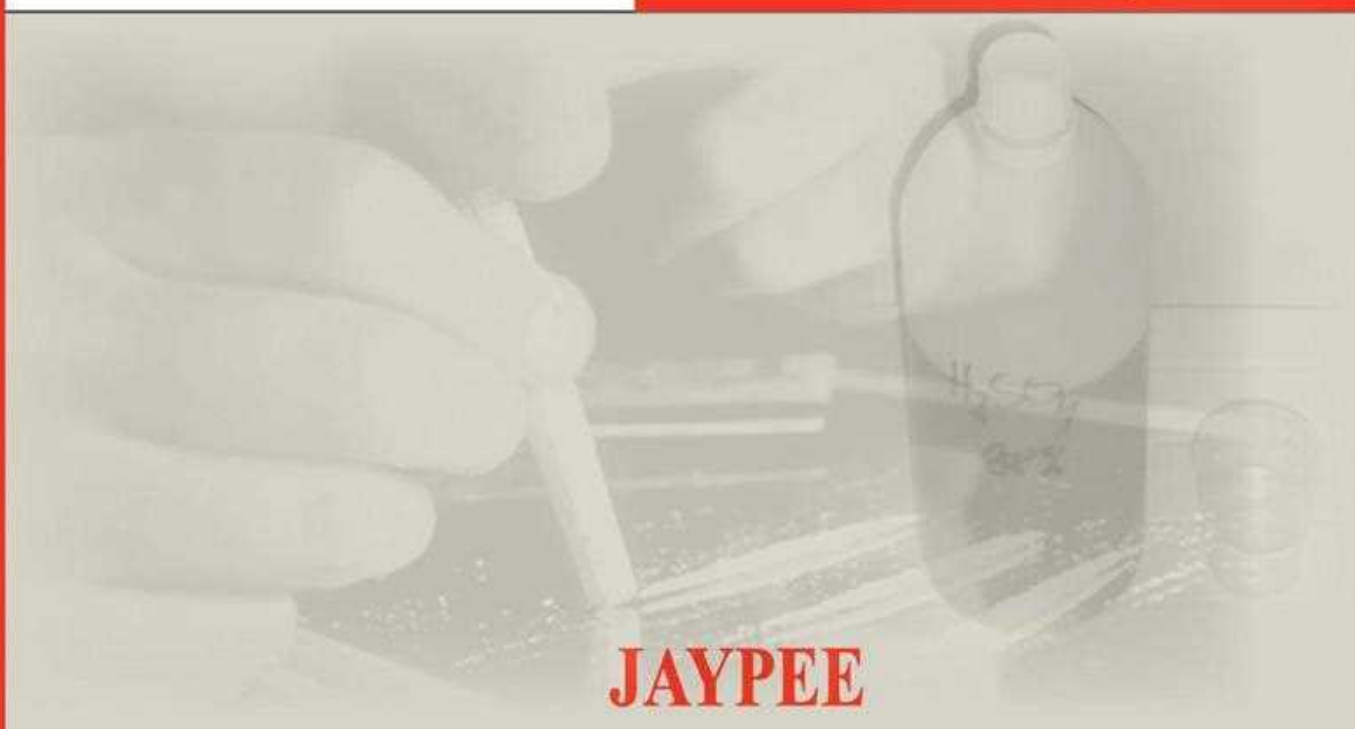**FOURTH EDITION**

MODERN MEDICAL TOXICOLOGY

Completely Updated, Revised & Profusely Illustrated

VV Pillay

JAYPEE

Modern Medical
Toxicology

If I can ease one life the aching,
Or cool one pain,
I shall not live in vain.

—Emily Dickinson

Modern Medical Toxicology

Completely Updated, Revised and Profusely Illustrated

4th Edition

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Foreword

Prem Nair

Dedicated to

the memory of
my father, Mr PV Pillay
and
my mentor, Professor ATS Iyengar

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Foreword

With this edition, *Modern Medical Toxicology (MMT)* celebrates its 17th year in circulation. When Dr VV Pillay wrote the 1st edition of this book back in 1995, he could not have realised the extent of popularity his book would engender among medical students, faculty and practitioners. MMT has now grown in size, but is still compact enough to be carried in the hand as a handbook.

Although the knowledge of medical toxicology has advanced substantially, the goal of MMT has not changed: to provide useful clinical information on poisons and poisoning to emergency room (ER) physicians, medical students, interns, residents, nurses, pharmacists, and other health care professionals in a concise, complete, and accurate manner. The text continues to cover all the topics expected in a book of this size, with detailed information on corrosives, irritant poisons, neurotoxic agents, cardiovascular drugs and poisons, asphyxiants, and even paediatric and obstetric poisons.

With poisoning cases constituting a significant proportion of hospital admissions, MMT quickly provides information that will help practitioners achieve optimal care. The more specialised the practice of medical toxicology becomes, the more important such information becomes. Specialists as well as generalists must at some time or the other require to quickly access information about various poisons.

The fourth edition of MMT is the culmination of an arduous but rewarding 5-year enterprise. Every chapter has been updated and completely rewritten. A number of original colour photographs and drawings have been included for the first time. Dr Pillay deserves a degree of gratitude that cannot be adequately expressed here, but we know he will feel sufficiently rewarded if his efforts serve your needs.

I congratulate Dr Pillay for this monumental work, and hope this edition will serve as an aid to you, compatible with your needs, and worthy of frequent use.

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Preface to the Fourth Edition

Modern Medical Toxicology (MMT) was conceived more than 15 years ago as an attempt to present current information on medical aspects of toxicology (especially diagnosis and management) to medical students and physicians. At the time it was first written, the only information on medical toxicology available was contained in the toxicology section of textbooks of forensic medicine, and as can be expected, much of it was outdated, incorrect or inappropriate. Physicians treating poisoned and overdosed victims were often in a quandary for accurate guidelines, and were forced to turn to Western sources of information which did not always help, since the toxicological scenario in the West was (and continues to remain) completely different from that which was encountered in India.

The need for a book exclusively designed to meet the needs of Indian physicians was dire, and it was at such a time that I wrote the first edition of *Modern Medical Toxicology*, taking great care to incorporate only information that was current and practically useful. In order to make it interesting to medical students, I had included a number of case histories, anecdotes and quotations. But, over a period of time, I realised that the information content with regard to toxicology for medicos had improved considerably in recent textbooks of forensic medicine (a possible, positive fallout of MMT), and the focus, therefore, should shift exclusively to physicians.

It is with this objective in mind that I have completely changed the format of MMT in this new fourth edition, and jettisoned the occasional frivolity, retaining only hardcore practical information that would be of use to a clinician at the bedside of a poisoned/overdosed victim. Thus, the new edition is shorn of historical cases, anecdotes and quotes, and embellished instead with precise and explicit practical tips for managing poisoned/overdosed patients, with incorporation of numerous colour images, many of them absolutely original contributions from renowned experts in this field. I sincerely hope that this radical shift will greatly benefit those whom this book is now directed at: general physicians, emergency physicians, critical care specialists, intensivists, paediatricians, clinical pharmacologists, and of course forensic medical experts and toxicologists.

I would be grateful for any comments and critical remarks that will serve to make subsequent editions even better. Do write to me or email me on *toxicology@aims.amrita.edu* or *drvvpillay@gmail.com*.

VV Pillay

Preface to the First Edition

The desire to write this book originated from a near catastrophic occurrence about three years ago. One evening, my daughter (then aged 8 months) swallowed some cockroach bait accidentally. We rushed her to the hospital where a stomach wash was carried out. Following this, none of the doctors present (including myself) had an inkling as to what further must be done. We did not even know the exact ingredients of the bait that my daughter had swallowed. Though it later transpired that the substance, which happened to be a newly introduced insecticide, while being poisonous to cockroaches was relatively non-toxic to humans. My wife and I spent a sleepless night observing our child's condition with great anxiety.

This incident brought me face to face with the dismal reality of ignorance and apathy on the part of the medical profession in our country in matters relating to poisoning. Though toxicology is today an important part of clinical medicine in the West, it is largely neglected in India. This, despite the well-known fact that cases of poisoning constitute a significant proportion of hospital admissions. There is an urgent need for doctors in India as in other Third World countries to realise the importance of toxicology in clinical medicine. This book is a humble contribution towards generating such an interest and providing practical guidelines in the treatment of poisoning. Though emphasis is on the clinical and pharmacological aspects, the book nevertheless deals extensively with forensic implications. After all, almost every case of poisoning has medicolegal overtones! Also, while the stress is on important fundamental information on commonly encountered poisons, an attempt has been made to enhance readability by including fascinating trivia (as Accessory Points), and landmark case histories involving the use or misuse of poisonous substances.

I have consulted innumerable journals and treatises for modern concepts in toxicology and have in addition corresponded with all major pharmaceutical companies and forensic science laboratories in India for information relating to various aspects. I hope all this has been worthwhile. If this book is found to be genuinely useful by medical students, doctors and all others concerned with toxicological matters, my efforts would have been vindicated. Suggestions and criticism for improving this book (which by no means is flawless) in subsequent editions would be particularly welcome.

VV Pillay

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  - **Dr Prem Nair** for his gracious Foreword.

- To all my distinguished peers and colleagues who have contributed to this book, and to this edition in particular.

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- As always to my wife **Dr Minnie** who has steadfastly stood by me and benevolently tolerated my obsession with my work, and of course my daughter **Roshni** who served as the initial inspiration to write *Modern Medical Toxicology*, since she survived a near catastrophic incident of poisoning when she was very young. She is now happily pursuing her undergraduate medical education with great enthusiasm and fervour.

- And above all to **Her Holiness Sri Mata Amritanandamayi Devi** for unwavering divine inspiration over the last decade, leading to my own sense of fulfillment and accomplishment.

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General Principles

Introduction

EPIDEMIOLOGY OF POISONING

It has been estimated that some form of poison directly or indirectly is responsible for more than 1 million illnesses worldwide annually, and this figure could be just the tip of the iceberg since most cases of poisoning actually go unreported, especially in Third World countries. The incidence of poisoning in India is among the highest in the world: it is estimated that more than 50,000 people die every year from toxic exposure.

The causes of poisoning are many—civilian and industrial, accidental and deliberate. The problem is getting worse with time as newer drugs and chemicals are developed in vast numbers. The commonest agents in India appear to be **pesticides** (*organophosphates, carbamates, chlorinated hydrocarbons, pyrethroids and aluminium/zinc phosphide*)**, sedative drugs, chemicals** (*corrosive acids and copper sulfate*)**, alcohol, plant toxins** (*datura, oleander, strychnos, and gastrointestinal irritants such as castor, croton, calotropis, etc.*), **and household poisons** (*mostly cleaning agents*). Among children the common culprits include **kerosene, household chemicals, drugs, pesticides,** and **garden plants**.

HISTORICAL OVERVIEW

The history of poisons and poisoning dates back several thousand years. Early poisons were almost exclusively plant and animal toxins, and some minerals. They were used mainly for hunting. Some were used as "**ordeal poisons***," for e.g. physostigmine from *Physostigma venenosum* (Calabar bean), and amygdalin from peach pits. Arrow and dart poisons were very popular for hunting animals (and sometimes fellow humans). In fact it is said that the term "toxicology" is derived from *toxicon*, a Greek word which when translated reads, "poison into which arrowheads are dipped". Common arrow poisons included strophanthin, aconitine, and extracts from *Helleborus* (a cardiotoxic plant), and snake venom.

One of the earliest classifications of poisons was done by the Greek physician **Dioscorides (AD 40–80)** who categorised poisons into 3 groups—animal, vegetable, and mineral.

Experimental toxicology perhaps began with **Nicander (204–135 BC)**, another Greek physician who experimented with animal poisons using condemned criminals as subjects. An early treatise on plant poisons is *De Historia Plantarum*, by **Theophrastus (370–286 BC)**. The ancient Indian text *Rig Veda* (**12th century BC**) also describes several plant poisons. The Greeks used some plant toxins as poisons of execution. **Socrates (470–399 BC)** was executed by the administration of hemlock.

Among mineral poisons, one of the earliest known elements was lead which was discovered as early as 3500 BC. Apart from its extensive use in plumbing, lead was also employed in the production of vessels and containers, which led to widespread chronic health problems. During the Roman period, lead acetate was widely used as a sweetening agent for wine resulting in a high incidence of plumbism, particularly among members of the aristocracy. In fact, the fall of the Roman empire is attributed to the debilitating effects of this scourge.

Homicidal poisoning has also had a hoary past. One of the earliest laws against the murderous use of poisons was the *Lex Cornelia* passed in Rome in **81 BC**. After the fall of the Roman empire, there was a lull in the development of Toxicology until **1198**, when **Moses Maimonides** published his classic work *Treatise on Poisons and Their Antidotes*. Then came the Renaissance toxicologists—**Paracelsus (1493–1541)**, **Ambroise Pare (1510–1590)**, and **William Piso (1611–1678)**. Paracelsus' study on the dose-response relationship is generally considered as the first time that a scientific approach was made in the field of toxicology.

Development of toxicology as a distinct speciality began in earnest in the 18th and 19th centuries with the pioneering work of **Bonaventure Orfila (1787–1853)**, who is generally regarded as the father of modern toxicology. He advocated the practice of autopsy followed by chemical analysis of viscera to prove that poisoning had taken place. His treatise *Traite des Poisons* published in 1814 laid the foundations of forensic toxicology. In 1829, one of his students, **Robert Christison (1797-1882)** published a simplified English version titled *A Treatise on Poisons*. The first published work on clinical toxicology was

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* Ingestion of these substances were believed to be lethal to the guilty and harmless to the innocent

A Practical Treatise on Poisons written by **O Costill**, and published in **1848**.

Subsequent to World War II, the role of Poison Control Centres began to be increasingly recognised in the prevention and treatment of poisoning, as well as in disseminating accurate information on toxicological matters to medical professionals and the general public.

POISON CONTROL CENTRES

Arising out of a growing concern over the rising incidence of poisoning worldwide, coupled with a lack of public awareness about its seriousness, **Poisons Information Services** made their first appearance in the Netherlands in 1949. In 1961, a telephone answering service was introduced in Leeds, England, which gave information to medical practitioners and others about the poisonous properties of a variety of household, agricultural, and therapeutic substances. On 2 September 1963, a National Poisons Information Service was established at Guy's Hospital, London. The same year, the Illinois Chapter of the American Academy of Pediatrics opened an Information Centre in Chicago, USA. Since then, all around the world similar Centres have sprung up, performing the invaluable functions of generating public awareness on poisoning, and imparting much needed toxicological diagnostic and therapeutic assistance to doctors.

India made a belated foray with the establishment of the **National Poisons Information Centre** at the **All India Institute of Medical Sciences, New Delhi** in December, 1994. A second Centre was subsequently opened at the **National Institute of Occupational Health, Ahmedabad**. Some more Regional Centres have come up in cities such as Chennai, and efforts are under way to establish similar Centres in other parts of the country. The author has established a full-fledged Centre at **Cochin** (in **Amrita Institute of Medical Sciences**, a multispecialty teaching hospital) with poison information and analytical services (**Box 1.1**). The Centre subscribes to POISINDEX, while the WHO has provided INTOX free of cost. An Analytical Laboratory attached to the Centre tests for common poisons or drugs in body fluids, as well as in water and medicinal preparations, and other commercial products.

Poison Centres provide immediate, round the clock toxicity assessment and treatment recommendation over the telephone for all kinds of poisoning situations affecting people of all ages, including ingestion of household products, overdose of therapeutic medication, illegal foreign and veterinary drugs, chemical exposures on the job or elsewhere, hazardous material spills, bites of snakes, spiders and other venomous creatures, and plant and mushroom poisoning. When a call about a poisoning is received, the poison information specialist obtains a history from the caller, assesses the severity of the poisoning, provides

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Box 1.1 The AIMS Poison Control Centre, Cochin

A full-fledged Poison Control Centre with poison information service and analytical laboratory was started at Amrita Institute of Medical Sciences and Research, Cochin, Kerala in July 2003. The Centre was converted into a separate department of Toxicology shortly thereafter, and today offers extensive facilities pertaining to poisons and poisoning to all hospitals, government doctors, private practitioners, as well as the lay public of Kerala State (and neighbouring regions). It is for the first time that such a department exclusively devoted to toxicology has been started in a hospital in the entire country. In less than a year since its inception, the department was officially recognised by the World Health Organization as an authorised Poison Control Centre. There are only 4 other such recognised Centres in the entire country. Recently, the Centre was accorded membership of the American Academy of Clinical Toxicology, another unique distinction.

The Department has state-of-the-art software packages (POISINDEX from Micromedex, USA and INTOX from the WHO) that have detailed information on more than 1 million poisons and drugs encountered worldwide.

Facilities offered:
- Toxicological analysis of blood, urine, or stomach contents (vomitus, aspirate, or washing) for evidence of any poisonous substance or drug.
- Screening of urine for substances of abuse.
- Toxicological analysis of water samples for pesticides and chemicals.
- Toxicological analysis of medicinal and other commercial products for toxic adulterants or contaminants.
- Toxicological screening for common chemicals and poisons in chronic, undiagnosed ailments (skin disease, respiratory illnesses, gastrointestinal disorders, neurological disorders).
- Advanced treatment facility at AIMS for all kinds of cases of poisoning (due to chemicals, drugs, plant products, animal bites or stings, food poisons, etc.).
- Instant access to detailed information (free of charge) on poisons and poisoning through telephone, email, postal mail, personal contact, etc.
- Free expert guidance on diagnosis and treatment of all kinds of poisoning.

How to Contact the Centre:
0484-4008056 (direct)
or 0484-2801234, ext: 8056 or 6034
09895282388 (24 hrs)
toxicology@aims.amrita.edu
poisonunit@aims.amrita.edu

treatment recommendations, and refers the patient for further medical attention when necessary. Referrals to health care facilities when made are later followed up with phone calls to assess progress, and provide additional recommendations until any medical problems related to the poisoning are resolved. Information from the beginning of the call to the final outcome are noted on preformatted case sheets, and quantifiable data is filled in by darkening respective bubbles on the sheet. The data generated is periodically analysed by the Centre and is also monitored for quality assurance of the information specialists. Upto 75% of poisonings reported to Poison Centres are managed entirely by telephone consultations without further necessity of additional costs for the health care system.

MORTALITY FROM POISONING

This varies from country to country depending on the kind of poisons encountered, the extent of awareness about poisoning, the availability of treatment facilities, and presence or absence of qualified personnel. While in developed countries the rate of mortality from poisoning is as low as 1 to 2%, in India it varies from a shocking 15 to 35%. Children under 15 years of age account for most cases of accidental poisoning, but fortunately they are associated with relatively low mortality. On the other

hand, most suicidal exposures are seen in individuals over 15 years of age but are associated with high mortality.

In poisoning cases, the attending physician is often asked to comment on the prognosis of the victim's condition. Unfortunately in cases of serious poisoning, it is very difficult to predict the outcome. There are many reasons for this. In a substantial number of cases, the doctor is unaware of the exact nature of the poison consumed; in others, the victim may have ingested several kinds of drugs simultaneously. Even in those cases where the exact identity and dose of a single ingested poison is known, the doctor may not have a clear idea as to its toxicity. In order to ameliorate the situation to some extent and help physicians have some idea as to the hazardous nature of various poisons, a system of "**toxicity rating**" has been evolved for common poisons. The higher the toxicity rating for a particular substance (over a range from 1 to 6), the greater its potency (**Table 1.1**). The rating is based on mortality, and is applicable only to the acute toxicity of a single dose taken orally. In the case of commercial products where various combinations of poisonous substances may have been used, one has to derive an estimate of the toxicity rating in totality, taking into consideration all the components put together, with particular reference to individual concentrations.

To assess and rate the toxicity of a drug, the **Usual Fatal Dose** (UFD) is taken into consideration which is derived from animal experimental data and statistics of human poisoning. The UFD is based on the **Minimum Lethal Dose** (MLD) which is usually indicative of the lethal dose that is fatal to 50% of animals (LD 50). While the UFD of virtually every poison/drug finds mention in this book under the relevant section, **Table 1.2** serves as a quick reference source for common agents.

POISONING SEVERITY SCORE

The European Association of Clinical Poison Centres and Clinical Toxicologists has proposed a guide for scoring

Table 1.1: Toxicity Rating

Usual Fatal Dose	Rating
Less than 5 mg/kg	6 (Super Toxic)
5 to 50 mg/kg	5 (Extremely Toxic)
51 to 500 mg/kg	4 (Very Toxic)
501 mg/kg – 5 gm/kg	3 (Moderately Toxic)
5.1 gm/kg – 15 gm/kg	2 (Slightly Toxic)
More than 15 gm/kg	1 (Practically Non-Toxic)

Table 1.2: Usual Fatal Dose of Common Toxic Agents

Acetyl salicylic acid (Aspirin) : 15 to 20 gm	Cyanide (salt) : 200 to 300 mg	Methanol : 60 to 250 ml
Acids (Mineral) : 10 to 15 ml	Datura : 50 to 75 seeds	Morphine : 200 mg
Aconite (Root) : 1 gm	DDT : 15 to 30 gm	Nicotine : 60 mg
Aluminium phosphide : 500 mg	Diazinon : 1 gm	Oleander : 5 to 15 leaves or 15 gm root
Arsenic trioxide : 250 mg	Ethanol : 5 to 8 gm/ kg	Opium : 500 mg
Atropine : 10 mg	Ethylene glycol : 100 ml	Organochlorines (except Lindane and DDT) : 2 to 6 gm
Long-acting Barbiturate : 3 gm	Formaldehyde : 30 to 60 ml	Oxalic acid : 15 to 20 gm
Short-acting Barbiturate : 1 to 2 gm	Heroin : 50 mg	Paracetamol : 12 to 20 gm
Benzene : 15 to 20 ml	Iron : 200 mg/kg	Parathion : 100 mg
Carbolic acid (Phenol) : 20 ml	Isopropanol : 200 to 250 ml	Phosphorus : 60 to 120 mg
Castor : 5 to 10 seeds	Lead acetate : 20 gm	Strychnine : 50 to 100 mg
Cocaine : 1 to 2 gm	Lindane : 15 to 30 gm	TEPP : 100 mg
Copper sulfate : 30 gm	Malathion : 1 gm	Thallium (salt) : 1 gm
Curare : 60 mg	Mercuric chloride : 1 to 2 gm	

poisoning severity, applicable to cases of acute poisoning in both adults and children. As per this system, there are basically 4 grades of severity:

None (0)—Nil/Minimal signs or symptoms
Minor (1)—Mild, transient and spontaneously resolving symptoms
Moderate (2)—Pronounced or prolonged symptoms
Severe (3)—Severe or life-threatening symptoms

In minor poisoning, symptomatic and supportive treatment is generally not required, whereas this normally is the case for moderate poisoning. In severe poisoning, advanced symptomatic and supportive treatment is always necessary.

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Diagnosis of Poisoning

A poisoning case can present to a doctor or hospital in any one of a number of ways. Broadly, there are four types of presentation:

1. **Fulminant**—Produced by a massive dose. Death occurs very rapidly, sometimes without preceding symptoms, the patient appearing to collapse suddenly.
2. **Acute**—Produced by a single dose or several small doses taken in a short period. Onset of symptoms is abrupt.
3. **Chronic**—Produced by small doses taken over a long period. Onset is insidious.
4. **Subacute**—Characterised by a mixture of features of acute and chronic poisoning.

The majority of poisoned patients presenting to the casualty (emergency) department are victims of acute exposure. Most of them are usually coherent enough to tell the doctor what the problem is, and indeed what they have taken or been exposed to. However, in an unconscious or uncooperative patient the diagnosis will have to be made on the basis of circumstantial or third party evidence. It is important to interrogate the persons accompanying the patient (relatives, friends, ambulance personnel, etc.), and to contact his or her family doctor as soon as possible. In spite of all this, unfortunately, in a significant proportion of cases the diagnosis remains uncertain. This is because unlike in other clinical conditions arising out of natural disease, there are only a very few **toxic syndromes** characterised by specific signs and symptoms (**Table 2.1**). In most cases, the poisoned patient presents with one or more of the following non-specific features:

1. Impairment of consciousness
2. Respiratory/Cardiovascular depression
3. Dehydration due to vomiting/diarrhoea
4. Hypothermia
5. Convulsions
6. Cardiac arrhythmias

However, there are some valuable clues afforded on detailed clinical examination which can help narrow down the differential diagnosis. Most of these will be dealt with in a subsequent section (**General Management**), but a few are discussed here for the sake of convenience.

1. **Ocular clues**: Several drugs/poisons affect the pupils of the eyes producing either miosis or mydriasis. A few produce nystagmus. These have been laid out in **Table 2.2**. Normally, both the pupils are equal in size, 3 to 4 mm under typical conditions, round, and react directly as well as consensually to increased light intensity by constricting. Pupillary

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Table 2.1: Toxic Syndromes

Anticholinergic syndrome

Causes: Antihistamines, antiparkinsonian drugs, atropine, scopolamine, amantadine, antipsychotic drugs, antidepressants, antispasmodics, skeletal muscle relaxants, many plants (especially Datura), and fungi (e.g. *Amanita muscaria*)

Symptomatology: Delirium with mumbling speech, tachycardia, dry hot skin, mydriasis, myoclonus, urinary retention, decreased bowel sounds. Convulsions and arrhythmias in severe cases

Cholinergic syndrome

Causes: Organophosphates, carbamates, parasympathomimetic drugs, and some mushrooms

Symptomatology: Confusion, CNS depression, salivation, lacrimation, urinary and faecal incontinence, vomiting, sweating, fasciculations, seizures, miosis, pulmonary oedema, tachy/bradycardia

Sympathomimetic syndrome

Causes: Cocaine, amphetamines, upper respiratory decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine)

Symptomatology: Paranoia, delusions, tachycardia, hypertension, hyperpyrexia, sweating, mydriasis, seizures, arrhythmias

Sedative syndrome

Causes: Opiates, barbiturates, benzodiazepines, ethanol, methaqualone, meprobamate, ethchlorvynol, glutethimide, clonidine

Symptomatology: Miosis, hypotension, bradycardia, hypothermia, CNS depression, hyporeflexia, coma, rarely convulsions

Table 2.2: Drugs/Poisons Producing Pupillary Changes

Miosis	*Mydriasis*	*Nystagmus*
Barbiturates	Alcohol (constricted in coma)	Alcohol
Benzodiazepines	Amphetamines	Barbiturates
Caffeine	Antihistamines	Carbamazepine
Carbamates	Carbon monoxide	Phencyclidine
Carbolic acid (Phenol)	Cocaine	Phenytoin
Clonidine	Cyanide	
Methyl dopa	Datura (Atropine)	
Nicotine	Ephedrine	
Opiates		
Organophosphates		
Parasympathomimetics		

constriction also occurs as part of the near reflex when a person focusses on near objects. All these functions result from the balance between cholinergic innervation of the iris sphincter (constrictor) by the oculomotor nerve, and sympathetic innervation of the radial muscle of the iris (dilator). Mydriasis can occur due to increased sympathetic stimulation by endogenous catecholamines or from systemic or ocular exposures to sympathomimetic drugs. Mydriasis can also result from inhibition of cholinergic mediated pupillary constriction. Because pupillary constriction in response to light is a major determinant of pupil size, blindness from ocular, retinal, or optic nerve disorders also leads to mydriasis. Pupillary constriction or miosis can result from increased cholinergic stimulation, or inhibition of sympathetic dilation. Other ophthalmological manifestations along with their respective causes are mentioned in **Table 2.3.**

2. **Olfactory clues:** Some poisons have distinctive odours which may be perceived in the vicinity of a poisoned patient, especially in the breath. Some important examples are mentioned in **Table 2.4**.

3. **Dermal clues:** Some poisons have characteristic dermal manifestations in acute toxicity, while certain others

Table 2.3: Toxic Ophthalmological Manifestations

Feature	Cause
Diplopia	Barbiturates, cannabis, ethanol, opiates, phenytoin, tetracycline, vitamin A
Blurred vision	Alcohol, anticholinergics, botulism, ethanol, lithium, MAOIs, methanol
Altered colour perception	Cannabis, CO, digitalis, hydrocarbons, ibuprofen, nalidixic acid
Corneal deposits	Chloroquine, vitamin D
Oculogyric crisis	Phenothiazines, butyrophenones, metoclopramide
Optic neuritis	Chloroquine, digitalis, disulfiram, ergot, heavy metals, methanol, penicillamine, quinine

Table 2.4: Diagnostic Odours

Odour	Substance
Acetone (apple-like)	Chloroform, ethanol, isopropanol, lacquer
Acrid (pear-like)	Chloral hydrate, paraldehyde
Bitter almond	Cyanide
Burnt rope	Marijuana (Cannabis)
Coal gas	Carbon monoxide (CO)
Disinfectant (hospital odour)	Carbolic acid, creosote
Garlicky	Arsenic, dimethylsulfoxide, organophosphates, phosphorus, selenium, tellurium, thallium
Mothballs	Camphor, naphthalene
Musty (fishy)	Aluminium phosphide, zinc phosphide
Rotten egg	Carbon di sulfide, disulfiram, hydrogen sulfide, mercaptans, N-acetylcysteine
Shoe polish	Nitrobenzene
Vinegar	Acetic acid
Wintergreen	Methyl salicylate

demonstrate skin signs on chronic exposure (**Table 2.5**). Several therapeutic drugs produce irritant dermatitis even in non-toxic doses, e.g. most antibiotics, INH, phenothiazines, sulfonamides, thiazides, NSAIDs, etc.

4. **Oral clues**: Careful examination of the mouth can afford valuable information about the aetiology of poisoning in some cases (**Table 2.6**).

Table 2.5: Dermal Manifestations of Poisoning

ACUTE		CHRONIC	
Poison/Drug	*Feature*	*Poison/Drug*	*Feature*
Datura, atropine	Dry, hot skin	Heroin, barbiturates, morphine, phencyclidine	Needle marks
Organophosphates, salicylates, arsenic, LSD	Profuse sweating	Bromides, iodides, coaltar products, phenytoin	Acne, brown colour
Carbon monoxide(CO)	Cherry pink colour	Arsenic	Rain drop pigmentation, hyperkeratosis, dermatitis
Cyanide	Brick red colour	Chlorinated hydrocarbons	Eczematous dermatitis
Barbiturates, CO, imipramine, methadone, nitrazepam	Blisters	Chloroquine, busulfan, clofazimine, phenothiazines, phenytoin	Dark pigmentation
Warfarin	Petechiae and purpuric spots	Bromides, iodides, penicillin, salicylates, tetracycline	Erythema nodosum
Clonidine, ergot, niacin, sympathomimetics, theophylline	Flushing		

Table 2.6: Drug-induced Oral Manifestations

Feature	Drug /Poison
Glossitis	Trimethoprim–sulfamethoxazole, diclofenac, naproxen, metronidazole, amoxycillin, erythromycin, piroxicam
Stomatitis	Cytotoxic drugs, penicillamine, gold salts, gentian violet dye
Sialadenitis	Phenylbutazone, isoproterenol, nitrofurantoin, iodine
Parotitis	Methyl dopa, clonidine, phenyl and oxyphenbutazone, thioridazine
Gingival hyperplasia	Phenytoin, sodium valproate, phenobarbitone, nifedipine, diltiazem, verapamil
Pigmentation	Cisplatin, oral contraceptives, antimalarials
Dental discolouration	Fluorides, tetracycline, chlorhexidine, iron tonic syrups
Dental caries	Cough and vitamin syrups, antibiotic suspensions
Xerostomia	Antipsychotics, tricyclics, antihistamines, anticholinergics, anticonvulsants, narcotics, diuretics, centrally acting antihypertensives
Sialorrhoea	Parasympathomimetics, iodides

FURTHER READING

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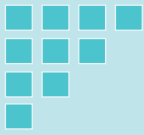
3 General Management of Poisoning

Stabilizations

The initial survey should always be directed at the assessment and correction of life-threatening problems, if present. Attention must be paid to the airway, breathing, circulation, and depression of the CNS (the **ABCD** of resuscitation).

Evaluation

If the patient is not in crisis, i.e. he is alert with normal speech and pulse, proceed to a complete, thorough, and systematic examination. As far as treatment is concerned, the emphasis should be on basic supportive measures.

Decontamination

This is with reference to skin/eye decontamination, gut evacuation and administration of activated charcoal.

Poison Elimination

Depending on the situation, this can be accomplished by diuresis, peritoneal dialysis, haemodialysis, haemoperfusion, etc.

Antidote Administration

Unfortunately, antidotes are available for less than 5% of poisonings.

Nursing And Psychiatric Care

General nursing care is especially important in comatose patients and those who have been incapacitated by the poison. Since some cases of poisoning leave behind persisting sequelae, adequate follow-up for a period of time may be necessary. Psychiatric intervention is frequently essential in suicidal overdose.

STABILISATION

ASSESSMENT

■ The Airway and Breathing

Symptoms of airway obstruction include dyspnoea, air hunger, and hoarseness. Signs comprise stridor, intercostal and substernal retractions, cyanosis, sweating, and tachypnoea.

Normal oxygen delivery requires adequate haemoglobin oxygen saturation, adequate haemoglobin levels, normal oxygen unloading mechanisms, and an adequate cardiac output. Increasing metabolic acidosis in the presence of a normal PaO_2 suggests a toxin or condition that either decreases oxygen carrying capacity (e.g. carbon monoxide, methaemoglobinaemia), or reduces tissue oxygen (e.g. cyanide, hydrogen sulfide).

The immediate need for assisted ventilation has to be assessed clinically, but the efficiency of ventilation can only be gauged by measuring the blood gases. Retention of carbon dioxide ($PaCO_2 > 45$ mmHg or 6 Kpa), and hypoxia ($PaO_2 < 70$ mmHg or 9.3 Kpa) inspite of oxygen being given by a face mask are indications for assisted ventilation. **Table 3.1** lists some substances which are known to cause respiratory depression. Some drugs stimulate the respiratory centre: amphetamines, atropine, cocaine, and salicylates. Some drugs are associated with non-cardiogenic pulmonary oedema, characterised by severe hypoxaemia, bilateral infiltrates on chest X-ray, and normal pulmonary capillary wedge pressure **(Table 3.2)**.

Some drugs cause or exacerbate asthma. The most important among them include NSAIDs, antibiotics like penicillins, cephalosporins, tetracycline, and nitrofurantoin, cholinergic drugs, chemotherapeutic drugs, and some diuretics.

■ Circulation

Several drugs produce changes in pulse rate and blood pressure **(Table 3.3)**, while others induce cardiac arrhythmias and heart block **(Table 3.4)**.

Table 3.1: Toxic Respiratory Depression	
Failure of Respiratory Centre	*Failure of Respiratory Muscles*
Antidepressants	Neuromuscular blocking agents
Antipsychotics	Nicotine
Ethanol	Organophosphates
Opiates	Shellfish poisoning
Sedatives	Snake bite (Cobra)
	Strychnine

Table 3.2: Agents Causing Non-cardiogenic Pulmonary Oedema

Amphetamines	Non-steroidal anti-inflammatory drugs
Anticoagulants	Opiates (especially heroin)
Aspirated oil, talc	Oxygen toxicity
Beta-blockers	Radiation
Calcium channel blockers	Salicylates
Carbon monoxide	Sulfonamides
Cocaine	Thiazide diuretics
Cytotoxic and immunosuppressive drugs	Tricyclic antidepressants
Irritant gases	

Table 3.3: Drugs Associated With Disturbances in Pulse Rate and Blood Pressure

Tachycardia & Normotension	Tachycardia & Hypotension	Tachycardia & Hypertension	Bradycardia & Hypotension	Bradycardia & Hypertension
Antihistamines, caffeine, cannabis, lomotil (atropine & diphenoxylate), thyroxine	Carbon monoxide, cyanide, phenothiazines, theophylline	Amphetamines, cocaine, phencyclidine, phenyl propanolamine	Clonidine, levodopa, MAOIs, organophosphates, opiates, tricyclic antidepressants	Phenylpropanolamine

Table 3.4: Drug/Toxin Induced Arrhythmias

Sinus Bradycardia or A-V Block	Sinus Tachycardia
Alpha adrenergic drugs, beta blockers, carbamates, cardiac glycosides, organophosphates, cyclic antidepressants	Amphetamines, anticholinergics, antihistamines, carbon monoxide, cocaine, phencyclidine, phenothiazines, theophylline, cyclic antidepressants

Table 3.5: Grading the Severity of CNS Intoxication

Depressants		Stimulants	
Grade	Features	Grade	Features
0	Asleep, but can be aroused	—	—
1	Semicomatose, withdraws from painful stimuli, reflexes intact	1	Restlessness, irritability, insomnia, tremor, hyperreflexia, sweating, mydriasis
2	Comatose, does not withdraw from painful stimuli, reflexes intact	2	Confusion, hypertension, tachypnoea, tachycardia, extrasystoles
3	Comatose, most reflexes lost, no depression of CVS or respiration	3	Delirium, mania, arrhythmia, hyperpyrexia
4	Comatose, reflexes absent, respiratory and/or circulatory failure	4	Convulsions, coma, and circulatory collapse

■ Depression of Central Nervous System

This is generally defined as an unarousable lack of awareness with a rating of less than 8 on the **Glasgow Coma Scale (Appendix 1)**. However, the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) are of the opinion that this scale while being very useful for trauma patients is inappropriate for acute poisoning. Several other scales have been proposed, including **Reaction Level Scale, Comprehensive Level of Consciousness Scale (CLOCS), Coma Recovery Scale, Innsbruck Coma Scale, Reed's Classification,** etc., but the predictive value of all these scales remains to be ascertained. A practical guide that can be easily applied and is quite reliable is mentioned in **Table 3.5**, which also has the additional advantage that it takes into account not only CNS depressants producing true coma, but also CNS stimulants which produce coma only in the last stage.

There are numerous causes for coma of which one of the most important is acute poisoning. A number of substances can induce coma, and it will require a great deal of astuteness and expertise to pinpoint the poison. Before proceeding to an elaborate exercise in diagnosis however, it may be desirable to first ascertain for sure that the patient is really comatose and not just pretending (**psychogenic** or **hysterical coma**). This is often encountered in cases of "*suicide gesture*" in contrast to "*attempted suicide*". The former is an attention drawing gambit, where there is no real intention of ending one's life. The telltale fluttering eyelids, the patient who is half-walked, half-dragged in by relatives, an elaborate suicide note, a phone call to a friend or relative informing them of the act, pill bottles strewn about, all may point to such a suicide gesture. In addition, the signs and symptoms manifested by the patient usually are out of proportion to the ingestion itself.

So the question is, how does the doctor humanely determine whether the coma is true or fake? Several methods have been recommended of which the following constitute barbaric acts and must never be employed :

Pinching nipples or genitals, or repeatedly pinching any part of the body.

Slapping the face hard, repeatedly.

Cotton pledgets or sterile applicator tips soaked with ammonia solution being inserted into the nostrils.

Instead, the following steps are recommended:

Perform a quick physical examination with particular attention to the breathing, vital signs, and the gag reflex. If these are normal, the coma is almost certainly psychogenic. Another indication is a tightly clenched jaw when attempts are made to open the mouth. However, first rule out seizure disorders.

A useful technique is to lift the patient's hand directly above his face and letting it drop. A psychogenic aetiology is almost a certainty if the hand falls gently to his side, rather than obeying the law of gravity and landing on the face. Pinching the shoulder may also be tried, but must not be repeated more than twice. Some clinicians advocate rubbing the patient's sternum with the knuckles of the clenched fist.

The key to successfully manage a patient with psychogenic loss of consciousness is to avoid humiliating the patient in front of either relatives, friends, or hospital staff. Making it known (loudly) to the patient that friends and relatives are waiting outside, and that the poison should be "wearing off about now", explaining what has to be done and why in a firm, non-emotional tone, and avoiding physical abuse or humiliation will often enable the patient to "regain consciousness" over a period of a few minutes with his dignity and self respect intact.

If the patient resists all the above manoeuvres and the attending doctor is sure that he is dealing with a known ingestion that is harmless, it is better to leave the patient alone for sometime. If however there is any doubt as to the seriousness of the ingested substance, gastric lavage must be initiated ensuring all necessary precautions.

MANAGEMENT

■ Respiratory Insufficiency

First establish an open airway:
- Remove dentures (if any).
- Use the chin lift and jaw thrust, to clear the airway obstructed by the tongue falling back.
- Remove saliva, vomitus, blood, etc. from the oral cavity by suction or finger-sweep method.
- Place the patient in a semi-prone (lateral) position.
- If required, insert an endotracheal tube.
- If ventilation is not adequate, begin artificial respiration with Ambu bag.

Oxygen therapy:

This is done to raise the PaO_2 to at least 45–55 mmHg (6.0 Kpa to 7.3 Kpa). Begin with 28% oxygen mask. Depending on the response as assessed by periodic arterial gas analysis, either continue with 28% or progress to 35%. If the condition is relentlessly deteriorating, consider assisted ventilation.

■ Circulatory Failure

- Correct acidaemia, if present.
- Elevate foot end of the bed (**Trendelenberg position**).
- Insert a large bore peripheral IV line (16 gauge or larger), and administer a fluid challenge of 200 ml of saline (10 ml/kg in children). Observe for improvement in blood pressure over 10 minutes. Repeat the fluid bolus if BP fails to normalise and assess for signs of fluid overload.* Haemodynamic monitoring should be considered in those adult patients who do not respond to 2 litres of infusion and short-term low-dose vasopressors such as dopamine and noradrenaline.
- Obtain an ECG in hypotensive patients and note rate, rhythm, arrhythmias, and conduction delays.**
- In patients, who do not respond to initial fluid challenges, monitor central venous pressure and hourly urinary output. Patients with severe hypotension may need more sophisticated haemodynamic monitoring (pulmonary artery catheter and intra-arterial pressure monitoring).
- Vasopressors of choice include dopamine and norepinephrine. The doses are as follows:
  - ❖ **Dopamine**: Add 200 mg (1 ampoule usually), to 250 ml of 5% dextrose in water to make a solution of 800 micrograms/ml. Begin with 1 to 5 micrograms/kg/min (maximum being 15 to 30 micrograms/kg/min), and titrate the dose to maintain systolic BP between 90 and 100 mmHg. Monitor BP every 15 minutes.
  - ❖ **Noradrenaline**: Add 8 mg (2 ampoules usually) to 500 ml of 5% dextrose solution to make a concentration of 16 micrograms/ml. Start at 0.5 to 1 ml/min and titrate to a clinical response. Monitor BP every 5–10 minutes until a clear trend is established.

■ Cardiac Arrhythmias

- Obtain an ECG, institute continuous cardiac monitoring and administer oxygen.
- Evaluate for hypoxia, acidosis, and electrolyte disturbances (especially hypokalaemia, hypocalcaemia, and hypomagnesaemia).
- Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Amiodarone and sotalol should be used with caution if a substance that prolongs the QT interval and/or causes torsades de pointes is involved in the overdose.
- Unstable rhythms require cardioversion.
- Atropine may be used when severe bradycardia is present and PVCs are thought to represent an escape complex.
  - ❖ **Lignocaine:**
    - – Dose -
      - - *Adult*: 1 to 1.5 mg/kg IV push. For refractory VT/VF an additional bolus of 0.5 to 0.75 mg/

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* Rales, S3 heart gallop, neck vein distension.
** PR>0.2 second, QRS>0.1 second or QT interval>50% of PR interval.

kg can be given over 3 to 5 minutes. Total dose should not exceed 3 mg/kg or more than 200 to 300 mg during a one hour period. Once circulation has been restored begin maintenance infusion of 1 to 4 mg per minute. If arrhythmias recur during infusion repeat 0.5 mg/kg bolus and increase the infusion rate incrementally (up to a maximum of 4 mg/minute).

- *Child:* 1 mg/kg initial bolus IV; followed by a continuous infusion of 20 to 50 micrograms/kg/minute.

– Lignocaine Preparation:
- Add 1 gm of lignocaine to 250 ml of dextrose 5% in water, to make a 4 mg/ml solution. An increase in the infusion rate of 1 ml/minute increases the dose by 4 mg/minute.

■ CNS Depression

Till recently it was recommended that in every case where the identity of the poison was not known, the following three antidotes (called the **Coma Cocktail**) must be administered (intravenously):

- *Dextrose*—100 ml of 50% solution
- *Thiamine* (Vitamin B$_1$)—100 mg
- *Naloxone*—2 mg

The rationale for the **coma cocktail** was that since a significant proportion of poisoned comatose patients in whom the identity of the poison was unknown comprise cases of overdose from opiates, alcohol, and hypoglycaemic agents, these drugs would work in such cases to at least indicate the possible diagnosis. Even if a particular case was not due to any of these causes, administration of these antidotes was considered relatively harmless. However, there is an increasing dissatisfaction among toxicologists with regard to the true benefits of the coma cocktail, and the view is gaining ground that it has no place in practice.

All patients with depressed mental status should receive 100% oxygen in a mask, (high flow—8 to 10 litres/min).

EVALUATION

In all those poisoned patients where there appears to be no immediate crisis, a detailed and thorough clinical examination should be made with special reference to the detection and treatment of any of the following abnormalities :

■ Hypothermia

Some common drugs which produce hypothermia are mentioned in **Table 3.6**. It is essential to use a low reading rectal thermometer. Electronic thermometers with flexible probes are best which can also be used to record the oesophageal and bladder temperatures.

Treatment:

- Rewarming
  ❖ For mild cases, a warm water bath (115ºF) is sufficient until the core temperature rises to 92º F, when the patient is placed in a bed with warm blankets. The rate of rewarming should not exceed 5º F per hour.
  ❖ Heating the inspired air is recommended by some as very effective in raising the core temperature.
  ❖ Others advocate gastric lavage with warmed fluids, or peritoneal lavage with warmed dialysate.
- In addition, it may be necessary to correct other associated anomalies such as hypotension, hypoventilation, acidosis, and hypokalaemia.

■ Hyperthermia

Oral temperature above 102ºF is referred to as hyperthermia. If it exceeds 106ºF (which is very rare), there is imminent danger of encephalopathy. In a few individuals there is a genetic susceptibility to hyperthermia, especially on exposure to skeletal muscle relaxants, inhalation anaesthetics, and even local anaesthetics—**malignant hyperthermia**. This should be distinguished from **neuroleptic malignant syndrome**, which is also characterised by high fever apart from other neurological signs, but is the result of adverse reaction to antipsychotic or neuroleptic drugs, and has no genetic basis. **Table 3.7** lists some

Table 3.6: Drugs Producing Hypothermia
Alcohols
Antidepressants
Barbiturates
Benzodiazepines
Carbon monoxide
Hypoglycaemics
Opiates
Phenothiazines
Sedative-hypnotics

Table 3.7: Agents Inducing Hyperthermia		
Muscular Hyperactivity	*Increased Metabolic Rate*	*Impaired Thermoregulation*
Amphetamines	Dinitrophenol	Anticholinergics
Antidepressants	Salicylates	Antihistamines
Cocaine	Thyroid hormones	Antipsychotics
MAO Inhibitors		Ephedrine
Phencyclidine		Phenylpropanolamine Phenothiazines
Strychnine		
Withdrawal (alcohol/opiates)		

of the important toxicological causes of hyperthermia along with postulated mechanism. Complications include coagulopathy, rhabdomyolysis, renal failure, and tachyarrhythmias.

Treatment :

- Remove all clothes, and pack the neck and groin with ice.
- Immersion in cold water bath (77ºF) is very effective but dangerous in the elderly and in heart patients.
- Stop cooling measures when core temperature falls below 102ºF, and nurse the patient in bed in a cool room.
- Administration of dantrolene may be beneficial in some cases.
- Do not use antipyretic drugs like paracetamol. They are ineffective.

■ Acid-Base Disorders

Serum electrolytes to evaluate for metabolic acidosis should be obtained if there is any possibility of mixed ingestion or uncertain history. The diagnosis of these acid-base disorders is based on arterial blood gas, pH, $PaCO_2$, bicarbonate, and serum electrolyte disturbances. It must be first determined as to which abnormalities are primary and which are compensatory, based on the pH (**Table 3.8**). If the pH is less than 7.40, respiratory or metabolic alkalosis is primary.

In the case of metabolic acidosis, it is necessary to calculate the **anion gap**. The anion gap is calculated as follows:
$(Na^+ + K^+)–(HCO3^- + Cl^-)$
Normally this translates as
$140–(24 + 104) = 12$ mmol/L (*Range: 12 to 16 mmol/L*)

If the anion gap is greater than 20 mmol/L, a metabolic acidosis is present regardless of the pH or serum bicarbonate concentration. Several poisons are associated with increased anion gap (**Gap acidosis**), while others do not alter it (**Non-gap acidosis**). The common causes for the various acid-base disorders are mentioned in **Table 3.9**.
Treatment of metabolic acidosis:

Table 3.8: Acid-Base Disorders

Disorder	Parameter	Value	Interpretation
Acute respiratory alkalosis	pH	7.50	Alkalaemia
	$PaCO_2$	29 mm Hg	Respiratory alkalosis
	HCO_3	22 mmol/litre	Normal
Acute respiratory acidosis	pH	7.25	Acidaemia
	$PaCO_2$	60 mm Hg	Respiratory acidosis
	HCO_3	26 mmol/litre	Normal
Chronic respiratory acidosis with metabolic compensation	pH	7.34	Normal
	$PaCO_2$	60 mm Hg	Respiratory acidosis
	HCO_3	36 mmol/litre	Metabolic compensation
Metabolic alkalosis	pH	7.50	Alkalaemia
	$PaCO_2$	48 mm Hg	Respiratory compensation
	HCO_3	36 mmol/litre	Metabolic alkalosis
Metabolic acidosis	pH	7.20	Acidaemia
	$PaCO_2$	21 mm Hg	Respiratory compensation
	HCO_3	8 mmol/litre	Metabolic acidosis

Table 3.9: Causes of Acid-Base Disorders

Type of disorder	Causes	
Acute respiratory alkalosis	Anxiety, hypoxia, lung diseases, CNS disease, pregnancy, sepsis, hepatic encephalopathy, drugs—*salicylates, catecholamines, progestone, etc.*	
Acute respiratory acidosis	CNS depression, airway obstruction, neuromuscular disorders (myopathies, neuropathies), severe pneumonia or pulmonary oedema, impaired lung motion (haemothorax, pneumothorax)	
Chronic respiratory acidosis with metabolic compensation	Chronic lung disease, chronic neuromuscular disorders, chronic respiratory centre depression	
Metabolic alkalosis	Normal or high urinary chloride	Low urinary chloride
	Cushing's disease, Conn's syndrome, steroid administration, diuretic administration, alkali overdose	Vomiting, past use of diuretics, post-hypercapnia
Metabolic acidosis	Non-Gap	Gap*
	Diarrhoea, renal tubular acidosis, carbonic anhydrase inhibitors, aldosterone inhibitors, post-hypocapnia, bromism, iodism, and secondary to hyperkalaemia, hypercalcaemia	**M**ethanol **U**raemia **D**iabetes **P**araldehyde phenformin **I**diopathic lactic acidosis, iron, isoniazid **E**thanol, ethylene glycol **S**alicylates, solvents, starvation

*The important causes can be remembered by the acronym - MUDPIES.

The drug of choice is sodium bicarbonate (**Box 3.1**). It is widely considered to be the best antidote for acidosis of almost any aetiology.

■ Convulsions (Seizures)

There are several drugs and poisons which cause convulsions (**Table 3.10**). Improper treatment or mismanagement can lead to status epilepticus which is a life-threatening condition.

Treatment:

- Administer oxygen by nasal cannula or mask.
- Position patient's head for optimal airway patency.
- Establish IV line.
- Begin drug therapy with benzodiazepines (**Table 3.11**). Either lorazepam (0.1 mg/kg) at a rate of 2 mg/min, or diazepam (0.2 mg/kg) at a rate of 5 mg/min can be administered IV. If status persists, administer 15–20 mg/kg phenytoin at 50 mg/min (adults), or 1 mg/kg/min (children), by IV.*
- If status still persists, administer 20 mg/kg phenobarbitone IV at 100 mg/min. If this measure also fails, give anaesthetic doses of phenobarbitone, pentobarbitone, thiopentone, or halothane. In such cases obviously, ventilatory assistance and vasopressors become mandatory.
- Monitor ECG, hydration, and electrolyte balance. Watch out for hypoglycaemia and cerebral oedema.

■ Agitation

Several drugs and poisons are associated with increased aggression which may sometimes progress to psychosis and

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Box 3.1: Sodium Bicarbonate

Uses :
1. Salicylate overdose (to alkalinise urine)
2. Tricyclic antidepressant overdose (to alkalinise blood)
3. Correction of metabolic acidosis (especially in methanol and ethylene glycol poisoning)
4. Adjuvant in poisoning with barbiturates, phenothiazines, cocaine, and carbamazepine
5. Drug or toxin-induced myoglobinuria
6. As stomach wash for iron poisoning
7. Possible use in lactic acidosis, diabetic keto-acidosis, and cardiac resuscitation

Formulation :
50 ml ampoules of 8.4 and 7.5% solution containing 50 and 44.6 mEq of sodium bicarbonate respectively.

Dose :
Add 2 to 3 ampoules of 8.4% $NaHCO_3$ to 1 litre of 5% dextrose in water, infused intravenously over 3 to 4 hours. In paediatric patients, add 1 to 2 mEq $NaHCO_3$/Kg in 15 ml/Kg 5% dextrose on 0.45% normal saline over 3 to 4 hours.

Check urine pH in 1 hour. It should be at least 7.5, preferably 8. Maintain alkalinisation with continuous infusion of 100 to 150 mEq in 1 litre of 5% dextrose in water at 150 to 200 ml/hr. Half of this dose suffices for a child.

Mechanism of action :
1. Alters drug ionisation of weak acids. Alkalinisation of blood prevents movement of ionised drug within the tissues. Cellular membranes are impermeable to ionised compounds.
2. Changes sodium gradients and partially reverses the fast sodium channel blockade seen especially in tricyclic antidepressant overdose.
3. Titrates acid, and reverses life-threatening acidaemia.

Dangers :
1. Can precipitate fatal arrhythmia if given in the presence of hypokalaemia.
2. Can result in alkalaemia, if administered negligently.

Table 3.10: Toxic Causes of Convulsions

During Toxicity		During Withdrawal
Amphetamines	Cocaine	Barbiturates
Anticholinergics	Cyanide	Benzodiazepines
Antidepressants	Heavy metals	Ethanol
Antihistamines	Isoniazid	Methaqualone
Caffeine	Organophosphates	Opiates
Camphor	Strychnine	
Carbon monoxide	Sympathomimetics	
Chlorinated hydrocarbons	Xanthines (theophylline)	
Cholinergics		

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* Phenytoin is incompatible with glucose containing solutions. The IV should be purged with normal saline before phenytoin infusion.

Table 3.11: Common Drugs Used to Treat Status Epilepticus

Dose	Diazepam	Lorazepam	Phenytoin	Phenobarbitone
Adult IV dose (mg/kg)	0.15 – 0.25	0.1	15 – 20	20
Paediatric IVdose (mg/kg)	0.1 –1.0	0.05 – 0.5	20	20
Paediatric per rectal dose (mg/kg)	0.5	–	–	–
Maximum IV rate (mg/kg)	5	2	50	100
Duration of action (hours)	0.25 – 0.5	> 12 – 24	24	> 48
Side Effects				
CNS depression	10 – 30 min	Several hours	None	Several days
Respiratory depression	Occasional	Occasional	Infrequent	Occasional
Hypotension	Infrequent	Infrequent	Occasional	Infrequent
Cardiac arrhythmias	–	–	Occasional	–

Table 3.12: Drugs Associated with Agitation and Psychosis

During Toxicity		During Withdrawal
Amphetamines	Corticosteroids	Barbiturates
Anticholinergics	Datura (atropine)	Ethanol
Antidepressants	Digitalis	Opiates
Benzodiazepines	Ethanol	
(paradoxical agitation)	Hallucinogens	
Cannabis		
Cocaine		

violent behaviour (**Table 3.12**). This is especially likely if there are other predisposing factors such as existing mental disorder, hypoglycaemia, hypoxia, head injury, and even anaemia and vitamin deficiencies. **Delirium** is the term which is often used to denote such acute psychotic episodes, and is characterised by disorientation, irrational fears, hyperexcitability, hallucinations, and violence. **Dementia** refers to a more gradual decline in mental processes mainly resulting in confusion and memory loss, and though it is often organic in nature due to degenerative diseases, there are some drugs which can cause this especially on chronic exposure. Elderly patients are more vulnerable. Dementia due to drugs is usually reversible.

Treatment :

- Delirium is managed by chlorpromazine, diazepam, or haloperidol. Caution is however necessary, since sedation which is inevitable with these preparations may sometimes result in more harm than benefit. **Table 3.13** outlines measures for managing a violent patient in the casualty (Emergency department).

Movement Disorders

Exposure to several drugs and toxins can result in a wide variety of movement disorders ranging from full blown Parkinson's disease to isolated tremors. The most frequent culprits for **parkinsonian** manifestations are phenothiazines and major tranquillisers, though there are several others which have also been implicated. Symptoms of Parkinsonism usually appear in

Table 3.13: Tranquillisation of the Violent Patient

Type of violent behaviour	Therapeutic measure
Schizophrenia (or any other psychosis)	Lorazepam 2 to 4 mg IM, combined with haloperidol 5 mg IM
Extreme agitation	Lorazepam 2 to 4 mg IM, every hour
Personality disorder	Lorazepam 1 to 2 mg orally every 1 to 2 hours,Or 2 to 4 mg IM, every 1 to 2 hours
Alcohol withdrawal	Chlordiazepoxide 25 to 50 mg orally,as required,Or Lorazepam 2 mg orally
Cocaine/amphetamine toxicity	Diazepam 10 mg every 8 hours orally or IM
Phencyclidine toxicity	Diazepam 10 to 30 mg orally, or Lorazepam 2 to 4 mg, or haloperidol 5 mg IM

the first three months of exposure and may be indistinguishable from idiopathic Parkinson's disease.

Drug-induced **myopathies** may result from a direct toxic effect which may be local (e.g. injection of drug into muscle), or more diffuse when the drug is taken systemically. Repeated injections of antibiotics or drugs of addiction often lead to severe muscle fibrosis and contractures (*myositis fibrosa, myositis ossificans*). Clofibrate and aminocaproic acid can cause an *acute necrotising myopathy* with myoglobinuria and renal failure. Other drugs that can induce toxic myopathies

include succinylcholine, halothane, corticosteroids, chloroquine, D-penicillamine, alcohol, phenytoin, thiazide diuretics, amphotericin, procainamide, penicillin, and lipid-lowering drugs. Environmental causes include exposure to silica, certain types of food (e.g. adulterated rape seed oil), and medical devices such as silicone implants.

Tricyclic antidepressants, monoamine oxidase inhibitors, fluoxetine, lithium, buspirone, and levadopa are the principal causes of drug-induced **akathisia.** This is characterised by extreme restlessness with constant movement and muscular quivering. **Dystonia** usually manifests as facial grimacing or torticollis, and is mainly associated with phenothiazines, butyrophenones, metoclopramide, tricyclic antidepressants, phenytoin, and chloroquine. **Chorea**, which causes involuntary writhing movements of limbs is most commonly seen with anticonvulsants (especially phenytoin), anabolic steroids, amphetamines, levodopa, and sometimes with cimetidine, ethanol, and cocaine. Phenothiazines and metoclopramide are most often the culprits in drug-induced **tardive dyskinesia**, which is characterised by stereotyped, slow, rhythmic movements.

