug reactions, lupus erythematosus-like eruptions, pemphigus-like eruptions, and nonspecific vesiculoulcerative lesions.

Anaphylactic stomatitis arises after the drug enters the circulatory system and binds to IgE-mast cell complexes. Most commonly, penicillin (Fig. 16-6) and sulfa drugs produce anaphylactic stomatitis even though the number of drugs that can precipitate this condition is endless. The oral lesions

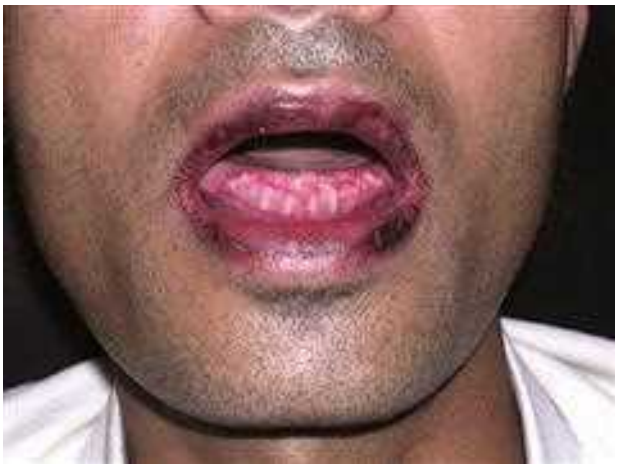


Figure 16-5. Stomatitis medicamentosa.
(Courtesy of Dr Poonja LS, Dr G Sriram, Dr Vaishali Natu, Nair Hospital Dental College, Mumbai).

may occur alone or in association with urticarial skin lesions or other signs and symptoms of anaphylaxis (like hoarseness, respiratory distress, and vomiting). The affected mucosa exhibits diffuse distribution of lesions, varying in appearance from multiple areas of erythema to extensive areas of erosion or ulceration.

Intraoral fixed drug eruptions may occur in patients who are administered on repeated occasions, a drug to which they are sensitive. This 'fixed' eruption is characterized in the appearance of a skin reaction at the same sites each time and is apparently due to local sensitization of the tissues. Nevertheless the skin 'patch' test is negative. Drugs commonly implicated in such allergic reactions include barbiturates, salicylates, phenazone derivatives, sulfonamides, and tetracycline. The oral lesions appear as localized areas of erythema and edema, commonly seen on the labial mucosa and can later develop into vesiculoulcerative lesions.

Lichenoid drug reactions, lupus erythematosus-like eruptions, and pemphigus-like eruptions resemble their namesakes clinically, histologically, and immunologically. Usually bilateral and symmetric oral lesions are seen in these drug reactions, commonly involving the posterior buccal mucosa and the lateral borders of the tongue, even though any mucosal surface may be involved. The list of drugs causing these chronic drug eruptions are endless and beyond the scope of this textbook.

Oral lesions of the gingiva often resemble necrotizing gingivitis or Vincent's infection. Hairy tongue, black, brown, or yellow, has been reported as a complication of antibiotic therapy, particularly with penicillin. In this condition, there is elongation and staining of the filiform papillae, producing a heavy coating of the tongue. It has been suggested that this reaction is not due to the direct effect of the antibiotic on the tongue, but to the alteration of oral bacterial flora, with an overgrowth of fungal elements and subsequent overgrowth of papillae. Alteration of intestinal flora with disturbances in elaboration of vitamins or vitamin components may also play some role, since vitamin deficiencies are readily mirrored in the tongue. The lingual papillae will sometimes be desquamated after antibiotic therapy, leaving a smooth, painful, inflamed tongue, which may become eroded.

Histologic Features. A nonspecific pattern of subacute mucositis with an admixture of lymphocytes, eosinophils, and neutrophils is observed in anaphylactic stomatitis. Similar features along with spongiosis and exocytosis of the epithelium, vacuolar change of the basal layer, and individual necrotic epithelial cells are characteristic of fixed drug eruptions. The drug reactions that resemble lichen planus, lupus erythematosus, and pemphigus resemble their namesakes. Even though these chronic drug eruptions cannot be separated from their primary associated immunologic disease, a distinctive annular fluorescence pattern, termed **string of pearl's** has been noted along cell membrane of the basal layer cells in lichenoid reactions, by indirect immunofluorescence. The detected circulating antibody in this instance has been termed **basal cell cytoplasmic antibody**.

Treatment and Prognosis. The signs and symptoms of drug allergy usually regress with discontinuance of the

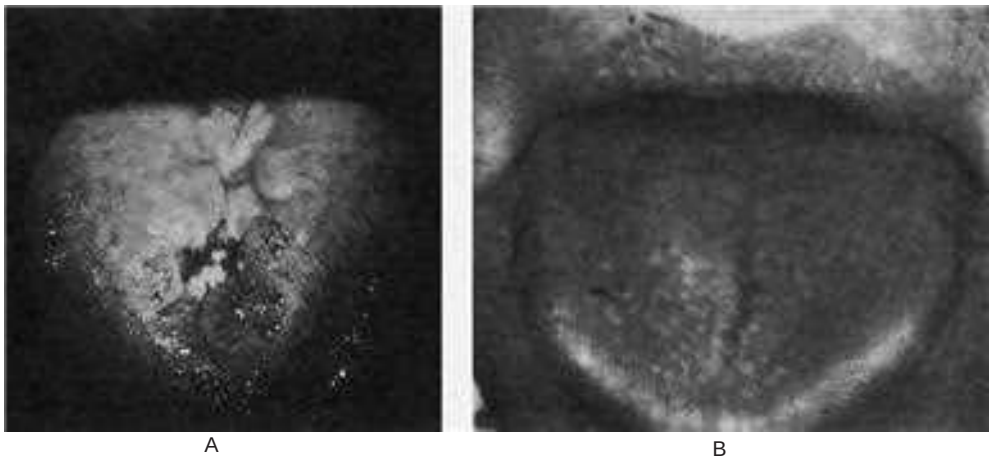


Figure 16-6. Allergic reactions to penicillin.
The tongue may become ulcerated **(A)** or denuded of papillae **(B)** in a penicillin reaction *(Courtesy of Dr Boynton H Booth).*

causative agent. The localized acute signs may be relieved by the administration of antihistaminic drugs or cortisone. Systemic manifestations warrant the use of adrenaline, corticosteroids, or antihistamines in case of anaphylactic stomatitis. Recurrence can be prevented only by complete abstinence from use of the particular drug involved.

Contact Stomatitis and Dermatitis

(Stomatitis and dermatitis venenata)

A contact allergy is a type of reaction in which a lesion of the skin or mucous membrane occurs at a localized site after repeated contact with the causative agent. These causative agents are chemical in nature (haptens) and require conjugation with proteins to become effective. This process occurs with the aid of the intraepithelial Langerhans cell where the hapten is converted into a competent antigen and is presented to the T lymphocytes for sensitization and production of IgE with specific receptors. Following antigenic rechallenge, local lymphocytes secrete chemical mediators of inflammation (lymphokines) that produce the clinical and histologic changes characteristic of this process.

There have been literally thousands of such allergens, varying from simple chemical elements to exceedingly complex organic substances. Many of these materials have come to represent hazards of occupation because of the wide use of organic compounds in industry. Certain initiating agents produce lesions upon contact because of their inherent irritating nature rather than as a result of an allergic phenomenon. In general, the reaction to the true contactant does not appear immediately as do reactions to simply irritating substances such as inorganic acids or other escharotics. It would be inappropriate to attempt to list even the more common contactants, which are recognized as causing dermatitis, because of the overwhelming numbers. But there is a well-recognized group of materials which frequently cause the oral lesion or stomatitis venenata, and which for this reason are of special interest to the dentist. These may be classified as follows:

1. **Dental or cosmetic preparations**
   - Dentifrices
   - Mouthwashes
   - Denture powders
   - Lipstick, candy, cough drops, chewing gum
2. **Dental materials**
   - Rubber dam
   - Vulcanite
   - Acrylic
   - Metal alloy base
3. **Dental therapeutic agents**
   - Alcohols
   - Antibiotics
   - Iodides
   - Phenols
   - Procaine
   - Volatile oils

Clinical Features. Contact dermatitis is manifested by the occurrence of an itching or burning sensation at the site of contact, followed shortly by the appearance of an erythema and then vesicle formation. After rupture of the vesicles, erosion may become extensive, and if secondary infection occurs, the lesions may be serious. In chronic contact, the skin may become thickened and dry.

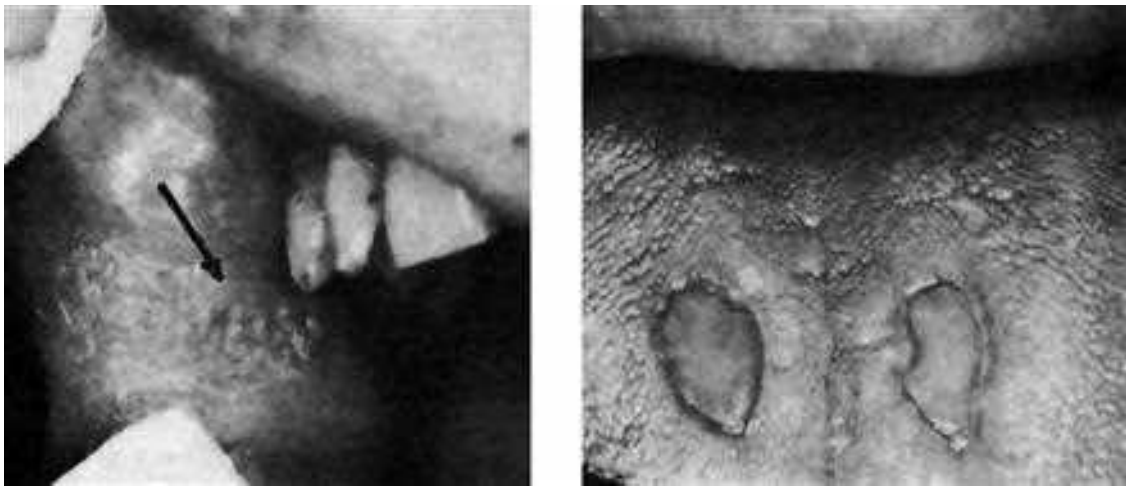
Oral Manifestations. Although the oral cavity is exposed to a wide variety of antigens, the frequency of a true allergic reaction to any one antigen from this contact appears to be rare. This is because the oral cavity is less sensitive than the skin surface, probably due to the shorter period of contact in the oral cavity, the fact that saliva dilutes and removes many antigens the possibility of rapid dispersal and absorption of antigens as facilitated by the anatomy of the oral mucosa, and the fewer chances for the antigen to be recognized considering the lower density of Langerhans cells and T lymphocytes.

Contact stomatitis or stomatitis venenata, demonstrates a variety of manifestations analogous to dermatitis venenata. After contact with some material to which the patient is sensitive, the mucosa becomes remarkably inflamed and edematous, the reaction imparting a smooth, shiny appearance to the surface. When the gingiva is involved, the tissue is uniformly bright red in all quadrants, in contrast to the plaque-induced gingivitis which is more localized and usually spares attached gingiva. Buccal mucosa is usually puffy and dark red, revealing engorged and ejected superficial capillaries on closer examination. Small vesicles may form, but these are transient and soon rupture to form small areas of erosion and ulceration, which may become extensive in some cases (Fig. 16-7). Such swollen and edematous features subject to erosion and ulceration are more common in the lips. Secondary infection is particularly common. These features are usually accompanied by a rather severe burning sensation. Itching, stinging, tingling, and edema may also be noted.

In chronic cases, the affected mucosa is typically in contact with the causative agent and may be erythematous or white and hyperkeratotic. The other common patterns in chronic contact include erosions, widespread erythema (usually associated with toothpastes), lip lesions similar to those induced by chronic irritation (chronic dryness, scaling, fissuring, or cracking of vermilion border of lip), symptoms identical to orolingual paresthesia, and plasma cell gingivitis (q.v.).

The reaction to various dental or cosmetic preparations is not especially common. Nearly every brand of dentifrice; however, has been reported to produce a contact stomatitis in certain persons. In most instances, the flavoring agent is responsible. The same holds true for mouthwashes, denture powders, candy, and chewing gum. Lipstick will sometimes incite a particularly violent reaction of the lips in a sensitized woman, producing severe edema and ulceration.

Certain dental materials have been implicated in causing a contact stomatitis. Acrylic has been reported occasionally to induce a contact allergy when used either as a denture base or as a filling material. The sensitivity may develop shortly after insertion of the denture or filling or not for a considerable



A B

Figure 16-7. Contact stomatitis.
The vesicular eruption of the buccal mucosa in **(A)** was due to chewing leaves of the poison ivy plant, while the ulcers of the tongue in **(B)** were caused by application of 'headache powder' *(A, Courtesy of Dr Henry M Swenson and B, of Dr Stephen F Dachi)*.

period of time, even many months. The tissues in contact with the material become highly inflamed and are painful. In most cases, the patient has been found by means of the patch test to be sensitive to the monomer and such sensitivity is most common in cases of incomplete polymerization of the acrylic. It is important to realize that the majority of cases of inflamed mucosa that appear to arise from contact with an acrylic denture are not due to an acrylic sensitivity, but to the fact that the denture does not fit properly and is physically irritating. Also, the predominant cause for the erythematous mucosa associated with dentures is oral candidal infection. True acrylic sensitivity is extremely uncommon. Allergy to metal base alloys is also rare.

Lea and his coworkers studied numerous compounds of epoxy resins, some of which are now in use in dental practice and have found that at least one uncured resin, one uncured resin modifier, and several amine curing agents were both irritating and sensitizing to skin and thus, presumably, to oral mucous membrane.

A variety of therapeutic agents used topically in the oral cavity may produce bothersome or even serious allergic reactions. These include such common materials as antibiotics, alcohol, chloroform, phenol, or volatile oils. In the case of antibiotic lozenges or troches, it is frequently the flavoring agent rather than the antibiotic itself, which causes the reaction. Of particular significance to the dentist is the fairly common allergy to procaine. This danger is of greater importance to the dentist than to patients, since the most common site of eruption is on the hands of the dentist. Considering the necessarily constant use of this local anesthetic agent, this can be professionally very serious. It may be necessary to discontinue all contact with and use of the solution, or to use rubber gloves when administering the anesthetic.

Besides these common contactants, two compounds, cinnamon and amalgam, demonstrate clinical and histopathological features that are sufficiently unique to justify separate descriptions. They are discussed in detail in the next part of the text.

Histologic Features. Intra- and inter-cellular edema of the epithelium along with vesicle formation within the epithelium or at the basement membrane is usually seen. Engorged and dilated blood vessels are seen in the connective tissue against a background of edema and an infiltrate of lymphocytes and plasma cells. In some lesions, the allergen elicits a heavy plasma cell response as observed in plasma cell gingivitis. Increased number of eosinophils is a common finding in allergic reactions.

Diagnosis. Patch test may be a useful investigation to identify the causative agent.

Treatment and Prognosis. The only treatment for contact dermatitis or stomatitis consists in discontinuing all contact with the offending material. When this is done, there is usually prompt remission of all lesions.

Contact Stomatitis from Cinnamon Flavoring

Cinnamon oil is used as flavoring agent in confectionery, ice cream, soft drinks, alcoholic beverages, processed meat, gum, candy, toothpastes, breath fresheners, mouthwash, and even dental floss. The flavoring constitutes up to 100 times that in the natural spice, and therefore oral reactions are commonly documented in products with prolonged or frequent contact like candy, chewing gum, and toothpaste.

Clinical Features. The clinical presentation in contact dermatitis due to toothpaste is more diffuse, characterized by plasma cell gingivitis (q.v.) like lesions of the gingiva, associated with enlargement, edema, and erythema. Other features include erythematous mucositis of buccal mucosa and tongue, exfoliative cheilitis, and circumoral dermatitis. Chewing gum and candy produce more localized lesions not involving the

vermilion border of lip or circumoral skin. The oral lesions commonly seen in the buccal mucosa are oblong hyperkeratotic lesions with an erythematous base, seen aligned along the occlusal plane. Lesions may also be observed on the lateral border of the tongue. Lingual keratosis may mimic oral hairy leukoplakia or carcinoma.

Histologic Features. Histologically, an acanthotic epithelium, with elongated rete ridges, thinned suprapapillary plates, hyperkeratosis, and neutrophil exocytosis is observed. The underlying connective tissue exhibits a diffuse chronic inflammatory infiltrate predominantly consisting of lymphocytes, with characteristic perivascular infiltration of lymphocytes.

Treatment and Prognosis. The reactions from cinnamon flavoring disappear within a week of discontinuance of cinnamon products. However, the lesions reappear within 24 hours if the patient resumes intake of the product.

Contact Stomatitis from Chronic Oral Mucosal Contact with Dental Amalgam

The widespread use of dental amalgam has been concurrently associated with numerous ailments like neurotoxicity, kidney dysfunction, reduced immunocompetence, alterations of oral and intestinal flora, birth defects, and adverse effects on general health. Even though no evidence is available to prove any relationship between these disorders and the use of amalgam, acute and chronic reactions to the mercury or a mercury-containing compound have been reported at a frequency of one case per million. These reactions clinically and histologically mimic lichen planus, with minimal or no clinical improvement of the lesions upon removal of the amalgam restorations. Among the patients previously diagnosed with lichenoid lesions, a subgroup exhibits lesions that do not migrate, usually involving only the mucosa directly in contact with the amalgam restoration, and resolving rapidly after removal of the dental amalgams. These lesions are termed as contact lichenoid reactions to amalgam.

P Koch and FA Bahmer based on their study involving 194 patients concluded that sensitization to mercury is an important factor in oral lichenoid lesions.

Clinical and Histologic Features. Such amalgam induced contact reactions are commonly observed in the posterior buccal mucosa, ventral border of the tongue, and gingival cuffs adjacent to subgingival amalgam restorations. The lesions appear white or erythematous with or without striae. Histologically, features similar to lichen planus like hydropic degeneration of basal cell layer, hyperkeratotic or atrophic epithelium, and dense band-like chronic inflammatory infiltrate consisting predominantly of lymphocytes are observed, occasionally with perivascular lymphoid aggregates.

Treatment and Prognosis. Management should be aimed at improving oral hygiene, smoothening, polishing, and recontouring of the restoration before adopting aggressive measures. If unsuccessful, the amalgam in question should be removed and replaced with a non-metallic restoration.

Lichenoid Reaction

(Lichenoid mucositis, lichenoid drug reaction, lichenoid lesions)

Lichenoid reactions (LR) represent a group of lesions similar to lichen planus clinically and histologically. These may involve skin or oral mucosa. As early as in 1929 drug-induced oral lichenoid reactions were mentioned, and were later cited in 1971 by Almeyda and Levantine. But unlike lichen planus the underlying cause is identifiable and withdrawal of the same leads to remission of these lesions.

Etiology. The exact mechanism of the development of lichenoid reaction is not known, but a series of triggering factors, such as dental restorative materials, graft-versus-host disease, a broad range of drugs, flavoring agents, and tobacco chewing are identified in the causation of LR.

Drugs such as antimalarials, non-steroidal anti-inflammatory drugs, antihypertensive agents, oral hypoglycemics, and beta blockers were reported to be associated with LR. Scully and Diz Dios have reported oral lichenoid reactions associated with antiretroviral therapy in HIV infection. Dental restorative materials such as silver amalgam, gold, cobalt, palladium, chromium and epoxy resins, preservatives and flavoring agents commonly used in foods and dentifrices also trigger LR.

Contact hypersensitivity to dental restorative materials was attributed to galvanism in the past. But recent studies have suggested a cell mediated contact hypersensitivity to dental materials in the susceptible individuals, and the contact allergy to dental materials mostly involves type IV delayed hypersensitivity reaction. Oral lichenoid reactions are considered to be a part of the spectrum of graft-versus-host disease.

Daftary and coworkers as early as in 1980 reported lichen planus-like lesion in tobacco chewers.

Clinical Features. They are present as reticular, erythematous, erosive lesions or ulcerations, with whitish streak similar to that of Wickham's striae of lichen planus. Clinical manifestations of LR are very much similar to that of lichen planus. An important factor which distinguishes LR from lichen planus is its atypical location and absence of bilateral occurrence.

Diagnosis. There is no specific test for the diagnosis of LR. The widely accepted criterion is based on the observation of disappearance of the lesions after withdrawal of triggering agent and recurrence of the lesions when they are reintroduced.

Histologic Features. Though histologically LR has superficial resemblance to lichen planus there are notable differences. The inflammatory infiltrate is diffuse and extends deeper into the lamina propria unlike the sharp band of infiltrate seen in lichen planus. Inflammatory infiltrate consists of plasma cells and eosinophils in addition to lymphocytes. Increased numbers of colloid or Civatte bodies may be present in LR. A perivascular chronic inflammatory cell infiltrate can be seen in drug related lichenoid lesions, which is not commonly found in lichen planus. Epithelial dysplasia associated with a band-like inflammatory infiltrate which on low-power can mimic lichen planus and is known as **lichenoid dysplasia**, and which may be seen in proliferative verrucous leukoplakia

(PVL), an unusual form of leukoplakia, shares some demographic and clinical similarities with lichen planus. PVL occurs most commonly in older female patients and is not associated with tobacco usage.

Treatment and Prognosis. Identification and elimination of the triggering factors play a major role in the management of LR. Lichenoid lesions can take many months or longer to resolve. As per Haute and coworkers, the malignant transformation rate is reportedly higher in oral lichenoid lesions which do not have all the typical clinical and histologic features of oral lichen planus.

Perioral Dermatitis

A unique inflammatory skin disease of the circumoral area has been reported to arise as an idiosyncratic response to the use of exogenous substances such as tartar-control toothpaste, bubblegum, moisturizers, night creams, and other cosmetic products. Termed as perioral dermatitis, this condition is worsened by the use of topical corticosteroids and thus a majority of patients report use of topical corticosteroids as the possible inciting agent.

Clinical Features. Classically, the lesions present as papules or papulopustules, involving the skin surface surrounding the vermilion border of the lips, with a zone of spared skin immediately adjacent to the vermilion border. Pruritus may be present. Such lesions are increasingly seen in women pointing to the use of cosmetic products. The lesions associated with tartar-control toothpastes present as a zone of erythema, without the papules or pustules, immediately adjacent to the vermilion border without the classic sparing of this area. Such lesions are specially referred to as circumoral dermatitis.

Histologic Features. A chronic lymphohistiocytic dermatitis or a rosacea-like pattern mimicking sarcoidosis has been commonly observed.

Treatment and Prognosis. Management consists of discontinuance of the topical corticosteroids and prescribing topical metronidazole, with or without topical tetracycline. Recurrences are uncommon.

Latex Allergy

Latex allergy has been reported frequently in last few years. Dental surgeons, dental students, and other healthcare providers appear to be at the risk of latex allergy in spite of the fact that the present situation warrants the use of protective gloves. Though latex allergy is usually of type I hypersensitivity reaction, contact dermatitis also could occur due to other irritants. The immediate reactions are urticaria, rhinitis, and edema around eyelids. Use of nonlatex products or cotton liners is advocated to such latex allergic individuals. Acute systemic reactions may be life-threatening at times.

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SECTION V

Diseases of Specific Systems

SECTION OUTLINE

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CHAPTER 17

Diseases of Bone and Joints

(Non-neoplastic and Non-infectious Disorders of Bone, Skeletal Dysplasias/Dysostoses, Constitutional Bone Disorders)

CHAPTER OUTLINE

The diseases of bone to be considered in this chapter do not include specific infections, neoplasms or other recognized injuries restricted to the jaws, but constitute a group of generalized skeletal diseases which frequently manifest involvement of the maxilla or mandible and therefore the use of the term 'diseases' should be viewed with caution, but is adapted here more in a general context. The category of diseases described here may be better called constitutional bone disorders due to the reasons mentioned. Bone is a dense calcified tissue which is specifically affected by a variety of diseases that often cause it to react in a dynamic fashion. Some of these diseases involve the entire bony skeleton, while others affect only a single bone. It is characteristic for certain of these conditions to follow a strict Mendelian pattern of heredity, although sometimes a specific disease will be inherited in one case and apparently not in another.

The maxilla and mandible, like other bones, suffer from both the generalized and the localized forms of skeletal diseases. Although the basic reactions are the same, the peculiar anatomic arrangement of teeth embedded partially in bone, through which the bone may be subjected to an unusual variety of stresses, strains and infections, often produces a modified response of bone to the primary injury.

Skeletal **dysplasias** are a heterogeneous group of disorders, which result in disproportionate short stature. The nomenclature of these disorders remains confusing. In an attempt to develop uniformity, an international nomenclature and classification was proposed in 1969 and then updated many times later. In the 1992 revision, the classification was based on radiodiagnostic and morphologic criteria. In the 1997 revision, the groups of disorders were rearranged based on current etiopathogenetic information regarding the gene and/or protein defect in these disorders (Table 17-1). In the 2001 revision, the term **dysostoses** was incorporated in the nomenclature. All these revisions merely reflect the complexity of skeletal-genetic phenotypes. Over the recent years the accumulation of knowledge on genes and proteins responsible for genetic disorders of the skeleton has been unprecedented. A molecular pathogenetic classification of skeletal dysplasias based on the structure and function of the causative gene and protein was recently proposed (Table 17-2).

DEFINITIONS

Osteochondrodysplasias refer to abnormalities of cartilage or bone growth and development. This term denotes a generalized disorder of the skeletal system encompassing multiple bones at the time of presentation.

Dysostoses refer to malformations of individual bones, single or in combination, and does not refer to a generalized disorder of the skeleton. Many disorders that were previously referred to as dysostoses are now listed with the osteochondrodysplasias, since they are due to mutations of genes associated with dysplasias, and therefore, of a more generalized nature.

The clinical evaluation should start with a complete medical history that includes previous milestones of growth. Since skeletal dysplasias may become apparent at various ages, study of growth points since birth may help to narrow the differential diagnosis. The family history should include information about other affected family members and possible consanguinity. Parents should be examined for evidence of disproportionate stature or other evidence of a skeletal dysplasia. Physical

Table 17.1. International nosology and classification of genetic disorders of bone —2006

Disorder	Inheritance	Locus	Gene name	Protein	Notes
1. FGFR3 group					
Thanatophoric dysplasia type 1 (TD1)	AD	4p16.3	FGFR3	FGFR3	Includes previous San Diego type PLSD. See also severe spondylodysplastic dysplasias (Group 13)
Thanatophoric dysplasia type 2 (TD2)	AD	4p16.3	FGFR3	FGFR3	
Achondroplasia	AD	4p16.3	FGFR3	FGFR3	
Hypochondroplasia	AD	4p16.3	FGFR3	FGFR3	
SADDAN (severe achondroplasia-developmental delay-acanthosis nigricans)	AD	4p16.3	FGFR3	FGFR3	
Hypochondroplasia-like dysplasia	AD, SP				Similar hypochondroplasia but unlinked to FGFR3, probably to heterogeneous
See also Group 30 for craniosynostosis syndromes due to FCFR3 mutations; Torrance dysplasia (Group 2) and the severe spondylodysplastic dysplasias (Group 12)					
2. Type 2 collagen group					
Achondrogenesis type 2 (ACG2; Langer-Saldino)	AD	12q13.1	COL2A1	Type 2 collagen	
Platyspondylic dysplasia, Torrance type	AD	12q13.1	COL2A1	Type 2 collagen	See also severe spondylodysplastic dysplasias (Group 13)
Hypochondrogenesis	AD	12q13.1	COL2A1	Type 2 collagen	
Spondyloepiphyseal dysplasia congenital (SEDC)	AD	12q13.1	COL2A1	Type 2 collagen	
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	AD	12q13.1	COL2A1	Type 2 collagen	
Kniest dysplasia	AD	12q13.1	COL2A1	Type 2 collagen	
Spondyloperipheral dysplasia	AD	12q13.1	COL2A1	Type 2 collagen	
Mild SED with premature onset arthrosis	AD	12q13.1	COL2A1	Type 2 collagen	Includes SED Namaqualand type 1
Stickler syndrome type 1	AD	12q13.1	COL2A1	Type 2 collagen	
Stickler syndrome, other					Unlinked to either COL2A1, COL11A1 or COL11A2
3. Type 11 collagen group					
Stickler syndrome type 2	AD	1p21	COL11A1	Type 11 collagen alpha-1 chain	
Marshall syndrome	AD	1p21	COL11A1	Type 11 collagen alpha-1 chain	
Otospondylomegaepiphyseal dysplasia (OSMED), recessive type	AR	6p21.3	COL11A2	Type 11 collagen alpha-2 chain	
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type; Weissenbacher-Zweymuller syndrome; Stickler syndrome type 3	AD	6p21.3	COL11A2	Type 11 collagen alpha-2 chain	
See also Stickler syndrome type 1 in Group 2					
4. Sulfation disorders group					
Achondrogenesis type 1B(ACG1B)	AR	5q32-33	DTDST	SLC26A2 sulfate transporter	
Atelosteogenesis type 2 (A02)	AR	5q32-33	DTDST	SLC26A2 sulfate transporter	Includes de la Chapelle dysplasia and McAlister dysplasia
Diastrophic dysplasia (DTD)	AR	5q32-33	DTDST	SLC26A2 sulfate transporter	
MED, autosomal recessive type (rMED; EDM4)	AR	5q32-33	DTDST	SLC26A2 sulfate transporter	See also multiple epiphyseal dysplasias in Group 9
SEMD Omani type	AR	10q22.1	CHST3	Chondroitin 6-sulfotransferase	See also SEMD group (Group 11)
SEMD Pakistani type	AR	10q23-q24	PAPSS2	PAPS-synthetase 2	See also SEMD group (Group 11)
5. Perlecan group					
Dyssegmental dysplasia, Silverman-Handmaker type	AR	1q36-34	PLC (HSPG2)	Perlecan	Relationship (radiographically) to dysseg-mental dysplasia, Rolland-Desbuquois type (Group 11) unclear
Schwartz-Jampel syndrome (myotonic chondrodystrophy)	AR	1q36-34	PLC (HSPG2)	Perlecan	Includes previous Burton dysplasia
6. Filamin group					
Frontometaphyseal dysplasia	XLD	Xq28	FLNA	Filamin A	
Osteodysplasty Melnick-Needles	XLD	Xq28	FLNA	Filamin A	
Otopalatodigital syndrome type 1 (OPD1)	XLD	Xq28	FLNA	Filamin A	
Otopalatodigital syndrome type 2 (OPD2)	XLD	Xq28	FLNA	Filamin A	
Atelosteogenesis type 1 (AOI)	AD	3p14.3	FLNB	Filamin B	Includes Boomerang dysplasia, Piepkorn dysplasia

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Atelosteogenesis type 3 (A03)	AD	3p14.3	FLNB	Filamin B	
Larsen syndrome	AD	3p14.3	FLNB	Filamin B	
Spondylocarpotarsal dysplasia	AR	3p14.3	FLNB	Filamin B	
7. Short-rib dysplasia (SRP) (with or without polydactyly) group					
Chondroectodermal dysplasia (Ellis-van Creveld)	AR	4p16 4p16	EVC1 EVC2	EvC gene 1 EvC gene 2	
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	AR				
SRP type 2 (Majewski)	AR				
SRP type 4 (Beemer)	AR				
Oral-facial-digital syndrome type 4 (Mohr-Majewski)	AR				
Asphyxiating thoracic dysplasia (ATD; jeune)	AR				
Thoracolaryngopelvic dysplasia (Barnes)	AD				
8. Multiple epiphyseal dysplasiasand pseudoachondroplasia group					
Pseudoachondroplasia (PSACH)	AD	19p12-13.1	COMP	COMP	
Multiple epiphyseal dysplasia (MED) type 1 (EDM1)	AD	19p13.1	COMP	COMP	
Multiple epiphyseal dysplasia (MED) type 2 (EDM2)	AD	1p32.2-33	COL9A2	Collagen 9 alpha-2 chain	
Multiple epiphyseal dysplasia (MED) type 3 (EDM3)	AD	20q13.3	COL9A3	Collagen 9 alpha-3 chain	
Multiple epiphyseal dysplasia (MED) type 5 (EDM5)	AD	2p23-24	MATN3	Matrilin 3	
Multiple epiphyseal dysplasia (MED) type 6 (EDM6)	AD	6q13	COL9A1	Collagen 9 alpha-1chain	
Multiple epiphyseal dysplasia (MED), other types					Many MED cases not linked to known genes
Familial hip dysplasia (Beukes)	AD	4q35			
See also multiple epiphyseal dysplasia, recessive type (rMED; EDM4) in sulphation disorders (Group 4)					
9. Metaphyseal dysplasias group					
Metaphyseal dysplasia, Schmid type (MCS)	AD	6q21-22.3	COL10A1	Collagen 10 alpha-1 chain	
Cartilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	AR	9p13	RMRP	RNA component of RNAse H	Includes anauxetic dysplasia
Metaphyseal dysplasia, Jansen type	AD	3p22-21.1	PTHR	PTH/PTHrP receptor	See also Eiken dysplasia in Group 25
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Bodian-Diamond syndrome, SBDS)	AR	7q11	SBDS	'SBDS gene,' function still unclear	
Metaphyseal anadysplasia	AD		MMP13	Matrix metallo-proteinase 13	See also SEMD Missouri type in Group 11
Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID)	AD	1q44	CIAS1	Cryopyrin	
Metaphyseal dysplasia, Spahr type	AR				
Metaphyseal Acroscyphodysplasia (various types)	AR				
10. Spondylometaphyseal dysplasias (SMD) group					
Spondylometaphyseal dysplasia Kozlowski type	AD				
Spondylometaphyseal dysplasia, Sutcliffe/comer fracture type	AD				
SMD with severe genu valgum	AD				Includes Schmidt and Algerian types of SMD
SMD with cone-rod dystrophy	AR				
See also SMD Sedaghatian type (Group 12)					
11. Spondylo-epi-metaphyseal dysplasias (SE(M)D) group					
Dyggve-Melchior-Clausen dysplasia (DMC)	AR	18q12-21.1	DYM	Dymeclin	Includes Smith-McCort dysplasia
Immuno-osseous dysplasia (Schimke)	AR	2q34-36	SMARCAL1	SWI/SNF-related regulator of chromatin subfamily A-like protein 1	
Progressive pseudorheumatoid dysplasia (PPRD)	AR	6q22-23	WISP3	WNT1-inducible signaling pathway protein 3	
SED Kimberley type	AD	15q26.1	AGC1	Aggrecan	

Disorder	Inheritance	Locus	Gene name	Protein	Notes
SED Wolcott-Rallison type	AR	2p12	EIF2AK3	Translaion initiation factor 2- alpha kinase-3	
SEMD Matrilin type	AR	2p23-p24	MATN3	Matrilin 3	See also matrilin-related MED in Group 8
SEMD Missouri type	AD	11q22.3	MMP13	Matrix metallo-proteinase 13	See also metaphyseal anadysplasia in Group 9
Metatropic dysplasia (various forms)	AD/AR				
X-linked SED tarda (SED-XL)	XLR	Xp22	SEDL	Sedlin	
Dyssegmental dysplasia, Rolland-Desbuquois type	AR				Unclear whether related to Perlecan or not
SPONASTRIME dysplasia	AR				
SEMD Maroteaux type (pseudo-Morquio type 2)	AR				
SEMD short limb-abnormal calcification type	AR				See also other dysplasias with stippling in Group 20
SEMD with joint laxity (SEMD-jL) Beighton type	AR				
SEMD with joint laxity (SEMD-JL) leptodactylic (or Hall) type	AD				
SEMD Handigodu type	AD				Includes Mseleni joint disease
Late onset SED	AR				
See also opsismodysplasia (Group 74), SEMDs (Group 71), mucopolysaccharidosis type 4 (Morquio syndrome) and other conditions in Group 26					
12. Severe spondylodysplastic dysplasias group					
Achondrogenesis type 1A (ACG1A)	AR				
SMD Sedaghatian type	AR				
Opsismodysplasia	AR				
Fibrochondrogenesis	AR				
Schneckenbecken dysplasia	AR				
See also thanatophoric dysplasia, types 1 and 2 (Group 1); achondrogenesis type IB (ACCIB, Group 4), ACC2 and Torrance dysplasia (Group 2)					
13. Moderate spondylodysplastic dysplasias (brachyolmias) group					
Brachyolmia, Hobaek/Toledo types	AR				
Brachyolmia, autosomal dominant type	AD				
See also SED tarda and late-onset SED (Group 11)					
14. Acromelic dysplasias group					
Trichorhinophalangeal dysplasia types 1/3	AD	8q24	TRPS1	Zinc finger transcription factor	
Trichorhinophalangeal dysplasia type 2 (Langer-Giedion)	AD	8q24	TRPS1 EXT1	Zinc finger transcription factor Exostosin 1	Microdeletion syndrome; see also multiple cartilaginous exostoses in Group 28
Acrocapitofemoral dysplasia	AR	2q33-q35	IHH	Indian hedgehog	
Angel-shaped phalangoepiphyseal dysplasia (ASPED)	AD	20q11.2	GDF5	Growth and differentiation factor 5	See also brachydactyly type C (Group 34)
Weill-Marchesani syndrome, recessive type	AR	19p13	ADAMTS10	Metalloproteinase with thrombospondin-like repeats	
Weill-Marchesani syndrome, dominant type	AD	15q21.1	FBN1	Fibrillin 1	see also Shprintzen-Goldberg syndrome (Group 30)
Brachydactyly-hypertension syndrome (Bilginturian)	AD	12p12.2-11.2			
Acrodysostosis	AD				
Acrolaryngeal dysplasia	AD				
Acromicric dysplasia	AD?				
Cranioectodermal dysplasia (Sensenbrenner)	AR				
Craniofacial conodysplasia	AD				
Familial digital arthropathy with brachydactyly	AD				
Geleophysic dysplasia	AD?				
Saldino-Mainzer dysplasia	AR				
See also short-rib dysplasias (Group 7)					
15. Acromesomelic dysplasias group					
Acromesomelic dysplasia type Maroteaux	AR	9p13-12	NPR2	Natriuretic peptide receptor 2	
Grebe dysplasia	AR	20q11.2	GDF5	Growth and differentiation factor 5	Includes acromesomelic dysplasia Hunter-Thompson type; see also brachydactylies (Group 34)

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Fibular hypoplasia and complex brachydactyly (DuPan)	AR	20q11.2	GDF5	Growth and differentiation factor 5	See also brachydactylies (Group 34)
Acromesomelic dysplasia with genital anomalies	AR	4q23-24	BMPR1B	Bone morphogenetic protein receptor 1B	
Acromesomelic dysplasia, Osebold-Remondini type	AD				
16. Mesomelic and rhizo-mesomelic dysplasias group					
Dyschondrosteosis (Leri- Weill)	Pseudo-AD	Xpter-p22.32	SHOX	Short stature-homeobox gene	Includes Reinhardt-Pfeiffer dysplasia
Langer type (homozygous dyschondrosteosis)	Pseudo-AR	Xpter-p22.32	SHOX	Short stature-homeobox gene	
Robinow syndrome, recessive type	AR	9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2	Includes previous COVESDEM (costo-vertebral segmentation defect with mesomelia); see also brachydactyly type B, Group 34
Robinow syndrome, dominant type	AD				
Mesomelic dysplasia, Nievergelt type	AD				
Mesomelic dysplasia, Kozlowski-Reardon type	AR				
Mesomelic dysplasia, Kantaputra type	AD	2q24-32			
Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type)	AD				
Mesomelic dysplasia, Savarirayan type (triangular tibia-fibular aplasia)	SP				Possibly related to Nievergelt dysplasia
Omodysplasia, dominant type	AD				
Omodysplasia, recessive type	AR				
17. Bent bones dysplasias group					
Campomelic dysplasia (CD)	AD	17q24.3-25.1	SOX9	SRY-box 9	Includes acampomelic campomelic dysplasia (ACD)
Stuve-Wiedemann dysplasia	AR	5p13.1	LIFR	Leukemia inhibitory factor receptor	Includes formerly neonatal Schwartz-Jampel syndrome or SJS type 2
Kyphomelic dysplasia, several forms					dimming syndrome Probably heterogeneous
Bent bones at birth can be seen in a variety of conditions, including Antley-Bixler syndrome, cartilage-hair hypoplasia, hypophosphatasia, osteogenesis imperfecta, dyssegmental dysplasia, and others					
18. Slender bone dysplasia group					
3M syndrome	AR	6p21.1	CUL7	Cuilin 7	
Kenny-Caffey dysplasia type 1	AR	lq42-q43	TBCE	Tubulin-specific chaperone E	
Kenny-Caffey dysplasia type 2	AD				
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	AR				Includes Taybi-Linder cephaloskeletal dysplasia
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	AR				
Microcephalic osteodysplastic dysplasia, Saul-Wilson type	AR				
IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies)	XLR	Chr. X			
Osteocraniostenosis	SP				
19. Dysplasias with multiple joint dislocations group					
Desbuquois dysplasia	AR	17q25.3			
Recessive Larsen-like syndrome	AR				Includes La Reunion Island dysplasia
Pseudodiastrophic dysplasia	AR				
See also atelosteogenesis type 3 and Larsen syndrome (Group 6); SEMDs with joint laxity (Group 11)					
20. Chondrodysplasia punctata (CDP) group					
CDP Conradi-Hunermann type (CDPX2)	XLD	Xpl 1	EBP	Emopamil-binding protein	
CDP X-linked recessive, brachytelephalangic type (CDPX1)	XLR	Xp22.3	ARSE	Arylsulfatase E	

Disorder	Inheritance	Locus	Gene name	Protein	Notes
CHILD (congenital hemidysplasia, ichthyosis, limb defects)	XLD	Xpl 1	NSDHL	NAD(P)H steroid dehydrogenase-like protein	
CHILD (congenital hemidysplasia, ichthyosis, limb defects)	XLD	Xq28	EBP	Emopamil-binding protein	
Greenberg dysplasia	AR	1q42.I	LBR	Lamin B receptor, 3-beta-hydro xysterol delta (14)-reductase	Includes hydrops-ectopic calcification-moth-eaten dysplasia (HEM)
Rhizomelic CDP type 1	AR	6q22-24	PEX7	Peroxisomal PTS2 receptor	
Rhizomelic CDP type 2	AR	1q42	DHPAT	Dihydroxyace-tonep-hosphate acyltransferase	
(DHAPAT) Rhizomelic CDP type 3	AR	2q31	AGPS	Alkylglycerone-phosphate syn-thase (AGPS)	
Astley-Kendall dysplasia	SP				
CDP tibial-metacarpal type	AD				
Dappled diaphyseal dysplasia	AR				Possibly identical to Greenberg dysplasia
See also SEMD short limb-abnormal calcification type in Group 71. Stippling can occur in several syndromes such as Zellweger, Smith-Lemli-Opitz and others.					
21. Neonatal osteosclerotic dysplasias group					
Blomstrand dysplasia	AR	3p22-21.1	PTHR1	PTHR/PTHRP receptor	Caused by recessive inactivating muta-tions; see also Eiken dysplasia (Group 25) and Jansen dysplasia (Group 9)
Desmosterolosis	AR	1p33-31.l	DHCR24	3-beta-hydroxys-terol delta-24-reductase	See also other sterol-metabolism related conditions in Group 20
Caffey disease (including infantile and attenuated forms)	AD	17q21-22	COL1A1	Collagen 1, alpha-1 chain	See also the various forms of osteogen-esis imperfecta related to collagen 1 genes (Group 24)
Caffey disease (severe with prenatal onset)	AR				
Raine dysplasia	AR				
See also Astley-Kendall dysplasia in Group 20					
22. Increased bone density group (without modification of bone shape)					
Osteopetrosis, severe neonatal or infantile forms	AR	11q13	CIRG1	Subunit of ATPase proton pump	
	AR	16p13	CLCN7	Chloride channel	
	AR	6q21	GL(OSTMI)	Osteopetrosis associated transmembrane protein	
Osteopetrosis, intermediate form	AR	16p13	CLCN7	Chloride channel pump	
Osteopetrosis with renal tubular acidosis	AR	8q22	CA1	Carbonic anhydrase	
Osteopetrosis, late-onset form type 1	AD	11 ql 3.4	LRP5	Low density lipoprotein receptor-related protein 5	Includes Worth type osteosclerosis
Osteopetrosis, late-onset form type 2	AD	16p13	CLCN7	Chloride channel pump	
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	Xq28	IKBKG (NEMO)	NF-kB signaling	
Pyknodysostosis	AR	1q21	CTSK	Cathepsin K	
Osteopoikilosis	AD	12q14	LEMD3	LEM domain-containing 3	Includes Buschke-Ollendorff syndrome
Melorheostosis with osteopoikilosis	AD	12q14	LEMD3	LEM domain-containing 3	Includes mixed sclerosing bone dysplasia
Melorheostosis					No germline LEMD3 mutations identified so far
Dysosteosclerosis	AR				
Osteomesopyknosis	AD				

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Osteopathia striata with cranial sclerosis	XLD				
Osteopetrosis with infantile neuroaxonal dysplasia	AR?				
Osteosclerosis, Stanescu type	AD				
23. Increased bone density group with metaphyseal and/or diaphyseal involvement					
Craniometaphyseal dysplasia, autosomal dominant type	AD	5p15.2-14.2	ANKH	Homolog of mouse ANK (ankylosis) gene	
Diaphyseal dysplasia Camurati-Engelmann	AD	I9q13	TGFbetal	Transforming growth factor beta 1	
Diaphyseal dysplasia Camurati-Engelmann, type 2					Not linked to TGFbeta 1
Oculodentoosseous dysplasia (ODOD) mild type	AD	6q22-23	GJA1	Gap junction protein alpha-1	
Oculodentoosseous dysplasia (ODOD) severe type	AR				Possibly homozygous form of mild ODOD
Osteoectasia with hyperphosphatasia (juvenile Paget's disease)	AR	8q24	OPG	Osteoprotegerin	
Sclerosteosis	AR	17q12-21	SOST	Sclerostin	
Endosteal hyperostosis, van Buchem type	AR	17q12-21	SOST	Sclerostin	52 kb deletion downstream from SOST
Trichodentoosseous dysplasia	AD	17q21	DLX3	Distal-less homeobox3	
Craniometaphyseal dysplasia, autosomal recessive type	AR	6q21 -22			
Diaphyseal medullary stenosis with bone malignancy	AD	9p21-p22			
Craniodiaphyseal dysplasia	.	AR/ AD ?			
Craniometadiaphyseal dysplasia, Wormian bone type	AR				
Cranio-osteoarthropathy					
Endosteal sclerosis with cerebellar hypoplasia	AR				
Lenz-Majewski hyperostotic dysplasia					
Metaphyseal dysplasia, Braun-Tinschert type	XL				
Pachydermoperiostosis	AD/AR				
Pyle disease	AR				
Diaphyseal dysplasia with anemia (Ghosal)	AR				
24. Decreased bone density group					
Osteogenesis imperfecta type 1 COL1A2	AD	17q21-22 7q22.1	COL1A1	Collagen 1, alpha-1 chain Collagen 1, alpha-2 chain	
Osteogenesis imperfecta type 2	AD	17q21-22 7q22.1	COL1A1 COL1A2	Collagen 1, alpha-1 chain Collagen 1, alpha-2 chain	
Osteogenesis imperfecta type 3	AD	17q21-22 7q22.1	COL1A1 COL1A2	Collagen 1, alpha-1 chain Collagen 1, alpha-2	
Osteogenesis imperfecta type 3, recessive, alpha-2	AR	7q22.1	COL1A2	Collagen 1, chain deficient	Extremely rare alpha-2 chain
Osteogenesis imperfecta, recessive, unlinked to COL1A1 and COL1A2	AR				More common than alpha-2 chain deficient form; includes recessive OI, South African form
Osteogenesis imperfecta type 4	AD	17q21-22 7q22.1	COL1A1 COL1A2	Collagen 1, alpha-1 chain Collagen 1, alpha-2 chain	
Osteogenesis imperfecta type 5	AD				
Osteogenesis imperfecta type 6					
Osteogenesis imperfecta type 7 (rhizomelic form)	AR	3p22-p24.1	CRTAP	Cartilage-associated protein	
Osteoporosis-pseudoglioma syndrome	AR	11 q12-13	LRP5	LDL-receptor related protein 5	
Bruck syndrome type 2	AR	3q23-24	PLOD2	Procollagen lysyl hydroxylase 2	
Bruck syndrome type 1	AR	17p12			
Singleton-Merten dysplasia	AD				
Geroderma osteodysplasticum	AR				
Calvarial doughnut lesions with bone fragility	AD				
Idiopathic juvenile osteoporosis	SP				

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Cole-Carpenter dysplasia (bone fragility with craniosynostosis)	SP				See craniosynostosis syndromes in Group 30
Spondylo-ocular dysplasia	AR				Unlinked to collagen 1 and collagen 2 genes or LRP5
Osteopenia with radiolucent lesions of the mandible	AD				
25. Defective mineralization group					
Hypophosphatasia, perinatal lethal and infantile forms	AR	1p36.1-p34	ALPL	Alkaline phosphatase, tissue nonspecific (TNSALP)	
Hypophosphatasia, adult form	AD	1p36.1-p34	ALPL	Alkaline phosphatase, tissue nonspecific (TNSALP)	Includes odontohypophosphatasia
Hypophosphatemic rickets	XLD	Xp22	PHEX	X-linked hypophosphatemia membrane protease	
Hypophosphatemic rickets	AD	12p13.3	FGF23	Fibroblast growth factor 23	
Hypophosphatemic rickets with hypercalciuria	AR	9p	SLC34A3	Sodium-phosphate cotransporter	
Neonatal hyperparathyroidism, severe form	AR	3q13.3-21	CASR	Calcium-sensing receptor	
Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism	AD	3q13.3-21	CASR	Calcium-sensing receptor	
Eiken dysplasia	AR	3p22-21.1	PTHR1	PTHR/PTHrP receptor 1	See also Blomstrand dysplasia (Group 21) and metaphyseal dysplasia Jansen type (Group 9)
26. Lysosomal storage diseases with skeletal involvement (dysostosis multiplex group)					
Mucopolysaccharidosis type 1H/1S	AR	4p16.3	IDA	alpha-1-iduronidase	
Mucopolysaccharidosis type 2	XLR	Xq27.3-28	IDS	Iduronate-2-sulfatase	
Mucopolysaccharidosis type 3A	AR	17q25.3	HSS	Heparan sulfate sulfatase	
Mucopolysaccharidosis type 3B	AR	17q21	NAGLU	N-Ac-beta-D- glucosaminidase	
Mucopolysaccharidosis type 3C	AR	Chr. 14		Ac-CoA:alpha-glucosaminide N- acetyltransferase	
Mucopolysaccharidosis type 3D	AR	12q14	GNS	N-Acetylglucosamine 6-sulfatase	
Mucopolysaccharidosis type 4A	AR	16q24.3	GALNS	Galactosamine-6-sulfate sulfatase	
Mucopolysaccharidosis type 4B	AR	3p21.33	GLBI	beta-Galactosidase	
Mucopolysaccharidosis type 6	AR	5q13.3	ARSB	Arylsulfatase B	
Mucopolysaccharidosis type 7	AR	7q21.11	GUSB	beta-Glucuronidase	
Fucosidosis	AR	1p34	FUCA	alpha-Fucosidase	
alpha-Mannosidosis	AR	19p13.2-12	MANA	alpha-Mannosidase	
beta-Mannosidosis	AR	4q22-25	MANBA	beta-Mannosidase	
Aspartylglucosaminuria	AR	4q23-27	AGA	Aspartyl- glucosaminidase	
GM, Gangliosidosis, several forms	AR	3p21-14.2	GLBI	beta-Galactosidase	
Sialidosis, several forms	AR	6p21.3	NEU1	Neuraminidase (sialidase)	
Sialic acid storage disease (SIASD)	AR	6q14-q15	SLC17A5	Sialin (sialic acid transporter)	
Galactosialidosis, several forms	AR	20q13.I	PPGB	beta-Galactosidase protective protein	

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Multiple sulfatase deficiency	AR	3p26	SUMF1	Sulfatase-modifying factor-1	
Mucolipidosis II (I-cell disease)	AR	4q21-23	GNPTA	N-Acetylglucosamine 1 -phosphotransferase	
Mucolipidosis III (Pseudo-Hurler polydystrophy)	AR	4q21-23	GNPTA	N-Acetylglucosamine 1 -phosphotransferase	
27. Osteolysis group					
Familial expansile osteolysis	AD	18q22.1	TNFRSF11A	RANK	
Infantile systemic hyalinosis	AR	4q21	CMG2	Capillary morphogenesis gene 2	Includes juvenile hyaline fibromatosis and puretic syndrome
Mandibuloacral dysplasia type A	AR	1q21.2	LMNA	Lamin A/C	
Progeria, Hutchinson-Gilford type	AD	1q21.2	LMNA	Lamin A/C	
Mandibuloacral dysplasia type B	AR	1p34	ZMPSTE24	Zinc metallo proteinase	
Torg-Winchester syndrome	AR	16q13	MMP2	Matrix metalloproteinase 2	Includes nodulosis-arthropathy-osteolysis syndrome
Hadju-Cheney syndrome	AD				
Multicentric carpal-tarsal osteolysis with and without nephropathy	AD				
28. Disorganized development of skeletal components group					
Cherubism	AD	4pl6	SH3BP2	SH3 domain-binding protein 2	
Fibrous dysplasia, polyostotic form	SP	20q13	GNAS1	Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1	Somatic mosaicism and imprinting phenomena; includes McCune-Albright syndrome
Progressive osseous heteroplasia	AD	20q13	GNAS1	Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1	Gene subject to imprinting
Gnathodiaphyseal dysplasia	AD	11p15.1-14.3	TMEM16E	Transmembrane protein 16E	
Multiple cartilaginous exostoses 1	AD	8q23-24.1	EXT1	Exostosin-1	
Multiple cartilaginous exostoses 2	AD	11 pi 2-11	EXT2	Exostosin-2	
Multiple cartilaginous exostoses 3	AD	19p			
Osteoglophonic dysplasia factor receptor 1	AD	8p11	FGFR1	Fibroblast growth	See also cramosynostosis syndromes in Group 30
Carpotarsal osteochondromatosis	AD				
Cherubism with gingival fibromatosis (Ramon syndrome)	AR				
Dysplasia epiphysealis hemimelica (Trevor)	SP				
Enchondromatosis (Oilier)	SP				PTHR1 mutations found in a few cases
Spondyloenchondrodysplasia (SPENCD)	AR, AD?				Includes SPENCD with spasticity and basal ganglia calcifications
Enchondromatosis with hemangiomata (Maffucci)	SP				
Fibrodysplasia ossificans progressiva	AD	4q27-31			
Genochondromatosis	AD				
Metachondromatosis	AD				
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	SP				
Dysspondyloenchondromatosis	SP				
Cheiro-spondyloenchondromatosis	SP				
29. Cleidocranial dysplasia group					
Cleidocranial dysplasia	AD	6p21	RUNX2	Runt related transcription factor 2	
CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption)	AR	22q12-13			
Yunis-Varon dysplasia	AR				

Disorder	Inheritance	Locus	Gene name	Protein	Notes
30. Craniosynostosis syndromes and other cranial ossification disorders group					
Pfeiffer syndrome (FGFR1-related)	AD	8p12	FGFR1	Fibroblast growth factor receptor 1	All have FGFR1 P252R mutation (phenotype generally milder than FGFR2-related Pfeiffer)
Apert syndrome	AD	10q26.12	FGFR2	Fibroblast growth factor receptor 2	
Craniosynostosis with cutis gyrata (Beare-Stevenson)	AD	10q26.12	FCFR2	Fibroblast growth factor receptor 2	
Crouzon syndrome	AD	l0q26.12	FCFR2	Fibroblast growth factor receptor 2	
Pfeiffer syndrome (FGFR2-related)	AD	10q26.12	FGFR2	Fibroblast growth factor receptor 2	Includes Jackson-Weiss syndrome and Antley-Bixler variants caused by FGFR2 mutations (see below)
Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome)	AD	4p16.3	FGFR3	Fibroblast growth factor receptor 3	Defined by specific FGFR3 A391E mutation
Craniosynostosis Muenke type	AD	4p16.3	FGFR3	Fibroblast growth factor receptor 3	FGFR3 P250R mutation
Antley-Bixler syndrome	AR	7q11.23	POR	Cytochrome P450 oxidoreductase	Cases with FGFR2 mutations classified as Pfeiffer syndrome
Craniofrontonasal syndrome	XLD	Xq13.1	EFNB1	Ephrin B1	
Craniosynostosis Boston type	AD	5q35.2	MSX2	MSX2	Heterozygous PI 48H mutation in a single family
Saethre-Chotzen syndrome	AD	7p21.1	TWIST1	TWIST	
Shprintzen-Goldberg syndrome	AD				Some affected individuals reported to have FBN1 mutations
Baller-Gerold syndrome	AR	8q24.3	RECQL4	RECQ protein-like 4	RECQL4 might not account for all cases of Baller-Gerold
Parietal foramina (isolated)	AD	11q11.2	ALX4	Aristaless-like 4	
Parietal foramina (isolated)	AD	5q34-35	MSX2	Muscle segment homeobox 2	
Carpenter syndrome *See also Cole-Carpenter syndrome in Group 24 and CD AGS syndrome in Group 29*	AR				
31. Dysostoses with predominant craniofacial involvement group					
Mandibulo-facial dysostosis (Treacher-Collins, Franceschetti-Klein)	AD	5q32	TCOF1		
Oral-facial-digital syndrome type I (OFD1)	XLR	Xp22.3	CXORF5		
Weyer acrofacial (acrodental) dysostosis	AD	4p16	EVC		
Acrofacial dysostosis, Nager type	AD/AR				
Frontonasal dysplasia	SP				
Hemifacial microsomia	SP/AD				Includes Goldenhar syndrome and oculo-auriculo-vertebral spectrum; probably genetically heterogeneous
Miller syndrome (postaxial acrofacial dysostosis) *See also oral-facial-digital syndrome type IV in the short-rib dysplasias (Group 7)*	AR				
32. Dysostoses with predominant vertebral and costal involvement group					
Currarino syndrome	AD	7q36	HLXB9	Homeobox gene HB9	
Spondylocostal dysostosis type 1 (SCD1)	AR	19q13	DIB	Delta-like 3	
Spondylocostal dysostosis type 2 (SCD2)	AR	15q26	MESP2	Mesoderm posterior 2	
Spondylocostal dysostosis type 3 (SCD3)	AR	7p22	LFNG	Lunatic fringe	
Spondylocostal dysostosis, dominant type	AD				Includes previous spondylothoracic dysostosis, dominant type
Jarcho-Levin syndrome	AR				Unlinked to DIB or MESP2; includes previous spondylothoracic dysostosis, recessive type
Cerebro-costo-mandibular syndrome (rib gap syndrome)	AD/AR				
Ischio-spinal dysostosis	SP/AR				
Klippel-Feil anomaly with laryngeal malformation *See also spondylocarpotarsal dysplasia in Group 26*	AD				

Disorder	Inheritance	Locus	Gene name	Protein	Notes
33. Patellar dysostoses group					
Ischiopubic patellar dysplasia	AD	17q21-q22 TBX4	T-box gene 4		
Nail-patella syndrome	AD	9q34.1	LMX1B	LIM homeobox transcription factor 1	
Genitopatellar syndrome	AR?				
Ear-patella-short stature syndrome (Meier-Gorlin)	AR				
34. Brachydactylies (with or without extraskeletal manifestations) group					
Brachydactyly type A1	AD	2q35-36	IHH	Indian hedgehog	
Brachydactyly type A1	AD	5q31			
Brachydactyly type A2	AD	4q23	BMPR1B	Bone morphogenetic protein receptor, 1B	
Brachydactyly type A2	AD			Not linked to BMRP1B	
Brachydactyly type A3	AD				
Brachydactyly type B	AD	9q22	ROR2	Receptor tyrosine kinase-like orphan receptor 2	
Brachydactyly type B				Not linked to ROR2	
Brachydactyly type C	AD, AR	20q1 1.2	GDF5	Growth and differentiation factor 5	See also ASPED (group 14) and other GDF5 disorders
Brachydactyly type D	AD	2q31	HOXD13	Homeobox D13	
Brachydactyly type D					Not linked to HOXD1 3
Brachydactyly type E	AD	2q31	HOXD13	Homeobox D13	
Brachydactyly type E					Not linked to HOXD1 3
Feingold syndrome (microcephaly-oculo-digito-esophageal-duodenal syndrome)	AD	2p24.1	MYCN	NMYC oncogene	
Hand-foot-genital	AD	7pl4.2	HOXA13	Homeobox A13	
Keutel syndrome	AR	12p13.1 -12.3	MGP	Matrix Gla protein	
Pseudohypoparathyroidism (Albright hereditary osteodystrophy, AHO)	AD	20q13	GNAS1	Guanine nucleotide binding protein of adenylate cyclase - subunit	See also polyostotic fibrous dysplasia and progressive osseous heteroplasia, Group 28
AHO-like syndrome (brachydactyly-mental retardation syndrome)	SP	2q37			Microdeletion syndrome
Rubinstein-Taybi syndrome	AD	16p13.3	CREBBP	CREB-binding protein	
Catel-Manzke syndrome	XLR?				
Christian type brachydactyly	AD				
Coffin-Siris syndrome	AR				
Mononen type brachydactyly	XLD?				
Poland syndrome	SP				
See also Group 20 for other conditions with brachydactyly					
35. Limb hypoplasia-reduction defects group					
Acheiropodia	AR	7q36	LMBR1	Putative receptor protein	Partial LMBR1 deletion affecting expression of sonic hedgehog (SHH) gene
De Lange syndrome	AD	5p13.1	NIPBL	Nipped-B-like	
Fanconi anemia	AR		FANC A, B,C,D1,D 2,E,F,G,L		Several complementation groups and genes
Holt-Oram syndrome	AD	12q24.1	TBX5	T-box gene 5	
Okihiro syndrome (Duane-radial ray anomaly)	AD	20q13	SALL4	SAL-like 4	
Roberts syndrome	AR	8p21.1	ESC02	Homolog of establishment of cohesion-2	
Tetra-amelia	AR	17q21	WNT3	Wingless-type MMTV integration site family, member 3	
Ulnar-mammary syndrome	AD	12q24.1	TBX3	T-box gene 3	

Disorder	Inheritance	Locus	Gene name	Protein	Notes
Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC)	AD	3q27	P63 (TP63)	Tumor protein p63	
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome Type 3 (EEC3)	AD	3q27	P63 (TP63)	Tumor protein p63	
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 1 (EEC1)	AD	7q11.2-12.3			
Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 2 (EEC2)	AD	Chr.19			
Limb-mammary syndrome (including ADULT syndrome)	AD	3q27	P63 (TP63)	Tumor protein p63	
Split hand-foot malformation, isolated form, type 4 (SHFM4)	AD	3q27	P63 (TP63)	Tumor protein p63	
Split hand-foot malformation, isolated form, type 1 (SHFM1)	AD	7q21.3-22.1			
Split hand-foot malformation, isolated form, type 2 (SHFM2)	XL	Xq26			
Split hand-foot malformation, isolated form, type 3 (SHFM3)	AD	10q24	Dactylin	Dactylin	
Split hand-foot malformation, isolated form, type 5 (SHFM5)	AD	2q31			
Split hand-foot malformation with tibial hypoplasia	AD				
Adams-Oliver syndrome	AD				
Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia	AR				
Femoral hypoplasia-unusual facies syndrome	SP/AD?				
Femur-fibula-ulna syndrome	SP?				
Fuhrmann syndrome	AR				
Hanhart syndrome (hypoglossia-hypodactylia)	AD				
Icapulo-iliac dysplasia (Kosenow)	AD				
Tirombocytopenia-absent radius (TAR)	AR7/AD?				
See also CHILD in Group 20					
36. Polydactyly-syndactyly-triphalangism group					
Preaxial Polydactyly type 1 (PPD1)	AD	7q36	SHH	Sonic hedgehog	Regulatory mutation
Preaxial Polydactyly type 1 (PPD1)	AD				Some instances not linked to SHH
Preaxial Polydactyly type 2 (PPD2)/ triphalangeal thumb (TPT)	AD	7q36	SHH	Sonic hedgehog	Regulatory mutation
Preaxial Polydactyly type 2 (PPD2)/triphalangeal thumb (TPT)	AD				Some instances not linked to SHH
Preaxial Polydactyly type 3(PPD3)	AD				
Preaxial Polydactyly type 4 (PPD4)	AD	7p13	GLI3	Gli-Kruppel family member 3	
Greig cephalopolysyndactyly syndrome	AD	7p13	GLI3	Gli-Kruppel family member 3	
Pallister-Hall syndrome (or above with Greig)	AD	7p1 3	GLI3	Gli-Kruppel family member 3	
Fibulin 1 -associated complex synpolydactyly	AD	22q13.3	FBLN1	Fibulin 1	
Synpolydactyly	AD	2q31	HOXD13	HomeoboxD13	
Syndactyly type 3	AD	6q22-24	CX43	Connexin 43	
Townes-Brocks syndrome (renal-ear-anal-radial syndrome)	AD	16q12.1	SALL1	SAL-like 1	
Acrocallosal syndrome	AR	7pl 3			
Acro-pectoral syndrome	AD	7q36			
Acro-pectoro-vertebral dysplasia (F-syndrome)	AD	2q36			
Mirror-image polydactyly of hands and feet (Laurin-Sandrow syndrome)	AD	14q1 3			
Mirror-image polydactyly of feet with tibial hypoplasia	AD				
Syndactyly type 1	AD	2q34-36			
Postaxial polydactyly		Several loci			Heterogeneous
37. Defects in joint formation and synostoses group					
Multiple synostoses syndrome type 1	AD	17q22	NOG	Noggin	Includes symphalangism-brachydactyly-deafness syndrome
Multiple synostoses syndrome type 2	AD	20q11.2	GDF5	Growth and differentiation factor 5	
Proximal symphalangism type 1	AD	17q22	NOG	Noggin	
Proximal symphalangism type 2	AD	20q11.2	GDF5	Growth and differentiation factor 5	
Radio-ulnar synostosis with amegakaryocytic thrombocytopenia	AD	7p15-14.2	HOXA11	Homeobox All	
See also spondylo-carpal-tarsal dysplasia (Group 6); mesomelic dysplasia with acral synostoses (Group 16); Antley Bixler syndrome (Group 30)					

AD, Autosomal dominant; AR; autosomal recessive; SP, sporadic, XL; x linked; XID, X linked dominant; XLR, X linked recessive.

Table 17-2: Molecular-pathogenetic classification of genetic disorders of the skeleton

Gene or protein	Inheritance	Clinical phenotype
Group 1: Defects in extracellular structural proteins		
COL1A1, COL1A2 (collagen 1 α1, α2 chains)	AD	Family: Osteogenesis imperfecta
COL2A1 (collagen 2 α1 chain)	AD	Family: Achondrogenesis 2, hypochondrogenesis, congenital spondylepiphyseal dysplasia (SEDC), Kniest, Stickler arthro-ophthalmopathy, familial osteoarthritis, other variants
COL9A1, COL9A2, COL9A3 (collagen 9 α1, α2, α3 chains)	AD	Multiple epiphyseal dysplasia (MED; two or more variants)
COL 10A1 (collagen 10 α1 chain)	AD	Metaphyseal dysplasia Schmid
COL 11A1, COL 11A2 (collagen 11 α1, α2 chains)	AR, AD	Oto-spondylo-megaepiphyseal dysplasia (OSMED): Stickler (variant), Marshall syndrome
COMP (cartilage oligometic matrix protein)	AD	Pseudoachondroplasia, multiple epiphyseal dysplasia (MED, one form)
MATN3 (matrilin-3)	AD	Multiple epiphyseal dysplasia (MED; one variant)
Perlecan	AR	Schwartz-Jampel type 1; dyssegmental dysplasia
Group 2: Defects in metabolic pathways (including enzymes, ion channels, and transporters)		
TNSALP (tissue nonspecific alkaline phosphatase)	AR, AD	Hypophosphatasia (several forms)
ANKH (pyrophosphate transporter)	AD	Craniometaphyseal dysplasia
DTDST/SLC26A2 (diastrophic dysplasia sulfate transporter)	AR	Family: achondrogenesis 1B, atelosteogenesis 2, diastrophic dysplasia, recessive multiple epiphyseal dysplasia (rMED)
PAPSS2, phosphoadenosine-phosphosulfate-synthase 2	AR	Spondylo-epi-metaphyseal dysplasia Pakistani type
TCIRGI, osteoblast proton pump subunit	AR	Severe infantile osteopetrosis
CIC-7 (chloride channel 7)	AR	Severe osteopetrosis
Carboanhydrase II	AR	Osteopetrosis with intracranial calcifications and renal tubular acidosis
Vitamin K-epoxide reductase complex	AR	Chondrodysplasia punctata with vitamin K-dependent coagulation defects
MGP (matrix Gla protein)	AR	Keutel syndrome (pulmonary stenosis, brachytelephalangism, cartilage calcifications and short stature)
ARSE (arylsulfatase E)	XLR	X-linked chondrodysplasia punctata (CDPXI)
3-β-hydroxysteroid dehydrogenase	XLD	CHILD syndrome
3-β-hydroxysteroid D(8)D(7)-isomerase	XLD	X-linked chondrodysplasia punctata, Conradi-Hunermann type (CDPX2); Child syndrome
PEX7 (peroxisomal receptor/importer)	AR	Rhizomelic chondrodysplasia punctata 1
DHAPAT (Dihydroxyacetonphosphate-acyltransferase, peroxisomal enzyme)	AR	Rhizomelic chondrodysplasia punctata 2
Alkyl-dihydroxydiacetonphosphate synthase (AGPS; peroxisomal enzyme)	AR	Rhizomelic chondrodysplasia punctata 3
Group 3: Defects in folding and degradation of macromolecules		
Sedlin (endoplasmic reticulum protein with unknown function)	XR	X-linked spondyloepiphyseal dysplasia (SED-XL)
Cathepsin K (lysosomal proteinase)	AR	Pyknodysostosis
Lysosomal acid hydrolase and transporters (sulfatase, glycosidase, translocase, etc.)	AR, XLR	Lysosomal storage disease: mucopolysaccharidoses, oligosaccharidoses, glycoproteinoses (several forms)
Targeting system of lysosomal enzymes (GlcNAc-1-phosphotransferase)	AR	Mucolipidosis II (I-cell disease), mucolipidosis III
MMP2 (matrix metalloproteinase 2)	AR	Torg type osteolysis (nodulosis arthropathy and osteolysis syndrome
Group 4: Defects in hormones and signal transduction mechanisms		
25-α-hydroxycholecalciferol-1-hydroxylase	AR	Vitamin D-dependent rickets type 1 (VDDR1)
1, 25-α-dihydroxy-vitamin D3 receptor	AR	Vitamin D-resistant rickets with end-organ unresponsiveness to vitamin D3 (VDDR 2)
CASR (calcium 'sensor'/receptor)	AD	Neonatal severe hyperparathyroidism with bone disease (if affected fetus in unaffected mother); familial hypocalciuric hypercalcemia
PTH/PTHrP receptor	AD (activating mutations)	Metaphyseal dysplasia Jansen

Gene or protein	Inheritance	Clinical phenotype
	AR (inactivating mutation)	Lethal dysplasia Blomstrand
GNAS1 (stimulatory Gs alpha protein of adenylate cyclase)	AD	Pseudohypoparathyroidism (Albright hereditary osteodystrophy and osteodystrophy and several variants) with constitutional haploinsufficiency mutations; McCune-Albright syndrome with somatic mosaicism for activating mutations
PEX proteinase	XL	Hypophosphatemic rickets, X-linked semidominant type (impaired cleav age of FGF23)
FGF23, fibroblasts growth factor 23	AD	Hypophosphatemic rickets, autosomal dominant type (resistance to PEX cleavage)
FGFR 1 (fibroblast growth factor receptor 1)	AD	Craniosynostosis syndromes (Pfeiffer, other variants)
FGFR 2	AD	Craniosynostosis syndromes (Apert, Crouzon, Pfeiffer; several variants)
FGFR 3	AD	Thanatophoric dysplasia, achondroplasia, hypochondroplasia, SADDAN: craniosynostosis syndromes (Crouzon with acanthosis nigricans, Muenke nonsyndromic craniosynostosis)
ROR-2 ('orphan receptor tyrosine kinase')	AR	Robinow syndrome
TNFRSF11A (receptor activator of under factor kB; RANK)	AD	Familial expansile osteolysis
TGFβ1	AD	Diaphyseal dysplasia (Camurati-Engelmann)
CDMP1 (cartilage-derived morphogenetic protein 1)	AR	Acromesomelic dysplasia Grebe/Hunter-Thompson
	AD	Brachydactyly type C
Noggin ('growth factor,' TGF antegonist)	AD	Multiple synostosis syndrome; synphalangism and hypoacusis syndrome
DLL3 (delta-like 3, intercellular signaling)	AR	Spondylocostal dysostosis (one form)
IHH (Indian hedgehog signal molecule)	AD	Brachydactyly A1
C7orf2 (orphan receptor)	AR	Acheiropodia
SOST (sclerosin; cystine knot secreted protein)	AR	Sclerosteosis, van Buchem disease
LRPS (LDL receptor-related protein 5)	AR	Osteoporosis-pseudoglioma syndrome
WISP 3 (growth regulator/growth factor)	AR	Progressive pseudorheumatoid dysplasia
Group 5: Defects in nuclear proteins and transcription factors		
SOX9 (HMG-type DNA binding protein/ transcription factor)	AD	Compomelic dysplasia
GII3 (zinc finger gene)	AD	Greig cephalopolysyndactyly, polydactyly type A and others, Pallister-Hall syndrome
TRPS 1 (zine-finger gene)	AD	Tricho-rhino-phalangeal syndrome (types 1–3)
HVC (leucine-zipper gene)	AR	Chondroectodermal dysplasia (Ellis-van Creveld)
TWIST (helix-loop-helix transcription factor)	AD	Craniosynostosis Saethre-Chotzen
P63 (p53 related transcription factor)	AD	EEC syndrome, Hay-Wells syndrome, Limb-mammary syndrome, split hand-split foot malformation (some forms)
CBFA-1 (core binding factor	AD	Cleidocranial dysplasia
A1; runt-type transcription factor)		
LXM1B (LIM homeodomain protein)	AD	Nail-patella syndrome
DLX3 (distal-less 3 homeobox gene)	AD	Trichodentoosseous syndrome
HOXD 13 (homeobox gene)	Ad	Synpolydactyly
MSX2 (homeobox gene)	AD (gain of function)	Craniosynostosis, Boston type
	AD (loss of function)	Parietal foramina
ALX4 (homeobox gene)	AD	Parietal foramina (cranium bifidum)
SHOX (short stature-homeobox gene)	Pseudo-autosomal	Leri-Weill dyschondrosteosis, idiopathic short stature
TBX3 (T-box 3, transcription factor)	AD	Ulnar-mammary syndrome
TBX5 (T-box 5, transcription factor)	AD	Holt-Oram syndrome

Gene or protein	Inheritance	Clinical phenotype
EIF2AK3 (transcription initiation factor kinase)	AR	Wolcott-Rallison syndrome (neonatal diabetes mellitus and spondyloepiphyseal dysplasia)
NEMO (NFkB essential modulator; kinase activity)	LX	Osteopetrosis, lymphedema, ectodermal dysplasia and immunodeficiency (OLEDAID)
Group 6: Defects in oncogenes and tumor suppressor genes		
EXT1, EXT2 (exostosin-1, exostosin-2; heparan-sulfate polymerases)	AD	Multiple exostoses syndrome type 1, type 2
SH3BP2 (a-Abl-binding protein)	AD	Cherubism
Group 7: Defects in RNA and DNA processing and metabolism		
RNAse MRP-RNA component	AR	Cartilage-hair-hypoplasia
ADA (adenosine deaminase)	AR	Severe combined immunodeficiency (ACID) with (facultative) metaphyseal changes

Adapted from Superti-Furga A, Bonafe L, Rimoin DL. Molecular pathogenetic classification of genetic disorders of the skeleton. Am J Med Genet 2001; 106: 282–93.

examination should focus on anthropometric measurements. The osteochondrodysplasias are generalized disorders of the skeleton, which usually result in disproportionate short stature. A disproportionate body habitus may not be readily appreciated unless anthropometric measurements (i.e. arm span, upper to lower segment ratio, etc.) are carefully obtained. This assessment may help to determine if the disproportionate shortening affects primarily the trunk or the limbs [the proximal (rhizomelic), middle (mesomelic) or distal segment (acromelic)].

The next step in the evaluation of disproportionate short stature is to obtain a full set of skeletal radiographs including views of the skull, spine, pelvis, extremities, hands and feet. Attention should be paid to the specific parts of the skeleton that are involved, the location of the lesion within each bone (epiphysis, metaphysis, diaphysis) and the recognition of unique patterns of abnormal skeletal ossification. Review of radiographs taken at different ages or before and after puberty may be helpful, because the radiographic features of many of these disorders may change with age.

GROUP I: DEFECTS IN EXTRACELLULAR STRUCTURAL PROTEINS (BASED ON MOLECULAR PATHOGENETIC CLASSIFICATION OF GENETIC DISORDERS OF SKELETON)

Osteogenesis Imperfecta

('Brittle bones', fragilitas ossium, osteopsathyrosis, Lobstein's disease)

Osteogenesis imperfecta (OI) is a serious disease, the molecular pathogenesis of which is being elucidated and it bears a superficial relatedness to dentinogenesis imperfecta (refer Chapter 1, section on dentinogenesis imperfecta), a milder condition affecting mesodermal tissues. It is a condition resulting from abnormality in the type I collagen, which most commonly manifests as fragility of bones. Although osteogenesis imperfecta is generally recognized as representing a hereditary autosomal dominant characteristic, autosomal recessive and nonhereditary types also occur.

Table 17-3: Clinical types of osteogenesis imperfecta

Osteogenesis imperfecta, type I Osteogenesis imperfecta tarda Osteogenesis imperfecta with blue sclerae Gene map locus 17q21.31–q22, 7q22.1
Osteogenesis imperfecta congenita; type II Osteogenesis imperfecta congenita, neonatal lethal Vrolik type of osteogenesis imperfecta Gene map locus 17q21.31–q22, 7q22.1
Osteogenesis imperfecta, progressively deforming, with normal sclerae: type III Gene map locus 17q21.31–q22, 7q22.1
Osteogenesis imperfecta, type IV Osteogenesis imperfecta with normal sclerae Gene map locus 17q21.31–q22

Four types of osteogenesis imperfecta exist (Table 17-3), based on the classifications of Sillence et al (1979).

Researchers have defined three more types of osteogenesis imperfecta **(type V, type VI, and type VII)**, but the genetic causes have not yet been identified.

Type I collagen fibers are found in bones, organ capsules, fascia, cornea, sclera, tendons, meninges, and dermis. Structurally, this protein is composed of a left-handed helix formed by intertwining of pro-a1 and pro-a2 chains. Mutations in the loci coding for these chains (**COL1A1 on band 17q21** and **COL1A2 on band 7q22.1,** respectively) cause osteogenesis imperfecta. Qualitative defects (abnormal collagen I molecule) and quantitative defects (decrease in production of normal collagen I molecules) both exist in its causation.

Osteogenesis imperfecta is an inherited disorder. Type I is autosomal dominant, type II is autosomal dominant with new mutation, type III is autosomal dominant with new mutation (rarely recessive forms also are observed), and type IV which is autosomal dominant.

Clinical Features. The chief clinical characteristic of osteogenesis imperfecta is the extreme fragility and porosity of the bones, with an attendant proneness to fracture. The fractures heal readily, but the new bone is of a similar imperfect quality.

The age of onset of symptoms varies depending on the type of OI with fractures in type I and IV occurring during infancy and type II *in utero.* In type III, half the cases present fracture in utero, and other half in the neonatal period. No known differences based on gender exist. Prenatal screening by ultrasound during the second trimester shows bowing of long bones, fractures, limb shortening, and decreased skull echogenicity.

A second characteristic clinical feature of osteogenesis imperfecta is the occurrence of pale blue sclerae. The sclerae are abnormally thin, and for this reason the pigmented choroid shows through and produces the bluish color. However, the appearance of blue sclera is not confined to this disease since it may also be seen in osteopetrosis, fetal rickets, Turner syndrome, Paget's disease, Marfan syndrome, and Ehlers-Danlos syndrome, as well as in normal infants. While the blue sclerae are a prominent sign in this disease, they are not invariably present. In a series of 42 patients reported by Bauze and his associates, 12 of the patients had white sclerae, and these were generally found in the older patients with the more severe disease and earlier onset of fractures.

In a thorough review of osteogenesis imperfecta and dentinogenesis imperfecta by Winter and Maiocco, the following additional signs and symptoms were described as being characteristic of osteogenesis imperfecta: deafness due to otosclerosis, abnormalities of the teeth (identical to those of dentinogenesis imperfecta, or 'hereditary opalescent dentin'), laxity of the ligaments, a peculiar shape of the skull and an abnormal electrical reaction of the muscles.

Many patients with osteogenesis imperfecta also have a tendency towards capillary bleeding although no specific blood dyscrasia or defect has been demonstrated.

Physical features can vary depending on the type. It forms the basis for **Sillence classification.**

Type I: Osteogenesis imperfecta. This is the most common and mildest form. In subtype A, dentinogenesis imperfecta is absent, while in subtype B, dentinogenesis imperfecta is present. Symptoms of both subtypes include blue sclera, *in utero* fractures in 10% of patients (fractures are more common during infancy), mild-to-moderate bone fragility with frequency of fractures decreasing after puberty, kyphoscoliosis, hearing loss, easy bruising and short stature.

Type II: Osteogenesis imperfecta. Osteogenesis imperfecta type II exhibits extreme bone fragility and frequent fractures. *In utero* fractures are present in 100% of cases. Many are stillborn, and 90% die before four weeks of age. Blue sclera may be present. Hearing loss is not common to type II OI. Dentinogenesis imperfecta may be present along with small nose, micrognathia and short trunk.

Type III: Osteogenesis imperfecta. Type III is associated with dentinogenesis imperfecta, sclera of variable hue, limb shortening and progressive deformities, triangular facies with frontal bossing and pulmonary hypertension. *In utero* fractures occur in 50% of cases. The remaining half of the cases have fractures in the neonatal period. No hearing loss has been reported in this type.

Type IV: Osteogenesis imperfecta. In subtype A, dentinogenesis imperfecta is absent, while in subtype B, dentinogenesis imperfecta is present. Symptoms of both subtypes include normal sclera, normal hearing, fractures that begin in infancy (*in utero* fractures are rare) and mild angulation and shortening of long bones. Bleeding diathesis have not been reported in this type.

Oral Manifestations. Osteogenesis imperfecta is basically a disturbance of mesodermal tissues, particularly the calcified tissues. When a widespread congenital disturbance in bone formation exists, it is only logical to expect a concomitant disturbance in dentin formation. The large head size, frontal and temporal bossing, and exaggerated occiput create a greater percentage of class III malocclusions. Anterior and posterior cross bites and open bites are also frequent. These conditions seem to be caused by maxillary hypoplasia rather than mandibular hyperplasia. A surprising large number of impactions and ectopic teeth have been reported. In permanent dentition, OI patients often have unerupted first and second molars, a condition which is rare in the general population. These abnormalities have no relation to the existence of dentinogenesis imperfecta. Dentinogenesis imperfecta represents the disturbance in tooth formation associated with OI, and is one of the most significant clinical patterns of OI. It can be the only abnormality noted at times amongst the spectra of clinical manifestations. Therefore, clinical and radiological evaluations of the dentition may be the only affirmative component in the diagnosis of a questionable case of OI.

Radiographic Features. The radiographic hallmarks of osteogenesis imperfecta include osteopenia, bowing, angulation or deformity of the long bones, multiple fractures, and wormian bones (sutural bone) in the skull.

Histologic Findings. The bones in patients with osteogenesis imperfecta exhibit thin cortices, sometimes being composed of immature spongy bone, while the trabeculae of the cancellous bone are delicate and often show microfractures (Fig. 17-1). Osteoblastic activity appears retarded and imperfect, and for this reason the thickness of the long bones is deficient. The basic defect appears to lie in the organic matrix with failure of fetal collagen to be transformed into mature collagen. Qualitative defects (abnormal collagen I molecule) and quantitative defects (decrease in production of normal collagen I molecules) both exist. There is some evidence that the progressive intermolecular cross-linkage of adjacent collagen molecules, which is an essential characteristic of normal collagen maturation, is defective in this disease. Calcification proceeds normally. Defective microvascular system and decreased collagen fibril diameter have also been observed. The length of the long bones is usually normal unless multiple fractures have caused undue shortening.

Treatment and Prognosis. There is no known treatment for osteogenesis imperfecta. No medical therapy is involved, other than the treatment of infections when they occur. The prognosis varies from relatively good to very poor. In type IA, life expectancy is similar to that of general population; type II,

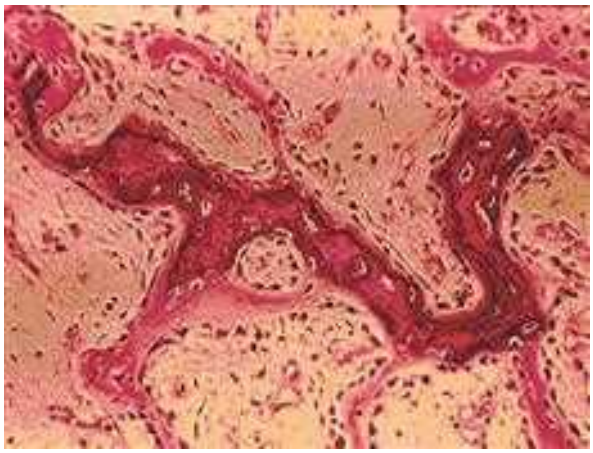


Figure 17-1. Osteogenesis imperfecta (OI).
The typical microscopic changes of OI can be seen in a section of a long bone of a severely affected child. The bone cortex is thin and porous. The bone trabeculae are thin, delicate, and widely separated. Many osteoblasts and osteocytes are present, but the formation and organization of osteoid is deficient. There is less bone tissue than normal and most of it is woven or nonlamellar bone with collagen fibers of small size and random distribution. The woven bone has an increase in basophilic ground substance (shown by blue staining in H and E sections) *(Courtesy of Dr Robert C Mellors)*.

most patients die within the first year of life. A slight decrease in life expectancy has been observed in the other types.

Marfan Syndrome
(Marfan-Achard syndrome, arachnodactyly)

Marfan syndrome is a spectrum of disorders caused by a heritable genetic defect of connective tissue that has an autosomal dominant mode of transmission, one of the more famous instances being that of president Abraham Lincoln. The defect itself has been isolated to **FBN1 gene** on **chromosome 15, bands q15–q23,** which codes for the connective tissue protein, fibrillin. Abnormalities in this protein cause a myriad of distinct clinical problems, of which the musculoskeletal, cardiac, and ocular problems predominate.

Several investigators studied various molecules that are found in the extracellular matrix over many years in attempts to elucidate the cause of Marfan syndrome. These included collagen, elastin, hyaluronic acid, and more recently, fibrillin. Several point mutations have now been identified in the fibrillin gene, most of which affect cysteine residues within the microfibril. These mutations are thus thought to cause defective fibrillin to be produced. Fibrillin's structure and function are altered by abnormal protein folding due to the alteration of bonding between cysteine residues, which in turn causes defective microfibril production (conformational protein change).

Clinical Features. The estimated incidence of Marfan syndrome ranges from 1 in 5,000 to 1 in 10,000 births which includes stillbirths. The wide variation in the sites of mutations noticed in the fibrillin gene causes the varied phenotypic manifestations of this syndrome. Several other diseases present similar to Marfan syndrome, making it exceedingly difficult to determine the exact incidence. The skeleton typically displays multiple deformities including arachnodactyly, dolichostenomelia (i.e. long limbs relative to trunk length), and thoracolumbar scoliosis. The shape of the skull and face is characteristically long and narrow, and commonly suggests the diagnosis of the disease (Figs. 17-2, 17-3). Other features of the disease include hyperextensibility of joints with habitual dislocations, kyphosis and flat feet. In the cardiovascular system, aortic dilation, aortic regurgitation, and aneurysms are the most worrisome clinical findings. Mitral valve prolapse requiring valve replacement can occur as well. Ocular findings include myopia, cataracts, retinal detachment, and superior dislocation of the lens.

Oral Manifestations. According to Baden and Spirgi, who have reviewed the oral manifestations of this disease, a high, arched palatal vault is very prevalent and may be a constant finding. Bifid uvula is also reported as well as malocclusion. In addition, multiple odontogenic cysts of the maxilla and mandible have occasionally been reported, most recently by Oatis and his coworkers. One additional finding sometimes present, is temporomandibular dysarthrosis (Fig. 17-4).

Figure 17-2. Marfan syndrome.

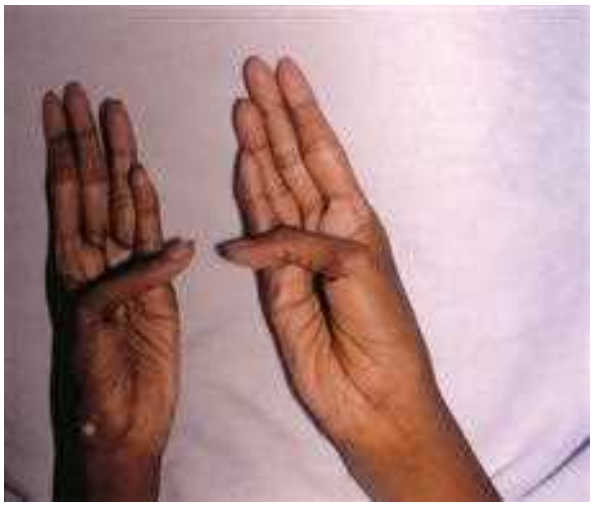


Figure 17-3. Marfan syndrome.
Showing disproportionately long and thin extremities.

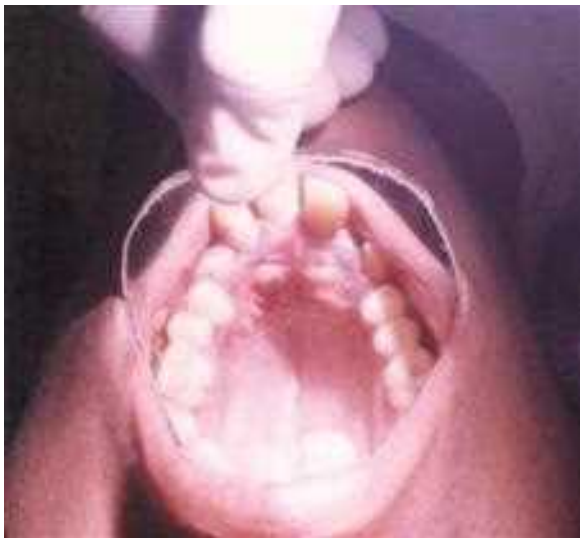


Figure 17-4. Intraoral photograph showing high arched palatal vault as well as malocclusion of maxilla.

Radiographic Features. Skull radiographs (AP and lateral) may demonstrate a high arched palate, increased skull height, and an enlarged frontal sinus.

Treatment and Prognosis. There is no specific treatment for this condition. Recent strides in the management of the cardiovascular manifestations of Marfan syndrome have led to a significant decrease in morbidity and mortality. Patient longevity now approaches that of persons without Marfan syndrome, although cardiovascular compromise is still the most common cause of patient death.

Achondrogenesis

Marco Fraccaro first described achondrogenesis in 1952. By the 1970s, researchers concluded that achondrogenesis was a heterogeneous group of chondrodysplasias lethal to neonates; **achondrogenesis type I (Fraccaro-Houston-Harris type)** and **type II (Langer-Saldino type)** were distinguished on the basis of radiological and histological criteria. In 1983, a new radiological classification of achondrogenesis (types I-IV) by Whitley and Gorlin was adopted in the McKusick catalog.

Etiology. Type IA is an autosomal recessive disorder with an unknown chromosomal locus. Type IB is an autosomal recessive disorder resulting from mutations of the DDST (diastrophic dysplasia sulfate transporter) gene, which is located at **5q32–q33.** Type II is an autosomal dominant type collagenopathy resulting from mutations in the **COL2A1** (collagen 2 αl chain) gene, which is located at **12q13.1–q13.3.** Different mutations in the gene encoding type II collagen (COL2A1) cause achondrogenesis type II as well as other type II collagenopathies (e.g. spondyloepiphyseal dysplasias, hypochondrogenesis).

In the late 1980s, structural mutations in collagen II were shown to cause achondrogenesis type II, which thus constitutes the severe end of the spectrum of collagen II chondrodysplasias. Achondrogenesis type I was subdivided further in 1988 on the basis of convincing histological criteria. It was subdivided into type IA (Houston-Harris type achondrogenesis) which has apparently normal cartilage matrix but inclusions in chondrocytes, and type IB, (Fraccaro type achondrogenesis) which has an abnormal cartilage matrix. The classification of type IB as a separate group has been confirmed recently by the discovery of its association with mutations in the diastrophic dysplasia sulfate transporter (DDST) gene, making it allelic with diastrophic dysplasia.

Clinical Features. Achondrogenesis type I results in still-birth more frequently than type II. Males and females are affected equally. Achondrogenesis is detected prenatally or at birth because of typical clinical, radiographic, histological, and molecular findings.

In **achondrogenesis type I,** the **craniofacial features** include a disproportionately large head, soft skull, sloping forehead, convex facial plane, flat nasal bridge, occasionally associated with a deep horizontal groove, small nose, often with anteverted nostrils, long philtrum, retrognathia, increased distance between lower lip and lower edge of chin and double chin appearance (often). In **achondrogenesis type II,** the features seen are a disproportionately large head, large and prominent forehead, flat facial plane, flat nasal bridge, small nose with severely anteverted nostrils, normal philtrum (often), micrognathia (Fig. 17-5). The differential diagnoses include achondroplasia, hypophosphatasia, osteogenesis imperfecta and thanatophoric dysplasia.

Radiographic Features. The radiographic features may vary, and no single feature is consistently noticed. Distinction between type IA and type IB on radiographs is not always possible. Degree of ossification is age dependent, and caution is needed when comparing radiographs at different gestational ages.

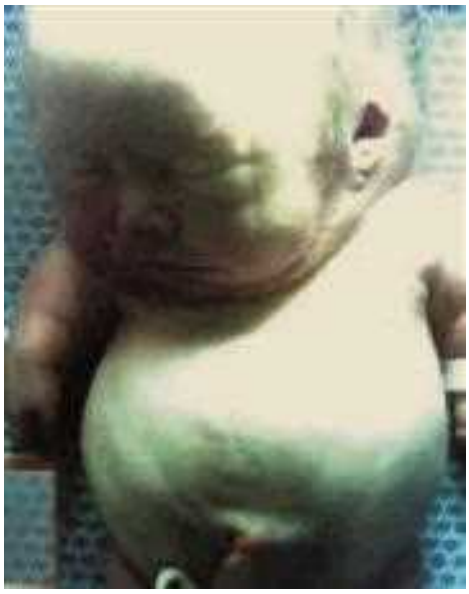


Figure 17-5. An infant with achondrogenesis type II.
Note the disproportionately large head, large and prominent forehead, flat facial plane, flat nasal bridge, small nose with severely anteverted nostrils, micrognathia, extremely short neck, short and flared thorax, protuberant abdomen, and extremely short upper extremities.

Histologic Findings

Achondrogenesis type IA, has a normal cartilage matrix. No collagen rings are present around the chondrocytes. Vacuolated chondrocytes, intrachondrocytic inclusion bodies (periodic acid-Schiff stain [PAS] positive, diastase resistant), extraskeletal cartilage involvement, enlarged lacunas, and woven bone are all present.

Achondrogenesis type IB, has a cartilage matrix that shows coarsened collagen fibers that are particularly dense around the chondrocytes, forming collagen rings.

Achondrogenesis type II, has slightly larger than normal and grossly distorted (lobulated and mushroomed) epiphyseal cartilage. There is severe disturbance in endochondral ossification and hypercellular reserve cartilage with large, primitive mesenchymal (ballooned) chondrocytes with abundant clear cytoplasm. The cartilaginous matrix is markedly deficient.

Treatment and Prognosis. Medical care is supportive. No treatment is available for the underlying disorder. The condition is universally lethal.

Hypophosphatasia

Initially recognized by Rathbun in 1948, hypophosphatasia is a rare inherited metabolic disease of decreased tissue nonspecific alkaline phosphatase and defective bone mineralization. Varying widely in its clinical presentation, it has been subdivided into five categories known as **perinatal, infantile, childhood, adult, and odontohypophosphatasia.** The different clinical forms have different modes of presentation, history, and inheritance.

Etiology. Patients with hypophosphatasia have defects in mineralization of bone due to TNSALP (tissue nonspecific alkaline phosphatase) deficiency. A mutation in the gene coding for tissue nonspecific alkaline phosphatase is believed to be the cause of hypophosphatasia. The gene, designated **ALPL,** is located at band **1p36.1–34.**

Clinical Features. Hypophosphatasia affects all age groups; however, the severity of the disease differs with age. Males and females are affected equally. Hypophosphatasia occurs in all races. The perinatal form is considered lethal, while the infantile form has a mortality rate of 50%. Individuals with the other forms can reach adulthood, although often with increased morbidity. Patients with the childhood form often have rachitic deformities, and those with the adult type have increased morbidity from poorly healing stress fractures. All patients are affected by premature loss of dentition.

The **perinatal** form has the most severe manifestations. It is usually diagnosed at birth, and the infant rarely survives for more than a few hours. Death is due to respiratory failure. Marked hypocalcification of the skeletal structures is observed.

Patients with the **infantile** form may appear normal at birth; however, the clinical signs of hypophosphatasia appear during the first six months. This form also has respiratory complications due to rachitic deformities of the chest. Despite the presence of an open fontanelle, premature craniosynostosis is a common finding that may result in increased intracranial pressure. Hypercalcemia is also present and increased excretion of calcium may lead to renal damage.

Skeletal deformities, such as dolichocephalic skull and enlarged joints, a delay in walking, short stature, and a waddling gait accompany the **childhood** form. A history of fractures and bone pain usually exists as well. Premature loss of dentition is common with the incisor teeth often being the first affected.

The **adult** form presents during middle age. The first complaint may be foot pain, which is due to stress fractures of the metatarsals. Thigh pain, due to pseudofractures of the femur, may also be a presenting symptom. Upon obtaining an in-depth history, many of these patients will reveal that they had premature loss of deciduous teeth.

The only physical finding in the **odontohypophosphatasic** form is the premature loss of teeth.

Oral Manifestations. The earliest manifestation of the disease may be loosening and premature loss of deciduous teeth, chiefly the incisors. There are varying reports of gingivitis; however it does not seem to be a consistent feature of the disease. The differential diagnoses include achondrogenesis, osteogenesis imperfecta, rickets and thanatophoric dysplasia.

Radiographic Features. The childhood form is characterized by rachitic deformities. Upon radiologic examination of the metaphysis, evidence of radiolucent projections from the epiphyseal plate into the metaphysis is present. This is not found in other types of rickets. Radiographic findings are normal for patients with odontohypophosphatasia. Dental radiographs generally reveal hypocalcification of teeth and the presence of large pulp chambers, as well as alveolar bone loss; however these findings have not been consistently reported.

Histologic Findings. Histologic examination of the skeleton will reveal rachitic abnormalities of the growth plates such as failure of cartilage calcification. Both osteoclasts and osteoblasts appear morphologically normal, but the latter lack membrane associated alkaline phosphatase (ALP) activity on histochemical testing. This disrupts incorporation of calcium into the matrix. The long bones characteristically exhibit an increased width of proliferating cartilage with widening of the hypertrophic cell zone, irregularity of cell columns, irregular penetration of the cartilage by marrow with persistence of numerous cartilage islands in the marrow, and formation of large amounts of osteoid which is inadequately calcified. These findings are indistinguishable from those in true rickets. Histological examination of the teeth reveals a decrease in cementum, which varies with the severity of the disease. This is presumably as a result of failure of cementogenesis, so that there is no sound functional attachment of the tooth to bone by periodontal ligament. This lack of attachment is thought to account for the early spontaneous exfoliation of the deciduous teeth. The pulp chamber also appears to be enlarged. The incisors tend to be the most affected. Bone biopsy findings are normal for patients with odontohypophosphatasia.

Treatment and Prognosis. Currently, no medical therapy is available. Various treatments have been attempted including zinc, magnesium, cortisone, plasma, and enzyme replacement therapy. The results have been inconsistent. Orthopedic surgical involvement may be necessary in patients with hypophosphatasia. The perinatal form is considered lethal. The infantile form is thought to be fatal in approximately 50% of patients. Longevity studies have not been conducted for the infantile and childhood forms. Individuals with the adult and odontohypophosphatasia forms are believed to have normal lifespans.

Osteopetrosis

(Marble bone disease, Albers-Schönberg disease, osteosclerosis fragilis generalisata)

Osteopetrosis is a rare hereditary bone disease of heterogeneous pathophysiology in which failure of osteoclastic bone resorption leads to increased bone mass. However, the bone has poor mechanical properties. A German radiologist, Albers-Schönberg, first described osteopetrosis in 1904.

Etiology. The primary underlying defect in all types of osteopetrosis is failure of the osteoclasts to resorb bone. This results in thickened sclerotic bones, which have poor mechanical properties. Increased bone fragility results from a failure of the collagen fibers to augment bone matrix and from defective remodeling of woven bone to compact bone. Heterogeneous molecular or genetic defects can result in impaired osteoclastic function. The exact molecular defects or sites of these mutations largely are unknown.

Clinical Features. Three distinct forms of the disease are based on age and clinical features. These are **adult onset, infantile,** and **intermediate.** Other rare forms have been described (e.g. lethal, transient, postinfectious). The infantile and intermediate types have an autosomal recessive mode of transmission, while the adult onset type shows autosomal dominant inheritance. If untreated, infantile osteopetrosis usually results in death by the first decade of life due to severe anemia, bleeding, or infection. Adult patients with osteopetrosis are usually asymptomatic and have good long-term survival rates.

Infantile osteopetrosis (also called malignant osteopetrosis) is diagnosed early in life. Failure to survive and growth retardation are symptoms. Bony defects occur. Nasal stuffiness due to mastoid and paranasal sinus malformation is often the presenting feature of infantile osteopetrosis. Cranial nerve entrapment neuropathies occur due to failure of the foramina in the skull to widen completely. Manifestations include deafness, proptosis, and hydrocephalus. Dentition might be delayed. Osteomyelitis of the mandible is common due to a deficient blood supply. Bones are fragile and can fracture easily. Defective osseous tissue tends to replace bone marrow, which can cause bone marrow failure with resultant pancytopenia. Patients might have anemia, easy bruising and bleeding (due to thrombocytopenia), and recurrent infections (due to inherent defects in the immune system). Extramedullary hematopoiesis might occur with resultant hepatosplenomegaly, hypersplenism, and hemolysis. Other manifestations include sleep apnea and blindness due to retinal degeneration.

Adult osteopetrosis (also called benign osteopetrosis) is diagnosed in late adolescence or adulthood. Approximately one half of the patients are asymptomatic, and the diagnosis is made incidentally (often in late adolescence because radiological abnormalities start appearing only in childhood) or is based on family history. Other patients might present with osteomyelitis or fractures. Many patients have bone pain. Bony defects are common and include cranial nerve entrapment neuropathies (e.g. with deafness, with facial palsy), carpal tunnel syndrome, and osteoarthritis. Bones are fragile and might fracture easily. Approximately 40% of patients have recurrent fractures. Osteomyelitis of the mandible occurs in 10% of patients. Bone marrow function is not compromised. Other manifestations include visual impairment due to retinal degeneration and psychomotor retardation. Physical findings are related to bony defects and include short stature, frontal bossing, a large head, nystagmus, hepatosplenomegaly, and genu valgum in infantile osteopetrosis. The differential diagnoses include hypoparathyroidism, myeloproliferative disease, Paget's disease, pseudohypoparathyroidism and lead toxicity.

Oral Manifestations. The jaws are involved in the same manner as the other bones in the body, and the oral manifestations have been reviewed by Kaslick and Brustein. However, a clear distinction has usually not been made as to the type of the disease present, benign or malignant. The medullary spaces of the jaws are remarkably reduced in both dominant and recessive osteopetrosis so that there is a marked predilection for the development of osteomyelitis should infection gain entrance to the bone. This is a complication of dental extraction which

has been reported frequently and discussed by Dyson. Similar findings were noted by Bjorvatn and his associates in four children with the malignant form of the disease. They stressed the necessity of administering large doses of antibiotics to control the recurring infection, which even then did not prevent the progressive osseous destruction. Fracture of the jaw during tooth extraction, even when the extraction is performed without undue force, may also occur because of the fragility of the bone. It has been reported that the teeth are of defective quality, enamel hypoplasia, microscopic dentinal defects and arrested root development all having been described. However, this may not be true in the benign dominant form of the disease. It is also reported that the teeth are especially prone to dental caries. Since dental findings have been recorded in so few cases, this observation is difficult to evaluate. An additional rather constant finding is retardation of tooth eruption due to the sclerosis of bone.

Radiographic Features. Radiographic features are usually diagnostic. Because the disease is a heterogeneous group of disorders, the findings vary depending on the subtype. Patients usually have generalized osteosclerosis. Bones may be uniformly sclerotic, but alternating sclerotic and lucent bands may be noted near the ends of long bones (Fig. 17-6). The bones might appear club like or show an appearance of a bone within bone (endobone). The entire skull is thickened and dense, especially at the base. Sinuses are small and underpneumatized. Vertebrae are extremely radiodense. They may show alternating bands, known as the **'rugger-jersey'** sign. Radiographs may show evidence of fractures or osteomyelitis. When the jaws are affected, the density of the bone may be such that the roots of the teeth are nearly invisible on the dental radiograph.

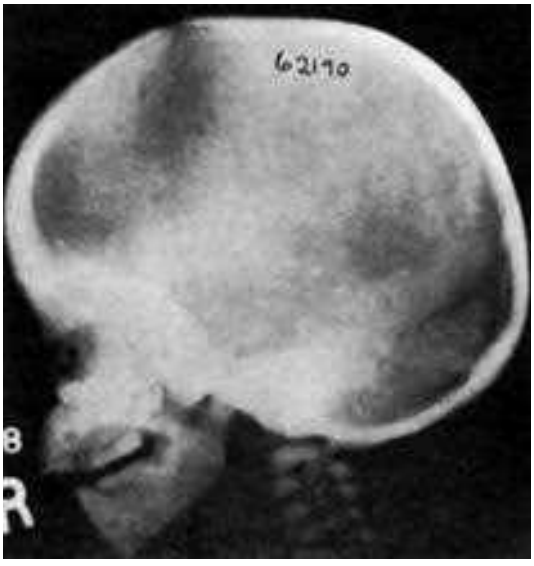


Figure 17-6. Osteopetrosis.
The skull and jaws evidence dense diffuse radiopacity *(Courtesy of Dr John A Campbell)*.

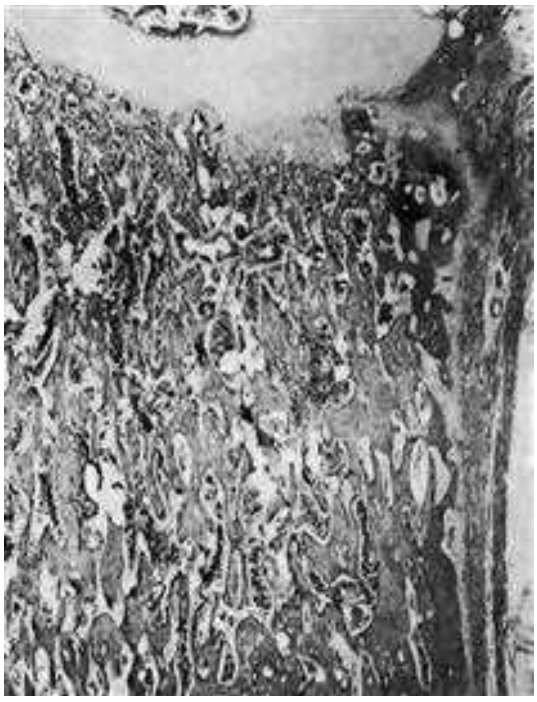


Figure 17-7. Osteopetrosis.
A photomicrograph of a long bone showing replacement of the marrow by endosteal bone *(Courtesy of Dr Frank Vellios)*.

Laboratory Findings. The patients manifest a myelophthisic anemia due to the displacement of hematopoietic marrow tissue by bone. Hypocalcemia can occur and cause rickets if it is severe enough. Parathyroid hormone (PTH) is often elevated (secondary hyperparathyroidism). Acid phosphatase and creatinine kinase (CK-BB) levels are increased due to increased release from defective osteoclasts.

Histologic Features. Bone biopsy is not essential for diagnosis because radiographs are usually diagnostic. Osteopetrosis is characterized by the endosteal production of bone with an apparent concomitant lack of physiologic bone resorption (Fig. 17-7). Osteoblasts are prominent, but osteoclasts are seldom found in significant numbers in tissue sections. The predominance of bone formation over resorption typically leads to the persistence of cartilaginous cores of bony trabeculae long after their replacement should have occurred in endochondral bones. The trabeculae themselves are disorderly in arrangement, and the marrow tissue present is usually fibrous.

It has been reported by Johnston and his associates; however, that adult patients with benign osteopetrosis do not appear to have a deficiency in osteoclastic activity but rather an abnormality in the type and structure of bone. They found osteoblastic and osteoclastic activity with prominent remodeling of bone. However, by polarized light, the bone was found to be markedly deficient in collagen matrix fibrils and these seldom crossed from one osteon to another. This deficiency of fibrils could account for the tendency for fracture in these patients.

Treatment and Prognosis. Infantile osteopetrosis warrants treatment due to the adverse outcome associated with the disease. Calcitriol appears to help by stimulating dormant osteoclasts, and thus, stimulating bone resorption. Erythropoietin can be used to correct anemia. Corticosteroids have been used with the hope of stimulating bone resorption and treating the anemia. Treatment with gamma interferon has been shown to produce long-term benefits. Adult osteopetrosis requires no treatment by itself, though complications of the disease might require intervention. No specific medical treatment exists for the adult type. If untreated, infantile osteopetrosis usually results in death by the first decade of life due to severe anemia, bleeding, or infections. Patients fail to survive, have growth retardation, and increased morbidity. Prognosis can change remarkably in some patients after bone marrow transplantation. Patients with adult osteopetrosis have good long-term survival rates.

Chondrodysplasia Punctata

Chondrodysplasia punctata is a rare congenital syndrome caused by a peroxisomal dysfunction and was first described in 1914. It is one of the four syndromes of the **peroxisome biogenesis disorders** resulting from anomalous enzymatic function of the metabolism of the fatty acids. It has been defined as erratic cartilage calcification during growth which produces the heterogeneous group of disorders that result in small ossification centers in the epiphyseal cartilage of the long bones and spine, skin lesions, cataracts, **craniofacial dysmorphism**, joint contractures, and cardiac malformation. In surviving children, abnormal growth leads to dysmorphism, kyphoscoliosis, limb shortness, and luxation of the hip.

Classification

- Autosomal dominate type (nonrhizomelic)
- Autosomal recessive type (rhizomelic)
- X-linked dominant type
- X-linked recessive type
- Sheffield, mild type
- Other variants.

Autosomal Dominant Type

(Nonrhizomelic, nonlethal type, dysplasia epiphysealis congenita, stippled epiphyses, chondrodysplasia punctata dominant type, chondrodysplasia epiphysealis punctata, chondrodystrophia calcificans congenita, Conradi-Hunermann syndrome)

Autosomal dominant type is the most common of all chondrodysplasia punctata; most are new mutations. An autosomal dominant inheritance is observed with a male: female ratio of 3:1.

Major Diagnostic Criteria

Craniofacial dysmorphism. Asymmetric head, frontal bossing; flat nasal bridge; dysplastic auricles; mongoloid palpebral fissures; hypertelorism; high arched palate.

Ocular abnormalities. Cataract; corneal opacity; nystagmus; microphthalmos; microcornea; glaucoma; and dislocated lens.

Cutaneus abnormalities. Ichthyosis and hyperkeratosis; alopecia; layered and split nails.

Skeletal abnormalities. Asymmetric mild shortening of all long bones; bowing; stippled epiphysis; vertebral scoliosis, clefting; or wedging; flexion contracture of the joints; clubfoot or valgus deformity.

Associated findings such as mild mental retardation and postaxial polydactyly has been rarely described. Complex congenital cardiac disease and central nervous system anomalies have also been reported.

Radiographic Features. Mild shortening of all long bones with multiple epiphyseal punctate calcific deposits in the infantile cartilaginous skeleton, which may or may not be seen by ultrasound after 14 weeks. Vertebral body deformities and scoliosis can also be seen. Stippling of the proximal humerus may also help to identify the condition.

Prognosis. The prognosis is excellent. Affected individuals usually have a normal life span and intelligence.

Pyknodysostosis

The disorder was first described and named by Maroteaux and Lamy in 1962. Andren et al, simultaneously and independently delineated this syndrome. The features are deformity of the skull (including wide sutures), maxilla and phalanges (acro-osteolysis), osteosclerosis, and fragility of bone. Pyknodysostosis is inherited as an autosomal recessive trait. The locus for the dysplasia has been mapped to chromosome **1q21.** Mutations in this region lead to cathepsin K deficiency. Cathepsin K is a cysteine protease that is highly expressed in osteoclasts. The estimated prevalence of pyknodysostosis is 1 per million.

Clinical Features. This dysplasia is characterized by a short-limbed stature. There is hypoplasia or absence of the lateral portion of the clavicles, and hypoplasia of the terminal phalanges of the digits (termed **acro-osteolysis**), leading to short, stubby hands with large finger nails. The skull has widened sutures and persistent open fontanels, even into adulthood. The mandible is small, and the angle of the mandible is obtuse, leading to a very small chin. The nose is protuberant. The teeth are delayed in appearance and disordered when present.

Radiographic Features. Radiographs show generalized osteosclerosis. The medullary canal is always present, but it is small and irregular. The sclerotic bone has a propensity to fracture, with fractures generally occurring in the lower extremities. Bone formation and resorption are simultaneously diminished. MRI studies have shown the cortex to be of normal thickness, whereas the space within the medullary canal was limited as a result of the increase in trabecular bone. Bone scan reveals increased uptake.

Histologic Features. Microscopic examination of bone biopsy specimens are similar to those in osteopetrosis. Meredith and associates (1978) proposed that normal osteoblasts and osteoclasts fail to respond as they should to the demands of stress on the bone. Although osteoclast are present, they do not appear to function properly in resorbing bone. At fracture sites, all cellular elements of fracture repair are present.

The differential diagnosis includes osteopetrosis. Unlike osteopetrosis, pyknodysostosis does not lead to aplastic anemia, because the medullary canal is partially preserved. Cleidocranial dysostosis may be considered because of the hypoplasia of the clavicles; however, osteosclerosis is not seen in cleidocranial dysostosis.

Treatment and Prognosis. Orthopedic treatment consists of fracture care. Life expectancy is normal. Chronic osteomyelitis of the jaw occurs frequently and is resistant to standard forms of treatment.

The types of MPS linked to specific enzyme deficiencies are listed below; some have been assigned an enzyme commission (EC) number.

- MPS type I-H (Hurler syndrome): Alpha-L-iduronidase deficiency (EC 3.2.1.76)
- MPS type I-S (Scheie syndrome, formerly MPS type V): Alpha-L-iduronidase deficiency
- MPS type I-H/S (Hurler-Scheie syndrome): Alpha-L-iduronidase deficiency
- MPS type II, mild (Hunter syndrome, mild form): L-sulfoiduronate sulfatase deficiency
- MPS type II, severe (Hunter syndrome, severe form): L-sulfoiduronate sulfatase deficiency (EC 3.1.6.13)
- MPS type III-A (Sanfilippo syndrome type A): Heparan sulfate sulfamidase deficiency (EC 3.1.6.14)
- MPS type III-B (Sanfilippo syndrome type B): N-acetyl-alpha-D-glucosaminidase deficiency (EC 3.2.1.50)
- MPS type III-C (Sanfilippo syndrome type C): Acetyl-CoA: alpha-glucosamide N-acetyltransferase deficiency (EC 2.3.1.3)
- MPS type III-D (Sanfilippo syndrome type D): N-acetyl-alpha-D-glucosamine-6-sulfatase deficiency (EC 3.1.6.14)
- MPS type IV-A (Morquio syndrome, classic form): N-acetylgalactosamine-6-sulfatase (gal-6-sulfatase) deficiency (EC 3.1.6.4)
- MPS type IV-B (Morquiolike syndrome): Beta-galactosidase deficiency (EC 3.2.1.23)
- MPS type VI (Maroteaux-Lamy syndrome, mild form): N-acetylgalactosamine-4-sulfatase (arylsulfatase B) deficiency
- MPS type VI (Maroteaux-Lamy syndrome, severe form): N-acetylgalactosamine-4-sulfatase (arylsulfatase B) deficiency (EC 3.1.6.1)
- MPS type VII (Sly syndrome): Beta-glucuronidase deficiency (EC 3.2.1.31)

Mucopolysaccharidoses Types I–VII

(Lysosomal storage disease)

Mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases, each of which is produced by an inherited deficiency of an enzyme involved in the degradation of acid mucopolysaccharides (now called glycosaminoglycans [GAG]). These diseases are autosomal recessive, except for MPS type II, which is X-linked.

Etiology. Glycosaminoglycans (GAG) are long, linear polysaccharide molecules composed of repeating dimers, each of which contains a hexuronic acid (or galactose in the case of keratan sulfate) and an amino sugar. The large proteoglycan molecules made up of protein cores and GAG branches are secreted by cells and constitute a significant fraction of the extracellular matrix of the connective tissue. The turnover of these molecules depends on their subsequent internalization by endocytosis, their delivery to the lysosomes, and their digestion by lysosomal enzymes. The enzyme deficiencies lead to the accumulation of mucopolysaccharides in the lysosomes of the cells in the connective tissue and to an increase in their excretion in the urine.

The enzyme synthesis is controlled at the following gene loci:

- 4p16.3 (Hurler syndrome, Scheie syndrome)
- 12q14 (Sanfilippo syndrome)
- 6q24.3 (Morquio syndrome): The deficiency of enzymes in Morquio syndrome type A or type B leads to the accumulation of keratan sulfate and chondroitin-6-sulfate in the connective tissue, the skeletal system, and the teeth
- 5q11–q13 (Maroteaux-Lamy syndrome)
- Xq27.3–q28 (Hunter syndrome)

Clinical Features. Onset usually occurs in early childhood. Skeletal findings include dwarfism, with rather characteristic radiologic changes of the hands and the lumbar vertebral column; stiff articulations; and coarse facies. Patients with Hurler syndrome usually die by the time they are aged 5–10 years. The life expectancy of patients with Scheie syndrome may be nearly normal. They can live until the fifth or sixth decade of life, and they can have healthy offspring. As for patients with Hunter and Sanfilippo syndrome, death usually occurs by the time of puberty. In the classic form of Morquio syndrome, long-term survival is rare, with death occurring in persons aged 20–40 years. In patients with the severe form of Maroteaux-Lamy syndrome, death usually occurs by early adulthood.

Differential diagnoses include Gaucher disease, Niemann-Pick disease, syphilis, osteogenesis imperfecta, vitamin D-resistant rickets, nephrogenic osteopathy, spondyloepiphysial dysplasia, metaphysial dysplasia.

Treatment. No cure for MPS exists, treatment is symptomatic and supportive. However, possible treatments are being investigated in several clinical trials.

Rickets

Rickets is an entity that commonly affects children leading to decreased mineralization at the level of the growth plates with resultant growth retardation and delayed skeletal development. Osteomalacia is found in adults which affects trabecular bone, and results in undermineralization of osteoid. By definition, rickets is found only in children prior to the closure of the growth plates, while osteomalacia occurs in persons of any age. The term rickets is said to have been derived from the ancient English word 'wricken', which means to bend. In several European countries, rickets is also termed English disease, which appears to stem from the turn of the 19th century in England when rickets was endemic in larger cities.

Etiology. Rickets results either from a deficiency or abnormal metabolism of vitamin D or from abnormal metabolism or excretion of inorganic phosphate. Histologic changes are seen at the level of the growth plates, or more specifically, at the level of the hypertrophic zone, where an increased number of disorganized cells is found. The increased number of cells results in increased width and thickness of the hypertrophic zone (rachitic metaphysis).

In most developing countries, rickets is seldom seen, supposedly due to high exposure to sunlight. An exception occurs in groups of women who are rarely allowed to leave the house (largely for religious reasons) or who must wear veils when they do. Since these women may have low vitamin D levels, their babies are at a higher risk of developing rickets. When patients receive adequate treatment, no mortality is associated with this disease; however concomitant diseases, such as pneumonia, tuberculosis, and enteritis, occur with a higher frequency and may cause death. Boys and girls are affected equally with rickets. There is a form of genetic rickets, called X-linked hypophosphatemic rickets, in which some children, often girls, may be only moderately affected, although girls with X-linked hypophosphatemic rickets can have rickets symptoms that are just as severe as those in boys. By definition, rickets occurs only in children whose growth plates have not closed. The growth plates close at the end of puberty, at approximately age of 17 years in females and age of 19 years in males. Premature neonates are especially at risk because their requirements for vitamin D, calcium, and phosphate are higher than the requirements in full-term neonates (for details, refer to Chapter 15 on Oral Aspects of Metabolic Disease).

Hyperparathyroidism

The parathyroid glands regulate serum calcium and phosphorus levels by its secretion and maintenance within physiological limits of its hormone, parathyroid hormone (PTH). Under normal conditions, the rate of secretion of parathyroid hormone is inversely proportional to the serum calcium level. Secretion of PTH is mainly controlled through the interaction of calcium with specific calcium-sensing receptors on the membrane of parathyroid cells. Hyperparathyroidism is a syndrome of hypercalcemia resulting from excessive release of parathyroid hormone. Most cases of hyperparathyroidism are discovered accidentally when hypercalcemia is noted during a routine serum chemistry examination. In most patients, symptoms are mild at the time of presentation and resolve with surgical correction of the disorder.

Etiology. In 85% of affected persons, **primary hyperparathyroidism** results from an adenoma in a single parathyroid gland. Hypertrophy of the parathyroid glands causes hyperparathyroidism in 15% of patients. Parathyroid malignancies account for a small number of hyperparathyroidism cases. Hyperparathyroidism is common in patients with type I and type II multiple endocrine neoplasia (MEN) and in patients who received radiation therapy to the head and neck during childhood for benign diseases. Also, a syndrome of familial hyperparathyroidism has been observed. **Secondary hyperparathyroidism** occurs when the parathyroid glands become hyperplastic after long-term stimulation to release PTH in response to chronically low serum calcium. Chronic renal failure, rickets, and malabsorption syndromes are the most frequent causes. In secondary hyperparathyroidism, high levels of PTH do not cause hypercalcemia because the primary problem makes calcium unavailable. With long-term hyperstimulation, the glands eventually function autonomously and continue to produce high levels of parathyroid hormone even after the chronic hypocalcemia has been corrected. Hypercalcemia caused by autonomous parathyroid function after long-term hyperstimulation is referred to as **tertiary hyperparathyroidism**.

A useful mnemonic for remembering the findings of rickets is as follows:

- Reaction of the periosteum (may occur)
- Indistinct cortex
- Coarse trabeculation
- Knees, wrists, and ankles affected predominantly
- Epiphyseal plates, widened and irregular
- Tremendous metaphysis (cupping, fraying, splaying)
- Spur (metaphyseal)

Clinical Features. Of the endocrine disorders, only diabetes mellitus and hyperthyroidism occur more frequently than hyperparathyroidism. Hereditary hyperparathyroidism occurs most frequently as part of a syndrome of multiple endocrine neoplasia (MEN). MEN 1 consists of hyperparathyroidism with tumors of the pituitary and pancreas. MEN 2A consists of hyperparathyroidism, pheochromocytoma, and medullary carcinoma of the thyroid. Although hyperparathyroidism can occur at any age, it is most common in the fifth and sixth decades of life. Prevalence is higher in females than in males, with a male-to-female ratio of approximately 1 : 2. At least one half of patients with hyperparathyroidism are asymptomatic. Manifestations of hyperparathyroidism may be subtle, and the disease may run a benign course for many years. Less commonly, hyperparathyroidism may worsen abruptly and cause severe hypercalcemic complications (e.g., profound dehydration, coma). This is referred to as **hypercalcemic parathyroid crisis**.

The skeletal and neuromuscular changes manifest as bone pain and/or tenderness, muscle fatigue, weakness and spontaneous fractures; nonspecific myalgias, osteoporosis, osteopenia, cystic bone lesions, vertebral collapse, chondrocalcinosis and pseudogout can develop. Patients have a tendency to develop pancreatitis and/or pancreatic calcification and peptic ulcer disease which can result in abdominal distress, constipation, vomiting, anorexia and weight loss. Neuropsychiatric illness and altered mental status such as anxiety, depression, psychosis and apathy have been reported. Signs of hypertension and congestive heart failure may be apparent.

Radiographic Features *(Refer to Chapter 15)*

Laboratory Findings. The diagnosis of hyperparathyroidism is made by demonstrating elevated parathyroid hormone levels in the setting of high serum calcium. Almost all other causes of hypercalcemia suppress the release of parathyroid hormone, which is measured by radioimmunoassay. Other findings include elevated serum chloride levels, decreased serum phosphate level (less than 2.5 mg/dl (0.81 mmol/L), decreased serum carbon dioxide, hyperchloremic metabolic acidosis, increase in urine cyclic adenosine monophosphate (cAMP).

Histologic Features *(Refer to Chapter 15)*

Treatment and Prognosis. The emergency management of hyperparathyroidism is focused on the treatment of the hypercalcemia. Specifically, the goal of treatment is to reduce the calcium level to below 11.5 mg/dl, less than the level in which most patients have resolution of hypercalcemia-induced symptoms.

Hypoparathyroidism

Primary hypoparathyroidism is caused by a group of heterogeneous conditions in which hypocalcemia and hyperphosphatemia occur as a result of deficient parathyroid hormone (PTH) secretion. This most commonly results from surgical excision of, or damage to, the parathyroid glands. However, genetic forms of hypoparathyroidism due to decreased secretion of PTH are known (Table 17-4).

Clinical Features. The signs and symptoms of hypoparathyroidism include evidence of latent or overt neuromuscular hyperexcitability due to hypocalcemia. The effect may be aggravated by hyperkalemia or hypomagnesemia, but there is wide variation in the severity of the symptoms. Patients may complain of circumoral numbness, paresthesia of the distal extremities or muscle cramping which can progress to carpopedal spasm or tetany. Laryngospasm or bronchospasm and seizures may also occur. Other less specific manifestations include fatigue, irritability, and personality disturbance. Patients with chronic hypocalcemia may have calcification of the basal ganglia or more widespread intracranial calcification, detected by skull X-ray or CT scan. Also seen are extrapyramidal neurological symptoms (more often with intracranial calcification), subcapsular cataracts, band keratopathy, and abnormal dentition.

Table 17-4: Forms of hypoparathyroidism having a genetic basis

1. Isolated
   - *Autosomal dominant*
     - PreproPTH signal peptide mutation
     - CASR activating mutation
   - *Autosomal recessive*
     - PreproPTH RNA splice-site mutation
     - Gcm-2 mutation
   - *X-linked*
2. Congenital multisystem syndromes
   - DiGeorge and velocardiofacial
   - Barakat/HDR
   - Kenny-Caffey
3. Metabolic disease
   - Mitochondrial neuromyopathies
   - Long-chain hydroxyacyl-CoA dehydrogenase deficiency
   - Heavy-metal storage disorders
4. Autoimmune disease
   - APECED
5. Pseudohypoparathyroidism

In hypoparathyroidism, serum calcium concentrations are decreased and serum phosphate levels are increased. Serum PTH is low or undetectable (the important exception is PTH resistance—pseudohypoparathyroidism—discussed below). Usually, serum 1,25(OH)2D is low, but alkaline phosphatase activity is normal. Despite an increase in fractional excretion of calcium, intestinal calcium absorption and bone resorption are both suppressed. The renal filtered load of calcium is decreased, and the 24-hour urinary calcium excretion is reduced; nephrogenous cyclic AMP excretion is low and renal tubular reabsorption of phosphate is elevated. After parenteral administration of biologically active PTH, plasma and urinary cyclic AMP and inorganic phosphate excretion increase — a test (the **Ellsworth-Howard test**) that differentiates hypoparathyroidism from pseudohypoparathyroidism. Hypoparathyroidism is a feature common to various kinds of inherited disorders. Although familial occurrences are reported, sporadic cases are common. Autoimmune hypoparathyroidism can occur as an isolated endocrine condition or with other glandular deficiencies in a pluriglandular autoimmune syndrome, and it can occur as a congenital hypoplasia/aplasia with or without other congenital anomalies such as lymphedema, nephropathy, nerve deafness or cardiac malformation. It also occurs as an isolated finding.

Autoimmune parathyroid gland ablation or destruction. Antibodies directed against parathyroid tissue have been detected in over 30% of patients with isolated hypoparathyroid disease, and over 40% of patients having hypoparathyroidism combined with other endocrine deficiencies. It remains to be seen whether the autoantibodies are of primary or secondary importance in these cases.

Pseudohypoparathyroidism. Several clinical disorders characterized by end-organ resistance to PTH have been described collectively by the term pseudohypoparathyroidism (PHP). They are associated with hypocalcemia, hyperphosphatemia, and increased circulating PTH, but target

tissue unresponsiveness to the hormone manifests as a lack of increased cAMP excretion in response to PTH administration.

Treatment. The goal of treatment in hypoparathyroid state is to raise the serum calcium sufficiently to alleviate acute symptoms and prevent the complications of chronic hypocalcemia. The calcium concentration required for this purpose is generally the low-normal range. Acute or severe symptomatic hypocalcemia is best treated with intravenous calcium infusion. Initial doses of 2–5 millimoles of elemental calcium as the gluconate salt can be given over a 10–20 minute period, followed by 2 millimoles elemental calcium per hour as a maintenance dose, to be adjusted according to symptoms and biochemical response.

Fibrous Dysplasia

Fibrous dysplasia is a skeletal developmental anomaly of the bone-forming mesenchyme that manifests as a defect in osteoblastic differentiation and maturation. Virtually any bone in the body can be affected. It is a nonhereditary disorder of unknown cause.

Etiology. The exact cause of fibrous dysplasia is not known. The condition is **not** believed to be hereditary. Fibrous dysplasia is usually caused by a mutation in the **GNAS1** gene **(20q13.2).** The GNAS1 **(guanine nucleotide-binding protein, α-stimulating activity polypeptide)** gene encodes a G-protein that stimulates the production of cAMP. The mutation results in a continuous activation of the G-protein leading to overproduction of cAMP in affected tissues. This results in a hyperfunction of affected endocrine organs, frequently giving rise to precocious puberty, hyperthyroidism, growth hormone and cortisol overproduction. Secondly, there is an increased proliferation of melanocytes resulting in large *café-au-lait* spots with irregular margins as opposed to the regular outlined *café-au-lait* spots in neurofibromatosis. Thirdly, cAMP is thought to have an effect on the differentation of osteoblasts leading to fibrous dysplasia. In fibrous dysplasia, the medullary bone is replaced by fibrous tissue, which appears radiolucent on radiographs, with the classically described **ground-glass** appearance. Trabeculae of woven bone contain fluid-filled cysts that are embedded largely in collagenous fibrous matrix, contributes to the generalized hazy appearance of the bone.

Clinical Features. The following three disease patterns are recognized:

1. Monostotic form
2. Polyostotic form
3. Craniofacial form.

The initial manifestations of fibrous dysplasia are most commonly found in persons aged 3–15 years. Two-thirds of patients with polyostotic disease are asymptomatic before they are aged 10 years. With monostotic disease, patients as old as 20 or 30 years are asymptomatic. No specific racial predilection exists. The incidence is equal in males and females. Clinical findings of increasing pain and an enlarging soft tissue mass suggest malignant change.

Monostotic form. Approximately 70–80% of fibrous dysplasias are monostotic. This form most frequently occurs in the rib (28%), femur (23%), tibia, **craniofacial bones** (10–25%), and humerus, in decreasing order of frequency. This form may present with pain or a pathologic fracture in patients aged 10–70 years. The degree of bone deformity is relatively less severe compared with that of the polyostotic type. No clearly documented evidence supports the conversion from the monostotic form to the polyostotic form.

Polyostotic form. Approximately 20–30% of fibrous dysplasias are polyostotic. Polyostotic fibrous dysplasia more frequently involves the skull and facial bones, pelvis, spine, and shoulder girdle. The sites of involvement are the femur, tibia, pelvis, ribs, skull and facial bones, upper extremities, lumbar spine, clavicle, and cervical spine in decreasing order of frequency. The dysplasia may be unilateral or bilateral, and it may affect several bones of a single limb or both limbs with or without axial skeleton involvement. Although the polyostotic variety tends to occur in a unilateral distribution, involvement is asymmetric and generalized when disease is bilateral.

Two-thirds of patients are symptomatic before they are 10 years of age. Often, the initial symptom is pain in the involved limb associated with a limp, spontaneous fracture, or both. In one series, pathologic fracture was present in 85% of polyostotic fibrous dysplasias. Leg-length discrepancy of varying degrees occurs in about 70% of patients with limb involvement. The structural integrity of the bone is weakened, and the weight-bearing bones become bowed. The curvature of the femoral neck and proximal shaft of the femur markedly increase causing a **Shepherd's crook** deformity, which is a characteristic sign of the disease. Overgrowth of adjacent soft tissues may be present. Two apparently separate types of polyostotic fibrous dysplasia are described:

- Fibrous dysplasia involving a variable number of bones, although most of the skeleton is normal, accompanied by pigmented lesions of the skin or '*café-au-lait*' spots (**Jaffe's type**).
- An even more severe fibrous dysplasia involving nearly all bones in the skeleton and accompanied by pigmented lesions of the skin, and in addition, endocrine disturbances of varying types (**Albright's syndrome**).

Craniofacial form. This pattern of the disease occurs in 10–25% of patients with the monostotic form and in 50% with the polyostotic form. It also occurs in an isolated craniofacial form. In the isolated variety, no extracranial lesions are present. Sites of involvement most commonly include the frontal, sphenoid, maxillary, and ethmoidal bones. The occipital and temporal bones are less commonly affected. Hypertelorism, cranial asymmetry, facial deformity, visual impairment, exophthalmos, and blindness may occur because of involvement of orbital and periorbital bones. Involvement of the sphenoid wing and temporal bones may result in vestibular dysfunction, tinnitus, and hearing loss. When the cribriform plate is involved, hyposmia or anosmia may result.

Cherubism. This is an entirely different entity having microscopic similarity more with giant cell lesions than fibrous dysplasia, and is an autosomal disorder of variable penetrance. The gene for cherubim was mapped to chromosome 4p16. The gene mutated was identified as SH3BP2 within this locus. It is believed that mutations in the gene may lead to pathologic activation of osteoclasts and disruption of jaw development. Regression may occur after adolescence. The jaw is broad and protruding. Involvement of the maxilla and the mandible is symmetric.

The only significant laboratory abnormality is an elevated alkaline phosphatase level. Differential diagnoses include enchondroma and enchondromatosis, eosinophilic granuloma, fibrous cortical defect and nonossifying fibroma, giant cell tumor, central hemangioma, hyperparathyroidism, primary neurofibromatosis type 1 and Paget's disease.

Radiographic Features. The usual appearance of fibrous dysplasia in long and short tubular bones includes a lucent lesion in the diaphysis or metaphysis, with endosteal scalloping and with or without bone expansion and the absence of periosteal reaction. The lucent lesion has a thick sclerotic border and is called the **rind sign.** Among skull and facial bones the frontal bone is involved more frequently than the sphenoid, with obliteration of the sphenoid and frontal sinuses. Single or multiple, symmetric or asymmetric, radiolucent or sclerotic lesions in the skull or facial bones may be present. Most commonly, maxillary and mandibular involvement has a mixed radiolucent and radiopaque pattern, with displacement of the teeth and distortion of the nasal cavities.

Oral Manifestations. The oral manifestations of polyostotic fibrous dysplasia are related to the severe disturbance of the bony tissue. One-third of the polyostotic patients in the series of Van Horn and his associates had lesions in the mandible. The occurrence of maxillary lesions was not mentioned, although Harris and his group stated that maxillary and mandibular involvement was not rare.

There may be expansion and deformity of the jaws, and the eruption pattern of the teeth is disturbed because of the loss of normal support of the developing teeth. The endocrine disturbance also may alter the time of eruption of the teeth. A classic case with involvement of the maxilla has been reported by Church. In this instance there was no intraoral pigmentation, although it has been reported to occur.

Histologic Features. The lesions are composed of fibrillar connective tissue within which are numerous trabeculae of coarse, woven immature bone, irregular in shape but evenly spaced, showing no relation to functional patterns. The osteocytes are quite large, and collagen fibers of these trabeculae can often be seen extending out into the fibrous tissue. Bone formation by stellate osteoblasts can be observed, although rows of cuboidal osteoblasts lined up on the surfaces of trabeculae are absent (osteoblastic riming). These trabeculae typically have wide osteoid seams. Osteoclastic activity may be seen where the calcification of osteoid extends to the surface of the trabeculae.

Treatment and Prognosis. Treatment is usually conservative and primarily to prevent deformity. Any underlying endocrine disturbances should be treated. In upper extremity lesions, more than 80% respond to nonsurgical management. No specific medical treatment exists for the bone disease, although early evidence suggests that vitamin D and bisphosphonates (after epiphyseal closure) may be helpful in ameliorating pain and possibly in reconstituting lesions with normal bone. Surgical therapy with curettage and replacement of the bone defect with autograft or allograft usually results in resorption of the graft at the surgical site. Use of allograft or cortical autograft usually delays this conversion, as it is more resistant to resorption and replacement by dysplastic bone.