Myasthenic crisis, a sudden onset of severe muscular weakness, may be precipitated by aminoglycosides, polymyxin, penicillamine, tetracycline, quinidine, lignocaine, quinine, curare, succinylcholine, procainamide, and some opiates.

Fasciculations are contractions of muscle fibres within an individual motor unit, and appear as twitching of affected muscles. **Table 3.14** lists the major toxicological causes of fasciculations. Drug induced **tremors** are of several types, and are listed in **Table 3.15**.

Treatment of movement disorders:

Most of the movement disorders induced by toxins or drugs are dose and duration related. Withdrawal of the incriminating agent commonly results in recovery. The usual measures undertaken in the management of the respective drug overdose (or abuse) must be instituted wherever applicable.

Table 3.16 will serve as a quick reference source for common culprits of drug or toxin induced movement disorders.

■ Electrolyte Disturbances

1. *Hyperkalaemia*—(i.e. potassium level more than 5.5 mEq/L)

The causes include digitalis, beta$_2$ antagonists, potassium sparing diuretics, NSAIDs, fluoride, heparin, succinylcholine, and drugs producing acidosis. Manifestations include abdominal

Table 3.14: Toxic Causes of Fasciculations

Amphetamines	Lithium
Barium salts	Manganese
Black widow spider bite	Mercury
Caffeine	Nicotine
Camphor	Phencyclidine
Cholinergic excess	Quaternary ammonium
Cocaine	compounds
Fluorides	Scorpion sting
Hypoglycaemics	Shellfish poisoning
Lead	Strychnine

Table 3.15: Drug-induced Tremor

Type	Cause
Resting (most pronounced at rest)	Same as for drug-induced Parkinsonism
Postural (most pronounced in an outstretched hand)	Beta agonists, phenytoin, valproic acid, tricyclics, lithium, arsenic, alcohol withdrawal, amphetamines, caffeine, cocaine, theophylline, CO
Kinetic (most pronounced with movement)	Chronic alcoholism, mercury, lithium, acute sedative-hypnotic overdose
Choreoid (repetitive writhing movements of hands)	Same as for chorea. Also anticholinergics, amantadine, bromocriptine, manganese
Dystonic (muscle group spasms)	Neuroleptics, anti-emetics, cocaine, and chloroquine

Table 3.16: Drug-induced Movement Disorders at a Glance

Drug	Disorders
Amoxapine	Parkinsonism
Amphetamines	Hyperkinetic movements
Antihistamines	Orofacial dystonia, myoclonic jerking
Butyrophenones	Parkinsonism, orofacial dystonia, opisthotonus, trismus
Caffeine	Myoclonic jerking
Carbamazepine	Orofacial dystonia
Carbon monoxide	Parkinsonism
Monoamine oxidase inhibitors	Rigidity, opisthotonus
Nicotine	Flaccid fasciculations
Organophosphates	Flaccid fasciculations
Pethidine	Tremor, muscle jerking
Phencyclidine	Generalised rigidity, trismus, orofacial dystonias, twitching
Phenothiazines	Orofacial and other dystonias
Phenytoin	Choreoathetosis
Strychnine	Rigidity, opisthotonus, trismus
Tricyclic antidepressants	Twitching, myoclonic jerking

pain, diarrhoea, myalgia, and weakness. ECG changes are important – tall, peaked T waves, ST segment depression, prolonged PR interval, and QRS prolongation. In severe cases there is ventricular fibrillation.

Treatment: Glucose, insulin infusion, sodium bicarbonate, and calcium gluconate. Haemodialysis and exchange resins may be required.

2. *Hypokalaemia*—(i.e. potassium level less than 3.5 mEq/L)

The causes include beta$_2$ agonists, theophylline, insulin, chloroquine, caffeine, dextrose, loop diuretics, thiazide diuretics, oral hypoglycaemics, salicylates, sympathomimetics, drug-induced gastroenteritis, and metabolic acidosis. Manifestations include muscle weakness, paralytic ileus, and ECG changes—flat or inverted T waves, prominent U waves,

ST segment depression. In severe cases there is A-V block and ventricular fibrillation.

Treatment: Oral or IV potassium.

3. *Hypernatraemia*—(i.e. sodium level more than 150 mEq/L)

The causes include colchicine, lithium, propoxyphene, rifampicin, phenytoin, alcohol, mannitol, sorbitol, sodium salts, excessive water loss, IV saline solutions, and salt emetics.

Treatment: Water restriction with or without loop diuretics.

4. *Hyponatraemia*—(i.e., sodium level less than 130 mEq/L)

The causes include carbamazepine, chlorpropamide, NSAIDs, amitryptiline, biguanides, sulfonylureas, captopril and other ACE inhibitors, lithium, imipramine, oxytocin, and excessive water intake.

Treatment: Hypertonic saline.

5. *Hypocalcaemia*—(i.e. calcium level less than 4 mEq/L)

The causes include hydrogen fluoride, oxalates, aminoglycosides, ethanol, phenobarbitone, phenytoin, theophylline, and ethylene glycol.

Treatment: Calcium gluconate IV (10% solution, 10 ml at a time, slowly).

Drug-induced hypercalcaemia is uncommon.

DECONTAMINATION

EYE

Irrigate copiously for at least 15 to 20 minutes with normal saline or water. Do not use acid or alkaline irrigating solutions. As a first-aid measure at home, a victim of chemical burns should be instructed to place his face under running water or in a shower while holding the eyelids open. During transportation to hospital the face should be immersed in a basin of water (while ensuring that the patient does not inhale water).

SKIN

Cutaneous absorption is a common occurrence especially with reference to industrial and agricultural substances such as phenol, hydrocyanic acid, aniline, organic metallic compounds, phosphorus, and most of the pesticides. The following measures can be undertaken to minimise absorption*—

- Exposed persons should rinse with cold water and then wash thoroughly with a non-germicidal soap. Repeat the rinse with cold water.
- Corroded areas should be irrigated copiously with water or saline for at least 15 minutes. Do not use "neutralising solutions".
- Remove all contaminated clothes. It is preferable to strip the patient completely and provide fresh clothes, or cover with clean bedsheet.
- Some chemical exposures require special treatment :
  - ❖ Phenolic burns should be treated by application of polyethylene.

- ❖ Phosphorus burns should be treated with copper sulfate solution.
- ❖ For hydrofluoric acid burns, use of intradermal or intra-arterial calcium gluconate decreases tissue necrosis.
- ❖ For tar, bitumen, or asphalt burns, first irrigate the affected skin with cold water and then clean and apply solvents such as kerosene, petrol, ethanol, or acetone. However, since these substances can not only be locally cytotoxic, but also be absorbed through the skin, it is preferable to use mineral oil, petrolatum, or antibacterial ointments in a petrolatum base. Prolonged irrigating applications may be required.

GUT

The various methods of poison removal from the gastrointestinal tract include:
- Emesis
- Gastric lavage
- Catharsis
- Activated charcoal
- Whole bowel irrigation.

■ Emesis

The only recommended method of inducing a poisoned patient to vomit is administration of **syrup of ipecacuanha** (or **ipecac**). However, the initial enthusiasm associated with the use of ipecac in the 1960s and 1970s in Western countries has declined substantially in recent years owing to doubts being raised as to its actual efficacy and safety. **The current consensus is that syrup of ipecac must NOT be used, except in justifiable circumstances.**

*Syrup of Ipecac***

- Source—Root of a small shrub (*Cephaelis ipecacuanha* or *C. acuminata*) which grows well in West Bengal (**Fig 3.1**).
- Active principles: Cephaeline, emetine, and traces of psychotrine.
- Indications: Conscious and alert poisoned patient who has ingested a poison not more than 4 to 6 hours earlier.
- Mode of action:
  - ❖ Local activation of peripheral sensory receptors in the gastrointestinal tract.
  - ❖ Central stimulation of the chemoreceptor trigger zone with subsequent activation of the central vomiting centre.
- Dose:
  - ❖ 30 ml (adult), or 15 ml (child), followed by 8 to 16 ounces, i.e. 250 to 500 ml approximately, of water.
  - ❖ The patient should be sitting up.
  - ❖ If vomiting does not occur within 30 minutes, repeat the same dose once more. If there is still no effect, perform stomach wash to remove not only the ingested poison but also the ipecac consumed. However the

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* For potentially toxic substances subject to skin absorption, health personnel should wear impermeable gloves and gowns.
**Not to be confused with fluid extract of ipecac, which was formerly used as an amoebicide and is very toxic.

Fig 3.1: *Cephaelis ipecacuanha*—Plant and dried roots

therapeutic doses of ipecac recommended above are not really harmful.

- Contra-indications:
  - ❖ *Relative :*
    - – Very young (less than 1 year), or very old patient
    - – Pregnancy
    - – Heart disease
    - – Bleeding diathesis
    - – Ingestion of cardiotoxic poison
    - – Time lapse of more than 6 to 8 hours
  - ❖ *Absolute :*
    - – Convulsions, or ingestion of a convulsant poison
    - – Impaired gag reflex
    - – Coma
    - – Foreign body ingestion
    - – Corrosive ingestion
    - – Ingestion of petroleum distillates, or those drugs which cause altered mental status (phenothiazines, antihistamines, opiates, ethanol, benzodiazepines, tricyclics).
    - – All poisons which are themselves emetic in nature
- Complications:
  - ❖ Cardiotoxicity (bradycardia, atrial fibrillation, myocarditis).
  - ❖ Aspiration pneumonia.
  - ❖ Oesophageal mucosal or Mallory Weiss tears (due to protracted vomiting).

Other Emetics

The only other acceptable method of inducing emesis that is advocated involves the use of **apomorphine**. Given subcutaneously, it causes vomiting within 3 to 5 minutes by acting directly on the chemoreceptor trigger zone. The recommended dose is 6 mg (adult), and 1 to 2 mg (child). Since apomorphine

is a respiratory depressant it is contraindicated in all situations where there is likelihood of CNS depression.

In some cases, **stimulation of the posterior pharynx** with a finger or a blunt object may induce vomiting by provoking the gag reflex. Unfortunately, such mechanically induced evacuation is often unsuccessful and incomplete, with mean volume of vomitus about one third of that obtained by the other two methods.

Obsolete Emetics

The use of **warm saline** or **mustard water** as an emetic is not only dangerous (resulting often in severe hypernatraemia), but also impractical since many patients, especially children refuse (fortunately) to drink this type of concoction and much valuable time is lost coaxing them to do so. One tablespoon of salt contains at least 250 mEq of sodium, and if absorbed can raise the serum level by 25 mEq/L in for instance, a 3-year old child.* It is high time that the use of salt water as an emetic be deleted once and for all from every first-aid chart or manual on poisoning.

Copper sulfate induces emesis more often than common salt, but significant elevations of serum copper can occur leading to renal and hepatic damage. It is also a gastrointestinal corrosive.

Zinc sulfate is similar in toxicity to copper sulfate, and has in addition a very narrow margin of safety.

■ Gastric Lavage (Stomach Wash)

The American Academy of Clinical Toxicology (AACT), and the European Association of Poison Centres and Clinical Toxicology (EAPCCT) have prepared a draft of a position paper directed to the use of gastric lavage, which suggests that gastric lavage should not be employed routinely in the management of poisoned patients. There is no certain evidence that its use improves outcome, while the fact that it can cause significant morbidity (and sometimes mortality) is indisputable. Lavage should be considered only if a patient has ingested a life-threatening amount of a poison and presents to the hospital within 1 to 2 hours of ingestion.

But in India, very often caution is thrown to the wind and the average physician in an average hospital embarks on gastric lavage with gusto the moment a poisoned patient is brought in. A sad commentary on the existing lack of awareness and a reluctance to change old convictions in spite of mounting evidence against the routine employment of such "established procedures".

- Indications—
  - ❖ Gastric lavage is recommended mainly for patients who have ingested a life-threatening dose, or
  - ❖ Who exhibit significant morbidity and present within 1 to 2 hours of ingestion. Lavage beyond this period may be appropriate only in the presence of gastric concretions, delayed gastric emptying, or sustained release preparations. Some authorities still recommend lavage upto 6 to 12 hours post-ingestion in the case of salicylates, tricyclics, carbamazepine, and barbiturates.

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* "Salt is only an occasionally successful emetic, but a frequently successful poison."

■ Precautions—
  ❖ Never undertake lavage in a patient who has ingested a non-toxic agent, or a non-toxic amount of a toxic agent.
  ❖ Never use lavage as a deterrent to subsequent ingestions. Such a notion is barbaric, besides being incorrect.
■ Contraindications—
  ❖ *Relative*: Haemorrhagic diathesis, oesophageal varices, recent surgery, advanced pregnancy, ingestion of alkali, coma.
  ❖ *Absolute*: Marked hypothermia, prior significant vomiting, unprotected airway in coma, and ingestion of acid or convulsant or petroleum distillate, and sharp substances.
■ Procedure—
  ❖ Explain the exact procedure to the patient and obtain his consent. If refused, it is better not to undertake lavage because it will amount to an assault, besides increasing the risk of complications due to active non-co-operation.
  ❖ Endotracheal intubation must be done prior to lavage in the comatose patient.
  ❖ Place the patient head down on his left lateral side (20° tilt on the table).
  ❖ Mark the length of tube to be inserted (50 cm for an adult, 25 cm for a child).*
  ❖ The ideal tube for lavage is the **lavacuator** (clear plastic or gastric hose).
  ❖ In India however, the **Ewald tube** is most often used which is a soft rubber tube with a funnel at one end (**Fig 3.2**). Whatever tube is used, make sure that the inner diameter corresponds to at least 36 to 40 French

size.** A nasogastric tube used for gastric aspiration is inadequate and should never be used. In a child, the diameter should be at least 22 to 28 French, (**Ryle's tube** may be sufficient – **Fig 3.3**).
  ❖ The preferred route of insertion is oral. Passing the tube nasally can damage the nasal mucosa considerably and lead to severe epistaxis. Lubricate the inserting end of the tube with vaseline or glycerine, and pass it to the desired extent. Use a mouth gag so that the patient will not bite on the tube.
  ❖ Once the tube has been inserted, its position should be checked either by air insufflation while listening over the stomach, or by aspiration with pH testing of the aspirate, (acidic if properly positioned).
  ❖ Lavage is carried out using small aliquots (quantities) of liquid. In an adult, 200 to 300 ml aliquots of warm (38°C) saline or plain water are used. In a child, 10 to 15 ml/kg body weight of warm saline is used each time. Water should preferably be avoided in young children because of the risk of inducing hyponatraemia and water intoxication. It is advisable to hold back the first aliquot of washing for chemical analysis.
  ❖ In certain specific types of poisoning, special solutions may be used in place of water or saline (**Table 3.17**).
  ❖ Lavage should be continued until no further particulate matter is seen, and the efferent lavage solution is clear. At the end of lavage, pour a slurry of activated charcoal in water (1 gm/kg), and an appropriate dose of an ionic cathartic into the stomach, and then remove the tube.
■ Complications -
  ❖ Aspiration pneumonia.
  ❖ Laryngospasm.
  ❖ Sinus bradycardia and ST elevation on the ECG.
  ❖ Perforation of stomach or oesophagus (rare).

■ Catharsis

Catharsis is a very appropriate term when used in connection with poisoning, since it means purification. It is achieved by

Fig 3.2: Gastric lavage (Ewald) tube (*Pic:* Dr Anu Sasidharan)

Fig. 3.3: Ryle's tube

* Alternatively, mark off the length corresponding to the distance between the xiphoid process and the bridge of the nose of the patient.
** Each unit of the French scale equals 0.3 mm.

Table 3.17: Solutions for Gastric Lavage	
Poison	**Solution**
Most poisons (known or unknown)	Water or saline
Oxidizable poisons (alkaloids, salicylates, etc.)	Potassium permanganate (1 : 5000 or 1 : 10000)
Cyanides	Sodium thiosulfate (25%)
Oxalates	Calcium gluconate

purging the gastrointestinal tract (particularly the bowel) of all poisonous material.

- The two main groups of cathartics* used in toxicology include
  - ❖ **Ionic or Saline**:
    - These cathartics alter physico-chemical forces within the intestinal lumen leading to osmotic retention of fluid which activates motility reflexes and enhances expulsion. However, excessive doses of magnesium-based cathartics can lead to hypermagnesaemia which is a serious complication.
    - The doses of recommended cathartics are as follows:
      - Magnesium citrate: 4 ml/kg
      - Magnesium sulfate: 30 gm (250 mg/kg in a child)
      - Sodium sulfate: 30 gm (250 mg/kg in a child).
  - ❖ **Saccharides**:
    - Sorbitol (D-glucitol) is the cathartic of choice in adults because of better efficacy than saline cathartics, but must not be used as far as possible in young children owing to risk of fluid and electrolyte imbalance (especially hypernatraemia).
    - It occurs naturally in many ripe fruits and is prepared industrially from glucose, retaining about 60% of its sweetness. Sorbitol is used as a sweetener in some medicinal syrups, and the danger of complications is enhanced in overdose with such medications when sorbitol is used as a cathartic during treatment.
    - Dose of sorbitol: 50 ml of 70% solution (adult).
  - ❖ Efficacy of catharsis:

While cathartics do reduce the transit time of drugs in the gastrointestinal tract, there is no real evidence that it improves morbidity or mortality in cases of poisoning.
  - ❖ Contraindications:
    - Corrosives
    - Existing electrolyte imbalance
    - Paralytic ileus
    - Severe diarrhoea
    - Recent bowel surgery
    - Abdominal trauma
    - Renal failure.

Oil based cathartics should never be used in poisoning since they increase the risk of lipoid pneumonia, increase the absorption of fat soluble poisons, and inactivate medicinal charcoal's effects when administered along with them. The last mentioned reason also applies to conventional laxatives, and hence they are also not recommended in poisoning.

■ Activated (Medicinal) Charcoal

A number of studies have documented clearly the efficacy of activated charcoal as the sole decontamination measure in ingested poisoning, while emesis and lavage are increasingly being associated with relative futility.

Activated charcoal is a fine, black, odourless, tasteless powder (**Fig 3.4**) made from burning wood, coconut shell, bone, sucrose, or rice starch, followed by treatment with an activating agent (steam, carbon dioxide, etc.). The resulting particles are extremely small, but have an extremely large surface area. Each gram of activated charcoal works out to a surface area of 1000 square metres.

- Mode of action—

Decreases the absorption of various poisons by adsorbing them on to its surface (**Fig 3.5**). Activated charcoal is effective to varying extent, depending on the nature of substance ingested (**Table 3.18**).

Fig 3.4: Activated charcoal powder
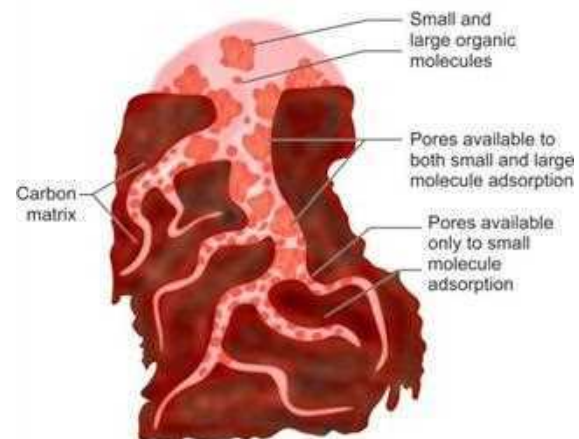
Fig 3.5: Activated charcoal powder—Mode of action

Small and large organic molecules
Pores available to both small and large molecule adsorption
Carbon matrix
Pores available only to small molecule adsorption

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* Not the same as laxatives or purgatives! A laxative is an agent which promotes soft formed or semifluid stool within a few hours or days. A cathartic promotes rapid, watery evacuation within 1 to 3 hours. Purgatives induce even stronger evacuation.

Table 3.18: Adsorption of Toxins to Activated Charcoal

Well Adsorbed		Moderately Adsorbed	Poorly Adsorbed
Aflatoxins	Cimetidine	Antidiabetic drugs	Alcohols
Amphetamines	Dapsone	Kerosene	Carbamates
Antidepressants	Digitalis	Paracetamol	Corrosives
Antiepileptics	NSAIDs	Phenol	Cyanide
Antihistamines	Opiates	Salicylates	Ethylene glycol
Atropine	Phenothiazines		Heavy metals
Barbiturates	Quinine, Quinidine		Hydrocarbons
Benzodiazepines	Strychnine		Organophosphates
Beta blockers	Tetracycline		
Chloroquine	Theophylline		

■ Dose—
  1 gm/kg body weight (usually 50 to 100 gm in an adult, 10 to 30 gm in a child).
■ Procedure—
  ❖ Activated charcoal is most effective when administered within one hour of ingestion. Administration in the prehospital setting has the potential to significantly decrease the time from toxin ingestion to activated charcoal administration, although it has not been shown to affect outcome.
  ❖ Add four to eight times the quantity of water to the calculated dose of activated charcoal, and mix to produce a slurry or suspension. This is administered to the patient after emesis or lavage, or as sole intervention. The slurry should be shaken well before administration.
    – Multiple-dose Activated Charcoal: The use of repeated doses (amounting to 150 to 200 gm of activated charcoal) has been demonstrated to be very effective in the elimination of certain drugs such as theophylline, phenobarbitone, quinine, digitoxin, phenylbutazone, salicylates and carbamazepine. The actual dose of activated charcoal for multiple dosing has varied considerably in the available medical literature, ranging from 0.25 to 0.5 gm/kg every 1 to 6 hours, to 20 to 60 gm for adults every 1, 2, 4, or 6 hours. The total dose administered is more important than frequency of administration.
■ Disadvantages—
  ❖ Unpleasant taste*
  ❖ Provocation of vomiting
  ❖ Constipation/diarrhoea
  ❖ Pulmonary aspiration
  ❖ Intestinal obstruction (especially with multiple-dose activated charcoal).
■ Contraindications—
  ❖ Absent bowel sounds or proven ileus

  ❖ Small bowel obstruction
  ❖ Caustic ingestion
  ❖ Ingestion of petroleum distillates.

■ Whole Bowel Irrigation (Whole Gut Lavage)

This is a method that is being increasingly recommended for late presenting overdoses when several hours have elapsed since ingestion. It involves the instillation of large volumes of a suitable solution into the stomach in a nasogastric tube over a period of 2 to 6 hours producing voluminous diarrhoea. Previously, saline was recommended for the procedure but it resulted in electrolyte and fluid imbalance. Today, special solutions are used such as **PEG-ELS** (i.e. polyethylene glycol and electrolytes lavage solution combined together, which is an isosmolar electrolyte solution), and **PEG-3350** (high molecular weight polyethylene glycol) which are safe and efficacious, without producing any significant changes in serum electrolytes, serum osmolality, body weight, or haematocrit.

■ Indications—
  ❖ Ingestion of large amounts of toxic drugs in patients presenting late (> 4 hours post-exposure)
  ❖ Overdose with sustained-release preparations.
  ❖ Ingestion of substances not adsorbed by activated charcoal, particularly heavy metals.
  ❖ Ingestion of foreign bodies such as miniature disc batteries (button cells), cocaine filled packets (**body packer syndrome**),** etc.
  ❖ Ingestion of slowly dissolving substances: iron tablets, paint chips, bezoars, concretions, etc.
■ Procedure—
  ❖ Insert a nasogastric tube into the stomach and instil one of the recommended solutions at room temperature, at a rate of 2 litres per hour in adults, and 0.5 litre per hour in children. The patient should preferably be seated in a commode. The use of metoclopramide IV, (10 mg in adults, 0.1 to 0.3 mg/kg in children) can minimise the incidence of vomiting. The procedure should be continued until the rectal effluent is clear, which usually occurs in about 2 to 6 hours.

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* It is gritty or sand-like in consistency, and has an unappetising look, being black in colour.
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- Complications—
  - ❖ Vomiting
  - ❖ Abdominal distension and cramps
  - ❖ Anal irritation.
- Contraindications—
  - ❖ Gastrointestinal pathology such as obstruction, ileus, haemorrhage, or perforation.

ELIMINATION

The various methods of eliminating absorbed poisons from the body include the following:
- Forced Diuresis
- Extracorporeal techniques
  - ❖ Haemodialysis
  - ❖ Haemoperfusion
  - ❖ Peritoneal dialysis
  - ❖ Haemofiltration
  - ❖ Plasmapheresis
  - ❖ Plasma perfusion
  - ❖ Cardiopulmonary bypass.

■ Forced Diuresis

Most drugs taken in overdose are extensively detoxified by the liver to produce inactive metabolites which are voided in the urine. Sometimes hepatic degradation produces active metabolites, but the secondary compounds are then converted to non-toxic derivatives. Under these circumstances, forced diuresis is inappropriate.

The procedure should be undertaken only if the following conditions are satisfied:
- A substantial proportion of the drug is excreted unchanged.
- The drug is distributed mainly in the extracellular fluid.
- The drug is minimally protein-bound.
- Principle—
  - ❖ Most drugs are weak electrolytes and exist partly as undissociated molecules at physiological pH. The extent of ionisation is a function of the ionisation constant of the drug (Ka for both acids and bases), and the pH of the medium in which it is dissolved. Ionisation constants are usually expressed in the form of their negative logarithm, pKa. Hence the pKa scale is analogous to the pH notation : the stronger an acid the lower its pKa, and the stronger a base the higher its pKa.
  - ❖ Thus when pKa = pH, the concentrations of ionised and non-ionised drugs are equal. Cell membranes are most permeable to substances that are lipid soluble and in the non-ionised, rather than the ionised form. Thus the rate of diffusion from the renal tubular lumen back into the circulation is decreased when a drug is maximally ionised. Because ionisation of acidic drugs is increased in an alkaline environment, and that of basic drugs is increased in an acid solution, manipulation of the urinary pH enhances renal excretion.

- **Forced alkaline diuresis :**
  - ❖ This is most useful in the case of phenobarbitone, lithium, and salicylates.
  - ❖ Administer 1500 ml of fluid IV, in the first hour as follows :
    - – 500 ml of 5% dextrose
    - – 500 ml of 1.2 or 1.4% sodium bicarbonate
    - – 500 ml of 5% dextrose.
- **Forced acid diuresis :**
  - ❖ Forced acid diuresis is no longer recommended for any drug or poison, including amphetamines, strychnine, quinine or phencyclidine.

■ Extracorporeal Techniques

1. **Haemodialysis (Fig 3.6)**
- Haemodialysis was first used in 1913 in experimental poisoning, but was not applied clinically until 1950, when it was used for the treatment of salicylate overdose. It was widely employed in the subsequent two decades accompanied by much adulatory reportage of its efficacy in medical journals. However, the popularity of haemodialysis has declined since then owing to authentic observation of its lack of utility in several types of poisoning, and the high incidence of complications such as infection, thrombosis, and air embolism.
- All drugs are not dialysable, and so it must be ensured before embarking on this procedure that the following conditions are satisfied:
  - ❖ The substance should be such that it can diffuse easily through a dialysis membrane.
  - ❖ A significant proportion of the substance should be present in plasma water or be capable of rapid equilibration with it.
  - ❖ The pharmacological effect should be directly related to the blood concentration.
  - ❖ **Table 3.19** outlines the various factors in a toxin which can affect the outcome of haemodialysis. Extensive plasma protein binding, insolubility in water, and high molecular weight are the three most important factors in making haemodialysis ineffective.
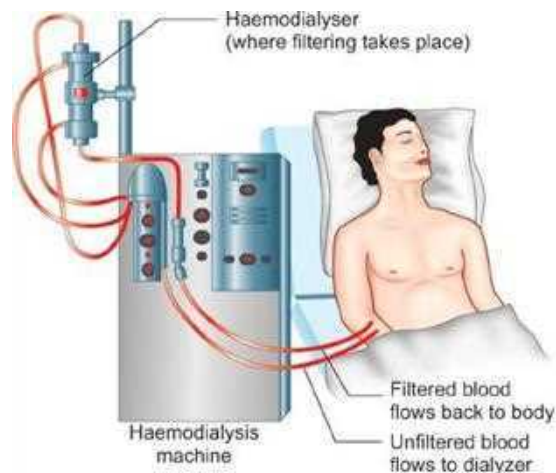
Fig 3.6: Procedure of Haemodialysis

Table 3.19: Factors Affecting the Efficacy of Haemodialysis	
Molecular weight	Volume of distribution
Charge	Tissue binding
Lipid protein binding	Total body clearance

- Procedure—
  - ❖ The three basic components of haemodialysis are the *blood delivery system*, the *dialyser* itself, and the *composition and method of delivery of the dialysate*. For acute haemodialysis, catheters are usually placed in the femoral vein and passed into the inferior venacava. Blood from one is pumped to the dialyser (usually by a roller pump) through lines that contain equipment to measure flow and pressure within the system. Blood returns through the second catheter. Dialysis begins at a blood flow rate of 50 to 100 ml/min, and is gradually increased to 250 to 300 ml/min, to give maximal clearance.
- Indications for haemodialysis—
  - ❖ Haemodialysis may be considered in those patients not responding to standard therapeutic measures while treating a dialysable toxicant (*vide infra*). It may also be considered a part of supportive care whether the toxicant is dialysable or not in the following situations: Stage 3 or 4 coma, or hyperactivity caused by a dialysable agent which cannot be treated by conservative means, marked hyperosmolality which is not due to easily corrected fluid problems, severe acid-base disturbance not responding to therapy, or severe electrolyte disturbance not responding to therapy.
    - – Best indications: Dialysis should be initiated, regardless of clinical condition, in the following situations: after heavy metal chelation in patients with renal failure, and following significant ethylene glycol or methanol ingestion.
    - – Very good indications: Dialysis is usually effective in patients with severe intoxications with the following agents:
      - - Lithium
      - - Phenobarbitone
      - - Salicylates
      - - Theophylline.
    - – Fairly good indications: Dialysis may be initiated following exposure to the following agents, if clinical condition deems the procedure necessary (patient deteriorating despite intense supportive care):
      - - Alcohols
      - - Amphetamines
      - - Anilines
      - - Antibiotics
      - - Boric acid
      - - Barbiturates (short acting)
      - - Bromides
      - - Chlorates
      - - Chloral hydrate
      - - Iodides
      - - Isoniazid
      - - Meprobamate
      - - Paraldehyde
      - - Fluorides
      - - Quinidine
      - - Quinine
      - - Strychnine
      - - Thiocyanates.
    - – Poor indications: Dialysis can be considered as a supportive measure in the presence of renal failure, following exposure to:
      - - Paracetamol
      - - Antidepressants
      - - Antihistamines
      - - Belladonna alkaloids
      - - Benzodiazepines
      - - Digitalis and related glycosides
      - - Glutethimide
      - - Opiates
      - - Methaqualone
      - - Phenothiazines
      - - Synthetic anticholinergics.
- Complications—
  - ❖ Infection (especially AIDS, hepatitis B)
  - ❖ Thrombosis
  - ❖ Hypotension
  - ❖ Air embolism
  - ❖ Bleeding (due to use of heparin as a systemic anticoagulant).

2. **Haemoperfusion (Fig 3.7)**

This is a technique that is increasingly becoming popular since it is capable of removing many of the toxins that are not removed well by haemodialysis (**Table 3.20**).

- Procedure—
  - ❖ An arteriovenous shunt or a double-lumen venous catheter is inserted into the patient's vascular tree. The haemoperfusion column and lines are primed with heparinised saline in accordance with the manufacturer's instructions and connected to the shunt or catheter. On commencement of perfusion, a bolus of heparin is injected into the arterial line and heparinisation is continued by administering an infusion of heparinised saline.
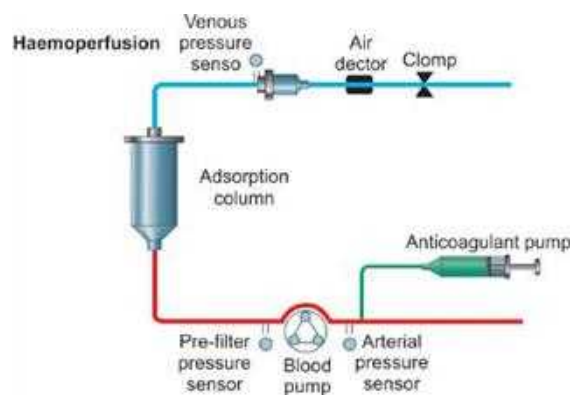
Fig 3.7: Procedure of Haemoperfusion

Table 3.20: Toxins Removed by Haemoperfusion (more efficiently than haemodialysis)

Amanitin	Paracetamol
Barbiturates (all categories)	Paraquat
Carbon tetrachloride	Phenols
Chloral hydrate	Phenylbutazone
Chlorpromazine	Promethazine
Dapsone	Propoxyphene
Diazepam	Quinidine, quinine
Digoxin	Salicylates
Diphenhydramine	Theophylline
Organophosphates	Tricyclic antidepressants

- Complications—
  - Bleeding (because of heparinisation)
  - Air embolism
  - Infection
  - Thrombocytopenia
  - Hypocalcaemia
  - Hypotension.

3. Peritoneal Dialysis

Although widely available, peritoneal dialysis today is almost never recommended for detoxification. In general, it is only 10 to 25% as effective as haemodialysis, and often only slightly more effective than forced diuresis. It is also time consuming, requiring 24 hours for successful completion as compared to the 2 to 4 hour cycles of haemodialysis and haemoperfusion. The only advantages are that it does not require anticoagulation and uses minimal equipment.

- Procedure—
  - Peritoneal dialysis works on the same principle as haemodialysis, allowing the diffusion of toxins from mesenteric capillaries across the peritoneal membrane into the dialysate dwelling in the peritoneal cavity. It involves the placing of a stylet catheter at the bedside under local anaesthesia, or the surgical insertion of a Tenckhoff catheter in the abdomen. Dialysate fluid is instilled, and 1 to 2 litres is exchanged each hour.
- Complications—
  - Pain
  - Haemorrhage (from vascular laceration)
  - Perforation of viscus
  - Bacterial peritonitis
  - Arrhythmias
  - Volume depletion/overload
  - Pneumonia
  - Pleural effusion
  - Hyperglycaemia
  - Electrolyte imbalance.

4. Haemofiltration

Haemofiltration is performed similar to haemodialysis except that the blood is pumped through a haemofilter. An arteriovenous pressure difference induces a convective transport of solutes through a hollow fibre flat sheet membrane. This allows a substantial flow of plasma water, and a high permeability to compounds with molecular weight less than 40,000. The procedure can be done intermittently at high ultrafiltrate rates of upto 6 litres/hour, or continuously at rates of 100 ml/hour (**Continuous Arteriovenous Haemofiltration, or CAVH**). The latter is preferred in the treatment of poisoning.

The main advantage of haemofiltration is that it can remove compounds of large relative molecular weight (4,500–40,000). Such compounds include aminoglycoside antibiotics and metal chelates (such as iron-desferrioxamine). CAVH is also useful in poisoning with lithium, methanol, ethanol, and ethylene glycol.

5. Haemodiafiltration

This is a combination of haemofiltration with haemodialysis. It has been undertaken very rarely, and nothing much is known as to its actual advantages, if any.

6. Plasmapheresis

Plasmapheresis is a technique of separating cellular blood components from plasma. The cells are resuspended in either colloids, albumin, or fresh frozen plasma, and then reinfused. It is very effective in eliminating toxic substances but exacts a heavy toll: a part of the patient's plasma proteins are sacrificed in the process. Plasmapheresis has been used in cases of overdose with theophylline, carbamazepine, amanita, mercury, hemlock, etc., but serious complications greatly limit its utility.

- Complications—
  - Bleeding disorders: DIC, thrombocytopenia
  - Hypercoagulation: Cerebral thrombosis, pulmonary embolism, myocardial infarction.
  - Anaphylaxis.
  - Fluid overload: Hypertension, congestive heart failure.
  - Infection.
  - Vessel perforation, air embolism.
  - Dysequilibrium syndrome: Vomiting, hypovolaemia.
  - Citrate toxicity: Paraesthesias, tetany, chills, arrhythmias.
  - Convulsions.
  - Metabolic alkalosis.

7. Plasma Perfusion

This is a combination of plasmapheresis and haemoperfusion, and has rarely been used in poisoning.

8. Cardiopulmonary Bypass

This is another rarely used experimental procedure in the treatment of poisoning, and has been shown to be useful in certain cases of overdose involving cardiac depressants such as verapamil and lidocaine.

ANTIDOTE ADMINISTRATION

In the majority of cases of acute poisoning, all that is required is intensive supportive therapy with attention to all the details mentioned in the preceding pages of this chapter. Specific antidotes are rarely necessary, besides the fact that only a few genuine antidotes exist in actual practice, though there is no denying the dramatic results that can be achieved with some of them in appropriate circumstances. Proper antidotal therapy can be life-saving in some situations.

Antidotes work in any one of a number of ways. Common modes of action are as follows:

1. **Inert complex formation**

    Some antidotes interact with the poison to form an inert complex which is then excreted from the body, e.g. chelating agents for heavy metals, Prussian Blue for thallium, specific antibody fragments for digoxin, dicobalt edetate for cyanide, etc.

2. **Accelerated detoxification**

    Some antidotes accelerate the detoxification of a poison, e.g. thiosulfate accelerates the conversion of cyanide to non-toxic thiocyanate, acetylcysteine acts as a glutathione substitute which combines with hepatotoxic paracetamol metabolites and detoxifies them.

3. **Reduced toxic conversion**

    The best example of this mode of action is provided by ethanol which inhibits the metabolism of methanol to toxic metabolites by competing for the same enzyme (alcohol dehydrogenase).

4. **Receptor site competition**

    Some antidotes displace the poison from specific receptor sites, thereby antagonising the effects completely. The best example is provided by naloxone, which antagonises the effects of opiates at stereo-specific opioid receptor sites.

5. **Receptor site blockade**

    This mode of action is best exemplified by atropine which blocks the effects of anticholinesterase agents such as organophosphates at muscarinic receptor sites.

6. **Toxic effect bypass**

    An example of this type of antidotal action is provided by the use of 100% oxygen in cyanide poisoning.

Table 3.21 represents a list of genuine antidotes recommended in toxicological practice today. In addition, there are certain therapeutic agents which are not antidotes as per the accepted definition, but which through their importance and sometimes specific role in the treatment of poisons, border on the concept of "antidotes". **Table 3.22** represents a list of such substances. Unfortunately in India, cumbersome governmental regulations and a lack of economic incentives for manufacturers have restricted availability of a substantial number of these life-saving drugs. As a result, doctors still use some substances which are more readily available as antidotes, but are generally considered obsolete or even dangerous in Western countries (**Table 3.23**). It is imperative that medical professionals strive to phase out these obsolete drugs, while working out strategies to make genuine antidotes more readily available.

NURSING AND PSYCHIATRIC CARE

NURSING CARE

This is especially important in comatose patients, and involves the following measures:

- Attention to pressure points to prevent the development of decubitus ulcers—hourly turning, a pillow between the legs, use of a ripple mattress if available, etc.

- In the absence of spontaneous blinking, avoid exposure keratitis by methyl cellulose eye drops, and if necessary, secure the eyelids with adhesive tape.
- Change bed linen frequently if it gets soaked with urine or stained with faeces.
- Urinary incontinence can be managed with a sheath urinal for a male, but for a female, an indwelling silastic catheter inserted with aseptic precautions is necessary.
- Inhalation of gastric contents is a frequent problem which can lead to pneumonitis. This can be prevented by positioning the patient semiprone with the head slightly dependent, and intubating if necessary.
- Adequate bronchial toilet is essential, with regular aspiration of secretions.
- Passive physiotherapy may be advisable to prevent stiffness and muscle atrophy.
- Prophylactic antibiotics, if necessary.

PSYCHIATRIC CARE

A significant proportion of overdose cases comprise suicide attempts. After medical stabilisation, the most important aspect of management consists of psychiatric counselling in order to prevent recurrence of suicide ideation once the patient has been discharged. The medico-legal aspects of these cases are discussed in **Chapter 4**.

Any patient who has taken an overdose or manifests suicidal ideation should get psychosocial assessment and support as early as possible. The initial evaluation can be performed prior to a total clearing of the patient's sensorium, but a final assessment should not be made unless the patient is completely alert. Recognition that the patient is possibly suicidal, with a precise analysis of the potential for suicide is essential. Carefully analysing the patient's psychologic state (*depressed, uncooperative, unresponsive, agitated, anxious, violent, or psychotic*), will allow for a realistic appraisal of the psychosocial alternatives with respect to immediate and long-term treatment, disposition, and continued follow-up, or outpatient care.

It is estimated that among adolescents, suicide accounts for a third of all unnatural deaths, while in college students, suicide is the second leading cause of unnatural death. According to one survey, oral ingestions account for 78% of the cases, 13% are inhalational, while 5% are due to parenteral intake. Patients suffering from depression commit suicide 50 times more frequently than the general population. Alcoholics and chronic dialysis patients have a suicide rate 6 times higher than the population at large. After the age of 40 years, the suicide rate begins to climb, with a dramatic increase after 65. Women attempt suicide 3 times more often than men, but men are more successful by a ratio of 3:1.

Significantly, 75% of all those who commit suicide do so shortly after seeing a doctor. Usually it is the family physician, not a psychiatrist who sees these patients, many of whom clearly need psychiatric support. With prompt recognition and referral, many suicides may be prevented. A patient with a past history of previous suicide attempts, vague health problems of recent onset, recent surgery, alcoholism, drug abuse,

Table 3.21: Specific Antidotes

Antidote	Main Indication	Other Applications
Acetylcysteine	Paracetamol	Amanitin
Amyl nitrite	Cyanide	Hydrogen sulfide
Ascorbic acid	Organic peroxides (Osmium)	—
Atropine	Cholinergic agents	—
Aurintricarboxylic acid (ATA)	Beryllium	—
Benzyl penicillin	Amanitins	—
β aminoproprionitrile	Acids	—
Calcium salts	Oxalates, fluorides	Calcium antagonists
Dantrolene	Malignant hyperthermia	Malignant neuroleptic syndrome
Desferrioxamine	Iron, aluminium	Paraquat
Diazepam	Chloroquine	—
Dicobalt edetate	Cyanide	—
Digoxin specific antibody fragments	Digitalis glycosides	—
Dimercaprol	Arsenic	Copper, gold, mercury
4,Dimethyl aminophenol (4 -DMAP)	Cyanide	Hydrogen sulfide
Ethanol	Methanol, ethylene glycol	—
Flumazenil	Benzodiazepines	—
Glucagon	Beta blockers	—
Glucose	Insulin	—
Guanidine	Botulism	—
Hydroxocobalamin	Cyanide	—
Isoprenaline	Beta blockers	—
Methionine	Paracetamol	—
4, Methylpyrazole	Ethylene glycol, methanol	Disulfiram, coprin
N-Acetylpenicillamine	Mercury	—
Naloxone	Opiates	—
Neostigmine	Peripheral anticholinergics	—
Oximes	Organophosphates	—
Oxygen	Cyanide, carbon monoxide, hydrogen sulfide	—
Oxygen (Hyperbaric)	Carbon monoxide	Cyanide, hydrogen sulfide, carbon tetra-chloride
Penicillamine	Copper	Gold, lead, mercury
Pentetic acid (DTPA)	Radioactive metals	—
Phentolamine	Alpha adrenergics	—
Physostigmine	Central anticholinergics	—
Phytomenadione (Vitamin K)	Coumarin derivatives	—
Potassium hexacyanoferrate (Prussian Blue)	Thallium	—
Propranolol	Beta adrenergics	—
Protamine sulfate	Heparin	—
Pyridoxine	Isoniazid	Ethylene glycol, gyrometrine, hydrazines
Sodium nitrite	Cyanide	Hydrogen sulfide
Sodium nitroprusside	Ergotism	—
Sodium salicylate	Beryllium	—
Sodium thiosulfate	Cyanide	Bromate, chlorate, iodine
Succimer (DMSA)	Lead, mercury	—
Tocopherol	Carbon monoxide	Oxygen toxicity
Toluidine blue	Methaemoglobinaemia	—
Trientine (triethylene tetramine)	Copper	—
Unithiol (DMPS)	Arsenic	Copper, nickel, lead, cadmium, mercury

Table 3.22: Adjunctival Antidotes

Agent	Indication
Activated charcoal	For most poisons (Refer Table 3.18)
Benztropine	Dystonia
Chlorpromazine	Psychotic states
Corticosteroids	Acute allergic reaction, laryngeal oedema
Diazepam	Convulsions
Diphenhydramine	Dystonia
Dobutamine	Myocardial depression
Dopamine	Myocardial depression, vascular relaxation
Epinephrine	Anaphylactic shock, cardiac arrest
Furosemide	Fluid retention, left ventricular failure
Glucose	Hypoglycaemia
Haloperidol	Psychotic states
Heparin	Hypercoagulability
Lidocaine	Ventricular arrhythmias
Mannitol	Cerebral oedema, fluid retention
Oxygen	Hypoxia
Pancuronium	Convulsions
Promethazine	Allergic reactions
Salbutamol	Bronchoconstriction
Sodium bicarbonate	Metabolic acidosis

Table 3.23: Obsolete Antidotes

Agent	Indication
Copper sulfate	Phosphorus
Cysteamine	Paracetamol
Diethyldithiocarbamate	Thallium
Fructose	Ethanol
Levallorphan	Opiates
Nalorphine	Opiates
Silibinin	Amanitin
Tocopherol	Paraquat
Universal antidote	Ingested poisons

and mental unsoundness (especially psychosis), is at high risk. Stress is also a major factor leading to suicide ideation; recent bereavement, loss of a job, financial loss, etc. are well recognised as trigger factors. Hypochondriasis, pessimism, hopelessness, and other signs of depression may signal a potential suicide and should alert the clinician.

Unfortunately, there are a number of misconceptions about suicide. For example, many people believe that those who talk about suicide will never actually commit suicide and those who resort to frequent suicide "gestures" are not really serious. However, studies show that of all those who successfully commit suicide, 80% have threatened to do so in the past, and may have even made previous attempts. It is therefore essential that every patient who talks about suicide or who presents with a suicide gesture no matter how trivial, should be referred to a psychiatrist before leaving the emergency department.

Today, psychosocial assessment has become an important component in the comprehensive evaluation of toxicologic emergencies. It has to be initiated in every case by interviewing collateral sources (accompanying family members or friends), before talking to the patient himself. Delay in obtaining psychosocial information can have serious consequences, for example, in cases where an overdosed adult patient may have small children who were left unattended.

FURTHER READING

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4

Medicolegal Aspects of Poisoning

Virtually every case of poisoning, whether acute or chronic, has medicolegal overtones. Basically there are three categories of medicolegal cases: **accidental, suicidal,** and **homicidal**. The vast majority constitute either accidental or suicidal poisoning, while homicidal cases are quite rare. Whatever the nature, every hospital (Government run or privately owned) is under a legal obligation to treat to the best possible extent, and no case can be turned away on the pretext that the hospital concerned is not "authorised" to handle medicolegal cases.* If adequate facilities do not exist for proper treatment, the victim should be administered first-aid and such other medical or surgical help that is possible under the circumstances before referring him to the nearest hospital where required facilities exist.

MEDICOLEGAL DUTIES OF A DOCTOR IN SUSPECTED/ACTUAL POISONING

1. If a case of poisoning is indubitably accidental or suicidal in nature, the attending doctor is under no legal obligation to notify the police in case he is working in a private hospital. But if the patient dies, the police has to be informed. Death certificate must not be issued.
2. Doctors working in government hospitals are required to report every case of poisoning regardless of the nature, to the police.
3. All cases of homicidal poisoning (definite or suspected) must be compulsorily reported to the police as per section **39** of the **Criminal Procedure Code (CrPC)**. Failure to do so will make him culpable under section **176** of the **Indian Penal Code (IPC)**.
4. If the police require information on any case of poisoning which is either suicidal or homicidal in nature, the attending doctor has to divulge it. There is no scope for professional secrecy in such matters (**175 CrPC**). If information is witheld or wrong information is provided, the doctor becomes culpable under section **202** and **193 IPC** respectively.
5. Every effort must be made by the attending doctor to collect and preserve evidence suggestive of poisoning.

Deliberate omission to do so can attract punishment under section **201 IPC**.
6. Collect vomitus, faeces, stomach washings, contaminated food, incriminating substance, etc., and despatch the same for chemical analysis to the nearest *Forensic Science Laboratory*.
7. If a poisoned patient is conscious but on the verge of death, record a dying declaration relating to the circumstances. It is preferable to call a magistrate for this purpose, but if death appears imminent, or if there is likelihood of delay in the arrival of the magistrate, the attending doctor must himself record the declaration as per section **32**, clause **1**, of the **Indian Evidence Act (IEA)**. Even when a declaration is taken down by a magistrate, the presence of a doctor is desirable to certify that the dying victim was in possession of his senses, and there was no clouding of judgement or coherence which is sometimes encountered in the final moments before death.
8. If a patient dies before the exact diagnosis could be made out, or he was brought dead to the hospital, the duty doctor must notify the police who will in all probability order an autopsy to be done. Death certificate must not be issued.
9. Detailed written records should be made with respect to every case of poisoning and kept in safe custody.
10. If a doctor comes across a case of food poisoning from a public eatery (canteen, café, restaurant, etc.), he must notify the **public health authority** concerned.

INDIAN STATUTES ON DRUGS/POISONS

Several legal acts have been passed regulating and controlling the manufacture, sale, distribution, and possession of drugs and poisons. The principal acts include the following:

■ The Poisons Act (1919)

This Act was amended in 1958 and repealed in 1960. It deals with the import of poisonous substances into India, license issuance for possession of certain specified poisons, and restrictions

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* As per the Supreme Court judgement passed in 1989, in response to a public interest litigation petition.

in the sale of such substances (mostly chemicals) as poisons, over which control is to be exercised.

Drugs And Cosmetics Act (1940)

This Act was amended in 1964, and very recently in 2008, and is today referred to as the **Drugs And Cosmetics Amendment Act (2008).** It deals with the import, manufacture, distribution, and sale of all kinds of drugs (allopathic, ayurvedic, unani, siddha, etc.) and cosmetics. As per the Act, every patented or proprietary medicinal preparation should display on the label of the container, either the exact formula or a list of the ingredients. The amended Act has enhanced the scale of punishment for various offences, including sale of spurious drugs, adulteration of drugs and cosmetics, toxic contamination, etc.

The Drugs And Cosmetics Rules (1945)

This is an offshoot of the **Drugs and Cosmetics Act** of **1940**, and is concerned mainly with the standard and quality of drugs, apart from exercising control over the manufacture, sale, and distribution, of drugs and cosmetics.* It was amended in 1988, and is now referred to as **Drugs And Cosmetics Rules (Eigth Amendment) 1988**. All types of drugs used in therapeutics have been included: *allopathic, homeopathic, ayurvedic, unani,* and *siddha*. All drugs and cosmetics are required to be labelled and packed appropriately. To advise the Central and State Governments on technical matters relating to drug control, the following Boards have been set up: the **Drugs Technical Advisory Board**, the **Ayurvedic** and **Unani Technical Advisory Boards**, and the **Drugs Consultative Committee**.

In order to facilitate the analysis or testing of drug samples to assess their quality, the **Central Drugs Laboratory** was established in 1962. Individual states have set up **Drug Control Laboratories**. Stringent punishments have been laid down for manufacture, stocking, or sale of substandard or spurious drugs. Guidelines for conducting clinical trials for new drugs have been made more strict (Schedule Y).

The Drugs and Cosmetics Rules have classified drugs into various *Schedules* as follows:

Schedule C and C1—Biological products, e.g. serums and vaccines.

Schedule D—Substances not intended for medicinal use—condensed or powdered milk, oats, spices and condiments, etc.

Schedule E1—List of poisonous substances under the Ayurvedic (including Siddha) and Unani Systems of Medicine.

Schedule G—Chemotherapeutic agents for cancer, antihistaminics, and hypoglycaemic agents.

Schedule H and L—Injectables, antibiotics, antibacterials and other prescription drugs.

Schedule J—Diseases and ailments (by whatever name described) which a drug may not purport to prevent or cure or make claims to prevent or cure, e.g. AIDS, cancer, cataract, congenital malformations, deafness, blindness, hydrocoele, hernia, piles, leucoderma, stammering, paralysis, etc.

Schedule O—Standards to be followed with regard to disinfectant fluids.

Schedule S—Standards to be followed with regard to cosmetics and allied products.

Schedule X drugs—Barbiturates and certain other sedatives, amphetamines, etc.

A list of drugs banned for sale in India as per **The Drugs and Cosmetics Rules** is listed in **Appendix 2**.

The Pharmacy Act (1948)

The objective of this Act is to allow only registered pharmacists to compound, prepare, mix, or dispense any medicine on the prescription of a registered medical practitioner. Under this Act, the **Pharmacy Council of India** has been constituted which regulates the study of pharmacy throughout the country. Individual states have **State Pharmacy Councils** for registration of pharmacists.

The Drugs Control Act (1950)

This Act regulates the supply and distribution of drugs, and also guides the manufacturer or dealer in fixing the maximum price for every drug.

The Drugs and Magic Remedies (Objectionable Advertisement) Act (1954)

The objective of this Act is to ensure that ethical standards are maintained when drugs are advertised by the manufacturers. Advertisements which offend decency or morality can be banned under this Act. Also, those which claim magical powers for certain drugs, e.g. enhancement of potency, cure for incurable diseases, etc. Magical remedies include the use of talismans or charms such as "*mantras*", "*kavachas*", etc.

The Medicinal And Toilet Preparation (Excise Duty) Act And Rules

This Act deals with regulatory problems arising out of the use of alcohol in various medicinal and toilet preparations. It has helped greatly in curbing the large scale inter-state smuggling of alcoholic medicinal, and toilet preparations which existed previously due to different rates of excise duties in different states. This Act has made uniform rates of duty applicable throughout the country.

Narcotic Drugs and Psychotropic Substances Act (1985)

The **Narcotic Drugs and Psychotropic Substances Act (NDPS Act)** was enacted in India and subsequently amended in 1988, to implement the provisions of the *Convention on Psychotropic Substances* (1971), and the *Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances* (1988), both held in Vienna. This Act renders obsolete three

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* A cosmetic is defined as any substance that is intended to be rubbed, poured, sprinkled, sprayed on, or introduced into the human body, or over any part thereof, for cleaning, beautifying, promoting attractiveness, or altering physical appearance of any person.

previous Acts—the **Opium Act (1857),** the **Opium Act (1878),** and the **Dangerous Drugs Act (1930)**.

The term "narcotic" in the legal sense is quite different from that used in the medical context which denotes a sleep-inducing agent. Legally, a narcotic drug could be an opiate (a true narcotic), cannabis (a non-narcotic), or cocaine (the very antithesis of a narcotic, since it is a stimulant). The term "psychotropic substance" is with reference to mind-altering drugs such as LSD, phencyclidine, amphetamines, barbiturates, methaqualone, benzodiazepines, mescaline, psilocybine, and designer drugs (MDMA, DMT, etc.).

The **NDPS Act** imposes complete prohibition on the cultivation of coca, poppy, and cannabis plants, and the manufacture, sale, purchase, use, or transport of any narcotic drug or psychotropic substance except for medical or scientific purposes.

The minimum punishment for any offence committed under the Act is 10 years rigorous imprisonment and fine of Rs.1 lakh, while the maximum punishment is 20 years rigorous imprisonment and fine of Rs.2 lakhs. There is also sufficient scope under the **NDPS Act** for enhanced punishment for repeat offences especially after previous convictions, which includes the imposition of even the death penalty. The minimum quantity of drug seized in the subsequent offence should be as per **Table 4.1**, if death penalty is to be imposed. To constitute an offence the first time around, the minimum quantity seized should be equal to or over 250 mg for heroin, 5 gm for hashish or charas, 5 gm for opium, 125 mg for cocaine, and 500 gm for ganja.

A new Chapter, Chapter V-A, was introduced into the Act in May 1989 to provide for the investigation, freezing, seizure and forfeiture of property derived from illicit trafficking in narcotic drugs and psychotropic substances. This Chapter prohibits any person from holding any property derived

from drugs trafficking and authorises officers empowered under the Act to investigate, identify and seize such property. The Chapter also sets out a quasi-judicial procedure for the forfeiture of such property consequent to which it shall vest in the Central Government.

In addition to persons directly involved in trafficking narcotic drugs and psychotropic substances, any person who finances trafficking, or harbours a person involved in trafficking, or abets, or is a party to a criminal conspiracy, including a criminal conspiracy to commit an offence outside India is also liable to the same scale of punishments.

However, immunity from prosecution is given to addicts volunteering for detoxification. **Section 64-A** of the **NDPS Act** states that any addict who is not charged with any offence punishable under **Sections 15 to 25**,* or **Section 27-A**,** and who voluntarily seeks to undergo medical treatment for detoxification or de-addiction from a hospital or an institution maintained or recognised by the government or a local authority, and undergoes such treatment shall not be liable to prosecution under **Section 27** of the Act (once in his lifetime). Such immunity granted may be withdrawn if the addict does not undergo the complete treatment, and in such circumstances the accused shall be prosecuted for the said offence.

Further, the Act makes a distinction between possession for personal consumption and trafficking, the punishment for the former being limited to between six months and one year only. The application of this provision is subject to the following two qualifications:

The quantity of the drug involved in the offence should be a small quantity as specified by the Central Government.

The onus is on the accused to establish that the drug in question was meant for personal consumption and not for sale, distribution, etc.

The Central Government of India constituted a **Narcotics Control Bureau** in 1986 with its headquarters at New Delhi, and zonal offices at Mumbai, Kolkata, Chennai, and Varanasi. In 1988, the Central Government constituted the **Narcotic Drugs and Psychotropic Substances Consultative Committee**, consisting of a chairman (the minister of finance/minister of state in the ministry of finance), and 18 members from diverse fields who would among other functions, conduct periodic review of the **NDPS Act**.

While the **NDPS Act** prohibits the cultivation of poppy, cannabis, and coca plants, it does not impose a total ban. Restricted cultivation of these plants is allowed under strict control for scientific or medical use. Prior sanction in the form of license is necessary from the Central Government for this purpose. For instance, poppy can be cultivated only in certain specified tracts in the states of *Rajasthan, Uttar Pradesh,* and *Madhya Pradesh* during a specified period, the opium year commencing on the first day of October every year, and ending on the 30th day of September the following year. These policy controls are backed by strict enforcement on the ground which include the measurement of fields, periodical crop surveys,

Table 4.1: Minimum quantity of seizure (in repeat offence) for imposition of death penalty

	Narcotic drug / Psychotropic substance	Quantity (Kg)
1.	Opium	10
2.	Morphine	1
3.	Heroin	1
4.	Codeine	1
5.	Thebaine	1
6.	Cocaine	0.5
7.	Hashish	20
8.	Any mixture of the above drugs	1.5
9.	LSD (Lysergic acid diethylamide)	0.5
10.	THC (Tetrahydrocannabinol)	0.5
11.	Amphetamines	1.5
12.	Methaqualone	1.5
13.	Salts and preparations of above (**9 to 12**)	1.5

* Relate to illegal cultivation or import/export of narcotic drugs and psychotropic substances.
** Relates to financing illicit drug trafficking, or harbouring offenders.

and physical checks to prevent diversion. Failure to tender the entire yield to the Government is treated as a serious offence and any cultivator who embezzles the opium produced by him, is in terms of section 19 of the Act, punishable with rigorous imprisonment for a term of between 10 to 20 years, and a fine which shall not be less than Rs.100,000/- but which may extend to Rs.200,000/-.

The 1998 UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances to which India is a signatory, requires countries to impose controls over the manufacture, internal distribution, and import and export of chemicals which can be used in the illicit manufacture of substances of abuse. In order to implement India's obligations under this Convention, the NDPS Act was amended in 1998 in order to empower the Central Government to declare any substance as a controlled substance and to regulate its manufacture, import and export, etc. (Section 9-A). Violations relating to such substances were established as criminal offences punishable with imprisonment for upto 10 years (Section 25-A). In 1993, the Government of India promulgated the NDPS (Regulation of Controlled Substances) Order, to regulate the manufacture, distribution, etc. of any substance declared to be a "Controlled Substance".

In exercise of its powers under the Act, the Central Government has so far notified acetic anhydride, which is used in the processing of opium into heroin, N-acetylanthranilic acid which is used in the illicit manufacture of methaqualone, and ephedrine and pseudoephedrine which are used in the illicit manufacture of amphetamine type stimulants as "controlled substances".

TOXICOLOGY AND THE CRIMINAL LAW

The criminal law of India is codified in the **Indian Penal Code** (**IPC**), and the **Criminal Procedure Code** (**CrPC**). The former is the substantive law dealing with the definition of specific offences and the nature of punishment to be administered, while the latter is the procedural or adjective law dealing with the elaboration of judicial proceedings at various stages of enquiry and trial.

The following sections of the **IPC** deal directly or indirectly with offences involving poisons:

■ 284

This section deals with negligent conduct in relation to poisons, and states, "*Whoever does with any poisonous substance any act in any manner so rash or negligent as to endanger human life or to be likely to cause hurt or injury to any person, or knowingly or negligently omits to take such order with any poisonous substance in his possession as is sufficient to guard against any probable danger to human life from such poisonous substance, shall be punished with imprisonment (up to 6 months), or fine (up to Rs.1000), or both*".

The gist of this offence is culpable negligence with respect to poisonous substances. The fact that a person has the custody

of any dangerous substance suffices itself to impose upon him the duty of being careful.

■ 299:

This section deals with culpable homicide. It states, "*Whoever causes death by doing an act with the intention of causing death, or with the intention of causing such bodily injury as is likely to cause death, or with knowledge that he is likely by such act to cause death, commits the offence of culpable homicide*".

Such acts include the use of poisonous substances, apart from conventional weapons of assault.

■ 300

The issue of murder is dealt with in this section which is very similar in definition to culpable homicide, but lays more emphasis on deliberate intention and premeditation.

The punishment for culpable homicide can be any term of imprisonment up to a maximum of life sentence, but that for murder can extend to the imposition of death penalty (capital punishment), the minimum sentence being life imprisonment.

However, poisoning homicides are among the most difficult to detect and bring to justice.

■ 304-A

There are two sub-sections under section **304**.* Sub-section A deals with death caused by a rash or negligent act and states, "*Whoever causes the death of any person by doing any rash or negligent act not amounting to culpable homicide, shall be punished with imprisonment (up to 2 years), or fine, or both*".

Such acts of negligence can be with reference to the handling or storage of poisonous substances, apart from carelessness in the use of a vehicle or machinery. For example, if a pharmacist leaves a cupboard containing toxic drugs unlocked leading to the death of a child who consumes any such drug out of curiosity, he will be held guilty under this section. It is interesting to note that in such a case, section **284** can also be applied.

■ 324

This section deals with the causing of hurt by any dangerous weapon or means (including the use of a poisonous substance). It states, "*Whoever voluntarily causes hurt by means of any instrument for shooting, stabbing, or cutting, or any instrument which when used as a weapon of offence is likely to cause death, or by means of fire or any heated substance, or by means of any poison or any corrosive substance, or by means of any substance which is deleterious to the human body to inhale, to swallow, or to receive into the blood, or by means of any animal, shall be punished with imprisonment (up to 3 years), or fine, or both.*"

■ 326

This section deals with the causing of grievous hurt by any dangerous weapon or means (including the use of a poisonous

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* Sub-section B deals with the definition and punishment for "dowry death", and has little relevance to toxicology.

substance). The wording of this section is very similar to that of section **324**, except for the fact that the injury caused should be of any of the eight types mentioned under section **320**, namely,

- Emasculation.
- Permanent privation of sight, or
- Hearing, or
- Any member or joint, or
- The impairment of the power of any member or joint.
- Permanent disfiguration of head or face.
- Fracture or dislocation of any bone or tooth.
- Any hurt which endangers life, or causes the sufferer to be in severe bodily pain, or unable to follow his ordinary pursuits for a minimum period of 20 days.

The punishment can be any term of imprisonment from 10 years to life imprisonment, and can also involve the imposition of a fine.

■ 328

Like section **284**, this section deals specifically with poisons. It states, "*Whoever administers to any person any poison, or any stupefying, intoxicating, or unwholesome drug with intent to cause hurt to such person, shall be punished with imprisonment (up to 10 years), and shall also be liable to fine.*"

MEDICOLEGAL PROBLEMS INVOLVING CONSENT

The consent of a patient is necessary for all diagnostic and therapeutic procedures, particularly those which are invasive or risky in nature.* Undertaking such procedures without consent having been obtained first can amount to an assault in the legal sense, even if done for the benefit of the patient unless extenuating circumstances exist.

A patient who has deliberately consumed a poisonous substance or overdosed on a therapeutic drug, is likely to be uncooperative and may resist all efforts at treating him. The attending physician may then be uncertain as to the legal implications of forcing treatment on the patient who may even threaten the doctor with a law suit if therapeutic procedures are forcefully carried out. It is however a fact that a patient who attempts suicide has lost the right to refuse treatment, and no court has so far upheld a patient's complaint of "forced treatment" in such circumstances. It is also true that in many such cases of toxic ingestions, the patient can be declared "not rational" enough to refuse treatment on account of depression or disturbance of mental functions which can be deemed to impair judgement. On the other hand, a physician may become liable for negligence if he does not do what is medically indicated.

There are times however, such as in a wildly agitated or extremely uncooperative patient, when overzealous attempts to remove a poison or drug overdose may place the patient at greater risk of physical harm than the ingestion itself. In such cases, the patient should be observed or partially restrained until cooperation or lethargy ensues. But if the patient has ingested an imminently life-threatening poison, then no effort should be spared in restraining the patient physically or even pharmacologically if necessary, in order to eliminate the toxin before it exerts its harmful effect.

In the case of a comatose patient, consent must be obtained from the next of kin. However, if it is an emergency and consent is being refused on unreasonable grounds, the physician can go ahead with the necessary treatment even in the absence of consent. In such cases, the court will always uphold his decision if it comes to a legal action, since it was made in good faith with the well being of the patient as the prime consideration. Special problems arise when medical examination is requested to be done on a person who is alleged to be drunk, in order to ascertain as to whether the allegation is true. This may be with reference to offences such as disorderly behaviour in public, rash driving, or commission of assault. Even if the individual concerned consents to examination, the question arises as to how valid it is, since if at the conclusion of the examination the doctor is of the opinion that the individual was intoxicated, then such consent becomes invalid because of the legal presumption that a person under the influence of alcohol is not in a fit enough mental state (**Section 90 IPC**).

It is pertinent to note that if an accused person has been arrested and then brought for examination where it can be reasonably believed that such examination can afford valuable evidence as to the commission of an offence, it is not necessary for consent to be obtained from the individual. Medical examination can be caried out in such cases on the basis of a request made by a police officer not below the rank of a Sub-Inspector (**Section 53 CrPC**). Even "reasonable" force can be used to accomplish the examination, which can also include the collection of blood or urine sample for analysis. However, if the person to be examined is a woman, the examination should be conducted by or under the supervision of a lady doctor.

TOXICOLOGY AND THE WORKMEN'S COMPENSATION ACT

The **Workmen's Compensation Act** (**1923**), provides for the payment of compensation by certain classes of employers to their employees for injury or accident sustained in the course of employment. An occupational disease contracted by a workman while in the service of an employer for a continuous period of not less than six months is deemed to be an injury or an accident.

When a workman gives notice of an accident, the employer should arrange to have him examined free of charge by a qualified medical practitioner. If the workman refuses to be examined or treated, or after agreeing to be examined disregards instructions regarding treatment, the injury or disablement will be deemed to be of the same severity as it may have been reasonably expected to be with proper medical attention.

In case a medical officer is asked to examine a workman and give his opinion as to whether he is partially or totally disabled from an accident or occupational disease, he should undertake the examination with great care. Among the list of

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* If the patient happens to be a child under the age of 12 years, or a mentally unsound person, the consent of the parent or guardian should be taken.

occupational diseases mentioned under the Act, the following poisons/toxins are implicated as causative agents—arsenic, benzene, bichromates, carbondisulfide, chromic acid, halogenated hydrocarbons, lead, manganese, mercury, nitrous fumes, organophosphates, and phosphorus. However, the WHO has identified many more chemicals as disease-causing in the field of occupational health (**Table 4.2**).

POSTMORTEM EXAMINATION IN A CASE OF POISONING

Poisoning cases being invariably medicolegal in nature, if the patient dies, an inquest will have to be done, followed by postmortem examination by a forensic pathologist. This is for the purpose of ascertaining the circumstances in which poisoning occurred, and to establish the exact cause and manner of death.

The general procedure of examination is the same as for any medicolegal autopsy, with particular attention being paid to those aspects which can afford a clue to the detection of and identification of the poison involved. The following is a summary of the important points to be noted:

■ External Examination

1. Stains or marks of vomit, faecal matter, etc., on the clothing, or on the body.
2. There may be evidence of corrosion in the form of discolouration and sloughing especially around the mouth, in caustic ingestion (acid/alkali).
3. Presence of jaundice suggests a hepatotoxic poison, or one which causes haemolytic anaemia.
4. Odour: Several poisons have characteristic odour which may be perceptible in the vicinity of the mouth. (**Table 2.4**, page no. 8).
5. Colour of postmortem lividity*: Certain poisons impart characteristic colouration, for example—

a.	Carbon monoxide	Cherry pink
b.	Cyanide	Brick red
c.	Hydrogen sulfide	Greenish blue
d.	Phosphorus	Brown
e.	Nitrobenzene, aniline, potassium chloride	Brownish red

6. Putrefactive changes: Some poisons are said to retard the rate of decomposition of a dead body, e.g. arsenic, organophosphates.
7. Injection marks : Especially likely in a victim who had been a drug addict in life.

■ Internal Examination

1. Odour: It is preferable to open the cranial cavity first, since poisons impart a faint odour to the brain which may be difficult to perceive in the presence of overpowering odours from the thorax or abdomen if they have been opened earlier. Examples of such poisons include alcohol, chloroform, cresol, cyanide, and phenol.
2. Evidence of inflammation: Ingested poisons may cause softening, reddening, corrosion, or even perforation of the gastrointestinal tract. Sometimes the poisonous substance in the form of tablets, powder, plant parts, or fluid may still be present. There may be associated odour.
3. The state of the other organ systems: Liver and kidneys are invariably congested. In some cases, there is evidence (gross or microscopic) of degenerative changes or even necrosis. Brain may be congested or oedematous, particularly in the case of neurotoxic poisons. Petechiae in the white matter are often seen with asphyxiant poisons, which also produce pulmonary oedema with consequent froth in the airways. The heart may demonstrate petechiae or degenerative changes in the case of cardiotoxic poisons. Subendocardial haemorrhages are said to be characteristic (though not pathognomonic) of acute arsenic poisoning.

CHEMICAL ANALYSIS

In every case of death due to poisoning, an attempt must be made to demonstrate the presence of poison by standardised analytical methods. For this purpose, the pathologist conducting the autopsy must collect certain of the viscera and body fluids,

Table 4.2: Toxic Agents Causing Occupational Diseases (WHO)

Gases	Dusts	Metals	Chemicals	Solvents
Ammonia	*Inorganic:*	Arsenic	Acids	Mercury
Carbon dioxide	Asbestos	Beryllium	Alkalies	Benzene
Carbon monoxide	Coal	Cadmium	Pesticides	Chloroform
Carbon disulfide	Iron	Chromium		Trichloro-ethylene
Hydrogen cyanide	Silica	Lead		
Hydrogen sulfide	*Organic :*	Manganese		
Nitrogen	Cotton dust	Mercury		
Sulfur dioxide	Hay			
	Sugarcane fibre			
	Tobacco			

* Normal colour is purplish

and despatch them through the police to the nearest forensic science laboratory. While submitting the samples for analysis it must be ensured that the correct quantity has been preserved in appropriate preservative in suitable, sealed containers. The materials to be collected are mentioned in **Table 4.3**, while the recommended preservatives are mentioned in **Table 4.4**.

■ Sample Collection and Preservation

The stomach is cut between double ligatures at the cardiac and pyloric ends, and transferred to a clean tray. It is slit open along the greater curvature and the contents examined. The stomach is then placed along with its contents in a clean, wide-mouthed glass bottle of 1 litre capacity. It is preferable to preserve the contents separately in a different container. Similarly, the first part of the jejunum is identified and a length of about 30 cm is cut between double ligatures at either end, and transferred to a tray. It is then slit open and placed along with its contents into the same container as the stomach. However, the contents can be preserved separately.

The liver is removed from the body in the usual manner, and about 500 grams portion is cut and preserved in another container of 1 litre capacity. It is desirable to include the gall bladder, since some drugs are concentrated in the bile, such as paracetamol, barbiturates, and opiates. The liver should always be sliced into pieces before placing it in the container, so that the preservative can exert its action more thoroughly.

The kidneys are dissected out of the body and one half of each is sliced and placed in the same container as the liver. Preserving one kidney alone may not be advisable, since it may happen to be dysfunctional.

It is important that the blood collected for analysis should never be withdrawn directly from the heart or scooped out of the thoracic or abdominal cavities, since some poisons such as alcohol and barbiturates can diffuse passively after death from the stomach or intestines into adjacent organs or cavities leading to erroneous results. Blood should always be collected into a clean syringe from a peripheral vein such as those in the neck or the limbs. The femoral vein is most suitable for withdrawing

Table 4.3: Viscera and Body Fluids to be Preserved in Suspected Poisoning

1. Routine Viscera & Body Fluids—(to be preserved routinely for analysis, in every case of poisoning)

	Specimen	Quantity
1	Stomach	Entire
2	Stomach contents	Entire (preferably)
3	Small intestine (jejunum)	30 cm (entire length in infants)
4	Small intestinal contents	Up to 100 gm
5	Liver (portion containing gall bladder)	500 gm (entire liver in infants)
6	Kidney	One half of each kidney (both kidneys in infants)
7	Urine	30 – 50 ml
8	Blood	10 – 20 ml

2. Special Viscera—(all or any of these should be preserved in addition to routine viscera, in certain specific cases of poisoning)

	Specimen	Quantity	Poison
1	Cerebrospinal fluid	As much as can be withdrawn	Alcohol
2	Brain	Half (one hemisphere)	Alcohol, anaesthetics, barbiturates,carbon monoxide, cyanide, opiates, strychnine
3	Spinal cord	Entire length	Gelsemine, strychnine
4	Lung	One	Inhaled poisons
5	Skin (with underlying tissues)	Affected portion	Corrosives, injected poisons
6	Long bone (preferably femur)	10 cm length	Heavy metals
7	Scalp hair (plucked)	15 to 20 strands	Heavy metals

Table 4.4: Preservatives for Viscera and Body Fluids

	Specimen	Preservative
1	Viscera	Rectified spirit* or Saturated saline
2	Blood	For every 10 ml, use 30 mg potassium oxalate and 100 mg sodium fluoride**
3	Urine	100 mg sodium fluoride for every 10 ml

* Not to be used in poisoning due to alcohol, phosphorus, acetic acid, phenol, and paraldehyde.
** For carbon monoxide and other gaseous/volatile poisons, use glass or plastic tube, and ensure that there is very little headspace after filling

a blood sample and can easily be approached percutaneously. A 30 or 50 ml syringe with a wide-bore needle must be used. The vein is located in the inguinal canal midway between the anterior superior iliac spine and the pubic tubercle, just medial to the femoral artery. The needle should be inserted perpendicularly. Do not "milk" the limb while collecting the blood sample since this can produce significant alterations in drug concentrations in the expressed blood. About 10 to 20 ml is withdrawn and transferred to a clean vial or bottle which should be capped tightly and sealed with molten wax to minimise evaporation of volatile poisons.

In putrefying bodies, it may be difficult to obtain blood from peripheral veins, besides the fact that the results of analysis may be vitiated by postmortem generation of alcohol as a result of decomposition. In such cases, it may be preferable to use cerebrospinal fluid or vitreous humor for analysis. Some investigators suggest that if alcohol is detected in blood but not in urine and vitreous humour, it should be assumed that postmortem synthesis of alcohol has occurred.

Urine can be collected by puncturing the bladder with a needle and syringe, and aspirating about 30 to 50 ml. However, if there is very little urine it may be necessary to make a small incision on the anterior bladder wall and scoop out the urine with a spoon, or aspirate it with a syringe or pipette. Care should be taken to ensure that the urine obtained is not contaminated with blood. The collected sample should be transferred into a clean vial or bottle and capped and sealed in the same way as described for the blood sample.

In some cases, additional viscera or body fluids may have to be preserved depending on the nature of the poison (**Table 4.3**). Cerebrospinal fluid is difficult to obtain by lumbar puncture at autopsy. It is easier to collect it by cisternal puncture. With the neck flexed, palpate the atlanto-occipital membrane in the midline and using a needle and syringe, gently introduce the needle through the skin at that point, directing the needle towards the bridge of the nose. As the atlanto-occipital membrane is punctured at a depth of approximately 2 cm, loss of resistance will be felt, at which point the CSF can easily be aspirated. As an alternative, CSF can be aspirated anteriorly after evisceration by introducing a needle into the spinal theca via the spinal foramina between the 1st and 2nd lumbar vertebrae. If lung is to be preserved for analysis (in inhaled poisons and solvent abuse), it is preferable to place it inside a nylon bag and then heat-seal the bag.

If all the specimens collected for chemical analysis can be despatched to the laboratory immediately and analysis can be done within 24 hours, no preservative need to be added to any of the specimens. However this is almost never possible in reality, and so either the samples should be sent in an insulated ice box with sufficient crushed ice, or suitable preservative must be added to all the containers before despatching (**Table 4.4**). It is important to label all the containers with details as to the postmortem number, crime number (if any), name of the deceased (if known), police station to which the case belongs, the date of collection, the exact nature and quantity

of the specimen, the nature of preservative, and the name, designation, and signature of the pathologist. A sample of the preservative used should be sent separately so that it can be analysed as to its purity and presence of contaminants, if any. All containers should be properly packed and sealed with sealing wax.

It is important to remember that chemical analysis reports are not always infallible, and the medical officer would do well to consider all other aspects including clinical notes, eye witness accounts, and his own observations at autopsy, before pronouncing the cause of death.

HISTOPATHOLOGICAL EXAMINATION

Since poisons can cause degenerative changes in target organs, histopathological evidence of such damage can be a valuable corroborative adjunct. Microscopic examination of tissues may also sometimes help to substantiate a suspicion of long standing abuse which could have contributed to the cause of death. Tissues submitted for histopathology must always be preserved in formalin.

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Section

2

Corrosive (Caustic) Poisons
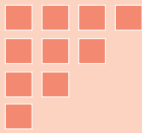
Mineral Acids (Inorganic Acids)

CAUSTICS

The term *caustic* is often mistakenly presumed to denote an alkali, while actually it has a much broader meaning and refers to any substance which is corrosive and burning in nature. Obviously this would include apart from alkalis, the more important group comprising acids (inorganic and organic). **Table 5.1** lists the common caustic substances encountered in toxicological practice, while **Table 5.2** mentions some ubiquitous commercial products containing corrosives.

All caustics are highly injurious locally and produce burns of varying severity and intensity. Three phases have been recognised—

1. **Acute inflammatory phase** (upto 7 days): Characterised by vascular thrombosis and cellular necrosis. The necrotic mucosa sloughs by the 3rd or 4th day, and an ulcer forms.
2. **Latent granulation phase** (1 to 2 weeks): The sloughed area of mucosa shows evidence of fibroplasia, and fresh granulation tissue is formed. Collagen starts to replace the granulation tissue by the end of the 1st week. Perforation is most common during this phase.
3. **Chronic cicatrisation phase** (after 2 weeks): There is formation of excessive scar tissue around the submucosa and muscularis mucosa resulting in contractures.

ACIDS

Acids are hydrogen containing substances that on dissociation in water produce hydronium ions. They are potent desiccants with the ability to produce coagulation necrosis of tissues on contact.* There is however eschar (slough) formation which has a self-limiting effect, minimising the extent of further damage. When a strong acid (especially inorganic) is dissolved in a solvent, an exothermic reaction ensues resulting in the emanation of heat which is referred to as the **heat of solution**.** This thermochemical reaction is postulated to be the cause for eschar formation. It is interesting to note that while generally speaking, the lower the pH of an acid the higher is its corrosive effect, it is not the pH alone which is the determinant of severity. For instance, lemon juice which has a very low pH of 2 is not corrosive in nature at all. More important determinants include molarity, concentration, and complexing affinity for hydroxyl ions.

Ingestion of acid causes more damage to the stomach than the oesophagus because the squamous epithelium of the latter is more resistant to acids, while it is just the opposite in the case of alkali ingestion where the columnar epithelium of the stomach is more resistant. However the current concept is that the minimal oesophageal damage in acid ingestion is more probably because of rapid oesophageal transit and limited

Table 5.1: Common Caustics

Acids		Alkalis	Others
Inorganic (Mineral)	**Organic**		
Boric	Acetic	Ammonia	Hydrogen peroxide
Chromic	Carbolic	Calcium hydroxide	Iodine
Hydrochloric	Citric	Potassium carbonate	Potassium permanganate
Nitric	Formic	Potassium hydroxide	Quaternary ammonium compounds
Phosphoric	Oxalic	Sodium carbonate	
Sulfuric		Sodium hydroxide	

* Hydrofluoric acid is a prominent exception, since it produces liquefactive necrosis.
** This should be differentiated from the heat of neutralisation which occurs when an acid is neutralised by any alkali (or vice versa). It is also an exothermic reaction.

Table 5.2: Commercial Products Containing Caustics

Acids	Alkalis	Others
Anti-rust preparations	Bleaches**	Antiseptics
Automobile batteries	Detergents	Cockroach powders
Disinfectants	Disc batteries	Deodorants
Metal cleaners and polishes	Jewellery cleaners	
Stain removers	Oven cleaners	
Toilet and drain cleaners*	Paint removers**	
Varnishes	Shampoos and soaps	
	Washing powders	

*Some drain cleaners contain alkalis such as sodium or potassium hydroxide
**Some bleaches and paint removers contain acids such as oxalic acid

penetrating ability, rather than from any special protective properties of the columnar epithelium. Acid burns of the stomach most commonly involve the antrum and pylorus.

INORGANIC ACIDS

Most of the information mentioned in the foregoing section actually pertains to inorganic or mineral acids, while corrosion is not really a prominent feature of organic acids. But on account of better absorption, organic acids display prominent systemic effects (*page no. 67*).

■ Sulfuric Acid

Synonym

Oil of vitriol; Oleum; Battery acid.

Physical Appearance

Sulfuric acid is a heavy, oily, colourless, odourless, non-fuming liquid (**Fig 5.1**). It is *hygroscopic*, i.e. it has great affinity for water with which it reacts violently, giving off intense heat.

Fig 5.1: Sulfuric acid

Sulfuric acid is mainly used in two forms:
- Commercial concentrated sulfuric acid is usually a 93–98% solution in water.
- Fuming sulfuric acid is a solution of sulfur trioxide in sulfuric acid.

Uses/Sources

Sulfuric acid is probably the most widely used industrial chemical in most parts of the world including India.
- It is used as a feedstock in the manufacture of a number of chemicals, e.g. acetic acid, hydrochloric acid, phosphoric acid, ammonium sulfate, barium sulfate, copper sulfate, phenol, synthetic fertilisers, dyes, pharmaceuticals, detergents, paint, etc.
- Storage batteries utilise sulfuric acid as an electrolyte.
- Sulfuric acid is also used in the leather, fur, food processing, wool, and uranium industries, for gas drying, and as a laboratory reagent.
- Sulfuric acid can be formed in smog from the photochemical oxidation of sulfur dioxide to sulfur trioxide and subsequent reaction with water. It is a major component of acid rain.

Usual Fatal Dose

About 20 to 30 ml of concentrate sulfuric acid. Deaths have been reported with ingestion of as little as 3.5 ml.

Toxicokinetics

Systemic absorption of sulfuric acid is negligible.

Mode of Action

Produces coagulation necrosis of tissues on contact.

Clinical Features

1. Burning pain from the mouth to the stomach. Abdominal pain is often severe.
2. Intense thirst. However, attempts at drinking water usually provoke retching.
3. The vomitus is brownish or blackish in colour due to altered blood (*coffee grounds vomit*), and may contain shreds of the charred wall of the stomach.

4. If there is coincidental damage to the larynx during swallowing or due to regurgitation, there may be dysphonia, dysphagia, and dyspnoea.
5. Tongue is usually swollen, and blackish or brownish in colour. Teeth become chalky white. There may be constant drooling of saliva which is indicative of oesophageal injury.
6. There is often acid spillage while swallowing with consequent corrosion of the skin of the face (especially around the mouth), neck, and chest (**Fig 5.2**). Burnt skin appears dark brown or black.
7. Features of generalised shock are usually apparent.
8. Renal failure and decreased urine output can occur after several hours of uncorrected circulatory collapse.
9. Because it is a strong acid, exposure to sulfuric acid may produce metabolic acidosis, particularly following ingestion. Acidosis may be due to severe tissue burns and shock, as well as absorption of acid.
10. Leukocytosis is common after exposure to strong mineral acids.
11. If perforation of stomach occurs, a severe form of chemical peritonitis can result. Rarely, perforation of duodenum (or even further down the small intestine) may occur.
12. If the patient recovers, there are usually long-term sequelae such as stricture formation which may lead to pyloric obstruction, antral stenosis, or an hour glass deformity of the stomach. The oesophagus may also be involved resulting in stenosis. There are indications of increased propensity for carcinomas.
13. Contact with the eyes can cause severe injury including conjunctivitis, periorbital oedema, corneal oedema and ulceration, necrotising keratitis, and iridocyclitis.
14. *Chronic Exposure* –
    a. Occupational exposure to sulfuric acid mist can cause erosion of teeth over a period of time, as also increased incidence of upper respiratory infections.

Fig 5.2: Sulfuric acid burns
(*Pic:* Dr Prateek Rastogi)

b. Sulfuric acid can react with other substances to form mutagenic and possibly carcinogenic products such as alkyl sulfates. Case reports suggest that chronic exposure to sulfuric acid fumes may be linked to carcinoma of the vocal cords and nasopharyngeal carcinoma. Occupational exposure to sulfuric acid may contribute to cases of laryngeal cancer.

Diagnosis

1. *Litmus test:* The pH of the saliva can be tested with a litmus paper to determine whether the chemical ingested is an acid or an alkali (turns red in acid, and blue in alkaline solution).*
2. Fresh stains in clothing may be tested by adding a few drops of sodium carbonate. Production of effervescence (bubbles) is indicative of an acid stain.
3. If vomitus or stomach contents are available, add 10% barium chloride. A heavy white precipitate forms which is insoluble on adding 1 ml nitric acid.

Treatment

1. Respiratory distress due to laryngeal oedema should be treated with 100% oxygen and cricothyroidotomy.**
2. Some authorities recommend administration of water or milk if the patient is seen within 30 minutes of ingestion (120–240 ml in an adult, 60–120 ml in a child). But no attempt must be made at neutralisation with alkalis, since the resulting exothermic reaction can cause more harm than benefit. Studies indicate that even administration of buffering agents such as antacids can produce significant exothermic reaction.
3. Remove all contaminated clothes and irrigate exposed skin copiously with saline. Non-adherent gauze and wrapping may be used. Deep second degree burns may benefit from topical silver sulfadiazine.
4. Eye injury should be dealt with by retraction of eyelids and prolonged irrigation for at least 15 to 30 minutes with normal saline or lactated Ringer's solution, or tap water if nothing else is available (**Box 5.1**). Anaesthetic agents and lid retractors may be necessary. It is desirable to continue with the irigation until normal pH of ocular secretions is restored (7.4), which can be tested with litmus paper or urine dipstick. Slit lamp examination is mandatory after decontamination, to assess the extent of corneal damage.
5. The following measures are **contraindicated**: oral feeds, induction of vomiting, stomach wash, and use of activated charcoal.
6. *Oral feeds:* Depends on degree of damage as assessed by early endoscopy. The following is a rough guide—
    a. Mild (grade I): may have oral feedings on first day.
    b. Moderate (grade II): may have liquids after 48 to 72 hours.
    c. Severe (grade III): jejunostomy tube feedings after 48 to 72 hours.

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* pH > 11.5 (alkali); pH < 2.0 (acid)
** Endotracheal intubation is contraindicated in the presence of laryngeal swelling.

Box 5.1: Management of Ocular Caustic Exposures

The most important first-aid measure for all patients with ocular caustic exposures should be immediate decontamination by irrigation, using copious amounts of water or any readily available safe aqueous solution such as normal saline, lactated Ringer's solution, or balanced salt solution. An ocular topical anaesthetic is usually required for effective irrigation. A complete irrigation must be done including the conjunctival recesses, internal and external palpebral surfaces, and corneal and bulbar conjunctiva. Lid retraction is invariably necessary. While concern has been expressed over the use of aqueous solutions for ocular irrigation in the case of exposure to substances which react with water leading to heat or mechanical injury (e.g. white phosphorus), there are hardly any documented case reports where this has actually happened.

The duration of ocular irrigation varies with the nature of exposure. After exposure to acids or alkalies, normalisation of the conjunctival pH is often suggested as a useful endpoint. A minimum of 2 litres of irrigant per affected eye should be used before any assessment of pH is done. After waiting for 5 to 10 minutes, the pH of the lower conjunctival fornix is checked. Thereafter, rechecks are done in cycles until the pH reaches 7.5 to 8.

Adjunctival treatment of ocular burns include application of topical antibiotic providing antistaphylococcal and antipseudomonal coverage, cycloplegics which not only reduce pain from ciliary spasm, but also decrease the likelihood of posterior synechiae formation, and the use of eye patches and systemic analgesics. Topical anaesthetic agents are not desirable. Topical steroids may help lessen the inflammation, but can interfere with healing and so must not be used for more than the first 7 days.

In every case of caustic ocular exposure, consultation with an ophthalmologist is essential after administration of first-aid and decontamination, to assess visual acuity, and to undertake slit lamp examination for detecting corneal damage. It may take 48 to 72 hours after the burn to assess correctly the degree of ocular damage. The basis of such an evaluation is the size of the corneal epithelial defect, the degree of corneal opacification and extent of limbal ischaemia.
- Grade 1: Corneal epithelial damage; no ischaemia.
- Grade 2: Cornea hazy; iris details visible, ischaemia less than one-third of limbus.
- Grade 3: Total loss of corneal epithelium; stromal haze obscures iris details; ischaemia of one-third to one-half of limbus.
- Grade 4: Cornea opaque; iris and pupil obscured, ischaemia affects more than one-half of limbus.

7. Administration of steroids has been shown to delay stricture formation (in animals) when given within 48 hours of acid ingestion, but the practice is generally not recommended because of increased risk of perforation.
   a. In case it is embarked upon, the dosage recommended is 60 to 100 mg/day of prednisolone for the first 4 days, followed by 40 mg/day for the next 4 days, and finally 20 mg/day for the subsequent 7 to 10 days. In children, the appropriate dose is 2 mg/kg/day.
   b. Alternatively 0.1 mg/kg of dexamethasone or 1 to 2 mg/kg of prednisone can be given for 3 weeks and then tapered off.
8. Administer antibiotics only if infection occurs. Prophylactic use is not advisable unless corticosteroid therapy is being undertaken.
9. Since there is often severe pain, powerful analgesics such as morphine may have to be given.
10. The use of flexible fibreoptic endoscopy is now standard practice in the first 24 to 48 hours of ingestion to assess the extent of oesophageal and gastric damage. If there are circumferential 2nd or 3rd degree burns, an exploratory laparotomy should be performed. If gastric necrosis is present, an oesophagogastrectomy may have to be done.
11. Emergency laparotomy is mandatory if there is perforation or peritonitis.
12. If the patient recovers, there may be long-term sequelae such as stenosis and stricture formation.* Follow-up is therefore essential to look for signs of obstruction—

nausea, anorexia, weight loss. Surgical procedures such as dilatation, colonic bypass, and oesophagogastrostomy may have to be undertaken.

Autopsy Features

1. Corroded areas of skin and mucous membranes appear brownish or blackish. Teeth appear chalky white.
2. Stomach mucosa shows the consistency of wet blotting paper.
3. There may be inflammation, necrosis, or perforation of the GI tract (**Fig 5.3**).

Fig 5.3: Sulfuric acid ingestion—perforation of GIT with peritonitis
(*Pic:* Dr Prateek Rastogi)

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* Some authorities recommend prophylactic bouginage to prevent stricture formation. Some gastroenterologists utilise a "string marker" to keep the lumen open; others employ an intraluminal splint (silastic tubing) as an initial prosthesis.

Forensic Issues

- Accidental poisoning may arise from mistaken identity since sulfuric acid resembles glycerine and castor oil. It is therefore imperative that it is stored in a distinctive bottle, clearly labelled, and kept in a safe place.
- Sulfuric acid is a rare choice for either suicide or homicide.
- In addition to routine viscera and body fluids, a portion of corroded skin should be cut out, placed in rectified spirit or absolute alcohol and sent for chemical analysis. Stained clothing must also be sent (preservative not necessary).
- Vitriolage:
    ❖ This term refers to the throwing of an acid on to the face or body of a person in order to disfigure or blind him (**Fig 5.4**). The motive is usually revenge or jealousy.
    ❖ Though sulfuric acid is commonly used (hence the term *vitriolage* which is derived from "oil of vitriol"), other acids are also employed. In fact any corrosive which is easy to hand may be used, including organic acids, alkalis, and irritant plant juices.
    ❖ Going by newspaper reports, vitriolage is a fairly common crime in India, though it is regarded as a serious offence (*grievous hurt*), and carries stiff punishment.*

■ Nitric Acid

Synonym

Aqua fortis; Azotic acid; Engraver's acid; Hydrogen nitrate.

Physical Appearance

Nitric acid is a colourless or yellowish fuming liquid (**Fig 5.5**) with an acrid, penetrating odour. It is essentially a solution of nitrogen dioxide (NO_2) in water and is available commercially in several forms.

Uses/Sources

- Nitric acid releases oxides of nitrogen into the air upon exposure to light. Therefore exposure to nitric acid potentially involves exposure to oxides of nitrogen, especially nitrogen dioxide.

Fig 5.4: Victim of vitriolage

Fig 5.5: Nitric acid

- Nitric acid is formed in photochemical smog from the reaction between nitric oxide and hydrocarbons. Individuals living in heavily polluted areas may receive chronic inhalation exposure to nitric acid.
- Workers in the following professions may be exposed to nitrogen oxides or nitric acid: glassblowing, engraving and electroplating, underground blasting operations, farming (silage and fertilisers), welding, fire fighting, and industrial chemistry.

Usual Fatal Dose

- About 20 to 30 ml.

Toxicokinetics

Systemic absorption is negligible.

Mode of Action

Nitric acid is a powerful oxidising agent and reacts with organic matter to produce trinitrophenol, liberating nitrogen monoxide (*xanthoproteic reaction*). Corrosion is less severe when compared to sulfuric acid.

Clinical Features

The general picture is the same as in the case of sulfuric acid, with the following differences:
1. Corroded areas appear yellowish due to xanthoproteic reaction (**Fig 5.6**). Stains on clothing and teeth also appear yellowish.
2. More severe eructation and abdominal distension due to gas formation.
3. Perforation of GI tract is less common.
4. Inhalation of fumes can produce coughing, rhinorrhoea, lacrimation, dyspnoea, and pulmonary oedema.

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* See page no. 44 for a more detailed discussion on grievous hurt.

Fig 5.6: Xanthoproteic reaction

Diagnosis

1. *Litmus test:* (*page no. 41*).
2. Drop a small piece of copper into the stomach contents and heat it. Pungent, dark brown heavy fumes will emanate if nitric acid is present in sufficient concentration.

Treatment

Same as for sulfuric acid. Respiratory distress is present more often and requires special attention.

Autopsy Features

1. Corroded areas of skin, teeth, and mucous membranes appear yellowish. Stains on clothing also show yellowish discolouration.*
2. Gastrointestinal perforation is less common.

Forensic Issues

Same as for sulfuric acid. Mistaking it for glycerine or castor oil, however is rare because it is a fuming liquid.

■ Hydrochloric Acid

Synonyms

Muriatic acid; Spirit of salts.

Physical Appearance

Hydrochloric acid is a colourless, fuming liquid which may acquire a yellowish tinge on exposure to air (**Fig 5.7**). It is actually hydrogen chloride in water.

Uses

- Bleaching agent (less than 10% HCl)
- Dyeing industry
- Metal refinery
- Flux for soldering
- Metal cleaner, drain cleaner
- Laboratory reagent.

Fig 5.7: Hydrochloric acid

Usual Fatal Dose

- About 30 to 40 ml.

Diagnosis

1. *Litmus test:* (*page no. 41*).
2. If an open bottle of concentrate ammonia solution is placed near the stomach contents or vomitus, copious white fumes of ammonium chloride will emanate. Though normal stomach contents contain hydrochloric acid, this is usually too dilute (0.2 to 0.5%) to vitiate the value of this test.

   The rest of the information on HCl is practically the same as for H_2SO_4, except that corroded areas are more likely to be greyish, and symptoms are generally less severe. But respiratory manifestations are more pronounced.

■ Hydrofluoric Acid

Physical Appearance

Hydrofluoric acid is a colourless, fuming liquid. It is a unique acid, in that most of its toxicity is due to the anion, fluoride, and not to the cation, hydrogen. Most acids cause burns and necrosis from liberated hydrogen ions. Undiluted hydrofluoric acid is a strong acid. Upon dilution, hydrofluoric acid is only weakly acidic at 0.1M.

Uses

- Industry:
  - ❖ 90% solution: petroleum refining, pharmaceutics, and germicides.
  - ❖ 10% solution: tanning, glass and metal etching, and rust removal.

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* To differentiate this from stains produced by iodine, apply ammonia solution. Iodine stains will be decolourised, while those due to nitric acid will deepen in intensity and turn to orange.

- Laboratory chemical.
- Window cleaning.

Usual Fatal Dose

- Unclear, but is probably in the range of 10 to 15 ml.

Toxicokinetics

Ingestion of hydrofluoric acid may be associated with significant systemic absorption and manifestations such as hypocalcaemia, acidosis, and shock.

Mode of Action

Hydrofluoric acid burns result in severe progressive tissue and bone destruction, and excruciating pain. Unlike other inorganic acids, hydrofluoric acid rapidly traverses the skin barrier and invades deeper tissue planes. The fluoride ion then proceeds to affect tissue integrity and metabolism in 3 ways:

1. Liquefactive necrosis.
2. Decalcification and destruction of bone.
3. Production of insoluble salts—calcium and magnesium fluoride.
   These effects result in hypocalcaemia and hypomagnesaemia.

Clinical Features

1. Hydrofluoric acid burns can range in severity from 1st to 3rd degree. Characteristic features include severe pain and a predilection for the sub-ungual area (i.e. under the nail) of fingers with destruction and loss of nail, and sometimes even the entire terminal phalanx.
   a. A hallmark of dermal exposure to low concentrations of hydrofluoric acid is pain that is out of proportion to the physical examination. Severe pain may be obvious, while only erythema of the exposed skin is observed.
   b. Hydrofluoric acid readily penetrates the skin and mucous membranes, causing deep tissue destruction (**Fig 5.8**). Severity and timing of effects depends on the concentration, duration of exposure, and penetrability of the exposed tissue; pain may be delayed.
   c. The fluoride ion may cause decalcification and corrosion of bone beneath the area of dermal burn. Bone destruction is extremely painful.
2. Inhalation causes severe throat irritation, cough, dyspnoea, cyanosis, lung injury and noncardiogenic pulmonary oedema.
3. Ingestion is associated with severe, burning pain followed by retching and vomiting. There is often haemorrhagic gastritis and frank haematemesis.
4. Systemic fluoride toxicity from ingestion or dermal or injection exposure to hydrofluoric acid may result in severe hypocalcaemia, hypomagnesaemia, hyperkalaemia, metabolic acidosis, and cardiac arrhythmias (QTc prolongation, torsade de pointes, and ventricular arrhythmias including bigeminy, ventricular tachycardia, refractory ventricular fibrillation, and cardiac arrest). Cardiac toxicity generally manifests within six hours of an exposure.

Fig 5.8: Hydrofluoric acid burn

Treatment

1. Patients with a history of significant exposure or with significant symptomatology should be admitted to an intensive care unit and observed with continuous ECG monitoring for a minimum of 24 to 48 hours.
2. Obtain at least hourly serum electrolytes including serial total or ionised calcium, magnesium, and potassium levels. Total calcium may not reflect true hypocalcaemia, but usually has a more rapid turnaround. Therapy should be directed toward signs and symptoms of toxicity. Serum fluoride level may be used to confirm hydrofluoric acid exposure.
3. Obtain serial ECGs looking for signs of hypocalcaemia (prolonged QTc interval) and hyperkalaemia (peaked T waves). Institute continuous cardiac monitoring.
4. Several methods have been suggested to deactivate the injurious fluoride ion which is responsible for most of the serious manifestations of hydrofluoric acid poisoning. The most widely accepted method is outlined below:
   ❖ *First Aid:*
   – Wash burnt areas copiously with water, preferably under a shower or tap for at least 15 to 30 minutes.
   – Soak the affected portion in iced solution of 25% magnesium sulfate, or any high molecular weight quaternary ammonium compound such as benzethonium or benzalkonium.*
   – If hydrofluoric acid has been ingested, attempt immediate administration of a fluoride binding substance. Options include milk (one-half to one glassful), chewable calcium carbonate tablets, or milk of magnesia. Avoid large amounts of liquid, since this may induce vomiting.
   – Stomach wash is risky and best avoided. But it may

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* The ice retards diffusion of fluoride ion, while the magnesium or quaternary ammonium compound interacts with the ion to prevent invasion of deeper tissues.

be done if spontaneous vomiting has not occurred, and the time between ingestion and treatment is less than 90 minutes. Addition of 10% calcium gluconate to the lavage fluid may provide some free calcium to bind the fluoride.

– Inhalation injury is treated by removing the victim from the scene into fresh air, followed by decontamination of the clothes and skin. The patient should be subsequently observed for signs of laryngeal oedema, pneumonitis, and pulmonary oedema.

– Ocular exposure should be treated with copious irrigation of the eye for at least 30 minutes. Local ophthalmic anaesthetic drops may be instilled to obtain patient compliance for the prolonged irrigation. The pH of the eye fluid should be periodically checked with litmus paper, and irrigation is continued until it is normal. Subsequently, an ophthalmic consultation is mandatory.

❖ *Topical Skin Therapy:*
  – For exposure to weak solutions of hydrofluoric acid (less than 20%), local application of 2.5% calcium gluconate gel is the treatment of choice. Since this gel is not available in India, it has to be prepared by the physician by mixing 3.5 grams of calcium gluconate powder with 150 ml of a water soluble lubricant such as K-Y jelly, which will result in a 2.5% gel. Repeated applications may be necessary.
  – After applying the gel, an occlusive barrier can be used (e.g. vinyl gloves or plastic wrap).
  – For skin lesions resulting from exposure to concentrate hydrofluoric acid, local infiltration (injection) of 10% calcium gluconate is necessary (0.5 ml/cm² of skin, with a 30 gauge needle).
  – Do not inject calcium chloride into the tissues locally, since it is itself a corrosive and can accentuate tissue damage. Similarly, local infiltration of magnesium sulfate or calcium gluconate are also not recommended today by several clinicians, though there are a few who still advocate their use. If it is decided to be done, a 10% solution should be injected with a 30 gauge needle in amounts no greater than 0.5 ml/cm² into and around the affected area.

❖ *Intra-arterial Therapy:*
  – Hydrofluoric acid burns often occur on the fingers where intradermal calcium injections can be hazardous. For these cases, an intra-arterial infusion regimen has been suggested:
    - Estimate the serum calcium, magnesium, and phosphorus levels, as well as the prothrombin time (PT), and partial thromboplastin time (PTT).
    - The appropriate artery is cannulated with a 20 gauge, 4 French or 5 French arterial catheter. If fingers are involved, the brachial artery is cannulated; if the foot is involved, the femoral artery is cannulated.

- It is imperative to admit the patient to the ICU for arterial pressure wave monitoring.
- An intra-arterial infusion of 10 ml of 10% calcium chloride diluted with 40 ml of normal saline is given over 4 hours.
- The arterial wave form is checked hourly and the arterial line is flushed with heparinised saline.
- After infusion of the calcium chloride solution, flush out the tubing with 10 ml of normal saline over a 15 minute period.
- Catheter clotting can be prevented by adding 500 units of heparin to the infusion mixture. In case such clots do occur, they can be lysed with 5000 units of urokinase.
- At the end of 4 hours, the affected extremity is checked for residual pain and tenderness. If this persists, repeat the infusion.
- Estimate serum calcium, magnesium, phosphorus, PT, PTT, 1 hour after completion of the infusion. If the magnesium level has fallen by 0.3 mg% (or falls below 1.7 mg%), an IV infusion of magnesium sulfate is begun using 1.015 mEq/hr to 4.06 mEq/hr.
- The process of 4 hours of infusion followed by 4 hours of rest is repeated until there is no residual tenderness to gentle pressure.

❖ *Intravenous Therapy:*
  – Regional intravenous perfusion of 5 ml of 10% calcium gluconate in 20 ml of normal saline is reported to give immediate relief of pain in a burnt extremity.
  – Ingestion of hydrofluoric acid resulting in hypocalcaemia or hypomagnesaemia may require multiple IV doses of calcium gluconate and magnesium sulfate (together with repeated cardioversion for ventricular fibrillation) until normal blood calcium and magnesium levels are achieved.
  – Patients should be monitored for laboratory and/or ECG evidence of hyperkalaemia after ingestion of hydrofluoric acid. Fluoride-induced hyperkalaemia, once developed, may be irreversible. Therapeutic intervention to prevent development of elevated serum potassium is essential. Quinidine has been shown to be effective in preventing the K+ efflux from cells and preventing cardiotoxicity. Intravenous calcium has no effect on circulating potassium levels, but it antagonises cardiac toxicity in patients demonstrating cardiac signs and/or symptoms of hyperkalaemia. Administer intravenous sodium bicarbonate to shift potassium intracellularly.

5. *Ventricular arrhythmia:* Evaluate for and treat hypocalcaemia, hypomagnesaemia and hyperkalaemia. Because amiodarone has potassium channel blocking effects, it may be the preferred antiarrhythmic in the setting of hydrofluoric acid poisoning.

6. Systemic acidosis should be corrected with appropriate IV doses of sodium bicarbonate.

7. Hypotension should be managed with volume expansion and vasopressors.

Autopsy Features

Essentially the same as for sulfuric or hydrochloric acid. There is evidence of more severe tissue destruction.

Forensic Issues

Most cases are due to accidental exposure at the work place.

■ Phosphoric Acid

Physical Appearance

Phosphoric acid is a clear, colourless, odourless, unstable, orthorhombic crystalline solid, or a syrupy liquid with a pleasing acid taste (when suitably diluted).

Uses

- Phosphoric acid is used as a flavouring material, an acidulant, and a synergistic antioxidant and sequestrant in carbonated beverages.
- Phosphoric acid is also utilised in dental ceramics, for water treatment, in engraving processes, for the rust-proofing of metals prior to painting, for metal pickling, in the coagulation of rubber latex, and as an analytic reagent in laboratories.
- Dilute phosphoric acid has been used in preparations for the management of nausea and vomiting, and in Great Britain, a technical grade of orthophosphoric acid in water, 1:330, is an approved disinfectant for foot-and-mouth disease.

Usual Fatal Dose

- About 300 to 500 ml.

Clinical Features

1. Corrosion of GI tract, sour acrid taste, vomiting, abdominal pain, bloody diarrhoea, acidosis, convulsions, coma, death.
2. Hyperphosphataemia and hypocalcaemia are common findings. There may also be hypomagnesaemia.

Diagnosis

Add 2 ml of ammonium molybdate solution, followed by 1 ml of nitric acid to a small quantity of gastric aspirate and heat for 1 minute. A canary yellow precipitate is specific for phosphoric acid.

Treatment

On general lines, as for other corrosives, (*see under "Sulfuric acid"*). Convulsions can be managed with benzodiazepines or barbiturates. Hyperphosphataemia (if severe) can be treated by haemodialysis.

■ Boric Acid

Boron is an inorganic, non-metallic element, the derivatives of which include the following:
- Boric acid—5.55% boron

- Sodium borate, biborate, pyroborate, and tetraborate—21.50% boron
- Boron oxide, trioxide, and sesquioxide, boric anhydride, boric oxide, borax, and tincal—33% boron
- Sodium perborate—7.03% boron
- Sodium metaborate—16.44% boron
- Magnesium perborate—14% boron

Physical Appearance

- Boric acid is a white powder or crystalline solid.
- Sodium tetraborate anhydrous is a light grey odourless solid.
- Sodium tetraborate decahydrate and pentahydrate are white odourless, crystalline solids.

Uses

1. *Medical*
   a. Borates have been used in a wide variety of pharmaceutical preparations including medicated powders, skin lotions, mouthwash, toothpaste, and eyewash solutions.
   b. Boric acid and borax are used in cosmetics and oral hygiene products.
   c. Boric acid has been used as a preservative for urine samples.
2. *Household*
   a. Borates have been used as a home remedy for diaper rash and oral discomfort in infants.
   b. Boric acid powder mixed with flour or sugar is used to kill ants and cockroaches in the home. Commercially available insecticides and herbicides used in the home may contain borates.
3. *Industrial*
   a. Borates are used in making heat-resistant glass, glazes, enamels, fire-resistant materials and agents, paints, photographic agents, and as insecticides and herbicides.
   b. They are used to preserve wood, and also as flame retardants in wood and textiles.

Usual Fatal Dose

- About 15 to 30 grams.

Toxicokinetics

Absorption occurs through GI tract when ingested (though quite slowly), through lungs when inhaled (especially in the form of pentaborate gas), and possibly also through skin.

Serum and urine borate levels do not correlate well with the clinical state, though symptoms of toxicity generally occur only when blood levels exceed 100 to 150 mg/ml.

Clinical Features

1. Acute Poisoning—
   ❖ GIT: nausea, vomiting (bluish green), haematemesis, diarrhoea (bluish green), epigastric pain.
   ❖ CNS: headache, tremor, convulsions, delirium, coma.
   ❖ CVS: hypotension, shock.
   ❖ Renal: oliguria, anuria, renal failure.
   ❖ Acid-base: metabolic acidosis.

❖ Dermal: erythema, desquammation, and exfoliation (*"boiled lobster syndrome"*) (**Fig 5.9**).

2. Chronic Poisoning—

Usually seen in children who have been treated with a boric acid preparation for diaper rash. Apart from skin manifestations, there may be oliguria, renal tubular necrosis, and renal failure. There may also be hypo- or hyperthermia, alopecia, and hypoplastic anaemia. Fatalities have been reported.

Diagnosis

1. *Urine test:* One drop of the patient's urine acidified with HCl is added to turmeric paper. Development of a brownish red colour is suggestive of boric acid or borates.
2. Blood borate levels may be useful to establish the diagnosis of borate intoxication.
3. Monitor renal function tests, cardiovascular status, fluid and electrolyte balance in symptomatic patients.

Treatment

1. Induction of emesis or gastric lavage.
2. Administration of a cathartic (e.g. magnesium sulfate).
3. *Forced diuresis:* Rule out renal damage. Urinary elimination may be enhanced by administration of 0.45% saline in 5% dextrose in water IV, along with a diuretic (e.g. furosemide 1 mg/kg, upto 40 mg/dose). Urine flow should be maintained between 3 to 6 ml/kg/hour.
4. Peritoneal or haemodialysis.
5. *Supportive measures:* Correction of shock, convulsions, etc.
6. Skin exposure must be treated by washing the affected area several times with soap and water. Eye contact is treated by irrigation with water for at least 20 minutes. Ophthalmological consultation may be required.

Autopsy Features

1. Gastric mucosa is often bright red in colour.
2. Blood may have the cherry red colour commonly associated with carbon monoxide poisoning.
3. Characteristic skin lesions (*boiled lobster syndrome*) may be present.
4. It is advisable to include one cerebral hemisphere for chemical analysis apart from the routine viscera, since the poison is often concentrated in the brain.

Fig 5.9: Boric acid powder burn
(*Pic:* Dr S Senthilkumaran)

Forensic Issues

Almost all the reported cases have been accidental or iatrogenic in nature.

■ Chromic Acid

It is a derivative of the metal chromium, being one of the hexavalent chromium compounds, while bivalent and trivalent compounds include chromic oxide, chromic phosphate, and chromic sulfate.

Clinical Features

The hexavalent compounds (chromium trioxide, the anhydride of chromic acid, chromates, dichromates, and polychromates) are corrosive in nature, and can cause oral burns and tissue ulceration.

Symptoms include vomiting, diarrhoea, GI bleeding, and manifestations of renal failure. Other features include intense gastrointestinal irritation or ulceration and corrosion, epigastric pain, vertigo, fever, muscle cramps, haemorrhagic diathesis, intravascular haemolysis, circulatory collapse, peripheral vascular collapse, liver damage, acute multisystem shock, coma, and even death, depending on the dose.

Bivalent and trivalent compounds are relatively non-toxic. Trivalent chromium is in fact an essential nutrient for glucose metabolism. However, prolonged chromic phosphate therapy in the form of intraperitoneal administration for early stage ovarian carcinoma can result in bowel perforation or obstruction.

Occupational exposure to hexavalent chromium has been associated with an increased incidence of lung cancer.

Treatment

Chelation therapy with BAL may be helpful. Haemodialysis and exchange transfusion have also been successfully tried. Dimercapto-propane-sulfonic acid (DMPS) is a new drug with promising results.

Dichromates (sodium, potassium, and ammonium) are important hexavalent chromium compounds which display some significant differences when compared to other chromium compounds. Ingestion of dichromates can cause vertigo, abdominal pain, vomiting, convulsions, severe coagulopathy, intravascular haemolysis, and hepatorenal failure.

Chronic inhalation of chromate dust causes conjunctivitis, lacrimation, ulceration of nasal septum, and respiratory cancer.

Treatment of acute dichromate poisoning involves administration of BAL and large doses of ascorbic acid (IV). Stomach wash can also be done with a solution of ascorbic acid. There are reports of favourable results with N-acetylcysteine.

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Chapter 5 ◆ Mineral Acids (Inorganic Acids)
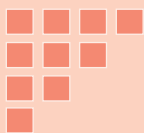
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Organic Acids

Organic acids differ from inorganic acids in two major respects:
- They are weaker in action locally.
- They are better absorbed into the systemic circulation, and therefore have more powerful remote action.

■ Acetic Acid

Synonyms

Ethanoic acid; Ethylic acid; Methane carboxylic acid; Pyroligenous acid.

Physical Appearance

Colourless, volatile liquid with a characteristic pungent odour. At 10^0C to 15^0C, the acid occurs in crystalline form (glacial acetic acid).

Uses

- 60% solution: printing, dyeing, plastics, and rayon manufacturing, hat making.
- 6 to 40% solution: disinfectant, pharmaceuticals, hair wave neutraliser.
- 4 to 5% solution: vinegar (**Fig 6.1**).

Usual Fatal Dose

About 50 to 100 ml of concentrate acetic acid.

Fig 6.1: Pure vinegar

Mode of Action

In concentrated form, acetic acid is a corrosive (albeit mild), while in dilute form it acts as an irritant. Systemic absorption leads to haemolysis, haemoglobinuria, and renal failure.

Clinical Features

A. **Local effects**: Mild grey-brown corrosion with concentrated acid. Chronic exposure to fumes causes darkening of skin.
B. **Ingestion**: Pain, haematemesis, haemolysis, diarrhoea, disseminated intravascular coagulation, and renal failure (**Table 6.1** lists some common nephrotoxic poisons).
C. **Inhalation**: Bronchopneumonia, pulmonary oedema. Chronic exposure leads to erosion of front teeth, chronic rhinitis, pharyngitis, and bronchitis.

Diagnosis

1. Odour of vinegar in the vicinity of the patient.
2. When a small quantity of stomach contents is gently heated with ethyl alcohol and 1 drop of sulfuric acid, there is emanation of a fruity odour.

Table 6.1: Nephrotoxic Poisons
Heavy metals
Arsenic, bismuth, chromium, copper, lead, mercury, platinum, thallium
Solvents
Carbon tetrachloride, toluene, trichloroethylene
Glycols
Diethylene glycol, ethylene glycol, propylene glycol
Antimicrobials
Acyclovir, aminoglycosides, amphotericin, cephalosporins, fluoroquinolones, polymyxins, sulfonamides, tetracycline
Non-steroidal anti-inflammatory drugs
Anti-arthritic drugs
Antineoplastic drugs
Miscellaneous
Aluminium phosphide, chelating agents, paraquat

Treatment

This is on general lines, with special attention paid to correction of acidosis and renal damage. Stomach wash can be done with caution if the patient is seen early.

Autopsy Features

1. Odour of vinegar around the mouth and in the gastric contents.
2. The affected areas of skin and mucosa may be greyish brown.
   Viscera meant for chemical analysis must not be preserved with rectified spirit. Saturated saline should be used instead.

Forensic Issues

Most cases of poisoning are accidental. There are however occasional reported cases of suicide.

It is pertinent to mention here that if paraldehyde meant for therapeutic use is stored improperly (e.g. in badly stoppered, transparent glass containers), it degrades into acetic acid with resultant iatrogenic poisoning when administered to a patient.

■ Formic Acid

Synonyms

Aminic acid; Formylic acid; Hydrogen carboxylic acid; Methanoic acid.

Physical Appearance

Colourless liquid with a pungent, penetrating odour.

Uses/Sources

- Formic acid is a natural constituent of some fruits (apples, pears, plums, apricots), nuts, and dairy products. Some wines may contain formic acid.
- Formic acid is an important toxic metabolite produced in methanol poisoning.
- *Industrial uses—*
  - ❖ Component of descaling and stain-removing agents
  - ❖ Reducing agent in wool/textile dyeing
  - ❖ Leather tanning, plumping and dehairing product for hides
  - ❖ Coagulation of latex rubber
  - ❖ Electroplating
- *Agricultural uses—*
  - ❖ Animal feed additive
  - ❖ Food preservative, flavour enhancer: Formic acid has been used as a food additive in small amounts (e.g. 0.1 to 6 ppm) in ice cream, ices, candy, and baked goods.
- *Therapeutic uses—*
  - ❖ Removal of tattoos
  - ❖ Component in some external preparations for the treatment of musculoskeletal and joint disorders.