Of special concern is malignant degeneration and metabolic changes in patients with fibrous dysplasia. The estimated frequency of malignant transformation is 0.4–1% in fewer than 50 reported cases. The interval from the diagnosis of fibrous dysplasia to the development of malignancy varies and is usually years or decades. Most often, skull and facial bones undergo malignant change in monostotic disease, whereas femoral and facial bones undergo malignant change in polyostotic disease. Osteosarcoma and fibrosarcoma are the most common tumors. Chondrosarcomas occur less frequently. Radiographic features suggestive of malignant degeneration include a rapid increase in the size of the lesion and a change from a previously mineralized bony lesion to a lytic lesion. Clinical findings of increasing pain and an enlarging soft tissue mass suggest malignant change.

Monostotic Fibrous Dysplasia of the Jaws

Monostotic fibrous dysplasia, though less serious than polyostotic fibrous dysplasia, is of greater concern to the dentist because of the frequency with which the jaws are affected. Nearly every bone has, at one time or another, been reported involved. In a series of 67 cases of monostotic fibrous dysplasia, Schlumberger found the following distribution:

Ribs	29 cases	Humerus	2 cases
Femur	9 cases	Ulna	2 cases
Tibia	8 cases	Vertebra	1 case
Maxilla	7 cases	Pelvis	1 case
Calvarium	5 cases	Fibula	1 case
Mandible	2 cases		

There is now evidence to indicate; however, that the incidence of jaw lesions is proportionately far greater than this study would indicate. It is now recognized that some cases of jaw lesions which in the past were diagnosed under a variety of other names are now embraced by the term 'fibrous dysplasia'. As an example, certain cases of so-called central giant cell tumors of the jaws have been found upon re-evaluation to be classifiable as fibrous dysplasia. This has been emphasized particularly by Jaffe, Lichtenstein and Portis and by Waldron. In past years the designation 'ossifying fibroma' (q.v.) was a common one for a certain group of jaw lesions which occurred with considerable frequency. Many authorities now view at least some of these lesions as a type of monostotic fibrous dysplasia. Another lesion of bone, the nonosteogenic

fibroma, also is considered by some investigators to be a form of fibrous dysplasia. The clinical term 'leontiasis ossea' has often been applied to cases of fibrous dysplasia which affect the maxilla or facial bones and give the patient a leonine appearance. Thus it can be appreciated that fibrous dysplasia of bone has come to include a number of lesions once described by other terms. Although investigators differed as to the desirability of inclusion of certain bony lesions in this group, the trend in the past few years had been to recognize monostotic fibrous dysplasia as an entity with considerable clinical and histologic variation, probably dependent upon the stage or phase of the disease.

In contrast; however, it has been suggested that this trend to classify many fibro-osseous lesions of the jaws under the term 'fibrous dysplasia' may be unfortunate, and many pathologists have now reverted again to the 'purist' idea that fibrous dysplasia does represent a specific entity with well-defined microscopic and radiographic features. This would man that there are certain fibro-osseous lesions of the jaws which would not be designated as fibrous dysplasia, and until more knowledge of the true nature of the lesions accumulates, some workers have simply classified them as 'fibro-osseous lesions', after first being certain that they do not represent some specific entity.

Clinical Features. Monostotic fibrous dysplasia of the jaws occurs with apparently equal predilection for males and females, although some reports show a mild predominance of females. It is more common in children and young adults than in older persons. The mean age of occurrence in the 69 patients reported by Zimmerman and his associates was 27 years, while in 53 patients with craniofacial fibrous dysplasia reported by Gardner and Halpert, the mean age was 34 years.

The first clinical sign of the disease is a painless swelling or bulging of the jaw. The swelling usually involves the labial or buccal plate, seldom the lingual aspect, and when it involves the mandible it sometimes causes a protuberant excrescence of the inferior border. There may be some malalignment, tipping or displacement of the teeth due to the progressive expansile nature of the lesion, and tenderness may ultimately develop. The mucosa is almost invariably intact over the lesion.

Fibrous dysplasia of the maxilla is an especially serious form of the disease since it has a marked predilection for occurrence in children and is almost impossible to eradicate without radical, mutilating surgery (Fig. 17-8). These lesions

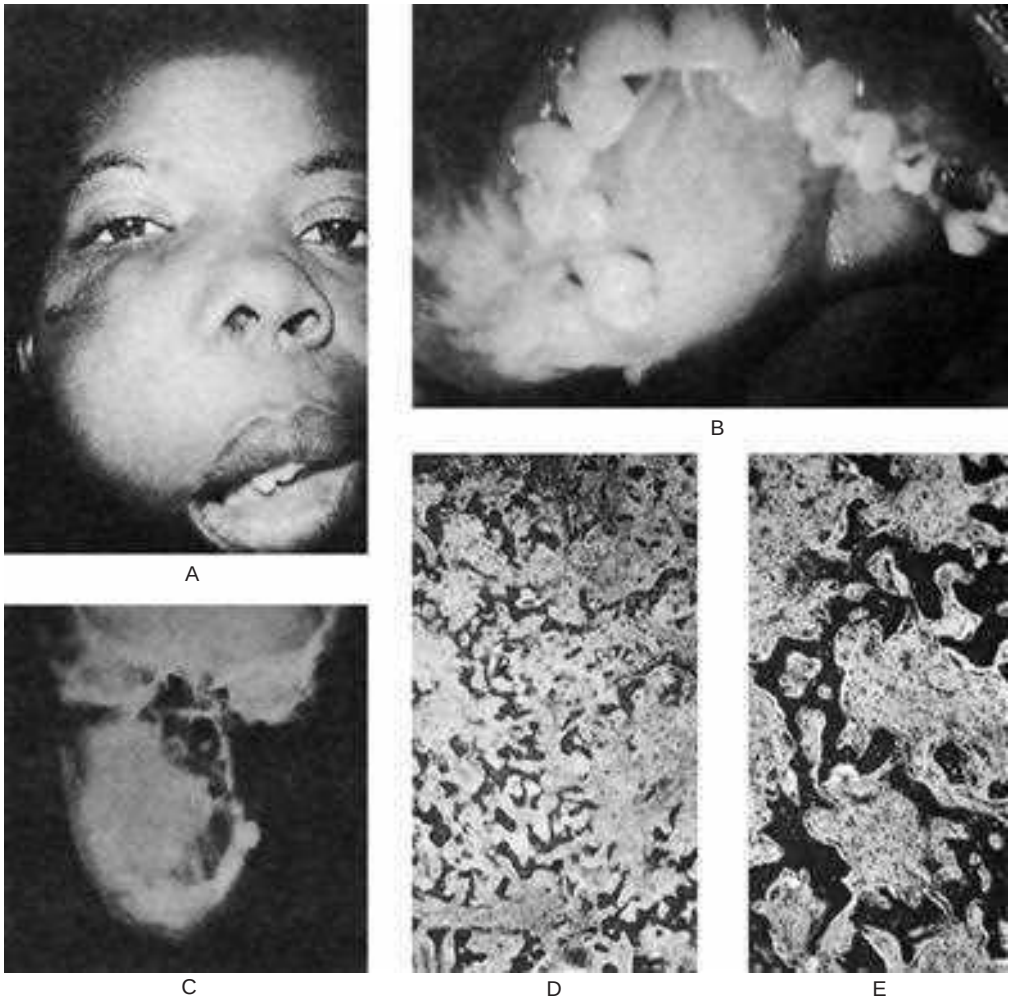


Figure 17-8. Fibrous dysplasia of the maxilla in childhood.
(Courtesy of Dr Edward M Pfafflin).

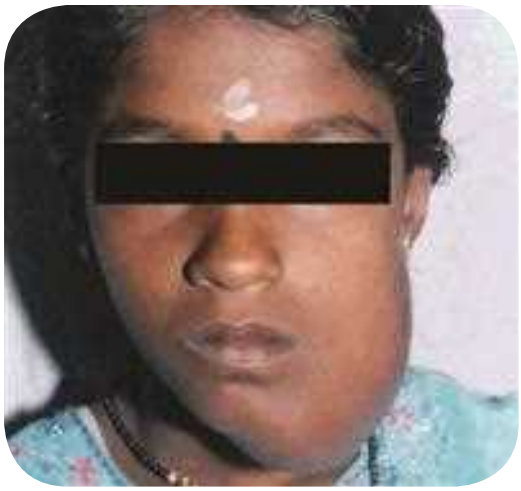


Figure 17-9. Fibrous dysplasia of the mandible in a girl of 16 years.

are not well circumscribed, commonly extend locally to involve the maxillary sinus, the zygomatic process and the floor of the orbit, and even extend back toward the base of the skull. Severe malocclusion and bulging of the canine fossa or extreme prominence of the zygomatic process, producing a marked facial deformity, are typical sequelae of this disease in this location need not be truly monostotic, but neither is it usually classified as a polyostotic type. It has sometimes been referred to as craniofacial fibrous dysplasia, since it does affect the craniofacial complex and is so characteristic in its clinical and radiographic features that it closely resembles a distinct entity (Fig. 17-9). This form of the disease has been described in detail by Waldron and Giansanti and by Eversole and his associates.

Radiographic Features. The radiographic appearance of fibrous dysplasia of the jaw is extremely variable (Fig. 17-10). There are three basic patterns which may be seen. In one type, the lesion is generally a rather small unilocular radiolucency or a somewhat larger multilocular radiolucency, both with a rather well-circumscribed border and containing a network of fine bony trabeculae. In the second type, the pattern is similar except that increased trabeculation renders the lesion more opaque and typically mottled in appearance. The third type of quite opaque with many delicate trabeculae gives a 'ground-glass' or '*peau d'orange*' appearance to the lesion. This latter type characteristically is not well circumscribed but instead blends into the adjacent normal bone. Any of the three types may be found in either maxilla or mandible. In all types, generally the cortical bone becomes thinned because of the expansile nature of the growth, but seldom is this bony plate perforated, or is periosteal proliferation obvious. The roots of teeth in the involved areas may be separated or moved out of normal position but only occasionally exhibit severe resorption. In some cases, the bone appears so opaque that the roots of teeth may be indistinct or not visible.

It is of interest that, in craniofacial fibrous dysplasia, there is characteristic radiographic thickening of the base of the skull.

Histologic Features. There is considerable microscopic variation in cases of monostotic fibrous dysplasia of the jaws. The lesion is essentially a fibrous one made up of proliferating fibroblasts in a compact stroma of interlacing collagen fibers (Fig. 17-11A, B). Irregular trabeculae of bone are scattered throughout the lesion with no definite pattern of arrangement. Characteristically, some of these trabeculae are C-shaped, or as described by one author, Chinese character-shaped. These trabeculae are usually coarse woven bone but may be lamellar, although not as well organized as normal lamellar bone. The relationship of osteoblasts and osteoclasts to the trabeculae is similar to that seen in the polyostotic form of the disease. Large lesions may show variation from area to area and sometimes present a greater bony reaction around the periphery of the lesion than in the central portion.

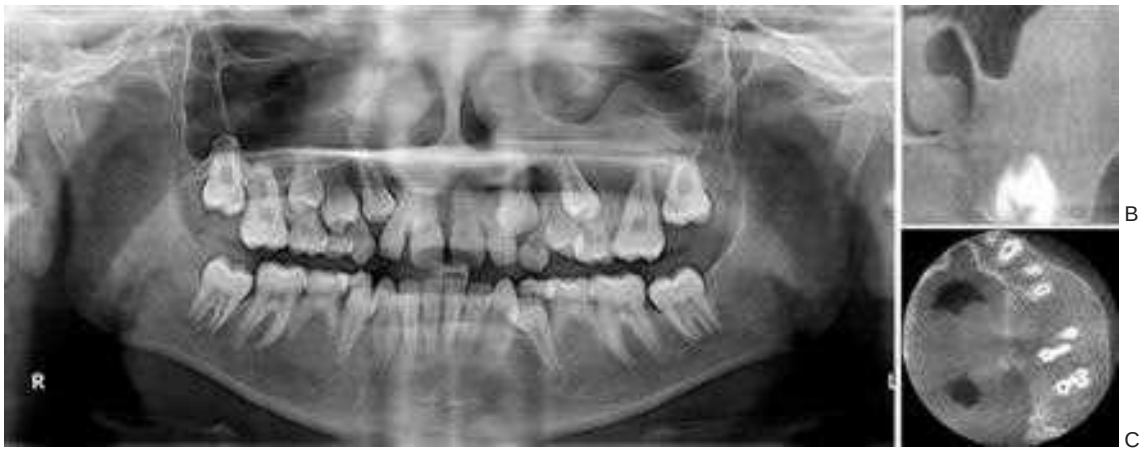
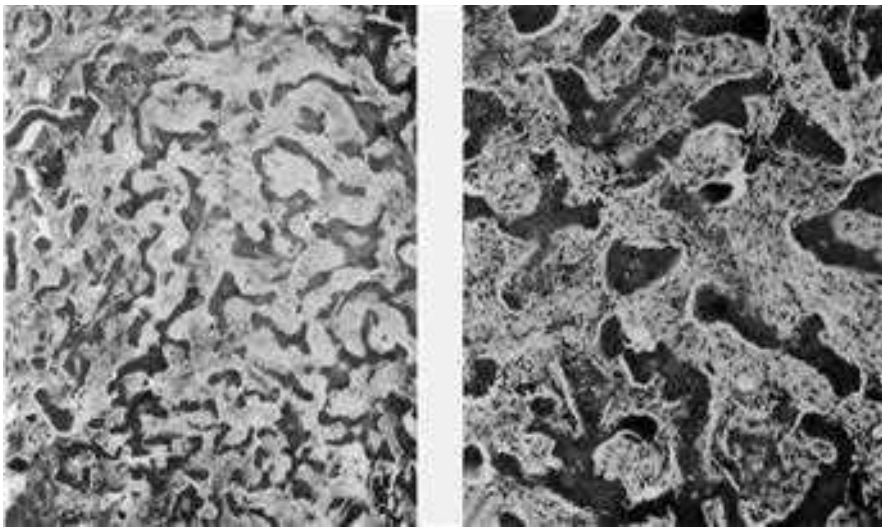


Figure 17-10. Monostotic fibrous dysplasia of bone.
Fibrous dysplasia in the left maxillary molar region. **(A)** Panoramic radiograph shows anterior displacement of the left maxillary second premolar and displacement of the floor of the sinus. **(B)** Coronal section of the same patient shows grainy alveolar bone and displacement of the floor of the sinus. **(C)** Axial section shows significant buccal-palatal expansion of the alveolar bone in the premolar-molar region. Area of fibrous dysplasia does not have clear demarcation.



A B

Figure 17-11. Monostotic fibrous dysplasia of bone.

Some of the earlier literature dealing with this disease suggested that it represents a permanent maturation arrest in the woven bone stage and proposed that lesions demonstrating lamellar bone transformation should not be diagnosed as fibrous dysplasia. However, it is generally well accepted now, particularly on the basis of the work of Waldron and Giansanti, that lesions of fibrous dysplasia of the jaws, especially the craniofacial type, will mature over a period of time and the lesional tissue may show lamellar bone.

McCune-Albright Syndrome
(Polyostotic fibrous dysplasia)

McCune-Albright syndrome or polyostotic fibrous dysplasia (PFD) is defined as the association of polyostotic fibrous dysplasia, precocious puberty, *café-au-lait* spots, and other endocrinopathies due to hyperactivity of various endocrine glands. Fuller Albright first described this syndrome in 1937. McCune-Albright syndrome has been shown to be due to a postzygotic activating mutation of the GS alpha gene in the affected tissues. The GS alpha subunit is the component of the G-protein complex, which couples hormone receptors to adenylate cyclase (the intracellular second messenger) in a submembrane site. It then mediates the cellular effects of hormone binding.

Clinical Features. Precocious puberty associated with the condition is gonadotrophin-independent. Among the endocrine disturbances described in association with Albright syndrome are:

- Hyperthyroidism
- Acromegaly
- Gonadotrophin—McCune-Albright syndrome
- Hyperprolactinemia
- Cushing syndrome
- Hyperparathyroidism
- McCune-Albright syndrome
- Hypophosphatemic rickets.

Some severely affected patients may present with associated hepatic, cardiac, and GI dysfunction (i.e. elevated hepatic transaminases, GI polyposis, and cardiomyopathy).

Cutaneous pigmentation is the most common extraskeletal manifestation in fibrous dysplasia and occurs in more than 50% of cases of the polyostotic form. Cutaneous pigmentation in polyostotic fibrous dysplasia is ipsilateral to the side of bony lesions, a feature that differentiates this disease from pigmentation in neurofibromatosis. The pigmented macules or *café-au-lait* spots (Fig. 17-12) are related to increased amounts of melanin in the basal cells of the epidermis. They tend to be arranged in a linear or segmental pattern near the midline of the body, usually overlying the lower lumbar spine, sacrum, buttocks, upper back, neck, and shoulders. Similar lesions may occur on the lips and oral mucosa. Pigmentation may occur at birth, and in fact, they occasionally precede the development of skeletal and endocrine abnormalities.

The association of fibrous dysplasia and intramuscular myxoma is a rare disease known as **Mazabraud's syndrome.** Both lesions tend to occur in the same anatomical region. The relationship between fibrous dysplasia and myxoma remains unclear, whereas an underlying localized error in tissue metabolism has been proposed to explain this occasional coexistence. Patients with soft tissue myxomas should be thoroughly examined for fibrous dysplasia. The greater risk of sarcomatous transformation in fibrous dysplasia with Mazabraud's syndrome has been reported.

Only a few cases of malignant transformation of skeletal lesions have been described in the setting of McCune-Albright syndrome. Malignancies described in this include:

- OsteosarcoMcCune-Albright syndrome (most common)

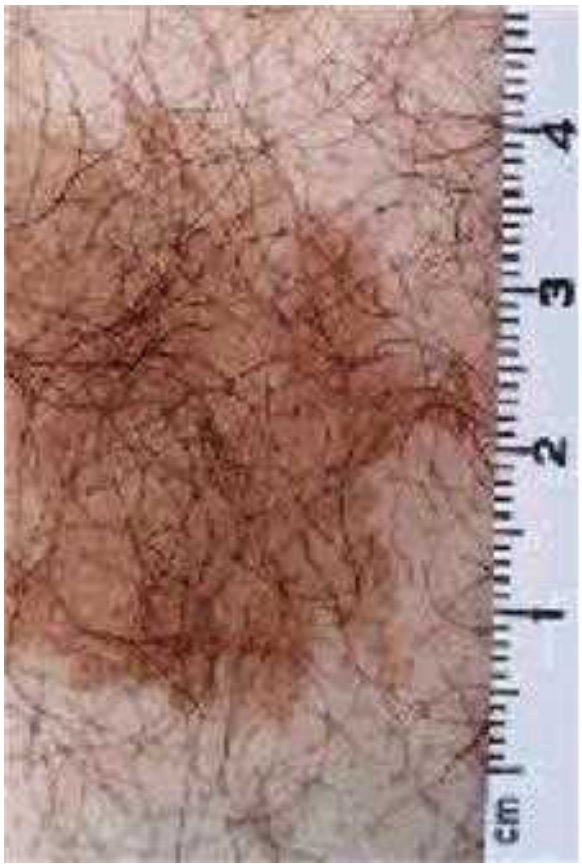


Figure 17-12. *Café-au-lait* pigmentation of skin.

- ChondrosarcoMcCune-Albright syndrome
- FibrosarcoMcCune-Albright syndrome
- LiposarcoMcCune-Albright syndrome.

These malignancies occur most commonly in the setting of therapeutic irradiation exposure. Females may have a greater risk for breast cancer, probably due to their prolonged exposure to elevated estrogen levels. The underlying GS alpha gene mutation also may play a role in this. For the same reasons, these patients also appear to be at an increased risk of thyroid and secondary osseous malignancies. Hypophosphatemic rickets is another potential complication that may worsen the bone disease associated with polyostotic fibrous dysplasia. While on vitamin D and phosphorus supplements, patients with McCune-Albright syndrome and hypophosphatemic rickets must be monitored closely for hypercalcemia and secondary hyperparathyroidism.

Laboratory Findings. There are no consistent significant changes in the serum calcium or phosphorus, although the serum alkaline phosphatase level is sometimes elevated. Premature secretion of pituitary follicle-stimulating hormone has been reported, as well as moderately elevated basal metabolic rate.

Histologic Findings. The bone affected by polyostotic fibrous dysplasia has areas of fibrous metaplasia within flat and tubular bones. The basic anomaly in fibrous dysplasia lesions is a progressively expanding fibrous lesion of bone-forming mesenchyme. The lesions typically expand concentrically from the medullary cavity outwards (i.e. towards the cortex). The bony lesions are well defined, although invariably not encapsulated. The lesions are rich in spindle-shaped fibroblasts, with a swirled appearance within the marrow space and erratically arranged 'tongues' of woven bone. Islands of cartilaginous tissue also may be interspersed within the lesions. Some parts of the affected bones may have cystic lesions lined by multinucleated giant cells akin to ostitis fibrosa cystica (of severe hyperparathyroidism) but with a paucity of osteoblasts.

Treatment and Prognosis. McCune-Albright syndrome is a multisystem condition with a host of variable presentations. Management often is challenging and requires a multidisciplinary approach. Apart from the small subgroup of patients that has increased mortality and those who develop malignancies, McCune-Albright syndrome is not associated with a significantly increased mortality risk. Deformities associated with polyostotic fibrous dysplasia result in variable degrees of morbidity, ranging from mild to very severe.

Cherubism

(Familial fibrous dysplasia of jaws, disseminated juvenile fibrous dysplasia, familial multilocular cystic disease of jaws, familial fibrous swelling of jaws)

An autosomal dominant fibro-osseous lesion of the jaws involving more than one quadrant that stabilizes after the growth period, usually leaving some facial deformity and malocclusion.

Cherubism, a non-neoplastic hereditary bone lesion that is histologically similar to central giant cell granuloma, affects the jaws of children bilaterally and symmetrically, usually producing the so-called cherubic look (Fig. 17-13). The disease was first described in 1933 by Jones, who called it familial multilocular disease of the jaws. The term 'cherubism', was introduced by Jones and others to describe the clinical appearance of affected patients. According to the WHO classification, cherubism belongs to a group of non-neoplastic bone lesions affecting only the jaws. It is a rare, benign condition with autosomal dominant inheritance, and it is one of the very few genetically determined osteoclastic lesions in the human body. It appears to have 100% penetrance in males and only 50–70% penetrance in females. There is great variation in the clinical expression. Although the condition is known to be hereditary, in some cases there has been no detectable family history, and although it usually occurs bilaterally, there have also been cases of unilateral involvement, perhaps because of incomplete penetrance or new mutations. Some investigators believe that cherubism arises from the mutation of a nonsex-linked gene responsible for the development of the jaw bones. Typically, the jaw lesions of cherubism remit spontaneously when affected children reach puberty, but the reason for this remission is unknown. The reduction in osteoclast formation caused by sex steroids and the increase in plasma concentrations of estradiol and testosterone at puberty both suggest that the genetic defect responsible for

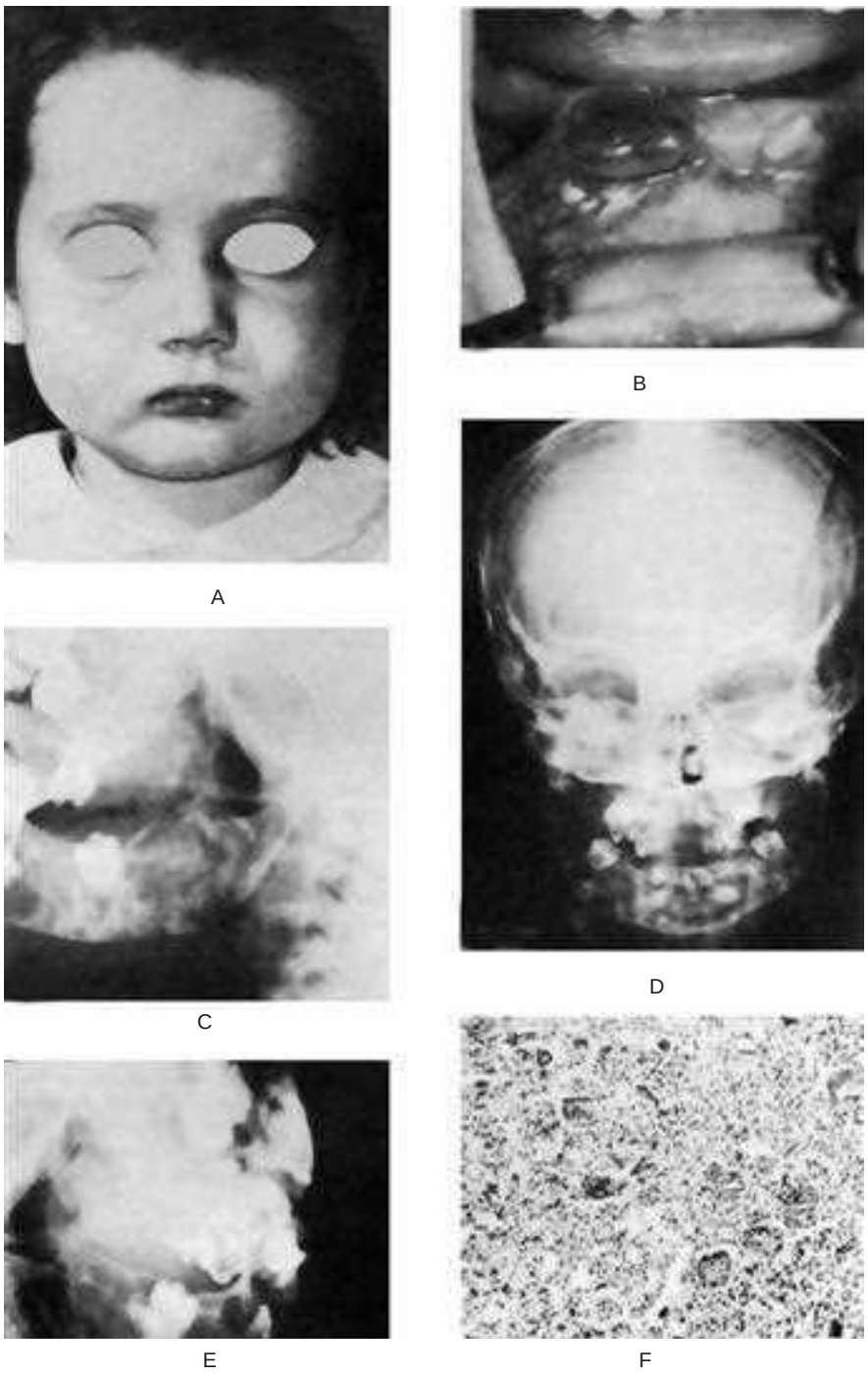


Figure 17-13. Cherubism.
The patient has a cherubic appearance owing to the expansion of the jaws **(A)**. Occasionally the mucosa will be perforated by the underlying bony lesion **(B)**. The bilateral involvement of the mandible is seen in the lateral jaw and skull radiographs **(C, D, E)** where there has been serious destruction of bone. A biopsy of the bone lesion reveals a cellular fibrous mass with many interspersed multinucleated giant cells **(F)** *(Courtesy of Dr Ralph E McDonald: Am J Dis Child, 89: 354, 1955)*.

the localized increase in osteoclasts in cherubism is overridden and normalized by the increased synthesis of sex steroids. The gene related to cherubism was located on chromosome **4p16.3.**

Genetics. Mutations in the SH3BP2 (SH3 domain binding protein 2) gene have been identified in about 80% of people with cherubism. In most of the remaining cases, the genetic cause of the condition is unknown.

The SH3BP2 gene provides instructions for making a protein whose exact function is still unclear. The protein plays a role in transmitting chemical signals within cells, particularly cells involved in the replacement of old bone tissue with new one (bone remodeling) and certain immune system cells.

Mutations in the SH3BP2 gene lead to the production of an overactive version of this protein which is expected to

disrupt critical signaling pathways in cells associated with the maintenance of bone tissue and some immunologic effecter cells. The overactive protein likely causes inflammation in the jaw bones and triggers the production of osteoclasts, which cause breakage of bone tissue while remodeling. A combination of bone loss and inflammation likely underlies the cyst-like growths characteristic of cherubism. Atleast 11 mutations in the SH3BP2 gene have been identified in people with cherubism.

Clinical Features. Affected children are normal at birth and are without clinically or radiographically evident disease until 14 months to 3 years of age. At that time, symmetric enlargement of the jaws begins. Typically, the earlier the lesion appears, the more rapidly it progresses. The self-limited bone growth usually begins to slow down when the patient reaches five years of age, and stops by the age of 12–15 years. At puberty the lesions begin to regress. Jaw remodeling continues through the third decade of life, at the end of which the clinical abnormality may be subtle. The signs and symptoms depend on the severity of the condition and range from clinically or radiographically undetectable features to grotesquely deforming mandibular and maxillary overgrowth with respiratory obstruction and impairment of vision and hearing. The jaw lesions are usually painless and symmetric and have florid maxillary involvement. The lesions, which are firm to palpation and nontender, most commonly involve the molar to coronoid regions, the condyles always being spared, and are often associated with cervical lymphadenopathy. Enlargement of the cervical lymph nodes contributes to the patient's full-faced appearance and is said to be caused by lymphoid hyperplasia with fibrosis. The lymph nodes become enlarged before the patient reaches 6 years of age, decrease in size after the age of 8 years and are rarely enlarged after the age of 12 years. Intraoral swelling of the alveolar ridges may occur. When the maxillary ridge is involved, the palate assumes a V shape. A rim of sclera may be visible beneath the iris, giving the classic 'eye to heaven' appearance.

Oral Manifestations. Numerous dental abnormalities have been reported, such as agenesis of the second and third molars of the mandible, displacement of the teeth, premature exfoliation of the primary teeth, delayed eruption of the permanent teeth, and transpositions and rotation of the teeth. In severe cases, tooth resorption occurs. Although cherubism was initially described as a familial disease affecting the jaws, cases without any apparent hereditary origin have been reported. In a few cases, cherubism has been described as being connected with other diseases and conditions such as **Noonan's syndrome,** a lesion in the humerus, gingival fibromatosis, psychomotor retardation, orbital involvement and obstructive sleep apnea. The deciduous dentition may be shed prematurely, beginning as early as 3 years of age. The permanent dentition is often defective, with absence of numerous teeth and displacement and lack of eruption of those present. The oral mucosa is usually intact and of normal color.

Grading System. Arnott (1978) suggested the following grading system for the lesions of cherubism: **grade I** is characterized by involvement of both mandibular ascending rami, **grade II** by involvement of both maxillary tuberosities as well as the mandibular ascending rami, and **grade III** by McCune-Albright syndrome involvement of the whole maxilla and mandible except the coronoid process and condyles.

Radiographic Features. Radiologically, cherubism is characterized by bilateral multilocular cystic expansion of the jaws. Early lesions occur in the posterior body of the mandible and the ascending rami. Maxillary lesions may occur at the same time but escape early radiographic detection because of overlap of the sinus and nasal cavities. Displacement of the inferior alveolar canal has been reported. The presence of numerous unerupted teeth and the destruction of the alveolar bone may displace the teeth, producing a radiographic appearance referred to as **floating tooth syndrome** (Fig. 17-14). With adulthood, the cystic areas in the jaws become re-ossified, which results in irregular patchy sclerosis. There is a classic (but nonspecific) **ground glass** appearance because of the small, tightly compressed trabecular pattern.

Histologic Features. Histologic examination of the lesions usually reveals numerous multinucleated giant cells. These multinucleated cells show strong positivity for tartrate-resistant

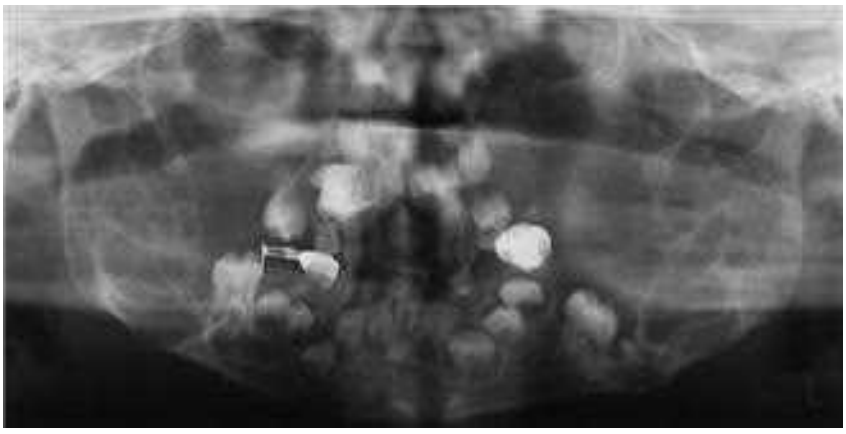


Figure 17-14. Cherubism.
Panoramic radiograph shows derangement of the teeth, many cyst like lesions, and expansion of the cortical plates.

acid phosphatase, which is characteristic of osteoclasts. The collagenous stroma, which contains a large number of spindle-shaped fibroblasts, is considered unique because of its water-logged, granular nature. Numerous small vessels are present, and the capillaries exhibit large endothelial cells and perivascular cuffing. The eosinophilic cuffing appears to be specific to cherubism. However, these deposits are not present in many cases, and their absence does not exclude the diagnosis of cherubism. Older, resolving lesions of cherubism show an increase in fibrous tissue, a decrease in the number of giant cells and formation of new bone. The microscopic findings seldom permit a specific diagnosis of cherubism in the absence of clinical and radiological information.

The differential diagnoses of cherubism consist of giant cell granuloma of the jaws, osteoclastoma, aneurysmal bone cyst, fibrous dysplasia and hyperparathyroidism.

Treatment. As Laskin (1985) stated, "the treatment of cherubism should be based on the known natural course of the disease and the clinical behavior of the individual case". Therefore, surgery to correct the jaw deformities of cherubism is rarely indicated. If necessary, surgery is usually undertaken after puberty, when the remission phase of the lesions have been reached, unless esthetic considerations or severe functional problems justify earlier treatment. Although exacerbation has sometimes been reported after surgery, it is believed that surgery ultimately accelerates the involution process.

Vitamin D-resistant Rickets

(Familial hypophosphatemic rickets, refractory rickets, phosphate diabetes)

Since the early 20th century, ultraviolet radiation or vitamin D ingestion has been recognized as a cure for nutritional rickets, although certain forms of rachitic diseases have remained refractory to this therapy. Study of these refractory cases has revealed low serum phosphate concentration as a common factor. Familial occurrence of this condition led to the diagnosis of familial hypophosphatemic rickets. Treatment with vitamin D produced no change in the rachitic state of these patients, even at rather high doses, leading to the term vitamin D-resistant rickets.

Etiology. Several of the most vexing questions about the underlying mechanism causing the clinical phenotype of X-linked hypophosphatemia remain unanswered. Great strides have been made in recent years, particularly with the cloning of the mutant gene known as **PEX.** This gene, found on the X chromosome, is thought to produce a currently unknown hormone involved in phosphate regulation. The gene for hypophosphatemic rickets has been localized. The X-linked dominant form of the disease is attributed to mutations in the PEX gene, located at **Xp22.1**. The gene locus for autosomal dominant hypophosphatemic rickets has been located on chromosome **12p13**. The pathogenesis of this disorder is clear; phosphate wasting at the proximal tubule level is the basis of the affected individual's inability to establish normal ossification. This phenomenon is secondary to defective regulation of the sodium-phosphate cotransporter in the epithelial cell brush border. Normal phosphate reabsorption in response to 1,25-dihydroxycholecalciferol (calcitriol) provides clear evidence that the sodium-phosphate cotransporter is capable of proper function and is not intrinsically defective.

Clinical Features. As in all genetic disorders, the disease is present from conception. Affected newborns are of normal weight, but infants may show growth retardation. Intellectual development is unaffected. Although serum phosphate levels are depressed similarly in affected males and females, the degree of bone involvement is substantially less severe in heterozygous females. All hemizygous males are clinically affected. Widened joint spaces and flaring at the knees may become apparent in children by their first birthday, particularly in boys. When a child begins to stand and walk, bowing of the weight-bearing long bones quickly becomes clinically evident. Dentition may be absent or delayed in very young children due to abnormal tooth formation; older children may experience multiple dental abscesses.

Laboratory Findings. Laboratory evaluation of rickets begins with assessment of serum calcium, phosphate, and alkaline phosphatase levels. In hypophosphatemic rickets, calcium levels may be within or slightly below reference ranges; alkaline phosphatase levels are significantly above reference ranges. Serum phosphate levels must be carefully evaluated in the first year because the concentration reference range for infants (5.0–7.5 mg/dl) is high compared to adults (2.7–4.5 mg/dl). Hypophosphatemia can be missed easily in a baby. Serum parathyroid hormone level is within reference ranges to slightly elevated, while calcitriol level is low or in the lower reference range. Most importantly, urinary loss of phosphate is above reference ranges.

Radiographic Features. In all cases of rickets, the study of choice is radiography of the wrists, knees, ankles, and long bones. No pathognomonic sign on X-ray distinguishes hypophosphatemic rickets from other variants of rickets.

Oral Manifestations *(Refer to Chapter 15)*

Histologic Features *(Refer to Chapter 15)*

Treatment and Prognosis. Treatment can be administered safely on an outpatient basis, although serum calcium concentrations must be monitored periodically and carefully. Conscientious follow-up is essential. The usual vitamin D preparations are not useful for treatment in this disorder because they lack significant 1-alpha-hydroxylase activity. Original treatment protocols advocated vitamin D at levels of 25,000–50,000 U/d (at the lower limit of toxic dosage), which placed the patient in jeopardy of frequent hypercalcemic episodes. Now more widely available, calcitriol substantially diminishes but does not eliminate this risk. Amiloride and hydrochlorothiazide are administered to enhance calcium reabsorption and to reduce the risk of nephrocalcinosis. Surgical care involves osteotomy to realign extremely distorted leg curvatures in children whose diagnosis was delayed or whose initial treatment was inadequate. Skull deformity may require treatment for synostosis. Spontaneous abscesses often

require periodic dental procedures. Apart from the short stature of most affected adults, the prognosis for a normal lifespan and normal health is good.

Craniosynostosis Syndromes

Craniosynostosis consists of premature fusion of one or more cranial sutures, often resulting in an abnormal head shape. It may result from a primary defect of ossification (primary craniosynostosis), or more commonly, from a failure of brain growth (secondary craniosynostosis). **Simple craniosynostosis** is a term used when only one suture fuses prematurely. **Complex or compound craniosynostosis** is used to describe premature fusion of multiple sutures. When children with craniosynostosis, usually complex, also display other body deformities, this is termed **syndromic craniosynostosis.**

Etiology. Multiple theories have been proposed for the etiology of primary craniosynostosis, but the most widely accepted is a primary defect in the mesenchymal layer ossification in the cranial bones. Secondary craniosynostosis typically results from systemic disorders such as endocrine disorders, hypothyroidism, hypophosphatemia, vitamin D deficiency, renal osteodystrophy, hypercalcemia, and rickets; hematologic disorders that cause bone marrow hyperplasia (e.g. sickle cell disease, thalassemia) and inadequate brain growth, including microcephaly and its causes.

The syndromic causes appear to result from genetic mutations responsible for **fibroblast growth factor receptors 2 and 3**. A gene locus for single suture craniosynostosis has not been identified. Primary craniosynostosis results when one or more sutures fuse prematurely, skull growth can be restricted perpendicular to the suture. If multiple sutures fuse while the brain is still increasing in size, intracranial pressure can increase. Secondary craniosynostosis is more frequent than the primary type, and results from early fusion of sutures due to primary failure of brain growth. Since brain growth drives the bony plates apart at the sutures, a primary lack of brain growth allows premature fusion of all the sutures. Intracranial pressure usually is normal, and surgery seldom is needed. Typically, failure of brain growth results in microcephaly. Intrauterine space constraints may play a role in the premature fusion of sutures in the fetal skull. This has been demonstrated in coronal craniosynostosis.

Clinical Features. Craniosynostosis may be evident at birth or in infancy from craniofacial abnormalities. It is equally distributed in both genders. It may become evident later when the child exhibits neurodevelopmental delays. Typically, careful examination alone can make the diagnosis. Craniosynostosis sometimes is associated with sporadic craniofacial syndromes such as Crouzon, Apert, Chotzen, Pfeiffer, or Carpenter syndromes. In this context, facial features, typically craniofacial abnormalities, suture ridging, and early closure of fontanels, suggest the diagnosis. Raised intracranial pressure is rare with fusion of a single suture. Intracranial pressure may be elevated in primary multiple suture craniosynostosis, such as cloverleaf skull and the syndromic synostoses. Signs include sun-setting eyes, papilledema, vomiting, and lethargy. Differential diagnoses include benign skull tumors, hydrocephalus, mental retardation, neural tube defects, syringomyelia, thyroid disease and torticollis.

Radiographic Features. Skull X-ray with anteroposterior, lateral, and Waters' views show prematurely fused sutures which are easily identified by the absence of sutures and associated ridging of the suture line. Sutures either are not visible or have evidence of sclerosis.

Treatment and Prognosis. In the past 30 years, a better understanding of the pathophysiology and management of craniosynostosis has developed. Currently, surgery is usually cosmetic for infants with fusion of one or two sutures that result in a misshapen head. For infants with microcephaly (i.e. secondary craniosynostosis), surgery usually is not required. Surgery typically is indicated for increased intracranial pressure or for cosmetic reasons. Patients with primary craniosynostosis must be monitored after surgery. In secondary craniosynostosis, prognosis is dependent upon underlying etiology.

Craniofacial Dysostosis
(Crouzon disease or syndrome)

The craniosynostosis syndromes constitute a group of conditions each characterized by premature craniosynostosis occurring in association with a variety of other abnormalities. These may or may not occur with syndactyly, anomalies of the hands and feet. The most common of the craniosynostotic syndromes occurring without syndactyly is craniofacial dysostosis, or Crouzon disease. The most common one occurring with syndactyly is the Apert syndrome, which is otherwise similar to Crouzon disease. Crouzon syndrome, described in 1912 as one of the varieties of craniofacial dysostosis, is caused by premature obliteration and ossification of two or more sutures, most often coronal and sagittal. Some authors connect those syndromes as one, calling it Crouzon-Apert syndrome, but symptomatologic differentiation makes classification difficult. Acanthosis nigricans is the main dermatologic manifestation of Crouzon syndrome.

Dysplasias of the skeleton (including craniofacial dysostosis) are caused by the malformations of the mesenchyme and ectoderm. The unknown teratogenic factors are taken into account. Dysplasias are inherited in an autosomal dominant pattern. Mutation of the fibroblast growth factor receptor **(FGFR)-2** gene could be responsible for Crouzon syndrome. Moreover, the mutation in the transmembrane region of **FGFR3** was detected in this syndrome.

Clinical Features. Although there is considerable individual variation in the appearance of patients with craniofacial dysostosis, the signs are all basically due to early synostosis of the sutures. Facial deformity is observed at birth, followed — with time — by other features of the syndrome. Coronal and sagittal sutures are obliterated; fontanels remain not obliterated and pulsating for a long time. Lateral and anteroposterior flattening of the acrocranium is observed, growing only at the vertical axis.

Anteroposterior diameter is smaller than transverse diameter. The forehead is high and wide. Wide face and hypoplastic maxilla producing pseudoprognathism are observed. Deviation of the nasal septum, narrowed or obliterated anterior nares, and wide beaked nose are present. Hypertelorism, divergent squint, eyelid seems antimongoloid, and upper eyelid mimicking 'frog face' are observed. The upper lip is shortened and sometimes cleaved. Progressing optic nerve atrophy leads to vision impairment because of the intracranial hypertension. Impairment of hearing indicates disorders of the middle ear. Malocclusion, malposed teeth, and dysphasia are noted. Short stature and no physiologic spinal curvature are observed. The skin usually is dark. Syndromic acanthosis nigricans appears in the axillary fossa, the angle of the mouth, and on the lips in children. Patients report headache. Convulsions often occur; mental retardation is frequently observed (Fig. 17-15).

Radiographic Features. Skull, spine, and hand radiography is usually necessary to confirm the diagnosis. Skull radiography reveals the following: obliterated sutures (mostly coronal, sagittal); shallow eye sockets (exophthalmos); shortened anterior cranial fossa; underdeveloped lateral nasal sinuses; tympanic membranes fixed obliquely, narrowed external auditory canals, and small pyramids with symptoms of sclerosis; On spine radiography, the presence of bifid spinous process is possible, and slight symptoms of achondroplasia may be visible. Radiographic examination of the metacarpal bones and fingers reveals slight achondroplasia.

Treatment and Prognosis. A neurosurgical procedure is recommended in cases of intracranial hypertension leading to further optic atrophy. The surgery is difficult, and the procedure must be considered and undertaken in stages. Plastic surgery of the face could be of great help. It is one of the few syndromes where the cosmetic results of the surgery can be strikingly effective. These patients may ultimately come to lead a relatively normal life.

Mandibulofacial Dysostosis
(Treacher Collins-Franceschetti syndrome)

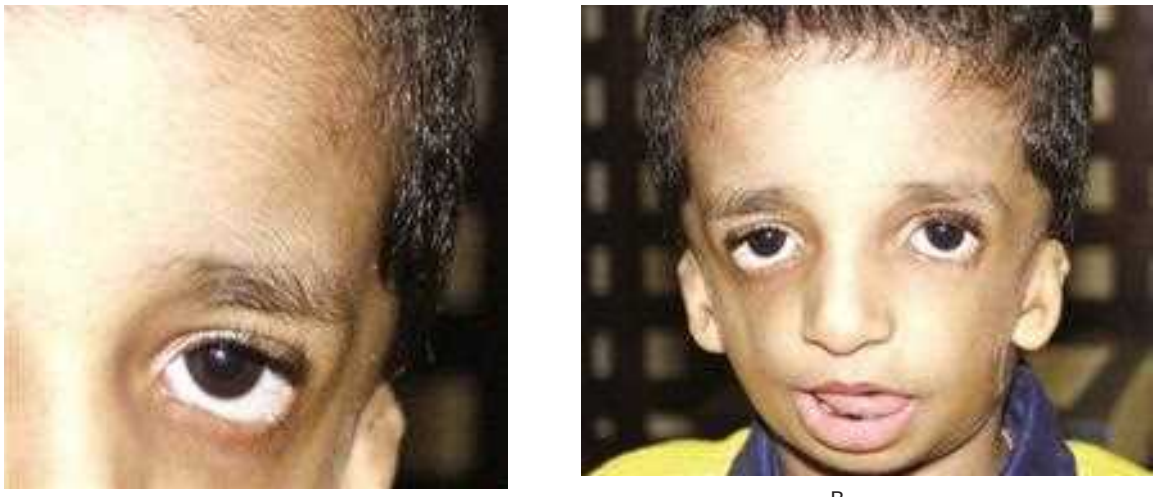
The mandibulofacial dysostosis syndrome encompasses a group of closely related defects of the head and face, often hereditary or familial in pattern, following an irregular form of dominant transmission. A historic review of the disease was made by Pavsek, who, in addition to reporting an additional case, summarized the embryologic faults of the conditions.

The occurrence of Treacher Collins syndrome is in the range of 1 in 25,000 to 1 in 50,000 live births. Inheritance is autosomal dominant: males and females are equally affected; inheritance may be from one parent; multiple generations are affected. The gene for Treacher Collins syndrome was mapped to chromosome **5q32–q33.1**. More than 50 Treacher Collins syndrome families have been analyzed. DNA diagnosis can be performed indirectly by linkage analysis in a family with more than one affected member, with greater than 95% accuracy if relevant DNA markers are informative within the family.

Clinical Features. Wide variations in the clinical expression of this syndrome are recognized, ranging from a complete, typical form manifesting all abnormalities listed below through incomplete, abortive, and atypical forms. The important clinical manifestations of the disease are:

- Antimongoloid palpebral fissures with a coloboma of the outer portion of the lower lids, and deficiency of the eyelashes (and sometimes the upper lids).
- Hypoplasia of the facial bones, especially of the malar bones and mandible.
- Malformation of the external ear, and occasionally of the middle and internal ears.
- Macrostomia, high palate (sometimes cleft) and abnormal position and malocclusion of the teeth.
- Blind fistulas between the angles of the ears and the angles of the mouth.

Figure 17-15. Craniofacial dysostosis.
A father (at an early age) and his two daughters are all affected by the condition *(Courtesy of Dr David Bixler and Dr Stephen G Kaler)*.



A B

Figure 17-16. Mandibulofacial dysostosis.
(Courtesy of Dr SM Balaji, Balaji Dental and Craniofacial Hospital, Chennai).

- Atypical hair growth in the form of a tongue-shaped process of the hairline extending towards the cheeks.
- Other anomalies such as facial clefts and skeletal deformities (Fig. 17-16).

The characteristic faces of the patients have often been described as being **bird like** or **fish like** in nature.

The syndrome is thought to result from a retardation or failure of differentiation of maxillary mesoderm at and after the 50 mm stage of the embryo. The fact that the teeth of the upper jaw are usually unaffected, and ordinarily are present by the sixth week, is further evidence of retardation or arrest of differentiation at or after the second month of fetal life. The first visceral arch of the visceral mesoderm also advances secondarily to form the mandible, and again retardation occurs on the same basis.

A disease that has sometimes been confused with mandibulofacial dysostosis because of certain clinical features in common is **hemifacial microsomia** (also known as **oculoauriculovertebral dysplasia** or **Goldenhar syndrome**). However, hemifacial microsomia is sporadic in the vast majority of cases, although familial cases have been reported. In addition as the name implies, this disease is unilateral and has been suggested to be related to an abnormality in the vascular supply of the head. It has been discussed in detail by Gorlin and his associates.

Radiographic Features. As Pavsek pointed out, the bodies of both malar bones tend to be grossly and symmetrically underdeveloped in mandibulofacial dysostosis. There may be agenesis of the malar bones with nonfusion of the zygomatic arches, as well as absence of the palatine bones. Cleft palate may be visible on the radiograph. There is usually hypogenesis, and sometimes agenesis of the mandible. The paranasal sinuses are grossly underdeveloped. The auditory ossicles are often absent, and the cochlea and vestibular apparatus may be deficient. The cranial vault is normal in most instances.

Treatment and Prognosis. There is no treatment for this condition, but the prognosis is good, most patients living a normal life span.

Pierre Robin Malformation

(Pierre Robin syndrome, Robin sequence, Pierre Robin anomalad, Robin complexes, Pierre Robin malformation complex)

Robin sequence, previously known as Pierre Robin syndrome and Pierre Robin anomalad, consists of three essential components which include:

- Micrognathia or retrognathia
- Cleft palate
- Glossoptosis, often accompanied by airway obstruction. (The tongue is not actually larger than normal, but because of the small mandible, the tongue is large for the airway and therefore causes obstruction. Rarely, the tongue is smaller than normal).

Robin sequence occurs as an isolated defect, as part of a recognized syndrome, or as part of a complex of multiple congenital anomalies. The condition is named after the French dental surgeon Pierre Robin (1867–1950).

Etiology. Three pathophysiological theories exist to explain the occurrence of Pierre Robin sequence:

1. ***The mechanical theory.*** This is the most accepted theory. Initially, mandibular hypoplasia occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios could play a role in the etiology since the lack of amniotic fluid could cause deformation of the chin and subsequent impaction of the tongue between the palatal shelves.
2. ***The neurological maturation theory.*** A delay in neurological maturation has been noted on electromyography of the

tongue musculature, the pharyngeal pillars, and the palate, as has a delay in hypoglossal nerve conduction. The spontaneous correction of the majority of cases with age supports this theory.

3. ***The rhombencephalic dysneurulation theory.*** In this theory, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

Clinical Features. This heterogeneous birth defect has a prevalence of approximately 1 per 8,500 live births. The male-to-female ratio is 1:1. Micrognathia is reported in the majority of cases (91.7%). The mandible has a small body, obtuse gonial angle, and a posteriorly located condyle. The mandibular hypoplasia; however, resolves and the child attains a normal profile by the age of five to six years. Glossoptosis is noted in 70–85% of reported cases. Macroglossia and ankyloglossia are relatively rare findings, noted in 10–15% of reported cases. The combination of micrognathia and glossoptosis may cause severe respiratory and feeding difficulty in the newborn. Obstructive sleep apnea may also occur. The prevalence of cleft palate varies from 14–91%. It can affect the soft and hard palate and is usually U-shaped (80%) or V-shaped (Fig. 17-17). Occasionally, it may present as a bifid or double uvula or as an occult submucous cleft. Velopharyngeal insufficiency is usually more pronounced in these patients than in those with isolated cleft palate.

Other associated anomalies are also seen which include; otitis media, hearing loss, nasal deformities, dental and philtral malformations. Anomalies involving the musculoskeletal system are the most frequent systemic anomalies (noted in 70–80% of cases). They include syndactyly, dysplastic phalanges, polydactyly, clinodactyly, hyperextensible joints, and oligodactyly in the upper limbs. Central nervous system (CNS) defects such as language delay, epilepsy, neurodevelopmental delay, hypotonia, and hydrocephalus may occur.

Treatment and Prognosis. A multidisciplinary approach is required to manage the complex features involved in the case of these children. Treatment is prioritized according to the severity of airway compromise followed by the extent of feeding difficulties. Infants with pronounced micrognathia may experience severe respiratory distress or failure to thrive. Surgical intervention is necessary in these cases.

Figure 17-17. Pierre Robin malformation.
U- and V-shaped cleft palates.

Apert Syndrome
(Acrocephalosyndactyly)

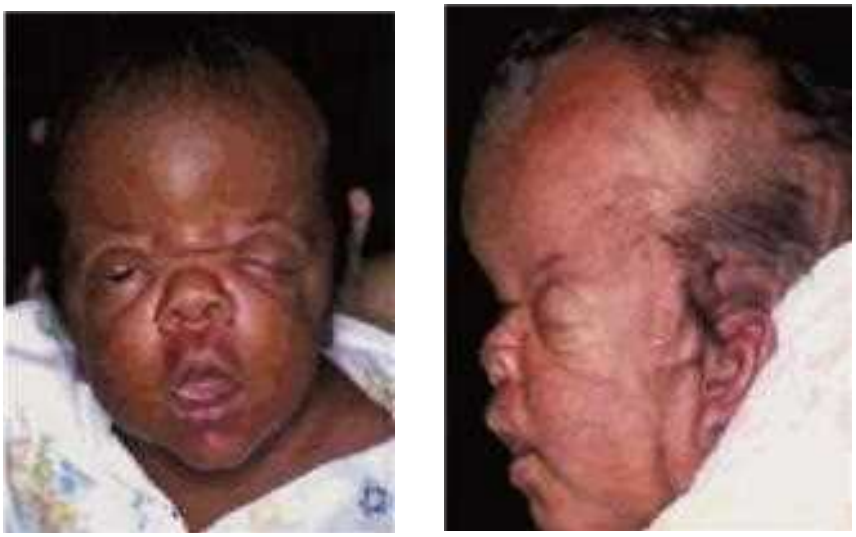
Apert syndrome is named after the French physician who described the syndrome acrocephalosyndactylia in 1906. It is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. It probably is the most familiar and best-described type of acrocephalosyndactyly.

Etiology. More than 98% of cases of Apert syndrome are caused by specific missense substitution mutations (i.e. **Ser252Trp, Ser252Phe, Pro253Arg**) involving **fibroblast growth factor receptor 2 (FGFR2)**, which maps to chromosome bands **10q25–q26**. The remaining cases are due to mutations in or near **exon 9 of FGFR2.** Fibroblast growth factor receptor 2 (FGFR2) mutations lead to an increase in the number of precursor cells that enter the osteogenic pathway. Ultimately, this leads to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development. The order and rate of suture fusion determine the degree of deformity and disability. The evidence that syndactyly of Apert syndrome could be a keratinocyte growth factor receptor (KGFR)-mediated effect has also been reported.

Clinical Features. Apert syndrome is detected in the neonatal period due to craniosynostosis and associated findings of syndactyly in the hands and feet. Asians have the highest reported prevalence (22.3 per million live births). No gender predilection is seen. Craniostenosis is present and most commonly involves the coronal sutures, resulting in acrocephaly, brachycephaly, flat occiput, and high prominent forehead. Large late-closing fontanels and a gaping midline defect are seen. Patients have apparent low-set ears with occasional conductive hearing loss. Eyes exhibit down-slanting palpebral fissures, hypertelorism, shallow orbits, proptosis and exophthalmos. The nose has a markedly depressed nasal bridge. It is short and wide with a bulbous tip, parrot-beaked appearance, and choanal stenosis or atresia (Fig. 17-18A, B).

The jaw shows a prominent mandible, maxillary hypoplasia, drooping angles of the mouth, high arched palate, bifid uvula, cleft palate, crowded upper teeth, malocclusion, delayed and ectopic eruption, shovel-shaped incisors, supernumerary teeth, V-shaped maxillary dental arch, and bulging alveolar ridges.

Syndactyly involves the hands and feet with partial-to-complete fusion of the digits, often involving second, third, and fourth digits. These often are termed **mitten hands** and **sock feet** (Fig. 17-19). In severe cases, all digits are fused, with the palm deeply concave and cup-shaped and the sole supinated (Fig. 17-20). Intelligence varies from normal to subnormal mentality. Malformations of the CNS may be responsible for most cases. Papilledema and optic atrophy with loss of vision may be present in cases of subtle increased intracranial pressure. Hyperhidrosis is commonly seen. Cardiovascular manifestations like atrial septal defect, patent ductus arteriosus, ventricular septal defect and pulmonary stenosis are present. Gastrointestinal, genitourinary and respiratory symptoms may be present in a small percentage of cases.



A B

Figure 17-18. Apert syndrome.
(A) An infant with Apert syndrome is shown. Note the characteristic ocular hypertelorism, down-slanting palpebral fissures, proptotic eyes, horizontal groove above the supraorbital ridge, break of the continuity of eyebrows, depressed nasal bridge, and short wide nose with bulbous tip. **(B)** In this profile, turribrachycephaly, high prominent forehead, proptosis, depressed nasal bridge, short nose, and low-set ears are prominent *(Courtesy of Dr Harold Chen)*.

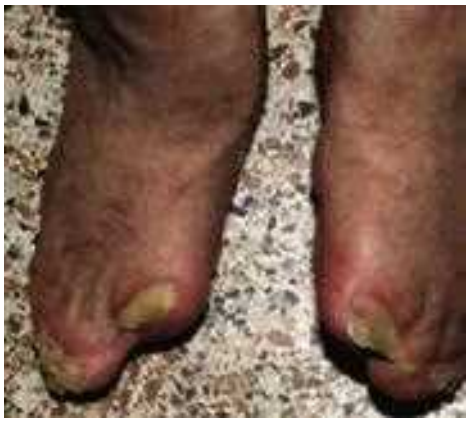


Figure 17-19. Apert syndrome.
Note the sock appearance of the feet with syndactyly involving the second, third, fourth, and fifth toes. The patient also has contiguous nail beds (synonychia). *(Courtesy of Dr Harold Chen)*.

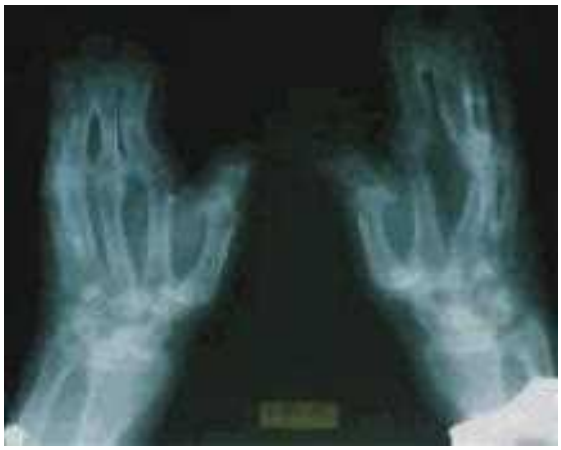


Figure 17-20. Apert syndrome.
Note osseous syndactyly involving the second, third, fourth, and fifth fingers; multiple synostosis involving distal phalanges and proximal fourth and fifth metacarpals; symphalangism of interphalangeal joints; shortening and radial deviation of distal phalanx; and delta-shaped deformity of proximal phalanx of the thumbs.

Treatment. Surgical care involves early release of the coronal suture and fronto-orbital advancement and reshaping. Prognosis largely depends on the age at operation. Craniosynostosis can result in brain compression and mental retardation unless relieved by early craniotomy.

Thanatophoric Dysplasia

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia that is lethal in the neonatal period. It is an autosomal dominant disorder resulting from sporadic *de novo* mutations in the **FGFR3** gene. Characteristics of TD include severe shortening of the limbs, a narrow thorax, macrocephaly, and a normal trunk length. It is divided into two clinically defined subtypes. **TD type 1**, the most common subtype, features a normally shaped skull and curved long bones (shaped like a telephone receiver) with the femurs affected most. **TD type 2** features a cloverleaf-shaped skull and straight femurs.

Clinical Features. A macrocephalic head with a frontal bossing, a flattened nasal bridge, and proptotic eyes has been observed. In TD2, a cloverleaf-shaped skull resulting from premature closure of the cranial sutures. Narrow thorax with small ribs, micromelic limbs with brachydactyly, protuberant abdomen, hydrocephalus and other cerebral parenchymal

abnormalities are seen. Characteristic orodental abnormalities are not described associated with this syndrome.

Prognosis. TD is usually lethal in the first few days of life. Death is caused by respiratory insufficiency.

Achondroplasia
(Chondrodystrophia fetalis)

Achondroplasia is a common nonlethal form of chondrodysplasia. It is transmitted as an autosomal dominant trait with complete penetrance. *De-novo* mutations cause 75–80% of cases.

Etiology. Achondroplasia is caused by mutations in the gene for fibroblast growth factor receptor-3 (**FGFR3**). The gene has been mapped to band **4p16.3**. The common mutations cause a gain of function of the FGFR3 gene, resulting in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix production.

Clinical Features. Frequency is believed to be 1 case per 15,000–40,000 births worldwide (Fig. 17-21). Cardinal features include short stature, rhizomelic shortening of the arms and legs, a disproportionately long trunk, trident hands, midfacial hypoplasia, prominent forehead (frontal bossing), thoracolumbar protuberance, true megalencephaly, and characteristic limitation of joint motion. The incongruous appearance of the achondroplastic dwarf is in contrast to that of the pituitary dwarf, and the incongruity becomes more pronounced as he/she approaches adulthood and later life, chiefly because of the disproportionate size of the head in relation to the remainder of the body. Despite their misshapen appearance, achondroplastic dwarfs are of normal intelligence. Often they are also endowed with unusual strength and agility, characteristics which have led some to adopt the occupation of professional wrestler.

Figure 17-21. Achondroplasia.
The mother and son present the typical dwarfed appearance *(Courtesy of Dr Ralph E McDonald).*

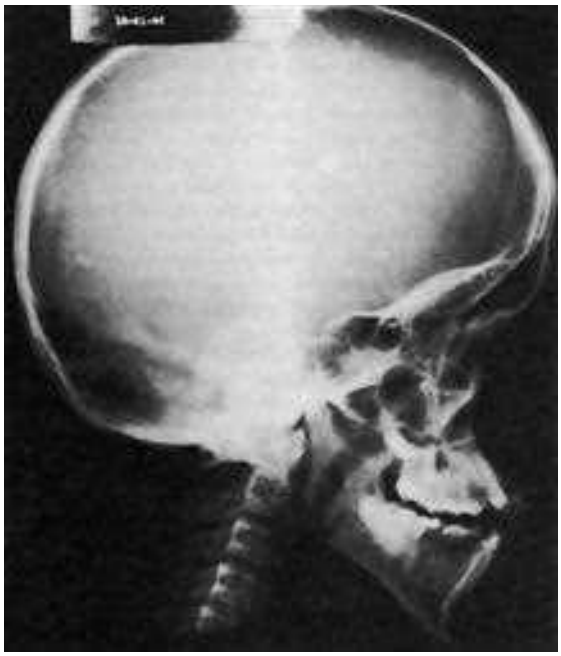


Figure 17-22. Achondroplasia.
The lateral skull film illustrates the retruded maxilla which contributes to the characteristic facial appearance of the patient *(Courtesy of Dr Ralph E McDonald).*

Oral Manifestations. The maxilla is often retruded because of restriction of growth of the base of the skull, and the retrusion may produce a relative mandibular prognathism (Fig. 17-22). The resultant disparity in size of the two jaws produces an obvious malocclusion. The dentition itself is usually normal, although congenitally missing teeth with disturbance in the shape of those present have been reported.

Radiographic Features. Radiographs of the skull, spine, and extremities reveal the characteristic features. A lateral skull radiograph demonstrates midface hypoplasia, enlarged calvaria, frontal prominence, and shortening of the base of the skull. The size of the foramen magnum is diminished. The long bones are shorter than normal, and there is thickening or mild clubbing of the ends. The epiphyses generally appear normal, but may close either early or late. The bones at the base of the skull fuse prematurely. Except for the retrusion of the maxilla and the malocclusion between the two jaws, there are no changes in the jawbones.

Histologic Features. The abnormality seen in the bone of patients with achondroplasia is failure of endochondral ossification. Intramembranous and periosteal ossification are undisturbed. Histologic studies have shown disarray of the chondrocytes, with loss of columnation and loss of normal chondrocyte proliferation. Fibrous tissue is present in the zone of provisional calcification, but bone trabeculae present

are irregular. Because endochondral growth is affected, the orderly longitudinal growth of bone is disrupted, resulting in stunting of the bone. Intramembranous ossification is normal, leading to normal clavicles and skull. Because the width of the long bones is a product of intramembranous periosteal ossification, these bones are of normal diameter.

Treatment and Prognosis. There is no treatment for achondroplasia. There may be delay in motor milestones but speech is normal. The frequent middle ear infections and dental crowding require attention. If the patient survives the first few years of life, the chances are excellent that he/she will have the life expectancy of a normal person.

Robinow Syndrome

Around 1969, Dr Meinhard Robinow identified a new syndrome, which was unreported before. He named it **fetal face** syndrome, based upon his views of the facial features of an eight-month old fetus. Later the name was changed to 'Robinow' syndrome.

Two types of this syndrome have been described, **dominant and recessive.** The dominant type is the most common and the parents are usually not carriers of the dominant gene that produces the syndrome. In the recessive type, which is the rarer of the two, both parents carry the recessive gene (but are not affected) and have a 25% chance of producing an affected offspring. The recessive form is caused by mutation in **ROR2** gene. This gene is located in chromosome **9q22** and works in cartilage and bone formation. The gene responsible for the dominant form has not been established yet, but genes related to ROR2 are being studied as candidates.

Clinical Features. The features described refer to both types of this syndrome. The patients usually have most of these signs in varied proportions.

Skeletal system. Mild to moderate short stature (dwarfism), short lower arms (mesomelic brachymelia), small hands with clinodactyly usually of the fifth finger (abnormal lateral or medial bending of one or more fingers or toes) and brachydactyly (abnormally short fingers or toes) and small feet.

Craniofacial. Hypertelorism, short upturned nose, broad nasal bridge, anteverted nares, triangular mouth, frontal bossing, long or short philtrum, micrognathia, wide and downslanting palpebral fissures, ear abnormality, facial nevus and normal intelligence.

Oral. Dental abnormalities including malaligned teeth, gingival hyperplasia, abnormal uvula, cleft lip and/or palate (nonmidline), shortened tongue sometimes with midline indentation.

Complications. These include frequent ear infections and hearing loss, hypotonia, risk for developmental delays, breathing or respiratory problems, feeding difficulties, photophobia (light sensitivity) and esophageal reflux.

Hyperostosis Corticalis Generalisata

(van Buchem's disease, hyperphosphatasemia tarda, endosteal hyperostosis, autosomal recessive)

This disease of bone, described by van Buchem and his associates in 1955, appears to represent an excessive deposition of endosteal bone throughout the skeleton in a pattern suggestive of a hereditary condition with an autosomal recessive characteristic. The disease gene has been mapped to chromosome **17q11.2.**

Clinical Features. The disease is usually not discovered until adult life, and in nearly all reported cases, has been a chance finding. The facial appearance of these patients may be altered and this may be the reason that they seek professional advice. Such a case has been reported by Dyson. The face may appear swollen, particularly with widening at the angles of the mandible and at the bridge of the nose. Some patients also have loss of visual acuity, loss of facial sensation, some degree of facial paralysis and deafness, all due to cranial nerve involvement through closure of foramina. Intraorally, there is sometimes overgrowth of the alveolar process. Most patients, except for the facial appearance, appear normal and are free of symptoms, including bone tenderness.

Radiographic Features. A skeletal survey will reveal increased density of many bones of the body, although some bones, such as those of the hands and feet, may be unaffected. The skull also exhibits diffuse sclerosis, as may the jaws.

Histologic Features. The bone is normal dense bone but without evidence of remodeling.

Differential Diagnosis. Three other diseases must also be considered in the diagnosis inasmuch as they may also present widespread sclerosis: osteopetrosis, osteitis deformans and progressive diaphyseal dysplasia.

Treatment and Prognosis. There is no treatment for the disease, although the patients usually lead a normal life.

Chondroectodermal Dysplasia

(Ellis-van Creveld syndrome)

Ellis-van Creveld is an extremely rare form of dysplasia first described by Ellis and van Creveld in 1940. It is characterized by four components: chondrodysplasia; polydactyly; ectodermal dysplasia affecting the hair, teeth, and nails; and congenital heart failure (Fig. 17-23). The dysplasia is one of the short-rib polydactyly syndromes. As its name implies, this syndrome affects both mesodermal and ectodermal tissues. The prevalence of Ellis-van Creveld dysplasia is 0.1 per million.

Ellis-van Creveld syndrome is inherited as an autosomal recessive disorder. The locus gene has been mapped to chromosome **4p16.1.**

Clinical Features and Oral Manifestations (*Refer to Chapter 19)*

Treatment. During infancy, cardiac surgery is often required to treat congenital malformations.

Cleidocranial Dysplasia

(Marie and Sainton's disease, Scheuthauer-Marie-Sainton syndrome, mutational dysostosis)

A congenital disorder of bone formation manifested with clavicular hypoplasia or agenesis with a narrow thorax, which allows approximation of the shoulders in front of the chest.

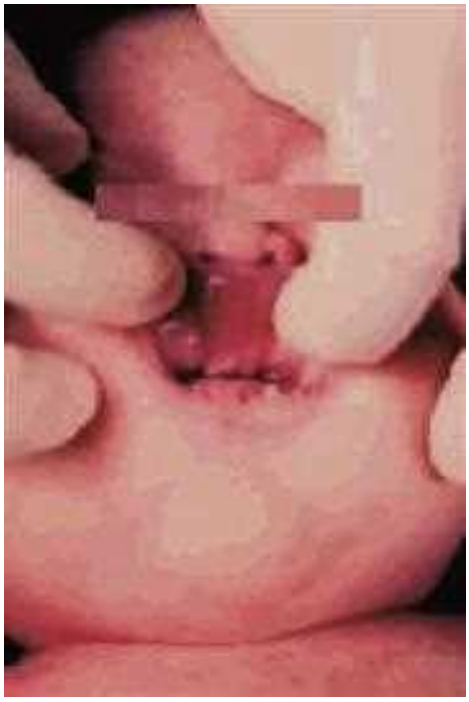


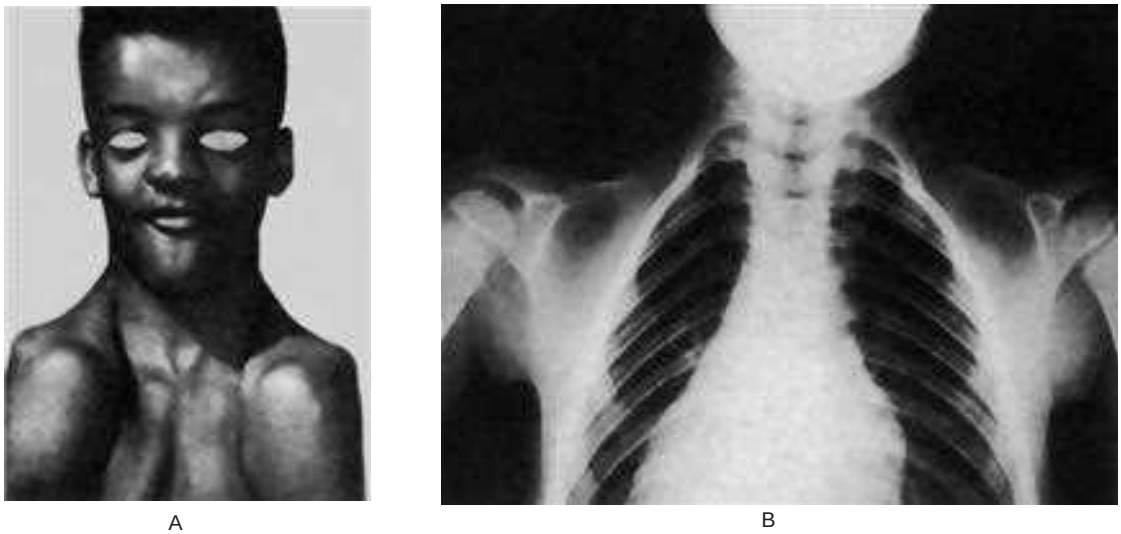
Figure 17-23. Ellis-van Creveld syndrome.
Natal teeth and lip tie.

Delayed ossification of the skull, excessively large fontanels, and delayed closing of the sutures are prominent features of this disorder. The fontanels may remain open until adulthood, but the sutures often close with interposition of wormian bones. Bossing of the frontal, parietal, and occipital regions give the skull a large globular shape with small face. The characteristic skull abnormalities are sometimes referred to as the **Arnold head** named after the descendants of a Chinese who settled in South Africa and changed his name to Arnold. More than 100 additional anomalies may be associated, including wide pubic symphysis, dental abnormalities, short middle phalanges of the fifth finger, delayed skeletal maturation, hearing deficiency, and mild mental retardation in some cases.

The syndrome is familial and is transmitted as an autosomal dominant trait. Several chromosome abnormalities have been reported to be associated with this syndrome, including rearrangement of long arm of chromosome **8(8q22)** and the long arm of chromosome **6**. Mutations in the **core-binding factor alpha-1 (CBFA1)** gene, located on chromosome **6p21**, have been shown to be the cause of cleidocranial dysplasia.

Clinical Features. Cleidocranial dysplasia is characterized by abnormalities of the skull, teeth, jaws and shoulder girdle as well as by occasional stunting of the long bones. In the skull the fontanels often remain open or at least exhibit delayed closing, and for this reason tend to be rather large. The sutures also may remain open and wormian bones are common. The sagittal suture is characteristically sunken, giving the skull a flat appearance. Frontal, parietal, and occipital bones are prominent and the paranasal sinuses are underdeveloped and narrow. Based on the cephalic index, the head is brachycephalic, or wide and short, with the transverse diameter of the skull being increased. A variety of other skull abnormalities are sometimes present. Additional abnormalities include calvarial thickening in the supraorbital part of the frontal bone, squamous part of the temporal bone and the occipital bone; occasional absence of the parietal bones, faulty development of the foramen magnum, and dysplasia of the paranasal sinuses. An excellent review and discussion of the varied clinical findings in cleidocranial dysplasia has been published by Kalliala and Taskinen.

The defect of the shoulder girdle, from which the condition derives a portion of its name, ranges from complete absence of clavicles, in about 10% of cases, to partial absence or even a simple thinning of one or both clavicles (Figs. 17-24 A, 17-25). Because of this clavicular disturbance, the patients have an unusual mobility of the shoulders and may be able to bring their shoulders forward until they meet in the midline



A B

Figure 17-24. Cleidocranial dysplasia.
The typical hypermobility of the shoulder **(A)** is made possible by the complete absence of the clavicles **(B)**. *(Courtesy of Dr Wilbur C Moorman).*

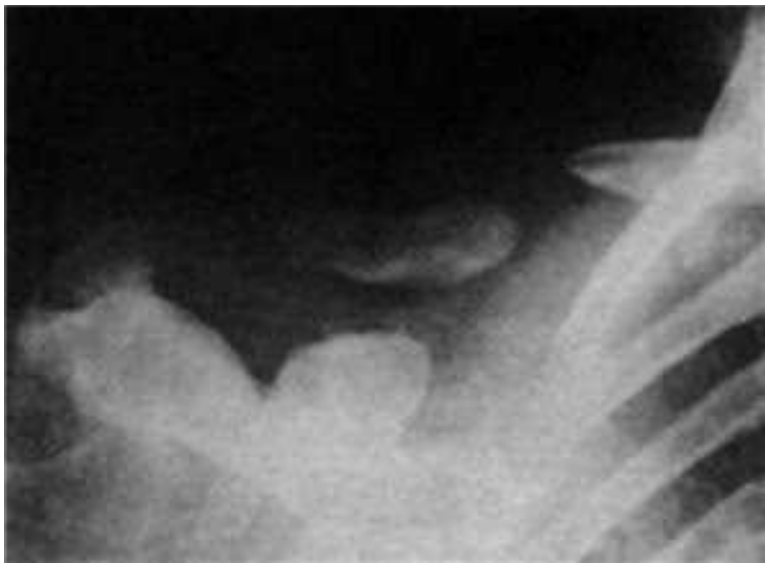


Figure 17-25. Cleidocranial dysplasia.
There may be only hypoplasia of the clavicle rather than its complete absence.

(Fig. 17-24B). Defects of the vertebral column, pelvis and long bones, as well as bones of the digits, are also relatively common. Thus cleidocranial dysplasia, once thought to be a disease involving only membranous bones, is now recognized as affecting the entire skeleton. In addition, changes outside the skeleton, such as anomalous muscles, have been reported, but these may be secondary to the bony involvement.

Oral Manifestations. Patients with cleidocranial dysplasia characteristically exhibit a high, narrow, arched palate, and actual cleft palate appears to be common. The maxilla is almost invariably reported to be underdeveloped and smaller than normal in relation to the mandible. However, Davis has reported that in a series of patients studied by cephalometric analysis all showed that the maxilla was of normal size and the position was either normal or anteriorly positioned in all cases. In addition, 70% of the affected patients had larger mandibles than those of controls, which suggests that patients with cleidocranial dysplasia have enlarged mandibles rather than small maxillae, as reported in the literature. These findings remain to be confirmed. The lacrimal and zygomatic bones are also reported to be underdeveloped.

One of the outstanding oral findings is prolonged retention of the deciduous teeth and subsequent delay in eruption of the succedaneous teeth. Sometimes this delay in tooth eruption is permanent. The roots of the teeth are often somewhat short and thinner than usual and may be deformed.

In addition, Rushton reported that there is absence or paucity of cellular cementum on the roots of the permanent teeth, and this may be related to the failure of eruption so frequently seen. This has also been studied by Smith, who confirmed the absence of cellular cementum on both deciduous and permanent teeth. A surprising and unexplained feature was the absence of this cementum on the erupted teeth in both dentitions, with no increased thickening of the primary acellular cementum. The manner of anchorage of periodontal fibers and the maintenance of periodontal ligament width are also not understood in this disease. Furthermore, it is characteristic for numerous unerupted supernumerary teeth to be found by radiographic examination (Fig. 17-26). Crypt formation around impacted teeth, and ectopic teeth have been reported.

These are most prevalent in the mandibular premolar and incisor areas. Interestingly, partial anodontia has also been recorded in this condition but is rare.

Radiographic Examination. Reveals the widely patent anterior fontanel and sutures with wormian bones in cranium. The clavicles typically are reduced to single or double fragments on each side with middle part being deficient. Frequently the changes are asymmetric. Marked delay in ossification of pelvic bones especially pubic and ischial bones is regulary observed. Spina bifida occulta is observed in the cervical and upper thoracic levels. Hands and feet demonstrate various anomalies including shortening and broadening of carpal, metacarpal, tarsal, metatarsal bones.

Treatment and Prognosis. There is no specific treatment of cleidocranial dysplasia, although care of the oral conditions is important. The retained deciduous teeth should be restored if they become carious, since their extraction does not necessarily induce eruption of the permanent teeth. However, in recent years, there has been increasing use of a multidisciplinary approach to treatment of these patients, utilizing the pedodontist, the orthodontist, and the oral surgeon. It has been found, as in the case reviewed by Hutton and his associates, that the permanent teeth do have the potential to erupt and that correct timing of surgical procedures for uncovering teeth and orthodontic repositioning can give excellent functional results. Life expectancy is normal. Complications may arise during delivery in cases with narrow pelvis.

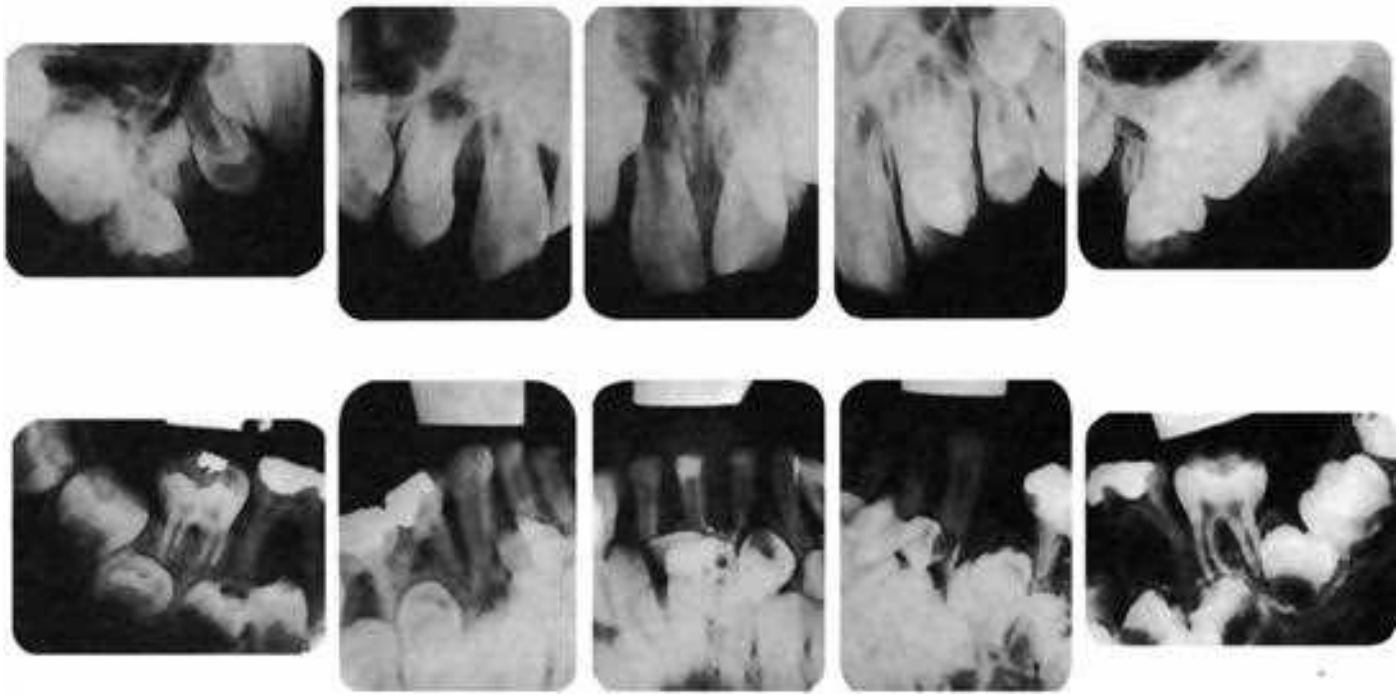


Figure 17-26. Cleidocranial dysplasia.
There are numerous unerupted and supernumerary teeth *(Courtesy of Dr Wilbur C Moorman).*

Tricho-dento-osseous Syndrome

The tricho-dento-osseous (TDP) syndrome is a hereditary condition which chiefly involves the hair, teeth, and bones. Individuals with this syndrome are born with a full head of kinky hair, which sometimes tends to straighten with age. Nails are thin and likely to peel or fracture. The sweat glands are developed normally. The chief bony abnormality in patients with the condition are bones which are found to be more dense than normal. In some families, the skull bones are excessively thick. These abnormalities are of no clinical significance and should not cause individuals with this syndrome any problem. They are, however, helpful in making the diagnosis. There is no evidence that people who have this condition are shorter or taller than normal.

Teeth may become infected and dental abscesses are common during the first few years of life. They have thin, pitted and yellow-brown enamel. On dental X-ray, large pulp chambers (**taurodontia**) are found. In addition, teeth may remain unerupted for long giving the condition of partial anodontia. Intelligence is normal, as is life span. The condition is inherited as an autosomal dominant disorder. Prenatal diagnosis for this syndrome is not yet possible. The disorder has been mapped to locus **17q21.3–q22**.

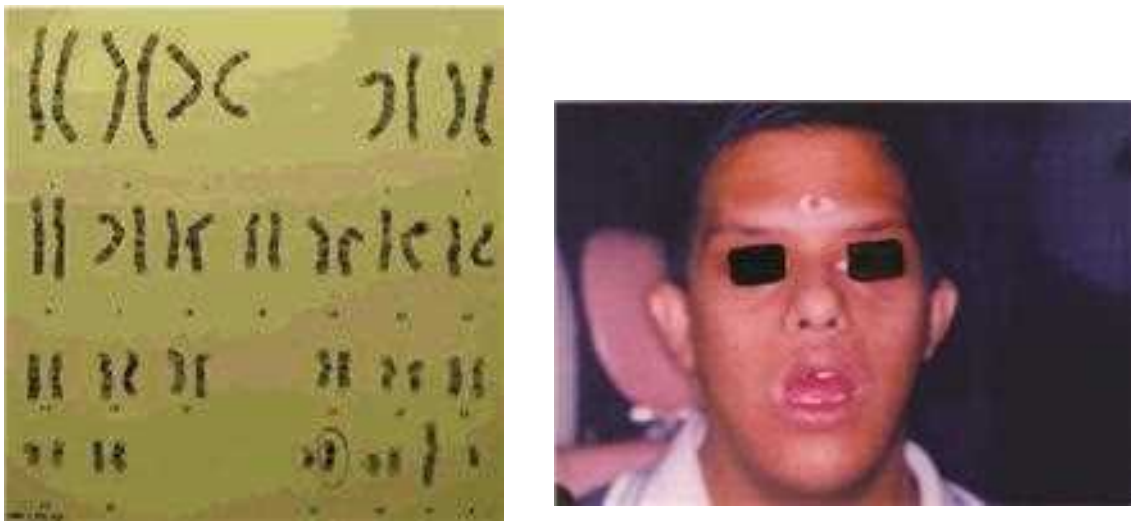
There may be **three distinct types** of TDO syndrome that have similar but not identical characteristics. Some researchers suggest that these variants may be differentiated mainly by whether the calvaria and/or long bones exhibit abnormal hardening (sclerosis), thickening, and/or density. Other symptoms also vary among the three types.

Down Syndrome

(Down's syndrome, trisomy 21 syndrome, mongolism, congenital acromicria syndrome)

Down syndrome is a frequent form of mental retardation associated with characteristic morphologic features (mongolism) and many somatic abnormalities due to a number of chromosomal aberrations. The characteristic clinical features that discriminate the syndrome from other mental deficiencies were first described by John Langdon Down in 1866.

Three cytogenetic variants cause Down syndrome: trisomy 21, chromosomal translocation, and mosaicism. Trisomy 21 accounts for nearly 95% of all patients with Down syndrome. It is now generally accepted that there are at least three forms of Down syndrome: one in which there is the typical trisomy 21 with 47 chromosomes (accounting for about 95% of cases); another termed the translocation type, in which there appear to be only 46 chromosomes, although the extra chromosome material of number 21 is translocated to another chromosome of G or D group, either 21/22 translocation or 21/21 translocation (about 3% of cases); and another that is the result of chromosomal mosaicism (about 2%) (Fig. 17-27). Children with the translocation type of Down syndrome are more commonly born to mothers over 30 years of age. The incidence of mongolism in subsequent siblings may be greatly increased in such instances. Mothers over 40 years rarely have translocation mongoloids. In contrast, the risk of having an affected child of the typical trisomy 21 type is approximately one in 2,000 live births in women under 30 years of age but rises dramatically to one in 50 live births in women over 45 years of age.



A B

Figure 17-27. Down syndrome.
(A) A G-banded karyotype showing trisomy 21 of ISO chromosome arm 21 q type [46 × 4i (q 10)]. **(B)** Frontal view of a patient with Down syndrome *(Courtesy of Dr Harold Chen).*

Clinical Features. Down syndrome is the most common autosomal abnormality and occurs in approximately 1 per 700 live births. Down syndrome accounts for the majority of mentally handicapped children in the preschool age category. It has been reported in people of all races. Both genders are affected equally. Characteristic morphologic features of mongolism can be recognized immediately at birth, but they are obvious in children older than one year. The major features of Down syndrome are mental retardation which can be mild to severe with an intelligence quotient (IQ) of 25–50; characteristic head appearance; small head (brachycephaly), flat facies with increased interocular distance (hypertelorism), depressed nasal bridge, flat occiput, and broad short neck. Narrow, upward and outward slanting of the palpebral fissures, medial epicanthal folds, strabismus, cataract and retinal detachment are the ocular anomalies. Small and misshapen ears with anomalies of the folds are observed. Skeletal anomalies include short stature; broad and short hands, feet, and digits; short curved fifth finger (dysplasia of the midphalanx), clinodactyly of the fifth finger; dysplasia of the pelvis; joint laxity; a wide gap between the first and second toes; and atlanto-occipital instability. Muscle hypotonia in newborns with decreased response to normal stimuli has been reported.

- The incidence of this syndrome at various maternal ages is as follows:
  - 15–29 years : 1 case in 1,500 live births
  - 30–34 years : 1 case in 800 live births
  - 35–39 years : 1 case in 270 live births
  - 40–44 years : 1 case in 100 live births
  - Older than 45 years : 1 case in 50 live births
- On rare occasions, the disease can be observed in a few members of a family

Protuberant abdomen (with or without an umbilical hernia), hypogenitalism, hypospadia, cryptorchism, and delayed and incomplete puberty. Congenital defects of the heart, or endocardial defects (40%), duodenal atresia, Hirschsprung disease, polydactylia, and syndactylia are reported. Other features include recurrent respiratory infections, leukemia (1%), epilepsy (10%), hypothyroidism (3%), and presenile dementia.

Oral Manifestations. Small mouth with protrusion of the tongue (macroglossia) with difficulty in eating and speaking, scrotal tongue, hypoplasia of the maxilla, delayed tooth eruption, partial anodontia, enamel hypoplasia, juvenile periodontitis, and cleft lip or palate (rare) are noticed commonly. Fissuring and thickening of the lips and angular cheilitis are frequent and gets increased in incidence and severity with age. Cheilitis occurs with greater frequency in children with Down syndrome than in unaffected persons. It is explained by mechanical factors, trauma, actinic influence, atopy, avitaminosis, or low-grade infections (candidiasis). A fissured tongue (plicated or scrotal) occurs in as many as 80% of children with Down syndrome, but it affects about 5% of the general population. Geographic tongue occurs in 11.3% of patients with Down syndrome. Juvenile periodontitis is a feature of Down syndrome, and its incidence among the various age groups parallels the occurrence of cheilitis but without significant correlation.

Treatment and Prognosis. No specific therapy exists for the congenital problems of patients with Down syndrome. About 25–30% of patients with Down syndrome die during the first year of life. The most frequent causes of death are respiratory infections (bronchopneumonia) and congenital heart disease.

DISEASES OF BONE OF QUESTIONABLE ETIOLOGY

Infantile Cortical Hyperostosis

(Caffey's disease, Caffey-Silverman syndrome, familial infantile cortical hyperostosis, sporadic infantile cortical hyperostosis)

Infantile cortical hyperostosis was originally described independently by Caffey and Silverman and by Smyth and his coworkers as a syndrome of unknown etiology in which unusual cortical thickening occurred in certain bones of infants. It was soon discovered that none of a variety of diseases which may produce cortical thickening, such as scurvy, rickets, syphilis, bacterial osteitis, neoplastic disease and traumatic injury are present in this condition. Infantile cortical hyperostosis is a self-limited disorder that affects infants and causes bone changes, soft tissue swelling, and irritability. Although the etiology is not completely understood, familial and sporadic forms appear to exist.

Etiology. This is an inflammatory process of unclear etiology. In early stages, inflammation of the periosteum and adjacent soft tissues is observed. As this resolves, the periosteum remains thickened and subperiosteal immature lamellar bone is observed. Mature specimens show hyperplasia of lamellar cortical bone without inflammation or subperiosteal changes. While the etiology is not clear, evidence of genetic transmission exists. Some believe that transmission may occur via an infectious agent with a long latency period. Other theories include a primary arterial abnormality and allergic reaction.

Clinical Features. Infantile cortical hyperostosis is a self-limited condition. No sex predilection has been established. Infantile cortical hyperostosis is now believed to exist in two forms, **familial** and **sporadic**. These forms differ in their onset and presentation. The familial form seems to have an earlier onset; 24% of these cases are present at birth. Incidence of mandibular involvement is lower, and incidence of lower extremity involvement is higher in the familial form than that observed in the sporadic form. The tibia is the most frequently involved bone. The average age at onset is six to eight weeks. The disease appears to be inherited in an autosomal dominant fashion with variable penetrance. The sporadic form is becoming less common. It has a higher incidence of mandibular involvement than does the familial form. The average age at onset is 9–11 weeks. The classic presentation includes a triad of irritability, swelling, and bone lesions. The swelling appears suddenly. It is deep and firm and may be tender. Fever may occur. Babies may refuse to eat, especially if they have mandibular involvement, creating an appearance of failure to survive. Almost all cases are evident in infants by age of five months.

The mandible and the clavicles are the bones most frequently affected, the jaw involvement usually being manifested as a facial swelling. In fact, mandibular involvement is such a constant and striking feature of the disease that the question has been raised as to whether the diagnosis of the disease should ever be made in its absence. However, Saul and his coworkers reported that in the familial form of the disease mandibular involvement is less frequent and lower extremity involvement more frequent. Other bones which commonly demonstrate hyperostosis are the calvarium, scapula, ribs and tubular bones of the extremities, including the metatarsals. The soft-tissue swellings are associated with deep muscles and occur in general in the locations in which the hyperostoses subsequently arise. These swellings have been described in the scalp, face, neck, thorax and extremities.

Other signs and symptoms of the condition which have been described in some patients, but which are not inevitably present, include fever, pseudoparalysis, dysphagia, pleurisy, anemia, leukocytosis, monocytosis, elevated sedimentation rate and increased serum alkaline phosphatase.

Oral Manifestations. The oral aspects of the disease have been studied by Burbank and his associates in a series of patients who had suffered from the condition during infancy. After careful follow-up examinations they found that some patients manifested a residual asymmetric deformity of the mandible, usually in the angle and ramus area, even several years after the disease had subsided. A few patients with this deformity also had severe malocclusion. Despite the febrile component of the disease, no cases of enamel hypoplasia were observed. Care must be taken not to confuse this disease with cherubism, in which bilateral enlargement of the mandible also occurs.

Radiographic Features. Radiographic examination reveals periosteal new bone formation that can be quite florid and subsequently becomes compact causing pronounced cortical thickening (Fig. 17-28). The periosteal new bone is seen in bones underlying areas of soft tissue swelling. The distribution is patchy and asymmetric but is multifocal, although cases of monostotic involvement have been reported. The mandible is almost invariably involved and other commonly affected areas include the clavicles, ribs and long bones of the limbs. Typically, the periosteal new bone or periosteal 'cloaking' is confined to the diaphyses of the long bones, sparing the metaphyses and epiphyses. There are a few reports of lytic areas affecting the skull vault and facial bones but this is uncommon. The spine, phalanges and pelvis are hardly ever involved. Increased uptake of radioisotope from a radioisotope bone scan shows areas of involvement before radiographic changes are present.

Histologic Findings. In early stages, inflammation of the periosteum and adjacent soft tissues is observed. As this resolves, the periosteum remains thickened and subperiosteal immature lamellar bone is observed. The bone marrow spaces contain vascular fibrous tissue. Mature specimens show hyperplasia of lamellar cortical bone without inflammation or subperiosteal changes.

Treatment. No specific treatment exists for infantile cortical hyperostosis. The disease ultimately resolves without sequelae in six to nine months. Some periods of exacerbations and remissions may occur during the course. Corticosteroids may be helpful in alleviating symptoms in severe cases, but

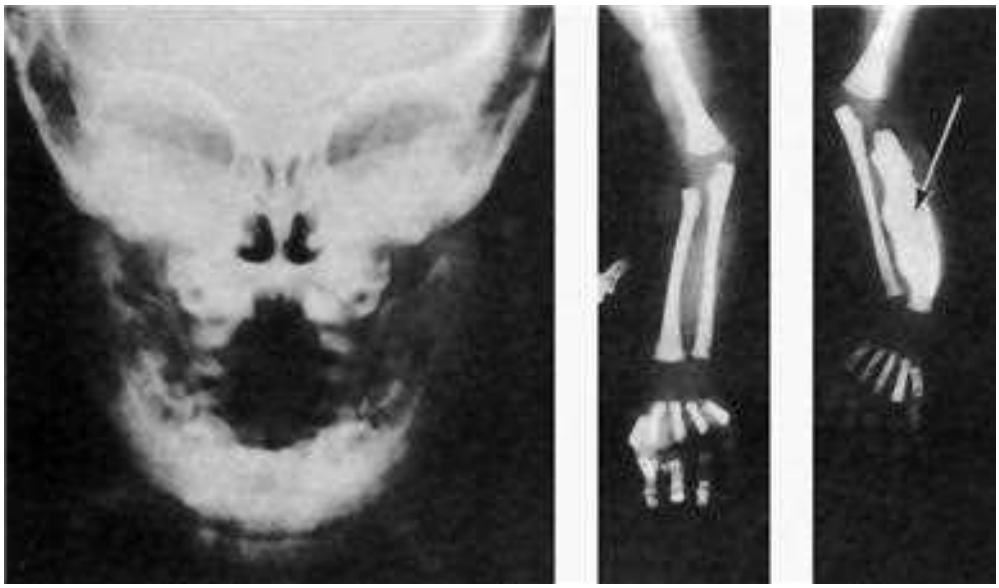


Figure 17-28. Infantile cortical hyperostosis.
There is thickening of the mandible **(A)** and of the radius in **(C)** as compared to the normal radius in **(B)** *(A, Courtesy of Dr F Brooksaler: J Pediatr, 48: 739, 1956).*

they do not have any effect on bone lesions. NSAIDs may also be used for symptoms. On occasion, residual skeletal changes may persist into adult life. In addition, occasional cases of recurrence of pain and cortical thickening of bone in later childhood have been reported.

Paget's Disease
(Paget's disease of bone, osteitis deformans)

Paget's disease, which is characterized by excessive and abnormal remodeling of bone, is a common disorder in middle-aged and elderly patients. The excessive remodeling gives rise to bones that are extensively vascularized, weak, enlarged, and deformed with subsequent complications. Paget's disease is named after Sir James Paget, an English surgeon who described the clinical course of this disorder and originally named the condition osteitis deformans, as he believed the disease was caused by chronic inflammation.

Etiology. The etiology of Paget's disease is still **unknown**. Evidence exists of a genetic link, as a 7-fold to 10-fold increase in incidence of Paget's disease was observed in relatives of patients diagnosed with the condition. The overall pattern of apparent transmission suggests an autosomal dominant inheritance. Another possible etiology is related to **viral infection**. Some studies have shown the presence of viral inclusion particles in pagetic osteoclasts. Furthermore, dense fibrillar material associated with some inclusions is similar to that found in the nuclei of virus-infected cells. Certain immunocytologic data and viral antibody titers against the measles virus reinforce the viral hypothesis. The presence of minimal inflammation and few inflammatory cells in bone and peripheral blood is consistent with a chronic infectious process. Other suggested etiologies include an **inflammatory cause,** which is supported by evidence of clinical improvement after treatment with anti-inflammatory medications. Elevated parathyroid hormone in Paget's disease also has been observed; however, no firm evidence links the two disorders. Furthermore, one case of Paget's disease was diagnosed in a patient with idiopathic hypoparathyroidism. **Autoimmune, connective tissue,** and **vascular disorders** are proposed as other possible etiologies.

Paget's disease of bone is characterized by enhanced resorption of bone by giant multinucleated osteoclasts with formation of disorganized woven bone by osteoblasts. This process evolves through various phases of activity, followed by a quiescent stage. Hence, Paget's disease typically consists of the following three phases:

- Lytic
- Mixed lytic and blastic
- Sclerotic or burned out.

Clinical Features. The prevalence of Paget's disease increases with age. Paget's disease is recognized most commonly after age 50 years and is rarely diagnosed in people younger than 20 years. By the ninth decade of life, prevalence reaches nearly 10% of the peer group. The male-to-female ratio is approximately 1 : 1. There is also a marked geographic predilection for occurrence, the disease being common in England, France and Germany but rare in certain other European countries, Africa, and the Middle and Far East.

Many individuals with Paget's disease are asymptomatic. Clinical features are extremely variable and depend on which bones are affected. The diagnosis most commonly is made incidentally during an unrelated radiographic or biochemical investigation. On occasion, the disease manifests with severe musculoskeletal impairments with neurologic and cardiovascular complications. Paget's disease has a predilection for the axial skeleton and may be widespread at the time of

diagnosis. The condition commonly affects the pelvis and spine, particularly the lumbar spine with a frequency of 30–75%. The sacrum is involved in 30–60% of cases and the skull in 25–65% of cases. The proximal long bones, especially the femur, also are affected frequently (in 25–35% of cases). Involvement of the shoulder girdle and proximal humerus is not uncommon. Though any bone may be affected, the fibula, ribs, and bones in the hands and feet are involved only infrequently. Paget's disease may affect one bone and then remain limited in its course or progress from a few localized areas to the rest of the skeleton. The most common presenting complaint is pain. The bone pain is perceived as a dull constant aching pain deep below the soft tissues. It may persist or exacerbate during the night. The involved bones become warm to the touch because of the increased vascularity. Other typical findings and complaints of patients with Paget's disease may include the following: pathologic fractures commonly result from weakened pagetic bone, nonspecific headaches, impaired hearing, and tinnitus are common symptoms of Paget's disease with skull involvement. The patient's hat size may increase or change due to skeletal deformity and enlargement, especially of the skull bones. Cranial nerve palsies can affect nerves other than the auditory nerve; however, this development is uncommon. Changes in vision may occur secondary to optic nerve involvement. Back and neck pain are common complaints, as Paget's disease frequently affects the spine, especially the lumbar and sacral regions. Softened bone at the base of the skull may lead to **platybasia,** the descent of the cranium onto the cervical spine. Progressive pain, paresthesias, limb paresis, gait difficulties (waddling gait), or bowel and bladder incontinence may be caused by compression of the spinal cord or spinal nerve secondary to platybasia or vertebral fractures. Nausea, dizziness, syncope, ataxia, incontinence, and dementia can be observed with hydrocephalus, basilar invagination, and cerebellar or brainstem compressive syndromes.

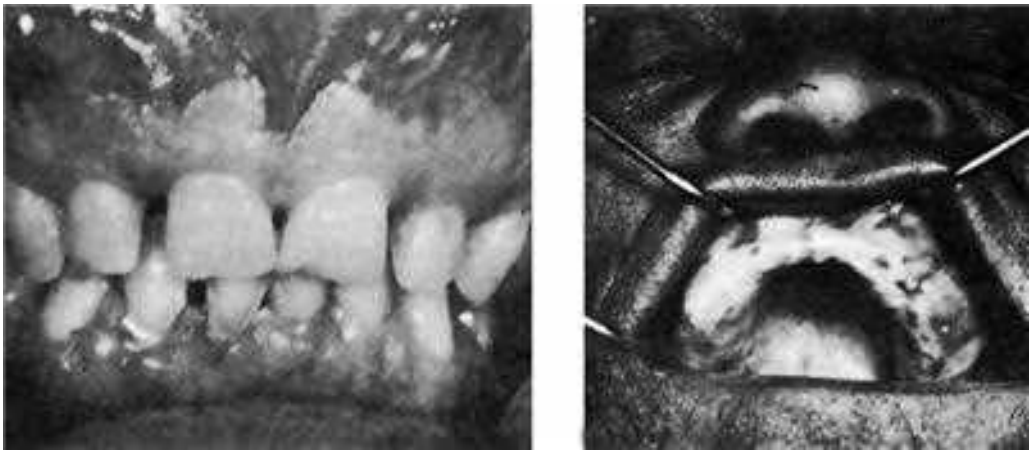
Involvement of the facial bones is occasionally seen. It has sometimes been called **leontiasis ossea** (lion-like facies) but because this term is nonspecific, Drury advocated discontinuing its use in referring to this disease.

Oral Manifestations. Involvement of the jaws in osteitis deformans is a rather common occurrence. Stafne and Austin reported 20 cases involving the maxilla and three cases involving the mandible in a series of 138 cases of generalized osteitis deformans, an incidence of 17% jaw involvement. This predilection for the maxilla has also been noted in most other studies. A number of cases have been reported in which both jaws of a patient were involved. Cooke also provided an excellent study of 15 cases of Paget's disease of the jaws, while Tillman has reported 24 cases. Smith and Eveson also have reviewed this disease with particular reference to dentistry, analyzing 152 cases involving the jaws previously reported in the literature. Of these, 98 involved the maxilla, 28 the mandible and 26 both jaws. Thus, the ratio of involvement of maxilla to mandible was approximately 2.3 : 1.

The maxilla exhibits progressive enlargement, the alveolar ridge becomes widened and the palate is flattened (Figs. 17-29, 17-30). If teeth are present, they may become loose and migrate, producing some spacing. When the mandible is involved, the findings are similar, but not usually as severe as in the maxilla. As the disease progresses, the mouth may remain open, exposing the teeth, because the lips are too small to cover the enlarged jaw.

Edentulous patients with dentures, commonly complain of an inability to wear their appliance because of increasing tightness due to expansion of the jaw. The dentures may be remade periodically to accommodate this increase in size of the jaws.

When the jaws are involved by Paget's disease, there is usually involvement of the skull as well. But there have been some cases reported in which the skull showed no evidence of the disease.



A B

Figure 17-29. Osteitis deformans.
There is diffuse enlargement of the maxilla and thickening of the dentulous **(A)** and edentulous **(B)** alveolar ridge. In addition, tipping of the teeth due to enlargement of the maxilla is obvious *(B, Courtesy of Dr Robert J Gorlin)*.

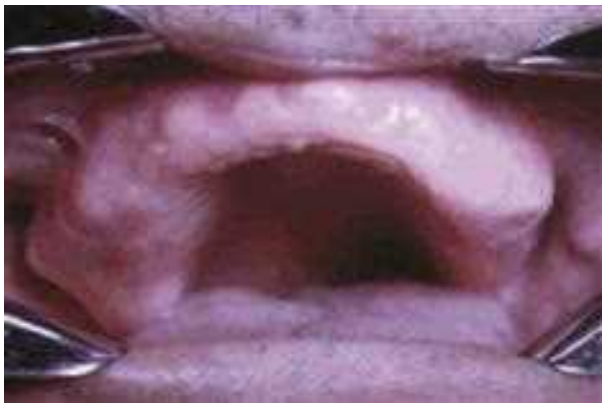


Figure 17-30. Paget's disease.
Note the enlargement on the right maxilla. The patient was unable to use his denture.

Radiographic Features. The radiographic features of osteitis deformans are varied and depend upon the stage of the disease encountered. Paget's disease has sometimes been described as a disorder characterized by an initial phase of deossification and softening, followed by a bizarre, dysplastic type of reossification not related to functional requirements, the two processes taking place simultaneously or alternately. With this in mind, the protean radiographic manifestations can be easily reconciled. Thus osteolytic areas of the skeleton are commonly associated with areas of osteoblastic activity. These destructive lesions may be multiple and diffuse or isolated. The isolated lesion in the skull, when large, is sometimes referred to as **osteoporosis circumscripta**.

The osteoblastic phase of osteitis deformans is the more commonly recognized one and inevitably occurs regardless of pre-existing osteolytic lesions. The osteoblastic areas, which appear as opacities in the radiograph, tend to be patchy in distribution, eventually becoming confluent, but often still showing minute areas of variation in radiodensity. This patchiness has been termed a 'cotton-wool' appearance and is especially well demonstrated in the skull and jaws (Fig. 17-31A).

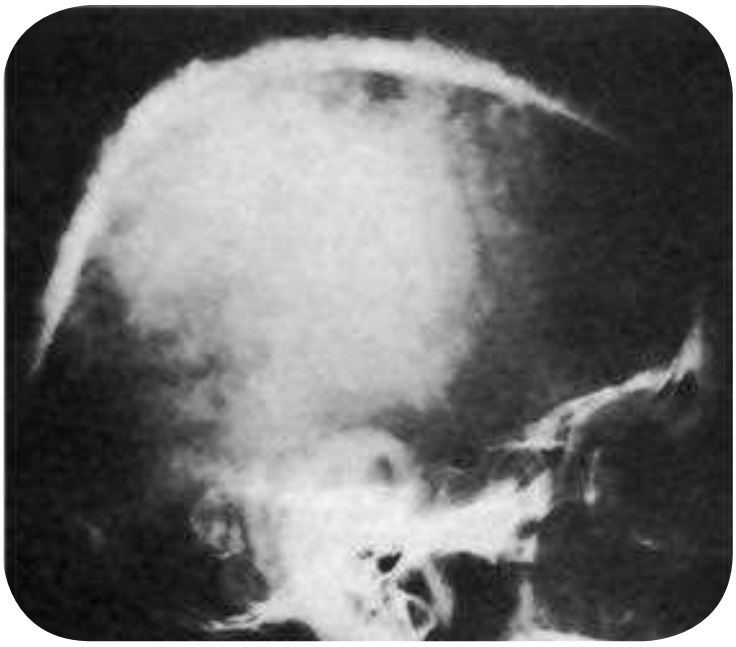
Radiographs of the jaws may demonstrate even very early phases of the disease, although such phases may not be so specific as to be pathognomonic. An excellent description of the oral manifestations of early osteitis deformans has been provided by Spilka and Callahan. In such cases, poorly defined areas of osteoporosis may be noted, although of more diagnostic significance is the finding of loss of normal trabeculation and the appearance of irregular osteoblastic activity, again giving rise to the typical **cotton-wool** appearances of 'Paget's bone' (Fig. 17-31B). Although the disease is usually bilateral, it may show radiographic evidence of only unilateral involvement of the jaw, especially early in the course of the disease. This may closely simulate chronic, diffuse, sclerosing osteomyelitis.

The teeth themselves and adjacent bone present significant radiographic changes suggestive of osteitis deformans also. These consist characteristically of a rather pronounced hypercementosis, and often, loss of a well-defined lamina dura around the teeth. Root resorption has been reported in some cases, but this is unusual.

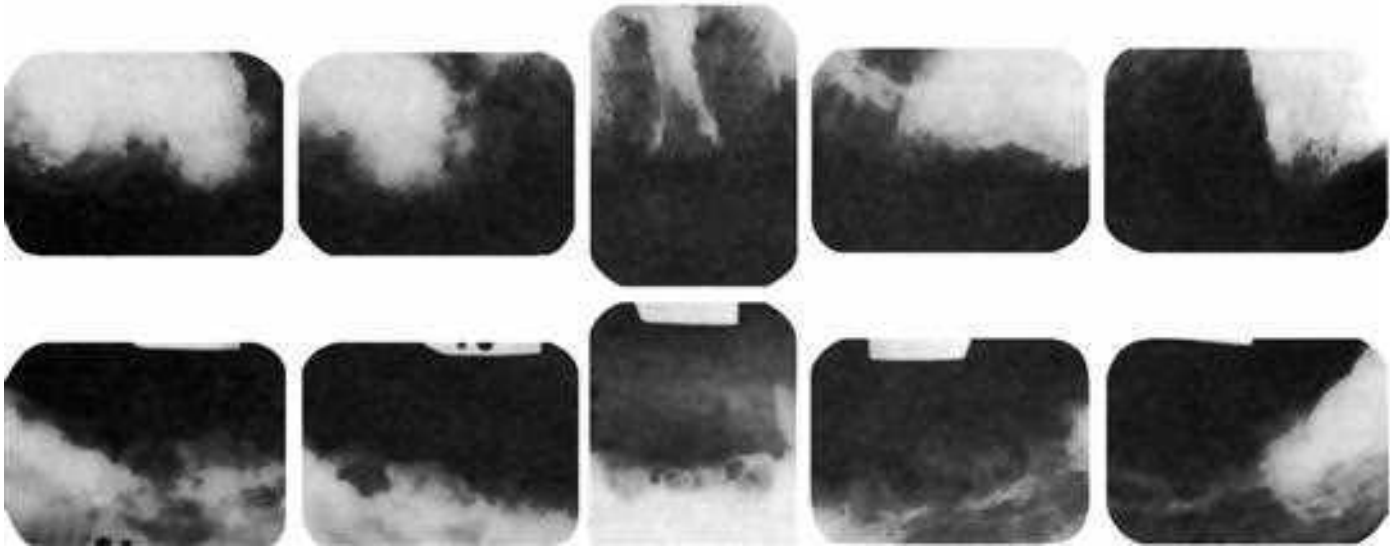
Laboratory Findings. The serum calcium and serum phosphorus levels are usually within normal limits, even in cases of advanced osteitis deformans. The serum alkaline phosphatase level may be elevated; however, to extreme limits. Values as high as over 250 Bodansky units have been reported, particularly in patients in the osteoblastic phase of the disease, when there is rapid formation of new bone and when there is polyostotic involvement. In fact, there is no other disease of bone in which the serum alkaline phosphatase level may be as high as in Paget's disease. In the monostotic form of the disease, the alkaline phosphatase level seldom exceeds 50 Bodansky units. In the very early stage of the disease this phosphatase level may not be significantly elevated, although it is simply a matter of time before this does occur. The serum acid phosphatase level is not increased. In Paget's disease, urinary **hydroxyproline** levels are elevated as they reflect increased osteoclastic activity and bone resorption. Hydroxyproline is a product of collagen breakdown. More recently, measurement of the urinary excretion of bone-specific **pyridinium collagen cross-links** has been found to be a sensitive and specific index of bone resorption. **Urinary N-telopeptide (NTX) and alpha-C telopeptide (CTX)** have emerged recently as sensitive biochemical markers for bone resorption. An abnormally high alpha-CTX: beta-CTX ratio is present with active Paget's disease. This ratio returns to the reference range following treatment with bisphosphonates.

Histologic Features. The microscopic appearance of the bone in cases of osteitis deformans varies remarkably, depending upon the stage of the disease encountered. The initial osteolytic phase is marked by disordered areas of resorption by an increased number of overtly large osteoclasts. These abnormal osteoclasts may contain as many as 100 nuclei. The subsequent osteoblastic phase follows with haphazard laying of new bone matrix and formation of woven bone without regard to the patterns of stress. Repeated episodes of bone removal and formation results in the appearance of many small irregularly shaped bone fragments that appear to be joined in a **jigsaw** or **mosaic pattern** with deeply staining hematoxyphilic reversal lines (Fig. 17-32). This pattern is the histologic hallmark of Paget's disease. As the disease progresses, the osteoblastic phase predominates, and excessive abnormal bone formation occurs, causing more compact and dense bone. The pagetic bone is coarse and fibrous, with an avidity for calcium and phosphorus. Marrow spaces are filled with loose highly vascularized connective tissue. The hypervascular bone combined with cutaneous vasodilation causes an increase in the regional blood flow and accounts for the rise in skin temperature seen clinically. The hypervascularity consists of an increased number of patent capillaries and dilated arterioles, as well as of larger venous sinuses (Fig. 17-33).

The normal trabecular appearance is distorted with a mosaic pattern of irregular cement lines joining areas of lamellar bone. Pagetic bone shows no tendency to form Haversian systems



A



B

Figure 17-31. Osteitis deformans.
The radiographs of the skull **(A)** and the jaws **(B)** demonstrate the typical 'cotton-wool' appearance *(A, Courtesy of Dr John A Campbell).*

or to center on blood vessels; the bones are very hard and dense. Eventually, the osteoblastic activity diminishes, and an osteoporotic or burned-out phase predominates (Figs. 17-34, 17-35). The new bone is disordered, poorly mineralized, and lacks structural integrity. The proliferation of bone and concomitant hypercementosis sometimes result in obliteration of the periodontal ligament.

Treatment and Prognosis. There is no specific treatment for osteitis deformans. Vitamin, hormone and radiation therapy have all been utilized with sporadic reports of cures, but these have not been confirmed. Very promising results have recently been obtained in the treatment of this disease by the use of calcitonin, the parathormone antagonist produced by the thyroid gland which suppresses bone resorption. Biphosphonates have also been used with some success, since they also inhibit bone resorption as well as bone mineralization. Finally, one of the cytotoxic antibiotics, mithramycin, has been used therapeutically but has serious side effects. The use of these agents has been reviewed in detail by Smith and Eveson. The general outlook for patients with Paget's disease is good, especially if treatment is administered before major changes in the bones have occurred. Treatment does not cure

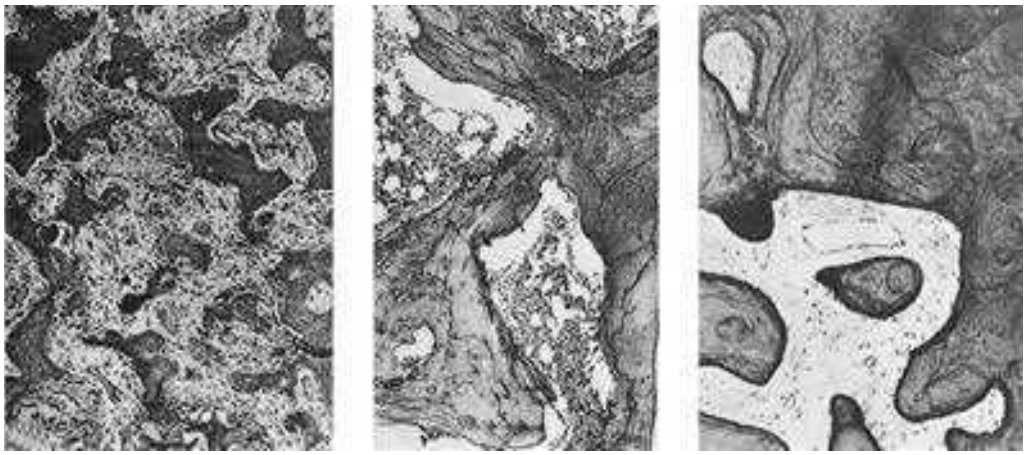


Figure 17-32. Osteitis deformans.
Photomicrographs of bone in different stages showing **(A)** reactive phase, **(B)** mosaic pattern, and **(C)** resting phase. Note the prominent resting and reversal lines in B.

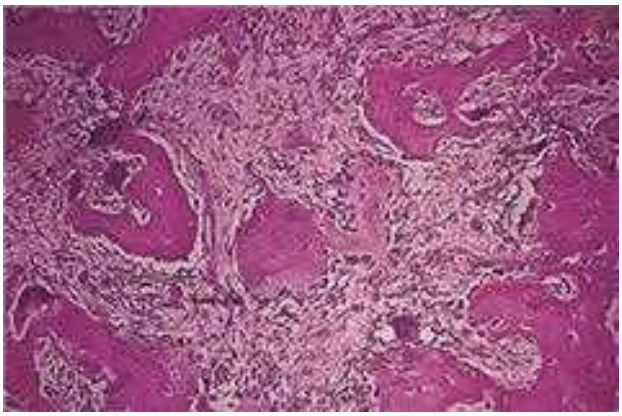


Figure 17-33. This photomicrograph taken from a bone biopsy from a patient with Paget's disease of bone shows several bone spicules in a highly vascularized connective tissue stroma.
These areas of bone formation alternate with areas of bone resorption characterized by the presence of osteoclasts. Typically, the osteoclasts are seen inside of Howship lacunae.

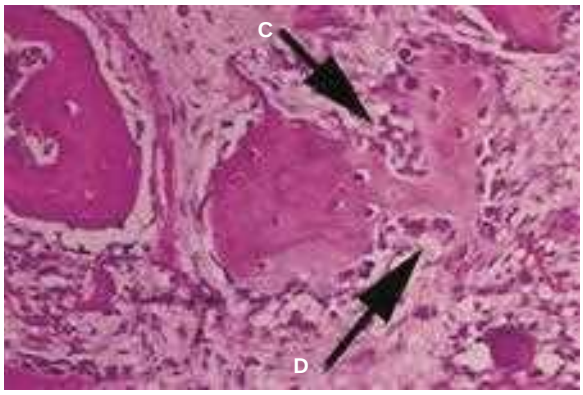


Figure 17-34. This is a higher magnification of the previous microscopy. Arrow A points to osteoclasts in Howship lacunae and arrow B points to osteoblasts in the process of bone formation.

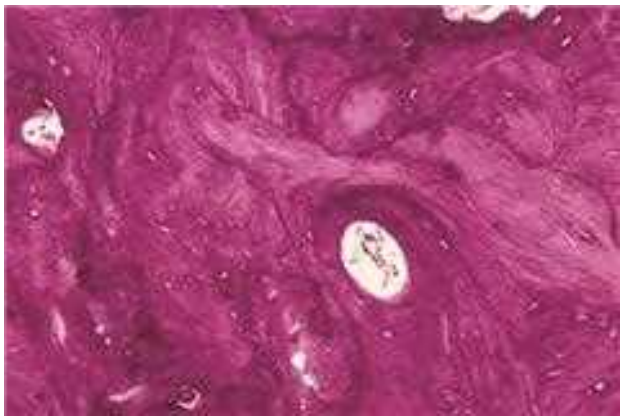


Figure 17-35. This is another photomicrograph taken from a bone biopsy from a patient with PDB from a mostly radiopaque area.
Note the apposition lines and the reversal (resorption) lines. The combination of these two lines give this biopsy a mosaic appearance.

Paget's disease but can control it. Patients with severe polyostotic Paget's disease have a less favorable prognosis than those with monostotic disease. Patients with polyostotic disease are at higher risk for complications.

Complications. Incomplete stress fractures frequently occur in Paget's disease. Mild injuries may cause acute true pathologic fractures in weakened pagetic bone. Pathologic fractures are more common in women than men. The most frequent site of these fractures is the femur, but fractures commonly occur in the tibia, humerus, spine, and pelvis. Sarcomatous degeneration of pagetic bone is a deadly complication. Pagetic sarcoma follows a rapid and fatal course. Sarcomatous degeneration may occur in 5–10% of patients with extensive pagetic skeletal involvement. In less widespread involvement, osteosarcoma occurs in fewer than 1% of patients with Paget's disease. Men are affected with sarcomatous degeneration slightly more frequently than women. Peak incidence is in the

seventh and eighth decades of life. The femur (most common) and proximal humerus are the sites most commonly affected; however, no bone is exempted, including sites of previously healed fractures.

Degenerative joint disease is associated with Paget's disease. Cardiovascular abnormalities such as increased cardiac output has been observed in patients with widespread Paget's disease. Left ventricular hypertrophy is an associated finding. Increased soft tissue and pagetic bone vascularity has been implicated as a contributing factor. High-output congestive heart failure may occur, but it is rare.

Massive Osteolysis

(Vanishing bone, disappearing bone, phantom bone, progressive osteolysis, Gorham syndrome)

Massive osteolysis is an unusual and uncommon disease characterized by spontaneous, progressive resorption of bone with ultimate total disappearance of the bone. Disappearing, or 'Phantom' bone disease, also called Gorham's disease, may be a form of hemangioma of bone. This relatively rare condition, usually occurring in children or young adults, is characterized by the dissolution, in whole or in part, of one or several adjacent bones. A cavernous, angioma-like permeation may be a prominent pathologic feature of the affected bones. The process is self-limited, but the extent of progression is unpredictable. It is not genetically transmitted.

Clinical Features. Massive osteolysis is most common in older children and young and middle-aged adults, affecting both genders equally. About 50% of all patients report an episode of trauma before the diagnosis, but this is often trivial in nature. Usually only one bone is affected in a given patient, although polyostotic cases have been reported. The most commonly affected bones are the clavicle, scapula, humerus, ribs, ilium, ischium, and sacrum.

The disease, which may or may not be painful, begins suddenly and advances rapidly until the involved bone is replaced by a thin layer of fibrous tissue surrounding a cavity. All laboratory values are usually normal.

Oral Manifestations. A number of cases have been reported involving the mandible and other facial bones, and these have been reviewed by Ellis and Adams and by Murphy and his coworkers. In only two of these cases was there destruction of the entire mandible. In at least three cases, there was concomitant involvement of the maxilla. The patient may present with pain or facial asymmetry, or both. One of the consistent findings in the disease has been pathologic fracture following minor trauma.

Histologic Features. The typical histologic findings is replacement of bone by connective tissue containing many thin-walled blood vessels or anastomosing vascular spaces lined by endothelial cells. It does not represent a hemangioma of bone, which remains a localized lesion, although the term 'hemangiomatosis' has been applied. Most authorities do not believe that the disease is due to increased osteoclastic activity, although osteoclasts may often be found in the tissues. On the other hand, their absence in areas of active resorption is often quite striking.

Treatment and Prognosis. There is no specific treatment. Radiation therapy has been of benefit in some cases, while surgical resection has stopped the progress of the disease in others. Left untreated, the disease commonly progresses to total destruction of the involved bone.

Cementoblastoma

(True cementoma)

The benign cementoblastoma is probably a true neoplasm of functional cementoblasts which form a large mass of cementum or cementum-like tissue on the tooth root. It is quite distinctive but relatively uncommon.

Clinical Features. The benign cementoblastoma occurs most frequently under the age of 25 years, with no significant gender predilection. More than half of the tumors have occurred in persons under 20 years of age, although the range has been 10–72 years. When the site has been specified, the mandible is affected three times more frequently than the maxilla. The mandibular first permanent molar is the most frequently affected tooth. In fact, only one case is reported involving the deciduous dentition. Involvement of this mandibular first molar has accounted for approximately 50% of all reported cases. However, other teeth involved have included mandibular second and third molars, mandibular bicuspids, maxillary bicuspids and first, second and third molars. The associated tooth is vital unless coincidentally involved. The lesion is slow-growing and may cause expansion of cortical plates of bone, but is usually otherwise asymptomatic. Pain has been reported, but this may have been related to associated caries rather than to the lesion.

Radiographic Features. The tumor mass is attached to the tooth root and appears as a well-circumscribed dense radiopaque mass often surrounded by a thin, uniform radiolucent line. The outline of the affected root is generally obliterated because of resorption of the root and fusion of the mass to the tooth.

Histologic Features. The main bulk of the tumor mass is composed of sheets of cementum-like tissue, sometimes resembling secondary cellular cementum but other times being deposited in a globular pattern resembling giant cementicles. Reversal lines scattered throughout this calcified tissue are often quite prevalent. There is a variable soft-tissue component consisting of fibrillar, vascular and cellular elements. Many of the cemental trabeculae in area of activity are bordered by layers of cementoblasts. Away from these trabecular surfaces, cementoclasts may be evident. In such active areas, the lesion is frequently microscopically indistinguishable from the benign osteoblastoma or giant osteoid osteoma, and this relationship has been discussed by Larsson and his associates. In fact, some areas are so cellularly active that they bear strong resemblance to osteosarcoma.

This calcified mass will be found united to the tooth root through obliteration of the periodontal ligament, resorption of portion of the root and replacement by the tumor tissue. The periphery of the tumor generally shows a soft tissue cellular layer

resembling a capsule. At this periphery, the cemental trabeculae are almost invariably arranged at right angles.

Treatment and Prognosis. Because of the tendency for expansion of the jaw, it is believed that extraction of the tooth is justified despite the fact that the pulp is vital. Care must be taken to distinguish this lesion from severe hypercementosis or chronic focal sclerosing osteomyelitis (i.e. condensing osteitis), both of which it may superficially resemble. The lesion does not appear to recur.

Bisphosphonate Therapy

Bisphosphonates are small inorganic molecules that bind to hydroxyapatite on the surface of damaged bones. They belong to a class of drugs that are used to prevent bone loss by demineralization of bone. At the sites of bone damage, osteoclasts are inhibited and destroyed. Since bone damage is caused by increased numbers and activity of these osteoclast bone cells, bisphosphonates reduce new bone damage and allow an opportunity for bone healing to occur. Bisphosphonates are approved for the treatment of osteoporosis, often seen in post-menopausal females, hypercalcemia of malignancy and in metastatic disease to bone (cancer spreading to bone tissue).

Bisphosphonates therefore have several beneficial effects, including:

- Preventing further bone damage
- Reducing bone pain and the need for pain relieving drugs
- Correcting and preventing hypercalcemia
- Reducing the need for radiotherapy
- Reducing pathologic fractures due to bone occupying/destroying lesions
- Improving quality of life
- Improving the chances of healing and recovery of strength of the bone

Possible Side Effects of Bisphosphonates. Bisphosphonates are generally very well tolerated. The most common side effects are fever, vein irritation, general aches and pains, kidney dysfunction and osteonecrosis of the jaws (ONJ).

Osteonecrosis of the Jaws. Recently cases have been reported of individuals having difficulty in healing after undergoing tooth extraction or other invasive dental procedures, associated with a phenomenon called osteonecrosis of the jaws (ONJ). The only common factor in these patients was that they were taking bisphosphonate drugs. As a consequence, an agreement was reached that there is an association between osteonecrosis of the jaw and bisphosphonate therapy, although the drugs are not the only factor involved.

Overall, the risk is thought to be less than 1% for patients taking IV bisphosphonates, and at least ten times less likely than that for patients taking the drugs by mouth. Most reported cases occur after oral trauma (tooth extraction or oral surgical procedures). Tobacco use, treatment with corticosteroids, long term use of bisphosphonates, treatment with more than one kind of bisphosphonates, and diabetes may increase the risk of this condition developing.

Signs of Bisphosphonate-associated Osteonecrosis. The hall marks of this condition are gum wounds that heal very slowly or do not heal at all for six weeks or more after a procedure that exposes bone. Some patients report that this begins with a feeling of 'roughness' on the gum tissue. If these open wounds become infected, suppuration or swelling in the adjacent gum tissue develop. Many times, the condition is painless in the beginning, and pain is experienced only after the exposed bone becomes infected. If this infection lasts long enough, there may even be numbness, especially in the lower jaw.

Unfortunately at this time most reported treatments are slow to resolve osteonecrosis of the jaw, so the best treatment is prevention. Current treatment methods that are used include antiseptic rinses, systemic antibiotics, and cleaning/removal of dead bone from the affected area. Generally, therapy focuses on controlling pain and preventing infection so that the body can heal properly.

If problems persist and/or if healing is slow, consideration can be given to stopping bisphosphonate therapy for 2–4 months to facilitate recovery. There is every reason to hope that with appropriate awareness and early management, serious problems from osteonecrosis can be avoided.

Patients with documented myeloma related bone disease should not take bisphosphonates. This means that, in general, patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering (early/clinically not established) myeloma without bone disease do not need or benefit from bisphosphonates. However, this remains an area of ongoing research and clinical trials.

Bisphosphonates must be used with caution in patients with pre-existing kidney disease or known elevation in serum creatinine, especially > 3.0 mg/dl but also any value above the normal range.

Patients who have allergic reactions or are intolerant to bisphosphonates should not be recruited to therapy.

DISEASES OF TEMPOROMANDIBULAR JOINT

The temporomandibular joints (TMJs) are one of the most commonly used joints and also one of the most complex joints. These joints play crucial roles in mastication and speech. Disorders of TMJs include congenital and developmental conditions, traumatic disturbances, arthritis, benign and malignant tumors, dysfunction of the articular disks and ligaments, disorders inside or outside the TMJ capsule, and disorders associated with mandibular or temporal bones. Disorders of TMJs are high; some studies reports as high as 86% of the population has some kind of TMJ related signs or symptoms. Progress in cross-sectional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI) and cone beam computed tomography (CBCT), has allowed better evaluation of the TMJs. Plain radiographs and panoramic radiographs have limited values in diagnosing TMJ disorders. With current clinical knowledge and treatment options available, management of TMJ related conditions are difficult and not always successful.

The following sections provide a brief overview of the most common TMJ-related disorders.

DEVELOPMENT DISTURBANCES OF TEMPOROMANDIBULAR JOINT

At the time of birth, the TMJs are incompletely formed. Therefore, developmental disturbance to the TMJs can occur either before or after birth. Kaneyama et al, have classified developmental disturbances as follows:

1. Hypoplasia or aplasia of the condyle
   a. Congenital or primary hypoplasia or aplasia
   b. Acquired or secondary hypoplasia or aplasia
2. Condylar hyperplasia
3. Bifid condyle.

Condylar Hypoplasia or Aplasia

Condylar aplasia is failure of development of the mandibular condyle, while condylar hypoplasia is underdevelopment of the condyle. Aplasia or hypoplasia may be congenital or acquired, and may occur unilaterally or bilaterally (Fig 17-36A, B).

Congenital or **primary** hypoplasia or aplasia is characterized by unilateral or bilateral underdevelopment of the condyle, usually due to disturbances in the first or second branchial arches. Conditions that show congenital hypoplasia or aplasia include Treacher Collins syndrome (Fig. 17-36C, D), oculo-auriculo-vertebral syndrome, hemifacial macrosomia, Pierre Robin sequence, and Hurler syndrome. In congenital variety, both the joints are usually affected but the primary clinical findings may be unilateral.

The **acquired** or **secondary** form of hypoplasia may be due to any agent which interferes with the normal development of the condyle. Local causes that may initiate condylar hypoplasia include trauma, infection of the mandible or middle ear, and therapeutic dose of irradiation.

Clinical Features. Hypoplasia or aplasia is frequently associated with other anatomically related defects such as a defective or absent external ear, an underdeveloped mandibular ramus or macrostomia. Unilateral involvement is the most common clinical type. If the disturbance is unilateral, there is obvious facial asymmetry, and both occlusion and mastication may be altered. A shift of the mandible towards the affected side occurs during opening. A mild disturbance presents only lesser degree of these features, perhaps accompanied by a mandibular midline shift during opening and closing. The distortion of the mandible in this pathognomonic pattern results from lack of downward and forward growth of the body of the mandible due to the arrest of the chief growth center of the mandible, the condyle. Some growth continues at the outer posterior border of the angle of the mandible, resulting in thickening of the bone in this area. The older the patient at the time of the growth disturbance, the less severe will be the facial deformation.

In bilateral hypoplasia or aplasia, deviation of the jaws is not present. However, micrognathia is a prominent feature of bilateral hypoplasia or aplasia. Along with micrognathia, dental crowding and open bite may be present. The severity of the clinical findings depends on the age of the patient when the injury occurred, the duration of the injury and its severity. In aplasia or severe hypoplasia, persistent airway obstruction may occur due to posterior positioning of the tongue into the pharyngeal airway. Feeding is thus compromised as well as speech.

Treatment. Treatment of condylar aplasia or hypoplasia is difficult since there are no available means of stimulating its growth locally or compensating for its failure. Singh and Bartlett have reported different treatment modalities conducted on a series of 266 patients over a period of 27 years. Early diagnosis and intervention are important in managing the occlusion, speech and other functions. Although the condition itself is not necessarily a progressive one, the resulting disturbance may become more severe as the patient approaches puberty. Cartilage or bone transplants have been used to build-up the underdeveloped parts, preceded in some cases by unilateral or bilateral sliding osteotomy, to improve the appearance of the patient with asymmetry and retrusion. If the derangement is severe, osteoplasty may be considered as an option. If the patient exhibits little difficulty, surgical intervention is not warranted, although cosmetic surgery may aid in correcting facial deformity. Infants with condylar aplasia who exhibit respiratory difficulty may require tracheotomy.

Hyperplasia of Mandibular Condyle

Condylar hyperplasia is a rare unilateral enlargement of the condyle (Fig. 17-37A,B, C) which should not be confused with a neoplasm of this structure, although it may superficially resemble an osteoma or chondroma. The cause of this condition is obscure, but it has been suggested that mild chronic inflammation, resulting in a condition analogous to a proliferative osteomyelitis, stimulates the growth of the condyle or adjacent tissues. The unilateral occurrence strongly suggests a local phenomenon. Obewegeser and Makek have classified condylar hyperplasia into three categories. Type A is hemimandibular hyperplasia, causing asymmetry in the vertical plane. In this type, the growth is unilateral in the vertical plane, with minimal deviation of the chin. Typically, maxilla shows compensatory growth. In absence of the maxillary growth, an open bite may be present on the same side. Type B is hemimandibular elongation, causing asymmetry in the transverse plane. In this type, the chin is deviated towards the contralateral side with no vertical asymmetry. Patient may exhibit cross-bite. Type C is a combination of type A and type B, and exhibits hyperplastic features unilaterally or bilaterally.