Usual Fatal Dose

Ingestions of less than 10 grams in children have resulted in oropharyngeal burns; no deaths were reported. Solutions of 10% or less are generally considered noncorrosive. Ingestions between 5 and 30 grams may result in symptomatic burns of the gastrointestinal tract and haematemesis, but death is unusual. Ingestions between 45 to 200 grams often result in death within the first 36 hours post-ingestion.

Toxicokinetics

Formic acid is readily absorbed from the GI tract.

Mode of Action

- Coagulative necrosis type of corrosive action on the GI mucosa.
- Damages clotting factors and causes haemolysis leading to acute renal failure.
- At the cellular level, it has an inhibitory action on aerobic glycolysis with consequent diminution of ATP synthesis.

Clinical Features

1. **GIT**: Burning pain, salivation, vomiting, mucosal corrosion and ulceration, haematemesis.
2. **CNS**: Drowsiness, weakness, coma. Pupils are dilated.
3. **CVS**: Tachy/bradycardia, hyper/hypotension.
4. **Blood**: Haemolysis, DIC.
5. **RS**: Acute respiratory distress, aspiration pneumonitis, "shock lung".
6. **Metabolic**: Acidosis, acute tubular necrosis, shock, and death.
7. **Skin**: Erythema, blisters.

Treatment

1. *First-aid* : Immediate dilution, by administering milk.
2. Induction of emesis, gastric lavage, and use of activated charcoal are all **contraindicated**.
3. High dose folinic acid (1 ml/kg IV bolus, followed by 6 doses of 1 mg/kg IV at 4 hourly intervals) is recommended by some investigators, since it is supposed to enhance formate degradation by the liver.
4. Supportive measures, with particular emphasis on dialysis, exchange transfusion, intubation, ventilatory support, and correction of metabolic acidosis and renal failure.

Autopsy Features

Blackish corrosion of GI mucosa, pulmonary oedema.

Forensic Issues

- Accidental and suicidal poisoning with formic acid is relatively common in those areas where the chemical is easily available, for instance in Kerala where manufacturing rubber is a major industry.
- Methanol poisoning (*page no. 193*), is associated with formic acid toxicity, since it is metabolised in the body to produce formaldehyde and formic acid.

■ Carbolic Acid

Synonyms

Hydroxybenzene; Phenol; Benzenol; Phenyl alcohol.

Physical Appearance

- Colourless, needle-like crystals which turn pink and liquefy when exposed to air. It is a coal tar derivative (creosote).
- Commercial phenol is a brownish liquid containing impurities like cresol (**Fig 6.2**). Household phenol (often sold as phenyle) contains 5% phenol in water. It has a characteristic, aromatic odour ("hospital odour").
- Derivatives:
  - ❖ Catechol, cresols, menthol, resorcinol, thymol: *Toxic*
  - ❖ Hexyl resorcinol, naphthol: *Less Toxic*
  - ❖ Tannic acid: *Least Toxic.*

Uses

Carbolic acid was introduced as a disinfectant in the **19th century** by **Lemaire**, and quickly became popular ever since **Lord Lister** (**Fig 6.**3) advocated its use in surgery for asepsis. Even today it is popular as a hospital and household disinfectant along with its related counterpart **Lysol**,* even though several safer and more effective alternatives have been developed including cetrimide, chlorhexidine (**Savlon**), chloroxylenol, parachlorometaxylenol (**Dettol**), terpineol, and xylenol.

The various uses of carbolic acid are as follows

- *Antiseptic and disinfectant:* especially for sterilising floors, walls, furnishings, glassware, and instruments.
- *Preservative:* Phenol is a commonly used preservative in injectable medications, e.g. glucagon, pethidine, neostigmine, quinidine, and epinephrine.
- *Pharmaceuticals*
- *Medical uses:*
  - ❖ "Face peel" in plastic surgery.
  - ❖ Neurolysis for spasticity (by injecting phenol solution into neuromuscular junctions).
  - ❖ Phenol is still used in preparations for treatment of localised skin disorders (Castellani's paint), and as a local anaesthetic.

Fig 6.2: Phenol

Fig 6.3: Lord Lister

Usual Fatal Dose

- Probable oral lethal dose is reported at 50 to 500 mcg/kg. Ingestion of 1 gram of phenol has caused death.
- 25 to 50 ml of household phenol can cause death. Fatalities have been reported even with much less quantities.
- The UFD for Lysol is 60 to 120 ml.

Toxicokinetics

Carbolic acid is rapidly absorbed through GI mucosa, lungs, and even intact skin. Dilution may actually increase absorption and enhance toxicity.

Mode of Action

Carbolic acid is actually a very mild corrosive, but has profound systemic effects after absorption. There is CNS depression, metabolic acidosis, and renal damage.

Clinical Features

1. **Acute Poisoning**
   a. *Local*: Skin or mucosal contact results in mild corrosion with hardening and whitish discolouration. However the white eschar (especially in the skin) drops off in a few days, leaving a brown stain. Locally there may be burning pain followed by tingling, numbness, and anaesthesia.
   b. *Systemic*:
      i.   GIT—Burning pain, vomiting.
      ii. CNS—Vertigo, convulsions, coma. Pupils are constricted.
      iii. RS—Tachypnoea, bronchospasm, pulmonary oedema.
      iv. CVS—Tachycardia, hypotension, cardiac arrhythmias

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* Protected trade mark in some countries, hence always use initial capital letter or face legal action! It consists of 50% cresol in saponified vegetable oil.

v. Blood—Haemolysis, methaemoglobinaemia.
vi. Metabolic—Hypothermia, with cold and clammy skin, metabolic acidosis.
vii. Hepatorenal—Oliguria, with scanty urine which turns greenish or brownish on exposure to air because of phenolic metabolites (hydroquinone and pyrocatechol). Later there is renal and hepatic failure.

Deaths have occurred even after skin contact with carbolic acid. **Table 6.2** lists the agents which can cause serious poisoning through dermal absorption.

2. Chronic Poisoning (*Phenol Marasmus*)

This was common in earlier days among medical personnel when phenol was routinely used as a skin disinfectant. It is characterised by anorexia, weight loss, headache, vertigo, dark urine, and pigmentation of skin and sclerae (*ochronosis).*

Diagnosis

1. Typical odour in the vicinity of the patient.
2. Urine collected and stored in a transparent container shows a gradual change in colour to brown or green (**Table 6.3** contains a list of poisons and drugs which discolour urine).
3. To 10 ml of urine, add 1 ml of 10% ferric chloride. A purple or blue colour which persists even on heating indicates phenol poisoning. Cresol is associated with green colour.
4. When 10 ml of urine is boiled with Millon's reagent,* a red colour is produced.

Treatment

1. Decontaminate skin by copious washing.
2. Stomach wash can be done preferably with sodium or magnesium sulfate solution.
3. Activated charcoal in the usual manner.
4. Treatment of methaemoglobinaemia (with methylene blue).
5. Convulsions can be managed with benzodiazepines or barbiturates.
6. Supportive measures.

Table 6.2: Substances Producing Serious Toxicity Through Dermal Absorption

Acrylamide
Aniline and derivatives
Arsenic compounds
Benzene
Chlorinated hydrocarbons
Cyanide and its salts
Formaldehyde
Hydrofluoric acid
Mercury compounds
Nitrates
Organic solvents
Pesticides—fumigants, fungicides, insecticides, and rodenticides
Phenol
Sulfides and sulfites
Toluidine

Table 6.3: Poisons/Drugs Which Discolour Urine

Urine Colour	Poison/Drug
Orange	Phenothiazines, rifampicin, phenolphthalein (*acidic urine*)
Red or Pink	Aminopyrine, aniline, ibuprofen, phenacetin, phenothiazines, phenytoin Anthraquinone, eosin, rhubarb (*alkaline urine*) Anisindione, beetroot (*acidic urine*)
Purple	Porphyrins Phenolphthalein (*alkaline urine*)
Reddish-brown	Chloroquine, ibuprofen, iron, sorbitol, phenacetin, phenothiazines, phensuximide, phenytoin, trinitrophenol Anisindione, methaemoglobin, metronidazole (*acidic urine*) Anthraquinone, levodopa, methyldopa (*alkaline urine*)
Brownish-black	Homogentisic aid, nitrobenzene, phenol, cresol, naphthol
Yellowish-brown	Furazolidone, nitrofurantoin, primaquine, sulfamethoxazole Anthraquinone, rhubarb (*acidic urine*)
Yellow	Fluorescin dye, phenacetin, riboflavin, trinitrophenol Quinacrine (*acidic urine*) Beetroot (*alkaline urine*)
Yellowish-orange	Aminopyrine, warfarin, carrots, vitamin A Anisindione, sulfasalazine (*alkaline urine*)
Greenish-blue	Chlorophyll Breath Mints (Clorets®), methylene blue, thymol, resorcinol, methocarbamol
Brownish-green	Cresol, phenol, methocarbamol, resorcinol

Autopsy Features

1. Distinct odour of phenol, especially around the mouth and in the stomach contents.
2. Corroded areas are at first white, but if death has been delayed they turn brownish (**Fig 6.4**).

Fig 6.4: Carbolic acid burns

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* Millon's reagent: Dissolve 10 gm mercury in 20 ml nitric acid. Dilute with an equal amount of distilled water. Allow to stand for 2 hours. Decant.

3. Gastric mucosa is greyish white, swollen, and hardened (leathery), but Lysol poisoning is asociated with soapy and soft mucosa.
4. Urine is greenish or brownish.

Forensic Issues

Most cases of poisoning are accidental in nature arising out of occupational exposure or therapeutic misuse. Formerly, suicidal ingestions were common. Poisoning with phenolic derivatives causes similar but usually less severe manifestations, and must be treated on the same lines as phenol.

■ Oxalic Acid

Synonyms

Ethanediolic acid; Dicarboxylic acid; Salt of sorrel.

Physical Appearance/Derivatives

Oxalic acid, the simplest dicarboxylic acid, is a potentially toxic chemical which is synthesised commercially and is also naturally present as a salt in many plants. Oxalic acid is a relatively strong acid, and forms a white, dihydrate precipitate.

Uses/Sources

- Oxalic acid occurs naturally in plants and vegetables such as wood sorrel (**Fig 6.5**), rhubarb (**Fig 6.6**), and spinach (**Fig 6.7**). Alkali extraction of sawdust and the metabolism of many moulds will also produce oxalic acid.
- Oxalic acid is used in paint, stain and varnish removers, rust and ink stain removers, and ceramics. It is also used in general metal and equipment cleaning, wood cleaning, process engraving, printing and dyeing, bleaching, textile finishing, leather tanning, and photography.

Usual Fatal Dose

About 15 to 30 grams of oxalic acid.

Fig 6.5: Wood sorrel

Fig 6.6: Rhubarb

Fig 6.7: Indian spinach

Mode of Action

Liquid oxalic acid has moderate corrosive action on skin and mucosa. Systemic absorption leads to hypocalcaemia, since it reacts with calcium in plasma, and insoluble calcium oxalate is precipitated which accumulates in the liver, kidneys, heart, lungs, and blood, and is excreted in the urine.

Clinical Features

1. Local:

Whitish or yellowish corrosion (mucosa), or discolouration (skin), with underlying congestion. The corroded mucosa is

often referred to as "scalded" in appearance. Production of acid haematin however can turn the mucosa blackish.

2. Systemic :

Vomiting and diarrhoea, followed by signs and symptoms of hypocalcaemia (**tetany**), characterised by tonic muscle spasms, cramping, and *accoucher's hand** *(Fig 6.8)*. There is often a positive *Trousseau's**(Fig 6.9)*, and *Chvostek's**** sign *(Fig 6.10)*. Pupils are usually dilated. Later there may be metabolic acidosis, ventricular fibrillation, and renal failure. Calcium oxalate crystals can be deposited in the liver resulting in hepatic necrosis and failure in severe cases. Milder cases may manifest as elevated serum liver enzymes.

Diagnosis

1. Demonstration of urinary oxalate crystals (**Fig 6.11**) which may occur either as monohydrates (prism or needle-like), or dihydrates (tent or envelope shaped).
2. Oxalic acid can be measured in the urine by colourimetry. The normal upper limit is 40 to 50 mg/24 hours.
3. Average serum oxalate concentration is said to be 1.4 mg/L.

Fig 6.8: Accoucher's hand

Fig 6.9: Trousseau's sign

Eliciting chvostek's sign

Begin by telling the patient to relax his facial muscles. Then stand directly in front of him, and top the facial nerve either just anterior to the earlobe and below the zygomatic arch or between the zygomatic arch and the corner of his mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity fo hypocalcemia

Fig 6.10: Chvostek's sign
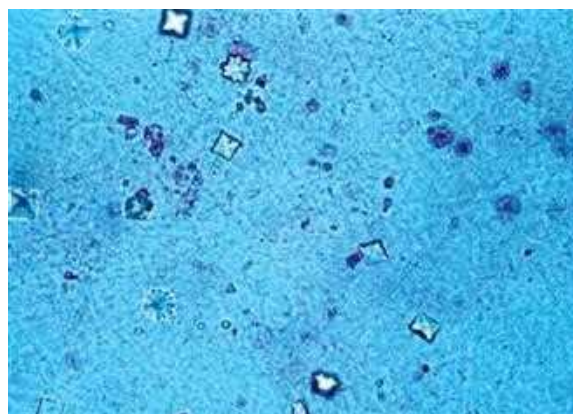
Fig 6.11: Calcium oxalate crystals
(*Pic:* Dr S Senthilkumaran)

Treatment

1. Stomach wash with calcium gluconate or lactate solution.
2. Calcium gluconate IV (10 ml, 10% solution).
3. Dialysis or exchange transfusion for renal failure.
4. Affected skin or eye should be washed copiously with water.

Autopsy Features

1. "Scalded" mucosa of GI tract (especially stomach). Sometimes there is a brown or black colour due to acid haematin. Crystals of calcium oxalate may be demonstrated in scrapings of the mucosa, (examine with polarising mico-scope).
2. Whitish or yellowish discolouration of corroded areas.
3. Microscopic evidence of renal damage.

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* Due to carpopedal spasm.
** Trousseau's sign: Spasm resulting from pressure applied to nerves and vessels of upper arm.
*** Chvostek's sign: Spasm of facial muscles following a tap on the facial nerve area.

Forensic Issues

- Most cases of oxalic acid or oxalate poisoning result from accidental causes, e.g. mistaking the substance for Epsom salt, sodium bicarbonate, etc. Accidental poisoning may also result from excessive ingestion of certain vegetables rich in oxalates (rhubarb leaves,* sorrel, etc.). Even tea is said to contain significant amounts of oxalate.
- Chronic consumption of oxalic acid can lead to renal calculi with consequent renal colic.
- Occasional cases of suicide and homicide with oxalic acid have been reported.

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* The stalk of a rhubarb plant is non-toxic and edible.
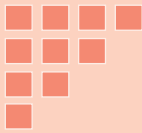
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Alkalis and Other Caustics

ALKALIS

Alkalis commonly encountered in poisoning include ammonia (usually in the form of ammonium hydroxide), carbonates of sodium and potassium, and hydroxides of sodium, potassium, and calcium. Sodium hypochlorite is also increasingly being implicated.

■ Physical Appearance

Most of these occur as white powders or colourless solutions. Ammonia gas is colourless with a pungent, choking odour.

Uses

- *Ammonia gas*—Smelling salts.*
- *Ammonium hydroxide* (*32.5% ammonia*)—Paint, oil, and dirt remover, refrigerant.
- *Sodium hydroxide* (*caustic soda*)—Drain cleaner, oven cleaner.
- *Potassium hydroxide* (*caustic potash*)—Drain cleaner, hearing aid batteries.
- *Sodium carbonate* (*washing soda*)—Household cleaning agent, detergent.
- *Potassium carbonate*—Household cleaning agent.
- *Sodium hypochlorite*—Household bleach.

Usual Fatal Dose

- About 10 to 15 gm for most alkalis.
- About 15 to 20 ml for ammonia.

Mode of Action

Locally, alkalis produce liquefaction necrosis which results in extensive penetrating damage because of saponification of fats and solubilisation of proteins. Production of ulcers is common which may persist for several weeks. Oesophagus is more severely affected than the stomach in contrast to acids (*page no. 39*).

Clinical Features

1. Corrosion of GI mucosa with greyish pseudomembrane formation. Oesophagus is often severely affected resulting in dysphagia, vomiting, drooling, and haematemesis. Stridor is an important indicator of severe oesophageal injury.
2. There are four categories of alkali induced oesophagitis:
   a. **Non-ulcerative oesophagitis**—from ingestion of mild irritants, resulting in 1st degree burns.
   b. **Mild ulcerative oesophagitis**—from ingestion of weak bases. 2nd degree burns are produced. Strictures may develop.
   c. **Severe ulcerative oesophagitis**—from ingestion of strong bases. There is severe dysphagia with vomiting which may subside after 2 to 3 days only to reappear as slowly progressive dysphagia after 4 to 6 weeks due to stricture formation. This may lead to total obstruction.
   d. **Oesophagitis with complications**—apart from oesophagitis, there are complications such as mediastinitis, perforation, pericarditis, pulmonary oedema, laryngeal obstruction, etc.
      It is important to perform oesophagoscopy and make accurate assessment as to the extent of local injury (**Table 7.1**). Contraindications to oesophagoscopy include upper airway obstruction and GI perforation.
3. Abdominal pain, diarrhoea, tenesmus.
4. Skin involvement results in greyish, soapy, necrotic areas without charring.
5. Eye involvement can produce serious complications, and constitutes an ophthalmologic emergency.
6. Ammonia ingestion causes manifestations which are essentially similar to those seen with other alkalis, but respiratory symptoms are commonly super-added due to inhalation of fumes while swallowing.

Diagnosis

1. In stomach contents:
   a. White, solid, slimy lumps, flakes, or granules.
   b. Turns litmus paper blue.
   c. Becomes warm on addition of water.
   d. If exposed to air, becomes moist and gets dissolved.

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* Glass capsule (usually enclosed in fibre mesh) containing 0.33 ml of a mixture of 18% ammonia and 36% alcohol. Used as first aid for treatment of syncope, weakness, etc.

Table 7.1: Oesophagoscopic Findings in Alkali Burns	
Acute	*Chronic*
1. *1st degree or Grade I:* Hyperaemia, with superficial desquammation of epithelium	1. *2nd week :* Granulation tissue, with neovascularisation
2. *2nd degree or Grade II:* Blisters, ulcers, and patchy membranous exudate on the mucosa	2. *3rd week :* Narrowed lumen, with resultant dysphagia
3. *3rd degree or Grade III:* Total loss of oesophageal epithelium with formation of granulation tissue	3. Persistent inflammation lasting for several months

   e.   Soapy or slimy feeling when touched with fingers.
   f.   Sharp penetrating odour in the case of ammonia.
2. **Platinum wire flame test**: Touch platinum wire to the unknown substance and then place it in a flame. Sodium gives an intense persistent yellow flame. Potassium gives a deep purple flame.
3. **Fume test for ammonia**: Place an open bottle of concentrate HCl near a sample of stomach contents, aspirate, or vomitus. Copious white fumes of ammonium chloride will emanate if ammonia is present. The test can also be done to detect the presence of ammonia in the atmosphere.

Treatment

1. Respiratory distress (especially in the case of ammonia) may require endotracheal intubation, cricothyroidotomy, or tracheostomy, depending on severity. Oxygen must be administered as necessary.
2. Diluents such as milk or water may be given as a first aid measure for alkali ingestion (no more than one or two glasses for an adult). If more than one hour has elapsed, this is usually not efficacious.
3. The following are absolutely **contraindicated** : *emesis, gastric lavage, catharsis,* and *activated charcoal.*
4. Withhold all oral feeds initially.
5. Assess fluid and electrolyte balance.
6. Watch for development of complications and attend to them accordingly.
7. Some investigators recommend early surgical intervention and use of an intraluminal stent in patients with 2nd or 3rd degree oesophageal burns because perforation which requires surgical repair may otherwise be missed. Others have suggested that if the serum pH is less than 7.20 (because of lactic acidosis resulting from severe tissue necrosis), surgery should be immediately undertaken.
8. If circumferential 2nd degree or 3rd degree burns of the oesophagus are seen, exploratory laparotomy should be undertaken followed by gastric resection and oesophagectomy, in case gastric necrosis is evident at laparoscopy.
9. In the past, administration of corticosteroids was recommended to prevent stricture formation which was based on animal studies. But today most investigators appear to be of the opinion that high dose corticosteroid therapy in caustic ingestion predisposes the patient to infection and perforation as well as masks symptoms of developing peritonitis or mediastinitis, and hence should be avoided. However, steroids may be effective in patients with dyspnoea, stridor, hoarseness, and other evidence of respiratory compromise, and may decrease laryngotracheal oedema thereby lessening respiratory dysfunction.
10. Use of prophylactic antibiotics is not recommended today. Most investigators feel that antibiotics should be administered only if there are signs of perforation or secondary infection.
11. An oesophagogram should be done at 3 weeks to evaluate the formation of strictures. Patients should be instructed to seek medical attention immediately whenever they develop dysphagia.
12. Alkali injuries to the eye and skin should be irrigated copiously with water or saline for at least 20 to 30 minutes. Ophthalmologic consultation is mandatory. Topical antibiotics and steroids may help.
13. Patients who have suffered from stricture formation require long-term endoscopic follow-up for the presence of neoplastic changes of the oesophagus which may occur with a delay of several years or decades.

Autopsy Features

1. Characteristic odour (in the case of ammonia).
2. Brownish or greyish staining of skin.
3. Inflammatory oedema with corrosion and sliminess of the tissues of the oesophagus and stomach. The mucosa may be brownish owing to formation of alkaline haematin.
4. Congestion of respiratory tract and pulmonary oedema (especially in the case of ammonia).

Forensic Issues

- Accidental poisoning occurs usually by mistaking an alkali solution for water, lemonade, beer, etc., because of careless storage of these chemicals in inadequately labeled, ordinary looking bottles or jars.
- Industrial accidents involving these substances are reported from time to time.
- Suicidal cases are occasionally encountered. Homicides are quite rare.
- Ammonia may sometimes be sprayed or thrown on a victim to facilitate robbery.

OTHER CAUSTICS

Potassium Permanganate

Synonyms

Condy's crystals; Chameleon mineral; Purple salt.

Physical Appearance

At room temperature, potassium permanganate exists as dark purple or bronze-coloured, odourless, sweetish, astringent orthorhombic crystals (**Fig 7.1**) that are almost opaque by transmitted light and have a blue, metallic sheen by reflected light. On contact with water it produces potassium hydroxide which probably accounts for its corrosive effects. Oxygen and manganese dioxide are also generated on contact with water.

Uses

- Potassium permanganate's industrial uses include bleaching resins, waxes, fats, oils, cotton, silk and other fibres; dyeing wood; printing fabrics; purifying air and water; etching rubber and plastic; and tanning leathers. It is also used as a fungicide; insecticide; miticide; algicide; bacteriocide; germicide; antiseptic; oxidiser; disinfectant; deodorant; sanitiser; chemical in photography; and reagent in analytical and synthetic organic chemistry.
- Therapeutically, potassium permanganate is used as a topical anti-infective. In veterinary medicine it is used as a topical antiseptic, astringent, and deodorant.
- Illicit uses have included the production of drugs of abuse, and as an abortifacient by topical application to the vaginal wall.

Usual Fatal Dose

About 5 to 10 grams.

Mode of Action

In concentrations exceeding 1:5000 (as a solution), potassium permanganate is an irritant, and in highly concentrated form it acts as a corrosive. It also exhibits systemic toxicity.

Clinical Features

1. Intense burning pain with difficulty in swallowing, abdominal pain, vomiting, and diarrhoea. There is usually severe thirst. Vomitus may be purple brown in colour. Stools are often black due to manganese sulfide.
2. Skin and mucosa are usually stained deep brown or black due to manganese dioxide.
3. If potassium permanganate comes in contact with air passages, it can provoke severe inflammatory oedema leading to dyspnoea and stridor.

Fig 7.1: Potassium permanganate crystals

4. Complications: shock, hepatic and renal failure, acute haemorrhagic pancreatitis, and methaemoglobinaemia, which manifests as dyspnoea, headache, fatigue, CNS depression, tachycardia, acidosis, etc.
5. Use as an abortifacient may result in vaginal or cervical burns and erosions, with extensive bleeding, shock, severe scarring and miscarriage as possible complications.
6. Chronic ingestion of potassium permanganate may result in manganese poisoning.

Diagnosis

Permanganate stains are decolourised by oxalic acid plus a trace of sulfuric acid, or by hydrogen peroxide.

Serum and urine manganese levels are often elevated after exposure, but their prognostic value is not clear.

Treatment

1. Immediate dilution with water or milk may help.
2. Gastric lavage is best avoided. However, if corrosion is not severe, it can be done with dilute hydrogen peroxide (10 ml of 3% solution in 100 ml of water).
3. Treatment of methaemoglobinaemia with methylene blue: 1 to 2 mg/kg/dose (0.1 to 0.2 ml/kg/dose) intravenously over 5 minutes as needed every 4 hours.
4. Chelation with EDTA and sodium para-aminosalicylic acid has been used in patients with manganese intoxication. While there is no experience with potassium permanganate exposure, chelation might be considered in patients with neurologic effects after chronic or subacute intoxication.
5. Supportive measures.

Autopsy Features

1. Brownish black staining of tissues.
2. Corrosion of oesophagus and stomach.
3. Evidence of hepatic and renal damage.
4. Congestion of airways; pulmonary oedema.

Forensic Issues

- Accidental poisoning occurs in the following ways
  - Children swallowing the attractive looking crystals, mistaking them for sweets, or out of plain curiosity.
  - *Therapeutic misuse:* Potassium permanganate was formerly used as treatment for amenorrhoea, as an abortifacient, as a gastric lavage solution, and as an irrigant of the urethra and bladder in the treatment of gonorrhoea.
  - Industrial exposure.
- Suicidal ingestions have been reported from time to time.

■ Iodine

Physical Appearance

Blue-black, glittering crystals which constantly give off violet coloured vapour (a process called *sublimation*) (**Fig 7.2**) with a peculiar odour.

Fig 7.2: Iodine sublimation

Uses

- Antiseptic preparations:
  - ❖ *Lugol's iodine* (5% iodine with 10% potassium iodide in water).
  - ❖ *Tincture of iodine* (2.5% iodine and 2.5% potassium iodide, or 2% iodine, 2.4% sodium iodide, 47% alcohol, and water).
  - ❖ *Povidone-iodine* (5 to 10% iodophor, i.e. mixture of polyvinyl-pyrrolidone and iodine).*
  - ❖ *Iodex* (iodine with methyl salicylate).
- As a component of some expectorants (e.g. potassium iodide, iodinated glycerol), anti-asthmatics (e.g. iophylline), anti-arrhythmics (e.g. amiodarone), anti-amoebics (e.g. iodoquinol), antifungals (e.g. vioform), antithyroid drugs (e.g. potassium iodide), and radiographic contrast agents (e.g. diatrizoate sodium, iopanoic acid, ipodate sodium, etc.).
- As a solution for prepaing patients for thyroid surgery (e.g. collosol liquid, which contains 8 mg iodine/5 ml).
- Iodochlorhydroxyquinolone (clioquinol), which is an iodinated hydroxyquinoline, is used sometimes in amoebiasis.
- Iodine is used commonly to treat drinking water to make it potable.

Usual Fatal Dose

About 2 to 5 grams of free iodine, or 1 to 2 ounces of strong iodine tincture. The presence of food in the stomach inactivates iodine by converting it to iodide which is relatively innocuous.

Mode of Action

Locally, strong iodine solution can be an intense irritant. Systemic toxicity is due to combination of free iodine with serum sodium bicarbonate, leading to metabolic acidosis.

Clinical Features

1. Initial manifestations of iodine poisoning include rhinorrhoea, conjunctivitis, and cough (especially if fumes have been inhaled).

2. There is burning pain extending from the mouth to the abdomen, salivation, metallic taste, vomiting, and diarrhoea.
   a. Vomitus and stools may appear yellowish (or sometimes bluish) in colour. Blue coloured emesis indicates the presence of food (starch) in the stomach and the conversion of iodine to iodide.
3. Skin and mucous membranes are stained yellowish brown. Prolonged exposure to tincture of iodine can induce superficial necrosis. Eye exposure can result in severe ocular burns.
4. The following features have also been reported: glottic oedema, pulmonary oedema, delirium, hallucinations, convulsions, tachycardia, hypotension, metabolic acidosis, and renal failure.
5. Hypersensitivity reactions including angioedema and a serum sickness-like reaction may occur following oral, topical, vaginal (douche), or IV administration of iodine.
6. Iodides and iodophores (e.g. povidone-iodine), are much less toxic and usually require only supportive treament.
   a. But chronic poisoning can result from long-term therapeutic intake of iodide salts leading to *iodism* which is characterised by metallic taste, anorexia, insomnia, lymphadenopathy, parotid swelling ("iodide mumps"), stomatitis, pharyngitis, conjunctivitis, rhinorrhoea, and skin manifestations (erythema, urticaria, acne, etc. together referred to as "ioderma").
7. Hypothyroidism, hyperthyroidism, and thyrotoxicosis have been reported secondary to iodine exposure.
8. Iodine is a confirmed human reproductive hazard.
   a. Excess iodine is harmful to the unborn, as shown in many cases of pregnant women taking iodine-containing drugs. Several iodine-containing drugs have been associated with foetal goitre, including ammonium iodide, potassium iodide, and sodium iodide.
   b. Iodine deficiency is also harmful to the unborn. This has become evident in certain areas of the world where either the low iodine content of the soil or the practice of eating cassava as a major portion of the diet results in endemic congenital cretinism. Iodine deficiency can cause congenital goitre, delayed skeletal maturation, developmental delays, and perhaps a higher incidence of birth defects.

Diagnosis

1. Specific Tests :
   a. Iodine
      i. Yellowish stains of clothing, skin (**Fig 7.3**), and mucosa (see *page no. 44* for distinguishing these stains from nitric acid stains).
      ii. Characteristic odour.
      iii. Vomitus or stomach contents when heated in a beaker will cause the iodine to sublime on a cold surface (e.g. a watch glass placed on top of the beaker with some ice).

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* Povidone-iodine mouthwashes contain only 1% solution.

Fig 7.3: Iodine stains (around abrasions)

iv. To 10 ml of vomitus or gastric aspirate, add 1 ml of starch solution. A blue-black colour will develop.

v. Urine Test: Add 5 ml of chloroform and a few drops of nitric acid to 10 ml of urine. Allow to stand for 3 minutes. A pinkish-violet chloroform layer forms.

b. *Iodides*

i. To 10 ml of vomitus or gastric aspirate, add 1 ml of 10% silver nitrate solution and 1 ml nitric acid. Formation of a yellow precipitate which is insoluble in ammonia is characteristic of iodides. Whitish precipitate (soluble in ammonia) is characteristic of chlorides, while bromides produce brown precipitate which is insoluble in ammonia.

2. Ancillary Tests:

Serum iodine levels are elevated, as also aminotransferase. There is also hyperbilirubinaemia, neutropenia and hypoxaemia.

Treatment

1. Decontamination:
   a. Skin: Wash thoroughly with soap and water, or 20% alcohol.
   b. Eyes: Irrigate with water for 15 minutes.
   c. GIT: If oesophageal injury is not present or suspected, gastric lavage can be attempted with starch solution, or 5% solution of sodium thiosulfate, or even plain milk. It has been suggested that soluble starch be administered, which forms a complex with iodine that is purple in colour and, therefore, may aid in the removal of iodine from the stomach by gastric lavage by making the iodine highly visible. Activated charcoal binds iodine, and can be administered.

2. Sodium bicarbonate IV for metabolic acidosis.

3. There is no specific antidote for iodine or bound iodine. Treatment is primarily supportive and includes monitoring for the development of gastroenteritis, renal failure, tachycardia, hypotension, and circulatory collapse. Anaphylactic type reactions may occur as well.

4. Osmotic diuresis, chloruretic diuresis, and salt loading may enhance elimination.

5. Iodism is treated by ceasing iodide intake while enhancing the intake of sodium chloride which promotes excretion of iodides. Chloride competes with iodide at the level of the renal tubules.

Autopsy Features

1. Brownish or yellowish stains of skin and mucosa. The mucosal staining in the GI tract will appear bluish if starch solution had been administered while attempting to treat the patient.
2. Characteristic odour (rarely perceptible).
3. Congestion of viscera, especially the kidneys.

Forensic Issues

■ Most cases result from accidental therapeutic exposure where iodine or iodides had been administered in excess. Deaths have been reported even with excessive local applications of povidone-iodine. The commonest abnormalities reported with such iodophore applications (repeatedly) are acid-base disturbances and metabolic acidosis.

■ Chronic poisoning can occur from prolonged therapy with iodides, or may be a result of occupational exposure.

■ Iodinated radiologic contrast agents are well known to produce anaphylactic reactions.

■ Hydrogen Peroxide

Synonyms

Albone; Carbamide peroxide; Hydrogen dioxide; Urea peroxide.

Physical Appearance

Commercial topical solution of hydrogen peroxide is a clear, colourless liquid with a faint ozone-like odour and bitter taste. It deteriorates on standing, repeated agitation, or exposure to light.

Uses

■ Disinfectant

■ *Radiology:* A mixture of hydrogen peroxide with barium can help identify the exact site of gastrointestinal haemorrhage under fluoroscopy, since bubbles are formed when blood is brought in contact with hydrogen peroxide.

■ Treatment of inspissated meconium, constipation, and faecal impaction.

■ Mouth wash/gargle.

■ Hair and teeth bleaching.

■ Vaginal douche.

■ *Industry:*
   ❖ Synthesis of various compounds, bleaching agent for paper and textiles, and in rocket fuel.
   ❖ The 3% solution is used in plastics manufacturing; in bleaching hair, feathers, silk, and textile fabrics; in renovating paintings and engravings; as an oxidiser in the manufacture of dyes; in disinfecting water and hides; in artificially aging wines, liquors, etc.
   ❖ Hydrogen peroxide is also used as a source of organic and inorganic peroxides, in foam rubber, in glycerol manufacturing, in electroplating, as a laboratory

reagent, as an oxidising and bleaching agent in foods, as a seed disinfectant, and as a substitute for chlorine in water and wastewater treatment.

- "Food grade" hydrogen peroxide solutions have recently been marketed in health-food stores in the West, to be diluted and used in "hyper-oxygenation therapy" to treat conditions ranging from arthritis to cancer to AIDS. This has resulted in an increased number of accidental exposures to these products.
- Hydrogen peroxide is effective in loosening cerumen (ear wax) that occludes the auditory canal, and can clear blocked ventilation tubes used in the treatment of conductive hearing loss caused by otitis media with effusion.

Usual Fatal Dose

Not clear. Fatalities are mostly associated with industrial grade solutions.

Mode of Action

Hydrogen peroxide decomposes to water and oxygen. When used in closed spaces or under pressure, liberated oxygen cannot escape. Systemic oxygen embolisation and surgical emphysema can occur.

Clinical Features

1. Household hydrogen peroxide (3 to 9%) is mildly irritating to mucus membranes. In general, ingestion, ocular, or dermal exposure to small amounts of dilute hydrogen peroxide will cause no serious problems.
   a. 1 ml of a 3% solution liberates 10 ml of oxygen. Therefore ingestion of a large amount of hydrogen peroxide solution even if it is very dilute can result in gastric distension. Irritation of gastrointestinal tract often results in vomiting.
   b. Oral contact with dilute (3%) solutions may induce oral gingival ulceration or enhance prior injuries of the mucous membranes of the mouth. Hypertrophy of the papillae of the tongue may occur from chronic use of hydrogen peroxide mouthwash.
2. Ingestion of industrial strength hydrogen peroxide (35 to 90%) can cause severe burns of GI mucosa with a tendency to gastric perforation (due to oxygen liberation). Oxygen emboli can also be produced which can be life-threatening. Foam formation can result in respiratory tract obstruction and respiratory failure. Metabolic acidosis and convulsions have also been reported.
3. Dermal exposure to concentrated solutions has resulted in burns and gangrene. If contact with the skin is relatively short no damage will occur beyond a whitening or bleaching accompanied by a tingling sensation. The skin returns to normal within 2 to 3 hours if it has been washed promptly after contact. However, hair may remain permanently bleached.

Diagnosis

1. *Clinical:* Foaming at mouth or nose, gastric distension, cerebral oedema.
2. Radiological:
   a. Gas in mesenteric, gastric, splenic, or portal venous systems.
   b. Gas in inferior vena cava or right ventricle.
   c. Gastric or duodenal distension.

Treatment

1. Aggressive airway management comprising endotracheal intubation, oxygen administration and mechanical ventilation.
2. Following ingestion, administer water immediately to dilute the peroxide. Spontaneous vomiting is common.
3. After endotracheal intubation, cautious gastric lavage may be attempted with iced saline.
4. Supportive measures with particular reference to control of metabolic acidosis and convulsions.
5. Laparotomy may be required if there is evidence of air in the GI tract.
6. Hyperbaric oxygen therapy may help alleviate life threatening gas embolisation.

Autopsy Features

1. *Gross* –
   a. Foam at the mouth or nose.
   b. Frothy blood in venous systems.
   c. "Frosty coating" of GI tract.
   d. Crepitus of liver.
   e. Diffuse cerebral oedema with cerebellar and uncal tonsillar notching.
   f. Visceral congestion.
   g. Petechiae of thymus, pericardium, and other viscera.
2. *Microscopic* –
   a. Evidence of gastritis, duodenitis, or colitis.
   b. Clear vacuoles in the submucosa of GI tract, GI veins, lymphatics, and mesenteric lymph nodes.
   c. Organ vacuolisation (gas emboli).
   Chemical analysis of viscera is a futile exercise.

Forensic Issues

Most cases of poisoning result from therapeutic misadventure. A few may be related to suicidal intent.

■ Cetrimide

Cetrimide (atrimonium bromide) is a quaternary ammonium compound. It is commonly used as a disinfectant. Common Indian preparations of cetrimide include *Cetavlon* (20% solution), *Cetrilak* (5% solution), and *Savlon* (15% solution with 7.5% chlorhexidine*).

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* Chlorhexidine is a cationic biguanide compound which is found also in skin cleansers and mouthwashes. It has low toxicity, but eye exposure can cause corneal damage.

Ingestion of cetrimide causes gastrointestinal irritation with vomiting. Systemic effects include a curare-like paralysis (because of depolarising neuromuscular blocking action), CNS depression, hypotension, and respiratory failure.

Usual fatal dose is said to be about 3 grams.

Treatment is the same as for all caustics. Administration of soap solution orally as a first-aid measure may help inactivate its toxic effect.

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Section

3

Chemical Poisons

8

Non-Metallic Chemical Poisons

There are innumerable substances which can be included under the term *inorganic non-metallic elements*. But this chapter concerns itself only with some of the relatively important (or common) examples encountered in toxicological practice such as phosphorus and the halogens.

■ Phosphorus

Physical Appearance

The name "phosphorus" is derived from Greek, meaning "light-bearing".

There are two main varieties (**Fig 8.1**):

1. Yellow (or White) Phosphorus—

    This is a yellowish, waxy, crystalline solid with a garlicky odour. On exposure to air, it oxidises into whitish fumes of phosphorus pentoxide. Hence, it is generally stored under water. Yellow phosphorus is highly combustible and ignites into flame at 34^0C. It is luminescent and glows in the dark (*phosphorescence*).

2. Red Phosphorus—

    This is a reddish or brownish, amorphous, odourless substance. It is insoluble and relatively harmless, since it is not absorbed from the GI tract.

    "Black phosphorus" is the inert, nontoxic allotropic form of elemental phosphorus.

    Derivatives and related compounds of phosphorus include phosphoric acid, phosphine, aluminium phosphide and zinc phosphide.

Uses

1. *Matches:* Yellow phosphorus was extensively used in the manufacture of friction matches during the 19th century. However, because of its propensity to produce chronic poisoning in workers of the match industry, most countries agreed at an international convention in Berne, Switzerland in 1906 to prohibit the manufacture and import of yellow phosphorus for the making of matches. Hence, these so-called "lucifer matches" gradually (and fortunately) faded out (**Fig 8.2**). Today's "safety match" contains only potassium chlorate and antimony sulfide (**Fig 8.3**). It has to be struck against a prepared surface to ignite it, which is provided by the sides of the match box being coated with powdered glass and red phosphorus.

Fig 8.1: Red and White (yellow) phosphorus

Fig 8.2: Lucifer matches

Fig 8.3: Safety matches

2. *Fireworks:* Although the use of yellow phosphorus in fireworks is prohibited in Western countries, it is still an important ingredient in several types of fireworks manufactured in India.
3. *Military uses:* Yellow phosphorus is an ingredient of tracer bullets, incendiary bombs, smoke screens, and air-sea rescue flares.
4. *Insecticide and rodenticide:* There are several pastes and powders available in India which contain phosphorus (or zinc phosphide) used for killing cockroaches and rats. Such pastes are usually mixed with molasses or butter and spread on bread as bait. Obviously, unintentional ingestion by children is quite possible leading to serious poisoning.
5. *Fertiliser*

Usual Fatal Dose

About 60 mg (roughly 1 mg/kg body weight).

Mode of Action

- Yellow phosphorus, a protoplasmic poison is a potent hepatotoxin (**Table 8.1**).
- In large doses, it can cause shock and cardiovascular collapse since it is also toxic to the heart.

- Locally, it produces severe irritation of skin and mucosa.
- Rate of absorption is greatly enhanced if phosphorus is administered in an oily vehicle.

Clinical Features

1. **Fulminant Poisoning:**
   This results from ingestion of a massive dose, i.e. more than 1 to 2 grams. The dominant clinical picture is one of peripheral vascular collapse. Death usually occurs in 12 to 24 hours, and signs of hepatic or renal damage are not seen.
2. **Acute Poisoning:**
   Today, most cases of phosphorus poisoning fall in this category. The clinical manifestations characteristically occur in three stages.
   a. *First Stage* (upto 3 days)—
      i. Local effects include severe burning pain, vomiting, diarrhoea, and abdominal pain.
      ii. Breath smells of garlic.
      iii. Vomitus and stools may be luminous in the dark. There may be haematemesis. Faint fumes may emanate from the stools (*Smoky stool syndrome*).
   b. *Second Stage* (upto several days after the first stage subsides)—
      This is an essentially symptom-free (treacherous) period, and the patient may feel well enough to be discharged from the hospital.
   c. *Third Stage*—
      i. This is due to the systemic effects of phosphorus after it has been absorbed.
      ii. There is a return of the digestive symptoms with increased severity.
      iii. In addition, manifestations of liver damage are prominent—tender hepatomegaly, jaundice which may progress to an olive green hue, pruritis, bleeding from multiple sites, and finally hepatic encephalopathy characterised by drowsiness, confusion, ataxia, flapping tremor of hands (*asterixis*), stupor, and coma. At this stage there is a mousy odour to the breath (*foetor hepaticus*).
      iv. Renal damage results in oliguria, haematuria, albuminuria, and acute renal failure.

Table 8.1: Hepatotoxic Agents

Acute Hepatocellular Injury	Cholestasis	Steatosis	Chronic Active Hepatitis
Arsenic	Chlorpromazine	Ethyl alcohol	Isoniazid
Carbon tetrachloride Disulfiram	Chlorpropamide	Nucleoside analogues	Methyldopa
Ethyl alcohol	Ethyl alcohol	(Zidovudine)	Nitrofurantoin
Halothane	Erythromycin	Sodium valproate	Trazodone
Iron	Nitrofurantoin	Tetracycline	
Isoniazid	Rifampicin		
Methotrexate			
Methyldopa			
Paracetamol			
Phenytoin			
Phosphorus (Yellow)			
Procainamide			
Tetracycline			

v. ECG changes include tachycardia, ST and T waves changes, QTc prolongation, low voltage QRS, and various arrhythmias.

vi. There may be terminal convulsions before death supervenes.

vii. Early hypoglycaemia has a grave prognosis. Survival for three or more days is a good prognostic sign.

Recent reports on phosphorus poisoning have indicated that the classical three phases of toxicity are not always encountered in these patients. The incidence of phosphorescent vomitus or faeces, oral mucosal burns, and presence of a garlicky odour on the breath or in gastric contents are also quite rare. Therefore, the absence of these findings does not preclude serious toxicity.

Diagnosis of Acute Poisoning

- Garlicky odour of breath and vomitus.
- Fuming or luminous vomitus and stools.
- Evidence of hepatic and renal failure.
- Hypokalaemia, hyperchloraemia, hypocalcaemia and both hyperphosphataemia and hypophosphataemia have been reported.
- Hypoprothrombinaemia and thrombocytopenia may occur following ingestion, and lead to a delayed onset of haematemesis, haematochezia, haematuria, and haemorrhages into the skin and mucous membranes.

3. **Dermal contact** with phosphorus results in acutely painful corrosion with yellow, necrotic, severely painful second or third degree chemical burns emitting garlic-like odour. Absorption from damaged skin may result in acute systemic phosphorus poisoning.

4. **Chronic Poisoning:**
   a. This usually results from long-term occupational exposure to the fumes of phosphorus pentoxide and results in the condition called *Phossy Jaw* (*Glass Jaw, Lucifer's Jaw*) (**Fig 8.4**) which was first described by **Bristowe** in **1862**.
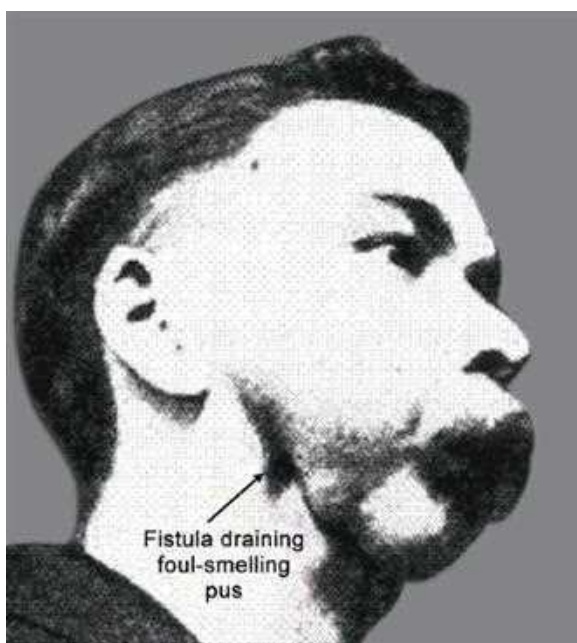
Fig 8.4: Phossy jaw

i. Main features include toothache (usually originating in a carious tooth), which because of its recurrence would be eventually extracted leading to exposure of bone followed by necrosis, sequestration, and osteomyelitis of jaw (invariably the lower jaw).

b. Chronic exposure to red phosphorus or phosphorus sesquisulfide may cause dermatitis.

Treatment

1. **Acute Poisoning:**
   a. Gastric lavage with potassium permanganate (1:5000), which oxidises phosphorus into relatively less toxic phosphoric acid and phosphates. Some authorities recommend administration of copper sulfate solution (250 gm in a glass of water), which converts phosphorus to non-toxic copper phosphide. Alternatively, a 0.2% solution of copper sulfate may be used for stomach wash. It must however be noted that copper sulfate being a highly toxic substance by itself is not a desirable antidote, and in fact is placed in the international list of obsolete antidotes.
   b. Do not administer milk or any oily/fatty foods, since this will enhance the absorption of phosphorus.
   c. Vitamin K by IV drip (65 mg) slowly, to combat hypoprothrombinaemia.
   d. *Intravenous fluids—*
      i. Isotonic saline and sodium lactate to treat shock, dehydration, and acidosis.
      ii. Glucose to combat hypoglycaemia.
      iii. Calcium gluconate for hypocalcaemia.
   e. Whole blood/fresh frozen plasma to correct coagulation defects.
   f. Steroids and inotropic support for shock.
   g. Anticonvulsants for seizures.
   h. Some investigators suggest the use of N-acetylcysteine (NAC) in patients with stage I phosphorus toxicity. A dose regimen of 150 mg/kg in 200 cc D5W for 15 minutes, followed by 50 mg/kg in 500 cc D5W for 4 hours, and then 100 mg/kg in 1000 cc D5W for 16 hours is recommended. It is presumed that NAC may be effective in preventing progression of liver damage when given in stage I of the illness.
   i. *Treatment of dermal burns:*
      i. After initial flushing with large volumes of water to remove any residual chemical material, clean wounds with a mild disinfectant soap and water. Loose, nonviable tissue should be removed by gentle cleansing with surgical soap or formal skin debridement. Intravenous analgesia may be required.
      ii. Removal and debridement of closed blisters is controversial. Current consensus is that intact blisters prevent pain and dehydration, promote healing, and allow motion; therefore, blisters should be left intact until they rupture spontaneously or healing is well underway, unless they are extremely large or inhibit motion.

iii. Prophylactic topical antibiotic therapy with silver sulfadiazine is recommended for all burns except superficial partial thickness (first-degree) burns. For first-degree burns bacitracin may be used, but effectiveness is not documented.

iv. Depending on the site and area, the burn may be treated open (face, ears, or perineum) or covered with sterile nonstick porous gauze. Alternatively, a petrolatum fine-mesh gauze dressing may be used alone on partial-thickness burns. Daily dressing changes are indicated if a burn cream is used; changes every 3 to 4 days are adequate with a dry dressing.

v. Analgesics such as paracetamol with codeine may be used for pain relief if needed.

vi. Phosphorus particles in dermal burns can be visualised by employing the use of Wood's lamp. Phosphorus will fluoresce under ultraviolet light. With the exposed areas immersed in water, loose or embedded phosphorus particles that are visualised under UV light can be mechanically but delicately removed safely under water. This technique may be a safer alternative than either the use of copper sulfate or silver nitrate, and may be the method of choice.

2. **Chronic Poisoning:**
   a. Removal of patient from source of exposure.
   b. Dental treament and follow-up.

Autopsy Features

1. Garlicky odour in the vicinity of the mouth and in the gastric contents.
2. Jaundice.
3. Bleeding points in the skin (subcutaneous haemorrhages).
4. Luminous gastric contents.* The contents will fluoresce under UV light.
5. Congestion and inflammation of affected skin and mucosa.
6. Enlarged fatty liver. Later there is evidence of aute yellow atrophy. Histopathological examination may reveal features of acute fulminant hepatitis: collapsed reticulin framework, with fibrosis between the hepatocytes showing bubbly, vacuolated cytoplasm.
7. There may also be fatty degeneration of heart and kidneys.
8. Viscera for chemical analysis must be preserved in saturated saline and not rectified spirit, otherwise luminosity especially of the stomach contents will be lost.

Forensic Issues

■ *Accidental poisoning:* This used to be common in the past because of unrestricted use of phosphorus in matches and fireworks. Today, most cases of accidental poisoning result from inadvertent ingestion of cockroach or rat poison by children, or because of contamination of food by these substances.

■ *Suicidal poisoning:* This was also previously quite common, especially in Western countries. A popular method appears to have been to soak several "lucifer" match heads in water or brandy, mix with sugar, and consume the resultant potion. Today, rat pastes containing phosphorus are occasionally implicated in suicidal ingestions.

■ *Homicidal poisoning:* Formerly, phosphorus was quite frequently employed for committing murder. Several accounts are mentioned in the literature where poisoning was accomplished by mixing phosphorus in soup, jam, or rum, and administered to unsuspecting victims.

■ Phosphoric Acid

See page no. 47

■ Phosphine

Synonyms

Hydrogen phosphide; Phosphoretted hydrogen.

Physical Appearance

Colourless, flammable gas with an odour of garlic or decaying fish.

Uses

■ Fumigant.
■ Grain preservative in the form of aluminium phosphide.
■ Rat poison in the form of zinc phosphide.

Usual Fatal Dose

Inhalation of phosphine at a concentration of 400 to 600 ppm can be lethal in 30 minutes. Exposure to 50 ppm is considered dangerous to life and health.

Mode of Action

Phosphine produces widespread organ damage due to cellular hypoxia as a result of binding with cytochrome oxidase, an important respiratory enzyme. The organs with the greatest oxygen requirements appear to be especially sensitive to damage and include the brain, kidneys, heart, and liver.

Clinical Features

1. Inhalation produces vertigo, headache, restlessness, chest pain, vomiting, and diarrhoea.
2. In severe cases there may be onset of adult respiratory distress syndrome (ARDS), pulmonary oedema, tachycardia, hypotension, cardiac arrhythmias, ataxia, tremor, diplopia, paraesthesias, convulsions, coma, and hepatorenal damage.
3. ECG abnormalities may include sinus tachycardia, sinus arrhythmia with ST segment depression in lead II, III, AVF, and T wave inversion in V5-6, and ventricular premature complexes followed by ventricular tachycardia.

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* Examine in the dark.

4. Ingestion of phosphine-releasing compounds such as aluminium or zinc phosphide produces predominantly gastrointesinal manifestations. But systemic toxicity can produce most of the symptoms mentioned earlier. Metabolic acidosis, hypokalaemia, hypo- or hypermagnesaemia may also be encountered.

5. Chronic poisoning, characterised by anaemia, bronchitis, gastrointestinal disturbances and visual, speech and motor disturbances, may result from prolonged exposure to low concentrations.

Diagnosis

1. *Silver Nitrate Test:* To 1 ml of gastric contents in a test tube, add 1 ml of water. Take two strips of filter paper impregnated with 0.1 N silver nitrate* and place one over the mouth of the test tube, while the other is placed over a clean open surface. Gently heat the tube at 50°C for 15 to 20 minutes. Remove the filter paper strip and dry it. Darkening of filter paper (due to deposition of silver) indicates a positive test. The other strip of filter paper acts as a control. If this shows darkening it means there is contamination of the atmosphere (usually by hydrogen sulfide).

   $PH_3 + 8AgNO_3 + 4H_2O \rightarrow 8Ag^+ + H_3PO_4 + 8HNO_3$
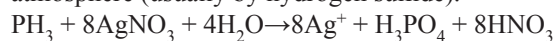
   This test can be done on the breath of the patient instead of gastric contents in the following manner. Use the impregnated filter paper as a mask and ask the patient to breathe through it for 15 to 20 minutes. Blackening indicates the presence of phosphine. However it is less reliable (*page no. 72*).

Treatment

1. Stomach wash with 1:5000 potassium permanganate is claimed by some physicians to be useful, by oxidising phosphine to non-toxic phosphate.

2. Activated charcoal as a slurry in the usual manner.

3. Magnesium sulfate is a disputed antidote claimed by some investigators to be very effective, while others are doubtful about its actual role. Magnesium sulfate has membrane stabilising effect and may help in controlling the cardiac arrhythmias produced by phosphine. The usual dose recommended is 3 grams as IV bolus followed by 6 grams infusion over 12–24 hours for 5 to 7 days.

4. For convulsions:
   a. *Diazepam*—5 to 10 mg IV over 2 to 3 minutes (adult). 0.25 to 0.4 mg/kg IV over 2 to 3 minutes (child).
   or
   b. *Phenytoin*—10 to 15 mg/kg IV at 30 to 50 mg/min (adult & child).
   or
   c. *Phenobarbitone*—12 to 15 mg/kg IV in 60 ml of normal saline at 25 to 50 mg/min (adult & child).

5. For shock:
   a. *Dopamine*—4 to 6 mcg/kg/min IV.
   b. *IV fluids*—4 to 6 litres over 6 hours.

6. For metabolic acidosis:
   Sodium bicarbonate—50 mEq/15 min.

7. For pulmonary oedema:
   Furosemide—20 to 40 mg IV.

8. For local irritation of GI tract:
   Ranitidine—50 mg IV, 8th hourly.

9. For respiratory failure:
   Ventilatory support.

Autopsy Features

1. Garlicky or decayed fish odour.
2. Pulmonary oedema.
3. Centrilobular necrosis of liver.
4. Focal myocardial necrosis.

Forensic Issues

Many cases of poisoning result from occupational exposure in agriculture, or domestic exposure from rat pastes or powders.

But today it is suicidal ingestion of aluminium phosphide which has assumed alarming proportions, especially in the central and northern states of India.

■ Aluminium Phosphide

Physical Appearance

Aluminium phosphide is marketed in India under various trade names (*Alphos, Bidphos, Celphos, Chemfume, Delicia, Fumigran, Phosphotek, Phosphume, Phostoxin, Quickphos, Synfume,* etc.).

It is generally available as greyish green tablets of 3 grams each, mixed with urea and ammonium carbonate (**Fig 8.5**). These tablets are sold in sealed, airtight containers of tens and twenties. Each tablet liberates 1 gram of phosphine.

Uses

■ *Grain preservative:* Aluminium phosphide is said to be the most ideal grain preservative since it is relatively cheap

Fig 8.5: Aluminium phosphide tablets

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* Impregnation is done by soaking the filter paper in saturated silver nitrate solution in methanol, and drying it at room temperature.

while being very effective in repelling pests. The required number of tablets are removed from the airtight container and placed among the grain. On exposure to moisture, phosphine is released which percolates among the grain. When fumigated grains are subsequently well aerated, phosphine evaporates rapidly leaving behind virtually no residue. Traces of phosphite and hypophosphite of aluminium may be present, but they are non-toxic.

Usual Fatal Dose

One to three tablets.

Mode of Action

When exposed to air and moisture, aluminium phosphide liberates phosphine which causes multi-organ damage (*page no. 70*).

$$AlP + 3H_2O \rightarrow Al(OH)_3 + PH_3$$
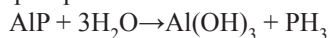
Clinical Features

1. Common presenting symptoms include metallic taste, vomiting, garlicky (or fishy) odour of breath, intense thirst, burning epigastric pain, and diarrhoea.
2. In severe cases, there are cardiovascular manifestations such as:
   a. Hypotension
   b. Tachy/bradycardia, and
   c. ECG abnormalities: sinus tachycardia, sinus arrhythmia with ST segment depression in lead II, III, and AVF, ST elevation, atrial fibrillation, T wave inversion in V5-6, sinus arrest, chaotic atrial pacemaker, complete heart block, bundle branch block, and ventricular premature complexes followed by ventricular tachycardia.
   d. Massive focal myocardial injury with elevated serum levels of cardiac enzymes may occur.
3. Convulsions have been reported in some cases. Coma supervenes in later stages.
4. Hepatic damage, renal failure, and metabolic acidosis are possible.
5. Respiratory distress is invariably present with cyanosis, and cold, clammy skin.

Diagnosis

1. Garlicky odour in the breath.
2. Urinalysis may reveal occult blood, bilirubin, glucose, and albumin.
3. Liver function tests are often abnormal.
4. Blood urea and serum creatinine are usually higher than normal.
5. Hypo/hypermagnesaemia; hypo/hyperphosphataemia.
6. ECG changes (mentioned under *Clinical Features*).
7. Qualitative tests for detecting phosphine in the breath and gastric aspirate:
   a. *Breath test*: A piece of filter paper impregnated with 0.1 N silver nitrate solution is used in the form of a mask through which the patient is asked to breathe in and out for 5 to 10 minutes. Blackening of the paper is indicative of the presence of phosphine in the breath, since silver nitrate is reduced to silver on exposure to it. Similar reaction is also produced by hydrogen sulfide.
   b. *Biological sample test*: A small amount of gastric apirate (5 to 10 ml) or minced tissue (5 to 10 gm of liver)* is taken into a steam distillation flask to which an equal quantity of water is added and then acidified with dilute HCl or H_2SO_4, followed by heating upto 50^0C for 15 minutes. The distillate is collected in an ice cold receiver containing 5 ml of 1% silver nitrate solution by dipping the adapter into it. If phosphine is present, the solution will turn black.
      i. For confirmation, add 5 ml of concentrate.HNO_3 to the black precipitate and boil till the solution becomes clear. Then add 5 ml of ammonium molybdate solution and heat for a minute. Formation of a yellow precipitate confirms the presence of phosphine.
      ii. A variation of this test involves placing 0.1 N lead acetate filter paper over the mouth of the distillation flask containing the sample (prepared in the same manner as detailed above). The flask is heated for 15 minutes at 50°C. Phosphine will blacken the silver nitrate paper, while hydrogen sulfide will blacken both papers.

Treatment

1. Emesis is not to be induced. Though there is often intense thirst, do not administer water since whatever aluminium phosphide is still remaining in the stomach will react with it, releasing phosphine. For the same reason, stomach wash is contraindicated. While activated charcoal can be administered, it should be mixed with sorbitol (and not water), using 240 ml for every 30 grams. However, some authorities recommend the performance of gastric lavage as well as the administration of activated charcoal using aqueous solutions.
2. While there were initial reports eulogising the efficacy of magnesium sulfate, particularly in relieving cardiovascular manifestations, later studies could not sustain such a view.
3. Presently the suggested measures include the following:
   a. Management of circulatory shock with IV fluids (4 to 6 L over 6 hours), while monitoring the central venous pressure and/or pulmonary wedge pressure. Dopamine can be given IV at a dose of 4 to 6 mcg/kg/min (maximum 10 mcg/kg/min).
   b. Management of respiratory distress with 100% humidified oxygen, intubation, and assisted ventilation.
   c. Management of metabolic acidosis with sodium bicarbonate (50 mEq/15 min) until the arterial bicarbonate rises above 15 mmol/L.
   d. Control of convulsions with anticonvulsants (benzodaizepines, barbiturates, etc.).

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* Applicable only to autopsied cases.

e. *Magnesium sulfate therapy*:* Magnesium sulfate is said to be beneficial in the management of cardiac arrhythmias. Conventional antiarrhythmic drugs such as digoxin and lidocaine are ineffective.

   i. Magnesium sulfate is given IV as a 3 grams bolus, followed by 6 grams infusion over 24 hours for 5 to 7 days.

   ii. Alternatively, 1 gram can be given IV to begin with, followed each hour by the same dose for 3 consecutive hours, and then 1 gram every 6 hours for 5 days.

4. Ranitidine 50 mg IV 8th hourly to counter the severe epigastric pain.

Autopsy Features

1. There is widespread hypoxic organ damage with congestion and petechiae.
2. Contents of stomach are often haemorrhagic with mucosal shedding, and there is usually an intense garlicky odour.
3. Microscopy reveals necrotic changes in liver and kidneys.
4. Heart shows features of toxic myocarditis with fibrillar necrosis.
5. Lungs may demonstrate evidence of ARDS (adult respiratory distress syndrome) with or without pulmonary oedema.

Forensic Issues

Prior to 1980, aluminium phosphide poisoning was virtually unreported in India. Today it is the leading cause of suicidal (and sometimes accidental) death in northern Indian states such as Punjab, Haryana, Uttar Pradesh, Madhya Pradesh, and Rajasthan. Southern states have so far not been significantly affected since aluminium phosphide is yet to make inroads into the agricultural sector here. But there are ominous indications of a gradual rise in the number of cases being reported.

■ Zinc Phosphide

Physical Appearance

Zinc phosphide is available as dark grey tetragonal crystals or crystalline powder marketed under various trade names (*Agrophos, Commando, Sudarshan, Ratoff, Ratol, Robart, etc.*). It has a repulsive odour of rotten fish.

Uses

Rodenticide

Usual Fatal Dose

About 2 to 4 grams.

Mode of Action, Clinical Features, Diagnosis, Treatment and Autopsy Features

Same as for aluminium phosphide.

Forensic Issues

Accidental and suicidal poisonings have been reported involving the consumption of rat pastes containing zinc phosphide. Some of these brands are marketed in tubes that look very similar to toothpaste tubes leading to accidental use (**Fig 8.6**).

■ HALOGENS

Iodine and iodides have been discussed under **Caustics** (*page no. 59*). The other halogens of importance include chlorine, bromine, and fluorine. All halogens combine with hydrogen to form acids, and with metals to form salts.

■ Chlorine

Physical Appearance

Chlorine is a greenish-yellow gas with a pungent odour.

Uses/Sources

- Chlorine is not found free in nature due to its reactivity with other chemicals. Instead, it is found as sodium chloride in land-locked lakes, as rock salt in underground deposits, in brines, and in natural deposits of sylvite and carnallite.
- Swimming pool chlorinator tablets or pellets may result in chlorine gas exposure.
- Chlorine is used to manufacture a number of chemicals including solvents such as carbon tetrachloride, trichloroethylene, tetrachloroethylene, and methylene chloride, pesticides and herbicides, plastics, vinyl chloride, etc. It is also used in making refrigerants and propellants such as halocarbons and methyl chloride.

Fig 8.6: Tooth paste and rat paste tubes

- Chlorine is used to make sodium hypochlorite, an ingredient in bleach, deodorisers and disinfectants. Household bleach (5% sodium hypochlorite) when brought into contact with an acidic toilet bowl cleaner or drain cleaner will cause the release of chlorine gas.
- It is used extensively in pulpmills, where wood chips are processed into pulp as part of the paper manufacturing process.
- Chlorine is employed in purifying drinking and swimming water, for sanitation of industrial and sewage wastes and other disinfecting uses.
- It has been used as a poisonous gas for military purposes under the name **bertholite**.

Usual Fatal Dose

Concentrations of over 50 to 100 ppm when inhaled can be rapidly fatal. Instant death can occur at concentrations over 1000 ppm. **Table 8.2** gives an overview of effects to varying degrees of exposure to chlorine gas.

Mode of Action

- Chlorine is an extremely active oxidising agent and causes rapid and extensive destruction of organic tissue. It combines with tissue water to produce HCl, producing injury and reactive oxygen species.
- Chlorine gas in concentrated amounts may be caustic to mucous membranes when inhaled or ingested; otherwise it is a strong irritant. When in contact with moist tissue, nascent oxygen or "active oxygen" is released as hydrogen is removed from H_2O. Nascent oxygen is a potent oxidiser, resulting in tissue damage. Secondary irritation occurs from acids formed during this reaction.
- Contact with respiratory epithelium produces initial alveolar capillary congestion followed by focal and confluent patches of high fibrinogen oedematous fluid. Acute lung injury peaks in 12 to 24 hours. The fluid is interstitial at first but can fill the alveoli. Once this occurs, copious frothy, blood-tinged sputum is observed.

Table 8.2: Effects of Exposure to Chlorine

0.2–3 ppm	Odour detection (some tolerance develops)
3–5 ppm	Mild mucous membrane irritation that can be tolerated for up to 1 hour
5–10 ppm	Extremely irritating to the eyes, nose and respiratory tract
14–21 ppm	Immediate irritation of the throat; Dangerous if exposed for 30–60 minutes
30 ppm	Severe irritation of the upper respiratory tract; Immediate chest pain, vomiting, dyspnoea, cough
35–50 ppm	Lethal in 60–90 minutes
Over 100 ppm	Lethal in 30 minutes
1,000 ppm	Fatal within a few minutes

* See page no. 57 for a similar test done in the case of ammonia leak.

Clinical Features

1. Chlorine is an irritant gas and inhalation provokes rhinorrhoea, lacrimation, coughing, chest pain, and shortness of breath.
2. Major exposure results in laryngeal oedema, stridor, pneumonitis, and pulmonary oedema.
3. In addition, the following features of systemic toxicity are seen: vomiting, vertigo, headache, ventricular ectopic beats, and metabolic acidosis.
4. Liquid chlorine can cause cutaneous and mucosal burns.
5. Gaseous chlorine is a dermal irritant and may cause burns in high concentrations
6. Chronic exposure to chlorine gas may cause cough, sore throat, dyspnoea, palpitations, chest pain, reactive upper airways dysfunction syndrome (RADS), dental enamel erosion, and an increased susceptibility to viral respiratory infections.
   a. Conjunctivitis, anosmia, and green discolouration of hair have also been reported.
   b. Chronic exposure to chlorine gas is one of the most frequent causes of occupational asthma.

Diagnosis

1. Characteristic odour.
2. Chlorine gas leak into the atmosphere can be detected by opening a bottle of concentrated ammonium hydroxide which will cause the production of heavy, white fumes of ammonium chloride.*

Treatment

1. Mild poisoning can be managed with bed rest and oxygen administration.
2. Cough can be controlled with codeine and bronchodilators.
3. Nebulised sodium bicarbonate (3.75% solution) is claimed to be effective in ameliorating respiratory symptoms by neutralising the acid formed when chlorine comes into contact with water in the airways. This can however provoke an exothermic reaction and doubts have been expressed as to its efficacy and safety.
4. The role of corticosteroids in the treatment of pulmonary oedema is also controversial.
5. Severe cases of poisoning will require intermittent positive pressure ventilation.
6. Eye exposure must be treated with copious irrigation of water or saline. Expert ophthalmic consultation is advisable to rule out corneal damage.

Autopsy Features

1. Characteristic odour.
2. Massive pulmonary oedema.
3. Denudation of respiratory epithelium.

Forensic Issues

Most cases of poisoning are accidental arising out of domestic or industrial exposure. Sometimes, exposure occurs at swimming pools where chlorine is often used as a disinfectant.

▪ Bromine

Bromine is a dark reddish-brown, heavy liquid with irritant brown fumes. By itself it is rarely encountered in poisoning cases, while the salts (bromides) have often been implicated, especially in the past when they were used extensively in therapeutics as sedative-hypnotics. Even today there are several therapeutic drugs (many of them over-the-counter preparations) which contain bromide ion and have the potential for chronic toxicity (**Table 8.3**). Methyl bromide is used in soil fumigation which can result in bromide levels as high as 380 mg/kg in vegetables such as lettuce, spinach, tomatoes, radishes, and cucumbers among others. Ethylene dibromide is used in the postharvest fumigation of warehouses, ships' holds, and quarantine chambers affecting fruits, wheat, almonds, tobacco, and dried mushrooms; achieving levels as high as 300 mg/kg.

Usual Fatal Dose

Blood bromide level of 300 mg/100 ml is potentially lethal. Levels greater than 50 to 100 mg/100 ml are usually associated with signs and symptoms of toxicity.

Acceptable daily intake: 1 mg/kg.

Clinical Features

1. Bromine is extremely corrosive to the eyes, skin, bronchial tree and mucous membranes in liquid or vapour form.
2. Ingestion may cause severe corrosive injury to the gastro-intestinal mucosa, abdominal pain, haemorrhagic gastro-enteritis, and circulatory collapse.
3. Inhalation causes respiratory tract irritation, cough, bronchospasm, upper airway oedema and delayed pulmonary oedema.
4. Ocular exposure results in irritation, lacrimation, inflammation, blepharospasm and photophobia.
5. Skin contact causes burns with brown discolouration and slowly healing ulcers.
6. Acute poisoning with bromides causes severe gastrointesinal irritation with nausea and vomiting, which usually prevents absorption of large doses.
7. Methyl bromide or ethylene dibromide inhalation provokes cough, dyspnoea, pneumonitis, pharyngitis, and pulmonary oedema. Eye exposure results in conjunctivitis and keratitis. Dermal contact produces redness and blistering. Ingestion results in headache, vertigo, vomiting, diarrhoea, metabolic acidosis, ventricular fibrillation, convulsions, and hepato-renal damage.
8. When therapeutic drugs containing bromides are taken for a long period, chronic poisoning results refered to as **bromism**:
   a. Anorexia, nausea, salty taste, halitosis, lassitude, low-grade fever, drowsiness, amnesia, slurred speech, abnormal gait, tremor, nystagmus, visual disturbances, and psychosis. Impotence and loss of libido have been reported.
   b. Bromide rash is sometimes seen, which is an acneiform eruption beginning in the face and spreading gradually to the rest of the body (**Fig 8.7**). It may progress to pustular lesions and ulceration (*bromoderma tuberosum*).
9. Bromides cross the placenta and may be detected in the milk of nursing mothers. Case reports suggest that prenatal exposure may cause growth retardation, craniofacial abnormalities and developmental delay.

Diagnosis

1. *Urine test*: Add 5 ml chloroform and a few drops of nitric acid to 10 ml urine. Allow to stand for 3 minutes. A yellow chloroform layer is diagnostic for bromide intoxication.
2. Decreased anion gap.
3. Serum bromide level: more than 100 mg per 100 ml is significant.
4. Bromides are often radiopaque. Abdominal X-ray may be helpful in confirming diagnosis of acute ingestion and detecting bezoar formation.

Table 8.3: Drugs with Bromide Ion

Drug	Bromide Concentration (%)
Bromocriptine	Unclear
Brompheniramine maleate	25
Carbromal	34
Dextromethorphan hydrobromide	43
Halothane hydrobromide	81
Homatropine methylbromide	29
Neostigmine bromide	38
Pancuronium bromide	37
Potassium bromide	67
Propantheline bromide	17
Pyridostigmine bromide	30
Quinine hydrobromide	17
Scopolamine hydrobromide	29

Fig 8.7: Bromide rash

Treatment

1. Acute Poisoning—
a. Milk or water can be administered as a first-aid measure.
b. Activated charcoal in the usual manner (for organic bromide compounds).
c. Treatment of convulsions with diazepam or phenytoin or babiturates.
d. Decontamination of skin and eye.
e. Sodium chloride orally or intravenously (*vide infra*).
f. Supportive measures.
g. Haemodialysis in severe cases.

2. Chronic Poisoning—
a. Stop bromide ingestion.
b. Oral or intravenous sodium chloride. It promotes excretion of bromides. Discontinue when symptoms have improved, and the serum bromide level is less than 100 to 150 mg/dL Administration of diuretics such as furosemide (10 mg IV, 4th or 6th hourly) can improve bromide clearance.
c. If saline administration is contraindicated for any reason, administer ammonium chloride, or undertake haemodialysis.

■ Fluorine

Physical Appearance

- Fluorine is a diatomic halogen gas. It is a very corrosive and toxic gas, and is found in the soil in combination with calcium. It is released into the atmosphere by the burning of soft coal, and during manufacturing processes involving superphosphate, aluminium, steel, lead, copper, etc.
- Salts (referred to as fluorides) include sodium fluoride and sodium fluoroacetate. Both are crystalline, white, odourless, tasteless, and strongly alkaline.

Uses

1. Sodium fluoride and sodium fluoroacetate are widely used as cockroach and rat killers.
2. In dentistry, fluorides are used in toothpastes, topical gels, and mouthwashes.

Usual Fatal Dose

- 70 to 140 mg/kg of fluoride ion. In general, 2.2 mg of sodium fluoride contains 1 mg of fluoride ion.
- Fatal blood fluoride level: more than 0.2 mg/100 ml.
- Urinary fluorine output of less than 5 mg/L is used as an index of safe working level for long-term exposure.
- The safe upper limit for fluorine gas is 1 ppm.

Mode of Action

Fluorine and fluorides act as direct cellular poisons by interfering with calcium metabolism and enzyme mechanisms. Fluoride combines with hydrochloric acid in the stomach to form hydrofluoric acid which is a powerful corrosive (*page no. 44*). After absorption, fluoride ions combine with cations in the serum, particulaly calcium and magnesium leading to hypocalcaemia and hypomagnesaemia. Hyperkalaemia is often an added hazard.

Dermal cutaneous burns are caused by the violent reaction between the skin and fluorine producing a thermal burn.

Clinical Features

1. Acute Poisoning—
a. Fluorine is an extremely strong tissue irritant, causing caustic irritation of eyes, skin, and mucous membranes. Thermal burns or frostbite may occur.
b. Inhalation of fluorine gas leads to headache, respiratory distress, polydipsia, and polyuria.
c. Ingestion of fluorides in large amounts can cause the following manifestations:
    i. Metallic taste, salivation, vomiting, diarrhoea, abdominal pain.
    ii. Paraesthesias, paresis, tetany, convulsions.
    iii. Ventricular arrhythmias, cardiovascular collapse, coagulopathies.

2. Chronic Poisoning—
a. Leads to a condition called **fluorosis**:
    i. This is usually the result of high fluoride content in water supply. Fluoridation of water is done to prevent caries. When the water fluoride content is more than 3 to 5 ppm, chronic exposure leads to mottling of teeth (**Fig 8.8**). The enamel loses its lustre and becomes rough, pigmented, and pitted.
    ii. Skeletal fluorosis is a different entity which is also associated with high fluoride concentration in water and soil. In non-endemic areas it may occur as a result of occupational exposure (aluminium

Fig 8.8: Dental fluorosis

production, magnesium foundries, superphosphate manufacture, etc.). The effects are usually more severe in children.

- Main features include genu valgus or varum (bow legs or knock knees) (**Fig 8.9**), lateral bowing of femora, sabre shins, and deformities of thorax, vertebrae, pelvis, and joints. There may also be mottling of teeth.
- In adults there may be thickening of long bones, development of exostoses and osteophytes, calcification of ligaments and tendons, polyarthralgia, and contractures of hips and knees.

Treatment

1. **Acute Poisoning—**
   a. *Insecticide fluoride ingestion—*
      i. Stomach wash with magnesium sulfate, followed by activated charcoal and sorbitol.
      ii. Treat convulsions with anticonvulsants.
      iii. Supportive measures, including the use of haemo-dialysis.
   b. *Non-insecticide fluoride ingestion –*
      i. Mild:
         - Administer milk.
         - Watch the progress for at least 12 hours. If symptoms such as vomiting, diarrhoea or abdominal pain occur, treat as mentioned below.
      ii. Moderate to Severe:
         - Stomach wash (if vomiting has not occurred).
         - Administer milk, oral calcium salts, or aluminium (or magnesium) based antacids to bind fluoride.
         - Treat hypocalcaemia, hypomagnesaemia, and hyper/hypokalaemia.
         - Consider haemodialysis for severe poisoning.

Fig 8.9: Skeletal fluorosis

   c. *Frostbite—*
      i. Rewarming:
         - Place affected area in a water bath with a temperature of 40 to 42^{0}C for 15 to 30 minutes until thawing is complete. The bath should be large enough to permit complete immersion of the injured part, avoiding contact with the sides of the bath.
         - Correct systemic hypothermia.
         - Rewarming may be associated with increasing pain, requiring narcotic analgesics.
      ii. Wound Care:
         - Digits should be separated by sterile absorbent cotton; no constrictive dressings should be used. Protective dressings should be changed twice per day.
         - The injured extremities should be elevated and should not be allowed to bear weight.
         - Prophylactic antibiotics may be administered.
         - Clear blisters should be debrided but haemorrhagic blisters left intact.
         - Further surgical debridement should be delayed until mummification demarcation has occurred (60 to 90 days). Spontaneous amputation may occur.
         - Tetanus prophylaxis is advisable.
         - Topical aloe vera may decrease tissue destruction and can be applied every 6 hours.
         - Ibuprofen is a thromboxane inhibitor and may help reduce tissue loss. Adult dose of 200 milligrams every 12 hours is recommended.

Forensic Issues

Most cases of poisoning (acute or chronic) are accidental. Suicidal poisonings have been reported with fluoride-based rodenticides and cockroach killers.

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Heavy Metals

Many metallic elements in trace quantities are essential for various biological processes. Some of them activate enzymes, others facilitate exchange and utilisation of oxygen and carbon dioxide. While most of these trace elements are acquired in adequate quantities through food, excessive exposure (nutritional, occupational, or environmental) can lead to progressive accumulation and toxicity resulting in serious consequences. Though the general perception is that heavy metal poisoning is uncommon, the actual fact is just the converse. Heavy metal poisoning (acute or chronic) is a major cause of morbidity and mortality all over the world, and India is no exception.

■ Arsenic

Arsenic is thought to occur throughout the universe. It is the twentieth most common element in the earth's crust, having a concentration of 1.8 ppm. Arsenic is today the commonest source of acute heavy metal poisoning, and is second only to lead in the incidence of chronic toxicity.

Physical Appearance

- Arsenic is a metalloid i.e. it is an element which resembles a metal in some respects, and is by itself not very toxic. However, almost all the salts are toxic to varying degree.
- Arsenic is a silver-grey or tin-white, shiny, brittle, crystalline and metallic-looking element (**Fig 9.1**). It is rarely found in its isolated, elemental form. More commonly, it is present in mineral species, in alloys, or as an oxide or other compound form.
- **Table 9.1** displays the physical properties and uses of arsenic and its compounds.

Fig 9.1: Arsenic metal

Usual Fatal Dose

- 200 to 300 mg for arsenic trioxide.
- In general, the pentavalent form of arsenic (*arsenate*) is less toxic than the trivalent form (*arsenite*) because it is less water soluble.
- The most toxic form is arsine gas (25 to 30 ppm can be lethal in 30 minutes).

Toxicokinetics and Mode of Action

- Arsenic is absorbed through all portals of entry including oral, inhalational, and cutaneous routes.
- After absorption it is redistributed to the liver, lungs, intestinal wall, and spleen, where it binds to the sulfydryl groups of tissue proteins. Arsenic replaces phosphorus in the bone where it may remain for years. It gets deposited also in hair.
- While arsenic does not cross the blood-brain barrier easily, it crosses the placenta readily and can give rise to intrauterine death of the foetus. In less severe intoxications it can cause respiratory distress of the newborn due to pulmonary haemorrhage and hyaline membrane formation.

Clinical Features

Mentioned in **Table 9.2**.

Dermal pigmentation is consistently seen in chronic arsenic poisoning, and may also be encountered in exposure to certain other substances, (**Table 9.3**).

In West Bengal, thousands of people residing in more than 300 villages are known to consume arsenic-contaminated groundwater, and many of them have arsenical skin lesions. Conjunctivitis, depigmented lesions, melanosis, and hyperkeratosis (**Fig 9.2**), are most commony present, but malignant neoplasms and gangrenous lesions have also been found. Pulmonary lesions are also fairly common.

Diagnosis

1. *Urine level:* If the 24 hour excretion of arsenic exceeds 100 mcg, it is indicative of toxicity. However, ingestion of seafood can interfere with interpretation since considerable concentrations of organic arsenicals such as *arsenobetaine* and *arsenocholine* may be present in shellfish, cod, haddock, etc., although it is not associated with toxic

Table 9.1: Inorganic and Organic Arsenicals

Chemical Name	Synonyms	Physical Properties	Uses
Elemental arsenic	Metallic arsenic, grey arsenic	Shiny grey, brittle, metallic-looking substance	In alloys
Arsine	Arsenic trihydride, hydrogen arsenide, arseniuretted hydrogen	Colourless gas with garlicky odour	Lead plating, soldering, galvanising, and in electronic components
Trimethyl arsine	Gosio gas	Colourless gas	Present in sewage
Arsenic trioxide	Arsenic oxide, white arsenic, arsenic sesquioxide, arsenious anhydride	White powder (dissolvesslowly in water to formarsenious acid)	Manufacture of glass, insecticide, rodenticide. Previously used in medicine for treating fever (e.g. *Fowler's solution*)
Arsenic trichloride	Butter of arsenic	Yellowish, oily liquid	Pottery
Sodium arsenite	Meta-arsenite, arsenious acid sodium	White or greyish powder	Insecticide, wood preservative, veterinary use
Arsenic pentoxide	Arsenic acid, arsenic anhydride	White powder (dissolves rapidly in water to form arsenic acid)	Manufacture of coloured glass, insecticide, wood preservative
Lead arsenate	Acid lead arsenate	Heavy, white powder	Insecticide
Sulfides of arsenic	Red realgar (*disulfide*) Yellow orpiment (*trisulfide*)	Red powder Yellow powder	Depilatory Depilatory & colour pigment
Copper arsenite	Scheele's green	Greenish powder	Colouring agent for toys,wall paper, etc.
Copper acetoarsenite	Paris or Emerald green	Greenish powder	Insecticide
Organic arsenicals (*carbarsone, tryparsamide, glycobiarsol, melarsoprol, etc.*)	—	—	Previously used in therapeutics
Arsenic compounds are also used in paints, and the tanning industry			

Table 9.2: Arsenic Poisoning

System	Acute	Chronic
Dermal	Hair loss, transverse bands of opacity in nails (*Mees' lines*)* (**Fig 9.3**)	Melanosis (neck, eyelids, nipples), Bowen's disease, facial oedema, hyperkeratosis, hyperpigmentation (*rain drop pattern*) (**Fig 9.4**), skin cancer
Ocular	Conjunctivitis, lacrimation	Dimness of vision
Gastrointestinal	Abdominal pain, metallic taste, dysphagia,vomiting, bloody or rice-water diarrhoea.** There may be garlicky odour in the breath	Anorexia, nausea, vomiting, diarrhoea,weight loss
Airways	Irritation of upper airways	Perforation of nasal septum, chronic laryngitis, bronchitis
Liver	Fatty degeneration	Hepatomegaly, jaundice, cirrhosis
Kidney	Oliguria, uraemia	Nephritic changes
Neurological	Hyperpyrexia, convulsions, coma	Encephalopathy, polyneuritis (*glove & stocking type*), tremor, ataxia, limb tenderness,difficulty in walking
Haematological	—	Anaemia, leucopenia, thrombocytopenia, basophilic stippling, karyorrhexis, pancytopenia
Cardiac	Tachycardia, hypotension, cardiac arrhythmias***	Hypertension, myocarditis

*After 2 weeks
**May mimic cholera
***ECG changes include ST-T wave changes and prolonged QT interval

effects. In such cases, the analysis must be repeated after 2 days of "no fish" diet.

2. *Blood level:* This is less reliable than urine level because of short half-life of arsenic in the blood. However, a blood level of arsenic less than 7 mcg/100 mL (70 mcg/L) is generally considered in the normal range.

3. *Hair level:* Although considered to be an important diagnostic criterion, it is actually virtually useless since it cannot discriminate between external deposition and toxic accumulation. If hair is sent for arsenic quantitation, pubic hair instead of scalp hair should be sent because of the

Table 9.3: Substances Producing Dermal Pigmentation on Ingestion

Bluish	Brownish	Reddish	Yellowish
Bismuth	Arsenic	Borates	Carotene
Gold (sun exposure)	Bleomycin (*linear*)	Clofazimine	Chloroquine
Mercury	Busulfan	Mercury	Epoxy resins
Minocycline	Chromium	Rifampicin	Methylenedianiline
Oxalic acid	Cyclophosphamide (sun exposure)		Nitrazepam
Phenothiazines	Dioxin		Picric acid
Quinine	Fluorouracil		Quinacrine
Silver	Imipramine		Sodium nitrate
Tetracycline	Levodopa		
	Methyldopa		
	Nitrates/nitrites		
	Phenacetin		

Fig 9.2: Arsenic poisoning—Hyperkeratosis

Fig 9.3: Mees' Lines

Fig 9.4: Raindrop pigmentation—arsenic poisoning

possibility of scalp hair being contaminated with arsenic from the environment.

4. *Radiography:* Since arsenic is radiopaque, abdominal x-ray may reveal its presence in the gastrointestinal tract in acute poisoning. **Table 9.4** presents a list of radiopaque poisons commonly encountered in practice.

5. *Additional investigations:*
   a. Monitor CBC, serum electrolytes, urinalysis (for proteinuria, haematuria or pyuria), liver and renal function tests.
   b. Obtain an ECG and institute continuous cardiac monitoring in symptomatic patients.
   c. Obtain a chest radiograph in patients with severe poisoning or pulmonary effects.
   d. Initial and periodic biological monitoring and medical surveillance are required for employees exposed to arsenic.

Treatment

1. *Supportive measures:* gastric lavage, intravenous fluids, cardiac monitoring, etc.

Table 9.4: Radiopaque Poisons

Inherently Radiopaque	Radiopaque by Bezoar
Acetazolamide	Aluminium hydroxide
Acetylsalicylic acid	Bromides
Ammonium chloride	Calcium phosphate
Busulfan	Cholestyramine
Carbon tetrachloride	Meprobamate
Chloral hydrate	Nifedipine
Chloroform	Theophylline (sustained release)
Enteric coated tablets	
Heavy metals	
Iodides, iron	
Methotrexate	
Penicillin G & K	
Phenothiazines	
Potassium chloride, iodide, and permanganate	
Pseudoephedrine	
Sodium chloride	
Vitamins	

2. *Chelation therapy:* This can be done with BAL (British Anti Lewisite or dimercaprol), penicillamine, DMSA (Dimercapto succinic acid), or DMPS (Dimercapto propane sulfonic acid).
    a. The usual agent employed is BAL at a dose of 3 to 5 mg/kg intramuscularly every 4 hours until the urinary arsenic excretion dips below 50 mcg/24 hours. Usual duration of therapy is 7 to 10 days.
    b. In patients who are not allergic to penicillin, penicillamine can be given orally at a dose of 100 mg/kg/day, 6th hourly for 5 days.
    c. DMSA and DMPS said to be superior to BAL and penicillamine, are currently not available in India.
    d. *Principles of chelation:*
        i. Begin chelation therapy in symptomatic patients. The urine arsenic level which should prompt chelation in an asymptomatic patient has been recommended as 200 mcg/litre.
        ii. Repeat courses of chelation therapy should be prescribed in severe poisonings until the 24-hour urine arsenic level falls below 50 mcg/litre. Observation for return of symptoms is strongly recommended.
        iii. Chelation therapy is not very effective for chronic poisoning, and is totally ineffective in arsine poisoning. The latter should be treated with emphasis on respiratory stabilisation and haemodialysis.
3. *Haemodialysis or exchange transfusion.*

Autopsy Features

1. Gastrointestinal congestion is a noteworthy feature in acute arsenic poisoning and varies from a mere reddening of mucosa (*red velvet*) to frank haemorrhagic gastritis. Focal haemorrhages giving rise to a *flea bitten* appearance is said to be characteristic. The intestines may be inflamed and may contain "rice water" contents.
2. Subendocardial haemorrhages are often seen in the heart.
3. There may be evidence of fatty degeneration of heart, liver, and kidneys.
4. Chronic arsenic poisoning may present features of non-specific gastrointestinal inflammation, as well as renal and hepatic damage, at autopsy.
5. It is conventional to preserve apart from the routine viscera and body fluids, a piece of long bone (preferably femur), a bunch of pulled scalp hair, a wedge of muscle, and a small portion of skin (from the back of the trunk) for chemical analysis.

Forensic Issues

- Arsenic has had an outstanding reputation as an ideal homicidal poison especially in the West, particularly United Kingdom in the Victorian era. Several celebrated murders are said to have been accomplished with the help of arsenic during this period. One of the most shocking cases which remained speculative until recently, when scientific evidence finally established the truth beyond reasonable doubt, was that of Napoleon Bonaparte.
- Arsenic trioxide being almost tasteless and colourless in solution can be administered without arousing the suspicion of a victim. The main obstacle is relative insolubility. But the solubility can be greatly enhanced if hot solutions are used such as coffee, tea, cocoa, porridge or gruel, and soups. The only problem is that on cooling, much of the dissolved arsenic will separate out to yield a gritty deposit. On chronic successful administration to a victim, arsenic produces insidious but relentlessly progressive symptoms which are likely to be mistaken even by a medical practitioner for natural causes such as neurological disease, alcoholism, tuberculosis, and hepatic or renal afflictions, while acute poisoning may be confused with gastroenteritis or cholera.
- However the popularity of arsenic has declined in recent times because of various factors, and today most cases of arsenic poisoning are accidental, though murders are still reported from time to time. Accidental poisoning may be the result of industrial or occupational exposure, or it may be due to consumption of contaminated water or food.
    - In the past, certain allopathic drugs used to contain arsenic and iatrogenic poisoning was not uncommon. Today ayurvedic preparations constitute the main hazard, some of which can contain substantial concentrations of arsenic that can produce chronic poisoning on prolonged use.
    - One of the most important sources of chronic accidental poisoning in India is consumption of well water. There are indications that sizeable populations of several Asian countries are exposed to arsenic tainted water, particularly tube well water. A devastating health crisis (*endemic hydroarsenicism*) began to unfold in West Bengal in the early 1980s due to exposure to arsenic laced well water. High levels of arsenic have

Fig 9.5: Various lesions – Arsenic poisoning

been demonstrated which probably leached from natural underground sources into thousands of village wells affecting more than 250,000 people who display overt manifestations (especially related to the skin) such as hyperkeratosis, pigmentation, and skin cancer (**Fig 9.5**), while more than 1 million who are continuing to drink the tainted water may develop lesions over a period of time. While the exact cause for this wide-spread contamination of water could not be pinpointed, it is believed that the problem is related to the large scale withdrawal of ground water. Whatever the under-lying mechanism, the fact remains that analysis of water from more than 200,000 tube wells demonstrated arsenic content above the WHO permissible limit of 0.01 mg/L in more than 60% samples (some as high as 3.7 mg/L). Hair, urine, skin, and nail samples from people drinking the water have also been shown to contain high levels of arsenic. In order to counter this tragedy, the West Bengal government is in the process of arranging the supply of arsenic-free piped water from the Ganges river, but the full implementation of such a programme may take several years, and involve the expenditure of millions of dollars of foreign aid. The most alarming question raised by this tragedy is how many tens of millions of people may be exposed to high levels of arsenic in areas not yet tested for contamination elsewhere in India.

Lead

Lead is the commonest metal involved in chronic poisoning. It was one of the first metals known to man and has been widely used during the last two thousand years for domestic, indus-trial, and therapeutic purposes. Lead is abundant in soil, being distributed throughout the earth's crust.

Physical Appearances and Uses

Elemental lead exists as a highly lustrous, heavy, silvery-grey metal (**Fig 9.6**) with a cubic crystal structure that assumes a bluish tint as it tarnishes in air. It is quite soft and malleable. Several of its salts occur as variously coloured powders or liquids and are used widely in industry and at home producing

Fig 9.6: Elemental lead

cumulative toxicity on chronic exposure. Lead acetate (*sugar of lead*) has been used in therapeutics,* lead carbonate (*white lead*) is still used in paints, lead oxide (*litharge*) is essential for glazing of pottery and enamel ware, and tetraethyl lead is mixed with petrol as an antiknock to prevent detonation in internal combustion engines. Among cosmetics, lead tetroxide is the most common compound in vermilion (*"sindoor"*) (**Fig 9.7**) applied by married Hindu women to the parting of their scalp hair, while lead sulfide is used as a collyrium (*"surma"*) (**Fig 9.8**) for the eyes by Muslims.**

The various situations in which lead salts are used resulting in chronic occupational, environmental, or domesic exposure are listed in **Table 9.5**.

Summary of some of the common non-occupational sources:
- Candle with lead-containing wicks
- Ayurvedic medicines
- Paint
- Retained bullets
- Ink
- Automobile storage battery casing; battery repair shops
- Ceramic glazes
- Lead pipes
- Silver jewellery workers
- Renovation/modernisation of old homes.

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* Has a sweetish astringent taste, and so was also used to sweeten wine in the olden days, leading to chronic poisoning in wine drinkers ("Dry gripes").
** Sometimes mercuric sulfide is used as "sindoor," while antimony sulfide is used as "surma."

Exposure to lead in the general population occurs from inhalation of contaminated air and dust of various types, or ingestion of food and water containing lead with a fairly even split between ingestion and inhalation exposure routes. About 5–15% of ingested lead is absorbed by adults with less than 5% retained. Children, however, absorb approximately 50% of ingested lead and retain about 30%.

Fig 9.7: Sindoor powder

Fig 9.8: Surma being applied to the eyes

Usual Fatal Dose

This is not really relevant to lead since acute poisoning is very rare. The average lethal dose is said to be 10 gm/70 kg for most lead salts, while it is 100 mg/kg for tetraethyl lead.

Toxicokinetics

■ Lead is absorbed through all portals of entry. Occupational exposure results mainly from inhalation, while in most other situations the mode of intake is ingestion. Tetraethyl lead can be absorbed rapidly through intact skin.

■ Following absorption, it is stored in the bones as phosphate and carbonate. In children about 70% of total body lead is skeletal, while in adults over 95% is in osseous tissues. Lead is drawn to those areas of the skeleton which are growing most rapidly. These include the radius, tibia, and femur, which are the most metabolically active. The hypermineralisation is reflected in the form of densities which are the classic **"lead lines"** observed on X-ray (**Fig 9.9**).

  ❖ The width of the lead lines is related to the duration of exposure.

  ❖ Significant amounts of skeletal lead are released from bone into the blood stream periodically resulting in symptoms of toxicity. The conditions favouring this include acidosis, fevers, alcoholic intake, and even exposure to sunlight.

■ Absorbed lead which is not retained in the body is excreted primarily in the urine (about 65%) and bile (about 35%).

Mode of Action

1. Lead combines with sulfhydryl enzymes leading to interference with their action.

Table 9.5: Sources of Lead Exposure

Environmental	Domestic	Occupational
Automobile exhaust *	Ceramic ware +	Autorepair works *
Drug abuse (*glue sniffing*) ·	Coloured picture books (*comics*) ·	Battery making *
Soil ·	Contaminated flour ·	Glass manufacture *
Water ·	Cosmetics ·	Mining *
	"Health" foods ·	Plastics manufacture *
	House paint *	Plumbing +
	Indigenous medicines ·	Pottery +
	Pencils ·	Printing ·
	Toys ·	Rubber industry ·
		Ship building or ship breaking *
		Smelting & refining *
		Soldering (*electronics*) +
		Steel welding & cutting *

* High-risk for lead poisoning + Moderate risk · Low-risk

Fig 9.9: Lead lines at the ends of long bones

2. It decreases haeme synthesis by inactivating the enzymes involved such as *aminolaevulinic acid dehydrase, aminolaevulinic acid synthetase, coproporphyrinogen oxidase* (or *decarboxylase*), and *ferrochelatase.* This results in anaemia.
3. Lead increases haemolysis as a result of which immature red cells are released into circulation such as reticulocytes and **basophilic stippled cells** (the result of aggregation of ribonucleic acid due to inhibition of the enzyme pyrimidine-5-nucleotidase which normally eliminates degraded RNA) (**Fig 9.10**).
4. In the CNS, lead causes oedema and has a direct cytotoxic effect leading to decreased nerve conduction, increased psychomotor activity, lower IQ, and behavioural/learning disorders. Children are especially susceptible. The highest brain concentrations of lead are found in hippocampus, cerebellum, cerebral cortex, and medulla.
5. Lead also has deleterious effects on the CVS (hypertension and myocarditis), kidney (nephritis),* and reproductive organs (infertility). Lead nephropathy after chronic lead
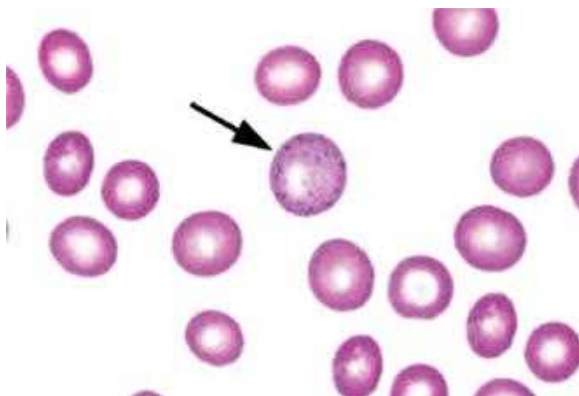
Fig 9.10: Basophilic stippled cell (*arrowed*)

exposure has been well described. Interstitial nephritis, reduced glomerular filtration rate, and nonspecific proximal tubular dysfunction are typical. In addition, lead can decrease uric acid renal excretion, thereby raising blood urate levels and predisposing to gout (*saturnine gout*). Elevated urinary levels of N-acetyl-3-D-glucosaminidase and beta-2-microglobulin may serve as early markers of renal injury.

6. **Permissible lead intake and blood levels:**
   a. There is much controversy over this at the present time. Lead appears as a trace metal in virtually all foods and beverages, though fortunately absorption from such sources is relatively low.
   b. Adults ingest 300 mcg and inhale 15 mcg of lead approximately each day, of which only 10% is absorbed, but children may absorb upto 50%.
   c. An important source of food based lead poisoning is the use of lead-soldered canned food and drink. While in USA measures have been taken to ban lead soldering of cans, the Indian canned food industry may still be persisting with lead soldered seams, though there is no clear information on this.
   d. Lead in drinking water may be absorbed to greater extent than that in food. The concentration of lead which may not really be very high in ground or surface water may progressively rise as it passes through the distribution system because of contact with lead connectors, lead service lines or pipes, lead soldered joints, lead containing coolers, and lead impregnated fixtures such as brass taps.
   e. Because of the reasons mentioned, minute quantities of lead are always present in the blood of even normal individuals. Only when the concentration is high, do features of intoxication begin to manifest. Today the accepted upper level for blood lead (BL) is fixed as 35 mcg/100 ml. However there are reports that adverse effects especially on the haematopoietic system can occur at levels as low as 10 mcg/100 ml. Neurobehavioural disorders in children can occur at BL as low as 25 mcg/100 ml. Hence, the current trend is to consider even levels as low as 10 mcg/100 ml as unacceptable, especially in children.

Clinical Features

1. *Acute poisoning—*
   a. This is rare. Many reported cases of acute poisoning may actually be exacerbations of chronic lead poisoning when significant quantities of lead are suddenly released into the bloodstream from bone.
   b. Symptoms include metallic taste, abdominal pain, constipation or diarrhoea (stools may be blackish due to lead sulfide), vomiting, hyperactivity or lethargy, ataxia, behavioural changes, convulsions, and coma.
2. *Chronic poisoning—*
   a. **Mild Toxicity** (*BL 40 to 60 mcg/100 ml*):

* Acute intoxication can cause haematuria, aminoaciduria, glycosuria, and hyperphosphaturia (Fanconi syndrome).

- Myalgia
- Paraesthesia
- Fatigue
- Irritability
- Abdominal discomfort.

b. **Moderate Toxicity** (*BL 60 to 100 mcg/100 ml*) :
  - Arthralgia (especially nocturnal)
  - Muscular exhaustibility
  - Tremor
  - Headache
  - Diffuse abdominal pain
  - Anorexia, metallic taste, vomiting
  - Constipation
  - Weight loss
  - Hypertension.

c. **Severe Toxicity** (*BL more than 100 mcg/100 ml*) :
  - *Lead palsy:* Wrist drop (**Fig 9.11**) or foot drop.
  - A bluish black *lead line* on gums (*Burton's line*) (**Fig 9.12**).*
  - *Lead colic*: Intermittent severe abdominal cramps. There may be tenderness around the umbilicus.
  - *Lead encephalopathy:* It is more common in children and is often associated with organic lead toxicity, especially tetraethyl lead or TEL which is

Fig 9.11: Wrist drop

Fig 9.12: Burton's line

lipid soluble and is distributed widely in lipophilic tissues such as the brain. TEL is metabolised to triethyl lead which is the major toxic compound. There is sudden onset of vomiting, irritability, headache, ataxia, vertigo, convulsions, psychotic manifestations, coma, and death. Mortality rate is around 25%. Even if recovery occurs, there is often permanent brain damage manifesting as mental retardation, cerebral palsy, optic neuropathy, hyper-kinesis, and periodic convulsions.

■ Note:

- Facial pallor, especially circumoral is said to be a characteristic feature of chronic lead poisoning and is due to vasospasm, though anaemia may contribute to a significant extent.
- The anaemia that is encountered in plumbism is similar to that due to iron deficiency, i.e. it is hypochromic and microcytic in type; but anaemia due to the latter is neither associated with reticulocytosis, nor are basophilic stippled cells seen. Anaemia is not a prominent feature in organic lead poisoning. Basophilic stippled cells are also not commonly encountered.
- Increasing blood lead levels in children have been correlated with hearing impairment, developmental delay, aggressive, hyperactive and antisocial behaviour, visual problems, and growth retardation.
- Lead is transferred across the placenta. It can affect reproduction in males and females, and affects neurodevelopmental milestones in children with both prenatal and postnatal exposure. Lead poisoning during pregnancy has been associated with prematurity, low birth weight, and impaired foetal growth.
- Lead is increasingly being implicated as a carcinogen. Some lead salts have produced tumours in experimental animal studies.

■ Diagnosis

- It has been suggested that all children should be screened for lead levels (BL) on their 1st birthday, and if possible at yearly intervals thereafter until they are 6 years old. If at any time the BL is more than 20 mcg/100 ml, therapeutic intervention is indicated, and if it exceeds 70 mcg/100 ml, it should be treated as a medical emergency.
- The current paediatric practice in the West is to first measure the free erythrocyte protoporphyrin before carrying out a blood lead quantification. Historically, the terms free erythrocyte protoporphyrin (FEP) and zinc protoporphyrin (ZnP) were used interchangeably, which is actually incorrect. The reason for this error was the inability to differentiate FEP from ZnP by the older techniques. Contemporary technology overcomes this, and both can be measured separately showing a normal ratio of 10 is to 9 between FEP and ZnP. Quantification of ZnP is generally perceived

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* May also be seen around the anal margin, and is due to bacterial action on blood lead precipitating insoluble lead sulfide. A similar dark line is sometimes seen in poisoning due to mercury, iron, thallium, silver, or bismuth

as one of the earliest and most reliable indicators of the impairment of haeme biosynthesis. But ZnP can be elevated in iron deficiency anaemia while the blood lead level is actually within normal limits. Hence when ZnP is raised, it is mandatory to confirm lead poisoning by performing a blood assay for lead level.

- While urine levels of aminolaevulinic acid (ALA) can also serve as a sensitive indicator of lead poisoning, ALA excretion rises only when blood lead concentrations exceed 40 mcg/100 ml.
- **Laboratory tests for lead:**
  1. **Blood**
     - *Complete blood count and peripheral smear*— General and non-specific findings include low haematocrit and haemoglobin values with normal total and differential cell counts. The peripheral smear may either be normochromic or hypochromic, and microcytic. Basophilic stippling is usually seen only in patients who have been significantly poisoned for a prolonged period. Hypochromia and basophilic stippling are strongly suggestive of lead intoxication, but their absence does not rule out lead poisoning. It must be borne in mind that such stippled RBCs may also be seen in arsenic and zinc poisoning.
     - *FEP and ZnP levels (>50 mcg/100 ml)*—An elevated FEP level indicates impairment of the haeme biosynthetic pathway and may result from lead poisoning or iron deficiency. In order to confirm whether it is due to the former, the BL must be estimated. Today ZnP levels are more commonly studied than FEP (*vide supra*). It is to be noted that both FEP and ZnP are not significantly elevated at lower levels of lead poisoning. In fact, the ability to reliably use zinc protoporphyrin levels as a screening tool to detect low blood levels is under serious question.
     - *Blood lead level* (*BL*)—BL can change rapidly in response to lead intake (e.g. ingestion of lead paint chips). For short exposure periods, it usually has a linear relationship to intake levels. Blood lead levels reflect recent exposure or exposure over a period of up to 3 to 5 weeks. In individuals with high or chronic past exposure, BL usually under-represents the total body burden because most lead is stored in the bone and may be found at normal levels in the blood. However, during stressful circumstances, patients with a high body burden may have elevated BL because of the release of lead stored in bones.
       - The recommended methods of estimating blood lead level (BL) include atomic absorption spectroscopy (AAS), electrothermal atomic absorption spectroscopy (EAAS), anodic stripping voltammetry (ASV), inductively coupled plasma atomic emission spectroscopy (ICP-AES), and X-ray fluorescence spectroscopy. Alternative methods include proton-induced

X-ray emission (PIXE), fast neutron activation analysis (FNAA), mass spectrometry (MS), and microwave plasma detection. EAAS and ASV are the methods of choice. In recent years, ICP-AES has become the technique of choice owing to superior specificity and sensitivity. It provides highly accurate and rapid results.

  2. **Urine**
     - The concentration of ALA in urine is widely used as a measure of lead toxicity in workers who are exposed occupationally. For this purpose colourimetric methods were employed previously, but today fluorometry (after separation by HPLC) is preferred.
     - *Urine lead level* : If this is above 150 mcg /litre it is a significant finding, but it is unfortunately not very reliable.
     - *Calcium disodium EDTA mobilisation test* : This test is done mainly in children to find out whether a child whose BL is between 25 and 41 mcg/100 ml will respond to chelation therapy with a brisk lead diuresis. Children whose BL is more than 45 mcg/100 ml should not receive this provocative test; they should be referred for chelation therapy immediately.
       - Procedure:
         » First the patient is asked to empty the bladder. Then CaNa$_2$EDTA is administered at a dose of 500 mg/m^2 in 5% dextrose infused over 1 hour. All urine must be collected with lead-free equipment over the next 8 hours. Preferably, urine should be voided directly into polyethylene or polypropylene bottles which have been cleaned in the usual way, then washed in nitric acid and thoroughly rinsed with de-ionised distilled water. For children who are not toilet trained, plastic paediatric urine collectors can be used. In the laboratory, the urine volume should be carefully measured and stored at 20° C until the lead concentration is measured.
         » To obtain the total lead excretion (mcg), the concentration of lead in the urine (mcg/ml) is multiplied by total urinary volume (ml). The total urinary excretion of lead (mcg) is divided by the amount of CaNa$_2$ EDTA given (mg) to obtain the lead excretion ratio.
         » An 8 hour *CaNa$_2$EDTA chelation provocative test* is considered positive if the lead excretion ratio is more than 0.6 (though some clinicians use a cut-off of 0.5). Children with positive chelation test results should undergo a 5-day course of chelation.
     - *Urine porphyrin level:* Patients with lead poisoning usually excrete elevated levels of porphyrins in the urine.

3. **Bone**
   – The X-ray fluorescence technique is brief and non-invasive and carries low-risk. It is based on the specific atomic property of lead to emit characteristic X-rays upon stimulation induced by external irradiation. The stimulated radiation is monitored externally by a solid state detector and can be expressed in terms of lead concentration in the bone. Because emitted radiation is considerably attenuated by the overlying tissue, the tibial shaft is chosen as the measurement site because of its thin overlying skin. Calibration of the system can be done from a cadaver leg, and subsequent atomic absorption analysis from the same site. Published regression equations that could be used to estimate mean skeletal lead concentration of the entire body and also to predict the lead concentration are available. Many investigators now recommend such an "in-vivo analysis" of bone lead concentration as superior to the more cumbersome *CaNa$_2$EDTA chelation provocative test.*
   – Radiology: This involves evaluation of the ends of long bones for arrest of growth line, and of the abdomen for radiopaque densities. Radiological examination of the abdomen may show radiopaque foreign material, if the material has been ingested during the preceding 24 to 36 hours. The significant finding in bone is the appearance of dense transverse bands or *lead lines* extending across the metaphyses of the long bones, and along margins of flat bones such as the iliac crest. The width of the *lead line* varies depending upon the amount of lead ingested and the length of time it has taken. It usually takes 4 to 8 weeks of heavy exposure for dense bands to develop.

Treatment

1. *Severe acute poisoning with encephalopathy:* This is a medical emergency and the following measures must be undertaken immediately –
   a. BAL 4 mg/kg immediately (in children).
   b. Cranial CT scan: to rule out cerebral oedema.
      – If there is cerebral oedema, it can be managed by the following measures:
        - Controlled hyperventilation, maintaining an arterial CO2 tension of 25 to 30 mmHg, can reduce intracranial pressure in patients with rapidly worsening mental status, lateralising neurologic findings or evidence of impending herniation. Prolonged hyperventilation is not desirable in general. Monitor intracranial pressure continuously. Monitor cardiovascular function, renal function, and serum electrolytes carefully.
        - Diuretics
          » Mannitol 20%: *Adult:* 1 to 1.5 gm/kg by infusion over 10 to 20 minutes. *Child:* 0.5 to 1 gm/kg by IV infusion over 10 to 20 minutes.
          » Glycerol: 0.3 to 1 gm/kg orally.
          » Loop Diuretics: Furosemide and/or ethacrynic acid may be useful as an adjunct in the treatment of cerebral oedema.
          » Corticosteroids:
            ◌ Dexamethasone—*low dose* - 16 mg/day in divided doses.
            ◌ Dexamethasone—*high dose*— 1 to 2 mg/kg/day in divided doses.
   c. KUB: to rule out lead chips in GI tract.
   d. For seizures: Treat seizures with intravenous diazepam (*Adult:* up to 10 mg slowly, repeat if necessary; *Children:* 0.1 to 0.3 mg/kg slowly). Seizures from lead encephalopathy may be resistant to anticonvulsant therapy; barbiturate coma and aggressive control of ICP may be needed.
   e. Foley catheterisation: to monitor urinary specificic gravity, sediment, lead level.
   f. CaNa$_2$ EDTA 75 mg/kg/day IV infusion.
   g. After the initial dose of BAL, repeat the same dose at 4 hourly intervals until blood lead level falls below 40 mcg/100 ml. Then reduce BAL to 12 mg/kg/day in 3 divided doses.
   h. Reduce CaNa$_2$ EDTA to 50 mg/kg/day as condition improves.
      – Continue the above regimen until patient is asymptomatic and can tolerate oral chelation with D-penicillamine or DMSA.
2. *Severe acute poisoning without encephalopathy:* (BL more than 70 mcg/100 ml) –
   a. BAL 12 mg/kg/day.
   b. EDTA 50 mg/kg/day.
   c. Discontinue BAL when the BL falls below 40 mcg/100 ml, but continue EDTA for 5 more days.
   d. Change to oral chelation subsequently which may have to be continued until the BL falls below 15 mcg/100 ml, or 3 months have been completed.
3. *Moderate poisoning:* (BL between 45 and 70 mcg/100 ml) –
   a. EDTA 50 mg/kg/day.
   b. When blood lead falls below 40 mcg/100 ml, begin oral chelation.
4. *Mild poisoning:* (BL between 20 and 35 mcg/100 ml) –
   a. D-Penicillamine 30 mg/kg/day in 3 divided doses. Start with ¼th of the calculated dose. Double this after 1 week. Double again (to full dose) after 1 week. Continue this until the BL falls to less than 15 mcg/100 ml, or 3 months have been completed.

In addition to the above protocol, the following supportive measures must be instituted as applicable –
- Thiamine 10 to 50 mg/kg is said to improve neurological manifestations of lead poisoning.
- In acute poisoning, or in the event of radiopacities in the GI tract on X-ray, stomach wash can be done.
- Lead colic usually responds to IV calcium gluconate.

- Correct iron deficiency if present.*
- IV fluids, (maintain specific gravity of urine under 1020).
- If intracranial pressure is high due to cerebral oedema, administer mannitol or steroids as required (*vide supra*).
- Organic lead poisoning is mainly managed symptomatically. Chelation is done only if there is production of inorganic lead in the body from organic lead.
- After one round of chelation therapy, allow an interval of 2 weeks and then esimate the BL. Repeat chelation if necessary. Rebounds are common.
- And finally the *sine qua non* of treament of heavy metal poisoning: remove the patient from the source of exposure.

  In recent times, a new chelating agent called **Succimer** has been introduced in the management of lead poisoning in Western countries. It is said to be more efficacious and less toxic.

5. *Treatment guidelines for children:*
   a. BL less than 10 mcg/100 ml—Re-evaluate and rescreen patients in 1 year. No additional action required.
   b. BL 10–19 mcg/100 ml—Lead education and referrals should be provided. If the result of screening test is 10–14 mcg/100 ml, perform diagnostic test for lead on venous blood within 3 months, and at least one follow-up test within 3 months. If the result of screening test is 15–19 mcg/100 ml, perform diagnostic test for lead on venous blood within 2 months, and at least one follow-up test within 2 months. Follow according to guidelines in 20–44 mcg/100 ml range if BL persists in 15–19 mcg/100 ml range.
   c. BL 20–44 mcg/100 ml—Lead education and referrals should be provided. Provide clinical evaluation and management. If the result of screening test is 20–29 mcg/100 ml, perform diagnostic test for lead on venous blood within 1 month. If the result of screening test is 30–44 mcg/100 ml, perform diagnostic test for lead on venous blood within 1 week. Follow-up testing should be performed every 1 to 2 months.
   d. BL 45–69 mcg/100 ml—Lead education and referrals should be provided. Provide coordination of care (case management) within 48 hours. Perform clinical evaluation and management within 48 hours. Provide diagnostic testing within 24–48 hours and follow-up testing (in accordance with chelation therapy, at least once a month).
   e. BL equal to or greather than 70 mcg/100 ml - A medical emergency. Hospitalise the patient and begin immediate chelation therapy.
6. *Occupational exposure:*
   a. Employees whose blood lead level is equal to or greater than 50 mcg/100 ml should be temporarily removed from exposure until their blood lead level is at or below 40 mcg/100 ml.
   b. Employees may also be removed from exposure for medical reasons even if their blood lead levels are within 40 mcg/100 ml.

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* Not if BAL is being administered.

Autopsy Features

1. Pale skin, conjunctivae, and mucosa (*anaemia*).
2. Emaciation.
3. Burtonian line.
4. Lead lines on X-ray.
5. Pathological lesions or changes are sometimes found in kidneys, liver, male gonads, nervous system, blood vessels.

Forensic Issues

- Metallic lead has been part of the human environment for over 5000 years, and is today detectable in practically all phases of the inert environment and in all biological systems worldwide. Because of its malleability and low melting point, it was one of the first metals smelted and used by early human societies. Hippocrates is credited with the earliest description of chronic lead poisoning when he associated persistent abdominal colic in a man, with his occupation of extracting metals (around 370 BC). The ancient Romans were however the first to experience the metal's adverse effects on a massive scale mainly because of chronic poisoning through lead acetate which was used to sweeten wine in those days. Chemical analyses of the bones of Roman rulers have demonstrated high lead content and the madness of some of the Roman aristocracy (*Nero, Caligula*), may actually have been the result of lead poisoning.
- Today chronic lead poisoning is said to be the most important environmental health problem, particularly among young children. Children are especially susceptible to lead poisoning because of their increased absorption of lead from the GIT when compared with the adult. The child with pica is in enhanced danger because of the tendency in such a case to lick lead-based paints off walls, furniture, toys, pencils, etc. Sadly, a child's environment (particularly in countries such as India) is full of lead. Exposure can occur through paint, petrol, soil, food, water, and even air. Millions of children are probably affected annually leading to permanent neurological sequelae. The increasing antisocial behaviour of street urchins and slum dwelling children in congested and polluted cities may also be the offshoot of chronic lead poisoning, since studies have demonstrated a high incidence of plumbism in juvenile boys with delinquent behaviour. In addition, the alarming rise in recent years of learning disabilities, lowered IQ, and memory problems of children may be related to the effects of plumbism.
- Strategies to minimise, and if possible totally eliminate lead poisoning were evolved in the last two decades in Western countries such as the USA, and have met with significant success. Actually the first law in this regard was passed in Australia banning the use of lead in house paint. In 1971, the USA enacted a similar law. But the most important legislation passed was in 1980 when leaded petrol was banned in many of these countries.
- In India, the first National Emission Standards for lead were issued in February 1990, but the stipulated permissible

limit of 0.56 gm/L was still much higher than the recommended limit of 0.013 gm/L prevailing in the Western countries. Today petrol has finally made its entry into the entire country, and the situation is expected to improve in the coming years.