Clinical Features. Condylar hyperplasia occurs more frequently in females. Patients of any age may be affected, although most common occurrence is in the third decade

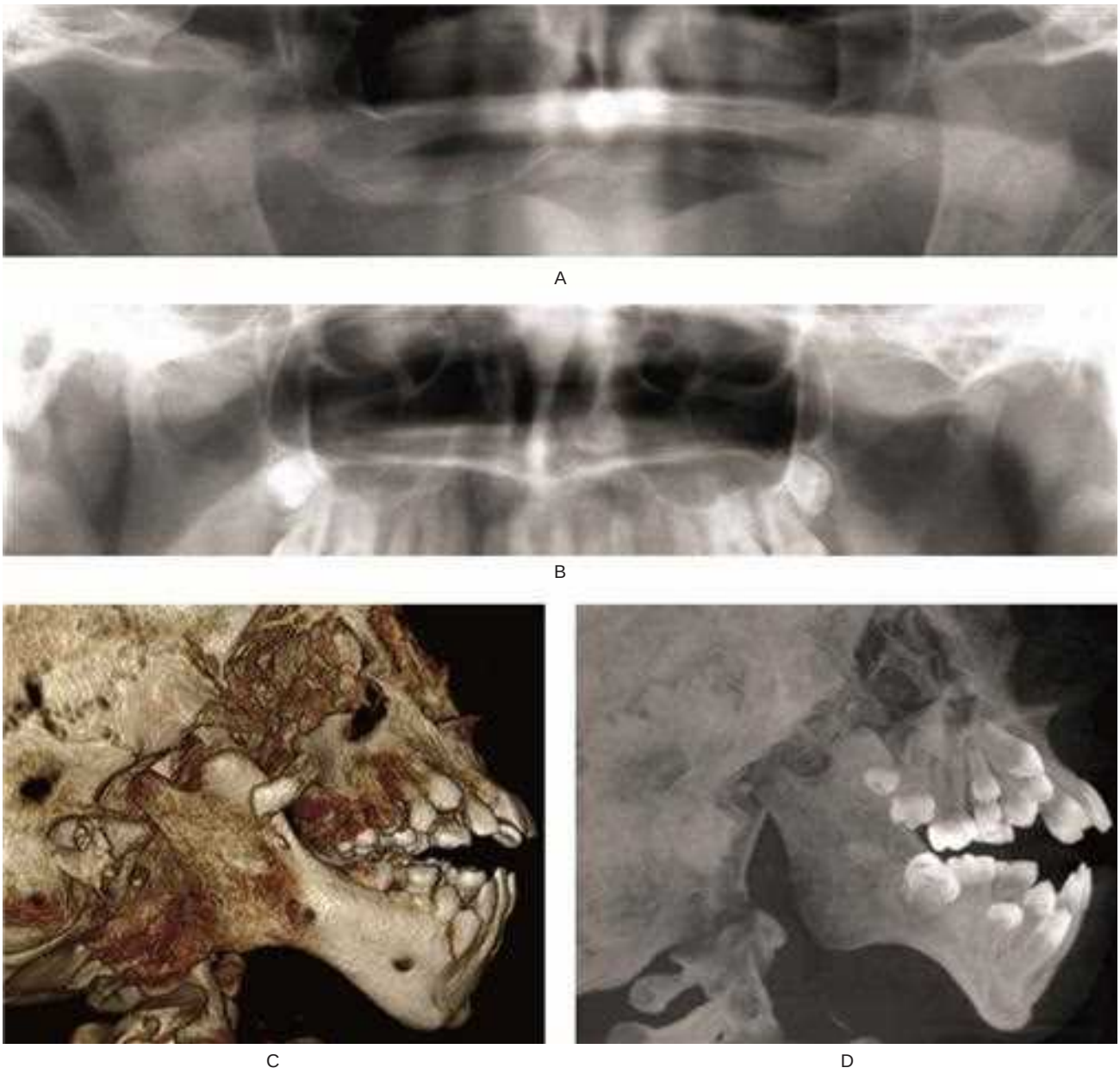


Figure 17-36. Developmental disturbances of temporomandibular joints.
Aplasia and hypoplasia of the TMJ. **(A)** Cropped panoramic radiograph showing bilateral aplasia of the TMJs. The finding is worse on the left side. The coronoid processes appear hyperplastic. **(B)** Cropped panoramic radiograph showing hypoplasia of the right condylar head. Compared to the left condylar head, the anteroposterior dimension of the right condylar head is small. The left condylar head has flattening of the lateral surface, consistent with degenerative joint disease. **(C)** Treacher Collins syndrome, 3-D reconstruction of a cone beam computed tomography data. **(D)** Same patient as in Figure C. Maximum intensity projection of cone beam computed tomography data. Figures C and D showing hypoplastic condylar head and coronoid process. Zygomatic arch is partially formed. Anterior teeth are protruded. Antegonial notch is prominent. In Treacher Collins syndrome, hypoplasia of the condylar heads is bilateral.

of life. Diagnosis of condylar hyperplasia is made by a combination of clinical and radiographic findings. The patients usually exhibit a unilateral, slowly progressive elongation of the face with deviation of the chin away from the affected side. The enlarged condyle may be clinically evident or at least palpated and presents a striking radiographic appearance in both coronal and sagittal views. The affected joint may or may not be painful. A malocclusion is a usual sequel of the condition.

Treatment. The treatment of condylar hyperplasia is usually surgical. Surgical options are condylectomy or orthognathic surgery or a combination of both. Depending on the severity of the hyperplasia, orthodontic treatment may be needed.

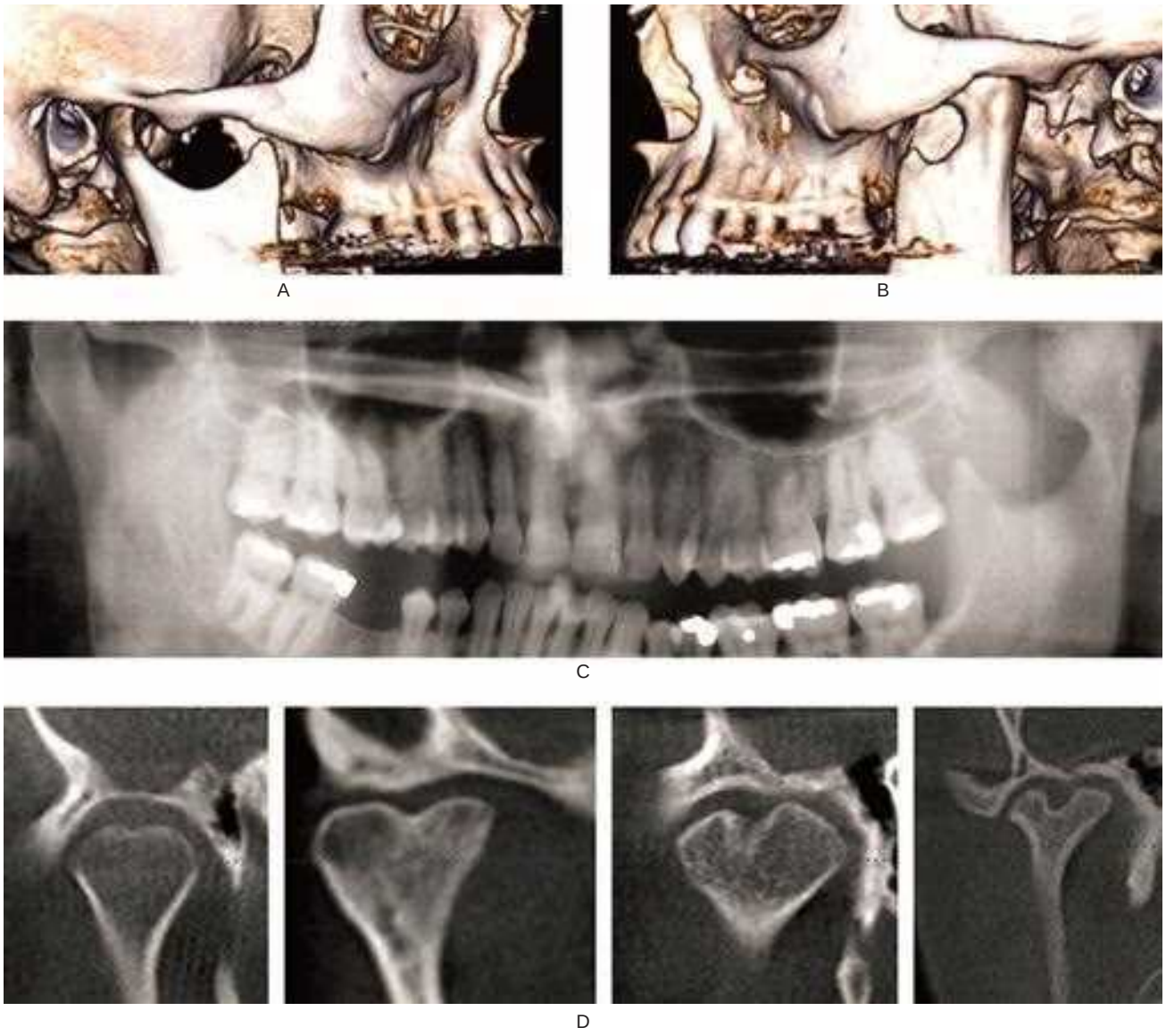


Figure 17-37. Developmental disturbances of temporomandibular joints.
Figures **(A and B)** are from the same patient. Three-dimensional reconstruction of a computed tomography data. The left condylar head is hyperplastic. Please note that left condylar head is too large for the articular fossa, and is permanently dislocated anterior to the articular eminence. **(C)** Cropped panoramic radiograph shows hyperplasia of the left condylar head. **(D)** Axially corrected coronal views of the temporomandibular joints from four different patients from cone beam computed tomography scans. Bifid condyles may have slight midline depression to almost a duplication of the condylar head.

Bifid Condyle

Bifid condyle is characterized by a varying depth of groove or depression around the midline of the condylar head (Fig. 17-37D). The depression may be visible on coronal or sagittal orientation. A deep groove may result into an appearance of duplicity of the condylar head. Usually, bifidity is unilateral, although bilateral bifid condyles have been reported. Bifidity is a rare condition, effecting less than 1% of the population. Even rarer are trifid condyles. The etiology of bifidity is controversial. Two etiologies of bifid condyles have been suggested. One theory speculates that bifidity may originate in embryo where blood supply to the condylar head is limited. Another theory suggests trauma being the cause of bifidity, either due to birth trauma or fracture of the condylar head. Usually patients with bifid condyles are asymptomatic and do not require any treatment. Relationship of bifid condyles to articular disks is not clearly known.

TRAUMATIC DISTURBANCES OF TEMPOROMANDIBULAR JOINT

Dislocation of the Condyles

Condylar dislocation can primarily be of two types: anterior dislocation and cranial dislocation. Cranial dislocation, where the condylar head is dislocated into the cranial fossa due to trauma, is rare. The causative trauma is mostly motor vehicle or sports related. Trauma may also dislocate the condylar head posteriorly.

Anterior dislocation of the TMJ is more common than cranial dislocation. Anterior dislocation occurs when the head of the condyle moves anteriorly over the articular eminence into such a position that it cannot be returned voluntarily to its normal position. Some researchers believe that this inability to retrude the mandible is caused by spasm of the temporal muscle initiated by myotatic reflex. Thus, in movements of the mandible involving forward translation of the condyle, tension may be placed on the temporalis and leads to the formation of the muscle spasm.

Anterior dislocations can be 'luxation' or 'subluxation'. Luxation of the joint refers to complete dislocation, which cannot be reduced by the patient (non-self-reducing). Subluxation is a partial or incomplete dislocation, which can be reduced by the patient (self-reducing). Some investigators hold the view that subluxation is actually a form of hypermobility, and should not be viewed as a form of dislocation. Anterior dislocation may occur repeatedly, and condylar reduction may become easier with successive dislocation. Repeated anterior dislocation and self-reduction is referred as **habitual** or **recurrent dislocation.**

Anterior dislocation may be acute, owing to a sudden traumatic injury resulting in fracture of the condyle (*see Figure 7-42E, F for examples of traumatic dislocation*), or more frequently, only in stretching of the capsule, usually at the point of attachment for the external pterygoid muscle into the capsule. There is often some tearing of the tendon at this insertion point. Most commonly, however, dislocation is a result of yawning or having the mouth opened too widely, as during extraction of teeth or during procedures such as tonsillectomy or endoscopy.

Clinical Features. The typical form of anterior dislocation is characterized by sudden locking and immobilization of the jaws when the mouth is open, accompanied by prolonged spasmodic contraction of the temporal, internal pterygoid and masseter muscles, with protrusion of the jaw. The patient experiences severe pain of the TMJs, excessive salivation and depression of the skin in the preauricular area. All activities requiring motion of the mandible, such as eating or talking, become impossible. The mouth cannot be closed, and the patients frequently become panicky, especially if it is their first experience.

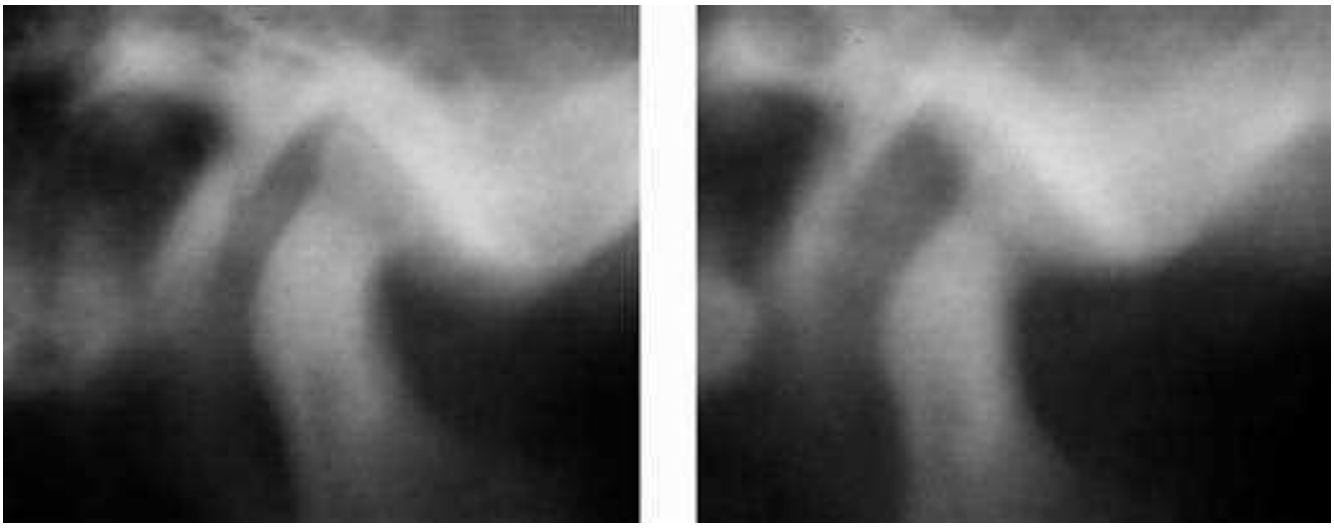
Treatment. Reduction of an anteriorly dislocated condyle is accomplished by inducing relaxation of the muscles and then guiding the head of the condyle under the articular eminence into its normal position by an inferior and posterior pressure of the thumbs in the mandibular molar area. The necessary relaxation can sometimes be brought about only by means of general anesthesia or by tiring the masticatory muscles by cupping the chin in the palm of the hand and applying a posterior and superior pressure for 5–10 minutes. Treatment of recurrent dislocation may be achieved by altering the ligaments, associated musculature, and bony anatomy.

Ankylosis (Hypomobility)

Ankylosis of the TMJ is a disorder in which adhesion of joint components takes place by fibrous or bony union, resulting into loss of function (Fig. 17-38).

Etiology. The most frequent causes of ankylosis of the TMJ are traumatic injuries and local or systemic infections. Other causes of ankylosis include systemic diseases such as ankylosing spondylitis, rheumatoid arthritis, psoriasis, or previous TMJ surgery. Bilateral ankylosis is often a result of rheumatoid arthritis.

Classification. Sawheny in 1986 had classified ankylosis of the TMJ is into four different types. In his study of 55 patients, type I ankylosis was least common, while type IV was most



Closed mouth Open mouth

Figure 17-38. Ankylosis of the temporomandibular joint.
The images are tomography of the left temporomandibular joint in the closed and open mouth positions. A radiopaque band of tissues extends from the condylar head to the anterior slope of the articular fossa. On the open mouth view, the condylar head barely translated.

common. In another study by Zhi et al, type III ankylosis was most common.

- **Type I:** The condylar head is flattened or deformed. Presence of fibrous adhesion makes movement impossible.
- **Type II:** The condylar head is deformed and a small bony adhesion exists between the condyle and articular fossa. The articular surfaces are mostly well-defined.
- **Type III:** A bony bridge extends from the ramus to the zygomatic arch. On the medial aspect, atrophic and displaced condylar head is still present. The articular surface of the fossa is intact. The articular disk is also probably intact.
- **Type IV:** The architecture of the joint is lost due to bony bridge extending from the ramus to the temporal bone.

A simpler classification of TMJ ankylosis identifies two types of ankylosis: **intra-articular** and **extra-articular.** In intra-articular ankylosis, the joint undergoes progressive destruction of the meniscus with flattening of the mandibular fossa, thickening of the head of the condyle and narrowing of the joint space. The ankylosis is basically fibrous, although ossification in the scar may result in a bony union.

Extra-articular ankylosis results in a 'splinting' of the TMJ by a fibrous or bony mass external to the joint proper, as in cases of infection in surrounding bone or extensive tissue destruction.

Clinical Features. Ankylosis of the joint occurs at any age, but most cases occur before the age of 10 years. Distribution is approximately equal between the genders. The patient may or may not be able to open his/her mouth to any appreciable extent, depending on the type of ankylosis. In complete ankylosis, bony fusions will absolutely limit any motion. There is usually somewhat greater motion in fibrous ankylosis than in bony ankylosis.

If the injury which brought about the ankylosis was sustained in infancy or childhood, at least before the age of 15 years, there is nearly always an associated facial deformity. The type of deformity is partially dependent upon whether the ankylosis is unilateral or bilateral. In unilateral ankylosis occurring at an early age, the chin is displaced laterally and backward on the affected side because of a failure of development of the mandible. When an attempt is made to open the mouth, the chin deviates toward, the ankylosed side, if any motion is present. Bilateral ankylosis occurring in childhood results in underdevelopment of the lower face; a receding chin and micrognathia (Fig. 17-39). The maxillary incisors often manifest overjet due to failure of this mandibular growth.

Radiographic Features. In fibrous ankylosis, the joint space is often limited. The articulating surfaces of the condyle and the fossa may be irregular. Irregular surfaces appear to interdigitate in a locking fashion. In bony ankylosis, a bony bridge exists from condylar head to the articular fossa.

Treatment. Treatment of TMJ bony ankylosis is surgical. Early surgical intervention in childhood can reduce the adverse effect on facial development. Different surgical procedures, including condylectomy, gap arthroplasty, interpositional arthroplasty, joint reconstruction have been attempted. Sometimes re-ankylosis can occur following arthroplasty. Fibrous ankylosis may be treated by functional methods.

Figure 17-39. Ankylosis of the temporomandibular joint.
The receding chin is characteristic in these cases.

Injuries of Articular Disk: Internal Derangement

Internal derangement of the TMJ is defined as an abnormality of the internal components of the joint, where the articular disk is displaced from its normal functional relationship with the condylar head and the articular fossa of the temporal bone (Fig. 17-40). According to Barkin and Winberg, internal derangement is considered to have four clinical stages. In stage I, the articular disk is displaced in closed mouth position and reduces to normal contact (the central part of the disk is in contact with the condylar head and articular eminence) in open mouth position. In stage II, the disk is displaced in closed mouth position, and intermittently locks in open mouth position. In stage III, the disk is displaced in closed mouth position, and does not reduce to normal contact in open mouth position (closed lock). In stage IV, the disk is displaced without reduction and with perforation of the disk or posterior attachment tissues.

Etiology. The etiology of internal derangement is not known. The possible causes of internal derangement may be injury to the condylar region, variation of normal function, muscle hyperactivity or excessive opening of the mouth. The trauma causing disk displacement may be a single event

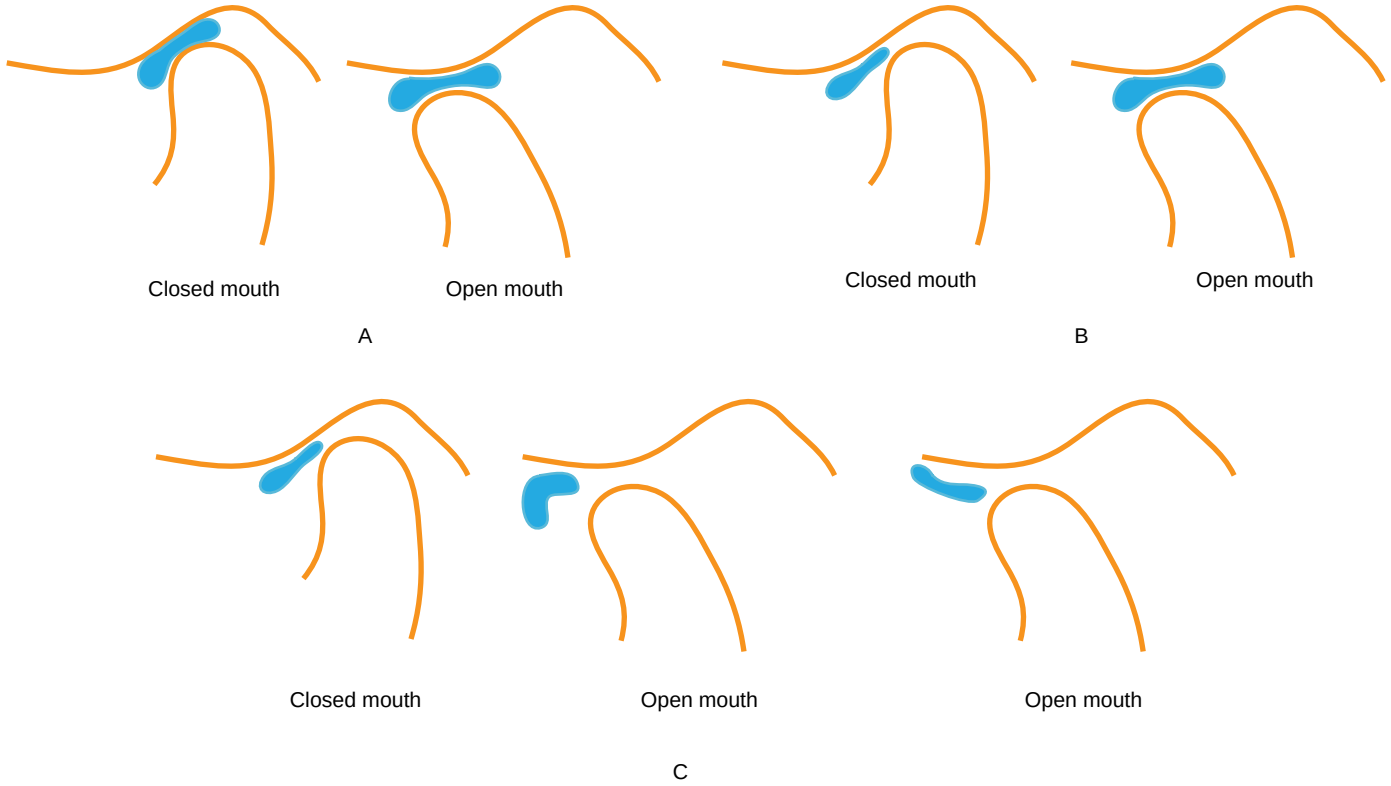


Figure 17-40. Diagrammatic representation of the relationship between bone and articular disk of the temporomandibular joint.
(A) Normal disk location in closed and open mouth position. In the closed mouth position, the posterior band of the articular disk is located between 11:30 and 12:30 of a clock face. The central narrow zone of the disk is in contact with the condylar surface as well as the articular fossa. In the open mouth position, the central narrow zone of the disk remains in contact with the condylar head and the articular eminence. **(B)** Disk displacement with reduction (DDWR). In the closed mouth position, the posterior band of the articular disk is displaced anterior to 11:30. The central narrow zone of the disk is not in contact with the condyle or the articular fossa. In the open mouth position, the central narrow zone of the disk is in contact with the condylar head and articular eminence. **(C)** Disk displacement without reduction (DDWOR). In the closed mouth position, the posterior band of the articular disk is displaced anterior to 11:30. The central narrow zone of the disk is not in contact with the condyle or the articular fossa. In the open mouth position, the disk is anteriorly displaced, and may assume normal biconcave shape or become deformed.

(macrotrauma) or multiple excessive forces over a period of time (microtrauma), such as bruxism.

Clinical Features. Internal derangements are far more common in females than in males, the ratio being as high as 8:1. Young adults are more frequently affected than children or persons past 40 years of age.

Patients with internal derangement can be asymptomatic. Patients who have disk displacement with reduction may have normal range of jaw movement. Some patients who have disk displacement with reduction may have limitation of movement, primarily due to pain. Clinical examination may reveal clicking or joint sound during opening and closing of the mouth. Patients who have disk displacement without reduction have limited range of mouth opening. In these patients, during opening, the mouth may deviate towards the involved joint. The patient may have pain during closed mouth position as the condyle rests on the retrodiskal tissues.

Magnetic resonance imaging of the TMJ in both closed and open positions is necessary for study of the condition (Fig. 17-41). Other radiographic examinations, such as panoramic radiography or computed tomography, are not useful in determining the location of the disk. In some patients with history of trauma, fluid effusion may be present. Effusion can be identified with T_2-weighted MR images, where effusion has high signal intensity.

Treatment. The treatment of disk displacement can be surgical or nonsurgical. Current understanding of the function of TMJs and the roles of articular disks suggest that it may not be necessary to re-establish the position of the disk. An anterior positioning appliance may be helpful in patients who have disk displacement with reduction. The treatment for each case depends upon careful individual evaluation, and no definite guidelines have been established.

Condylar Fracture

About 17–52% mandibular fractures involve condylar fracture. Zachariades et al have provided a thorough review of condylar fractures. Condylar fractures may be classified according to the anatomic location, e.g. the condylar head (intracapsular), the condylar neck (extracapsular) and the subcondylar region. Condylar fractures may also be classified as non-displaced, deviated, displaced (medial or lateral), and dislocated (Fig. 17-42). Another classification is according to the

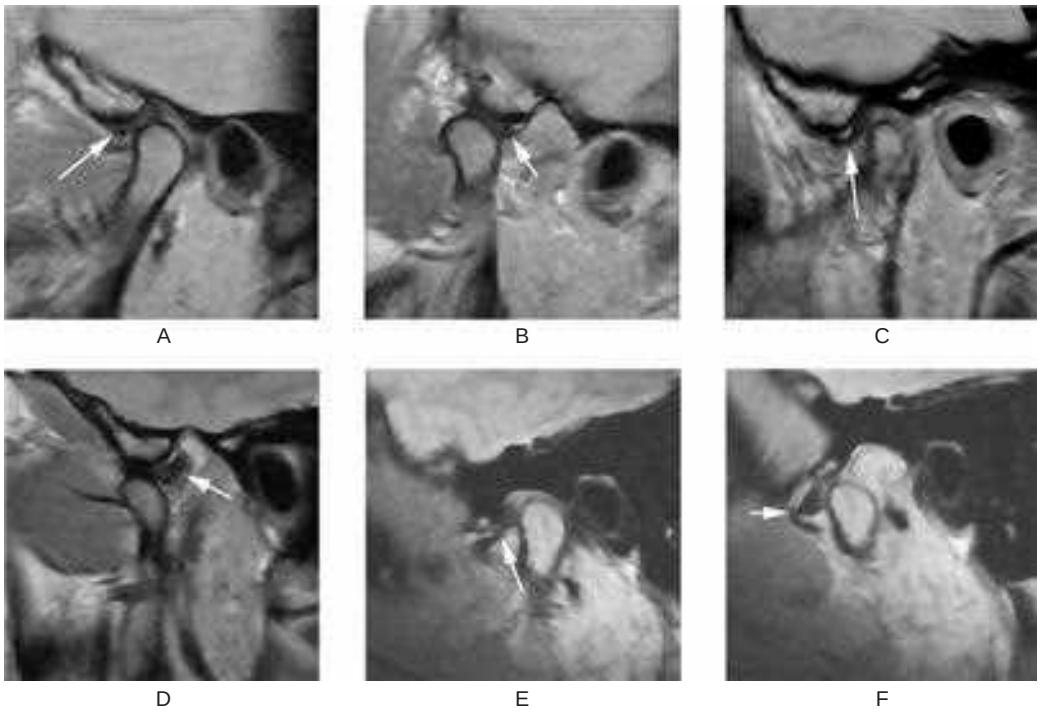


Figure 17-41. Magnetic resonance imaging of the temporomandibular joints.
(A, B) From the same patient, in closed (A) and open (B) mouth position. (A and B) show Normal disk relationship with the condylar head and articular fossa/eminence. **(C, D)** From the same patient, in closed (C) and open (D) mouth position. (C, D) show disc displacement with reduction (DDWR). **(E, F)** From the same patient, in closed (E) and open (F) mouth position. (E and F) show disc displacement without reduction. (DDWOR) The arrows point to the articular discs.

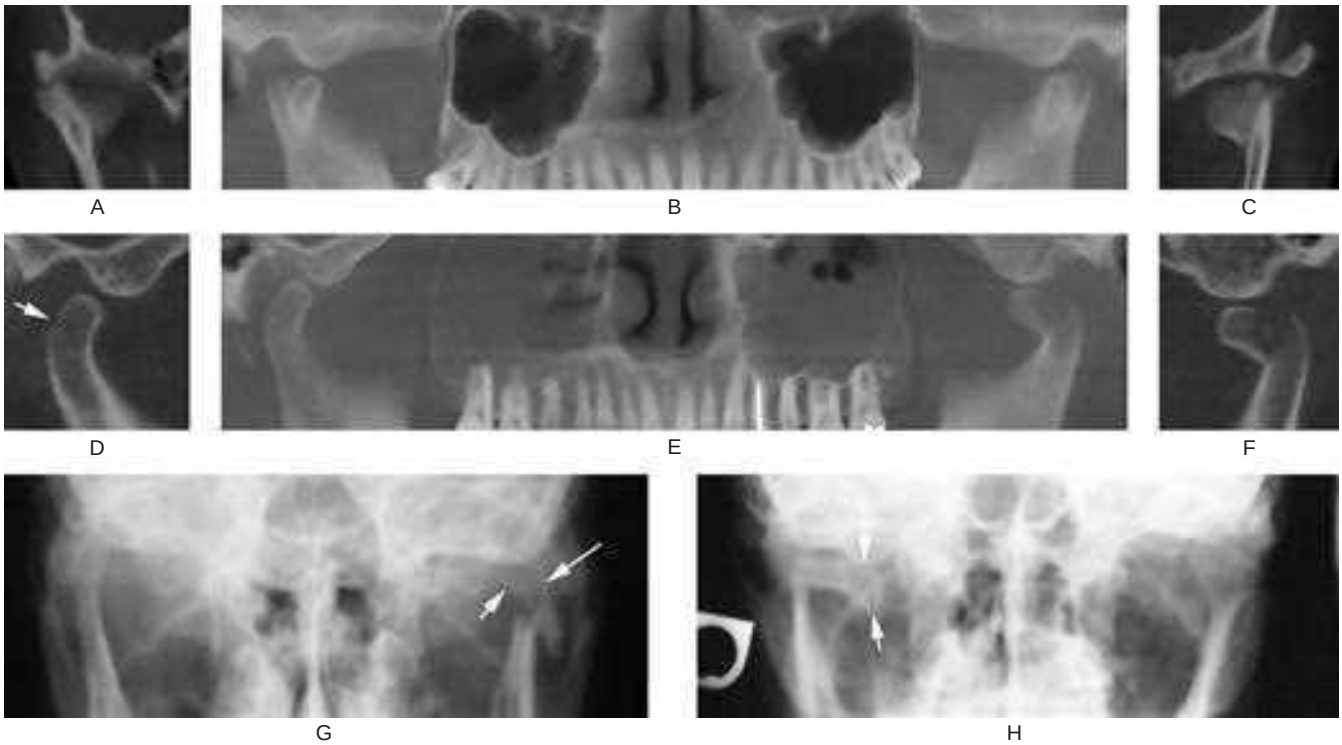


Figure 17-42. Fracture of the condylar temporomandibular joints.
(A, B, and C) From the same patient's cone beam computed tomography scan. Both the condylar heads are vertically fractured. The reconstructed panoramic view (B) shows the fractured fragments of the condylar heads are dislocated anteriorly. **(D, E, and F)** From the same patient's cone beam computed tomography scan. D, Shows a hairline fracture (arrow) of the right condylar head. Figure E shows fractured and anteriorly displaced left condylar head. Both the maxillary sinuses are cloudy. F, shows fractured left condyle, and that fracture fragment is displaced to the peak of the articular eminence. **(G)** Fracture of the left side at the condylar neck region. Open mouth Towne's radiograph shows the fractured fragment (arrows) is medially inclined. **(H)** Fracture of the right side at the condylar neck region. Open mouth Towne's radiograph shows the fractured fragment (arrows) is displaced medially and is horizontally oriented.

orientation of the fracture line, e.g. horizontal, vertical or compression type. Condylar fracture results from an acute traumatic injury to the jaw and is accompanied by limitation of motion and pain and swelling over the involved condyle. The fractured condyle fragment is frequently displaced anteriorly and medially into the infratemporal region because of the forward pull of the external pterygoid muscle, and reduction of the fracture is often difficult because of this displacement. In unilateral fracture of the condyle, the body of the contralateral mandible is also likely to fracture. In fatal automobile accidents, a fracture condyle may be dislocated into the cranium. Open reduction of the fracture fragments is indicated in case of limited range of motion or loss of function. Surgical reduction of the fracture fragments may not be necessary if the patient has adequate function.

INFLAMMATORY DISTURBANCES OF TEMPOROMANDIBULAR JOINT

Arthritis or inflammation of the joints is one of the most prevalent chronic diseases. Temporomandibular joint may suffer from any form of arthritis. Following three are the most common types of arthritis of TMJ:

- Osteoarthritis, or degenerative joint disease
- Rheumatoid arthritis
- Septic arthritis.

Osteoarthritis (Degenerative Joint Disease)

Osteoarthritis is the most common type of arthritis and has been said to develop, at least to some degree, in all persons past 40 years of age. Although its etiology is unknown, it is a disease associated with the aging process. The joints first involved are those which bear the weight of the body and are thus subjected to continued stress and strain: the joints of the knees, hips and spine. In case of TMJ, degenerative joint disease is assumed to initiate after disk is displaced and bony contact exists between the condyle and articular fossa (Fig. 17-43).

Clinical Features. Clinical signs and symptoms of osteoarthritis are often remarkably absent even in the face of severe histologic or radiographic joint changes. Since the TMJ is not a weight-bearing joint, changes here are insignificant even though arthropathy may be present in other joints. Those changes that do occur may be a result of disturbed balance of the joint due to loss of all teeth or due to external injury. Patients with osteoarthritis of other joints may complain of clicking and snapping in the TMJ, but pain is not necessarily a feature. This joint noise is probably due to atypical disk motion resulting from discordant mandibular condyle-disk function on the basis of the changes in the articular cartilage. Limitation of motion or ankylosis rarely occurs.

Histologic Features. The changes in the articular cartilage consist of surface erosions of varying degrees of severity, with the presence of vertical cracks extending often from the surface through the cartilaginous plate into the subchondral bone. The cartilage cells often exhibit degeneration, and there may be complete destruction of cartilage in localized areas.

Radiographic Features. Degenerative joint disease is diagnosed radiographically. CBCT and CT are the reliable examinations to diagnose degenerative changes (Fig. 17-44). MRI and panoramic radiographs have limited value in diagnosing early degenerative changes. Ahmad et al, have described the diagnostic criteria for degenerative joint disease. Radiographically, a joint is considered osteoarthritic if it fulfils any of the

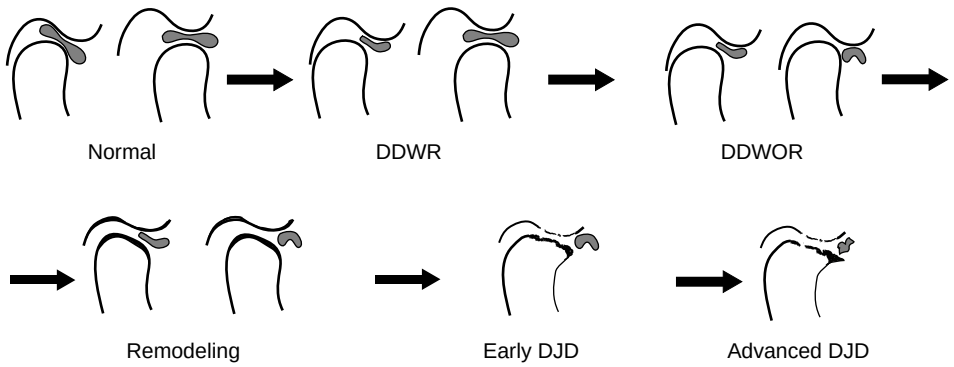


Figure 17-43. Diagrammatic representation of the progression from normal condyle to degenerative joint disease.
In normal stage, the condylar head and the articular fossa/eminence are smooth and well-defined. The posterior band of the articular disk and the central narrow zone are in normal positions. In stage II, the disc is anteriorly displaced in closed mouth position, but reduces during opening (disc displacement with reduction=DDWR). In stage III, in the open mouth position, the displaced disc does not reduce (disc displacement without reduction = DDWOR). In stage IV, the condylar head and the articular fossa/eminence are slightly flattened and sclerosed, indicating remodeling of the joint. In stage V, the margins of the condylar head and articular fossa are irregular and slightly eroded, indicating early degenerative joint disease. In stage VI, condylar and fossa margins are eroded. A prominent osteophyte is present at the anterior margin of the condylar head. These signs indicate advanced degenerative joint disease. The disc is deformed in advance degenerative disease.

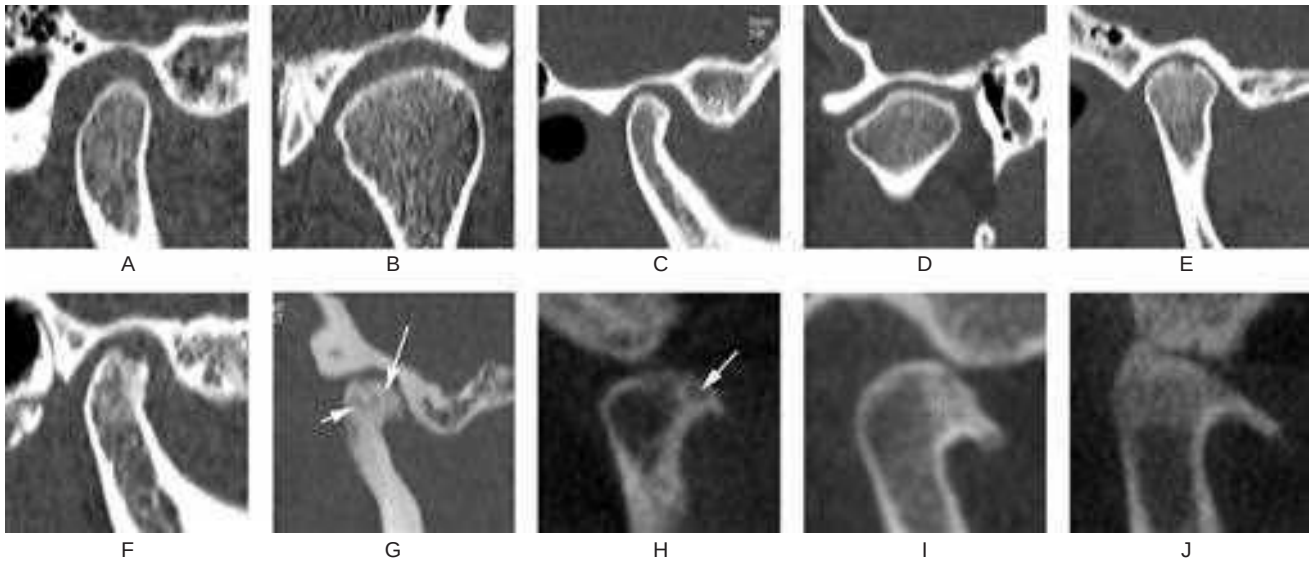


Figure 17-44. Computed tomographic findings of normal and osteoarthritic temporomandibular joints.
(A) Sagittal view of a normal temporomandibular joint, which has smooth, rounded and well-defined cortical margin of the condyle and the fossa. **(B)** Axially corrected coronal view of a normal temporomandibular joint which has smooth, rounded and well-defined cortical margins. **(C)** Sagittal view of a temporomandibular joint that shows signs of remodeling. Anterior slope of the condylar head is flat. **(D)** An axially corrected coronal view showing remodeling of the condylar head. The lateral slope of the condylar head is flat. **(E–J)** Images of joints with degenerative joint disease. **(E, F)** Sagittal views showing erosion of the condylar heads. The continuity of the cortical margin is lost. **(G)** A condyle with generalized sclerosis, osteophyte at the anterior margin, and several subcortical pseudocysts (arrows). **(H–J)** From cone beam computed tomography. **(H)** An osteophyte at the anterior margin of the condylar head and a subcortical pseudocyst (arrow). **(I)** A prominent osteophyte, which often appears as a bird's beak. **(J)** A prominent anterior osteophyte, sclerosis of the superior part of the condylar head, and flattening of the articular eminence.

following criteria: (i) the condyle has osteophytes, (ii) condyles or fossa/eminence has subcortical erosion or (iii) condyles or fossa/eminence has subcortical pseudocysts. An osteophyte is defined as a marginal hypertrophy with sclerotic borders and exophytic angular formation of osseous tissue arising from the surface of the condyle. Subcortical erosion is defined as loss of continuity of articular cortex. A subcortical pseudocyst is defined as a cavity below the articular surface that deviates from normal marrow pattern.

Treatment. For TMJ osteoarthritis, the treatment is limited to reducing joint stress, anti-inflammatory drugs to control secondary inflammation, and improving joint mobility. Surgery is reserved for extreme cases.

Rheumatoid Arthritis

Rheumatoid arthritis is a disease of unknown etiology which commonly begins in early adult life (35–50 years) and affects women more frequently than men, in a ratio of at least 3:1. It is a chronic, systemic, autoimmune inflammatory disorder. This is an aggressive condition that can damage a joint within 2 years. Although this disease is apparently not due to a specific bacterial infection, there is evidence to indicate that it may be a hypersensitivity reaction to bacterial toxins, specifically streptococci. The distribution of joint involvement is nearly always polyarticular and frequently symmetrically bilateral. Patients usually manifest a long series of episodic exacerbations and remissions. TMJ involvement in cases of rheumatoid arthritis is not particularly common despite the fact that this is a polyarticular disease. Treister and Glick have provided a thorough review of rheumatoid arthritis of the TMJ and dental care plan.

Clinical Features. Rheumatoid arthritis, in its early stages, may be manifested by slight fever, loss of weight and fatigability. The joints affected are swollen, and the patient complains of pain and stiffness. Involvement of the TMJ may occur concomitantly with the other joint lesions or may arise at any subsequent time. Radiographically, joints may be irregular (Fig. 17-45). Articular surfaces become flat. Subcortical pseudocysts and osteophytes may be present.

Movement of the jaw, as during mastication or talking, causes pain and may be limited because of the stiffness. The stiffness is commonly at its height in the morning and tends to diminish throughout the day with continued use of the jaw. Clicking and snapping of the joint are not common, but when they occur are due to alterations in the articular cartilage and meniscus. Over a period of years there may be ankylosis of the joint, but this is not inevitable.

Juvenile idiopathic arthritis (JIA) or juvenile rheumatoid arthritis or Still's disease is a common rheumatic disease in children. TMJ involvement in JIA patients may be as high as 87%. Some studies indicate that TMJ can be the only joint involved with JIA. The patient may be asymptomatic, without any clinical signs and symptoms. The first clinical signs may be asymmetry of the mandible and class II malocclusion. When this diagnosis is made, irreversible condylar resorption has

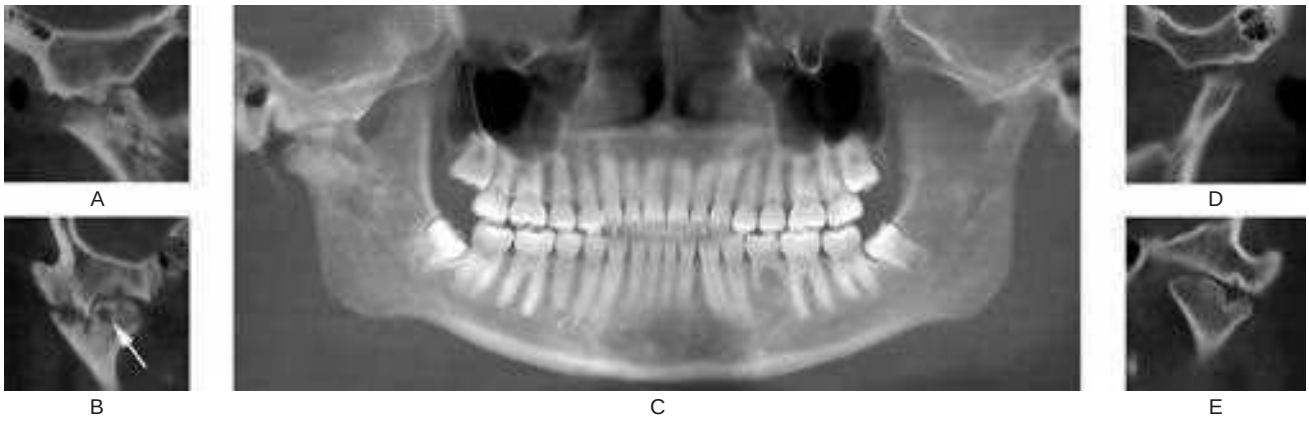


Figure 17-45. Cone beam computed tomography of a patient with bilateral involvement with rheumatoid arthritis.
(A) Sagittal view of the right joint. Superior margin of the condylar head is irregular. **(B)** An axially corrected coronal view of the right joint, which shows inter-digitation of bony projections that lead to ankylosis of the joint. A subcortical pseudocyst (arrow) is present in the condylar head. **(C)** A reconstructed panoramic radiograph from the cone beam scan. The dentition appears within normal limits, with the exception of congenitally missing mandibular left second premolar. **(D, E)** Sagittal and coronal sections of the left joint. Superior margin of the left condylar head is irregularly flat and has prominent notching. The articular fossa is also flat.

already taken place. Radiographic findings include low density of the condylar head, erosion of the surface of the condyle, eminence and fossa. In severe cases, the resorbed condylar head may assume the shape of a pencil.

Histologic Features. There has been little opportunity for microscopic examination of the TMJ in cases of rheumatoid arthritis, and findings have been reported in but few cases. There is; however, no reason to expect the histologic features to be significantly different from those in other joints. Elsewhere, the disease is characterized by the ingrowth of granulation tissue to cover the articular surfaces, the invasion of cartilage and its replacement by granulation tissue, and the ultimate destruction of the articular cartilage. Eventually fibrous adhesions occur; the articular disk may become eroded, and fibrous ankylosis results. Occasionally the connective tissue becomes ossified and a true bony ankylosis occurs.

Treatment and Prognosis. There is no specific treatment for rheumatoid arthritis, although remarkable benefit may result from the administration of adrenocorticotropic hormone (ACTH) or cortisone. Once limitation of motion and deformity have occurred, surgical intervention in the form of condylectomy may be necessary to regain movement. There is; however, a great tendency for recurrence of the ankylosis. For patients with JIA, the management includes orthodontic treatment and functional appliances. Nonsteroidal antiinflammatory drug (NSAID) therapy has shown mixed benefit. Intra-articular corticosteroid injection has shown promising results in JIA patients. Arabshahi and Cron have reported benefits of different treatment modalities for JIA.

Septic (Infectious) Arthritis

The incidence of arthritis due to a specific infection is low when compared to the occurrence of degenerative joint disease and rheumatoid arthritis. Until recently, about 40 cases have been reported in English literature. Leighty et al, have reviewed the existing literature, which showed that most common organism is *Staphylococcus aureus*. The spread of infection is either directly from a penetrating wound or from hematogeneous origin. Cai et al, have recently reported another 40 cases that were treated in a hospital in China. In this study, majority of the patients had hematogeneous source of infection.

Clinical Features. Patients suffering from acute infectious arthritis complain chiefly of sudden severe pain in the joint, with extreme tenderness on palpation or manipulation over the joint area. The pain is of such intensity that motion is severely limited. Healing of this form of arthritis often results in ankylosis, either osseous or fibrous. A fibrous ankylosis is more common, but in either event there is severe limitation of motion. Diagnosis of the condition is usually achieved by clinical examination, radiographic evaluation and aspiration of the fluid in the joint area.

Histologic Features. Depending upon the severity of involvement, there is a variable amount of destruction of the articular cartilage and articular disk. Osteomyelitis with destruction of bone of the condyle may develop. The joint spaces become narrower in the healing phase by the development of granulation tissue and its subsequent transformation into dense scar tissue.

Treatment. For septic arthritis, treatment of choice is antibiotics and arthrocentesis under low pressure. If treatment is instituted in the acute phase, the sequelae will be less deforming or disabling than if the disease has been allowed to enter a chronic phase. After infection subsides, physiotherapy may help in improving mobility of the joint.

NEOPLASTIC DISTURBANCES OF TEMPOROMANDIBULAR JOINT

Neoplasms and tumor like growths, benign and malignant, may involve the TMJ, but such involvement is relatively uncommon. Such tumors may originate from the condyle, either the bone or the articular cartilage, or from the joint capsule. As might be expected, the connective tissue, cartilage, and bone give rise to the majority of these tumors. Occasionally metastatic tumors have also been reported to involve the TMJ. The rarity of these lesions precludes their discussion here, particularly since they exhibit no features significantly different from those of similar tumors occurring in other locations in and about the oral cavity which have already been described.

LOOSE JOINT BODIES

Synovial Chondromatosis

Synovial chondromatosis is a rare benign condition where nodular cartilaginous or osteocartilaginous entities proliferate in the joint synovium (Fig. 17-46). These entities may become loose from the synovium, and continue to grow in size.

Clinical Features. Mean age of patients with synovial chondromatosis is about 45 years. It is more common in females. Bilateral synovial chondromatosis is rare. Patients may be asymptomatic. However, Guarda-Nardini et al, have reported three cardinal signs and symptoms of synovial chondromatosis. These include: (i) pain in the preauricular area, (ii) swelling, facial asymmetry, and joint deformity, and (iii) limited joint function. Additional signs and symptoms include occlusal changes, headache, and joint sound. CT and MRI are useful imaging examinations for diagnosis and treatment planning.

Treatment. Surgery is the treatment of choice. Arthroscopy and open surgery are used to remove the loose joint bodies and resection of the diseased synovial tissues. After surgical removal, recurrence is low.

TEMPOROMANDIBULAR DISORDERS

TMJ Syndrome

Temporomandibular joint (TMJ) syndrome or temporomandibular disorder (TMD) is the most common cause of facial pain after toothache. No unequivocal definition of the disease exists; discrepancies concerning the terminology, definitions, and practical treatment methodologies exist. TMD can be classified broadly as TMD secondary to myofacial pain and dysfunction (MPD), and TMD secondary to true articular disease.

The two types can be present at the same time, making diagnosis and treatment more challenging. The MPD type forms the majority of the cases of TMD and is associated with pain without apparent destructive changes of the TMJ on radiograph. It is frequently associated with bruxism and daytime jaw clenching in a stressed and anxious person. True intra-articular disease can be grouped under disk displacement disorder, chronic recurrent dislocations, degenerative joint disorders, systemic arthritic conditions, ankylosis, infections, and neoplasia.

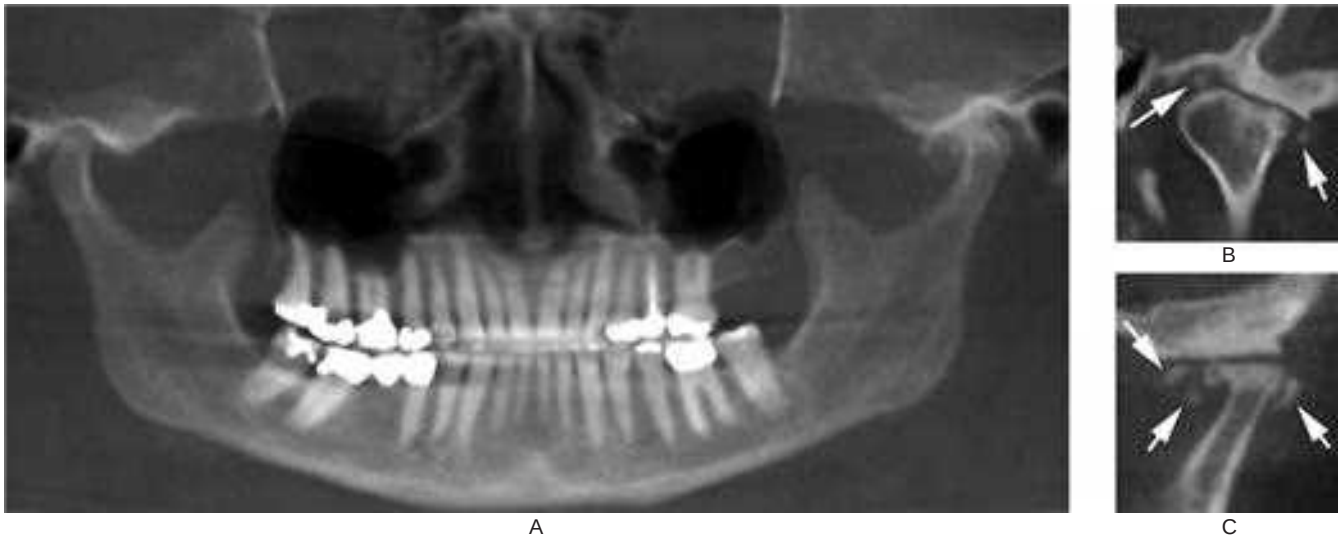


Figure 17-46. Synovial chondromatosis of the left temporomandibular joint as shown in a cone beam computed tomography.
(A) Normal right temporomandibular joint, and synovial chondromatosis associated with the left temporomandibular joint. **(B)** An axially corrected coronal view of the left temporomandibular joint. Loose joint bodies (arrows) are present at the superior and lateral margins of the condylar head. The condylar head is flattened and has subcortical sclerosis. **(C)** Sagittal view of the left temporomandibular joint. The condylar head and articular fossa are flat and sclerosed. Loose joint bodies (arrows) are present at the anterior and posterior margins of the condylar head.

Etiology. The etiology of MPD is multifactorial and includes malocclusion, jaw clenching, bruxism, personality disorders, increased pain sensitivity, and stress and anxiety. The principal factors responsible for the clinical manifestations in MPD (i.e. pain, tenderness, and spasm of the masticatory muscles) are muscular hyperactivity and dysfunction due to malocclusion of variable degree and duration. The significance of psychological factors has been recognized during the past few years. Of the causes of TMD of articular origin, disk displacement is the most common. Other diseases such as degenerative joint disorders, rheumatoid arthritis, ankylosis, dislocation, infection, neoplasia, and congenital anomalies may contribute to pain. In TMD of articular origin, the spasm of the masticatory muscles is secondary in nature. One study found that in patients with chronic inflammatory connective tissue disease, the pain on mandibular movement and tenderness to palpation of TMJ is related to the level of tumor necrosis factor alpha (TNF-α) in the synovial fluid.

Clinical Features. TMD primarily affects young women aged 20–40 years. The male-to-female ratio is 1:4. A comprehensive, chronological history and physical examination of the patient, including dental history and examination, is essential to diagnose the specific condition to decide further investigations, if any, and to provide specific treatment. There are four cardinal signs and symptoms of the syndrome: (1) pain, (ii) muscle tenderness, (iii) a clicking or popping noise in the TMJ, and (iv) limitation of jaw motion, unilaterally or bilaterally in approximately an equal ratio, sometimes with deviation on opening. The pain is usually periauricular, associated with chewing, and may radiate to the head but is not like the common headache. It may be unilateral or bilateral in MPD, and usually is unilateral in TMD of articular origin, except in rheumatoid arthritis. In MPD, the pain may be associated with history of bruxism, jaw clenching, stress, and anxiety; the pain may be more severe during periods of increased stress. Clicking, popping, and snapping sounds usually are associated with pain in TMD. An isolated click is very common in the general population and is not a risk factor for development of TMD. Limited jaw opening due to pain or disk displacement may be seen. TMD may act as a trigger in patients prone to headaches, and when present in association with TMD, they tend to be severe in nature. Other symptoms associated with TMD are otalgia, neck pain and/or stiffness, shoulder pain, and dizziness. About one third of these patients have a history of psychiatric problems. History of facial trauma, systemic arthritic disease, and recurrent dislocation also should be elicited. Differential diagnoses include cluster headache, migraine headache, post herpetic neuralgia, temporal/giant cell arteritis, trigeminal neuralgia and middle ear infections.

Laboratory Findings. Blood examination is required if systemic illness is suspected to be the cause of TMD. A complete blood count is done if infection is suspected. Rheumatoid factor (RF), ESR, antinuclear antibody (ANA), and other specific antibodies are checked if rheumatoid arthritis, temporal arteritis, or a connective tissue disorder is suspected. Uric acid should be checked for gout.

Radiographic Features. Radiographic findings in TMJ correlate to the etiology of TMD; in cases of rheumatoid arthritis and seronegative spondyloarthropathies, conventional radiographs show erosions, osteophytes, subchondral bony sclerosis, and condylar-glenoid fossa remodeling. A variety of new imaging techniques are being used and perfected to study TMJ. CT scan can explore both bony structures and muscular soft tissues. It is relatively less expensive and can be done with contrasting material injected into the joint cavity. MRI, though costly, should be used as the study of choice if an articular or meniscal pathology is suspected and an endoscopic or surgical procedure is contemplated in a case of traumatic TMD. Diagnostic arthroscopy is an invasive diagnostic approach. It should be used mainly in patients suffering from internal TMJ derangements resistant to conservative treatments. A good MRI study should be obtained before contemplating arthroscopy.

Treatment and Prognosis. Most TMDs are self-limiting. Conservative treatment involving self-care practices, rehabilitation aimed at eliminating muscle spasms, and restoring correct coordination, is all that is required. NSAIDs should be used on a short-term, regular basis. On the other hand, treatment of chronic TMD can be difficult and the condition is best managed by a team approach, consisting of a primary care physician, a dentist, a physiotherapist, a psychologist, a pharmacologist, and in small number of cases, a surgeon. The different modalities include patient education and self-care practices, medication, physical therapy, splints, psychological counseling, relaxation techniques, biofeedback, hypnotherapy, acupuncture, and arthrocentesis. Most cases of TMD respond to simple treatment and the prognosis is good. Symptoms usually remit with simple care. In cases of secondary involvement of TMJ, the prognosis depends on the primary disease.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a disease that primarily affects bone but occasionally may also affect other organ systems and present in a multisystemic pattern. Despite advances in understanding the clinical picture, disease course and molecular profiling, the pathogenesis of LCH is still enigmatic. The use of different terminology to describe this condition adds to this puzzle and the search for its etiology. In the past the terms that have been used to define LCH and associated conditions include histiocytosis X, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, type II histiocytosis and non-lipid reticuloendotheliosis. The term LCH is generally preferred to the older term, histiocytosis X. This new name emphasizes the histogenesis of the condition by specifying the type of lesional cell and removes the connotation of the unknown (X) because its cellular basis has now been clarified. Unique features of Langerhans cells revealed by cytoplasmic

immunostaining with S100 antigen distinguishes them from other histiocytes. The presence of HX bodies or **Birbeck granules** (rod-shaped with characteristic periodicity and some times a dilated terminal end called **tennis racket** appearance, intracellular in location, identified by electron microscopy) and the presence of CD1a antigen on the cell surface and HLA-DR positivity confirms the Langerhans cell origin of this disease.

The annual incidence of LCH is reported at 5.4 million children per year (Bhatia S et al, 1997). Males are affected to slightly greater degree than females. It is predominantly a disease of childhood, with more than 50% of cases diagnosed between the ages of one and 15 years: there is a peak in the incidence between the ages of one and four. Although diagnosis is often made in childhood, many cases progress eventually into adult life.

The term histiocytosis is a collective designation for a variety of proliferative disorders of histiocytes or macro-phages. Some such as the rare histiocytic lymphomas are clearly malignant, whereas others such as reactive histiocytic proliferation in the lymph nodes are clearly benign. Between these two extremes lies the condition called Langerhans cell histiocytosis. It is a group of idiopathic disorders characterized by the clonal proliferation of specialized bone marrow-derived, antigen presenting dendritic cells called Langerhans cells (LCs) and mature eosinophils. The clinical spectrum includes on one end, an acute fulminant, disseminated disease called **Letterer-Siwe disease,** and on the other end, solitary or few, indolent and chronic lesions of bone or other organs called **eosinophilic granuloma**. The intermediate clinical form is called **Hand-Schüller-Christian disease**.

Pathogenesis. The pathogenesis of LCH has remained a mystery despite intensive search in this direction. Current theories suggest a role for environmental, infectious, immunologic and genetic causes; others believe that LCH is a neoplastic process. Flowcytometric sorting coupled with polymerase chain reaction (PCR) confirmed that the CD1a + Langerhans cells in LCH lesions are clonal. However, a clonal proliferation does not necessarily mean that LCH is a neoplastic process. The favorable natural history in most cases, the high probability of survival for patients older than two years of age, and the failure to detect aneuploidy or consistent karyotypic abnormalities support the idea that LCH is not a neoplastic process or malignancy. However, the proliferation of LCs may be a physiological rather than a pathologic response.

Langerhans cell histiocytosis may represent a reaction to a virus, but there is no convincing evidence at this point. A comprehensive analysis of nine different viruses by *in situ* hybridization and PCR failed to prove an association among 56 specimens obtained from osseous lesions and lymph nodes (McClain K et al, 1994). A role for HHV-6 has been suggested by other studies. One report detected HHV-6 in 14 of 30 (47%) pediatric cases of LCH using PCR on archival tissues (Leahy, MA et al, 1993). The abnormal immunological response noted in this disease state may be secondary to a viral infection of LCs and the lymphocytes. This also suggests that cells other than the pathologic LCs may play a key role in the pathogenesis of LCH. In fact there are other indirect evidences supporting a viral etiology. Aberrant or uncontrolled cytokine production is known to play a role in reactive histiocytic disorders. Likewise, LCH patients may abnormally produce at least 10 different cytokines (Egeler RM et al, 1999). Most of these are of T-cell origin and may explain the recruitment of LCs, other inflammatory cells, over expression of adhesion molecules, fibrosis, bone resorbtion, and necrosis. The presence of different kinds of chromosomal alterations as well as a high variability in the number of chromosomal breaks noted in this disease is consistent with a hypothesis of a viral etiology for LCH.

Treatment. Many cases demonstrate a favorable natural history without treatment. The major difficulty in treatment decision rests with reconciling the status of the disease as either reactive or neoplastic proliferation of LCs. Because of this there have been major discrepancies in the search to find appropriate treatment for patients.

Hand-Schüller-Christian Disease
(Multifocal eosinophilic granuloma)

Hand-Schüller-Christian disease is characterized by widespread skeletal and extraskeletal lesions and a chronic clinical course. It occurs primarily in early life, usually before the age of five, but it has been reported in adolescents and even in young adults. It is more common in boys than in girls, with a gender ratio of approximately two to one.

Hand-Schüller-Christian disease has certain features in common with Letterer-Siwe disease and eosinophilic granuloma, and some features which serve to distinguish it from the others. In all three diseases, the proliferative cell is the histiocyte. In Hand-Schüller-Christian disease both the skeletal system and soft tissues may be involved, while in eosinophilic granuloma, only the bone is affected, although soft-tissue extension is often observed. Letterer-Siwe disease is an acute, fulminating disease with widespread lesions of both skeletal and extraskeletal tissues, including the skin.

Clinical Features. Hand-Schüller-Christian disease is characterized by the classic triad of single or multiple areas of 'punched-out' bone destruction in the skull, unilateral or bilateral exophthalmos, and diabetes insipidus with or without other manifestations of dyspituitarism such as polyuria, dwarfism, or infantilism. The complete triad occurs in only about 25% of affected patients. Involvement of the facial bones, which is frequently associated with soft-tissue swelling and tenderness, causes facial asymmetry. Otitis media is also common. Other bones are frequently involved, particularly the femur, ribs, vertebrae, pelvis, humerus, and scapula. Any of the visceral organs also may be involved, and the skin sometimes exhibits papular or nodular lesions, as discussed by Winkelmann.

Oral Manifestations. Oral manifestations may be one of the earliest signs of the presence of the disease. In reported series, the frequency of oral involvement varies widely, ranging from 5% to over 75% of patients.

These oral manifestations are often nonspecific and include sore mouths, with or without ulcerative lesions; halitosis,

gingivitis and suppuration; and unpleasant taste; loose and sore teeth with precocious exfoliation of teeth; and failure of healing of tooth sockets following extraction (Fig. 17-43). Loss of supporting alveolar bone mimicking advanced periodontal disease is characteristic, and this finding in a child should always be viewed with suspicion. The oral findings have been discussed by Sedano and his associates and by Jones and his coworkers.

Radiographic Features. The individual lesions, particularly in the skull, are usually sharply outlined, although the lesions in the jaws may be more diffuse. The lesions in the jaws are usually manifested simply as destruction of alveolar bone with tooth displacement (Fig. 17-43).

Histologic Features. Hand-Schüller-Christian disease is usually considered as manifesting in four stages during the progression of the characteristic lesion. These are:

- A proliferative histiocytic phase with accumulation of collections of eosinophilic leukocytes scattered throughout the sheets of histiocytes.
- A vascular-granulomatous phase with persistence of histiocytes and eosinophils, sometimes with aggregation of lipid-laden (cholesterol) macrophages.
- A diffuse xanthomatous phase with abundance of these 'foam cells'.
- A fibrous or healing phase (Fig. 17-47).

Laboratory Features. Anemia and, less frequently, leukopenia, and thrombocytopenia are occasionally found. The serum cholesterol level is nearly always normal, although the tissue cholesterol content may be elevated remarkably.

Treatment and Prognosis. The prognosis in Hand-Schüller-Christian disease is good. Approximately half of the patients undergo spontaneous remission over a period of years. The treatment of choice is curettage or excision of lesions. Inaccessible lesions may be irradiated. Some patients benefit from chemotherapeutic drugs, including prednisone, vinblastine, and cyclophosphamide. One of the most significant factors influencing the morbidity and mortality of the disease is the extent of the disease at the time of initial diagnosis and number of organ systems involved.

Eosinophilic Granuloma

(Unifocal eosinophilic granuloma)

The term 'eosinophilic granuloma of bone' was introduced by Lichtenstein and Jaffe in 1940, although the lesion to which it referred had been described by others before them. The term is used to describe a lesion of bone which is primarily a histiocytic proliferation, with an abundance of eosinophilic leukocytes but no intracellular lipid accumulation. This disease occurs primarily in older children and young adults, and the proportion of males to females is about two to one.

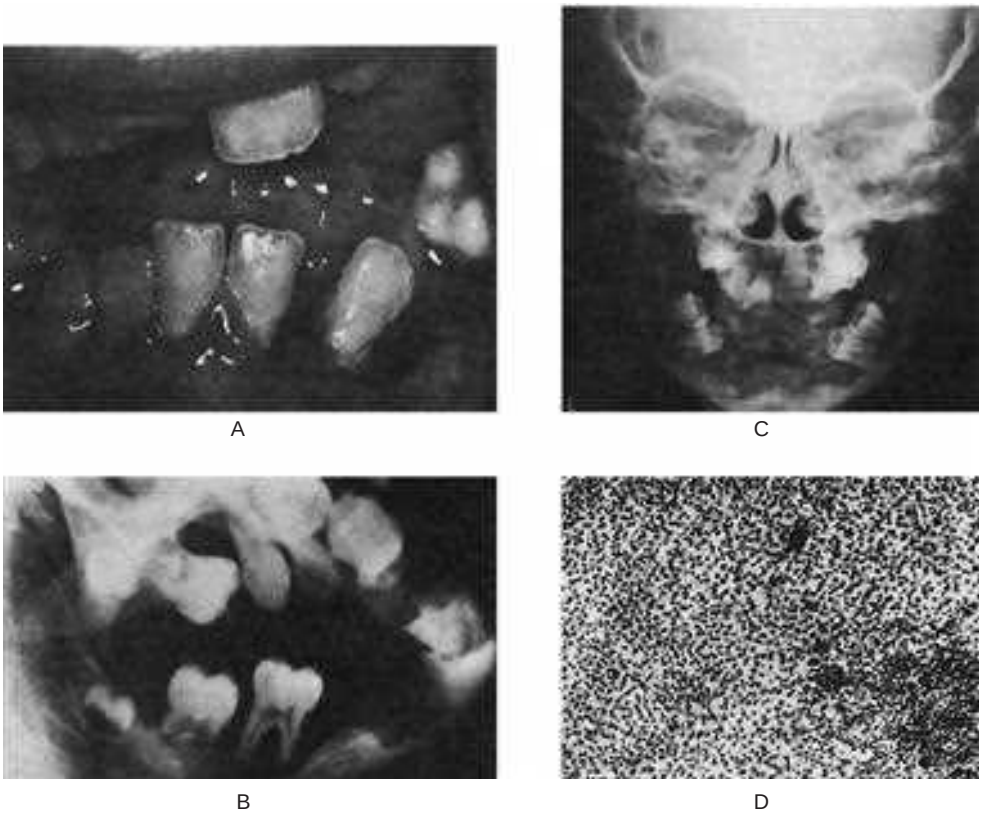


Figure 17-47. Hand-Schüller-Christian disease.
Clinically **(A)** the teeth are loose and have migrated. The gingiva is red, tender, swollen and hyperplastic. The radiographs **(B, C)** show lesions in the maxilla and mandible with severe loss of supporting bone. The microscopic appearance **(D)** is characteristic, showing sheets of proliferating histiocytes.

Clinical Features. Clinically, the lesion may present no physical signs or symptoms and may be found only upon an incidental radiographic examination of the bones of the head or other areas. On the other hand, there may be local pain, swelling, and tenderness. The lesion may occur in the jaw and overlying soft tissues of the mouth, so that the differential diagnosis between eosinophilic granuloma and some form of dental disease becomes imperative. Although the skull and mandible are common sites of involvement, the femur, humerus, ribs, and other bones may also be affected. General malaise and fever occasionally accompany the eosinophilic granuloma of bone. The lesions are destructive and are well demarcated, roughly round or oval in shape. The area destroyed is replaced by a soft tissue, the composition of which varies, depending upon the stage at which the lesion is examined. The tissue of the early lesion is soft and brown and, since there is no necrosis, is not friable. Later the lesion becomes fibrous and grayish.

Radiographic Features. The lesions appear as irregular radiolucent areas usually involving superficial alveolar bone (Fig. 17-48). The cortex is often destroyed, and pathologic fractures may occur. If the lesions are in the jaw, they usually appear as single or multiple areas of rarefaction which may be so well circumscribed as to resemble cysts of the jaw, periapical granulomas or even periodontal disease (Fig. 17-49).

Histologic Features. Microscopically (Fig. 17-50), the primary cell is the histiocyte, which grows in sheets or sheetlike collections. The histiocytes may coalesce and form multinucleated giant cells, but this is quite uncommon. The early lesions also contain large numbers of focal collections of

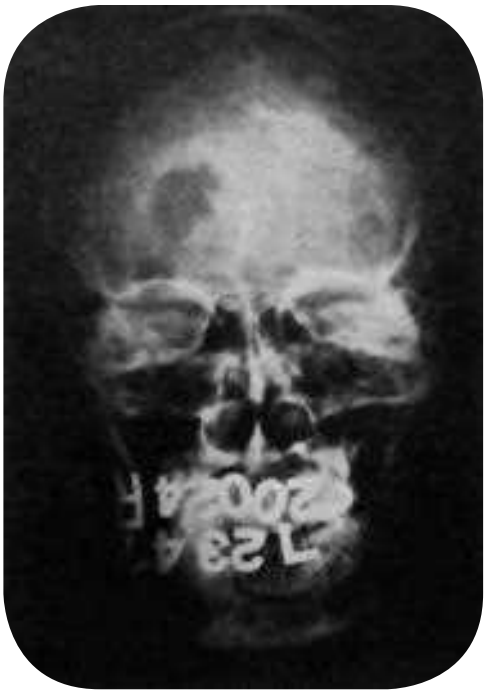


Figure 17-48. Eosinophilic granuloma.
The radiograph shows the typical irregular radiolucent areas of the skull *(Courtesy of Dr M Pleasure, Bronx Veterans Administration Hospital).*

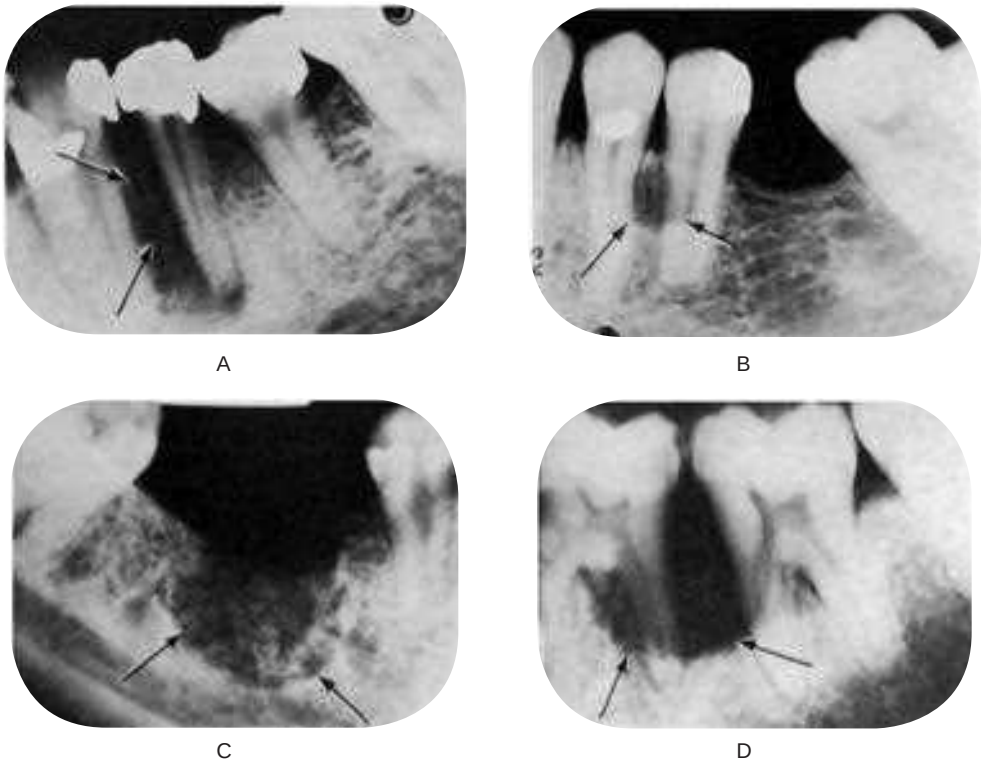


Figure 17-49. Eosinophilic granuloma of the jaws.
These four cases exemplify the variable radiographic appearance of the disease in the jaws *(D, Courtesy of Dr Charles A Waldron).*

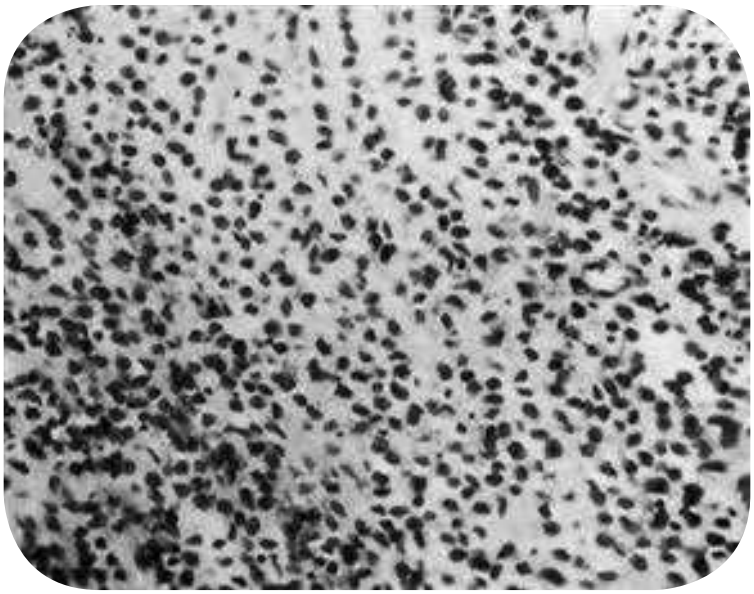


Figure 17-50. Eosinophilic granuloma.
The photomicrograph shows sheets of histiocytes and many eosinophils.

eosinophils. When the lesion matures, fibrosis occurs. In these older lesions, the eosinophils become less numerous, and they may even disappear so that the lesion approximates the histologic picture of Hand-Schüller-Christian disease.

Treatment and Prognosis. The prognosis in the majority of cases is excellent, since curettage and/or X-ray therapy are curative, symptoms usually subsiding within two weeks after treatment.

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CHAPTER 18

Diseases of the Blood and Blood-forming Organs

CHAPTER OUTLINE

Hematologic abnormalities are varied in nature, in its causation as well as in its clinical manifestations, most of which manifest in the oral cavity. In fact the oral site in many instances could act as the forerunner of its manifestations before overt systemic signs and symptoms express. The need of a thorough oral examination is a requisite in any attempt to look into manifestations of hematologic abnormalities and therefore its role as a clinical adjunct cannot be overemphasized.

The symptoms of hematologic disorders are so varied and nonspecific that in themselves they may not suggest a hematologic problem. Thus, unexplained fever, extreme fatigability, or recurrent infections may or may not be caused by a hematologic condition. Likewise, physical examinations may or may not direct attention to the hematopoietic system. Certain details of history must receive special enquiry. These include exposure to physical or chemical agents that may have caused injury and to drugs prescribed or self-medicated. Also deserving special enquiry is the diet, the degree and frequency of chronic blood loss, and the presence or absence of fever. In addition, family history is important in the differential diagnosis of hematologic disorders. Knowledge of ethnic origin or a history of jaundice, anemia, or bleeding in male rather than in female members of the family, for example, may offer useful clues. Furthermore, history alone may be insufficient. Although symptoms may be denied, a palpable spleen on physical examination or morphologic changes seen in blood smear, may direct attention to a hitherto unsuspected hereditary disorder. A family history is only as good as the thoroughness of the enquiry (Wintrobe, 1998).

The formed elements of the blood, as well as its liquid portion, play extraordinary roles in many physiologic mechanisms and processes in the human body. When a disturbance of one of these constituents occurs, severe clinical manifestations result. In some cases, the alteration of cells, serum, or other components is a result of a hereditary diathesis, nutritional deficiency, or exposure to certain chemicals. Other times, a focal or disseminated infection or a defect in one of the elements associated with the clotting mechanism causes the disturbance. A neoplastic overproduction of white cells is recognized as one of the most dreaded of blood dyscrasias.

The various blood diseases present polymorphic clinical expressions, one of which is the relatively constant involvement of oral structures. The dentist is often consulted by the patient suffering from one of the hematologic disorders who, unaware of his condition, only seeks relief of his harassing physical discomforts. Oral manifestations of many diseases of the blood are clinically similar to those lesions which occur in the oral cavity as a result of some local phenomenon, usually irritation or infection. For this reason a specific diagnosis of blood dyscrasia is difficult, if not impossible, to establish on the basis of the oral findings alone.

The hematologic disorders discussed in the following section are grouped, for ease of consideration, according to the cell type involved. No attempt is made to describe every known blood disease or even all the common ones. The sole criterion for inclusion in this section is the occurrence of oral manifestations and their obvious dental implications.

DISEASES INVOLVING RED BLOOD CELLS

ANEMIA

Anemia is defined as an abnormal reduction in the number of circulating red blood cells, the quantity of hemoglobin and the volume of packed red cells in a given unit of blood. The etiologies of the condition are extremely varied, and the classification presented in Table 18-1 based upon causes has been offered by Wintrobe.

In addition to this etiologic classification, a morphologic classification (Table 18-2) has been found of great value. It expresses the characteristic changes in the size and hemoglobin content of the red blood cell and thus acts as a guide to treatment. A recent classification based on cellular kinetic parameters was suggested (Table 18-3).

A number of different types of anemia may exhibit oral manifestations. These may be unusually varied, but often are so characteristic that the dentist should at least strongly suspect, if not actually confirm, the diagnosis of the anemia. In the discussion to follow, only those forms of anemia which are known to exhibit specific oral signs and symptoms will be considered.

Pernicious Anemia

(Vitamin B_{12} deficiency, Addisonian anemia, Biermer anemia, Hunter-Addison anemia, Lederer anemia, Biermer-Ehrlich anemia, Addison-Biermer disease)

Pernicious anemia is a relatively common chronic hematologic disease. It is an adult form of anemia that is associated with gastric atrophy and a loss of intrinsic factor production in gastric secretions and a rare congenital autosomal recessive form in which intrinsic factor (IF) production is lacking without gastric atrophy. The term pernicious anemia is reserved for patients with vitamin B_{12} deficiency due to a lack of production of IF in the stomach. Intrinsic factor in gastric secretions is necessary for the absorption of dietary vitamin B_{12}. Vitamin B_{12}, a substance now thought to be synonymous with the 'erythrocyte-maturing factor' or 'hemopoietic principle' and present in many foods, particularly liver, beef, milk and dairy products. Body stores of the vitamin usually exceed 1000 mcg and the daily requirement is about 1 mcg.

Pernicious anemia probably is an autoimmune disorder with a genetic predisposition and the disease is associated with human leucocyte antigen (HLA) types A2, A3, and B7 and A blood group. Antiparietal cell antibodies occur in 90% of patients with pernicious anemia but in only 5% of healthy adults. Similarly, binding and blocking antibodies to IF are found in most patients with pernicious anemia. A greater association than anticipated exists between pernicious anemia and other autoimmune diseases, which include thyroid disorders, type I diabetes mellitus, ulcerative colitis, Addison disease, and acquired agammaglobulinemia. An association between pernicious anemia and *Helicobacter pylori* infections has been postulated but not clearly proven.

Clinical Features. Pernicious anemia is rare before the age of 30 years and increases in frequency with advancing age. In the United States, males are affected more commonly than females; in other countries, notably Scandinavia, females are more commonly affected. No apparent racial predilection is noticed.

Table 18-1: Etiologic classification of the anemia

- I. Loss of blood
  - A. Acute posthemorrhagic anemia
  - B. Chronic posthemorrhagic anemia
- II. Excessive destruction of red corpuscles
  - A. Extracorpuscular causes
    1. Antibodies
    2. Infection (malaria, etc.)
    3. Splenic sequestration and destruction
    4. Associated disease states, e.g. lymphoma
    5. Drugs, chemicals, and physical agents
    6. Trauma to RBC
  - B. Intracorpuscular hemolytic disease
    1. Hereditary
       (a) Disorders of glycolysis
       (b) Faulty synthesis or maintenance of reduced glutathione
       (c) Qualitative or quantitative abnormalities in synthesis of globin
       (d) Abnormalities of RBC membrane
       (e) Erythropoietic porphyria
    2. Acquired
       (a) Paroxysmal nocturnal hemoglobinuria
       (b) Lead poisoning
- III. Impaired blood production resulting from deficiency of substances essential for erythropoiesis
  - A. Iron deficiency
    Experimentally; also copper and cobalt deficiencies
  - B. Deficiency of various B vitamins
    Clinically, B_{12} and folic acid deficiencies (pernicious anemia and related macrocytic, megaloblastic anemias); pyridoxine-responsive anemia
    Experimentally, pyridoxine and niacin deficiencies; possibly also riboflavin, pantothenic acid and thiamine deficiencies
  - C. Protein deficiency
  - D. Possibly ascorbic acid deficiency
- IV. Inadequate production of mature erythrocytes
  - A. Deficiency of erythroblasts
    1. Atrophy of bone marrow: aplastic anemia
       (a) Chemical or physical agents
       (b) Hereditary
       (c) Idiopathic
    2. Isolated erythroblastopenia (pure red cell aplasia)
       (a) Thymoma
       (b) Chemical
       (c) Antibodies
  - B. Infiltration of bone marrow
    1. Leukemia, lymphomas
    2. Multiple myeloma
    3. Carcinoma, sarcoma
    4. Myelofibrosis
  - C. Endocrine abnormality
    1. Myxedema
    2. Addisonian adrenal insufficiency
    3. Pituitary insufficiency
    4. Sometimes, hyperthyroidism
  - D. Chronic renal disease
  - E. Chronic inflammatory disease
    1. Infections
    2. Noninfectious diseases, including granulomatous and collagen diseases
  - F. Cirrhosis of liver

Modified from MM Wintrobe: Clinical Hematology. 8th ed. Lea and Febiger, Philadelphia, 1981.

Table 18-2: Morphologic classification of the anemia

Type of anemia	Description		Most common causes
1. Macrocytic	Increased normal	MCV; increased MCH; MCH conc	Lack of erythrocyte-maturing factors ('extrinsic' and 'intrinsic' factors)
2. Normocytic	Reduction normal normal	Only in RBC number; MCV; normal MCH; MCH conc	Hemorrhage; hemolysis; lack of blood formation; dilution of blood with fluid
3. Simple microcytic	Reduced normal	MCV; reduced MCH; MCH conc	Associated with infections and inflammatory diseases
4. Hypochromic microcytic	Reduced reduced	MCV; reduced MCH; MCH conc	Iron deficiency

MCV = mean corpuscular volume (Volume/RBC).
MCH = mean corpuscular hemoglobin (Hb/RBC).
MCH conc = mean corpuscular hemoglobin concentration (Hb/Vol).

Table 18-3: Kinetic classification of anemia

Impaired erythrocyte production (reticulocyte production index less than 2)
- a) Hypoproliferative
  - Iron-deficient erythropoiesis
    - Iron deficiency
    - Anemia of chronic disorders
  - Erythropoietin deficiency
    - Renal disease
    - Endocrine deficiencies
  - Hypoplastic anemia
    - Aplastic anemia
    - Pure red cell aplasia
  - Infiltration
  - Leukemia
  - Metastatic carcinoma
  - Myelofibrosis
- b) Ineffective
  - Megaloblastic
    - Vitamin B_{12} deficiency
    - Folate deficiency
    - Other causes
  - Microcytic
    - Thalassemia
    - Certain sideroblastic anemia
  - Normocytic

Increased erythrocyte production (reticulocyte production index greater than 3)
- Hemolytic anemia
  - Hereditary
  - Acquired
- Treated nutritional anemia

Adopted from Wintrobe's Clinical Haematology. 10th ed. Lippincott Williams and Wilkins, Philadelphia, 1998.

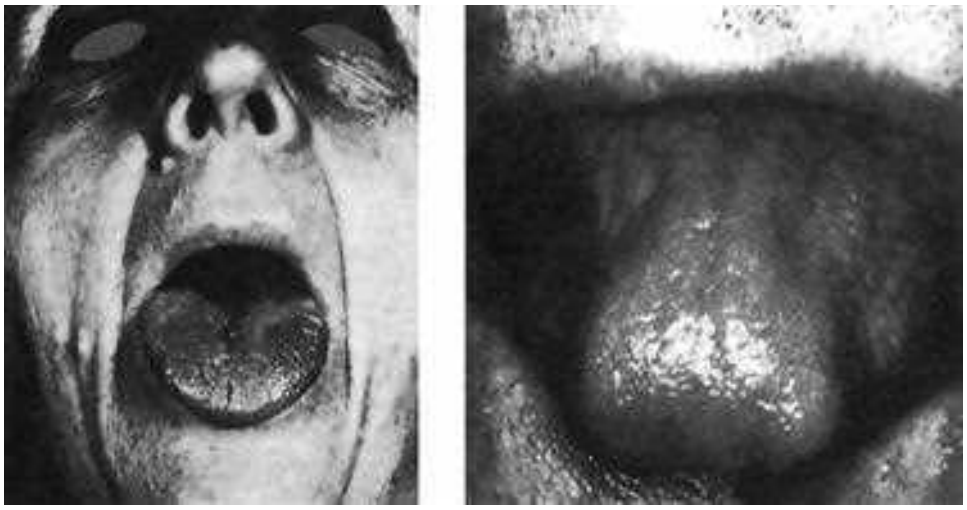
The disease is often characterized by the presence of a triad of symptoms: generalized weakness, a sore, painful tongue, and numbness or tingling of the extremities. In some cases the lingual manifestations are the first sign of the disease. Other typical complaints are easy fatigability, headache, dizziness, nausea, vomiting, diarrhea, loss of appetite, shortness of breath, loss of weight, pallor and abdominal pain.

Patients with severe anemia exhibit a yellowish tinge of the skin and sometimes of the sclerae. The skin is usually smooth and dry. Nervous system involvement is present in over 75% of the cases of pernicious anemia, and this consists of sensory disturbances including the paresthetic sensations of the extremities described above, weakness, stiffness and difficulty in walking, general irritability, depression or drowsiness as well as incoordination and loss of vibratory sensation. These nervous aberrations are referable to the degeneration of posterior and lateral tracts of the spinal cord with loss of nerve fibers and degeneration of myelin sheaths. Degeneration of the peripheral nerves also occurs.

Oral Manifestations. Glossitis is one of the more common symptoms of pernicious anemia. The patients complain of painful and burning lingual sensations which may be so annoying that the dentist is often consulted first for local relief.

The tongue is generally inflamed, often described as 'beefy red' in color, either in entirety or in patches scattered over the dorsum and lateral borders (Fig. 18-1). In some cases, small and shallow ulcers — resembling aphthous ulcers — occur on the tongue. Characteristically, with the glossitis, glossodynia and glossopyrosis, there is gradual atrophy of the papillae of the tongue that eventuate in a smooth or 'bald' tongue which is often referred to as Hunter's glossitis or Moeller's glossitis and is similar to the 'bald tongue of Sandwith' seen in pellagra. Loss or distortion of taste is sometimes reported accompanying these changes. The fiery red appearance of the tongue may undergo periods of remission, but recurrent attacks are common. On occasion, the inflammation and burning sensation extend to involve the entire oral mucosa but, more frequently, the rest of the oral mucosa exhibits only the pale yellowish tinge noted on the skin. Millard and Gobetti have emphasized that a nonspecific persistent or recurring stomatitis of unexplained local origin may be an early clinical manifestation of pernicious anemia. Not uncommonly the oral mucous membranes in patients with this disease become intolerant to dentures.

Farrant and Boen and Boddington have reported that cells from buccal scrapings of patients with pernicious anemia presented nuclear abnormalities consisting of enlargement, irregularity in shape and asymmetry. These were postulated to be due to a reduced rate of nucleic acid synthesis with a reduced rate of cell division. These epithelial cell alterations are rapidly reversible after administration of vitamin B_{12}.



A B

Figure 18-1. Pernicious anemia.
The tongue is inflamed and painful in each case, and there is beginning of atrophy of the papillae in **(A)** and advanced atrophy in **(B)** *(Courtesy of Dr Boynton H Booth and Dr Stephen F Dachi).*

Laboratory Findings

Blood. This chronic disease often exhibits periods of remission and exacerbation, and the blood changes generally parallel these clinical states. The red blood cell count is seriously decreased, often to 1,000,000 or less per cubic millimeter. Many of the cells exhibit macrocytosis; this, in fact, is one of the chief characteristics of the blood in this disease, although poikilocytosis, or variation in shape of cells, is also present (Fig. 18-2). The hemoglobin content of the red cells is increased, but this is only proportional to their increased size, since the mean corpuscular hemoglobin concentration is normal. A great many other red blood cell abnormalities have been described, particularly in advanced cases of anemia, including polychromatophilic cells, stippled cells, nucleated cells, Howell-Jolly bodies and Cabot's rings punctate basophilia. Leukocytes are also often remarkably reduced in number, but are increased in average size, in number of lobes to the nucleus (becoming the so-called macropolycytes) and anisopoikilocytosis. Mild to moderate thrombocytopenia is noticed. Coexistent iron deficiency is common because achlorhydria prevents solubilization of dietary ferric iron from foodstuffs. Striking reticulocyte response and improvement in hematocrit values after parenteral administration of cobalamin is characteristic.

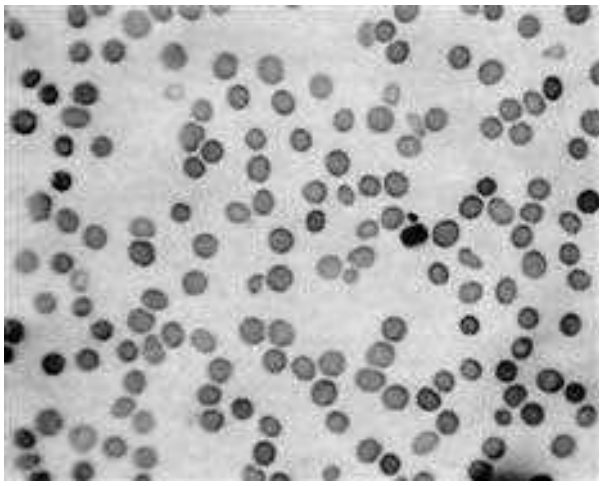


Figure 18-2. Pernicious anemia.
The peripheral blood smear from a typical case of pernicious anemia exhibits macrocytosis and poikilocytosis. The variation in size of erythrocytes is obvious. In addition, characteristic pear-shaped or 'tear-drop' erythrocytes are also present.

Serum. The indirect bilirubin may be elevated because pernicious anemia is a hemolytic disorder associated with increased turnover of bilirubin. The serum lactic dehydrogenase usually is markedly increased. The serum potassium, cholesterol, and skeletal alkaline phosphatase often are decreased. Serum antibodies for IF are highly specific.

Gastric secretions. Total gastric secretions are decreased to about 10% of the reference range. Most patients with pernicious anemia are achlorhydric, even with histamine stimulation. IF is either absent or is markedly decreased.

Bone marrow. The bone marrow biopsy and aspirate usually are hypercellular and show trilineage differentiation. Erythroid precursors are large and often oval. The nucleus is large and contains coarse motley chromatin clumps, providing a checkerboard appearance. Nucleoli are visible in the more immature erythroid precursors. Imbalanced growth of megakaryocytes is evidenced by hyperdiploidy of the nucleus and the presence of giant platelets in the smear. Lymphocytes and plasma cells are spared from the cellular gigantism and cytoplasmic asynchrony observed in other

cell lineages. The bone marrow histology is similar in both folic acid and cobalamin deficiency.

Treatment. The treatment of pernicious anemia consists of the administration of vitamin B_{12} and folic acid. Early recognition and treatment of pernicious anemia provides a normal, and usually uncomplicated, lifespan. Delayed treatment permits progression of the anemia and neurological complications. The mental and neurological damage can become irreversible without therapy.

Celiac Sprue

(Celiac disease, nontropical sprue, gluten-sensitive enteropathy, Gee-Herter disease)

Sprue is one disease of a large group which constitutes the 'malabsorption syndrome'. It is a chronic disease of the digestive tract that interferes with the absorption of nutrients from food. **Sprue is not basically an anemic disorder**. It is considered here; however, because it presents so many signs and symptoms in common with pernicious anemia that the differentiation is often difficult. This disease, also called 'idiopathic steatorrhea' to distinguish it from steatorrhea resulting from fibrocystic disease of the pancreas with resultant decrease in pancreatic enzyme secretion.

People with celiac sprue cannot tolerate gluten, a protein commonly found in wheat, rye, barley, and sometimes, oats. When affected individuals ingest gluten, the mucosa of their small intestine is damaged by an immunologically mediated inflammatory response, resulting in maldigestion and malabsorption. Genetics play an important role in celiac sprue. The incidence of disease in relatives of celiac sprue patients is significantly higher than in the general population. The prevalence in first-degree relatives of celiac sprue patients is approximately 10%. Concordance for the disease in HLA identical siblings is about 30% and that for identical twins approaches 70%. Strong association exists between the disease and two human leukocyte antigen (HLA) haplotypes, DR3 and DQw2.

Clinical Features. Sprue occurs both in tropical countries and in temperate zones in persons of all ages, including infants. For example, the frequency of the disease is between 1 in 250 persons and 1 in 300 persons in Italian and Irish populations. In comparison, the disease is rare in Africans or Asians. The symptoms of untreated celiac sprue are divided into gastrointestinal and extraintestinal symptoms.

Gastrointestinal symptoms include diarrhea, which is the most common symptom in untreated celiac sprue due to maldigestion and malabsorption of nutrients. Malabsorption of ingested fat (steatorrhea) resulting in excessive amount of fat passed in the stools. Flatulence results from the release of intestinal gas by the bacterial flora flourishing on undigested and unabsorbed food materials. In infants and young children with untreated celiac sprue, failure to gain weight and growth retardation is common. Other symptoms include weakness and fatigue, severe abdominal pain and excessive malodorous flatus. Occasionally, severe hypokalemia due to the loss of potassium in the stool can cause muscle weakness.

Extraintestinal symptoms include anemia which is usually due to impaired absorption of iron or folate from the proximal small intestine. In severe disease with ileal involvement, absorption of vitamin B_{12} might be impaired. A bleeding diathesis caused by prothrombin deficiency due to impaired absorption of fat-soluble vitamin K. Excessive amounts of fat are passed in the stools, inducing a concomitant excessive loss of calcium, which in turn causes a calcium deficiency with ensuing low blood calcium levels and occasional tetany. Bone pain occurs due to osteoporosis as a result of calcium and vitamin D deficiency. Nervous irritability as well as numbness and tingling of the extremities occurs, but seldom is there spinal cord involvement as in pernicious anemia. Malaise and generalized weakness are also common. The skin changes are often identical with those of pernicious anemia, but also include irregular brownish pigmentation, particularly on the face, neck, arms and legs, and drying of the skin with a scaly eruption.

Oral Manifestations. The oral changes in sprue are similar to those of pernicious anemia and have been described by Adlersberg from observation of 40 cases. There may be a severe glossitis with atrophy of the filiform papillae, although the fungiform papillae often persist for some time on the atrophic surface. Painful, burning sensations of the tongue and oral mucosa are common, and small, painful erosions may occur. These severe oral manifestations are seldom absent in cases of sprue (Fig. 18-3). Tyldesley has reviewed this problem recently and concluded that there is an association between recurrent oral ulceration, or recurrent aphthous ulcers, and celiac disease and that proper dietary treatment leads to remission of the oral lesions.

Laboratory Findings. The blood and bone marrow changes are often identical with those of pernicious anemia and include a macrocytic anemia and leukopenia. Hypochromic

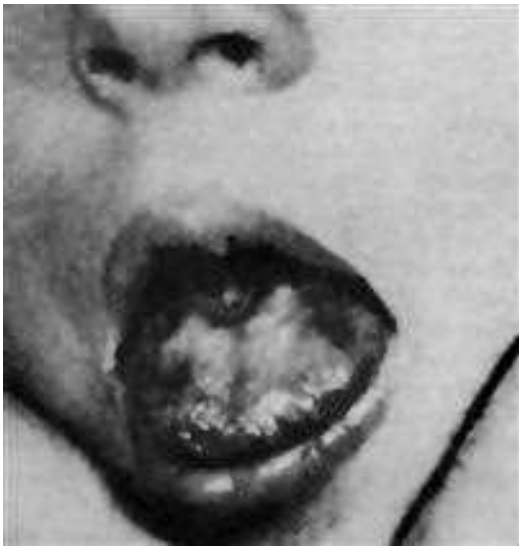


Figure 18-3. Sprue.
There is ulceration and inflammation of the tongue accompanied by a painful, burning sensation *(Courtesy of Dr Boynton H Booth)*.

microcytic anemia occasionally occurs. A low serum iron level is common. The prothrombin time (PT) might be prolonged because of malabsorption of vitamin K. The patients do not usually exhibit achlorhydria, nor is the 'intrinsic' factor absent.

Small intestinal biopsy, along with appropriate serum antibodies, usually will establish the diagnosis.

Histologic Findings. Celiac sprue primarily involves the mucosa of the small intestine. The submucosa, muscularis, and serosa usually are not involved. The villi are atrophic or absent, and crypts are elongated. The cellularity of the lamina propria is increased with a proliferation of plasma cells and lymphocytes. The number of intraepithelial lymphocytes per unit length of absorptive epithelium is increased.

Treatment. Sprue responds well in most cases to the administration of vitamin B_{12} and folic acid, although the diet must be carefully supervised and supplemented with vitamins and minerals. Use of food grains containing gluten should be avoided. A small percentage of celiac sprue patients fail to respond to a gluten free diet. In some patients who are refractory, corticosteroids might be helpful. The patients who fail to respond to corticosteroids, other conditions such as lymphomas of the small intestine should be suspected.

Aplastic Anemia

Aplastic anemia is a bone marrow failure syndrome characterized by peripheral pancytopenia and general lack of bone marrow activity. It may affect not only the red blood cells but also the white cells and platelets, resulting in a pancytopenia. The clinical manifestations of the disease vary according to the type of cell chiefly affected. Paul Ehrlich, introduced the concept of aplastic anemia in 1888 when he studied the case of a pregnant woman who died of bone marrow failure. However, it was not until 1904 when this disorder was termed aplastic anemia by Chauffard.

It is common to recognize two chief forms of aplastic anemia, primary and secondary. **Primary aplastic anemia** is a disease of unknown etiology which occurs most frequently in young adults, develops rapidly and usually terminates fatally. A disease known as **Fanconi's syndrome** consists of congenital, and sometimes familial, aplastic anemia associated with a variety of other congenital defects including bone abnormalities, microcephaly, hypogenitalism and a generalized olive-brown pigmentation of the skin.

Secondary aplastic anemia, on the other hand, is of known etiology, occurs at any age and presents a better prognosis, particularly if the cause is removed. The etiology of this secondary anemia is the exposure of the patient to various drugs or chemical substances or to radiant energy in the form of X-rays, radium or radioactive isotopes. In many cases the development of aplastic anemia after exposure to the drug or chemical seems to be an allergic phenomenon, since the amount of the substance absorbed is too small to result in an actual poisoning or intoxication. The chemicals which have been found most frequently to cause the development of this condition are acetophenetidine, amidopyrine, organic arsenicals, particularly sulfarsphenamine, benzol, chloramphenicol, quinacrine hydrochloride (Atabrine), trinitrotoluene, dinitrophenol, colloidal silver, bismuth, mercury, sulfonamides and penicillin, although many others have also produced the disease. On few occasions aplastic anemia is preceded by infection by hepatitis viruses, Epstein-Barr virus (EBV), HIV, parvovirus, and mycobacterial infections.

The effect of irradiation is usually more pronounced on the white blood cell series, although the development of aplastic anemia after exposure to X-ray radiation is well recognized.

Clinical Features. The clinical manifestations of aplastic anemia are referable not only to the anemia, but also to the leukopenia and thrombocytopenia which are variably present. There are few differences in the clinical features of the primary and secondary forms of the disease except in the ultimate prognosis. The onset is insidious, with the initial symptom relating to anemia or bleeding, but fever or infections often are noted at presentation.

The patients usually complain of severe weakness with dyspnea following even slight physical exertion and exhibit pallor of the skin. Numbness and tingling of the extremities and edema are also encountered due to anemia. Petechiae in the skin and mucous membranes occur, owing to the platelet deficiency, while the neutropenia leads to a decreased resistance to infection.

The role of an immune dysfunction was suggested in 1970, when autologous recovery was documented in a patient with aplastic anemia who had failed to engraft after marrow transplantation. It was proposed that the immunosuppressive regimen used for conditioning promoted the return of normal marrow function. Subsequently, numerous studies have shown that, in approximately 70% of patients with acquired aplastic anemia, immunosuppressive therapy improves marrow function. Although the inciting antigens that breach immune tolerance with subsequent autoimmunity are unknown, HLA-DR2 is over represented among European and American patients with aplastic anemia.

Suppression of hematopoiesis likely is mediated by an expanded population of the cytotoxic T lymphocytes (CD8 and HLA-DR+), which are detectable in both the blood and bone marrow of patients with aplastic anemia. These cells produce inhibitory cytokines, such as gamma interferon and tumor necrosis factor, which are capable of suppressing progenitor cell growth. These cytokines suppress hematopoiesis by affecting the mitotic cycle and cell killing through induction of Fas-mediated apoptosis. It also has been shown that these cytokines induce nitric oxide synthase and nitric oxide production by marrow cells, which contributes to immune-mediated cytotoxicity and elimination of hematopoietic cells.

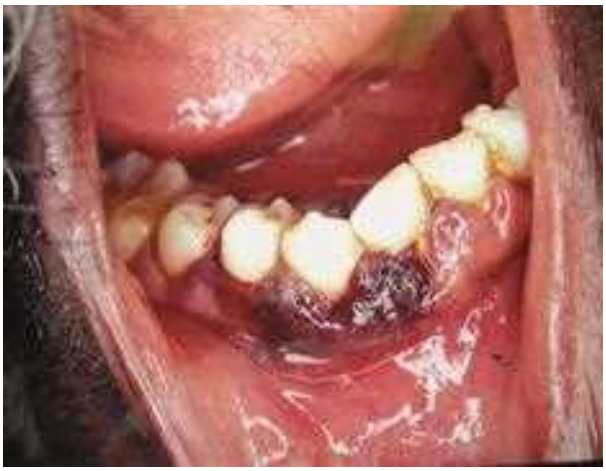


Figure 18-4. Primary aplastic anemia.
The patient suffered from spontaneous hemorrhage from the gingiva.

Oral Manifestations. Petechiae purpuric spots or frank hematomas of the oral mucosa may occur at any site, while hemorrhage into the oral cavity, especially spontaneous gingival hemorrhage, is present in some cases. Such findings are related to the blood platelet deficiency (Fig. 18-4). As a result of the neutropenia there is a generalized lack of resistance to infection, and this is manifested by the development of ulcerative lesions of the oral mucosa or pharynx. These may be extremely severe and may result in a condition resembling gangrene because of the lack of inflammatory cell response.

Laboratory Findings. The red blood cell count is remarkably diminished, often to as low as 1,000,000 cells per cubic millimeter, with a corresponding reduction in the hematocrit and hemoglobin levels. A paucity of granulocytes, monocytes, and reticulocytes is found. The thrombocytopenia results in a prolonged bleeding time; the clotting time remains normal. Clot retraction is poor and the tourniquet test is positive. The degree of cytopenia is useful in assessing the severity of aplastic anemia. The presence of teardrop poikilocytes and leucoerythroblastic changes suggest marrow aplasia from infiltrative and dysplastic causes.

Bone marrow smears exhibit variable findings depending on the extent of the anemia and/or pancytopenia. If only an anemia exists, there is erythropoietic depression. Occasionally, however, the marrow appears normal or even hyperplastic. In pancytopenia there is hypoplasia of all marrow elements, and only occasional cells of any type may be found. In cases of less severe damage, moderate numbers of primitive cells persist. In severe cases, hypocellular bone marrow with fatty replacement and relatively increased nonhematopoietic elements such as plasma cells and mast cells may be found. Hemoglobin electrophoresis and blood group testing may show elevated fetal hemoglobin and red cell 1 antigen suggesting stress erythropoiesis, which is observed in both aplastic anemia and myelodysplastic syndromes.

Treatment. Patients with aplastic anemia require transfusion support until the diagnosis is established and specific therapy can be instituted. Infections should be treated appropriately as it is the major cause of mortality. Other treatment options are bone marrow transplantation and immunosuppressive therapy.

Thalassemia

(Cooley's anemia, Mediterranean anemia, erythroblastic anemia)

Thalassemic syndromes are genetically determined disorders of hemoglobin synthesis with decreased production of either alpha or beta polypeptide chains of hemoglobin molecules, which results from markedly decreased amounts of globin messenger ribonucleic acid. Features first described by Thomas B Cooley in 1925 are seen primarily in Mediterranean populations, in races bordering the Eastern Mediterranean sea or in families originating from these areas (*thalassa* means 'sea' in Greek).

Normal adult hemoglobin is a large complex molecule in which an iron-containing pigment (heme) is conjugated to a complex protein (globin). The globin component consists two pairs of unlike polypeptide chains, alpha and nonalpha chains (e.g. beta, gamma, delta). In the normal adult hemoglobin (HbA), which constitutes over 95% of the hemoglobin in normal persons older than one year, the globin component consists of two alpha and two beta chains. The thalassemia group of anemias is a heterogeneous group characterized by diminished synthesis of the alpha (α)-or beta (β)-globin chain of hemoglobin A. The disease is termed α thalassemia when there is deficient synthesis of the α-chain and β-thalassemia when the β-chain is deficient. Thus, in β-thalassemia there is an excess of α-chains, producing 'unstable hemoglobins' that damage the erythrocytes and increase their vulnerability to destruction. In heterozygotes, the disease is mild and is called **thalassemia minor** or **thalassemia trait**. It represents both α-and β-thalassemia. Homozygotes may exhibit a severe form of the disease that is called **thalassemia major** or **homozygous β-thalassemia**, in which the production of β-chains is markedly decreased or absent, and a consequent decrease in synthesis of total hemoglobin occurs. This results in severe hypochromic anemia. Furthermore, excess α-chains, which synthesize at the normal rate, precipitate as insoluble inclusion bodies within the erythrocytes and their precursors. The presence of such intracellular inclusion bodies (**Fessas bodies**) leads to increased erythrocyte hemolysis and severe ineffective hematopoiesis. Approximately 70–85% of marrow normoblasts are destroyed in severely affected patients. These processes result in profound anemia and an associated increase in marrow activity, which is estimated to increase 5- to 30-fold.

Two other forms of thalassemia major that represent α-thalassemia also exist. These are:

- Hemoglobin H disease, which is a very mild form of the disease in which the patient may live a relatively normal life.
- Hemoglobin Bart's disease, with hydrops fetalis, in which the infants are stillborn or die shortly after birth.

Clinical Features. In high-risk areas (i.e. Greek and Italian islands), 10% of the population may have homozygous

β-thalassemia; 5% in Southeast Asian populations; and 1.5% in African and American black populations. The onset of the severe form of the disease (homozygous β-thalassemia) occurs within the first two years of life, often in the first few months. Siblings are commonly affected. The child has a yellowish pallor of the skin and exhibits fever, chills, malaise and a generalized weakness. Splenomegaly and hepatomegaly may cause protrusion of the abdomen. The face often develops mongoloid features due to prominence of the cheek bones, protrusion or flaring of the maxillary anterior teeth, and the depression of the bridge of the nose which gives rise to the characteristic **rodent facies.** The child does not appear acutely ill, but the disease follows an ingravescent course which is often aggravated by intercurrent infection. Some patients; however, die within a few months, especially when the disease is manifested at a very early age. Logothetis and his associates have shown that the degree of cephalofacial deformities in this disease (including prominent frontal and parietal bones, sunken nose bridge, protruding zygomas and mongoloid slanting eyes) is closely related to the severity of the disease and the time of institution of treatment.

Thalassemia minor (thalassemia trait) is generally without clinical manifestations.

Oral Manifestations. An unusual prominence of the premaxilla has been described in cases of erythroblastic anemia, such as that reported by Novak, and this results in an obvious malocclusion. The oral mucosa may exhibit the characteristic anemic pallor observed on the skin.

Laboratory Findings. The pronounced anemia is of a hypochromic microcytic type, the red cells exhibiting a poikilocytosis and anisocytosis. These cells are extremely pale, but in some instances appear as 'target' cells with a condensation of coloring matter in the center of the cell. The presence of typical **safety-pin** cells and of normoblasts or nucleated red blood cells in the circulating blood is also a characteristic feature. The white blood cell count is frequently elevated, often as high as 10,000–25,000 or more per cubic millimeter. Supravital staining (methyl violet) of peripheral blood can demonstrate inclusion bodies. Bone marrow smears show cellular hyperplasia with large numbers of immature, primitive and stem forms of red blood cells, all indicating maturation arrest. The serum bilirubin in these patients is also elevated, indicative of the severe hemosiderosis which is almost invariably present. This systemic hemosiderosis has suggested a possible block in iron utilization with accumulation of iron pigment and subsequent inadequate formation of hemoglobin.

Radiographic Features. The skeletal changes in thalassemia are most striking and have been thoroughly described by Caffey. A frequent finding in rib has been referred to as the **rib-within-a-rib** appearance and is noted particularly in the middle and anterior portions of the ribs. The finding consists of a long linear density within or overlapping the medullary space of the rib and running parallel to its long axis. In the skull, there is extreme thickening of the diploe (medulla), the inner and outer plates (cortices) become poorly defined, and the trabeculae between the plates become elongated, producing a bristle like **crew-cut** or **hair-on-end** appearance of the surface of the skull (Fig. 18-5). Because of the lack of hematopoietic marrow, the occipital bone usually is not involved.

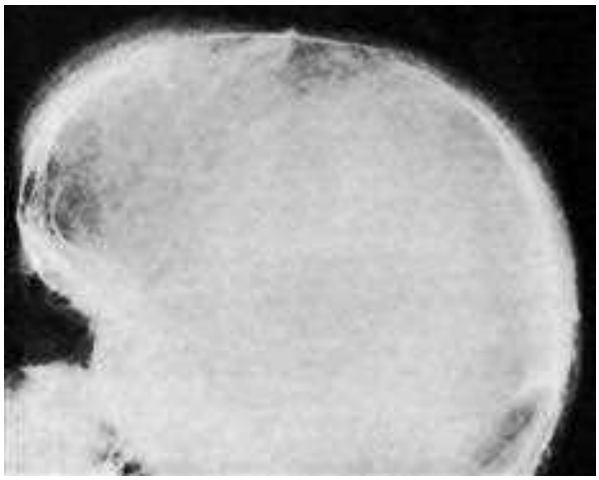


Figure 18-5. Thalassemia.
The 'hair-on-end' effect is well demonstrated in the radiograph *(Courtesy of Dr Robert J Gorlin).*

Both the skull and long bones exhibit some degree of osteoporosis, but spontaneous fracture of bones is not common. There is typically a widening of the medulla with thinning of the cortices of the long bones. The bony changes may occur early in life and tend to persist, particularly those in the skull.

Proliferation of marrow within the frontal and facial bones impedes pneumatization of the paranasal sinuses. This results in hypertrophy of osseous structures and a consequent prominence of the lateral margins of the malar eminences, together with anterior and medial displacement of developing teeth. Characteristically, ethmoidal sinuses are not involved, a factor attributable to the absence of red marrow in the sinus walls.

Intraoral radiographs in some cases reveal a peculiar trabecular pattern of the maxilla and mandible, characterized by an apparent coarsening of some trabeculae and the blurring and disappearance of others, resulting in a **salt and pepper** effect. In general, thinning of the lamina dura and circular radiolucencies in the alveolar bone are also found (Dewey et al).

Gall bladder imaging and ultrasound evaluation may reveal pigment stones. Splenic ultrasound may reveal splenomegaly.

Treatment. There is no treatment for this form of anemia. The administration of liver extract, iron or vitamin B_6 is fruitless. Blood transfusions do provide temporary remissions. Bone marrow transplantation may be a definitive treatment option, but long-term results from transplants already performed are not available. The disease is usually fatal, although mild forms which are compatible with life apparently exist. Generally, the earlier in infancy the disease occurs, the more rapidly it proves fatal. Death is generally due to intercurrent infection, cardiac damage as a result of anoxia, or liver failure.

Sickle Cell Anemia
(Sickle cell disease)

Sickle cell anemia is a hereditary type of chronic hemolytic anemia transmitted as a mendelian dominant, nongender-linked characteristic, which occurs almost exclusively in blacks, and in whites of Mediterranean origin. Malaria is possibly the selecting agent for sickle cell disease because a concordance exists between the prevalence of malaria and HbS. The name is derived from the peculiar microscopic appearance of sickle-or crescent-shaped erythrocytes found in the circulating blood. Normal adult hemoglobin (HbA) is genetically altered to produce sickle hemoglobin (HbS) by the substitution of valine for glutamine at the sixth position of the β-globin chain. In the heterozygote, only about 40% of the hemoglobin is HbS, so that the individual has only the sickle-cell trait and manifests clinical evidence of sickling only under conditions of severe hypoxia. About 8% of American blacks are heterozygous for hemoglobin S. In the homozygote, nearly all hemoglobin is HbS, and the individual suffers from sickle cell anemia. This occurs in about 1 in 600 American blacks.

Deoxygenation of the heme moiety of HbS leads to hydrophobic interactions between adjacent HbS molecules, which then aggregate into larger polymers, distorting the red blood cell (RBC) into the classic sickle shape. The RBCs with sickle shape become much less deformable; therefore, obstructing the microcirculation and thus caused tissue hypoxia, further promotes sickling. Sickle-shaped RBCs are rapidly hemolyzed and have a life span of only about 10–20 days.

The clinical manifestations of sickle cell anemia are diverse, and any organ system may be affected. These manifestations commonly are divided into vaso-occlusive, hematologic, and infectious crises.

Clinical Features. Sickle cell anemia is more common in females and usually becomes clinically manifest before the age of 30 years. Patients manifest a variety of features related to the anemia *per se.* Thus the patient is weak, short of breath and easily fatigued. Pain in the joints, limbs and abdomen, as well as nausea and vomiting, is common. Systolic murmur and cardiomegaly also occur. One additional feature characteristically seen is packing of red blood cells in peripheral vessels with erythrostasis and subsequent local tissue anoxia. An infarct of the mandible on this basis has been reported by Walker and Schenck. Sickle cell crises (vaso-occlusive, hematologic, and infectious crises) may occur under a variety of situations, including the administration of a general anesthetic, probably as a result of decreased oxygenation of the blood. Other triggering causes of deoxygenation may include exercise or exertion, infections, pregnancy or even sleep.

Oral Manifestations. According to the studies of Robinson and Sarnat, a majority of patients with sickle cell anemia exhibit significant bone changes in the dental radiographs. These alterations consist of a mild to severe generalized osteoporosis and a loss of trabeculation of the jaw bones with the appearance of large, irregular marrow spaces. The trabecular change is prominent in the alveolar bone. There are no alterations in the lamina dura or periodontal ligament. Similar findings were reported by Morris and Stahl and by Prowler and Smith, not only in patients with sickle cell anemia but also in many with only the sickling trait. However, in a study of 80 patients with sickle cell anemia who were compared with an apparently normal group of patients, Mourshed and Tuckson stated that these two radiographic features of the jaws—increased radiolucency and coarse trabeculation—cannot be considered reliable diagnostic criteria for the disease.

Goldsby and Staats have reported morphologic alterations in the nuclei of epithelial cells in scrapings of the oral mucosa in 90% of all studied cases of patients with homozygous sickle cell disease. These changes were chiefly nuclear enlargement, binucleation and an atypical chromatin distribution. These changes are similar to those that have been reported occurring in pernicious anemia and sprue (Fig. 18-6A, B).

Radiographic Features. Radiographs of the skull exhibit an unusual appearance, with perpendicular trabeculations radiating outward from the inner table producing a 'hair-on-end' pattern, identical to that seen in thalassemia, congenital hemolytic jaundice and sometimes in chronic iron deficiency anemia and secondary polycythemia of cyanotic congenital heart disease. The outer table of bone may appear absent and the diploe thickened. Generalized osteoporosis may be present. The long bones of children may exhibit enlarged medullary cavities with thin cortices, while the same bones in adults become sclerotic with cortical thickening due to fibrosis of the marrow.

Laboratory Findings. The red blood cell count may reach a level of 1,000,000 cells or less per cubic millimeter with a decreased hemoglobin level. High reticulocyte count indicates anemia and increased marrow response. A major drop in hemoglobin (i.e. more than 2 gm/dl) from previous values indicates a hematological crisis. If the reticulocyte count is low, an aplastic crisis is the probable cause.

On the blood smear, typical sickle-shaped red blood cells are commonly seen, although they are present also in cases of the sickle trait without clinical evidence of the disease (Fig. 18-6C). Elevated levels of lactate dehydrogenase and decreased levels of haptoglobin confirm the presence of hemolysis. Hemoglobin electrophoresis can be done to differentiate homozygous from heterozygous.

Treatment. Treatment strategies include the following five goals:

- Management of vaso-occlusive crisis
- Management of chronic pain syndromes
- Management of the chronic hemolytic anemia
- Prevention and treatment of infections
- Management of the complications and the various organ damage syndromes associated with the disease.

Because this is a lifelong disease, prognosis is not good. The goal is to achieve a normal lifespan with minimal morbidity.

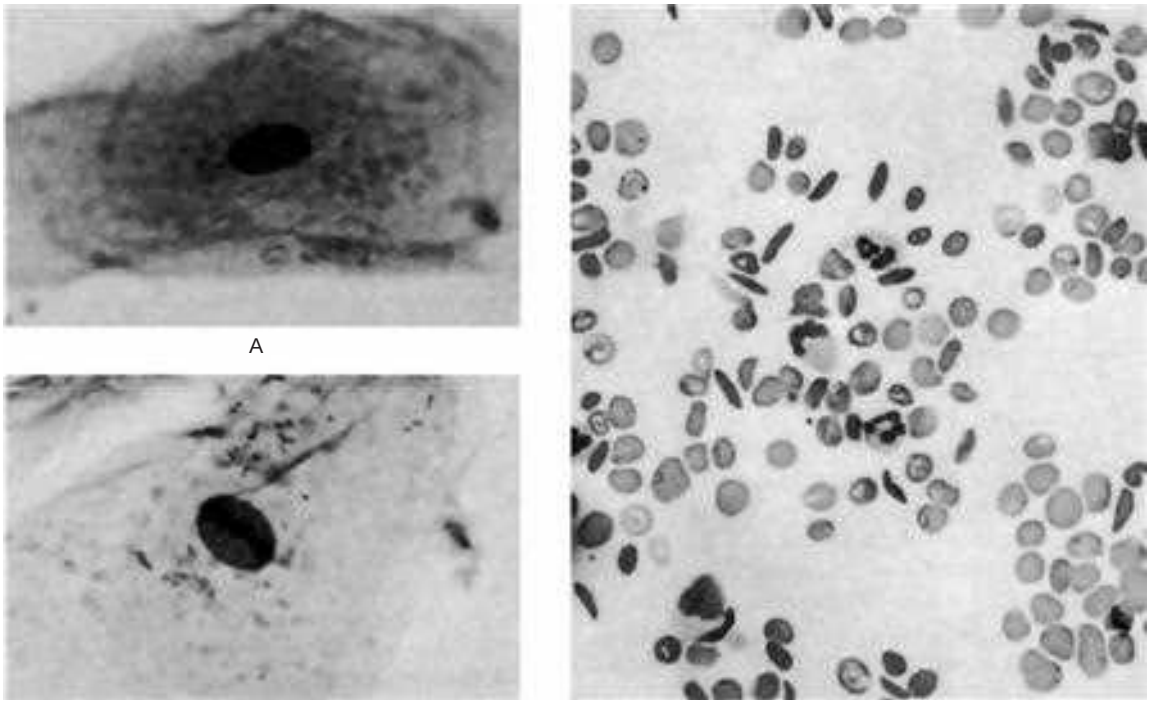


Figure 18-6. Sickle cell anemia.
Atypical chromatin bars are seen in cytologic smears from buccal mucosa **(A, B)**, while numerous typical sickle-shaped erythrocytes are present in the peripheral blood smear **(C)**.

Erythroblastosis Fetalis

Congenital hemolytic anemia due to Rh incompatibility results from the destruction of fetal blood brought about by a reaction between maternal and fetal blood factors.

The Rh factor, named after the rhesus monkey, was discovered by Landsteiner and Wiener in 1940 as a factor in human red blood cells that would react with rabbit antiserum produced by administration of red blood cells from the rhesus monkey. The Rh factor, a dominant hereditary characteristic, is present in the red blood cells of approximately 85% of the Caucasian population of the United States.

Pathogenesis. Erythroblastosis fetalis is essentially due to the inheritance by the fetus of a blood factor from the father that acts as a foreign antigen to the mother. The transplacental transfer of this antigen, actually transplacental leaks of red cells, from the fetus to the mother results in immunization of the mother and formation of antibodies which, when transferred back to the fetus by the same route, produce fetal hemolysis. Occasionally, the ABO system may produce a similar type of immunization and hemolysis.

The basic inheritance of the Rh factor is relatively simple. If both parents are homozygously Rh-positive (have the Rh factor), the infant will be Rh-positive, but maternal immunization cannot occur, since both mother and fetus have the same antigen. If the mother is homozygously positive, but the father Rh-negative, the same situation actually exists, since both the mother and the fetus have the same antigen and no immunization can occur. If the father is Rh-positive and the mother Rh-negative; however, the fetus inherits the paternal factor, which may then act as an antigen to the mother and immunize her with resultant antibody formation.

The problem is complicated; however, by the occurrence of numerous immunologically distinct Rh antigens. The strongest of these antigens have been termed C, D and E, and the presence of any one of them constitutes an Rh-positive person. Each of these antigens is normally present in a specific gene, but, if absent, their place is taken by less potent Hr antigens, known as c, d and e. Thus, three Rh or Hr genes are inherited from each parent, constituting three pairs of factors. Any combination of C, D, E and c, d, e is therefore possible, but the only combination producing an Rh-negative person is cde-cde. The D antigen, by far the strongest, is most frequently responsible for the clinical manifestations of erythroblastosis fetalis, and the 85% of the population generally considered Rh-positive actually have the D antigen homozygously (D-D) or heterozygously (D-d). The 15% who are Rh-negative have the d antigen homozygously (d-d). Mathematically, according to the laws of random mating, there should be 10 cases of erythroblastosis fetalis in every 100 pregnancies. Clinically, it has been found that only one case in every 200 pregnancies occurs. There are several possible explanations for this discrepancy:

- In some cases the mother may be unable to form antibodies even though immunized by the Rh-positive fetus.
- Even though the fetus is Rh-positive, transplacental transfer of the antigen does not occur, so that there is no maternal immunization.

- Immunization may occur, but its level is so low as to be clinically insignificant. Recent evidence has shown that, in general, women have a reduced immunologic responsiveness during pregnancy.

Subsequent pregnancies might cause further immunization with increased antibody formation, so that in ensuing pregnancies clinical hemolysis does occur. This latter explanation is plausible since it explains adequately why the first pregnancy is often uneventful, while erythroblastosis frequently occurs in succeeding pregnancies.

It is of great interest to note that the frequency of erythroblastosis fetalis of Rh incompatibility has shown a dramatic decrease in the past few years and that the eventual elimination of the disease through immunization prevention techniques is a probability. At present, Rh-negative mothers are being given anti-D gamma globulin to prevent immunization, since it binds to antigenic receptor sites on fetal red cells, making them nonimmunogenic.

Clinical Features. The manifestations of the disease depend upon the severity of the hemolysis. Some infants are stillborn. Those that are born alive characteristically suffer from anemia with pallor, jaundice, compensatory erythropoiesis, both medullary and extramedullary, and edema resulting in fetal hydrops. It is of considerable interest that the severe anemia and jaundice do not begin to develop until at least several hours after birth and frequently not for several days. The most important aid in diagnosis of the disease is a positive direct Coombs test on cord blood.

Oral Manifestations. Erythroblastosis fetalis may be manifested in the teeth by the deposition of blood pigment in the enamel and dentin of the developing teeth, giving them a green, brown or blue hue (Fig. 18-7). Ground sections of these teeth give a positive test for bilirubin. The stain is intrinsic and does not involve teeth or portions of teeth developing after cessation of hemolysis shortly after birth.

Enamel hypoplasia is also reported occurring in some cases of erythroblastosis fetalis. This usually involves the incisal edges of the anterior teeth and the middle portion of the deciduous cuspid and first molar crown. Here a characteristic ring-like defect occurs which has been termed the **Rh hump** by Watson.

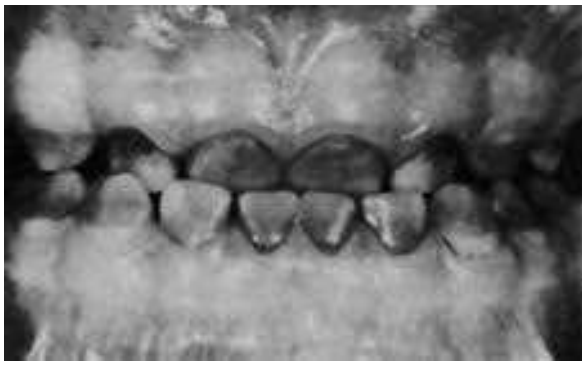


Figure 18-7. Pigmentation of teeth in erythroblastosis fetalis.
The teeth had a definite blue cast. The sharp line of separation between affected and unaffected tooth substance is seen near the cervical area of the mandibular cuspids and first molars *(Courtesy of Dr Ralph E McDonald).*

Many infants with this disease are stillborn, but an increasing number of those born alive have survived after a total replacement of their blood by transfusion at birth. Thus the dentist may expect to see more children with the peculiar pigmentations of teeth characteristic of the condition, and should be aware of its nature.

Laboratory Findings. The red blood count at birth may vary from less than 1,000,000 cells per cubic millimeter to near a normal level. There are characteristically large numbers of normoblasts, or nucleated red cells, in the circulating blood. Ultimately, severe anemia usually develops within a few days. The icterus index is invariably high and may reach a level of 100 units.

Treatment. No treatment for the tooth pigmentation is necessary, since it affects only the deciduous teeth and presents only a temporary cosmetic problem.

Iron Deficiency Anemia and Plummer-Vinson Syndrome

(Paterson-Brown-Kelly syndrome, Paterson-Kelly syndrome, sideropenic dysphagia)

Iron deficiency is an exceedingly prevalent form of anemia, particularly in females. Iron deficiency is the most prevalent single deficiency state on a worldwide basis. It has been estimated that between 5 and 30% of women in the United States are iron deficient, while in some parts of the world, this may reach 50% . Men are only rarely affected. In healthy people, the body concentration of iron (approximately 60 parts per million) is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron. Persistent errors in iron balance lead to either iron deficiency anemia or hemosiderosis.

The iron deficiency leading to this anemia usually arises through:

- Chronic blood loss (as in patients with a history of profuse menstruation
- Inadequate dietary intake
- Faulty iron absorption
- Increased requirements for iron, as during infancy, childhood and adolescence and during pregnancy.

An adult male absorbs and loses about 1 mg of iron from a diet containing 10–20 mg of iron daily. During childbearing years, an adult female loses an average of 2 mg of iron daily (extra 500 mg of iron with each pregnancy, menstrual losses are highly variable is about 4–100 mg of iron) and must absorb a similar quantity of iron in order to maintain equilibrium. Growing children must obtain approximately 0.5 mg more iron daily.

The Plummer-Vinson syndrome is one manifestations of iron-deficiency anemia and was first described by Plummer in 1914 and by Vinson in 1922 under the term ‘hysterical dysphagia’. Not until 1936; however, was the full clinical

significance of the condition recognized. Ahlbom then defined it as a predisposition for the development of carcinoma in the upper alimentary tract. It is, in fact, one of the few known predisposing factors in oral cancer. It is thought that the depletion of iron-dependent oxidative enzymes may produce myasthenic changes in muscles involved in the swallowing mechanism, atrophy of the esophageal mucosa, and formation of webs as mucosal complications. It is also thought to be an autoimmune phenomenon as the syndrome is seen in association with autoimmune conditions such as rheumatoid arthritis, pernicious anemia, celiac disease, and thyroiditis. Other factors such as nutritional deficiencies, genetic predisposition are thought to play roles in the causation of this disease.

Clinical Features. While an iron-deficiency anemia may occur at any age, the Plummer-Vinson syndrome occurs chiefly in women in the fourth and fifth decades of life. Presenting symptoms of the anemia and the syndrome are cracks or fissures at the corners of the mouth (angular cheilitis), a lemon-tinted pallor of the skin, a smooth, red, painful tongue (glossitis) with atrophy of the filiform and later the fungiform papillae, and dysphagia limited to solid food resulting from an esophageal stricture or web. These oral findings are reminiscent of those seen in pernicious anemia. The mucous membranes of the oral cavity and esophagus are atrophic and show loss of normal keratinization. Koilonychia (spoon-shaped fingernails) or nails that are brittle and break easily have been reported in many patients; splenomegaly has also been reported in 20–30% of the cases.

The depletion of iron stores in the body, manifested as iron-deficiency anemia, may be the direct cause of the mucous membrane atrophy, since the integrity of epithelium is dependent upon adequate serum iron levels. The atrophy of the mucous membranes of the upper alimentary tract predisposes to the development of carcinoma in these tissues. This relationship was first noted by Ahlbom, who reported that half of all women with carcinoma of the hypopharynx and upper part of the esophagus seen at Radiumhemmet in Stockholm suffered from Plummer-Vinson syndrome. Subsequently the predisposition to the development of oral carcinoma was also established.

Laboratory Findings. Blood examination reveals a hypochromic microcytic anemic of varying degree, while sternal marrow examination shows no megaloblasts typical of pernicious anemia. The red blood cell count is generally between 3,000,000 and 4,000,000 cells per cubic millimeter, and the hemoglobin is invariably low. That the anemia is of an iron-deficiency type can be confirmed by lack of a reticulocyte response following administration of vitamin B_{12}. A low serum iron and ferritin with an elevated total iron binding capacity (TIBC) are diagnostic of iron deficiency. There is an absence of free hydrochloric acid in the stomach. The achlorhydria is generally the cause of the faulty absorption of iron, since the absence of hydrochloric acid prevents the conversion of unabsorbable dietary ferric iron to the absorbable ferrous state. The absence of stainable iron in a bone marrow aspirate is further diagnostic of iron deficiency. Unusual alterations in exfoliated squamous epithelial cells of the tongue in cases of severe iron-deficiency anemia have been reported by Monto and his associates. These changes consisted of a deficiency of keratinized cells, a reduced cytoplasmic diameter of cells with a paradoxical enlargement of the nucleus, and abnormal cellular maturation characterized by a disturbed nuclear pattern, an increase in nucleoli, presence of double nuclei and karyorrhexis. Testing stool for the presence of hemoglobin is useful in establishing gastrointestinal bleeding as the etiology of iron deficiency anemia; however, they produce a high incidence of false-positive results in people who eat meat.

Treatment and Prognosis. The anemia responds well to iron therapy and a high-protein diet. Because of the predisposition to the development of carcinoma of oral mucous membranes, it is essential that the diagnosis be established early so that treatment may be instituted as soon as possible. Dysphagia may improve with iron replacement alone, particularly in patients whose webs are not substantially obstructive. Dysphagia caused by more advanced webs is unlikely to respond to iron replacement alone, and thus is managed with mechanical dilation.

Polycythemia

Polycythemia is defined as an abnormal increase in the number of red blood cells in the peripheral blood, usually with an increased hemoglobin level. Three forms of the disease are recognized: relative polycythemia; primary polycythemia or erythremia (polycythemia rubra vera) of unknown etiology; and secondary polycythemia or erythrocytosis, due to some known stimulus.

Relative polycythemia is an apparent increase in the number of circulating red blood cells that occurs as a result of loss of blood fluid with hemoconcentration of cells, and is seen in cases of excessive loss of body fluids such as chronic vomiting, diarrhea, or loss of electrolytes with accompanying loss of water. This increase in the number of red blood cells is only relative to the total blood volume, and therefore, is not a true polycythemia.

Primary polycythemia, or **polycythemia rubra vera,** is characterized by a true idiopathic increase in the number of circulating red blood cells and of the hemoglobin level. It is characterized by bone marrow with an inherent increased proliferative activity.

Secondary polycythemia is similar to primary polycythemia except that the etiology is known. Secondary polycythemia is caused due to absolute increase in red blood cell mass resultant to enhanced stimulation of red blood cell production. In general, the stimulus responsible for producing a secondary polycythemia is either bone marrow anoxia or production of an erythropoietic stimulating factor. Bone marrow anoxia may occur in numerous situations such as pulmonary dysfunction, heart disease, habitation at high altitudes or chronic carbon monoxide poisoning. Erythropoietic stimulatory factors include a variety of drugs and chemicals such as coal-tar derivatives, gum shellac, phosphorus, and

various metals such as manganese, mercury, iron, bismuth, arsenic and cobalt. Some types of tumors such as certain brain tumors, liver and kidney carcinomas and the uterine myoma have also been reported associated with polycythemia. The mechanism for increased production of the red blood cells by these tumors is unknown, but has been postulated as due to elaboration of a specific factor which stimulates erythropoiesis.

Polycythemia Vera

(Polycythemia rubra vera, erythremia, Vaquez's disease, Osler's disease)

Polycythemia vera (PV) is a chronic stem cell disorder with an insidious onset characterized as a panhyperplastic, malignant, and neoplastic marrow disorder. The most prominent feature is an absolute increase in the number of circulating red blood cells and in the total blood volume because of uncontrolled red blood cell production. This is accompanied by increased white blood cell (myeloid) and platelet (megakaryocytic) production, which is due to an abnormal clone of the hematopoietic stem cells with increased sensitivity to the different growth factors for maturation.

The bone marrow of patients with polycythemia vera shows normal and abnormal stem cells (Figs. 18-8, 18-9, and 18-10). The clonal proliferation of abnormal stem cells interfere with or suppress normal stem cell growth and maturation. Evidence indicates that the etiology of this panmyelosis is unregulated neoplastic proliferation. The cause of the stem cell transformation remains unknown.

All clinical manifestations of this disease are identical with those of secondary polycythemia, so the two conditions are considered together here.

Clinical Features. Polycythemia vera often manifests itself primarily by headache or dizziness, weakness and lassitude, tinnitus, visual disturbances, mental confusion, slurring of the speech and inability to concentrate. The skin is flushed or diffusely reddened, as a result of capillary engorgement and high red cell mass, as though the patient were continuously blushing. This condition is most obvious on the head, neck and extremities, although the digits may be cyanotic. Increased red blood cell mass increases blood viscosity and decreases tissue perfusion, and also predisposes for thrombosis. If secondary

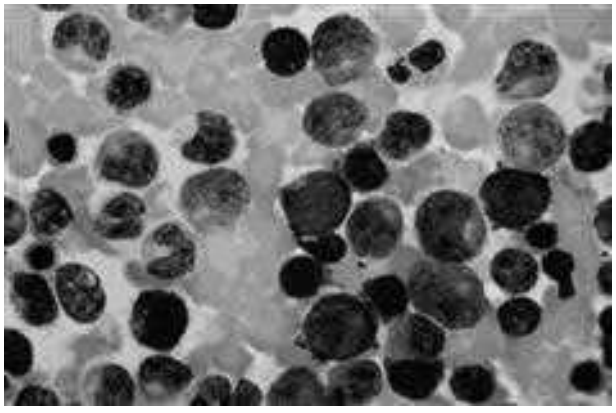


Figure 18-8. Polycythemia vera, bone marrow aspirate.
Increased number of both erythroid and myeloid precursors are seen. PV results in a panhyperplasia of marrow cell elements (Wright Giemsa, Oil).

Cytogenetic studies show the presence of an abnormal karyotype in the hematopoietic progenitor cells in approximately 34% of patients with PV, depending on the stage of the disease. Approximately 20% of patients have cytogenetic abnormalities at diagnosis, increasing to more than 80% for those with more than 10 years of follow-up care.

The chromosomal abnormalities observed in patients with PV are deletion of **20q** (8.4%), deletion of **13q** (3%), trisomy **8** (7%), trisomy **9** (7%), trisomy of **1q** (4%), deletion of **5q** or monosomy **5** (3%), deletion of **7q** or monosomy **7** (1%). These are similar to the abnormal karyotypes observed in patients with myelodysplastic syndromes and other myeloproliferative disorders.

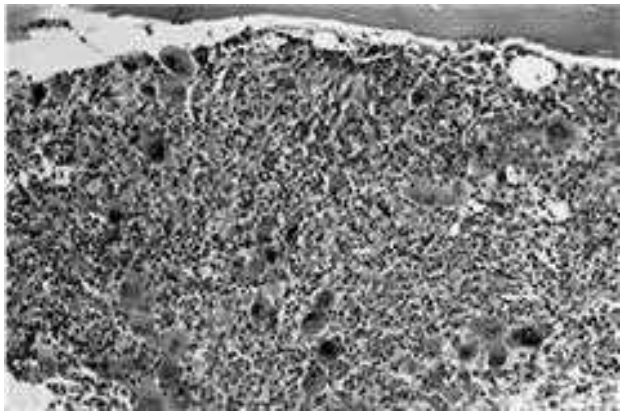


Figure 18-9. Polycythemia vera, bone marrow core biopsy.
Hypercellular, megakaryocytes are increased.

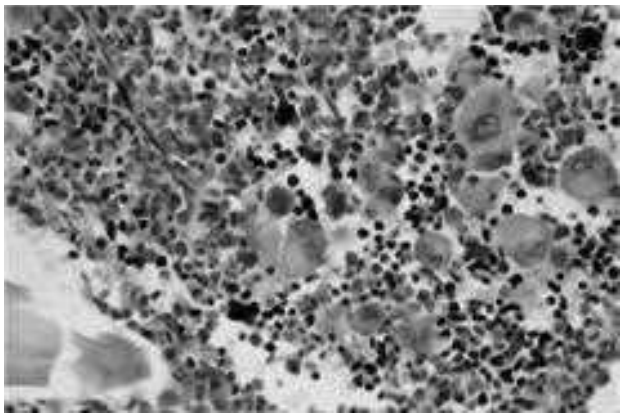


Figure 18-10. Polycythemia vera, megakaryocytes proliferation.
This biopsy illustrates the proliferation of megakaryocytes in PV.

polycythemia is secondary to hypoxia, patients can also appear cyanotic or may have acrocyanosis which is caused by sluggish blood flow through small blood vessels. The skin of the trunk is seldom involved. Splenomegaly is one of the most constant features of polycythemia vera, and the spleen is sometimes painful. Gastric complaints such as gas pains, belching and peptic ulcers are common, and hemorrhage from varices in the gastrointestinal tract may occur. Pruritus results from increased histamine levels released from increased basophils and mast cells and can be exacerbated by a warm bath or shower in up to 40% of patients. The disease is more common in men and usually occurs in middle age or later.

Oral Manifestations. The oral mucous membranes appear deep purplish red, the gingiva and tongue being most prominently affected. The cyanosis is due to the presence of reduced hemoglobin in amounts exceeding 5 gm/dl. The gingivae are often engorged and swollen and bleed upon the slightest provocation. Submucosal petechiae are also common, as well as ecchymoses and hematomas. Intercurrent infection may occur, but this is not related directly to the disease.

Laboratory Findings. Red blood cell mass and plasma volume can be measured directly using radiochromium-labeled red blood cells which show an increase in mass with a normal or slightly decreased plasma volume. The red blood cell count is elevated and may even exceed 10,000,000 cells per cubic millimeter (Figs. 18-11). The red blood cells in patients with PV are usually normochromic normocytic. The hemoglobin content of the blood is also increased, often as high as 20 gm/dl, although the color index is less than 1.0. Because of the great number of cells present, both the specific gravity and the viscosity of the blood are increased.

Leukocytosis is usual, as is a great increase in the number of platelets (400,000–800,000/dl) (Figs. 18-12, 18-13); in addition, the total blood volume is elevated through distention of even the smallest blood vessels of the body. The leukocyte alkaline phosphatase score is elevated (>100 U/L) in 70% of patients. There is usually hyperplasia of all elements of the bone marrow. Bleeding and clotting times are normal.

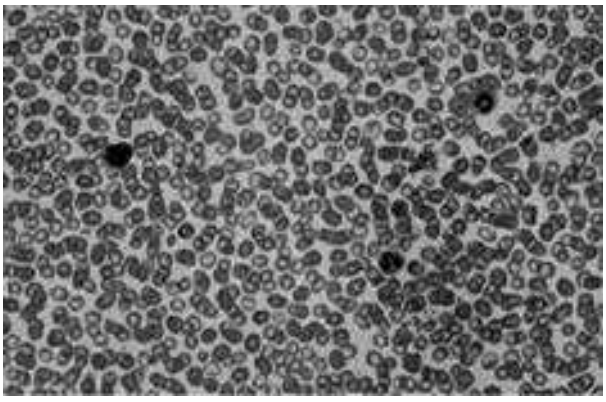


Figure 18-11. Polycythemia vera, peripheral blood.
It is often difficult to prepare a good peripheral blood smear in PV due to the increased viscosity of the blood. The red cells are crowded together (Wright Giemsa).

Treatment. No specific treatment for polycythemia is known, although several methods are used for relieving its symptoms. The patient may be periodically bled, or substances may be administered either to destroy blood cells (phenylhydrazine) or to interfere with its formation (nitrogen mustard or even X-ray radiation). In recent years, the radioactive isotope of phosphorus, P^{32}, has been used. Any such treatment; however, produces only a remission of the disease; it does not affect a cure. The course of the disease may be protracted over many years.

DISEASES INVOLVING WHITE BLOOD CELLS

LEUKOPENIA

Leukopenia is an abnormal reduction in the number of white blood cells in the peripheral blood stream. This decrease involves predominantly the granulocytes, although any of the cell types may be affected. The etiology of this particular sign of disease is extremely varied, but the classification shown in Table 18-4 has been devised by Wintrobe.

Oral lesions are present in certain diseases that are characterized by a reduction in the number of white cells. These lesions are related to the inability of the tissues to react in the usual manner to infection or trauma. Because of the dangerous sequelae which may result if the disease is not recognized, the dentist must be fully acquainted with each disorder and its serious consequences.

Agranulocytosis

(Granulocytopenia, agranulocytic angina, malignant leukopenia or neutropenia)

Agranulocytosis is a serious disease involving the white blood cells. It is characterized by decreased number of circulating granulocytes. It is often classified with reference to etiology as primary or secondary in type, **primary agranulocytosis** being that form of the disease in which the etiology is unknown, and **secondary agranulocytosis** being that form in which the cause is recognized. Since the clinical and laboratory findings in both forms are identical, the disease will be discussed here as a single entity.

Etiology. The most common known cause of agranulocytosis is the ingestion of any one of a considerable variety of drugs (Table 18-5) and infections. Those compounds chiefly responsible for the disease are also those to which patients commonly manifest idiosyncrasy in the form of urticaria, cutaneous rashes and edema. For this reason and because often only small amounts of these drugs are necessary to produce the disease, it appears that the reaction may be an allergic phenomenon, although attempts to demonstrate antibodies in affected patients have not been successful. Moreover, in the case of some of the drugs, the disease occurs only after continued administration.

Table 18-4: Causes of leukopenia

I. Infections
- A. Bacterial
  1. Typhoid fever
  2. Paratyphoid fever
  3. Brucellosis
  4. Tularemia (rarely)
- B. Viral and rickettsial
  1. Influenza
  2. Measles
  3. Rubella
  4. Chickenpox
  5. Infectious hepatitis
  6. Colorado tick fever
  7. Dengue
  8. Yellow fever
  9. Sandfly fever
- C. Protozoal
  1. Malaria
  2. Relapsing fever
  3. Kala-azar
- D. Any overwhelming infection
  1. Miliary tuberculosis
  2. Septicemia

II. Cachectic and debilitating states and inanition

III. Hemopoietic disorders, especially splenic
- A. Gaucher's disease
- B. Banti's disease
- C. Pernicious anemia (relapse)
- D. Aplastic anemia
- E. Chronic hypochromic anemia
- F. Myelophthisic anemia
- G. 'Aleukemic' leukemia
- H. Agranulocytosis

IV. Chemical agents
- A. Agents commonly producing leukopenia in all patients if given in sufficient dose
  1. Mustards (sulfur and nitrogen mustards, triethylenemelamine [TEM], etc)
  2. Urethane, busulfan, demecolcine
  3. Benzene
  4. Antimetabolites (antifolic compounds, 6-mercaptopurine, etc)
- B. Agents occasionally associated with leukopenia, apparently a result of individual sensitivity
  1. Analgesics, sedatives and anti-inflammatory agents (e.g. aminopyrine, dipyrone, phenacetin, phenylbutazone)
  2. Antithyroid drugs (e.g. the thiouracils)
  3. Anticonvulsants
  4. Sulfonamides
  5. Antihistamines
  6. Antimicrobial agents
  7. Tranquilizers (e.g. phenothiazines and others)
  8. Miscellaneous (e.g. dinitrophenol, phenindione, cimetidine, tolbutamide, chlorpropamide, carbutamide, gold salts, industrial chemicals)
  9. Many other drugs infrequently

V. Physical agents
- A. X-ray radiation and radioactive substances

VI. Anaphylactoid shock and early stages of reaction to foreign protein

VII. Certain diseases of unknown etiology, including hereditary and congenital
- A. Liver cirrhosis
- B. Felty's syndrome
- C. Disseminated lupus erythematosus
- D. Primary splenic neutropenia
- E. Cyclic neutropenia
- F. Chronic hypoplastic neutropenia

Modified from MM Wintrobe: Clinical Hematology, 8th ed. Lea and Febiger, Philadelphia, 1981.

Table 18-5: Risks of agranulocytosis associated with select drugs

Drug	RR	Excess risk
Antithyroid drugs	97	5.3
Macrolides	54	6.7
Procainamide	50	3.1
Aprindine	49	2.7
Dipyrone	16	0.6
Trimethoprim-sulfamethoxazole	16	2.4
Thenalidine	16	2.4
Carbamazepine	11	0.6
Digitalis	2.5–9.9	0.1–0.3
Indomethacin	6.6	0.4
Sulfonylureas	4.5	0.2
Corticosteroids	4.1	
Butazones	3.9	0.2
Dipyridamole	3.8	0.2
β-Lactams	2.8	0.2
Propranolol	2.5	0.1
Salicylates	2.0	0.0006

From the International Aplastic Anemia and Agranulocytosis Study.
RR = multivariant relative risk estimate; excess risk is expressed as number of cases per 1 million users in 1 week. Reproduced from Young NS. Agranulocytosis. JAMA 271: 935–938, 1995.

Kracke, in 1931, was one of the first to point out that a rapid increase in the number of cases of agranulocytosis occurred at the time of the introduction of certain coal-tar derivatives for use in therapy. The following drugs and compounds are some of those which have been reported to produce agranulocytosis in some persons:

Amidopyrine
Barbiturates (including amobarbital and phenobarbital)
Benzene
Bismuth
Chloramphenicol
Cinchophen
DDT
Dinitrophenol
Gold salts
Organic arsenicals
Phenacetin
Phenothiazines and related compounds (including chlorpromazine promazine, mepazine, prochlorperazine and imipramine)
Phenylbutazone
Quinine
Sulfonamides (including sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine)
Thioglycolic acid
Thiouracil
Tolbutamide
Trimethadione
Tripelennamine

Most persons can be exposed to these drugs with near impunity; the hematologic reaction to the compounds is actually an uncommon one.

The mechanism that causes agranulocytosis is not understood completely. In drug-induced agranulocytosis, the drug may act as a hapten and induce antibody formation.

Thus produced antibodies destroy the granulocytes or may form immune complexes which bind to the neutrophils and destroy them. Autoimmune neutropenia due to antineutrophil antibodies is seen in few cases.

Other uncommon causes of agranulocytosis include **Kostmann syndrome** (severe congenital neutropenia) which is most often inherited in autosomal recessive pattern. Autosomal dominant and sporadic cases have also been reported, most often due to mutations in the granulocyte colony-stimulating factor (G-CSF) receptor.

Chronic severe neutropenia has an underlying unknown cause. Myelodysplasia occurs in early infancy and is associated with recurrent infections. The condition is due to accelerated apoptosis and decreased expression of bcl-x in neutrophil precursors.

Clinical Features. Agranulocytosis can occur at any age, but is somewhat more common in adults, particularly women. The disease frequently affects workers in the health professions and in hospitals (e.g. physicians, dentists, nurses, hospital orderlies, and pharmacists), probably because they have easy access to the offending drugs and often use drug samples injudiciously.

The disease commences with a high fever, accompanied by chills and sore throat. The patient suffers malaise, weakness and prostration. The skin appears pale and anemic, or in some cases, jaundiced. The most characteristic feature of the disease is the presence of infection, particularly in the oral cavity, but also throughout the gastrointestinal tract, genitourinary tract, respiratory tract and skin. Regional lymphadenitis accompanies the infection in any of these locations. If treatment is not promptly instituted, the infection progresses to generalized sepsis, which may be life threatening.

The clinical signs and symptoms develop rapidly in the majority of cases, usually within a few days, and death may occur within a week.

Oral Manifestations. The oral lesions constitute an important phase of the clinical aspects of agranulocytosis. These appear as necrotizing ulcerations of the oral mucosa, tonsils and pharynx. Particularly involved are the gingiva and palate. The lesions appear as ragged necrotic ulcers covered by a gray or even black membrane (Fig. 18-12). Usually no purulent discharge is noticed. Significantly, there is little or no apparent inflammatory cell infiltration around the periphery of the lesions, although hemorrhage does occur, especially from the gingiva. In addition, the patients often manifest excessive salivation.

It is obvious that all oral surgical procedures, particularly tooth extraction, are contraindicated in cases of agranulocytosis.

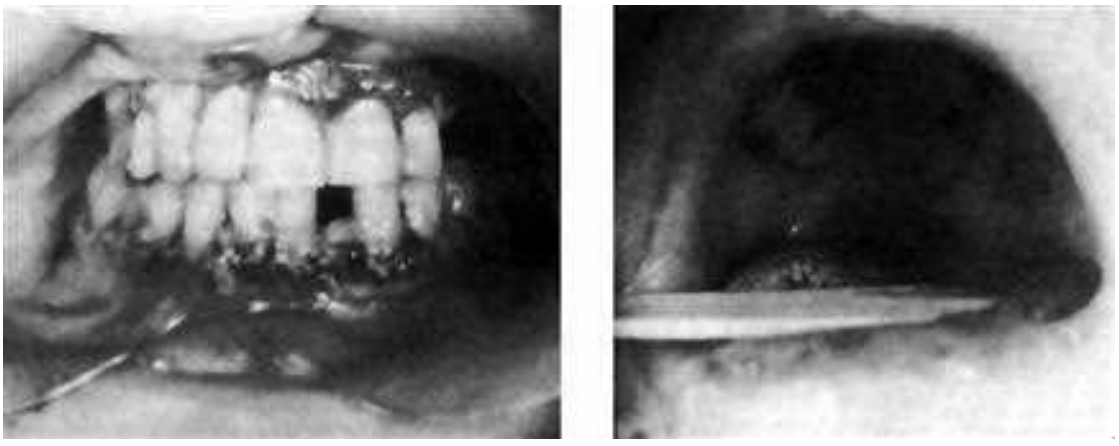
Histologic Features. The microscopic appearance of sections through the ulcerated oral lesions is a pathognomonic one and accounts for certain clinical features of the disease. Since the essential fault is the lack of development of normal granular leukocytes, the ulcerated areas exhibit no polymorphonuclear reaction to the bacteria in the tissues, and rampant necrosis ensues.

Bauer studied the microscopic appearance of the jaws in agranulocytosis and reported necrosis of the gingiva, beginning adjacent to the sulcus and spreading into the free gingiva, periodontal ligament and even alveolar bone. Rapid destruction of the supporting tissues of the teeth follows.

Laboratory Findings. The white blood cell count in agranulocytosis is often below 2000 cells per cubic millimeter with an almost complete absence of granulocytes or polymorphonuclear cells. The red blood cell count and platelet count are usually normal, although occasionally anemia is present.

The bone marrow is relatively normal except for the absence of granulocytes, metamyelocytes and myelocytes. Promyelocytes and myeloblasts are usually present in near normal numbers; however, and for this reason it appears that the basic defect is an arrest in cell maturation.

Treatment and Prognosis. The treatment of agranulocytosis is not specific, but should consist principally in recognition and withdrawal of the causative drug and in administration of antibiotic drugs to control the infection.



A B

Figure 18-12. Agranulocytosis.
The necrotizing areas of ulceration on the gingivae **(A)** and palate **(B)** occurred after the use of a barbiturate *(Courtesy of Dr Edward V Zegarelli).*

Death is usually related to massive infection, and for this reason the disease carried a high mortality before the advent of the antibiotics. Today, although it is still a serious disease, agranulocytosis has a good prognosis if the responsible agent is discovered. Agranulocytosis secondary to viral infections is usually self-limited, and patients with such conditions have a good prognosis.

Cyclic Neutropenia

(Periodic neutropenia, cyclic agranulocytic angina, periodic agranulocytosis)

Cyclic neutropenia is an unusual form of agranulocytosis characterized by a periodic or cyclic diminution in circulating polymorphonuclear neutrophilic leukocytes as a result of bone marrow maturation arrest, accompanied by mild clinical manifestations, which spontaneously regresses only to recur subsequently in a rhythmic pattern. The etiology of this disease is unknown. Excellent reviews of cyclic neutropenia with its oral manifestations have been published by Page and Good, Becker and his coworkers, and Gorlin and Chaudhry. Although the role of hormonal and allergic factors in the etiology of the disease has been suggested by some workers, there is no sound evidence to indicate that this is the case. There appear to exist at least two additional rare hereditary forms of the disease, one cyclic and the other noncyclic. In addition, a chronic idiopathic neutropenia, noncyclic and nonfamilial, associated with severe persistent gingivitis has been reported by Kyle and Linman.

Clinical Features. This type of agranulocytosis may occur at any age, although the majority of cases have been reported in infants or young children. The symptoms are similar to those of typical agranulocytosis except that they are usually milder. The patients manifest fever, malaise, sore throat, stomatitis and regional lymphadenopathy, as well as headache, arthritis, cutaneous infection and conjunctivitis. In contrast to other types of primary agranulocytosis, rampant bacterial infection is not a significant feature (Table 18-6), presumably because the neutrophil count is low for such a short time. Entities closely mimic the clinical characteristics of cyclic neutropenia are variable, encompassing a wider spectra (Table 18-7).

Oral Manifestations. Patients with this disease typically exhibit a severe gingivitis, sometimes a stomatitis with ulceration, which corresponds to the period of the neutropenia and is due to bacterial invasion, chiefly from the gingival sulcus, in the absence of a defense mechanism (Fig. 18-13). With return of the neutrophil count to normal, the gingiva assumes a nearly normal clinical appearance. In children, the repeated insult of infection often leads to considerable loss of supporting bone around the teeth (Fig. 18-14). The widespread severe ulceration usually seen in agranulocytosis does not often occur. However, isolated painful ulcers may occur which persist for 10–14 days and heal with scarring. On this basis, it has been suggested by Gorlin and Chaudhry that some cases diagnosed clinically as periadenitis mucosa necrotica recurrens may actually be cyclic neutropenia.

Table 18-6: Infection associated with neutropenia

Viruses and viral illness	Bacterial
Colorado tick fever	Brucellosis
Cytomegalovirus	Gram-negative septicemia
Dengue fever	Paratyphoid fever
Epstein-Barr virus	Tuberculosis
Hepatitis virus	Tularemia
Herpes simplex virus	Typhoid fever
Human immunodeficiency virus type A and B	**Fungal**
Influenza	Histoplasmosis
Measles	**Protozoal**
Mumps	Leishmaniasis
Parvovirus	Malaria
Poliomyelitis	**Rickettsial**
Psittacosis	Rickettsial pox
Respiratory syncytial virus	Rocky Mountain
Roseola	spotted fever
Rubella	Typhus fever
Sandfly fever	
Smallpox	
Varicella	
Yellow fever	

Adapted from Wintrobe's Clinical Hematology. 10th ed. Williams and Wilkins, 1998.

Radiographic Features. The intraoral radiographs typically exhibit mild to severe loss of superficial alveolar bone, even in children, as a result of the repeated cyclic gingivitis, advancing to periodontitis. In children, this loss of bone around multiple teeth has sometimes been termed 'prepubertal periodontitis', and it is frequently indicative of a serious systemic disease. Cohen and Morris have discussed the periodontal manifestations of cyclic neutropenia.

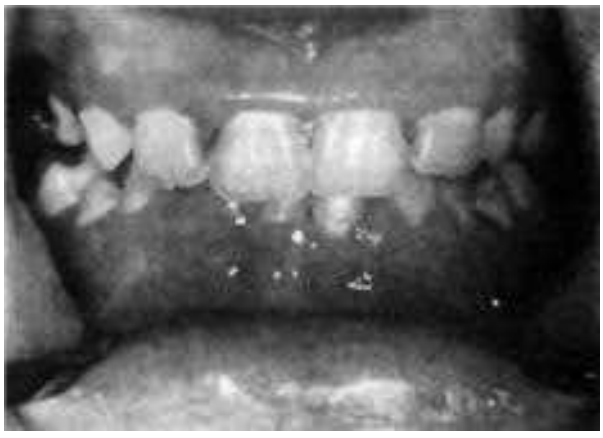


Figure 18-13. Cyclic neutropenia.
The gingivitis in this young boy was periodic and corresponded to the neutropenia.

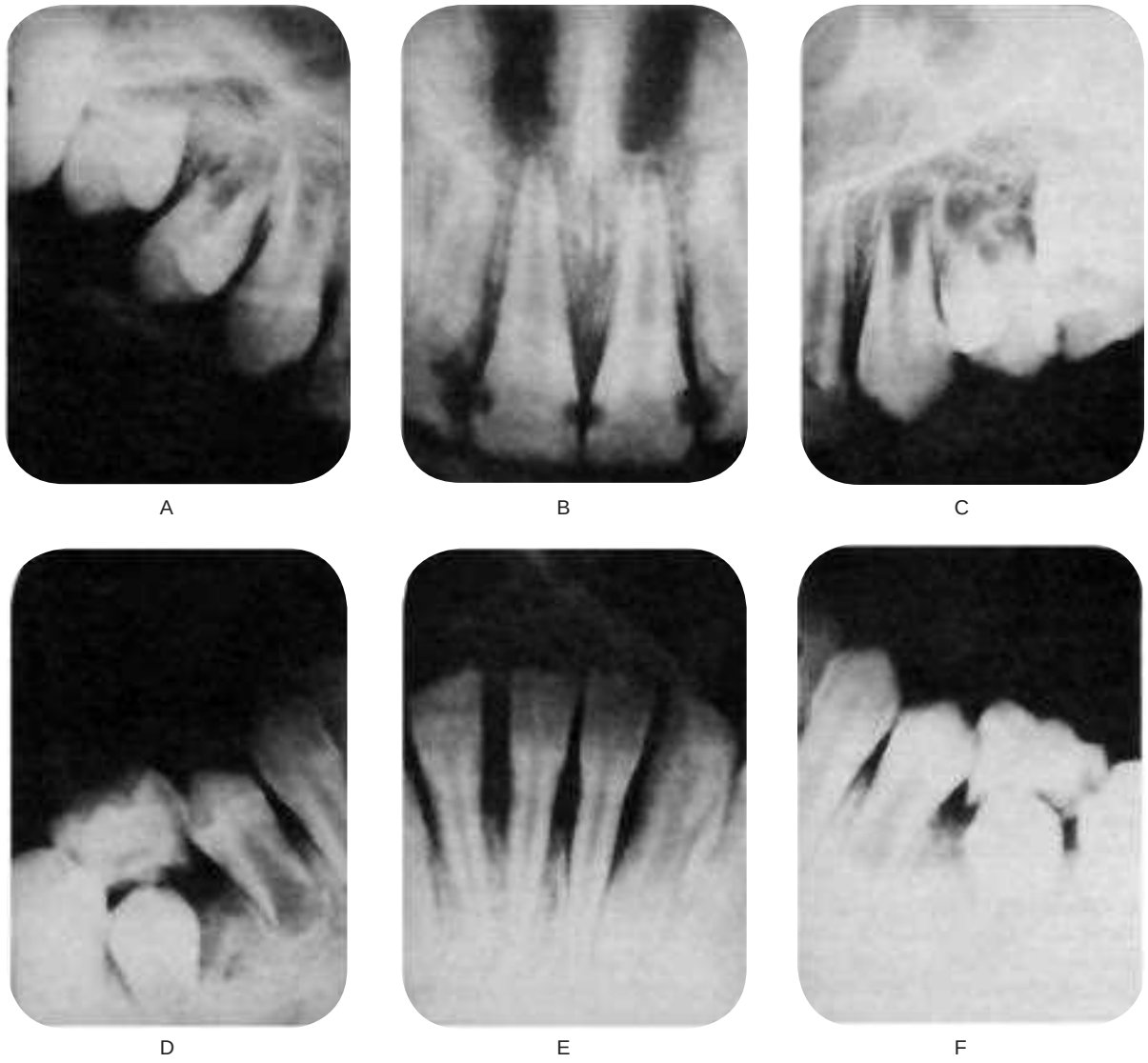


Figure 18-14. Cyclic neutropenia.
The radiographs demonstrate beginning of loss of alveolar bone even at an early age, due to the repeated episodes of gingival infection and inflammation.

Laboratory Findings. Cyclic neutropenia is an unusual disease which manifests the clinical signs and symptoms and blood changes in a periodic fashion. The cycle commonly occurs every three weeks, although in some cases it may be several months or even longer in duration.

The patient may exhibit a normal blood count which, over a period of four to five days, begins to show a precipitous decline in the neutrophil count compensated by an increase in monocytes and lymphocytes. At the height of the disease, the neutrophils may completely disappear for a period of one or two days. Soon; however, the cells begin to reappear, and within four to five days the blood cell count and differential count are essentially normal.

Treatment and Prognosis. There is no specific treatment for the disease, although in some instances splenectomy has proved beneficial. Death occasionally results, usually from intercurrent infection, but the prognosis is generally far better than in typical agranulocytosis. The patients may suffer from their periodic disease for years.

Chediak-Higashi Syndrome
(Béguez César syndrome, Chédiak-Steinbrinck-Higashi syndrome)

Chédiak-Higashi syndrome (CHS) was described by Béguez Cesar in 1943, Steinbrinck in 1948, Chédiak in 1952, and Higashi in 1954. Chédiak-Higashi syndrome is an autosomal recessive immunodeficiency disorder characterized by abnormal intracellular protein transport.

Clinical Features. Chédiak-Higashi syndrome affects all races and usually appears soon after birth or in children younger than five years. This disease is characterized by immune deficiency; partial oculocutaneous albinism; easy bruisability and bleeding as a result of deficient platelet dense bodies; recurrent infections with neutropenia, impaired chemotaxis,

Table 18-7: Differential diagnosis of neutropenia

- Pseudoneutropenia
- Acquired neutropenia
  - Infections
    - Bacterial
    - Viral
    - Protozoal
    - Rickettsial
    - Fungal
  - Drugs and chemicals
  - Nutritional
    - Cachexia and debilitated states
    - B_{12} and folate deficiencies
    - Copper deficiency
  - Immune neutropenia
    - Isoimmune neonatal neutropenia
    - Chronic autoimmune neutropenia
    - T-γ lymphocytosis
    - Miscellaneous immunologic neutropenia
  - Felty syndrome
  - Neutropenia associated with complement activation
    - Dialysis, bypass
    - Extracorporeal membrane oxygenation
    - Anaphylactoid shock
  - Splenic sequestration
- Congenital or chronic neutropenias
  - Severe congenital neutropenia (Kostmann syndrome)
  - Cyclic neutropenia
  - Chronic benign neutropenia
    - Familial
    - Nonfamilial (chronic granulocytopenia of childhood)
  - Idiopathic chronic severe neutropenia
  - Neutropenias associated with congenital immune defects
    - Neutropenia with immunoglobulin abnormality
    - Neutropenia with defective cell-mediated immunity
  - Reticular dysgenesis
  - Neutropenias associated with phenotypic abnormalities
    - Shwachman syndrome
    - Cartilage-hair hypoplasia
    - Dyskeratosis congenita
    - Barth syndrome
    - Chediak-Higashi syndrome
  - Myelokathexia
  - Lazy leukocyte syndrome
- Metabolic disease

Adapted from Wintrobe's Clinical Hematology, 10th ed. Williams and Wilkins, 1998.

and bactericidal activity; and abnormal natural killer (NK) cell function.

The Chédiak-Higashi syndrome gene was characterized in 1996 as the ***LYST*** or ***CHS1*** gene and is localized to bands **1q42–43** which encodes a lysosomal trafficking regulator. The CHS gene affects the synthesis and/or maintenance of storage or secretory granules in these cells, e.g. lysosomes of leukocytes and fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, and melanosomes of melanocytes. The impaired function in the polymorphonuclear leukocytes may be due to abnormal microtubular assembly. Defective melanization of melanosomes, i.e. autophagocytosis of melanosomes results in oculocutaneous albinism in CHS.

The disease is often fatal in childhood as a result of terminal phase characterized by nonmalignant lymphohistiocytic lymphoma like infiltration of multiple organs that occurs in more than 80% of patients. This stage is precipitated by virus infection, particularly by the Epstein-Barr virus. It is associated with anemia, bleeding episodes, and overwhelming infections leading to death. Infections secondary to abnormal functioning of polymorphonuclear leukocytes commonly involve the skin, the lungs, and the respiratory tract. Infections are usually caused by *Staphylococcus aureus, Streptococcus pyogenes,* and Pneumococcus species. Very few patients live to adulthood and in these patients, a progressive neurologic dysfunction may be the dominant feature. Neurologic involvement is variable but often includes peripheral neuropathy.

Oral Manifestations. Ulcerations of the oral mucosa, severe gingivitis, and glossitis are the commonly described oral lesions, as in the case report of Gillig and Caldwell. Hamilton and Giansanti have pointed out that periodontal breakdown, probably related to defective leukocyte function, may also be a common oral feature.

Laboratory Findings. Hematologic studies show that the patients classically exhibit giant abnormal granules in the peripheral circulating leukocytes, in their marrow precursors, and in many other cells of the body as well. These granules are the hallmark of the syndrome and are invariably present. They are thought to represent abnormal lysosomes and bear resemblance to toxic granulations and Dohle bodies. Pancytopenia is sometimes present. Ultrastructurally viable dividing bacteria, along with abnormal granules, are found in the cytoplasm of periodontal polymorphonuclear leukocytes.

Treatment and Prognosis. There is no specific treatment for the disease. It is often fatal, with death occurring before the child reaches the age of 10 years.

LEUKOCYTOSIS

Leukocytosis is defined as an abnormal increase in the number of circulating white blood cells. This condition is usually considered to be a manifestation of the reaction of the body to a pathologic situation. Any increase in the number of circulating white blood cells, particularly when involving only one type of cell, should prompt suspicion of and investigation for a particular disease, especially when the laboratory findings are correlated with the clinical findings in the patient. Care must be exercised in separating an absolute from a relative leukocytosis. But this should offer little difficulty.

A tabulation of the various conditions in which a pathologic increase in the number of each form of white blood cell is found has been compiled by Wintrobe. This classification is presented in Table 18-8. In addition, a transient peripheral plasmacytosis, a cell not normally seen in circulating blood, may be found occasionally in a variety of pathologic situations or conditions listed in Table 18-9.

Table 18-8: Causes of neutrophilia, eosinophilia, basophilia, lymphocytosis, and monocytosis

Neutrophilia
1. Acute infections, including localized infections, especially coccal, certain bacilli, fungi, spirochetes, viruses and parasites. Certain general infections, such as rheumatic fever, diphtheria and smallpox
2. Inflammatory conditions, such as coronary thrombosis, gout, collagen vascular disease, burns and hypersensitivity reactions
3. Intoxications a. Metabolic: uremia, diabetic acidosis, eclampsia b. Poisoning by chemicals and drugs: lead, mercury, digitalis; insect venoms: black widow spider; foreign proteins, after a preliminary leukopenia
4. Acute hemorrhage
5. Acute hemolysis
6. Malignant neoplasms when growing rapidly, especially in gastrointestinal tract, liver or bone marrow
7. Physiologic in the newborn, during labor, after strenuous exercise, after repeated vomiting, convulsions, paroxysmal tachycardia, after epinephrine injection
8. Myelocytic leukemia, polycythemia, myelofibrosis and myeloid metaplasia
9. Miscellaneous: chronic idiopathic neutropenia, hereditary neutrophilia, adrenocorticosteroids
Eosinophilia
1. Allergic disorders: bronchial asthma, urticaria, angioneurotic edema, hay fever, some drug sensitivity
2. Skin diseases, especially pemphigus and dermatitis herpetiformis
3. Parasitic infestations, especially parasites which invade the tissues: e.g. trichinosis, echinococcus disease; less regularly in intestinal parasitism
4. Certain infections: e.g. scarlet fever, chorea, erythema multiforme
5. Certain diseases of the hemopoietic system: chronic myelocytic leukemia, polycythemia vera, Hodgkin's disease, after splenectomy, pernicious anemia
6. Malignant disease of any type, especially with metastasis or necrosis
7. Following irradiation
8. Loeffler's syndrome and pulmonary infiltration and eosinophilia
9. Tropical eosinophilia
10. Miscellaneous: periarteritis nodosa, rheumatoid arthritis, sarcoidosis, certain poisons, etc
11. Inherited anomaly
12. Idiopathic
Basophilia
1. Blood diseases: chronic myelocytic leukemia, erythremia, chronic anemia, chlorosis and Hodgkin's disease
2. Splenectomy
3. Infections: chronic inflammation of accessory sinuses, smallpox, chickenpox
4. After injection of foreign proteins
5. Myxedema
6. Some cases of nephrosis
Lymphocytosis
1. Certain acute infections: pertussis, infectious mononucleosis, acute infectious lymphocytosis, infectious hepatitis
2. Chronic infections, such as tuberculosis, secondary and congenital syphilis and undulant fever
3. Lymphocytic leukemia, acute and chronic, some cases of lymphosarcoma, heavy chain disease
4. Hemopoietic disorders: relative lymphocytosis, in most conditions associated with neutropenia, exanthems, after the initial stage, especially in mumps and German measles, during convalescence from an acute infection, in thyrotoxicosis
Monocytosis
1. Certain bacterial infections: tuberculosis, subacute bacterial endocarditis, syphilis, brucellosis, rarely in typhoid
2. During subsidence of acute infections and recovery phase of agranulocytosis
3. Many protozoal and some rickettsial infections: malaria, Rocky Mountain spotted fever, typhus, kala-azar, trypanosomiasis, Oriental sore
4. Lymphoma, leukemia and other hematologic disorders: Hodgkin's disease and other lymphomas, monocytic leukemia, chronic myelocytic leukemia and 'myeloproliferative' disorders, multiple myeloma
5. Lipid storage diseases, such as Gaucher's disease
6. Malignant neoplasms: carcinoma of ovary, stomach and breast
7. Collagen vascular disease: lupus erythematosus and rheumatoid arthritis
8. Granulomatous diseases: sarcoidosis, ulcerative colitis and regional arteritis
9. Tetrachloroethane poisoning
10. Chronic high-dose steroid therapy

Modified from MM Wintrobe: Clinical Hematology, 8th ed. Lea and Febiger, Philadelphia, 1981.

Table 18-9: Causes of peripheral plasmacytosis

I. Infections
- A. Viral
  - 1. Rubella
  - 2. Rubeola
  - 3. Varicella
  - 4. Infectious mononucleosis
- B. Bacterial
  - 1. Streptococcal
  - 2. Diplococcal
  - 3. Syphilis
  - 4. Tuberculosis
- C. Protozoal
  - 1. Malaria
  - 2. Trichinosis

II. Serum sickness
- A. Drugs
  - 1. Penicillin
  - 2. Sulfisoxazole
- B. Antitoxins
  - 1. Equine tetanus
  - 2. Equine diphtheria

III. Neoplasia
- A. Hematologic
  - 1. Plasma-cell leukemia
  - 2. Chronic lymphocytic leukemia
- B. Nonhematologic
  - 1. Breast
  - 2. Prostate

IV. Miscellaneous
- A. Pokeweed mitogen
- B. Transfusion
- C. Hyperimmunization
- D. Trauma

Infectious Mononucleosis
(Glandular fever)

Infectious mononucleosis was first described by Sprunt and Evans in the Johns Hopkins Medical Bulletin in 1920. These authors described the clinical characteristics of Epstein-Barr virus (EBV) infectious mononucleosis, and, at the time, their paper was entitled 'Mononuclear leukocytosis in reaction to acute infection (infectious mononucleosis)'. Since the 1800s, infectious mononucleosis has been recognized as a clinical syndrome consisting of fever, pharyngitis, and adenopathy. The term glandular fever was first used in 1889 by German physicians and was termed **Drusenfieber**.

The disease occurs chiefly in children and young adults. It has been transmitted experimentally to monkeys by the administration either of emulsified material from lymph nodes or of Seitz filtrate of the blood from affected human beings. EB virus is transmitted via intimate contact with body secretions, primarily oropharyngeal secretions and one important means is thought to be through 'deep kissing' or intimate oral exchange of saliva. For this reason, the condition has sometimes been called the 'kissing disease'. It is known that oral excretion of the EB virus may continue for as long as 18 months following onset of the disease, although this excretion may be either constant or intermittent.

Clinical Features. Frequently seen in epidemic form, infectious mononucleosis is characterized by fever, sore throat, headache, chills, cough, nausea or vomiting and lymphadenopathy (bilateral and symmetrical). Splenomegaly and hepatitis also occur with considerable frequency. Most patients with EBV infectious mononucleosis can be asymptomatic.

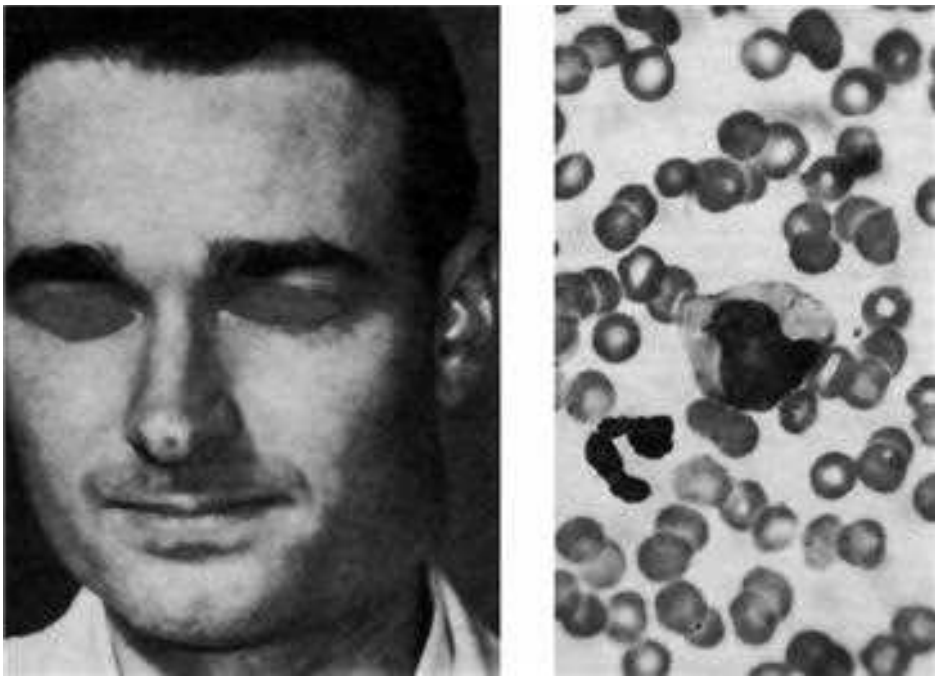
The cervical lymph nodes are usually the first to exhibit enlargement, followed by the nodes of the axilla and groin (Fig. 18-15A). Pharyngitis and tonsillitis are common, but not invariably present, and skin rash has occasionally been reported.

The majority of cases in children appear to be asymptomatic. However, the peak incidence of the disease occurs in the 15 to 20-year-old age group. There does not appear to be a sex or seasonal predilection for occurrence.

Oral Manifestations. There are apparently no specific oral manifestations of infectious mononucleosis, although secondary lesions do occur. An excellent review of the literature and study of the oral lesions occurring in 140 patients with infectious mononucleosis was reported by Fraser-Moodie. The oral manifestations consisted chiefly of acute gingivitis and stomatitis, the appearance of a white or gray membrane in various areas, palatal petechiae and occasional oral ulcers. Of his entire series of 140 patients, 32% exhibited oral manifestations, and interestingly, in 50% of the patients with stomatitis the oral lesions were the first sign of the disease. Edema of the soft palate and uvula has also been reported in some cases.

Reports by Shiver and his coworkers and by Courant and Sobkov emphasized the finding of petechial hemorrhages of the soft palate near the junction with the hard palate as an early manifestation of infectious mononucleosis (Fig. 18-16). These have been described as pinpoint petechiae, numbering from a dozen to several hundred, which appeared a few days after other symptoms in 50–65% of the patients in these series. The lesions persisted for 3–11 days and then gradually faded. They must be differentiated from areas of increased vascularity and pigmented areas. This occurrence of palatine petechiae as an early clinical diagnostic sign of infectious mononucleosis has also been confirmed by Schumacher and Barcay. They reported that approximately 7% of a series of 452 patients with this disease had hemorrhagic manifestations, nearly half of these presenting with palatine petechiae. About one-third of the patients with the hemorrhagic tendency exhibited oronasopharyngeal bleeding, including bleeding from the gingiva.

Laboratory Findings. The patient exhibits atypical lymphocytes in the circulating blood, as well as antibodies to the EB virus and an increased heterophil antibody titer (Fig. 18-15B). However, the increased heterophil is present only in a small minority of children with the disease. The normal titer of agglutinins and hemolysins in human blood against sheep red blood cells does not exceed 1 : 8. In infectious mononucleosis; however, the titer may rise to 1 : 4096. This is referred to as a positive Paul-Bunnell test and is both characteristic and pathognomonic of the disease. Agglutination of horse RBCs on exposure to EB virus heterophile antibodies (Monospot test) is a highly specific test. In acute



A B

Figure 18-15. Infectious mononucleosis.
Severe cervical lymphadenopathy is present **(A)**, while the peripheral blood smear exhibits numerous atypical lymphocytes with indented nuclei such as that illustrated in **(B)**.

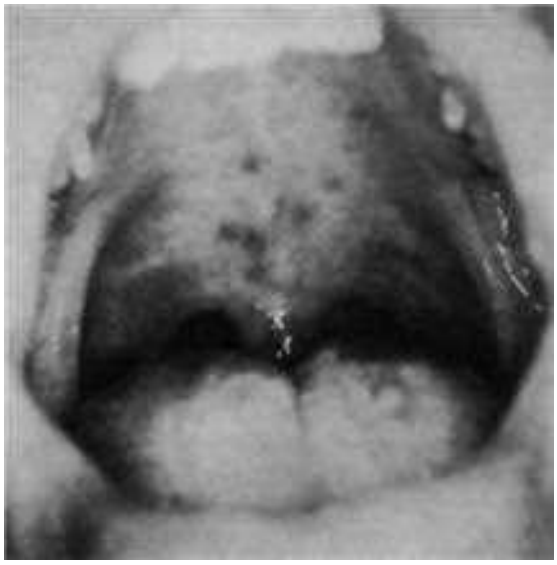


Figure 18-16. Infectious mononucleosis.
Palatal petechiae occurred as a prodromal manifestation of the disease.

infection, the viral core antigen antibody of IgM class titer against EBV is increased. Later in the course of infection, the increase in IgM viral core-antigen (VCA) antibodies may be accompanied by an increase in IgG VCA antibodies and an increase in IgG EBNA (EBV nuclear antigen antibodies). EBNA appears after one to two months and persists throughout life. Thus the presence of this antibody suggests previous exposure to the antigen. The erythrocyte sedimentation rate is elevated in most patients with EBV infectious mononucleosis.

An increase in the white blood cell count is also common, and this is almost invariably a lymphocytosis. In fact, infectious mononucleosis is defined partly on the basis that the patient has more than a 50% lymphocytosis, of which 10% or more are the 'atypical' forms. These 'atypical' forms consist of either oval, horseshoe-shaped or indented nuclei with dense, irregular nuclear chromatin and a basophilic, foamy or vacuolated cytoplasm. A thrombocytopenia is also present in some patients. It is an interesting finding that during the acute phase of infectious mononucleosis, patients frequently have a normal sedimentation rate.

Treatment. There is no specific treatment for this disease. The various antibiotics have been used without great success. Bed rest and adequate diet are probably of as great a benefit as any other form of therapy. Short-term steroid therapy has occasionally been used, but the results have been somewhat inconsistent. The disease generally runs its course in two to four weeks, and there seldom are complications.

Leukemia

Leukemia is a disease characterized by the progressive overproduction of white blood cells which usually appear in the circulating blood in an immature form. This proliferation of white blood cells or their precursors occurs in such an uncoordinated and independent fashion that leukemia is generally considered a true malignant neoplasm, particularly since the disease is so often fatal. Any of the white blood cells may be involved by this disorder, and for this reason the disease is often classified according to the following types:

1. Lymphoid (lymphoblastic, lymphocytic) leukemia—involving the lymphocytic series.
2. Myeloid (myelogenous) leukemia—involving progenitor cell that gives rise to terminally differentiated cells of the myeloid series (erythrocytes, granulocytes, monocytes and platelets), e.g. acute myelogenous leukemia, acute promyelocytic leukemia, acute monocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia (Cotran et al, 2001).

This classification may be modified to indicate the course of the disease by application of the terms 'acute', 'subacute', and 'chronic'. An acute form of leukemia is one in which survival is less than six months; chronic leukemia implies a survival of over one year, and the subacute form lies between these two. In general, the course of the disease closely parallels the degree of anaplasia of the malignant cells; thus the more undifferentiated the cell, the more acute is the course. The relation of the leukemias to other malignant diseases of the lymphoid tissues is discussed under the section dealing with the malignant lymphomas.

Etiology. The etiology of leukemia is unknown. Certain aspects of the disease have suggested an infectious origin to some investigators, but a specific causative organism has never been isolated. Of these, viruses have been suspected for many years of being most closely related to this disease. It has been recognized for many years that a variety of animal leukemias were almost certainly of viral origin. It has been shown by Stewart and Eddy that the 'polyoma' virus is capable of producing numerous different types of neoplasms in a variety of animals, one of these neoplasms being leukemia.

It is rather well accepted by most workers in the field of viral oncology today that avian, feline and murine leukemia are caused by leukemogenic viruses. However, the animals must be rendered immunologically vulnerable and it is possible that, in the human as well as in the experimental animal, radiation and a variety of chemicals, both of which have been closely associated with leukemia for many years, may be at least one key to this immunologic susceptibility. Not only is the incidence of leukemia among radiologists approximately 10 times higher than among general practitioners of medicine, but also the data indicate a general rise in the incidence of this disease among the Japanese exposed to the atomic bomb blasts at Hiroshima and Nagasaki. In addition, chronic exposure to benzol, aniline dyes and related chemicals has been recognized for many years as being associated with the development of leukemia.

The Epstein-Barr (EB) virus, a herpes like virus, has been implicated as being the most likely leukemogenic virus in humans because of the high antibody titer against this virus in leukemic patients, as well as the finding in leukemic cells of viruses with a morphologic similarity to the EB virus. Human T-cell leukemia virus-1 (HTLV-1) is known to be associated with a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin.

It is also recognized that chromosomal abnormalities commonly occur in leukemic patients. One such abnormality is the finding of the Philadelphia chromosome in between 85 and 95% of patients with chronic myeloid leukemia. This Philadelphia chromosome, at one time thought to be a partial deletion of the long arm of chromosome 22, is now recognized as a translocation of chromosomal material from chromosome 22 to chromosome 9. In about 5% of cases, the translocation occurs to other chromosomes. It is interesting to note that this chromosome disappears from the circulation during remission of the disease in many cases but will reappear when there is a relapse. In addition, a variety of other chromosomal abnormalities also have been recognized as occurring in over 50% of patients with different forms of poorly differentiated leukemia.

It should be remembered that mongolism or Down syndrome is due to a defect or trisomy of chromosome 21. Interestingly, it has been found that the incidence of leukemia in mongoloids is between three and 15–20 times that of the general population. However, this type of leukemia in mongoloids is generally an acute form of leukemia in contrast to the chronic leukemia associated with the Philadelphia chromosome.

The importance of various cofactors or predisposing characteristics, such as genetics, age, hormones, immune competence and stress, must all be considered in determining the susceptibility to tumor development of an individual infected with an oncogenic virus. Only when this has been accomplished can there be any attempt at specific cure or even prevention of the disease.

Clinical Features. The age of the patients affected by leukemia varies remarkably, but generally may be correlated with the course of the disease. Thus acute leukemia occurs more commonly in children and young adults, while chronic leukemias are most frequently seen in adults of middle age or older. There are; however, many exceptions to this general rule. There is some difference in the gender predilection, males being affected more often than females. No notable differences exist in the clinical manifestations of the morphologic forms of leukemia except that most cases of acute leukemia in adults are of the monocytic variety; thus all types of acute leukemia present a similar clinical picture and cannot be differentiated without recourse to laboratory studies. The same is true for chronic leukemia. For this reason the clinical features of leukemia can be discussed under the general categories of acute and chronic forms of the disease.

Acute leukemia. The development of acute leukemia is sudden, characterized by weakness, fever, headache, generalized swelling of lymph nodes, petechial or ecchymotic hemorrhages in the skin and mucous membranes and evidence of anemia. The lymphadenopathy is often the first sign of the disease, although many cases are recorded in which the oral lesions were the initial manifestation. In a survey of children with acute lymphoblastic leukemia, White has shown that in at least two-thirds of the cases, cervical lymph nodes are palpable before diagnosis and treatment of the disease have been established.

Numerous organs, such as the spleen, liver and kidney, become enlarged, owing to leukemic infiltration, especially in

cases of long duration. In the fulminating variety of the disease there is not time for gross pathologic changes to develop. Hemorrhages are common due to the decrease in platelets incident to involvement of the bone marrow and decrease in megakaryocytes. Terminal infection is frequent and may be related to the crowding out of myeloid tissue which ordinarily produces granulocytes.

Chronic leukemia. In contrast to acute leukemia, chronic leukemia develops so insidiously that the disease may be present for months or even several years before the symptoms lead to discovery. It is not unusual for this form of leukemia to be found by a routine hematologic examination in which an unexplained leukocytosis is noted.

The patient may appear in excellent health or exhibit features such as an anemic pallor and emaciation suggestive of a chronic debilitating disease. Lymph node enlargement is common in chronic lymphatic leukemia, but uncommon in myeloid leukemia, as might be expected, particularly in the early stages of the disease. The protracted course of the disease allows sufficient time for full development of splenomegaly and hepatomegaly. Enlargement of the salivary glands and tonsils also may occur, owing to leukemic infiltration, and this results in xerostomia.

The skin is frequently involved in chronic leukemia and may manifest petechiae or ecchymoses. In other instances there may be leukemids: papules, pustules, bullae, areas of pigmentation, herpes zoster, itching and burning sensations or a variety of other disturbances. Finally, nodular lesions composed of leukemic cells may occur on the skin.

Destructive lesions of bone are reported in some cases of chronic leukemia, and these may result in pathologic fracture or osteomyelitis.

Laboratory Findings. Hematologic examination constitutes the basis for the final diagnosis of any type of leukemia. It is recognized; however, that 'subleukemic' or 'aleukemic' forms of the disease exist in which the white blood cell count of the peripheral blood is normal or even subnormal and in which these are or are not abnormal or immature leukocytes present.

Acute leukemia. Anemia and thrombocytopenia are both characteristic of acute leukemia. As a result, in some instances, both bleeding time and coagulation time are prolonged. The tourniquet test is usually positive.

The leukocyte count may be subnormal, particularly in the early stages of the disease, but it usually rises in the terminal stages to 100,000 or more cells per cubic millimeter, and there is a corresponding increase in the proportion of the involved cell in the differential count. This increase in cells is due to a single cell type, usually very immature. In myeloid leukemia the predominant cell often resembles the myeloblast, or undifferentiated myelocyte. The cells of lymphoid leukemia may exhibit considerable variation in degree of differentiation. Monocytic leukemia also manifests poorly differentiated cells (Fig. 18-17).

In many instances, it is difficult if not impossible for even an experienced hematologist to distinguish the exact type of acute leukemia. The term 'stem cell leukemia' is sometimes applied to those types in which the leukemic cells are highly undifferentiated. Such cases are most difficult to diagnose.

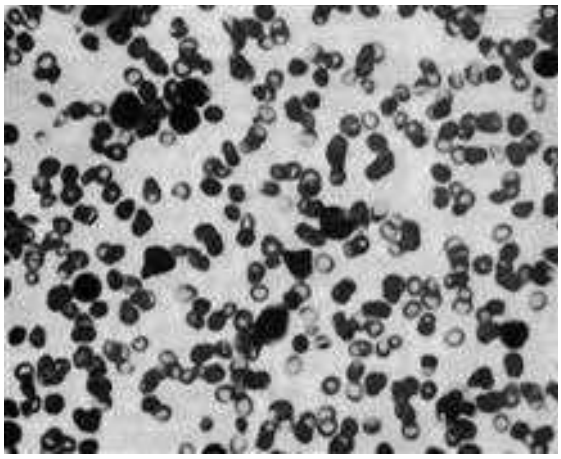


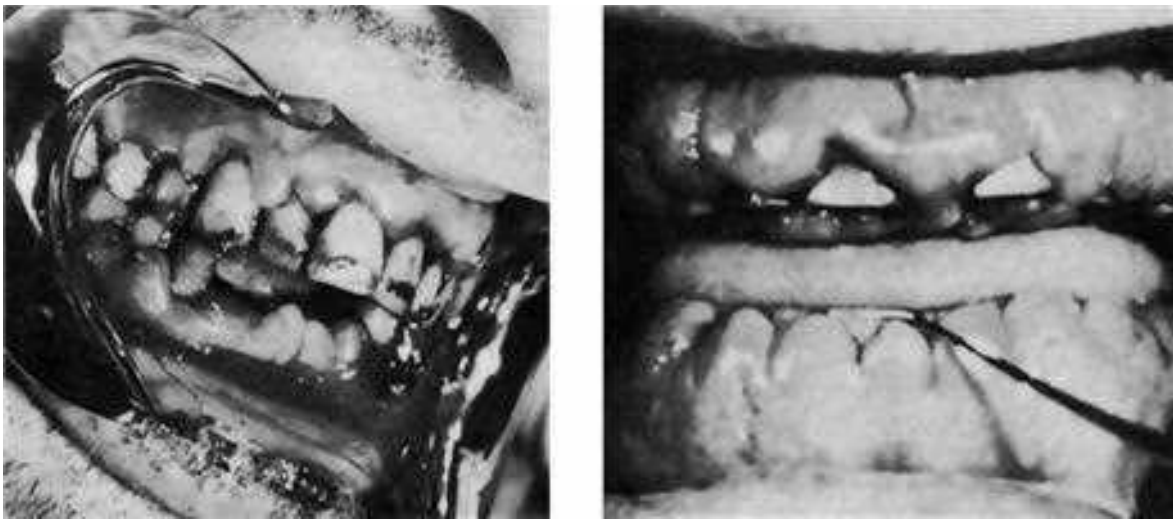
Figure 18-17. Monocytic leukemia, acute.
Vast numbers of atypical, pleomorphic monocytes are present in the peripheral blood smear.

Chronic leukemia. Anemia and thrombocytopenia are also common in the chronic form of leukemia. The leukocytosis may be great, and white blood cell counts of over 500,000 cells per cubic millimeter are not uncommon. On the other hand, very low white blood cell counts also occur. In all forms of the chronic dyscrasia the differential count is elevated in the cell type involved, and often over 95% of the total number of cells are leukemic cells.

Oral Manifestations. Oral lesions occur in both acute and chronic forms of all types of leukemia: myeloid, lymphoid and monocytic. These manifestations are far more common; however, in the acute stage of the disease, and according to Burket, are most common in monocytic leukemia. In a series of cases he reported oral lesions in 87% of patients with monocytic leukemia, in 40% of patients with myeloid leukemia, and in 23% of those with lymphoid leukemia. Osgood found a similar high incidence of oral manifestations in monocytic leukemia, reporting that 80% of affected patients exhibited gingival hyperplasia. An 80% incidence of positive oral findings was reported in a series of 38 leukemic patients by Duffy and Driscoll. Interestingly, those patients not manifesting oral lesions were either very young children or edentulous persons. In a study of 292 children with leukemia of different types, Curtis found that only slightly less than 30% had oral findings suggestive of leukemia. He pointed out that this infrequency of oral manifestations in childhood leukemia is due primarily to the high incidence of acute lymphocytic leukemia in this age group, since this type is least likely to produce oral lesions.

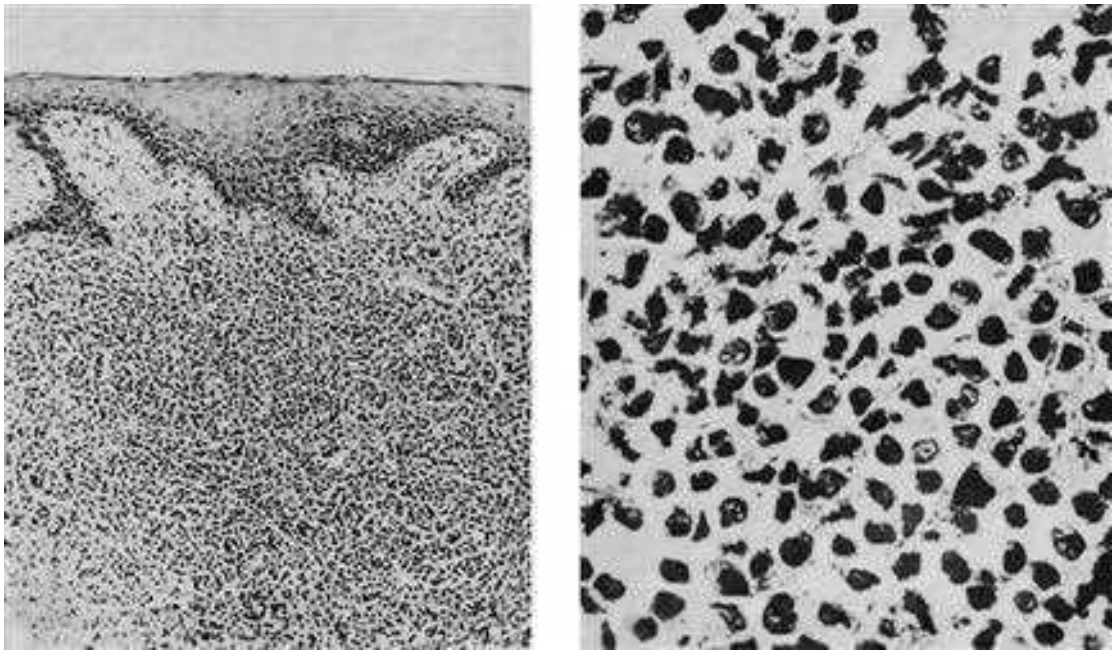
Often a patient with leukemia presents himself to his/her dentist for treatment of oral lesions, not suspecting that they are more than local in nature. These primary clinical manifestations of the disease may consist of gingivitis, gingival hyperplasia, hemorrhage, petechiae and ulceration of the mucosa.

The gingival hyperplasia, which may be one of the most constant features of the disease except in edentulous patients,



A B

Figure 18-18. Monocytic leukemia.
The severe gingival hyperplasia may develop within a few weeks.



A B

Figure 18-19. Monocytic leukemia.
The gingival tissue is densely infiltrated by atypical blood cells **(A)** with a mononuclear configuration **(B)**.

is usually generalized and varies in severity. In severe cases the teeth may be almost completely hidden (Fig. 18-18). The gingivae are boggy, edematous and deep red. They bleed easily. The gingival swelling is due to the leukemic infiltration in areas of mild chronic irritation (Fig. 18-19). Purpuric lesions of the oral mucosa analogous to the cutaneous ecchymoses may also be seen.

The gingival hemorrhage which commonly occurs is due to ulceration of the sulcus epithelium and necrosis of underlying tissue. Since the normal white blood cells distribution is greatly disturbed, a normal inflammatory response to even a mild infection is impossible. For this reason severe ulceration of the oral mucosa and even the development of a noma-like condition is not unusual. Thrombosis of gingival vessels appears to contribute to this phenomenon.

Rapid loosening of the teeth due to necrosis of the periodontal ligament has been reported, and destruction of alveolar bone also occurs in some cases. The use of panoramic radiographs in a study of 214 children with acute leukemia has been reported by Curtis to be useful in demonstrating previously overlooked changes in the jaws. Of this group, approximately 63% exhibited osseous changes in the jaws, including alterations in developing tooth crypts, destruction

of lamina dura, displacement of teeth and poor radiographic definition of bone, sometimes extending to the crest of alveolar bones, with destruction of the bone in this area.

It is imperative that the dentist maintain a high index of suspicion in cases of periodontal lesions with a somewhat unusual appearance. The complaint of a patient that he/she has experienced sudden gingival bleeding or gingival hyperplasia should suggest the possibility of leukemia. As Michaud and her coworkers have indicated in a study of 77 children with the disease, the oral manifestations of acute leukemia may be varied; they are not pathognomonic. Any disease that causes immunosuppression, bone marrow suppression, and disease of the blood-forming organs may have one or more of the oral findings of acute leukemia at the time of its initial diagnosis.

Treatment. Spectacular advances have been made in the treatment of the leukemias over the past few years. At one time, the prognosis for this disease was almost hopeless. Today, a wide array of chemotherapeutic drugs, radiation therapy and corticosteroids under certain circumstances offer prolonged remissions and apparent cures in at least some forms of the disease. For example, the most common form of leukemia in children, acute lymphocytic leukemia, once almost always fatal within a few months, now has a prolonged remission and a probable cure rate approaching 50%. Because this area of treatment is changing so rapidly with the introduction of new drugs and new techniques, to cite data on therapeutic responses would not be meaningful. It is sufficient to note that while leukemia is still a serious disease, the outlook for the leukemic patient today is far more promising than it was only a few decades ago and will probably continue to improve.

DISEASES INVOLVING BLOOD PLATELETS

Blood platelets have a variety of unique and very necessary functions which include:

- Adhesion to a variety of substances, primarily collagen fibrils in the damaged vessel wall, which initiates a secretory process in which these are extruded from the cell (**release reaction**) granules including serotonin, adenosine triphosphate (ATP) and adenosine diphosphate (ADP). ADP can directly **aggregate** platelets, thus accounting for the primary and temporary arrest of bleeding after vascular wall disruption.
- Participation in the blood-clotting mechanism by providing a lipid or lipoprotein surface that may catalyze on or more reactions in the conversion of prothrombin to thrombin. This thrombin, in addition to converting fibrinogen to fibrin, can also aggregate platelets. An additional function, recently discovered, is their synthesis of certain prostaglandins which act as potent inhibitors of platelet aggregation in normal blood flow.

There has been very extensive research within the past two decades to clarify our understanding of platelet function, and particularly, our understanding of the exact mechanisms involved in some of the bleeding disorders which may be encountered clinically. Thus, the finding of a prolonged bleeding time in a patient with a normal platelet count would suggest some disturbance in platelet function. This could be a result of an inherent defect of the platelets, which is the usual case, or a deficiency of a plasma factor necessary for some certain aspects of platelet function.

Platelet physiology and abnormalities in their function have been thoroughly reviewed by Weiss and by Zieve and Levin, and the reader is referred to these sources for a discussion of hemostasis. Only the more common and well-recognized diseases involving blood platelets can be discussed in this section, but it should be emphasized that new pathologic entities in this area are being reported frequently.

Purpura

Purpura is defined as a purplish discoloration of the skin and mucous membranes due to the spontaneous extravasation of blood, and in itself, is a symptom rather than a disease entity. There are many causes of purpura, and the clinical manifestations of the condition are widely diversified.

Blood platelets play an obviously important role in the clotting mechanism, and if the platelets are defective or deficient, purpura may result (Fig. 18-20, Table 18-10). On the other hand, many times purpura will occur even though there are adequate numbers of thrombocytes in the circulating blood; in such cases the purpura is due to an unexplained increase in capillary fragility. This variability in presence or absence of blood platelet deficiency in cases of purpura has formed the basis of the following classification:

1. Nonthrombocytopenic purpura
2. Thrombocytopenic purpura
   (a) Primary or 'essential' purpura
   (b) Secondary or symptomatic purpura.

Nonthrombocytopenic Purpura

Nonthrombocytopenic purpura constitutes a heterogeneous group of diseases which have in common only the fact that they may cause purpura. As the name indicates, this type of purpura is not mediated through changes in the blood platelets, but rather through alteration in the capillaries themselves that result in many instances in increased permeability. The most common causes of nonthrombocytopenic purpura or conditions with which this form of purpura is associated are shown in Table 18-11.

The oral manifestations of this form of purpura vary considerably both in incidence of occurrence and in nature, and many of these will be discussed in other sections dealing with the specific etiologic agents. In general terms, the oral purpuric lesions resemble those to be described under thrombocytopenic purpura.

Thrombocytopenic Purpura

Thrombocytopenia is a disease in which there is an abnormal reduction in the number of circulating blood platelets. When this occurs, the patient develops focal hemorrhages into various tissues and organs, including the skin and mucous membranes.

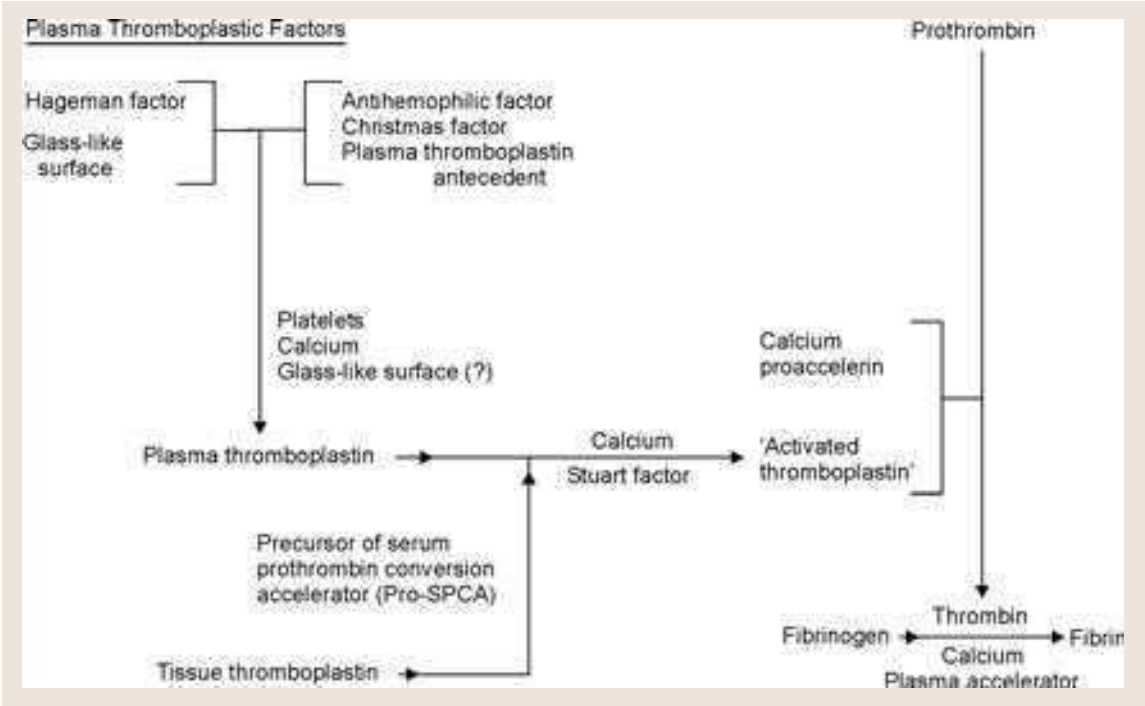


Figure 18-20. The mechanism of blood clotting.
From OD Ratnoff: Bleeding syndromes: A Clinical Manual. Springfield, III, Charles C Thomas, 1960.

Table 18-10: International nomenclature of blood clotting factors

Factor	Preferred synonyms
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin
IV	Ionized calcium
V	Accelerator globulin
	Proaccelerin
	Labile factor
VI	Term no longer used; factor VI-activated factor V
VII	Serum prothrombin conversion accelerator (SPCA)
	Convertin
	Stable factor
VIII	Antihemophilic globulin (AHG)
IX	Plasma thromboplastin component (PTC)
	Christmas factor
X	Stuart factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin stabilizing factor

Table 18-11: Bleeding disorders mainly due to vascular abnormalities (nonthrombocytopenic purpura)

I. Autoimmune
1. Allergic purpuras
2. Drug-induced vascular purpura
3. Purpura fulminans

II. Infections
1. Bacterial (meningococcemia and septicemia due to other organisms, typhoid fever, scarlet fever, diphtheria, tuberculosis, endocarditis, bacterial products, leptospirosis, others)
2. Viral (smallpox, influenza, measles, others)
3. Rickettsial (Rocky Mountain spotted fever, typhus, others)
4. Protozoal (malaria, toxoplasmosis)

III. Structural malformations
1. Hereditary hemorrhagic telangiectasia
2. Hereditary disorders of connective tissue (Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum)
3. Acquired disorders of connective tissue (scurvy, corticosteroid purpura, Cushing's disease, senile purpura, 'cachectic' purpura)

IV. Miscellaneous
1. Autoerythrocyte sensitization and related syndromes (DNA hypersensitivity, cutaneous hyper-reactivity to hemoglobin, psychogenic purpura, vicarious bleeding)
2. Paraproteinemias (hyperglobulinemic purpura, cryoglobulinemic purpura, Waldenström's macroglobulinemia, others)
3. Purpura simplex and related disorders ('orthostatic' and 'mechanical' purpura, factitial purpura)
4. Purpura in association with certain skin diseases (annular telangiectatic purpura, angioma serpiginosum, Schamberg's disease, pigmented purpuric lichenoid dermatitis)
5. Others (blood-borne tumor emboli, Kaposi's sarcoma, snake venoms, hemochromatosis, amyloidosis, other chronic diseases)

Modified from MM Wintrobe: Clinical Hematology, 8th ed. Lea and Febiger, Philadelphia, 1981.

Two basic forms of thrombocytopenia are recognized: primary, which is of unknown etiology; and secondary, which may be due to a wide variety of situations listed in Table 18-12. One subtype, thrombotic thrombocytopenic

Table 18-12: Etiological classification of secondary thrombocytopenia

I. Conditions associated with a reduction of platelet production
- A. Hypoplasia or aplasia of megakaryocytes
  1. Ionizing radiation
  2. Drugs and chemicals (e.g. certain oncolytic compounds, organic solvents, chemotherapeutic agents, antibiotics, anticonvulsants, antihistamines, sedatives and tranquilizers, heavy metals, hair dyes and shoe polishes, insecticides, antithyroid drugs, antidiabetic drugs and a variety of others)
  3. Congenital hypoplastic anemia
  4. Fanconi's familial anemia
  5. Congenital thrombocytopenia with absent radii
  6. Aplastic anemia with thymoma
  7. Agnogenic myeloid metaplasia
  8. 'Idiopathic'
- B. Infiltration of marrow by abnormal cells
  1. Leukemia
  2. Metastatic tumors
  3. Multiple myeloma
  4. Histiocytoses
- C. Megaloblastic anemia
- D. Metabolic disorders
  1. Azotemia
  2. Hypothyroidism
- E. Infection (e.g. many bacterial diseases, including pneumococcal pneumonia, meningococcal infection, erysipelas, scarlet fever, diphtheria, tuberculosis, bacterial endocarditis and others; certain spirochetal infections, including syphilis; certain rickettsial infections; many viral infections, including measles, chickenpox, mumps, influenza, smallpox, cat-scratch fever, infectious hepatitis and infectious mononucleosis; certain protozoan and metazoan diseases)

II. Conditions associated with a reduction of platelet lifespan
- A. Diseases related to immune mechanism
  1. Sensitivity to drugs (e.g. certain sedatives, antipyretics, chemotherapeutic agents, cardiac therapeutic agents, antihistaminics, antidiabetic drugs and a variety of others)
  2. Experimental anaphylaxis
  3. Infections (same as those listed in I, E above)
  4. Hemolytic anemias (e.g. acute idiopathic hemolytic anemia, toxemia of pregnancy, incompatible transfusion reactions)
  5. Systemic lupus erythematosus
  6. Thrombotic thrombocytopenic purpura
  7. Idiopathic thrombocytopenic purpura
- B. Diseases resulting in platelet sequestration or utilization at an excessive rate
  1. Splenomegaly (e.g. congestive splenomegaly, Gaucher's disease, sarcoidosis, miliary tuberculosis)
  2. Platelet sequestration (e.g. congenital hemangiomatosis, Kaposi's sarcoma, experimental hypothermia)
  3. Intravascular coagulation: amniotic fluid embolism

III. Thrombocytopenia due to dilution of platelets by transfusion of platelet-poor blood

IV. Conditions in which thrombocytopenia is of idiopathic pathogenesis
- A. Infections (same as those listed in I, E above)
- B. Congenital thrombocytopenia with eczema and repeated infections
- C. Familial thrombocytopenia
- D. Onyalai
- E. Thermal burns
- F. Heat stroke
- G. Kwashiorkor
- H. Macroglobulinemia
- I. Hypofibrinogenemia with carcinoma, premature separation of placenta, etc.
- J. Paroxysmal nocturnal hemoglobinuria

Modified from OD Ratnoff: Bleeding Syndromes: A Clinical Manual. Springfield, Ill, Charles C Thomas, 1960.

purpura, will be discussed separately because of its unusual clinical and histologic features.

Primary Thrombocytopenia
(Werlhof's disease, purpura hemorrhagica and idiopathic purpura)

Primary thrombocytopenia is thought by some investigators to be an autoimmune disorder in which a person becomes immunized and develops antibodies against his/her own platelets. The discovery in the serum of thrombocytopenic patient of an antiplatelet globulin which results in a decrease in the number of circulating platelets when administered to normal patients has given credence to this theory. However, some cases appear due to the absence of a platelet-stimulating or megakaryocyte-ripening factor. The acute form of the primary type of disease commonly occurs in children, often following certain viral infections, while the **chronic** type occurs most frequently in adults, especially women of childbearing age.

The various manifestations of primary and secondary thrombocytopenic purpura are nearly identical, and for this reason, may be described together.

Clinical Features. Thrombocytopenic purpura is characterized by the spontaneous appearance of purpuric or hemorrhagic lesions of the skin which vary in size from tiny, red pinpoint petechiae to large purplish ecchymoses and even massive hematomas. The patient also exhibits a bruising tendency.

Epistaxis, or bleeding from the nose, is a common manifestation of the disease, as are bleeding in the urinary tract, resulting in hematuria, and bleeding in the gastrointestinal tract, producing melena or hematemesis. A possible complication is intracranial hemorrhage, which may result in hemiplegia. The spleen is usually not palpable. If it is palpable, leukemia should be suspected instead of thrombocytopenic purpura.

According to Wintrobe and his associates, over 80% of cases of primary thrombocytopenic purpura occur before the age of 30 years, with the greatest incidence before 10 years. Many patients present a familial history of purpura. Secondary thrombocytopenia has no particular age predilection.

Oral Manifestations. One of the prominent manifestations of thrombocytopenic purpura is the severe and often profuse gingival hemorrhage which occurs in the majority of cases (Fig. 18-21). This hemorrhage may be spontaneous and often arises in the absence of skin lesions.

Petechiae also occur on the oral mucosa, commonly on the palate, and appear as numerous tiny, grouped clusters of reddish spots only a millimeter or less in diameter. Actual ecchymoses do occur occasionally.

The tendency for excessive bleeding contraindicates any oral surgical procedure, particularly tooth extraction, until the deficiency has been compensated.

Laboratory Findings. The thrombocytopenia may be exceptionally severe, and the platelet count is usually below 60,000 platelets per cubic millimeter. As a consequence, the bleeding time is prolonged, often to one hour or more. The

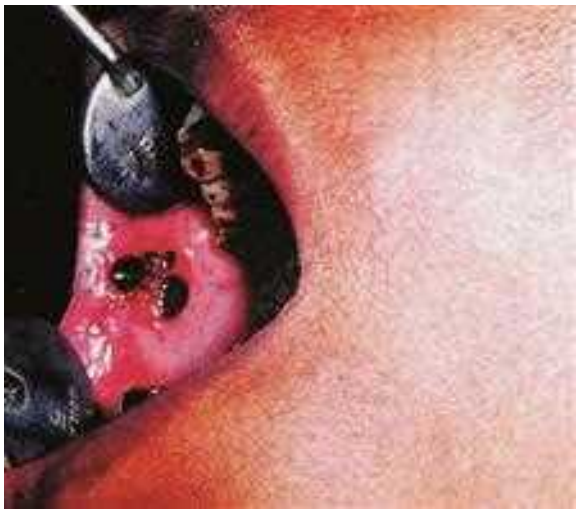


Figure 18-21. Primary thrombocytopenic purpura.
(Courtesy of Dr Sheeba, Thiruvananthapuram).

coagulation time is normal, although the clot does show failure of retraction. As might be expected from the clinical findings, the capillary fragility is increased and the tourniquet test is strongly positive. The red and white blood cell counts are normal unless secondarily disturbed by frequent episodes of hemorrhage or drug or X-ray-induced pancytopenia. Giant platelets on peripheral smear suggest congenital thrombocytopenia.

It is important to understand the basic mechanisms underlying the determination of bleeding and clotting times. Cessation of bleeding as measured by the bleeding time, depends upon the physical blockade of severed capillaries by platelets; as long as the number of platelets present in the blood stream is normal and the platelets aggregate properly, there is no alteration in bleeding time. But if the number of circulating platelets is decreased, the normal platelet plugging of the capillaries occurs more slowly and the bleeding time is consequently prolonged. On the other hand, the role of the platelets in the blood clotting mechanism is through release of a thromboplastic factor from agglutinated platelets. This is present in sufficiently large quantities so that, even when there is a reduction in the number of circulating platelets, sufficient thromboplastic substance is released to maintain normal coagulation. Therefore, in thrombocytopenia, the coagulation time remains normal.

The blood platelets are probably also related to capillary fragility, although the exact mechanism is unknown. It has been suggested that all capillaries undergo 'daily wear and tear' with minor injuries to their walls which are normally plugged by the platelets. If the platelets are diminished; however, there is failure of this maintenance of capillary integrity, resulting in an apparent increase in the capillary fragility.

Treatment and Prognosis. There is no specific treatment for this disease, although splenectomy probably has proved more beneficial than any other form of therapy aside from symptomatic relief such as transfusions and bed rest. Corticosteroids have been used in many cases with excellent results, although remissions may be temporary. The prognosis for patients with this disease is fairly good, since remissions are common. Unfortunately, exacerbations are also common. When death ensues, it is usually from sudden severe hemorrhage.

In secondary thrombocytopenia, correction or removal of the etiologic factor is essential.

Thrombotic Thrombocytopenic Purpura
(Moschcowitz disease)

Thrombotic thrombocytopenic purpura (TTP), an uncommon form of thrombocytopenic purpura, is a life-threatening multisystem disorder of an obscure nature but may be immunologically mediated. It was first described by Eli Moschcowitz in 1924. TTP and hemolytic uremic syndrome (HUS) are thrombotic microangiopathies characterized by microvascular lesions with platelet aggregation.

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome share the same pathophysiological etiology and may be varied expressions of the same underlying disease process. TTP is more common in adults and is associated with pregnancy; diseases such as HIV, cancer, bacterial infection, and vasculitis; bone marrow transplantation; and drugs.

The TTP syndrome is characterized by microangiopathic hemolysis and platelet aggregation/hyaline thrombi in microcirculation, whose formation is unrelated to coagulation system activity. The thrombi partially occlude the vascular lumina with overlying proliferative endothelial cells. The endothelia of the kidneys and brain are particularly vulnerable to TTP. No inflammatory changes are seen, but the partial occlusion causes fragmentation of erythrocytes and hemolysis.

Clinical Features. The disease generally occurs in young adults and is more common in females than in males. It is characterized by thrombocytopenia, hemolytic anemia, fever, transitory neurologic dysfunction and renal failure.

Histologic Features. The major findings in this disease are the widespread microthrombi in the arterioles, venules, and capillaries in all tissues and organs throughout the body. These intravascular thrombi are composed of loose aggregates of platelets that become organized into amorphous plugs, which are then replaced by fibrin. All of the clinical features can be traced to the thrombosed microcirculation.

It has been reported by Goldenfarb and Finch that biopsy of gingival tissue in patients suspected of having this disease will frequently confirm the diagnosis. Although tissue from many other sites may be used, they believe that gingival tissue is preferable because of its accessibility to rapid hemostasis. The characteristic microscopic gingival changes are described as occlusive subintimal deposits of PAS (periodic acid-Schiff)-positive material at arteriolocapillary junctions.

Laboratory Findings. On blood examination thrombocytopenia and anemia can be noted. Fragmented RBCs (schistocytes) consistent with hemolysis are noticed in peripheral smear. Reticulocyte count is also elevated in few cases. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are within normal limits. LDH levels are increased.

Indirect bilirubin is elevated due to extensive hemolysis. Urinalysis shows proteinuria and microscopic hematuria.

Treatment and Prognosis. At one time, this disease was almost uniformly fatal. However, many patients now survive with the help of modern therapeutic drugs and techniques, including corticosteroids, platelet aggregation inhibitors, splenectomy and exchange transfusions.

Wiskott-Aldrich Syndrome
(Hypogammaglobulinemia M)

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive genetic condition with variable expression, commonly includes immunoglobulin M (IgM) deficiency. This disorder is a severe congenital immunodeficiency, found almost exclusively in boys. This syndrome results from an X-linked genetic defect in a protein now termed Wiskott-Aldrich syndrome protein **(WASp).** The gene resides on **Xp11. 22–23,** and its expression is limited to cells of hematopoietic lineage. The exact function of WASp is not fully elucidated, but it seems to function as a bridge between signaling and actin polymerization in the cytoskeleton.

Clinical Features. The disease is characterized by thrombocytopenic purpura, eczema, usually beginning on the face, and a markedly increased susceptibility to infection due to cellular and humoral immunodeficiency and an increased risk of autoimmune disease and hematologic malignancy. Petechiae and a purpuric rash or ecchymoses of the skin may be early signs of the disease. The eczema has been thought to be allergic in nature. These patients commonly manifest boils, otitis media, bloody diarrhea, and respiratory infection. The increased susceptibility to infection appears related to an antibody deficiency—in particular, a poor antibody response to protein antigens. Serum IgM levels are low, IgG levels are relatively normal, but IgA and IgE levels may be normal or elevated. Thus, patients are unable to form antibody against polysaccharide-containing organisms such as pneumococci, *Hemophilus influenzae* and coliform bacilli. It is generally agreed that these patients have T- and B-cell abnormalities, although these cells may be relatively normal during early infancy.

One of the important features of the disease is the occurrence of a lymphoreticular malignant neoplasm, commonly a malignant lymphoma, which is often discovered incidentally at autopsy, although it is the specific cause of death in about 10% of cases.

Oral Manifestations. Spontaneous bleeding of the gingiva is frequently seen as well as bleeding from the gastrointestinal tract and nose. Palatal petechiae may also be present.

Laboratory Findings. One of the basic defects appears to be both a qualitative and quantitative abnormality of the platelets. Because of the thrombocytopenia, generally between 18,000 and 80,000 per cubic millimeter, these patients have a prolonged bleeding time. In addition, there is considerable anisocytosis—alterations in the size and shape of platelets, with most platelets being smaller than normal. At the electron microscope level there are alterations in the cell membrane, while biochemically there is a deficiency of the adenosine diphosphate nucleotide storage pool, although platelets can aggregate. Quantitatively, there appears to be decreased production and defective maturation of platelets since normal megakaryocytes may be seen in the marrow, but little platelet formation. There also seems to be accelerated platelet clearance from peripheral blood.

Treatment and Prognosis. There is no specific treatment for the disease, and death usually occurs within the first five years of life as a result of secondary infection or hemorrhage. Some patients have been treated with antibiotics and platelet transfusions, bone marrow transplantation, and even transfer factor. The eventual prognosis, however, is poor.

THROMBOCYTASTHENIA

'Thrombocytasthenia' is the term used to designate a variety of diseases characterized by a qualitative defect in blood platelets. Some forms are congenital and/or familial, while others are acquired.

Familial Thrombasthenia
(Glanzmann thrombasthenia or disease)

Familial thrombasthenia is a hereditary, chronic hemorrhagic disease transmitted as an autosomal recessive trait. There appears to be at least several varieties or forms of Glanzmann disease, thus accounting for the heterogeneous nature of various descriptions of the condition and the bewildering array of biochemical alterations cited.

Clinical Features. Patients with this disease exhibit the usual characteristics of excessive bleeding, either spontaneous or following minor traumatic injury. Both genders may be affected, and in females, the onset of menarche may be a critical event. Purpuric hemorrhages of skin are common, as are epistaxis and gastrointestinal bleeding. Hemarthrosis has also been reported.

Oral Manifestations. Spontaneous bleeding from the oral cavity, particularly gingival bleeding, is often seen in these patients as are palatal petechiae.

Laboratory Findings. The bleeding time is prolonged in familial thrombasthenia, while clot retraction characteristically is impaired. However, the platelet count is normal, as is the clotting time. The aggregation of platelets by epinephrine, ADP and thrombin is defective. In addition, it is now recognized that there are reduced amounts of certain membrane glycoproteins on the surface of platelets in this disease. This membrane abnormality may be at least partly responsible for the hemostatic defect.

Treatment. There is no specific treatment. However, Perking and his coworkers have discussed this disease and reported two cases of patients requiring oral surgery who were treated with a microfibrillar collagen preparation and with a fibrinolytic inhibitor, c-aminocaproic acid, to control postoperative hemorrhage.

Thrombocytopathic Purpura
(Thrombocytopathia)

Thrombocytopathic purpura is a group of rare diseases of unknown etiology in which the patient manifests a bleeding tendency referable to qualitative defects in the blood platelets. It is not related to thrombocytopenic purpura, since the platelet count is usually normal, although the two diseases have been reported to occur simultaneously. It is clinically indistinguishable from thrombasthenia. An acquired form is also recognized associated with a variety of disease conditions such as uremia.

Clinical Features. Patients with thrombocytopathic purpura have a severe bleeding tendency and bruise easily after only minor trauma. Spontaneous ecchymoses are common, although petechial hemorrhages are rare. Epistaxis and bleeding into the gastrointestinal tract are frequent clinical findings. In some cases, menstrual bleeding has been so severe as to require blood transfusions.

Oral Manifestations. The oral manifestations are those that might be expected in such a hemorrhagic disorder. Spontaneous gingival bleeding is common, while mucosal ecchymoses occasionally occur. Excessive and prolonged bleeding from dental extractions may be a serious management problem.

Laboratory Findings. The platelet count is nearly always normal, but the bleeding time is either normal or prolonged. This is generally due to defective platelet aggregation, even though there is normal release of ADP and ATP, so that normal capillary plugging is impaired. This failure of normal aggregation can often be seen in routine blood smears. Since there are a number of forms of this disease, a variety of different platelet defects seem to exist. For example, in one type called 'storage pool disease', there is a deficiency in the nonmetabolic storage pool of platelet adenine nucleotides. Another form is the 'Portsmouth syndrome', discussed by Roser and his associates, in which there is normal ADP-induced platelet aggregation but abnormal or absent collagen-induced aggregation. In the Bernard-Soulier syndrome, there is normal platelet aggregation to collagen and ADP but an abnormal response to fibrinogen.

Treatment. There is no satisfactory treatment for this disease, although conventional hemostatic agents and blood transfusions aid in controlling the severe hemorrhage. Apparently, death due to prolonged bleeding is rare, but obviously could occur.

Thrombocythemia
(Thrombocytosis)

Thrombocythemia is a condition characterized by an increase in the number of circulating blood platelets. As in thrombocytopenia, two forms are recognized: primary (or 'essential') and secondary. The etiology of primary thrombocythemia is unknown. Secondary thrombocythemia may occur after traumatic injury, inflammatory conditions, surgical procedures or parturition. In addition, a number of cases have been reported to occur in association with polycythemia and myeloid leukemia, anemia, tuberculosis and sarcoidosis, hyperadrenalism, rheumatoid arthritis and bronchial carcinoma with osseous metastases. Secondary thrombocytosis may be due to the overproduction of proinflammatory cytokines, such as IL-1, IL-6, and IL-11, that occurs in chronic inflammatory, infective, and malignant states. The presence of elevated IL-1, IL-6, C-reactive protein, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in individuals with this condition suggests that these cytokines may be involved in reactive thrombocytosis.

Clinical Features. No gender or age predilection is seen. Patients with thrombocythemia almost invariably show a bleeding tendency in spite of the fact that their platelet count is elevated. Epistaxis and bleeding into the gastrointestinal tract as well as bleeding into the genitourinary tract and central nervous system are common. Hemorrhage into the skin is also found. Few patients can be asymptomatic and are identified on routine blood counts.

Oral Manifestations. Spontaneous gingival bleeding is one of the more commonly reported findings in cases of thrombocythemia, but petechiae are rare. Excessive and prolonged bleeding also frequently occurs after dental extractions. Pogrel has discussed this disease as a cause of oral hemorrhage.

Laboratory Findings. The platelet count in thrombocythemia is greatly increased, and it has been suggested that this high concentration interferes with the formation of thromboplastin. One case reported in the literature showed 14,000,000 platelets per cubic millimeter by a method whereby the normal value was approximately 250,000. In addition, there is abnormal platelet aggregation in response to several aggregating agents. The clotting time, prothrombin time, clot retraction and tourniquet test are all normal, although the bleeding time is frequently prolonged. In primary thrombocythemia, both the red and white blood cell counts are normal. But in secondary thrombocythemia, there may be alterations in the red and white cell counts, depending upon the associated condition.

Treatment. The most common treatment has been the administration of radioactive phosphorus (P32) and blood transfusions in cases of severe hemorrhage. Certain cytotoxic drugs, heparin during thrombotic episodes, corticosteroids and aspirin have also been used with some degree of success.

DISEASES INVOLVING SPECIFIC BLOOD FACTORS

Hemophilia
(Bleeder's disease, disease of the Hapsburg, the disease of Kings)

Hemophilia is a blood disease with a long and interesting history. It is characterized by a prolonged coagulation time and hemorrhagic tendencies. The disease is hereditary, the defect being carried by the X chromosome, and is transmitted as a gender-linked Mendelian recessive trait; thus hemophilia occurs only in males, but is transmitted through an unaffected daughter to a grandson. The sons of a hemophiliac are normal

and are not carriers of the trait; the heterozygous daughters carry the defect to half of their sons and as a recessive trait to half of their daughters. The occurrence of hemophilia is theoretically possible in a homozygous female, and occasional rare cases have been recorded.

Etiology. There are a number of different types of hemophilia, and there has been extensive investigation and clarification of this disease in recent years. In light of our present knowledge, three chief forms of hemophilia may be described: hemophilia A (classic hemophilia), B, and C. Each of these differs from the others only in the particular deficiency of the blood clotting factor involved:

Type	Clotting factor deficiency
Hemophilia A	Plasma thromboplastinogen (antihemophilic globulin, AHG, factor VIII)
Hemophilia B	Plasma thromboplastin component (PTC, factor IX)
Hemophilia C	Plasma thromboplastin antecedent (PTA, factor XI)

The genes for factor VIII and factor IX are located on the long arm of the X chromosome in bands **q28 and q27,** respectively. Genetic abnormalities include deletions of variable size, abnormalities with stop codons, and frame-shift defects. Recent data suggest that 45% cases of severe hemophilia A result from an inversion mutation. In hemophilia B several mutations such as partial and total deletions, missense mutations that result in the decrease or absence of factor IX or the production of an abnormal molecule. The factor XI gene is located on chromosome 4. Mutations of factor XI gene cause failure, reduced production of the active protein, and rarely production of an abnormal molecule result in factor XI deficiency.

A deficiency of AHG (factor VIII) results in the occurrence of **hemophilia A,** which is the most common type of hemophilia. However, recent studies now show that factor VIII is a glycoprotein which contains three distinct components:

- A clot-promoting factor that corrects the coagulation defect in patients with classic hemophilia.
- A factor VIII antigen that is present in patients with classic hemophilia but deficient in those with von Willebrand's disease (q.v.).
- A component called the von Willebrand factor that is synthesized by endothelial cells that will correct the platelet adherence defect in von Willebrand's disease.

Therefore, in hemophilia A (classic hemophilia), there is only an absence of the clot-promoting factor. **Hemophilia B,** due to a PTC deficiency, is also known as Christmas disease (named after the first patient in whom it was described). Apparently two forms of hemophilia B exist: one in which there are apparently normal levels of the inactive protein, another in which there are deficient levels of the coagulant factor. A PTA deficiency is the cause of **hemophilia C.** Despite the fact that different blood components are involved in each of these diseases, their clinical and oral manifestations are identical. They will therefore be described together as a single disease. In addition, some of the characteristics of the various hemophilioid disorders are shown in Table 18-13.

Clinical Features. Patients with hemophilia exhibit persistent bleeding, either spontaneous or following even slight trauma that produces the mildest of abrasions or cuts. Hemorrhage into the subcutaneous tissues, internal organs, and joints is also a common feature and may result in massive hematomas. It is of interest, though still unexplained, that there is a wide range in the degree of severity of factor VIII deficiencies, with some patients showing only rare and mild bleeding, and others frequent and severe bleeding.

The disease is usually present from birth, but may not become clinically apparent for several years. Approximately, 30–50% of patients with severe hemophilia present with manifestations of neonatal bleeding such as prolonged bleeding from the umbilical cord. Spontaneous cyclic remissions and exacerbations of hemophilia are common.

Table 18-13: Characteristics of the hemophilioid disorders

Disorder	Mode of inheritance	Prothrombin time (PT)	Partial thromboplastin time (PTT)*	Bleeding time
Hemophilia A	Sex-linked recessive	Normal	Prolonged	Normal
Hemophilia B	Sex-linked recessive	Normal	Prolonged	Normal
Vascular hemophilia	Autosomal dominant	Normal	Usually moderately prolonged	Prolonged
Factor II deficiency	?	Prolonged	Prolonged	Normal
Factor V deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
Factor VII deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
Factor X deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
PTA deficiency	Incomplete recessive	Normal	Slightly prolonged	Normal
Fibrinogen deficiency	Autosomal recessive	Prolonged (or incoagulable)	Prolonged (or incoagulable)	Normal⁺
Factor XII deficiency	Autosomal recessive	Normal	Normal	Normal

**Either original test or activated test (kaolin, etc). may be used.*
⁺May occasionally be prolonged.
Courtesy of Dr Harold R Roberts. Modified from HR Roberts and KM Brinkhous: Blood coagulation and hemophilioid disorders. Postgrad Med, 43: 114, 1968.

Table 18-14: Classification of hemophilia

Classification	Factor activity (percentage)	Cause of hemorrhage
Mild	>5	Major trauma or surgery
Moderate	1–5	Mild-to-moderate trauma
Severe	<1	Spontaneous, hemarthrosis, soft tissue bleeding

Petechiae usually do not occur in patients with hemophilia because they are manifestations of capillary blood leaking, which typically is the result of vasculitis or abnormalities in the number or function of platelets.

Hemophilia is classified according to the clinical severity as mild, moderate, or severe (Table 18-14).

Hemophilia C can be distinguished from hemophilias A and B by the absence of bleeding into joints and muscles and by its occurrence in individuals of either genders.

Oral Manifestations. Hemorrhage from many sites in the oral cavity is a common finding in hemophilia, and gingival hemorrhage may be massive and prolonged. Even the physiologic processes of tooth eruption and exfoliation may be attended with severe prolonged hemorrhage. The oral manifestations of the various forms of hemophilia have been discussed by Spiegel and by Steg and his coworkers. In addition, mandibular 'pseudotumor' of hemophilia has been reported by Stoneman and Beierl, a condition in which there is subperiosteal bleeding, with reactive new bone formation causing tumor like expansion of the bone.

The problem of dental extractions is a difficult one in hemophiliacs. Without proper premedication, even a minor surgical procedure may result in death from exsanguination. Tooth extraction by means of rubber bands has often been used successfully, the rubber band being placed around the cervix of the tooth and allowed to migrate apically, causing exfoliation of the tooth through pressure necrosis of the periodontal ligament.

Laboratory Findings. The characteristic defect of hemophilia is a prolonged coagulation time. The bleeding time is normal, as is the prothrombin time and platelet aggregation. Usually, the activated partial thromboplastin time (aPTT) is prolonged; however, normal aPTT does not exclude mild or even moderate disease. Functional assay of factors is useful in diagnosing hemophilia caused due to dysfunction of coagulation factors. The combination of low factor VIII and low von Willebrand's factor indicate von Willebrand's disease. *In vitro,* the deficiency of the clot-promoting factor in the plasma of hemophiliacs impairs clotting because it appears to retard development of the substance responsible for conversion of prothrombin to thrombin. Separation of the various forms of hemophilia and proper diagnosis depends upon demonstration that the plasma of a patient with a known form of hemophilia does not correct the plasma clotting defect in the patient under observation.

Treatment and Prognosis. There is no known cure for hemophilia. The affected persons should be protected from traumatic injuries.

If a surgical procedure such as tooth extraction must be carried out, the operation should be considered a major one, to be performed only in a hospital.

The greatest number of fatalities in hemophiliacs have resulted from surgical procedures, including tooth extraction. Preoperative transfusion of whole blood and the administration of antihemophilic factor concentrate are recommended. Nevertheless, oral surgery is a dangerous procedure and should be avoided whenever possible. Unfortunately, a small percentage of hemophiliacs have circulating anticoagulant, probably an antibody, which specifically inactivates antihemophilic factor, negating the effects of transfusion.

The prognosis is variable, and many affected persons die during childhood.

von Willebrand's Disease

(Pseudohemophilia, vascular hemophilia, vascular purpura)

von Willebrand's disease, or pseudohemophilia, is a disease characterized by the tendency to excessive bleeding in patients who have a normal platelet count, normal clotting time, normal serum fibrinogen and normal prothrombin time. Only the bleeding time is prolonged. Therefore, other diseases characterized by an abnormal bleeding time must be ruled out before the diagnosis is established. It is the most common

von Willebrand disease is due to an abnormality, either quantitative or qualitative, of the vWF, which is a large multimeric glycoprotein that functions as the carrier protein for factor VIII. vWF also is required for normal platelet adhesion. It functions in both primary (involving platelet adhesion) and secondary (involving factor VIII) hemostasis. In primary hemostasis, vWF binds on platelets to its specific receptor glycoprotein Ib on nonactivated platelets and the receptor glycoprotein IIb/IIIa on activated platelets and acts as an adhesive bridge between the platelets and damaged subendothelium at the site of vascular injury. In secondary hemostasis, vWF protects factor VIII from degradation and delivers it to the site of injury.

vWD can be classified into three main types:

Type 1: vWD is characterized by a **partial quantitative** decrease of normal vWF and factor VIII.

Type 2: vWD type 2 is a variant of the disease with primarily **qualitative** defects of vWF. Type 2 vWD can be either autosomal dominant or recessive.

Type 3: is the most severe and rarest form of vWD. In the homozygous patient, type 3 vWD is characterized by marked deficiencies of both vWF and factor VIII in the plasma, the absence of vWF from both platelets and endothelial cells, and a lack of the secondary transfusion response. This type is characterized by severe clinical bleeding and is inherited as an autosomal recessive trait and common in case of consanguineous marriage. Occasionally in heterozygotes disease may be less severe.

hereditary bleeding disorder first described by Erik Adolf von Willebrand in 1926. It is now accepted to be a hereditary disease, inherited as an autosomal dominant trait transmitted by and manifested in both males and females but detected more often in females. von Willebrand disease (vWD) is a family of bleeding disorders caused by an abnormality of the von Willebrand factor (vWF).

von Willebrand disease is caused by an inherited defect in the amount and/or quality of vWF. A gene on chromosome **12p** (**vWF** gene) codes for the synthesis of this macromolecule. A variety of point mutations, insertions, and deletions at the vWF locus have been described. Acquired forms of vWD can be observed in the conditions such as Wilms tumor, systemic lupus erythematosus, etc.

Clinical Features. Prevalence worldwide is estimated at 0.9–1.3%. Many children with vWD are asymptomatic and are diagnosed as a result of a **positive family history** or during routine preoperative screening. Excessive bleeding, either spontaneously or following even minor trauma, is the chief feature of the disease. The most common sites of bleeding are nose, skin, and gingiva. Spontaneous nosebleeds and spontaneous cutaneous ecchymoses can be seen in these cases. Bleeding into the gastrointestinal tract and severe menorrhagia are also common, although hemarthrosis is rare. However, a wide variation in the clinical manifestations exists, even for the members of the same family. This bleeding tendency is often cyclic or sporadic.

Oral Manifestations. Gingival bleeding occurred in this same series in 39% of the patients. In some instances this was spontaneous bleeding; in other cases bleeding occurred only after brushing of the teeth.

The disease may be discovered after dental extractions because of the prolonged and excessive bleeding. The profuse bleeding may commence at the time of the extraction and continue indefinitely, or it may begin several hours subsequent to surgery and result in an almost unmanageable flow.

Laboratory Findings. The bleeding time of patients with this disease is increased to an extremely variable degree. Bleeding times of over 300 minutes have been recorded, but more often they range between several minutes and one hour. The bleeding time also shows wide variation in the same patient at different times. Prothrombin time (PT) is normal and aPTT increased in approximately 25% of type 1 vWD. The clotting time of the blood is usually normal, but may be slightly prolonged, while capillary fragility is reportedly increased with a positive tourniquet test in about 50% of cases. The clot retraction is normal. Characteristically, poor platelet adherence is also demonstrable.

Treatment. Bleeding episodes are best treated by transfusions of plasma and/or antihemophilic factor and by local control of hemostasis. Unfortunately, some patients become refractory to this treatment after repeated transfusions, and occasionally patients develop antibodies against antihemophilic factor.

Death from bleeding in pseudohemophilia is reportedly rare despite what appears to be excessive loss of blood. Nevertheless inherent dangers of tooth extraction should be recognized by the dentist so that if such a procedure is absolutely necessary, he/she may be on guard to institute prompt measures to control bleeding, should it occur. In general, all surgical procedures of an unessential nature should be avoided.

Parahemophilia

Parahemophilia is a rare hemorrhagic disorder, clinically similar to hemophilia, but caused by a deficiency of an unrelated blood factor, proaccelerin (factor V), which is one of the substances responsible for the conversion of prothrombin to thrombin.

Clinical Features. Parahemophilia is generally thought to be inherited as an autosomal recessive trait. Both genders are affected. Patients with parahemophilia exhibit a severe bleeding tendency. Spontaneous epistaxis, bleeding into the gastrointestinal tract and menorrhagia are common. Cutaneous ecchymoses and hematomas are frequently seen, although petechiae are rare. Intraocular hemorrhage and hemorrhage into the central nervous system have been reported in some patients, but hemarthrosis is seldom seen.

Oral Manifestations. Spontaneous gingival bleeding occurs in some cases of parahemophilia. Petechiae of the oral mucosa are rare. Prolonged bleeding following dental extractions is common, and this may terminate fatally.

Laboratory Findings. The blood platelet level is normal in cases of parahemophilia. Both the clotting time and prothrombin time are prolonged, but the bleeding time is normal. The basic defect in the disease is the reduction of plasma proaccelerin.

Treatment. There is no effective treatment for parahemophilia. Transfusions, as well as freshly frozen plasma, are given to replace blood lost through hemorrhage or prior to a necessary surgical procedure. The prognosis is good, although a few deaths have been reported as a result of the hemorrhage.

Afibrinogenemia and Hypofibrinogenemia
(Hypofibrinogenopenia)

Afibrinogenemia is an uncommon disease in which the patient has little or no fibrinogen present in either his/her plasma or tissues. For this reason the blood cannot clot, even after the addition of thrombin.

A fibrinogen deficiency may be either congenital or acquired. **Congenital afibrinogenemia** is a rare hereditary disease, probably an autosomal recessive trait, occurring in both genders, but with some predilection for males. It is present from the time of birth and appears to be due to an inability of the patient to synthesize fibrinogen rather than any excessive destruction of fibrinogen.

Acquired hypofibrinogenemia generally occurs secondary to defective fibrinogen formation, to an increase in fibrinogen consumption during intravascular clotting, or to destruction or digestion of fibrinogen by fibrinolytic or proteolytic enzymes circulating in the blood stream. It may also occur in extravascular sequestration of the protein, in loss

of blood through hemorrhage, in a transfusion reaction and in association with other conditions, including amyloidosis, polycythemia, certain neoplasms, and pregnancy.

There is generally not a complete absence of fibrinogen in the acquired form of the disease as there is in the congenital type, and this accounts for the difference in use of the terms 'afibrinogenemia' and 'hypofibrinogenemia'. But since the clinical features in both forms of the disease are almost identical, they will be described together.

Clinical Features. Patients with hypofibrinogenemia or afibrinogenemia exhibit severe bleeding episodes, throughout their lives in the congenital type, and the disease is clinically indistinguishable from hemophilia. However, characteristically in the congenital type, the patients may have long periods of freedom from bleeding. Epistaxis, bleeding into the gastrointestinal tract and central nervous system, and cutaneous ecchymoses and hematomas are all common. Hemarthrosis is not as prominent as in hemophilia. In affected females, menstrual bleeding is usually normal.

Oral Manifestations. The oral manifestations of congenital afibrinogenemia have been reviewed by Kranz and Ruff, and those of the acquired type by Rose. These consist of spontaneous gingival bleeding and prolonged and excessive bleeding following dental extractions. Petechiae of the oral mucosa are rare.

Laboratory Findings. Patients with congenital afibrinogenemia have normal red blood cell, white blood cell and platelet counts, although thrombocytopenia has been occasionally reported. The bleeding time may be normal or slightly prolonged. The most dramatic feature is that the clotting time and prothrombin time are infinite, although this is not necessarily the case in hypofibrinogenemia. The peripheral blood fails to clot even after the addition of thrombin. The tourniquet test in these patients is normal. Finally, the erythrocyte sedimentation rate is zero, the cells remain suspended even after 24 hours.

Treatment. There is no specific treatment for the disease except for transfusions, particularly of concentrated fibrinogen, during bleeding episodes. Occasional patients develop antibodies against the administered fibrinogen, thus disrupting therapy. Unfortunately, the prognosis is poor, and many patients die of hemorrhage during infancy or early childhood. Some patients do reach adult life. The acquired form of the disease is less serious if recognized in time.

Dysfibrinogenemia

Dysfibriongenemia is a congenital disease probably transmitted as an autosomal dominant characteristic which appears to represent a group of familial disorders rather than a single entity. For example, there may be impairment of the rate at which thrombin cleaves fibrinopeptides from fibrinogen. There may be replacement of one amino acid residue by another in the NH2 terminal part of the A<chain of fibrinogen, as in fibrinogen detroit, in which arginine replaces serine. In fibrinogen Philadelphia, the abnormal protein is catabolized at an accelerated rate.

Fibrinogen is usually present in normal amounts in this disease, but is defective in its structure and coagulability so that the aggregation of fibrin monomers is impeded. In one variant, the abnormality of fibrinogen appears to be one manifesting defective cross-linking between fibrin strands after clotting has occurred.

Acquired dysfibrinogenemias, often called dysfibrinogenemia of liver disease, commonly due to severe liver disease secondary to cirrhosis, hepatoma, or hepatitis exhibit bleeding complications.

The disease manifests itself clinically by a mild to severe bleeding tendency although, interestingly, paradoxical thrombosis has also been reported. (Fibrinogen Oslo I is an abnormal fibrinogen that is associated with thromboembolic complications. The abnormal fibrinogen in these patients forms a fibrin clot that is resistant to fibrinolysis by plasmin).

Laboratory Findings. Prothrombin time (PT) is prolonged (the most sensitive screening test). Activated partial thromboplastin time (aPTT) may be prolonged.

Treatment. Medical treatment is not required in majority of patients. Fresh frozen plasma or cryoprecipitate may be transfused in case of bleeding.

Fibrin-stabilizing Factor Deficiency
(Factor XIII deficiency)

Congenital factor XIII or fibrin-stabilizing factor (factor XIII) deficiency, originally recognized by Duckert in 1960, is a rare autosomal recessive disease, with a high incidence of consanguinity. Acquired factor XIII deficiency has been described in association with hepatic failure, inflammatory bowel disease, and myeloid leukemia.

Inherited factor XIII deficiency is usually due to mutations in the gene encoding the catalytic α subunit, located on **chromosome 6**. More than 40 different mutations have been identified, half of which are missense mutations. In patients homozygous for this defect, the α subunit is absent in plasma, platelets, and monocytes, resulting in a severe bleeding diathesis; the concentration of β subunits is relatively normal. Biochemically, thrombin appears to activate factor XIII from an inactive precursor form. This activated factor XIII then cross-links fibrin or stabilizes it by transamidation. In the absence of this factor, there is failure of permanent peptide bonds between fibrin molecules so that the fibrinogen monomer aggregates (fibrins) break up under certain conditions. Factor XIII covalently binds fibronectin, 2-plasmin inhibitor, and other molecules to the fibrin plug; this enhances adherence to the wound site, resistance to fibrinolysis, and wound healing.

Clinical Features. Patients with this deficiency have severe postsurgical bleeding episodes which are typically delayed for 24–36 hours, hemarthrosis and defective wound healing. Bleeding and clotting times are both normal. Bleeding from the stump of the umbilical cord within the first days

to weeks of life is a characteristic sign that occurs in 80% of affected individuals. Soft tissue bleeding and bruising are very common, as is bleeding into the mouth and gums during teething.

Laboratory Findings. Measurement of clot stability is the most commonly used screening test for factor XIII deficiency. In the absence of factor XIII, the clot dissolves in minutes to hours. Factor XIII α and factor XIII β antigen levels can be quantified by means of enzyme-linked immunosorbent assay (ELISA) techniques.

Treatment. Plasma, cryoprecipitate, and factor XIII concentrates have been used for replacement of factor XIII and the treatment of bleeding.

Macroglobulinemia

(Waldenstrom hypergammaglobulinemia, macroglobulinemia of Waldenstrom)

Macroglobulinemia is not specifically a blood 'factor' disease, but is included here because of the hemorrhagic tendency of the disease, thus mimicking the other hemorrhagic diatheses previously described. The condition was first described as an entity by Waldenstrom in 1948, and, by 1958, he found over 100 cases in the literature in his classic review of the disease. Since then many more cases have been discovered, and this disease should not be considered rare.

Etiology. The etiology of macroglobulinemia is unknown. It has been suggested to be related to:

- A variant of multiple myeloma, IgM monoclonal gammopathies of undetermined significance (MGUS) are considered a precursor of Waldenstrom macroglobulinemia.
- The Bing-Neel syndrome (hyperglobulinemia with central nervous system involvement on a toxi-infectious basis).
- A variety of plasmacytoma.
- An altered immunologic reaction.
- Reports of familial cases suggest a genetic predisposition.

It is now generally classified as a plasma cell dyscrasia (monoclonal gammopathies) so that the excessive proliferation of B-lymphocytes, the precursor of the plasma cell, results in the production of large amounts of electrophoretically homogeneous M-type IgM globulins which characterize the disease.

The clinical presentation of WM is similar to that of multiple myeloma (MM) except that organomegaly is common in WM and is uncommon in MM, and lytic bony disease and renal disease are uncommon in WM but are common in MM.

Clinical Features. The protean clinical manifestations of this rare disorder result from two important components of the disorder. First, secretion of the IgM paraprotein leads to hyperviscosity and consequent vascular complications because of certain physical, chemical, and immunological properties of this paraprotein. The monoclonal IgM causes hyperviscosity syndrome; cryoglobulinemia types 1 and 2; coagulation abnormalities; polyneuropathies; cold agglutinin disease and anemia; primary amyloidosis; and tissue deposition of amorphous IgM in skin, the GI tract, kidneys, and other organs.

Second, neoplastic lymphoplasmacytic cells infiltrate tissue. The abnormal clone of lymphoplasmacytic cells infiltrate the bone marrow, spleen, lymph nodes, liver, lungs, GI tract, kidneys, skin, eyes, and CNS. The infiltration of these organs causes numerous organ specific clinical symptoms and signs. Occasionally, IgM paraprotein has rheumatoid factor activity, antimyelin activity that can contribute to peripheral neuropathy, and immunologically related lupus anticoagulant activity.

Macroglobulinemia occurs most frequently in persons over the age of 50 years, seldom under 40 years. Males and females are about equally affected.

The chief clinical signs are pallor, weakness and weight loss, lymphadenopathy and hepatomegaly occurring commonly. Hemorrhages from the nasal and oral cavity are characteristic of the disease, and subarachnoid and ocular hemorrhages are also frequently seen, according to Voight and Frick. Bone lesions such as those that occur in myeloma are exceedingly rare.

Oral Manifestations. Oral lesions are common in macroglobulinemia, and these have been reviewed by Gamble and Driscoll. They consist of spontaneous gingival hemorrhage, often with continued oozing of blood; bleeding oral ulcers on the tongue, palate, buccal mucosa or gingiva; and focal areas of hyperemia which appear edematous and are painful. Severe and prolonged bleeding following dental extractions is common. Salivary gland involvement with xerostomia has also been reported.

These bleeding diatheses appear to be related to protein-protein interactions, with formation of complexes between IgM globulins and coagulation factors such as fibrinogen, thrombin and factors V and VII, as well as interference with platelet agglutination and capillary damage.

Laboratory Findings. Waldenstrom was the first to demonstrate by ultracentrifugation technique that the serum of patients with this disease contained a fraction in the serum proteins, presumably globulins, with molecular weights near 1,000,000 as contrasted to the highest normal globulin molecular weight of 150,000. In addition to the macroglobulinemia and hyperglobulinemia, these patients generally manifested severe anemia with hemoglobin levels near 4–6 gm/dl, an extremely elevated sedimentation rate, demonstrable euglobulins and frequent gelling of the serum upon cooling to room temperature or lower. The viscosity of the blood serum was usually extremely high.

The white blood cell and platelet counts, as well as the bleeding, clotting, and prothrombin times, are usually within normal limits, although lymphocytosis, neutropenia, and thrombocytopenia are occasionally observed.

Bone marrow smears are generally confusing, since they show an increase in mononuclear cells that have been interpreted variously as plasma cells, lymphoid cells, or lymphoid reticulosis.

Bence Jones proteinuria is present in a limited number of patients with macroglobulinemia. Serum protein electrophoresis results indicate evidence of a monoclonal spike.

Treatment. There is no specific treatment for the disease other than supportive therapy with whole blood replacement. Chlorambucil in relatively high doses has produced prolonged remissions in many patients. Repeated plasmapheresis has often been used for temporary treatment.

Cryoglobulinemia
(Cryoproteinemia)

Cryoglobulinemia is a disease characterized by the presence of cryoglobulins in varying amounts in the blood. These cryoglobulins are globulins which have the ability to precipitate on exposure to cold and redissolve upon return to body temperature. This condition has been discussed in detail by Brouet and his associates.

A mild cryoglobulinemia has been found to occur in a large variety of diseases including some of the collagen diseases such as rheumatoid arthritis, periarteritis nodosa and systemic lupus erythematosus, as well as in certain of the malignant lymphomas including lymphosarcoma, Hodgkin's disease and lymphatic leukemia. It is also sometimes found in polycythemia, heart disease and cirrhosis. In multiple myeloma, it has occasionally been found in large quantities. In some cases there is no apparent associated disease, and in these instances, it has been referred to as 'essential cryoglobulinemia', or mixed IgG-IgM cryoglobulinemia. The etiology of this disease is not known.

The current system of **classification** of the types of cryoglobulinemia (by composition) includes the following:

Type I cryoglobulinemia, or simple cryoglobulinemia, is the result of a monoclonal immunoglobulin, usually immunoglobulin M (IgM) or immunoglobulin G (IgG) observed in lymphoproliferative disorders (e.g. multiple myeloma, Waldenström macroglobulinemia).

Type II and type III cryoglobulinemia (mixed cryoglobulinemia) contain rheumatoid factors (RF), which usually are IgM. These RFs form complexes with the fragment crystallizable (Fc) portion of polyclonal IgG. The actual RF may be monoclonal (in type II cryoglobulinemia) or polyclonal (in type III cryoglobulinemia) immunoglobulin. This type is observed in lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL), chronic liver disease, infections, and coexistent connective tissue diseases.

Cryoglobulinemia does not usually produce clinical manifestations. On occasion, however, spontaneous bleeding from the nose and mouth with purpuric hemorrhages into the skin and retina may be found. Other sequelae are related directly to cryoprecipitation *in vivo*, including plugging and thrombosis of small arteries and capillaries in the extremities (gangrene) and glomeruli (acute renal failure). Circulating large-molecular weight cryoprotein complexes, even when unprecipitated *in vivo*, can lead to clinical hyperviscosity syndrome.

Treatment. The goal of therapy is the limitation of precipitant cryoglobulin and the resultant inflammatory effects; however, asymptomatic cryoglobulinemia does not require treatment. In case of secondary cryoglobulinemia underlying malignancy or associated disease should be treated. Otherwise, cryoglobulinemia is treated simply by suppression of the immune response.

Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are multipotent stem cells that give rise to all the blood cell types from the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T cells, B cells, NK cells). HSCs are a heterogeneous population. Three classes of stem cells exist, distinguished by their ratio of lymphoid to myeloid progeny (L/M) in blood. Myeloid-biased (My-bi) HSC have low L/M ratio (>0, <3), whereas lymphoid biased (Ly-bi) HSC show a large ratio (>10). The third category consists of the balanced (Bala) HSC for which 3< L/M<10. Much work is currently being undertaken to investigate the properties of these different classes of HSCs, but it appears that only the myeloid–biased and balanced HSCs have durable self-renewal properties.

HSCs are found in the bone marrow of adults, which includes femurs, hip, ribs, sternum, and other bones. Cells can be obtained directly by removal from the hip using a needle and syringe, or from the blood following pre-treatment with cytokines, such as G-CSF (granulocyte colony-stimulating factors), that induce cells to be released from the bone marrow compartment. Other sources for clinical and scientific use include umbilical cord blood, peripheral blood in which a small number of stem and progenitor cells circulate in the blood stream. These cells can migrate from marrow to blood in greater numbers by injecting the donor with a cytokine, such as G-CSF. As stem cells, HSCs are defined by their ability to replenish all blood cell types (multipotency) and their ability to self-renew. It is known that a small number of HSCs can expand to generate a very large number of daughter HSCs. This phenomenon is used in bone marrow transplantation, when a small number of HSCs reconstitute the hematopoietic system. This indicates that, subsequent to bone marrow transplantation, symmetrical cell divisions in-to two daughter HSCs must occur.

Stem cell self-renewal is thought to occur in the stem cell niche in the bone marrow, and it is reasonable to assume that key signals present in this niche will be important in self-renewal. There is much interest in the environmental and molecular requirements for HSC self-renewal, as understanding the ability of HSC to replenish themselves will eventually allow the generation of expanded populations of HSC *in vitro* that can be used therapeutically.

HSCs have a higher potential than other immature blood cells to pass the bone marrow barrier, and thus, may travel in the blood from the bone marrow in one bone to another bone. If they settle in the thymus, they will develop into T cells. In the case of fetuses and other extramedullary hematopoiesis, HSCs may also settle in the liver or spleen and develop. This ability is the reason why HSCs may be harvested directly from the blood.

With regard to morphology, HSCs resemble lymphocytes. They are non-adherent, and rounded, with a rounded nucleus and low cytoplasm-to-nucleus ratio. Since peripheral HSC cannot be isolated as a pure population, it is not possible to identify them under a microscope. The above description is based on the morphological characteristics of a heterogeneous population, of which PHSC are a component.

Hematopoietic stem cells are identified by their surface markers, many of these markers belong to the cluster of differentiation (CD) series, like: CD34, CD38, CD90, CD133, CD105, CD45, and also c-kit, the receptor for stem cell factor. There are many differences between the human and mice hematopoietic cell markers for the commonly accepted type of HSCs.

Hematopoetic stem cells cannot be easily observed directly and, therefore, their behaviors need to be inferred indirectly. Clonal studies are likely the closest technique for single cell *in vivo* studies of HSC. Here, sophisticated experimental and statistical methods are used to ascertain that, with a high probability, a single HSC is contained in a transplant administered to a lethally irradiated host. The clonal expansion of this stem cell can then be observed over time by monitoring the percent donor-type cells in blood as the host is reconstituted. The resulting time series is defined as the repopulation kinetic of the HSC.

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CHAPTER 19

Diseases of the Skin

■ R RAJENDRAN

CHAPTER OUTLINE

Dermatology, the specialized study of skin diseases, has become an important subdivision of the practice of medicine not only because of the many primary diseases that affect the skin, but also because of the common cutaneous manifestations of deeper visceral or systemic diseases. The dermatologist is well aware that many primary cutaneous diseases also involve the mucous membranes throughout the body, including the oral mucosa.

It is especially important for the dentist to recognize not only that some dermatoses exhibit concomitant lesions of the oral mucous membranes, but also that manifestation of some of the diseases may be preceded by oral lesions. Thus the dentist may be in a position to establish the diagnosis of a dermatologic disease before the cutaneous lesions become apparent.

There is no universally accepted classification of these dermatologic diseases. However, several broad groups of diseases may be separated out, all of which have significant interest to dentistry, on the basis of the nature of the disease process or the nature of the lesion itself.

One large group of specific lesions which has been recognized in recent years is that known as the **genodermatoses**. These basically represent hereditary skin disorders, many of which are also accompanied by various systemic manifestations of different altered enzyme functions. Some of these genodermatoses are characterized particularly by alterations in the normal keratinization process and these have been specifically referred to as **genokeratoses**. Unfortunately, there are numerous defects and considerable overlap in even such a simple scheme. There are, for example, numerous diseases characterized by alterations in the keratinization process which are not genetically transmitted, and therefore, are not genokeratoses. There is considerable value in classifying certain dermatologic diseases as vesiculobullous diseases because of the aid provided in the differential diagnosis of a given case in which vesicles and bullae are present. However, some of the vesiculobullous diseases are genetically transmitted and thus could also be classified as genodermatoses, while others have no hereditary pattern.

Ectodermal Dysplasia

(Hereditary ectodermal dysplasia, ectodermal dysplasia syndrome)

Ectodermal dysplasia syndrome (EDS) is a large, heterogeneous group of inherited disorders, the manifestations of which could be seen in more than one ectodermal derivatives. These tissues primarily are the skin, hair, nails, eccrine glands, and teeth. Defects in tissues derived from other embryologic layers are not uncommon. The current classification of ectodermal dysplasia (ED) is based on clinical features. The disorders are congenital, diffuse, and nonprogressive. To date, more than 150 distinctive syndromes have been described with all possible modes of inheritance. The most common syndromes within this group are **hypohidrotic (anhidrotic) ED** and **hidrotic ED.** Several EDSs may manifest in association with midfacial defects, mainly cleft lip and palate.

Etiology. Ectodermal dysplasia syndrome results from aberrant development of ectodermal derivatives in early embryonic

life. Genes responsible for the varied syndromes are located on different chromosomes and may be mutated or deleted.

- X-linked hypohidrotic ED has been mapped in the proximal area of the long arm of band **Xq-12-q13.1.** Decreased expression of the epidermal growth factor receptor has been proposed as playing a causal role in this condition's phenotype. The gene **ED1** responsible for the disorder has been identified.
- Autosomal recessive disorders, phenotypically indistinguishable from the X-linked forms, exist in humans. A candidate gene has recently been identified at the **dl locus (downless)** that is mutated in mice.
- The gene that causes hidrotic ED (Clouston syndrome) has been identified to be **GJB6,** which encodes for connexin-30. GJB6 has been mapped to the pericentromeric region of chromosome 13q.
- Mutations of the gene **PVRL1,** encoding a cell-to-cell adhesion molecule/herpesvirus receptor, have been reported in those with cleft lip/palate ED.

Clinical Features. Individuals affected by EDS have abnormalities in different structures. Some EDS types are mild, while others are devastating. EDSs have been reported most often in whites, but they have also been observed in persons of other races. X-linked hypohidrotic ED has full expression only in males. Female carriers outnumber affected men, but females show little or no signs of the condition. The remaining EDSs have no gender predilection. Obvious manifestations of the disorders are not clinically apparent in newborns. Dental, hair, and nail anomalies are evident during infancy or childhood. The number of hair follicles, sweat glands, and sebaceous glands varies. Symptoms of a reduction in hair follicles vary from sparse scalp hair (usually short, fine and dry) to a complete absence of hair. Hair bulbs may be distorted, bifid, and small. Eccrine sweat glands may be absent or sparse and rudimentary, particularly in those with hypohidrotic EDS. In some cases, mucous glands are absent in the upper respiratory tract and in the bronchi, esophagus, and duodenum. The mouth may be dry from hypoplasia of the salivary glands; lacrimal glands also may be deficient. Teeth show abnormal morphogenesis or are absent. Nails are often brittle and thin or show abnormal ridging, but they may be grossly deformed. Other signs and symptoms like lack of breast development, deficient hearing or vision, cleft lip and/or palate and missing fingers or toes are also seen. The presence or absence of these abnormalities defines the different syndromes. Following are the best-defined syndromes within this group.

Hypohidrotic (anhidrotic) ED (Christ-Siemens-Touraine syndrome) is the most common phenotype in this group and is usually inherited as an X-linked recessive trait; autosomal recessive and autosomal dominant forms have been reported but are rare. It is characterized by several defects (e.g. hypohidrosis, anomalous dentition, onychodysplasia, hypotrichosis). Typical facies are characterized by frontal bossing; sunken cheeks; saddle nose; thick, everted lips; wrinkled, hyperpigmented skin around the eyes; and large, low-set ears. Because such characteristics are not obvious at birth, clinical clues for diagnosis in the neonatal period are extensive scaling of the skin and unexplained pyrexia. Dental manifestations include conical or pegged teeth, hypodontia or complete anodontia, and delayed eruption of permanent teeth. The prevalence of atopic eczema is high. Other common signs are short stature, eye abnormalities, decreased flow of tears and photophobia. Intelligence is normal.

Oral Manifestations. The oral findings are of particular interest, since patients with this abnormality invariably manifest anodontia or oligodontia, complete or partial absence of teeth, with frequent malformation of any teeth present, both deciduous and permanent dentitions (Fig. 19-1B and C). Where some teeth are present, they are commonly truncated or cone shaped. It should be pointed out that even when complete anodontia exists, the growth of the jaw is not impaired. This would imply that the development of the jaws, except for the alveolar process, is not dependent upon the presence of teeth. However, since the alveolar process does not develop in the absence of teeth, there is a reduction from the normal vertical dimension resulting in the protuberant lips. In addition, the palatal arch is frequently high and a cleft palate may be present (Fig. 19-2).

According to Bessermann-Nielsen, the salivary glands, including the intraoral accessory glands, are sometimes hypoplastic in this disease. This results in xerostomia, and the protuberant lips may be dry and cracked with pseudorhagades formation. As a related phenomenon, there may be hypoplasia of the nasal and pharyngeal mucous glands which leads to chronic rhinitis and/or pharyngitis, sometimes with associated dysphagia and hoarseness.

Hidrotic ED (Clouston syndrome) is inherited in an autosomal dominant manner; the homozygous state may be lethal. Clinical features include nail dystrophy associated with hair defects and palmoplantar dyskeratosis. Nails are thickened and discolored; persistent paronychial infections are frequent. Scalp hair is very sparse, fine, and brittle. Eyebrows are thinned or absent. Patients have normal facies, normal sweating and **no specific dental defect is seen.**

Histologic Findings. Skin histopathology documents the reduction in the number of sweat glands, hair follicles, and sebaceous glands associated with the different syndromes. In hypohidrotic EDS, the epidermis is thin and flattened. Eccrine sweat glands are few or poorly developed or are very rudimentary. Beyond the skin, mucous glands in the upper respiratory tract and bronchi are often reduced in number. Salivary glands may show ectasia of ducts and inflammatory changes.

Treatment. There is no treatment for the condition; however affected individuals with dental defects could be subjected to early dental evaluation and intervention beginning with dentures as early as two years.

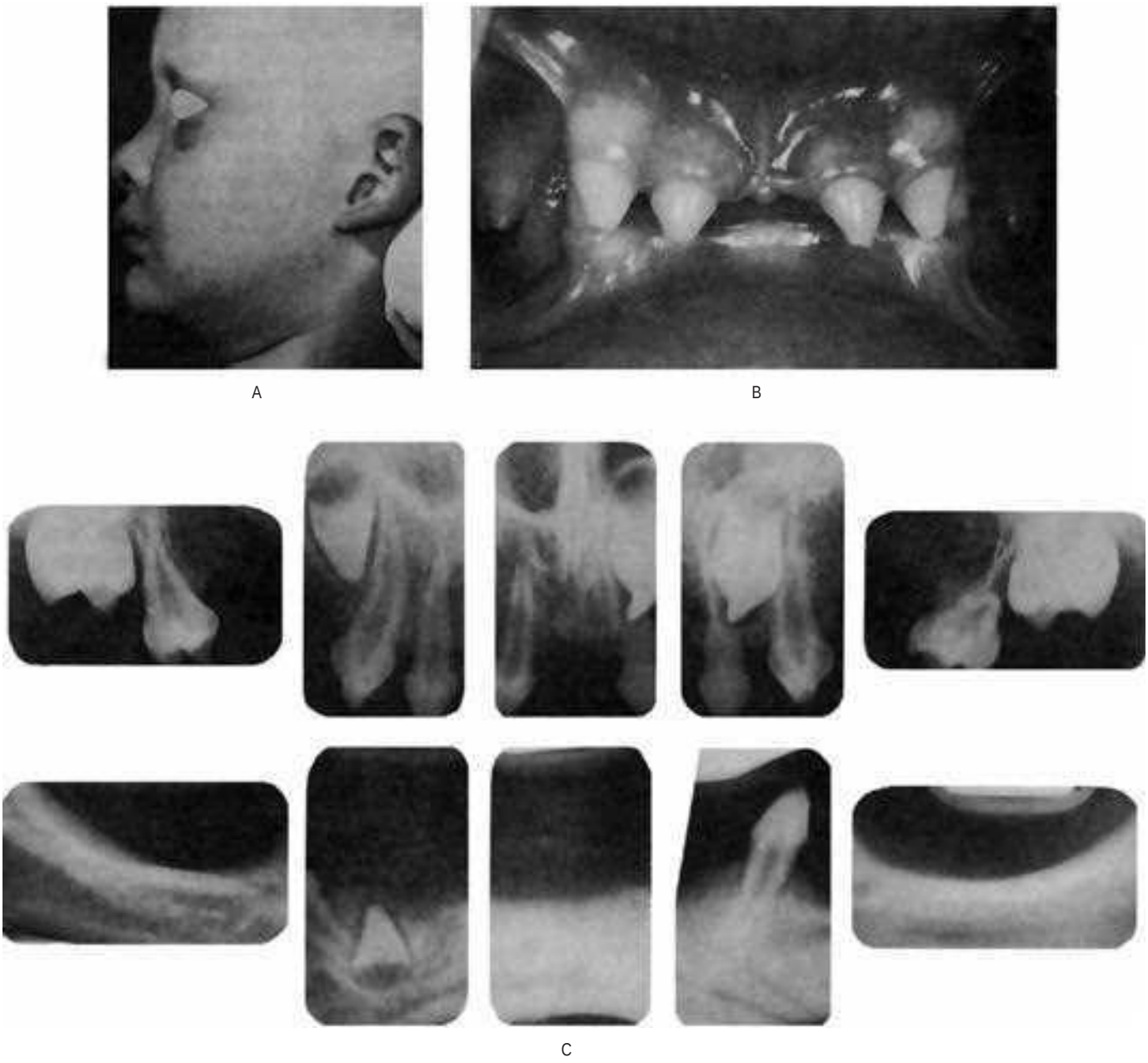


Figure 19-1. Hereditary ectodermal dysplasia.
(A) The protuberant lips, the thin, scanty hair and the saddle-nose are characteristic of the disease. **(B)** The teeth are cone-shaped. **(C)** Radiographs showing congenitally missing teeth *(Courtesy of Dr Ralph E McDonald).*

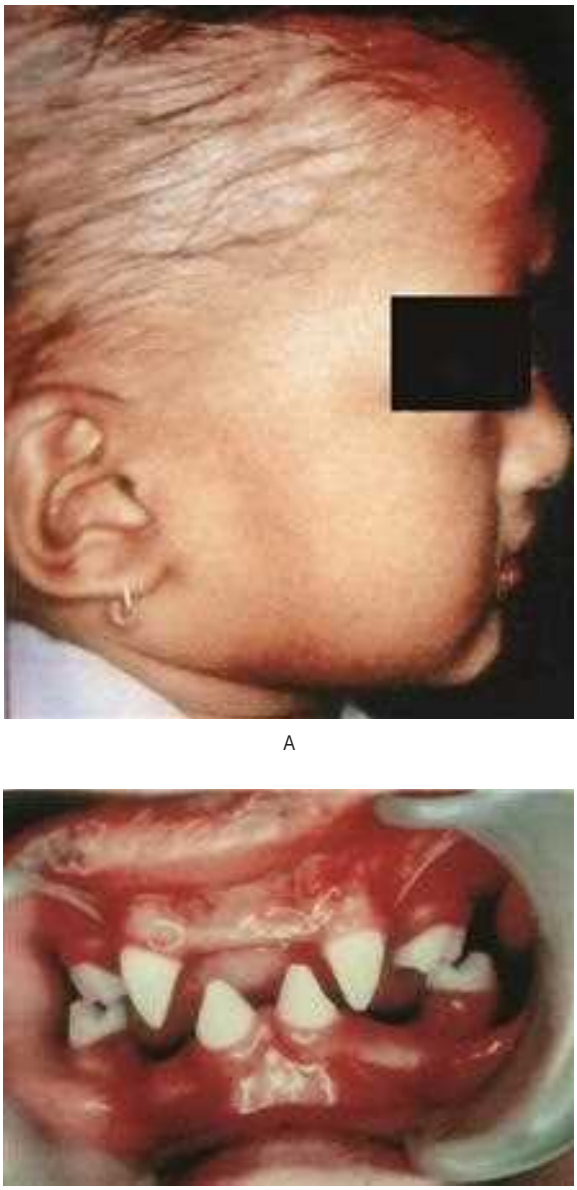
Chondroectodermal Dysplasia
(Ellis-van Creveld syndrome)

This uncommon disease is not classified as a dermatologic disease but is discussed here because of the similarity of certain of its features to those of hereditary anhidrotic ectodermal dysplasia. The disease appears to be inherited as an autosomal recessive characteristic with parental consanguinity in about 30% of the cases. McKusick and his coworkers reported 52 cases of this condition among 30 families in an Amish isolate.

Clinical Features. Chondroectodermal dysplasia is characterized by a number of ectodermal disturbances, including involvement of the nails and teeth as well as chondrodysplasia, polydactyly and sometimes congenital heart disease.

The nails are generally hypoplastic with marked koilonychia. The sweat mechanism has been reported to be normal in contrast to that in hereditary anhidrotic ectodermal dysplasia. The arms and legs are shortened and thickened. The bilateral polydactyly affects the hands and occasionally the feet. Many additional malformations are often present, although cardiac abnormalities are present in only about half of all cases.

Oral Manifestations. A discussion of both the systemic and oral manifestations of the disease has been published by



A

B

Figure 19-2. Ectodermal dysplasia.
(A) Lateral view showing frontal bossing, collapse of the middle third face, and sparse hair on the scalp. **(B)** Intraoral view showing peg-shaped incisors *(Courtesy of the Department of Oral Pathology and Microbiology, KLE's Institute of Dental Sciences, Belgaum).*

Gorlin and Pindborg, by McKusick and his associates, and by Winter and Geddes.

The most constant oral finding is a fusion of the middle portion of the upper lip to the maxillary gingival margin eliminating the normal mucolateral sulcus. Thus, the middle portion of the upper lip appears hypoplastic.

Natal teeth, prematurely erupted deciduous teeth, frequently occur as well as congenital absence of teeth, particularly in the anterior mandibular segment. Tooth eruption is often delayed and those erupted are commonly defective, being small, cone-shaped, irregularly spaced and demonstrating enamel hypoplasia. Supernumerary teeth are also reported.

Treatment. There is no treatment for the disease. Some patients die in early childhood.

Oral Lichen Planus
(Lichen ruber planus)

Oral lichen planus (OLP) is a common mucocutaneous disease. It was first described by Wilson in 1869 and is thought to affect 0.5–1% of the world's population. The condition can affect either the skin or mucosa or both. It can cause bilateral white striations, papules, or plaques on the buccal mucosa, tongue, and gingivae. Erythema, erosions, and blisters may or may not be present. The involvement of the oral mucous membrane is so frequent and accompanies or precedes the appearance of lesions on the skin and genital mucous membrane.