- Another important step taken in the West to minimise the incidence of plumbism was to ban lead-based household paints, while such paints are still freely available in India. It has been proved that even occasional nibbling of pencils or toys painted with lead containing compounds, or licking of wall paint can lead to significant lead intoxication. In the USA, the Consumer Product Safety Commission stipulated that the maximum permissible level of lead in household paints should not exceed 0.06% and recommended to house owners that painted surfaces containing in excess of 0.7 mg/cm² of surface lead be stripped and repainted (*lead abatement*). However, industrial paints for cars, machinery, bridges, highway stripes, etc., still contain 10 to 20% lead even in USA, while in India this may be upto 40%.
- Though today lead pipes are hardly used for supplying drinking water in most parts of India, the latter even now constitutes an important source of lead poisoning. Contamination can occur through atmospheric lead or industrial wastes, or from the soldered joints in the water distribution system.
- Lead intake through various food stuffs and beverages has been discussed in the preceding sections of this chapter.
- The most sizeable chunk of plumbism occurs from occupational exposure among workers exposed to lead such as miners, plumbers, battery makers, plastic manufacturers, garage workers, etc. (**Table 9.5**, *page no. 85*).
- Apart from all the conventional sources of lead exposure mentioned, novel situations are reported from time to time: ingestion of indigenous pharmaceuticals (especially *Ayurvedic* preparations) containing lead, home-made acidic beverages and fruit juices stored in ceramic ware, infant formula milk reconstituted with lead containing water, illicit alcohol (especially whiskey) distilled in lead soldered stills, and lead contaminated flour originating from negligently maintained mills.
- As would be evident from the foregoing, lead poisoning is almost always accidental or inadvertent in nature. Instances of suicide or homicide with lead-based compounds are extremely rare.

■ Mercury

Synonyms

Quicksilver; Liquid silver.

Physical Appearance

Metallic or elemental mercury (Hg°) is a heavy, silvery liquid (**Fig 9.13**) which is *per se* non-toxic, but vapourises at room temperature to give off a toxic vapour: mercuric mercury. Volatilisation is greatly enhanced by heating. In its solid state, mercury is a tin-white, ductile metal that is malleable enough to be cut with a knife.

Fig 9.13: Liquid mercury

Salts or compounds of mercury may be inorganic or organic in nature. Inorganic salts are of two types—mercuric (bivalent, i.e. Hg++) and mercurous (monovalent, i.e. Hg+). Common mercuric salts include mercuric chloride (*corrosive sublimate*) which is a white crystalline corrosive powder, mercuric oxide which is a red crystalline powder that turns yellow when treated with caustic soda or potash, and mercuric sulfide (*vermilion* or *sindoor*) which is a red crystalline powder. The most important mercurous salt is mercurous chloride (*calomel*) which is fibrous and heavy.

Organic mercurials are generally more toxic and comprise mainly compounds such as phenyl and methoxymethyl mercury, and alkyl compounds such as ethyl and methyl mercury. Mercurochrome is also an organic mercurial and exists as iridescent green scales readily soluble in water. The most toxic compound of mercury is methyl mercury.

Uses

Listed in **Table 9.6**.

Uses/Sources

- Breaking of mercury fluorescent light bulbs, heating of mercury-gold amalgams in order to extract gold, and the use of mercury-containing latex paint or building materials.
- Ingestion or handling of liquid mercury following breakage of thermometers or other mercury-containing devices.
- Insertion or removal of dental amalgam restorations can generate mercury vapour or respirable particulates. Bruxism, chewing, and tooth brushing may increase amalgam release of mercury vapour.
- Occupations which have the greatest exposure to mercury vapours include mining and processing of cinnabar ore, the chloralkali industry, and occupations in which mercury-containing instruments or materials are manufactured or handled.
- Dietary exposure to mercury (in the form of methyl

Table 9.6: Uses of Mercury Compounds

Industry	*Medicine and Dentistry*	*Miscellaneous*
1. Barometer, thermometer, etc.	1. Antiseptic and disinfectant	1. Electroplating
2. Ceramics	2. Dental amalgam	2. Embalming
3. Dry cell batteries	3. Diuretic	3. Fabric softener
4. Electrical appliances(mercury switches)	4. Purgative	4. Fingerprint powder
5. Explosives and fireworks		5. Fungicide
6. Felt hats		6. Gold and silver extraction
7. Fluorescent and mercury vapour lamps		7. Grain preservative
		8. Paints
		9. Pesticides
		10. Taxidermy

mercury) from consumption of fish, shellfish and marine mammals.

Usual Fatal Dose

- The amount of ingested mercury that would be fatal to a man is estimated at 100 grams.
- Mercuric chloride: 0.5 to 1 gm/70 kg
- Mercurous chloride : 1.5 to 2 gm/70 kg

Toxicokinetics

After inhalation, elemental mercury is readily absorbed through the alveolar membrane and enters the blood stream. Ingestion of mercury salts is asociated with slower rate of absorption. Mercury is rapidly converted to mercuric ions (Hg_{++}) in the blood which can lead to renal tubular damage during excretion. In the central nervous system, mercury acts mainly upon cerebellum, temporal lobe, basal ganglia, and corpus callosum.

Both organic and inorganic mercurials can be absorbed through intact skin.

Clinical Features

A. Poisoning with elemental mercury and inorganic salts:
1. *Acute poisoning—*
   – **Inhalation:**
     - This usually occurs while heating metal in a closed room, or following gold refining in an enclosed area.
     - Symptoms (which may be delayed upto 4 hrs) include dyspnoea, cough, fever, headache, chills, GI disturbances, metallic taste, and blurring of vision. Stomatitis, swelling of the salivary glands and gingivitis may develop within a few days of acute exposure to mercury. Teeth may become loose due to gum inflammation.
     - In severe cases there may be non-cardiogenic pulmonary oedema, dyspnoea, convulsions, etc.
     - Sometimes manifestations similar to *Kawasaki disease* (*mucocutaneous lymph node syndrome*) are seen especially in children, which may be mistaken for scarlet fever: conjunctival congestion, fever, reddened palms and soles,

deep red oral mucosa with "strawberry tongue" (**Fig 9.14**), skin rash (**Fig 9.15**), and cervical lymphadenopathy.
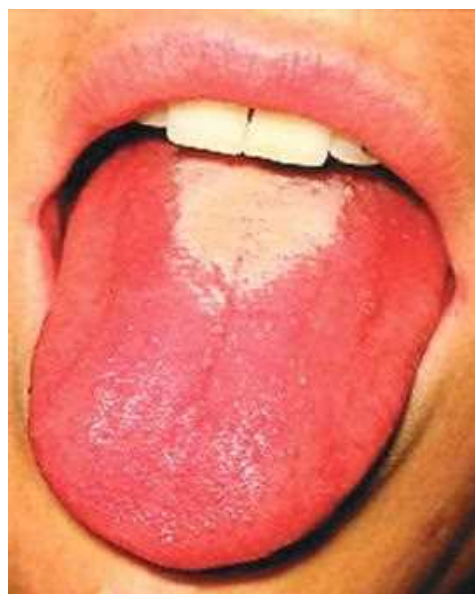
Fig 9.14: Strawberry tongue

Fig 9.15: Skin rash – Mucocutaneous lymph node syndrome

- **Ingestion:**
  - Small quantities of elemental mercury usually cause no harm on ingestion. Sometimes even a relatively large amount may pass out of the body uneventfully (egged on by a mild laxative). It is however advisable to take X-rays to monitor the progress of the elemental mercury through the GI tract.
  - Ingestion of mercuric salts produces corrosion leading to abdominal pain, vomiting, diarrhoea, and shock. The mucosa of the GI tract usually appears greyish. There may be haematemesis. In severe cases there is onset of renal failure, pulmonary oedema, and coma. Urine may appear pinkish.
  - Ingestion of button (or disc) batteries (**Fig 9.16**) poses special problems since they contain a variety of caustic substances apart from mercury. These batteries are used in hearing aids, watches, calculators, and some hand-held computer games. They range in size from 7 to 25 mm and can easily be swallowed by children. Each such battery contains a heavy metal (usually mercury) along with a variety of caustic alkalies, especially sodium or potassium hydroxide.
    - » In the majority of cases of button battery ingestion there are no serious consequences, and the object usually passes out in the stools quite uneventfully over a period of 1 to 4 days, However if the contents of the battery leak out during transit, there can be production of burns by the caustic alkalies, and a theoretical risk of mercury poisoning (so far unreported).
    - » **Management**:
      - ⌂ Airway assessment and stabilisation.
      - ⌂ Antero-posterior and lateral chest radiographs that visualise the neck, chest, and abdomen.
      - ⌂ Patients with batteries in the airway or lower respiratory tract require emergency removal via bronchoscopy.

Fig 9.16: Button (Disc) batteries

- ⌂ If the battey is visualised in the oesophagus, it requires immediate endoscopic removal by forceps or magnet.
- ⌂ Intact batteries located past the stomach in asymptomatic patients can be followed up by serial stool examinations, checking for battery passage.
- ⌂ If the battery fails to pass the pyloric region within 48 hours, endoscopic retrieval may be necessary.
- ⌂ The use of polyethylene glycol solution in whole bowel irrigation can be considered in patients with poor mobility of batteries in the GI tract.

- **Injection:**
  - Subcutaneous or intramuscular injections of elemental mercury may cause abscess formation wih ulceration, extruding tiny droplets of mercury.
  - Intravenous injection can result in *mercurialism* characterised by thrombophlebitis, granuloma formation, and pulmonary embolism. Repeated haemoptysis is a characteristic feature.
  - Intra-arterial injection can result inadvertently from arterial blood gas sampling with syringes which contain liquid mercury as an anaerobic seal, or from arterial pressure monitors which employ a liquid mercury manometer connected directly to the intra-arteial needle. Leakage of mecury into arterial blood results in peripheral embolisation with ischaemia, and sometimes frank gangrene. There may also be abscess formation and ulceration. X-ray usually reveals multiple, tiny spheres in the veins draining the entry site. Mercury globules may also be seen in various organs.

2. *Chronic poisoning (Hydrargyrism)—*
   - **Inhalation:**
     - *Tremor*: It is one of the classical and most consistent manifestations of chronic mercury poisoning and is sometimes referred to as the *Danbury tremor*. It begins in the hands and is of a coarse, intentional type, interspersed with jerky movements. Later it progresses to the lips, tongue, arms, and legs. The advanced condition is referred to as *Hatter's shakes*,* when the tremor becomes so severe that daily activities involving some delicacy of movement become grossly impaired, e.g. shaving, writing, holding a tumbler or spoon, etc. The most severe form of the condition is referred to as *concussio mercurialis* when literally no activity is possible. Even years after exposure to mercury has ceased, tremor may persist.

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* So called because the condition was first described among felt hat workers.

- Ataxia, reeling gait. Fasciculations of the tongue and legs have been reported in paediatric patients after several months of exposure to elemental mercury.
- A Parkinsonian syndrome with resting and intention tremor, bradykinesia and cogwheel rigidity has been reported after long-term exposure to elemental mercury vapours. The syndrome improved after penicillamine chelation.
- Metallic taste (**Table 9.7**), anorexia, nausea, increased salivation.
- Gingivitis, halitosis, blue line on gums (similar to the *Burtonian line* of plumbism).
- Erythematous macular or papular rashes are common with mercury vapour poisoning. The rash usually involves the hands and feet. The trunk, axillae, popliteal and antecubital fossae may also be affected.
- *Erethism*: Another classic manifestation, it refers to a cluster of psychiatric symptoms including abnormal shyness, loss of self confidence, depression, irritability, amnesia, excitability, progressing in later stages to delirium with hallucinations, or suicidal melancholia, or manic depressive psychosis (*mad hatter*).*
- *Mercuria lentis*: Characterised by the brown reflex of anterior lens capsule of the eye. There may be fine punctate opacities. Visual blurring is often present, and sometimes there is concentric constriction of visual fields ("tunnel vision"). Mercuria lentis usually indicates chronic exposure to elemental mercury rather than toxicity. Diagnosis is made by slit lamp examination.
- Renal damage results in membranous glomerulonephritis with hyaline casts and fatty casts in the urine. It is more common in chronic ingestion of mercury salts.

– **Ingestion:**
  - Colitis.
  - Melanosis coli.
  - Dementia.
  - Tremor.
  - Renal failure.
  - *Acrodynia* (*Pink disease*) (**Fig 9.17**): This is seen mainly in children. Formerly most cases were related to chronic use of teething powders containing mercurous chloride. But almost any form of chronic mercury exposure can cause this condition including inhalation of elemental mercury vapour or cutaneous application of ammoniated mercury ointments. The onset is usually insidious with anorexia, insomnia, profuse sweating, skin rash, and photophobia. The hands and feet become puffy, *p*inkish, *p*ainful, *p*araesthetic, *p*erspiring and *p*eeling (*the*

Table 9.7: Poisons/Drugs Producing Metallic Taste

Acetaldehyde	Iodine
Allopurinol	Iron salts
Arsenicals	Lead
Cadmium	Lithium
Ciguatoxin	Mercury
Copper	Metoclopramide
Disulfiram	Metronidazole
Ethambutol	Mushroom (*Coprinus*)

Fig 9.17: Pink disease (Acrodynia)

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* Derived from a character of the same name in Lewis Carroll's "Alice's Adventures in Wonderland" published in 1865

child pees!). Teeth may be shed, with ulceration of gums. In older children and adults the disease is milder, and is characterised by antisocial behaviour, insomnia, aching extremities, and alopecia. Today the incidence of childhood acrodynia is uncommon since the use of mercurial teething powders and diaper rinses has been abandoned.

- Exposure to mercury at an early age is suggested as a possible factor in the aetiology of autism, as per recent studies. According to these investigators, the reported increased rates of autism in some Western countries over the last few decades could be associated with increased exposure to mercury through infant vaccines containing thimersol (also spelt thimerosal or thiomersal), dental amalgams, or RhoD immunoglobulin injections that the mother received during pregnancy.

B. Poisoning with organic mercurials:
1. Features are related mainly to the CNS and include dysarthria, ataxia, paraesthesias, neuropathies, diminished auditory and visual acuity, mental deterioration, and chorea.
2. A special type of organic mercurial poisoning relates to food poisoning through methyl mercury which has caused terrible tragedies in the past, and may well cause more havoc in the years to come, unless measures are devised to curb its far reaching effects. Between 1953 and 1970, on the island of Kyushu around Minimata Bay in Japan, more than 2000 people were diagnosed to be suffering from a curious cluster of neurological symptoms comprising paraesthesiae, narrowing of vision, dysarthria, diminution of hearing, amnesia, ataxia, staggering gait, weakness, and emotional instability. Some developed paralysis and became stuporous, and out of all the people afflicted nearly a hundred died. The condition came to be known as the ***Minimata disease*** (**Fig 9.18**), and intensive investigations pointed to one inescapable conclusion: it was caused by consumption of fish contaminated with methyl mercury, which originated from a nearby vinyl chloride plant. The most severely affected victims were actually infants who had been exposed in utero.

In 1964, a similar outbreak of poisoning was reported from another part of Japan: Niigata along the Agano river. Forty three cases were diagnosed as having the Minimata disease out of whom six died. Then came the shocking tragedy in Iraq in 1971–72, when 500 people died out of a total of 6530 victims due to consumption of imported wheat and barley meant for sowing, treated with methyl mercury. Nearly 95,000 tonnes of seed grain treated with methyl mercury was baked into bread.

Unlike inorganic mercury compounds, methyl mercury is a subtle, difficult to detect, long lasting poison. When large quantities of industrial waste and agricultural fungicides containing mercury are released

Fig 9.18: Minimata disease

into the ocean apart from volcanic discharges, methylation of this relatively inoffensive metal results in the production of methyl mercury which then enters the algae-fish-human food chain. This biological methylation is accomplished by a deep sea bacterium called *methanobacterium omelanskii*. These bacteria are consumed by plankton which in turn are eaten by fish. When human beings partake of such contaminated fish, the scene is set for a tragedy.

In the human body, methyl mercury is bound by haemoglobin and circulates in this form in the bloodstream for several weeks or months. Excretion is very slow and the estimated half life in man is 70 days, while in fish it is 200 days. It passes easily into the CNS where it selectively and irreversibly damages the cells of the granular layer of cerebellum and cerebral cortex. Methyl mercury is especially injurious to the CNS of infants and children.

Diagnosis

1. X-ray.
2. *Blood mercury level*: Flameless atomic absorption spectrometry is best for deducing this. Normal level is less than 3 mcg/100 ml. Symptoms of toxicity may occur at blood mercury concentrations of 5 mcg/100 ml or greater. Symptoms do not always correlate with blood mercury levels.
3. *Urine mercury level*: Urinary mercury is the best biological marker for chronic elemental or inorganic mercury exposure. Urinary mercury concentrations are also useful for assessing the response to chelation therapy. Normal level is less than 10 to 15 mcg/100 ml. Signs and symptoms of toxicity may begin to occur at urinary mercury concentrations of 20 to 100 mcg/100 ml. Urinary mercury levels, however, often do not correlate with clinical signs and symptoms of toxicity. There is a high degree

of intraindividual variation in urine mercury levels. The averaging of several urinary mercury determinations may be required. A 24-hour urine collection is recommended.

4. *Hair analysis*: Done by cold vapour atomic absorption spectrometry. External contamination can however vitiate the results.

Treatment

A. Acute Poisoning:
1. **Metallic mercury and inorganic compounds—**
   - Inhalation:
     - Supportive measures.
     - Chelation
   - Ingestion:
     - In elemental mercury ingestion, take X-ray and repeat it to study the progression. If mercury gets lodged in the appendix, perform appendectomy.
     - Administer laxatives.
     - Demulcents for corrosive compounds such as mercuric chloride.
     - Stomach wash: It may be advisable to add egg white or 5% albumin or just plain milk to the lavage fluid to bind the mercury.
     - Chelation.
   - Injection:
     - If there is abscess formation, perform repeated incisions to remove the mercury. If the globules are very minute and widely distributed in the intercellular spaces, excise the affected tissue.
     - Monitor the CNS and renal functions for evidence of toxicity.
     - Mercuric salts are relatively well adsorbed by activated charcoal.
     - Chelation.
2. **Organic mercurials**
   - Supportive measures.
   - Chelation is not very effective.
   - In severe manifestations with acute renal failure resulting from any type of exposure, the following may be tried: haemodialysis, haemofiltration, or plasma exchange. Haemoperfusion is said to be ineffective.

B. Chronic Poisoning:
1. **Chelation therapy—**
   - BAL (British Anti Lewisite)
     - 100 mg by deep IM, every 4 hours for 48 hours, followed by 100 mg every 8 hours for 8 to 10 days.
   OR
   - DMPS (2,3 DiMercapto Propane-1-Sulfonate)
     - 5 mg/kg IV, or 6 infusions of 250 mg/day, followed by 100 mg orally twice a day for 24 days.
   OR
   - DMSA (Meso 2,3 DiMercapto Succinic Acid, or Succimer)

   - 30 mg/kg/day orally for 5 days, followed by 20 mg/day for 14 days.
   OR
   - D-Penicillamine
     - 250 mg qid, for adults, (20 mg/kg/day) for 5 to 10 days.
2. Supportive measures.

Autopsy Features

1. In death due to acute mercury poisoning, the mucosa of the mouth, throat, oesophagus, and stomach appears greyish in colour with softening and superficial corrosion. There may be haemorrhagic points.
2. If there had been survival for a few days, the large intestine may reveal ulceration.
3. Kidneys are often pale and swollen due to oedema of renal cortex. Microscopy usually demonstrates necrotic changes in the renal tubules.

Forensic Issues

- Mercury and its compounds constitute important industrial, agricultural, and occupational toxic hazards. In the past when mercury was used in its various forms for the therapy of a wide variety of ailments including syphilis, iatrogenic poisoning was common. Even today calomel (mercurous chloride) is sometimes recommended as a laxative. Prolonged use can cause colitis dementia, tremor, and renal failure. Acrodynia resulting from teething powders containing calomel has fortunately become a rarity.
- The tragic consequences of chronic industrial exposure to mercury have been outlined in the foregoing sections.
- Domestic exposure though not often reported is today a distinct threat. Such exposure may result from inadvertent mercury spills (broken thermometers), or from home gold-ore processing.
- An important area that must be considered in relation to chronic mercury exposure is dentistry. Dental amalgams used for fillings often contain mercury. Dental surgeons may get chronically exposed due to this reason. Many dentists still knead the amalgam mass in the palms of their hands. In squeezing the mass to express excess mercury, droplets of the metal sometimes fall to the floor where they are allowed to remain and vapourise. Significant concentrations may be detectable even in the reception room environment. Recent studies of mercury levels in dental surgeons suggest that they are at high-risk for developing mercury related polyneuropathies, psychopathies, and visual disturbances. However patients wih mercury amalgam fillings are not at risk even though such fillings may remain intact for years.
- Food poisoning (especially involving fish) through mercury compounds can give rise to manifestations akin to the Minimata disease.
- A relatively new hazard concerns dry cell batteries used in cameras, hearing aids, torches, and watches.

■ Iron

Physical Appearance

Metallic iron is silvery white in colour, occurring naturally as *haematite*, *magnetite*, etc. and usually causes no problems. In fact it is an essential element and deficiency results in anaemia. Even if there is more than the required intake daily, the excess is excreted. But in some individuals with inborn errors, even normal dietary iron can cause toxic effects due to accumulation, e.g. haemochromatosis (*bronze diabetes*).

Various iron salts are administered therapeutically in individuals with iron deficiency anaemia which can result from a wide variety of causes. Iron poisoning is related in most instances to overdose of such salts. One of the commonest is ferrous sulfate (*green vitriol*) which occurs as bluish green crystals (**Fig 9.19**). Iron (ferric) oxide, i.e. rust does not cause iron poisoning.

Uses/Sources

- Dietary Sources:
  - ❖ The required daily amount of iron of 10–20 mg for adults is supplied through average diet. The required intake increases to 25–30 mg in pregnancy.
  - ❖ The average daily intake for adults is 15 mg.
- Environmental Sources:
  - ❖ Iron is found in 5.1% of the earth's crust. It is the second most abundant metal, and the fourth most abundant element. It is believed that the earth's core consists mainly of iron.

Fig 9.19: Ferrous sulfate

- Uses:
  - ❖ Industrial uses—
    - Iron is primarily used in powder metallurgy and serves as a catalyst in chemical reactions.
    - Iron is a component of carbon steels, cast iron, high-speed steels, high-strength low-alloy steels, manganese alloy steels, and stainless steels.
    - Steel is the most important alloy of iron. It contains 0.25–2% of carbon. Alloyed with carbon (C), manganese (Mn), chromium (Cr), nickel (Ni) and other elements, iron is used to form steel.
    - Wrought iron is almost pure iron.
    - Iron uses include magnets, dyes, pigments, and abrasives.
  - ❖ Biological uses
    - Iron is essential to life. It is a constituent of biological pigments such as haemoglobin, cytochromes and ferrichromes.

Usual Fatal Dose

Commonly used iron salts in therapeutics along with respective iron content are mentioned in **Table 9.8**.

The amount of iron in a particular iron salt (e.g. sulfate, gluconate, fumarate, etc.) is not the same. Take the total molecular weight of iron in the compound, and divide it by the molecular weight of the compound and multiply by 100. Multiply the total number of milligrams of the compound ingested by the percentage of iron in the compound. Another fast method to remember the approximate amount of iron in a preparation is FSG:359. This means the amount of ferrous Fumarate divided by 3; Sulfate divided by 5 and Gluconate divided by 9 is the amount of elemental iron in the preparation.

The usual fatal dose corresponds to about 200 to 250 mg of elemental iron per kg of body weight. This can be calculated from the percentage of elemental iron in a particular preparation, e.g. a single 150 mg tablet of anhydrous ferrous sulfate which contains 37% of elemental iron will contain a total of 55 mg of elemental iron. But such calculations can be misleading since serious hepatotoxicity can result at much lower concentrations of iron in the body which can lead to death. In practice, this can be as low as 60 mg of elemental iron/kg. Hence just a handful of these tablets (15 to 20 in number), can be lethal to a young child.

Table 9.8: Elemental Iron Content of Iron Salts

Iron Salt	Iron Content (%)	Iron Salt	Iron Content (%)
Ferrous gluconate	12	Ferrous fumarate	33
Ferric pyrophosphate	12	Ferric chloride (anhydrous)	34
Ferric ammonium citrate	14 to 18	Ferrous succinate	35
Ferroglycerine sulfate	16	Ferrous sulfate (anhydrous)	37
Ferrous sulfate (hydrated)	20	Ferric phosphate	37
Ferric chloride (hydrated)	20	Ferrous chloride (anhydrous)	44
Ferrous chloride (hydrated)	28	Ferrous carbonate	48

Toxicokinetics

Iron poisoning occurs when serum iron level exceeds the total iron-binding capacity (TIBC), resulting in free circulating iron in the bloodstream.

Mode of Action

Free iron causes:
a. Massive postarteriolar dilatation which results in venous pooling.
b. Increased capillary permeability resulting in decreased plasma volume.
c. Oxidation of ferrous to ferric iron releasing hydrogen ions. Subsequent hydration of ferric iron results in metabolic acidosis.
d. Inhibits mitochondrial function leading to hepatic damage, hypoglycaemia, and hypoprothrombinaemia.
e. Inhibits thrombin-induced conversion of fibrinogen into fibrin.
f. Has a direct corrosive action on the GI mucosa.

Clinical Features

Most cases occur in children. There are 5 stages:
- *Stage I* (0.5 to 2 hours) includes vomiting, haematemesis, abdominal pain, diarrhoea, haematochezia, lethargy, shock, acidosis, and coagulopathy. Necrosis to the GI tract occurs from the direct effect of iron on GI mucosa. Severe gastro-intestinal haemorrhagic necrosis with large losses of fluid and blood contribute to shock. Free iron and ferritin produce vasodilatation that may also contribute to shock.
- *Stage II* (after *Stage I*) includes apparent recovery and may contribute to a false sense of security. Observe closely.
- *Stage III* (2 to 12 hours after *Stage I*) includes profound shock, severe acidosis, cyanosis and fever. Increased total peripheral resistance, decreased plasma volume, haemo-concentration, decrease in total blood volume, hypotension, CNS depression, and metabolic acidosis have been reported.
- *Stage IV* (2 to 4 days) includes possible hepatotoxicity, convulsions, and coma. Thought to be a direct action of iron on mitochondria. Monitor liver function tests and bilirubin. Acute lung injury may also occur.
  - ❖ The primary site of hepatic injury is the periportal areas of the hepatic lobule (the principal site for hepatic regeneration), which may explain the increase in mortality and poorer prognosis. Iron induced hepato-toxicity is a presumed result of free radical generation and lipid peroxidation. Iron catalyses hydroxyl radical formation (the most potent-free radical), which initiates lipid peroxidation. Based on limited data, antioxidants may have a hepatoprotective role in iron poisoning.
- *Stage V* (days to weeks) includes GI scarring and strictures. GI obstruction secondary to gastric or pyloric scarring may occur due to corrosive effects of iron. Evaluate with barium contrast studies. Sustained-release preparations have resulted in small intestinal necrosis with resultant scarring and obstruction.

These stages of iron poisoning may not occur in all patients.

After massive overdose, patients may present in shock. With less serious overdoses, the initial gastrointestinal symptoms may be the only findings to develop even without treatment.

Diagnosis

1. X-ray: Like all other heavy metals, iron and its compounds are radiopaque. However, chewable iron tablets and liquid iron formulations are usually not visualised on X-ray. Completely dissolved iron tablets/capsules may also not be radiopaque.
2. Serum iron level: Poisoning is indicated if this exceeds 150 mcg/100 ml, and serious toxicity is usually associated with levels beyond 500 to 600 mcg/100 ml. Peak levels are seen around 4 hours after ingestion. Measuring the total iron binding capacity and relating it to the serum iron level is often misleading and unreliable.
3. Total leucocyte count (TLC), electrolytes, glucose, blood gas, clotting studies, liver function and renal function tests are useful estimates.
4. Chelation challenge test: Desferrioxamine in a dose of 25 mg/kg (maximum 1 gm) is given IM. If the serum iron has exceeded iron binding capacity, the excess iron is chelated to desferrioxamine and the complex is excreted as a pinkish (*vin rosé*) colour in the urine (**Fig 9.20**). But a negative result does not rule out iron poisoning.
5. Qualitative desferrioxamine colour test (QDCT): 2 ml of gastric fluid and 2 drops of 30% hydrogen peroxide are placed in 2 plastic tubes. 0.5 ml of solution of desferriox-amine (500 mg in 4 ml distilled water) is added into one tube and the resulting colour change is compared with the other tube (control). If the test is positive, an orange to red colour will develop in the tube in which desferrioxamine was added. The test must be done within 2 hours of inges-tion of iron.

Treatment

1. Stomach wash with normal saline performed gently may be of benefit in massive ingestions. Desferrioxamine must not be used for lavage.
2. Activated charcoal is ineffective.
3. Magnesium hydroxide solution (1%) administered orally may help reduce absorption of iron by precipitating the

Fig 9.20: Iron overdose: *Vin rose* urine (Left to right—dark, medium, normal urine of the same patient as he recovered) (*Pic:* Dr. S Senthilkumaran)

formation of ferrous hydroxide. Magnesium hydroxide and calcium carbonate containing antacids may safely be used in therapeutic doses to help reduce iron absorption.

4. Obtain serum iron levels, creatinine, electrolytes, blood haemoglobin concentration, blood prothrombin time, baseline liver function tests, and arterial blood gases in seriously poisoned patients.

5. Correction of hypovolaemia, and metabolic acidosis.

6. Chelation therapy:
  a. This is indicated in any of the following situations:
    – More than one episode of vomiting or diarrhoea.
    – Significant abdominal pain, hypovolaemia, or acidosis.
    – Multiple radiopacities on abdominal radiograph.
    – Serum iron level greater than 350 mcg/100 ml.
  b. Chelation can be done either with desferrioxamine (*parenteral*) or deferiprone (*oral*).
    – *Dose (desferrioxamine):*
      - Intravenous Dose: Administer by continuous infusion at a rate of up to 15 mg/kg/hr. Faster rates or IV boluses may cause hypotension in some individuals. Infusion rates up to 35 mg/kg/hr have been used in children with severe overdoses without adverse effects.
      - Intramuscular Dose: Administer 90 mg/kg, up to a maximum of 1 gm/dose, every 8 hours as needed. Pain and induration at the injection site are often experienced.
      - Total Daily Dose: The recommended total intravenous or intramuscular daily dose should not generally exceed 6 grams.
      - Duration of Infusion: Duration of infusion is guided by the patient's clinical condition. Patients with moderate toxicity are generally treated for 8 to 12 hours, those with severe toxicity may require desferrioxamine for 24 hours or longer. Patients should be re-evaluated for evidence of recurrent toxicity (hypotension, metabolic acidosis) several hours after the infusion is discontinued. Infusion duration of greater than 24 hours has been associated with the development of ARDS.
      - Therapy Endpoint/Colour Change: Monitor urine for characteristic pink to orange-red colour ("*vin rose*") indicating the excretion of ferrioxamine (chelated iron) although frequently a urine colour change is not seen. In patients who demonstrate a colour change, desferrioxamine therapy may be discontinued when the urine loses the "*vin rose*" colour, indicating a decrease in concentration of chelated complex, if the patient is generally asymptomatic.
    – *Adverse Effects:*
      - Sepsis: The use of desferrioxamine in iron-overdosed children has been associated with *Yersinia enterocolitica* septicaemia and mucormycosis. In such circumstances desferrioxamine may

have provided the iron siderophore complex growth factor needed by the bacteria to induce overgrowth.
      - Visual Toxicity: Continuous intravenous administration of desferrioxamine, often in the presence of low iron stores, has produced visual toxicity (decreased visual acuity, night blindness, colour blindness, retinal pigmentary abnormalities). Visual toxicity has also been associated in patients with rheumatoid arthritis and chronic renal failure. The mechanism remains unclear.
      - Ototoxicity: In one study, some patients receiving desferrioxamine had abnormal audiograms, with a few requiring hearing aids. Risk factors include desferrioxamine dose, duration of therapy and the presence of a low serum ferritin.
      - Pulmonary Toxicity: A "pulmonary syndrome" has been associated with high dose IV (10 to 25 mg/kg/hr) desferrioxamine therapy for several days for acute and chronic iron overload patients. Features include severe tachypnoea, hypoxaemia, fever, eosinophilia, preceding urticaria, and pulmonary infiltrates.
      - Hypotension appears to be rate related. One study has suggested that intravenous desferrioxamine be administered at a dose NOT to exceed 15 mg/kg/hr. At present, a safe administration rate has not been established and is based on empiric data.
      - Renal Toxicity: Elevated creatinine levels and decreased creatinine clearances have been reported.
  c. Continuous arteriovenous haemofiltration (CAVH) may be helpful in severe poisoning.
  d. Liver transplantation is the only therapeutic avenue open in the presence of fulminant hepatic failure.

Autopsy Features

1. Haemorrhagic necrosis of gastric mucosa. In ferrous sulfate poisoning, gastric contents may appear bluish green in colour.
2. Hepatic and renal necrosis.

Forensic Issues

Acute iron poisoning has assumed grave significance in recent years and cases of accidental poisoning are being reported with alarming frequency in young children. Since most iron preparations (syrups and tablets) are brightly coloured and pleasantly flavoured, they constitute an irresistible, fatal attraction for these innocent victims. To compound the tragedy, in several instances the parents themselves are ignorant about the toxicity of these preparations and tend to dismiss them as "harmless vitamins". It is imperative that public awareness be generated about the treacherous lethality of iron preparations. Introduction of childproof containers would be very effective in

minimising inadvertent ingestions by children as demonstrated by the Western experience.

■ Copper

Physical Appearance

- Copper is a lustrous, ductile, malleable, odourless solid with a distinct golden-red or reddish-brown colour. It is an essential trace element, being the third most abundant trace element in the body, and is an important catalyst for haeme synthesis and iron absorption. Metallic copper itself probably has little or no toxicity, although reports in the literature are conflicting.
- Copper salts produce toxicity. Soluble salts, such as copper sulfate (**Fig 9.21**), are strong irritants to skin and mucous membranes (**Table 9.9**).

Uses

- Elemental Copper:
  - ❖ Copper has excellent electrical conductivity, corrosion resistance, malleability and ductility, which make it very useful as an industrial metal.
  - ❖ Copper is widely used in applications for which high electrical and thermal conductivity are needed. Copper whiskers are used in thermal and electrical composites.
  - ❖ Copper is used in important alloys such as bronze (copper alloyed with as much as 10% tin) and brass (copper alloyed mainly with zinc). Money metal, another copper alloy, is copper alloyed with nickel.

Fig 9.21: Copper sulfate

Table 9.9: Toxic Salts of Copper

Chemical Name	Common Name
Copper acetoarsenite	*Paris green*
Copper arsenite	*Scheele's green*
Copper carbonate (native)	*Mountain green*
Copper carbonate (with chalk)	*Brunswick green*
Copper subacetate	*Verdigris*
Copper sulfate	*Blue vitriol*

- Copper is useful in electroplated coatings and under-coatings for products made from nickel, chromium, and zinc, and in cooking utensils. Copper is also made into corrosion-resistant plumbing pipes, used in heating and roofing materials for building construction, and has applications in industrial machinery and in automobiles.
- ❖ Copper's contraceptive effects (as a spermatocide) are exploited for intrauterine devices. Its contraceptive effects permit the use of a smaller device, resulting in fewer side effects such as pain and bleeding.
- Copper Compounds:
  - ❖ Copper oxide: Cupric oxide (black copper oxide) (CuO), or Cuprous oxide (red copper oxide) (Cu_2O)— Copper oxide is used as a catalyst and a pigment for ceramic, glass, enamel, and porcelain; it is used in copper metallurgy, pyrotechnics and welding and in the manufacture of rayon; and it is found in batteries, electrodes, desulfurising oils, paints fungicides and insecticides.
  - ❖ Copper acetate: Cupric acetate or Cuprous acetate— Copper acetate is used as a paint pigment, insecticide, and fungicide.
  - ❖ Copper carbonate: Cupric carbonate—Copper carbonate is used in pigments, pyrotechnics, insecticides, fungicides and brass colouring.
  - ❖ Copper chloride: Cupric chloride ($CuCl_2$) or Cuprous chloride (CuCl)—Copper chloride is used as a disinfectant, in metallurgy, for the preservation of wood pulp, in photography, in water purification, and as a feed additive.
  - ❖ Copper nitrate: Cupric nitrate (CuN_2O_6)—It shares many uses with copper chloride and, in addition, is used preferentially in pharmaceutical preparations and in paints, varnishes and enamels.
  - ❖ Copper cyanide: Cuprous cyanide (CuCN)—Its chief use is in the electroplating of copper on iron.
  - ❖ Copper sulfate/sulfide: Cupric sulfate, Cupric sulfide (CuS), or Cuprous sulfide (Cu_2S)—It is used as a fungicide, molluscicide and wood preservative, for water treatment as a bactericide and algaecide, as a mordant, in leather tanning and hide preservation, and in some fertilisers. It is also used medicinally as an emetic, and in several intrauterine contraceptive devices.

Usual Fatal Dose

About 10 to 20 grams of copper sulfate.

Toxicokinetics

The safe daily intake of dietary copper is 2 to 3 mg/day, while the actual requirement is only 0.8 mg/day. It is required for the functioning of enzymes such as catalase and peroxidase.

Copper is normally present in serum in two forms—one which is bound to albumin (7% of total serum copper), and one which is bound to the copper enzyme caeruloplasmin (93%). Urine normally contains only traces of copper (5 to 25

mcg/day). About 0.1 to 1.3 ng of copper is excreted through the bile daily and lost in the faeces. Total body copper content is 150 mg.

Copper can be absorbed through GI mucosa, and from intact skin.

Clinical Features

1. **Acute Poisoning:**
   a. Copper intoxication is characterised by myalgia, abdominal pain, vomiting (bluish or greenish),* diarrhoea, acidosis, pancreatitis, methaemoglobinaemia, haemolysis, jaundice, oliguria, renal failure, seizures, delirium and coma.
   b. Hepatomegaly, liver tenderness, increased levels of transaminase and jaundice may occur on the second or third day after ingestion of copper salts.
   c. Acute renal failure develops in 20 to 40 percent of patients with acute copper sulfate intoxication and is believed to be mainly due to intravascular haemolysis. This might also occur after ingestion of other copper salts. Anuria or oliguria may develop 24 to 48 hours after ingestion, accompanied by an increase in BUN.
   d. Inhalation of copper dust or fumes can cause cough, sore throat, and conjunctivitis, while copper oxide is one of the incriminating agents in metal fume fever.
   e. Eye exposure to copper can result in conjunctivitis and corneal ulceration or turbidity as well as palpebral oedema. Copper or copper alloy foreign bodies lodged in the eye (*chalcosis lentis*) can result in uveitis, abscess, serious injury or loss of the eye; over time, the copper may dissolve and disseminate to the lens, cornea and iris, where it may produce a greenish-brown discolouration of the anterior capsule visible by slit-lamp microscope.

2. **Chronic Poisoning:**
   a. Chronic inhalation of copper sulfate spray used as an insecticide in vineyards can cause *vineyard sprayer's lung disease* characterised by a histiocytic granulomatous lung. Liver damage is also common.
   b. Chronic contact with swimming pool water containing algicidal copper chemicals can cause green hair discolouration.
   c. Churches in some developing countries distribute "spiritual green water" to devotees which contains copper sulfate. When this is ingested, serious toxicity and even death can result.
   d. Cooking in copper or brass vessels can cause copper poisoning due to verdigris. Copper poisoning can also result from the leaching of copper containers in which carbonated water, citrus fruit juices, and other acidic beverages have been stored.
   e. Chronic copper toxicity is the hallmark of Wilson's disease, an autosomal recessive genetic disorder in which there is deficiency of caeruloplasmin. Discolouration of the peripheral part of the cornea (Kayser-Fleischer ring) (**Fig 9.22**) is a pathognomonic feature of this condition characterised by deposition of copper in parenchymal tissue. A 'sunflower-like' discoloration of the most anterior layers of the lens has also been reported in patients with Wilson's disease.
   f. Metal fume fever, wheezing and rales have been reported in workers exposed to fine copper dust. Dyspnoea has developed after oral copper exposure.
   g. Skin exposure can produce severe irritation, itching, erythema, dermatitis and eczema.

Diagnosis

1. Serum caeruloplasmin level: A value of 35 mg% or less at 24 hours is associated with serious toxicity.
2. Blood copper level: If this is elevated beyond 1.5 mg/100 ml, there is likelihood of serious toxicity. Average normal levels are 1.09 mg/L for men, 1.20 mg/L for non-pregnant women and 2.39 mg/L for pregnant women.
3. Urine level: Normal daily excretion of copper in the urine is less than 0.6 micromole/day.
4. Radiography: Metallic copper is radiopaque. X-rays may be useful to establish diagnosis. Copper salts are not considered radiopaque.

Treatment

1. Haemodialysis is said to be useful in the early stages of poisoning when the metal is still circulating in the bloodstream as free copper.
2. Administration of egg white or milk orally may help in detoxifying copper resulting in the formation of an albuminate.
3. Stomach wash can be done with a solution of potassium ferrocyanide. It converts the copper salt (especially copper sulfate) into insoluble cupric ferrocyanide.
4. Induction of emesis is contraindicated.

Fig 9.22: Kayser-Fleischer ring

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* Bile is also greenish but can be differentiated by adding ammonium hydroxide. The vomitus becomes deep blue in colour in copper poisoning, while bile will not change colour.

5. There is little clinical experience in the use of chelators in the setting of acute copper intoxication. Data on efficacy is derived from patients with chronic copper intoxication (Wilson's disease, Indian childhood cirrhosis) and animal studies.

   a. **D-penicillamine** is considered the drug of choice for Wilson's disease, a condition of chronic copper overload. Chelation therapy is generally recommended in symptomatic patients. If the patient is asymptomatic, confirmation from the laboratory may be received before instituting chelation therapy.
      – Usual Adult Dose: 1000 to 1500 mg/day divided every 6 to 12 hours, before meals.
      – Usual Paediatric Dose: Initially 10 mg/kg/day, gradually increase to 30 mg/kg/day divided in two or three doses as tolerated. Doses up to 100 mg/kg/day in four divided doses may be used depending on the severity of poisoning and adverse effects. Give before meals; maximum 1 gm/day.
      – Pregnancy: Use of penicillamine in pregnancy has been associated with connective tissue abnormalities, hydrocephalus, cerebral palsy, cardiac and great vessel anomalies, webbing of fingers and toes, and arthrogryposis multiplex. However, the teratogenic effect when used in low doses or for short periods of time, as in metal chelation, has yet to be determined.

   b. **Dimercaprol** has been used in patients with acute copper sulfate intoxication but data regarding efficacy are lacking. The usual dose is 3 to 5 mg/kg/dose deep IM every 4 hours for 2 days, every 4 to 6 hours for an additional 2 days, then every 4 to 12 hours for up to 7 additional days.

   c. **Unithiol** is not FDA-approved in USA, but it has been used with beneficial effects by some investigators. The usual dose is 5% solution IM or SC 5 mg/kg three or four times during the first 24 hours, 2 to 3 times on day two, and 1 to 2 times daily thereafter.

   d. **Calcium disodium edetate** has been used to treat patients with acute copper sulfate intoxication but data regarding efficacy are lacking. The usual dose is 75 mg/kg/24 hours deep IM, or slow IV infusion given in 3 to 6 divided doses up to 5 days; may be repeated for a second course after a minimum of 2 days; each course should not exceed a total of 500 mg/kg body weight.

6. Symptomatic measures—antacids and ranitidine for prevention of gastric erosions, dopamine for shock, etc.

7. Eye exposure—
   a. Remove contact lenses and irrigate exposed eyes with copious amounts of room temperature 0.9% saline or water for at least 15 minutes.
   b. If irritation, pain, swelling, lacrimation, or photophobia persist after 15 minutes of irrigation, an ophthalmologic examination should be performed.

8. Dermal exposure—
   a. Remove contaminated clothing and wash exposed area extremely thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists after washing.
   b. Metallic copper embedded in the skin has produced increased serum copper concentrations. Monitor serum and urine copper concentrations in patients with significant dermal exposure.
   c. Chelation therapy should be considered if copper concentrations are excessive.

9. Disorder of hair colour—Use of shampoos containing penicillamine (250 mg in 5 ml of water and 5 ml of shampoo) or EDTA have been effective in removing green colour from hair due to copper exposure.

Autopsy Features

1. Jaundiced skin and conjunctivae.
2. Greenish or bluish stomach contents.
3. Hepatic and renal necrosis.

Forensic Issues

In India, the incidence of suicidal ingestion of copper sulfate was quite high till recently. Of late, there has been a decline.

OTHER METALS AND METALLIC ELEMENTS

(In alphabetical order)

■ Antimony

The important derivatives of antimony include antimony oxide, antimony trichloride (*butter of antimony*), antimony sulfide, potassium antimony tartrate (*tartar emetic*), stibine gas and antimonials used in therapeutics.

Uses

- Alloys
- Plating
- Pigments
- Batteries
- Ant paste (insecticide)
- Matches
- Therapeutics: In the past, tartar emetic was quite popular as an emetic, diaphoretic, and indirect expectorant. Today virtually the only indication for the use of antimonials in medicine is leishmaniasis for which relatively safe pentavalent antimony compounds are used such as sodium stibogluconate and meglumine antimoniate.
- Antimony trichloride and stibine (which is a gas) are mainly encountered in the industry.
- Antimony sulfide may be used as *kohl* to darken the eyebrows, or as collyrium for the eyes in place of lead sulfide (*surma*).

Clinical Features

1. Ingestion of antimony compounds produces abdominal pain, vomiting, diarrhoea, haematemesis, dermatitis, EEG changes, oliguria, and renal and hepatic failure.
2. Exposure to the dust and fumes may cause gingivitis, rhinitis, chest tightness, shortness of breath, bronchitis, pulmonary oedema, headache, and dizziness.

3. Inhalation of stibine gas (released when antimony alloys are treated with acids) causes respiratory irritation, vomiting, headache, haemolytic anaemia, haematuria, myoglobinuria, and renal failure.
4. Signs and symptoms of chronic exposure may include ECG changes, laryngitis, tracheitis, bronchitis, pneumonitis, pneumoconiosis, ulceration of the nasal septum and larynx, and contact allergy to metal. Skin contact with antimony compounds can cause papules and pustules around sweat and sebaceous glands. QT prolongation and T wave changes have been reported on ECG.
5. Side effects associated with pentavalent antimonial therapy include arthralgias, myalgias, and EEG changes, and are usually reversible.
6. Antimony has been found to cause premature births and spontaneous abortions in women, along with growth retardation in children. Russian studies have suggested that workers exposed to antimony have shown sexual dysfunction in males and increased incidence of gynaecological problems in females.

Treatment

1. Chelation with BAL (as in arsenic poisoning).* It is given intramuscularly for 10 days. However, DMSA may be more effective. D-penicillamine is less effective but may be useful. EDTA is not effective.
2. Haemodialysis.
3. Stomach wash may help if the patient is seen early, in the case of oral ingestions.

■ Barium

Important derivatives include barium sulfate, sulfide, chloride, and carbonate.

Uses

- Rat poison—*barium carbonate, hydroxide, or chloride*.
- Depilatory—*barium sulfide*.
- Gastrointestinal X-ray—*barium sulfate* (the "barium meal").
- Golf balls—*barium sulfate* (along with calcium carbonate, zinc sulfide, castor oil, and fish oils).

All water or acid soluble barium salts are highly toxic. The most commonly involved in poisoning (accidental or intentional) are the following: barium carbonate (a white powder), barium fluoride, barium sulfide, barium oxide (a white to yellowish powder), barium chloride, barium acetate, and barium sulfate (water-insoluble, white or yellowish, odourless, tasteless, fine, heavy orthorhombic powder or crystalline solid).

Usual Fatal Dose

- Barium carbonate—60 to 70 mg/kg
- Barium chloride—12 to 20 mg/kg
- It has been reported that the LD50 for barium ingestion is 1 gram.

Mode of Action

1. Hypokalaemia (**Table 9.10**), and neuromuscular blockade: The rapid onset of the marked hypokalaemia so characteristic of barium intoxication is due to sequestering of potassium by muscle cells. Barium clogs the exit channel for potassium ions in skeletal muscle cells.
2. Barium stimulates striated, smooth, and cardiac muscle resulting in violent peristalsis, arterial hypertension and arrhythmias.

Clinical Features

1. *GIT*—Salivation, vomiting, abdominal pain, diarrhoea.
2. *CNS*—Mydriasis, paraesthesias, depressed tendon reflexes, headache, confusion, convulsions.
3. *CVS*—Hypertension, cardiac arrhythmias (premature ventricular complexes, ventricular tachycardia, bradycardia and ventricular fibrillation asystole/fibrillation.
4. *LMS*—Myoclonus, myalgia, cramps, dysarthria, flaccid quadriplegia.
5. *RS*—Pulmonary oedema, respiratory failure.
6. Hypokalaemia, metabolic and respiratory acidosis, and renal failure are commonly reported. In fact, quadriplegia is usually the result of severe hypokalaemia.
7. Oral or rectal barium sulfate administration may cause constipation, impaction, obstruction, cramping, diarrhoea, and perforation of the bowel. Appendicitis, bowel perforation, peritonitis and proctitis have been reported after oral or rectal barium sulfate use in radiologic procedures. ECG abnormalities have also been reported. Aspiration of barium sulfate may cause pneumonitis, granuloma formation, severe dyspnoea, and hypoxaemia. Barium sulfate is almost insoluble and lacks the severe toxicity characteristic of ingestion of other salts.
8. Allergic reactions (including anaphylaxis) can occur following barium sulfate administration for radiologic purposes.

Diagnosis

1. X-ray of abdomen.
2. Blood barium level.

Treatment

1. Gastric decontamination (emesis, lavage). For lavage, 5 to 10 grams sodium sulfate can be added to the solution.
2. Monitor cardiac rhythm and serum potassium. Cardiac

Table 9.10: Substances Producing Hypokalaemia	
Barium	Terbutaline
Corticosteroids	Theophylline
Salbutamol	Toluene (chronic)
Strychnine	Vitamin B$_{12}$

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* May not be useful for stibine gas exposure.

arrhythmias usually respond to potassium administration. If not, consider lignocaine, amiodarone, or procainamide.

3. IV fluids (liberally, to flush out barium by diuresis). Administer 0.45% NaCl in D5W, and a diuretic such as intravenous furosemide (1 mg/kg to a maximum of 40 mg/dose) to obtain a urine flow of 3 to 6 ml/kg/hr. Saline and furosemide forced diuresis has been reported to enhance barium elimination. If initial hydration is necessary, administer 0.45% saline to which sodium bicarbonate has been added to bring to isotonic 80 mEq/L at 20 to 30 ml/kg/hr for the first few hours.

4. 30 grams magnesium sulfate through a nasogastric tube (250 mg/kg for children). It precipitates the compound ingested into insoluble barium sulfate. In the past intravenous magnesium sulfate was recommended. This should be avoided because renal injury may result due to intrarenal precipitation of barium sulfate.

5. Treat hypokalaemia with potassium infusions (up to 250 mEq administered over 24 hours has been effective).

6. Haemodialysis.

7. Mild to moderate allergic reactions to barium sulfate administration can be managed with antihistamines, with or without inhaled beta agonists, corticosteroids or adrenaline. Treatment of severe anaphylaxis necessitates oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring, and IV fluids.

Autopsy Features

1. Haemorrhagic gastritis and duodenitis.
2. Pulmonary oedema.

Forensic Issues

- Most cases are accidental, usually the result of mistaken identity, when a soluble barium salt is administered for a "barium meal" instead of the insoluble barium sulfate. Barium salts are sometimes also mistakenly ingested in place of Epsom salt, Glauber's salt, or even common salt. Inhalation of a "barium meal" can produce granulomas in the lungs.

- A few cases of mass poisonings have been reported, the most remakable being *Pa Ping* an endemic form of periodic paralysis which occurred in the early 1940s in the Szechuan province of China. This was due to massive contamination of table salt by barium chloride.

■ Cadmium

Cadmium is a bluish, lustrous, and light metal which is a common contaminant of several metal ores such as lead, copper, and zinc. Cadmium is highly resistant to corrosion and is widely used in industry. An important derivative is cadmium acetate which is a white metallic salt.

Daily cadmium intake from food averages 10 to 25 mcg/day. Shellfish such as mussels, scallops, and oysters may be a major source of dietary cadmium, and may contain 100 to 1,000 mcg/kg. Smokers usually have twice the body burden of cadmium as non-smokers due to cadmium in cigarettes (up

_____
* Japanese for Ouch-Ouch!

to 30 mcg/pack) producing inhalation of 2 to 4 mcg cadmium/pack smoked.

Uses

- Welding.
- Electroplating: of automobile engine parts, aircraft parts, radio and TV parts, and nuts and bolts.
- Alloys: in jewellery making.
- Batteries (nickel-cadmium).
- Pigments.
- Shampoo: as a 1% solution for the treatment of seborrheic dermatitis and dandruff.

Mode of Action

1. Cadmium's toxic effects may be due to the displacement or substitution of cadmium for zinc in critical metabolic processes. Cadmium interferes with the uptake, distribution and action of zinc.

2. Cadmium may also cause apoptosis (programmed cell death), based on a study involving cultured human T cells.

3. Oral or inhaled cadmium is transported to the liver where it induces metallothionein, which binds and detoxifies cadmium. A slow release of this complex produces cadmium-metallothionein complex in all organs, particularly the kidney. Half of a non-smoker's body burden of 15 to 30 mg cadmium is in the liver and kidneys. Cadmium bound to metallothionein is filtered through the renal glomeruli, reabsorbed and released in the tubules. Unbound cadmium stimulates synthesis of new metallothionein which then binds cadmium in the renal tubular cells. If this step does not occur, toxic effects can result.

4. The kidney accumulates cadmium over a lifetime. Renal damage is believed to occur once the cadmium concentration in the kidney cortex reaches or exceeds about 200 micrograms per gram of kidney weight. Low levels of metallothionein, excessive accumulation of cadmium in the renal cortex, high concentrations of cadmium-metallothionein complexes which may directly affect the brush border membranes, interference with zinc-containing enzymes, and autoimmunological processes have been proposed as mechanisms involved in nephrotoxicity.

Clinical Features

1. **Acute Poisoning:**
   a. Ingestion—
      i. Nausea, metallic taste, salivation, vomiting, abdominal pain, diarrhoea, and myalgia. Sudden muscle cramps can cause the victim to cry out in pain periodically (*Itai-Itai* disease*, or *Ouch-Ouch disease*).
      ii. There is also bone demineralisation with osteomalacia and pathological fractures.
      iii. Vertigo, shock, unconsciousness and convulsions have been reported.
      iv. Death can occur due to dehydration or renal failure.

b. Inhalation—
  i. The symptoms of acute poisoning after inhalation exposure may be delayed 12 to 36 hours. These include chest pain, cough (with bloody sputum), difficulty breathing, sore throat, 'metal fume fever' (shivering, sweating, body pains, headache) dizziness, irritability, weakness, nausea, vomiting, diarrhoea, tracheobronchitis, pneumonitis and pulmonary oedema.

2. Chronic Poisoning:
  a. Yellow staining of teeth (*yellow teeth line*).
  b. Vertigo.
  c. Anorexia, fatigue.
  d. Rhinitis and anosmia (due to damage to olfactory nerve).
  e. Musculoskeletal pain (due to osteopenia-osteomalacia).
  f. Dyspnoea, emphysema.
  g. Hypochromic or normochromic normocytic anaemia.
  h. Renal damage producing microhaematuria, proteinuria, leukocyturia, urinary calculi).
  i. Hypertension.
  j. Cadmium is said to be carcinogenic, and increased incidence of lung, prostate, pancreas and bladder cancers in humans have been reported.

Diagnosis

1. Normal blood cadmium level in non-smokers is 0.4 to 1 mcg/L, and in smokers 1.4 to 4 mcg/L.
2. Urinary cadmium excretion of more than 2 mcg/24 hrs or 10 mcg/L is potentially nephrotoxic.
3. *Radiography:*
  a. Chest X-ray findings after acute inhalation exposures may indicate diffuse pulmonary oedema. Later they are those of bronchopneumonia (proliferative interstitial pneumonitis).
  b. In chronic poisoning, X-ray findings are characteristic of osteomalacia and may show multiple fractures.

Treatment

1. Chelation with CaNa$_2$ EDTA or DMSA for acute poisoning. BAL is contraindicated since it can aggravate nephrotoxicity.
  a. Dosage of CaNa$_2$ EDTA is as follows: 75 mg/kg/24 hrs deep intramuscular or slow IV infusion, given in 3 to 6 divided doses for up to 5 days. May be repeated for a second course after a minimum of 2 days drug holiday; each course should not exceed a total of 500 mg/kg body weight.
  b. For DMSA, the initial dose is 10 mg/kg orally every 8 hours for 5 days. The dosing interval then is increased to every 12 hours for the next 14 days. Repeat course may be given if indicated by elevated blood levels. A minimum of 2 weeks between courses is recommended.
2. Chronic poisoning may not require chelation. Removal from exposure and supportive treatment usually will suffice.

Forensic Issues

▪ Most cases of poisoning result from occupational or industrial exposure.
▪ Cadmium contamination of the environment can occur through soil, water, and food. The outbreak of *Itai-Itai disease* in Japan occurred in 1945 and was the result of consumption of rice grown in paddy fields which were irrigated by the local Jintzu river containing cadmium contaminated water (as a result of effluents from a nearby mine). The drinking water was also found to be contaminated.
▪ Certain types of soil have high cadmium content, and consumption of vegetables grown in such soil can result in elevated blood cadmium levels. This may be a factor in the aetiology of some cases of hypertension and renal failure.
▪ Tobacco smoke contains cadmium, and significant concentrations may be inhaled by chronic smoking, especially unfiltered cigarettes. Accumulation occurs mainly in the lung and kidney with resultant inflammatory and degenerative changes.
▪ Some types of industrial and laboratory fires can release significant quantities of cadmium fumes and produce serious consequences in firemen. It is imperative that such fires should be tackled only after wearing self-contained breathing apparatus.
▪ Consumption of acid fruit juices stored in cadmium-plated metal ware can cause poisoning in families. Other sources of food contamination include pots and pans with cadmium-containing glazing, and vending machines for hot/cold drinks in which cadmium soldering has been done.

▪ Cobalt

Cobalt is a hard, steel-grey or silver-grey coloured, somewhat malleable, magnetic, ductile metal, which exists in two allotropic forms with the hexagonal (alpha) form more stable at ambient temperatures than the cubic (beta) form. It is usually available in the form of hard metal which is actually an alloy of cobalt (5 to 25%) and tungsten carbide (75 to 95%). Toxicity is due to the former while the latter is relatively inert and harmless. Cobalt has exceptional magnetic properties in alloys.