Epidemiology. The overall prevalence of oral lichen planus among Indians was 1.5%; it was highest (3.7%) in those people with mixed oral habits and lowest (0.3%) in nonusers of tobacco. The annual age-adjusted incidence rate was 2.1 and 2.5 per 1,000 among men and women, respectively (Bhonsle et al, 1979). The relative risk for oral lichen planus was highest (13.7) among those who smoked and chewed tobacco.

Etiology. The data available suggests that oral lichen planus is a T-cell-mediated autoimmune disease in which cytotoxic CD8+ T-cells trigger the apoptosis of oral epithelial cells. However, the precise cause of OLP is unknown. The CD8+ lesional T-cells may recognize an antigen associated with the major histocompatibility complex (MHC) class I on keratinocytes. After antigen recognition and activation, CD8+ cytotoxic T-cells may trigger keratinocyte apoptosis. Activated CD8+ T-cells (and possibly keratinocytes) may release cytokines that attract additional lymphocytes into the developing lesion. The lichen planus antigen is unknown, although it may be a self-peptide. The expression or unmasking of the lichen planus antigen may be induced by drugs **(lichenoid drug reaction),** contact allergens in dental restorative materials or toothpastes (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), viral infection, or unidentified agents. It is interesting to note that the disease is seldom seen in carefree persons; the nervous, high-strung person is almost invariably the one in whom the condition develops. The course of the disease is long, from months to several years, frequently undergoing periods of remission followed by exacerbations which often correspond to periods of emotional upset, overwork, anxiety or some form of mental strain. Other causes suggested include traumatism (since outbreaks often develop along scratch lines), malnutrition and infection.

An interesting association of lichen planus, diabetes mellitus and vascular hypertension has been described by Grinspan, the triad being described as **Grinspan's syndrome** by Grupper. However, the reported associations between OLP and systemic diseases may be coincidental, because OLP is relatively common, it occurs predominantly in older adults, and many drugs used in the treatment of systemic diseases trigger the development of oral lichenoid lesions as an adverse effect.

Clinical Features. Oral lichen planus affects all racial groups, with a female-to-male ratio of 1.4:1. It predominantly occurs in adults older than 40 years, although younger adults and children can be affected. The skin lesions of lichen planus appear as small, angular, flat-topped papules only a few millimeter in diameter. These may be discrete or gradually coalesce into larger plaques, each of which is covered by a fine, glistening scale. The papules are sharply demarcated from the surrounding skin. Early in the course of the disease the lesions appear red, but they soon take on a reddish, purple or violaceous hue. Later, a dirty brownish color develops. The center of the papule may be slightly umbilicated. Its surface is covered by characteristic, very fine grayish-white lines, called **Wickham's striae.** The lesions may occur anywhere on the skin surface, but usually are distributed in a bilaterally symmetrical pattern, most often on the flexor surfaces of the wrist and forearms, the inner aspect of the knees and thighs, and the trunk, especially the sacral area. The face frequently remains uninvolved. In chronic cases, hypertrophic plaques may develop, especially over the shins. The primary symptom of lichen planus is a severe pruritus that may be intolerable. In patients with OLP, scalp involvement (lichen planopilaris) and nail involvement is rare.

Oral Manifestations. The majority of patients with dermal lichen planus have associated oral lesions of the disease, according to the study of Shklar and McCarthy. Conversely, in a study of 115 patients with oral lichen planus by Andreasen, only 44% had skin lesions as well.

In the oral cavity, the disease assumes a somewhat different clinical appearance than on the skin, and classically is characterized by lesions consisting of radiating white or gray, velvety, thread-like papules in a linear, annular or retiform arrangement forming typical lacy, reticular patches, rings and streaks over the buccal mucosa and to a lesser extent on the lips, tongue and palate. A tiny white elevated dot is frequently present at the intersection of the white lines, known here also as the striae of Wickham. When plaque-like lesions occur, radiating striae may often be seen on their periphery.

Shklar and McCarthy have reported the following distribution of oral lesions: buccal mucosa, 80%; tongue, 65%; lips, 20%; gingiva, floor of mouth and palate, less than 10% (Fig. 19-3). These oral lesions produce no significant symptoms, although occasionally patients will complain of a burning sensation in the involved areas.

Vesicle and bulla formation has been reported in oral lesions of lichen planus, but this is not a common finding, and the diagnosis of lichen planus from the clinical appearance of the lesions is extremely difficult. This **bullous** form of lichen planus has been discussed by Shklar and Andreasen. Still another type, the so-called **erosive** form of lichen planus, usually begins as such and not as a progressive process from 'nonerosive' lichen planus. Nevertheless the vesicular or bullous form of the disease may clinically resemble erosive lichen planus when the vesicles rupture. Eroded or frankly ulcerated lesions are irregular in size and shape and appear as raw, painful areas in the same general sites involved by the simple or reticular form of the disease (Fig. 19-4). Despite the erosion of the mucosa, the characteristic radiating striae may often be noted on the periphery of the individual lesions.

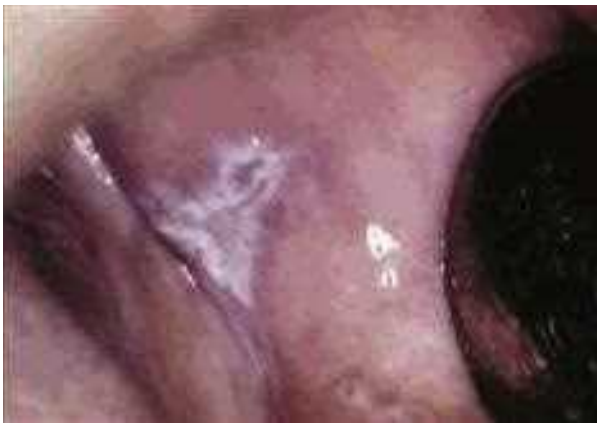


Figure 19-3. Oral lichen planus.
Plaque-like oral lichen planus on the buccal mucosa on the left side.

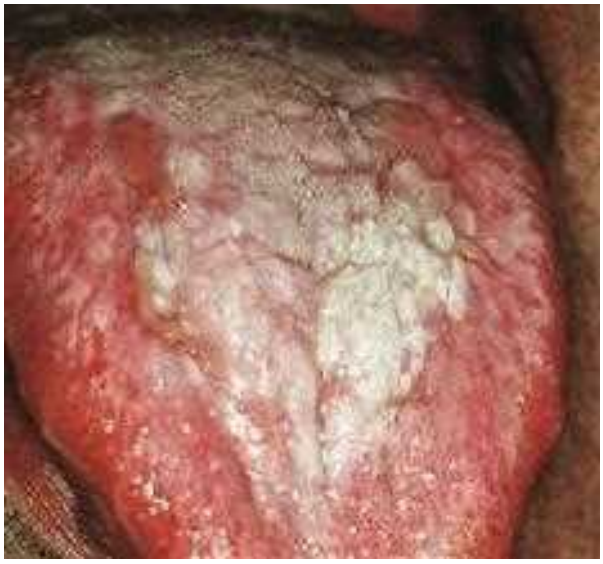


Figure 19-4. Oral lichen planus.
Ulcerative oral lichen planus on the dorsum of the tongue.

An **atrophic** form of lichen planus occurs with some frequency and appears clinically as smooth, red, poorly defined areas, often but not always with peripheral striae evident. The term 'chronic desquamative gingivitis' was at one time used to describe a red, diffuse, painful condition of the gingiva, usually found in postmenopausal women and generally quite refractory to therapy. It is now generally accepted that this is not an entity but represents a variety of conditions including the oral manifestations of several dermatologic diseases, one of which is lichen planus (usually the atrophic or erosive form), occurring on the gingiva.

A **hypertrophic** form of lichen planus may also occur on the oral mucosa, generally appearing as a well-circumscribed, elevated white lesion resembling leukoplakia. In such cases biopsy is usually necessary to establish the diagnosis.

The oral manifestations of lichen planus may occur weeks or months before the appearance of the skin lesions; in fact, in the clinical experience of most investigators, the great majority of patients exhibiting oral lichen planus do not have skin lesions present at the time of presentation of the oral lesions. Indeed, many patients with oral lichen planus never manifest the cutaneous form of the disease, although most patients are not followed up for a sufficiently long time to be absolutely certain of this. Other mucous membranes may be affected also, such as those of the penis, vagina and epiglottis. The genitals are involved in as many as 25% of women with OLP, compared with only 2–4% of men with OLP. Involvement of these locations may occur concomitant with or independent of oral lesions.

A variety of drugs may cause lesions that appear clinically similar to lichen planus and are termed as lichenoid lesions. **Oral mucosal lichenoid lesions** may occur after the administration of systemic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonylureas, antimalarials, beta-blockers, and some angiotensin-converting enzyme (ACE) inhibitors. The period between the commencement of the drug therapy and the clinical appearance of OLP-like disease varies. In rare cases, oral mucosal lichenoid lesions occur after a dental restoration is performed or after the patient starts using a denture; the lag period varies. Patients with an associated allergy to metals or components of the appliance should be evaluated by means of patch testing. In many patients, a cause for the oral lichenoid lesions cannot be identified; in these patients, the disease is called **idiopathic OLP.** Oral lichenoid reactions are considered to be a part of the spectrum of graft-versus-host disease.

They are present as reticular, erythematous, erosive lesions or ulceration, with whitish streak similar to that of Wickham's striae of lichen planus. Clinical manifestations of LR are very much similar to that of lichen planus. An important factor which distinguishes LR from lichen planus is its atypical location and absence of bilateral occurrence.

There is no specific test to diagnose LR. The widely accepted criterion is based on the observation of disappearance of the lesions after withdrawal of triggering agent and recurrence of the lesions when it is reintroduced.

Though histologically LR has superficial resemblance to lichen planus there are notable differences. The inflammatory infiltrate is diffuse and extends deeper into the lamina propria unlike the sharp band of infiltrate seen in lichen planus. Inflammatory infiltrate consists of plasma cells and eosinophils in addition to lymphocytes. Increased numbers of colloid or Civatte bodies may be present in LR compared to lichen planus. A perivascular chronic inflammatory cell infiltrate can be seen in drug related lichenoid lesions, which is not commonly found in lichen planus.

Proliferative verrucous leukoplakia, an unusual form of leukoplakia shares some demographic and clinical similarities with lichen planus. It occurs most commonly in older female patients and is not associated with tobacco usage. Microscopically it exhibits epithelial dysplasia with a band-like inflammatory infiltrate which on low-power can mimic lichen planus and is known as **lichenoid dysplasia**.

Identification and elimination of the triggering factors play a major role in the management of LR. Lichenoid lesions can take many months or longer to resolve. The malignant transformation rate is reportedly higher in oral lichenoid lesions which do not have all the typical clinical and histologic features of oral lichen planus.

Histologic Findings. Histopathologic examination of lesional tissue is the most relevant investigation in cases of OLP. Typical findings include hyperparakeratosis or hyperorthokeratosis with thickening of the granular layer, acanthosis with intracellular edema of the spinous cells in some instances, the development of a 'saw tooth' appearance of the rete pegs. Band-like subepithelial mononuclear infiltrate consisting of T-cells and histiocytes; increased numbers of intraepithelial T-cells; and degenerating basal keratinocytes that form colloid **(Civatte, hyaline, cytoid)** bodies, which appear as homogenous eosinophilic globules are consistently seen.

Degeneration of the basal keratinocytes and disruption of the anchoring elements of the epithelial basement membrane and basal keratinocytes (e.g. hemidesmosomes, filaments, fibrils) weakens the epithelial-connective tissue interface. As a result, histologic clefts (i.e. **Max-Joseph spaces**) may form, and blisters on the oral mucosa (bullous lichen planus) may be seen at clinical examination. B cells and plasma cells are uncommon findings (Fig. 19-5).

Immunoglobulin or complement deposits are not a consistent feature of OLP. In some instances, fibrinogen and fibrin are deposited in a linear pattern in the basement membrane zone. Colloid bodies contain fibrin, IgM, C3, C4, and keratin. Laminin and fibronectin staining may be absent in areas of heavy fibrin deposition and colloid body formation; this finding suggests basement membrane damage in these areas. Direct immunofluorescent studies of lichen planus by Daniels and Quadra-White have shown that nearly all specimens from oral lesions of this disease react with antifibrinogen and exhibit an intensely positive fluorescence that outlines the basement membrane zone with numerous irregular extensions into the superficial lamina propria. This particular pattern is characteristic of both lichen planus and lupus erythematosus. This is not present in pemphigoid or erythema multiforme, in both of which the fluorescence instead tends to form a patchy linear pattern, nor is it seen in pemphigus, in which the fluorescence has a granular pattern. These workers reported a general absence of immunoglobulins in lichen planus lesions while only a few specimens exhibited a fine granular fluorescence with anti-C3 (complement) at the basement membrane zone. They concluded that the pattern of fibrinogen deposition, in the absence of fluorescence by other reagents, is sufficiently unique to be used as a diagnostic criterion for oral mucosal lichen planus.

In OLP, electron microscopy is used principally as a research tool. The ultrastructure of the colloid bodies suggests that they are apoptotic keratinocytes, and recent studies of the end-labeling method revealed DNA fragmentation in these cells. Electron microscopy shows breaks, branches, and duplications of the basement membrane in OLP.

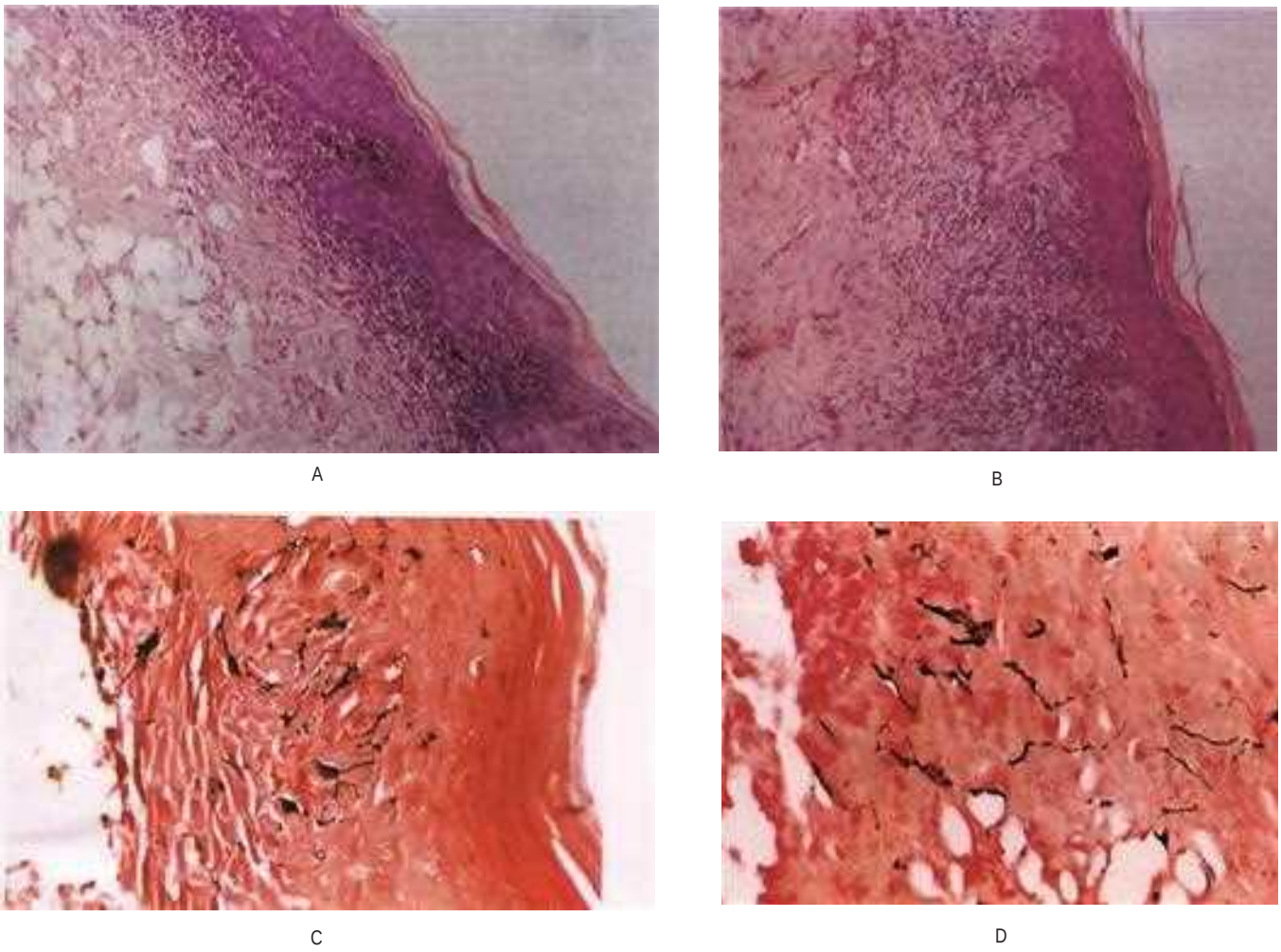


Figure 19-5. Oral lichen planus.
(A) Note the basilar degeneration and band-like infiltration of inflammatory cells in the subepithelial zone. **(B)** Histopathology of lichenoid mucositis (H and E x 100). Note the diffuse infiltration of inflammatory cells involving parts of submucosa. **(C)** Photomicrograph of Langerhans cells in lichen planus (Gold Chloride staining x400). **(D)** Photomicrograph of Langerhans cells in lichenoid mucositis (Gold Chloride staining x400) *(Courtesy of the Dept of Oral Pathology, Ragas Dental College and Hospital, Chennai).*

Differential Diagnosis. It is important that lichen planus be differentiated from other lesions of the oral cavity which may present a similar clinical appearance, but which may have a different prognosis. Oral lesions which bear superficial resemblance to lichen planus include lichenoid reactions, leukoplakia, candidiasis, pemphigus, cicatricial pemphigoid, erythema multiforme, syphilis, recurrent aphthae and lupus erythematosus (q.v.). Although microscopic examination of tissue may be necessary to establish a definitive diagnosis, the clinical characteristics of these various diseases are often sufficient to differentiate one from the other.

Malignant Transformation. There is some controversy regarding its malignant potential. There seems to be a slightly higher incidence of oral squamous cell carcinoma in patients with oral lichen planus than in the general population. The actual overall frequency of malignant transformation is low, varying between 0.3 and 3%. The forms that more commonly undergo malignant transformation are the erosive and atrophic forms.

Treatment. At present there is no cure, although various agents have been tried. Due to its minimal potential for malignant transformation, these patients used to be kept on long-term follow-up. Medical treatment of OLP is essential for the management of painful, erythematous, erosive, or bullous lesions. The principal aims of current OLP therapy are the resolution of painful symptoms, the resolution of oral mucosal lesions, the reduction of the risk of oral cancer, and the maintenance of good oral hygiene. As it is an autoimmune mediated condition, corticosteroids are recommended. In patients with recurrent painful disease, another goal is the prolongation of their symptom free intervals. The main concerns with the current therapies are the local and systemic adverse effects and lesion recurrence after treatment is withdrawn. Patients should be observed periodically, particularly those with the

erosive or atrophic forms and those who also have a history of alcohol and tobacco misuse, because of the risk of malignant transformation.

Psoriasis

Psoriasis is a noncontagious skin disorder that most commonly appears as inflamed, edematous skin lesions covered with a silvery white scale. The most common type of psoriasis is plaque psoriasis and is characterized by patches on the scalp, trunk, and limbs. The nails may be pitted and/or thickened. In rare instances it has been reported to manifest oral mucous membrane lesions.

Etiology. The cause of psoriasis is unknown. Patients do have a genetic predisposition for the disease; the disease has a strong association with **HLA Cw6** and **B57** region. Recent evidence suggests that in addition to these regions many other gene loci such as **19p13, 17q25,** and **1q21** may also increase the susceptibility to this disease. The trigger event may be unknown in most cases but is likely to be an immunologic event. Significant evidence is accumulating that psoriasis is an autoimmune disease. Lesions of psoriasis are associated with increased activity of T-cells in underlying skin. Also of significance is that 2.5% of persons with HIV develop psoriasis during the course of the disease. Perceived stress can cause exacerbation of psoriasis. Some authors suggest that psoriasis is a stress-related disease and offer findings of increased concentrations of neurotransmitters in psoriatic plaques. The pathogenesis of psoriatic lesions is due to an increase in the turnover rate of dermal cells, from the normal turnover duration of 23 days to three to five days in affected areas (Fig. 19-6). As would be expected, there is also a dramatic increase in the mitotic index of psoriatic skin which is said to even surpass that of epidermoid carcinoma.

Clinical Features. Psoriasis of the skin is characterized by the occurrence of small, sharply delineated, dry papules, each covered by a delicate silvery scale which has been described as resembling a thin layer of mica. If the deep scales are removed, one or more tiny bleeding points are disclosed, a characteristic feature termed **Auspitz's sign**. After removal of the scale the surface of the skin is red and dusky in appearance.

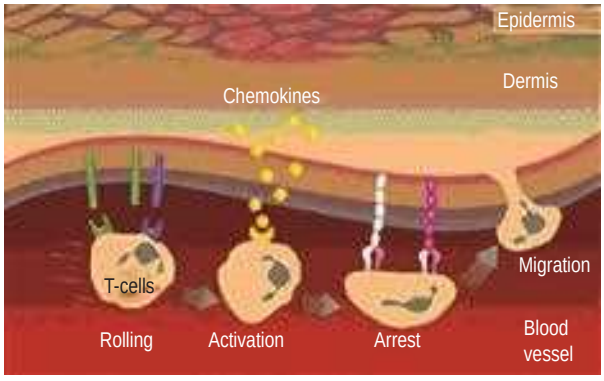


Figure 19-6. Psoriasis and T-cell trafficking across the endothelium. *(Courtesy of Dr Andrew Chan).*

The cutaneous lesions, which are painless and seldom pruritic, may be few in number or extensive in distribution. The papules enlarge at the periphery and tend to become slightly infiltrating and elevated, smaller lesions coalescing to form large plaques of irregular outline. They are roughly symmetrical and are most frequently grouped on the extensor surfaces of the extremities, particularly the elbows and knees, the scalp, back and chest, face and abdomen. Involvement of the hands and feet, with the exception of the fingernail, is uncommon.

The disease commences with the appearance of a few small papules, which gradually increase in size. New lesions slowly arise over a period of weeks, months or even years. The disease may remain static for a long time, progresses slowly to involve more and more skin area, or exhibits acute generalized exacerbations. The disease is more severe in the winter and less severe in the summer as a result of increased exposure to ultraviolet light; patients who move to a warm sunny climate usually undergo improvement in their condition. Mental anxiety or stress almost invariably appears to increase the severity of the disease or induce acute exacerbations. Arthritis is a complication in about 12% of persons with psoriasis, according to Allen. Psoriasis is uncommon in children, and seldom does a primary attack occur after the age of 45 years; it most frequently arises in the second and third decades of life. The median age at onset is 28 years. Psoriasis is slightly more common in women.

Oral Manifestations. Most authorities consider psoriatic involvement of oral mucosa extremely rare and point out that many oral lesions occurring concomitant with psoriasis of the skin are actually other diseases such as leukoplakia or lichen planus. In fact some investigators deny the existence of oral psoriasis. For example, in a study of 100 patients with dermal psoriasis, Buchner and Begleiter found none with oral lesions of the disease. However, they did note in these patients an 11% incidence of angular cheilosis, 6% incidence of fissured tongue and 5% incidence of benign migratory glossitis. Nevertheless it has been reported that in occasional cases oral lesions have exhibited all histologic features of psoriasis and in some instances have been identical with the coexisting skin lesions.

Such lesions have been reported on the lips, buccal mucosa, palate, gingiva and floor of the mouth (Fig. 19-7). Clinically, they are described as gray or yellowish-white plaques; as silvery white, scaly lesions with an erythematous base; as multiple papular eruptions which may be ulcerated; or as small, papillary, elevated lesions with a scaly surface. Reports by Goldman and Bloom and by Levin emphasized the vagaries in the clinical appearance of oral psoriasis. Psoriasis of the gingiva was reported by Brayshaw and Orban and that of the alveolar ridge by Wooten and his associates in patients without skin lesions; however, cases of mucosal involvement without skin manifestations must be viewed with caution even though the histologic sections of the lesions do present a psoriasi-

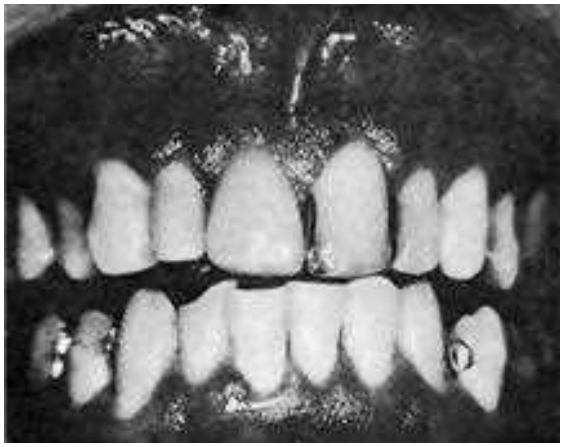


Figure 19-7. Psoriasis.
The patient manifested typical psoriasis of the skin, and in addition, presented granular gingival lesions which microscopically exhibited the characteristic psoriasiform pattern *(Courtesy of Dr Robert J Gorlin and Dr Frank Vellios).*

form pattern. White and his associates have reviewed the literature on intraoral psoriasis while reporting an additional case. Fischman and his coworkers studied an oral lesion in a patient with skin lesions of psoriasis utilizing light and electron microscopy, as well as immunologic methods, and noted in all instances that the findings in the oral lesion were similar to those in the skin lesions. They concluded that true oral lesions do occur in psoriasis.

The general problem of 'psoriasiform' lesions of the oral mucosa has been reviewed by Weathers and his associates. These lesions included psoriasis, Reiter's syndrome, benign migratory glossitis and 'ectopic geographic tongue', and the authors concluded that their exact interrelationship, if any, is still unknown.

Histologic Features. The microscopic appearance of psoriasis is characterized by uniform parakeratosis, absence of the stratum granulosum and elongation and clubbing of the rete pegs (Figs. 19-8, 19-9). The epithelium over the connective tissue papillae is thinned, and it is from these points that bleeding occurs when the scales are peeled off. Tortuous, dilated capillaries extending high in the papillae are prominent. Intraepithelial microabscesses (**Monro's abscesses**) are a common but not invariable finding; they are reported by Pisanty and Ship to be absent in oral psoriasis (Fig. 19-10). Mild lymphocytic and histiocytic infiltration of the connective tissue is also typical, particularly perivascular and periadnexal in location.

Treatment. The lesions are usually benign but a few cases may be refractory to treatment. Treatments for more general or advanced psoriasis include UV-A light, psoralen plus UV-A light (PUVA), retinoids (e.g., isotretinoin, acitretin), methotrexate (particularly for arthritis), cyclosporine, and alefacept.

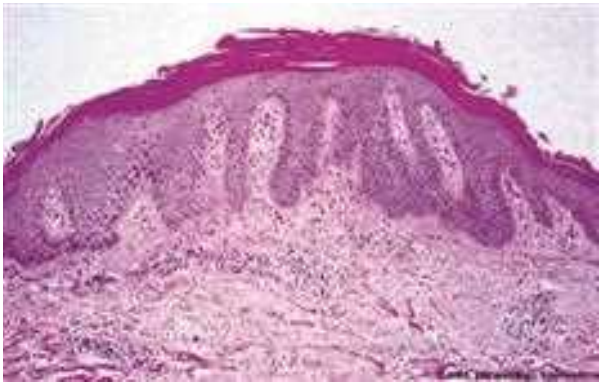


Figure 19-8. Psoriasis
Photomicrograph of skin psoriasis exhibits the pathognomonic features of the disease *(Courtesy of Dr Mary Sebury Stone)*.

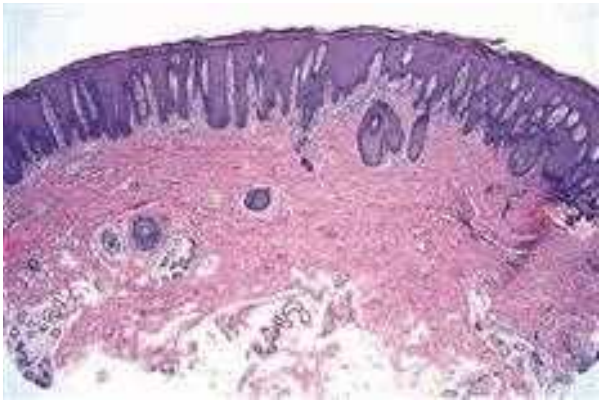


Figure 19-9. Psoriasis.
Note the 'test tube'-shaped rete ridges.

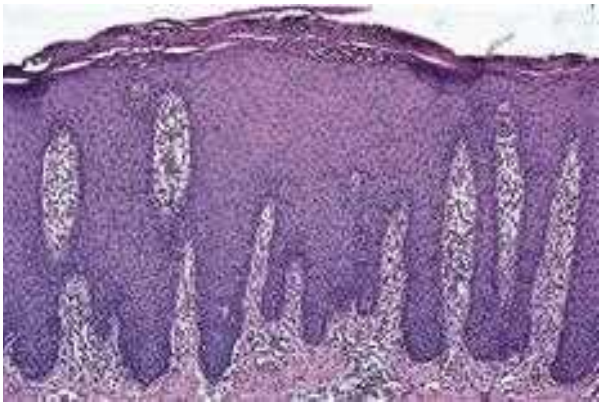


Figure 19-10. Psoriasis.

Pityriasis Rosea

Pityriasis rosea (PR) is a common benign papulosquamous disease causing acute skin eruption of unknown etiology. Pityriasis denotes fine scales, and rosea implies rose-colored or pink. It can have a number of clinical manifestations and

its diagnosis is important because it may resemble secondary syphilis.

Etiology. Pityriasis rosea has often been considered to be a viral exanthem. Its clinical presentation supports this concept. It has an increased incidence in individuals who are immunocompromised. As with viral exanthems, a single outbreak tends to elicit lifelong immunity. Despite these tendencies, no single virus has been proven to cause the disease. A number of viruses have been studied for a link to PR, which include picornavirus and parvovirus B19. Other recent work demonstrated human herpesvirus 7 (HHV-7) viral DNA in the lesions and the plasma of patients with PR. However, because HHV-7 is frequently found in healthy individuals, its etiologic role is controversial. Lesions are also thought to be increased in individuals with high stress levels.

Clinical Features. The disease is more common in hot, dry climate countries like Australia, Malaysia and India. PR is more common in women than in men and commonly develops in children and young adults, although any age group can be affected. Pityriasis rosea is characterized by the appearance of superficial light red macules or papules, either generalized over most of the skin surface, with the usual exception of the face and hands, or localized to certain areas such as the trunk, thighs, axillae or groin. This generalized outbreak is frequently preceded by the appearance of a **'primary lesion'** or **'herald spot'** 7–10 days previously. This spot is brighter red and larger (3–4 cm in diameter) than the multiple eruptions which follow its appearance. The individual exanthematous lesions are commonly ovoid, with the long axis parallel to the natural lines of cleavage of the skin, and are covered by a thin silvery scale.

The lesions often manifest mild itching sometimes accompanied by headache and low-grade fever; cervical lymphadenopathy may also be present.

Pityriasis rosea usually runs its course in three to six weeks and seldom recurs. It is interesting that the disease occurs seasonally, being far more common in the spring and autumn than at other times.

Oral Manifestations. It was pointed out by Guequierre and Wright, and confirmed by others, that involvement of the oral mucous membranes occurs with some frequency in pityriasis rosea. The oral lesions appear either concomitantly with or subsequent to the skin manifestations; they are not present throughout the clinical course of the disease, but are usually prominent during its most severe phase.

The oral lesions usually occur only on the buccal mucosa, although both tongue and palatal lesions have also been recorded. They appear as erythematous macules with or without a central area of grayish desquamation. The lesions may be single or multiple, are irregular in shape, occasionally show a raised border and vary in size from a few millimeters to 1 or 2 cm in diameter. These lesions are asymptomatic and of no clinical significance. They clear simultaneously with the skin lesions.

Histologic Features. The microscopic changes in pityriasis rosea are not pathognomonic, but consist of slight acanthosis and focal parakeratosis with microvesiculation or simply sprinkling of leukocytes within the epithelium. In addition, edema, hyperemia and perivascular infiltration of lymphocytes, plasma cells and histiocytes are prominent in the superficial connective tissue. Increased amounts of CD4 T-cells and Langhans cells are present in the dermis; this observation may indicate viral antigen processing and presentation. The histologic features suggest little more than a nonspecific dermatitis.

Treatment. The most important part of treating patients with PR is reassurance that the rash will resolve. Relief of pruritus is helpful and can be accomplished by using topical steroids, oral antihistamines, topical menthol-phenol lotions, and oatmeal baths. Systemic steroids are not recommended. Although they suppress pruritus, systemic steroids do not shorten the overall disease; in fact, they may prolong or exacerbate the disease. Ultraviolet B (UV-B) light therapy may rapidly relieve pruritus in resistant cases. One must take into consideration the possibility of postinflammatory pigmentation with light therapy. The prognosis for PR is excellent. Patients may return to work or school because they are not considered to be contagious.

Erythema Multiforme

(Stevens-Johnson syndrome, erythema multiforme major, erythema multiforme minor, herpes-induced EM major, herpes-associated erythema multiforme, drug-induced Stevens-Johnson syndrome)

Erythema multiforme (EM) is an acute self-limiting dermatitis characterized by a distinctive clinical eruption manifested as the iris or target lesion. EM may present with a wide spectrum of severity. **EM minor** represents a localized eruption of the skin with mild or no mucosal involvement. **EM major** and **Stevens-Johnson syndrome (SJS)** are more severe mucosal and skin diseases and are potentially life-threatening disorders. Recently, different workers have suggested that EM and SJS could be separated as two distinct clinical disorders with similar mucosal reactions but different patterns of cutaneous lesions. The clinical picture is as follows: erythema multiforme major is characterized by mucosal erosions of **raised atypical target lesions**. These are usually located on the extremities and/or on the face. The characteristic findings of SJS are mucosal erosions plus widespread distribution of **flat atypical targets** or purpuric macules. The lesions may be present on the trunk, the face, and on the extremities.

Etiology. Many suspected etiologic factors have been reported to cause EM. EM and SJS are both caused by drugs, but infectious agents are considered to be the major cause of EM. Today, EM minor is regarded as being triggered by HSV in nearly 100% of cases; many instances of idiopathic EM minor may be precipitated by subclinical HSV infection. A herpetic etiology also accounts for 55% of cases of EM major. Among the other infections, *Mycoplasma* infection appears to be a common cause. Drugs are reported in many documented cases of SJS and EM major. Sulfa drugs are the most common triggers.

Clinical Features. Erythema multiforme occurs chiefly in young adults, although it may develop at any age, the highest incidence is in the second to fourth decades of life and affects males more frequently than females. This disease is characterized by the occurrence of asymptomatic, vividly erythematous discrete macules, papules or occasionally vesicles and bullae distributed in a rather symmetrical pattern most commonly over the hands and arms, feet and legs, face and neck. The individual lesions may vary considerably in size even in the same patient, but are generally only a few centimeters or less in diameter. A concentric ring-like appearance of the lesions, resulting from the varying shades of erythema, occurs in some cases and has given rise to the terms 'target', 'iris', or 'bull's eye' in describing them (Fig. 19-11). They are most common on the hands, wrists and ankles. Mucous membrane involvement, including the oral cavity, is common. The lesions make their appearance rapidly, usually within a day or two, and persist from several days to a few weeks, gradually fading and eventually clearing. Recurrence of the disease over a period of years is common, however.

The **oral mucous membrane** lesions are not usually a significant feature of the disease except for the pain and discomfort they cause. The hyperemic macules, papules or vesicles may become eroded or ulcerated and bleed freely. The tongue, palate, buccal mucosa and gingiva are commonly diffusely involved (Fig. 19-12). Occasionally, mucous membrane lesions occur before the cutaneous manifestations, but oral involvement without dermal lesions has been questioned. Nevertheless, Lozada and Silverman have reported that 12 of 50 patients with erythema multiforme had oral lesions only.

Stevens-Johnson syndrome. At one time considered to be a separate disease, Stevens-Johnson syndrome is now recognized as simply a very severe bullous form of erythema multiforme with widespread involvement typically including the skin, oral cavity, eyes and genitalia. It commences with the abrupt occurrence of fever, malaise, photophobia, and eruptions of the oral mucosa, genitalia and skin. The cutaneous lesions in this mucocutaneous-ocular disease are similar to those of erythema multiforme, although they are commonly hemorrhagic and are often vesicular or bullous.

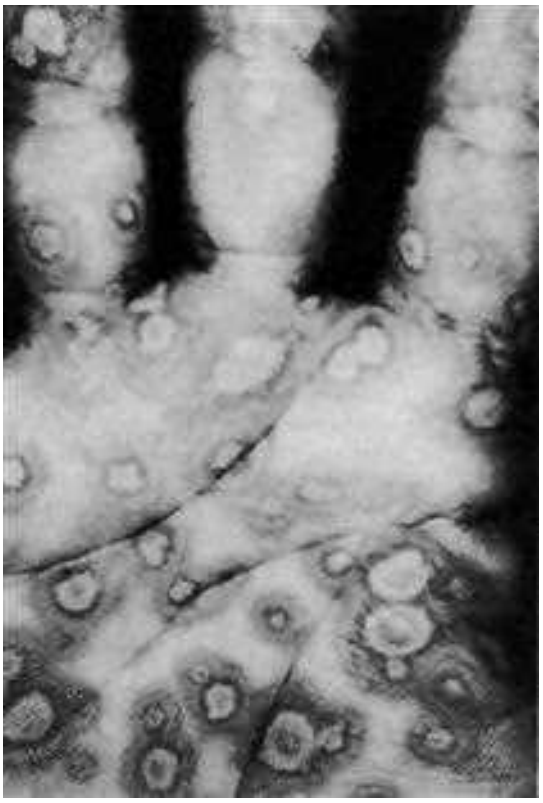
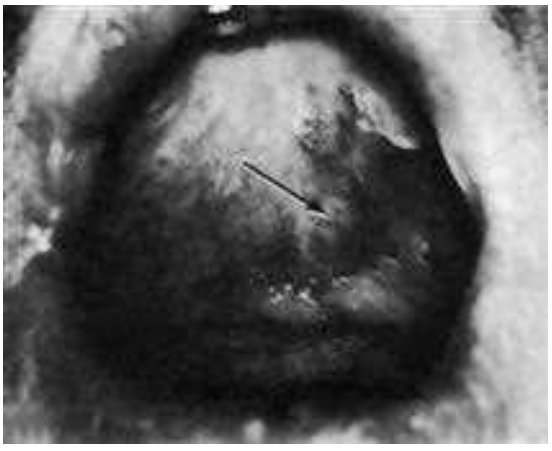
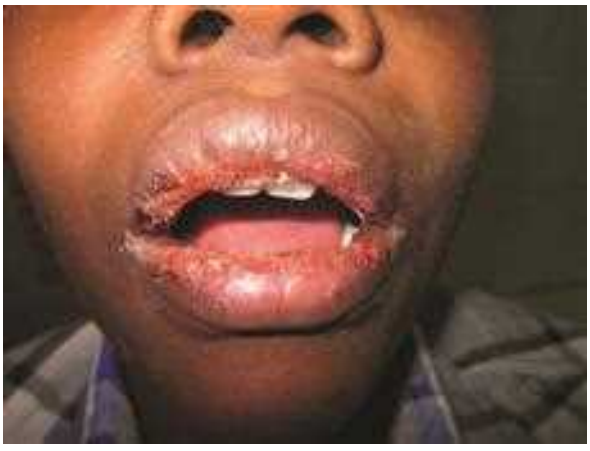


Figure 19-11. Erythema multiforme.
Typical 'target' or 'bull's eye' lesions of hand.

Oral mucous membrane lesions may be extremely severe and so painful that mastication is impossible. Mucosal vesicles or bullae occur which rupture and leave surfaces covered with a thick white or yellow exudate. Erosions of the pharynx are also common. The lips may exhibit ulceration with bloody crusting



A



B

Figure 19-12. Erythema multiforme.
Lesions of the palate **(A)** and lip **(B)**. *(B, Courtesy of Meenkashi Ammal Dental College, Chennai).*

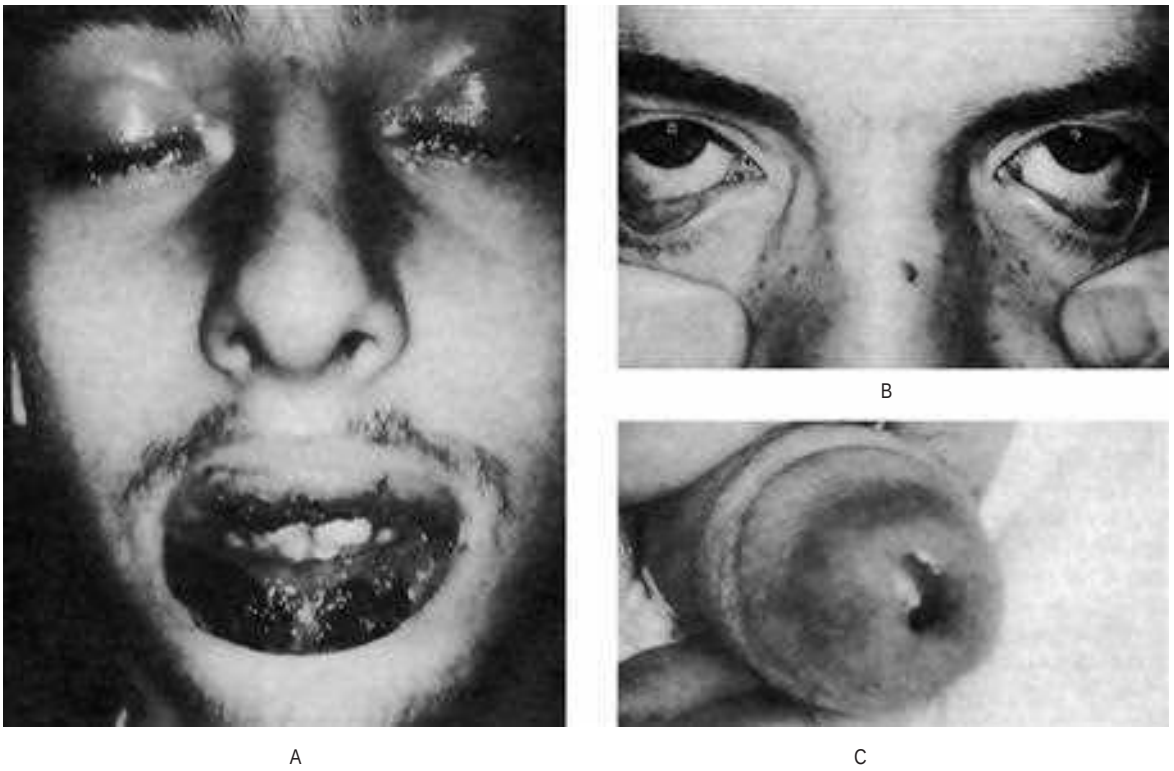


Figure 19-13. Stevens-Johnson syndrome.
Crusting ulcerated lesions of the oral cavity and lips **(A)**, conjunctivitis **(B)**, urethritis **(C)** are characteristics of the disease.

and are painful (Fig. 19-13A). The oral lesions may be the chief complaint of the patient, and understandably, have been mistaken for acute necrotizing ulcerative gingivostomatitis. Interestingly, however, it has been reported that the organisms of Vincent's infection are scarce in patients with this disease. The mucosal involvement in SJS is more severe and extensive than in EM major.

Eye lesions consist of photophobia, a characteristic of the disease referable to the conjunctivitis, corneal ulceration and panophthalmitis which may occur (Fig. 19-13B). Keratoconjunctivitis sicca also has been described. Blindness may result chiefly from intercurrent bacterial infection.

Genital lesions are reported to consist of a nonspecific urethritis, balanitis and/or vaginal ulcers (Fig. 19-13C).

Other reported complications are related to respiratory tract involvement such as tracheobronchial ulceration and pneumonia. The patients usually recover unless they succumb to a secondary infection.

Histologic Features. The microscopic appearance of erythema multiforme is not diagnostic. Although considerable variation occurs, corresponding to the variation in clinical appearance, the cutaneous or mucosal lesions generally exhibit intracellular edema of the spinous layer of epithelium and edema of the superficial connective tissue which may actually produce a subepidermal vesicle. In a study of oral lesions, Shklar has also described a zone of severe liquefaction degeneration in the upper layers of the epithelium, intraepithelial vesicle formation and thinning with frequent absence of the basement membrane. Dilatation of the superficial capillaries and lymphatic vessels in the uppermost layer of connective tissue is prominent, and a varying degree of inflammatory cell infiltration, chiefly lymphocytes, but often neutrophils and eosinophils, is also present. Similar findings were described by Buchner and his coworkers in a series of 25 cases. The findings have been confirmed in an electron microscopic study by von Bulow and his coworkers.

Differential Diagnosis. The varied nature of the disease may present difficulty in diagnosis, particularly when the occurrence of cutaneous lesions is minimal. In the presence of oral lesions, aphthous stomatitis, contact dermatitis or stomatitis and acute necrotizing gingivitis must be considered, as well as pemphigus, dermatitis herpetiformis, bullous lichen planus, herpes zoster, chickenpox and toxic epidermal necrolysis (Lyell's disease).

Toxic epidermal necrolysis is a very serious, often fatal, bullous drug eruption, so severe that large sheets of skin peel off, giving the appearance of a widespread scalding burn. Oral erosions may also occur and have been described by Giallorenzi and Goldstein. It is now considered to be a confluent form of Stevens-Johnson syndrome. Toxic epidermal necrolysis must be differentiated from the **staphylococcal scalded skin syndrome,** which appears clinically similar even though the latter is a milder disease with a better prognosis.

Treatment. Identification of the cause should be made if possible. If a drug is suspected, it must be withdrawn. Infections should be appropriately treated after cultures and/or serologic tests have been performed. For all forms of EM, symptomatic

treatment, including oral antihistamines, analgesics, local skin care, and soothing mouthwashes, is of great importance. Topical steroids may be considered. Oral antacids may be helpful for discrete oral ulcers. The use of liquid antiseptics, such as 0.05% chlorhexidine, during bathing is preferable. Systemic corticosteroids are controversial, and some believe they may predispose to complications.

Mucocutaneous Lymph Node Syndrome
(Kawasaki disease)

An acute self-limiting febrile illness in a large number of Japanese children was first described in 1967 by Dr Tomisaku Kawasaki. Since then, Kawasaki disease (KD) has been observed worldwide in children and adult patients of all races.

Mucocutaneous lymph node syndrome, Kawasaki syndrome or KD, is a systemic vasculitis of unknown etiology and the most common cause of acquired heart disease in children in Japan and the United States. However, Asians are most commonly affected. The hallmarks of KD are fever of unknown origin for more than five days, generalized erythema and desquamation of skin, cervical nonsuppurative lymphadenopathy, and swelling of the hands and the feet.

Etiology. The cause of Kawasaki disease is unknown. Evidence suggests an abnormal inflammatory response triggered by a neoantigen or a conventional antigen from one or more etiologic agents. Several infectious causes of KD have been theorized; these include Epstein-Barr virus; retroviruses; *Streptococcus pyogenes; Streptococcus viridans; Staphylococcus species; Chlamydia* infections; *Propionibacterium,* and *Pseudomonas* species. However, conventional bacterial and viral cultures and serologic studies have not confirmed an infectious cause. Other postulated etiologic agents are immunization; medications; and environmental agents, such as house dust mites.

Clinical Features. The vast majority of cases have occurred in children between three months and 12 years of age, although it has also been reported in adults. KD occurs more often in boys than in girls, with a ratio of about 1.4 : 1. The most frequent symptoms of the disease are:

- Fever for five days or more, with no response to antibiotics.
- Bilateral congestion of ocular conjunctiva.
- Changes in the extremities including indurative edema, erythema of palms and soles and membranous desquamation of fingers and toes.
- Changes in lips and mouth including dryness, redness and fissuring of lips, strawberry-like reddening and swelling of tongue papillae and diffuse reddening of oral and pharyngeal mucosa, sometimes with gingival ulceration.
- Polymorphous exanthema of torso without vesicles or crusts.
- Acute, nonpurulent swelling of cervical lymph nods of 1.5 cm or more. Other less common findings include diarrhea, arthralgia, proteinuria, leukocytosis, increased sedimentation rate and positive C-reactive protein.

One of the unfortunately common complications of the disease is cardiac abnormality. While the vast majority of cases are self-limiting and nonfatal, occasional deaths do occur, almost invariably a result of the cardiac complications, usually a coronary thrombosis or vascular damage related to infantile periarteritis nodosa. The implications of dental treatment in these patients have been reviewed by Taylor and Peterson.

Differential Diagnosis. Unfortunately, there are no laboratory tests available for confirmation of the diagnosis of the disease. Therefore, its diagnosis is based entirely on clinical manifestations. It must be carefully distinguished from scarlet fever, erythema multiforme or Stevens-Johnson syndrome.

Histologic Findings. Sparse perivascular lymphocytic and histiocytic inflammatory infiltrates are seen. Marked papillary dermal edema, dilatation of blood vessels, and exocytosis of lymphocytes are observed. Evidence of vasculitis is most severe in medium-sized arteries.

Treatment. The initial therapy is aimed at reducing fever and inflammation of the myocardium and coronary artery wall to prevent subsequent cardiac sequelae. Recommended therapy for KD in the acute phase includes intravenously administered gammaglobulin (IVGG).

Pachyonychia Congenita
(Jadassohn-Lewandowsky syndrome, polykeratosis congenita [Touraine])

Pachyonychia congenita (PC) is a rare form of hereditary palmoplantar keratoderma (PPK), extremely uncommon in occurrence. In the dermatologic literature, PC is better known as Jadassohn-Lewandowsky syndrome. The condition is rare, but more than 250 cases have been reported. Various classifications for PC have been proposed. Currently two distinct syndromes of PC are recognized:

- **PC-1 (the Jadassohn-Lewandowsky type)**
- **PC-2 (the Jackson-Lawler type).**

Etiology. PC results from mutations in the genes encoding epidermal keratinocyte keratins, specifically **K6a, K6b, K16,** and **K17.** In most cases, an autosomal dominant mode of inheritance is described; however, autosomal recessive inheritance is also mentioned in the literature. Cockayne (1933) was the first to express the opinion that the presence of an additional factor, probably a second genetic mutation, is necessary for the expression of the disease. Munro (1994) was the first to propose that the genetic defect in PC is linked to the keratin gene cluster on **chromosome 17.**

Clinical Features. The skin lesions of pachyonychia congenita usually occur shortly after birth; both genders are affected equally and consist of dystrophic changes in the fingernails and toenails, hyperkeratotic calluses of the palms and soles, follicular keratosis about the knees and elbows, and hyperhidrosis or excessive sweating of the hands and feet. The nail changes from which the disease derives its name consist of marked thickening, increasing toward the free border, with the nail bed becoming filled with yellowish keratotic debris, often causing the nail to project upward at the free edge. Associated sparse hair and corneal dyskeratosis producing corneal opacities have been reported also.

Oral Manifestations. Oral lesions are nearly always present, according to Gorlin and Chaudhry. They consist of either focal or generalized, white, opaque thickening of the mucosa involving the buccal mucosa, tongue or lips. These leukoplakic oral lesions should not be confused clinically with lichen planus. These have even been reported present at birth. Angular cheilosis is also reported to be commonly seen. Teeth present at birth, natal teeth, have been found on a number of occasions. Cases with typical oral lesions have been reported by Maser and by Young and Lenox.

Histologic Findings. The hyperkeratotic lesions of the skin and oral mucosa show acanthosis, hyperkeratosis, and parakeratosis. Premalignant changes are not observed. Electron microscopy shows thickened and clumped intermediate filaments, as well as enlarged keratohyalin granules. In the broadened granular layer, thick masses of tonofilaments and large, irregular keratohyalin granules are present. In the spinous layer, thick masses of tonofilaments are found at the periphery of the cells.

Treatment. Currently, there is no treatment for this disease, which is not considered to be a serious condition.

Keratosis Follicularis
(Darier disease, Darier-White disease)

Keratosis follicularis, also known as Darier disease (DD) or Darier-White disease, is a dominantly inherited genodermatosis that is characterized by hyperkeratotic papules in seborrheic regions and various nail abnormalities. The disease was first reported independently by Darier and White in 1889.

Etiology. Abnormal cell-cell adhesion and aberrant epidermal keratinization are the primary features of DD. Electron microscopy reveals loss of desmosomes, breakdown of desmosome-keratin intermediate filament attachment, and perinuclear aggregates of keratin intermediate filaments. These observations suggest that the molecules responsible for cell-cell adhesion, such as desmosomal cadherins, desmosomal plaque proteins, or intermediate filament proteins, may be involved in the disease process. However, recently, mutations in the gene **ATP2A2 (located in band 12q23-24.1)** were found in patients with DD.

Clinical Features. Keratosis follicularis is usually manifested during childhood or adolescence and has an equal gender distribution. The cutaneous lesions appear as small, firm papules, which are red when they first appear, but characteristically become grayish brown or even purple, ulcerate and crust over (Fig. 19-14). Especially in the skin folds, the lesions tend to coalesce and produce verrucous or vegetating macerated, foul-smelling masses. They are generally distributed on the forehead, scalp, neck and over the shoulders, but often spread to the limbs, chest and genitalia. Palmar and plantar keratotic thickening may be so severe as to interfere with function. In severe cases, all the intertriginous areas are involved. Characteristic nail changes are also seen consisting of splintering, fissuring, longitudinal streaking and subungual keratosis.

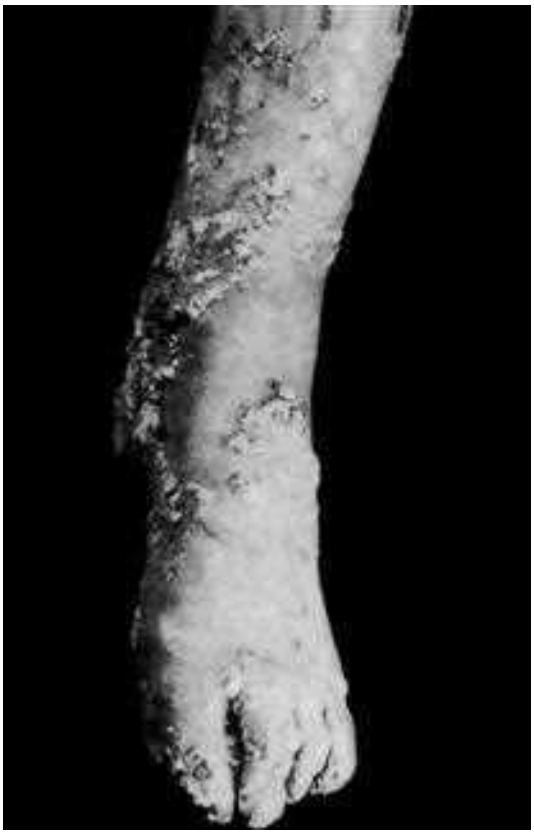
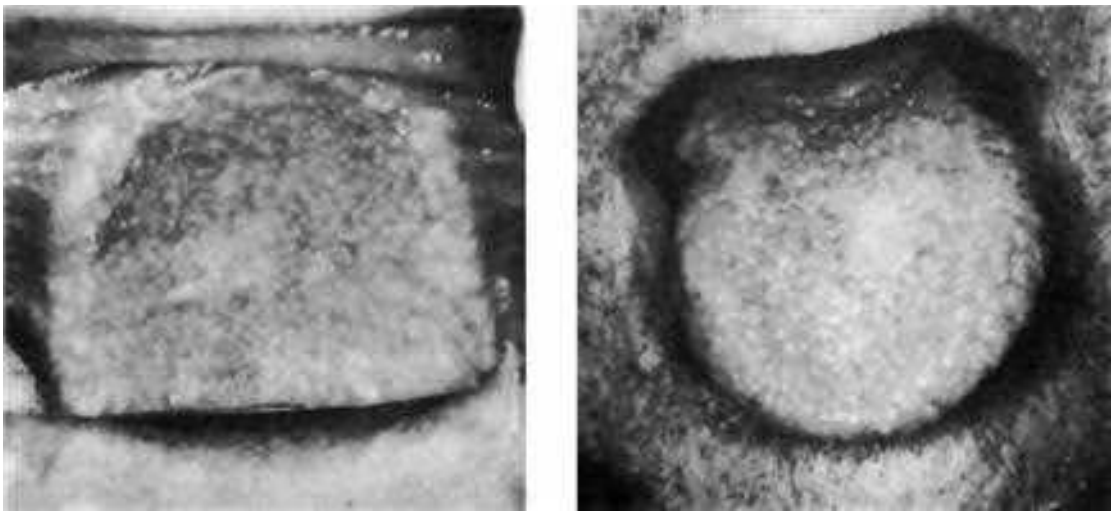


Figure 19-14. Keratosis follicularis.
(Courtesy of Dr Dwight R Weathers. Arch Dermatol, 100: 50, 1969).

Oral Manifestations. The oral mucosa is probably more commonly involved than is generally realized, according to Gorlin and Chaudhry, who found a number of reports of oral lesions in the literature. In addition, they pointed out that other mucosal surfaces such as vulva, pharynx and larynx have also been reported as sites of the disease. Mucosal lesions have been said to be apparent only when there is extensive skin involvement. However, Weathers and Driscoll have stated that severe skin involvement is not necessary for the occurrence of oral lesions, although the severity of oral involvement did tend to parallel that of the skin. Nevertheless, oral involvement has been reported in as high as 50% of all cases.

The oral lesions appear as minute, whitish papules which feel rough upon palpation. Some cases have been described as rough, pebbly areas with verrucous white plaques or as having a cobblestone appearance as in the cases of Weather and his associates and Prindiville and Stern. These are most frequently found on the gingiva, tongue, hard and soft palates, buccal mucosa and even the pharynx (Fig. 19-15).

Histologic Features. The disease is misnamed, since the changes are not restricted to the hair follicles. The characteristic findings in skin lesions are hyperkeratosis, papillomatosis, acanthosis and a peculiar benign dyskeratosis. This benign dyskeratosis is characterized by rather typical cells called **corps ronds** and **grains**. The corps ronds are larger than normal squamous cells and have a round, homogeneous, basophilic nucleus with a dark eosinophilic cytoplasm and a



A B

Figure 19-15. Keratosis follicularis.
(Courtesy of Dr Dwight R Weathers. Arch Dermatol, 100: 50, 1969).

distinct cell membrane. These are found usually in the granular layer and superficial spinous layer. The grains are small, elongated parakeratotic cells situated in the keratin layer. Both corps ronds and grains represent partially keratinized cells and are found also in the typical slit-like intradermal vesicle just above the basal layer of cells, the typical suprabasilar cleavage. Acantholytic cells are commonly found floating in the lacunae produced by this intraepithelial separation. The microscopic features of the oral lesions are identical except that the hyperkeratotic changes are generally not pronounced.

In an excellent review of keratosis follicularis, Spouge and his associates have also described a peculiar hyperplasia of the epithelial rests of Malassez in the periodontal ligament with a maturation of these individual cells into prickle cells, some of which even exhibited individual cell keratinization.

The cytologic findings in scrapings taken from the deeper portion of oral mucosal lesions have been described by Burlakow and his coworkers. They pointed out that, while some of the cells might be mistaken for malignant cells, the general cell population, the presence of grain cells and corps ronds and the 'leafing-out' pattern of the parabasal cells should permit the correct diagnosis from such cytologic smears.

It has been demonstrated by the electron microscope that the basic defect in epidermal synthesis, turnover and resultant keratinization is related to a defect in the desmosome-tonofilament complex. It is also reported that there is a sevenfold decrease in turnover time of this epithelium.

Treatment. Oral retinoids have been the most effective medical treatment for DD. However, long-term treatment with oral retinoids is needed in DD. Unfortunately, prolonged use of oral retinoids can cause significant adverse effects, and many patients have to stop taking them because of the toxicity. A few authors reported symptomatic and cosmetic improvement in DD by using surgical procedures. Overall, patients with DD have a life expectancy similar to that of the general population.

Warty Dyskeratoma
(Isolated dyskeratosis follicularis, isolated Darier's disease)

The warty dyskeratoma is a lesion which bears marked histologic similarity to keratosis follicularis but, in contrast to the latter, is usually a single isolated focus. The suggested origin of the lesion from the pilosebaceous apparatus would seem somewhat unlikely since oral lesions are known to occur.

Clinical Features. The skin lesions have occurred on the face, scalp or neck and upper chest in the majority of reported cases. They are almost invariably single lesions varying in size from only 1–10 mm in diameter. They appear as elevated nodules, somewhat umbilicated, with a raised border and varying in color from yellow or brown to gray or black. Purulent drainage as well as bleeding frequently occurs.

There were 80 males and 32 females in a group of 112 cases of this lesion reviewed by Tanay and Mehregan and the majority occurred in middle-age or in older adults. In nearly every case, careful examination will reveal a hair passing through the lesion.

Oral Manifestations. Oral lesions are rare but do occur, three cases having been reported by Tomich and Burkes and several solitary cases reviewed by Patibanda and by Danforth and Green. These lesions were described as small whitish areas of the mucosa with a central depression and were situated on the alveolar ridge and palate. The patients were aware of the presence of these lesions and in at least two of these cases discomfort was present.

Histologic Features. The microscopic findings in the skin and mucosal lesions are identical except for the absence of a pilosebaceous structure in the oral lesions. The intraoral

lesions exhibit a central orthokeratin or parakeratin core beneath which the epithelium shows a suprabasilar separation resulting in a cleft-like space containing acantholytic and benign dyskeratotic cells. The connective tissue papillae are covered usually by a single layer of basal cells while the underlying connective tissue shows a nonspecific chronic inflammatory cell infiltrate.

The term **focal acantholytic dyskeratosis** was suggested by Ackerman in 1972 for a clinically heterogeneous group of dermatologic conditions all characterized by certain histologic features which they share in unison but with no implied common etiology or pathogenesis. The warty dyskeratoma is one of the groups fulfilling the criteria, and an intraoral case has been reported under the more inclusive generic term by Freedman and his associates.

Treatment and Prognosis. The lesions should be treated by surgical excision. There appears to be no malignant transformation in these lesions.

Incontinentia Pigmenti
(Bloch-Sulzberger syndrome)

Incontinentia pigmenti (IP), sometimes termed Bloch-Sulzberger syndrome, is an X-linked dominant single-gene disorder with neurologic, ophthalmologic, and dental involvement, as well as cutaneous findings. Bloch and Sulzberger defined the condition as a clinical syndrome with a constellation of unique features, which include typical cutaneous lesions. Since then, a large number of small series and individual case reports have been published.

Etiology. The patchy distribution of the skin lesions is thought to be the result of tissue mosaicism due to random X-inactivation. Normal X chromosomes are active in unaffected skin, and mutated X chromosomes are active in skin affected with IP.

Clinical Features. The disease generally appears shortly after birth. More than 95% of reported cases occur in females, but the disease does occur in males and is characterized by the appearance of erythematous and vesiculobullous lesions on the trunk and extremities which frequently disappear, then reappear. This phase is often associated with a marked eosinophilia. These are gradually replaced by white keratotic, lichenoid, papillary or verrucous lesions which then persist for some months.

The third type of characteristic skin lesions in these infants are brownish-gray macules in a streaked, patchy distribution over the trunk and extremities, occurring subsequent to the verrucous, keratotic lesions. This pigmentation begins to fade within a few years. It is the heavy melanin pigmentation of the epithelium, dropping down into clusters of chromatophores in the upper dermis (incontinence), which gives the disease its name and is considered the hallmark of the syndrome.

A variety of associated defects are often seen in **incontinentia pigmenti**, including local or generalized baldness; ophthalmologic lesions including cataracts, optic atrophy, strabismus and retrolental fibroplasia; central nervous system involvement and lesions of the skeletal system.

Oral Manifestations. Oral changes in this disease have been described by Gorlin and Anderson and by Russell and Finn, among others, and appear limited to the teeth. Dental abnormalities are seen in 80% of patients. Both the deciduous and permanent dentitions may be affected. These dental changes have been described as consisting of delayed tooth eruption, peg or cone-shaped tooth crowns, congenitally missing teeth, malformed teeth and additional cusps. The cone-shaped teeth are very similar to those seen in hereditary ectodermal dysplasia.

Treatment. Treatment of the cutaneous lesions is usually not required. The vesicles of the inflammatory stage should be left intact, and the skin should be kept clean to prevent secondary bacterial infection. Oral hygiene and regular dental care is necessary, and dental restoration may be indicated. The prognosis of IP is generally good.

Porokeratosis of Mibelli

Porokeratosis of Mibelli is an uncommon genokeratosis characterized by faulty keratinization of the skin followed by atrophy. It appears to be inherited as a simple dominant characteristic, although many sporadic cases are known. There is no adequate documentation that the lesions of porokeratosis, despite the name of the disease, have their origin in the epidermal pores of sweat glands.

Clinical Features. The majority of cases begin in early childhood but the progression of the lesions is generally exceedingly slow. It appears to occur in males with greater frequency than in females. The lesions themselves consist initially of crateriform keratotic papules which gradually enlarge to form elevated plaques ranging in size from a few millimeters to several centimeters. The lesions have a predilection for the extremities, particularly the hands and feet, as well as the shoulders, face and neck, and the genitalia. The nails commonly become thickened and ridged. The central portion of the lesions ultimately becomes atrophic, leaving permanent scarring. Epidermoid carcinoma has been reported developing in this atrophic skin. Lesions of the oral cavity are said to occur with considerable frequency in patients with this disease.

Histologic Features. The elevated horny margin of the lesion exhibits hyperkeratosis and acanthosis with a deep groove filled with parakeratin and a characteristic absence of the usual underlying granular layer. This constitutes the 'cornoid lamella' which is characteristic of the lesion. The central portion of the lesion shows epithelial atrophy and occasionally dyskeratosis. The connective tissue beneath the cornoid lamella may exhibit a lymphocytic infiltrate.

Treatment. There is no treatment for the disease except for removal of individual lesions.

Dyskeratosis Congenita
(Zinsser-Engman-Cole syndrome, Hoyeraal-Hreidarsson syndrome)

Dyskeratosis congenita (DKC) is a well recognized but rare genodermatosis characterized by cutaneous reticulated hyperpigmentation, nail dystrophy, premalignant leukoplakia of

the oral mucosa, and progressive pancytopenia. The importance of the syndrome lies in the high incidence of oral cancer which develops in the young affected adults.

Etiology. Mutations in **DKC1** have been shown to cause the X-linked form of DKC. The inheritance pattern of most cases of DKC is X-linked recessive, but autosomal dominant and recessive patterns have been reported.

Clinical Features. Dyskeratosis congenita is a rare syndrome, with approximately 180 individuals reported in the literature. Because this disorder is primarily X-linked recessive, the male-to-female ratio is approximately 10 : 1. The nail changes are usually the first manifestation of the disease, becoming dystrophic and shedding some time after the age of five years. The grayish-brown skin pigmentation appears at the same time or a few years later and is distributed over the trunk, neck, and thighs. The skin may become atrophic and telangiectatic and the face appears red.

Occasional cases have also been reported with a wide spectrum of other minor manifestations including a frail skeleton, mental retardation, small sella turcica, dysphagia, transparent tympanic membranes, deafness, epiphora and eyelid infections, urethral anomalies, small testis, dental abnormalities and, commonly, hyperhidrosis of the palm and soles.

Oral Manifestations. Mucosal leukoplakia typically occurs on the buccal mucosa and can affect the tongue and oropharynx. The leukoplakia may become verrucous, and ulceration may occur. Other mucosal sites may be involved (e.g. esophagus, urethral meatus, glans penis, lacrimal duct, conjunctiva, vagina, anus). Constriction and stenosis can occur, with the development of dysphagia, dysuria, phimosis, and epiphora. Patients have an increased incidence of malignant neoplasms, particularly squamous cell carcinoma of the skin, mouth, nasopharynx, esophagus, rectum, vagina, and cervix. These often occur within sites of leukoplakia. Patients also may have an increased incidence and severity of dental caries and tooth loss.

Histologic Findings. Skin biopsy specimens from the areas of reticulated pigmentation typically show mild hyperkeratosis, epidermal atrophy, telangiectasia of the superficial blood vessels, and melanophages in the papillary dermis. Interface changes have also been reported, with mild basal layer vacuolization and a lymphocytic inflammatory infiltrate in the upper dermis. Oral lesions have not been thoroughly studied but the leukoplakic lesions appear to be nonspecific hyperparakeratosis or hyperorthokeratosis and acanthosis. Depending on the stage of the disease, the epithelium may show dysplasia. The exact nature of the preceding vesicles and ulcers has not been described.

Laboratory Findings. Many cases have been characterized also by hematologic changes including anemia, leukopenia, thrombocytopenia and pancytopenia. Some patients have developed Fanconi's anemia. In fact, the suggestion has been made that Fanconi's syndrome, or Fanconi's familial pancytopenia, is simply a varied expression of dyskeratosis congenita.

Treatment. Short-term treatment options for bone marrow failure in patients with DKC include erythropoietin and granulocyte colony-stimulating factor; however, the only long-term, curative option is allogenic bone marrow transfer. The high frequency of malignant transformation of oral lesions would necessitate careful periodic examination of the patient for such an occurrence.

White Sponge Nevus

(Familial white folded dysplasia of mucous membrane, white folded gingivostomatitis, oral epithelial nevus, congenital leukokeratosis, Cannon's disease)

Familial white folded dysplasia is a relatively uncommon condition of the oral mucosa described by Cannon in 1935. The disease appears to follow a hereditary pattern as an autosomal dominant trait but with irregular penetrance and no definite sex predilection.

Clinical Features. This mucosal abnormality is congenital in many instances. In other cases it does not appear until infancy, childhood or even adolescence, by which time it has generally reached the full extent of its severity.

The oral lesions may be widespread, often involving the cheeks, palate, gingiva, floor of the mouth and portions of the tongue. The mucosa appears thickened and folded or corrugated with a soft or spongy texture and a peculiar white opalescent hue (Fig. 19-16). There is sometimes a minimal amount of folding present. Ragged white areas may also be present which can be removed sometimes by gentle rubbing without any ensuing bleeding (Fig. 19-17A, B). The lesions themselves are almost invariably asymptomatic. Banoczy and her associates have provided a detailed review and discussion in their report of 45 cases of this disease. In occasional cases

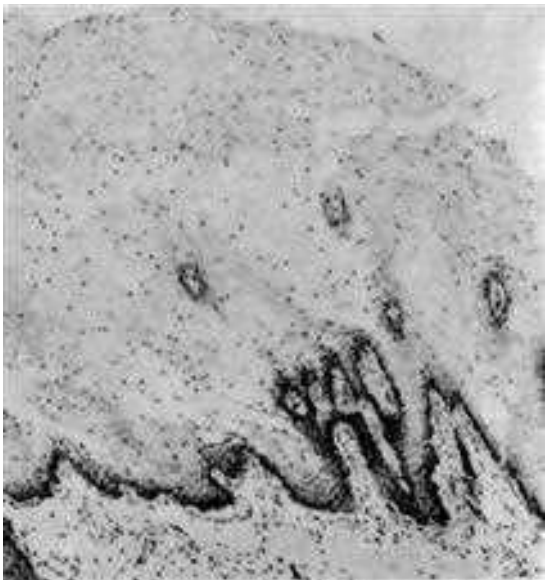
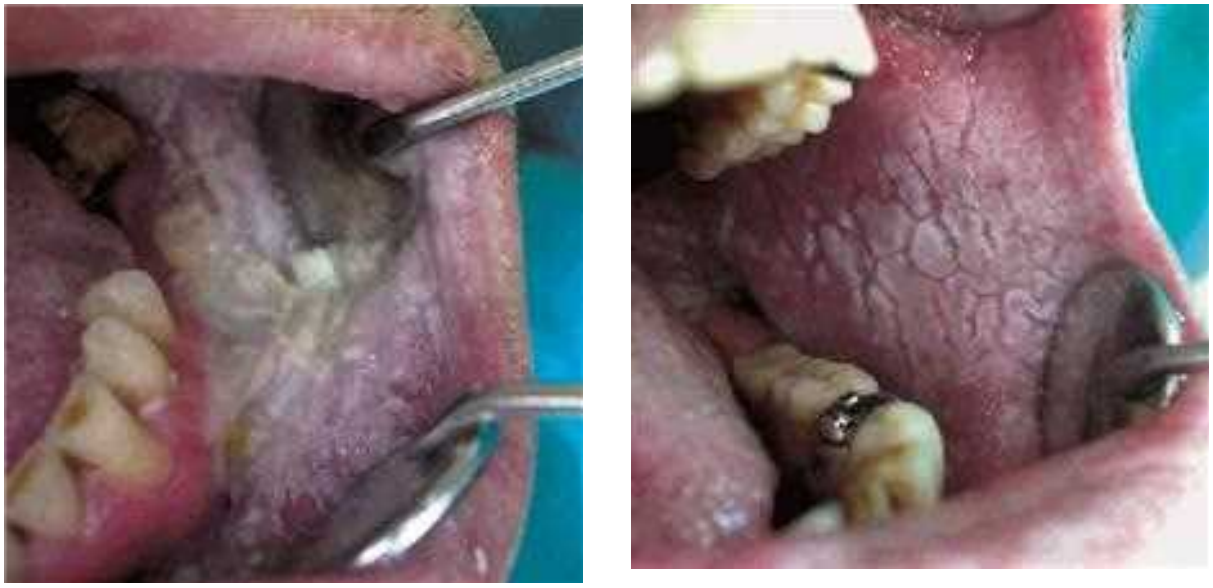


Figure 19-16. White sponge nevus.
The typical intracellular edema and cellular pyknosis of the spinous cells *(Courtesy of Dr Carl J Witkop).*



A B

Figure 19-17. White sponge nevus.
The folded, spongy texture of the buccal mucosa is apparent in the figures.

reported in the literature, the oral lesions were accompanied by similar lesions of other mucosal surfaces, including the vagina and labia, anus, rectum and nasal cavity.

Histologic Features. The microscopic findings in familial white folded dysplasia are characteristic but not entirely pathognomonic of the disease. The epithelium is generally thickened, showing both hyperparakeratosis and acanthosis, and the basal layer is intact. The cells of the entire spinous layer, continuing to the very surface, exhibit intracellular edema (Fig. 19-16). These vacuolated cells may show pyknotic nuclei. In addition, parakeratin plugs running deep into the spinous layer are typically found. The submucosa may show a mild inflammatory cell infiltration, but this is not consistent.

Several electron microscopic investigations of the white sponge nevus have been reported, the first being that of Whitten, and subsequent studies, those of McGinnis and Turner and of Frithiof and Banoczy. There is some lack of agreement on interpretation of the ultrastructural findings in the various studies so that, until these are resolved, their discussion in explanation of the light microscopic findings should be deferred.

Treatment and Prognosis. There is no treatment for the condition, but since it is perfectly benign, the prognosis is excellent. There are no serious clinical complications.

Hereditary Benign Intraepithelial Dyskeratosis

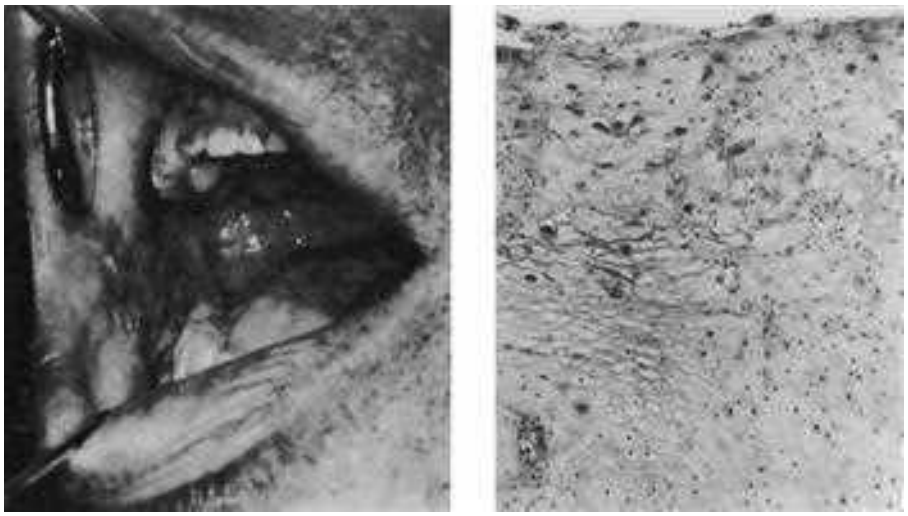
This unusual hereditary syndrome was discovered in 1954 in a racial isolate group of mixed Caucasian, Indian and Negro ancestry living in North Carolina. Since that time it has been thoroughly studied and described by Witkop and his coworkers. The disease appears superficially similar to familial white folded dysplasia or white sponge nevus in its hereditary pattern, although the clinical and microscopic features are different.

Clinical Features. The oral lesions of hereditary benign intraepithelial dyskeratosis appear generally as white, spongy, macerated lesions of the buccal mucosa, with or without folds (Fig. 19-18A). They are also described on the floor of the mouth, ventral and lateral surfaces of the tongue, the gingiva and palate. These lesions vary from delicate, opalescent white membranous areas to a rough, shaggy mucosa. Lesions frequently involve the corners of the mouth and appear as soft plaques with pinpoint elevation when the mucosa is stretched.

Patients with this disease also manifest lesions of the eye characterized by superficial, foamy, gelatinous white plaques overlying the cornea, sometimes producing temporary blindness. In addition, the conjunctivae are usually intensely congested. Interestingly, these eye lesions in some cases show a seasonal variation, tending to appear or increase in severity in the spring and disappear, sometimes by spontaneous shedding of the pseudomembrane, in late summer or fall.

Histologic Features. Sections of the buccal mucosa exhibit thickening of the epithelium with pronounced hydropic degeneration. In addition, numerous round, waxy-appearing eosinophilic cells resembling minute epithelial pearls are evident, the 'dyskeratotic' cells (Fig. 19-18B). An excellent detailed description of the microscopic features of this disease has been provided by Witkop. Sadeghi and Witkop also have described ultrastructural differences between the mature dyskeratotic cells in this disease and in other dyskeratotic conditions of the mucous membranes.

Treatment and Prognosis. Witkop and his associates indicate that there is no increase in the death rate or in death



A B

Figure 19-18. Hereditary benign intraepithelial dyskeratosis.
The white, macerated appearance of the lesions on the buccal mucosa is seen in **(A)**. The peculiar 'dyskeratotic' cells are shown in **(B)** *(Courtesy of Dr Carl J Witkop).*

from neoplastic disease in these patients, and therefore no treatment is indicated.

Acanthosis Nigricans

Acanthosis nigricans (AN) is an unusual dermatosis, the first documented case was reported in 1889. Acanthosis nigricans is divided into two broad categories, **benign and malignant.** Patients with the benign form of acanthosis nigricans experience very few, if any, complications of their skin lesions. However, many of these patients have an underlying insulin-resistant state that is the cause of their disease. Malignant acanthosis nigricans is associated with significant complications because the underlying malignancy is often an aggressive tumor (e.g. adenocarcinomas of various internal organs, particularly the stomach or malignant lymphomas). The average survival time of patients with signs of malignant acanthosis nigricans is two years.

Etiology. The definitive cause for acanthosis nigricans has not yet been ascertained, although several possibilities have been suggested. Acanthosis nigricans is most likely caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation. In the benign form of acanthosis nigricans, the factor is probably insulin or an insulin-like growth factor (IGF) that stimulate the epidermal cells. In malignant acanthosis nigricans, the stimulating factor is hypothesized to be a substance secreted either by the tumor or in response to the tumor. Exogenous medications also have been implicated as etiologic factors.

Clinical Features. Acanthosis nigricans is much more common in people with darker skin. The incidence is equal in men and women. Lesions of benign acanthosis nigricans may be present at any age, including at birth, although it is found more commonly in the adult population. Malignant AN occurs more frequently in elderly persons; however, cases have been reported in children with Wilms tumor. The skin lesions in all forms of the disease are similar although the severity of the lesions and their distribution may vary from case to case. Generally, the skin lesions vary from a symmetric, mild hyperpigmentation and mild papillary hypertrophy of only small patchy areas to heavily pigmented, aggressively verrucous lesions involving much of the skin, especially the axillae, palms and soles, and face and neck (Fig. 19-19A). The verrucous lesions are often pedunculated. Generalized pruritus is also a common finding.

Oral Manifestations. Oral mucous membrane involvement has been reported in between 25 and 50% of all cases of acanthosis nigricans. The oral findings in the benign form have been described by Pindborg and Gorlin, and in the malignant form, by Bang. These oral findings in both forms appear essentially the same.

The tongue and lips appear to be most frequently involved and to the greatest degree. There is hypertrophy of the filiform papillae producing a shaggy, papillomatous surface to the dorsal tongue. The lips may be enlarged and covered by papillomatous growths, particularly at the angles of the mouth. The buccal mucosa is less frequently involved, but generally shows a velvety white appearance with occasional papillary lesions. Similar findings may be seen in other areas, including the palate (Fig. 19-19B, C, D). In addition, gingival enlargement has been reported, clinically resembling idiopathic fibromatosis.

Histologic Findings. The histologic findings are characteristic but not pathognomonic. Histologic examination reveals hyperkeratosis, papillomatosis, and slight irregular acanthosis with minimal or no hyperpigmentation. The dermal papillae project upward as finger-like projections, with occasional thinning of the adjacent epidermis (Fig. 19-20A, B). Pseudohorn cysts may be present. Clinical discoloration is secondary to the hyperkeratosis and not to increased melanocytes or increased melanin deposition.

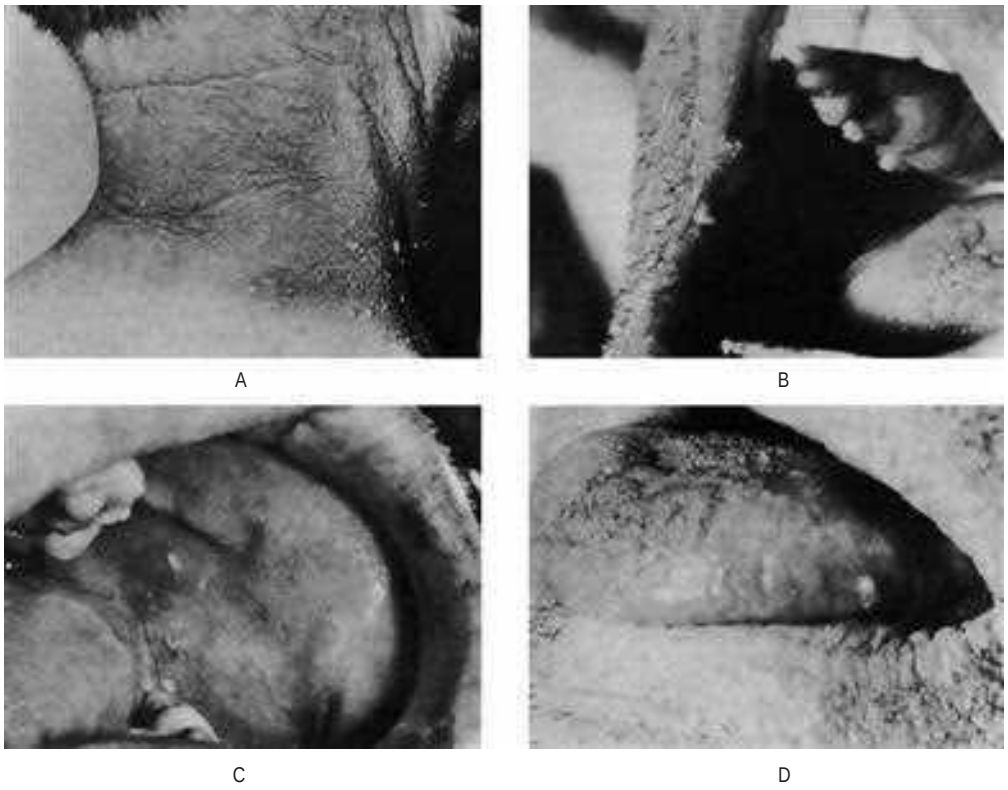


Figure 19-19. Acanthosis nigricans maligna.
Lesions of the skin **(A)**, and intraoral lesions of the commissure **(B)**, buccal mucosa **(C)**, and tongue **(D)** are illustrated *(Courtesy of Dr Gisle Bang. Oral Surg 29: 370, 1970).*

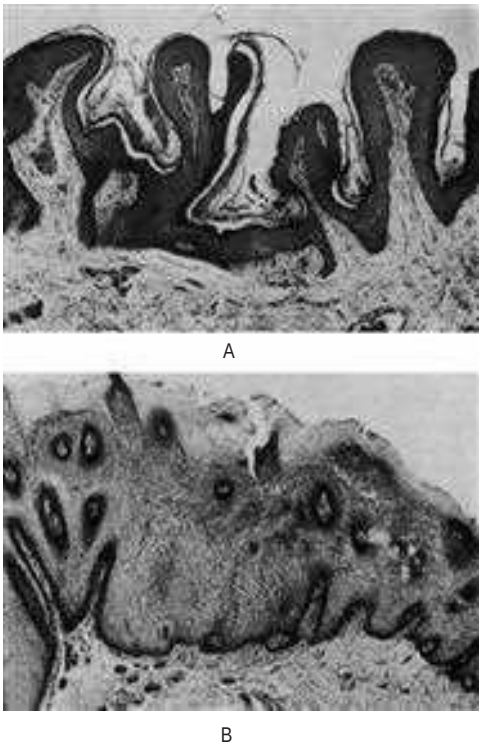


Figure 19-20. Acanthosis nigricans maligna.
Photomicrographs of lesions of the skin **(A)** and buccal mucosa **(B)** show the typical changes in each location *(Courtesy of Dr Gisle Bang. Oral Surg, 29: 370, 1970).*

Treatment. The goal of therapy is to correct the underlying disease process. Treatment of the lesions of AN is for cosmetic reasons only. Correction of hyperinsulinemia often reduces the burden of hyperkeratotic lesions. The prognosis for patients with malignant AN is often poor.

PEMPHIGUS

Pemphigus is a serious chronic skin disease characterized by the appearance of vesicles and bullae, small or large fluid-filled blisters that develop in cycles. Pemphigus is derived from the Greek word *pemphix* meaning bubble or blister. Pemphigus describes a group of chronic bullous diseases, originally named by Wichman in 1791. The term pemphigus once included most bullous eruptions of the skin, but diagnostic tests have improved, and bullous diseases have been reclassified. Pemphigus includes a group of autoimmune blistering diseases of the skin and mucous membranes characterized histologically by intradermal blisters and immunologically by the finding of circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes.

The three primary subsets of pemphigus include pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus. Each type of pemphigus has distinct clinical and immunopathologic features. Pemphigus vulgaris accounts for approximately 70% of pemphigus cases.

Pemphigus Vulgaris

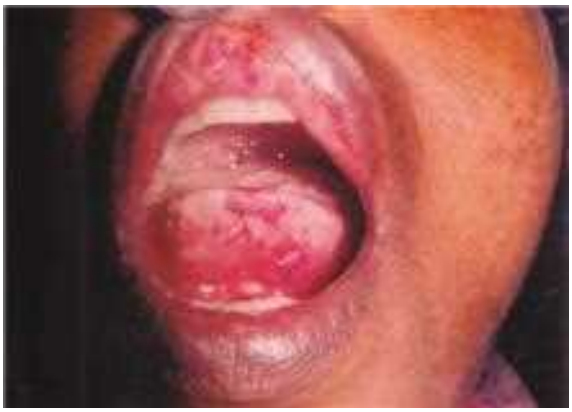
Pemphigus vulgaris (PV) is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membranes and is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. Clinical and experimental observations indicate that the circulating autoantibodies are pathogenic. An immunogenetic predisposition is well established. Blisters in PV are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or PV antibodies bind to keratinocyte desmosomes and to desmosome free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-cell adhesion.

Intercellular adhesion in the epidermis involves several keratinocyte cell surface molecules. Pemphigus antibody binds to keratinocyte cell surface molecules desmoglein 1 and desmoglein 3. Patients with the active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 and G4 subclasses. Disease activity correlates with antibody titer in most patients. Pemphigus antibody fixes components of complement to the surface of epidermal cells. Antibody binding may activate complement with the release of inflammatory mediators and recruitment of activated T-cells.

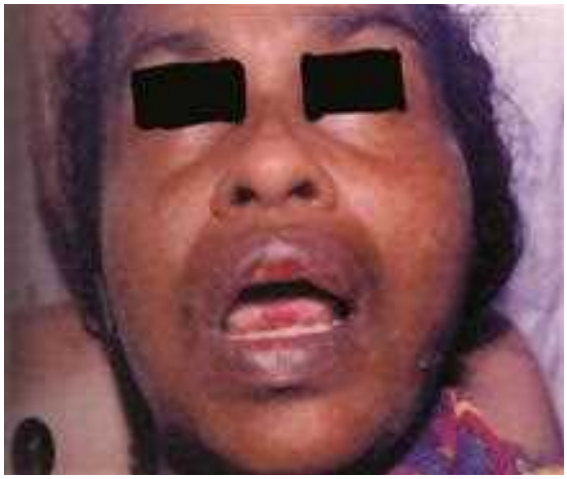
Clinical Features. Pemphigus vulgaris affects all races, with an equal gender distribution among males and females. The mean age of onset is approximately 50–60 years; however, the range is broad, and disease onset in older individuals and in children has been described. Patients are younger at presentation in **India** than in western countries.

Pemphigus vulgaris is characterized by the rapid appearance of vesicles and bullae, varying in diameter from a few millimeters to several centimeters, in such numbers that large areas of the skin surface may be covered (Fig. 19-21). These lesions contain a thin, watery fluid shortly after development, but this may soon become purulent or sanguineous. When the bullae rupture, they leave a raw eroded surface identical with that seen when focal areas of epithelium slide off either under oblique pressure or spontaneously without the prior formation of a vesicle or bulla (Fig. 19-22A, B). The loss of epithelium occasioned by rubbing apparently unaffected skin is termed **Nikolsky's sign.** It is a characteristic feature of pemphigus and is caused by prevesicular edema which disrupts the dermal-epidermal junction. The course of pemphigus vulgaris is a variable one, the disease terminating in death or recovery within a few days or weeks, or being prolonged over a period of months or even years.

Figure 19-21. Pemphigus vulgaris.
Unruptured bullae and vesicles on the skin.



A



B

Figure 19-22. Pemphigus vulgaris.
(A) Oral mucosal involvement. **(B)** Lesions of the lip.

Pemphigus vegetans is an uncommon variant of pemphigus vulgaris. It occurs in 1–2% of pemphigus vulgaris cases. The median age of onset is 40–50 years. Two clinical subtypes of pemphigus vegetans exist, characterized initially by flaccid bullae and erosions (Neumann) or pustules (Hallopeau). Both subtypes subsequently develop into hyperpigmented vegetative plaques with pustules and hypertrophic granulation tissue at the periphery. Lesions are typically located at intertriginous areas and the oral mucosa. Oral involvement is present in nearly all pemphigus vegetans cases. A characteristic feature of pemphigus vegetans is the **cerebriform tongue,** characterized by a pattern of sulci and gyri on the dorsum of the tongue.

Oral Manifestations. Mucous membranes typically are affected first in PV. Mucosal lesions may precede cutaneous lesions by months. The disease involves mucosa in 50–70% of

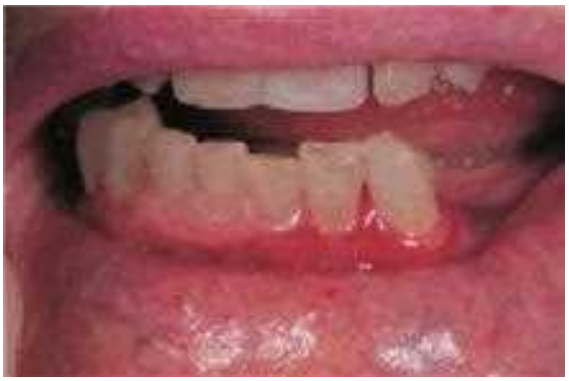


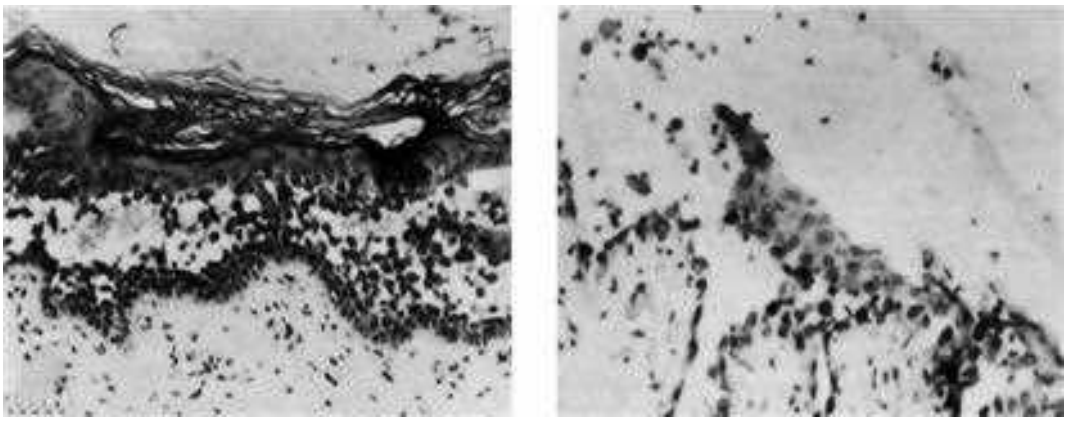
Figure 19-23. Pemphigus vulgaris of the gingiva.

patients. Intact bullae are rare in the mouth. More commonly, patients have ill-defined, irregularly shaped, gingival, buccal or palatine erosions, which are painful and slow to heal (Fig. 19-23). The erosions extend peripherally with shedding of the epithelium. Erosions may be seen on any part of the oral cavity and can be scattered and often extensive. Erosions may spread to involve the larynx with subsequent hoarseness. The patient is often unable to eat or drink adequately because the lesions are so uncomfortable. Other mucosal surfaces may be involved, including the conjunctiva, esophagus, labia, vagina, cervix, penis, urethra, and anus. The oral lesions are similar to those occurring on the skin.

Histologic Features. Pemphigus as an entity is characterized microscopically by the formation of a vesicle or bulla entirely intraepithelially, just above the basal layer producing the distinctive suprabasilar 'split' (Fig. 19-24A, B). Prevesicular edema appears to weaken this junction, and the intercellular bridges between the epithelial cells disappear. This results in loss of cohesiveness or acantholysis, and because of this, clumps of epithelial cells are often found lying free within the vesicular space (Fig. 19-24A, B). These have been called 'Tzanck cells' and are characterized particularly by degenerative changes which include swelling of the nuclei and hyperchromatic staining. These changes are particularly obvious in cytologic smears taken from early, freshly opened vesicles (Fig. 19-25). Such smears form the basis for a rapid supplemental test for pemphigus, the 'Tzanck test', and these cytologic findings have been discussed in detail by Medak and his associates as well as by Shklar and Cataldo. Shklar has also reported that there is a marked increase in RNA in the cytoplasm of these acantholytic cells as well as in the epithelial cells at the floor of the vesicle.

The fluid in most vesicles, particularly those more than a day or two old, contains variable numbers of polymorphonuclear leukocytes and lymphocytes. The relative scarcity of inflammatory cell infiltration; however, in both the vesicular fluid and in the connective tissue at the base of the vesicle or bulla, is suggestive of pemphigus, since most other bullous diseases manifest marked inflammation. Once secondary infection occurs, this feature is masked (Fig. 19-26).

Immunofluorescent testing has proven to be of great value in establishing the diagnosis of pemphigus, especially when the clinical or microscopic findings are inconclusive. In this test, **direct immunofluorescence** is used to demonstrate the presence of immunoglobulins, predominantly IgG but sometimes in combination with C3, IgA and IgM, in the intercellular spaces or intercellular substance in either the oral epithelium of the lesions or of clinically normal epithelium adjacent to the lesions. This test is carried out by incubating a biopsy specimen (either frozen section or one specially fixed in Michel solution) with a fluorescein-conjugated antiglobulin. **Indirect immunofluorescence** has also been used to substantiate the diagnosis of pemphigus. This is accomplished basically by incubating normal animal or human mucosa with serum from the patient suspected of having the disease and adding the fluorescein-conjugated human antiglobulin. A positive reaction in the tissue indicates the presence of circulating immunoglobulin antibodies. Daniels and Quadra-White have reported positive direct immunofluorescence for IgG in 10 biopsies of 10 patients (100%) with pemphigus vulgaris



A B

Figure 19-24. Pemphigus vulgaris.
(A) Early stage of vesiculation with suprabasilar cleavage accompanied by prominent acantholysis and numerous Tzanck cells. **(B)** In the bullous stage, acantholysis is still evident with occasional leukocytes in the bullous fluid *(Courtesy of Dr Frank Vellios and Dr Charles A Waldron)*.

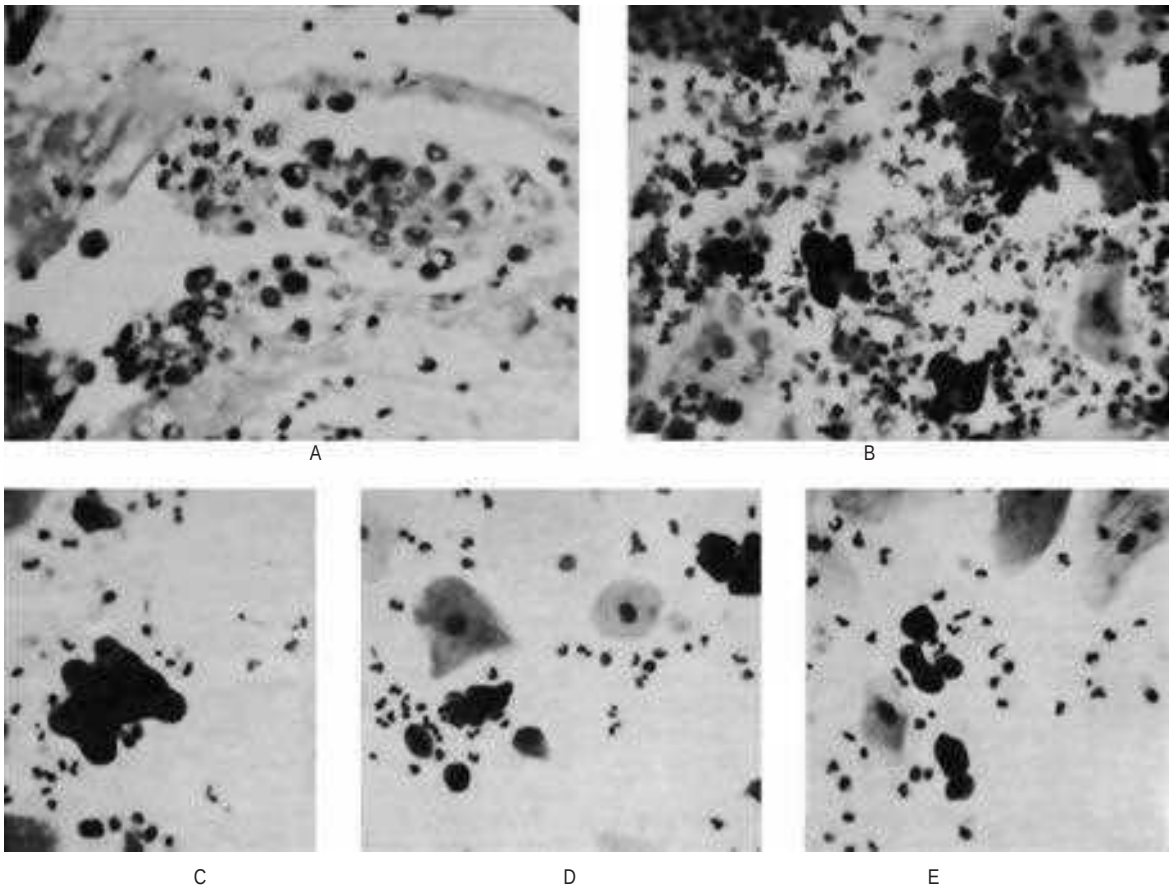


Figure 19-25. Pemphigus vulgaris.
The characteristic acantholytic cells are seen in the histologic section of the vesicle **(A)**. These same cells are found on cytologic smear of the vesicle **(B, C, D, E)**.

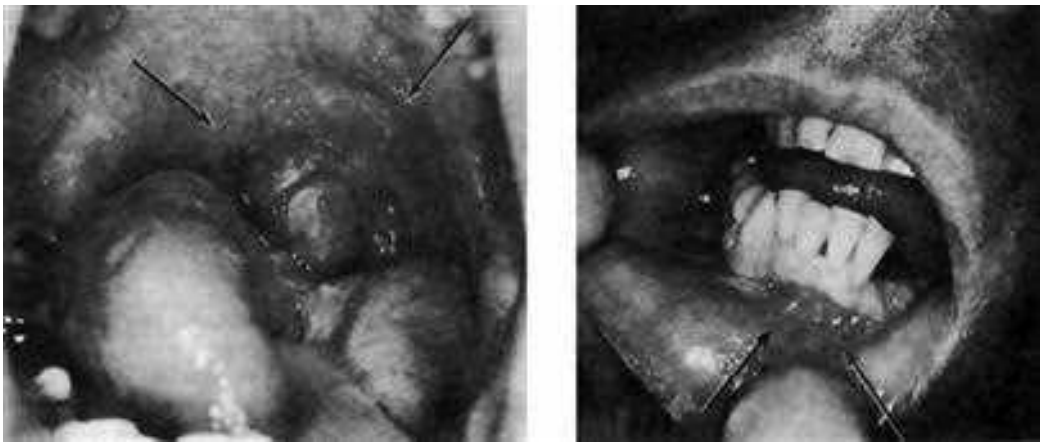


Figure 19-26. Pemphigus vulgaris.
Rupture of bullae of the oral mucous membranes results in large, denuded, painful lesions *(Courtesy of Dr Wilbur C Moorman).*

(Fig. 19-27). Six of these 10 were also positive for C3, while only one each was positive for IgA and IgM. Laskaris has also found, in testing a series of 58 patients with pemphigus vulgaris limited to the oral cavity, positive direct immunofluorescence in 57 (98%), demonstrating intercellular substance deposition of IgG, either alone or in combination with C3, IgA, and IgM. By indirect immunofluorescence, Laskaris also reported that, when normal human oral mucosa was used as the substrate,

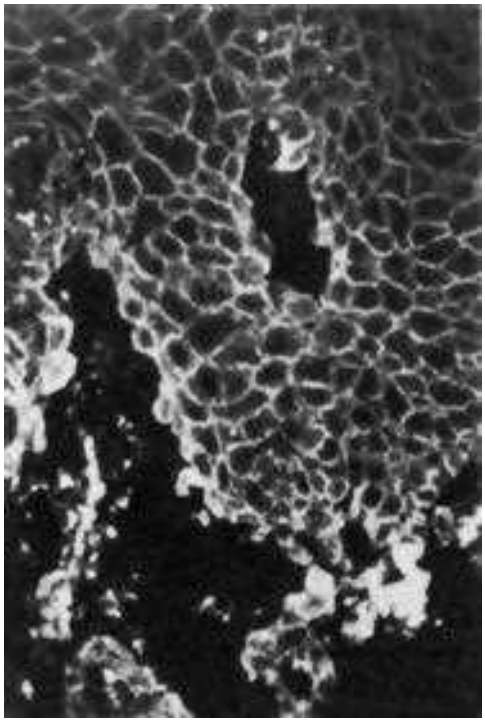


Figure 19-27. Pemphigus vulgaris.
Oral specimen showing intercellular space fluorescence throughout the epithelium with anti-IgG. At lower left there is an intraepithelial vesicle above the basal epithelial cells attached to the basement membrane zone *(Courtesy of Dr Troy E Daniels and CV Mosby Company. From TE Daniels, and C Quadra-White. Direct immunofluorescence in oral mucosal disease: a diagnostic analysis of 130 cases. Oral Surg, 51: 38, 1981).*

circulating intercellular substance antibodies were present in 50 of the 58 patients (86%).

Differential Diagnosis. Oral lesions constitute an important feature of pemphigus, and for this reason pemphigus must always be considered in the differential diagnosis of blister-like eruptions of oral mucous membranes. Some difficulty may be experienced in differentiating pemphigus from other bullous diseases such as dermatitis herpetiformis, erythema multiforme bullosum, bullous lichen planus, epidermolysis bullosa and other chronic bullous dermatoses such as bullous pemphigoid and cicatricial pemphigoid. Clinical experience, however, aided by the histologic appearance of the lesions, usually suffices to separate the diseases.

Treatment. The aim of treatment in PV is the same as in other autoimmune bullous diseases, which is to decrease blister formation, promote healing of blisters and erosions, and determine the minimal dose of medication necessary to control the disease process. Therapy must be tailored for each patient, taking into account pre-existing and coexisting conditions. Patients may continue to experience mild disease activity while under optimal treatment.

Pemphigus Foliaceus
(Superficial pemphigus, fogo selvagem)

Pemphigus foliaceus (PF) is generally a benign variety of pemphigus. It is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis), resulting in the formation of superficial blisters. It is typified by clinical involvement of healthy-appearing skin that blisters when rubbed (the Nikolsky sign). Pemphigus foliaceus is characterized by a chronic course, with little or no involvement of the mucous membranes. It includes the following six subtypes: pemphigus erythematosus (PE), pemphigus herpetiformis (PH), endemic pemphigus foliaceus, immunoglobulin A (IgA) pemphigus foliaceus, paraneoplastic pemphigus foliaceus (PNPF), and drug-induced pemphigus foliaceus.

Superficial blisters in PF are induced by immunoglobulin G (IgG) (mainly IgG4 subclass) autoantibodies directed against a cell adhesion molecule, **desmoglein 1,** expressed mainly in the granular layer of the epidermis. Precipitating factors include medications and ultraviolet light radiation. It was recently suggested that both factors enhanced autoantibody epidermal binding and preferential neutrophil adhesion to UV-irradiated epidermis which contribute to acantholysis in photo-induced PF.

Clinical Features. Pemphigus foliaceus is manifested by characteristic early bullous lesions which rapidly rupture and dry to leave masses of flakes or scales suggestive of an exfoliative dermatitis or eczema. The disease may originate in this form or may develop from one of the other types of pemphigus. It is a relatively mild form of pemphigus, which is most common in older adults but may occur in young children as well.

Brazilian pemphigus (fogo selvagem or Brazilian wildfire) is a mild endemic form of pemphigus foliaceus found in tropical regions, particularly in Brazil, that often occurs in children and frequently in family groups. The course of the disease is similar to that of pemphigus foliaceus. Oral lesions in pemphigus foliaceus are rare, according to Perry and Brunsting (1965) in their extensive study of this form of the disease.

Histologic Findings. Pemphigus foliaceus begins as acantholysis of the upper epidermis. It usually enlarges and detaches without bullae formation, though a bulla may form showing acantholysis at both the roof and the floor. More established lesions may have acanthosis and mild-to-moderate papillomatosis. Hyperkeratosis and parakeratosis may also be evident, with dyskeratotic cells within the granular layer. These features may be particularly pronounced in long-standing pemphigus erythematosus. A mild dermal lymphocytic infiltrate occurs, often with the presence of eosinophils.

Treatment. Therapy for PF is usually less aggressive than that for pemphigus vulgaris because of their lower morbidity and mortality rates. Few results indicate that nonsteroidal treatment of pemphigus is possible. Mestinon may be used to slow down progression of the disease and to treat mild cases with chronic lesions on limited areas.

Paraneoplastic Pemphigus

Anhalt et al, first described paraneoplastic pemphigus in 1990. The authors reported five patients with underlying neoplasms who developed oral erosions and bullous skin eruptions. Since

then, more than 60 patients with paraneoplastic pemphigus have been reported, and patients previously believed to have other diseases have been retrospectively diagnosed. Skin biopsy samples showed both suprabasal acantholysis and interface dermatitis. Immunofluorescence tests revealed intraepidermal intercellular staining with immunoglobulin G (IgG).

A summary of criteria for the diagnosis of paraneoplastic pemphigus includes the following:

- Painful mucosal erosions, sometimes with a skin eruption that eventually results in blisters and erosions, in the setting of confirmed or occult malignancy.
- Histopathologic changes of acantholysis, keratinocyte necrosis, and interface dermatitis.
- Direct immunofluorescence (DIF) typically reveals IgG and complement (C3) within the epidermal intercellular spaces as well as at the epidermal basement membrane.
- Indirect immunofluorescence (IDIF) observation of circulating antibodies specific for stratified squamous or transitional epithelia (transitional epithelium) is found.
- Immunoprecipitation of a complex of proteins with typical molecular weights.

Tumor antigens are hypothesized to evoke an immune response that leads to the development of an autoimmune response to intercellular adhesins (plakins). This autoantibody response leads to blistering in mucosa and other epithelia. Paraneoplastic pemphigus is often fatal. Mortality rates approach 90%. Causes of death include sepsis, with resultant multiorgan failure and respiratory failure due to the direct effects of the disease on the respiratory epithelium. The susceptibility to infection caused by the loss of skin integrity is exacerbated by the potent immunosuppressive medications used to treat the condition.

Clinical Features. The mean age at onset is 60 years. Patients ranging in age from 7 to 76 years have been reported. Males and females are affected equally. With the exception of a few patients, all patients with paraneoplastic pemphigus have had tumors, most of which have been malignant. The most common malignancy associated with paraneoplastic pemphigus is non-Hodgkin lymphoma. Other associated malignancies include chronic lymphocytic leukemia, Castleman tumor, giant cell lymphoma (reticulum cell sarcoma), Waldenström macroglobulinemia, thymoma, poorly differentiated sarcoma, bronchogenic squamous cell carcinoma, and follicular dendritic cell sarcoma.

Oral Manifestations. Most patients with paraneoplastic pemphigus present with oral erosions or ulcerations. Patients present with painful oral erosions, often accompanied by a generalized cutaneous eruption. The eruption can assume a wide variety of morphologies, including morbilliform, urticarial, bullous, papulosquamous, or erythema multiforme-like lesions. Some patients complain of pruritus or pain. The erosions can occur anywhere in the mouth, including the buccal, the labial, the gingival, and the lingual mucosa. Erosions and subsequent crusting on the vermilion of the lips are typical and similar to that seen in Stevens-Johnson syndrome. The nose, the pharynx, and the tonsils can be affected, as can the genital mucosal surfaces. Nasal ulcers may cause epistaxis.

Histologic Findings. Vesicular lesions express the most characteristic histopathologic features. Oral and cutaneous lesions show variable epidermal necrosis, suprabasal acantholysis, dyskeratotic keratinocytes, vacuolar interface dermatitis, and lymphocytic infiltration. Oral mucosal lesions show the greatest acantholysis, while some skin lesions may not have any acantholysis at all. A distinctive feature of paraneoplastic pemphigus is dyskeratosis. Dyskeratosis is a constant feature, but the number of dyskeratotic keratinocytes is variable. Dyskeratotic keratinocytes are found at all levels in the epidermis, especially within the zones of acantholysis, and they can be found in cutaneous adnexa. The presence of dyskeratosis in a suprabasal acantholytic bullous disorder is a clue to the presence of paraneoplastic pemphigus.

Treatment. Initial care is aimed at treating superinfection, if present. Warm compresses, nonadherent wound dressings, and topical antibiotic ointments are helpful. Potent immunosuppressive agents are required to decrease blistering, but they are often ineffective. In general, skin lesions are more responsive to therapy than mucosal lesions. Other therapeutic options include plasmapheresis and immunopheresis. For solid neoplasms, curative resection should be attempted when appropriate. The prognosis of paraneoplastic pemphigus is poor.

Familial Benign Pemphigus
(Hailey-Hailey disease)

Familial benign pemphigus was originally described by Hailey brothers in 1939. It is a chronic autosomal dominant disorder with incomplete penetrance. Approximately two-thirds of patients have a family history of the disorder. A history of multiple relapses and remissions is characteristic. Many hypotheses exist concerning the pathogenesis of familial benign pemphigus. It is hypothesized to result from a genetic defect in a calcium pump protein. The pump mutation is in **ATP2C1,** a gene localized on chromosome 3. This gene defect is similar to the genetic defect in Darier disease, which also is a calcium pump defect. In addition to the primary gene defect in Hailey-Hailey disease, contributing factors like heat, friction, and infection are known to exacerbate the disease.

Clinical Features. The disease first manifests itself during adolescence or young adult life, although there are occasional exceptions. There is no apparent predilection for occurrence in either gender. The lesions themselves develop as small groups of vesicles appearing on normal or erythematous skin, which soon rupture to leave eroded, crusted areas. These lesions then appear to enlarge peripherally but heal in the center. Nikolsky's sign is present. It has been frequently noted that heat and sweating amplify the outbreak of the lesions while spontaneous remissions may occur in cold weather. The lesions themselves develop most commonly on those areas of skin which are exposed to friction, e.g. flexure surfaces of the axillae and groin, the neck and the genital area. Tender and enlarged regional lymph nodes may also be present.

It has been recognized that bacterial infection also appears to precipitate the appearance of lesions, and more recently, infection by *Candida albicans* has been implicated.

Oral Manifestations. Oral lesions occasionally occur in patients with familial benign chronic pemphigus, and these are similar to those occurring on the skin. The lesions develop as crops of vesicles which rapidly rupture leaving raw eroded areas.

Histologic Features. The histologic appearance of the epithelial lesions in familial benign chronic pemphigus bears remarkable similarity to that seen in pemphigus vulgaris and in keratosis follicularis or Darier's disease. However, in familial benign chronic pemphigus there is generally more extensive acantholysis than in pemphigus vulgaris and there is usually less damage to the acantholytic cells. One of the characteristic features of this disease is that occasional intercellular bridges persist so that adjacent epithelial cells still adhere to each other and are not entirely acantholytic.

This appearance has been given the classic description of the **dilapidated brick wall** effect. Finally, benign dyskeratotic cells similar to the corps ronds of Darier's disease may be present.

Treatment. Familial benign pemphigus waxes and wanes in intensity. Soothing compresses (aluminum acetate) followed by intermittent use of mild corticosteroid preparations and topical antibiotics (clindamycin or erythromycin) result in transient improvement. More widespread flares may require systemic antibiotics to suppress protease activation and acantholysis. Erythromycin and tetracycline are favored. Bacterial culture and sensitivity can help guide appropriate therapy.

Cicatricial Pemphigoid

(Benign mucous membrane pemphigoid, ocular pemphigus)

Cicatricial pemphigoid (CP) is an autoimmune blistering disease that predominately affects the mucous membranes, including the mouth and the oropharynx, the conjunctiva, the nares, and the genitalia. Patients with cutaneous involvement present with tense blisters and erosions, often on the head and the neck or at sites of trauma. Blisters heal with scarring and pigmentation. Sequelae of mucosal involvement include decreased vision, blindness, and supraglottic stenosis with hoarseness or airway obstruction.

Etiology. Cicatricial pemphigoid is an autoimmune blistering disease associated with autoantibodies directed against basement membrane zone target antigens. Autoantibodies of the IgG subclass, particularly IgG4, are associated with CP; however, IgA antibodies have also been detected. The two major antigens associated with CP are bullous pemphigoid antigen 2(BPAG2) and epiligrin (laminin-5).

Clinical Features. The disease occurs nearly twice as frequently in females as it does in males with the peak age of involvement being between 40 and 50 years. Typically, the vesiculobullous lesions occur on the oral mucous membranes and conjunctiva. Lesions also occur on the skin, particularly around the genitalia and near the body orifices in about 25% of cases. Typically, these lesions heal by scar formation, particularly on the conjunctiva. Other mucous membrane surfaces may be involved such as the nose, larynx, pharynx, esophagus, vulva, vagina, penis and anus.

The ocular involvement is probably the most serious complication of this disease. Following the initial conjunctivitis, adhesions develop between the palpebral and bulbar conjunctivae resulting in obliteration of the palpebral fissure, with opacity of the cornea frequently leading to complete blindness.

Oral Manifestations. The most consistent oral lesions to occur are those involving the gingivae, although ultimately other sites in the oral cavity become involved. The mucosal lesions are also vesiculobullous in nature but appear to be relatively thick-walled, and for this reason, may persist for 24–48 hours before rupturing and desquamating. Eventually their rupture does occur leaving a raw, eroded, bleeding surface. The gingivae frequently manifest a persistent erythema for weeks or even months after the original erosions have healed (Fig. 19-28A). These oral lesions rarely scar. In the past, this disease has often been diagnosed as 'chronic desquamative gingivitis,' a term now used only in the descriptive sense and not as a specific disease entity.

Histologic Features. The histologic findings in cicatricial pemphigoid, in contrast to pemphigus vulgaris, are nonspecific. The vesicles and bullae are subepidermal rather than suprabasilar and there is no evidence of acantholysis (Fig. 19-28B). The basement membrane structure appears to detach with the epithelium from the underlying connective tissue, as shown in the electron microscopic studies of Susi and Shklar. There is a nonspecific chronic inflammatory infiltrate in the connective tissue, chiefly lymphocytes, plasma cells and eosinophils.

Immunofluorescence studies have revealed the presence of tissue-bound basement membrane zone antibodies in most patients with this disease as well as circulating antibasement membrane zone antibodies in the serum of some patients. Daniels and Quadra-White reported the results of direct immunofluorescence examinations in 33 patients with cicatricial pemphigoid. Of these, they found that 17 (51%) showed a linear basement membrane zone pattern of IgG, 10 (33%) IgA, 12 (36%) IgM, and 32 (97%) C3 (Fig. 19-29). Laskaris and Angelopoulos also reported both direct and indirect immunofluorescent studies on 33 patients with cicatricial pemphigoid and found 32 of the 33 (97%) had a direct total positive basement membrane zone pattern (IgG 32/33; IgA 9/33; IgM 4/33; C3 26/33; fibrin 13/33), while only 12 of the 33 (36%) had an indirect positive using the patients' serum and a substrate of normal human oral mucosa (IgG only; all others negative). These authors pointed out that the immunofluorescence pattern of cicatricial pemphigoid was indistinguishable from the pattern observed in bullous pemphigoid and that this gave support to the possibility that the two diseases may represent variants of the same entity.

Differential Diagnosis. Because of the nonspecific microscopic findings on biopsy, a variety of other diseases must be considered in the differential diagnosis. The chief of these are

A B

Figure 19-28. Cicatricial pemphigoid.
Erythematous and eroded areas are seen in **(A)**, while the typical subepidermal separation is apparent in **(B)** *(A, Courtesy of Dr Richard W Henry).*

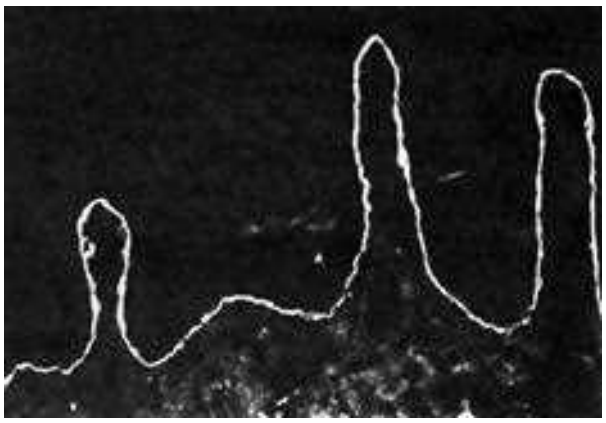


Figure 19-29. Cicatricial pemphigoid.
Oral specimen showing continuous linear fluorescence in the basement membrane zone with anti-C'3 *(Courtesy of Dr Troy E Daniels and CV Mosby Company. From TE Daniels, and C Quadra-White. Direct immunofluorescence in oral mucosal disease: a diagnostic analysis of 130 cases. Oral Surg, 51: 38, 1981).*

pemphigus vulgaris, bullous pemphigoid, erosive lichen planus, and bullous erythema multiforme.

Treatment. The goal of treatment is to suppress extensive blister formation, to promote healing, and to prevent scarring. The lowest dose of medication to suppress disease activity and to minimize the risk for the patient should be used. This disorder is extremely difficult to treat. Even with optimum control, blisters may continue to develop in some patients. The risks and the benefits of therapy must always be evaluated for each patient. Complications of CP include visual loss or blindness, airway stenosis, esophageal stricture, or cutaneous blistering with scarring and milia formation.

BULLOUS PEMPHIGOID

(Parapemphigus)

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal, blistering skin disease that rarely involves mucous membranes. It is characterized by the presence of immunoglobulin G (IgG) autoantibodies specific for the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1) and BP180 (BPAg2). IgG autoantibodies bind to the skin basement membrane and activate complement and inflammatory mediators. Activation of the complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells in turn are postulated to release proteases, which degrade hemidesmosomal proteins and lead to blister formation. Eosinophils are characteristically present, although their presence is not an absolute diagnostic criteria.

Clinical Features. Bullous pemphigoid is basically a disease of elderly persons, approximately 80% of patients being over 60 years of age. Nevertheless, it can occur earlier in life. There appears to be no gender predilection.

The cutaneous lesions begin as a generalized nonspecific rash, commonly on the limbs, which appears urticarial or eczematous and which may persist for several weeks to several months before the ultimate appearance of the vesiculobullous lesions. The vesicles and bullae arise in these prodromal skin lesions as well as in normal skin. In addition to the occurrence on the limbs, the abdomen is frequently affected. These vesicles and bullae are relatively thick-walled and may remain intact for some days. Rupture does not always occur, although when it does it leaves a raw, eroded area which heals rapidly.

Oral Manifestations. Oral lesions occur far less frequently in bullous pemphigoid than in cicatricial pemphigoid, varying from approximately 10–45% in various reported series. These oral lesions of bullous pemphigoid have been reviewed by Shklar and his associates and are usually described as vesicles and areas of erosion and ulceration. An important feature of the oral involvement is the similarity of gingival lesions to those of cicatricial pemphigoid. This gingival involvement generally involves much, if not all, of the gingival mucosa and is exceedingly painful. The gingival tissues appear extremely erythematous and may desquamate as the result of even minor frictional trauma. The vesicles and ultimate erosions may develop not only on the gingival tissues but in any other area such as the buccal mucosa, palate, floor of the mouth the tongue.

Histologic Features. The vesicles and bullae in this disease are subepidermal and nonspecific. There is no evidence of acantholysis of epithelial cells; in fact, the epithelium appears relatively normal. The vesicles contain a fibrinous exudate admixed with occasional inflammatory cells.

Electron microscopic studies have shown that, in contrast to cicatricial pemphigoid, the basement membrane remains attached to the connective tissue rather than to the overlying separated epithelium. In addition, these ultrastructural studies have shown that the primary changes in bullous pemphigoid appear to occur in the connective tissue where the blood vessels show alterations in their penetrability. The basement membrane also shows thickening, with interruption of continuity.

Bullous pemphigoid is thought to be an autoimmune disease and circulating basement membrane zone antibodies have been found by the indirect immunofluorescence technique in about 80% of patients with this disease, according to the study of 29 patients reported by Laskaris and Nicolis. Direct immunofluorescent studies of these same patients revealed tissue-bound antibasement membrane zone antibodies of the IgG class in all oral mucosal biopsies (100%) of patients who had both mucosal and skin lesions (14 patients), but in only 80% of oral mucosal biopsies in the group of patients who had only skin lesions (15 patients).

Treatment. The goal of therapy is to decrease blister formation, to promote healing of blisters and erosions. Therapy must be individualized for each patient, keeping in mind preexisting conditions and other patient-specific factors. Most patients affected with BP require therapy for 6–60 months, after which many patients experience long-term remission of the disease. However, some patients have long-standing disease requiring treatment for years.

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. Historically, epidermolysis bullosa subtypes have been classified according to skin manifestations. Recent discoveries of the molecular basis of EB have resulted in the development of new diagnostic tools, including prenatal testing.

Epidermolysis bullosa is classified into three major categories including:

- **Epidermolysis bullosa simplex** (EBS) (intraepidermal skin separation)
- **Junctional epidermolysis bullosa** (skin separation in lamina lucida or central basement membrane zone)
- **Dystrophic epidermolysis bullosa** (sublamina densa basement membrane zone separation).

Researchers have recently proposed a new category termed hemidesmosomal epidermolysis bullosa (HEB), which produces blistering at the hemidesmosomal level in the most superior aspect of the basement membrane zone. EBS is usually associated with little or no extracutaneous involvement, while the more severe hemidesmosomal, junctional, and dystrophic forms of EB may produce significant multiorgan system involvement.

Etiology. Most cases of epidermolysis bullosa simplex (EBS) are associated with mutations of the genes coding for keratins 5 and 14. The level of skin separation is at the mid-basal cell associated with variable intermediate filament clumping. Junctional epidermolysis bullosa (JEB) has a highly variable molecular etiology and represents a collection of different diseases. These diseases all cause blistering in the lamina lucida and variable hemidesmosomal abnormalities. More than one half of JEB cases are caused by one of two recurrent nonsense mutations in the **LAMB3** gene, which is helpful for mutation analysis and prenatal testing. Dystrophic epidermolysis bullosa (DEB) thus far has been associated in all cases with mutations of the gene coding for type VII collagen (COL7A1). Anchoring fibrils are affected in patients with DEB, and the degree of involvement ranges from subtle changes to complete absence.

Epidermolysis Bullosa Simplex

Clinical Features. The **generalized** form of epidermolysis bullosa simplex is inherited as an autosomal dominant characteristic, manifests itself at birth or shortly thereafter and is characterized by the formation of vesicles and bullae, chiefly on the hands and feet at sites of friction or trauma. The knees, elbows and trunk are only rarely involved and the nails are only occasionally affected. When the blisters heal, usually within 2–10 days, it is an important feature that there is no resultant scarring or permanent pigmentation. The disease appears to improve at puberty and prognosis is good for a normal life span.

The **localized** form of the disease (Weber-Cockayne syndrome), which is also familial may occur early in childhood or later in life and is commonly recurrent. The bullae only develop on the hands and feet, are related to frictional trauma and tend to exacerbate in hot weather. There is no scarring upon healing.

Oral Manifestations. Bullae of the oral cavity have been reported in occasional cases of generalized epidermolysis bullosa simplex, but it is doubtful that they actually occur. In addition, the teeth are not affected.

Histologic Features. In the generalized form of epidermolysis bullosa simplex, the vesicles and bullae develop as a result of destruction of basal and suprabasal cells so that some nuclei may persist on the floor of the blister, according to Lowe. The individual cells become edematous and show dissolution of organelles and tonofibrils with displacement of the nucleus to the upper end of the cell. The PAS (periodic acid-Schiff)-positive basement membrane remains on the dermal side of the separation. The elastic, pre-elastic and oxytalan fibers in the connective tissue are normal.

In the **localized** form of the disease, the bullae are intraepidermal and suprabasal in location.

Junctional Epidermolysis Bullosa

It was earlier suggested by some workers that the junctional or lethal type is simply an extremely severe from of the dystrophic recessive form which is incompatible with prolonged survival. However, recent studies have proven that the two are distinctly different disorders.

Clinical Features. Three criteria have been established for the diagnosis of this form of the disease. These are:

- Onset at birth
- Absence of scarring, milia or pigmentation
- Death within three months of age.

The bullae are similar to those seen in the dystrophic recessive type except that they commonly develop spontaneously, and sheets of skin may actually be shed.

Oral Manifestations. Oral bullae are frequently very extensive, and because of their extreme fragility, produce serious feeding problems. Similar lesions also occur in the upper respiratory tract, the bronchioles, and the esophagus.

Severe disturbances in enamel and dentin formation of the deciduous teeth also occur but this is of only academic interest. These have been described by Arwill and his associates and by Gardner and Hudson in significant detail.

Histologic Features. The microscopic changes, including the location of the bullous cleavage, appear similar and probably identical to those occurring in the dystrophic recessive disease.

Epidermolysis Bullosa Dystrophic, Dominant

Clinical Features. This form of the disease may have its onset in infancy or it may be delayed until puberty. The blisters commonly develop on the ankles, knees, elbows, feet and head; healing results in scarring which is sometimes keloidal in type. In the majority of cases, the nails are thick and dystrophic, and milia are commonly present. However, the eye is never involved. Palmar-plantar keratoderma with hyperhidrosis also may occur as well as ichthyosis and sometimes hypertrichosis.

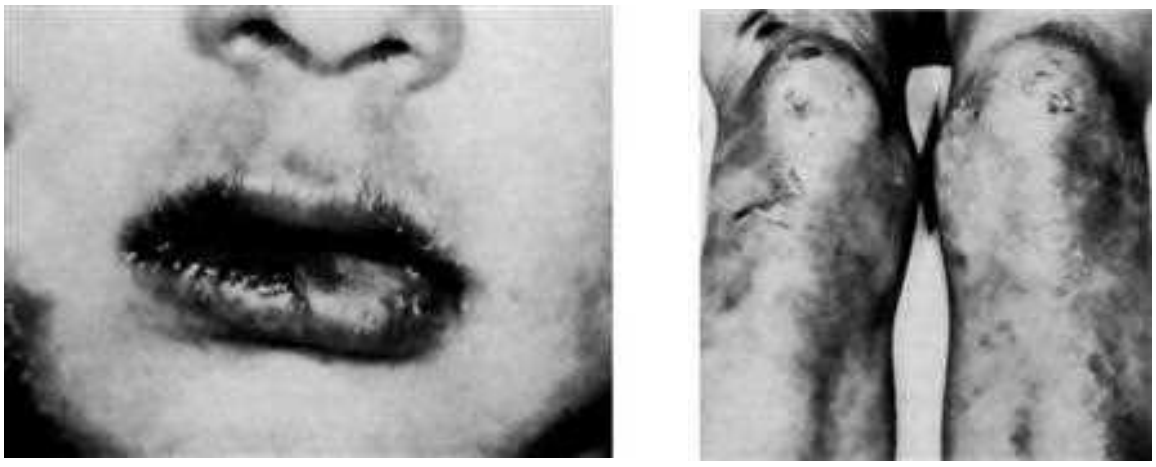
Oral Manifestations. Bullae of the oral cavity have been described as occurring in about 20% of cases of this type, and Andreasen has described oral milia. The teeth are unaffected.

Histologic Features. The bullae in this form of the disease develop as a result of separation through the very thin, irregular PAS-positive basement membrane which becomes divided. The basal layer appears normal although flattened on the roof of the blister. The underlying connective tissue shows an absence of elastic and oxytalan fibers.

Epidermolysis Bullosa Dystrophic, Recessive

Clinical Features. This type of epidermolysis bullosa (EB) is the best known and classic form of the disease. It has its onset at birth or very shortly thereafter and is characterized by the formation of bullae spontaneously or at sites of trauma, friction or pressure (Fig. 19-30A). The typical sites of involvement are the feet, buttocks, scapulae, elbows, fingers and occiput. The bullae contain a clear, bacteriologically sterile or sometimes blood-tinged fluid. When these bullae rupture or are peeled off under trauma or pressure, they leave a raw, painful surface. These patients frequently have a positive Nikolsky's sign. The bullae heal by scar, milia and pigmentation (Fig. 19-30B). This scarring may result in afunctional club-like fists. The hair may be sparse while the nails are usually dystrophic or absent.

Oral Manifestations. Oral bullae are common in this form of the disease. They may be preceded by the appearance of white spots or patches on the oral mucous membrane or the development of localized areas of inflammation. The bullae may be initiated by nursing or by any simple dental operative procedure in the oral cavity. Unless great caution is used, large



A B

Figure 19-30. Epidermolysis bullosa.
(A) The lower lip shows painful desquamation of the epithelium. **(B)** The bullae and the typical scarring of the knees are indicative of the dystrophic recessive form of the disease *(Courtesy of Dr John Mink).*

areas of mucous membrane may be inadvertently denuded. These bullae are painful, especially when they rupture or when the epithelium desquamates. Scar formation often results in obliteration of sulci and restriction of the tongue. Hoarseness and dysphagia may occur as a result of bullae of the larynx and pharynx. Esophageal involvement may produce serious stricture.

Dental defects have also been described, consisting of rudimentary teeth, congenitally absent teeth, hypoplastic teeth and crowns denuded of enamel. These have been discussed in detail by Arwill and his associates.

Histologic Features. The separation and bulla formation here occur immediately beneath the poorly defined PAS-positive basement membrane which remains attached to the roof of the blister. Fragments of the basement membrane may adhere to the dermis, however. The basal layer of cells is normal. The pre-elastic and oxytalan fibers in the connective tissue are increased in number. Elastic fibers are also increased but appear fragmented, according to Lowe.

Treatment. This group of diseases cannot be cured so that therapy is chiefly symptomatic. The simplex form of the disease requires little treatment; the lethal form will terminate fatally in most cases regardless of management. In the dystrophic forms, prevention of trauma may reduce the incidence of bulla formation, but this is almost impossible to achieve. Antibiotics are useful in controlling secondary infection and corticosteroids have sometimes been found effective. EB is a lifelong disease. Some subtypes, especially the milder EB forms, improve with age.

DERMATITIS HERPETIFORMIS

(Duhring-Brocq disease)

Dermatitis herpetiformis (DH) is a rare, benign, chronic, recurrent, immune-mediated blistering dermatologic disease with an associated, most often asymptomatic, gluten-sensitive enteropathy (GSE). Characteristic skin lesions found in patients with dermatitis herpetiformis are extremely itchy grouped vesicles most frequently located on extensor surfaces.

The pathogenesis of DH is associated with the presence of GSE; an increased expression of human leukocyte antigen1 (HLA-A1), human leukocyte antigen B8 (HLA-B8), human leukocyte antigen DR3 (HLA-DR3), and human leukocyte antigen DQ2 (HLA-DQ2) haplotypes; and granular deposition of IgA at the dermal-epidermal junction of the skin.

Clinical Features. The disease occurs chiefly between 20 and 55 years of age, although children are occasionally involved. A slight male predilection has been reported. The first manifestations of the disease are usually pruritus and severe burning, followed by the development of erythematous papules, vesicles, bullae or pustules. These occur most frequently on the extremities, trunk and buttocks as well as on the face, scalp and sometimes oral cavity. The vesicle is the most common and characteristic lesion, usually occurring symmetrically and in groups. Pigmentation of involved areas of skin ultimately develops in most cases. Patients frequently show increased severity of the disease in summer months.

Oral Manifestations. Vesicles and bullae which rupture rapidly to leave areas of superficial ulceration at any intraoral site are the characteristic finding. These have been described by Russotto and Ship.

Histologic Features. The lesions begin by accumulation of neutrophils and eosinophils in the dermal papillae producing a microabscess. The connective tissue becomes necrotic and the overlying epithelium separates, usually forming a subepithelial vesicle with destruction of basement membrane. The presence of eosinophils is generally prominent and characteristic, aiding in the differential diagnosis by excluding epidermolysis bullosa, erythema multiforme and pemphigus.

Direct immunofluorescent staining of uninvolved paralesional skin has been shown by Katz to be positive at the epidermal dermal junction. Almost invariably, IgA alone or in combination with the immunoglobulins IgG or IgM will be found in the upper dermis. When IgA deposits occur at the dermal-epidermal junction in a linear pattern (about 14% of cases) rather than as granules, the variant has been termed **linear IgA disease**. This has been discussed by Wiesenfeld and his colleagues, who also described the oral manifestations as being similar to those in the usual form of dermatitis herpetiformis.

Laboratory Findings. Some patients develop a blood eosinophilia of over 10%. Interestingly, these patients also show a sensitivity to the halogens (chlorine, bromine, iodine and fluorine) both by patch test and after ingestion.

Treatment. Skin lesions of dermatitis herpetiformis can be treated with dapsone, with relief of symptoms within 24–48 hours of the start of therapy. Alternatively, many patients can control the skin disease with a gluten-free diet, often without medication. Prognosis is good for patients who can tolerate dapsone and for the few who maintain a gluten-free diet.

ACRODERMATITIS ENTEROPATHICA

(Zinc deficiency)

Acrodermatitis enteropathica (AE) is an autosomal recessive disorder characterized by periorificial and acral dermatitis, alopecia, and diarrhea. The nature of the metabolic defect continues to be debated. However, two new fibroblast proteins that are absent in the fibroblasts of patients with acrodermatitis enteropathica have recently been discovered. These proteins may be responsible for decreased zinc uptake and abnormal zinc metabolism. Symptoms of acrodermatitis enteropathica occur within the first few months after birth and tend to appear shortly after discontinuation of breastfeeding. This phenomenon has led many to believe that human milk has a beneficial role, which bovine milk lacks.

Clinical Features. The disease begins in the first few weeks or months of life with a localized eruption of the skin,

particularly near the body orifices. Shortly, there is loss of hair and gastrointestinal disturbance accompanied by diarrhea. The skin lesions are vesiculobullous in nature and tend to occur in crops. These lesions rupture and become crusted and ultimately erythematous, scaling with a psoriasiform pattern. The skin lesions, and oral lesions as well, are prone to secondary infection, especially by *Candida albicans.* This is probably related to the deficiency in cell-mediated immunity reportedly manifested by the children.

Oral Manifestations. The oral mucosa, chiefly the buccal mucosa, becomes erythematous and edematous with erosive desquamative lesions. These oral lesions have been described in the cases of Danbolt.

Histologic Features. Histopathologic examination reveals parakeratosis of the stratum corneum with occasional neutrophils and intracellular edema. The granular cell layer is diminished, and the upper epidermis demonstrates pallor and edema. Focal dyskeratosis is seen. The epidermis may be psoriasiform or atrophic. Occasionally, subcorneal pustules are seen.

Laboratory Findings. Plasma zinc levels are low. Determining hair, urine, and parotid saliva zinc levels as well as serum alkaline phosphatase activity (which lowers later in the disease) may be helpful. Analysis of maternal breast milk zinc concentrations may also help in differentiating AE from acquired zinc deficiency.

Treatment. Treatment of AE involves greater than 1–2 mg/kg of oral zinc supplementation per day for life. Further progression and even death may occur if AE is left untreated.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibodies, immune complex formation, and immune dysregulation resulting in damage to essentially any organ, including the kidney, skin, blood cells, and the CNS. The natural history of this illness is unpredictable; patients may present with many years of symptoms or with acute life-threatening disease. Because of its protean manifestations, lupus must be considered in the differential diagnosis of many problems, including fevers of unknown origin, arthralgia, anemia, nephritis, psychosis, and fatigue. Early diagnosis and careful treatment tailored to individual patient symptoms has improved the prognosis from what was once perceived as an often fatal disease.

Etiology. The specific cause of SLE remain undefined. Research suggests that many factors, including genetics, hormones, and the environment (e.g. sunlight, drugs), contribute to the immune dysregulation observed in lupus. In lupus, greater production of autoantibodies leads to immune complex formation and tissue damage due to direct binding and/or immune complex deposition in tissues. Whether these antibodies are produced in reaction to exposure of normally nonexposed self-antigens or as a consequence of a broad spectrum of immune dysregulation resulting in excessive production of many antibodies without regard to prior stimulation is unclear. Patients with SLE produce autoantibodies against DNA, other nuclear antigens, ribosomes, platelets, erythrocytes, leukocytes, and other tissue-specific antigens. Thus, the resulting immune complexes result in widespread tissue damage. Cell-mediated autoimmune responses also play a pathophysiologic role.

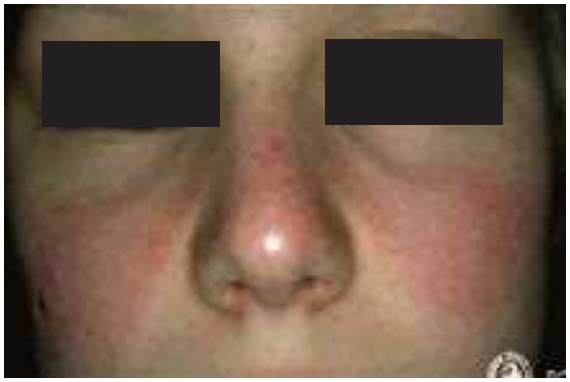


Figure 19-31. Systemic lupus erythematosus (butterfly rash of lupus).

Clinical Features. Systemic lupus erythematosus is a serious cutaneous-systemic disorder which characteristically manifests repeated remissions and exacerbations. This disease has its peak age of onset at about 30 years in females but about 40 years in males. The disease may occur in childhood as reported by Jacobs. Prevalence rates are higher in females than in males. A female-to-male ratio of approximately 2 : 1 occurs before puberty, and a ratio of 4 : 1 occurs after puberty.

The cutaneous lesions consist of erythematous patches on the face which coalesce to form a roughly symmetrical pattern over the cheeks and across the bridge of the nose in a so-called butterfly distribution (Fig. 19-31). Also involved are the neck, upper arms, shoulders and fingers. These lesions may present itching or burning sensations as well as areas of hyperpigmentation. The acute erythematous patches either arise on previously uninvolved skin or develop in old chronic lesions. Their severity is intensified by exposure to sunlight.

The generalized manifestations of the systemic disease are referable to involvement of various organs, including the kidney and heart. In the kidney, fibrinoid thickening of glomerular capillaries occurs, producing the characteristic 'wire loops,' which may be sufficient to result in renal insufficiency. The heart may suffer from an atypical endocarditis involving the valves, as well as fibrinoid degeneration of the epicardium and myocardium. The widespread tissue involvement and the nature of the lesions have led to the inclusion of this disease in that group known as the 'collagen diseases,' which also includes rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, scleroderma and dermatomyositis.

Oral Manifestations. Oral mucous membrane involvement is reported in 20–50% of cases of discoid lupus erythematosus,

and slightly more frequently in the systemic form of the disease, according to Andreasen. With the oral mucous membranes affected in such a high percentage of cases, the dentist must be aware of this problem. The oral mucosa reportedly may be involved either prior to or following the development of skin lesions or even in the absence of skin manifestations.

Oral lesions are found in **systemic** lupus erythematosus. These are very similar to those found in discoid lupus except that hyperemia, edema and extension of the lesions is sometimes more pronounced, and there may be a greater tendency for bleeding, petechiae and superficial ulcerations which are surrounded by a red halo as a result of localized telangiectasis. Superimposed oral moniliasis as well as xerostomia have also been reported.

Sugarman pointed out that great variation in the oral lesions exists and that these frequently simulate other diseases, chiefly leukoplakia and lichen planus. For this reason, diagnosis based upon the clinical appearance of the oral lesions should not be encouraged. In fact, it has been stressed by Schiodt and his coworkers in a long-term follow-up study of 52 patients with discoid lupus erythematosus that those oral lesions which had undergone a transition into the leukoplakia-like lesions over a period of time even showed histopathologic and immunopathologic features similar to leukoplakia not preceded by lupus erythematosus.

Histologic Features. The histologic appearance of systemic lupus erythematosus and discoid lupus erythematosus is similar, differing only in the degree of certain of the findings. According to Lever, discoid lupus erythematosus of the skin is characterized by hyperkeratosis with keratotic plugging, atrophy of the rete pegs, liquefaction, degeneration of the basal layer of cells, perivascular infiltration of lymphocytes and their collection about dermal appendages, and basophilic degeneration of collagen and elastic fibers, with hyalinization, edema and fibrinoid change, particularly prominent immediately beneath the epithelium. Not all features are invariably present in each case, however. In the systemic form of the disease the cutaneous lesions are similar in appearance, although the degenerative features and collagen disturbance are usually more prominent and the inflammatory features less severe. The histologic appearance of the tissue from a cutaneous lesion of any type of lupus erythematosus is not pathognomonic of the disease, but is certainly suggestive.

The histologic findings in oral lesions of both discoid and systemic lupus erythematosus have been described in detail by Andreasen and Poulsen. Shklar and McCarthy have also discussed the histopathology of the oral lesions in 25 cases and concluded that it is sufficiently characteristic that a definitive diagnosis can be made. In the discoid form, the lesions exhibit hyperorthokeratosis and/or hyperparakeratosis alternating with areas of epithelial atrophy. In the majority of cases, keratotic plugging down into the spinous layer, acanthosis and pseudoepitheliomatous hyperplasia are present. Hydropic degeneration and liquefaction necrosis of the basal cell layer also invariably occur as well as subepithelial vesiculation or ulceration (Fig. 19-32). In most cases, a thickening of the basement membrane can be demonstrated as a homogeneous, broad, eosinophilic and PAS-positive acellular band. Finally, there is a diffuse infiltrate of lymphocytes with smaller numbers of plasma cells and occasional polymorphonuclear leukocytes in superficial and deep connective tissue. This is quite reminiscent of that seen in lichen planus. Small focal perivascular collections of lymphocytes are found also, as well as degeneration and disintegration of collagen.

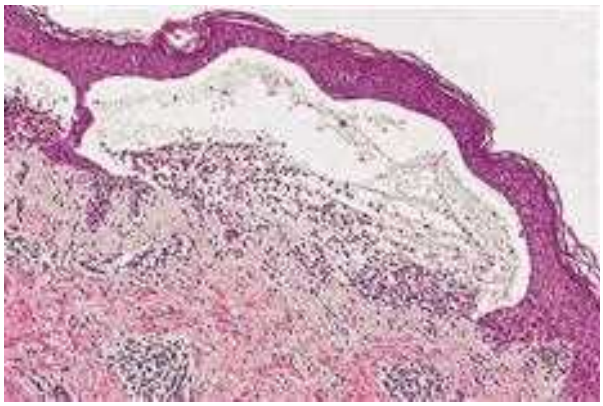


Figure 19-32. Systemic lupus erythematosus (bullous).

The systemic form of lupus exhibits histologic changes in the oral lesions that are virtually identical to those in the discoid type with the possible exception of the absence of keratinization.

Direct immunofluorescent testing is often used to confirm a suspected diagnosis of lupus erythematosus. It is basically a test used to detect the presence of immunoglobulins (IgG, IgM and IgA) at the epidermal-dermal junction or basement membrane zone of skin or oral mucosa of patients with the disease by incubating a biopsy specimen (either frozen section or one specially fixed in Michel solution) with a fluorescein-conjugated antiglobulin. The appearance of the immunoglobulins deposited in this location in discoid lupus generally is the 'particulate' (or 'speckled') pattern. These immunoglobulins were present at this specific histologic location in oral lesions in all patients with the systemic form and in nearly 75% of patients with the discoid form in a series of 52 patients with lupus erythematosus reported by Schiodt and his associates in 1981. They also found a high incidence of complement C3 and of fibrinogen at this same zone utilizing appropriate conjugates. Interestingly, these immunoglobulins may also be demonstrated in the uninvolved skin and mucosa of a significant percentage of patients with systemic lupus, as well as in lesional skin or mucosa, but almost never in normal or uninvolved skin or mucosa of discoid patients. In a retrospective study of 130 cases of oral mucosal disease by direct immunofluorescence technique, Daniels and Quadra-White have concluded that this can provide a valuable criterion in diagnosing chronic ulcerative or erosive disease of the oral mucosa if the biopsy specimens are taken from appropriate sites and have attached epithelium.

Laboratory Findings.* Routine clinical tests which suggest that the person has an active systemic disease include:

1. Sedimentation rate (ESR) and CRP (C-reative protein) binding, both of which are frequently elevated in inflammation from any cause.
2. Serum protein electrophoresis which may reveal increased gammaglobulin and decreased albumin.
3. Routine blood counts which may reveal anemia and low platelet and white cell counts.
4. Routine blood chemistry which may reveal:
   - Kidney involvement by increases in serum blood urea nitrogen and creatinine
   - Abnormalities of liver function tests
   - Increased muscle enzymes (such as CPK) if muscle involvement is present.

These abnormalities alert to the presence of a systemic disease with multiple organ involvement.

Commonly used blood tests in the diagnosis of SLE are:

1. Antinuclear antibody test (ANA) to determine if autoantibodies to cell nuclei are present in the blood
2. Anti-DNA antibody test to determine if there are antibodies to the genetic material in the cell
3. Anti-Sm antibody test to determine if there are antibodies to Sm, which is a ribonucleoprotein found in the cell nucleus
4. Serum (blood) complement test to examine the total level of a group of proteins which can be consumed in immune reactions
5. Complement proteins C3 and C4 test to examine specific levels.

Positive ANA. The immunofluorescent antinuclear antibody (ANA, or FANA) test is positive in almost all individuals with SLE (97%), and is the most sensitive diagnostic test currently available for confirming the diagnosis of SLE when accompanied by typical clinical findings. However, a positive ANA test, by itself, is not proof of lupus since the test may also be positive in other connective tissue diseases, such as, scleroderma, Sjogren's syndrome, rheumatoid arthritis, thyroid diseases, liver diseases, juvenile arthritis and in individuals being treated with certain drugs like procainamide, hydralazine, isoniazid, chlorpromazine, etc. in viral illnesses, such as, infectious mononucleosis, in other chronic infections such as, hepatitis, lepromatous leprosy, subacute bacterial endocarditis, malaria, etc. in other autoimmune diseases, including thyroiditis, multiple sclerosis, etc. and in as many as 30–40% of asymptomatic first-degree relatives of people with lupus.

A positive ANA does not equate to having a disease.

Other Autoantibodies

- Antibodies to DNA are found primarily in SLE.
- Antibodies to histones (DNA packaging proteins) are usually found in people with drug induced lupus (DIL), but may also be found in those with SLE.
- Antibodies to the Sm antigen are found almost exclusively in lupus, and often help to confirm the diagnosis of SLE.
- Antobodies to RNP (ribonucleoprotein) are found in a number of connective tissue diseases. When present in very high levels, RNP antibodies are suggestive of mixed connective tissue disease (MCTD), a condition with symptoms like those of SLE, polymyositis, and scleroderma.
- Antibodies to Ro/SS-A are found in people with either lupus or Sjogren's syndrome, and are almost always found in babies who are born with neonatal lupus.
- Antibodies to Jo-1 are associated with polymyositis.
- Antibodies to PM-Scl are associated with certain cases of polymyositis that also have features of scleroderma.
- Antobodies to centromere (structure involved in cell division) are found in people with a limited form of scleroderma which tends to have a chronic course.

Complement. Laboratory tests which measure complement levels in the blood may also be helpful in making a diagnosis of SLE. The most common complement tests are C3, C4, and CH50 (total hemolytic complement). If the total blood complement level is low, or the C3 or C4 complement values are low and the person also has a positive ANA, the findings are more suggestive of lupus. Low C3 or C4 complement levels with a positive ANA may signify the presence of active disease.

Disease activity correlates with a rise in:

1. CRP (C-reative protein) binding
2. ESR or sedimentation rate
3. Anti- DNA
4. Liver and kidney function tests (AST, ALT, BUN, creatinine)
5. CPK (muscle enzyme)
6. Urine protein or cellular casts.

Disease activity correlates with a fall in:

1. CBC or complete blood count (WBC, hemoglobin, platelets)
2. Complement components
3. Serum albumin.

Treatment. The most important tool in the medical care of the patient with SLE is careful and frequent clinical and laboratory evaluation to tailor the medical regimen and to provide prompt recognition and treatment of disease flare, which is the cornerstone of successful intervention. Lupus is a lifelong illness, and patients must be monitored indefinitely. SLE is a high-risk disease with the possibility of end-organ damage to any organ, vital or otherwise. This damage can severely affect organ function and can lead to decreased quality of life.

Discoid Lupus Erythematosus

Discoid lupus erythematosus (DLE) is a chronic, scarring, atrophy producing, photosensitive dermatosis. DLE may occur

*Source: Lupus Foundation of America, Inc. http://www.lupus.org/

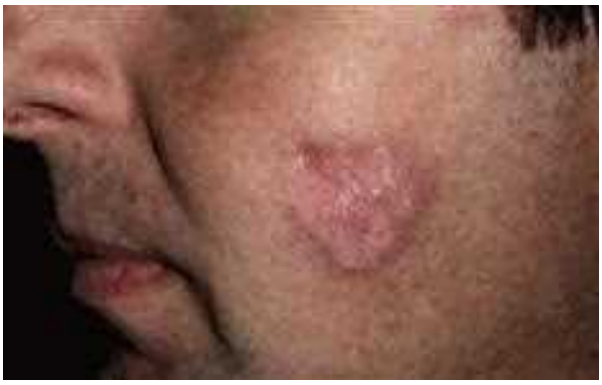


Figure 19-33. Discoid lupus erythematosus on the face.

in patients with systemic lupus erythematosus (SLE), and some patients (<5%) with DLE progress to SLE. Serologic abnormalities are uncommon. Patients with DLE rarely have clinically significant systemic disease. Lesions may produce scarring or atrophy. Scarring alopecia is particularly disturbing.

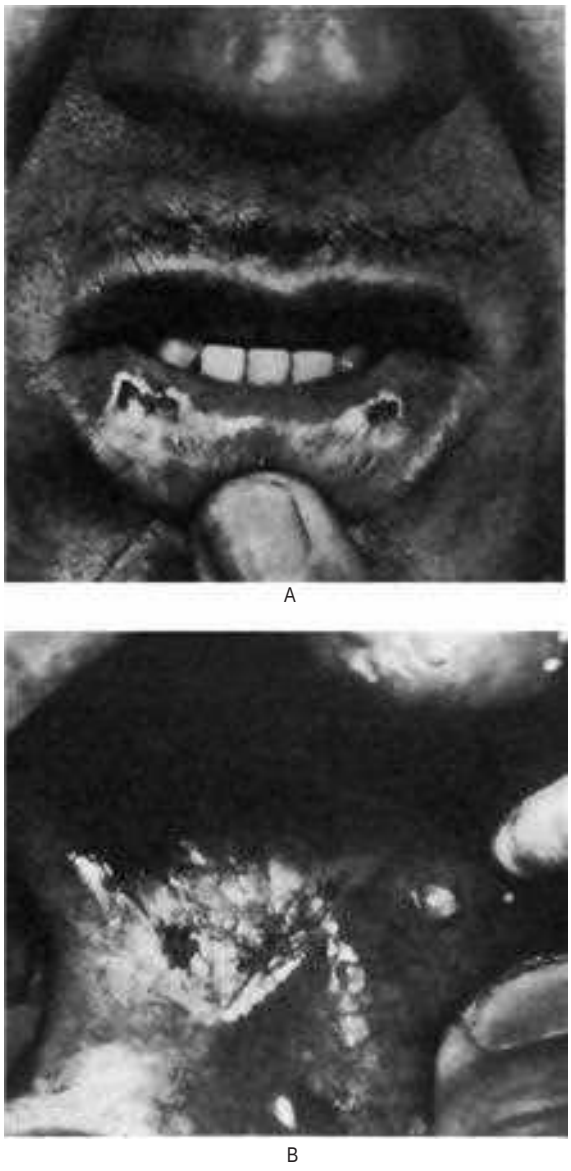
Etiology. DLE probably occurs in genetically predisposed individuals, but the exact genetic connection has not been determined. The pathophysiology of DLE is not well understood. It has been suggested that a heat shock protein is induced in the keratinocyte following ultraviolet (UV) light exposure or stress, and this protein may act as a target for T-cell-mediated epidermal cell cytotoxicity.

Clinical Features. Discoid lupus erythematosus is a relatively common disease which, like the systemic form, occurs predominantly in the third and fourth decades. It is also considerably more common in women than in men. Although any skin area may be involved by the discoid form of lupus erythematosus, the most common sites are the face (Fig. 19-33), oral mucous membranes, chest, back and extremities.

The typical cutaneous lesions are slightly elevated red or purple macules that are often covered by gray or yellow adherent scales. Forceful removal of the scale reveals numerous 'carpet tack' extensions which had dipped into enlarged pilosebaceous canals. The lesions increase in size by peripheral growth, this feature partially characterizing the disease. The periphery of the lesion appears pink or red, while the center exhibits an atrophic, scarred appearance indicative of the long-standing nature of the disease with characteristic central healing. The discoid form of the disease may also assume a typical 'butterfly' distribution on the malar regions and across the bridge of the nose. Since this is not a constant feature of the disease and since a similar distribution of lesions may occur in certain other diseases, its diagnostic significance should not be overemphasized.

Epidermoid carcinoma, and less commonly, basal cell carcinoma have been reported developing in healed scars of discoid lupus. This is only an occasional finding, and is thought to occur only in cases of 20 years duration or more.

Oral Manifestations. Oral mucous membrane involvement is reported in 20–50% of cases of discoid lupus erythematosus,



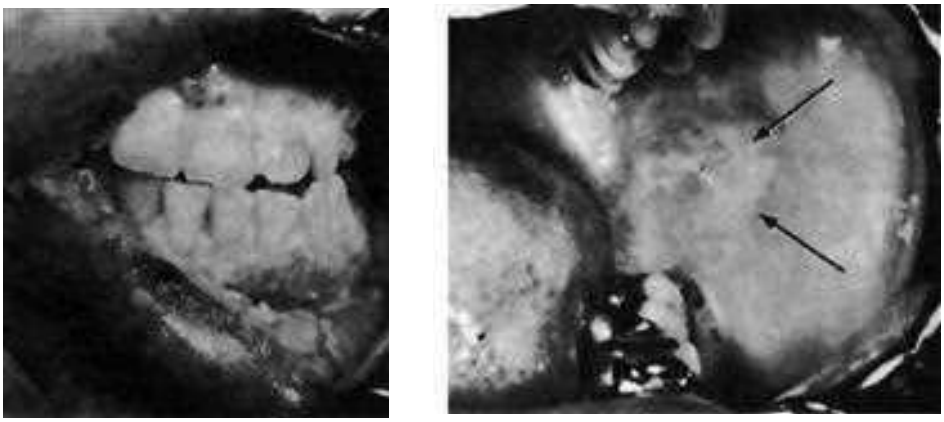
A

B

Figure 19-34. Lupus erythematosus, chronic discoid.
Typical lesions of the lip **(A)** and buccal mucosa **(B)** *(Courtesy of Dr Boynton H Booth).*

and slightly more frequently in the systemic form of the disease, according to Andreasen. With the oral mucous membranes affected in such a high percentage of cases, the dentist must be aware of this problem. The oral mucosa reportedly may be involved either prior to or following the development of skin lesions or even in the absence of skin manifestations.

The oral lesions in the **discoid** form begin as erythematous areas, sometimes slightly elevated but more often depressed, usually without induration and typically with white spots. Occasionally, superficial, painful ulceration may occur with crusting or bleeding but no actual scale formation as is seen on the skin (Figs. 19-34, 19-35). The margins of the lesions are not sharply demarcated but frequently show the formation of a narrow zone of keratinization. Often, fine white striae radiate out from the margins. Central healing may result in depressed scarring. These lesions, which were symptomatic in



A B

Figure 19-35. Lupus erythematosus, chronic discoid.
(A, Courtesy of Dr Robert J Gorlin and B, of Dr Nathaniel H Rowe).

75% of a group of 32 patients with oral manifestation described by Schiodt and his associates, are most common on the buccal mucosa, palate and tongue. In the case of the tongue, atrophy of the papillae and severe fissuring are also seen. The vermilion border of the lips, particularly the lower, is a very common site for these lesions. The erythematous, atrophic plaques, surrounded by a keratotic border, may involve the entire lip and extend onto the skin surface. Malignant transformation of these lip lesions occurs with some frequency, and the reported cases have been reviewed by Andreasen.

Treatment. The goals of management are to improve the patient's appearance, to control existing lesions and limit scarring, and to prevent the development of further lesions. The prognosis of patients with chronic DLE is favorable regarding mortality; however, many patients continue to experience pain in their lesions or may experience disfigurement from the scars or atrophy that can develop.

SYSTEMIC SCLEROSIS

(Scleroderma, dermatosclerosis, hidebound disease)

Systemic sclerosis (SSc) is a systemic connective tissue disease, characterized by vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs (e.g. alimentary tract, lungs, heart, kidney, CNS); with associated immunologic disturbances.

Etiology. Systemic sclerosis is an autoimmune disease of unclear etiology; however, different factors, including genetic, environmental, and vascular factors are involved in SSc pathogenesis. One theory states that antigens from the human leukocyte antigen (HLA) histocompatability complex, including HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52, and HLA-DQB2, are involved in SSc. Some data suggest that apoptosis and the generation of free radicals may be involved in the pathogenesis of SSc. Increased collagen deposition in tissues is a characteristic feature of SSc.

Clinical Features. Progressive systemic sclerosis is a disease characterized by the ultimate induration of the skin and fixation of the epidermis to the deeper subcutaneous tissues. It may begin in children or young adults, although the greatest incidence is between 30 and 50 years of age, and exhibits a definite gender predilection, females being affected more frequently then males (3-6:1). Systemic sclerosis usually begins on the face, hands or trunk. Simultaneously with the development of the early typical indurated edema of the skin, neuralgia and paresthesia may occur as well as arthritis or simply vague joint pain. Erythema usually accompanies this cutaneous change. The disease progresses at a variable rate, but eventually much, if not all, of the body surface becomes involved. The skin takes on a yellow, gray or ivory-white waxy appearance. Brown pigmentation of the skin may also occur, but this is usually a late manifestation of the disease. Sometimes deposition of calcium in affected areas is also found. The skin becomes hardened and atrophic and cannot be wrinkled or picked up because of its firm fixation to the deep connective tissue. This contracture of the skin gives a mask-like appearance to the face (Fig. 19-36) and a claw-like appearance to the hands (Figs 19-37, 19-38).

Progressive diffuse systemic sclerosis may ultimately involve many internal organs by fibrosis, loss of smooth muscle and loss of visceral function. Those organs most frequently involved are the gastrointestinal tract, lungs cardiovascular-renal system, musculoskeletal system, and central nervous system.

One variant of systemic sclerosis is the CREST syndrome, an acronym of the five major findings: calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia. This form of the disease is sometimes not as severe as the usual systemic type.

Circumscribed scleroderma, commonly termed **morphea,** is manifested by the appearance of one or more well-defined, slightly elevated or depressed cutaneous patches, which are white or yellowish and are surrounded by a violaceous halo. The plaques are varied in both size and

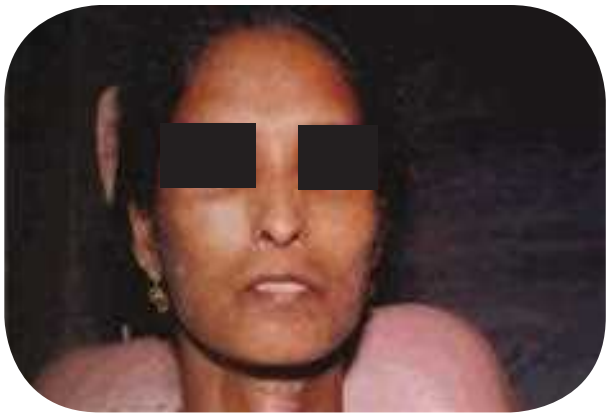


Figure 19-36. Progressive systemic sclerosis.
Characterized by induration of the skin and fixation of the epidermis with the deeper subcutaneous connective tissue.

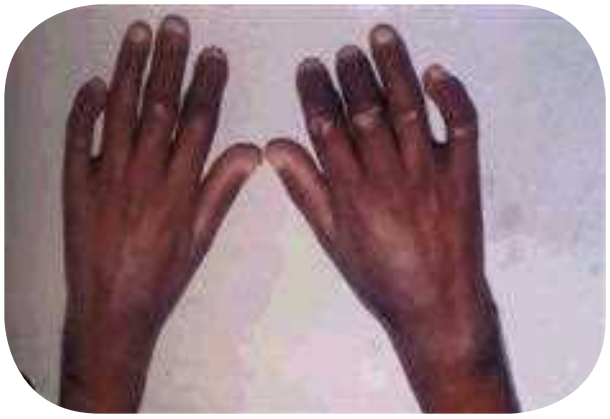


Figure 19-37. Scleroderma of the hand.

shape. The lesions commonly occur on the sides of the chest and the thighs.

Occasionally the lesions occur as linear bands or ribbons on the face, particularly the forehead, on the chest and trunk or on an extremity. This has been termed **linear scleroderma**. Such a band, made up of a furrow with an elevated ridge on one side, is often termed a ***coup de sabre,*** since it resembles the mark produced by the blow of a saber. The circumscribed lesions eventually become stiff and hard. It has been reported that facial hemiatrophy is associated with this form of the disease occurring in children. The lesions are generally asymptomatic, although prickling, tingling and itching sensations have been described. The disease may persist for several months to many years, but, in this form, causes no deaths.

Oral Manifestations. The tongue, soft palate and larynx are the intraoral structures usually involved in progressive systemic sclerosis. Early mild edema of these structures is gradually followed by atrophy and induration of mucosal and muscular tissues. The tongue often becomes stiff and board like, causing the patient difficulty in eating and speaking (Fig. 19-39). The gingival tissues are pale and unusually firm.

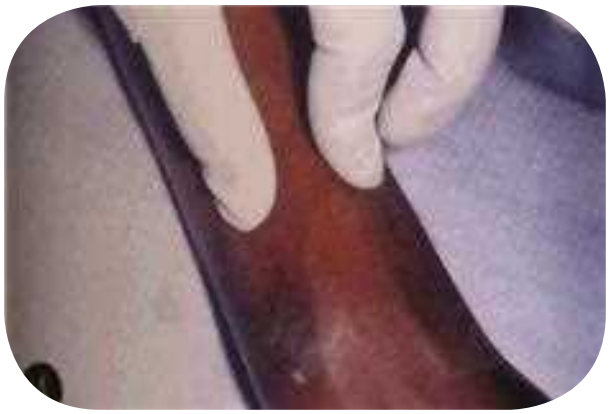


Figure 19-38. Scleroderma.
With extreme fixation of the skin to the subjacent connective tissue.

The lips become thin, rigid and partially fixed, producing microstomia. Dysphagia, a choking sensation, inability to open and close the mouth and difficulty in breathing also occur. The reduced opening of the mouth and fixation of the jaw are a result of involvement of the peritemporomandibular joint tissues, and make dental care very difficult. Limitation of mouth opening was found in 80% of a series of these patients by Marmary and his coworkers. Both Smith and Wade also have reviewed this disease with particular emphasis on the oral manifestations.

In addition, Alarcon-Segovia and his coworkers, studying 25 patients with progressive systemic sclerosis, found that all had pathologic changes in the minor salivary glands characteristic of Sjögren's disease: lymphocyte infiltration, duct cell proliferation and collagen infiltration. Weisman and Calcaterra also reported evidence of alterations of salivary gland function characteristic of the sicca syndrome in 12% of 71 patients with scleroderma.

Radiographic Features. Extreme widening of the periodontal ligament, two to four times normal thickness, has been reported originally by Stafne and Austin as characteristic

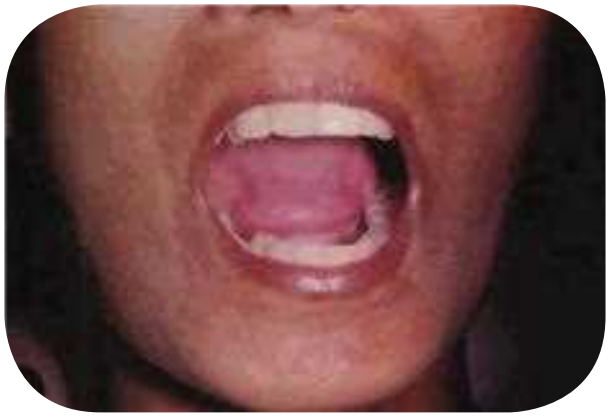


Figure 19-39. Scleroderma.
Difficulty in mouth opening due to involvement of perioral skin.

Figure 19-40. Systemic sclerosis.
The extreme widening of the periodontal ligament is obvious in the dental radiograph *(Courtesy of Dr Edward C Stafne).*

of scleroderma (Fig. 19-40). This may be so striking that, once the association is recognized, the occurrence of the periodontal disturbance as found on routine dental radiographs may be sufficient to establish a tentative diagnosis of systemic sclerosis. This has been confirmed by many studies such as those of White and his coworkers and of Marmary and his associates.

Bone resorption of the angle of the mandibular ramus, usually bilaterally, has also been reported by numerous investigators as occurring frequently in this disease. One additional radiographic feature reported has been partial or complete resorption of condyles and/or coronoid processes of the mandible.

Histologic Features. Diffuse systemic sclerosis is characterized microscopically by thickening and hyalinization of the collagen fibers in the skin, the loss of dermal appendages, particularly the sweat glands, and atrophy of the epithelium with loss of rete pegs and increased melanin pigmentation. There is an increase in PAS-positive, diastase-resistant material present in the areas of the homogeneous collagen. Subcutaneous fat disappears, and the walls of the blood vessels become sclerotic. Mucous membrane changes are similar to those occurring in the skin.

The microscopic changes in the periodontal ligament consist of a widening due to an increase of collagen and oxytalan fibers as well as an appearance of hyalinization and sclerosis of collagen with a diminution in the number of connective tissue cells usually found. These changes have been described by Fullmer and Witte.

Treatment. There is no adequate treatment for progressive diffuse systemic sclerosis, although partial remissions have been reported following cortisone therapy. Circumscribed scleroderma has an excellent prognosis, since spontaneous remission usually occurs.

EHLERS-DANLOS SYNDROME

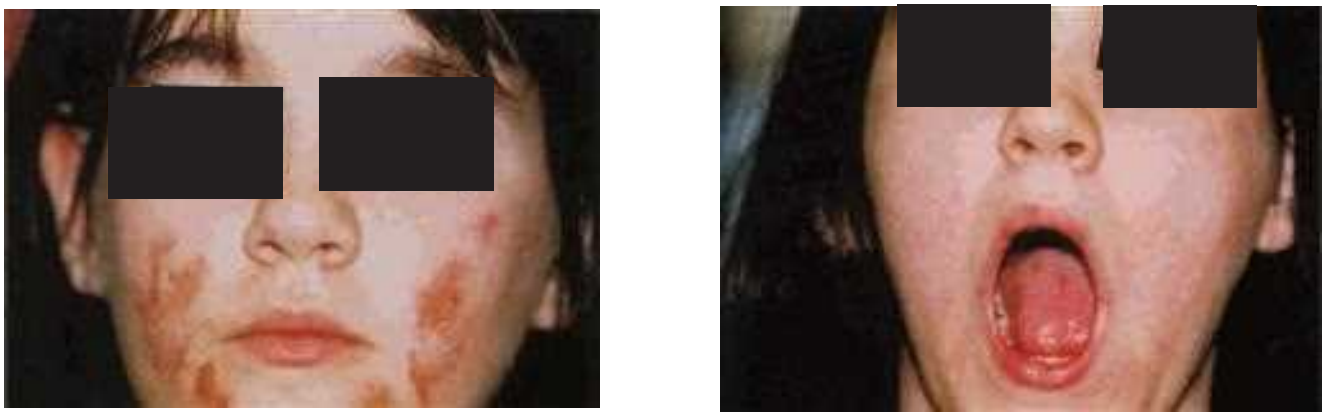
(Tenascin-X deficiency syndrome, lysyl hydroxylase deficiency syndrome, cutis hyperelastica)

Ehlers-Danlos syndrome (EDS) is the name given to a group of more than 10 different inherited disorders; all involving a genetic defect in collagen and connective-tissue synthesis and structure. EDS can affect the skin, joints, and blood vessels. This syndrome is clinically heterogeneous; the underlying collagen abnormality is different for each type. Clinical recognition of the types of EDS is important. One type, type IV, is associated with arterial rupture and visceral perforation, with possible life-threatening consequences.

In EDS types I and II, the classic variety, causative mutations may involve the *COL5A1, COL5A2,* and tenascin-*X* genes. Type IV is characterized by a decreased amount of type III collagen. Types V and VI are characterized by deficiencies in hydroxylase and lysyl oxidase, an important post-translational modifying enzyme in collagen biosynthesis. Type VII has an amino-terminal procollagen peptidase deficiency. Type IX has abnormal copper metabolism. Type X has nonfunctioning plasma fibronectin.

Etiology. Ehlers-Danlos syndrome is a heterogeneous group of inherited connective-tissue disorders characterized by joint hypermobility, cutaneous fragility, and hyperextensibility. The collagen defect has been identified in only six of the 11 types of EDS.

Clinical Features. The characteristic clinical features of this disease are the hyperelasticity of skin, hyperextensibility of the joints, and fragility of the skin and blood vessels resulting in excessive bruising as well as defective healing of skin wounds (Fig. 19-41). However, there may be considerable variation in the clinical manifestations depending upon the type of the syndrome present in the patient (Table 19.1). For example, hyperextensibility of skin and joints is striking in EDS I and EDS III but very limited in EDS II and EDS IV. EDS IV is often called the **ecchymotic** type, since rupture of even large arteries as well as the intestine often occurs, producing a life-threatening situation. In instances in which the skin extensibility is pronounced, the patient has become known as the circus **rubber man** (Fig. 19-42). The facies are frequently distinctive with hypertelorism, a wide nasal bridge and epicanthic folds being common features. Protruding ears and frontal bossing are often present. Freely movable subcutaneous nodules are frequently found, and these appear



A B

Figure 19-41. Ehlers-Danlos syndrome.
(A) Bilateral bleeding in the cheeks following episodes of luxation. **(B)** Luxation of the temporomandibular joint in a 12–year-old patient.

Table 19-1: Classification of Ehlers-Danlos syndrome

Type	Transmission	Clinical features
I: Severe or classic	AD[a]	Skin hyperelasticity and fragility Dystrophic scars Joint hypermobility Abnormal bleeding tendency
II: Moderate	AD	Symptoms less pronounced than in type I
III: Familial hypermobility	AD	Joint hypermobility Multiple dislocations Skin hyperelasticity Absence of dystrophic scars Normal coagulation
IV: Vascular (Sack-Barabas) A, B, C, D	AD (A, B, C) AR[b] (D)	Vascular fragility (arterial rupture) Moderate hypermobility of the finger joints Perforation of certain hollow organs (uterus, intestine)
V: Chromosome X-linked	XL[c]	Similar to types II and III
VI: Ocular A, B	AR (A, B)	Hyperelasticity of the skin Joint hypermobility Detached retina Severe scoliosis
VII: Arthrochalasis multiplex congenita A, B, C	AD (A, B) AR (C)	Congenital luxation of the hips Multiple joint dislocations Moderate hyperelasticity of the skin Small stature
VIII: Periodontal	AD	Generalized early-onset periodontitis Moderate joint hypermobility Variable skin hyperelasticity Shin ecchymoses

[a]AD Autosomal dominant; [b]AR Autosomal recessive; [c]XL Chromosome X-linked
Approximate percentage including all other types (V-XI, Hernandez, Friedman-Harrod, Beasley-Cohen, Viljoen).

to represent fibrosed lobules of fat. The scarring of the skin following wound healing in these patients is unusual inasmuch as the scars tend to spread rather than contract in time.

Oral Manifestations. The oral manifestations of this disease have been described in detail by Barabas and Barabas. In their series of cases, they found that the oral mucosa was of normal color but was excessively fragile and bruised easily. Although the mucosa did not hold sutures satisfactorily, healing was only slightly retarded and there was no defective scar formation. No remarkable hyperextensibility of mucous membrane could be demonstrated, and the patients had no difficulty in wearing dentures. The gingival tissues appeared fragile and bled after toothbrushing, gingival hyperplasia and fibrous nodules were also noted. Tooth mobility was not increased.

A B C

Figure 19-42. Ehlers-Danlos syndrome.
(A) Note the abnormal ability to elevate the right toe. **(B)** Dorsiflexion of all the fingers is easy and absolutely painless. **(C)** Joint hypermobility is less intense than with other conditions *(Courtesy of Enrico Ceccolini, MD)*.

Hypermobility of the temporomandibular joint, resulting in repeated dislocations of the jaw, has been reported.

Alterations in the structure of the teeth have also been reported by Barabas and these consist of a lack of normal scalloping of the dentinoenamel junction, the passage of many dentinal tubules into the enamel, the formation of much irregular dentin and an increased tendency to form pulp stones. Hypoplastic changes in the enamel have also been reported, the teeth have been reported to be fragile and have a tendency for fracture.

Several families have also been reported with apparent Ehlers-Danlos syndrome with extensive periodontal destruction. This has been reviewed by Linch and Action, who described an additional case.

Histologic Features. Histologic study of skin and connective tissues by routine techniques generally fails to reveal any characteristic or diagnostic abnormality. Ultrastructural changes in collagen have been reported in some forms of the disease, according to Byers and his associates.

Treatment. There is no known treatment for the disease. Surgical procedures should be carried out with care because difficulty in suturing and healing problems may exist. With the exception of EDS type IV, all the other variants of this syndrome are not too dangerous, and affected individuals can live a normal life with a few restrictions.

FOCAL DERMAL HYPOPLASIA SYNDROME

(Goltz's syndrome)

Focal dermal hypoplasia (FDH) is an uncommon genetic disorder characterized by distinctive skin abnormalities and a wide variety of defects that affect the eyes, teeth, and skeletal, urinary, gastrointestinal, cardiovascular, and central nervous system. The name is somewhat of a misnomer because the skin lesions appear to evolve as accumulations of fat rather than hypoplasia of the dermis. The mnemonic FOCAL can be used to remember some of the key features of this syndrome: Female sex; Osteopathia striata; Coloboma; Absent ectodermis-, mesodermis-, and neurodermis-derived elements; and Lobster claw deformity. Affected individuals are recognized at birth or prenatally, but cases involving a minor expression of the syndrome may be diagnosed later. Focal dermal hypoplasia is also known as Goltz syndrome; this is not to be confused with Gorlin or Goltz-Gorlin syndrome, which is also known as basal cell nevus syndrome.

Etiology. Focal dermal hypoplasia has an X-linked dominant inheritance pattern and is usually lethal in males. The underlying molecular defect in FDH is not clear. On the basis of common findings of syndactyly, oligodactyly, and polydactyly, the fetal expression of FDH is postulated to occur before the eighth week of gestation; by the eighth week, the hands and feet have differentiated and developed separate and elongated digits.

Clinical Features. The syndrome is characterized by relative focal absence of the dermis associated with herniation of the subcutaneous fat into the defects; skin atrophy, streaky pigmentation and telangiectasia; multiple papillomas of the mucosa and/or skin; anomalies of the extremities including syndactyly, polydactyly and adactyly; an asymmetrical face with pointed chin and notched nasal alae, asymmetrical ears; sunken eyes with sparse eyebrows and scalp hair; eye anomalies, most frequently iris and choroid colobomata and strabismus; and dental and oral anomalies. Mental retardation is often present as is some retardation of physical growth. In addition, many other anomalies have also been reported with varying frequency.

Oral Manifestations. Papillomas of the lips have been a striking feature in a number of these patients as well as papillomas of the buccal mucosa or gingiva. In addition, the teeth are commonly defective in size, shape or structure. Microdontia is a common finding as is enamel hypoplasia. Cleft lips/cleft palate has also been described in several cases. Details of the disease have been discussed by Gorlin and his associates.

Histologic Features. The atrophic reticulated patches of skin reveal attenuation of dermal collagen fibers with partial-to-complete absence of significant portions of the dermis. An accompanying change is the appearance of adipose cells in the dermis. In mild cases, adipocytes may be noted only around blood vessels; in severe cases, they may replace all or part of the dermal connective tissue. A layered effect sometimes

occurs, with attenuated collagenous connective tissue lying both above and beneath an adipose layer. If the accumulation of adipose tissue is pronounced, it may cause the apparent herniation of subcutaneous tissue through the thinned skin. The papillomatous lesions typically consist of a fibrovascular stalk composed of loose connective tissue with dilated vessels and a variable perivascular admixture of inflammatory cells.

Treatment. Management is targeted toward the various soft-tissue and skeletal anomalies, with the goal of achieving optimal functional and cosmetic results.

SOLAR ELASTOSIS

(Senile elastosis, actinic elastosis)

Solar elastosis is a dermatologic disease which is essentially a degenerative condition of skin associated with the general process of aging which itself may be influenced by hereditary factors including skin coloration or pigmentation or its absence, and exposure to the elements, especially sunlight and wind. Such skin, damaged by prolonged exposure to elements of the weather, has often been termed **sailor's skin** or **farmer's skin**. It is interesting that this disease, though common, has not been widely reported.

Clinical Features. This disturbance seldom occurs on the oral mucous membranes, but does involve the lip with considerable frequency. Although not confined to elderly patients, it is most common in this age group. The affected skin is wrinkled and appears dry, atrophic and flaccid. On the lip there may be mild keratosis and subtle blending of the vermilion with the skin surface.

Histologic Features. The chief microscopic characteristic is the apparent increase in the amount of elastic connective tissue fibers, a phenomenon that is best observed by special stains. In routine hematoxylin and eosin stained sections, the connective tissue may appear hyalinized, but it stains with hematoxylin rather than with eosin, and this has been termed basophilic degeneration.

Treatment. There is no treatment for solar elastosis any more than of approaching old age in general.

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CHAPTER 20

Diseases of the Nerves and Muscles

■ R RAJENDRAN

CHAPTER OUTLINE

DISEASES OF THE NERVES

One of the responsibilities of the dentist is the diagnosis and treatment of pain involving oral or paraoral structures. Although many of the cases of pain that confront him are directly associated with the teeth, others arise from diseases of nerves themselves and thus are not closely connected with the teeth. A comprehensive understanding of the disorders affecting the nerve pathways and the nerve supply of the various anatomic sites and structures associated with the oral cavity is essential for the dentist if he/she is to determine successfully the true nature of the pain and take appropriate measures to effect its relief.

DISTURBANCES OF FIFTH CRANIAL NERVE

Trigeminal Neuralgia

(Tic douloureux, trifacial neuralgia, Fothergill's disease)

Trigeminal neuralgia (TN) is an archetype of orofacial neuralgias which follows the anatomical distribution of the fifth cranial nerve. It mainly affects the second and third divisions of the trigeminal nerve and almost always exhibits a trigger zone, stimulation of which initiates paroxysm of pain. The pain is often accompanied by a brief facial spasm or tic. Pain distribution is unilateral and lasts for a few seconds to a minute. Physical examination eliminates alternative diagnoses. Signs of cranial nerve dysfunction or other neurologic abnormality exclude the diagnosis of idiopathic TN and suggest that pain may be secondary to a structural lesion.

Etiology. The etiology of trigeminal neuralgia is as much a mystery today as it has been for several centuries. The proximity of the teeth to the site of the pain and particularly to the nerves involved, suggested long ago that the teeth might be the source of the difficulty. When, however, the extraction of countless teeth in an effort to cure the disease failed to accomplish that purpose, the conclusion was finally reached that trigeminal neuralgia is most likely not dental in origin. Periodontal disease and traumatogenic occlusion have also been suggested as causes, but with little foundation in fact.

The causative mechanism of pain in this condition still remains controversial. One theory suggests that peripheral injury or disease of the trigeminal nerve may be causative but failure of central inhibitory mechanisms may be involved as well. Most cases are idiopathic, but compression of the trigeminal roots by tumors or vascular anomalies may cause similar pain. Abnormal vessels, aneurysms, tumors, chronic meningeal inflammation, or other lesions may irritate trigeminal nerve roots along the pons. Uncommonly, an area of demyelination, such as may occur with multiple sclerosis, may be the precipitant. In most cases, no organic lesion is identified, and the etiology is labeled as idiopathic. Development of trigeminal neuralgia in a young person suggests the possibility of multiple sclerosis. Lesions of the entry zone of the trigeminal roots within the pons may cause a similar pain syndrome. Thus, although TN is typically caused by a dysfunction in the peripheral nervous system (the roots or trigeminal nerve itself), a lesion within the central nervous system may rarely cause similar problems. Infrequently, adjacent dental fillings composed of dissimilar metals may trigger attacks (galvanism).

Clinical Features. Older adults are more commonly affected by trigeminal neuralgia than young persons, the disease seldom occurring before the age of 35 years. Females are more commonly

affected (3:2). It is a well-established fact, but a completely unexplained one, that the right side of the face is affected in more patients than the left by a ratio of about 1.7:1.

The pain itself is of a searing, stabbing, or lancinating type which many times is initiated when the patient touches a 'trigger zone' on the face. The term 'tic douloureux' is properly applied only when the patient suffers from spasmodic contractions of the facial muscles although, through custom, this term is often used interchangeably with 'trigeminal neuralgia'. In the early stages of the disease the pain is relatively mild, but as the attacks progress over a period of months or years, they become more severe and tend to occur at more frequent intervals. The early pain has been termed 'pretrigeminal neuralgia' by Mitchell and is sometimes described as dull, aching or burning or resembling a sharp toothache. Later, the pain may be so severe that the patient lives in constant fear of an attack, and many sufferers have attempted suicide to put an end to their torment. Each attack of excruciating pain persists for only a few seconds to several minutes and characteristically disappears as promptly as it arises. As the attack occurs, the patient may clutch his/her face as if in terror of the dreaded pain. The patient is free of symptoms between the attacks, but unfortunately the frequency of occurrence of the painful seizures cannot be predicted.

The 'trigger zones', which precipitate an attack when touched, are common on the vermilion border of the lips, the alae of the nose, the cheeks, and around the eyes. Usually any given patient manifests only a single trigger zone. The patient learns to avoid touching the skin over the trigger area and frequently goes unwashed or unshaven to forestall any possible triggering of an attack. In some cases, it is not necessary that the skin actually be touched to initiate the painful seizure; exposure to a strong breeze or simply the act of eating or smiling has been known to precipitate it.

Any portion of the face may be involved by the pain, depending upon which branches of the fifth nerve are affected. The mandibular and maxillary divisions are more commonly involved than the ophthalmic; in some instances two divisions may be simultaneously affected. The disease is unilateral in nearly all cases, and seldom, if ever, does the pain cross the midline.

Differential Diagnosis. The unusual clinical nature of the disease—the presence of a 'trigger zone', the fleeting but severe type of pain occasioned and the location of the pain—usually provides the key for establishing the diagnosis of trigeminal neuralgia. There are, however, a variety of diseases and conditions which may mimic this disease and which must be considered in the differential diagnosis.

One of the more common conditions mistaken for trigeminal neuralgia is migraine or migrainous neuralgia (Horton's syndrome, histamine headache, histamine cephalgia), but this severe type of periodic headache is persistent, at least over a period of hours, and has no 'trigger zone'. Sinusitis, on occasion, also has been confused with this disease so completely that radical sinus operations have been performed in the full expectancy of curing the patient of the 'neuralgia'. Again, the various clinical aspects of trigeminal neuralgia should exclude this diagnosis. The so-called Costen syndrome has also been reported to produce symptoms suggestive of trigeminal neuralgia.

Tumors of the nasopharynx can produce a similar type of pain, generally manifested in the lower jaw, tongue and side of the head with an associated middle ear deafness. This symptom complex, caused by a nasopharyngeal tumor, has been called **Trotter's syndrome** and was found to occur in 30% of a series of patients with this type of neoplasm reported by Olivier. These patients also exhibit asymmetry and defective mobility of the soft palate and affected side. As the tumor progresses, trismus of the internal pterygoid muscle develops, and the patient is unable to open his/her mouth. The actual cause of the neuralgic pain in Trotter's syndrome is involvement of the mandibular nerve in the foramen ovale through which the tumor invades the calvarium.

A condition clinically similar to trigeminal neuralgia often occurs after attacks of herpes zoster of the fifth nerve. Termed **postherpetic neuralgia**, the pain usually involves the ophthalmic division of the fifth cranial nerve, but commonly regresses within two to three weeks. It may persist, however, particularly in elderly patients. The history of skin lesions prior to the onset of the neuralgia usually aids in the diagnosis.

Trigeminal neuritis or trigeminal neuropathy is a poorly understood condition which has a variety of presumed causes:

- Some dental surgical procedure
- Pressure of a denture on the dental nerve
- Surgical (other than dental) or mechanical trauma
- The therapeutic use of hydroxystilbamidine isethionate
- Tumors of the head and neck
- Intracranial aneurysms. Some cases are idiopathic.

It differs from trigeminal neuralgia by being described more often as an ache, variously stated as a burning, boring, pulling, drawing or pressure sensation. This continues over a period of hours, days or weeks rather than the instantaneous jolt of pain in trigeminal neuralgia. A series of patients with trigeminal neuritis has been studied by Goldstein and his coworkers who have emphasized the dental causes of the disease.

Finally, pain of dental origin may be of such a localized or referred nature that it simulates this disease. By careful observation and questioning of the patient; however, one can usually establish the correct diagnosis. However, an extremely diligent search is sometimes necessary to establish the dental origin of pain, particularly in cases of a split tooth or an interradicular periodontal abscess.

Laboratory Findings. Patients with characteristic history and normal neurologic findings may be treated without further work-up. Some physicians recommend elective MRI for all patients to exclude an uncommon space occupying lesion or aberrant vessel compression on the nerve roots.

Treatment. The treatment of trigeminal neuralgia has been extremely varied over the years, and the degree of success which has resulted has not been outstanding. Each of the many types of treatment suggested has its advocates, but none is successful in all cases.

One of the earliest forms of treatment was peripheral neurectomy—sectioning of the nerve at the mental foramen, or at the supraorbital or infraorbital foramen. Since any relief

afforded is temporary, this form of treatment has not been extensively used in recent years. The injection of alcohol either into a peripheral nerve area or centrally into the gasserian ganglion has had many proponents throughout the years, despite its temporary benefit and attendant dangers. The patient may experience respite from all symptoms for a period of six months to several years after alcohol injection. The injection of boiling water into the gasserian ganglion has also been reported to be beneficial in causing respite from pain. Surgical sectioning of the trigeminal sensory root by any of a number of techniques has come to be recognized by many surgeons as the treatment of choice when attempting to obtain a permanent cure.

In the past few years, the use of phenytoin (dilantin) in the management of trigeminal neuralgia has been found to be efficacious in some cases. Many reports of its use have now been published, and, though not uniformly successful, it does appear to afford good control of the neuralgia in early cases as well as in some advanced cases. The use of the drug must be continuous, since most reports indicate that cessation of its use is followed by return of pain. In case of failure to obtain relief with this drug, carbamazepine is often used. In fact, this drug is frequently used as a therapeutic challenge to the diagnosis of trigeminal neuralgia. Thus, if a patient who is presumed to have this disease does not respond rapidly to carbamazepine in 24–48 hours, then the diagnosis is seriously in doubt.

One of the newest procedures for the management of trigeminal neuralgia is microsurgical decompression of the trigeminal root. This treatment has been reported to produce good results.

Paratrigeminal Syndrome

(Raeder's syndrome, paratrigeminal neuralgia)

The paratrigeminal syndrome is a disease characterized by severe headache or pain in the area of the trigeminal distribution with signs of ocular sympathetic paralysis. The sympathetic symptoms and homolateral pain in the head or eye occur without vasomotor or trophic disturbances. These signs and symptoms usually appear suddenly. The disease appears to be most common in males, chiefly those of middle age.

Paratrigeminal syndrome presents some of the signs of Horner's syndrome (q.v.), but can be differentiated from it by the presence of pain and little or no change in sweating activity on the affected side of the face. The cause of the disease is unknown, but in the case reported by Lucchesi and Topazian, dramatic improvement occurred after elimination of dental infection. This may have been a fortuitous finding.

Sphenopalatine Neuralgia

(Sphenopalatine ganglion neuralgia, lower-half headache, Sluder's headache, vidian nerve neuralgia, atypical facial neuralgia, histamine cephalgia, Horton's syndrome, cluster headache, periodic migrainous neuralgia)

Sphenopalatine neuralgia is a pain syndrome originally described by Sluder as a symptom complex referable to the nasal ganglion. Subsequently Vial described a similar syndrome, but believed that it involved the vidian nerve and concluded that the condition reported by Sluder should be termed 'vidian neuralgia'. In recent years, the term 'periodic migrainous neuralgia' has been used to describe this clinical syndrome, and Eggleston has helped clarify some of the confusion surrounding the disorder. At the present time, it is considered by most investigators as an idiopathic syndrome consisting of recurrent brief attacks of sudden, severe, unilateral periorbital pain.

Etiology. The pathophysiology of sphenopalatine neuralgia is not understood entirely. Its typical periodicity has been attributed to hypothalamic hormonal influences. Pain is thought to be generated at the level of the pericarotid/cavernous sinus complex. This region receives sympathetic and parasympathetic input from the brainstem, possibly mediating occurrence of autonomic phenomena during an attack. The exact roles of immunologic and vasoregulatory factors, as well as the influence of hypoxemia and hypocapnia, are still controversial. Cases of this syndrome affecting multiple members within a single family have been reported, suggesting that a genetic predisposition may exist in some individuals.

Clinical Features. Sphenopalatine ganglion neuralgia, or periodic migrainous neuralgia is characterized by unilateral paroxysms of intense pain in the region of the eyes, the maxilla, the ear and mastoid, base of the nose, and beneath the zygoma. Sometimes the pain extends into the occipital areas as well. These paroxysms of pain have a rapid onset, persist for about 15 minutes to several hours, and then disappear as rapidly as they began. There is no 'trigger zone'. In a series of 35 cases reported by Brooke, over 50% of the patients described their pain as a toothache. Unfortunately, the attacks develop regularly, usually at least once a day, over a prolonged period of time. Interestingly, in some patients the onset of the paroxysm occurs at exactly the same time of day, and for this reason, the disease has been referred to as **alarm clock** headache. After some weeks or months, the attacks disappear completely and this period of freedom may persist for months or even years. However, all too frequently there is subsequent recurrence of paroxysms.

In addition to the pain sensation experienced by the patient, a number of other complaints may be noted as an accompaniment of this disease. Sneezing, swelling of the nasal mucosa and severe nasal discharge often appear simultaneously with the painful attacks, as well as epiphora, or watering of the eyes, and bloodshot eyes. Paresthetic sensations of the skin over the lower half of the face also are reported. It has been noted by many investigators that attacks are precipitated in some patients by either emotional stress or injudicious intake of alcohol. Men are affected more commonly than women (5:1) and the majority of patients experience their first manifestations of the disease before the age of 40 years.

Treatment. Numerous methods of treatment of the sphenopalatine ganglion syndrome have been proposed, none of which is successful in every instances. One of the most widely

used of these has been cocainization of the sphenopalatine ganglion or alcohol injection of this structure. Resection of the ganglion has been carried out in some instances, as well as surgical correction of septal defects. It has been found that ergotamine will often produce immediate and complete relief of symptoms. In those cases where it is not totally effective, combining it with methysergide, an antiserotonin agent, appears to produce a synergistic action usually providing total relief. However, both drugs carry some risk of serious side effects if given in large doses or over a prolonged period. Invasive nerve blocks and ablative neurosurgical procedures all have been implemented successfully in refractory cases.

Burning Mouth Syndrome

Burning mouth syndrome (BMS) is a burning or stinging of the mucosa, lips, and/or tongue, in the absence of visible mucosal lesions. van der Waal defined the term **burning mouth syndrome** to refer only to idiopathic cases in which the main symptoms are located in the oral mucosa, with or without involvement of any other part of the body. There is a strong female predilection, with most female patients being postmenopausal and the age of onset being approximately 50 years. The causes of BMS are multifactorial and remain poorly understood.

Clinical Features. The history of this illness in most cases seems to be protracted with the patients experience symptoms of the disorder for a long time. The burning sensation may be felt either as a continuous or intermittent discomfort which most frequently affects the tongue, and sometimes the lips or palate. Other oral mucosal sites may also be involved. Onset of the symptoms may be sudden or gradual over months, and it has been suggested that psychosomatic factors are associated with the onset of BMS. No oral mucosal lesions will be detected on examination. Up to 50% of patients with BMS report an associated sensation of dry mouth which is not confirmed on investigation. Some of these may also notice increased thirst. In addition affected patients may report altered taste sensation either with reduction in taste perception or the presence of a persistent unusual taste, most frequently bitter or metallic. Unlike most other oral disorders, BMS usually does not interfere with sleeping. Drinking or eating may temporarily reduce the severity of symptoms. Patients may have associated anxiety or depression.

Treatment. Treatment modalities which may be considered in BMS patients include antidepressants, vitamins or dietary supplements such as alpha lipoic acid; analgesic sprays or mouthwashes such as benzydamine hydrochloride, and in postmenopausal female patients, hormone replacement or topical estrogen applied to the oral mucosa. Where a dry mouth is a prominent symptom then saliva substitutes may be considered.

Etiology

Local causes

- Dry mouth (xerostomia)
- Mucosal disorders—geographic tongue (erythema migrans), lichen planus, etc.
- Trauma to oral mucosa (e.g. poorly fitting dentures)
- Repetitive oral habits (such as 'tongue thrusting')
- Gastroesophageal reflux disease
- Sensory nerve damage (e.g. due to trauma)

Systemic medical causes

- Vitamin B_{12}, folate, iron deficiencies
- Medication (e.g. angiotensin converting enzyme [ACE] inhibitors such as captopril)
- Immunologically-mediated diseases (e.g. Sjögren's syndrome)
- Psychogenic disorders (e.g. depression, anxiety, fear of cancer)
- Psychosocial stresses (e.g. stressful life events such as bereavement)
- Diabetes mellitus
- Menopause

Orolingual Paresthesia

(Glossodynia or painful tongue, glossopyrosis or 'burning' tongue)

Paresthesia of the oral mucous membrane is a common clinical occurrence. It presents a great problem to the dentist because he/she is frequently unable to discover a cause for the complaint. The condition undoubtedly represents a symptom rather than a disease entity, but because of its clinical frequency and the specific nature of the complaint it is included in this section on diseases of the nerves and nervous system.

Etiology. A great variety of local and systemic disorders have been implicated in the cause of orolingual paresthesia. These have been reviewed by Karshan and his associates and include the following:

- Deficiency states such as pernicious anemia and pellagra
- Diabetes
- Gastric disturbances such as hyperacidity or hypoacidity
- Psychogenic factors
- Trigeminal neuralgia
- Periodontal disease
- Xerostomia
- Hypothyroidism
- Referred pain from abscessed teeth or tonsils
- Angioneurotic edema
- Mercurialism
- Moeller's glossitis
- Oral habits such as excessive use of tobacco, spices, and the like
- Antibiotic therapy
- Local dental causes such as dentures, irritating clasps or new fixed bridges.

In addition, Shafer pointed out two other possible etiologic factors: an electrogalvanic discharge occurring between dissimilar metallic dental restorations, and temporomandibular joint disturbances.

A great number of cases of orolingual paresthesia are undoubtedly based on psychogenic factors, the most common being emotional conflict, sexual maladjustment, and cancerophobia. A considerable series of patients were reviewed by Ziskin and Moulton, who emphasized this nervous background, but nevertheless applied the term 'idiopathic orolingual pain' to the disease.

Clinical Features. The tongue is most frequently the site of the paresthetic sensations, thus the origin of the terms 'glossodynia' and 'glossopyrosis'; however, any site in the oral cavity may be affected by these varying symptoms. The sensations most commonly encountered are pain, burning, itching and stinging of the mucous membranes. It is significant that the appearance of the tissues is usually normal; there are no apparent lesions to explain the untoward complaints.

The disease most frequently occurs in women past the menopause, although men are occasionally seen with this paresthesia. It is rare in children.

Treatment. A vast variety of therapeutic agents have been used in an attempt to relieve the symptoms of this disease. Kutscher and his coworkers reported the results of nearly 50 different drugs of various types, including topical anesthetics, analgesics, smooth-and skeletal-muscle relaxants, sedatives, antibacterial and antifungal agents, antihistamines, vitamins, enzyme digestants, CNS stimulants, salivary stimulants, vasodilators and sex hormones. They concluded that, except in occasional instances, permanent remission of the condition cannot be expected after drug therapy.

Auriculotemporal Syndrome
(Frey's syndrome, gustatory sweating)

The auriculotemporal syndrome is an unusual phenomenon, which arises as a result of damage to the auriculotemporal nerve and subsequent reinnervation of sweat glands by parasympathetic salivary fibers.

Etiology. The syndrome follows some surgical operation such as removal of a parotid tumor or the ramus of the mandible, or a parotitis of some type that has damaged the auriculotemporal nerve. After a considerable amount of time following surgery, during which the damaged nerve regenerates, the parasympathetic salivary nerve supply develops, innervating the sweat glands, which then function after salivary, gustatory or psychic stimulation. Some cases of gustatory sweating appear to be due to transaxonal excitation rather than to actual anatomic misdirection of fibers.

Clinical Features. The patient typically exhibits flushing and sweating of the involved side of the face, chiefly in the temporal area, during eating. The severity of this sweating may often be increased by tart foods. Of further interest is the fact that profuse sweating may be evoked by the parenteral administration of pilocarpine or eliminated by the administration of atropine or by a procaine block of the auriculotemporal nerve.

There is a form of gustatory sweating which occurs in otherwise normal individuals when they are eating certain foods, particularly spicy or sour ones. This consists of diffuse facial sweating, not simply a perioral sweating, and may even be on a hereditary basis, as suggested by Mailander.

There is a somewhat similar condition known as 'crocodile tears' in which patients exhibit profuse lacrimation when food is eaten, particularly hot or spicy foods. It generally follows facial paralysis, either of Bell's palsy type or the result of herpes zoster, head injury or intracranial operative trauma. According to Golding-Wood, whenever an autonomic nerve degenerates from injury or disease, any closely adjacent normal autonomic fibers will give out sprouts which can connect up with appropriate cholinergic or adrenergic endings; thus, a salivary-lacrimal reflex arc is established resulting in 'crocodile tears'.

The auriculotemporal syndrome is not a common condition. Nevertheless the possibility of its occurrence must always be considered after surgical procedures in the area supplied by the ninth cranial nerve. The syndrome is a possible complication not only of parotitis, parotid abscess, parotid tumor and ramus resection, but also of mandibular resection for correction of prognathism, as in the case of Chisa and his associates. It has been reported as a complication in as high as 80% of cases following parotidectomy. In a study reported by McGibbon and Paletta, it was found that 14% of a series of 70 patients who had had a radical neck dissection during the treatment of a tumor later had manifestations of gustatory sweating when eating. A review of the affected patients indicated that all had had the tail of the parotid gland excised.

Treatment. Treatment of the auriculotemporal syndrome by intracranial division of the auriculotemporal nerve has been reported to be successful.

DISTURBANCES OF SEVENTH CRANIAL NERVE

Bell's Palsy
(Seventh nerve paralysis, facial paralysis)

Bell's palsy is one of the most common neurologic disorders affecting the cranial nerves. It is an abrupt, isolated, unilateral, peripheral facial nerve paralysis without detectable causes. Idiopathic facial paralysis was first described more than a century ago by Sir Charles Bell; however much controversy still surrounds its etiology and management. Bell's palsy is the most common cause of facial paralysis worldwide. It is important to keep in mind that Bell's palsy is a diagnosis of exclusion.

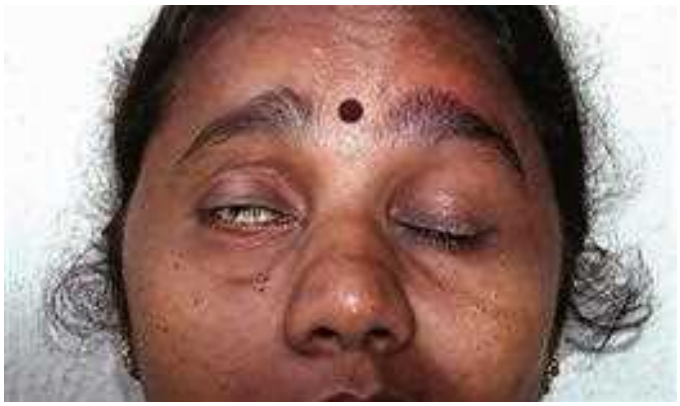
Etiology. Bell's palsy is considered an idiopathic facial paralysis; however, an infectious cause has been reported. Herpes simplex virus (HSV) has been isolated in many patients with Bell's palsy and is most likely the infectious agent. There is more than one etiologic agent with a shared common pathway leading to facial neuropathy. Actual pathophysiology is unknown. A popular theory proposes that the inflammation of the facial nerve with resultant edema causes nerve compression while it passes through the temporal bone. Various inflammatory, demyelinating, ischemic, or

compressive processes may impair neural conduction at this unique anatomic site.

Clinical Features. Bell's palsy begins abruptly as a paralysis of the facial musculature, usually unilaterally. Familial occurrence of Bell's palsy has been reported on a number of occasions, such as the case of Burzynski and Weisskopf, and hereditary factors may play a role in the etiology of the disease. Women are affected more commonly than men, and the middle-aged are most susceptible, although no age group is exempt. The disease arises more frequently in the spring and fall than at other times of the year. It may develop within a few hours or be present when the patient awakens in the morning. In some cases it is preceded by pain on the side of the face which is ultimately involved, particularly within the ear, in the temple or mastoid areas, or at the angle of the jaw.

The muscular paralysis manifests itself by the drooping of the corner of the mouth, from which saliva may run, the watering of the eye, and the inability to close or wink the eye, which may lead to infection. When the patient smiles, the paralysis becomes obvious, since the corner of the mouth does not rise nor does the skin of the forehead wrinkle or the eyebrow raise (Fig. 20-1). The patient has a typical mask like or expressionless appearance. Speech and eating usually become difficult, and occasionally the taste sensation on the anterior portion of the tongue is lost or altered.

A



B

Figure 20-1(A, B). Bell's palsy due to facial nerve paralysis.
The patient demonstrates the typical unilateral paralysis of the facial musculature with inability to smile or close the eye on the affected side *(Courtesy of Dr Ajay-prakash, Department of Oral Pathology, Kamineni Institute of Dental Sciences, Andhra Pradesh).*

In many cases of a mild nature, the disease regresses spontaneously within several weeks to a month. Any residual manifestation of the disease which persists for over one year is apt to represent a permanent alteration.

Recurrent attacks of facial paralysis, identical with Bell's palsy, associated with multiple episodes of nonpitting, noninflammatory painless edema of the face, cheilitis granulomatosa, and fissured tongue or lingua plicata is known as the **Melkersson-Rosenthal syndrome**. The facial edema resembles angioneurotic edema and involves the upper lip, occasionally the lower, and sometimes the nose, tongue or maxillary alveolar process. The fissured or scrotal tongue has been reported to be present in only about 25–40% of cases with the other manifestations. An excellent review and a discussion of this syndrome have been presented by Vistnes and Kernahan.

Treatment. There is no specific treatment for Bell's palsy, since the etiology of the disease is unknown. The use of vasodilator drugs, e.g. histamine, has proved beneficial in some cases. Administration of physiologic flushing doses of nicotinic acid has produced excellent results in a series of cases reported by Kime, when treatment was instituted within a week after onset of the disease. In permanent paralysis surgical anastomosis of nerves has been carried out with some success. An attempt should be made to prevent infection of the involved eye, but other special precautions are seldom necessary.

DISTURBANCES OF NINTH CRANIAL NERVE

Glossopharyngeal Neuralgia

Pain similar to that of trigeminal neuralgia may arise from the glossopharyngeal nerve. This condition is not as common as trigeminal neuralgia, but when it occurs, the pain may be as severe and excruciating. The condition has been reviewed by Bohm and Strang.

Clinical Features. This neuralgia occurs without gender predilection in middle-aged or older persons and manifests itself as a sharp, shooting pain in the ear, the pharynx, the nasopharynx, the tonsil or the posterior portion of the tongue. It is almost invariably unilateral, and the paroxysmal, rapidly subsiding type of pain characteristic of trigeminal neuralgia is also a feature here. Numerous mild attacks may be interspersed by occasional severe ones. The patient usually has a 'trigger zone' in the posterior oropharynx or tonsillar fossa. These zones are difficult to localize but can be found by careful probing. Because of the location of these trigger zones, certain actions are recognized as inciting the episodes of pain. These include such simple acts as swallowing, talking, yawning or coughing. The etiology of glossopharyngeal neuralgia is unknown. Neural ischemia has been suggested, but without conclusive evidence.

Treatment. The treatment of glossopharyngeal neuralgia has generally consisted in resection of the extracranial portion of

the nerve or intracranial section. The injection of alcohol into the glossopharyngeal nerve has not been as widely accepted as has similar treatment in the case of trigeminal neuralgia. Periods of remission with subsequent recurrence are common in this disease.

MISCELLANEOUS DISTURBANCES OF NERVES

Motor System Disease

(Motor neuron disease, amyotrophies)

Motor system disease constitutes a group of closely related conditions of unknown etiology which occur in three clinically variant forms usually referred to as progressive muscular atrophy, amyotrophic lateral sclerosis, and progressive bulbar palsy. They are called the motor system disease, since they all manifest corticospinal and anterior horn cell degeneration and exhibit either bulbar (tongue, pharyngeal, laryngeal) or limb muscle involvement.

Clinical Features. Progressive muscular atrophy is characterized by progressive weakness of the limbs with associated muscular atrophy, reflex loss and sensory disturbances. It shows a strong hereditary pattern, affects males more frequently than females and tends to occur in childhood. The initial symptoms usually consist of difficulty in walking, with leg pain and paresthesia. Atrophy of the foot, leg and hand muscles ultimately occurs with the appearance of a typical foot-drop, steppage gait and stork legs.

Amyotrophic lateral sclerosis generally occurs between the ages of 40 and 50 years and affects males more frequently. Precipitating factors in the appearance of the disease have often been described, and these include fatigue, alcohol intoxication, trauma and certain infections such as syphilis, influenza, typhus and epidemic encephalitis. A genetically determined form of the disease is known to occur in Guam and the Pacific Islands but a hereditary type in the western world has yet to be proven. Nevertheless, Fleck and Zurrow have reported familial amyotrophic lateral sclerosis in which four of five siblings in a family were involved. The initial symptoms consist of weakness and spasticity of the limbs, difficulty in swallowing and talking with indistinct speech and hoarseness. Atrophy and fasciculations of the tongue with impairment or loss of palatal movements may also occur. The oral findings have been discussed by Roller and his coworkers.

Progressive bulbar palsy is characterized by difficulties in swallowing and phonation, hoarseness, facial weakness and weakness of mastication. It generally occurs in patients in the fifth and sixth decades of life with a familial pattern in some instances. The initial symptoms are gradual in onset and consist of difficulty in articulation, with impairment and finally loss of swallowing. Chewing is difficult as the facial muscles become weakened. These patients exhibit atrophy of the face, masseter and temporal muscles, and tongue with fasciculations of the face and tongue. There is also impairment of the palate and vocal cords.

Pseudobulbar palsy is a disease unrelated to the 'motor system disease'. It results from loss or disturbance of the cortical innervation of the bulbar nuclei, usually seen in patients with multiple cerebral thrombi as a result of cerebral arteriosclerosis. The typical patient with pseudobulbar palsy has suffered a cerebrovascular accident with paralysis of one arm and leg but no swallowing difficulty. A subsequent 'stroke', however, may result in paralysis of the opposite limbs with impairment of swallowing and talking, associated with loss of emotional control. In this disease there is hypertonia and failure of voluntary muscle control rather than spasticity.

Treatment and Prognosis. There is no specific treatment for motor system disease. In most instances, the disease is fatal, although temporary remissions sometimes occur.

Multiple Sclerosis

(Disseminated sclerosis)

Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disease of the central nervous system (CNS). Patients commonly present with an individual mixture of neuropsychological dysfunction, which tends to progress over years.

Etiology. Multiple sclerosis commonly is believed to result from an autoimmune process. What triggers the autoimmune process is not clear, but the nonrandom nature of its geographic distribution suggests an isolated or additive environmental effect and/or inadvertent activation and dysregulation of immune processes by a retroviral infection that was perhaps acquired in childhood. On the basis of research findings, some authorities implicate human herpes virus-6 (HHV-6), while others implicate *Chlamydia pneumoniae* as causative agents. Polygenic inheritance accounts for a familial rate of 10–20%. Most studies confirm that a monozygotic twin has only a 30% risk of acquiring this disease, suggesting the contributory role of environmental agents to genetic predisposition in the causation of this disorder.

Clinical Features. Multiple sclerosis rarely occurs in those younger than 20 years or those older than 50 years. Onset of symptoms is most frequently seen between the ages of 20 and 40 years. There is a female gender predilection (2:1), and a familial incidence is often observed. The disease is characterized by:

- A variety of ocular disturbances, including visual impairment as a manifestation of retrobulbar neuritis, nystagmus and diplopia.
- Fatigability, weakness and stiffness of extremities with ataxia or gait difficulty involving one or both legs.
- Superficial or deep paresthesia.
- Personality and mood deviation toward friendliness and cheerfulness.
- Autonomic effector derangements, such as bladder and/or rectal retention or incontinence.

Charcot's triad is a well-known diagnostic triad characteristic of multiple sclerosis but not invariably present. It consists of

intention tremor, nystagmus and dysarthria or scanning speech, an imperfect speech articulation.

Facial and jaw weakness occurs in some patients, and a staccato type of speech has been described. In addition, both Bell's palsy and trigeminal neuralgia have been reported in some patients with multiple sclerosis, but these are not common and the findings may be fortuitous.

Treatment. There is no treatment for multiple sclerosis. Although remissions of the disease frequently occur, patients usually follow an ingravescent course leading to death, often from supervening infection.

Orofacial Dyskinesia

Orofacial dyskinesia is a condition thought to result from either an extrapyramidal disorder or a complication of phenothiazine therapy. However, a similar situation has been reported as a result of disruption of dental proprioception. Thus, Sutcher and his associates have reported a group of edentulous patients wearing full upper and lower dentures in gross malocclusion, who exhibited the involuntary movements typical of orofacial dyskinesia but in somewhat less severe form. These patients showed either a marked diminution or total disappearance of symptoms when dentures with proper physiologic craniomandibular relationships were constructed.

Clinical Features. This disorder occurs more frequently in persons over the age of 60 years than in the young. It is characterized by severe, involuntary, dystonic movements of the facial, oral and cervical musculature. Thus, irregular and involuntary movements such as lip-smacking and lip-licking, protrusion of the lips as in pouting, protrusion of the tongue and mandible with uncoordinated movements, and grimacing are all typical manifestations. The dyskinesia may occur alone or in association with torticollis or generalized dystonia.

Treatment. Surgical operations similar to those carried out in the treatment of Parkinson's disease generally cause improvement in the symptoms of the disease, although antiparkinsonian drug therapy has met with only limited success. It has also been suggested that correction of denture occlusion may be an effective therapeutic procedure.

Ménière's Disease

(Ménière's disease, Ménière's syndrome, endolymphatic hydrops)

Ménière syndrome, also known as **endolymphatic hydrops**, is an inner ear (labyrinthine) disorder in which there is an increase in volume and pressure of the endolymph of the inner ear. It typically presents with waxing and waning, hearing loss and tinnitus associated with vertigo.

Etiology. The exact cause of Ménière syndrome is unknown. The current theory is that it is the response of the inner ear to injury. Autopsy studies involving patients with Ménière syndrome have shown an increase in the volume of endolymph with distention of the entire endolymphatic system. This distention and increased fluid results in permanent damage to both the vestibular and cochlear apparatuses.

Clinical Features. This disease is characterized by deafness, tinnitus and vertigo usually beginning in middle age, and if untreated, persisting indefinitely with occasional periods of remission. It commences with tinnitus and deafness which are unilateral in approximately 90% of the cases. The low-pitched tinnitus has been described as a roar or hum, or in some cases, as a hissing sound, while the deafness has been described as an inner-ear deafness of the conductive type which fluctuates in degree. Vertigo is often a late symptom of the disease and many times is accompanied by attacks of nausea and vomiting which may be incapacitating. The vertigo usually has a sudden explosive onset and persists for several minutes to several hours. Some patients can foretell an attack by alteration in the pitch or intensity of the tinnitus.

These same signs and symptoms commonly occur in cases of cardiovascular disorders or with cerebral arteriosclerosis. True Ménière's disease; however, has specific histopathologic changes in the labyrinth, which were originally described in 1938 by Hallpike and Cairns. The nonspecific term 'Ménière's syndrome' is often used to describe conditions characterized by labyrinthine vertigo not necessarily associated with the changes reported by these investigators. In true Ménière disease there is dilatation of the endolymphatic spaces of the labyrinth with absence of an inflammatory reaction. The increased endolymphatic fluid pressure appears to diminish and distort the response to stimulation of the end-organs of the labyrinth and cochlea.

The basis of the endolymphatic dilatation is unknown. It has been suggested that the basic cause of this disorder is either an autonomic vasomotor dysfunction or an intrinsic allergy. The suggestion of a nutritional deficiency does not seem valid in view of the typical unilateral occurrence.

Treatment. No treatment of Ménière's disease is wholly effective. Management by drugs is generally unsuccessful, although some patients react favorably to vasodilators such as histamine or niacin. When conservative treatment fails, surgical intervention may be considered to relieve the vertigo. This consists in section of the eighth nerve or destructive labyrinthotomy, both of which appear equally effective in eliminating acute attacks of vertigo.

Migraine

(Migraine syndrome)

Migraine is a term applied to certain headaches with a vascular quality. However, overwhelming evidence suggests that migraine is a dominantly inherited disorder characterized by varying degrees of recurrent vascular headache, photophobia, sleep disruption, and depression.

Etiology. The mechanisms of migraine are not completely understood. However, the advent of new technologies has allowed formulation of current concepts that may explain parts of the migraine syndrome. For many years, headache during a migraine attack was thought to be a reactive hyperemia in response to vasoconstriction-induced ischemia during aura (Fig. 20-2). This explained the throbbing quality

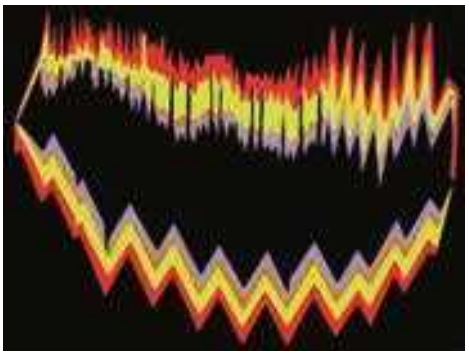


Figure 20-2. Migraine headache.
Example of a visual migraine aura as described by a person who experiences migraine. This patient reported that these visual auras preceded her headache by 20–30 minutes *(Courtesy of Dr Amelito Malapira).*

of the headache, its varied localization, and the relief obtained from ergots; however, it does not explain the prodrome and associated features.

Clinical Features. Migraine usually begins during the second decade of life and is especially common in professional persons. Migraine headaches are reported to affect women more than men. The frequency of attacks is extremely variable. They may occur at frequent intervals over a period of years or on only a few occasions during the lifetime of the patient.

A prodromal stage (preheadache phenomenon) is noted by some patients, consisting of lethargy and dejection several hours before the headache. Visual phenomena such as scintillations, hallucinations or scotomas are often described. Other less common prodromal phenomena include vertigo, aphasia, confusion, unilateral paresthesia or facial weakness.

The headache phase consists of severe pain in the temporal, frontal and retro-orbital areas, although other sites such as parietal, postauricular, occipital or suboccipital are also occasionally involved. The pain is usually unilateral, but may become bilateral and generalized. The pain is not necessarily confined to the same side of the head in successive attacks. The pain is usually described as a deep, aching, throbbing type.

At the time of headache the patient may appear extremely ill. The face is usually pale, sallow, and sweaty. The patient is irritable and fatigued, and the memory and concentration are impaired. Anorexia and vomiting may occur, as well as a variety of visual disturbances. Prolonged and painful contraction of head and neck muscles is found in some patients.

Treatment. The treatment of migraine includes a wide variety of drugs ranging from acetylsalicylic acid and codeine to ergotamine, methysergide and norepinephrine. The prognosis of the disease is good, since the condition is not dangerous and may undergo complete and permanent remission.

Temporal/Giant Cell Arteritis

Temporal arteritis is a cause of headache which is frequently diagnosed erroneously as 'atypical migraine'. It is a relatively uncommon condition, as is any arteritis or periarteritis of cranial arteries.

It is basically a focal granulomatous inflammation of arteries, especially the cranial vessels, although in severe cases arteries throughout the body may be involved. The temporal arteries are particularly prone to develop these lesions. Occasionally, similar lesions are found throughout the skeletal muscles related to their vasculature, and this condition has been termed 'polymyalgia arteritica'.

Etiology. Giant cell arteritis is primarily a disease of cellular immunity. The vasculitic damage is mediated by activated CD4+ T helper cells responding to an antigen presented by macrophages. The primary inflammatory response affects the internal elastic lamina. Multinucleated giant cells, which are a histologic hallmark of this condition, may contain elastic fiber fragments. The actual inciting antigen remains unknown, but elastin remains an important suspect.

Clinical Features. Temporal arteritis occurs most frequently in older persons usually between the ages of 55 and 80 years. It affects women far more frequently than men.

The onset of the disease may be slow and insidious, or the disease may develop suddenly with a headache or a burning, throbbing type of pain, sometimes beginning elsewhere than over the course of the temporal artery. A general malaise, chills and fever and weight loss with anorexia, nausea, and vomiting may precede any manifestations of pain. These are sometimes followed by aching and stiffness of the muscles of the shoulders and hips, which is often termed 'polymyalgia rheumatica'.

The pain frequently may be localized first in the teeth, temporomandibular joint, scalp, or occiput. Nearly one-half of patients complain of tiredness, fatigue and pain on repetitive chewing. This jaw claudication probably represents an external insufficiency of the carotid artery and musculature ischemia. Ultimately, however, there is localized inflammation or cellulitis over the swollen, nodular, tortuous artery.

Eye pain, photophobia, diplopia and even blindness may accompany the temporal symptoms. According to Sandok, permanent visual loss occurs in 25–50% of patients.

The erythrocyte sedimentation rate is markedly elevated in the majority of these patients and a mild leukocytosis may also be found. These are nonspecific findings; however, and do not establish the diagnosis.

Histologic Features. The histopathology of the diagnostic arterial lesion includes intimal proliferation with resulting luminal stenosis, disruption of the internal elastic lamina by a mononuclear cell infiltrate, invasion and necrosis of the media progressing to panarteritic involvement by mononuclear cells, giant cell formation with granulomata within the mononuclear cell infiltrate, and less consistently, intravascular thrombosis.

Treatment and Prognosis. The response of temporal arteritis to corticosteroid therapy is excellent, and clinical manifestations subside within a few days. In occasional cases in which there is widespread systemic vascular involvement, the course of the disease may be progressively downhill and may terminate fatally.

Complex Regional Pain Syndrome
(Causalgia, reflex sympathetic dystrophy syndrome)

Causalgia is a term applied to severe pain which arises after injury to or sectioning of a peripheral sensory nerve. Although few reports of this condition exist in the dental literature, cases do occur after the extraction of teeth. It has readily identifiable signs and symptoms and is treatable if recognized early; however, the syndrome may become disabling if unrecognized.

Etiology. Some authors believe that development of causalgia requires the following triad of conditions: an injury, an abnormal sympathetic response, and a predisposing personality. Others, however, dispute the need for an underlying personality disorder.

Clinical Features. Causalgia may develop in patients of any age. It usually follows extraction of a multirooted tooth, particularly when the extraction is difficult or traumatic. The pain arises within a few days to several weeks after the extraction and has a typical burning quality from which the condition derives its name. The pain itself develops locally at the site of the injury and is evoked by contact or by application of heat or cold. It is an interesting feature of the disease that an attack may be elicited not only by actual touch stimulation but also by emotional disturbances.

Behrman reported 10 cases of causalgia following tooth extraction, while Elfenbaum reported 30 cases following similar surgical procedures. In both series it was reported that the pain was intensified by the application of heat, by ingestion of alcohol, during the menstrual periods, or at times when the patient became frustrated or upset.

It is surprising, considering the great numbers of teeth extracted, that far more cases of causalgia have not been reported. Possibly the condition has not been recognized as such, but rather has been ascribed simply to the patient's imagination or to the trauma occurring during the surgical procedure. Behrman suggested that the manifestation of causalgia in some patients but not in others may be due to an abnormality in the nerves of individual patients rather than to a peculiarity in the nature of the lesion *per se*.

Differential Diagnosis. Causalgia should be differentiated from local pain due to simple traumatic injury to soft tissue or bone during the extraction procedure. In addition, there is another interesting disease which typically produces referred pain in the posterior portion of the mandible: **subacute thyroiditis**. The etiology of subacute thyroiditis is unknown, although its incidence of occurrence appears to be increasing. The mechanisms for referral of pain to the jaw in this disease is not clear, but has been reported to occur in over 35% of patients with thyroiditis, according to the report by Tolman and his associates. Since patients may seek dental treatment for relief of their symptoms, the possibility of the thyroid condition must be remembered. Treatment of the thyroiditis almost invariably results in subsidence of the jaw pain.

Treatment. The treatment of intraoral causalgia is indeed a difficult one. The injections of procaine, alcohol nerve block, phenol cauterization and surgical curettement of the bone in the involved area have generally proved ineffective. In some instances resection of the nerves in the retrogasserian region has afforded relief. Unfortunately, the typical history in these cases reveals that the patient submits to numerous procedures, but still continues to suffer from the severe pain.

Atypical Facial Pain
(Atypical facial neuralgia, facial causalgia)

Atypical facial pain constitutes a group of conditions in which there is a vague, deep, poorly localized pain in the regions supplied by the fifth and ninth cranial nerves and the second and third cervical nerves. The pain is not associated with trigeminal neuralgia, glossopharyngeal neuralgia, postherpetic neuralgia, or with diseases of the teeth, throat, nose, sinuses, eyes or ears. The distribution of this pain is unanatomic, since it involves portions of the sensory supply of two or more nerves and may cross the midline. This pain, which lacks a trigger zone, is constant and persists for weeks, months or even years. Atypical facial pain occurs in the territory of the trigeminal nerve, but the discomfort is not typical of trigeminal neuralgia. It may be as severe as trigeminal neuralgia, but its pattern and quality are different. The distinction is important for making treatment decisions, because surgery, usually rhizotomy or vascular decompression, is highly effective for trigeminal neuralgia, whereas surgery is not appropriate for atypical facial pain.

Etiology. Atypical facial pain is usually without a specific cause. However, injury of any peripheral or proximal branch of the trigeminal nerve due to facial trauma or basal skull fracture can produce the disorder.

The difficult problem of atypical facial pain has been reviewed by Rushton and his associates, who suggested that designation by this term should be reserved for only those cases in which a definite diagnosis is not possible and in which there is realization that surgical treatment holds little promise of aiding the patients. A large group of the series of patients presented by Rushton and his coworkers were classified as psychogenic with regard to possible origin of the neuralgia, although many other patients showed no reliable cause for their condition.

One condition which must always be considered in the differential diagnosis of any vague or atypical orofacial pain is **Eagle's syndrome**. This syndrome consists of either elongation of the styloid process or ossification of the stylohyoid ligament causing dysphagia, sore throat, otalgia, glossodynia, headache, vague orofacial pain or pain along the distribution of the internal and external carotid arteries.

Probably the most consistent symptom is pharyngeal pain. It is common for the difficulty to arise following tonsillectomy, presumably from fibrous tissue that forms and is stretched and rubbed over the elongated styloid process. However, many cases are not preceded by tonsillectomy, and this is especially true of the form known as the **carotid artery syndrome**,

in which pressure exerted by either a deviant styloid process or an ossified ligament causes impingement on the internal or external carotid arteries between which the styloid process normally lies. This entire problem has been reviewed in detail by Ettinger and Hanson, by Russell, by Sanders and Weiner and by Baddour and his associates.

Treatment. Medical treatment of atypical facial pain is less satisfactory than that of trigeminal neuralgia. Of the non-narcotic drugs, tricyclic antidepressants give best results; phenytoin is of intermediate effectiveness, and carbamazepine is least effective. Any of these may be best in a particular patient.

Horner's Syndrome
(Sympathetic ophthalmoplegia)

Horner's syndrome is a condition characterized by:

- Miosis, or contraction of the pupil of the eye due to paresis of the dilator of the pupil.
- Ptosis, or drooping of the eyelid due to paresis of the smooth muscle elevator of the upper lid.
- Anhidrosis and vasodilatation over the face due to interruption of sudomotor and vasomotor control.

Its chief significance lies in the fact that it indicates the presence of a primary disease. The exact features of the syndrome depend upon the degree of damage of sympathetic pathways to the head and the site of this damage. Thus lesions in the brainstem, chiefly tumors or infections, or in the cervical or high thoracic cord occasionally will produce this syndrome. Preganglionic fibers in the anterior spinal roots to the sympathetic chain in the low cervical and high thoracic area are rather commonly involved by infection, trauma or pressure as by aneurysm or tumor to produce Horner's syndrome. Finally, involvement of the carotid sympathetic plexus by lesions of the gasserian ganglion or an aneurysm of the internal carotid artery may produce the typical facial sweating defect as well as facial pain and sensory loss.

Marcus Gunn Jaw-winking Syndrome
(Trigemino-oculomotor synkinesis)

This interesting condition consists of congenital unilateral ptosis, with rapid elevation of the ptotic eyelid occurring on movement of the mandible to the contralateral side. It is commonly recognized in the infant by the mother when, on breastfeeding her baby, she notices one of its eyelids shoot up, as in the case reported by Smith and Gans. In 1883, Marcus Gunn described a 15-year-old girl with a peculiar type of congenital ptosis that included an associated winking motion of the affected eyelid on movement of the jaw. This synkinetic jaw-winking phenomenon now bears his name.

At least some cases are hereditary, although it is reported that the phenomenon may begin in later life following an injury or disease. From reported cases, it appears that males are affected more frequently than females, and the left upper eyelid is involved more frequently than the right. It is also thought that about 2% of all cases of congenital ptosis are due to this condition.

Marcus Gunn jaw-winking is a form of synkinetic ptosis. An aberrant connection exists between the motor branches of the trigeminal nerve (CN V3) innervating the external pterygoid muscle and the fibers of the superior division of the oculomotor nerve (CN III) that innervate the levator superioris muscle of the upper eyelid.

An interesting condition known as the **Marin Amat syndrome** or **inverted Marcus Gunn phenomenon** is usually seen after peripheral facial paralysis. In this condition, the eye closes automatically when the patient opens his/her mouth forcefully and fully, as in chewing, and tears may flow.

DISEASES OF THE MUSCLES

Diseases of the skeletal muscles of the face and oral cavity occur with sufficient frequency to be of considerable concern to the dentist. Many of these primary diseases manifest a generalized muscular involvement so that facial and oral manifestations constitute only a minor portion of the clinical problem. In other instances, the facial or oral manifestations represent a major feature of the disease, and these may present serious functional problems that must be met and solved. Secondary diseases of muscle are seen with somewhat greater frequency, and they also present difficulties in diagnosis and clinical management.

Little attention was directed to diseases and dysfunctions of the muscular system by the dental profession until recent years, when the physiologic and pathologic function of muscle became an obviously important clinical responsibility. Thus, the specialty practices of orthodontics, prosthodontics and periodontics, among others, are especially allied in their interests in muscle diseases.

Remarkable advancements have been made in recent years in the development and application of new techniques to the study of muscle physiology and pathology. One such technique, electromyography, has found extensive clinical application to dental problems, and though such investigations are still preliminary, the technique offers great promise in our ultimate understanding of some of the clinical problems in dentistry.

There is no satisfactory classification of the various diseases of muscles, owing in part to their obscure etiology in many instances and our often fragmentary knowledge of the disease

Classification of diseases of muscle

I. Primary myopathies, limited to or predominant in muscle
   - Dystrophies
   - Myotonias (dystrophic, congenital, acquired)
   - Hypotonias
   - Myasthenias
   - Myositis (including dermatomyositis and myositis ossificans)
   - Metabolic defects (glycolytic, myoglobinuria)
   - Miscellaneous (amyoplasias, contractures, degenerations)

II. Secondary myopathies, representing muscular reaction to primarily extramuscular disease
- Atrophy (traumatic, neuropathic secondary to metabolic, vascular, nutritional, infectious and toxic processes)
  - Denervation
  - Disuse and fixation
  - Aging and cachexia
- Hypertrophy
  - Developmental
  - Functional
- Endocrine
- Internal environment
  - Chemical
  - Vascular
- Infection
  - Specific (Trichinella, Toxoplasma, coxsackievirus)
  - General (rickettsial, typhoid, pneumococcal pneumonia)
  - Postinfectious asthenia

processes. The classification proposed by Lilienthal, based chiefly on etiology of the diseases, is of practical use even though it has certain disadvantages. In a modified form, it is presented below.

No attempt will be made in this chapter to discuss all diseases of muscles shown in the foregoing classification. Instead, only those conditions which have been reported to present facial or oral manifestations will be considered. Furthermore, specific tumors of muscle and certain infections which may involve muscle are not included in the classification and will not be considered in this section, since they are discussed in other chapters.

DYSTROPHIES

Muscular dystrophy is a primary, progressively degenerative disease of skeletal muscle. The basic disorder lies within the muscle fiber itself, since the muscular nerves and nerve endings at the neuromuscular junction are normal. Actually, a number of different diseases fall within this category, all characterized by:

- Symmetric distribution of muscular atrophy
- Retention of faradic excitability in proportion to the remaining power of contraction
- Intact sensibility and preservation of cutaneous reflexes
- Liability to heredofamilial incidence
- Unknown etiology.

The important forms of muscular dystrophy include:

- Severe generalized familial muscular dystrophy
- Mild restricted muscular dystrophy
- Myotonic dystrophy
- Ophthalmoplegic dystrophy
- Late distal muscular dystrophy.

Only the first two will be discussed here, since they present prominent orofacial findings. Myotonic dystrophy will be discussed under the section on myotonias. Zundel and Tyler have published an excellent review of all the muscular dystrophies.

Severe Generalized Familial Muscular Dystrophy
(Pseudohypertrophic muscular dystrophy of Duchenne)

This disease is best described as a rapidly progressive muscle disease usually beginning in early childhood, presenting strong familial transmission usually through unaffected females, and occurring predominantly in males, with or without pseudohypertrophy. It is the most common form of muscular dystrophy.

Clinical Features. Severe generalized familial muscular dystrophy begins in childhood, usually before the age of six years and rarely after 15 years. The earliest signs are inability to walk or run, the children falling readily, with muscular enlargement and weakness. The muscles of the extremities are generally those first affected, but even the facial muscles may be involved. This muscular enlargement ultimately proceeds to atrophy; however, and the limbs appear flaccid. Atrophy from the onset of the disease is apparent in certain groups of muscles, chiefly those of the pelvis, lumbosacral spine and shoulder girdle. It is this atrophy which is responsible for the postural and ambulatory defects, such as the waddling gait.

The muscles of mastication, facial and ocular muscles, and laryngeal and pharyngeal muscles are usually involved only late in the course of the disease.

Histologic Features. There is gradual disappearance of muscle fibers as the disease progresses, until ultimately no fibers may be recognized, being replaced entirely by connective tissue and fat. Persistent fibers show variation in size in earlier stages of the disease, some being hypertrophic, but others atrophic.

Laboratory Findings. The serum creatine phosphokinase level is elevated in all males affected by this disease and in about 70% of the female carriers as well. It is significant that this CPK elevation occurs prior to the clinical manifestations of the disease in the males.

Treatment. There is no treatment for this disease, and despite modern advances in gene therapy and molecular biology, the disease remains incurable. With proper care and attention, patients have a better quality of life, but most still die by the time they are 30 years of age, usually as a result of cardiopulmonary failure.

Mild Restricted Muscular Dystrophy
(Facioscapulohumeral dystrophy of Landouzy and Dejerine)

Mild restricted muscular dystrophy is a slowly progressive proximal myopathy which primarily involves the muscles of

the shoulder and face and has a weak familial incidence. It frequently presents long remissions and sometimes complete arrest. One variant of this disease is a slowly progressive one without facial weakness.

Etiology. It is an autosomal dominant disease in 70–90% of patients and is sporadic in the rest. One of the causative genes has been localized to chromosome band **4q35**.

Clinical Features. This disease begins at any age, from 2–60 years, although the onset in the majority of cases is in the first two decades of life. Frequency of occurrence is higher in males. Frequently no familial history can be found, but some cases appear to be transmitted as an autosomal dominant trait.

The earliest signs of the condition may be inability to raise the arms above the head and inability to close the eyes even during sleep as a result of weakness of facial muscles. The lips develop a characteristic looseness and protrusion which have been described as 'tapir-lips', a part of the 'myopathic facies', and the patients are unable to whistle or smile. The scapular muscles become atrophic and weak, with subsequent alteration in posture, as do the muscles of the upper arm.

Cardiac abnormalities, including cardiomegaly and tachycardia, are often present, and many patients die of sudden cardiac failure.

Histologic Features. No specific microscopic findings are found in this disease. There is some variation in the size of muscle fibers and moderate infiltration of fiber bundles by connective tissue. Individual fibers ultimately become atrophic.

Treatment. There is no treatment for the disease. Some patients undergo temporary periods of remission or even complete arrest. There may be mild disability. The possibility of cardiac failure is always present, however.

MYOTONIAS

Myotonia is a failure of muscle relaxation after cessation of voluntary contraction. It occurs in three chief forms: dystrophic, congenital, and acquired myotonia, and though each presents the same basic defect, there are sufficient differences between the three types to warrant their separation. Paramyotonia is a disorder related to the other myotonias, but differing from them in several important aspects.

Dystrophic Myotonia

(Myotonic dystrophy, dystrophia myotonica)

Dystrophic myotonia has been described by Adams and his associates as a steadily progressive, familial, distal myopathy with associated weakness of the muscles of the face, jaw and neck, and levators of the eyelids, a tendency for myotonic persistence of contraction in the affected parts, and testicular atrophy. It is inherited as an autosomal dominant characteristic.

Clinical Features. Atrophy of muscles is a characteristic feature of this disease, generally manifested first in the muscles of the hands and forearms. This muscular wasting does not appear usually until the third decade of life, but may be seen earlier, even in childhood.

Alterations in the facial muscles are one of the prominent features of the disease. These consist of ptosis of the eyelids and atrophy of the masseter and sternocleidomastoid muscles. The masseteric atrophy produces a narrowing of the lower half of the face which, with the ptosis and generalized weakness of the facial musculature, gives the patient a characteristic 'myopathic facies' and 'swan neck'. In addition, the muscles of the tongue commonly show myotonia but seldom atrophy. Thus it is obvious that myotonia and atrophy, although frequently associated, are not necessarily related.

Pharyngeal and laryngeal muscles in patients with dystrophic myotonia also exhibit weakness manifested by a weak, monotonous, nasal type of voice and subsequent dysphagia. Recurrent dislocation of the jaw is also reported to be common in this disease.

Other clinical features frequently associated with dystrophic myotonia include testicular atrophy, which is so common as to be considered an integral part of the syndrome; cataracts, even in a high percentage of young patients; hypothyroidism with coldness of extremities, slow pulse and loss of hair; and functional cardiac changes.

Histologic Features. Enlargement of scattered muscle fibers and the presence of centrally placed muscle nuclei in long rows have been described as being characteristic of atrophy. True hypertrophy of some fibers is almost invariably found, as well as isolated fibers which show extreme degenerative changes, including nuclear proliferation, intense basophilic cytoplasmic staining and phagocytosis. In advanced muscular atrophy, fibers appear small, and there may be interstitial fatty infiltration.

Treatment and Prognosis. There is no treatment for this disease. It progresses inevitably over a period of many years, producing disability and ultimately death.

Congenital Myotonia

(Thomsen's disease, myotonia congenita)

Congenital myotonia is an anomaly of muscular contraction in which an inheritance pattern has been established in about 25% of the reported cases. Thus, it is an autosomal dominant trait but with incomplete penetrance in some families. The characteristic feature of the disease is myotonia associated with muscular hypertrophy.

Clinical Features. Congenital myotonia commences early in childhood and may be first noticed because of difficulties in learning to stand and walk. The degree of myotonia varies, but is generally severe and affects all skeletal muscles, especially those of the lower limbs.

Muscular contraction induces severe, painless muscular spasms, actually a delay in relaxation. Electrical or physical stimulation of a muscle produces characteristic prolonged contraction or 'percussion contraction'.

The muscles are large, and patients with this disease are described as presenting a Herculean appearance. The muscles

of the thighs, forearms and shoulders are especially affected, as well as the muscles of the neck and the masseter muscles of the face. The muscles of the tongue are not reported to be affected by the hypertrophy, although they may be involved by the myotonia.

Blinking with strong closure of the eyes will sometimes produce a prolonged contraction of the lids. Spasms of the extraocular muscles may lead to convergent strabismus. Interestingly, a sudden movement such as sneezing often produces a prolonged spasm of the muscles of the face, tongue, larynx, neck and chest, and there may be respiratory embarrassment.

A subjective increase in disability following exposure to cold has been described by many patients with this disease.

Histologic Features. Muscle biopsy reveals no alterations from normal except for hypertrophy of all muscle fibers.

Treatment and Prognosis. There is no specific treatment of the disease, but the prognosis is good. In fact, some regression of the disease occurs in occasional patients.

Acquired Myotonia

Acquired myotonia, as described here, refers to spasms of muscles, although such spasms are generally considered to be more intense than those occurring in typical myotonia. Nevertheless, the similarity in physiologic response of muscle in true myotonia and in muscular spasm justifies its inclusion here as a form of myotonia. If these spasms are intermittent, the condition is called **clonus** (myoclonic contractions); if constant, the term **trismus** is applied (myotonic contractions). All gradations in the degree of spasmodic contraction occur, ranging from slight muscular twitches to severe, painful, prolonged muscular cramps.

Spasm involving the facial muscles is seen in a variety of situations such as epilepsy, diseases of the CNS and tetany. Such spasms on a local basis are far more common; however, and these occur in a variety of conditions such as pericoronal infection, especially of third molars; infectious myositis; and hysteria (hysterical trismus).

The spasms, which are usually painful, may be transitory or may persist for a period of several days or until the cause of the disease is treated.

Hemifacial Spasm

(Facial myoclonus, facial dystonia)

Hemifacial spasm is a disease characterized by repeated, rapid, painless, irregular, nonrhythmic, uncontrollable, unilateral contractures of the facial muscles in adults, chiefly women. The cause of this condition is unknown, but appears to be a peripheral facial nerve lesion. Some studies indicate that there may be compression of the facial nerve in the facial canal adjacent to the stylomastoid foramen.

Clinical Features. Hemifacial spasm usually begins in the periorbital muscles, but soon spreads to the entire half-face. It is first manifested as a brief transitory twitching, but may progress to sustained spasms. These spasms are often triggered by fatigue, tension or facial activity and are of brief duration, usually only a few seconds. Interestingly, they may continue through sleep and even awaken the patient.

In cases of long-standing hemifacial spasm, mild facial contracture may occur, as well as lid closure and lip pursing.

Hemifacial spasm must be differentiated from emotional tics and focal convulsive seizures, but this is usually not difficult.

Treatment and Prognosis. There is no treatment for this disease, but decompression of the facial nerve in its canal has offered relief in some cases. It is a progressive, nonfatal illness. It almost always responds favorably to treatment.

Periodic Paralyses

(Paramyotonia)

The heterogeneous group of muscle diseases known as periodic paralyses (PP) is characterized by episodes of flaccid muscle weakness occurring at irregular intervals. Most of the conditions are hereditary and are more episodic than periodic. They can be divided conveniently into primary and secondary disorders. General characteristics of primary PP include the following:

- They are hereditary
- Most are associated with alteration in serum potassium levels
- Myotonia sometimes coexists
- Both myotonia and PP result from defective ion channels.

Clinical Features. Paramyotonia is manifested by cramping, stiffness and weakness of the muscles of the face and neck, fingers and hands upon exposure to cold. The eyelids are closed, and the face assumes a mask-like appearance. The tongue may exhibit a similar cramping after drinking cold liquids, and the speech becomes slurred. In many cases, myotonia of the tongue may be induced by percussion, although this is not true of other muscles. Although the muscular cramping may disappear within an hour, the weakness may persist for several days.

Histologic Features. Reports of microscopic study of muscles from patients with paramyotonia are almost entirely lacking. Information available indicates that there are no significant histologic changes in muscle fibers.

Treatment and Prognosis. There is no specific treatment for paramyotonia, but the prognosis is excellent with frequent improvement during adult life.

Hypotonias

Hypotonia is a reduction or complete absence of tonus in muscles. There are many causes of hypotonia and delay in motor development in infants, so that this condition should be regarded only as a symptom which may be found in many diseases. Certain congenital diseases may result in hypotonia, such as:

- Diseases of the central nervous system (e.g. atonic diplegia)
- Lipoid and glycogen storage diseases (e.g. Tay-Sachs disease)

- Mongolism
- Cretinism
- Achondrodysplasia.

Hypotonia also may result from strictly neuromuscular diseases, however, including:

- Infantile muscular atrophy
- Infantile muscular dystrophy
- Amyotonia congenita
- Congenital nonprogressive myopathy
- Neonatal myasthenia gravis.

Many of these latter diseases, all occurring in infancy, have certain features in common, including hypotonia, reduced tendon reflexes and muscular weakness. Because of the difficulty encountered in their separation, the term 'floppy infant syndrome' has sometimes been applied to describe the chief clinical manifestation of these unfortunate children. As the term would imply, these infants have a generalized weakness so that their bodies hang limply with inability to sit, stand or walk. The hypotonia involves the muscles of the face and tongue as well, but these findings are secondary to the generalized condition. For this reason this particular group of diseases warrants no detailed consideration.

MYASTHENIAS

Myasthenia is an abnormal weakness and fatigue in muscle following activity. The myasthenias constitute a group of diseases in which there is a basic disorder of muscle excitability and contractility and include myasthenia gravis; familial periodic paralysis; and aldosteronism. The rarity of the latter two diseases and their lack of clinical manifestations of significant interest to the dentist preclude their discussion here.

Myasthenia Gravis

Myasthenia gravis (MG) is an acquired autoimmune disorder characterized clinically by weakness of skeletal muscles and fatigability on exertion. Thomas Willis reported the first clinical description in 1672.

Etiology. Myasthenia gravis is idiopathic in most patients but autoimmunity is also implicated to be responsible. The antibodies in MG are directed toward the acetylcholine receptor (AChR) at the neuromuscular junction (NMJ) of skeletal muscles.

Clinical Features. Myasthenia gravis occurs chiefly in adults in the middle-age group, with a predilection for women, and is characterized by a rapidly developing weakness in voluntary muscles following even minor activity. Of interest to the dentist is the fact that the muscles of mastication and facial expression are involved by this disease, frequently before any other muscle group. The patient's chief complaints may be difficulty in mastication and in deglutition, and dropping of the jaw. Speech is often slow and slurred. Disturbances in taste sensation occur in some patients.

Diplopia and ptosis, along with dropping of the face, lend a sorrowful appearance to the patient. The neck muscles may be so weak that the head cannot be held up without support. Patients with this disease rapidly become exhausted, lose weight, become further weakened and may eventually become bedfast. Death frequently occurs from respiratory failure.

The clinical course of patients with myasthenia gravis is extremely variable. Some patients enter an acute exacerbation of their disease and succumb very shortly, but others live for many years with only the slightest evidence of disability. On this basis, two forms of the disease are now recognized: one, a steadily progressive type; the other, a remitting, relapsing type.

Histologic Features. There are usually no demonstrable changes in the muscle. Occasionally, focal collections of small lymphocytes, or 'lymphorrhages', are found surrounding small blood vessels in the interstitial tissue of affected muscles. In a few cases, foci of atrophy or necrosis of muscle fibers have been described. There are no pathognomonic features, however.

Treatment. It is interesting that the drug of choice used in treatment of myasthenia gravis provides such remarkable relief of symptoms in such a short time that it is commonly used as the diagnostic test for the disease. Physostigmine, an anticholinesterase, administered intramuscularly, improves the strength of the affected muscles in a matter of minutes, although the remission is only temporary. No 'cure' for the disease is known, even though the prognosis is good in the relapsing type.

MYOSITIS

Myositis refers to an inflammation of muscle tissue and is entirely nonspecific, since a great many bacterial, viral, fungal or parasitic infections, as well as certain physical and chemical injuries, may give rise to the condition. In addition, a variety of diseases of unknown etiology may produce or at least be associated with myositis. Since the various diseases resulting in myositis are discussed elsewhere in this text, only four specific forms of myositis will be considered here: dermatomyositis; myositis ossificans, generalized and traumatic; proliferative myositis; and focal myositis.

Dermatomyositis

(Juvenile dermatomyositis, childhood dermatomyositis, polymyositis)

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) with characteristic cutaneous findings. Four of the five criteria are related to the muscle disease, and are as follows: progressive proximal symmetrical weakness, elevated muscle enzymes, an abnormal finding on electromyograph, and an abnormal finding on muscle biopsy. The fifth criterion is compatible cutaneous disease.

Bohan and Peter (1975) suggested five subsets of myositis, as follows: dermatomyositis, polymyositis, myositis with malignancy, childhood dermatomyositis/polymyositis, and myositis overlapping with another collagen-vascular disorder.

Etiology. The cause of DM is unknown. The pathogenesis of the cutaneous disease is poorly understood. Recent

The cause of DM is unknown; however, the following factors have been implicated:

- A genetic predisposition may exist. DM rarely occurs in multiple family members, but it may be linked to certain human leukocyte antigen (HLA) types (e.g. DR3, DR5, DR7).
- Immunological abnormalities are common in patients with DM. Patients frequently have circulating autoantibodies. Abnormal T-cell activity may be involved in the pathogenesis of both the skin and the muscle disease. In addition, family members may have other diseases associated with autoimmunity.
- Autoantibodies to nuclear antigens (ANA) and cytoplasmic (i.e. antitransfer RNA synthetases) antigens may be present. While their presence may help to define subtypes of DM and PM, their role in pathogenesis is uncertain.
- Infectious agents, including viruses, e.g. coxsackievirus, echovirus, human T-cell lymphotrophic virus type I (HTLV-I), HIV and Toxoplasma and Borrelia species, have been suggested as possible triggers of the disease.

Several cases of drug-induced disease have been reported. DM-like skin changes have been reported with hydroxyurea in patients with chronic myelogenous leukemia or essential thrombocytosis. Other agents that may trigger the disease include penicillamine, statin drugs, quinidine, and phenylbutazone.

studies of the pathogenesis of the myopathy have been controversial. Some suggest that the myopathy in DM and PM is pathogenetically different. DM is probably caused by complement-mediated (terminal attack complex) vascular inflammation, while PM is caused by the direct cytotoxic effect of $CD8^+$ lymphocytes on muscle. However, other studies of cytokines suggest that some of the inflammatory processes may be similar.

Clinical Features. Dermatomyositis may occur in patients of any age from very young children to elderly adults, but the majority of cases occur in the fifth decade of life. There is no sex predilection in its occurrence.

The more acute form of the disease, seen more commonly in children, begins with an erythematous skin eruption, edema, tenderness, swelling and weakness of the proximal muscles of the limbs. Accompanying these manifestations are fever and leukocytosis. The skin lesions frequently calcify and form calcium carbonate nodules with a foreign body reaction. This is known as calcinosis cutis, whereas the term **calcinosis universalis** is applied when these calcified masses are found generalized throughout the soft tissues.

The chronic form of the disease is similar, but may not show dermal involvement (polymyositis only), although all gradations are present between the two extremes. In some cases a long interval may supervene between the appearance of the dermal lesions and the muscle dysfunction. In addition, Raynaud's phenomenon or paroxysmal digital cyanosis may be an early manifestation. The muscular stiffness and weakness are often symmetric in distribution.

The cutaneous lesions usually consist of a diffuse erythema with desquamation, although other types of rashes have been described. This rash is most frequently seen on the face, eyelids, ears, anterior neck and overlying articulations.

Oral Manifestations. The oral lesions, consisting of diffuse stomatitis and pharyngitis, are extremely common. Telangiectatic lesions of the vermilion border of the lips and cheeks may also occur. In addition, involvement of the muscles of the jaws, tongue and pharynx may pose problems in eating and phonation. A detailed discussion of the oral and facial manifestations of dermatomyositis has been presented by Sanger and Kirby.

Histologic Features. The muscle fibers in dermatomyositis exhibit widespread degeneration and hyalinization. In advanced cases the muscle fibers disappear, leaving only the fibrous stroma. Many fibers show vacuolization, granulation and fragmentation with phagocytosis of disintegrating fibers. Diffuse leukocytic infiltration is also frequently pronounced.

Laboratory Findings. Patients with this disease sometimes manifest a mild anemia or leukocytosis. In addition, creatinuria is a constant finding, as well as elevated levels of serum transaminase and aldolase.

Treatment. There is no specific treatment for the disease, although symptomatic treatment may be of considerable benefit to the patient. In the more acute forms of the disease, death may occur rapidly. In other cases there may be recovery, sometimes with a residual disability.

HETEROTOPIC OSSIFICATION

The term heterotopic ossification (HO) describes bone formation at an abnormal anatomical site, usually in soft tissue. Stover et al (1975) classify HO into the following three types: myositis ossificans progressiva; traumatic myositis ossificans; and neurogenic heterotopic ossification.

Myositis Ossificans Progressiva

Generalized myositis ossificans is a disease of unknown etiology which affects the interstitial tissues of muscles as well as tendons, ligaments, fascia, aponeuroses and even the skin. Basically, masses of fibrous tissue and bone occur within these structures with secondary atrophy and destruction of the associated muscles due to pressure and inactivity. The differential diagnosis for this condition includes calcinosis universalis, which usually occurs in relation to scleroderma or polymyositis. In calcinosis, calcium deposition is noted in the skin, subcutaneous tissues, and connective tissue sheaths around muscles, as opposed to within muscles.

Clinical Features. Generalized myositis ossificans usually occurs in young children or adolescents with the development

of soft, fluctuant or firm nodular swellings anywhere on the body but frequently on the neck or back. These masses may develop spontaneously or after minor trauma. They vary considerably in size and shape and may disappear or become transformed into bony nodules. These are usually painless and are covered by a reddened skin which may ulcerate as a result of pressure from the underlying mass.

Any skeletal muscle may be affected, but those of the trunk and proximal limbs are most frequently involved. Interestingly, certain muscles tend to escape involvement: the tongue, larynx, diaphragm, and perineal muscles. Ultimately, entire groups of muscles become transformed into bone with resulting limitation of movement. The masseter muscle is often involved so that fixation of the jaw occurs. The patient becomes transformed into a rigid organism sometimes encountered in circuses as the 'petrified man'.

The differential diagnosis for this condition includes calcinosis universalis, which usually occurs in relation to scleroderma or polymyositis. In calcinosis, calcium deposition is noted in the skin, subcutaneous tissues, and connective tissue sheaths around muscles, as opposed to within muscles.

Histologic Features. The muscle in this disease is gradually replaced by connective tissue which undergoes osteoid formation and subsequently ossification. In some cases cartilage formation may also be evident. Characteristically, intact muscle fibers may be found within the bony tissue.

Treatment and Prognosis. There is no treatment for the disease. It is progressive until death results, usually from a pulmonary infection secondary to the respiratory difficulties arising from involvement of the intercostal muscles.

Traumatic Myositis Ossificans

In this condition, a painful area develops in muscle or soft tissue following a single blow to the area, a muscle tear, or repeated minor trauma. The painful area gradually develops masses of cartilaginous consistency, and within four to seven weeks, a solid mass of bone can be felt. Common sites include the pectoralis major, biceps, and thigh muscles. A nontraumatic type of myositis ossificans also may exist.

The exact mechanism of the ossification is not entirely clear. Several possible theories have been reviewed by Carey:

- Traumatization of the periosteum of an adjacent bone with the displacement of osteoblasts into the muscle and subsequent formation of bone.
- Activation of periosteal implants already present in muscle by trauma or hemorrhage.
- Metaplasia of the pluripotential intermuscular connective tissue into bone.
- Metaplasia of fibrocartilage, a normal constituent of many muscle tendons, into bone.

It is of significance that the attempts of Tweeddale and his associates to induce myositis ossificans experimentally in animals by traumatic injury to muscle and periosteum and injection of blood into muscle have met with uniform failure. Therefore some unknown factors favoring ossification must also be present, particularly since so few muscle injuries actually do ossify.

It is recognized that this typical ossifying lesion can occur in superficial tissue away from muscle. This has been discussed by Kwittken and Branche, who have proposed the term 'fasciitis ossificans' for such cases.

Clinical Features. Myositis ossificans developing after a single acute traumatic injury usually manifests as a firm, painful mass in the injured muscle within one to four weeks. In some cases motion is limited by the lesion. Chronic cases of myositis ossificans are usually asymptomatic and may be discovered accidentally. In some cases there is a mild discomfort associated with a progressive limitation of motion.

Oral Manifestations. Myositis ossificans involving the muscles of the face, particularly the masseter and temporal muscles, has been reported on numerous occasions, usually following a single acute traumatic injury. Goodsell, as well as Plezia and his associates, have reviewed the literature dealing with myositis ossificans of the masseter muscle and found that, in most reported cases, growth of the calcified lesions has been rapid, maximum size obtained, and then the lesion remained static or even diminished in size. Some difficulty in opening the mouth may be experienced by patients with myositis ossificans of the masseter muscle.

Radiographic Features. The radiographic pattern of myositis ossificans may appear either as a feathery type of calcification in muscle, following ossification of a hematoma which dissected along muscle bundles, or as a solitary irregular calcified mass occurring in a simple hematoma. The radiopaque calcification may be first seen within two to three weeks of the traumatic experience and show a progressive increase in radiodensity (Fig. 20-3).

Histologic Features. Traumatic myositis ossificans exhibits varying stages from hemorrhage, degeneration of muscle and connective tissue hyperplasia to chondrification and, ossification. The osteoid and bone trabeculae formed often

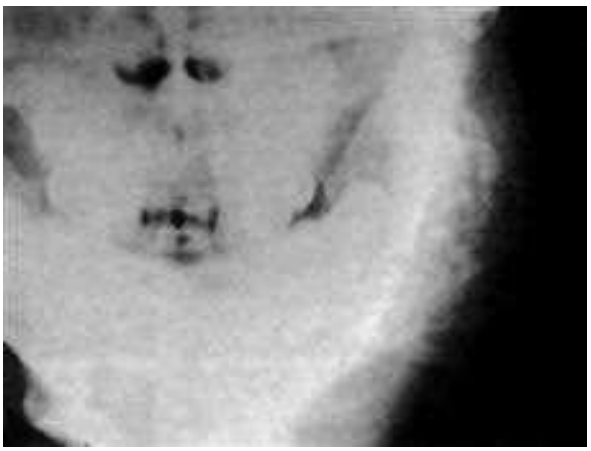


Figure 20-3. Traumatic myositis ossificans involving masseter muscle.

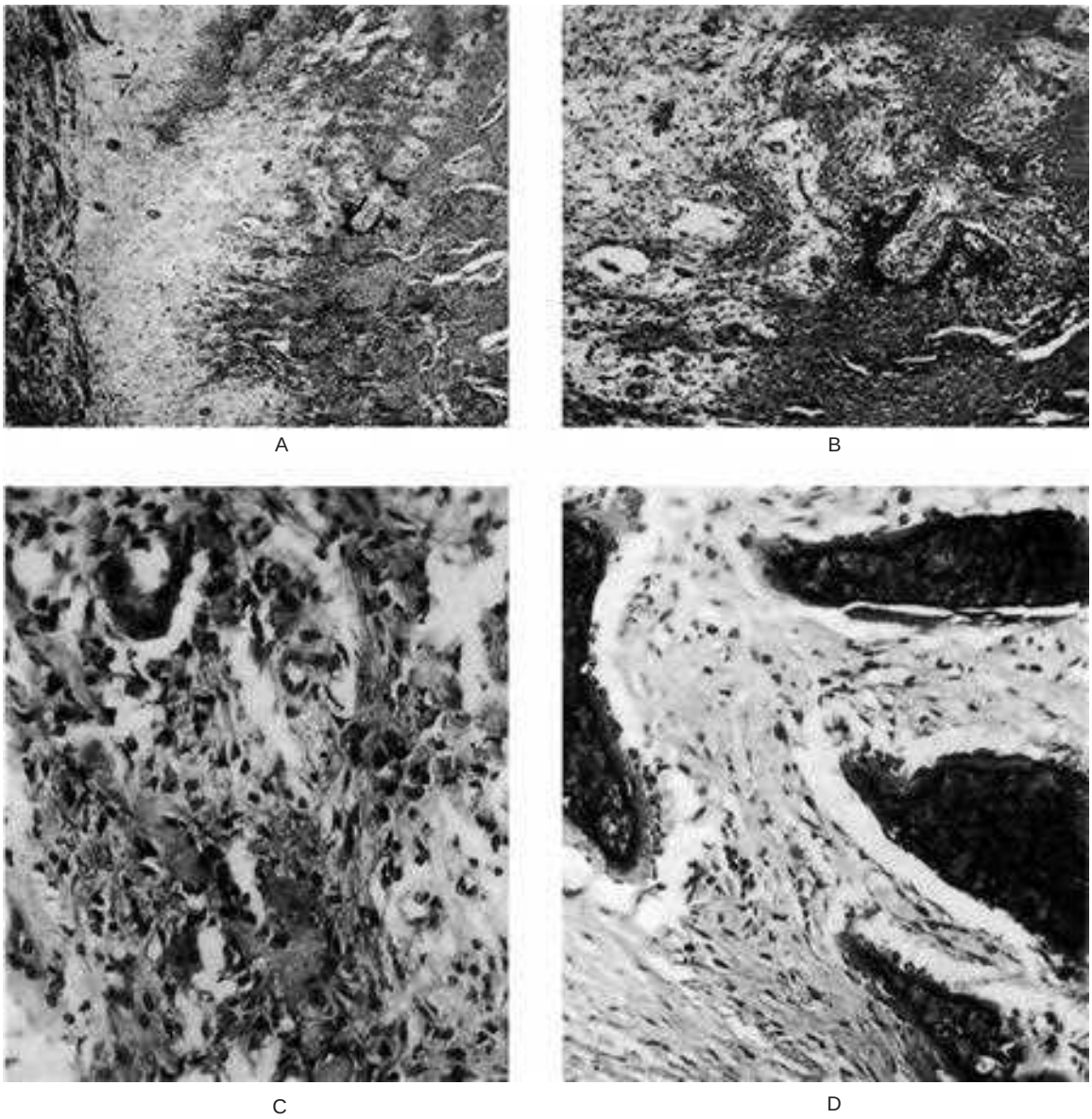


Figure 20-4. Myositis ossificans.
The characteristic features of connective tissue hyperplasia, myxomatous tissue, osteoid and bone are well demonstrated *(Courtesy of Dr William G Sprague).*

trap viable muscle fibers, but these may ultimately disappear. The trabecular pattern is often extremely bizarre, and with the cartilage and myxomatous tissue present may resemble callus formation. The more mature tissue is usually found on the periphery of the lesion.

The rapidly proliferating bony tissue often produces a sufficiently atypical microscopic picture to confuse the lesion with osteosarcoma, and this mistake has been made on numerous occasions in the past (Fig. 20-4). Ackerman carefully described the problems in microscopic differential diagnosis between these two diseases. The term 'pseudomalignant myositis ossificans' has even been applied by Lagier and Cox to emphasize their similarities. Although some reports in the literature have described transformation of myositis ossificans into osteosarcoma, this probably does not occur.

Treatment and Prognosis. Treatment of myositis ossificans is essentially surgical excision. Recurrence has been reported in some cases, but this is not characteristic. The prognosis is good, since the lesion is a localized, inflammatory one.

Neurogenic Heterotopic Ossification

This condition is the one that comes to mind when the generic phrase heterotopic ossification is used. In 1918, Dejerine and Ceilier first described heterotopic ossification in patients with spinal cord injury (SCI) from the First World War. Now it is recognized as a fairly common sequela of SCI, especially after traumatic cord injury. The condition also has been described with lesser frequency in other severe neurologic disorders (e.g. closed head injuries [CHI], stroke, encephalitis, polio,

tetanus, tabes dorsalis, syringomyelia, anoxic encephalopathy), as well as following severe burns.

PROLIFERATIVE MYOSITIS

Proliferative myositis has been defined by Enzinger and Dulcey as a pseudosarcomatous process of muscle characterized by an ill-defined proliferation of basophilic giant cells and fibroblasts chiefly involving the perimysium, epimysium and neighboring fascia. It is sometimes mistaken for a sarcoma because of its rapidity of growth, and histologically, its cellularity and the presence of giant cells. While mechanical trauma may play a role in the development of proliferative myositis, there may be other causes as well. It was first described by Kern in 1960.

Clinical Features. Patients afflicted by this condition have ranged in age from the early 20s to the early 80s, with a median age of 50 years. There is a slight predilection for occurrence in males. The lesion is manifested as a firm solitary nodule that is deep-seated and not attached to overlying skin. It grows rapidly but is seldom tender or painful. Four of the 33 cases reported by Enzinger and Dulcey occurred in the head and neck area.

Histologic Features. Proliferative myositis is characterized by a poorly demarcated fibroblastic proliferation involving the epimysium, perimysium, and endomysium and by the presence of large, basophilic giant cells resembling ganglion cells or rhabdomyoblasts. The process affects primarily stromal tissue and leaves muscle fibers virtually uninvolved. There is never complete replacement of muscle tissue over a large circumscribed area as in nodular fasciitis or myositis ossificans, from which proliferative myositis must be differentiated. It must also be separated from proliferative fasciitis, described by Chung and Enzinger, which is very similar to proliferative myositis, especially microscopically, except that the lesion is superficial and does not involve muscle.

Treatment. Proliferative myositis is treated by simple local excision and has no tendency to recur.

Focal Myositis

Focal myositis is a benign inflammatory pseudotumor of skeletal muscle first described by Heffner and his associates in 1977 as a new and distinct clinicopathologic entity. The actual etiology is unknown but, even though a history of trauma is absent in most cases, it is speculated that a subclinical injury, such as a muscle tear, might initiate the condition.

Clinical Features. Focal myositis presents as a rapidly enlarging mass within a single skeletal muscle. The most common sites reported are the lower leg, thorax, abdomen, and forearm; however, involvement of perioral musculature and submandibular and buccal mucosa has been reported by Ellis and Brannon.

There is no apparent gender predilection and the age range has been from 10 to over 65 years of age, with a mean of nearly 40 years of age. While lesions have a duration of only a few weeks, some lesions are present a year or longer. Some cases are asymptomatic; others are characterized by a dull, aching pain. There are no other local or systemic manifestations of disease present.

Histologic Features. There are microscopic changes in random muscle fibers, rather than grouped bundles, consisting of atrophy, hypertrophy, necrosis with phagocytosis, and regeneration. Lymphocytic infiltration is usually present in the interstitial tissue, as is an increase in fibrous connective tissue in endomysial and perimysial locations. It should be stressed that a careful consideration of both clinical and histologic findings is essential in order to establish a definitive diagnosis of focal myositis.

Differential Diagnosis. A variety of conditions, especially from the clinical aspect, must be considered in the differential diagnosis. These include a benign or malignant neoplasm within muscle, nodular fasciitis, proliferative myositis, myositis ossificans, polymyositis, and in the oral region, a salivary gland lesion.

Treatment. The lesion should be excised; it does not recur.

MISCELLANEOUS MYOPATHIES

Congenital Facial Diplegia
(Möbius syndrome)

Congenital facial diplegia is a nonfamilial deficient development of cranial muscles consisting of facial diplegia with bilateral paralysis of the ocular muscles, particularly the abducens. Although von Graefe described a case of congenital facial diplegia in 1880, the syndrome was reviewed and defined further by Möbius in 1888 and 1892. Because of these contributions, Möbius is now the eponym used to describe the syndrome. Möbius syndrome is due, in part, to loss of function of motor cranial nerves.

Etiology. Numerous theories exist concerning the primary underlying pathogenesis. Möbius believed that the condition was degenerative and involved the nuclei of the affected nerves. Some authors suggest that the underlying problem is congenital hypoplasia or agenesis of the cranial nerve nuclei. Approximately 2% of cases appear to have a genetic basis. Theories of vascular etiologies propose the disruption of flow in the basilar artery or premature regression of the primitive trigeminal arteries. A second vascular theory is that of subclavian artery supply disruption sequence, which also involves an interruption of embryonic blood supply. Simultaneous occurrence of limb malformations with cranial nerve dysfunction suggests a disruption of normal morphogenesis during a critical period in the development of the embryonic structures of these regions, most likely from four to seven weeks of gestation.

Clinical Features. Congenital facial diplegia is usually manifested in infancy during the first few days of life by failure to close the eyes during sleep. Because of the partial or complete facial paralysis, the infant exhibits no change in facial expression even when crying or laughing. The

prominent lips are often everted, and the mouth may remain partially opened.

There is difficulty in mastication; saliva frequently drools from the corners of the mouth, and speech is severely impaired.

The majority of patients have other associated congenital deformities, including external ophthalmoplegia, deformity of the external ears, deafness, defects of the pectoral muscles, paresis of the tongue, soft palate or jaw muscles, clubfoot, mental defects and epilepsy.

Histologic Features. There are no conclusive microscopic studies of muscle in patients with congenital facial diplegia.

Treatment. There is no treatment for the disease, but the prognosis appears to be good, barring complications.

Atrophy of Muscle

Atrophy of muscle refers to a decrease in the size of individual muscle fibers which were once normal. The condition is entirely nonspecific, since it occurs in many situations, some of which have been previously described. A partial listing of some of the recognized causes of muscle atrophy is given below:

1. Disuse and fixation
2. Aging and cachexia
3. Denervation
4. Muscular dystrophies
5. Nutritional disturbances
6. Infections and toxins
7. Muscular hypotonias
8. Metabolic disturbances
9. Vascular changes.

Atrophy of muscle has been confused occasionally with aplasia or agenesis of muscles. Thus, some diseases are a result of muscular aplasia, or actually hypoplasia, rather than an actual decrease in size of normal fibers. One form of muscle atrophy, facial hemiatrophy (q.v.), has been discussed in Chapter 1 on Developmental Disturbances of Oral and Paraoral Structures.

Hypertrophy of Muscle

Hypertrophy of muscle refers to an increase in size of individual muscle fibers. This should be separated from pseudohypertrophy, in which the overall increase in the size of a muscle is due to an increase in interstitial connective tissue.

The causes of muscular hypertrophy are also nonspecific and occur in a variety of situations listed as:

1. Developmental defects
2. Functional disturbances
3. Inflammations and infections
4. Metabolic changes
5. Neoplasms.

Two forms of muscular hypertrophy are of interest to the dentist: macroglossia, which has been discussed previously in Chapter 1 on Developmental Disturbances of Oral and Paraoral Structures; and hypertrophy of the masseter muscle.

Masseteric hypertrophy occurs usually in two situations: congenital facial hemihypertrophy (q.v.); and functional hypertrophy as a result of unusual muscle function through habit or necessity after certain surgical procedures involving the jaws. This condition has been reviewed by Bloem and van Hoof.

Specific Tumors of Muscles. Those tumors derived from muscle tissue are discussed in Chapter 2 on Benign and Malignant Tumors of the Oral Cavity.

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SECTION VI

Forensic Odontology

SECTION OUTLINE

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CHAPTER 21

Forensic Odontology

■ ASHITH B ACHARYA AND B SIVAPATHASUNDHARAM

CHAPTER OUTLINE

The word forensic, states Clark, is derived from the Latin *forensis,* which means 'before the forum'. According to Jones, in ancient Rome the forum was a public square where trials and debates took place and consequently served as a court of law. Odontology refers to the study of teeth, and in effect denotes dentistry. Forensic odontology, therefore, has been defined by the Fédération Dentaire Internationale (FDI) as 'that branch of dentistry which, in the interest of justice, deals with the proper handling and examination of dental evidence, and with the proper evaluation and presentation of dental findings'. It primarily deals with identification, based on recognition of unique features present in an individual's dental structures. Forensic dentistry plays a major role in identification in man-made or natural disasters—events which result in multiple fatalities that may not be identifiable through conventional methods such as visual recognition or even fingerprints. According to Harvey, the earliest known example of identification by dental means dates backs to 66 A.D. There have been numerous instances over the last two millennia in which dental remains played a major role in identification of deceased individuals. Elaborate dental records including radiographs and spare crowns identified the body of Adolph Hitler, probably the most publicized case of dental identification. In addition to postmortem identification, dental evidence can be crucial in crime investigation as in, for example, bite mark investigation and determination of whether an individual is a juvenile or an adult.

In the last half-century, forensic odontology has made great strides and has evolved as a separate specialty. It relies on sound knowledge of the teeth and jaws possessed by dentists and incorporate dental anatomy, histology, radiography, pathology, and dental materials.

Forensic odontologists delve into:

- Identifying unknown human remains through comparison of postmortem dental evidence with dental records of the presumed deceased.
- Assisting at the scene of a mass disaster and in the victims' identification.
- Eliciting the ethnicity/population affinity and assisting in building up a picture of lifestyle and diet of skeletal remains at forensic and archeological sites.
- Assessing the sex of skeletonized remains.
- Age estimation of both the living and deceased.
- Analysis and identification of bite marks found on human tissue, animal tissue, and inanimate objects/foodstuffs.
- Presenting evidence in court as expert witnesses.

PERSONAL IDENTIFICATION

Identification is the establishment of a person's individuality. Proper identification of the dead is required both for legal and humanitarian reasons. It may help in the settlement of property and insurance, facilitate remarriage of a surviving spouse, and allow the cremation or burial of the body, according to appropriate religious and cultural customs.

Traditional methods of identification have included visually recognizing the body, and personal property such as clothing, jewelry and the like. These methods, however, are not very reliable in establishing the identity. Visually identifying a body

that is burned or decomposed is not only unreliable but also can be a very traumatic experience for relatives and friends. The more appropriate approach is for forensic experts to analyze physical features present in the body, thus enabling a scientific means to identification.

In general, physical features may be inherited or acquired. While inherited features include characteristics such as hair color, height, and dental features such as Carabelli's trait, among others, acquired features may be surgical scars, previous fractures, or dental restorations. Physical features however are prone to change over time. Epidermal ridges on the fingers (that produce fingerprints) are exceptions but, like other soft tissue, undergo postmortem change.

Dental hard tissues gain importance in identification based on the condition of the human remains. Teeth are one of the strongest structures in the body, and are usually resistant to postmortem decomposition. Moreover, most materials used by the dentist for restoring and replacing teeth are also resistant to postmortem changes. Therefore, the use of dental evidence is the method of choice in establishing identity of badly burned, traumatized, decomposed, and skeletonized remains.

BASIS FOR DENTAL IDENTIFICATION

The basis for dental identification is the theory that human dentition is never the same in any two individuals. In a much cited work, Keiser-Nielsen has assessed the 'uniqueness' of teeth mathematically. The morphology and arrangement of teeth vary from person-to-person. Although teeth are relatively resistant to environmental insults after death, during life they are susceptible to physiologic and pathologic changes. As a result, teeth may have been restored. Those teeth that are beyond restoration may have been extracted and, thus, missing from the mouth. The number of combinations 16 missing teeth can produce is approximately 60 crore (600 million). Sixteen filled teeth produce a similar combination. Four missing and four filled teeth in a mouth combined can produce more than 70 crore combinations (700 million combinations). All teeth have five surfaces. If, instead of considering the whole tooth, the surfaces were taken individually, the variations produced would be astronomic. In fact, Fellingham and coworkers have calculated that there are 1.8×10^{19} possible combinations of 32 teeth being intact, decayed, missing or restored. Hence, dental identity has been defined by Acharya and Taylor as "the total of all characteristics of the teeth and their associated structures which, while not individually unique, when considered together provide a unique totality".

DENTAL IDENTIFICATION PROCEDURES

There are essentially two forms of dental identification: the first known as comparative identification, attempts conclusive identification by comparing the dead individual's teeth with dental records of the presumed individual. This is possible when some clue (through circumstantial evidence) exists about the possible identity of the deceased. The second, reconstructive identification or dental profiling, attempts to elicit the population affinity or race, sex, age, and occupation of the dead individual. This is undertaken when virtually no clue exists about the identity of the decedent.