Uses

▪ Manufacture of extremely hard steel and cutting tools. Also used in cemented carbide cutting tools, jet engines, as a co-ordination and complexing agent.
▪ Together with nickel, aluminium, copper, beryllium, chromium and molybdenum, cobalt is utilised in the electrical, automobile, aircraft and other industries.
▪ Manufacture of chemicals (cobalt salts); in alloys; cobalt steels for permanent magnets (in telephones, magnetic tape, microphones, speakers, computers, and motors) and for soft magnets and high-speed tool steels; in nuclear technology; and as oxidising agent.
▪ Used in alloys (nickel-aluminium-cobalt alloys), heat resistant alloys (gas turbines, electrical heating elements,

and aircraft engines), and high-strength alloys (specialised axles, space equipment, cobalt steels).

- Cobalt is found in lamp filaments, as a trace element in fertilisers, and as drying agent in printer inks, paints, and varnishes.
- Cobalt compounds are contained in enamels, glazes, glass, pottery and paints. They are also used in glass pottery, photography and electroplating processes.
- Cobalt chloride may be present in chemistry sets, and in crystal-growing sets sold in supermarkets and toy-stores.
- Cobalt is often added to beer to promote the formation of foam.
- A component of vitamin B_{12} (cyanocobalamin), cobalt plays an important role in human nutrition. Vitamin B_{12} is necessary for proper development of red blood cells; its absence causes pernicious anaemia. The recommended daily allowance of cobalt in the form of Vitamin B_{12} is 0.13 mcg/day. Cobalt is found naturally in foods, especially in fish, cocoa, bran, and molasses, and green leafy vegetables, such as lettuce, cabbage and spinach.

Clinical Features

1. The classic toxidrome of chronic cobalt poisoning is the tetrad of goitre, polycythaemia, cardiomyopathy, and metabolic acidosis.
2. Chronic exposure to cobalt in the form of inhalation results in *hard metal lung disease*, characterised by pulmonary fibrosis and an obstructive airway syndrome. It can induce or exacerbate asthma.
3. Regular consumption of beer to which cobalt chloride or sulfate has been added (to enhance foaming) over a period of time can result in cardiomyopathy, referred to as *beer drinker's heart* which carries a relatively high mortality of nearly 50%.
4. Dermal contact can cause "cobalt itch" or "carboloy-itch" (an allergic erythematous papular eruption). Chronic exposure can cause nerve deafness and optic atrophy.
5. Ingestion of magnets can cause acute cobalt toxicity.
6. Cobalt exposure has also been linked to an increased risk of cancer.

Mode of Action

1. Cobalt in its ionised form readily reacts with proteins, and may act as a hapten to induce allergic dermatitis and reactive airway disease.
2. A deleterious effect on myocardial mitochondria may be responsible for the development of cobalt-induced cardiomyopathy.
3. Protein deficiency (especially of tryptophan, DL-methionine, and L-cysteine) may be one important factor in the development of cobalt-induced cardiomyopathy.
4. Zinc and magnesium deficiencies may also play a part in the aetiology of cobalt-beer cardiomyopathy.

Diagnosis

1. Monitor haemoglobin, haematocrit, RBC counts, urinalysis, and thyroid function tests.

2. Monitor chest X-ray, arterial blood gases, ECG, and possibly echocardiogram if cardiomyopathy is present.
3. Monitor pulmonary function tests and chest X-ray if inhalation exposure or respiratory disease is present.

Treatment

1. If chronic ingestion has occurred, evaluate for the presence of cardiomyopathy, pericardial effusion, and polycythaemia. Chest X-ray, electrocardiogram, echocardiogram, arterial blood gases, and complete blood count should be obtained and monitored if abnormal.
2. Intensive supportive care may be required if cardiomyopathy is present. Digitalis preparations, diuretics, thiamine, and potassium replacement when indicated have been beneficial in some cases.
3. Nausea and vomiting may occur in acute ingestions from local gastrointestinal tract irritation. Maintain fluid and electrolyte balance as necessary.
4. Monitor red blood cell count and urinalysis. Monitor thyroid function tests if goitre is present.
5. Replacement of zinc and magnesium deficits, correction of metabolic acidosis with sodium bicarbonate, and administration of thiamine seemed to be beneficial in some cases of cobalt-beer cardiomyopathy.
6. Treat severe acidosis (pH < 7.1) with intravenous sodium bicarbonate. Begin with 1 to 2 mEq/kg in adults and 1 mEq/kg in children. Repeat every 1 to 2 hours as required. Monitor arterial blood gases to adjust dose.

7. **Chelation Therapy**

   a. *Dimercaprol:*
      i. Indications: BAL has been suggested for use in symptomatic cobalt poisoning although the indications for its use are not well defined. Chelation has not been reported to be effective therapy for cobalt-induced cardiomyopathy or respiratory disease.
      ii. Dose: 4 mg/kg IM (not more than 300 mg per dose) every 4 hours for the first day; then every 6 hours for the second day; then 3 times daily for approximately 7 days.
      iii. Alternative regimen: 3 to 5 mg/kg per dose deep IM every 4 hours for the first 2 days; then 2.5 to 3 mg/kg per dose IM every 6 hours for 2 days; and finally 2.5 to 3 mg/kg per dose IM every 12 hours for one week.

   b. *Calcium Disodium Edetate:* Some animal data have suggested that calcium EDTA may be useful in cobalt poisoning, although it has not been reported to be efficacious in treating either cobalt-induced myocardial or respiratory disease, and its indications for use are unclear.

8. **Other Measures**

   a. While systemic corticosteroid therapy has been used in patients with cobalt-induced interstitial lung disease, it has not been successful unless accompanied by removal from further cobalt exposure.

b. Patients who develop hypersensitivity reactive airway disease should be precluded from further cobalt exposure.

c. Acute bronchospasm resulting from cobalt hypersensitivity may require treatment with inhaled sympathomimetic agents. If more severe, other treatments effective in bronchospastic airway disease such as theophylline or corticosteroids may be required.

d. Some studies suggest that haemodialysis could be of some value in patients with renal failure, uraemic cardiomyopathy, and elevated serum cobalt levels. There is no evidence that haemodialysis would be beneficial in any other cobalt-induced disease.

■ Lithium

Lithium is strictly speaking not a heavy metal. It actually belongs to the same group of elements as sodium and potassium. However, convention demands that it be classed with the metals.

Lithium chloride was once used as a substitute for table salt in hypertensive patients. Numerous reports of toxicity led to its abandonment. Today lithium salts are mainly used for the treatment of manic depressive psychosis (or bipolar disorder), and depressive disorders. It has also been recommended for the treatment of alcoholism, amelioration of neutropenia induced by chemotherapy, and prevention of cluster headaches. The usual dosage recommended varies from 600 to 900 mg/day initially, and later reduced to an optimal maintenance dose (which produces a blood level of 0.7 to 1 mEq/L).

Lithium is also used industrially in nuclear reactors as a coolant, alkaline storage batteries, and alloys.

Clinical Features

1. Adverse effects—
   a. Common side effects of lithium (which unfortunately has a very narrow toxic therapeutic index), include thirst, polyuria, tremor, acne, hypothyroidism, dysarthria, ataxia, alopecia, and exacerbation of psoriasis.
   b. In about 10% of patients, nephrogenic diabetes insipidus can occur.
   c. GI effects are usually mild and reversible. 10 to 20% of patients experience diarrhoea, vomiting, abdominal pain, nausea, and anorexia in the early stages of treatment. Dehydration is a common finding in patients with chronic lithium intoxication.
   d. Other effects include exophthalmos, restlessness, and anxiety.
   e. A parkinsonian syndrome characterised by tremor, fasciculations and cogwheel rigidity may occur with or without other signs of toxicity.
   f. Hypercalcaemia with cardiac rhythm disturbances has been reported as a side effect of lithium treatment.
   g. Neutrophilia is a reported side effect of treatment with lithium, and significant leukocytosis may develop with lithium toxicity.
   h. There is evidence to indicate that lithium is teratogenic and may cause cardiac malformations.
   i. Toxicity has also been noted in newborn babies breastfed by lithium-ingesting mothers, manifesting as hypotonicity, lethargy, and cyanosis (*floppy baby syndrome*).

2. Lithium overdose is characterised by the following:
   a. *CNS*—Weakness, fatigue, tremor, confusion, ataxia, choreoathetosis, myoclonus, opisthotonus, blurred vision with nystagmus, dysarthria, seizures, and coma. A disorder similar to neuroleptic malignant syndrome (NMS) or serotonin syndrome has been associated with lithium therapy and toxicity.
   b. *CVS*—Arrhythmias with prolonged QT interval, and flattened, inverted T waves.
   c. *Blood*—Leukocytosis, aplastic anaemia.
   d. *Renal*—Polyuria, polydipsia (nephrogenic diabetes insipidus).
   e. *Endocrine*—Goitre, myxoedema.
   f. *Dermal*—Dermatitis, localised oedema, ulcers.
   g. *GIT*—Vomiting, diarrhoea.
   h. *RS*—Acute respiratory distress syndrome.

Diagnosis

1. Determine serum electrolytes (especially sodium) and lithium concentration. Correct any sodium deficiency.
2. *Monitoring*— Serum levels should be monitored regularly during treatment of intoxication. After termination of drug the plasma level drops by 1/2 every 2 to 3 days.
3. *Anion Gap*—Because lithium may be an unmeasured cation, an elevated level may result in a decreased or absent anion gap.
4. *Lithium Induced Renal Disease*—Serum B2 microglobulin has been found to be a more sensitive indicator than serum creatinine for monitoring glomerular filtration rates in patients on chronic lithium therapy.
5. *Toxicity*—
   a. Therapeutic Levels: 0.6 to 1.2 mEq/L
   b. Mild-Moderate Symptoms: 1.5 to 2.5 mEq/L
   c. Potentially Lethal: 3 to 4 mEq/L.
6. *Thyroid*—Periodic monitoring of thyroid function may help detect preexisting hypothyroidism or lithium-induced hypothyroidism.
7. *Urinalysis*—Perform urinalysis and determine serum creatinine to rule out impaired renal function.
8. *ECG*—The predominant change during intoxication is slowing of the dominant rhythm. These changes may persist for several days.
9. *Magnetic Resonance Imaging*—Brain and tissue lithium levels can be quantified using Li-7 magnetic resonance imaging.
10. *EEG*—Should be performed on all patients who present with altered sensorium, to assist in diagnosis of seizure activity.
11. Lithium is easily measured by atomic spectrophotometry, ion selective electrode, or by emission photometery.

Treatment

1. Activated charcoal does not adsorb lithium very well and must not be administered.

2. Whole bowel irrigation with polythelene glycol electrolyte lavage solution at a rate of 2 L/hr for 5 hours has been shown to be very useful in the early stages.

3. Haemodialysis: The indications for haemodialysis in lithium intoxication are inexact; some authors recommend haemodialysis for any patient with a level above 3.5 mEq/L. Other authors recommend haemodialysis for all patients with more than prodromal symptoms and slightly increased 12-hour serum lithium concentration. Lithium clearance during haemodialysis is approximately 100–120 ml/min, thus four hours of haemodialysis is equivalent to 24-hour clearance of 16–20 ml/min. Renal lithium clearance is 20 to 30% of creatinine clearance, thus those with renal impairment (calculated creatinine clearance less than 60 ml/min) are generally candidates for haemodialysis. Once begun, haemodialysis should be carried out as long as necessary to reduce the serum lithium concentration to less than 1 mEq/L after redistribution.

4. Continuous arteriovenous haemodiafiltration (CAVH), if available, is more efficacious than haemodialysis.

5. Administration of sodium polystyrene sulfonate can help reduce absorption of lithium.
   a. Dose—
      i. Adults: 60 ml of suspension (15 gm resin) given orally four times a day; 120 to 200 ml of suspension (30 to 50 gm resin) given rectally as retention enema following a cleansing enema.
      ii. Children and Infants: Dose is based on exchange ratio of about 1 mEq of potassium per 1 gram of resin or approximately 1 gram/kg/dose every 6 hours orally, or every 2 to 6 hours rectally.

6. Supportive measures: artificial ventilation, anticonvulsants, and correction of hypotension, dehydration, and hypovolaemia.

■ Magnesium

Magnesium is a white mineral element which is an important component of the human body present in soft tissue, muscle, bone, and body fluids. Normal magnesium level of serum varies from 1.5 to 2.5 mEq/L. Magnesium found in normal urine ranges from 2 to 4 mEq/L (1 to 6 mmol/L). A 24-hour urine specimen is important to assess magnesium excretion accurately due to circadian variation.

Magnesium is ingested via water and several types of food. Deficiency is rare, except in diarrhoea and malabsorption states and is characterised by neuromuscular hyperexcitability (sometimes accompanied by behavioural disturbances), absence of other electrolyte or toxic causes, failure to respond to IV calcium, and response to IV magnesium. Manifestations include muscular weakness, tremors, ataxia, vertigo, focal or generalised tonic-clonic seizures, irritability, depression or psychotic behaviour and decreased respirations.

Magnesium salts are used in pharmacotherapeutics as antacids (magnesium trisilicate, magnesium carbonate, magnesium hydroxide, i.e. milk of magnesia), laxatives (magnesium citrate, magnesium hydroxide or milk of magnesia, magnesium oxide, magnesium phosphate, and magnesium sulfate), antipyretic (magnesium salicylate), anticonvulsant (magnesium sulfate), and for correction of electrolyte disturbances as well as in dialysis solutions (magnesium chloride).

Magnesium salts rarely cause poisoning since the kidneys normally excrete the magnesium ion with sufficient rapidity to prevent its accumulation. However, hypermagnesaemia can occur in the presence of renal failure and certain other predisposing conditions (**Table 9.11**). In such situations, it is dangerous to administer repeated doses of magnesium salts unless careful monitoring is done of deep tendon reflexes, bowel motility, renal function, and serum calcium and magnesium levels.

Mode of Action

Hypermagnesaemia impairs neuromuscular junction transmission by decreasing acetylcholine release from the presynaptic membrane, by diminishing the depolarising action of acetylcholine at the postsynaptic junction, and by impairing postsynaptic junction sensitivity to acetylcholine.

Clinical Features

These have been correlated with the serum magnesium level and mentioned in **Table 9.12**.

Paediatric poisoning—Infants often manifest sleepiness, limp muscle tone, and poor suck reflex. Impaired renal function is the most common cause of hypermagnesaemia in the paediatric population. High dose (>48 grams) tocolytic magnesium sulfate therapy was reported to be associated with increased perinatal mortality among foetuses and

Table 9.11: Predisposing Conditions for Hypermagnesaemia

Common	Less Common	Uncommon
Acute renal failure	Rectal administration of Mg solutions	Lithium therapy
Chronic renal failure (with exogenous Mg intake)		Hypothyroidism
Toxaemia therapy		Viral hepatitis
		Hyperparathyroidism
		Milk-alkali syndrome
		Acute diabetic ketoacidosis
		Addison's disease

Table 9.12: Clinical Manifestations of Hypermagnesaemia

Serum Mg Level (mEq/L)	Symptoms
1.4 to 2.0	Normal serum level
3.0	Nausea, vomiting, flushing of skin
4.0	Decreased deep tendon relexes, drowsiness, unsteadiness, sweating
5.0	ECG changes (*QRS widening, PR prolongation*)
6.0 to 7.0	Somnolence, bradycardia, hypotension
10.0	Absent tendon reflexes, paralysis
15.0	Complete heart block, respiratory failure
17.0 to 20.0	Asystole

neonates weighing 700–1249 grams in one case-control study.

Treatment

- Discontinue magnesium intake.
- Eliminate magnesium by enema if it is in the bowel.
- Calcium gluconate is the antidote for hypermagnesaemia. 10% solution is administered IV (10 to 20 ml in adults, 100 mg/kg in children upto a maximum of 1 gram, slowly, over 5 to 10 minutes, with ECG monitoring). Alternatively calcium chloride 10% can be given IV (0.2 to 0.5 ml/kg/dose up to 10 ml/dose over 5 to 10 minutes). Repeat dose as needed. Monitor ECG and stop infusion if heart rate begins to decrease.
- Furosemide (40 mg in adults, 1 mg/kg in children) along with replacement of urine volume by 0.9% saline, may be useful as an altenative therapy.
- Haemodialysis or exchange transfusion.

■ Manganese

Manganese is a grey-white, silvery, hard, brittle, lustrous transition metal. It is found in several types of foods, and is essential in trace quantities for normal bone metabolism and many enzyme reactions.

Uses

- Metallic manganese is primarily used in the manufacture of steel and as an ingredient in the production of ferrous and nonferrous alloys. It is combined with aluminium, copper, nickel, silver and titanium.
- Manganese is also used as a bronze ingredient, in high-purity salts for various chemical processes, and as a scavenging and purifying agent in metal production.
- Manganese salts are utilised in fertilisers, as driers for linseed oil, for glass and textile bleaching, and for leather tanning. Manganese chloride is used as a catalyst, in dry-cell batteries, and as an animal feed supplement.
- Manganese and its compounds are utilised in the manufacture of dry-cell batteries, paints, varnishes, inks, dyes, matches, and fireworks, as decolourisers and colouring agents in the glass and ceramics industry, and as a fertiliser, disinfectant, bleaching agent, and laboratory reagent.
- An organic manganese compound (manganese ethylene

bis-dithiocarbamate) is contained in the fungicide Maneb. Other pesticides are reported to contain manganese and may cause manganism in agricultural workers.

Mode of Action

1. Neurotoxicity from manganese results from selective disruption of dopamine neurons and production of the neurotoxins dopamine quinone and hydrogen peroxide. Manganese also has an affinity for neuromelanin in addition to disrupting dopaminergic systems. Oxidation of dopamine by manganese ions produces cytotoxic free radicals probably via glutathione reduction, decreased glutathione peroxidase activity, or the inhibition of mitochondrial respiration.
2. Histopathological examination of brain has demonstrated loss of nerve cells in the inner globus pallidus and diffuse degeneration of cells in the cerebral cortex, palladium, caudate nucleus, putamen, basal ganglia and cerebellum. Some authors postulate that the neurologic features of manganism are mainly due to functional disturbances in striatal neurons.

Clinical Features

Acute manganese poisoning is extremely rare. Chronic exposure to manganese dust or fumes results in the following:
1. Dyspnoea, bronchitis, pneumonia.
2. Parkinson-like syndrome (manganism)—tremor, rigidity, ataxia, amnesia, and abnormal gait. In addition, there may be nystagmus, paraesthesia, "whispering speech", lumbosacral pain, urinary incontinence, impotence, etc.
3. *Manganese madness* (*"Locura manganica"*)—insomnia, confusion, anxiety, hallucinations, and bizarre behaviour.
4. Some manganese miners on an Australian island (Groote Eylandt) have been reported to be afflicted with a peculiar neurological disease characterised by upper motor neuron and cerebellar signs, and oculomotor symptoms (*Angurugu syndrome or Groote Eylandt syndrome*).
5. "Metal fume fever" has been reported after inhalation exposure to manganese oxide fumes.
6. Manganese exposure has not been related to cancer occurrence in humans. However, manganese deficiency has been related to cancer in humans.

Diagnosis

1. Blood manganese level more than 3 mcg/100 ml. Usual urine reference range is 0.1 to 0.8 mcg/100 ml. However, plasma and urine manganese levels do not correlate well with severity of symptoms or the clinical course of manganese toxicity.
2. MRI: may reveal manganese in the basal ganglia.

Treatment

1. Sodium para-aminosalicylic acid may help in ameliorating the neurological manifestations of chronic manganese toxicity. *Dose:* 6 gm/day in 500 ml of 10% glucose by IV drip for 4 days, followed by an interval of 3 days. The treatment is then repeated and continued with periodic intervals upto 4 months.
2. Other drugs have also been tried with varying degrees of success including L-dopa (3.5 gm to 12 gm/day), 5-hydroxytryptophan, scopolamine, procyclidine, and trihexyphenidyl.
3. Chelation therapy with CaNa$_2$ EDTA may help in some cases. *Dose:* 1 gram in 500 ml D5W or saline, given over 5 hours twice a day for 3 days.
4. Supportive measures.

■ Potassium (Kalium)

Potassium is a soft silvery white metal found in the earth's crust and is an essential electrolyte. Uses include treatment for potassium depletion, treatment of arrhythmias that are potassium dependant, as a salt substitute, in conjunction with anticholinesterase agents in restoring muscular strength, and in the treatment of thallium poisoning.

Potassium is the principal cation in intracellular fluid, and along with sodium and chloride, is essential for regulation of osmotic pressure and acid-base balance. A proper balance of potassium, calcium, and magnesium ions is necessary for normal excitability of muscle tissue, especially cardiac muscle. Normal serum potassium level varies from 3.8 to 5 mEq/L. In hypokalaemic states, potassium preparations are administered orally or parenterally. Several oral rehydration solutions used in diarrhoeas also contain potassium as one of the elements. Overdose can produce dangerous consequences (hyperkalaemia). Slow release potassium preparations are particularly hazardous.

Potassium salts are available in a variety of forms and are chiefly used as supplementation with diuretic therapy. Potassium supplements are available in "slow release" (enteric-coated) tablets, which can release large amounts of KCl over a relatively short segment of small bowel. These formulations have been implicated in small bowel ulcers, some of which caused fatalities. The newer slow release KCl formulations are somewhat safer, but can cause potential adverse effects if delayed intestinal transit is present.

The concentration of potassium in some common salts is given below:

Potassium (K) Salt	mEq K/gram of salt
K-Acetate	10.3
K-Bicarbonate	10
K-Chloride	13.3
K-Citrate H20	9.3
K-Iodide	6
K-Phosphate monobasic	7.4
K-Phosphate dibasic	11.4

Salt substitutes containing potassium can also cause serious poisoning. Potassium is also present in large amounts in certain foods (e.g. cantaloupe, citrus fruits, bananas, tomatoes, and potatoes). Water softeners can be a significant source of potassium, especially in patients with underlying renal insufficiency.

Potassium salts (other than phosphate, sulfate, and tartrate) are generally readily absorbed orally. Ninety percent is absorbed in the first half hour, most being absorbed in the small intestine. The rate is 25 to 50% that of sodium. Potassium distributes primarily intracellularly by complex transport mechanisms. Transcellular K "shifts" into and out of cellular water and is governed by numerous complex physiologic phenomena (extracellular pH, cellular adaption to K loads, endocrine function, extent of total body potassium depletion, etc.). The intracellular compartment contains most of the body's total of potassium (approximately 150 to 160 mEq/L). It distributes preferentially to kidney, gut, liver, skin, and muscle, in that order. Potassium leaves the plasma space very rapidly (half-life approximately 16 sec) by transcapillary transfer.

Common Causes Of Hyperkalaemia (K = > 5.5 mEq/L)

- Acute renal failure
- Use of potassium-sparing diuretics (spironolactone and triamterene)
- Potassium over-supplementation
- Drug overdose: digitalis, beta 2 agonists, NSAIDs, fluorides, heparin, succinylcholine, and drugs causing acidosis.

Clinical Features

- Vomiting, diarrhoea, listlessness, weakness, numbness of extremities, pallor, muscular cramps, hypotension, arrhythmias, heart block, and cardiac arrest.
- *ECG Changes*—Peaked T waves usually develop initially, followed by small or flattened P waves, deep S waves in the precordial leads, and widened QRS complexes. In severe cases sine waves may develop. Prolongation of the PR interval is also possible
- The following salts can be irritating or even corrosive in nature: potassium carbonate (potash), potassium hydroxide (caustic potash), and potassium oleate.

Diagnosis

1. Monitor serial electrolytes and obtain a serum creatinine. Normal serum potassium levels range from 3.5 mEq/L to 5 mEq/L.
   a. *Minimal Toxicity*—Potassium levels under 6.5 mEq/L.
   b. *Moderate Toxicity*—Potassium levels between 6.5 and 8 mEq/L (lassitude, fatigue, and weakness).
   c. *Severe Toxicity*—Potassium levels over 8 mEq/L (complete neuromuscular paralysis may dominate the

clinical picture; death from cardiac arrest occurs usually at 10 to 12 mEq/L).

2. Obtain an ECG and institute continuous cardiac monitoring. The ECG is fairly characteristic (i.e. peaked T waves, small P waves, QRS widening), except in patients with Addison's disease (i.e. the ECG may show generalised reduction and slowing).

3. Potassium preparations are reported to be consistently radiopaque. An abdominal film may be useful to assess if an ingestion has occurred or if gastric decontamination has been effective.

4. Postmortem Diagnosis: Studies have shown that the serum, plasma, and vitreous humour may be the best fluids to test for potassium overdose on postmortem.

Treatment

1. Activated charcoal is not useful. Whole bowel irrigation has been employed with benefit.

2. 10 ml calcium gluconate solution (10%), or calcium chloride solution (10%). May be repeated after 5 to 10 minutes. Calcium chloride is the preferred salt for resuscitation since it directly delivers ionised calcium, whereas calcium gluconate must be hepatically metabolised to release ionised calcium. However it is very irritating, and should only be given via a central venous catheter. It can also cause hypotension and bradycardia. *Caution:* All calcium salts are incompatible with bicarbonate.

3. Sodium bicarbonate IV: It helps to shift potassium intracellularly. *Adult Dose*—50 ml (50 mEq) intravenously over 5 minutes, repeated at 20 to 30 minute intervals. *Paediatric Dose*—1 to 2 ml/kg/dose (1 to 2 mEq/kg/dose) intravenously every 2 to 4 hours, or as required by pH. The onset is 15 minutes, the duration of action 1 to 2 hours.

4. Glucose/insulin (also enhances intracellular shift of potassium): *Adult Dose*—Administer 25 grams of dextrose (250 ml of a 10% solution) intravenously over 30 minutes, and then continue the infusion at a slower rate. Ten units of regular insulin are given subcutaneously or added to the infusion. Alternatively, 50 ml of a 50% dextrose solution with 5 to 10 units of regular insulin may be administered intravenously over 5 minutes. This regimen generally lowers serum potassium by 1 to 2 mEq/L within 30 to 60 minutes with the decrease lasting for several hours. *Paediatric Dose*—0.5 to 1 gm/kg/dose followed by 1 unit of regular insulin intravenously for every 4 grams of glucose infused; can be repeated every 10 to 30 minutes. *Caution:* 50% and 25% dextrose solutions are very hyperosmolar and can cause sclerosis of peripheral veins; administration of hypertonic solutions must always be preferred via central lines, if possible.

5. Haemodialysis (in severe cases).

Forensic Issues

- Most cases of hyperkalaemia result from iatrogenic overdose. Some cases result from inadvertent excessive ingestion of salt substitutes containing potassium, or mistaken identity leading to ingestion of salts such as saltpetre (potassium nitrate).

- Ingestion of match heads containing potassium dichromate can lead to death by acute renal failure, particularly in children.

- Poisoning with potassium permanganate has been dealt with in earlier sections (consult *Index)*.

■ Thallium

Thallium is a soft and pliable metal which is acquiring an increasingly notorious reputation as an ideal homicidal poison. Important derivatives include thallous sulfate, acetate, chloride, iodide, nitrate, and carbonate. Most of these salts (particularly thallous sulfate), are odourless, tasteless, and freely soluble in water.

Uses

- Glass and dye industry
- Rodenticide
- Depilatory
- Fireworks
- Cardiac perfusion imaging.

Mode of Action

1. Thallium is a cellular toxin. It behaves as a potassium analogue and is distributed intracellularly to all the tissues of the body, but changes in distribution occur with the passage of time. At low levels, thallium replaces potassium in the sodium-potassium ATPase pump; at high levels it competitively inhibits sodium potassium ATPase.

2. Thallium also has an affinity for sulfhydryl groups. The blocking of sulfhydryl cross-linking in keratin causes alopecia and abnormalities in nail growth which are manifested as Mees' lines.

Usual Fatal Dose

Average fatal dose of thallium sulfate varies from 12 to 15 mg/kg. The reported adult fatal dose is approximately 1 gram of absorbed thallium.

Clinical Features

Absorption can occur through inhalation, ingestion, or even across intact skin.

1. **Acute Poisoning:**
   a. Abdominal pain, gastroenteritis (sometimes with haematemesis, and haematochezia), tachycardia, and headache, followed by confusion, paraesthesias, hallucinations, convulsions, retrobulbar neuritis, and ophthalmoplegia. Death results from respiratory failure.
   b. Occasionally, patients develop hepatic or renal failure.
   c. There may be bone marrow depression.
   d. A characteristic, dark pigmented band is often noticed in the scalp hair in about 3 to 4 days.
   e. Urine that is first voided after poisoning may show a green discolouration.

2. **Chronic Poisoning:**
   a. *Alopecia* (**Fig 9.23**)—One of the pathognomonic signs of chronic thallium intake, it begins about 10 days after the

Fig 9.23: Alopecia – Thallium poisoning

first dose and may lead to total scalp hair loss in about a month if the intake is continued. Apart from scalp hair, the lateral halves of the eyebrows is (peculiarly) affected. Regrowth of the hair occurs if the patient survives the poisoning. **Table 9.13** lists some important substances which produce alopecia.

b. *Skin rash*—This is in the form of a papulomacular rash which often assumes a "butterfly" distribution on the face. There may be acneiform eruptions.

c. *Dystrophy of the nails* (Mees' stripes or lines)*

d. Painful ascending *peripheral sensorimotor neuropathy*. Pain and paraesthesias are most pronounced in the lower limbs, particularly the soles. Painful peripheral neuropathy and paraesthesia, primarily of the legs and feet, are among the first symptoms noted. Pain may be described as aching, tingling or burning and may be so severe as to prohibit walking. Paraesthesias may develop within 2 to 6 days in severe poisoning. Loss of pain, temperature, vibratory and position sense may all occur and an unsteady gait may develop.

e. *Ataxia*.

f. *Other neurological manifestations*—Cranial nerve

palsies, optic neuropathy, choreoathetosis, tremor, and encephalopathy. Psychotic behaviour may be noted.

g. *Ophthalmological manifestations*—Ptosis, ophthalmoplegia, nystagmus, keratitis, lens opacities, optic atrophy. Functional changes include abnormal colour vision (tritanomaly), impaired visual acuity, and central scotomas.

h. *Cardiovascular and haematological manifestations*—Hypertension, cardiomyopathy, ECG changes, leukocytosis, and thrombocytopenia. Cardiac arrhythmias, bradycardia, and T wave abnormalities have been reported. Severe cases of acute poisoning may result in refractory cardiogenic shock.

i. *Other symptoms and signs*—Autonomic dysfunction, testicular toxicity, hypokalaemia, renal failure, and hepatic dysfunction. A bluish line in the gums may appear 3 to 4 weeks post-ingestion. Respiratory failure often develops in patients with severe motor neuropathy. Prolonged ventilatory support may be required.

The outstanding combination of **alopecia and skin rash, painful peripheral neuropathy, and mental confusion with lethargy** (*thallium triad*), in any clinical case must immediately arouse the suspicion of chronic thallium poisoning. A high level of suspicion should be kept for thallium poisoning in patients with painful peripheral neuropathy and gastrointestinal symptoms, which appear much earlier than alopecia, since the prognosis is much better with early diagnosis and treatment.

The progression of symptoms may sometimes mimic other conditions, particularly Guillain Barre syndrome (Landry's paralysis, acute infectious polyneuritis), acute porphyria, psychosis, or thiamine deficiency.

Sequelae, including mental retardation, psychosis, abnormal reflexes, ataxia, tremor, flaccid paraparesis, cerebellar ataxia, and mental impairment have been reported. There are reports of neurological sequelae lasting more than 30 years.

Diagnosis

1. X-ray: may reveal opacities in the GIT or liver.
2. Tests of contrast sensitivity and colour vision are useful

Table 9.13: Substances Producing Alopecia		
Allopurinol	5-Fluorouracil	Oral contraceptives
Amphetamines	Gentamicin	Propylthiouracil
Androgens	Gold salts	Quinacrine
Anticoagulants	Heparin	Selenium
Arsenic	Hexachlorobenzene	Thallium
Carbamazepine	Iodine	Thiocyanates
Chloroquine	Lead	Valproic acid
Cimetidine	Levodopa	Vinblastine
Clofibrate	Mercury	Vincristine
Cyclophosphamide	Methotrexate	Vitamin A
Diphenylhydantoin	Methyldopa	Warfarin

* Also seen in other heavy metal poisonings, especially arsenic.

in the early detection of optic neuropathy in thallium poisoning.

3. Abnormal EEG and delayed peripheral nerve conduction.
4. Microscopy of scalp hair may reveal a diagnostic pattern of black pigmentation of hair roots.
5. Urine test: Combine a few drops of urine with 3 drops of saturated bromine water, 3 drops of sulfosalicylic acid, 1 drop of HCl, 2 drops of a solution of 0.05 gram of rhodamine B in 100 ml of concentrate HCl. Mixture add 1 ml of benzene, shake, centrifuge, and examine the benzene layer. A bright yellow or fluorescent red colour indicates a positive result.

    Preparation of reagents:

      Bromine solution—Dissolve 10 gram of sodium bromide in 10 ml of water. Add 20 ml of 6N HCl followed by 2.5 ml of liquid bromine.
      Sulfosalicylic acid—Mix 1 part saturated sulfosalicylic acid with 2 parts of 6N HCl.

6. Atomic absorption spectroscopy.
7. Urinary excretion of thallium in excess of 10–20 mg in 24 hours is considered diagnostic. Although less reliable for diagnosis than 24 hour urinary thallium excretion, whole blood thallium exceeding 100 mcg/dL indicates potential poisoning.
8. Hypocalcaemia—Monitor calcium levels during the acute phase.

Treatment

1. In acute poisoning, stomach wash can be done with Prussian Blue [potassium ferric ferrocyanide or potassium ferric hexacyanoferrate i.e. $KFe(Fe(CN)_6)$] which prevents the absorption of thallium by binding with it, exchanging potassium for thallium in its crystal lattice network. Prussian Blue is then instilled through a duodenal tube (125 mg/kg twice a day, with 50 ml of 15% mannitol).* This is continued until the urinary excretion falls below 0.5 mg/day.
2. Activated charcoal may be beneficial. Thallium is thought to undergo enterohepatic recirculation, and multiple dose activated charcoal may enhance its elimination.
3. Forced diuresis in conjunction with potassium chloride. Potassium chloride therapy has been reported to enhance excretion of thallium, but there are conflicting reports as to its efficacy in enhancing elimination.
4. Haemodialysis along with haemoperfusion can remove significant amounts of thallium from the blood.
5. Chelating agents such as BAL, EDTA, etc. are not effective.
6. Diethyldithiocarbamate (Dithiocarb) was till recently advocated as an antidote. However it sometimes leads to a worsening of the patient's condition and is therefore not recommended today.
7. Physiotherapy, to prevent muscle contractures.
8. Shaving the patient's head may reduce the psychological stress of hair loss, and improve the patient's morale.

9. Special attention must be paid to oral hygiene, otherwise a severe stomatitis may result.

If treatment is instituted in time, recovery from thallium poisoning is the rule, though this may take a long time. There may be residual effects such as amnesia, ataxia, tremor, and foot drop.

Autopsy Features

1. Alopecia.
2. Stomatitis.
3. Fatty degeneration of heart (with "tabby cat striation" of the ventricles) (**Fig 9.24**).
4. Fatty degeneration of liver.
5. Renal damage.
6. Pulmonary oedema.
7. Cerebral oedema with widespread degeneration of nerve cells and axons.

Forensic Issues

- Accidental poisoning occurs due to industrial or occupational exposure. It can also occur inadvertently from its use as a rodenticide. Several instances of accidental poisoning have been reported in children who have consumed cockroach or rat bait containing thallium.
- Suicides with thallium have always been rare in India, though they were relatively common abroad until the 1960s when legislation was passed in most Western countries greatly restricting its availability for use as pesticides. In 1975, USA banned its use altogether as a rodenticide.
- The most disturbing aspect about thallium today is its increasing deployment by poisoners to commit murder. There have been several celebrated cases of murder reported over a period of time, especially in Western countries.

Fig 9.24: Fatty degeneration of the heart

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* Prussian Blue can cause blue discolouration of sweat and tears.

■ Metal Fume Fever

Synonyms

Brass chills; Brass founder's ague; Brazier disease; Copper colic; Foundry fever; Galvanised shakes; "Galvo"; Metal ague; Metal shakes; Monday fever; The shakes; The smothers; Smelter shakes; Welder's ague; Zinc chills.

Occupations Affected

Welding, galvanising, smelting, metal refining, electroplating, metal polishing, metallic pigment manufacture, alloy making, ship breaking, etc.

Metals Involved

The syndrome is caused by inhalation of fumes produced when the following metals are heated above their melting point (*in decreasing order of importance*): zinc, copper, magnesium, iron, chromium, cadmium, nickel, manganese, mercury, cobalt, lead, antimony, selenium, beryllium, vanadium, silver, and aluminium.

Clinical Features

1. The syndrome resembles a flu-like illness, beginning 4 to 6 hours after exposure to fumes, and is characterised by chills, fever, myalgia, cough, dyspnoea, fatigue, metallic taste, salivation, thirst, sweating, tachycardia, tachypnoea, leukocytosis, cyanosis, and reduced pulmonary function tests. The chest X-ray may be clear.
2. Resolution of symptoms occurs 36 hours after stoppage of exposure, so that over the weekend usually the worker becomes allright only to succumb once again the following Monday (*Monday fever*).
3. Sequelae are uncommon. Pulmonary lesions and residual effects are extremely rare and are not generally considered classical signs of metal fume fever. However, exposure to chromium and nickel fumes has resulted in increased incidence of lung cancer.

Diagnosis

Heavy metal screens or specific metal assay may be necessary to identify a causal agent in patients with significant acute or chronic toxicity.

Treatment

1. Symptomatic and non-specific. Chelation therapy may be required.
2. Corticosteroids have occasionally been recommended to reduce inflammatory response in patients with serious pulmonary involvement. Recommended regimen: 60 mg of prednisone per day, which is then tapered over the next week, or single dose of methylprednisolone 250 to 500 mg IV. Controlled studies demonstrating the benefits of corticosteroids have not been performed.
3. Analgesics and antipyretics should be administered as necessary.
4. Prophylactic antibiotics are not generally recommended unless bacterial infection is suspected.
5. Specific antidotal therapy may be indicated for symptomatic toxic metal inhalation.

Prevention

- Implementation of engineering controls.
- General room ventilation.
- Local exhaust ventilation.
- Process enclosure.
- Down-draft or cross-draft tables.
- Use of fume extractors.

Related Syndromes

A condition very closely resembling *metal fume fever* called *polymer fume fever* results from inhalation of gases produced by burning of polytetrafluoroethylene (Teflon). It is similar in presentation to metal fume fever, with short-term, flu-like symptoms of sore throat, fever, shivering, and weakness. Symptoms are usually less severe than with metal fume fever and require only symptomatic treatment.

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Section

4

Organic Poisons (Toxins)

10

Irritant Plants

Since India is a tropical country, it is host to rich and varied flora of thousands of plants, some of which are extremely poisonous. Most people in rural areas depend for their food upon farms and gardens. Cases of accidental poisoning occur not infrequently due to mistaken ingestion of toxic plant products or contamination of foodstuffs. Some cases are related to intake of harmful herbal remedies and "traditional medicines". A substantial number of cases involve children for whom plants are accessible and attractive. In some Western countries, 5 to 10% of all human exposures reported to poison control centres involve plants. In India, the over-all percentage ranges from 6 to 15%, while if rural populations are taken in isolation, the percentage may be as high as 63%.

CLASSIFICATION

1. Oropharyngeal Irritant Plants
Caladium, Dumbcane, Elephant ear, Jack-in-the-pulpit, Philodendron, Pothos, Skunk cabbage.

2. Gastric Irritant Plants
Amaryllis, Black locust, Black nightshade, Buttercup, Castor, Colocynth, Croton, Daffodil, Glory lily, Ground cherry, Hyacinth, Marking nut, Mayapple, Narcissus, Potato, Rhubarb, Red pepper, Rosary pea, Spider lily, Tomato.

3. Intestinal Irritant Plants
Baneberry, English ivy, Horse chestnut, Pokeweed.

4. Dermal Irritant Plants
Agave, Beach apple, Bull nettle, Cashew, Congress grass, Cow parsnip, Creeping spurge, Garlic, Gingko, Lime, Mango, Pencil cactus, Poison ivy, Poison oak, Poison sumac, Primrose, Stinging nettle, Wild parsnip.

The toxicity of some of these plants has been discussed elsewhere (see *Index*). Of the remaining, only the common Indian plants will be dealt with in this section.

OROPHARYNGEAL IRRITANT PLANTS

■ Dumbcane

Other Common Names

Dumbplant; Mother-in-law's tongue; Tuftroot.

Botanical Name

Dieffenbachia species.

Physical Appearance

This plant belonging to family Araceae can grow up to 6 feet, and has a fleshy, waxy stem with large, smooth leaves that are generally green on the periphery and mottled white in the center (**Fig 10.1**).

Fig 10.1: Dumbcane

Uses

It is a popular ornamental houseplant. While most houseplants are non-toxic (**Table 10.1**), dumbcane is among the few exceptions.

Toxic Part

All parts, especially leaves.

Toxic Principle

Calcium oxalate crystals.

Mode of Action

- The leaves and stem contain high amounts of insoluble calcium oxalate in the form of needle-like crystals packaged in raphides and bundled into elongated idioblasts. The idioblasts are cigar shaped structures with specialised nozzles at each end, capable of firing the needle-like raphides in the form of projectiles when force is applied (e.g. chewing). Thus when a leaf is bitten into, thousands of idioblasts fire the needle-like calcium oxalate crystals which penetrate mucous membranes and deposit proteolytic enzymes. The latter stimulate a cascade of events leading to release of bradykinin and histamine.
- Studies on *Dieffenbachia picta* in guinea pigs demonstrated the most toxic part of the plant was the stem juice, which, when dropped into the mouths of the animals, caused lip and tongue oedema, nasal secretions and progressive respiratory difficulties.

Table 10.1: Non-Toxic Houseplants

Common Name	Botanical Name
African violet	*Episcia reptans*
Aluminium plant	*Pilea cadierei*
Aralia	*Fatsia japonica*
Baby tears	*Helxine soleirolii*
Bird's nest fern	*Asplenium nidus*
Bridal veil	*Tradescantia*
Coleus	*Coleus x hydrus*
Corn plant	*Dracaena fragrans*
Creeping jenny	*Lysimachia*
Dracaena indivisa	*Cordyline indivisa*
Dwarf schefflera	*Schefflera arboricola*
Emerald ripple	*Peperomia caperata*
Fiddle leaf fig	*Ficus lyrata*
Gardenia	*Gardenia jasminoides*
Grape ivy	*Cissus rhombifolia*
Jade plant	*Crassula argentea*
Wandering jew	*Tradescantia albiflora*
Wandering jew (red and green)	*Zebrina pendula*
Parlor palm	*Chamaedorea elegans*
Peacock plant	*Calathea*
Piggyback begonia	*Begonia hispida* (var. *Cuculifera*)
Piggyback plant	*Tolmiea menziesii*
Prayer plant	*Maranta leuconeura*
Rubber tree	*Ficus elastica decora*
Umbrella plant	*Schefflera arboricola*
Snake plant	*Sansvieria trifasciata*
Spider plant	*Chlorophytum comosum*
String of hearts	*Ceropegia woodii*
Swedish ivy	*Plectranthus verticillatus*
Velvet plant	*Gynura aurantiaca*
Wax plant	*Hoya carnosa*
Zebra plant	*Aphelandra squarrosa*

Clinical Features

1. Most cases of dumbcane poisoning involve oral exposure causing immediate and severe symptoms of pain and local swelling. Patients often describe the intense agony as akin to chewing powdered glass. There is severe swelling of the lips, mouth, and tongue, with salivation. There may be interference with swallowing and breathing. Oral paraesthesia, with severe pain and numbness in the perioral area may occur.
2. Ocular exposure to expressed sap may cause immediate pain, lacrimation, photophobia, corneal abrasions, and deposition of calcium oxalate crystals on the corneal epithelium.
3. Systemic toxicity due to calcium oxalate is rare. Bloody emesis and diarrhoea may occur. Vomiting may be profuse. Following large ingestions, oxalic acid is formed in the stomach and subsequently absorbed into the systemic circulation. There it binds with calcium, and may cause hypocalcaemia. This could lead to weak, irregular pulse, bradycardia, hypotension, and cardiac dysrhythmias.

Treatment

1. In patients with severe poisoning, examine the urine for calcium oxalate crystals. Also, monitor calcium and renal function (BUN, creatinine).
2. Local treatment with cold milk or ice cream as a demulcent is sufficient in most cases. Cold water or sucking on crushed ice will also relieve oral pain. Remove all visible evidence of plant debris from the oropharynx.
3. In severe cases, parenteral opioids, corticosteroids, IV fluids, and endotracheal intubation may be required. Tetany should be treated with intravenous calcium gluconate.
4. Ocular exposure to sap resulting in chemical conjunctivitis and corneal abrasions must be treated with copious irrigation, systemic analgesics, and expert ophthalmologic consultation.

■ Philodendron

There are over 200 species of Philodendron. They are epiphytic herbs, primarily with climbing stems. They rarely stand erect. Identification is difficult because of the many different sizes and shapes of the leaves.

Other Common Names

Panda plant; Parlor ivy.

Botanical Name

Philodendron.

Physical Appearance

Small plant with variously shaped, glossy, dark green leaves (**Fig 10.2**).

Uses

Popular houseplant.

Toxic Part

Leaves, stem.

Mode of Action

- This plant contains calcium oxalate crystals, and causes GI irritation and local swelling. The raphides are contained in ampoule-like cells that, when ruptured by chewing or crushing, eject their contents into tissue. It appears that the rupturing of these cells, and the injection of the cell contents occurs at the same time. Crystallographic evidence indicates that there is some free oxalic acid in the cells.
- The raphides may also be coated with various proteolytic enzymes which produce additional tissue damage.

Clinical Features

1. Mild GI distress: Dysphagia, nausea, vomiting, oral pain, and perioral swelling may occur. Stomatitis, swelling of the tongue, and excessive salivation may be seen after ingestion.
2. Hypocalcaemia and tetany are unlikely unless large amount has been ingested.
3. Cutaneous exposure results in delayed contact dermatitis in sensitised individuals, due to the presence of resorcinol (an alkyl agent). Allergic contact dermatitis has been reported in a number of cases.

Usual Fatal Dose

Philodendrons may have as much as 0.7% oxalates. As little as 5 grams may be fatal. This would represent over 700 grams of leaves.

Fig 10.2: Philodendron (Parlor ivy)

Treatment

1. General measures:
   a. Dilution with milk or water may be of benefit by washing out the crystals and assisting in decontamination of the oral pharynx.
   b. Cold water or ice pack application may relieve local pain in the mouth.
2. Analgesics may be required if the pain is intense.
3. If large amounts have been ingested, the urine may be examined for oxalate crystals, but so far, crystals have not been reported after philodendron ingestion.
4. Corticosteroid dressings have been recommended for treatment of allergic dermatitis.

GASTRIC IRRITANT PLANTS

■ Castor

Other Common Names

Mole bean; Moy bean; Palma Christi.

Botanical Name

Ricinus communis.

Physical Appearance

- This plant belonging to family Euphorbiaceae, is a vigorous, perennial, erect, branched plant (**Fig 10.3**), and is native to India, but is also encountered throughout the world in temperate and tropical climates. Dwarf forms are typically less than 2 metres in height, but most plants become tree-like with stout, fibrous roots and soft, woody, stems reaching a height of 6 to 9 metres.
- Stems and branches may be flushed red or maroon.
- Leaves have long, green or reddish stalks, and may be quite large (up to 1 metre across). They are generally notched into 5 to 11 palmate lobes with toothed margins.
- Clusters of greenish-white to rust coloured flowers form at the end of the branches on 6 to 12 inch long upright stems. Male and female flowers are separate, but on the same plant.

Fig 10.3: Castor Plant – Twig
(*Pic:* Dr Shashidhar C Mestri)

■ The fruit (seed pod) has a prickly capsule (**Fig 10.4**) and contains (usually) three shiny, mottled, hard-coated, greyish-brown seeds (**Fig 10.5**). Seed pods are green or red, about one inch long, and hold elliptical, glossy seeds, which may be mottled with black, brown, grey, or white colours, and are 1 to 2 cm in length.

Uses

1. Ornamental plant.
2. Oil extracted from the seeds is used medicinally as a purgative, and as a lubricant for engines.
3. Castor beans have found wide use, both systemically and topically, in stimulating breast milk production in many countries.
4. Ricin (the main active principle) has been used as a chemical warfare agent, a reagent for pepsin and trypsin, an experimental antitumour and immunosuppressive agent, and as a commercial mole killer.

Toxic Part

All parts, but the most toxic are the seeds.

Fig 10.4: Castor capsules
(*Pic:* Dr Shashidhar C Mestri)

Fig 10.5: Castor seeds

Toxic Principle

■ The main toxic principle is the phytotoxin *ricin* which is a toxalbumen. It is not present in castor oil which contains a much milder irritant—*ricinoleic acid*. Ricin is one of the supertoxic poisons of plant origin.*
  ❖ Toxalbumens cause severe gastrointestinal lesions with irritation of the oropharynx, oesophagus, or stomach when directly exposed. Although clinically similar to alkaline caustic burns, they are usually delayed two or more hours after exposure. Late complications result from cytotoxic effects on the liver, central nervous sytem, kidney, and adrenal glands, typically 2 to 5 days after exposure. The patient may be asymptomatic during the preceding 1 to 5 days.

Mode of Action

■ The seeds are harmless when ingested whole, since the outer coating resists digestion. However, if the seeds are crushed or chewed before swallowing, toxicity results due to the release of ricin. Poisoning is much more severe when ricin is injected parenterally.
■ Ricin contains two polypeptide chains (A and B) held together by a single disulfide bond; the total molecular weight is 66,000. Chain B is a lectin that binds to the surface of the cell to facilitate toxin entry into the cell. Chain A disrupts protein synthesis by activating the 60S ribosomal sub-unit. Sensitisation to castor bean (IgE response) may occur, with the main allergen being a 25 storage albumin (proposed name Ric cI). Both Type 1 (immediate) and Type IV (delayed) reactions have been reported.
■ Haemagglutination has been seen in animal and laboratory work, but is almost never seen in actual poisonings. It is now believed that the haemagglutinating agent is not ricin, but another lectin (sometimes called *ricine*).
■ The pulp of the seed contains allergenic glycoproteins which cause allergic dermatitis, rhinitis, and asthma in sensitised individuals.

Clinical Features

1. There is usually a delay of several hours before manifestations begin. There is at first a burning sensation in the GI tract which is followed by colicky abdominal pain, vomiting, and diarrhoea. Frequent stools, including bloody diarrhoea and tenesmus, are well known signs of toxalbumin toxicity.
2. In severe cases, there is haemorrhagic gastritis and dehydration. Urea nitrogen, amino acid hydrogen, and inorganic phosphate levels are usually elevated.
3. Delayed CNS toxicity may occur, especially involving the cranial nerves. Optic nerve damage has been reported with ricin.
4. Renal damage leads to acute renal failure. Haematuria is often seen. Serum creatinine is usually elevated.
5. Liver damage may occur in serious overdoses.

_____
* Other examples include abrin and aconitine

6. Major alterations in glucose metabolism have been shown to occur in experimental ricin intoxication. Glycogen stores decrease, gastrointestinal absorption of glucose decreases, and glucose concentrations fall.

Usual Fatal Dose

- It is generally believed that ingestion of a single castor seed can be lethal, whereas actually 8 to 10 seeds are required to produce a fatal outcome. However, even a single seed can occasionally cause death due to anaphylaxis.
- Parenteral injection of ricin can be fatal with a dose as low as 1 mg/kg body weight. But even ricin is a poorly absorbed substance, and it may take up to 5 days for toxic effects to manifest fully.

Treatment

The latent period between exposure and systemic symptoms requires observation for 8 hours following any substantial exposure to ricin.

1. *Decontamination*: stomach wash, activated charcoal, catharsis.
2. *Supportive measures:* IV fluids, monitoring for hypoglycaemia, haemolysis, and complications of hypovolaemia. Alkalinisation of urine probably has a role in preventing crystallisation of haemoglobin, and should be considered in severe poisonings.
3. Many antidotes have been investigated, but no specific treatments are available for toxalbumen exposures. Various antibodies have been developed, but are not used clinically.

Forensic Issues

- Reports from some countries suggest that it is not unusual to find a clustering of cases of toxic gastroenteritis among young children who ingest the seeds of castor. It is presumed that the unique marbled pattern of the seeds may be very attractive to children, and that the multiple seeds found in the pod may be shared between several children.
- The exaggerated notion about the lethality of castor (and more particularly ricin) stems from the celebrated case of **Georgi Markov**:

  Georgi Markov (**Fig 10.6**) was a 49 year old Bulgarian who had defected to the West, and was working as a broadcaster for the BBC World Service in London. On September 7, 1978, he was waiting for his evening bus home on Waterloo Bridge when a sharp jab in his right thigh caused him to turn in surprise. The man behind him dropped his furled umbrella (the tip of which had apparently accidentally poked into him), apologised, and moved away. He subsequently hailed a taxicab and left the scene. Puzzled and a little concerned, Markov caught his bus home. Late that night he fell ill with fever and vomiting. Next morning, his wife called their family doctor over who became quite alarmed at Markov's condition and rushed him to hospital. By now there was suspicion that his illness was connected somehow to the incident at the bus stop the previous day. The puncture wound in his thigh had become inflamed and painful. The body temperature

Fig 10.6: Georgi Markov

rose relentlessly and septicaemia was diagnosed. Over the weekend Markov became delirious, passed into coma, and died shortly thereafter.

Owing to the circumstances of the death, a high-level police investigation was launched. An autopsy was ordered, during the course of which the tissues around the puncture wound in the thigh were dissected and revealed the presence of a tiny pellet, the size of a pinhead. Electron microscopy revealed the pellet (made of an alloy of platinum and iridium) to have two small holes bored through it (**Fig 10.7**). To drill holes 0.35 mm wide in a pellet of 1.5 mm diameter, made of a notably hard substance, plainly indicated the involvement of someone with access to highly specialised equipment. The position of the pellet in the body suggested that the mysterious assailant's umbrella must have also been equally specialised. Investigators surmised that there must have been a firing device in the ferrule, silently powered by a gas cylinder.

Chemical analysis of the pellet did not reveal the presence of any poison. However, experimental injection of laboratory animals with a few of the known "supertoxic"

Fig 10.7: The pellet containing ricin

poisons suggested the possibility of ricin. The negative chemical analysis only reinforced this possibility, since ricin is known to get degraded rapidly in the body leaving behind no trace of its original presence.

The assassin with his lethal umbrella was never caught.

- Castor oil ingestion during pregnancy can cause terato-genic effects. Moderate growth retardation, craniofacial dysmorphia, absence deformity of limbs, vertebral segmentation defect, and seizures have been described in one case.

■ Colocynth

Botanical Name

Citrullus colocynthis

Physical Appearance

- This plant belonging to family Cucurbitaceae grows wild all over the country.
- The stem is diffuse or creeping, and is slender, angled, branched, and hirsute.
- Leaves are usually triangular in shape, 5–7 lobed, pale green distally and ashy proximally (**Fig 10.8**).
- Fruits are globular, 3 to 4 inches in diameter, variegated green and white, with a dry, spongy, bitter pulp (**Fig 10.9**).

Fig 10.8: *Citrullus colocynthis*

Fig 10.9: Colocynth fruit

- Seeds are 4 to 6 mm long and pale brown in colour.
- The root is bitter and pungent, and is used as a folk remedy for various ailments.

Uses

1. Dried fruit pulp is used as a purgative by rural folk.
2. Root is used by quacks for the treatment of jaundice, rheu-matism, constipation, etc.

Toxic Part

Fruit, root, leaf.

Clinical Features

Vomiting, diarrhoea, hypotension, shock.

Treatment

1. *Decontamination:* Stomach wash, activated charcoal.
2. IV fluids, dopamine.

■ Croton

Botanical Name

Croton tiglium

Physical Appearance

- This plant belonging to family Euphorbiaceae grows well in Assam, Bengal, and the Western Ghats.
- It is a small evergreen tree with ovate or elliptical leaves which are narrow-pointed, toothed, and 2 to 4 inches long, varying in colour from metallic green to bronze, orange, or yellowish (**Fig 10.10**).
- Seeds are oval, smooth, 1 to 2 cm long, and brownish in colour (**Fig 10.11**).

Fig 10.10: *Croton tiglium*

Fig 10.11: Croton seeds

Uses

The seeds, oil, and root extract are used as a drastic purgative in folk medicine.

Toxic Part

Stem, leaves, seeds.

Toxic Principles

- Crotin (toxalbumen).
- Crotonoside (glycoside).

Clinical Features

1. Plants in this family contain irritant diterpene esters that are strongly irritating. Rubbing the latex of these plants to the face, or chewing on the stem may result in erythema, swelling, and blistering. Initial symptoms of reddening and swelling occur in 2 to 8 hours, with vesicle and blister formation peaking in 4 to 12 hours. Severity depends on the amount of plant latex and the duration of contact.
2. Ingestion results in burning pain in the upper GI tract, vomiting, tenesmus, watery or blood-stained diarrhoea, hypotension, collapse, coma, and death.

Treatment

1. Decontamination.
2. Treatment of shock with IV fluids and dopamine.
3. Administration of cold milk may alleviate the GI irritation.

■ Glory Lily

Botanical Name

Gloriosa superba

Other Common Names

Climbing lily; Superb lily.

Physical Appearance

- This plant belonging to family Liliaceae is a large, herbaceous, climbing annual.

- It is a slender vine with a thick tuberous root, resembling a sweet potato.
- Leaves terminate in tendril-like, long, curling tips.
- Flowers are large, solitary, yellow or red, crinkled, and long-stalked (**Fig 10.12**). They appear to be "upside-down", with the stamens and pistils pointing downward.

Uses

1. The juice from the leaves is used as a pediculoside (to kill head lice).
2. The root is used to treat various ailments in folk medicine.

Toxic Part

Leaves, root.

Toxic Principles

Root contains colchicine and gloriosine. The tubers contain an estimated 6 mg/10 gm of tuber of colchicine along with gloriosine, which is a related alkaloid.

Clinical Features

1. Acute poisoning with the root results in severe vomiting, diarrhoea, tachycardia, chest and abdominal pain.
2. More severe effects such as hypotension, bradycardia, seizures, bone marrow suppression, coagulopathy, ECG changes, respiratory failure and death have been reported less commonly.
3. Acute colchicine overdose results in severe toxicity which may be delayed 2 to 12 hours postingestion. Toxic effects occur in three phases.
   a. **Early Phase** (2 to 24 hours): Severe GI symptoms (nausea, vomiting, abdominal pain, haemorrhagic gastroenteritis) with resulting electrolyte abnormalities, volume depletion, and hypotension. Ingestion often causes numbness of the lips, tongue and throat.
   b. **Second Phase** (24 to 72 hours): Multisystem failure, with fever and neurological (confusion, coma, ascending peripheral neuropathy), pulmonary, renal, hepatic, haematological, and cardiovascular toxicity. Seizures have been reported in children. Death may occur from respiratory

Fig 10.12: *Gloriosa superba*

failure, cardiovascular collapse, or sudden asystole. Sepsis is a common cause of death at 3 to 7 days.

c. **Third Phase** (7 to 10 days): Phase of recovery, and is characterised by a rebound leukocytosis and reversible alopecia. Fever may persist for several weeks.