COMPARATIVE DENTAL IDENTIFICATION

The circumstances of death may give adequate information of the possible identity of the decedent. For example in a car-crash, the licence plate gives an indication of the name and address of the driver who died. Using this information, the family is traced through whom the dentist who treated the deceased. Scientific methods of identification are then employed to confirm the identity of the dead individual from his or her teeth. Comparative dental identification is the conventional method of postmortem dental identification, and includes four steps, namely:

- Oral autopsy
- Obtaining dental records
- Comparing post- and antemortem dental data
- Writing a report and drawing conclusion.

ORAL AUTOPSY

Autopsy, also known as necropsy or postmortem examination, involves examining the deceased usually with dissection to expose the organs to determine the cause of death. Autopsy has a systematic protocol starting with critical examination of the external features of the body such as gender, ethnicity, build, wounds, scars, tattoos, and body piercing. Photographs, radiographs, fingerprints, fingernail scrapings, hair sample may be obtained, as necessary.

Oral examination is ideally an essential part of the postmortem examination (Fig. 21-1). The forensic dentist who conducts oral autopsy should have adequate knowledge about common postmortem findings such as rigor mortis, livor mortis, decomposition and postmortem artefacts. Rigor mortis may render the jaws rigid and the use of mouth-gags, trismus screws, or intraoral myotomy is essential for jaw separation. In cases of incinerated remains, additional challenges are faced—since teeth may be brittle following exposure to prolonged heat, they need to be reinforced with cyanoacrylate glue prior to examination. According to Griffiths and Bellamy, access for radiography in incinerated bodies can be obtained by removing the tongue and contents of the floor of the mouth in a 'tunneling' fashion from beneath the chin. Although oral examination may be challenging at times owing to certain postmortem alterations, the status of each tooth (whether visibly intact, carious/diseased, restored or missing) should be carefully noted. A thorough examination of soft tissue injuries, para-oral hard tissue fractures, and presence of foreign bodies is undertaken and samples of hard and soft tissues may be obtained for further investigations. All information pertaining to the body must be entered into the modified Interpol postmortem dental odontogram (Fig. 21-2).

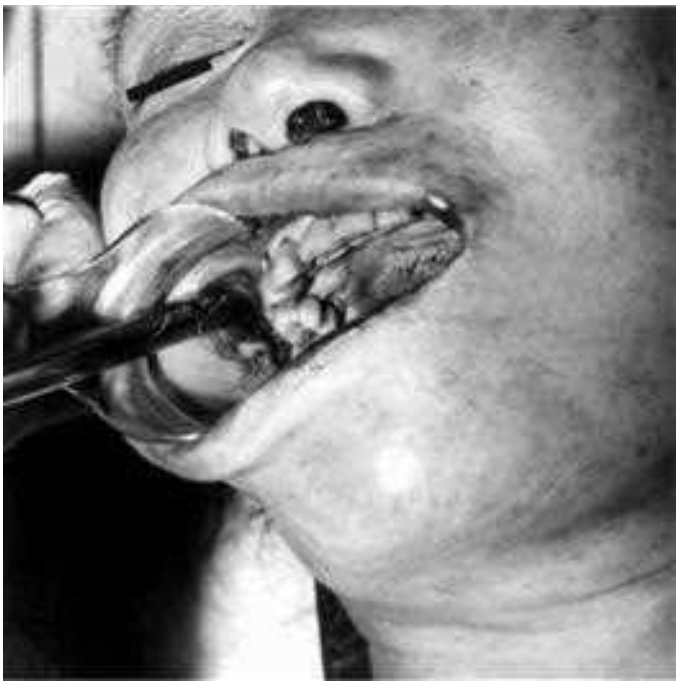


Figure 21-1: Postmortem dental examination must be thorough and should include a detailed status of the dentition, including whether the teeth are intact, decayed, restored or missing.
(Reprinted from Nakayama Y et al. Forced oral opening for cadavers with rigor mortis: two approaches for the myotomy on the temporal muscles. Forensic Sci Int 2001;118:37–42, with permission from Elsevier).

OBTAINING DENTAL RECORDS

Dental records contain information of treatment undergone and dental status of a person during his/her lifetime, and constitute the antemortem dental data. Dayal and colleagues state that dental records may be obtained from the treating dentist or hospital records. Whenever possible, the original record should be examined. Such records may be in the form of dental charts, radiographs, casts and/or photographs. It is likely that multiple dentists may have treated an individual. Hence, the contents of all available dental records should be transcribed onto the modified Interpol antemortem odontogram (Fig. 21-3).

COMPARING POST- AND ANTEMORTEM DENTAL DATA

Following postmortem examination and transcription of antemortem data, the two odontograms are compared. Features evaluated include tooth morphology and associated bony structures, pathology, and dental restorations (Fig. 21-4). An individual with multiple dental treatment and unusual features has a better likelihood of being identified than someone with no extraordinary dental characteristics. This, however, does not imply that identification relies on extensive dental treatment—comparison should take into account quality rather than quantity. Acharya and Taylor have concluded that a single point of concordance between post- and antemortem data may be sufficient to establish identity, considering, of course, the uniqueness of such a feature and circumstances of the case.

WRITING A REPORT AND DRAWING CONCLUSIONS

One needs to remember that any attempt at establishing identity is addressed to the law enforcers or legal authorities. Therefore, a detailed report and factual conclusion based on the comparison must be clearly stated. The quality and quantity of information required for establishing dental identity has not been fully determined. In fingerprinting, differences in the ante- and postmortem data rule out identification. This concept does not apply to dental identification so long as the inconsistencies are explainable. For example, the postmortem data may reveal a 'filling' on the right upper first molar but the dental records show the same tooth as 'intact.' This difference, however, may be explained on the basis that the restoration was made on a date *after* the available dental records by a different dentist, but for which no records are available. On the other hand, if the postmortem data shows an 'intact' right upper first molar, whereas the same tooth is 'filled' in the dental records, this would probably indicate a mismatch. It is essential to explain these considerations in the report for the purpose of clarity. Having compared and weighed the two sets of data, one should ask the questions: "Are the similarities significant?", "Can the differences be explained?". Based on this, a range of conclusions can be derived, which have been modified below from McKenna, Silverstein, and Acharya and Taylor.

Positive Identification

This indicates that the ante- and postmortem dental data match each other. The identity is proven 'beyond reasonable doubt' and must include post- and antemortem radiographs.

Probable Identification

There is high level of concordance between the two sets of data but may lack radiographic support. The data is consistent but a lack of quality post- and/or antetmortem information implies that one cannot confirm identity.

Possible Identification

The post- and antemortem data are in agreement but the available information is insufficient, usually in terms of quality. The available information neither permits a definitive identification nor enables the identity to be excluded.

Insufficient Information

The available post- and antemortem information is minimal or insufficient to draw a conclusion on the identity of the deceased.

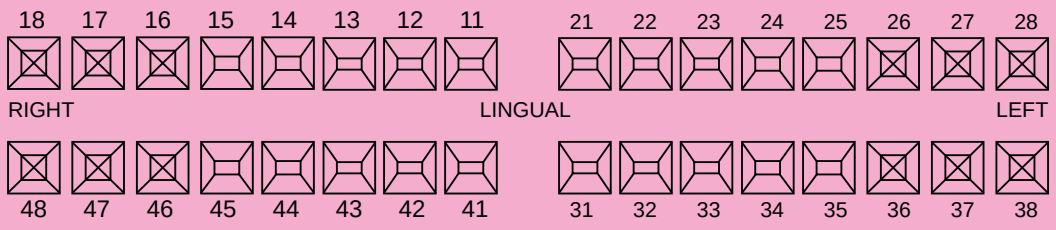
Excludes Identification

The post- and antemortem data are clearly inconsistent. The data contains unexplainable differences which comprehensively indicate a mismatch.

DENTAL STATUS OF HUMAN REMAINS

Site of discovery :	Date :
Condition of remains :	Body no :
Cause of death :	Ref. F/O :
	Sex

11			21
12			22
13			23
14			24
15			25
16			26
17			27
18			28



48			38
47			37
46			36
45			35
44			34
43			33
42			32
41			31

Occlusion :		Crowns :		Bridges :		Smoker
DENTURES :	P/U F/U P/L F/L	Material : Marks :		TEETH :	Type : Mould : Shade :	
MAXILLOFACIAL PROSTHESIS : IMPLANTS :				CLASPS :	Type :	
RADIOGRAPHS :	Bw.	Pa :	Occ.	Lat.	AP	OPG
PHOTOGRAPHS :	Clinical			Portrait		
SPECIAL TREATMENT	Endo.	Perio	Ortho.	Oral Surgery		C. & B.

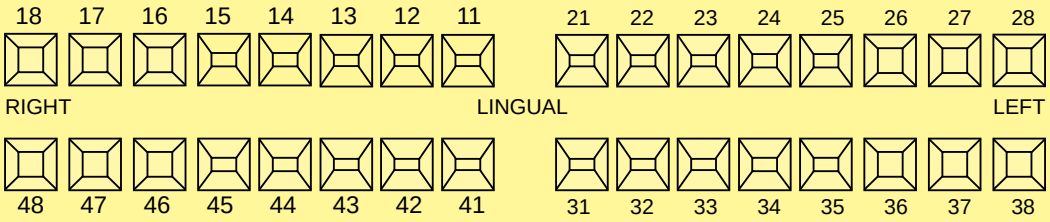
Figure 21-2: Modified Interpol postmortem odontogram.

DENTAL STATUS OF MISSING PERSON

Date :

Name :	Age :	D.O.B.	M/F
Address : Previous Address : Occupation :		Dentist School Clinic Hospital	
Police Reference :		Reference F/O :	

11			21
12			22
13			23
14			24
15			25
16			26
17			27
18			28



48			38
47			37
46			36
45			35
44			34
43			33
42			32
41			31

Occlusion :		Crowns :		Bridges :		Smoker
DENTURES : P/U F/U P/L F/L MAXILLOFACIAL PROSTHESIS : IMPLANTS :		Material : Marks :		TEETH : CLASPS :	Type : Mould : Shade : Type :	
RADIOGRAPHS : Bw. Pa : Occ. Lat. AP OPG PHOTOGRAPHS : Clinical Portrait						
SPECIAL TREATMENT	Endo.	Perio	Ortho.	Oral Surgery		C. & B.

(form 1)

Figure 21-3: Modified Interpol antemortem odontogram.

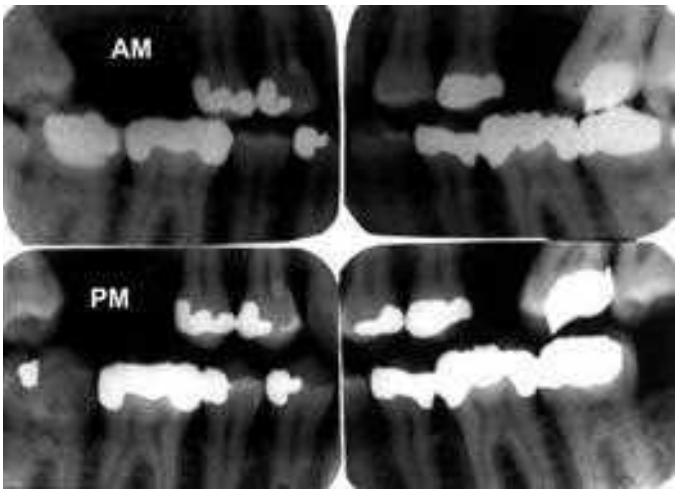


Figure 21-4: Antemortem (AM) and postmortem (PM) bitewing radiographs. The top two images are bitewing radiographs taken several years prior to death. The bottom two images were exposed on the body with a deliberate attempt to replicate and angulations of the antemortem (AM) images. There are discrepancies between the AM and postmortem (PM) images in terms of number of restorations, but they are explainable on account of the patient having undergone additional treatment in the interval between AM and PM examinations; the discrepancy in tooth 47 (lower right 2nd molar) is due to a dislodged restoration and fractured tooth, possibly due to trauma around the time of death. *(Reprinted from Wood RE. Forensic aspects of maxillofacial radiology. Forensic Sci Int 2006;159S:S47–S55, with permission from Elsevier).*

Use of Ameloglyphics in Personal Identification

Tooth prints are the pattern formed by the enamel rod ends at the crown surface of the tooth. Manjunath and coworkers recorded the enamel rod end pattern using acetate peel technique (a technique used to study the texture and surface details of rocks and fossils). Based on their recent study that examined 60 subjects and 120 teeth, they have categorized tooth prints into eight different patterns and demonstrated that no two teeth have similar pattern and coined the term ameloglyphics (Fig. 21-5). However they have raised doubts regarding its forensic value since enamel undergoes regressive changes and the course taken by the enamel rods vary at different levels of the enamel.

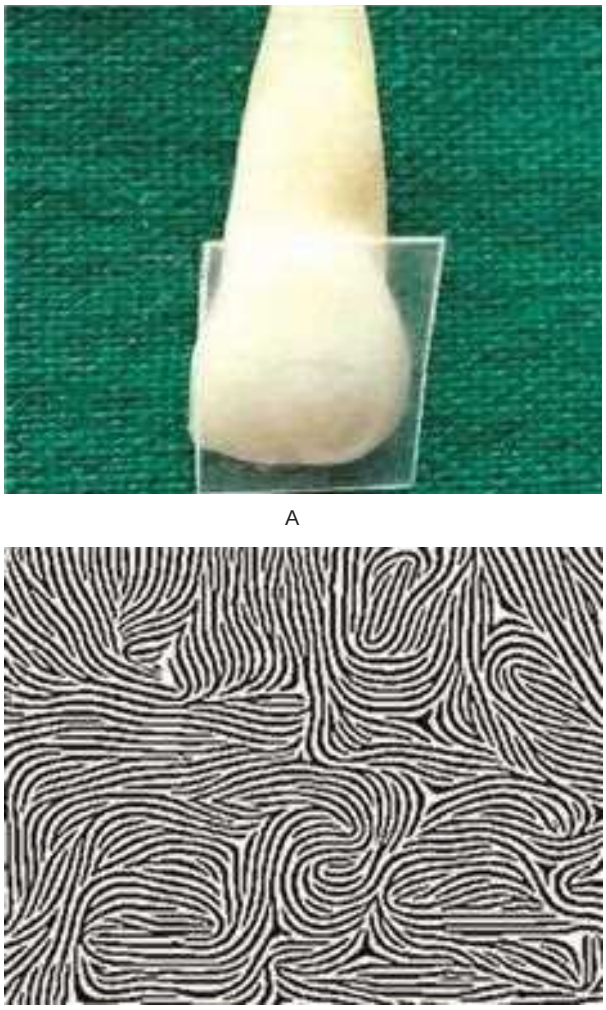


Figure 21-5: Tooth prints.
(Reprinted from Manjunath K et al. Journal of Forensic Odontology, 1:33–36, 2008.).

IDENTIFICATION IN DISASTERS

Disasters refer to natural calamities such as earthquakes, floods and tsunami and accidental or man-made events—such as airplane crashes or terrorist attacks—that result in multiple human fatalities. Such incidents require identification of the postmortem remains due to severe mutilation. The process of dental identification is essentially the same as described previously except, the magnitude of the event is far greater. It involves examining and comparing hundreds, sometimes thousands, of post- and antemortem data. Human remains in such events may be highly fragmented and, hence, only part of the body may be recovered. The bodies may be incinerated or commingled (i.e. parts of two bodies are mixed with each other). Vale and Noguchi state that disasters may involve exorbitant monetary lawsuits, making it an added reason for prompt and accurate identification; also, there are political and jurisdictional issues that may need to be addressed. For example, Keiser-Nielsen states that in some countries, an airplane is considered 'national territory'—in case an airplane registered in one country crashes in another, the victims may be considered as having died in the former country's territory. Hence, experts from that country may be required to assist in identification. Airplane crashes usually involve victims from diverse countries and acquiring relevant dental records from distant regions can be daunting.

DENTAL SECTION

Forensic dentists are usually part of a team of identification specialists that include anthropologists and fingerprint experts, to name a few. Each team has its own section where postmortem identification is carried out. According to Clark,

almost 50% of identifications in disasters are from dental evidence. Therefore, most disaster victim identifications have an odontology section. Representation on this section should be as broad as possible and inclusion of different specialists and dental auxiliaries can be useful. Each team member should be familiar with procedures to be followed in a disaster situation. Information about team activation, the tasks to be performed, and standardized charting methods should be known in advance. Tasks may range from taking radiographs to performing clerical duties. The Interpol's disaster victim identification guide as well as Vale and Noguchi suggest the division of the odontology section into three sub sections—postmortem unit, antemortem unit and the comparison and identification unit.

POSTMORTEM UNIT

According to Vale and Noguchi, it is useful if members of the forensic dental team are part of the search and recovery team at the site of disaster since dentists are more likely to recognize fragmented and burned teeth. They suggest that at the disaster site a sketch should be made of the scene. The location at which a body is recovered is noted and preliminary examination of the mouth is made on-site to evaluate the oral condition. The definitive dental examination however, is best performed at the temporary mortuary set-up for postmortem examination.

Clark states that dental examination is usually done **after** most other procedures such as photography, fingerprinting and medical autopsy. This allows sufficient time to organize the postmortem unit. Portable dental radiography apparatus should be installed at a convenient area within the temporary mortuary, taking precaution against the risk of radiation hazard. The postmortem unit is responsible for processing the radiographs and may also need to arrange for photography of teeth. Teeth and jaw specimens may be removed from a body for convenience of examination. These must be appropriately labeled to prevent a 'mix-up'.

ANTEMORTEM UNIT

Morlang considers the task of the antemortem unit as the most difficult. The members need to collect as much information as possible in the shortest period of time. This begins with locating the dental records of the victims, which requires an extensive network of communication with the police, relatives of the victim and the victim's dentists. It is essential to re-check the verbal information obtained with the victim's dentist. This dentist is requested to provide the written records, radiographs and study models to the antemortem unit. The Interpol's guide has stressed that personnel in this unit should be capable of reading and interpreting all dental records obtained. The quality, quantity, and variety of dental records present a major obstacle to this unit (see Box). Since transcribing and copying could reduce the quality of antemortem information, it is recommended that original records be obtained. All information gathered must be transferred onto the Interpol antemortem odontogram (Fig. 21-3).

Tribulations of interpreting dental records

The use of different types of tooth numbering system, non-standard abbreviations or charting errors by the treating dentist may pose problems in interpreting dental records. A common system of tooth numbering is, unfortunately, not followed around the world. While the FDI system is recommended, other numbering systems such as Zsigmondy/Palmer, ADA and Haderup are still employed in different countries. The use of abbreviations for recording dental treatment is common worldwide and varies from one dentist to another. Restorations are usually named by the letter of the tooth surface involved—mesial (M), distal (D), occlusal (O), buccal (B), etc. However, in some countries, buccal may be replaced with 'vestibular' or 'facial'. In the maxilla lingual may be described as palatal. Such varying descriptions, in addition to illegible handwriting, make accurate interpretation of records a time-consuming process for the forensic odontologist. This results in delayed identification or, worse, non-identification. One method of overcoming this is if the individual dentist is able to provide a legend for the abbreviations used in the dental records he/she maintains. A better solution is for the regional dental associations to implement standardized codes for various surfaces of the teeth as well as treatments performed.

COMPARISON AND IDENTIFICATION UNIT

This subsection handles comparison and confirmation of identity. In addition, the unit has the potential to exclude identity. Vale and Noguchi recommend commencing comparison and identification once postmortem information from all the victims is available. Antemortem information from all victims may or may not have been procured. The comparison may be done manually or by computer aid. When manual, Clark suggests that the data can be sorted by sex, age, presence or absence of restorations, etc. This eases comparison to some extent when hundreds of data exist. According to Vale and Noguchi, the antemortem data is taken individually and compared to the postmortem data that is spread out, for example, on a table. The Interpol's guide states that fragmentary remains will need to be cross-checked with individual bodies. When there is a match, one must ensure that all sets of documents relating to dental features are attached to the relevant sets of documents for the rest of the body.

A number of computer software programes such as IDENTIFY, ODONTID, CAPMI and IDIS have been developed over the last two and half decades to simplify comparison. In addition, the Interpol has recently facilitated access to and free use of a software program called 'Plass Data DVI System International'. Using Interpol's post- and antetmorten forms, the software allows the investigators to enter both post- and antemortem data, which is then analyzed and compared to enhance the matching process and assist

in identification. However, these programs merely sort the data, bringing down the number to a few likely post- and antemortem data. Clark stresses that the final identification should always be done by the dentist manually, which is based on personal evaluation of evidence. In problematic cases, it is useful to consult with other methods of identification, such as anthropologists and fingerprint experts. This is reciprocal in nature and adds to the ultimate success of identification in disasters. In fact, the Interpol's guide states that the success of disaster identification depends on the active participation and cooperation of different identification teams.

IDENTIFICATION FROM DENTAL DNA

The conventional method of dental identification described thus far requires one basic element that may not always be readily available—dental records. Lack of adequate or complete absence of antemortem records is not uncommon and is known to undermine the identification process; this, however, does not necessarily preclude identification. Since teeth can resist extreme conditions, Pretty and Sweet state that teeth are an excellent source of DNA. One may doubt the ability of teeth to yield sufficient quantities of DNA for analysis, particularly under circumstances when the postmortem interval ranges from a few months to years. However, Pötsh and coworkers successfully extracted DNA from the pulp of teeth recovered from decomposed and burned bodies, as well as victims of air crashes. Moreover, a routinely applied technique in forensic investigations—the polymerase chain reaction (PCR)—allows amplification of even highly degraded DNA. This facilitates comparison with a known biological antemortem sample of the decedent, such as hair from a comb, epithelial cells from a toothbrush or biopsy specimen. A major advantage of DNA analysis over comparative dental identification is that if a decedent's antemortem sample is unavailable, DNA pattern may be compared to that of parent(s) or sibling(s), thus facilitating confirmative identification.

TYPES OF DNA

Pretty and Sweet have pointed out the use of two types of DNA. The first is called genomic or nuclear DNA, which is located in the nucleus of cells and commonly used in forensic cases. The second, known as mitochondrial DNA (mtDNA), is present in the mitochondria of cells. While most cells have a single nucleus, Bender and associates point out that the major advantage of mtDNA is that each cell has a high copy number of mtDNA. For example, epithelial cells contain 5,000 mtDNA molecules and, hence, mtDNA can substitute in cases where nuclear DNA is unavailable. Also, mtDNA is exclusively inherited from the mother, and there is no contribution whatsoever of the father. Thus, an identical mtDNA pattern is observed among siblings, their mother and many maternal relatives. Moreover, due to their exclusive maternal inheritance, they can be used to establish identity in cases where there is a gap of several generations.

EXTRACTION OF DENTAL DNA

Owing to its neurovascular nature, the tooth pulp is considered to be the best source of dental DNA. Ajayprakash and coworkers isolated DNA from dental pulp and accurately determined personal identity using HLA-DQ amplification. Sweet and Hildebrand have advocated a method known as cryogenic grinding for extracting DNA. This involves cooling the whole tooth to extremely low temperatures using liquid nitrogen and then mechanically grinding it to fine powder. Using standard protocols, they were able to obtain sufficient amounts of DNA from intact, carious as well as root-filled teeth. Extraction of DNA from the latter implies that pulp tissue is not necessarily the only source of dental DNA—hard tissues such as dentin and cementum may be equally viable. This is of particular significance in skeletal remains. In fact, applying this method on a 3½ year-old skeletal specimen, Sweet and associates were able to accurately identify the remains.

The major drawback of cryogenic grinding is that the tooth needs to be completely crushed. This is a drawback since, in forensic investigation, methods that circumvent the need for tooth destruction are preferred as the tooth sample may need to be presented later as part of the evidence in courts.Therefore, Trivedi and coworkers have suggested a less destructive method for DNA isolation. Their method involves accessing the root canals through an opening similar to that made during root canal treatment, scraping the pulp area with a notched medical needle, and subsequent flushing of the tissue debris. This, the authors claim, 'retains the morphology and physiology of the tooth'. Most methods yield variable quantities of DNA from the same type of tooth. Hence, for optimal results, one may need to utilize multiple teeth.

PALATAL RUGAE IN IDENTIFICATION

In the preceding columns, identifying individuals from their teeth, either by comparison with antemortem dental records or to known DNA samples, has been elaborated. However, this approach is not practical in identifying the edentulous. A useful method of identifying edentate individuals is by examining the palatal rugae pattern. The rugae pattern on the deceased's maxilla or maxillary denture may be compared to old dentures that may be recovered from the decedent's residence, or plaster models that may be available with the treating dentist.

Palatal rugae are ridges on the anterior part of the palatal mucosa on each side of the mid-palatine raphae, behind the incisive papilla (Fig. 21-6). These asymmetric and irregular ridges are well protected by the lips, cheek, tongue, buccal pad of fat and teeth in incidents of fire and high-impact trauma. Furthermore, Muthu, Subramanian and colleagues have found that palatal rugae can also resist decomposition to an extent. Rugae pattern, like teeth, are considered unique to an individual. They seldom change shape with age and reappear after trauma or surgical procedures.

A B

Figure 21-6: Rugae pattern.
(Courtesy of Dr Dutiganti Santhosh Reddy, Meenakshi Ammal Dental College, Chennai).

Classification of Palatal Rugae

Attempts to categorize palatal rugae have spanned almost one hundred years. While many authors have suggested diverse classifications, the one suggested by Lysell is quoted most often. He measured rugae in a straight line, from their origin on the medial side to terminus on the lateral, and divided them into three types:

- Primary rugae (>5 mm)
- Secondary rugae (3–5 mm)
- Fragmentary rugae (2<3 mm)

(Rugae < 2 mm is not taken into consideration).

This is a rather simplified picture of the intricate form that rugae usually present. Therefore, Thomas and Kotze have further categorized the various patterns of primary rugae as branched, unified, cross-linked, annular, and papillary. Other authors, such as Kapali and associates, have grouped the rugae according to shape as straight, curved, wavy, and circular.

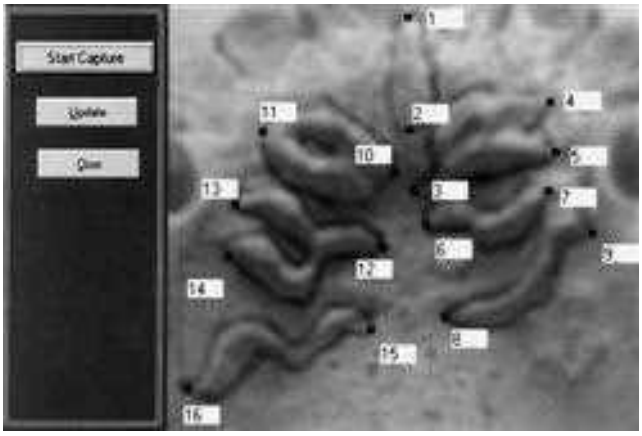


Figure 21-7: Points plotted manually on the image of palatal rugae.
(Reprinted from Limson KS and Julian R. Computerized recording of the palatal rugae pattern and an evaluation of its application in forensic identification. J Forensic Odontostomatol 2004;22(1):1–4, with permission of author and journal).

ANALYSIS OF RUGAE PATTERN

Thomas and van Wyk have manually traced rugae patterns from post- and antetmortem dentures on to clear acetate (transparent plastic sheets) and then superimposed these tracings on photographs of plaster models. More recently, Limson and Julian have developed a computer software program which makes use of the principle commonly employed in fingerprint analysis. The method used digitized images of the palate on which characteristic points were plotted on the medial and lateral extremities of all rugae (Fig. 21-7). The plotted points were assessed by the software program and the information stored sequentially, corresponding to the pixel position. These researchers obtained up to 97% accuracy in identifying individuals in a simulated post- and antemortem comparison of the palatal rugae. Significantly, in their analyses, the authors have bypassed any form of classification suggested previously. In fact, Thomas and Kotze state that, considering the complex nature of rugae patterns, a universally acceptable classification may not be feasible and, as long as the technique used to compare the rugae is accurate, one need not conform to a particular classification.

Furthermore, a recent study by Ohtani and coworkers suggests that high accuracy rates in postmortem identification from palatal rugae can be obtained using straightforward visual comparison of post- and antemortem rugae patterns obtained from dentures (Fig. 21-8), and neither a classification protocol nor computer-aided method is mandated. These authors did, however, infer that more complex the rugae pattern, greater the tendency for non-identification.

A B

Figure 21-8: Similar palatal rugae pattern on casts obtained from old (A) and new (B) dentures.
(Reprinted from Ohtani M et al. Indication and limitations of using palatal rugae for personal identification in edentulous cases. Forensic Sci Int 2008;176:178–182, with permission of Elsevier).

Palatal rugae in race and sex identification

A recent study by Nayak and coworkers suggests that rugae patterns are also useful in identifying an individual's population affinity or race. In particular, they examined straight, curved, wavy, and circular rugae shapes in populations originating from southern and western India and found significant differences in some of them—while straight rugae were more frequently found among southern Indians, curved rugae had greater incidence among Western Indians. Based on rugae shape, they were able to correctly identify an individual's population origin in 70% of cases. However, this study as well as others—including the one by Kapali and associates—was unable to observe significant sex differences in rugae pattern. On the other hand, teeth are reasonably good indicators of race and sex, both of which are important for reconstructive identification.

DENTAL PROFILING

To pinpoint identity of the dead is possible when some form of antemortem information is available. But, as is seen from time to time, circumstantial evidence may not be available to give an indication about the putative identity of the deceased and, consequently, dental records are not traceable. This could be the case in skeletal remains recovered in an isolated area and with no proof of identification. Such cases warrant building a postmortem profile for reconstructive identification. Dental profiling includes extracting a triad of information—the decedent's ethnic origin, sex, and age. According to Pretty and Sweet, 'the information from this process will enable a more focused search for antemortem records'.

IDENTIFYING ETHNIC ORIGIN FROM TEETH

Physically, humans are a diverse species. This diversity is the result of genetic influences as well as environmental factors such as climate and geographic location. Therefore, the people of the world look different. Traditionally, the human species has been categorized into three 'races'—Caucasoid, Mongoloid and Negroid. This classification, however, does not reflect human variation. Moreover, Relethford has emphasized that the concept of 'race' is rather ambiguous. Hence, it may not be an appropriate classification and has been discarded by biological anthropologists. Scott and Turner have divided humans based on geographic origin, which is the accepted approach today. Human diversity permeates to dental morphology as well, and dental anthropologists have cataloged this diversity. As a result, it is possible to identify an individual's ethnic origin based purely on the dentition.

Genetic and Environmental Influences on Teeth

Teeth have proven to be significant in the study of human variation. Scott and Turner suggest that characteristic dental features have evolved over time as a result of genetic and environmental forces that influenced different population groups. Dental features have a complex mode of inheritance and are a combination of hereditary factors and environmental effects to which a person is exposed. As a result, today, different populations show considerable diversity in their dentition. For population identification, those dental features that have a stronger genetic and weak environmental influence are useful.

Dental features used to describe population differences are broadly categorized as metric (tooth size) and non-metric (tooth shape) traits. Metric traits are based on measurements, and non-metric traits defined in terms of presence (or degree of expression) and absence of a particular feature, for example, whether Carabelli's cusp is present or not. Townsend cites numerous studies which indicate metric traits as being considerably influenced by intraoral environmental factors (e.g., missing lateral incisors cause compensatory increase in central incisors; space constraints in the jaws result in compression of third molars). On the other hand, nonmetric traits are more heritable and, therefore, dependable in establishing the population group to which an individual belongs.

Non-metric Dental Traits

More than 30 non-metric traits of the tooth crown and root have been described and analyzed in detail by Scott and Turner. Data exist for Indians for only a few features and these have been obtained from the preliminary studies of Vijapure and coworkers, and Angadi and Acharya, on a sample of 105 heterogeneous subjects. The following is a description of these traits:

Shoveling. Shoveling refers to the presence of mesial and distal marginal ridges on the lingual surface of the maxillary and mandibular anterior teeth. The marginal ridges may be absent, slightly developed or very prominent. The lingual fossa is a secondary reflection of marginal ridge development. The maxillary central incisors are the recommended teeth for observing the trait in assessing population differences. Virtually 0% shoveling was found in the preliminary heterogeneous Indian sample.

Carabelli's Trait. The Carabelli's cusp, or tubercle of Carabelli, is a cingular derivative expressed on the mesiolingual or lingual aspect of the mesiolingual (mesiopalatal) cusp of maxillary molars. The trait may be absent, expressed as minor depressions or well-developed tubercles with free apexes. For assessing population differences, the maxillary first molar is examined. In Indians, it is reported to be present in 26% of the population.

Three-cusped Maxillary Second Molar. The distolingual (distopalatal) cusp of the maxillary molars is usually retained on the first molar, but tends to be of reduced size or absent on the second molar. Such a three-cusped maxillary second molar was observed in 34% of Indians.

Winging. This is an indirect crown trait. It is characterised by the bilateral labial rotation of the distal margins of maxillary

Table 21.1: Incidence of some non-metric dental features for some populations of India

Feature	Haryana (Jats) (%)	Punjab (%)	Maharashtra (Andh tribe) (%)	Karnataka (%)
Carabelli's cusp	16.61	–	–	25.3
Shoveling	55.64	–	–	10.4
Three-cusp upper second molar	33.47	–	5.97	–
Four-cusp lower first molar	16.61	17.05	17.72	–
Four-cusp lower second molar	94.06	74.42	36.99	–
Y-groove pattern	22.34	25.58	67.57	–
X-groove pattern	23.71	0.00	12.16	–
+-groove pattern	53.95	74.4	20.27	–

Compiled from Sharma and Kaul (1977), Kaul and Prakash (1981), Kulkarni et al (1985) and Reddy (1985).

central incisors. The incisal edge of the central incisors, taken together, appears 'V' shaped from the occlusal aspect. Winging was observed in 16% of the Indian population.

Cusp 5. This is characterized by the presence of occlusal tubercles on the distal marginal ridge of maxillary molar(s), particularly the first molar. An incidence of 75% is observed in Indians.

Cusp 6. An additional cusp between distal and distolingual cusp of mandibular molar(s), particularly the first molar, is referred to as cusp 6. Approximately 57% of Indians have been shown to exhibit this feature.

Cusp 7. An additional cusp expressed between the lingual cusps of mandibular molar(s), particularly the first molar. It appears wedge-shaped from the occlusal aspect, with the base of the wedge placed lingually and apex towards the central pit. The feature is observed in just over 21% of Indians.

Mandibular Molar Groove Pattern. Occlusal groove pattern on the mandibular molars, particularly the second molar, is the result of varying modes of cusp contact at the central fossa:

- When the mesiolingual and distobuccal cusps are in contact, the resultant groove pattern is referred to as the Y-groove.
- When the mesiobuccal and distolingual cusps are in contact at the central fossa, the groove pattern is known as the X-groove.
- When all major cusps are in contact at the central fossa, the groove pattern takes the form of a '+' sign.

Four-cusped Mandibular Molars. Conventionally, the mandibular first molar is considered to have five cusps while the second molar is regarded as having four. However, the distal cusp may be absent on the first molar and/or expressed on the second molar. Therefore, both first and second mandibular molars are studied for the absence of the distal cusp. The frequency of four cusps is 11% for first molars and 90% for second molars in the preliminary Indian sample.

Table 21.1 reveals differences between populations from various regions of India for some of the features described above. Dissimilarities exist between different regions of the world, particularly between the major subdivisions of humankind, namely Eurasians, Africans, East Asians, and Native Americans. The range of dental variation among humans, however, is so great that several non-metric traits must be considered together before concluding on ethnic or population origin. Of the preceding features, some have aroused great interest owing to their high frequency in certain populations, while the occurrence of others is uncommon and, in some instances, rare. One must bear in mind that the high and low incidence of a non-metric trait is equally important in identifying a particular population/ethnic group. For example, people of European, West- and South-Asian origin (Eurasians) may exhibit four-cusped lower first molar, Carabelli's cusp and three-cusped upper second molar in relatively high frequency, but features such as shoveling and Y-groove pattern do not occur often among them. On the other hand, four-cusped lower second molar is infrequent while shoveling and three-cusped upper second molar is commonly seen among East Asians. One is advised to remember, however, that the frequency of occurrence of many non-metric traits overlap in different population groups. Therefore, the use of such morphological characters for identification should be used carefully and judiciously.

SEX DIFFERENTIATION

Assessing the sex, or sexing, of unknown human skeletal remains is the second step in the triad of building a dental profile. Sex can be assessed based on data from morphology of skull and mandible, tooth measurements and by analyses of DNA from teeth.

Sexing from Craniofacial Morphology and Dimensions

The use of morphological features of the skull and mandible (Table 21.2) is a common approach used by anthropologists in sexing. A number of features are known to show variation between the sexes. However Botha and Chandra Sekharan, in separate studies, caution that most of these features are not reliable until well after puberty. Even then, no single feature is characteristic and the use of multiple features tends

Table 21-2: Craniofacial morphologic indicators of sex

Skull features	Male	Female
Size/architecture	Big/rugged	Small/smooth
Frontal and parietal eminence	Small	Large
Forehead	Sloping	Vertical
Supraorbital ridges	Medium to large	Small to medium
Glabella	Moderate to marked curve	Flat or slight curve
Orbits	Squared, low, rounded margins	Rounded, high, sharp margins
Nasal aperture	High , thin sharp margins	Lower, wider rounded margins
Zygomatic arch	Extends	Does not
Occipital	Muscle lines marked	Muscle lines not marked
Mastoid process	Medium to large	Small to medium
Occipital condyles	Large	Small
Glenoid fossa	Deep	Shallow
Foramen magnum	Large and long	Small and round
Palate	Large, U-shaped	Smaller, parabolic
Mandible features		
General features	Large, broad ascending ramus	Small, narrow ascending ramus
Condyles	Large	Small
Shape of chin	Square	Rounded/pointed
Gonial angle	Less obtuse, flares	More obtuse, does not flare
Body height	High symphysis	Low symphysis

Modified from Biggerstaff (1977), de Villiers (1968), Krogman (1955,) and Williams and Rogers (2006).

to be more accurate. Williams and Rogers found that sex could be predicted correctly in 96% of cases using different features of the skull and mandible. Furthermore, they observed that using a constellation of just six traits—mastoid process, supraorbital ridge, size and architecture of skull, extension of the zygomatic arch beyond the external auditory canal, nasal aperture and gonial angle (on the mandible)—the accuracy of sex determination was 94%. This indicates that craniofacial morphology can be used to determine sex of skeletal specimens with a high degree of precision. While some authors believe that skull traits are affected by changes in old age, Williams and Rogers found no such effect.

SEX DIFFERENCES IN TOOTH SIZE

Teeth may be used for differentiating sex by measuring their mesiodistal (MD) and buccolingual (BL) dimensions. Lund and Mörnstad state that "this is of special importance in young individuals where skeletal secondary sexual characters have not yet developed". Teeth are not only important for sex determination of skeletal remains of non-adults but also of adults since other, more preferred parameters, such as the pelvic and long bones may be fragmented. The dentition's ability to survive postmortem degradation is what makes teeth important in this area. Numerous studies have shown that the male dentition is statistically larger than the female permanent and deciduous tooth crown dimensions. The average MD and BL dimension (in mm) of the maxillary and mandibular permanent teeth in a heterogeneous Indian sample is given in Table 21.3. Tooth measurements are population specific and vary from region-to-region. However, the canines have consistently shown the maximum sex difference in most studies. The molars are next to canines in exhibiting considerable male-female differences. Sex is determined from tooth measurements using statistical methods called discriminant function analysis and logistic regression analysis. Using the former, Prabhu and Acharya determined sex correctly in approximately 76% of Indians. The accuracy from tooth measurements is lower than the near-100% success obtained using the pelvis and skull. This can be attributed to an overlap existing between male and female tooth dimensions, which makes accurate diagnosis of sex challenging. The success is usually greater when all available teeth are used. Therefore, teeth are recommended as an adjunct or supplementary method rather than the sole indicator of sex.

Sex Determination by DNA Analysis

Forensic DNA analysis for sex determination can give highly accurate results. Sex can be determined with very minute quantities of DNA (as little as 20 pg), and from very old specimens of teeth. Sivagami and coworkers state "amelogenin (AMEL) is one of the major matrix proteins secreted by the ameloblasts of the enamel. The AMEL gene, coding for a highly conserved protein, is located on the X- and the Y-chromosomes in humans. The two alleles are

Table 21.3: Average male and female tooth measurements (in mm) on the right and left side combined

Tooth	Buccolingual		Mesiodistal	
	Male	Female	Male	Female
Maxilla				
CI	7.24	7.09	8.42	8.29
LI	6.35	6.27	6.61	6.50
CI	8.08	7.76	7.63	7.41
PM1	9.26	9.11	6.81	6.82
PM2	9.23	9.05	6.42	6.55
M1	11.16	10.83	9.85	9.80
M2	10.86	10.52	9.34	9.18
Mandible				
CI	5.85	5.86	5.35	5.26
LI	6.08	6.12	5.88	5.78
CI	7.36	7.00	6.66	6.46
PM1	7.93	7.74	6.77	6.82
PM2	8.54	8.26	6.85	6.88
M1	10.50	10.17	10.80	10.58
M2	10.07	9.85	9.83	9.71

Modified from Prabhu and Acharya (2009).

similar for the exonic sequences but differ in the intronic sequences. Thus the females (XX) have two identical AMEL genes but the males (XY) have two nonidentical genes". Preparing DNA from teeth by ultrasonication and subsequent PCR amplification, these authors obtained 100% success in determining sex of the individual. This was confirmed by the study of Ajayprakash and coworkers wherein DNA was isolated from dental pulp.

DENTAL AGE ESTIMATION

The final step in the triad of dental profiling, age estimation has applications both in postmortem identification as well as living individuals in whom the chronological age is under dispute. While different physiologic systems are used to estimate age, teeth are considered better suited than bones. Dental age is one of the few measures of physiologic development that is uniformly applicable from infancy to late adolescence. After attaining maturity, teeth continue to undergo changes, making age estimation possible in adults.

Dental Age Estimation Methods

Dental age estimation makes use of morphologic, radiographic, histological, and biochemical methods to examine age-dependant changes in teeth. Age estimation using the dentition may be grouped into three phases:

- Prenatal, neonatal and early postnatal period
- Children and adolescents
- Adults.

Age Estimation in Prenatal, Neonatal and Early Postnatal Period. The primary teeth begin to calcify at approximately 12-14 weeks *in utero* (IU), and the enamel formation of all deciduous teeth is usually complete by the first year. Among permanent teeth, the first molar commences calcificaqtion around the time of birth. Age estimation in this group of individuals can be very accurate. Aka and coworkers have devised a method of measuring the developing calcified teeth retrieved from skeletal remains or after maceration (removal of soft tissue), and correlating this to age; alternatively, Lalys and colleagues have recommended the use of CT scans, which they believe allow a 'non-invasive' method of tooth measurement. Another, simple, alternative in skeletonized specimens is to measure the dry weight of the mineralized tooth cusps of the deciduous central incisor, lateral incisor, and first molar. The method, developed by Stack, suggests that the combined weight of teeth in a child at six months IU is about 60 mg, 0.5 gm in a newborn and 1.8 gm at six months after birth.

The neonatal 'line' is considered as an indicator of live birth. Bowers attributes its formation to the slowing down of enamel prism growth rate, thus "creating an apparent line of demarcation". According to Ciapparelli, the neonatal line may take up to three weeks after birth to form. Hence, Bowers warns that a false result may be produced if one were to conclude that the absence of neonatal line indicates stillbirth. What is certain, however, is that if the neonatal line is present, the child was alive at birth. Estimating age in this age group may have legal implications in case of feticide and infanticide.

Age Estimation in Children and Adolescents. Two events that may be used to measure dental age in children and adolescents are tooth emergence (or 'eruption') and tooth calcification. Nystrom and colleagues consider estimating age from the study of tooth emergence to be a convenient clinical method. It involves visual assessment of teeth present in the mouth and requires little expertise or equipment. The use of tooth emergence for age estimation should, however, be limited to deciduous teeth. Their emergence is under genetic control and relatively regular, commencing approximately at six months after birth and completing by about 2½ years. On the other hand, emergence patterns of permanent teeth are under influence of the intraoral environment and affected by infection, arch space and premature tooth loss. Therefore, evaluating radiographs to assess calcification of permanent dentition is a much better alternative for age estimation, since:

- Calcification of teeth can be observed on radiographs for a period of several years.
- It is not altered by local factors such as lack of space, over-retention of deciduous teeth.
- The study of tooth calcification also allows us to assess age at periods when no emergence takes place (2½–6 years and >12 years).

In fact, dental calcification is considered by Schmeling and associates as one of the three most suitable methods of

estimating age for criminal procedures. The techniques used are simple and easy to master, even for the inexperienced dentist. Moreover, age estimation in this group is relatively accurate since a number of teeth, passing through various stages of calcification, are available. Hence, dental calcification has been accepted as a better indicator of age in the first two decades of life. For reasons of brevity, described below are just a few of the many methods that exist for estimating age in children and adolescents.

Schour and Massler's method. The chart of Schour and Massler was probably the first attempt at scientific dental age estimation. It describes 20 chronological stages of tooth development starting from five months IU until 21 years of age. The chart or atlas is based on histological sections and permit direct comparisons with radiographs. Bowers states that the charts were improved by Ubelaker, who included data from additional population studies (Fig. 21-9). Dental development of males and females were combined and each stage includes the amount of age variation. Bowers stresses that these improved charts should be used for age assessment, since the original Schour and Massler atlas has serious drawbacks.

Demirjian's method. Demirjian and coworkers have developed an age estimation method that assesses the mandibular left side teeth. The method is the most widely used technique for assessing age in children and adolescents, probably due to the detailed description and radiographic illustrations of tooth developmental stages, as well as its relative simplicity. While the method originally excluded the third molar, Chaillet and Demirjian proposed a modification that included this tooth. In the modified method, the calcification of the teeth was divided into 10 stages and numbered '0' to '9' (Fig. 21-10). For example, Stage '0' denotes that tooth calcification is yet to begin; Stage '5' indicates crown completion while Stage '9' represents completion of tooth calcification (complete formation of root apex). Based on the amount of calcification visible on the radiograph, each tooth is given an appropriate developmental stage. Depending on the developmental stage, each tooth is given a corresponding 'maturity score'.

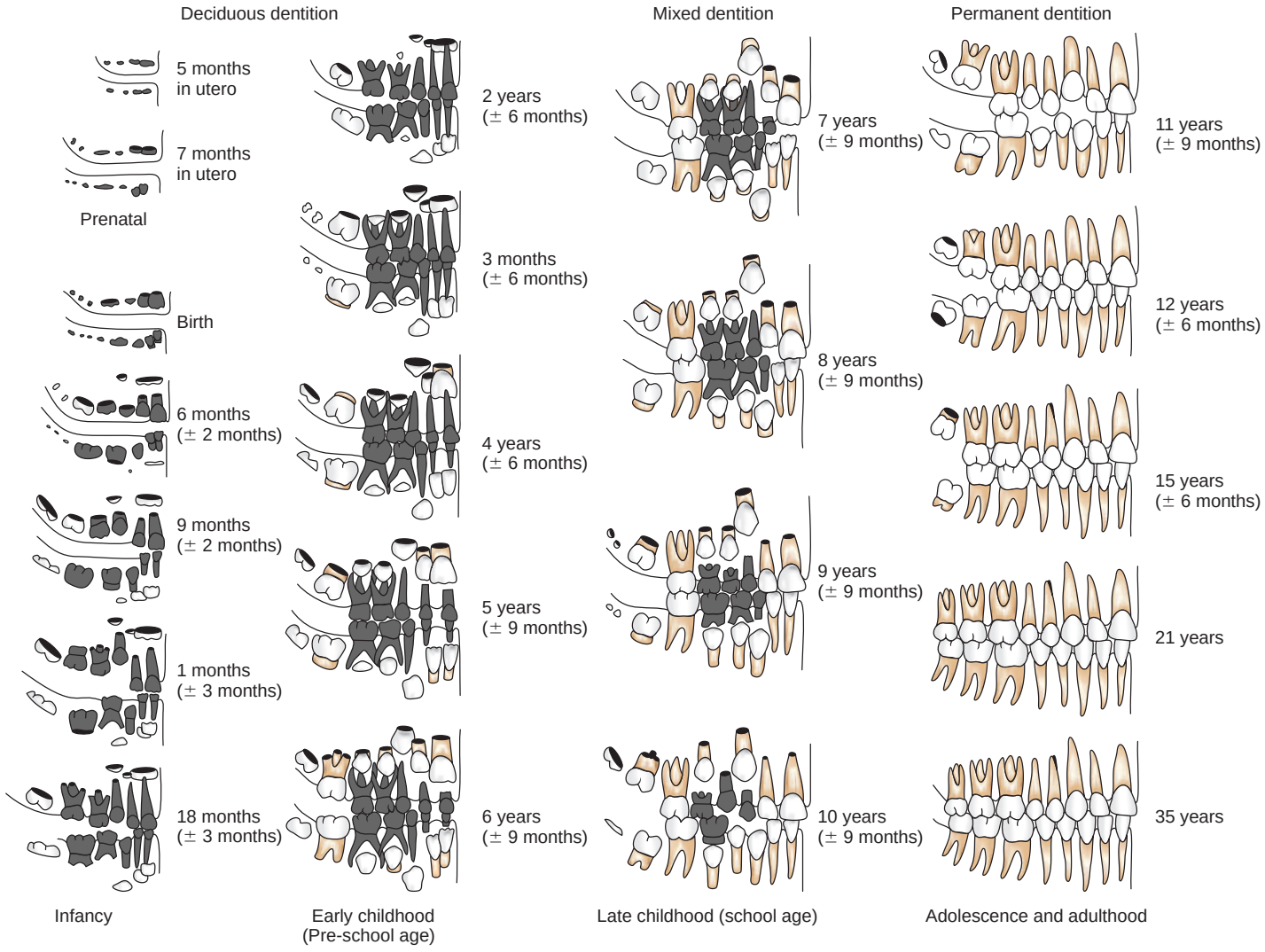


Figure 21-9: Schour and Massler pictorial representation of tooth development allows assessment of age by comparing the chart to radiographs.
(Reprinted from Ubelaker DH. Human skeletal remains: excavation, analysis and interpretation. 3rd ed. Taraxacum: Washington DC, 1999, with permission of author).

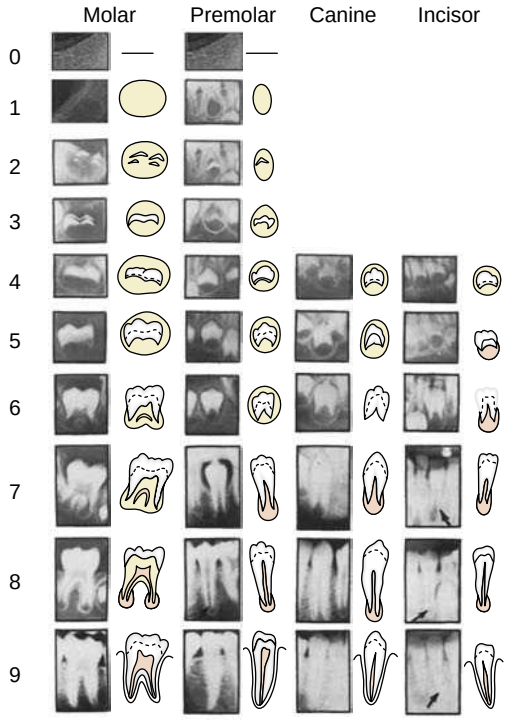


Figure 21-10: The 10-stage dental development chart of Demirjian and coworkers.
(Modified and reprinted from Demirjian A, Levesque GY. Sexual differences in dental development and prediction of emergence. J Dent Res 1980;59(7):1110-22, with permission of Sage Publications).

Considering differences in tooth development between males and females, Chaillet and Demirjian provided separate maturity scores for each sex (Tables 21.4 and 21.5). The score assigned for each of the eight teeth is added and a total maturity score (S) obtained. The total is substituted in regression formulae to derive age. The following formulae may be used when estimating age in Indians:

- Males: Age = $27.4351 - (0.0097 \times S^{2)} + (0.000089 \times S^3)$
- Females: Age = $23.7288 - (0.0088 \times S^2) + (0.000085 \times S^3)$

These formulae have been developed by Acharya on an Indian sample of 461 subjects whose age ranged between 7 and 25 years. Such an adaptation of a foreign-based method to the local sample is usually necessary and potentially increases the accuracy of age prediction. The average absolute error of these formulas in estimating age is ±1.43 years, and they are able to calculate age to within ±1 year of the actual age (which is considered as a 'good result') in about 44% of cases. Indian formulae have been shown to produce a dental age which, on the average, is closer to the real age by about six months when compared to Chaillet and Demirjian's original formulae. A difference of six months may be considered as useful when the subject who requires age assessment is a child or an adolescent.

Value of Third Molars in Age Estimation. Although the third molar is a valuable indicator of age in the 16–22 year-old age-group where all other teeth have completely developed, its accuracy in age estimation is questionable due to great variation in its genesis, position, morphology, and time of formation. However, Gunst and associates underscore its importance, particularly due to the relative inaccuracy of skeletal predictors of age in this age-group. In particular, the development of the third molar is important for determining whether an individual is a juvenile (<18 years) or an adult (≥18 years). In many countries, including India, 18 years is the threshold at which the law considers an individual to have attained adulthood and this has major legal ramifications. For example, the Juvenile Justice (Care and Protection of Children) Amendment Bill, 2006, states that a 'juvenile in conflict with law' (i.e., a juvenile alleged to have committed an offence), cannot be sentenced to death or life imprisonment or committed to prison. Instead, Juvenile Justice Boards exercise powers in relation to such individuals, who may only incur group counseling, community service, payment of fine or be remanded to a special home, usually for 3 years or until the time he/she attains adult status. Among teeth, at this age, the third molar is the only one still undergoing calcification. Therefore, this tooth has been utilized to determine juvenile/adult status. Recently, Acharya applied

Table 21.4: Maturity scores for males

	Tooth No.							
Stage	31	32	33	34	35	36	37	38
0							1.70	6.20
1					1.7		3.00	7.65
2				1.70	2.25		3.40	8.30
3			1.70	1.98	3.40		4.75	8.85
4			2.65	3.52	3.40		4.90	9.90
5	2.30	2.55	4.35	5.19	5.60	2.15	6.70	11.15
6	4.35	4.70	6.15	6.47	6.95	3.75	7.90	12. 25
7	5.15	5.75	7.60	8.18	8.70	4.95	9.10	13.65
8	6.55	6.95	9.50	9.84	10.65	7.00	11.15	14.05
9	10.70	10.90	12.55	12.57	13.10	11.20	13.65	15.30

Modified from Chaillet and Demirjian (2004).

Table 21.5: Maturity scores for females

	Tooth No.							
Stage	31	32	33	34	35	36	37	38
0								6.40
1							2.55	7.75
2					2.45			8.90
3				2.55	3.45		2.65	9.30
4			2.55	3.55	3.85		4.10	10.20
5	2.60	2.65	3.15	5.10	5.75	2.60	6.50	11.05
6	3.10	4.55	5.40	6.30	6.80	3.25	8.00	12.65
7	5.00	5.40	7.20	8.10	8.70	4.25	9.15	13.75
8	6.65	7.00	9.20	9.80	10.80	6.90	11.00	14.45
9	10.60	10.90	12.00	12.30	12.80	10.95	13.85	16.65

Modified from Chaillet and Demirjian (2004).

Demirjian's grading to the third mandibular molar in an Indian sample and found that this tooth correctly predicted juvenile/adult status in 73.2% of cases. This implies that just over one-fourth of subjects who need to be certified as a juvenile/adult may be categorized to the wrong age-group. This level of accuracy may be insufficient for the courts of law to rule with adequate levels of certainty about the juvenile/adult status of an individual using third molar development.

Growth variations exist between different population groups due to dissimilar genetic and environmental factors. Ideally, therefore, population specific developmental data is essential for optimized age estimation.

Age Estimation in Adults. Age estimation in adults is challenging when compared to younger age-groups. Ritz and colleagues state that following completion of growth, changes in the dentition used to estimate age "are influenced not only by the age of the individual, but also by numerous endogenous and exogenous factors, such as disease, nutrition, and physical strain".

Gustafson's method. In 1950, Gösta Gustafson proposed a method for age estimation based on morphological and histological changes of the teeth. The method assessed regressive changes such as attrition (A), secondary dentin deposition (S), loss of periodontal attachment (P), cementum apposition at the root apex (C), root resorption at the apex (R) and dentin translucency (T). For each of these regressive changes, or variables, Gustafson assigned different grades ranging from 0 to 3. This implies that a tooth can have any one of four grades for attrition (A0, A1, A2, or A3) and similar one of four grades for the other variables. Adding the allotted grade for each variable (e.g. A3 + S2 + P2 + C1 + R2 + T1 = X), a total score (X) was obtained. It was found that an increase in the total score corresponded with an increase in age. Age was estimated using the formula Age = 11.43 + (4.56 × X). Pillai and Bhaskar applied Gustafson's method on an Indian population and obtained an average error rate of about ± 8 years as against the original Gustafson's method that gave an error of ± 3.6 years. This may be a result of variable dental hygiene and habits such as beetle-leaf and tobacco chewing in Indians.

Later researchers discovered some statistical errors in Gustafson's method and modified them. In particular, the improvements made by Johanson are widely applied. Instead of four grades (0–3), Johanson proposed seven namely, 0, 0.5, 1, 1.5, 2, 2.5, and 3 (Fig. 21-11). The grade for the respective variable is substituted in a multiple regression formula to estimate age: Age = 11.02 + (5.14 × A) + (2.3 × S) + (4.14 × P) + (3.71 × C) + (5.57 × R) + (8.98 × T). Johanson observed that more the number of teeth used, more accurate was the age estimate.

Gustafson's method of age estimation is undoubtedly a significant contribution to forensic dentistry but his method *per se* has been discredited. The six variables he put forth are, however, valid and the modification suggested by Johanson is widely recommended for age assessment.

Dentin Translucency. Root dentin is considered to start becoming translucent in the third decade of life, beginning at the apex and advancing towards the cementoenamel junction (CEJ). The diameter of the dentinal tubules decreases as a result of increased intra-tubular calcification. Hence, the difference in refractive indices between intra-tubular organic and extra-tubular inorganic material is equalized, resulting in increased translucency of the affected dentin. Johanson recognized that dentin translucency contributed best to age estimation among the six variables of Gustafson. Hence a number of researchers focused on the use of this variable alone in estimating age. Bang and Ramm measured the length of translucency in individuals of different ages and reported that there was a predictable increase in root translucency as age advanced (Fig. 21-12). They suggested measuring translucency (as viewed from the proximal side of the tooth) from its apical limit up to the junction of translucent and non-translucent zone of dentin

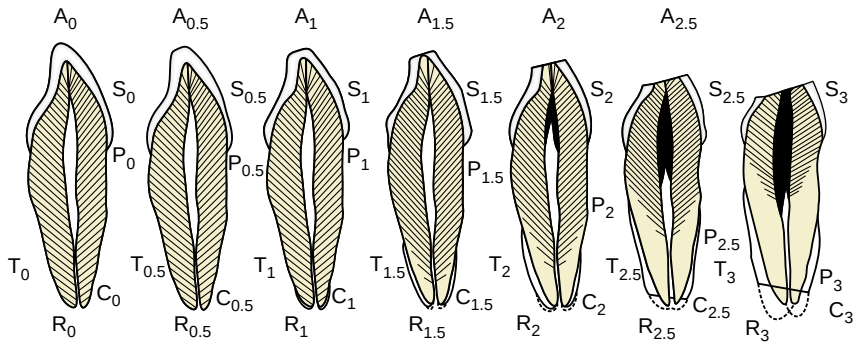


Figure 21-11: The seven grades proposed by Johanson for each of the six 'regressive' changes. For example, in a tooth, attrition may have any *one* of seven grades (A0, A0.5, A1, A1.5, A2, A2.5 or A3)
(Reprinted from Johanson G. Age determination from teeth. Odontologisk Revy 1971;22(suppl 21):90).

Figure 21-12: Tooth sections from three age-groups depicting progressive increase in translucency length with age.

coronally, approximately midway between the root surface and root canal; if translucency lengths (T) are different on the buccal/labial and lingual/palatal sides, separate measurements are taken and averaged.

Based on tooth type, Bang and Ramm provided different regression formula for age estimation. Recently, Acharya and Vimi found Bang and Ramm's method may also need adaptation to the Indian context. They have put forth the following India-specific formulae, which are common to all single-rooted teeth and produced marginally better age estimates than Bang and Ramm's formulae:

- Formula I: Age = $35.5619 + (3.4828 \times T)$
- Formula II: Age = $29.9074 + (7.4507 \times T) + (-0.4369 \times T^2)$

If the translucency measured is >9 mm, formula I is used for age estimation; if translucency length is ≤9 mm, formula II is used. Using these formulae, an average age estimation error of ±8.3 years was found for Indians, which may be categorized as 'moderately good' accuracy. Translucency may be measured on either intact extracted teeth or ground sections of teeth. Measuring translucency is a convenient approach to postmortem age estimation and even an inexperienced examiner can apply it. However, a major disadvantage is that the junction between translucent and non-translucent zones can sometimes be highly irregular, making it difficult to measure the length.

Age estimation from incremental lines of cementum. Kagerer and Grupe have suggested the possibility of age estimation from acellular cementum incremental lines. This makes use of mineralized, unstained cross-sections of teeth. The authors claim age estimation accuracy to within ±2 to ±3 years of actual age. In addition to age, hypomineralized bands in the incremental lines give an indication of events such as pregnancies (Fig. 21-13), skeletal trauma and renal

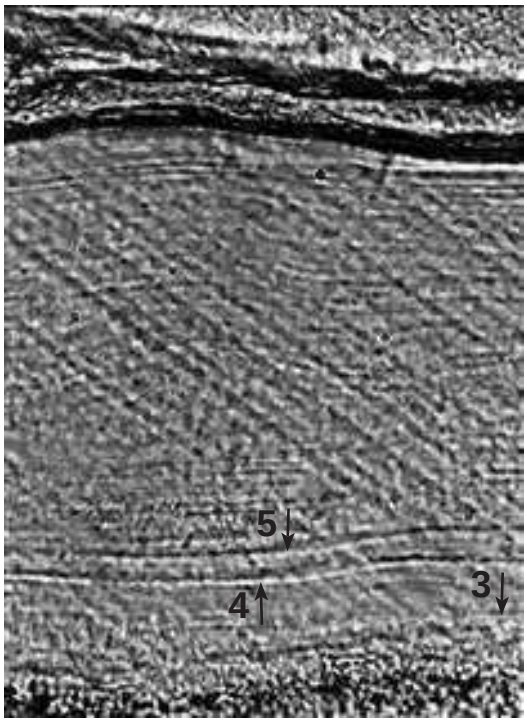


Figure 21-13: Cementum incremental line on tooth 43 (lower right canine) from an 86-year-old female. Arrow 1 indicates eruption line while arrows 2 and 3 correspond with two pregnancies, separated by four years.
(Reprinted from Kagerer P and Grupe G. Age-at-death diagnosis and determination of life-history parameters by incremental lines in human dental cementum as an identification aid. Forensic Sci Int 2001;118:75–82, with permission of Elsevier).

disorders, which can accurately be dated to an individual's life-history, thus facilitating identification. Valenzuela and coworkers believe that cementum apposition shows particular promise for ageing skeletal remains. A recent study by Renz and Radlanski has, however, questioned the use of counting cementum incremental lines for age estimation (Fig. 21-14). These authors found it difficult to obtain repeatable counts of cementum lines in the same area of a tooth section. For example, some teeth were found to differ markedly in the number of incremental lines in different sections of the same tooth as well as in different regions of the same section. Also the pathologic state of the periodontium may compromise the precision of ageing.

The above methods of estimating age in adults necessitate tooth extraction, sectioning and possible destruction. While this is feasible in dead individuals, it is not practical (and possibly unethical) in living adults. A 'non-destructive' radiographic technique developed by Cameriere and associates shows promise and may be used as an alternative. Radiography can also be used to assess age in the dead, since mortuaries usually have the requisite equipment.

Age estimation from pulp-to-tooth area ratio. Cameriere and associates suggested measuring the area of the pulp chamber/root canal and the tooth area of canines on radiographs and calculate their ratio (Fig. 21-15). This was named the pulp-to-tooth area ratio. The method is based on the principle of age-related secondary dentin deposition and, as age increases, the area of the pulp chamber/root canal reduces, which is reflected in the decrease in pulp-to-tooth area ratio. The ratio is calculated to compensate for and circumvent differences in magnification of radiographs and angulation between X-ray beam and film/sensor. Cameriere and associates developed the method on an Italian sample

Figure 21-14: Cementum incremental lines are less distinct, with a radiating pattern.
(Reprinted from Renz H and Radlanski RJ. Incremental lines in root cementum of human teeth—a reliable age marker? Homo 2006;57:29–50, with permission of Elsevier).

Biochemical indicators of age

Amino acid racemization. Helfman and Bada first suggested a relationship between age and the extent of aspartic acid racemization in dentin. Subsequently others including Ritz and associates as well as Ohtani and coworkers have explored this biochemical method and found it suitable for ageing. All humans use amino acids exclusively in protein synthesis. Aspartic acid is an amino acid that has a rapid rate of **racemization**, i.e. it gets spontaneously converted from one type (L-aspartic acid) to another (D-aspartic acid) with increasing age. Therefore, there is a constant change in the ratio of L- and D- aspartic acid at different ages and this D/L ratio may be used for age assessment. Due to constant replacement of proteins in metabolically active tissues (such as liver), no measurable amounts of D-aspartic acid is found. However, the D/L ratio can be measured in those proteins that are synthesized early in life and are not replaced. Such proteins are found in brain cells, crystalline lens, bone and teeth. Racemization rate of aspartic acid is found to be high in root dentin and therefore teeth are a valuable tissue for using this method. Waite and colleagues believe that this is an objective method that is very accurate, with age estimates within ±3 years of actual age.

Age estimation from ^{14}C levels. To further improve age estimates, scientists in Sweden and the US have recently proposed a highly unconventional and path-breaking concept of age assessment. This method, developed by Spalding and associates, looks at the amount of carbon-14 isotope (^{14}C) in enamel and compares it to recent atmospheric levels of ^{14}C. Atmospheric ^{14}C levels increased rapidly over the last 60 years following above-ground nuclear testing. Following cessation of such testing owing to the Partial Test Ban Treaty (PTBT) in 1963, however, their levels decreased exponentially through diffusion from the atmosphere into plants and animals. There is no turnover of enamel after it has been laid down and, hence, the ^{14}C concentration in enamel reflects that in the atmosphere at the time of enamel formation. Data for ^{14}C levels over the past 60-odd years is available and, using this as reference, age can be estimated. Examining a group of 22 individuals of known age, the researchers could determine age to within ±1.6 years of actual age. While both amino acid racemization and measuring ^{14}C levels have been shown to give precise estimates, a major disadvantage of both is the need for expensive equipment that may not be available in normal dental set-ups.

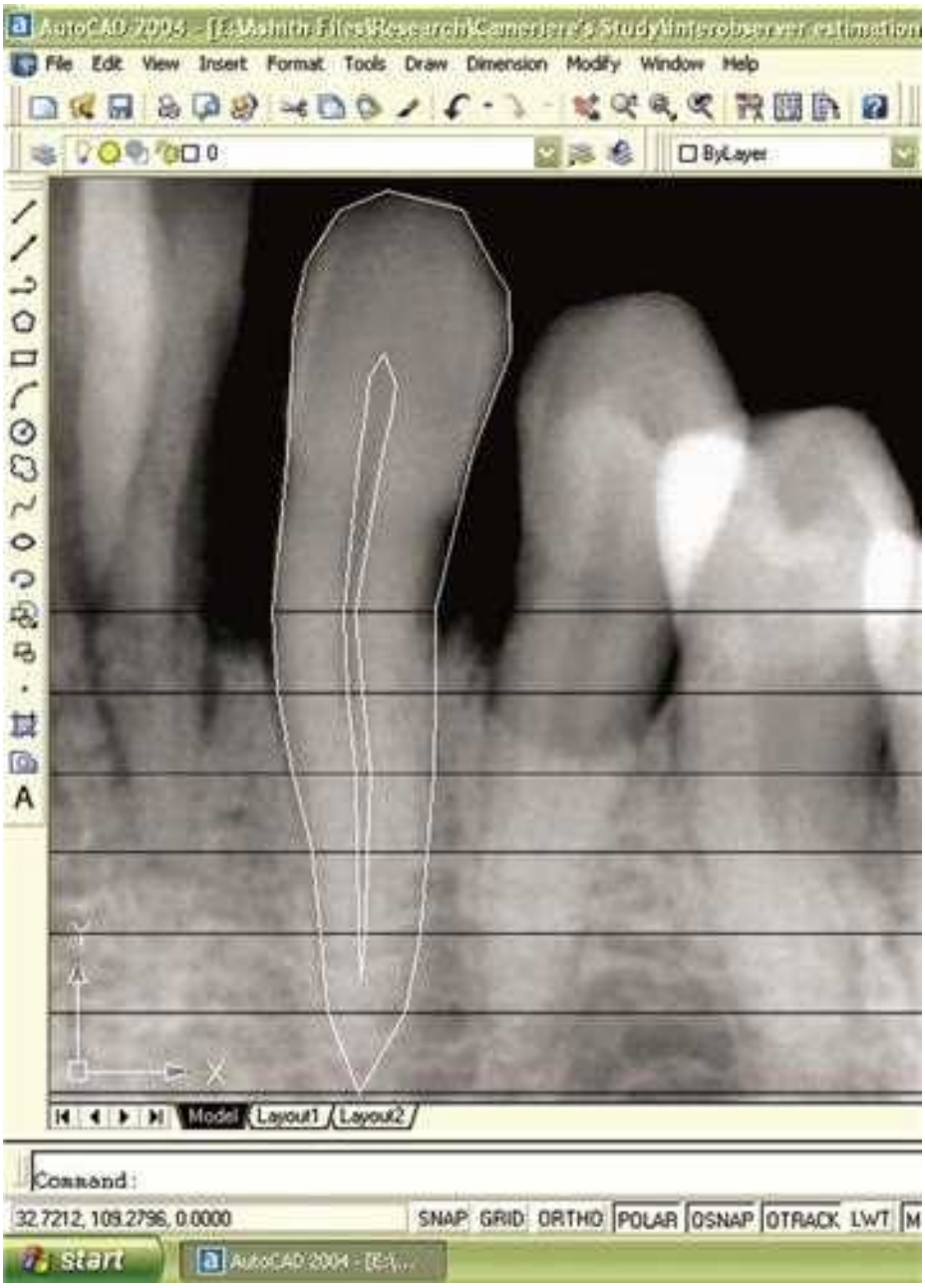


Figure 21-15: The tooth and pulp areas are delineated and measured on computer software programs such as AutoCAD, and their ratio calculated. The ratio are entered in a regression formula for estimating age.

and Babshet and coworkers found that customized Indian formulae predicted age better in Indians than the original Italian formulae. The following linear regression formula may be used in Indians: Age = 64.413 − (195.265 × PTR), where PTR is the pulp-to-tooth area ratio. This formula produced an average error of ±10.76 years, an error rate that borders on what may be considered as 'acceptable' in forensic age estimation.

Report and Conclusion of Age Estimation

As with dental identification, one must bear in mind that the report on age estimation is addressed to law enforcement authorities. Therefore, it is important that the wordings in the report reveal the underlying concepts of age estimation, the material(s) that were obtained for the purpose (such as radiographs or skeletal samples) and the method(s) used. In addition, it is important to address the validity of the method(s) to the population on which it was applied. It is important to note that dental age may not be expressed precisely, but as the most likely age.

CRIME INVESTIGATION

In the preceding passages, the forensic dentist's role in identifying the deceased, either through comparison with dental records, through DNA samples, or by reconstructing a dental

profile, has been elucidated. Forensic odontologists also play a vital role in crime investigation. While the frequency of such cases may not approach those of postmortem identification and age estimation, their significance is certainly no less. Crime investigation includes the investigation of bite marks, child abuse, and lip prints.

Bite Marks

Bite marks have been defined by MacDonald as "a mark caused by the teeth either alone or in combination with other mouth parts". Bite marks may be caused by humans or animals; they may be on tissue, food items or on objects. Biting is considered to be a primitive type of assault and results when teeth are employed as a weapon in an act of dominance or desperation. As a result, bite marks are usually associated with sex crimes, violent fights, and child abuse. Bite marks have also been recovered from scenes of theft. Hence, matching the bite mark to a suspect's dentition may enable the investigating officers to connect the suspect to the crime.

Sweet and Pretty believe that the size, shape, and pattern of the incisal or biting edges of upper and lower anterior teeth is specific to an individual, although there is considerable debate on this issue. Rawson and associates have mathematically calculated that biting edges (incisal edges) of the twelve anterior teeth can be arranged in 1.36×10^{26} different combinations. Hence, theoretically at least, a bite mark may accurately depict the 'unique' pattern of a biter's teeth. This may be crucial to identify a criminal or to exclude an innocent suspect, both of which are equally important.

Classification of Bite Marks

MacDonald has stated that as any field of specialization gets established, 'it requires the development of specific nomenclature and systems of classification'. Unsurprisingly, as the study of bite marks developed over the past five decades, numerous authors have tried to classify the injury. Listed below are a few.

Cameron and Sims' Classification. A relatively simple, wide-encompassing classification, this is based on the type of agent producing the bite mark and the material exhibiting it. Presented below is an abridged version.

Agents
- Human
- Animal.

Materials
- Skin, body tissue
- Foodstuff
- Other materials.

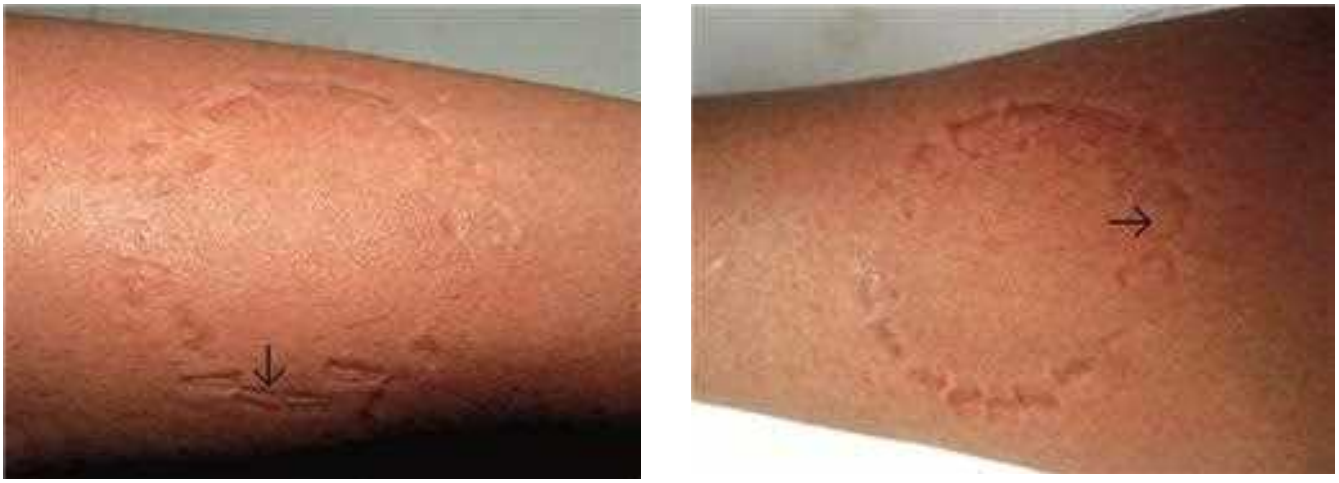
MacDonald's Classification. Probably the most cited, MacDonald suggested an etiologic classification. This is pertinent for human bite marks, but MacDonald adds, 'it is equally applicable to marks on other materials'.

Tooth pressure marks. Marks produced on tissue as a result of 'direct application of pressure by teeth'. These are generally produced by the incisal or occlusal surfaces of teeth (Fig. 21-16A).

Tongue pressure marks. When sufficient amount of tissue is taken into the mouth, the tongue presses it against rigid areas such as the lingual surface of teeth (Fig. 21-16B) and palatal rugae. The marks thus left on the skin are referred to as 'suckling,' since there is a combination of sucking and tongue thrusting involved.

Tooth scrape marks. These are marks caused due to scraping of teeth across the bitten material. They are usually caused by anterior teeth and present as scratches or superficial abrasions.

Webster's Classification. It is not uncommon to note bite marks on foodstuff. This is especially so in cases of theft or robbery at residences or commercial establishments, where the thief may bite on food items during the course of crime.



A B

Figure 21-16: Tooth pressure marks caused by the incisal surface of lower central incisors (arrow in A); as a result of the tongue pressing the bitten skin against the teeth, the lingual surface of the maxillary right canine is visible (arrow in B).

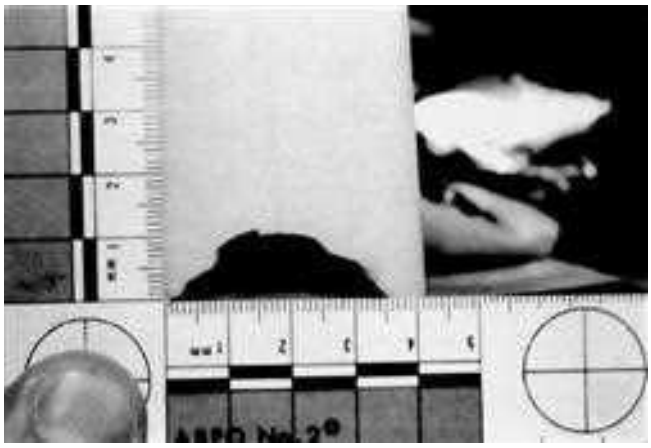


Figure 21-17: Type III bite mark produced on a piece of cheese.
(Reprinted from Arheart KL and Pretty IA. Results of the 4th ABFO bitemark workshop—1999. Forensic Sci Int 2001;124:104–111, with permission from Elsevier).

Type I. The food item fractures readily with limited depth of tooth penetration (e.g. hard chocolate).

Type II. Fracture of fragment of food item with considerable penetration of teeth (e.g. bite marks in apple and other firm fruits).

Type III. Complete or near complete penetration of the food item with slide marks (e.g. cheese, banana) (Fig. 21-17).

Bite Mark Appearance

Type of Injury. Compression of the skin surface due to tooth pressure during a bite initially causes indentations (Fig. 21-16). Indentations, while ideal for bite mark analysis, seldom persist for more than a few minutes unless the victim is dead (note that indentations may also be seen on healing lacerated wounds). Owing to the elastic nature of skin, indentations soon disappear as the skin regains its original contour. This is followed by a brief period of edema over the bite area, which usually obscures the bite mark completely. Once the edema subsides, subcutaneous bleeding is apparent. These are referred to as contusions or bruises (Fig. 21-18) and are the most common presentation of bite marks. Depending on the skin color they appear as reddish or purplish or dark brown discoloration on the skin surface and are due to the blood escaping into subcutaneous tissue from ruptured minute vessels. When the intensity of the bite is great, there may be a break in the integrity of skin surface, resulting in lacerations (Fig. 21-19). The most extreme form of bite mark injury is avulsion, where part of the tissue is bitten off.

Identifying the Injury as a Bite Mark. Sweet has suggested that a human bite mark may be identified by the following characteristics:

Gross charateristics. A circular or elliptical mark found on the skin with a central area of ecchymosis. The circular/elliptical mark is caused by the upper and lower arches while the central area of ecchymosis is apparently due to sucking action. A typical bite mark is usually distinct from an injury caused by anything else.

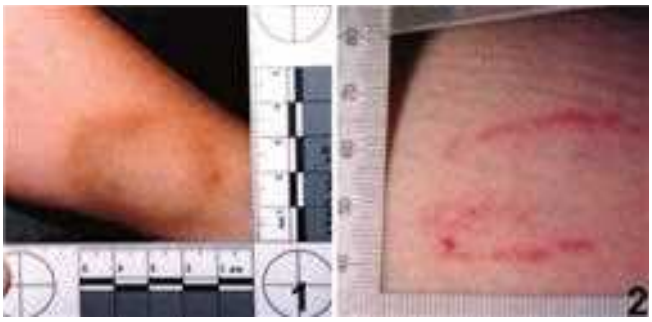


Figure 21-18: Bruising or contusion is the most common presentation of bite mark injuries. They may be very mild (1), with no obvious tooth marks, or show more distinct tooth patterns (2).
(Reprinted from Pretty IA. The barriers to achieving an evidence base for bitemark analysis. Forensic Sci Int 2006;159S:S110–S120, with permission from Elsevier).

Class charateristics. The marks produced by different classes of teeth are usually distinct, allowing one to differentiate the type of tooth within a bite mark. Incisors produce rectangular marks; canines are triangular or rectangular, depending on the amount of attrition; premolars and molars are spherical or point-shaped.

Individual charateristics. Class charateristics may, in turn, have features such as fractures, rotations, spacing, etc. Such attributes are referred to as individual features and make the bite mark distinct.

Site of Bite Marks. Bite marks may be found on any part of the body. However, Pretty and Sweet state that females are most often bitten on the breasts and legs (especially on the inner part of thigh)—a result of sexual assault. Male children are prone to be bitten on the genitals, a result of child sexual abuse (see box). However, adult males are

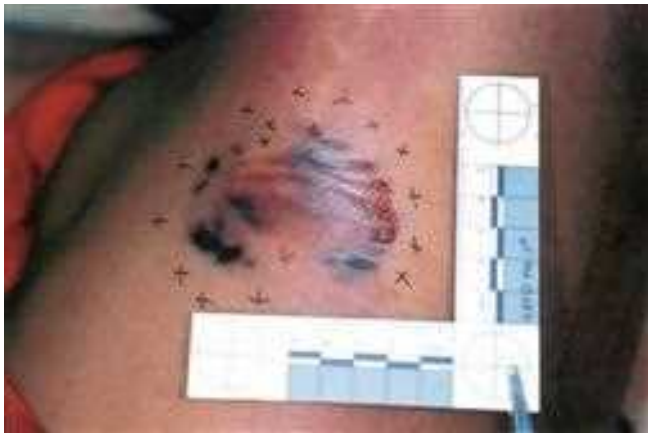


Figure 21-19: Lacerated wound caused by the mandibular anterior teeth.
(Reprinted from Thali MJ et al. Bite mark documentation and analysis: the forensic 3D/CAD supported photogrammetry approach. Forensic Sci Int 2003; 135(2):115–121, with permission from Elsevier).

bitten on the fingers, arms and shoulders, which are more often due to fights.

Bites and child abuse

Child abuse has been defined by Vale as "any act of commission or omission that endangers or impairs a child's physical or emotional health and development". Child abuse may broadly be categorized as physical abuse, sexual abuse, emotional abuse, and neglect of the child. Kenney and Clark have cited numerous studies which suggest that approximately 50% of injury in child abuse cases occur in the oral and perioral region. These include ocular injuries, marks caused by belt buckle or a slap from the hand. Blunt trauma, such as the latter, may result in tearing away of the labial mucosa from gingiva or a torn labial and lingual frenula. Blunt trauma may also result in mobile, fractured, and avulsed teeth. Gonococcal and syphilitic lesions of the mouth are commonly associated with sexual abuse. In addition to these, bite marks are also present in cases of child abuse. According to Beckstead and associates, bite marks in infants may be the result of punishment; in older children, it may occur due to sexual abuse. Kenney and Clark have attributed marks with an intercanine width greater than 3cm to adults. A smaller dimension may be the result of self-inflicted bites, as can occur when the child's arm is forced into the mouth to prevent it from screaming. One must also remember that children may bite each other casually during play.

Bite Mark Investigation

Preliminary Questions. Drinnan and Melton, as well as Sweet, have emphasized that any attempt at bite mark investigation should begin with the following questions:

- Is the injury a bite mark?
- If a bite, was it caused by human teeth?
- Was it caused by an adult or child?
- Does the age of the bite mark correspond to the time and type of crime?
- Are there any unique, individual characteristics in the bite mark?
- Can these characteristics be compared to the teeth of the suspect?

Once these questions have been answered adequately, one may proceed with the next step, collection of bite mark evidence.

Bite Mark Evidence Collection from the Victim. Ideally, bite mark evidence should be collected when it is first presented and observed. If a suspected bite mark is criminal in nature, it must be reported to law enforcement authorities. When a case with a suspected bite mark is identified, the primary concern is patient care. Therefore, at no time should collection of bite mark evidence interfere with timely patient treatment. This is emphasized since Pretty and associates have found human bites to be more infectious (includes transmission of HIV, hepatitis B and syphilis), especially when the bite injury presents as an abrasion or laceration. The protocol for bite mark evidence collection that follows has been recommended by the American Board of Forensic Odontology (ABFO) as well as accredited forensic dentists.

Case Demographics. Vital information pertaining to the case should first be noted. For example, name, age and sex of the victim as well as case number, date of examination and name of the examiner(s).

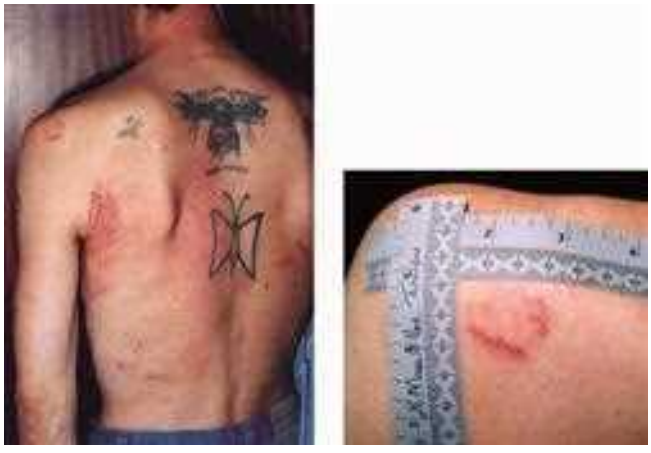
Visual Examination. Visually examine the bite mark and document the following:

- Orientation and location of the mark
- Type of injury
- Color, size, and shape
- Contour, texture, and elasticity of the bite site
- Differences between upper and lower arches and between individual teeth.

According to Brown, visual examination must be done **before** autopsy in the event the victim is dead.

Photography. Photographs provide a permanent record of bite marks. Therefore no time should be lost in obtaining pictures, since the injury changes appearance rapidly due to healing. Color and black-and-white photographs from different angles may be taken. It is desirable to have photographs from two views:

- Orientation photographs—photographs that depict the location of bite mark on the body (Fig. 21-20A).
- Close-up photographs—these should be made with a rigid reference scale (such as the ABFO No. 2 scale) that is placed on the same plane as the bite mark. The entire scale and mark must be visible on the photograph (Fig. 21-20B). A second close-up photograph depicting the bite mark without the scale can also be made to indicate



A B

Figure 21-20: Orientation photograph (A) must be complemented with a close-up photograph of the bite with a scale (B).
(Reprinted from Pretty IA. The barriers to achieving an evidence base for bitemark analysis. Forensic Sci Int 2006;159S:S110–S120, with permission from Elsevier).

that no part of the mark has been masked by the scale. The camera should be positioned directly over the injury site with the long axis of the lens perpendicular to the surface of the bitten skin. According to Sweet and Pretty, this decreases perspective distortion of the image due to off-angle camera position. If the bite is on a curved surface and the upper and lower arch marks are wide apart, separate photographs of each mark should be taken. Brown states that when the victim is alive, photographs can be repeated every 24-hours for 3–4 days to record progressive changes in the appearance of bite mark.

Saliva Swab. It is reasonable to assume that a bite can not be inflicted without leaving saliva behind. Saliva deposited on skin may have WBCs and sloughed epithelial cells which may be a source of DNA, enabling a direct link to the suspect. Hence, swabbing the bite area for saliva traces can prove invaluable in the investigation. Care should be taken to not wash the bite area before saliva swabbing. A cotton swab moistened with distilled water should be used for swabbing. This rehydrates the dried cells in the bitten area. The swab is air-dried at room temperature for about 30-minutes, placed in labeled paper envelopes and stored under refrigeration. The latter prevents degradation of salivary DNA and bacterial growth. Clark recommends that clothing must also be swabbed for saliva if the bite has occurred through it. The use of high-intensity alternative light source (such as UV light) to locate stains from body fluids enable saliva traces to be recovered even in the absence of visible bite marks.

Impressions. Impression of the bite area may be made when tooth indentations exist. The material of choice is Vinyl Polysiloxane. The impression material may be reinforced with dental stone, autopolymerizing acrylic or impression compound to prevent dimensional change. It is to be noted that if the bite mark is on an area accessible to the victim's own dentition, impressions of the victim's teeth should be made to rule out self-inflicted bites.

Evidence Collection from the Suspect. Evidence collected from a victim of a bite mark should be complemented with evidence from a suspect of the perpetrated bite. Such evidence must be obtained from the suspect using a signed and witnessed informed consent or a court order (warrant); infection control and asepsis protocols must be adhered to. Following a detailed clinical examination (extra- and intra-oral), the items of evidence recovered should include:

- Photographs of the suspect's teeth in occlusion and in open bite
- Maxillary and mandibular impressions made with rubber-base impression material or irreversible hydrocolloid, and models poured in dental stone. Bite registration on a thin sheet of wax may be made if impressions are unavailable.
- Saliva swabs, preferably from the buccal vestibule, should be obtained for comparing with the swab collected from the bite mark.

The above are steps in collecting evidence in potential criminal cases. Therefore, all evidence obtained must be stored in suitable containers and properly labeled. The labels should include the case number, date, time, place as well as witness(es) present during evidence collection. This is necessary to maintain 'chain of custody', which is the documentation and testimony that proves that the evidence has not been altered or tampered with in any way since it was obtained. This is essential both to assure its admissibility in the court and its probative value in preceding investigations.

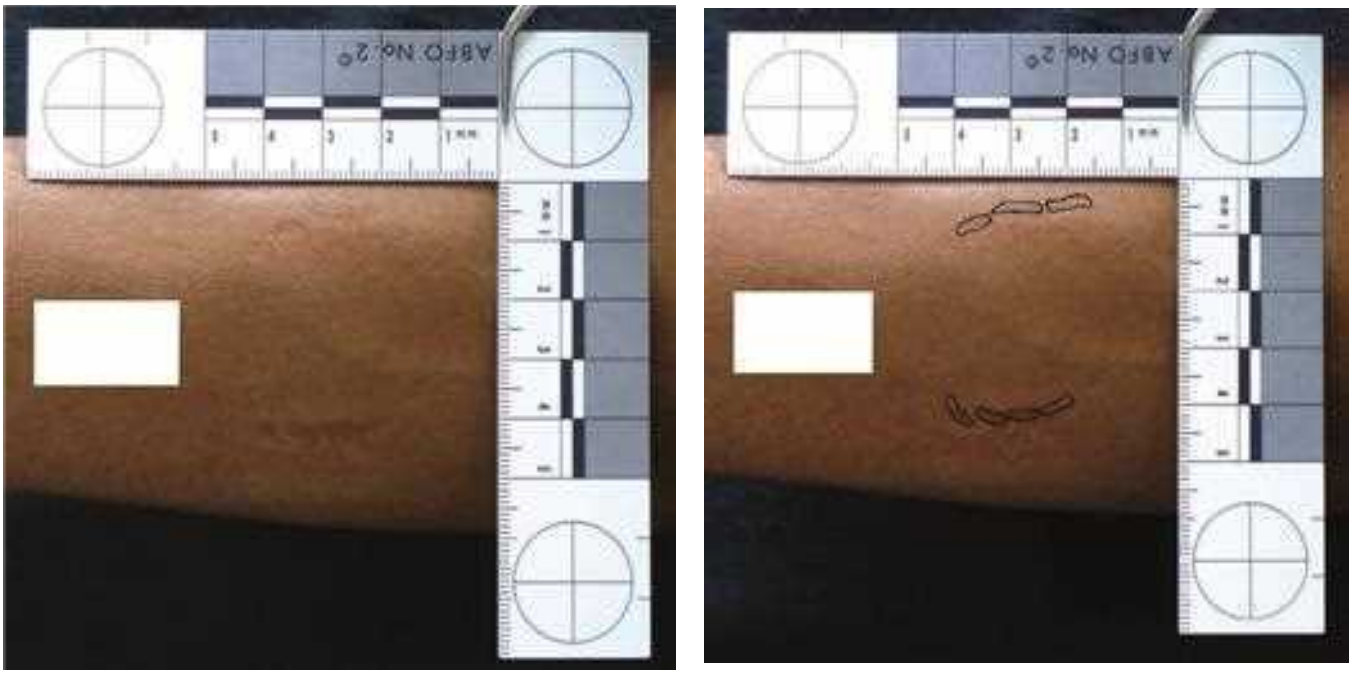
Bite Mark Analysis and Comparison

The dynamics of biting make analysis of the bite mark and its comparison to the suspect's teeth a highly challenging aspect of forensic dental investigsation. In addition to jaw movements, one needs to consider movement on part of the victim, the flexibility of the bitten tissue, as well as possible distortion introduced during photography. Bearing this in mind, one may proceed with the analysis. It is important to recognize uncommon characteristics of the bite mark such as presence or absence of a particular tooth, its dimension, rotation, fracture, diastema and other unusual features of the teeth as these can aid in implicating a suspect. The measurement of the mark constitutes 'metric analysis' and may be obtained using simple instruments such as a caliper or using computer software. Measurements obtained from the bite mark are compared to that of the suspect's dental model. Metric analysis, ideally, should not be undertaken independently, but in conjunction with 'pattern association' which involves matching the configuration of bite injury to the arrangement of teeth on the suspect's dentition. Ciapparelli and Hughes have pointed towards the 'direct method' of comparison, where the suspect's dental models are placed directly over the bite mark photograph or on the bite mark itself (i.e., *in situ*). Alternatively, the incisal and occlusal edges of the suspect's teeth may be traced onto clear acetate and superimposed on life-size bite mark photographs. This constitutes the 'indirect method'. However, the trend today has moved towards the application of 2D computer-based methods that use software programs such as Adobe® Photoshop®, as suggested by Johansen and Bowers (Fig. 21-21). The future, however, may well be the use of 3D methods, for example, Thali and coworkers have developed a 3D/CAD supported photogrammetry approach for bite mark analysis and comparison, while Martin-de las Heras and associates presented a new software program for producing outlines of the biting surfaces of teeth (called 'overlays') from 3D scans of dental casts. These methods, though more equipment-intensive, may be more accurate than 2D computer-based methods.

Conclusions in Bite Mark Analysis

Following comparison, a bite mark analysis may have one of the following concluding statements as suggested by Levine and the ABFO.

Definite Biter. There is reasonable medical certainty to indicate that the bite mark has been produced by the suspect's dentition: there is concordance of sufficient distinctive, individual characteristics to confer uniqueness within the population under consideration. There is absence of any



A B

Figure 21-21: A bite mark (A) superimposed with the bite edges of a suspect's dentition (B) generated using computer software such as Adobe® Photoshop®. Note the correspondence in alignment and rotation of both maxillary and mandibular teeth.

unexplainable discrepancies. This implies that there are characteristic matches between the bite mark dimensions/pattern and that of the suspect's teeth.

Probable Biter. Bite mark shows some degree of specificity to the suspect's teeth by virtue of a sufficient number of matching points, including some corresponding individual characteristics. There is absence of any unexplainable discrepancies.

Possible Biter. The bite mark and the suspect's dentition are consistent: although the suspect's teeth could have made the bite mark, there are no characteristic matches to be absolutely certain. The similarity is non-specific or there is similarity of class characteristics. Matching points are general and/or few and there are no incompatible inconsistencies that would serve to exclude the bite mark as having been caused by the suspect.

Not the Biter. The bite mark and the suspect's dentition are not consistent: features on the bite mark indicate that the suspect's teeth have definitely not caused them.

Investigating Animal Bites

Not infrequently, forensic dentists may be requested to investigate animal bites (Fig. 21-22). Such bites are usually produced by the dog family (dog, wolf, fox), cat family (domestic cat, tiger, leopard), rodents (rat, squirrels), snakes, sharks and crocodiles. A working knowledge of animal dental patterns is, therefore, required to investigate cases of non-human bites. The study of the dentition of different animal species is known as comparative dental anatomy. Animals are primarily classified as vertebrates (those with vertebral columns), and invertebrates. Vertebrates include fish, amphibians, reptiles and mammals. The following description of vertebrate dentition closely follows the compilation of Townsend and Winning.

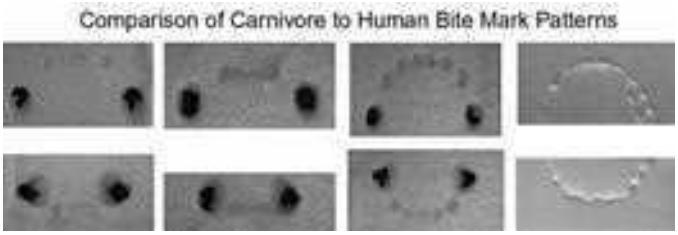


Figure 21-22: Same-scaled patterns showing family group differences and similarities, allowing a comparison of the bite marks. Note that the carnivores have six incisors and two very large canines per arch; humans (right) have only four incisors and much smaller canines.
(Reprinted from Murmann DC et al. A comparison of animal jaws and bite mark patterns. J Forensic Sci 2006 Jul;51(4):846–60, with permission from John Wiley and Sons).

Characteristics of Some Vertebrate Dentitions

Fish. The major function of teeth in fish is to seize or grasp prey and they usually have conical-shaped teeth. When all teeth are the same shape the dentition is known as homodont and this is characteristic of most fish. There are some fish, however, that have different shaped, or heterodont, teeth. Knowledge of specific morphologic patterns of fish dentition has application in investigating, for example, shark attacks and differentiating the causative shark species.

Reptiles. Reptiles use their teeth primarily in combat and to grasp prey. They typically have a row of only conical or only tricuspid teeth, which are homodont. However, they may vary in size, are ankylosed, simple rooted and polyphyodont (several sets of teeth). The teeth do not occlude and there is limited jaw movement. Hence, they usually select small-sized prey that can be consumed whole. Some reptiles have a more complex dentition (e.g. crocodiles and alligators have periodontal fibers). In some snakes, teeth are modified to form poison fangs, which contain a canal or groove for venom release. It is interesting to note that venomous and non-venomous snakes present different types of dentitions. While non-venomous snakes have two rows of maxillary teeth, venomous snakes have a single row. Palatal to this single row is a pair of poison fangs that deliver venom. The ability to distinguish venomous from non-venomous snakebites can prove critical at times. A victim of snakebite is under intense physical and psychological trauma, as one is usually unaware about the type of snake that caused the bite. By correlating snake dental pattern to the bite marks, it may be possible to arrive at an on-the-spot diagnosis about the nature of snakebite. This allows reassuring a victim of non-venomous snake bite, or facilitates appropriate therapy in case of venomous bites.

Mammals. Mammals are characterized by a heterodont dentition. Teeth are attached by periodontal ligament to the bony socket. Usually there are only two sets of dentition (diphyodont as opposed to polyphyodont), where the primary dentition is replaced by permanent teeth. Mammals also have accessional teeth (i.e. permanent molars emerge posterior to the deciduous teeth). The teeth usually consist of enamel, dentin and cementum and the posterior teeth are normally multi-rooted. Teeth are specialized for functions such as mastication, so the teeth occlude.

Dental Features of a Few Mammals

The dental formula for the dog family, or *canidae*, is $I\frac{3}{3}\ C\frac{1}{1}\ P\frac{4}{4}\ M\frac{2}{3}$. The incisors have a high central cusp with mesial and distal lobes adapted for holding, tearing and crushing. The canine tooth is long and strong while the upper fourth premolar and lower first molar are adapted as the carnassial teeth (see Box), which are used for shearing food.

The dental formula for the cat family, or *felidae*, is $I\frac{3}{3}\ C\frac{1}{1}\ P\frac{3}{2}\ M\frac{1}{1}$. The *felidae* have a dentition that is specialized for grasping and killing prey by slicing the flesh. The incisors are similar to the canidae but the canine is longer and stronger. In addition, the premolars and molars are reduced in number. The upper third premolar and lower molar form the carnassial teeth. Felines display a short snout, with the incisors arranged in an approximately straight line across the front of the mouth and large canines at the corners.

The bear family, or *ursidae*, generally have the dental formula $I\frac{3}{3}\ C\frac{1}{1}\ P\frac{4}{4}\ M\frac{2}{3}$. Murmann and coworkers state that ursidae differ from both the canidae and felidae but they are more like the cat family—the anterior portion of the maxillary arch is only slightly curved, and the corresponding region of the mandibular arch is very straight.

A characteristic feature of carnivores is the specialization of one posterior tooth in each quadrant called the carnassial tooth. These consist of a blade-like upper tooth that slices against the buccal surface of the opposing lower tooth, which produces a scissor-like cutting action.

In regions where there is a threat of accidental or predatory carnivorous attacks, the subsequent need to identify animal species causing the bite is essential from an investigative and ecological conservation point of view. For example, why did the attack take place? Have such attacks occurred before? How can it be prevented in the future?

Rodents. The rat family has chisel-shaped, continually erupting incisors with a diastema between the incisors and molars. They have no canines or premolars. The general dental formula is $I\frac{1}{1}\ C\frac{0}{0}\ P\frac{0}{0}\ M\frac{3}{3}$. The labial surface of the incisors is covered with enamel, while the lingual surface has cementum. Although rodents seldom attack humans, there are instances when these animals have nibbled at the extremities of dead bodies, producing peculiar injuries. It was, therefore, required to ascertain the nature of these injuries and rule out foul play. Also, Brown has reported cases where damage was inflicted on electric cables and fire extinguisher hoses. These were attributed to rat bites rather than suspected sabotage or vandalism.

Table 21.6 depicts some differences between human and carnivorous animal bite marks.

Lip Prints

The wrinkles and grooves visible on the lips have been named by Tsuchihashi as 'sulci labiorum rubrorum'. The imprint produced by these grooves is termed 'lip print', the examination of which is referred to as 'cheiloscopy'. These grooves are heritable and are supposed to be individualistic. Lip prints, therefore, can constitute material evidence left at a crime scene, similar to fingerprints. Lip prints were first classified by Santos into two categories:

Simple wrinkles

- Straight line
- Curved line
- Angled line
- Sine-shaped curve.

Table 21.6: Differences between human and carnivore bites

	Human	Animal
Arch size and shape	Broad, U-shaped; circular or oval	Narrow anterior aspect, V-shaped and elongated.
Teeth	Broad central and narrow lateral incisors; more blunt	Broad laterals, narrow centrals; sharper, longer canines
Injury pattern	Commonly bruising; laceration and avulsion less common	Severe laceration and avulsion; greater skin damage
Site	Breast, abdomen, nipple, thigh, back, shoulder	Extremities such as feet, legs, hands, arms; exposed skin

Compiled from Sweet (1995) and Brown (1992).

Compound wrinkles

- Bifurcated
- Trifurcated
- Anomalous.

Tsuchihashi later proposed a separate classification, dividing the pattern of grooves into six types (Fig. 21-23):

Type I – Clear-cut vertical grooves that run across the entire lip
Type I′ – Similar to type I, but do not cover the entire lip
Type II – Branched grooves
Type III – Intersected grooves
Type IV – Reticular grooves
Type V – Grooves that cannot be morphologically differentiated.

A combination of these grooves may be found on any given set of lips. To simplify recording, the lips are divided into quadrants similar to the dentition—a horizontal line dividing the upper and lower lip and a vertical line dividing right and left sides. By noting the type of groove in each quadrant, the individual's lip print pattern may be recorded. The above classification and method has enabled differentiation of lip print pattern between two individuals.

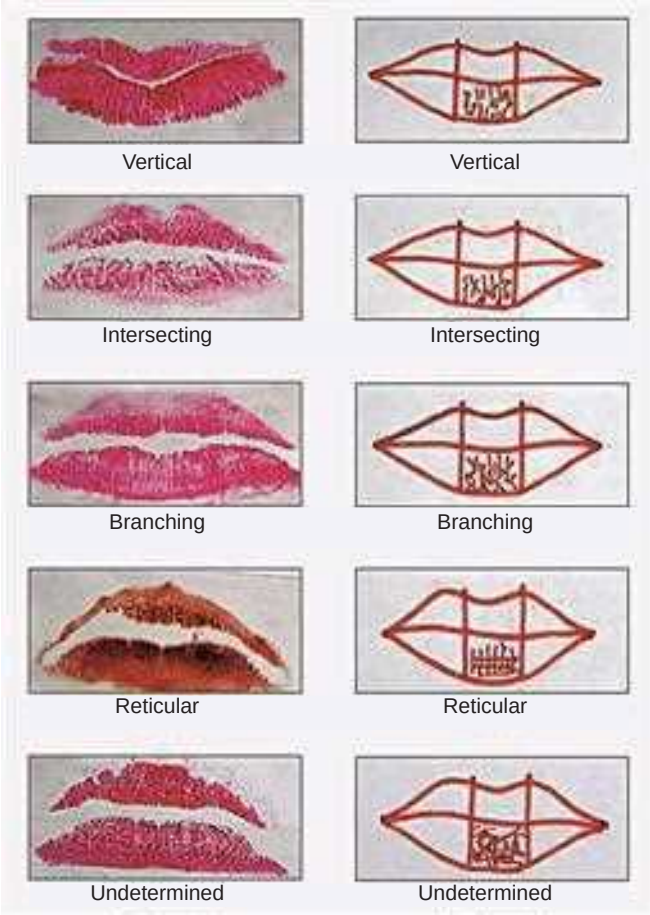


Figure 21-23: Different patterns of lip prints defined by Tsuchihashi. *(Courtesy of Sivapathasundharam B, Ajayprakash P, and Sivakumar G, Lip prints (chelioscopy). Indian J Dent Res 10:234–237, 2001.)*

Lip prints may be left at crime scenes and can provide a direct link to the suspect. Traditionally, the use of lipsticks was essential to leave behind colored traces of lip prints. In recent years, however, lipsticks have been developed that do not leave any visible trace after contact with surfaces such as glass, clothing, cutlery or cigarette butts. Nevertheless, these lipstick marks are characterized by their permanence and produce 'persistent' lip prints that can be recovered days after being produced. Although invisible, Alvarez and associates have shown that these prints can be developed and visualized using agents such as aluminum powder and magnetic powder. It is also interesting to note that the use of lipsticks is not indispensable for leaving lip prints. Ball states that the vermilion border has minor salivary glands and the edges of the lips have sebaceous glands with sweat glands in between. The secretions of oil and moisture from these enable development of 'latent' lip prints in most crime scenes, analogous to latent fingerprints, where close contact between the victim and culprit has occurred.

However, a major disadvantage of lip print investigation pertains to doubts about the permanence of lip groove patterns. While they are believed to remain unchanged throughout one's life, Sivapathasundharam and coworkers have cautioned that major trauma to the lips can result in scarring. They further add that surgical treatment rendered to correct any abnormality also affects the size and shape of the lips, thereby altering the pattern and morphology of the grooves. Another disadvantage, states Tsuchihashi, arises from the anatomic position of lip grooves on the zone of transition close to the vermilion border—a zone which is extremely mobile. Consequently, the prints produced may differ in appearance depending on the pressure applied and the direction of pressure. Hence, lip prints caused by one individual may be mistakenly identified as those from another. Therefore, Ball concludes that this sub-specialty of forensic odontology requires further study—first, to comprehensively establish the uniqueness of lip grooves and, second, to develop standard protocols for collecting and analysing lip prints, without which it will fail the rigors of court interrogation.

THE DENTIST AS AN EXPERT WITNESS

Forensic dentists who are associated with identification and crime investigation are usually required to provide testimony in the court of law in the capacity of an 'expert witness'. In addition, dental practitioners who assist in legal cases may, at times, be asked to do the same. According to Knight, "expert witnesses are those whose training, qualifications or experience enables them to give an opinion on a relevant matter where the ordinary person is not so enabled". Put simply, an expert witness is one who gives an opinion on facts that fall within the realm of his/her particular profession or specialization. Drinnan and Melton have pointed out that the Working Group on Forensic Odontology of the FDI has distinguished between the 'dental expert' and 'forensic dental expert'. While a qualified dentist can be an expert witness in dental matters, "additional

knowledge and experience" is essential for qualifying as a forensic expert; some courts may also deem it essential that a 'forensic dental expert' has a recognized qualification or board certification. Nevertheless, a qualified dentist, in the absence of a forensic odontologist, may be required to provide forensic dental related testimony. As experts, dentists may need to testify in cases involving malpractice, dental fraud, accidents and injuries, in addition to post-mortem identification, age estimation and bite mark investigation.

To the general practitioner not used to the nuances of court procedures, the experience can be intimidating. In any court hearing, the expert witness may appear for the prosecution or for the defense. It is useful at this point to draw attention to an expert's required attire. Knight and Clark suggest dressing well yet modestly, reflecting a professional persona. The adage 'image is everything' may not hold true, but image is something and complements the evidence given. The witness is usually first questioned by the side she/he is appearing for, followed by questioning by the lawyers of the opposing side. The latter is termed as cross-examination, and is the most challenging aspect of court testimony. The opposing counsel may indulge in character assassination, trying to weaken the expert witness and the evidence that is presented. Knight and Clark warn that "the temptation to become too partisan must be resisted, as a biased or angry witness is a careless and vulnerable witness, easily led into the traps" laid by shrewd lawyers. It is therefore advisable to control one's temper, keep calm, and be dispassionate. This, however, does not imply that the expert be timid. When in the witness box, the expert should speak up loud enough and with clarity, for everyone concerned to hear and comprehend.

It can be tempting to make bold statements while preparing reports and framing conclusions concerning postmortem dental identification, age estimation, or bite mark investigation. These signed statements form the basis of the expert's court testimony. Any change in opinion during questioning by the opposing lawyers can render the expert witness fallible. Stimson and Mertz advise that the expert witness must "always present the evidence and conclusions based on facts". Truth is paramount, and repeatable. Anything less is unethical, and possibly perjury (lying under oath). If the expert witness does not know the answer to a question raised by the lawyer, the expert should say so, and should never try to guess answers, or answer questions that are beyond one's expertise. To do so could be disastrous, with the opposing lawyer taking full advantage to undermine the expert's credibility. Opinion should be presented in such a way that it is accurate yet simple enough for the layperson to understand. The judge cannot be expected to be familiar with the technical terms of dentistry. It is also important to remember never to discuss matters pertaining to a case with anybody as long as the case is under trial. An exception is the lawyer on whose side the expert is testifying. The liberty to discuss the case with family, friends or colleagues may be taken only after judgment in the case has been passed. To summarize, the expert witness in particular, and the forensic odontologist in general, must be professional, unbiased, ethical, and truthful.

Acknowledgements

One of the authors (Ashith B Acharya) wishes to thank Prof C Bhasker Rao, former Director of SDM College of Dental Sciences and Hospital, Dharwad, for his encouragement and support to the development of forensic odontology. Many of the literature cited have been accessed from the Forensic Odontology Unit (FOU), School of Dentistry, The University of Adelaide, Adelaide (Australia), during this author's postgraduate study. The author wishes to thank Helen James, Director of the FOU, and other collegues from around the world for providing additional literature.

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Appendices

APPENDIX OUTLINE

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APPENDIX I

Introduction to Laboratory Analyses in Oral and Maxillofacial Pathology

■ PRAVEEN R ARANY

INTRODUCTION

The study of pathology involves the analysis of a variety of biological materials varying in their physiochemical compositions from viscous secretions to solid bone and enamel. The oral and maxillofacial region is an extremely complex milieu in terms of its functional composition of biological tissues and thereby the diagnostic techniques also involve a wide array of analytical methodology ranging from simple light rays to analyse enamel crystalline structure to sophisticated ultrastructural analyses of subcellular organelles.

This section is not an exhaustive summary of diagnostic methodology and is aimed at the dental student learning oral pathology and its diagnostic rationale. The emerging emphasis on molecular approaches is becoming a widely accepted norm in the clinics today and an attempt is made here to introduce these newer analyses without burdening the student with the intricate technical details. At the end of this chapter, an appendix of analytical techniques is provided with a brief description of its principle and application that are used routinely these days in a molecular pathology lab.

In an attempt to make a student appreciate the individual procedural steps in any pathobiological analyses, this section is divided into specific topics dealing with the collection and processing of the biological specimen followed by important conceptual rationale common to many of these methods. An attempt is also made to try and bridge the gap between the routine analyses and the more sophisticated molecular analyses by highlighting similarities between their principles and procedural components.

The practice of ancient medicine was entirely based on clinical manifestations and time-tested 'interventions' like blood letting or exotic herbs and concoctions. This form of medicine though potent in cases was not efficacious in its ability to treat every malady. All through the ages, basic sciences, without its numerous specialties as we know it nowadays, has largely developed autonomously of medicine. In the late 1800s the power of the microscope along with the hypothesis of **'germ theory'** bought the pathologist to the fore by his ability to assign a causative agent to many diseases. It was during this juncture that physicians realized that the rapidly developing field of basic sciences might benefit their own patient care. Thus began a rigorous effort to inculcate scientific reasoning and observations to every medical practice.

It is truly amazing that the predominant diagnosis of pathology even today is largely based on the clinical, histological and/or radiographic features despite having powerful technological tools available. It is prudent to point out that these simple yet time-tested analyses are usually sufficient for effective diagnosis and treatment planning for the majority of our clinical pathology cases. However, there is always the odd case that requires more sophisticated techniques, immunostaining being the most popular amongst them that are now used to unravel the subtle pathological markers. With the exponential growth of biomaterial and biomedical sciences, there is an increasing understanding of the infinitesimal components that contribute to the disease processes. The newer sophisticated techniques help us unravel these minuscule information that contribute to the pathology and thereby help us in our ultimate goals in improving patient care. Thus, the onus has shifted from the routine lab techniques to the more elaborate molecular analyses to accurately diagnose and prognosticate.

More importantly, the incessant quest for basic biological understanding of disease pathophysiology has nurtured the curiosity of the clinical-pathologist and the physician-scientist to use more elaborate analytical methodology. These clinical studies have, in turn, spawned the development of many basic sciences, techniques and applications. One classic example is the initial characterization of disease causing viruses by elaborate basic science techniques to isolate, culture, and characterize virus strains which have yielded tremendous amounts of information which we exploit nowadays by the use of virus-based techniques ranging from simple *in vitro* molecule transfer of recombinant DNA to *in vivo* clinical applications like gene delivery into tumors and gene therapy. As we unravel more details in the clinical presentations of nature's aberrations manifesting as pathologies by the use of using the more sophisticated tools developed in the labs at

our disposal, basic research has also gained many insights and avenues of potential mechanisms and manifestations.

SAMPLE ACQUISITION AND HANDLING

As the oral and maxillofacial region encompasses a range of extremely diverse tissue composition and architecture it is very important to customize the collection and storage of the specimen. There are two important aspects of specimen collection, nature of specimen and type(s) of analysis intended. In the pathology lab we deal with hard tissues like bone, enamel, dentin, cementum, aberrant calcifications, etc. and soft tissues like skin, mucosa, muscle, etc. as well as secretions like saliva, blood—whole, serum and plasma, gingival crevicular fluid, cystic excretions, etc. Due to this variability of the physical nature of specimens involved, there are many specialized reagents at our disposal but there is no universal collection buffer or solution for all possible analyses.

We will now briefly deal with the collection process requirements. Broadly, all sample collection protocols can be broadly classified based on their mechanism as physical, chemical agents or both. It is important to remember that the basis of this collection process is not to induce any artefactual changes by the process itself thereby retaining maximum 'original' information from the *in vivo* scenario, be it a physical or a chemical aberration, induced by the pathology. To cite an example of a physical agent, snap-freezing tissues in liquid nitrogen (–196°C) preserves molecules like the RNA and certain enzymes that would otherwise degrade at ambient room temperature. It is important to note however that tissues subjected to such a drastic physical manipulation may not retain their native morphological orientation making it unsuitable for certain architecture-based methods. Common examples of chemical reagents which are also the most routinely used for clinical collection are the buffered saline or formalin. An example of chemophysical agent is the cryo freezing of tissues with glycerol-alcohol mix (OCT compound) and dry ice.

For regular biochemical analysis, a good rule of thumb is to maintain the microenvironment similar to the local conditions existing in the tissues. That is, maintain similar pH, ionic balance and micromechanical (stretched versus curled) as in the sample's original anatomical location. Usually a good temporary (clinic to lab transit) would be buffered saline (all tissues) or formalin (usually soft tissue). It is important to note that prolonged storage (more than 12–24 hours) of the specimens even in these 'ideal' solutions might induce structural changes mimicking pathology and these are referred to as **'procedural or technical artifacts'.**

For molecular analysis, we have a variety of special reagents to help preserve and this primarily depends on the molecule of interest, broadly proteins or nucleic acids. There are other 'hybrid' or complex groups of molecules like glycoproteins or lipoproteins that usually require specialized methods of collection, processing and analyses.

In terms of ease of analysis, deoxyribose nucleic acid (DNA) is the easiest to work with because it is the most biologically robust molecule to procure and analyse even from archival specimens like hair, dried blood, fixed tissue sections or even exfoliated cells into secretions such as saliva. The other nucleic acid, ribose nucleic acid (RNA) is more fragile in terms of handling and storage due to the nature's abundance of RNA degrading enzymes (RNAses). Protein analysis is of intermediate stability as there are many protein chewing enzymes (proteases) in biological tissues capable of destroying protein structure but these are more easily kept in check with chemical inhibitors.

It is a common dilemma in a pathology lab to have a tissue routinely fixed in buffered formalin and paraffin embedded but following histopathology newer analyses might be desired. While this is not always possible, there is an increasing effort by many groups to attempt molecular analyses in these fixed tissues as seen by the growing literature available for wide ranging analyses ranging from polymerase chain reaction (PCR) to *in situ* hybridization protocols. A good lab practice, although not feasible in many clinical scenarios, is to always anticipate possible future analyses on encountering any clinical case so that appropriate measures are taken for tissue collection and storage.

SIGNIFICANCE OF BIOLOGICAL KINETICS: DYNAMICS AND REAL TIME ANALYSES

We must realize that once a specimen is removed from the subject (patient), it ceases to continue its biological activities, be it physiological or pathological. The observer must always appreciate that what we see outside the organism is a 'snap-shot' of its time-frozen biological dynamics. In pathology, it is imperative to realize that we study these snap-shots of aberrant tissue changes from the representative diseased tissues. In cases of biological responses to specific interventional treatment or progression of disease, a real time analysis involving serial or repeated specimens are most appropriate but are usually difficult in practice due to patient availability and ethical aspects of patient care (repeated biopsies). A simpler kinetic analysis in some situations is to utilize secretions like saliva or gingival crevicular fluid and/or noninvasive biopsy techniques like cytology and brush biopsies to follow the real time changes in disease or treatment parameters.

POSITIONAL INFORMATION AND USE OF QUALITATIVE VERSUS QUANTITATIVE ANALYTICAL TECHNIQUES

It is prudent to point out that the biological significance of a molecule is not dictated by its mere presence or absence but also other prime factors like its modulated expression or concentration (from physiological baseline) and its localization. The positional information is extremely important in determining if the molecule has any potent biological efficacy. For example, the mere presence of an increased levels of an extracellular secreted protein 'within' a cell does not subscribe to its functional relevance in terms of the tissue pathology being examined (Fig. AI-1).

Analytical techniques are broadly either **qualitative** or **quantitative,** that is; they either determine the presence or

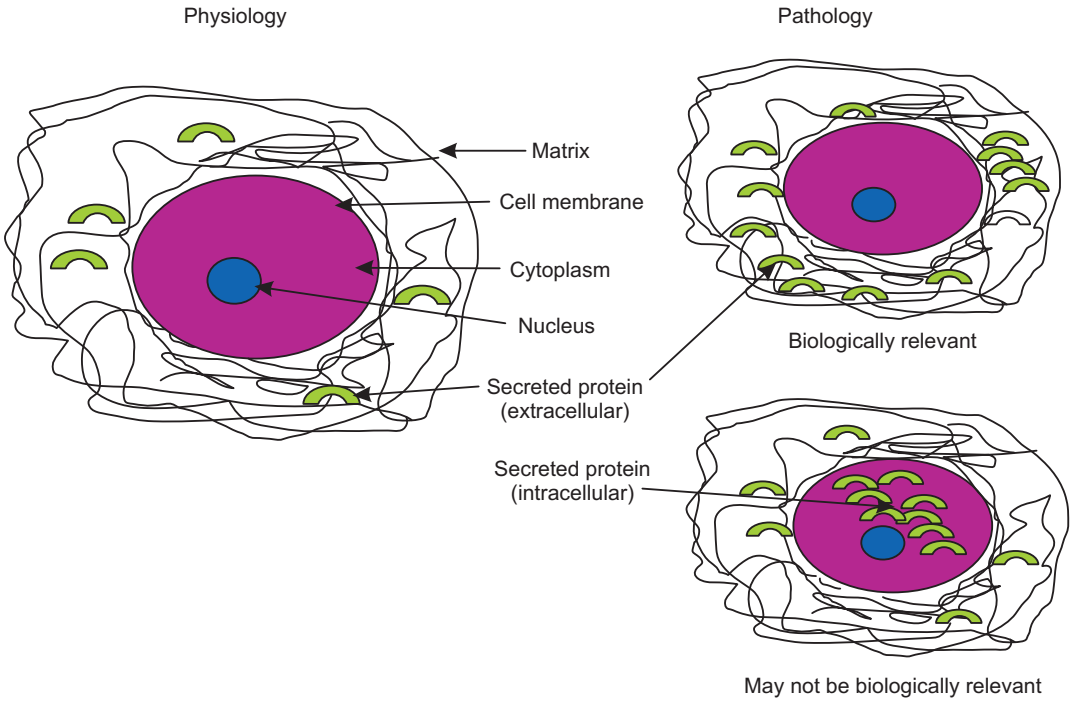

Figure AI-1. Importance of positional information of a molecule in elucidating pathophysiology.

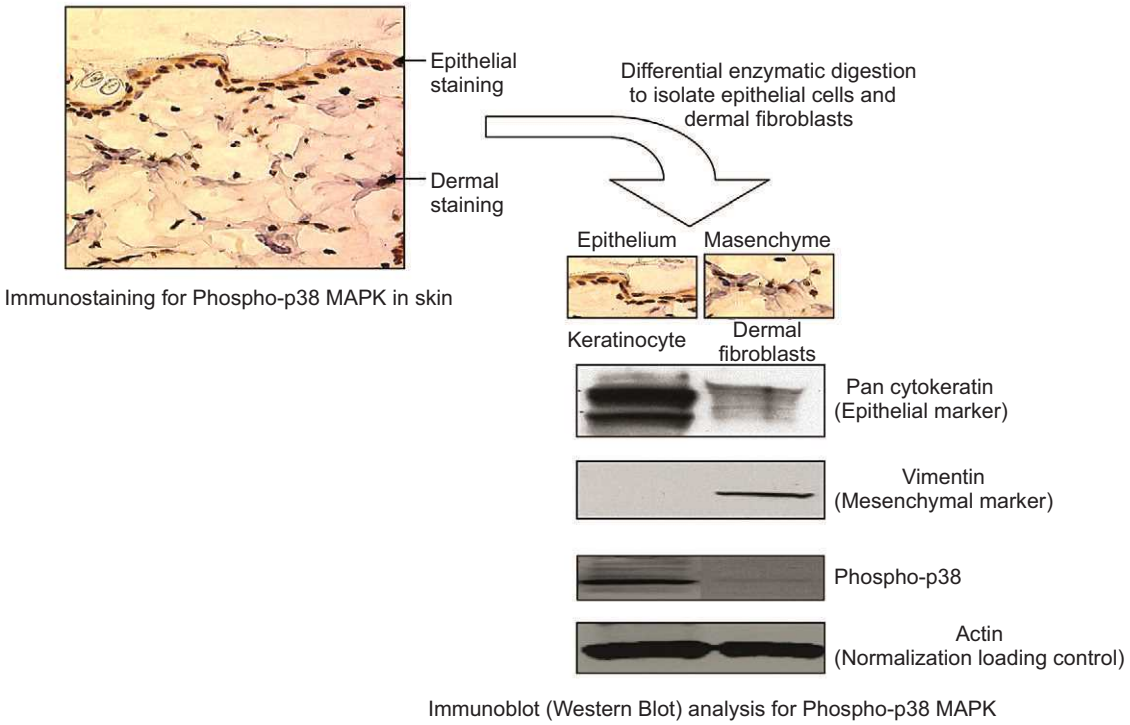

Figure AI-2. Qualitative versus quantitative analysis.

absence of a given molecule or define the precise stoichiometry. To cite an example for protein analyses, immunostaining for phospho-p38 MAPK (mitogen-activated protein kinase) in skin samples demonstrates qualitative positional information (epithelium versus mesenchyme or cytoplasmic versus nuclear) while an immunoblot (Western Blot) demonstrates the actual levels of phospho-p38 expression in the tissue fractions derived from the tissue sample (Fig. AI-2). Briefly, the skin was proteolytically digested with trypsin and collagenase to isolate fibroblasts and keratinocytes which

were then propagated in tissue culture before being analysed for their basal phospho-p38 activity by immunoblotting. The experiment shows the increased phospho-p38 MAPK expression observed in the epithelial compartment by immunostaining is also demonstrated quantitatively by the immunoblast as compared to its expression in the mesenchymal compartment.

It is also appropriate to point out that unlike in this mice experiment where we had sufficient tissue to proteolytic digest and isolate epithelial (keratinocytes) and dermal fibroblasts, the amount of routine human pathology tissue specimen is usually very limited. Thus, a better alternative to the proteolytic digestion in such small tissue samples would be techniques like laser capture microdissection or the now popular magnetic beads tagged with cell lineage specific antibodies.

It is always possible to use these qualitative techniques to obtain quantitative information and vice versa. The immunostaining pictures (qualitative) can also be analysed by histological densitometric analyses and an automated software programs (or manually by experienced histopathologists) for quantitation.

On the contrary using techniques to separate tissue sample component fractions like epithelium, fibroblasts and/or even subcellular organelles like golgi, mitochondria, or endoplasmic reticulum, etc. by the use of differential lysis buffer protocols, proteolytic digestion, magnetic bead separation, flow assorted cells sorting (FACS), laser capture microdissection (LCM) or differential elutriation (density dependent centrifugation) provide isolated fractions which can then be analysed quantitatively and also inherently provide positional (qualitative) information. A similar example for quantitative mRNA expression is northern blotting or qualitatively with *in situ* hybridization. It is important to emphasize again that every tissue sample that is procured might not be amenable to these different types on analyses, the primary determining factors being the amount and manner in which the sample is procured or received in the lab.

LEVELS OF INVESTIGATION

Classically, six levels of analytical investigations are utilized: **clinical** (gross), **histological** (tissues), **cytological** (cells), **organelle** (lysosomes, mitochondria, golgi, nucleolus, etc.) **molecular** (proteins, lipids, sugars, nucleic acids and their complexes) and **ultrastructural** (by electron microscopy). With the advent of newer exciting technologies like atomic force microscopy and nuclear magnetic resonance imaging the power of resolution is now in the nano (10^{9})—femto (10^{15}) meter range providing exciting avenues to explore the submolecular composition of biological tissues.

STRUCTURAL BASIS OF ANALYSES

Among the routine analytical techniques used in the pathology lab, it is amazing to note that most routine analyses still use the time-tested cornerstone of architectural changes to diagnose the disease pathology. The most popular and common analysis of hard tissue or soft tissue is to observe the changes in diseased sites compared to the 'normal' surrounding counterpart. The hard tissue analyses usually use the refractive properties of the differentially mineralized dental tissues (variable amount of crystalline inorganic deposits refract light differentially) and are observed with radiographs. The soft tissue analyses use the differential affinity of chemical dye components (or combination of dyes) to increase the contrast of their architectural constituents, e.g. hematoxylin and eosin.

It is appropriate at this point to elaborate the 'normal' or 'baseline' references that we use in our analyses. The commonly used counterparts are usually the clinically apparent nonaffected adjacent tissues or sometimes, if possible, the anatomic counterpart such as the 'normal' opposing buccal mucosa or retromolar pad. These are the best possible baselines for most anatomically discrete pathologies. Another common approach used is to compare tissues from similar anatomical sites between normal and diseased populations. While this approach may be appropriate in very large sample sizes to establish broad differences among the populations, it is inaccurate for smaller groups as it does not account for individual patient sample variations. Also certain parameters like disease progression or response to treatment are strictly dependent on the individual patient and on innumerable systemic, regional, and local variables like nutrition, circulatory factor, etc. and the most ideal analysis would be to use each patient as his/her own control by analyzing intrapatient parameters whenever possible.

These 'normal' references are usually erroneous for diffused pathologies like generalized manifestations of a systemic condition. A good example is oral lesions presenting in a patient with systemic sclerosis. Another significant area of pathology where these 'normalcy' is dubious is in the wide array of tumors we see in the oral and maxillofacial region. A controversial aspect is the use of adjacent 'normal' tissues from the 'safe margins' of resected tumors as these areas might have significant changes due to the advancing front of premalignant changes based on the concept of regional **'field cancerization'** first put forth by Slaughter in 1953. These reports raise critical questions about the use of the resected safe margins in many large-scale genomic or proteomic studies reported in the literature these days.

COMPONENTS OF ANALYTICAL METHODOLOGY

This section will deal with general principles of analytical methodology. Broadly, there are three major components of the analyses namely the **target,** the **probe** and the **visualization** procedure. Simplifying the methods would fit these three critical components and this basic foundation is to be appreciated by the student of oral biology. Some methods combine these components, inherently and are not seen as discrete components while the more sophisticated techniques have multiple steps for each component (Table AI-1).

Table AI-1: Components of analytical methodology

Analytical techniques	Target	Probe	Visualization process
Histochemical staining	Cells and tissues	Color stains	Microscopy
Immunostaining	Cellular and/or tissue protein components	Specific antibodies	Chemical or fluorescence tagged reaction
Western Blot	Proteins extracted from cells or tissues	Specific antibodies	Chemiluminescence
Fluorescent *in situ* hybridization (FISH)	Chromosomes	Specific oligonucleotides	Fluorescence
Southern blot	DNA	Specific oligonucleotides	Chemiluminescence or radioactivity

Target. A target is defined as the 'one to be influenced or changed by an action or event'. In analytical methodology it refers to a discrete entity that is to be examined by the analytical technique. It can be the whole organ like the tooth being studied in ground sections, the tissue in biochemical stains, the protein molecule in immunostaining, etc. The routine power of resolution is now at the ultrastructural level of cellular organelles and microfibrils while, as mentioned earlier, the advent of powerful new technological tools now has increased the power of ultrastructural resolution to the level of single atomic structures with techniques like atomic force microscopy.

The choice of a target can be based on its morphological nature or its chemical specificity. To cite examples of morphological targeting, the simple use of polarized light to examine crystalline dental structures or the use of immunological antibodies raised against the unique morphological structural conformations of specific proteins. The use of the chemical specificity to target molecules is one of the commonest methods when using biochemical dyes like hematoxylin and eosin which broadly target the acidic or basic nature of tissue components. A more sophisticated use of chemical targeting involves using the exquisitely specific chemical nature of nucleic acids encoded by their inherent base pair sequences (A, C, G and T or U) with techniques like southern blotting for DNA and northern blotting for RNA. Another popular technique is the use of polymerase chain reaction (PCR) where the primers are designed to bind extremely specifically to a given nucleotide sequence among the plethora of possible sequences within the cell.

Probe. A probe is defined as 'the act of exploring with a device or instrument'. In biology, a probe is defined as a substance that is radioactively labeled or otherwise marked and used to detect or identify another substance in a sample. In terms of analytical methodology, the broader use of the term probe can be extended to sources of electromagnetic radiations ranging from regular fiberoptic light devices to high power lasers, various biochemical dyes used to stain tissue or cell components, radiolabeled pieces of nucleic acids, immunological antibodies for proteins, etc.

The primary function of the probe is to ensure specificity to the target. A multicomponent probe, like a biochemical dye, can give a sufficient specificity for certain histopathology analysis while a critical degree of specificity is required for molecular analyses due to a similarity, at this level, of compositional constituents.

Visualization Process. The term visualization literally means to 'make visible'. This basically involves the procedural step(s) in detecting and demonstrating the probe-target complexes. Often the probing and visualization might be coupled to a single component like routine biochemical dyes or radioactive-labeled nucleic acid or primary antibodies. But the more sophisticated techniques usually utilize a multi step process including an amplification step after probing to increase the sensitivity along with the specificity of the analytical methodology. A standard protocol these days is to use two specific antigenic determinants on the target molecule to increase the specificity of the assay like the dual antibody **'Sandwich' ELISA techniques.** A common example of the amplification step is the use of high binding affinity complexes like the biotin-tagged secondary antibody and streptavidin-tagged enzyme or a similar gold-silver coupled complex. The final visualization with a provided substrate, like diaminobenzidine (DAB), completes the colorimetric determination (Fig. AI-3). The various color developing enzyme-substrate used are shown in Table AI-2.

The processes of visualization in the multi step analyses are divided into two parts, probe-coupled signal generation and detection. The detection itself utilizes five major approaches namely: microscopy, colorimetry specific fluorescence, chemical (enzyme-substrate) reactions or autoradiographic (radioactive isotope) assay. The colorimetry enzyme-substrate had been covered previously. The fluorescence emitting probes have the distinct advantage over the enzyme-substrate that unless excited by a particular wavelength of light (lasers) they are not visible and therefore allow simultaneous anatomical localization using multifluorescent probes on the same tissue section (Fig. AI-4). This figure demonstrates the simultaneous localization of the nucleus (with DAPI) and the F-actin organization throughout the cell with fluorescent labeled **Phalloidin**, a mushroom derived toxin that has very high affinity for actin. Some commonly used probes are listed in Table AI-3. An emerging new class of biological labels is the **'quantum dots'** that are tiny light-emitting particles on the nanometer scale with novel properties and applications that have opened new possibilities for ultrasensitive biochemical analysis and cellular imaging.

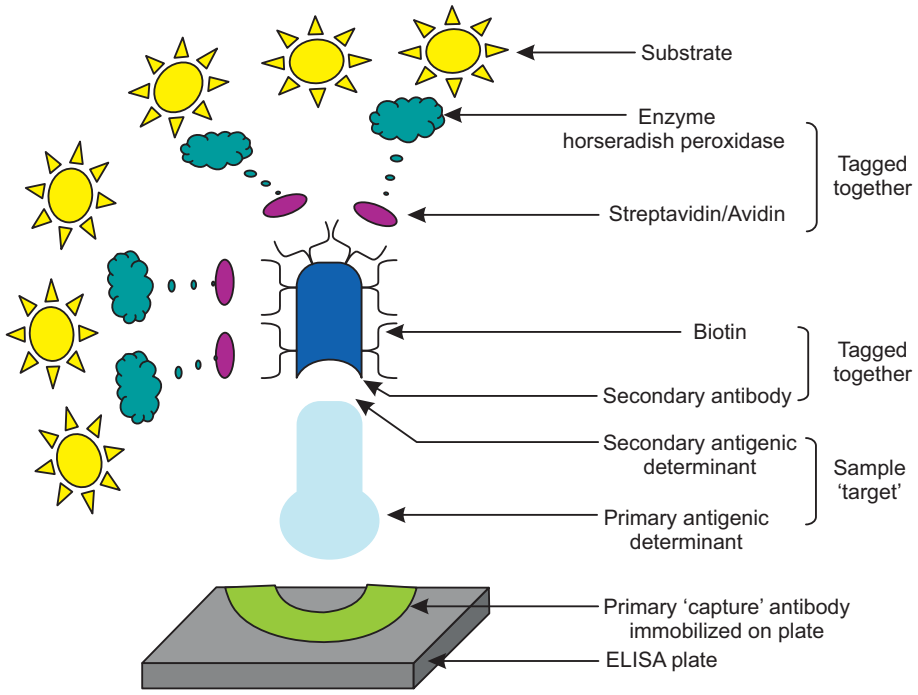

Figure AI-3. Amplification in analytical methodology.

Table AI-2: Color developing enzyme substrates

Enzyme label	Substrate	Dye	Color	Reading wavelength
	Hydrogen peroxide Hydrogen peroxide	Orthophenylene diamine (OPD) Tetra methylbenzidine (TMB)	Orange Yellow	492 nm 450 nm
Horseradish peroxidase	Hydrogen peroxide Hydrogen peroxide Hydrogen peroxide	2,2′-bis ethylbenzthiazoline sulfonic acid (ABTS) 5-aminosalicylic acid (5AS) Diaminobenzidine (DAB)	Green Black/brown Brown	414 nm 450 nm Visible by naked eye
Alkaline phosphatase	Paranitrophenyl phosphate (pnpp)	Paranitrophenyl phosphate (pnpp)	Yellow/green	405 nm

DAPI staining (360/460 nm) showing the nucleus of fibroblasts (single plane)

Phalloidin staining (496/520 nm) showing the F-actin or stress fibers in fibroblasts (single plane)

Digitally merged image showing cellular distribution of F-actin (multiple planes)

Figure AI-4. Fluorescence microscopy.

Table AI-3: Commonly used probes

Fluorochrome	Color	Excitation (nm)	Emission (nm)
4',6-diamidino-2-phenylindole (DAPI)	Blue	360	490–500
Propidium iodide (PI)	Red	340	600–610
Fluorescein isothiocyanate (FITC)	Green	490	525
Rhodamine	Red	596	615

IMMUNOLOGICAL-BASED TECHNIQUES

Due to the ever growing popularity, increasing applications and easy use of these immunological techniques, this section will try to give the student a brief rationale of the principle, development and limitations of this area.

The word 'immunity' comes form the Latin word *'immunis'* which means free of and was used in the context of being free of the burden of taxes or military conscription. The field of immunology is slightly more than 100 years old and Louis Pasteur is considered the 'father of immunology'. Cellular immunology has a more recent history beginning in the late 1950's. At the turn of the century, immunology developed into two schools of thought, the **humoralists** and the **cellularists.** The 'humoralists' believed that immunity was due to **humoral** substances, i.e. antibodies. Paul Ehrlich was a pioneer in this area who proposed the most plausible humoral theory of antibody formation, the **'side chain theory'.** Emil Von Behring, who worked at the Koch Institute in Germany, used serum to treat diseases. The 'cellularists' believed that immunity was due to the existence of **phagocytic** cells within our bodies. The pioneer of this concept was Eli Metchnikoff and became the strongest proponent of cellular immunity after observing water Daphnia phagocytose smaller materials and examining blood cells devour foreign bacteria in blood samples. Nowadays, we know that immunity is due to both of these facets of the immune system. With a better understanding of the intricacies of the immune system, researchers quickly learnt to exploit their new found knowledge to areas of analytical methodology. Amongst the earliest documented use of immunological based reagents in analytical technique was the insulin radioimmunoassay (RIA) by Solomon Berson and Rosalyn Yalow in 1959 for which Yalow was awarded the 1977 Nobel Prize in physiology and medicine.

In principle, all diagnostic methods in immunology involve the measurement of substances produced by the immune system. The use of the term immunological techniques in diagnostic pathology is often confusing as those that detect variances in the patient's immune system while others rely on the use of immunological reagents in their analytical methodology. The former 'immunological assays' are based on the generation of specific immunological molecules against native (autoimmune) or foreign antigens by the patient's immune system, for example, increased isotype specific immunoglobulins in multiple myeloma. While the latter termed 'immunodiagnostics' involves generation of specific molecule targeted immune reagents by introducing an 'antigenic gene product'. This is usually accomplished by injecting unique small peptide sequences of the target protein rather than the whole protein for ease of handling and increased specificity, in animals like rabbits, mice, donkey or goat. Another common method of generating antibodies is from cell cultures including the original B lymphocyte cell cultures called **'hybridomas'** and the now popular mammalian Chinese Hamster-Ovary (CHO) cell line. Examples are the generation of antibodies against specific molecules of interest like p53, collagens, cytokeratins, etc. An interesting historical anecdote here is that the origin of the Hybridoma technique was based on the original pathologist's observations of the single immunoglobulin secreting plasmacytomas. G Kohler and C Milstein used the Sendai virus to fuse B cells from the spleen of an immunized mouse with immortal myeloma cells in hopes that the hybrid cells (thus, hybridomas) would make antibodies specific to the antigen of interest and also grow continuously in tissue culture. They were awarded the Noble Prize in medicine in 1984 for pioneering this technique that has revolutionized various fields from the use of monoclonal antibodies in diagnostics to treating patients with various ailments.

Immunological diagnostic methods may be classified broadly into one of the following four groups: immunometric immunoassays (e.g. enzyme-linked immunosorbent assays/ fluorescence immunoassays or ELISA/FIA), competitive immunoassays (labeled analogs that compete with the substance being measured for binding to antibody), heterogeneous immunoassays (labeled antibody-bound material is separated from an unlabelled fraction before detection) and homogeneous immunoassays (no separation before detection).

The major limitation of these techniques is with the redundancy of the antigenic determinants which results in lower specificity (Fig. AI-5). Improved scientific techniques in terms of increased stringency with each assay done in duplicates or triplicates, use of multiple antigenic determinants along with multiple analytical assays have improved the accuracy, reliability and popularity of these immunodiagnostic techniques.

A summary of various laboratory analyses commonly employed in clinical practice is given in Table A1-4.

PROMISE OF THE GENOME

This chapter would seem incomplete without mentioning one of the most exciting scientific advancements of this century by the use of these very molecular techniques. The human genome has been unraveled by an international 13-year effort, formally begun in October 1990 and completed in 2003, to discover all the estimated 20,000–25,000 human genes along

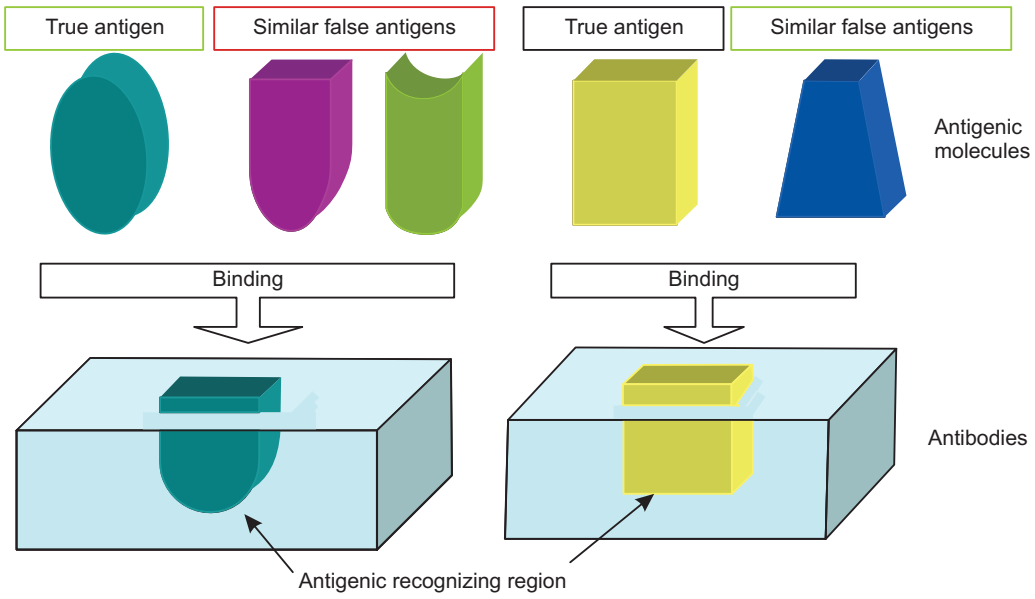

Figure AI-5. Redundancy of the antigenic determinations.

Table AI-4: Summary of laboratory analysis

Technique	Principle/mechanism	Target	Probe	Visualization
Flow cytometry	Sort cells based on their surface markers	Cells	Fluorescent labels, coulter machine (flow sorter)	Separated viable or nonviable cells, digital output
Elutriation	Sort cells or subcellular organelles based on their size and density	Cells	Centrifuge	Fractionated layers/ phases analysed further
Magnetic bead separation	Uses magnetic beads tagged to cell specific antibody that is then isolated by a strong magnet	Cells	Magnetic beads tagged to antibodies	Isolated cells are analysed/ cultured as desired
Enzymatic separation	Differential susceptibility of tissue components to enzymatic digestions	Tissues	Proteolytic digestion like trypsin, collagenase	Separated components are analysed further
Laser capture microscopy	Uses laser beams as 'optical tweezers' to isolate cells/ matrix components	Tissues	Laser beams	Microscopy
Electrophoresis	Separation of molecules based on their mobility (mass and charge) in an electrical field	DNA, RNA, proteins or their complexes	Electrical field and matrix gels or capillaries	Direct staining, radioactive labels, chemiluminescence
• Gel	Agarose (DNA & RNA) and acrylamide (proteins)			
• Free zone capillary electrophoresis	Performed in fused-silica capillaries			
Chromosome banding techniques	Banding due to differences in base composition, replication time, chromatin conformation and gene density	Cell nucleus	Stains like Giemsa, Leishman's, silver nitrate, quinacrine, diamino phenyl indole (DAPI), etc.	Microscopy fluorescence microscopes, digital outputs
• Solid staining	Chromosome breakage and fragile site studies			
• G banding	Highly condensed heterochromatin, AT rich most commonly used			
• Q banding	Fluorescence technique using the ability of quinacrine stain to bind DNA by intercalation of external ionic banding to study polymorphic variants on acrocentric chromosomes (1,3,9,16)			
• C banding	Dark staining of heterochromatin located at centromeres following DNA denaturation with alkali, also used to study chromosomal polymorphism			

Technique	Principle/mechanism	Target	Probe	Visualization
• R banding	Reverse pattern of G bands, stains the lighter G bands more darkly, GC rich, less condensed chromatin, stains telomeric regions of several chromosomes dark			
• Nucleolar organizer region (NOR) staining	Selective staining of active transcription sites of acrocentric chromosomes (13,14,15,21 and 22) encoding the constitutive genes 18S and 28S, used to study polymorphism and identifying small bisatellited marker chromosomes, and increased transcriptional activity of tumors			
• DAPI/distamycin staining	Uses stains Distamycin A-4 and 6-diamino-2-phenylindole to bind to AT rich regions, study small marker chromosomes derived from chromosome 15 and heterochromatin regions of other chromosomes			
Fluorescent *in situ* hybridization (FISH)	Used with interphase (nondividing) nucleus, gives molecular and cytogenetic information like characterizing chromosome and structural rearrangements, numerical abnormalities, microdeletions, duplications	Formalin fixed or frozen tissues, smears	Fluorochrome coupled single stranded complementary DNA probe	Fluorescence microscopy, digital imaging
• Primed *in situ* hybridization (PRINS)	Coupling FISH with denatured DNA and/or PCR amplification (cycling PRINS)			
• Fiber FISH	Denatured duplex DNA is stretched to obtain a high resolution DNA map			
Twenty-four color painting	Visualizes all 1-22 chromosomes and the sex chromosomes X,Y on the basis of their color, used to analyse markedly abnormal (tumor) cells and their derivative and marker chromosomes, marked chromosome rearrangements	Fixed or frozen tissues and smears	Uses five or more fluorochrome coupled single stranded complementary DNA probe	Fluorescence microscopy or inferometer (called spectral karyotyping) with digital imaging
Color banding	Complement G banding to detect rearrangements, deletions or duplications and further identify chromosome segment involved	Fixed or frozen tissues and smears	Fluorochrome coupled to Gibbon chromosomes which bind by complementarity to human chromosomes in a unique pattern	Fluorescence microscopy with digital imaging
Comparative genomic hybridization	Changes in DNA sequence copy numbers in terms of amplifications or deletions are tested by comparative hybridization of normal genomic reference DNA with test (tumor derived/diseased) genomic DNA to normal metaphase chromosome	Fixed or frozen tissues, smears genomic DNA	Differentially fluorochrome labeled reference and tumor	Fluorescence microscopy with digital imaging
DNAmicroarrays	Comparative hybridization on slides or membranes labeled with complementary DNA or oligonucleotides representing altered gene expression (DNA activity)	mRNA from tissues or cells	Spotted complementary sequences binding to differentially labeled (Cy3 or Cy5) reference and analytical mRNA	Fluorescence detectors with digital imaging
• RNA arrays	Direct hybridization on slides or membranes spotted with complementary single stranded DNA or oligonucleotides sequences	mRNA from tissues or cells	Spotted complementary sequences binding to chemically or radiolabeled mRNA	Autoradiography or chemiluminescence
Southern blot analysis	Complementarity of nucleic acid target to probe	Deoxyribonucleic acid (DNA)	Labeled single stranded DNA oligonucleotide (18–30 base pairs)	Gel electrophoresis film, digital imaging
Restriction fragment	DNA heterogeneity due to allelic length polymorphisms polymorphism, which may be inherited, makes an individual's genomes amenable to bacterial' restriction nuclease' digestions into specific patterns. Detects single/multiallelic mutations, similar inheritance patterns or genetic fingerprinting (forensics)	Genomic DNA	Restriction nucleases	Fragments can be visualized by southern blotting and radiolabelled probes or PCRs
• Variable number of tandem repeats (VNTR)	Larger repeats of 10–60 nucleotides			
• Micro-satellites (small tandem repeats)	Small individual repeats of 1–5 nucleotides. Microsatellite instability (MSI) is used in detecting genetic analysis of malignancies			

Technique	Principle/mechanism	Target	Probe	Visualization
• Single nucleotide polymorphism (SNIPs)	Individual nucleotide variations in DNA sequences			
Polymerase chain reaction	Uses compositional units of nucleic acids (nucleotides) with a DNA (Taq) enzyme to amplify and visualize them	DNA or RNA (reverse transcriptase- PCR) enzyme	Nucleotides, polymerase	Ethidium bromide agarose gel electrophoresis
Northern blot analysis	Complementarity of nucleic acid target to probe	Support-bound mRNA extracted from tissues or cells	Labeled single stranded nucleotide (18–30 base pairs)	Gel electrophoresis, film, digital imaging
RNA Mapping	Both are based on hybridization of RNA and antisense DNA protecting it from nuclease digestion	Low abundant mRNA	Complementary nucleic acid sequences	Nuclease protected fragments are visualized by electrophoresis or sequencing
Ribonuclease protection assay (RPA)	RPA uses A and T1 ribonuclease digestion for quantitative mRNA analysis			
S1 nuclease mapping	S1 mapping used S1 ribonuclease and is used for qualitative mRNA analysis like structure, intron-exon regions, 5′ or 3′ ends, mutational analysis			
In situ hybridization	Complementarity of nucleic acid target to probe, used for chromosome painting, analyse RNA localization, detection of viruses	Support -bound mRNA in tissue, cells or embryos	Radioactive or enzyme labeled complementary nucleic acid sequences (Oligos)	Autoradiography, fluorescence, chemiluminescence
Immunohistochemistry	Antibodies directed against antigenic immunocytochemistry determinant of a part or whole protein	Cells or tissues	Enzyme labeled antibodies	Chemiluminescence
Enzyme-linked immunoassay	Antibodies directed against antigenic determinant of the part/full protein	Protein from cell or tissue lysates, fluids like serum or plasma, secreted saliva, GCF	Enzyme labeled antibodies	Chemiluminescence
Protein electrophoresis	Based on differential migration of proteins depending on their isoelectric point in an electrical field	Cell or tissue lysates	Use of specific antibodies	Direct staining of gels, chemiluminesence
• Two dimensional				
• Western Blot				
Mass spectroscopy	Produces gas-phase ions from sample ionization and separated on the basis of their mass-to-charge ratio	Proteins	Ionization by chemicals, lasers, electrical fields	Digital readouts
Chromatography • Ion-exchange • Size exclusion • Hydrophobic interaction • Affinity • Gas • Reverse phase high pressure liquid (RPHPLC)	Broad range of physical methods used to separate and/or to analyse complex mixtures, components to be separated are distributed between two phases: a *stationary phase* bed and a *mobile phase* which percolates through the stationary bed	Lysates from cells or tissues	Different techniques	Digital readouts
Nuclear magnetic resonance (NMR) • 1D • 2D	Measures chemical shifts of the atoms' nuclei in the protein when it is placed in a powerful magnetic field allowing determination of its 3D structure	Tissues	Electrical field	Digital readouts

with the complete sequence of the 3 billion DNA subunits. This has ushered in a new era of molecular pathology as we now have the complete set of genetic informational pieces to correlate with pathological changes in form or function. These large scale 'global' changes in genetic information have helped us identify potential therapeutic targets while also giving us valuable clues about specific genetic susceptibility to many diseases allowing us to modify individual patient factors like diet, exercise or medications. These kind of large scale genetic analyses also allow us to better assess changes in the patient responses to therapy. The promise of gene therapy based on similar genetic analyses has also been realized in some hereditary diseases like severe combined immunodeficiency disease (SCID).

Although this explosion of information is extremely valuable in terms of our understanding the biological changes, it is also pertinent to point out that changes in DNA or RNA are not usually sufficient to extricate its complete biological function of the gene which is usually implicit with the protein levels. The presence, concentration, and location of the proteins either

structural or functional (e.g. enzymes) are extremely crucial to unravel its role in physiology as well as pathology. To cite an analogy, we now have alphabets of the human biological language but we need to further our understanding of how these are put together to make the words and sentences for the poetry of physiology and the prosaism of pathology.

The realization that the functional players also need to be elucidated has spurred many levels of investigations, especially the rapidly emerging field of 'proteomics', the study of all structural and functional proteins. The latter subgroup of functional 'signaling' or 'activating' (kinases) group of proteins is also referred to as the 'kinome'.

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APPENDIX II

Mucosal Response to Oral Prostheses: Some Pathological Considerations

■ MAHESH VERMA AND PRIYA KUMAR

The treatment modalities which deal with the replacement of missing teeth and contiguous structures with a suitable prosthesis can be broadly classified as removable and fixed.

Though the prostheses are designed and fabricated with the aim to conserve the tissues and perpetually maintain those structures that remain, there are occasions when the prosthesis acts as an etiological factor for certain pathologies either by virtue of an error from the operator, inadequate maintenance by the patient, or the properties of the material used.

The basic lesions which are caused by removable prostheses include oral mucosal lesions, burning mouth syndrome (BMS), allergic response to denture base materials and fungal infections related to soft liner, traumatic lesions associated with metallic clasps and the phenomenon of residual ridge resorption (which still remains an enigma).

With fixed prostheses the most common lesions are secondary caries, pulpal and periodontal inflammation due to improper contours and margins of restorations, allergic reactions, and occlusion-related problems which range from changes in muscles of mastication to temporomandibular joint disorders. The latest treatment modality of implant-supported prostheses also entails the pathology of peri-implantitis.

DENTURE IN THE ORAL ENVIRONMENT

Placement of a removable prosthesis in the oral cavity produces profound changes of the oral environment that may have an adverse effect on the integrity of oral tissues.

Mucosal reactions could result from:

- Mechanical irritation by the denture.
- Accumulation of microbial plaque on the denture.
- Occasionally, toxic or allergic reaction to constituents of the denture material.

The continuous use of dentures may have a negative effect on the residual ridge form because of bone resorption. Furthermore, wearing complete dentures that function poorly and that impair masticatory function could be a negative factor with regard to the maintenance of adequate muscle function and nutritional status, particularly in older persons.

There are several aspects of the interaction between the prosthesis and the oral environment. Surface properties of the prosthetic material may affect plaque formation on the prosthesis; however, the original surface chemistry of the prosthetic material is modified by the acquired pellicle and thus is of minor importance for the establishment of plaque. On the contrary, surface irregularities or microporosities greatly promote plaque accumulation by enhancing the surface area exposed to microbial colonization and by enhancing the attachment of plaque. Furthermore, plaque formation is greatly influenced by environmental conditions such as the design of the prosthesis, health of adjacent mucosa, composition of saliva, salivary secretion rate, oral hygiene, and denture-wearing habits of the patient.

The presence of different types of dental materials in the oral cavity may give rise to electrochemical corrosion, but changes in the oral environment due to bacterial plaque may constitute an important cofactor in this process. Corrosive galvanic currents have been implicated in BMS, oral lichen planus, and altered taste perception. Most often it is difficult to establish a definite causal relationship. For instance, local irritation of the mucosa by the dentures may increase mucosal permeability to allergens or microbial antigens. This makes it difficult to distinguish between a simple irritation and an allergic reaction against the prosthetic material, microbial antigens, or agents absorbed to the prosthesis capable of eliciting an allergic response.

The matter is further complicated by the fact that certain microorganisms are able to use methylmethacrylate as a carbon source, thereby causing a chemical degradation of the denture resin. In the interface between a prosthesis and the oral mucosa, microbial plaque may have important negative or harmful effects. Thus a prosthesis may promote infection of the underlying mucosa, caries, and periodontal disease adjacent to overdenture abutments, periimplant gingivitis, and chemical degradation or corrosion of prosthetic materials.

Sequelae Caused by Wearing Removable Prostheses

1. Mucosal reactions
2. Inflammation caused by galvanic currents
3. Altered taste perception
4. Burning mouth syndrome
5. Gagging
6. Residual ridge reduction
7. Periodontal disease (abutments)
8. Caries (abutments).

INTERACTION OF PROSTHETIC MATERIALS AND THE ORAL ENVIRONMENT

Surface Properties: Plaque Accumulation

Chemical stability
Adhesiveness
Texture
Microporosities
Hardness.

Chemical Properties

Corrosion
Toxic reactions
Allergic reactions.

Physical Properties

Mechanical irritation
Plaque accumulation.

Changes of Environmental Conditions

Plaque microbiology.

DIRECT SEQUELAE CAUSED BY WEARING DENTURES

Denture Stomatitis

The pathological reactions of the denture-bearing palatal mucosa appear under several titles and terms such as denture-induced stomatitis, denture sore mouth, denture stomatitis, inflammatory papillary hyperplasia, and chronic atrophic candidosis. The term **denture stomatitis** is used with the prefix **Candida-associated** if the yeast *Candida* is involved. In the randomized populations, the prevalence of denture stomatitis is about 50% among complete denture wearers. Detailed clinical and histologic features are discussed elsewhere.

Flabby Ridge

Flabby ridge (i.e. mobile or extremely resilient alveolar ridge) occurs due to replacement of bone by fibrous tissue. The bone may be grossly resorbed often upto level of anterior nasal spine. It is seen most commonly in the anterior part of the maxilla, particularly when there are remaining anterior teeth in the mandible, and is probably a sequela of excessive load of the residual ridge and unstable occlusal conditions. Histologically there is marked fibrosis, inflammation, and resorption of the underlying bone. Flabby ridges provide poor support for the denture, and it could be argued that the tissue should be removed surgically to improve the stability of the denture and to minimize alveolar ridge resorption. However, in a situation with extreme resorption of the maxillary alveolar ridge, flabby ridges should not be totally removed, as it would result in the elimination of vestibular sulcus. Indeed the resilient ridge may provide some retention for the denture. Such ridges may cause problems during implant placement as there will not be sufficient volume for implant placement without bone grafting.

Denture Irritation Hyperplasia

A common sequela of wearing ill-fitting dentures is the occurrence of hyperplasia of the mucosa in contact with the denture border. The lesions are the result of chronic injury by unstable dentures or by thin, overextended denture flanges. The proliferation of tissue may take place relatively quickly after placement of new dentures and is normally not associated with marked symptoms. However, this lesion may sometimes represent a squamous cell carcinoma that has proliferated around the denture flange, therefore excision and histopathological examination is a must.

The lesions may be single or quite numerous and are composed of flaps of hyperplastic connective tissue. It is characterized by the development of elongated rolls of tissue in the mucolabial or mucobucccal fold area into which the denture flange conveniently fits. It is less commonly seen along the lingual sulcus. Inflammation is variable; however, in the bottom of deep fissures, severe inflammation and ulceration may occur. After replacement or adjustment of the dentures, the inflammation and edema may subside and produce some clinical improvement of the condition. After surgical excision of the tissue and replacement of the denture, the lesions are unlikely to recur. A less commonly encountered variant of denture hyperplasia is **leaf-like denture fibroma**. This lesion is observed on the hard palate beneath a maxillary denture. It is a flattened pink mass attached to the palate by a narrow stalk. Usually, it lies in close approximation to the palate and fits into a cupped out depression. Edges of the lesion appear serrated and resemble a leaf. For further discussion refer Chapter 12—Physical and Chemical Injuries of the Oral Cavity.

Traumatic Ulcers

Traumatic ulcers or sore spots most commonly develop within one to three days after placement of new dentures. The ulcers are small, painful, covered by a gray necrotic membrane and surrounded by an inflammatory halo with firm, elevated borders. The direct cause is usually overextended denture flanges or unbalanced occlusion. Conditions that suppress resistance of the mucosa to mechanical irritation are predisposing (e.g. diabetes mellitus, nutritional deficiencies, radiation therapy, or xerostomia). In the systemically non-compromised host, sore spots will heal a few days after correction of the dentures. When no treatment is instituted,

the patient will often adapt to the painful situation, which subsequently may develop into a denture irritation hyperplasia.

Angular Cheilitis

(Angular cheilosis, perléche)

Angular cheilitis is a multifactorial disease affecting the commissure of the lips and is commonly seen in denture wearers. A clinical diagnosis of angular cheilitis is arrived at when other specific lesions of the lip such as recurrent herpes labialis, ulceration due to known trauma, environmental exposure, or syphilis are ruled out. This common condition of the lip has been associated with several predisposing factors such as infection, nutritional deficiencies, and reduced vertical dimension of the mouth as seen in old age and in long-term denture wearers.

In these patients, due to loss of occlusal height in old age or due to incorrectly designed or worn out dentures, deep folds of skin are produced at the corners of the mouth. Saliva tends to collect in these areas and the skin becomes macerated and fissured, predisposing to infection. A majority of infections are *Candida*-associated, with nearly 20% of the cases arising due to *Candida albicans* alone, 60% due to a combined infection with *Candida albicans* and *Staphylococcus aureus,* and 20% due to *Staphylococcus aureus* alone. Further, in nearly 80% of the cases of angular cheilitis, there is a co-existent denture stomatitis.

Nutritional deficiencies such as iron deficiency anemia, vitamin B, or folic acid deficiency have been strongly implicated in angular cheilitis, referred to as **perléche**. Ariboflavinosis induces circumoral lesions which are prone to become infected and when this happens, the lesions are indistinguishable from the pērleche of other causes. Other uncommon predisposing factors include diabetes, neutropenia, and AIDS.

Clinical Features. Angular cheilitis occurs in both young children and adults and is characterized symptomatically by a feeling of dryness and a burning sensation at the corners of the mouth. Clinically, the skin at the commissure appears wrinkled and somewhat macerated. In time, the wrinkling becomes more pronounced to form one or more deep fissures or cracks which appear ulcerated, but which do not tend to bleed, although a superficial exudative crust may form (Fig. AII-1). These fissures do not involve the mucosal surface of the commissure inside the mouth, but stop at the mucocutaneous junction. The severity of the lesions waxes and wanes. If the lesions are not treated, they often show a tendency for spontaneous remission. Subsequent exacerbation is common, however, and only rarely do the lesions completely disappear.

Cheilocandidiasis and **juvenile juxtavermilion candidiasis** refer to more extensive and often desquamative lesions affecting the full width of the lip, even extending into adjacent lesions. They are associated with habitual lip sucking, prolonged dental appointments, sunlight, and chronic candidal infection. Differential diagnoses of these lesion include perioral erythema and Id reaction (localized sterile vesiculopapular rash).

Treatment. The treatment of angular cheilitis is empirical at best because of the apparently varied etiology. It should be remembered that the infection present is secondary and that, unless the primary cause is corrected, treatment of the infection will not produce a permanent cure.

Oral Cancer in Denture Wearers

An association between oral carcinoma and chronic irritation of the mucosa by the dentures has often been claimed, but **no definite proof seems to exist.** Case reports have detailed the development of oral carcinomas in patients who wear illfitting dentures. The opinion is still valid that if a sore spot does not heal after correction of the denture, malignancy should be suspected. Patients with such lesions and clinically aberrant manifestations of denture irritation hyperplasia should be referred immediately to a pathologist. It should be recognized that the prognosis is poor for oral carcinomas, especially for those in the floor of the mouth.

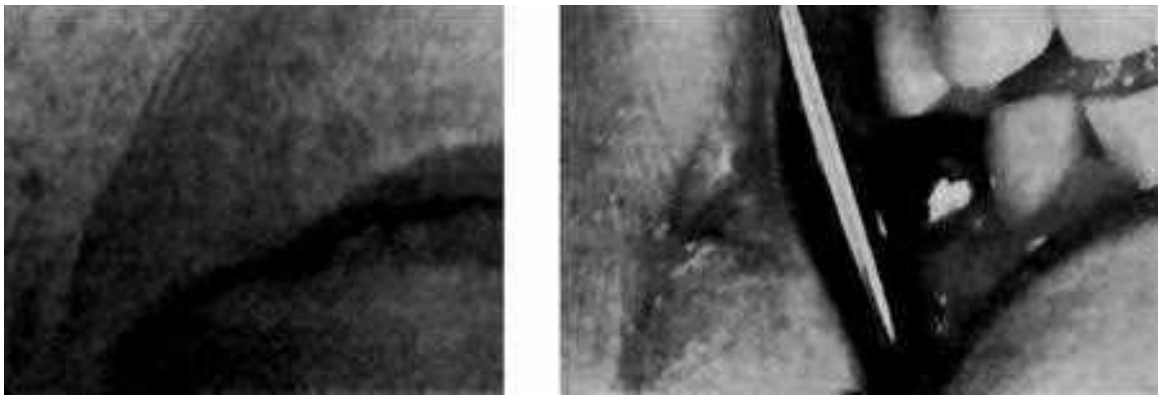

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Figure AII-1. Angular cheilitis associated with decreased intermaxillary space.
(A) Mouth closed, showing deep fissure at angle of mouth. **(B)** Mouth opened, showing typical lesions.

Burning Mouth Syndrome

Burning mouth syndrome could be a sequela of denture wearing and is characterized by a burning sensation in one or many areas in contact with the dentures. It is seen in around 5–7% of the denture wearing population. It is relevant to differentiate between **burning mouth sensations** and **BMS.** In the former group, the patient's oral mucosae are often inflamed because of mechanical irritation, infection, or an allergic reaction. In patients with BMS, the oral mucosa usually appears clinically healthy.

The vast majority of those patients affected by BMS are older than 50 years of age, female, and wear complete dentures. In the edentulous patient wearing complete dentures, burning sensations from the upper denture bearing tissues and the tongue are common complaints, particularly in postmenopausal women. Usually, there are no overt clinical signs, but the symptoms often appear for the first time in association with the placement of new dentures.

Characteristically, the symptoms have a gradual onset, and the pain is often present in the morning and tends to become aggravated during the day. The quality of pain is a burning sensation associated with a feeling of dry mouth and persistent altered taste sensation. Other associated symptoms may include headache, insomnia, decreased libido, irritability or depression. Aggravating factors include tension, fatigue, and hot or spicy foods, whereas sleeping, eating, and distraction reduce pain intensity.

BMS has been classified by Lamey and Lewis (1989) into the following three types:

Type I (33%)—There are no symptoms on waking. Burning sensations soon commence and increase as the day progresses. Symptoms are seen everyday.

Type II (55%)—Symptoms are present on waking and persist throughout the day and are seen everyday.

Type III (12%)—Intermittent symptoms throughout the day and symptom free days.

Etiological Factors. A multitude of causative factors have been described for BMS, which can be classified into three main categories: **local, systemic,** or **psychogenic.**

Possible Causes of Burning Mouth Syndrome

Local factors
- Mechanical irritation
  - Denture faults
  - Residual monomer
- Allergy
- Infection
- Parafunctional oral habits
- Myofascial pain
- Smoking
- Mouthwashes.

Systemic factors
- Vitamin deficiency
- Iron deficiency anemia
- Xerostomia
- Menopause
- Diabetes mellitus
- Parkinson's disease
- Medication.

Psychogenic factors
- Depression
- Anxiety
- Psychosocial stress.

Gagging

The gag reflex is a normal, healthy defense mechanism. Its function is to prevent foreign bodies from entering the trachea. Gagging can be triggered by tactile stimulation of the soft palate, the posterior part of the tongue, and the fauces. Usually, this may be due to a denture that is too loose, too thick or extended too far posteriorly onto the soft palate. However, other stimuli such as sight, taste, noise, as well as psychological factors, or a combination of these, may trigger gagging. In sensitive patients, the gag reflex is easily released after placement of new dentures, but it usually disappears in a few days as the patient adapts to the dentures. In wearers of old dentures, gagging may be a symptom of diseases or disorders of the gastrointestinal tract, adenoids or catarrh in the upper respiratory passages, alcoholism, or severe smoking. Psychological gagging is most difficult to treat since it is out of the dentist's control. In such cases, an implant supported palateless denture may have to be constructed.

Residual Ridge Reduction (RRR)

Longitudinal studies of the form and weight of the edentulous residual ridge in wearers of complete dentures have demonstrated a continuous loss of bone tissue after tooth extraction and placement of complete dentures. The residual ridge changes its shape and progressively reduces in size at varying rates. This ridge resorption rate varies in different individuals and in the same individual at different times. There is one school of thought that the RRR is a physiological phenomenon on the premise that the removal of the tooth eliminates the relevance of the alveolar bone. But RRR is not inevitable, and can proceed beyond the alveolar bone into the basal bone and hence widely believed to be a pathological process. The basic change in RRR is the reduction in the size of the bony ridge under the mucoperiosteum which may sometimes leave the overlying mucoperiosteum excessive and redundant. RRR does not stop with residual ridge, but may go well below where apices of teeth were, sometimes leaving only a thin cortical plate on the inferior border of the mandible or virtually no maxillary alveolar process of the upper jaw.

Overdenture Abutments: Caries and Periodontal Disease

The retention of selected teeth to serve as abutments under complete dentures is an excellent prosthodontic technique.

However, the wearing of overdentures is often associated with a high risk of caries and progression of periodontal disease of the abutment teeth. The reason for this is, the bacterial colonization beneath a close-fitting denture is enhanced, and good plaque control of the fitting denture surface is generally difficult to obtain. *Streptococcus* and *Actinomyces* predominating in denture plaque are well known for their major contributions to dental plaque on smooth enamel surfaces, as well as on cementum. The inflammatory potential of these species is illustrated by the finding that early dentogingival plaque (in which they also predominate) initiates gingivitis after one to three days of plaque accumulation when oral hygiene practices is discontinued. Caries rates, up to 30% after one year have been observed in patients wearing overdentures. For an increased success of overdentures, effective prevention of caries and periodontal diseases is necessary. The principal aim of the preventive measures should be to control accumulation of plaque on the exposed dentin of the abutment teeth as well as the root surface.

INDIRECT SEQUELAE

Atrophy of Masticatory Muscles

It is essential that the oral function in complete denture wearers is maintained throughout life. The masticatory function depends on the skeletal muscular force and the facility with which the patient is able to coordinate oral functional movements during mastication. Maximal bite forces tend to decrease in older patients. Furthermore, computed tomography studies of the masseter and the medial pterygoid muscles have demonstrated a greater atrophy in complete-denture wearers, particularly in women. This indicates that reduced bite force and chewing efficiency are sequelae caused by wearing complete dentures, resulting in impaired masticatory function. There is little evidence that the placement of a new denture significantly improves masticatory efficiency. Indeed, elderly denture wearers often find that their chewing ability is insufficient and that they are obliged to eat soft foods.

Nutritional Deficiencies

Aging is often associated with a significant decrease in energy needs as a consequence of a decline in muscle mass and decreased physical activity. Thus a 30% reduction in energy needs should be and usually is accompanied by a 30% reduction of food intake. However, with the exception of carbohydrates, the requirement for virtually all other nutrients does not decline significantly with age. As a consequence, the dietary intake by elderly individuals frequently reveals evidence of deficiencies, which is clearly related to the dental or prosthetic status.

It would appear that replacing missing teeth with removable or complete dentures would improve chewing and limit risk of nutritional problems. Indeed, change from poor natural dentition to edentulousness to complete dentures is generally accompanied by improved chewing efficiency and nutritional status. Properly fitted dentures may allow one to choose from a wide selection of food; however, a denture wearer does not have the chewing efficiency enjoyed by a person with natural teeth and studies have shown that the chewing efficiency of a denture wearer is 15–25% of that of an individual with natural teeth. More importantly, problems with denture fit, bone shrinkage, and gum tissues supporting the dentures compromise masticatory function and may negatively alter dietary intake.

Denture wearers generally avoid food that are difficult to manipulate and chew. Approximately, five times more effort is required for an average person wearing complete dentures to pulverize food to the same degree when compared to a person with natural dentition.

Severe nutritional deficiencies are rare among healthy individuals, even with poor masticatory function. However, in chronically ill or hospitalized patients nutritional deficiencies are frequent. In these patients, factors such as ill-fitting dentures, salivary gland hypofunction, or altered taste perception may have a negative effect on dietary habits and nutritional status.

Masticatory Ability and Performance

One of the strong indications for prosthodontic treatment is to improve masticatory function. In this context, the term **masticatory ability** is used for an individual's own assessment of his or her masticatory function, whereas **efficiency** is to be understood as the capacity to reduce or grind food during mastication.

As previously mentioned, the wearing of complete dentures greatly compromises both masticatory ability and performance as compared with a situation with natural teeth present. There is no striking evidence that malnutrition could be a direct sequela of wearing dentures. However, edentulous women have a higher intake of fat and a higher consumption of coffee and a lower intake of ascorbic acid compared with dentate subjects within the same age group.

Allergic Reactions

Intraoral contact allergy reactions are poorly described and understood, and are not very commonly dealt with in the specialized literature. Although such reactions appear to be scantily relevant, evidence suggests that they may be more frequent than previously believed. No single or specific clinical picture of intraoral contact allergy exists, though **lichenoid reactions** appear to be the most common manifestations. Epicutaneous patch testing, together with the clinical manifestations, constitute the most widely used diagnostic approach in such situations. Metals used in dental practice—particularly amalgams and base metal alloys (Ni)—are the most commonly reported causes of intraoral allergic reactions, though hypersensitivity to resins is mentioned in the literature as a consequence of their increasingly widespread use.

The systematic intraoral elimination or substitution of materials inducing cutaneous hypersensitivity has recently been

questioned while, on the other hand, it is not possible to discard an allergic component in some nonspecific stomatological disorders.

Fisher first described allergic sensitization of the skin and oral mucosa to acrylic resin denture materials in 1956, and methacrylates are now well recognized as contact allergens. Two reviews of patch testing with methacrylates have identified the most common allergens to be 2-hydroxyethylmethacrylate (2-HEMA), and triethylene glycol dimethacrylate. This cannot be interpreted as an accurate ranking because many methacrylate compounds contain undeclared 'other' components. In spite of the widespread use of methacrylates in dental materials, in a study of Swedish dentists with hand eczema only 5% showed positive patch test reactions to methacrylates, all of them reacting to HEMA and most also to ethyleneglycol dimethacrylate (EGDMA). Intraoral reactions in patients are less common. In a 15-year study of patch testing to methacrylates, 67 patients with positive reactions were identified, 47 of whom had been sensitized at work and no oral reactions in dental patients were reported. Methacrylates have rarely been implicated in oral lichenoid reactions. Two patients with severe gingivostomatitis have been described, caused by sensitivity to an epoxy diacrylate and the other to methyl methacrylate in a provisional crown.

The prevalence of intraoral contact allergy (IOCA) to the materials used in dental practice appears to be relatively low. The great majority of allergic reactions to dental materials correspond to type IV delayed hypersensitivity phenomena mediated by T lymphocytes. Dental amalgams are the most common origin of IOCA. The current very widespread use of acrylic materials will surely lead to an increase in the number of allergic phenomena. In order for a material (metal or otherwise) to induce allergic manifestations, it must first undergo corrosion and particle release. No single or pathognomonic IOCA lesion exists, though lichenoid reactions are the most frequent clinical manifestations associated with the disorder. Positive epicutaneous patch testing affords a diagnostic orientation that must be accompanied by clinical manifestations to secure a diagnosis of IOCA. Cutaneous and intraoral hypersensitivity reactions are not always analogous. The systematic withdrawal or replacement of restorations containing materials that yield a positive epicutaneous test is not warranted. Allergy can be included in the differential diagnosis of many nonspecific or unclear intraoral clinical disorders.

Peri-implantitis

Peri-implantitis is defined as an inflammatory process affecting the tissues around an osseointegrated implant in function, resulting in loss of supporting bone. The term periimplant mucositis is used for reversible inflammation of the soft tissues surrounding implants in function. It has also been described as 'a site-specific infection yielding many features in common with chronic adult periodontitis' or 'an inflammatory, bacterial driven destruction of the implant-supporting apparatus'. The overall frequency of peri-implantitis is reported to range from 5% to 8% in various long term studies.

The soft and hard tissues surrounding an osseointegrated implant show some similarities with the periodontium of the natural dentition (Fig. AII-2). A big difference lies in the collagen fibers being non-attached and parallel to the implant surface instead of being perpendicular and in a functional arrangement from bone to cementum as seen in periodontal ligament. Peri-implantitis is a periodontitis-like process

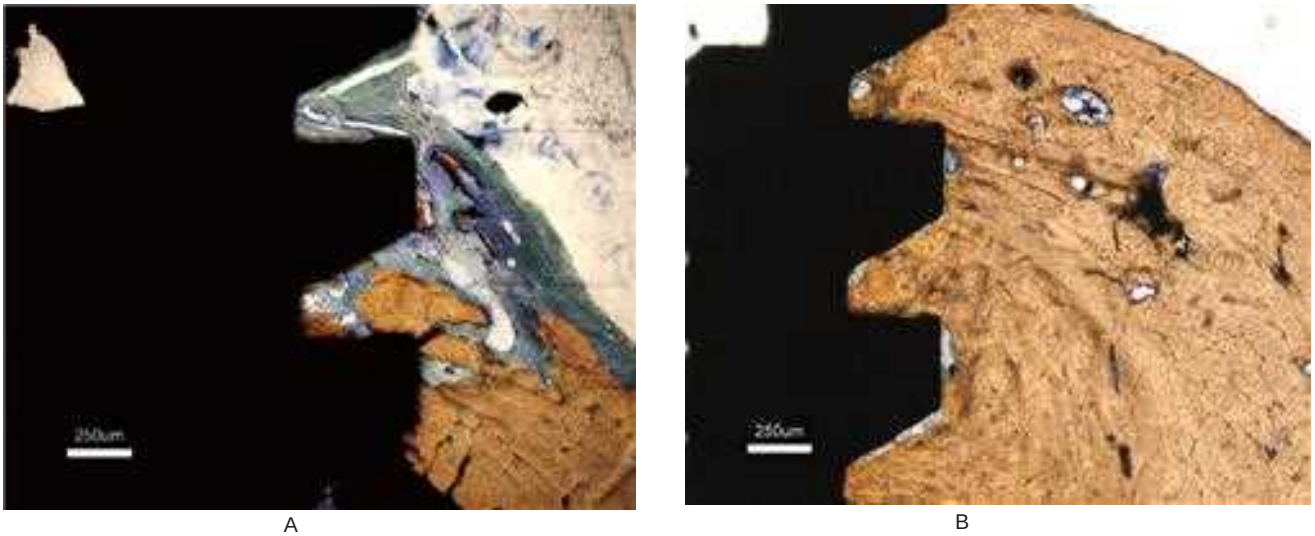

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Figure AII-2. Implant tissue interface in rabbit bone.
(A) 6 weeks post implant placement. New woven bone is noted partially filling one thread which is also partially filled with periosteal tissue; few bone chips are noted (Stevenels blue stain and Van Geison's Picrofuschin stain).
(B) 12 weeks post implant placement. Mature woven bone is observed extending from the endosteal aspect of cortical bone into implant thread. Most of this bone is in direct contact with implant surface. (Stevenels blue stain and Van Geison's Picrofuschin stain).
(Courtesy – Dr Mahesh Verma and Dr Naresh Bhatnagar, NMITLI Dental Implant Project (Maulana Azad Institute of Dental Sciences, New Delhi, in collaboration with CSIR)

affecting dental implants and ultimately leads to the loss of osseointegrated implant. Bacterial plaque plays a significant role in this, and as in periodontitis, failing implants include considerable gingival inflammation, deep pockets and progressive bone loss (Lindquist et al. 1988).

Etiology. The etiology for peri-implantitis is basically either infection with periodontal pathogens or increased trauma (retrograde peri-implantitis). The distinction between implant failure caused by infection with periodontal pathogens and implant failure associated with retrograde peri-implantitis (traumatic failure) is also reflected in the microflora. Rosenberg et al., in 1991 demonstrated that in failing implants with a primarily infectious cause 42% of the subgingival flora consists of *Peptostreptococcus* sp., *Fusobacterium* sp. and enteric gram-negative rods while the failing implants with a traumatic cause have a microflora more consistent with gingival health and composed primarily of streptococci.

Peri-implantitis due to periodontal pathogens. The view that microorganisms play a major role in the development of peri-implantitis is supported by several clinical findings. A cause-related effect between plaque accumulation and peri-implant mucositis has been shown in animals and humans. Moreover, the microbial colonization of implants follows the same pattern as that described around teeth. During peri-implant breakdown, a complex microbiota is established, closely resembling that found in adult periodontitis. When peri-implant tissue breakdown is induced by placing plaque-retentive ligatures submarginally in animals, a shift in the microflora occurs.

The bacterial flora at the failing implant site consists of gram-negative rods, including *Bacteroides* and *Fusobacterium* sp. Failing implants were characterized clinically by increased mobility and peri-implant radiolucency and probing depths greater than 6 mm were associated with periodontal pathogens, including *Actinobacillus actinomycetemcomitans, Prevotella intermedia* and *Porphyromonas gingivalis* (Becker et al). Mombelli and Meriscke-Stern studied the microflora from 18 edentulous patients with 'successful' implants and found 52.8% facultative anaerobic cocci and 17.4% facultative anaerobic rods, but only 7.3% gram negative rods and no *P. gingivalis* and no spirochetes.

Implants in the partially edentulous patients appear to be at a greater risk for peri-implantitis than implants in fully edentulous patients. It has been suggested that the pathogens in peri-implant infections propagate from the periodontopathic bacteria of natural teeth into the saliva and become transmitted to the vicinity of implants. Also, prospective longitudinal data show that the incidence and the prevalence of radiographic bone loss vary among patients. The higher the full-mouth clinical probing pocket depth and the greater the full-mouth attachment loss, the higher the attachment loss is to be expected around implants in the susceptible patient. In individuals with a history of chronic periodontitis, the incidence of peri-implantitis is usually four to five times higher than in individuals with no history of periodontitis. Implant failures due to infection are characterized by a complex peri-implant microbiota resembling that of adult periodontitis.

Quirynen and Listgarten in 1990 studied 24 partially edentulous implant patients in whom the proportion of coccoid forms, motile rods and spirochetes in implant pockets were 65.8, 2.3, and 2.1% respectively and 55.6, 4.9 and 3.6% for the same organisms in the natural tooth crevices. In the fully edentulous cases, more coccoid cells (71.3%), fewer motile rods (0.4%) and no spirochetes were found. The authors concluded that the flora in the partially edentulous patients was potentially more pathogenic. Organisms those are less frequently associated with periodontitis, such as *Staphylococcus* sp., enterics, and *Candida* sp., have also been found in peri-implant infections.

Peri- implantitis due to increased trauma (retrograde peri-implantitis). In this group, patients usually have no pain or suppuration and the failed implants have a microbiologic profile similar to that found at healthy implant sites.

Peri-implant tissues do not accommodate increased biomechanical stresses because:

1. Implants move minimally in bone compared to their natural tooth counterparts.
2. With overload, microfracturing of the bone occurs and this is irreversible even with the control of the overload.
3. A reduced area of support exists in the root-form implant compared with that of natural teeth.

In contrast,

1. The periodontal ligament hypertrophies with increased function allow for greater movement in bone.
2. With overload, mineralized bone volume may be reduced around natural teeth, but in the absence of inflammation the situation is reversible once the overload is eliminated or reduced.
3. The periodontal ligament is attached to a natural tooth with greater surface area and allows for off-axis loading.

Implants also have a less effective natural soft tissue barrier around their necks than natural teeth and are less resistant to infection. The predictability of a stable soft tissue attachment has not been confirmed and the perimucosal seal may just be a circular fiber arrangement.

Peri-implantitis due to smoking. The possible relationship between smoking and implant failures has also been repeatedly evaluated. In a retrospective analysis of the outcome of 2,194 implants placed in 540 subjects, Bain and Moy reported an overall failure rate of 11.3% in smokers in comparison to only 4.8% in non-smokers.

Clinical and Radiographic Appearance of Peri-implantitis. Peri-implantitis lesions are often asymptomatic and usually detected at routine recall appointments. Careful probing around teeth and implants should be routine procedures included at these check-up appointments. Increased clinical probing pocket depth, often accompanied by bleeding and sometimes suppuration, is an indicator of pathology in

peri-implant tissues. The radiographic appearance is often a radiolucency in the shape of a saucer or rounded beaker and most often extends the full circumference of the implant.

Treatment. Traditional periodontal infection control including plaque control regimens and mechanical instrumentation of the affected areas possessing surgical flap access should be performed. It is essential to inform the patient about the need for effective oral hygiene procedures (particularly around implants), and the use of necessary additional oral hygiene aids. Antimicrobial agents have been used with varying degrees of success.

To summarize, the microbiota associated with failing dental implants is similar to flora commonly associated with periodontally affected teeth. The gram-negative microorganisms composing a large portion of the flora produce endotoxin, a heat stable lipopolysaccharide that has been shown to initiate an acute inflammatory response in addition to producing the bone destruction whether about a tooth or implant. Some cases may be attributed to increased trauma and an increased incidence of failures in smokers has also been found. The treatment primarily involves determination of the etiology, its control along with hygiene techniques, instrumentation, and use of antimicrobials.

ORAL REACTIONS TO ORTHODONTIC APPLIANCES

Placement of orthodontic appliances of all types juxtaposes physical obstruction to the external surfaces of the teeth, which interferes with the natural food spillways that permit masticated food to move smoothly over the buccal and lingual surfaces and away from the teeth. The interference thus created traps food around the appliance keeping it in close contact with the teeth and gingival tissues leading to caries and inflammation. The degree of such damage varies and is influenced by factors such as oral hygiene compliances, innate factors of the patient and treatment characteristics.

Ulceration, pain and discomfort are frequent side effects that result from irritation caused mainly due to fixed appliances.

Effect on Teeth

Enamel. Enamel demineralization and caries are one of the most frequently encountered complications in orthodontics. Caries usually occurs on the smooth surfaces and the incidence is said to vary from 2% to 6% in various studies. Increased caries risk may result from:

- Difficulty in identifying such lesions.
- Lowering of resting pH.
- Increased volume of dental plaque.
- A rapid shift in dental flora.

Apart from caries, enamel damage usually stems from direct contact with orthodontic brackets; being worst for ceramic, metal and composite brackets. Extreme caution must be exercised to avoid direct contact between brackets and opposing teeth.

Debonding of brackets often results in enamel fracture, both with metal and ceramic brackets. Wearing down of enamel due to contact with both metal and ceramic brackets (abrasion) is also noteworthy.

Pulp. The application of a light continuous force to the tooth produces a mild and transient inflammatory response within the pulp. This is however reversible and produces no long term damage to the tooth. Pulp damage may be severe when a greater force is applied or when the duration of force applied is long. Although, it may rarely lead to loss of vitality, pulpitis is more common in teeth previously traumatised by orthodontic appliances.

Roots. Some degree of external root resorption is inevitably associated with fixed appliances although the extent may differ. Resorption is usually limited to 2mm and is more on the apical and lateral surfaces of the root. Risk factors associated with severe resorption are:

- Shorter than average roots.
- Previously traumatized teeth.
- Nonvital teeth.
- Teeth subjected to excessive forces.
- Combination of orthodontic and orthognathic procedures.

Effect on Periodontium

Gingival inflammation and recession are common sequelae of orthodontic procedures. Interproximal areas are affected more in facial and posterior teeth than anterior teeth. Bands induce more gingival inflammation than bonds as they are more plaque retentive and often have subgingival margins. An increase in the concentration of anaerobes and a decrease in facultative anaerobes in the plaque around bands has been reported rendering it peripathogenic.

When teeth are moved orthodontically in a setting of inflammation, gingival recession and bone loss are likely to follow. Various studies have reported increased frequency and severity of gingival inflammation in patients with poor oral hygiene status, and patients having fixed orthodontic appliances in comparison to removable appliances. Ay et al. have showed that oral hygiene motivation methods performed under the supervision of a clinician go a long way in preventing and minimising periodontal inflammation in orthodontic patients.

Effects on Lining Mucosa

Mucosal ulcerations, lacerations and erosions are the most frequent lesions encountered in fixed appliance wearers and are a direct consequence of trauma. The location of such lesions is usually on the buccal and vestibular mucosa where the archwire and brackets cause erosions and desquamations, and on the lower lip where brackets and wire cause ulcerations. They are particularly noted in instances where long unsupported

stretches of wire rest against the labial mucosa. Use of dental wax over brackets and rubber tubing over archwire may help prevent such lesions.

In the case of removable appliances, mucosal inflammation commonly under the palatal plate with superimposed candidal infection is usually encountered. Erosions result from irritation caused by interdental clasps or by deleterious habits such as tongue pushing a palatal screw and resulting in tongue injury. Reactions to removable appliances are in most instances similar to reaction to removable prostheses and has been discussed in the previous section.

Allergy

Allergy to materials used in orthodontic therapy is not a commonly reported phenomenon, although hypersensitivity reactions due to leaching of materials from appliances have been reported. This entails the release of known allergens such as nickel, chromium, cobalt , catalysts in bonding material, cold cure acrylics or latex used in elastics into the oral cavity. Allergy to nickel is more common in an extraoral setting as a result of contact with headgear or facebow strap.

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APPENDIX III

Routine Histotechniques, Staining and Notes on Immunohistochemistry

■ S ANIL AND R RAJENDRAN

HISTOTECHNIQUES: TISSUE PROCESSING

Histotechniques constitute the backbone of diagnostic pathology, enabling histologic diagnosis of diseased tissue possible for proper management. The protocol is rigid, custom made, based on scientific principles with the aim of avoiding procedural artifacts as far as possible. The exercise is more and more being automated but a good diagnostic slide avoiding the routine artifacts; its make is still an art and skill of a histotechnologist than dictated by any scientific principle. The commonly applied histotechniques, their principles and application in a routine diagnostic laboratory are discussed in this chapter.

SPECIMEN COLLECTION

Tissue specimens received in the surgical pathology laboratory have a request form that lists the patient information and history along with a description of the site of origin. The specimens are accessioned by giving them a number that will identify each specimen for each patient.

GROSS EXAMINATION

Tissues removed from the body for diagnosis arrive in the pathology department and are examined by a pathologist, pathology assistant, or pathology resident. Gross examination consists of describing the specimen and placing all or parts of it into a small plastic cassette which holds the tissue while it is being processed to a paraffin block.

MARGINATING THE GROSS SPECIMEN

When a malignancy is suspected, the specimen is often covered with ink in order to mark the margins of the specimen. Different colored inks can be used to identify different areas if needed. When sections are made and processed, the ink will mark the actual margin on the slide.

FIXATION: TYPES OF FIXATIVES

The purpose of fixation is to preserve tissues permanently in as life-like a state as possible. Fixation should be carried out as soon as possible after removal of the tissues (in the case of surgical pathology) or soon after death (with autopsy) to prevent autolysis. There is no perfect fixative, though formaldehyde comes the closest. Therefore, varieties of fixatives are available for use, depending on the type of tissue present and features to be demonstrated.

There are five major groups of fixatives, classified according to mechanism of action:

- Aldehydes
- Mercurials
- Alcohols
- Oxidizing agents
- Picrates.

Aldehydes. These include formaldehyde (formalin) and glutaraldehyde. Tissue is fixed by cross-linkages formed in the proteins, particularly between lysine residues. This cross-linkage does not harm the structure of proteins greatly, so that antigenicity is not lost. Therefore, formaldehyde is good for immunoperoxidase techniques. Formalin penetrates tissues well, but is relatively slow. The standard solution is 10% neutral buffered formalin. A buffer prevents acidity that would promote autolysis and cause precipitation of formol-heme pigment in the tissues.

Glutaraldehyde causes deformation of alpha-helix structure in proteins so is not good for immunoperoxidase staining. However, it fixes very quickly so is good for electron microscopy. It penetrates very poorly, but gives best overall cytoplasmic and nuclear detail. The standard solution is a 2% buffered glutaraldehyde.

Mercurials. These fix tissues by an unknown mechanism. They contain mercuric chloride and include such well-known fixatives as B-5 and Zenker's. These fixatives penetrate

relatively poorly and cause some tissue hardness, but are fast and give excellent nuclear details. Their best application is for fixation of hematopoietic and reticuloendothelial tissues. Since they contain mercury, they must be disposed of carefully.

Alcohols. Including methyl alcohol (methanol) and ethyl alcohol (ethanol), are protein denaturants and are not used routinely for tissues because they cause too much brittleness and hardness. However, they are very good for cytologic smears because they act quickly and give good nuclear detail. Spray cans of alcohol fixatives are marketed to physicians doing PAP smears, but cheap hairsprays do just as well.

Oxidizing Agents. These include permanganate fixatives (potassium permanganate), dichromate fixatives (potassium dichromate), and osmium tetroxide. They cross-link proteins, but cause extensive denaturation. Some of them have specialized applications, but are used very infrequently.

Picrates. These include fixatives with picric acid. Foremost among these is Bouin's solution. It has an unknown mechanism of action. It does almost as well as mercurials with nuclear detail but does not cause as much hardness. Picric acid is an explosion hazard in dry form. As a solution, it stains everything it touches yellow, including skin.

FIXATION: FACTORS AFFECTING FIXATION

There are a number of factors that will affect the fixation process:

- Buffering
- Penetration
- Volume
- Temperature
- Concentration
- Time interval.

Fixation is best carried out close to neutral pH, in the range of 6–8. Hypoxia of tissues lowers the pH, so there must be buffering capacity in the fixative to prevent excessive acidity. Acidity favors formation of formalin-heme pigment that appears as black, polarizable deposits in tissue. Common buffers include phosphate, bicarbonate, cacodylate, and veronal. Commercial formalin is buffered with phosphate at a pH of 7.

Penetration of tissues depends upon the diffusibility of each individual fixative, which is a constant. Formalin and alcohol penetrate the best, and glutaraldehyde the worst. Mercurials and others are somewhere in between. One way to get around this problem is sectioning the tissues thinly (2–3 mm). Penetration into a thin section will occur more rapidly than for a thick section.

The volume of fixative is important. There should be a 10:1 ratio of fixative to tissue. Obviously, we often get away with less than this, but may not get ideal fixation. One way to partially solve the problem is to change the fixative at intervals to avoid exhaustion of the fixative. Agitation of the specimen in the fixative will also enhance fixation.

Increasing the temperature as with all chemical reactions will increase the speed of fixation, as long as you do not cook the tissue. Hot formalin will fix tissues faster, and this is often the first step on an automated tissue processor. Concentration of fixative should be adjusted down to the lowest level possible, because you will expend less money for the fixative. Formalin is best at 10%; glutaraldehyde is generally made up at 0.25–4%. Too high a concentration may adversely affect the tissues and produce artifact similar to excessive heat.

Also very important is time interval from removal of tissues to fixation. The faster you can get the tissue fixed, the better. Artifact will be introduced by drying, so if tissue is left out, keep it moist with saline. The longer you wait, the more cellular organelles will be lost, and the more nuclear shrinkage and artefactual clumping will occur.

FIXATIVES: GENERAL USAGE

There are common usages for fixatives in the pathology laboratory based upon the nature of the fixatives, the type of tissue, and the histologic details to be demonstrated. Formalin is used for all routine surgical pathology and autopsy tissues when an H & E slide is to be produced. Formalin is the most forgiving of all fixatives when conditions are not ideal, and there is no tissue that it will harm significantly. Most clinicians and nurses can understand that formalin smells bad enough so they should be careful when handling it.

Zenker's fixatives are recommended for reticuloendothelial tissues including lymph nodes, spleen, thymus, and bone marrow. Zenker's fixative fixes nuclei very well and gives good detail. However, the mercury deposits must be removed (dezenkerized) before staining or black deposits will result in the sections. Bouin's solution is sometimes recommended for fixation of testis, GI tract, and endocrine tissues. It does not do a bad job on hematopoietic tissues either, and does not require dezenkerizing before staining.

Glutaraldehyde is recommended for fixation of tissues for electron microscopy. The glutaraldehyde must be cold and buffered and not more than 3 months old. The tissue must be as fresh as possible and preferably sectioned within the glutaraldehyde at a thickness not more than 1 mm to enhance fixation.

Alcohols, specifically ethanol, are used primarily for cytologic smears. Ethanol (95%) is fast and cheap. Since smears are only a cell or so thick, there is no great problem from shrinkage, and since smears are not sectioned, there is no problem from induced brittleness.

For fixing frozen sections, you can use just about anything–though methanol and ethanol are the best.

TISSUE PROCESSING

Once the tissue has been fixed, it must be processed to a form in which it can be made into thin microscopic sections. The usual way this is done is with paraffin. Tissues embedded in paraffin, which is similar in density to tissue, can be sectioned at anywhere from 3–10 microns, usually 4–6 routinely. The technique of getting fixed tissue into paraffin is called tissue sections processing. The main steps in this process are dehydration and clearing.

Wet fixed tissues (in aqueous solutions) cannot be directly infiltrated with paraffin. First, the water from the tissues must be removed by dehydration. This is usually done with a series of alcohols, say 70–100%. Sometimes the first step is a mixture of formalin and alcohol. Other dehydrants can be used, but have major disadvantages. Acetone is very fast, but a fire hazard, so is safe only for small, hand-processed sets of tissues. Dioxane can be used without clearing, but has toxic fumes.

The next step is called 'clearing' and consists of removal of the dehydrant with a substance that will be miscible with the embedding medium (paraffin). The most common clearing agent is xylene. Toluene works well, and is more tolerant of small amounts of water left in the tissues, but is 3 times more expensive than xylene. Chloroform works, but is a health hazard, and is slow. Methyl salicylate is rarely used because it is expensive, but it smells nice (it is oil of wintergreen). There are newer clearing agents available for use. Many of them are based on limolene, a volatile oil found in citrus peels. Others use long chain aliphatic hydrocarbons (Clearite). Although they represent less of a health hazard, they are less compatible with poorly fixed, dehydrated, or sectioned tissues.

Finally, the tissue is infiltrated with the embedding agent, almost always paraffin. Paraffins can be purchased that differ in melting point, for various hardnesses, depending upon the way the histotechnologist likes them and upon the lab conditions (warm vs. cold). A product called paraplast contains added plasticizers that make the paraffin blocks easier for some technicians to cut. A vacuum can be applied inside the tissue processor to assist penetration of the embedding agent. The above processes are almost always automated for the large volumes of routine tissues processed. Automation consists of an instrument that moves the tissues around through the various agents on a predetermined time scale. The 'Technicon' tissue processor is one of the most common and most reliable (a mechanical processor with an electric motor that drives gears and cams), though no longer made. Newer processors have computers, not cam wheels, to control them and have sealed reagent wells to which a vacuum and/or heat can be applied.

TISSUE PROCESSOR

Automated Tissue Processor

Tissues that come off the tissue processor are still in the cassettes and must be manually put into the blocks by a technician who must pick the tissues out of the cassette and pour molten paraffin over them (Fig. AIII-1). This 'embedding' process is very important, because the tissues must be aligned, or oriented, properly in the block of paraffin.

Tissue Embedding. Alternatives to paraffin embedding include various plastics that allow thinner sections. Such plastics include methyl methacrylate, glycol methacrylate, Araldite, and epon. Methyl methacrylate is very hard and therefore good for embedding undecalcified bone. Glycol methacrylate has the most widespread use since it is the easiest to work with. Araldite is about the same as methacrylate, but requires a more complex embedding process. Epon is routinely used for electron microscopy where very thin sections are required.

Figure AIII-1. Automated tissue processor.

Plastics require special reagents for dehydration and clearing that are expensive. For this reason, and because few tissues are plastic embedded, the processing is usually done by hand. A special microtome is required for sectioning these blocks. Small blocks must be made, so the technique lends itself to small biopsies, such as bone marrow or liver.

SECTIONING

Once the tissues have been embedded, they must be cut into sections that can be placed on a slide. This is done with a microtome. The microtome is nothing more than a knife with a mechanism for advancing a paraffin block standard distances across it.

SECTIONING WITH MICROTOME

Knives are either of the standard thick metal variety or thin disposable variety. The former type allows custom sharpening to one's own satisfaction, but is expensive. The latter costs less and are nearly as good. The advantage of the disposable blade becomes apparent when sectioning a block in which is hidden a metal wire or suture, which damages the cutting edge of the blade. Plastic blocks (methacrylate, Araldite, or epon) are sectioned with glass or diamond knives. A glass knife can section down to about 1 micron. Thin sections for electron microscopy (1/4 micron) are best done with a diamond knife which is very expensive.

Microtomes have a mechanism for advancing the block across the knife. Usually this distance can be set, for most paraffin embedded tissues at 4–6 microns. The more expensive the microtome, the better and longer-lasting this equipment will be. Sectioning tissues is a real art and takes much skill and practice. Histotechnologists are the artists of the laboratory. It is important to have a properly fixed and embedded block or

Figure AIII-2. Tissue floatation bath.

much artifact can be introduced in the sectioning. Common artifacts include tearing, ripping, 'venetian blinds' holes, folding, etc. Once sections are cut, they are floated on a warm water bath (Fig. AIII-2) that helps remove wrinkles. Then they are picked up on a glass microscopic slide.

Picking Sections up from Water Bath—Unstained Section on Glass Slide. The glass slides are then placed in a warm oven for about 15 minutes to help the section adhere to the slide. If this heat might harm such things as antigens for immunostaining, then this step can be bypassed and glue-coated slides are used instead to pick up the sections.

HARD TISSUE PROCESSING (BONE, TOOTH)

COMMON FIXATIVES IN HARD-TISSUE PROCESSING

Fixation is one of the most important steps in obtaining a good histological specimen. Its goal is to block all lytic enzyme activity as well as the activity of bacteria and other infectious agents in order to preserve the constituents of a tissue as they were in the living state. The most common solutions employed for fixation include 10–30% formalin, glutaraldehyde, paraformaldehyde, and alcohol-based solutions. Formalin penetrates tissues well, but its action is relatively slow. The standard solution used is 10% neutral buffered formalin (NBF). A buffered solution prevents acidity, which would promote autolysis, causing precipitation of formol-heme pigment in the tissues. The alcohol-based solutions have the advantage of preserving numerous enzymes, allowing the performance of many histochemical studies. All these fixatives are known as primary, and the rest as secondary. The latter are obtained by mixing together several primary fixatives (e.g. Bouin's fixative containing picric acid, formalin, and glacial acetic acid), in order to make use the different advantages presented by each component.

It is also important to reduce the size of the specimen to allow better fixation: the best size of the specimen appears to be 4–5 mm. Although formaldehyde is the best fixative, it is not the perfect one. Therefore, a variety of fixatives are available for use, depending on the type of tissue we want to study and on the features we want to analyse. For specimens with a diameter larger than 4–6 mm, glutaraldehyde and formalin are suggested, while for specimens smaller than 1–3 mm, alcoholic fixatives may be used.

POST-FIXATION TREATMENT AND SPECIMEN STORAGE

The fixed specimen must be washed in phosphate buffered saline (PBS) or running water to completely remove all the fixative solutions, which could affect the staining procedure. Washing in PBS is performed by immersing the specimen for 1 day in PBS, and changing the solution several times. Fixed specimens can be stored in alcohol or fixative for several weeks, but longer periods in alcohol tend to shrink the cells, altering the morphology. For large specimens, water tends to separate from alcohol and the latter also evaporates, leaving a large portion of the tissue under water and without alcohol. Formalin, after long period, tends to lose its fixing capability. If specimens must be preserved for more than several weeks, the best way is to infiltrate and embed them in resin. In this case, there is no time limit for storage.

EMBEDDING TECHNIQUES AND RESULTS IN DIFFERENT TYPES OF RESIN

Plastic-embedding technique generally does not require the removal of the resin before staining, a process that could introduce artifacts in the sections. The presence of the resin in the section makes the staining procedure different from routine paraffin-embedded tissues, and achieving satisfactory staining is more difficult.

An exception is methyl methacrylate (MMA) which is removed from the sections after cutting to permit staining. Embedding in MMA requires the removal of the resin with solvents. Glycol methacrylate cannot be removed because of the high number of crosslinking binding sites present in the chains of the polymer. Sectioning of blocks containing hard endosseous biomaterials (bone implants) can be made easier by the use of a system consisting of a special glycol methacrylate resin (Technovit 7200 VLC, Kulzer, Wehrheim, Germany), which provides good infiltration, polymerization, and subsequent easy sectioning by cutting and grinding the specimens. Although this system allows the precise observation of an intact interface between bone and endosseous biomaterials, the hardness of glycol methacrylate and its permanence in the tissues make any routine staining procedure very difficult.

During the last three decades, the increase in the use of medical and dental implants and techniques of bone regeneration has underlined the importance of the histological evaluation of the tissue-implant interface. Conventional methods of microscopic examination have shown to be inappropriate for studying undecalcified bone, implants, and biomaterials. Thus, various plastic-embedding methods have been used to produce sections in which both the implant material and the adjacent tissues are intact. Many biomaterials cannot be infiltrated with conventional embedding media, and they can

be more resistant to grinding than the embedding media and/or the surrounding hard tissues, producing sections of uneven thickness. Plastic embedding allows a distinction between mineralized bone and unmineralized osteoid, with an excellent preservation of the cellular structures.

It must be kept in mind that histological detail is critical for the morphometrical evaluation, diagnosis, and study of the bone pathology. For optimal and reproducible processing of the specimens, the following steps are necessary:

- Optimal procurement of the specimen
- Proper fixation
- Proper embedding
- Proper sectioning
- Proper staining.

Methacrylate-embedding medium is the method of choice for the study of bone. Glycol methacrylate-embedding provides good infiltration of cartilage and good preservation of osteoblast-associated alkaline phosphatase (ALP). Methyl methacrylate (MMA) produces a harder plastic that provides a superior support for cortical and trabecular bone and allows a better preservation than glycol methacrylate of ALP in cartilage matrix and of acid phosphatase (ACP) in osteoclasts. The use of MMA as an embedding medium has made possible the study of semi-thin sections of mineralized bone.

STAGES OF HARD TISSUE HISTOLOGICAL SPECIMEN PREPARATION

Dehydration

Dehydration follows fixation, and it has the goal of removing all the water contained within the specimen to allow uniform penetration of the resin into any biomaterial present. The dehydration process is essential because the resins employed are not water-soluble. The water is removed by immersing the specimen in alcohol solutions of increasing concentration (ascending grades). The time for each step will vary (from 15 minutes to 24 hours), depending on the size of the specimen. The alcohol concentrations used are as follows:

- 30% alcohol
- 50% alcohol
- 70% alcohol
- 90% alcohol
- 100% alcohol.

The time required for dehydration may be reduced when vacuum is applied. The dehydration process hardens the tissues, making resin penetration more difficult. To avoid this problem, a few drops of glacial acetic acid may be added to the 70% alcohol solution. For some resins, acetone dehydration can be performed.

Infiltration

Resins commonly used for infiltration and embedding are:

- Technovit 7200 Kulzer
- Technovit 8100 Kulzer
- Technovit 9100 Kulzer
- Epon
- L-R White
- Other MMA resins
- Spurr's resin.

All these resins are initially fluids, and solidify during polymerization. Resin embedding produces hard blocks containing the tissues to be trimmed and cut for examination. The resins must be put in appropriate embedding molds that do not react with the resin.

Embedding and Polymerization

After embedding, polymerization is performed for about 6–8 hours at a temperature not exceeding 40°C. The polymerized resin is very hard, and it is possible to cut and grind the specimen in a very uniform way with no alteration of the histological features. Polymerization may be accomplished either by using light polymerization or autopolymerization, depending on the type of resin used. Once the block is obtained, for light microscopy observation, it can be glued to either a base of Plexiglas or a clean glass slide. Several types of glue are suitable (e.g. Technovit 4000, Attack, Vitroresin). The surface to be examined must be positioned uppermost. Excess resin is removed in order to obtain a free surface of the specimen parallel to the holding slide. At this stage another slide is glued to the free surface. However, the most superficial portion of the resin usually remains fluid as the presence of oxygen in the air inhibits the polymerization process. This excess resin is removed with a knife or by grinding and the clean glass slide can be attached with glue.

Block Trimming

The polymerized blocks must be removed from their molds. Before trimming the plastic block, the orientation of the specimen in the block to the microtome blade has to be done. The cylindrical block containing a bone/implant core is flattened on a plane parallel to the length of the core. Flattening can be done on a grinder/polisher machine with coarse silicon carbide paper. The grinding paper should be flushed with a stream of water to prevent plastic particles from clogging the paper. Leave at least 1 mm of plastic between each cut and the bone specimen. To remove the excess plastic on the sides of the specimen, two more cuts are made, each perpendicular to the end of the first two cuts. The shape and preparation of the base of the block is done according to the microtome that is used for slicing.

Several techniques have been reported that describe the preparation of non demineralized bone specimens for study at both the light and electron microscopic levels.

Microtome Sectioning

Types of Microtomes for Sectioning Bone (Figs. AIII-3–AIII-5). Microtomes generally produce two movements: the **cutting movement** of the knife along the desired plane, and

A B

Figure AIII-3. (A) Rotary microtome. (B) Sliding microtome.

Figure AIII-4. The Leica SP1600 microtome uses a diamond-coated inner-hole saw blade.

the **feeding movement** of the specimen block perpendicular to the cutting plane. Microtomes of good quality have precise adjustable movements. Most microtomes from well-known manufacturers meet these demands. Large, bisectioned with a sliding or base sledge microtome, where specimens in either case remain stationary while the knife is passed through it. The knife is fastened in a holder, which slides back and forth on rails with the cutting edge of the blade in the lead. The specimen is advanced in small increments at a right angle into the path of the oncoming knife-edge. As the knife sweeps past the specimen, a thin slice or section is made. The uniform thickness and flatness of the section is determined by the sharpness of the blade, the stoutness of the cutting-edge, the steadiness of the knife motion, and the ability of the apparatus to absorb vibration. For this purpose, these microtomes are stable and robust, and are motorized to provide a slow and steady cutting motion.

Saw Microtome (Horizontal Diamond Saw). A horizontal rotation-sawing machine with diamond cutting edge on the inside diameter is used for sectioning of the dental implant/bone interface studies (Figs AIII-6, AIII-7). The inside diameter diamond saw blade consists of a thin circular steel core, which is tensioned at its outer edge in two clamp-

Figure AIII-5. Freezing microtome (cryostat for sectioning frozen tissue).

Figure AIII-6. A dental Implant embedded in methyl methacrylate (MMA) in rabbit femur during the sectioning.

ing rings. A rigid and vibration-free assembly is required to obtain exact thickness of the sections. A powerful and silent motor drives the saw. Samples of bone containing implanted

Figure AIII-7. Photomicrograph showing the bone and implant interface.

biomaterials are embedded in methyl methacrylate. After polymerization, the blocks are trimmed and firmly fixed to a flattened ball. The ball is tightly clamped into an arm-type holder that moves toward the diamond saw with a force of 0.2–2 Nm, using a 1:1 (v/v) glycerin/water mixture as a cooling lubricant. The block is fixed in the holder at a defined angle (free motions of 360° horizontally and 60° vertically). Thick sections are cut until the desired area of the specimen is reached, then the surface is etched for 30 seconds with 1% ethanol-HCl solution and rinsed with water. The surface of the sample is stained with methylene blue (1 minute) and basic fuchsin blue (30 seconds). After staining, the surface is rinsed with water and is carefully dried, then a glass coverslip is glued to the stained surface with a thin layer of UV adhesive; this coverslip stabilizes the thin section during the sectioning process. The block is raised using a high-quality micromanipulator (Mikrocontrol UT 100, Elmekanic®, Markelo, The Netherlands) with a reliable read-off system for a precise sample lift of 1 mm, enabling production of sections of exact thickness. After sawing, the previously stained section with cover slip attached is glued to a glass slide with Permacol and is ready for histological evaluation.

Staining

Toluidine blue, acid fuchsin, silver nitrate, acid and alkaline phosphatase are routinely used staining agents. Acid solutions may alter the resin properties, and can produce a background staining that does not allow an accurate morphologic evaluation. Deplasticized stained sections on glass slides are mounted in the same way as paraffin sections using alcohol dehydration, xylene clearing, and mounting with a synthetic mounting medium. Free floating sections tend to wrinkle, and while in clearing agent, can be flattened with a brush or rolled between pieces of smooth filter paper, then mounted with synthetic resin with a weight placed on top of cover glass to keep the section flat until the medium dries. Clamping devices maintain flat sections briefly but are too strong, causing the mounting media to retract later during storage. Sections cleared with terpineol and mounted with terpene based mounting media may be flatter initially, but this medium does not harden as well as the synthetic resins and results in an unstable mount.

Surface-stained sections surrounded by MMA cannot be dehydrated, cleared or mounted. Methylmethacrylate is softened by alcohols and is soluble in xylene and the solvents in mounting media, and any mounting results in ugly cracking of plastic in and around a section. To examine surface-stained sections, place a cover glass on top of the dry section without mounting media and examine with the brightest light setting on the microscope. Immersion oil can be used to mount these sections, but is temporary and leaves messy oil residue on stored sections.

Hematoxylin and Eosin for MMA-embedded Tissue. This method is useful for diagnosis of suspected osteomalacia and distinguishes mineralized bone from osteoid, with nuclei and other soft tissues stained similar to decalcified bone-paraffin sections.

Hematoxylin and Eosin

Reagents

Cole's hematoxylin and 1% aqueous eosin.

Method

1. Deplasticize with xylene and hydrate sections to distilled water.
2. Stain in freshly filtered Cole's hematoxylin, 60 minutes. with occasional agitation.
3. Wash well in alkaline tap water.
4. Stain in eosin solution, 30 minutes.
5. Wash in tap water.
6. Dehydrate, clear and mount.

Results

- Osteoid—*pink*
- Calcified bone—*purplish brown*
- Nuclei—*blue.*

Solochrome Cyanine Method

The solochrome cyanine stain differentiates osteoid from newly laid-down bone and older bone.

Solutions

- Stain solution
- Solochrome cyanine R—1 g
- Concentrated sulfuric acid—2.5 ml.

Mix well until dye incorporates into the resulting 'sludge', then add 500 ml of 0.5% aqueous iron alum (ferric ammonium sulfate), mix and filter.

Method

- Deplasticize with xylene and hydrate sections to distilled water.
- Stain in solochrome cyanine solution, 60 minutes.
- Using a microscope, differentiate in warm (30°C) alkaline tap water until mineralized areas appear blue and other areas light red. Over-differentiation causes all parts to become blue.
- Dehydrate, clear and mount.

Results

- Mineralized bone—*light blue*
- Calcification front—*dark blue*
- Osteoid—*light red-orange*
- Wide osteoid—*light red-orange with pale blue and orange bands*
- Nuclei—*blue.*

Staining for Bone Mineral

The classic von Kossa silver method is used to stain the mineral component in bone, (calcium phosphate) and basically is a negative stain for osteoid with the calcium component blackened by silver deposition. Osteoid is counterstained red by either van Gieson's or safronin O. This can also be used as a ground section surface stain but without the acid 'etching' removal of calcium. An alternative method is the rapid bone stain with van Gieson.

Modification of Von Kossa's Method

Solutions

- 1 % aqueous silver nitrate
- 2.5% sodium thiosulfate
- 1% safronin O or van Gieson's picro fuchsin.

Method

- Deplasticize with xylene, and hydrate sections to distilled water.
- Place in silver nitrate solution, expose to strong light for 10–60 minutes, and watch the mineralized bone turn dark-brown to black, indicating a completed reaction.
- Wash in three changes of distilled water.
- Treat with sodium thiosulfate, 5 minutes.
- Wash well in distilled water.
- Counterstain as desired.
- Dehydrate, clear and mount.

Results

- Mineralized bone—black
- Osteoid—red.

Long wavelength UV light from sunlight or a quartz halogen microscope lamp is preferable to a tungsten filament light bulb, and accelerates the reaction. van Gieson's picro fuchsin counterstaining may interfere with birefringence of osteoid.

Goldner's Trichrome Method

This staining technique can be more valuable than the von Kossa's method in investigations of metabolic diseases, i.e. Paget's, renal osteodystrophy and hyperparathyroidism, because of excellent staining of cells. Osteoblast and osteoclast activity is easily assessed, an important factor for both diagnosis and evaluating the effects of treatment in these disorders by repeated bone biopsies. An additional advantage is that metastatic tumor cells in bone marrow are easily identified.

Solutions

- Weigert's iron hematoxylin
- Ponceau-fuchsin-azophloxin stock solutions
- Ponceau de xylidine—0.75 g
- Acid fuchsin—0.25 g
- Acetic acid—1.0 ml mix, and add to 100 ml distilled water
- Azophloxin—0.5 g
- Acetic acid—0.6 ml
- Mix, and add to 100 ml distilled water
- Final working stain solution
  - Ponceau-fuchsin solution—5–10 ml
  - Azophloxin—2 ml
  - 0.2% Acetic acid solution—88 ml
- Light green solution
  - Light green—1 g
  - Acetic acid —1 ml
    Mix, and add to 500 ml distilled water
- Phosphomolybdic acid/orange G solution
  - Phosphomolybdic acid—3 g
  - Orange G—2 g

Dissolve in 500 ml of distilled water, and add a crystal of thymol.

Method

- Deplasticize with xylene and hydrate sections to water.
- Immerse sections in alkaline alcohol solution (90 ml of 80% ethanol and 10 ml of 25% ammonia), 1 hour.
- Rinse in water, 15 minutes.
- Stain in Weigert's hematoxylin, I hour.
- Rinse in tap water, 10 minutes.
- Rinse in distilled water, 5 minutes.
- Stain in final Ponceau-fuchsin-azophloxin solution, 5 minutes.
- Rinse in 1% acetic acid, 15 seconds.
- Stain in phosphomolybdic acid/orange G solution, 20 minutes.
- Rinse in 1% acetic acid, 15 seconds.
- Stain with light green, 5 minutes.
- Rinse in three changes of 1% acetic acid.
- Rinse in distilled water, blot dry and mount.

Results

Mineralized bone—green, Osteoid—orange/red, Nuclei—blue-gray, Cartilage—purple.

Frozen Sections. At times during performing surgical procedures, it is necessary to get rapid diagnosis of a pathologic process. The surgeon may want to know if the margins of his/her resection for a malignant neoplasm are clear from tumor before closing, or an unexpected disease process may be found and require diagnosis to decide what to do next, or it may be necessary to determine if the appropriate tissue has been obtained for further work-up of a disease process. This is accomplished through use of a frozen section. The piece(s) of tissue to be studied are snap frozen in a cold liquid or cold environment (-20 to -70 Celsius). Freezing makes the tissue solid enough to section with a microtome (Fig. AIII-5).

Frozen sections are performed with an instrument called a cryostat. The cryostat is just a refrigerated box containing a microtome. The temperature inside the cryostat is about -20 to -30 Celsius. The tissue sections are cut and picked up on a glass slide. The sections are then ready for staining.

STAINING

The embedding process must be reversed in order to get the paraffin wax out of the tissue and allow water soluble dyes to penetrate the sections. Therefore, before any staining can be done, the slides are 'deparaffinized' by running them through xylenes (or substitutes) to alcohols to water. There are no stains that can be done on tissues containing paraffin.

The staining process makes use of a variety of dyes that have been chosen for their ability to stain various cellular components of tissue. The routine stain is that of hematoxylin and eosin (H and E). Other stains are referred to as 'special stains' because they are employed in specific situations according to the diagnostic need.

Using Automated Stainer (Fig. AIII-8). Frozen sections are stained by hand, because this is faster for one or a few individual sections. The stain is a 'progressive' stain in which the section is left in contact with the stain until the desired tint is achieved (Fig. AIII-9).

Figure AIII-8. Automated linear slide stainer.

Figure AIII-9. Slide warmer.

Staining a Frozen Section

H and E Staining (Table AIII-1). Hematoxylin is the oxidized product of the logwood tree (*Haematoxylon campechianum*) known as hematein. Since this tree is very rare nowadays, most hematein is of the synthetic variety. In order to use it as a stain it must be 'ripened' or oxidized. This can be done naturally by putting the hematein solution on the shelf and waiting several months, or by buying commercially ripened hematoxylin or by putting ripening agents in the hematein solution.

Hematoxylin will not directly stain tissues, but needs a 'mordant' or link to the tissues. This is provided by a metal cation such as iron, aluminum, or tungsten. The variety of hematoxylins available for use is based partially on choice of metal ion used. They vary in intensity or hue. Hematoxylin, being a basic dye, has an affinity for the nucleic acids of the cell nucleus.

Hematoxylin stains are either 'regressive' or 'progressive'. With a regressive stain, the slides are left in the solution for a set period of time and then taken back through a solution such as acid-alcohol that removes part of the stain. This method works best for large batches of slides to be stained and is more predictable on a day to day basis. With a progressive stain the slide is dipped in the hematoxylin until the desired intensity of staining is achieved, such as with a frozen section. This is simple for a single slide, but lends itself poorly to batch processing.

Eosin is an acidic dye with an affinity for cytoplasmic components of the cell. There are a variety of eosins that can be synthesized for use, varying in their hue, but they all work about the same. Eosin is much more user friendly than hematoxylin and is less of a problem in the lab. The only problem you will see is overstaining, especially with decalcified tissues.

Coverslipping. The stained section on the slide must be covered with a thin piece of plastic or glass to protect the tissue from being scratched, to provide better optical quality for viewing under the microscope, and to preserve the tissue section for years to come. The stained slide must go through the reverse process that it went through from paraffin section to water. The stained slide is taken through a series of alcohol solutions to remove the water, then through clearing agents to a point at which a permanent resinous substance beneath the glass coverslip or a plastic film can be placed over the section.

Table AIII-1. H and E staining (paraffin)

Hydrate		
1.	Xylene	5 minutes
2.	Xylene	5 minutes
3.	Xylene	5 minutes
4.	100% EtOH	1 minute
5.	100% EtOH	1 minute
6.	95% EtOH	1 minute
7.	95% EtOH	1 minute
8.	70% EtOH	1 minute
9.	Deionized water	2 minutes
Stain		
1.	Hematoxylin (Gill's 2x)	2 minutes (filter when metallic scum appears on surface)
2.	Tap water rinse under running	
	water until water is clear	
3.	Bluing solution	1–2 dips
4.	Allow slides to stand in running	
	tap water for 5 minutes	
	(donot use ice-cold water)	
5.	80% EtOH	2 minutes
6.	Eosin	2–3 minutes
Dehydrate		
1.	80% EtOH	3–4 dips to rinse out excess Eosin
2.	95% EtOH	1 minute
3.	95% EtOH	1 minute
4.	100% EtOH	1 minute
5.	100% EtOH	1 minute
6.	Xylene	3 minutes
7.	Xylene	3 minutes
8.	Xylene	3 minutes

W Coverslip with Permount (Xylene based). After coverslipping, the chromatin in nuclei should be stained dark blue (hematoxylin) and the cytoplasm should be stained pink (eosin)
EtOH – Ethyl alcohol

Decalcification. Some tissues contain calcium deposits which are extremely firm and which will not section properly with paraffin embedding owing to the difference in densities between calcium and paraffin. Bone specimens are the most likely type here, but other tissues may contain calcified areas as well. This calcium must be removed prior to embedding to allow sectioning. A variety of agents or techniques have been used to decalcify tissue and none of them work perfectly. Mineral acids, organic acids, ethylene diamine tetra acetic acid (EDTA), and electrolysis have all been used.

Strong mineral acids such as nitric and hydrochloric acids are used with dense cortical bone because they will remove large

quantities of calcium at a rapid rate. Unfortunately, these strong acids also damage cellular morphology, so are not recommended for delicate tissues such as bone marrow. Organic acids such as acetic and formic acid are better suited to bone marrow, since they are not as harsh. However, they act more slowly on dense cortical bone. Formic acid in a 10% concentration is the best all-around decalcifier. Some commercial solutions are available that combine formic acid with formalin to fix and decalcify tissues at the same time. EDTA can remove calcium and is not harsh (it is not an acid) but it penetrates tissue poorly and works slowly and is expensive in large amounts. Electrolysis has been tried in experimental situations where calcium had to be removed with the least tissue damage. It is slow and not suited for routine daily use.

ARTIFACTS IN HISTOLOGIC SECTIONS AND TROUBLESHOOTING

A number of artifacts that appear in stained slides may result from improper fixation, from the type of fixative, from poor dehydration and paraffin infiltration, improper reagents, and poor microtome sectioning. The presence of a fine black precipitate on the slides, often with no relationship to the tissue (i.e. the precipitate appears adjacent to tissues or within interstices or vessels) suggests formalin-heme pigment has formed. This can be confirmed by polarized light microscopy, because this pigment will polarize a bright white (and the slide will look like many stars in the sky). Formalin-heme pigment is most often seen in very cellular or bloody tissues, or in autopsy tissues, because this pigment forms when the formalin buffer is exhausted and the tissue becomes acidic, promoting the formation of a complex of heme (from red blood cells) and formalin. Tissues such as spleen and lymph node are particularly prone to this artifact. Making thin sections and using enough neutral-buffered formalin (10:1 ratio of fixative to tissue) will help. If the fixative solution in which the tissues are immersed is grossly murky brown to red, then place the tissues in new fixative.

The presence of large irregular clumps of black precipitate on slides of tissues fixed in a mercurial fixative such as B-5 suggests that the tissues were not dezenkerized prior to staining. These black precipitates will also appear white with polarized light microscopy. Tissues that are insufficiently dehydrated prior to clearing and infiltration with paraffin wax will be hard to section on the microtome, with tearing artifacts and holes in the sections. Tissue processor cycles should allow sufficient time for dehydration, and final ethanol dehydrant solution should be at 100% concentration. In humid climates, this is difficult to achieve. Covering or sealing the solutions from ambient air will help. Air conditioning (with refrigerants, not with evaporative coolers) will also reduce humidity in the laboratory. Toluene as a clearing agent is more forgiving of poorly dehydrated tissues, but it is more expensive and presents more of a health hazard than other non-xylene clearing agents. Though alcohols such as ethanol make excellent fixatives for cytologic smears, they tend to make tissue sections brittle, resulting in microtome sectioning artifacts with chattering and a 'venetian blind' appearance. Bubbles under the coverslip may form when the mounting media is too thin, and as it dries air is sucked in under the coverslip. Contamination of clearing agents or coverslipping media may also produce a bubbled appearance under the microscope.

PROBLEMS IN TISSUE PROCESSING

This includes small pieces of tissue that appear on a slide that do not belong to it. They have floated in during processing. Floaters may arise from sloppy procedure on the cutting bench—dirty towels, instruments, or gloves can have tissue that is carried over to the next case. Therefore, it is essential that you do only one specimen at a time and clean thoroughly before opening the container of the next case. The best way to guard against unrecognized floaters is separate similar specimens in the numbering sequence. For example, if you have three cases with prostate chips, separate them in accessioning with totally different specimens such as uterus or stomach. That way, if numbers are transposed or labels written wrong or tissue carried over, then you will have an obvious mismatch. Carrying over one prostate to another, or transposing the numbers of identical tissues may never be recognized.

If reusable cassettes are employed, you must be aware that tissue may potentially be carried over and appear as 'floaters' even several days later, when the cassette is re-used. The problem arises when, during embedding, not all the tissue is removed from the cassette. Then, in the cleaning process, not all of the wax is removed. Then, the next person using the cassette does not pay attention to the fact that there is tissue already in the cassette and puts his/her specimen in it. The floater that appears on the slide will look well-preserved—it should, because it was processed to paraffin. Always be sure that you properly identify the tissue! This means that you make sure that the patient-label on the specimen container matches that of the request slip. An accession number is given to the specimen. This number must appear with the tissue at all times. You must never submit a cassette of tissue without a label. You must never submit a cassette of tissue with the wrong label. Mislabeling or unlabeling of tissues is courting disaster.

SAFETY IN THE LAB

The laboratory should be well-ventilated. There are regulations governing formalin and hydrocarbons such as xylene and toluene. There are limits set by the Occupational Safety and Health Administration (OSHA) that should not be exceeded. These limits have recently been revised to reduced levels. Every chemical compound used in the laboratory should have a materials safety data sheet on file that specifies the nature, toxicity, and safety precautions to be taken when handling the compound. The laboratory must have a method for disposal of hazardous wastes. Healthcare facilities processing tissues often contract this to a waste management company. Tissues that are collected should be stored in formalin and may be disposed by incineration or by putting them through a 'tissue

grinder' attached to a large sink (similar to a large garbage disposal unit).

Every instrument used in the laboratory should meet electrical safety specifications and have written instructions regarding its use. Flammable materials may only be stored in approved rooms and only in storage cabinets that are designed for this purpose.

Fire safety procedures are to be posted. Safety equipment including fire extinguishers, fire blankets, and fire alarms should be within easy access. A shower and eyewash should be readily available. Laboratory accidents must be documented and investigated with incident reports and industrial accident reports.

Specific hazards that you should know about include:

- Bouin's solution is made with picric acid. This acid is only sold in the aqueous state. When it dries out, it becomes explosive.
- Many reagent kits have sodium azide as a preservative. You are supposed to flush solutions containing sodium azide down the drain with lots of water, or there is a tendency for the azide to form metal azides in the plumbing. These are also explosive.
- Benzidine, benzene, anthracene, and naphthol containing compounds are carcinogens and should not be used.
- Mercury-containing solutions (Zenker's or B-5) should always be discarded into proper containers. Mercury, if poured down a drain, will form amalgams with the metal that build up and cannot be removed.

DIAGNOSTIC CYTOLOGY

Exfoliative cytology has been used as a diagnostic test for precancerous and cancerous lesions presenting in the oral cavity. George N Papanicolaou introduced cytology as a tool to detect cancer and precancer in 1928. It is now a widely accepted method for mass screening in asymptomatic population. However, in general, cytology has relied primarily on the personal judgement of the cytologist and not on the measurement of cellular parameters. Controversy has surrounded the use of cytology in the diagnosis of oral cancer. One of the main reasons for this is the occurrence of false negative results. A number of authors have suggested reasons for this which includes inadequate sampling, technical errors, misinterpretation of the results and observer bias. It is important that techniques are developed to aid in the diagnosis of early oral cancer especially in predicting the behavior of those lesions which display epithelial dysplasia but no overt malignancy (precancer). In 1981, Cowper and Longmore felt that the application of quantitative techniques to cytology could markedly improve its diagnostic sensitivity in detecting oral cancer. The quantitative techniques included DNA cytophotometry and cytomorphology (measurement of nuclear size, and later cell size).

The major value of cytology is the non-invasive nature of a simple and relatively painfree procedure which can provide intact cells from different layers within the epithelium. Cytology has been recommended for the early diagnosis of oral cancer and proved to be a reliable diagnostic test.

FIXATION OF CYTOLOGY SPECIMENS

Rapid fixation of smears is necessary to preserve cytologic details of cells spread on a glass slide. Fixation means prevention of degeneration of cells and tissue by the autolytic enzymes present in the cells and preservation of cells as close as possible to the living state. To achieve this, smears are placed in the fixative solution for specific periods of time before the staining procedure is started. Fixation changes the physical and chemical state of the cell and determines the subsequent staining reactions that could be carried out on the smears.

PROPERTIES OF CYTOLOGIC FIXATIVES

- Do not excessively shrink or swell cells.
- Do not distort or dissolve cellular components.
- Inactivate enzymes and preserve nuclear details.
- Kill microbes.
- Improve optical differentiation and enhance staining.
- Properties of the tissues and cell components are preserved.

CYTOLOGIC FIXATIVES

Wet Fixation

Routine Fixatives. The process of immersing freshly prepared smears immediately in a liquid fixative is called wet fixation. This is the ideal method for fixing all gynecological and non-gynecological smears, and any of the following alcohols can be used. All alcohol fixatives should be discarded or filtered (Whatman No: I filter paper) after each use.

- ***95% Ethyl alcohol (ethanol).*** The ideal fixative recommended in most of the laboratories for cytological specimen is 95% ethanol alone. It produces the characteristic desired effect on nucleus. It is a dehydrating agent and causes cell shrinkage as it replaces water. But it causes only the desired amount of cell contraction to yield optimal chromatin detail characteristic of cytological preparations. Absolute (100%) ethanol produces a similar effect on cells, but is much more expensive.
- ***Ether-alcohol mixture.*** This fixative was originally recommended by Papanicolaou. It consists of equal parts of ether and 95% ethyl alcohol. It is an excellent fixative, but ether is not used in most of the laboratories because of its safety hazards, odor and hygroscopic nature.
- ***100% Methanol.*** 100% methanol is an acceptable substitute for 95% ethanol. Methanol produces less shrinkage than ethanol, but it is more expensive than ethanol.
- ***80% Propanol and isopropanol.*** Propanol and isopropanol cause slightly more cell shrinkage than ether-ethanol or methanol. By using lower percentage of these alcohols, the shrinkage is balanced by the swelling effect of water on cells. Hence 80% propanol is a substitute for 95% ethanol.

- ***Denatured alcohol.*** It is ethanol that has been changed by the additives in order to render it unsuitable for human consumption. There are many different formulae for denatured alcohol; all of them contain methanol as the main ingredient, and hence this can be used at concentrations of 95% or 100%. One formula is 90 parts of 95% ethanol + 5 parts of 100% methanol + 5 parts of 100% isopropanol.

Time of fixation. Minimum 15 minutes fixation prior to staining is essential. Prolonged fixation for several days or even few weeks will not affect the morphology of cells. If smears are to be preserved over a long period of time in alcohol, it is better to store them in capped containers in the refrigerator.

Coating Fixative. Coating fixatives are substitutes for wet fixatives. They are either aerosols applied by spraying the cellular samples or a liquid base, which is dropped onto the slide. They are composed of an alcohol base, which fixes the cells and wax like substance, which forms a thin protective coating over the cells, e.g. Carbowax (polyethylene glycol) fixative. Diaphine fixative spray is a coating fixative (hairspray) with high alcohol content and a minimum of lanolin or oil is also an effective fixative.

Most of these agents have a dual action in that they fix the cells and, when dry, form a thin protective coating over the smear. These fixatives have practical value in situations where smears have to be mailed to a distant cytology laboratory for evaluation. This method is not recommended for smears prepared from fluid within the laboratory as in any good method of fixation the coating fixative should be applied immediately on fresh smears. The distance from which the slides are sprayed with an aerosol fixative affects the cytology details. 10–12 inches (25–30 cm) is the optimum distance recommended for aerosol fixative. Aerosol sprays are not recommended for bloody smears, because they cause clumping of erythrocytes. Waxes and oils from hairspray fixative alter staining reactions if they are not adequately removed. Prior to staining, the slides have to be kept overnight in 95% alcohol for removal of the coating fixative.

Special Purpose Fixative

Carnoy's fixative. This is a special purpose fixative for hematologic samples. The acetic acid in the fixative hemolyses the red blood cells. It is an excellent nuclear fixative as well as preservative for glycogen but results in considerable shrinkage of cells and tends to produce overstaining with hematoxylin. Overfixing in Carnoy's fixative also results in loss of chromatin material. Carnoy's fixative must be prepared fresh when needed and discarded after each use. It loses its effectiveness on long standing, and chloroform can react with acetic acid to form hydrochloric acid.

AAF Fixative. This is the ideal fixative used for cellblock preparation of fluid specimens.

Mailing of Unstained Smears—Glycerine Method for Mailing Slides. Smears are first fixed in 95% ethanol for 12 minutes. Two drops of glycerine are placed on smears and covered with a clean glass slide. This may be wrapped in wax paper and mailed to the laboratory in a suitable container. Coating fixative such as Carbowax fixative and spray coating fixative can be used primarily to facilitate transport of smears, mailing, etc.

Prefixation of Cytologic Material. Prefixation may preserve some specimens for days without deterioration of cells. Some of the disadvantages of prefixation are precipitation/coagulation of proteins, hardening of cells into spherical shapes and condensation of chromatin. The coagulation of proteins may interfere with the adherence of cells to glass slides. It also 'rounds up' the cells—causes the cells to clump together into tight clusters making stain absorption and interpretation difficult. Albuminized slides should be used to prepare smears from prefixed sample. The most common solutions used for this purpose are:

- Ethyl alcohol (50% solution)
- Saccomanno's fixative (50% alcohol with 2% Carbowax 1540)
- Mucolexx (a commercial mucoliquefying preservative for the collection of mucoid and fluid specimens).

Many other preservatives have been developed for use with automated cytology systems.

Rehydration of Air-dried Smears. Unfixed, air-dried gynecological smears received from peripheral areas can be used for Papanicolaou staining by rehydration method. The simplest rehydration technique is to place air-dried cytological specimens in 50% aqueous solution of glycerine for three minutes followed by two rinses in 95% ethyl alcohol, and then stained by the routine Papanicolaou method.

STAINING METHODS IN CYTOLOGY

PAPANICOLAOU STAINING METHOD

Papanicolaou staining method is the routine staining procedure used in cytopathology laboratory. This technique is named after Dr George N Papanicolaou, the father of exfoliative cytology and is devised for the optimal visualization of cells exfoliated from epithelial surfaces of the body. It is a polychrome staining reaction designed to display the many variations of cellular morphology showing degrees of cellular maturity and metabolic activity. The use of the Papanicolaou stain results in well-stained nuclear chromatin, differential cytoplasmic counterstaining and cytoplasmic transparency.

Steps of Staining Procedure (Table AIII-2)

1. **Fixation.** The cytology smears are fixed in 95% ethyl alcohol or in other substitutes for a minimum of 15 minutes.
2. **Nuclear Staining.** It is done by using hematoxylin stain. Harris hematoxylin or its modified form is used in Papanicolaou staining in regressive method, in which we deliberately overstain with hematoxylin and remove the excess stain by using a differentiating solution such as acid alcohol (0.05% HCl in 70% ethyl alcohol) or 0.05% aqueous solution of HCl alone. As hematoxylin is used in an acid pH, a pink color will form and it is not stable. In order to make it stable, the compound is brought to

Table AIII.2. Papanicolaou staining procedure

1. 90% Ethanol (fixation)	15 minutes(mt)
2. 80% Ethanol	2
3. 60% Ethanol	2
4. Distilled water	5 dips
5. Distilled water	5 dips
6. Hematoxylin stain	2
7. 0.05% HCl solution	2
8. Running tap water (Bluing)	10
9. 60 % Ethanol	2
10. 80% Ethanol	2
11. 80% Ethanol	2
12. 95% Ethanol	2
13. OG-6 stain	2
14. 95% Ethanol	2
15. 95% Ethanol	2
16. 95% Ethanol	2
17. EA-36 Stain	2
18. 95% Ethanol	2
19. 95% Ethanol	2
20. 95%Ethanol	2
21. 95% Ethanol	2
22. Absolute Ethanol	2
23. Absolute Ethanol	2
24. Absolute Ethanol	2
25. Absolute Ethanol+ Xylene (1:1)	2
26. Xylene	5
27. Xylene	5
28. Xylene	till clear
29. Mounting in DPX	

alkaline pH (bluing) by treating with a weak alkaline solution. Running tap water which is slightly alkaline (pH 8) is used as bluing solution in small laboratories. Ammonium hydroxide solution (15 ml of ammonium hydroxide 28–30% weight/volume to 985 ml of 70% ethanol) can also be used.

3. **Cytoplasmic Staining.** Cytoplasmic stains are OG-6 and EA-36. Both are synthetic stains and OG-6 is a monochrome stain while EA-36 is a polychrome stain.
4. **Dehydration.** Rinse the smears in absolute alcohol for two or three changes for the removal of water. Smears left in rinses for long will lose too much stain. Alternative to 100% ethanol are 100% isopropanol and 100% denatured alcohol. Rectified spirit affects the cytoplasmic staining and hence is not recommended.
5. **Clearing.** Cells are not transparent while the smear is in the staining or alcohol solutions. During clearing, alcohol is being replaced with xylene, which is also miscible in mounting medium. Xylene has a refractive index as that of glass and mounting medium and it prevents cellular distortion.
6. **Mounting of Slide.** The mounting media must be miscible with the clearing agent to prevent fading of the stains. Practice is essential to achieve well-mounted slides, free of air bubbles and artifacts. A minimum of mounting medium should be used. Too much mounting medium interferes with microscopic detail, making the cell film appear hazy or milky when examined under the high power objective. If the mounting medium and cover slip are applied too slowly, a common artifact appears as a brown refractile pigment like substance on the surface of the cell when xylene evaporates. If this artifact occurs, the slide must be soaked in xylene, absolute alcohol and 95% alcohol, rinsed in running tap water and restained in OG and EA. A possible means of preventing the 'brown artifact' is to coverslip slide behind a transparent chemical splash shield set at the front edge of the fume hood. The shield diverts air around the local workspace and reduces the rate of xylene evaporation. The usual size of the coverslip for a cervical smear is 22 × 30 mm. If the smear spread is beyond the coverslip area, ideally use another small coverslip or put a drop of DPX and spread evenly with the same coverslip without affecting the focus.

Precautions

- Immediate fixation of smears is essential.
- Smears should never be allowed to dry before placing the coverslip.
- Hematoxylin is filtered everyday before use.
- All solutions and stains are filtered before use, to keep them free of sediment.
- Avoid contamination from one smear to another.
- Keep stains and solutions covered when not in use.
- All dishes are washed daily.
- Stains are discarded and replaced as the quality of the stain deteriorates.
- Avoid contamination during placing of the coverslip, with the dropper used to dispense the mounting medium.
- Place the coverslip on the microslide slowly without trapping air bubbles.

Maintenance of Stains and Solutions

- Solutions may be used for longer period of time, if the slide carrier is rested on several layers of tissue paper (paper toweling) for a few seconds before transferring to the solutions.
- Stains keep longer if they are stored in dark colored, stoppered bottles.
- Hematoxylin keeps relatively constant staining characteristics and do not require frequent discarding if small amounts of fresh stain are added to replace stain loss due to evaporation.
- Use of coating or spray fixatives may cause contamination making frequent changes necessary.
- OG and EA stains lose strength more rapidly than hematoxylin and should be replaced each week or as soon as the cells appear without crisp staining colors.

- Bluing solution and HCl should be replaced at least once daily.
- Water rinses should be changed after each use.
- Alcohol used for the process of dehydration prior to the cytoplasmic stains may be replaced weekly. The alcohol rinses following the cytoplasmic stains are usually changed on a rotating basis after each use. The alcohol rinse immediately following the stain is discarded, and the other two rinses are moved to the first and second position, and fresh unused alcohol is replaced in third position. Ideally this rotation must continue after each staining run. The absolute alcohols should be changed weekly and can be kept water free by adding silica gel pellets.
- Xylene should be changed as soon as it becomes tinted with any of the cytoplasmic stains. Xylene becomes slightly milky if water is present in it and if so the clearing process may be disturbed. Tiny drops of water may be seen microscopically on a plane above the cell on a slide. Addition of silica gel pellets to the absolute alcohol will minimize water contamination of xylene.
- Agitation of the slides by occasional dipping is necessary to remove excess dye.
- Dipping should be done gently to avoid cell loss and the slide carrier should not hit the bottom of the staining dish.
- The quality of the stained slide is dependent on timing, solubility and percentage of dye concentration.

RAPID PAPANICOLAOU STAINING

The purpose is to save staining time and money by combining OG and EA and reducing the number of rinses. This procedure needs to be done only for emergency situations and not for routine use.

Contamination Control

All stains, hematoxylin, OG-6 and EA-36 should be filtered at least once daily. The alcohols used for rehydration, dehydration, and xylene must be filtered or replaced daily. Gynecological and non-gynecological materials may be stained separately. Specimens prone for shedding cells and those suspected to have large number of cancer cell should be stained at the end of the day using separate rack. Even with all these precautions, gross contamination may occur, and if this happens with malignant cells all solutions and stains must be immediately filtered or discarded.

HEMATOXYLIN AND EOSIN (H&E) STAINING METHOD

Some laboratories use routine H&E stain for non-gynecological smears. The benefits of using Papanicolaou stain are clear definition of nuclear details and differential counterstaining giving cytoplasmic transparency. H&E stain does not satisfy these criteria and hence unacceptable for cervical smears.

MAY-GRUNWALD-GIEMSA (MGG) STAINING METHOD

Many laboratories use MGG (Romanowski type stain) staining method for cytological diagnosis of non-gynecological specimens in addition to Pap and H&E stains. Combination of all these stains increases the efficiency of microscopic interpretations. MGG stain is performed on air-dried aspirates or fluids. Stock solutions of May-Grunwald reagent and Giemsa stain are available commercially.

Staining Procedure

1. May-Grunwald solution—5 mt
2. Running water—1 mt
3. Giemsa solution—15 mt
4. Running water—1–2 mt
5. Air-dry (no mounting necessary).

Labeling of Slides

After the slides have been cleaned, they are ready for labeling. Place a small square label on the edge of the slide on the same side as the cover slip. Use waterproof ink and record the institution, details, accession, year, nature of specimen, etc. on it.

Filing the Slides

The slides must be protected from breakage, light, moisture and dust. After microscopic interpretation, the slides must be filed in slide filing cabinets in serial order, in numbered slots. They are kept for a minimum of 5 years and are retrieved when necessary.

NOTES ON IMMUNOHISTOCHEMISTRY

Immunohistochemistry is the localization of antigens in tissue sections by the use of labeled antibody as specific reagents through antigen–antibody interactions that are visualized by a marker such as fluorescent dye, enzyme, radioactive element or colloidal gold.

Albert H Coons and his colleagues (Coons et al. 1941, 1955; Coons and Kaplan 1950) were the first to label antibodies with a fluorescent dye, and use it to identify antigens in tissue sections. With the expansion and development of immunohistochemistry techniques, enzyme labels have been introduced such as peroxidase (Nakane and Pierce 1966; Avrameas and Uriel 1966) and alkaline phosphatase (Mason and Sammons 1978). Colloidal gold (Faulk and Taylor 1971) label has also been discovered and used to identify immunohistochemical reactions at both light and electron microscopy level. Other labels include radioactive elements, and immunoreaction can be visualized by autoradiography.

Since immunohistochemistry involves specific antigen–antibody reaction, it has apparent advantage over traditionally used special enzyme staining techniques that identify only a

limited number of proteins, enzymes and tissue structures. Therefore, immunohistochemistry has become a crucial technique and widely used in many medical research laboratories as well as clinical diagnostics.

There are numerous immunohistochemistry methods that may be used to localize antigens. The selection of a suitable method should be based on parameters such as the type of specimen under investigation and the degree of sensitivity and specificity required.

FIXATION

Tissue preparation is the cornerstone of immunohistochemistry. To ensure the preservation of tissue architecture and cell morphology, prompt and adequate fixation is essential. However, inappropriate or prolonged fixation may significantly diminish the antibody binding capability.

There is no one universal fixative that is ideal for the demonstration of all antigens. However, in general, many antigens can be successfully demonstrated in formalin-fixed paraffin-embedded tissue sections. The discovery and development of antigen retrieval techniques further enhanced the use of formalin as routine fixative for immunohistochemistry in many research laboratories.

For best results, vertebrate tissues (especially neuronal tissues) usually require fixation by transcardial perfusion for optimal tissue preservation. The most common fixatives used for immunohistochemistry are:

1. 4% paraformaldehyde in 0.1M phosphate buffer.
2. 2% paraformaldehyde with 0.2% picric acid in 0.1M phosphate buffer.
3. PLP fixative: 4% paraformaldehyde, 0.2% periodate and 1.2% lysine in 0.1M phosphate buffer.
4. 4% paraformaldehyde with 0.05% glutaraldehyde (TEM immunohistochemistry).

Some antigens will not survive even moderate amounts of aldehyde fixation. Under this condition, tissues should be rapidly fresh frozen in liquid nitrogen (snap frozen) and cut with a cryostat. The sections should be kept frozen at −20° C or lower until fixation with cold acetone or alcohol. After fixation, the sections can be processed using standard immunohistochemical staining protocols.

SECTIONING

Since its introduction, paraffin wax has remained the most widely used embedding medium for diagnostic histopathology in routine histological laboratories. Accordingly, the largest proportion of material for immunohistochemistry is formalin-fixed, paraffin-embedded. Paraffin sections produce satisfactory results for the demonstration of majority of tissue antigens with the use of antigen retrieval techniques.

Certain cell antigens do not survive routine fixation and paraffin embedding. So, the use of frozen sections still remains essential for the demonstration of many antigens. However, the disadvantages of frozen sections include poor morphology, poor resolution at higher magnifications, special storage needed, limited retrospective studies, and cutting difficulty over paraffin sections.

Vibratome sections have some advantages when doing immunohistochemistry since the tissue is not processed through organic solvents or high heat, which can destroy the antigenicity. In addition, the morphology of tissue sections are not disrupted since no freezing and thawing needed. Vibratome sections are often used for floating immunostaining, especially for pre-embedding EM immunohistochemistry. The disadvantage of vibratome sections is that the sectioning process is slow and difficult with soft and poorly fixed tissues. In addition, the chatter marks or vibratome lines often appears in the sections.

WHOLE MOUNT PREPARATION

Small blocks of tissue (less than 5 mm thick) can be processed as whole mounts. The advantage of whole mount preparations is that the results provide three- dimensional information about the location of antigens without the need for reconstruction from sections. However, the major limitation of using whole mounts is antibody penetration may not be complete in the tissue, resulting in uneven staining or false negative staining. So Triton X-100 or saponin treatment is used routinely for whole mount immunohistochemistry to enhance penetration of the antibody.

The demonstration of many antigens can be significantly improved by pretreatment with the antigen retrieval reagent that breaks the protein cross-links formed by formalin fixation and thereby uncover hidden antigenic sites. The techniques involved the application of heat for varying lengths of time to formalin-fixed, paraffin-embedded tissue sections in an aqueous solution (commonly referred to as the retrieval solution). This is called 'heat induced epitope retrieval (HIER)'. Another method uses enzyme digestion and is called proteolysis induced epitope retrieval (PIER).

Microwave oven, pressure cooker, and steamer are the most commonly used heating devices. Other devices also include the use of autoclave and water bath. The heating length of 20 minutes appears to be the most satisfactory and the cooling usually takes about 20 minutes. **Citrate buffer of pH 6.0** is the most popularly used retrieval solution and is suitable for most of antibody applications. The **TRIS-EDTA of pH 9.0** and **EDTA of pH 8.0** are second most used retrieval solutions. **Proteinase K** is effective enzyme digestion reagent for membrane antigens such as integrins, CD31, vWF, etc.

PIER methods (such as **proteinase k**, **trypsin**, chymotrypsin, **pepsin**, **pronase** and various other proteases) have also been reported for restoring immunoreactivity to tissue antigens with different degrees of success. However, the use of enzyme digestion method may destroy some epitopes and tissue morphology. Therefore the optimal enzyme concentration and incubation time need to be tested.

Combination of heat mediated and proteolytic enzyme method is an alternative approach to unmask antigens if other methods did not work. It is especially useful when performing double or triple labeling of two or more antigens simultaneously.

Improving antibody penetration is also important for immunohistochemical staining of frozen and vibratome sections. Triton X-100 is by far the most popular detergent for improving antibody penetration for immunohistochemistry. However, it is not appropriate for the use of membrane antigens since triton X-100 destroy membranes. Some researchers prefer the freeze and thaw method for the improvement of antibody penetration. Sodium borohydride (1% in phosphate buffer) treatment is also widely used to unmask antigens, particularly in glutaraldehyde fixed tissue to reduce the glutaraldehyde linkages.

BLOCKING

Background staining may be specific or non-specific. Inadequate or delayed fixation may give rise to false positive results due to the passive uptake of serum protein and diffusion of the antigen. Such false positives are common in the center of large tissue blocks or throughout tissues in which fixation was delayed.

Antibodies, especially polyclonal antibodies are sometimes contaminated with other antibodies due to impure antigen used to immunize the host animal.

The main cause of non-specific background staining is non-immunological binding of the specific immune sera by hydrophobic and electrostatic forces to certain sites within tissue sections. This form of background staining is usually uniform and can be reduced by blocking those sites with normal serum.

Endogenous peroxidase activity is found in many tissues and can be detected by reacting fixed tissue sections with DAB substrate. The solution for eliminating endogenous peroxidase activity is by the pretreatment of the tissue section with hydrogen peroxide prior to incubation with primary antibody.

Many tissues also contain endogenous alkaline phosphatase (AP) activity and should be blocked by the pretreatment of the tissue section with levamisole if using AP as a label.

Some tissues such as liver and kidney have endogenous biotin. To avoid unwanted avidin binding to endogenous biotin if using biotin–avidin detection system, a step is necessary for these tissues by the pretreatment of unconjugated avidin which is then saturated with biotin.

Autofluorescence or natural fluorescence exists in some tissues and can cause background problems when fluorescent dyes are used in the experiments. The simplest test is to view the tissue sections with a fluorescence microscope before any antibody incubation. If autofluorescence is detected in the tissue sections, the best solution is to avoid use of fluorescent method but select enzyme or other labeling methods.

CONTROLS

Special controls must be run in order to test the protocol and for the specificity of the antibody being used.

Positive control is to test a protocol or procedure and make sure it works. It will be ideal to use the tissue of known positive as a control. If the positive control tissue showed negative staining, the protocol or procedure needs to be checked until a good positive staining is obtained.

Negative control is to test for the specificity of an antibody involved. First, no staining must be shown when omitting primary antibody or replacing a specific primary antibody with normal serum (must be from the same species as primary antibody). This control is easy to achieve and can be used routinely in immunohistochemical staining.

Second, the staining must be inhibited by adsorption of a primary antibody with the purified antigen prior to its use, but not by adsorption with other related or unrelated antigens. This type of negative control is ideal and necessary in the characterization and evaluation of new antibodies but it is sometimes difficult to obtain the purified antigen, therefore it is rarely used routinely in immunohistochemical staining.

DIRECT METHOD

Direct method is one-step staining method, and involves a labeled antibody (i.e. labeled conjugated antiserum) reacting directly with the antigen in tissue sections. This technique utilizes only one antibody and the procedure is short and quick. However, it is insensitive due to little signal amplification and rarely used since the introduction of indirect method.

INDIRECT METHOD

Indirect method involves an unlabeled primary antibody (first layer) which reacts with tissue antigen, and a labeled secondary antibody (second layer) that reacts with primary antibody (Note: The secondary antibody must be against the IgG of the animal species in which the primary antibody has been raised, i.e. raised in a different species of animal e.g. rabbit, sheep). This method is more sensitive due to signal amplification through several secondary antibody reactions with different antigenic sites on the primary antibody. In addition, it is also economic since one labeled second layer antibody can be used with many first layer antibodies (raised from the same animal species) to different antigens.

The second layer antibody can be labeled with a fluorescent dye such as FITC, rhodamine or Texas red, and this is called indirect immunofluorescence method. The second layer antibody may be labeled with an enzyme such as peroxidase, alkaline phosphatase or glucose oxidase, and this is called indirect immunoenzyme method.

PAP METHOD

Peroxidase anti-peroxidase method (PAP) is a further development of the indirect technique and it involves a third layer which is a rabbit antibody to peroxidase, coupled with peroxidase to make a very stable peroxidase anti-peroxidase complex. The complex, composed of rabbit gamma-globulin and peroxidase, acts as a third layer antigen and becomes bound to the unconjugated goat anti-rabbit gamma-globulin of the second layer. The sensitivity is about 100 to 1000 times higher since the peroxidase molecule is not chemically conjugated to the anti IgG but immunologically bound, and loses none of

its enzyme activity. It also allows for much higher dilution of the primary antibody, thus eliminating many of the unwanted antibodies and reducing non-specific background staining.

ABC METHOD

Avidin-biotin complex (ABC) method is standard immunohistochemistry (IHC) method and one of widely used techniques for immunohistochemical staining. Avidin, a large glycoprotein, can be labeled with peroxidase or fluorescein and has a very high affinity for biotin. Biotin, a low molecular weight vitamin, can be conjugated to a variety of biological molecules such as antibodies.

The technique involves three layers. The first layer is unlabeled primary antibody. The second layer is biotinylated secondary antibody. The third layer is a complex of avidin-biotin peroxidase. The peroxidase is then developed by the diaminobenzidine tetrahydrochloride (DAB) or other substrate to produce differently colored end products.

LSAB METHOD

Streptavidin, derived from *Streptococcus avidinii*, is a recent innovation for substitution of avidin. The streptavidin molecule is uncharged relative to animal tissue, unlike avidin which has an isoelectric point of 10, and therefore electrostatic binding to tissue is eliminated. In addition, streptavidin does not contain carbohydrate groups which might bind to tissue lectins, resulting in some background staining.

Labeled streptavidin biotin (LSAB) is technically similar to standard ABC method. The first layer is unlabeled primary antibody. The second layer is biotinylated secondary antibody. The third layer is enzyme-streptavidin conjugates horseradish peroxidase; AD–alkaline phosphatase (HRP*-streptavidin or AP*-streptavidin) to replace the complex of avidin-biotin peroxidase. The enzyme is then visualized by application of the substrate chromogen solutions to produce different colored end products. The third layer can also be fluorescent dye-streptavidin such as FITC-streptavidin if fluorescence labeling is preferred.

A recent report suggests that LSAB method is about 5–10 times more sensitive than standard ABC method.

POLYMERIC METHODS

These are based on dextran polymer technology. This unique chemistry permits binding of a large number of enzyme molecules (horseradish peroxidase or alkaline phosphatase) to a secondary antibody via the dextran backbone. The benefits are many, including increased sensitivity, minimized non-specific background staining, and a reduction in the total number of assay steps as compared to conventional techniques. The simple protocol is: (i) application of primary antibody, (ii) application of enzyme labeled polymer, and (iii) application of the substrate chromogen.

Polymerized Reporter Enzyme Staining System. It is based on a new method of polymerizing enzymes and attaching these polymers to antibodies. The novel approach employed to form enzyme 'micropolymers' avoids the intrinsic shortcomings of using large dextrans or other macromolecules as backbones. Attaching a unique micropolymer with a high density of very active enzyme to a secondary antibody generates a reagent that overcomes steric interference and provides enhanced accessibility to its target. The result is outstanding sensitivity, signal intensity, low background staining, and reduced non-specific binding. The simple protocol is: (i) application of primary antibody, (ii) application of enzyme labeled polymer, and (iii) application of the substrate chromogen.

Tyramide Signal Amplification (TSA). It is ideal for the following applications: (i) detecting small quantities of antigen, (ii) enhancing performance of low affinity mouse and rabbit antibodies, and (iii) enabling compatibility of certain 'tough' mouse and rabbit antibodies with paraffin embedded tissue sections. The simple protocol is as follows:

1. Application of primary antibody
2. Application of biotinylated linking antibody
3. Application of the tyramide amplification reagent
4. Application of streptavidin-HRP
5. Application of the substrate chromogen.

Biotin-free TSA System. It is a highly sensitive immunohistochemical (IHC) staining procedure incorporating a signal amplification method based on the peroxidase-catalyzed deposition of a fluorescein-labeled phenolic compound, followed by a secondary reaction with a peroxidase-conjugated anti-fluorescein. In the procedure, a mouse primary antibody is first detected with a peroxidase-conjugated secondary antibody. The next step utilizes the bound peroxidase to catalyze oxidation of a fluorescein-conjugated phenol (fluorescyl-tyramide) which then precipitates onto the specimen. The procedure is continued with detection of the bound fluorescein by a peroxidase-conjugated anti-fluorescein. Staining is completed using diaminobenzidine/hydrogen peroxide as chromogen/substrate, and can be observed with a light microscope. In comparison to standard immunohistochemical methods, such as labeled streptavidin biotin (LSAB) or avidin-biotin complexes (ABC), tyramide amplification methods have been reported to be many fold more sensitive. This reagent system utilizes fluorescyl-tyramide, rather than biotinyl-tyramide, and does not contain avidin/biotin reagents, thus eliminating potential background staining due to reactivity with endogenous biotin.

Principles of Procedure. The specimens are first incubated with peroxidase block for 5 minutes to quench endogenous

* HRP—Horseradish peroxidase; AP—alkaline phosphatase.

peroxidase activity. The specimens are then incubated for 5 minutes with a protein block to suppress nonspecific binding of subsequent reagents, followed by a 15-minute incubation with an appropriately characterized and diluted mouse primary antibody or negative control reagent (user provided). This is followed by sequential 15-minute incubations with anti-mouse immunoglobulins-HRP, fluorescyl-tyramide hydrogen peroxide (amplification reagent) and anti-fluorescein-HRP. Staining is completed by a 5-minute incubation with 3,3′ diaminobenzidine tetrahydrochloride (DAB)/hydrogen peroxide, which results in a brown precipitate at the antigen site.

MULTIPLE LABELING

It is often useful to be able to stain for two or more antigens in one common tissue section. This can be achieved by immunofluorescence method using different fluorescent dyes. Multiple staining can also be done with peroxidase conjugated antibodies developed with different chromogen substrates to produce the end products of different colors. There are three basic approaches in planning multiple staining: parallel, sequential, and adjacent. In addition, the antibody dilution and conditions are also important factors to be considered. Finally, appropriate color combination is also crucial since improper color combination may produce poor result and fail to demonstrate multiple antigens in the same section. For best result, the careful design and test of multiple staining protocols are necessary.

Immuno-electron Microscopy

Electron microscopic (EM) immunohistochemical techniques can be divided into two groups: (i) those where the immunostaining takes place prior to resin embedding are referred to as pre-embedding, and (ii) those methods where the immunolabeling is undertaken after resin embedding are known as post-embedding.

The choice of whether to apply pre- or post-embedding method to the detection of an antigen in any particular location will depend to a large extent upon the distribution and availability of the antigen and the characteristics of the primary antibody. Before starting immuno-EM labeling, a test for the characteristics and dilution of the primary antibody should be performed at light microcopy level.

Several recently developed methods rely on labeling with colloidal gold particles. These methods were originally introduced for electron microscopy (Faulk and Taylor 1971) as the gold particles are easily visible under the electron microscope, but they are also useful for light microscopy.

Since gold particles can be made in different sizes from 5–30 nm, it is possible to carry out multiple staining at the electron microscopic level, most easily by direct labeling of several first layer antibodies with different sized particles. The indirect techniques can also be used in double or triple labeling by parallel approach if the primary antibodies are from different species and by sequential approach if the primary antibodies are from same species.

STANDARD IHC METHOD

1. Cut paraffin sections and mount on adhesive slides.
2. Deparaffinize slides in xylene and graded alcohols to water.
3. Quench endogenous peroxidase activity. Rinse in buffer.
4. Incubate with 'blocking serum'. Rinse in buffer.
5. Perform epitope retrieval step (antigen retrieval or protease) if needed. Rinse in buffer.
6. Apply primary antibody, incubate, and rinse in buffer.
7. Apply secondary (link) antibody, incubate, and rinse in buffer.
8. Apply detection complex, incubate, and rinse in buffer.
9. Develop reaction product with chromogen, counterstain, dehydrate, coverslip, and view.

Influence of Decalcification on Immunohistochemical Staining of Formalin–fixed Paraffin–embedded Tissue

The pathologist often faces the situation where specimens are fixed and processed before it is known that immunohistochemical analysis may be required. It is now accepted that the adverse effects of routine formalin fixation and processing on the histochemistry of a variety of antigens can be overcome by digestion of tissue sections with proteases prior to immunostaining. However, some specimens containing hard tissue components must be decalcified, usually with dilute solutions of mineral or organic acids, prior to processing and sectioning. The effects of decalcification on the immunoreactivity of formalin fixed tissue has received little attention even though compound fixatives containing acetic acid seem to be effective in preserving tissue antigens in a form detectable without enzyme treatment.

Decalcification of tissues with 10% aqueous solutions of acetic and formic acids for periods up to five days after fixation in neutral formalin does not significantly alter immunoreactivity (JB Matthews, 1981). This is true of routine specimens containing mineralized components (bone and tooth) which have been decalcified in 10% formic acid. Proteins such as immunoglobulin heavy and light chains can withstand treatment with 70% formic acid without greatly affecting their antigenicity.

It is interesting to note that the adverse effects of fixation with neutral formalin were reversed, to a limited extent, by treatment with formic and acetic acid. Thus tissue immunoreactivity was marginally improved in the absence of enzyme digestion and maximal reactivity obtained with less 'unmasking' by trypsin. However the full protective effect of acetic acid (low pH) on tissue antigens would seem to depend upon its presence during primary fixation or post-fixation following a short period (4–8 hours) in neutral formalin.

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APPENDIX IV

Tables of Normal Values

Table AIV-1: Normal laboratory values

Test	Material used and comments	Normal*
Albumin	Serum (See *Protein)*	
Amino acid nitrogen	Serum	3.5–6.0
Amylase	Serum or plasma	80–150 units (Somogyi). (1 unit is 1 mg of reducing sugar liberated as glucose per 100 ml of serum)
Ascorbic acid	Serum or plasma	0.7–2.0
Basal metabolic rate (BMR)		Minus 15% to plus 15%
Bilirubin (van den Bergh)	Serum	Direct: 0–0.2 Total: 0.1–1.0
Bromide	Serum or plasma	Less than 50
Bromsulphalein test (BSP)	Serum. Liver function test. Method is valueless in patients with obvious jaundice	Less than 10% retained in 30 min
Calcium, diffusible	Serum, consists of ionized and nonionized calcium	4.5–5.0
Calcium, nondiffusible	Serum, nonionized calcium. Contains protein-bound calcium fraction	4.5–6.0
Calcium, total	Serum. Total calcium equals diffusible plus nondiffusible	9.0–11.5 (4.5–5.5 mEq/liter)
Calcium, total	Feces, 24-hour specimen	70–90% of ingested calcium eliminated in feces
Calcium, total	Urine, 24-hour specimen	10–30% of ingested calcium eliminated in urine
Carbon dioxide-combining power (CO_2 capacity)	Serum or plasma. Normal Milli-equivalent values expressed as bicarbonate or carbonic acid	Adults: 55–70 vols % (25–35 mEq/liter) Children: 40–55 vols % (18–25 mEq/liter)
Carotenoids	Serum	80–400 µg/100 ml
Cephalin flocculation	Serum. Liver function test	Below 2+ in 48 hours
Chloride	Serum or plasma	570–620 (as NaCl) 340–370 (as Cl) (96–105 mEq/liter as Cl)
Chloride	Spinal fluid	720–750
Chloride	Urine, 24-hour specimen	10–16 gm/24 hr
Cholesterol, esters	Serum or plasma	80–200
Cholesterol, total	Serum or plasma	120–260
Congo red test	Serum or plasma. Test for amyloidosis and nephrosis	10–30% eliminated from blood in 1 hr
Copper	Serum	100–200 µg/100 ml
Creatine	Whole blood	3–7
Creatine	Urine, 24-hour specimen	Adults: 0–200/24 hr Children: 10–15/24 hr
Creatinine	Serum	0.6–1.3
Creatinine	Urine, 24-hour specimen	1–1.8 gm/24 hr
Fatty acids, total	Serum	250–500
Fibrin	Plasma	0.3–0.6 gm/100 ml

Test	Material used and comments	Normal*
Glucose	Whole blood Serum Postprandial	60–90 70–105 Less than 140
Glucose	Spinal fluid	40–60
Hippuric acid	Urine. Liver function test	
Oral		3 gm benzoic acid excreted/4 hr
Intravenous		0.7–0.95 gm benzoic acid excreted/1 hr
Hydrogen ion concentration	Whole blood, serum or plasma	7.3–7.5 units
Icteric index	Serum	4–6 units
Iodine, protein–bound	Serum	3–8 micrograms/100 ml
Lecithin	Serum or plasma	225–250
Lipase	Serum	0.8–1.5 units (Alper) 0.2–1.5 units (Cherry-Crandall)
Lipids, total	Serum	470–750
Nitrogen, nonprotein	Whole blood	25–35
Nitrogen, urea	Whole blood	9–17
pH	Whole blood, serum or plasma	7.3–7.5 units
Phenolsulfonphthalein (PSP)	Urine. Renal function test	40–60% 1st hour 20–25% 2nd hour
Phosphatase, acid	Serum	0–2.5 units (King-Armstrong) 0–1.5 phenol units
Phosphatase, alkaline	Serum	Adults: 1.5–5.0 units (Bodansky) 5–10 units (King-Armstrong) 1.0–3.5 phenol units Children: 5–14 units (Bodansky) 5–20 units (King-Armstrong) 4–12 phenol units
Phospholipids	Serum	150–350
Phosphorus, inorganic	Serum	Adults: 3.0–4.5 Children: 4.5–6.0
Potassium	Serum	16–22 (4.1–5.6 mEq/liter)
Protein, total	Serum	6–8 gm/100 ml
Albumin		3.2–4.1 gm/100 ml
Alpha globulin		0.7–1.5 gm/100 ml
Beta globulin		0.7–1.3 gm/100 ml
Gamma globulin		0.7–1.3 gm/100 ml
Total globulin		2.6–3.8 gm/100 ml
Albumin-globulin ratio (A/G ratio)		1.5–2.5 : 1
Protein, total	Spinal fluid	20–40
Sodium	Serum	315–340 (137–147 mEq/liter)
Sulfates	Serum	2.5–5.0
Thymol turbidity	Serum. Liver function test	0–4 units
Uric acid	Whole blood	2–4
Urobilinogen	Feces, 4-day specimen	150–300
Urobilinogen	Urine, 24-hour specimen	8 or less
Vitamin A	Serum	15–60 µg/ml
Vitamin C	Serum or plasma	0.7–2.0
Volume, blood	Whole blood and plasma	70–100 cc blood/kg 35–50 cc plasma/kg
Zinc turbidity	Serum. Liver function test	2–8 units

**All values expressed as milligrams per 100 ml unless otherwise specified.*

Table AIV-2: Normal red blood cell values

Age	Red cell count (millions per cu mm blood)	Hemoglobin* (gm per 100 ml)	Hematocrit (vol packed cells per 100 ml)	Sedimentation rate in 1 hr (Wintrobe method)	Reticulocytes (% of erythrocytes)
Children					
First year	6.1–4.5	25–11.2	64–35	0–2 mm	2–6 (at birth)
	(Values decrease with increasing age; high at birth)			(At birth)	0.5–1.5 (2–5 days after birth)
2–10 years	4.6–4.7	11.5–12.9	35.3–37.5	3–13 mm	0.5–1.5
11–15 years	4.8	13.4	39		0.5–1.5
Adults					
Females	4.2–5.4	12–16	37–47	0–15 mm	
Males	4.6–6.2	14–18	40–54	0–65 mm	0.5–1.5

**Hemoglobin values by oxygen capacity method.*

Table AIV-3 Normal white blood cell values

Total white cell count per cu mm blood	
Infants:	8,000–16,500
4–7 years:	6,000–15,000 (average 10,700)
8–18 years:	4,500–13,500 (average 8,300)
Adults:	5,000–10,000 (average 7,000)

*Relative (differential) and absolute values for leukocyte counts in normal adults per cu mm blood**

Type of cell	Percentage	Absolute number		
		Average	Minimum	Maximum
Total leukocytes	—	7,000	5,000	10,0000
Myelocytes	0	0	0	0
Juvenile neutrophils	3–5	300	150	400
Segmented neutrophils	54–62	4,000	3,000	5,800
Eosinophils	1–3	200	50	250
Basophils	0–0.75	25	15	50
Lymphocytes	25–33	2,100	1,500	3,000
Monocytes	3–7	375	285	500

**From MM Wintrobe: Clinical Hematology (6th ed). Lea and Febiger, Philadelphia, 1967.*

Table AIV-4: Normal blood platelet values and associated phenomena

Total number of platelets: 150,000–400,000 per cu mm blood	
Bleeding time:	Under 5 minutes (Duke's method)
Clotting time:	1–7 minutes (Capillary tube method) 2.5–5 minutes (Kruse and Moses method) 5–10 minutes (Lee and White method)
Prothrombin time:	10–20 seconds (Quick method)
Clot retraction time: Qualitative begins 1–6 hours; completes at 24 hours Quantitative 80–90%	
Capillary fragility (tourniquet test): More than 10 petechiae per 1 inch circle—positive	
Heterophil antibodies (Sheep cell agglutination): Below 1 : 56 dilution	
Incidence of blood groups in normal population:	
Group O: 40% A: 45 B: 12 AB: 4	
Rh positive: 85%	
Negative: 15	

Table AIV–5: Normal average values of urine

Physical characteristics	
Volume, 24-hour specimen	1500 ml
Specific gravity	1.015–1.025
Turbidity	None
Color	Amber
Chemical characteristics	
pH	Slightly acid
Total acidity	25–40 ml N/10 NaOH to neutralize 100 ml urine
Water	95% of total urine
Inorganic constituents	
Chloride (as NaCl)	9.0 gm/liter
Phosphorus (as P_2O_5)	2.0 gm/liter
Total sulfur (as SO_3)	1.5 gm/liter
Sodium (as Na_2O)	4.0 gm/liter
Potassium (as K_2O)	2.0 gm/liter
Calcium (as CaO)	0.2 gm/liter
Magnesium (as MgO)	0.2 gm/liter
Iron	0.003 gm/liter
Organic constituents	
Urea	15.25 gm/liter
Uric acid	0.4–0.6 gm/liter
Creatinine	0.8–1.5 gm/liter
Ammonia	0.6 gm/liter
Undetermined N	0.6 gm/liter
Traces of other substances	

Table AIV–6: Normal chronological development of deciduous teeth

	Calcification begins (mods in utero)	Crown completed (mos)	Eruption (mos)	Root completed (yrs)	Root resorption begins (yrs)	Tooth shed (yrs)
Central incisor	4–5	2–4	6–9	1½–2	5–6	7–8
Lateral incisor	4–5	2–5	7–10	1½–2	5–6	7–9
Cuspid	5	9	16–20	2½–3	6–7	10–12
First molar	5	6	12–16	2–2½	4–5	9–11
Second molar	6	10–12	20–30	3	4–5	10–12

Adapted from original data of Logan and Kronfeld.

Table AIV–7: Normal chronological development of permanent teeth

	Calcification begins (yrs)	Crown completed (yrs)	Eruption (yrs)	Root completed (yrs)
Maxilla				
Central incisor	3–4 mos	4–5	7–8	10
Lateral incisor	1	4–5	8–9	11
Cuspid	4–5 mos	6–7	11–12	13–15
First bicuspid	1½–1¾	5–6	10–11	12–13
Second bicuspid	2–2½	6–7	10–12	12–14
First molar	Birth	2½–3	6–7	9–10
Second molar	2½–3	7–8	12–13	14–16
Third molar	7–9	12–16	17–25	18–25
Mandible				
Central incisor	3–4 mos	4–5	6–7	9
Lateral incisor	3–4 mos	4–5	7–8	10
Cuspid	4–5 mos	6–7	9–11	12–14
First bicuspid	1¾–2	5–6	10–12	12–13
Second bicuspid	2¼–2½	6–7	11–12	13–14
First molar	Birth	2½–3	6–7	9–10
Second molar	2½–3	7–8	11–13	14–15
Third molar	8–10	12–16	17–25	18–25

Adapted from original data of Logan and Kronfeld.

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