Usual Fatal Dose

The estimated fatal dose of pure colchicine is 7 to 60 mg. The colchicine content of tubers of *Gloriosa superba* is approximately 0.3%. A potentially lethal amount would therefore be contained in 2.5 to 5 grams of tubers.

Diagnosis

1. High-performance liquid chromatography-mass spectrometry has been described for the identification and quantification of colchicine in human serum following a toxic plant ingestion.
2. Radioimmunoassay and enzyme immunoassays have also been developed for colchicine.

Treatment

Following a substantial ingestion, the patient should be observed for at least 12 hours due to an asymptomatic latent period, which may last up to 12 hours.

1. *Decontamination:* Activated charcoal therapy may be effective. Colchicine is believed to undergo enterohepatic recirculation. Multiple dose activated charcoal may interrupt enterohepatic recirculation, though there is no clinical evidence that this decreases toxicity or improves outcome.
2. *Symptomatic and supportive measures*:
   a. Fluid and electrolyte status, especially potassium levels, should be followed closely, with administration of appropriate IV fluids.
   b. A complete blood count should be done daily, monitoring for bone marrow depression. Patients suffering from bone marrow depression should be isolated to protect the patient from infection.
   c. Analgesics or opiates (with an anticholinergic drug if necessary) may be used to control severe abdominal pain.
   d. Ascending paralysis with respiratory involvement requires aggressive supportive care including mechanical ventilation.

Forensic Issues

- Accidental poisoning may occur when the tuber of *Gloriosa superba* is mistaken for sweet potato.
- Suicidal ingestions are not uncommon wherever the plant grows well.

■ Marking Nut

Botanical Name

Semecarpus anacardium.

Physical Appearance

- This tree belonging to family Anacardiaceae grows well in many parts of the country, and bears oblong leaves rounded at the tip, ash grey to brownish in colour, with cartilaginous margins (**Fig 10.13**).
- The fruit is referred to as "marking nut". It is blackish in colour and is vaguely heart-shaped (**Fig 10.14**). The juice of the nut is oily and black.

Uses

1. The juice of the nut is used by *dhobies* (washermen) in India to mark washed laundry.
2. The extract of the nut is used to treat various ailments in folk medicine.
3. The bruised nut is sometimes used as an abortifacient by inserting it into the vagina.

Toxic Part

Nut.

Fig 10.13: Marking nut tree

Fig 10.14: Marking nuts

Toxic Principles

- Semecarpol
- Bhilawanol.

Clinical Features

1. Skin contact with the acrid juice results in irritation, inflammation, vesication, and ulceration.
2. Ingestion produces GI distress with blister formation in and around the mouth. Severe poisoning results in vomiting, abdominal pain, diarrhoea, hypotension, tachycardia, delirium, and coma. Pupils may be dilated.

Usual Fatal Dose

About 5 to 8 seeds, or 10 grams.

Treatment

1. Wash contaminated skin with soap and water, and treat lesions with help of a dermatologist.
2. *Decontamination* (if taken orally): activated charcoal, cathartic.
3. Milk may be beneficial in ameliorating the GI distress.
4. Supportive and symptomatic measures.

■ Mayapple (May Apple)

Other Common Names

American Mandrake.

Botanical Name

Podophyllum peltatum, Podophyllum hexandrum.

Physical Appearance

- This plant belonging to family Podophylaceae grows well in the hilly regions of Sikkim, Uttar Pradesh, Punjab, Himachal Pradesh, and Kashmir.
- It is a flowering herb with a creeping root stock with deeply lobed leaves having toothed margins (**Fig 10.15**).
- Flowers are usually solitary, cup-shaped, and white or pink in colour.
- Fruits are generally ovoid and bright scarlet.

Toxic Part

Leaves and rhizomes.*

Toxic Principle

1. Podophyllin (purified form: podophyllotoxin): Podophyllum is an amorphous caustic powder which is light brown to greenish-yellow or brownish-grey in colour having a characteristic odour, and is a mixture of at least 16 physiological compounds divided into two groups: lignans (wood extracts) and flavonols. It is present in the rhizomes and roots of the plant, and contains at least 50% podophyllotoxin. Commercial preparations usually contain 25% podophyllum resin in either tincture of benzoin,

Fig 10.15: Mayapple

or 10% benzoin and 72% isopropanol. Both podophyllum and podophyllotoxin have a colchicine-like and vinblastine-like effect, resulting in the following chemical effects:
   a. Antimitosis: arrest of mitosis in metaphase.
   b. Negative effect on axoplasmic transport.
   c. Inhibition of protein, RNA and DNA synthesis.
   d. Blocking of oxidation enzymes in tricarboxylic acid cycle.

Uses

1. Podophyllum and its resin are used as keratolytic agents whose caustic action is thought to be caused by the arrest of mitosis in metaphase.
2. Topical treatment of condyloma acuminata (venereal warts).
3. Podophyllum is also used in Homoeopathy.

Clinical Features

Ingestion or dermal application could both result in toxicity. The toxicity associated with podophyllum is colchicine-like, arresting cellular mitosis in metaphase. Symptoms generally begin 30 minutes to several hours following ingestion, and 12 to 24 hours after dermal absorption.

1. Exposure of eyes to podophyllum powder causes intense irritation with conjunctivitis, keratitis, corneal ulceration, and iritis.
2. Ingestion results in nausea, abdominal pain, vomiting, and diarrhoea, followed by fever, tachypnoea, peripheral neuropathy, tachycardia, hypotension, ataxia, dizziness, lethargy, confusion, and altered sensorium. Seizures may occur. Polyneuropathy generally appears in about a week, and progresses for 2 to 3 months.

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* The term "rhizome" refers to the underground stem which gives off roots and shoots.

3. After a few days, pancytopenia and hepatic dysfunction may occur, which generally resolves in 2 to 3 weeks.
4. Cardiotoxicity, ileus, coma, and hallucinations may also occur.
5. Autonomic dysfunction, including sinus tachycardia, urinary retention, paralytic ileus, and orthostatic hypotension may persist for several months.
6. Oliguria, anuria, and renal failure are rare complications.
7. Consumption of Chinese herbal products containing extracts of podophyllum have caused neuropathies and encephalopathy.
8. It has been suggested that podophyllum should not be used during pregnancy for the treatment of genital warts due to the potential for severe myelotoxicity and neurotoxicity in the mother. Also, there are indications that podophyllum may be teratogenic and carcinogenic. Squamous cell carcinoma-like changes have been reported following the dermal use of podophyllum in humans.

Treatment

Obtain baseline CBC, haemoglobin, electrolytes, calcium, and renal and liver function tests.
1. Gastric decontamination: Emesis is not indicated. Activated charcoal can help.
2. Symptomatic and supportive measures.
3. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline.
4. Monitor electromyography and nerve conduction velocity in all patients with symptoms of peripheral neuropathy.
5. Patients generally recover from thrombocytopenia and leukopenia within 1 month. Granulocyte colony-stimulating factor (G-CSF), or filgrastim may be effective in accelerating recovery from neutropenia following podophyllum poisoning.
6. Due to the large molecular weight of the compound it is unlikely that haemodialysis would be effective for removal of podophyllum. Early charcoal or resin haemoperfusion has been suggested by some investigators to be useful in facilitating neurological recovery in some patients. But there is no conclusive evidence regarding its usefulness.

Autopsy Features

In one reported case, postmortem examination revealed partial maturation arrest of granulocytopoesis and a severe decrease in megakaryocytes. There were multiple petechiae on the pleura, the peritoneal surfaces of many organs, and the gastric mucosa. Severe pulmonary congestion was present, as well as marked vascular congestion of the liver and kidneys. There was a small area of focal acute necrotising bronchial pneumonia, and the brain was oedematous.

■ Red Pepper

Other Common Names

Chilly; Chili pepper; Cayenne pepper; Cherry pepper; Cluster pepper; Christmas pepper; Cone pepper.

Botanical Name

Capsicum annuum, Capsicum frutescens.

Physical Appearance

It is a small herb belonging to family Solanaceae, bearing longish tapering fruits which become red when ripe (**Fig 10.16**) with a pungent odour and taste, and contain a number of small and flat yellowish seeds (**Fig 10.17**). The latter bear a superficial resemblance to Datura seeds and serious poisoning sometimes results from mistaken identity. **Table 10.2** lists salient points of difference. The fruits and seeds of *C. frutescens* are hotter to taste than those of *C. annuum*.

Uses

1. The fruit and seeds are very popular in Indian cuisine as a condiment and flavouring agent. It is also used in pickles and sauces.
2. In medicine it is sometimes used as an appetite stimulant and carminative.
3. The main active principle, capsaicin, is sometimes used in the treatment of neuralgia and diabetic neuropathy.
4. Capsaicin is sometimes used in self-protective repellents such as dog repellents and mace-like agents.

Toxic Part

Fruit and seeds.

Fig 10.16: *Capsicum annuum* (Chilly)

Fig 10.17: Chilly seeds

Table 10.2: Differences	
Chilly seed	*Datura seed*
Small	Large
Yellow	Brown
Rounded and smooth	Reniform and pitted
Pungent odour	Odourless
Pungent taste	Bitter taste
On section, the embryo is seen to curve inwards towards the hilum	Embryo curves outwards

Toxic Principles

Capsicum contains a mixture of seven or more closely related vanillyl acids with the following approximate composition: capsaicin (69%), dihydrocapsaicin (22%), nor-dihydrocapsaicin (7%), homocapsaicin (1%), homodihydrocapsaicin (1%), and nor-capsaicin (< 0.1%).

Mode of Action

The vanillyl acids are irritants which cause their effects by depleting nerve terminals of substance P. This results in local swelling and pain due to dilation of blood vessels, and intense excitation of sensory nerve endings. Following such an initial reaction, there is a period of relative insensitivity to various stimuli, which forms the basis for the use of capsaicin as an active ingredient in some analgesic creams.

Clinical Features

1. *Cutaneous exposure*: Burning, stinging, pain. Occupational handling of chillies can result in burning pain, irritation, and erythema ("chili burns"), or severe contact dermatitis ("Hunan hand").
2. *Ocular exposure*: Intense pain, lacrimation, conjunctivitis, and blepharospasm.
3. *Inhalation/aspiration of chilly powder*: Occupational exposure results in increased coughing ("chilly workers' cough").
4. *Ingestion*: Nausea, vomiting, burning pain, salivation, abdominal cramping, burning diarrhoea.

Treatment

1. *Cutaneous exposure:*
   a. Copious local washing with water.
   b. Local and systemic analgesics.
   c. Immersion in cool water and/or vegetable oils.
2. *Ocular exposure*: Copious local irrigation and local analgesics. Even severe cases usually resolve without sequelae in 24 hours.
3. *Ingestion*:
   a. Sips of cool water or crushed ice.
   b. Systemic analgesics.

Forensic Issues

- Occupational exposure results in health problems among workers (*vide supra*).

- Accidental deaths have been reported due to aspiration of pepper. Sometimes datura seeds (**Fig 10.18**) are consumed in mistake for chilly seeds giving rise to serious poisoning.
- Homicides have also been accomplished by inhalational route.
- The powder is occasionally used for torture or extortion by forcible introduction into the anus or vagina. Cases of child abuse have also been reported.
- Robbery, rape, etc., may be facilitated by rendering a victim suddenly agonised and helpless by throwing pepper into the eyes.
- Black pepper (*Piper nigrum* belonging to family Piperaceae) contains terpinoids such as d-limonene, L-pinene, linalool, and philadendrone, which are said to be carcinogenic.

■ Rosary Pea

Other Common Names

Jequirity bean; Indian bead; Buddhist rosary bead; Rosary pea; Seminole bead; Prayer bead; Jungle bead; Crab's eye; Weather plant; Love bean; Lucky bean; Ojo de pajaro; Indian liquorice.

Botanical Name

Abrus precatorius.

Physical Appearance

- This green vine belongs to family Leguminosae, and is a tropical, ornamental, twining, woody vine which grows to a height of 10 to 20 feet when supported by other plants.
- It has slender, tough branches with 5 to 10 cm long compound leaves bearing 10–20 pairs of leaflets (**Fig 10.19**). Leaves are alternate, opposite, pinnately divided (feather-like) with small oblong leaflets. Leaflets appear in 8 to 15 pairs, and are about ½ inch long.
- Stems are green when young, but develop grey bark as the plant matures.
- Flowers are pink, purple, or white and borne in clusters. They appear in the leaf axils along the stems.
- The distinctive part of the plant is the seed which is oval, 5 mm in diameter, and has an attractive hard glossy outer shell

Fig 10.18: Datura seeds

Fig 10.19: *Abrus precatorius*
(*Pic:* Dr S Sivasuthan)

that is usually scarlet red with a black centre (**Fig 10.20**).* The seeds are present inside fruit pods, each containing 3 to 5 seeds. The pods split open when ripe. The pod is a legume (pea-shaped pod), and is about 3 cm long.

Uses

■ The seeds are often used in rosary beads, necklaces, and folk jewellery.
■ Jewellers in India sometimes use the seeds as a weighing measure for gold or precious stones.

Fig 10.20: Abrus seeds
(*Pic:* Dr Shashidhar C Mestri)

■ Quacks use extracts of various parts of the plant for the treatment of a wide variety of ailments.

Toxic Part

Seeds, root, leaves.

Toxic Principles

Abrin, abric acid, glycyrrhizin, and N-methyl tryptophan.

The main active principle is abrin which is a toxalbumen very similar to ricin. It is a lectin composed of two polypeptide chains (A and B) connected by a disulfide bridge. This basic structure of two peptide chains linked by a single disulfide chain is similar to that of botulinum toxin, tetanus toxin, cholera toxin, diphtheria toxin, and insulin.

Mode of Action

Like castor, the seeds of abrus are harmless when ingested whole, since the hard outer shell resists digestion. However, chewing or crushing of the seed before swallowing will enable the toxins to be released. Abrin is a powerful gastrointestinal toxin, and one of its polypeptide chains (B) binds to the intestinal cell membrane, while the other chain (A) enters the cytoplasm. Once in the cell, the A chain acts on the 60S ribosomal sub-unit, preventing binding of elongation factor 2, thus inhibiting protein synthesis and leading to cell demise.

Clinical Features

1. Dermal contact: redness, rash.
2. Ocular exposure: reddening, swelling, blindness.
3. Ingestion:
   a. Burning pain in the mouth and throat
   b. Severe vomiting
   c. Abdominal pain
   d. Bloody diarrhoea
   e. Cardiac arrhythmias
   f. Convulsions
   g. CNS depression
   h. Cerebral oedema
   i. Elevations of liver enzymes.

Usual Fatal Dose

About 1 to 3 seeds.

A point to note is that there have been several cases of ingestion of large amounts of seeds, which have resulted in scant clinical effects. This may reflect variations in toxicity, and/or poor GI absorption. If the seeds of these plants are swallowed whole, symptoms are much less likely to occur.

Treatment

1. Gastric decontamination (lavage, charcoal).
2. Whole bowel irrigation is said to be helpful, but some investigators dispute this.
3. Supportive measures, with special emphasis on rehydration. Close attention should be given to haematological parameters.

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* Other varieties: black with a white centre, and white with a black centre.

4. Alkalinisation of the urine probably has a role in preventing crystallisation of haemoglobin, and should be considered in severe poisonings.
5. Treat convulsions in the usual manner with diazepam.
6. Renal failure can be managed by haemodialysis.
7. Ocular exposure necessitates copious irrigation with running water for at least 15 minutes.

Autopsy Features

Evidence of GI haemorrhage, oedematous bowel, cerebral oedema, and congested liver and kidneys.

Forensic Issues

- Accidental poisoning is not uncommon among children playing in the countryside who find the seeds very attractive and may bite or chew on them.
- The extract of the seed is used in rural India to kill cattle by injecting needles ("suis") made out of the dried seed paste.
- Homicides have been reported with "suis".

INTESTINAL IRRITANT PLANTS

The plants in this category are rarely encountered in the Indian scenario, and hence will not be discussed.

DERMAL IRRITANT PLANTS

These plants mainly act as irritants on skin contact, with resultant inflammation. Among the sensitising plants which induce plant dermatitis, the Compositae, the largest family of flowering plants are frequently found in homes and gardens. Severe eruptions are commonly associated with the highly sensitising plants of the genus Toxicodendron (Poison ivy, Poison oak, Poison sumac). Related species of Anacardiaceae (Lacquer tree, Ginkgo fruit tree, Marking nut tree, Cashew, and Mango) can also produce dermatitis. Some plants (Parsnip, Lime, Wild carrot) can cause photodermatitis, manifesting as erythema, blisters, or hypopigmentation, on exposure to ultraviolet A light.

Table 10.3 lists a glossary of common skin lesions associated with plant toxicity. **Table 10.4** lists some plants that cause dermatitis.

Table 10.3: Common Skin Lesions Resulting From Dermal Irritants

Vesicle (Blister)	A circumscribed, fluid filled elevation of less than 0.5 cm size
Macule	A flat, non-palpable discolouration less than 1 cm in diameter. It may be erythematous (red), hyperpigmented (brown or black), or hypopigmented (pale)
Papule	A circumscribed elevated lesion measuring up to 1 cm
Nodule	A papule greater than 1 cm
Patch	A macule greater than 1 cm
Plaque	Results from a confluence of papules or nodules, producing an elevated lesion measuring greater than 1 cm
Bulla	A blister larger than 0.5 cm
Erosion	Loss of epidermis up to full thickness, but not involving basement membrane
Ulcer	Loss of full thickness epidermis, as well as papillary dermis, reticulardermis, or subcutis
Lichenification	A compensatory pathologic process resulting in a plaque-like lesion due to constant rubbing or scratching

Table 10.4: Common Dermal Irritant Plants

Plant	Irritant Ingredient	Nature of Dermatitis
Garlic	Allium, Dially Idisulfide	ACD, ICD
Onion, Leek	Allyldisulfide	ICD
Tulips	Alpha methylene-gamma butyrolactone	ACD
Tansy	Arbusculin A	ACD
Chrysanthemum	Arteglassin A, Parthenolide	ACD (photoallergic)
Hyacinth	Calcium oxalate	ICD
Red pepper (Chilly)	Capsaicin	ICD
Cashew tree	Cardanol	ACD
Cinnamon	Cinnamic aldehyde	ACD
Eucalyptus	Citronellal	ICD, ACD
Pine tree	Colophony, Turpentine	ACD, ICD
Cloves	Eugenol	ACD, ICD, Cheilitis

Contd...

Contd...

Geranium	Geraniol	Lip dermatitis
Lavender	—	ICD, ACD
Gingko tree	Gingkolic acid	ACD, Cheilitis, Stomatitis
Dandelion	Glycopyronosid	ACD
Nettles	Histamine	Pruritis, Hives
Jasmine	Jasmine oil	ACD
Lettuce	Lactucopicrin	ACD
Laurel	Laurel oil	ACD
Lemon grass	Lemon grass oil	ICD
Citrus	Limonine citral	Photodermatitis, Irritant dermatitis
Mint	Menthol or Carvone	ICD
Congress grass	Parthenin	ACD
Primrose	Primrose oil	ACD, Conjunctivitis, Erythema multiforme
Carrot, Parsnip, Fig	Psoralen	ICD
Celery	Psoralen	Photodermatitis
Orchids	Quinone	ACD
Castor seed	Ricinoleic acid	ICD, ACD, Lip dermatitis
Black mustard	Senevols	ICD
Sandalwood	Santal oil	Photoallergy
Sesame oil	Sesamol or Sesamin	ICD, ACD
Thyme	Thyme oil	Cheilitis, ACD
Mango tree	Urushiol	ACD
Poison oak Poison ivy Poison sumac	Urushiol	ACD, Leukoderma
Marking nut tree	Urushiol	ACD
Narcissus	—	Dermatitis
Daffodil	—	Dermatitis
Dieffenbachia	—	ICD
Philodendron	—	ACD

ACD = Allergic Contact Dermatitis, ICD = Irritant Contact Dermatitis

■ Treatment of Contact Dermatitis

1. Topical corticosteroids—corticosteroid ointments with few or no additives are preferred. Optimal frequency of application is twice a day.
2. For acute or weeping lesions, saline or aluminium subacetate compresses can be applied 3 to 4 times a day to dry the skin.
3. Itching can be relieved by oral antihistamines and lotions with menthol (0.25 to 0.5%).
4. Oral corticosteroids may be required in addition to high-potency local applications for widespread eruptions (e.g. poison ivy dermatitis). Tapering the oral dose is necessary. Long-term local applications of corticosteroids must be avoided, since that may lead to atrophy, striae, purpura, folliculitis, and telengiectasiae.
5. Prevention of irritant and allergic contact dermatitis may be attempted with barrier creams.
6. Photosensitive reactions can be treated with antihistamines, topical antipruritic agents, topical corticosteroids, and compresses. Rarely, systemic corticosteroids may be required.

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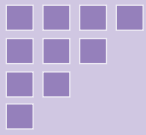
Plants of Special Importance

HEPATOTOXIC PLANTS

■ Neem

Other Common Names

Margosa tree.

Botanical Name

Azadirachta indica.

Physical Appearance

This tree belonging to family Meliaceae grows well in most parts of the country (**Fig 11.1**) and is revered highly for its medicinal properties. The seeds yield a yellowish oil (neem oil or margosa oil) which has a disagreeable odour and bitter taste.

Uses

Various parts of the tree as well as the oil have been used in the treatment of a wide variety of ailments.

Fig 11.1: Neem tree

Rural folk often chew on the twig of this tree to "clean" their teeth as an alternative to brushing with conventional dentifrices.

Toxic Part

Leaves (**Fig 11.2**) and seeds.

Toxic Principles

- Margosa oil and leaf extract contain stearic, oleic, palmitic, and linoleic acids.
- Aflatoxins may be present in unrefined oil.

Clinical Features

Ingestion of leaf extract or excess of margosa oil results in hepatotoxicity with vomiting, drowsiness, and encephalopathy. Metabolic acidosis is often present. Convulsions, myocarditis (with ventricular fibrillation), and pancreatitis have been reported.

Treatment

- Control of convulsions.
- Correction of acidosis.
- Management of cerebral oedema.
- Supportive measures.

Fig 11.2: Neem leaves

OTHER PLANTS

Autumn Crocus

Other Common Names

Meadow saffron; Meadow crocus; Naked lady; Son-before-the-father; Wild saffron.

Botanical Name

Colchicum autumnale.

Physical Appearance

- It is a perennial plant with whitish or pale purple flowers (**Fig 11.3**).
- The long, broad-lanceolate, dark green leaves are produced in spring, while the flowers bloom in succession from August to October, soon dying down.
- The bulb-like fleshy underground stems (corms) are about the size of a small tulip bulb, and lie from 6 to 10 inches deep in the soil.
- This plant grows well in England, Wales, and many European countries, but is relatively uncommon in Asia. However, it is encountered in the Himalayan region. The Indian variety usually bears yellowish flowers.

Uses

- The main active principle colchicine is used in the treatment of gout. It acts by reducing the inflammatory response to the deposited urate crystals, and also by diminishing phagocytosis. Deposition of urate is favoured by acid pH. Colchicine counters acid pH environment by inhibiting lactic acid production by leucocytes, thereby interrupting urate deposition and inflammatory response that sustains the acute attack.

Fig 11.3: Meadow saffron (*Colchicum autumnale*)

- The fruit capsule of Autumn crocus contains numerous dark brown seeds. The dried capsule is often used as a "rattle" by children. Each seed contains approximately 3.5 mg of colchicine. Ingestion of 2 seeds may be potentially lethal.

Toxic Part

All parts, especially fresh corms and ripe seeds.

Toxic Principles

- Colchicine
- Demecolcin.

Mode of Action

Colchicine is an antimitotic agent, blocking mitosis in metaphase and in the G_1 phase, preventing DNA synthesis.

Clinical Features

Listed in **Table 11.1**

Poisoning resulting from plant part ingestion is usually less severe than the pure alkaloid (colchicine) poisoning. Common manifestations after plant ingestion include nausea, vomiting, diarrhoea, abdominal pain, tachycardia, and chest pain. Hypotension, bradycardia, seizures, bone marrow suppression, coagulopathy, ECG changes, and death occur rarely.

Usual Fatal Dose

- 1 gram of the fresh corm.
- 7 to 60 mg of colchicine (0.5 mg/kg may be fatal).

Treatment

1. The following must be monitored:
   a. Fluid and electrolyte balance.
   b. Renal and liver function tests.
   c. Complete blood count (CBC) with differential and platelet count (daily in symptomatic patients).
2. All patients should be observed for at least 12 hours, because of occasional late onset of manifestations.
3. Colchicine is believed to undergo enterohepatic recirculation. Multiple dose activated charcoal may be beneficial because it interrupts enterohepatic recirculation, and should always be considered in patients with potentially serious or lethal ingestions.
4. Fluid and electrolyte status, especially potassium levels, should be followed closely, with administration of appropriate intravenous fluids for replacement.
5. Central nervous symptoms and ascending paralysis with respiratory involvement require aggressive supportive care including mechanical ventilation.
6. Patients suffering from bone marrow depression should be isolated to protect the patient from infection.
7. Granulocyte colony-stimulating factor, 300 mg/day, IV, helps in normalising leukocyte count.
8. *Antidote:* Specific goat colchicine Fab fragments administered as an infusion (400 to 500 mg). There are case reports of dramatic recovery from potentially lethal colchicine poisoning.

Table 11.1: Colchicine Poisoning

Phase I : 0 – 24 hours	Phase II: 2nd – 7th day	Phase III: After the 7th day
Abdominal pain, vomiting, diarrhoea, (sometimes haemorrhagic gastroenteritis)	Fever	Alopecia (reversible)
Leukocytosis	Bone marrow hypoplasia, leukopenia, thrombocytopenia	Rebound leukocytosis
Electrolyte disturbances, hypovolaemia, hypotension	Spontaneous haemorrhages, anaemia	Fever may persist for several weeks
Consumptive coagulopathy, fibrinolysis	Cardiac arrhythmias	
Massive cytolysis	Hepatotoxicity	
	Ascending peripheral neuropathy	
	Confusion, delirium, convulsions, coma	
	Multi-organ failure·	
	ARDS (Acute respiratory distress syndrome)	

9. Haemodialysis and exchange transfusion are not likely to be helpful because of the large apparent volume of distribution of colchicine.

Autopsy Features

1. Multiple petechiae and ecchymoses over visceral pleura, pericardium, and peritoneum.
2. Haemorrhagic oedema and congestion of lungs.
3. Inflammation of stomach and intestines.
4. Fatty degeneration of liver. Microscopy may reveal fatty changes and necrosis in the central portions of hepatic lobules with cells demonstrating "colchicine bodies", i.e. nuclei containing clumps of chromatin material. In a recently reported case, autopsy revealed hepatosplenomegaly (with significant haemorrhagic necrosis around central hepatic veins) and acute tubular necrosis. Hepatocytes showed hydropic or microvesicular fatty change, and portal triads were infiltrated by mononuclei. In addition, left cardiac ventricle hypertrophy and cerebral oedema were observed.
5. Kidneys may demonstrate evidence of acute tubular necrosis.
6. *Microscopy of bone marrow tissue*: hypocellular marrow with marked depletion of erythropoietic and granulopoietic cells, and moderate depletion of megakaryocytes.

■ Oduvan

Other Common Names

Oduvanthalai/Nillipalai (*Tamilnadu and Pondicherry*); Kadishe (*Andhra Pradesh*); Karlajuri (*West Bengal*); Garari (*Hindi speaking States of India*).

Botanical Name

Cleistanthus collinus.

Physical Appearance

- *Cleistanthus collinus* belongs to family Phyllanthaceae (sometimes placed in Euphorbiaceae), and grows wild in dry hills of various parts of India from Himachal Pradesh to Bihar, and southwards into Peninsular India (**Fig 11.4**).

Fig 11.4: Oduvan (*Cleistanthus collinus*)

- It is a small, deciduous tree with spreading, smooth branches. Leaves are orbicular, broadly ovate or elliptical, with rounded tips (**Fig 11.5**).
- Flowers are borne in small axillary clusters.
- The fruit capsule is large, somewhat trigonous, woody, dark-brown, and appears shining and wrinkled when dry. Seeds are globose and chestnut-brown in colour.

Fig 11.5: Oduvan leaves and fruit

Toxic Part and Principles

- All parts of the plant are poisonous.
- Extract of the various plant parts yield a multitude of compounds of which the glycosides, arylnaphthalene lignan lactones are toxic. These lignan lactones include cleistanthin A and B, collinusin and diphyllin, which in the past were known collectively as "oduvin".

Clinical Features

1. In one Indian case series, clinical features in those who died included vomiting, epigastric pain, breathlessness, visual disturbances (clouding/blurring/coloured vision), giddiness, drowsiness, fever, tachycardia, hypotension and/or respiratory arrest. Survivors were asymptomatic, or transiently symptomatic with abdominal pain, visual symptoms and giddiness.
2. A recent case report highlighted ARDS, distal renal tubular acidosis, and distributive shock secondary to inappropriate vasodilatation.
3. Neuromuscular weakness at presentation has been documented.

Diagnosis

1. ECG changes may include QTc prolongation and non-specific ST-T changes.
2. Blood biochemistry may reveal hypokalaemia, increased AST/LDH/CPK/CPK-MB levels, hyponatraemia, hyperbilirubinaemia and elevated urea levels.
3. ABG may show evidence of metabolic acidosis, hypoxia, and a widened alveolar- arterial O_2 gradient/difference (A-aDO$_2$ gap), especially in those with respiratory failure.

Treatment

1. Correction of metabolic acidosis with sodium bicarbonate.
2. Correction of hypokalaemia with IV potassium chloride.
3. N-acetylcysteine 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, and 100mg/kg over the next 16 hours, has been suggested as beneficial.

Forensic Issues

Cases of suicide accomplished with parts of the Oduvan plant have been on the increase in recent times, in several parts of India, especially Tamil Nadu and Andhra Pradesh. Accidental poisoning has also been reported.

■ Eucalyptus

Other Common Names

Blue gum tree.

Botanical Name

Ececalyptus globulus

Physical Appearance

- *Eucalyptus globulus* is a tree that grows well in the Nilgiris area in South India.

Fig 11.6: Eucalyptus trees

- The bark of the tree is smooth, and leaves are long and curved.
- Eucalyptus oil is obtained from the leaves and young shoots.
  - ❖ The oil is volatile, pale yellow or clear, with a distinctive fragrant odour and pungent, cooling taste.
  - ❖ It contains about 38 to 65% of eucalyptol (cineole), a monoterpenoid substance, as well as alpha pinene, phellandrene eudesmol, and other terpenes.

Uses

The oil is used in folk medicine for a variety of ailments (particularly those related to respiratory tract).

Clinical Features

1. Burning of mouth, abdominal pain, vomiting, diarrhoea.
2. Bronchospasm, bronchorrhoea, tachypnoea, chemical pneumonitis, apnoea.
3. Vertigo, slurred speech, delirium, ataxia, headache, drowsiness, coma. Sometimes convulsions occur. Pupils are often constricted. Mydriasis is encountered less commonly.
4. Tachycardia, hypotension.
5. There is odour of eucalyptus in the breath.
6. Aspiration of the oil results in chemical pneumonitis, with fever, dyspnoea, cyanosis, rales, and rhonchi.
7. Contact dermatitis and urticaria have been reported in sensitive persons after handling the foliage and other plant parts of *Eucalyptus globulus*.

Usual Fatal Dose

About 4 to 5 ml.

However, survival has been reported with 20 to 30 ml in children, and 120 to 240 ml in adults.

Treatment

1. Symptomatic and supportive measures.
2. Emesis is NOT recommended due to potential for aspiration, CNS depression, and seizures.
3. Activated charcoal is beneficial.
4. If the patient is coughing upon arrival at the hospital, aspiration may have already occurred. Monitor arterial blood

gases in cases of severe aspiration pneumonitis to assure adequate ventilation. Obtain baseline chest X-ray and vital signs.

5. Mechanical ventilation may be required in cases of severe respiratory depression or aspiration.
6. Mannitol, peritoneal dialysis, and haemodialysis were successfully used in some cases of substantial ingestion.

■ Physic Nut

Other Common Names

Purging nut.

Botanical Name

Jatropha curcas.

Physical Appearance

- This is a large, glabrous shrub belonging to family Euphorbiaceae, with greenish white, smooth bark that peels off in thin flakes.
- Leaves measure up to 15 mm in diameter, and are entirely or palmately lobed.
- Flowers are yellowish green in colour.
- The black seed of *Jatropha curcas* is known as "physic nut" or "purging nut", since it is a strong purgative. It contains a pale acrid oil, just like croton oil, and has the active principle *curcanoleic acid*. Apart from being used as a laxative, the oil is also applied to painful joints, and is said to have beneficial effects. However, the crude oil when applied externally causes irritation, and when ingested causes severe diarrhoea. The seeds possess a toxalbumin named *curcin*.

Clinical Features

Ingestion of the seeds results in salivation, sweating, abdominal pain, diarrhoea, weakness, and muscle twitching. Jatropha poisoning is generally non-fatal, even though some deaths in lower animals have been reported.

Treatment

Supportive and symptomatic measures.

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12 Venomous Bites and Stings

SNAKES

Snakes (also referred to as serpents) are limbless creatures with elongated bodies covered with scales. The body is divided into head, trunk, and tail. The head may be oval, triangular, or the same width as the trunk, ending as a blunt snout. The head bears two eyes, two nostrils, and a mouth. External ears are absent since snakes do not posses auditory apparatus. However, though a snake cannot perceive sounds, it senses vibrations on the ground, which enables it to hunt prey and keep clear of predators. The eyes of a snake lack eyelids, each being covered by a transparent scale. Pupils may be round or elliptical.

The mouth of a snake is extremely distensible, enabling it to swallow large animals whole, without mastication. Snakes are essentially carnivorous and feed mostly on mice, rats, lizards, or frogs. Water snakes feed on fish. Some are cannibals and feed on other snakes, e.g. krait, king cobra, etc. Snakes can survive for long periods of time without food, even up to several months or years. Most snakes have four rows of teeth in the upper jaw, and two rows of teeth in the lower jaw. Two of the upper rows are situated along the margins of the jaw, while the remaining two are located on the palate near the middle of the roof of the mouth (*palate teeth*). The lower rows are located along the margins of the lower jaw. Venomous snakes have modified teeth called *fangs* in addition to ordinary teeth. Fangs are usually two in number, invariably located one on each side of the upper jaw. They may be grooved or canalised, and are connected to the venom glands which are a pair of modified parotid salivary glands located one on each side, just below and behind the eye. All teeth are generally directed backwards which help in propelling a swallowed prey inwards, thereby minimising the possibility of it being disgorged.

The tongue of a snake is forked and can be flicked in and out of the mouth rapidly. It is not adapted for licking or sucking, but is actually a device to pick up scent particles from the exterior and transfer them to the Jacobson's organ in the roof of the mouth. Thus the snake is able to track its prey, locate suitable mates, and smell out predators such as mongoose or humans.

The nostrils enable a snake to inhale air into its lungs. Hissing is accomplished by the forcible expulsion of air through the nostrils, and is an act of aggression or defence. Russell's viper and puff adder are noted for their very loud hiss. In some (Crotalid) snakes, there is a pit between the eye and nostrils, which is a heat sensitive organ that helps in detecting warm-blooded prey.

Venomous snakes are found all over the world, except New Zealand, and most parts of the Arctic and Antarctic regions, as well as Ireland, Iceland, Chile, Hawaii, parts of Mediterranean and Caribbean regions, and some of the Pacific islands. In Britain, there is only one indigenous snake (*Vipera berus*), which seldom causes serious envenomation.

Snakes are encountered in all kinds of geographical locations, such as on land, in marshes, and in water (fresh water and the sea). Most snakes can climb trees, and a few can burrow into the ground. Land snakes can swim in water, but sea snakes cannot survive on land. Snakes are cold-blooded creatures, and their body temperature varies depending on the environmental conditions. They usually hibernate in the winter in secluded places, and go without food and water for several months. Stored body fat helps in sustenance during hibernation. However, tropical snakes may not hibernate at all, and may be seen in the open all year round.

Snakes regularly moult, i.e. they shed their skin periodically (usually every 2 months). The skin which is cast off, is turned inside out, in the manner of a glove being removed from the hand. Moulting enables a snake to become more alert and active.

The trunk (i.e. the main body) of a snake may be stout or slender, and may be variously coloured. Often there are vivid patterns or designs. The portion of the body distal to the vent is called the tail, which may end abruptly to a blunt point, or may taper gradually to a fine point. The vent is an opening situated in the posterior part of the undersurface of the body, which serves as a common orifice for the alimentary and genito-urinary tracts. The tail of a sea snake is flattened and paddle shaped, to enable it to swim.

Sexes are distinct in snakes. Each species breeds true, and hybrids are virtually unknown. Most snakes lay eggs (oviparous) while a few species bring forth their young alive (viviparous). Snakes usually survive for many years, a few species living up to 20 years or more.

■ Classification of Snakes

Snakes are classified on the basis of morphological characteristics such as arrangement of scales (*lepidosis*), dentition,

osteology, myology, sensory organs, and the form of the hemipenes, as well as on the basis of immunological analysis of venom and serum proteins, and sequence analysis of DNA that encodes mitochondrial and other enzymes.

There are about 3500 known species of snakes in the world, of which less than 350 species are venomous. Among non-venomous snakes, only the giant constrictors belonging to family Boidae are dangerous to man. Examples include rock python (*Python sebae*) of Africa, reticulated python (*Python reticulatus*) of South East Asia, especially Indonesia, and anaconda (*Eunectes murinus*) of South America. The Indian rock python is seen all over India, and grows up to 3 metres, but not a single case of human fatality has been reported that can be definitely attributed to this snake. The regal python of Nepal grows up to 10 metres in length, and is said to be the largest snake in the world. The giant constrictors act by coiling around the victim and crushing him to death.

Venomous snakes belong to 5 families:

1. **Colubridae:** This family includes almost 1400 species, or 75% of all the snake genera and 78% of all the snake species in the world. Approximately 400 of these species of Colubridae have short immobile fangs, or enlarged solid teeth at the posterior end of the maxilla. About one third of the Colubrid species possess rear fangs which deliver a toxic saliva delivered by a chewing motion. Colubrid snakes are the predominant species on all continents except Australia. Examples include mountain racer, Western and Eastern hognose snakes, parrot snake, rat snake, wandering garter snake, etc.

2. **Atractaspididae:** This family comprises African and Middle Eastern burrowing asps or stilleto snakes (also known as burrowing or mole vipers or adders, false vipers, side-stabbing snakes), which have very long front fangs used for immobilising their prey by a side-swiping motion. These fangs often protrude from the corner of the partially closed mouth.

3. **Elapidae:** These snakes have relatively short, fixed front (proteroglyph) fangs, which however may extend up to 10 mm long). They are anchored at the anterior portion of the maxilla. Examples include the following—
   a. Cobras (*Naja*)
   b. Kraits (*Bungarus*)
   c. Coral snakes (*Calliophis, Maticora, Micrurus*)
   d. Mambas (*Dendroaspis*)

4. **Viperidae:** These snakes have highly developed long curved, hinged, front fangs, which are channelised in the form of a hypodermic needle. There are two sub families—
   a. **Viperinae or true vipers:** Vipers and adders
   b. **Crotalinae or pit vipers:** Rattle snakes (*Crotalus, Sistrurus*), and Asian pit vipers (*Trimeresurus, Hypnale*).

5. **Hydrophidae:** This family comprises sea snakes, which have short fixed fangs as in the case of the elapids.

Approximately 330 species of snakes exist in India, of which about 70 species are venomous (40 land snakes and 30 sea snakes). The commonest Indian venomous snakes are referred to as the "Big Four", and comprise common krait (*Bungarus caeruleus*), common cobra (*Naja naja*), saw-scaled viper (*Echis carinatus*), and Russell's viper (*Vipera russelli*).

Other venomous snakes which are less commonly encountered include the common green pit viper or bamboo snake (*Lachesis gramineus*), large-spotted viper (*Lachesis monticola*), horse-shoe viper (*Trimeresurus strigatus*), Gray's viper (*Trimeresurus purpureomaculatus*), anamalai viper (*Trimeresurus anamallensis*), brown or common himalayan viper (*Agkistrodon himalayanus*), hump-nosed viper (*Agkistrodon hypnale*), Millard's viper (*Agkistrodon millardi*), large-scaled viper (*Lachesis macrolepis*), and mock viper (*Psammodynastes pulverulentus*), all of which are pit vipers. Of the remaining, the following are important: king cobra (*Ophiophagus hannah*), Bibron's coral snake (*Calliophis bibroni*), Maclelland's coral snake (*Calliophis macclellandi*), slender coral snake (*Calliophis trimaculatus*), and common Indian coral snake (*Hemibungarus nigrescens*). The commonest sea snake encountered in Indian seas is the hook-nosed sea snake (*Enhydrina schistosa*).

■ Identification of Venomous Snakes

India records a staggering 10,000 to 15,000 deaths annually from snakebite. While many of these deaths occur due to envenomation, a significant few result from terror following a non-lethal venomous, or non-venomous snakebite. The ability to distinguish the highly venomous snakes (especially cobra, krait, viper) from the mildly venomous or non-venomous snakes could therefore help mitigate such lethal fear, and reduce mortality. It is also true that correct identification of the exact variety of venomous snake involved in a particular case can be of great benefit in evolving effective treatment strategies. For these reasons, every doctor should possess fundamental knowledge in differentiating venomous from non-venomous snakes, as well as (preferably) identify the exact species. However, this is easier said than done, and the current view is not to attempt detailed examination if identification is difficult, but instead to rely on the clinical picture of the bitten victim. **Table 12.1** lists some common features of venomous snakes.

■ Common Indian Venomous Snakes

Indian Snakes of Medical Importance

The WHO classifies the following as Indian Snakes of Medical Importance:

Class I - Commonly cause death or serious disability: Cobra/ Russells Viper/Saw-Scaled Viper

Table 12.1: Features Indicative of Venomous Snake
• Usually dull coloured: brown, black, grey, dull green, etc.
• Stout body with abruptly tapering tail
• Compressed tail
• Broad belly scales extending across entire width of belly
• Small scales on triangular head
• Pit between eye and nostril
• Presence of hood with or without markings
• Presence of fangs
• Presence of rattle at the end of tail

Class II - Uncommonly cause bites but are recorded to cause serious effects (death or local necrosis): Krait/King Cobra
Class III - Commonly cause bites but serious effects are very uncommon.

It is interesting to note that the king cobra is present on this list. There are other snakes such as the hump-nosed pit viper that also qualify under these categories. The term 'The Big Four' has been used in India for many decades, to describe the common cobra, Russell's viper, common krait and saw-scaled viper. This was due to the belief that these four snakes were responsible for causing virtually all snakebite deaths in India. However, this has led to confusion when a death occurs resulting from snakebite. The assumption has been that the death must be due to one of the snakes on the Big Four list. This has led to major problems of species mis-identification, such as the hump-nosed pit viper being erroneously identified as *Echis carinatus*. With the emergence of a hump-nosed pit viper as a snake of medical importance, questions now exist over the other snakes in India and whether they are also capable of causing lethal envenomation and to what extent.

The Big Four

■ Common Cobra

Scientific Name

Naja naja.

Other Common Names

Indian Cobra.

Geographical Distribution

All over India.

Physical Appearance

- The common cobra is usually brown or black in colour.
- It is a distinctive snake growing up to 5 to 6 feet in length, with a distensible neck that can be expanded into a hood (**Fig 12.1**). On the dorsal side of the hood, there may be a monocellate (monocle) or binocellate (spectacle) mark (**Fig 12.2**).
    - ❖ The former is more common in the Bengal cobra (*Naja kaouthia*). The monocellate cobra is generally brown or black, with speckled or variegated, white or pale yellow appearance (**Fig 12.3**). It often has alternate wide and narrow, transverse, dark bands. Dorsal hood mark is a pale circle edged with black and has 1 to 3 spots; ventral hood mark has a pair of dark spots, or a wide dark band.
    - ❖ Another variety of cobra that is encountered in the Indian sub-continent is the Andaman cobra (*Naja sagittifera*).
- The hood markings distinguish the cobra from other species, and its habit of rearing up when alarmed make it distinctive but not definitive, as other species do this, notably the Trinket Snake.
- On the ventral surface of the hood are faint, broad, black

Fig 12.1: Common cobra (*Naja naja*)—Hood expanded
(*Pic:* Ashok Captain)

Fig 12.2: Common cobra – Binocellate mark on hood

stripes above which are two dark spots that extend over 3 to 4 scales.
- The head is small, and pupils are round.
- The most important distinguishing feature of this snake is the fact that the 3rd supralabial shield touches the eye and nose shield. Also, a small wedge-shaped scale ("cuneate") is present between the 4th and 5th infralabials. Another important feature is said to be the presence of 3 small scales just behind each eye.

Fig 12.3: Monocellate cobra (*Naja kaouthia*)

Habitat

- Grassy plains, fields, and mountainous regions (up to 15000 feet). They usually reside among piles of bricks, termite mounds, tangles of roots at the base of trees, and old masonry constructions.
- The spectacled cobra is encountered virtually over the whole of mainland India except the north-east.
- The black cobra (*Naja oxiana*) (**Fig 12.4**) occurs in the extreme north of India around Jammu and Kashmir, and also in Gujarat and Rajasthan, although these may be patternless versions of the spectacled cobra.
- The cobra is diurnal, but bites from cobras occur during both the day and the night. The cobra's principal diet is rats. It is known to enter human habitations in search of prey.

Nature of Venom

Predominantly neurotoxic.

■ Common Krait

Scientific Name

Bungarus caeruleus.

Other Common Names

Indian krait.

Geographical Distribution

All over India.

Fig 12.4: Black cobra (*Naja oxiana*)

Physical Appearance

- The common krait is a steel-blue snake growing up to 3 to 4 feet in length (sometimes up to 7 feet), with whitish bands or half-rings throughout its back (**Fig 12.5**). Occasionally, it may be grey or dark brown in colour. The markings consist of paired white bands which may be less distinct anteriorly.
- The common krait has small dark eyes, and the pupils are almost invisible. The upper lip is white or yellow, while the belly is very white.
- The most distinctive features comprise the following:
    ❖ A chain of hexagonal large scales throughout the mid-doral aspect of the body (**Fig 12.6**).
    ❖ The subcaudals (ventral scales distal to the vent) are undivided, unlike other elapids.
    ❖ The 4th infralabial scale is the largest of the infralabials.

Habitat

- The common krait is a reclusive snake which prefers to reside in crevices of rocks or logs of wood, and being nocturnal, emerges only during the night to hunt for prey. Its primary diet is other snakes. It can be found all over Peninsular India and often seeks habitation near human dwellings.

Fig 12.5: Common krait (*Bungarus caeruleus*)
(*Pic:* Dr HS Bawaskar)

Fig 12.6: Common krait: hexagonal large scales on mid-doral aspect of body (*Pic:* Ashok Captain)

- The common krait may enter houses and hide in dark corners, cupboards, bookshelves, etc. It does not hiss, but occasionally makes a faint whistling sound. These snakes prowl on hot humid nights; they often do not strike, but make a quick snapping bite.

Nature of Venom

Predominantly neurotoxic. It is the most venomous snake of India.

■ Saw-scaled Viper

Scientific Name

Echis carinatus.

Other Common Names

Carpet viper; "Phoorsa".

Geographical Distribution

All over India (especially plains and deserts).

Physical Appearance

- The saw-scaled viper is a small snake, about 1½ to 2 feet long, and is usually brown in colour (**Fig 12.7**). Occasionally, the colour appears greenish. There is a wavy white line along the entire length of each flank, while diamond-shaped markings extend over the back, numbering usually 25 to 30.
- The head is triangular with small scales. A characteristic whitish, arrow-shaped or crow's foot mark is often present on the head. The pupils are vertical.
- The saw-scaled viper is named as such because its scales are serrated. When agitated, it throws itself into a double coil (in the manner of a "figure of eight"), and rubs the coils together vigorously, producing a harsh, rasping sound, akin to the sound of a sandpaper being scraped over a rough surface. At the same time, it also hisses loudly by exhaling forcefully through the nostrils.
- Like other vipers, the saw-scaled viper is viviparous.
- The echis is an aggressive snake and may bite on the slightest provocation.

Habitat

This snake prefers desert regions, and is often found basking in the sun during the daytime, among rocks or in sandy soil. It may enter human habitations especially tents, in search of prey. In some parts of peninsular India, it is very uncommon, particularly in most parts of Kerala.

Nature of Venom

Vasculo- and haemotoxic.

■ Russell's Viper

Scientific Name

Vipera russelli, Daboia russelli.

Geographical Distribution

All over India.

Physical Appearance

- This is a brownish, stout snake, growing up to several feet in length (**Fig 12.8**).
- The head is triangular, with a 'V' shaped mark (apex pointing forward), and is covered with small scales. Pupils are vertical.
- Fangs are long, channelised, and hinged, being erected at the time of striking (**Fig 12.9**).
- There are 3 rows of chained dark spots over the entire body. The Russell's viper is known to hiss loudly when agitated. Like other vipers, it is viviparous.
- Russell's viper is a nocturnal snake, but unfortunately for humans, during the daytime it often rests up under bushes, at the base of trees, and in leaf litter. It is therefore frequently encountered by rural workers as they carry out general agricultural activities.

Nature of Venom

Predominantly vasculo- and haemotoxic, but is able to produce neurotoxic effects also. Acute renal failure and adrenal insufficiency have also been associated with this snake.

Fig 12.7: Saw-scaled viper (*Echis carinatus*)
(*Pic:* Dr HS Bawaskar)

Fig 12.8: Russell's viper (*Daboia russelli*)
(*Pic:* Ashok Captain)

Chapter 12 ◆ Venomous Bites and Stings

Fig 12.9: Russell's viper fangs (*Pic:* Ashok Captain)

OTHER SNAKES

King Cobra

Scientific Name

Ophiophagus hannah, Naja hannah, Naja bungarus.

Other Common Names

Hamadryad.

Geographical Distribution

Himalayan region, Bengal, Assam, and hills and forests of South India. The king cobra is a forest dweller primarily, but also inhabits mangrove, and occasionally tea and coffee estates. It feeds on other snakes, and is rarely encountered.

Physical Appearance

- The king cobra is the largest venomous snake in the world, and grows up to 8 to 12 feet or more in length (**Fig 12.10**).
- Like the common cobra, it has a hood, but lacks the monocellate or binocellate marking; the hood is much narrower than that of the common cobra.

- Colour varies from yellow to green, brown, or black.
- The head has two large occipital shields behind the parietals. This is a unique feature of this species. The 3rd supralabial touches the eye and nose shield as in the case of the common cobra, but cuneate is absent.

Nature of Venom

Predominantly neurotoxic. However, according to some reports they may be able to produce haemorrhagic activity also.

Banded Krait

Scientific Name

Bungarus fasciatus.

Geographical Distribution

Eastern parts of India.

Physical Appearance

- The most distinctive feature of this snake is the presence of glistening, broad bands of yellow, alternating with black (**Fig 12.11**). These alternating bands encircle the body and are almost equal in width.
- The banded krait has a marked vertebral ridge that gives it a permanently emaciated look with a distinct blunt tail. Considered a harmless snake, the banded krait rarely bites.

Nature of Venom

Predominantly neurotoxic

Pit Vipers

These vipers are characterised by the presence of a pit between the eye and nostril on each side. There are two kinds of Indian pit vipers:
1. Pit vipers with small head scales—
   a. Common Green Pit Viper (**Fig 12.12**): It is also referred to as the bamboo viper, and its scientific name is *Lachesis gramineus*. It is the commonest of the pit vipers, and is found in most of the hilly regions of India.

Fig 12.10: King cobra (*Naja hannah*)
(*Pic:* Dr Nishat Ahmed Sheikh)

Fig 12.11: Banded krait (*Bungarus fasciatus*)

Fig 12.12: Green pit viper (*Lachesis gramineus*)

It is vivid green or yellow in colour with a whitish or yellowish line on each flank. The head is flat, broad, and triangular. Pupils are vertically elliptical. Belly may be mottled. Length varies from 2 to 3 feet or more. As the name suggests, it prefers to reside among bamboo trees, though it is also commonly encountered on other trees.

b. Large Spotted Viper: The scientific name of this snake is *Lachesis monticola*. It is confined to the Himalayan region, and is brownish in colour, growing up to 3 feet in length. The head may have a V mark, because of which it is sometimes mistaken for Russell's viper.

c. South Indian Pit Vipers:
   i. The horse-shoe viper (*Trimeresurus strigatus*) and Anamalai viper (*Trimeresurus anamallensis*) are commonly encountered in the Western Ghats and the Nilgiris.
   ii. Other vipers encountered in this region include the large-scaled pit viper (*Trimeresurus macrolepis*), the Malabar pit viper (*T. malabaricus*) (**Fig 12.13**), and the horseshoe pit viper (*T. strigatus*). Envenomation with most of these snakes results in localised pain, swelling, and bleeding. No fatalities have been reported.
   iii. T. gramineus (Indian green tree viper) is said to be a common source of bites in Peninsular India, primarily hilly country with dense undergrowth, especially

among farmers, and those picking tea. Fatalities have been reported in children with this snake.
   iv. Envenomation with *T. purpureomaculatus* (Mangrove pit viper) causes local pain, swelling (which may extend to the entire limb), local necrosis, and enlarged lymph nodes. Coagulopathies are possible. Fatalities have been reported.

d. Pit Vipers of the North-East: mountain pit viper (*Ovophis monticola*), Jerdon's pit viper (*Protobothrops jerdonii*), Medo's pit viper (*T. medoensis*), Pope's pit viper (*T. popeiorum*) which is generally found in hilly regions up to 3,000 to 5,000 feet, and is common on tea plantations, spot-tailed pit viper (*T. erythurus*), and white-lipped pit viper (*T. albolabris*). Envenomation results in local pain, bruising, and swelling with extension beyond the bite area. Local blisters and necrosis are less likely to occur. Coagulopathies may occur; fatal intracranial bleeding has been reported in some cases.

2. Pit Vipers with shields on the head –
   a. Brown or Common Himalayan Viper (*Agkistrodon himalayans*):
      i. This is the commonest pit viper in the Himalayan region and Kashmir.
      ii. It grows up to 2 feet or more in length, is brownish in colour, and usually has mottled "carpet" patterns (dark longitudinal lines that are interrupted by paler cross bands) on the back. The belly may have red spots.
      iii. When agitated, it coils itself tightly, and vibrates the tail vigorously (like a rattle snake).
      iv. Envenomation results in immediate local pain, blistering, and swelling of the limb, which can be extensive and may last for several days. No systemic bleeding has been reported; patients usually recover with no apparent permanent disability.
   b. Hump-nosed Pit Viper (*Hypnale hypnale*) (**Fig 12.14**):
      i. The hump-nosed pit viper (Merrem's hump-nosed viper) is one of India's tiniest venomous snakes, its total length ranging from 28.5–55.0cm.
      ii. Its distinctive features include the weakly keeled body scales, a markedly triangular head with an up-turned snout, and the presence of five large

Fig 12.13: Malabar pit viper (*Trimeresurus malabaricus*)
(*Pic:* K Shaji Kumar & Dr Jaideep C Menon)

Fig 12.14: Hump-nosed pit viper (*Hypnale hypnale*)
(*Pic:* K Shaji Kumar & Dr Jaideep C Menon)

symmetrical plate scales (supraoculars, frontal and parietals) on the top of the head in addition to the smaller scales typical of all vipers. There are heat sensitive pits between the nostril and the eye.

iii. Colouration is very variable and includes grey, cream or brown on the dorsal surface, which is heavily marked with dark brown or black chevrons whose apices touch the mid-line, or with brown and/or black blotches. The ventral surface is grey, yellow or brownish, sometimes with brown or black spots.

iv. It is mainly nocturnal and both arboreal and terrestrial. It can be found in both wet and dry deciduous and secondary forest areas and plantations. It is a frequent cause of bites to rubber plantation workers who harvest latex before dawn. It often rests during the day in leaf litter beneath trees and bushes when it is most frequently encountered. Its habit of resting on bushes brings it into contact with plantation workers or agricultural workers who tend bushes.

v. Its geographical range is believed to be the Western Ghats as far north as Goa but may well be more extensive. It is also found throughout Sri Lanka.

vi. The hump-nosed pit viper's venom is anti-haemostatic and causes both coagulation abnormalities and acute renal failure. A common feature of *Hypnale* envenomation is the late onset of systemic symptoms. Disturbances in coagulation often do not appear for 12 hours and therefore it is vital that patients are monitored for 24 hours. The species can also cause severe local swelling although the only objective measure suggests not to a sufficient extent to require surgical intervention.

■ Coral Snakes

Coral snakes are generally small (2 to 3 feet), brightly coloured snakes which are not as venomous as the other elapids or viperids. They are considered rare, which may be more due to their secretive nature than actual rarity. These snakes are quiet and very rarely bite. Many authorities consider them harmless, but they can cause fatalities. They feed on cold-blooded animals.

There are 9 varieties seen in India, of which the commonest is the Common Indian coral snake or Gunther's coral snake (*Hemibungarus nigrescens*). It is found in the hills of Western and Southern India, and has nocturnal habits, but little in detail is known about it. When found, which is rare, it is usually located under leaf litter, soil, or underneath rotting logs. It is a reddish or brownish snake with spots or lines on the back (**Fig 12.15**). The head and neck are usually black. Other coral snakes are even more rarely encountered in toxicological practice.

The venom is predominantly neurotoxic, as in the case of all elapids, although fatalities have not been reported in India. Some tribals report considerable bleeding following presumed coral snake bites.

Fig 12.15: Coral snake (*Hemibungarus nigrescens*)

■ Sea Snakes

There are approximately 47 species of sea snakes (hydrophids) in 2 sub-families. They are easily distinguished from eels by their nostrils, whereas eels have gills, fins, and no scales. Sea snakes do not hiss as their land relatives, but produce a low pitched gurgling sound. They are all venomous and have fixed fangs with the venom duct opening near the fang's tip.

All the Indian seas (Indian Ocean, Bay of Bengal, and Arabian Sea) abound in venomous sea snakes which are characterised by their flattened, paddle shaped tails. The belly scales are generally not as broad as in the land snakes. These snakes are generally bluish, greyish, or greenish in colour, and may have conspicuous bands on the back. They generally grow up to 4 to 5 feet in length, but may occasionally be 9 feet long. There are 29 species of sea snake in Indian waters, and though they are all venomous, they generally do not bite humans. They feed entirely on fish, and favour coastlines, sometimes resting in puddles of sea water between rocks. Apart from the paddle shaped tail, these snakes can be distinguished by the nostrils which (unlike in land snakes) are situated on the top of the snout. This enables them to breathe while in water.

The venom of sea snakes is predominantly myotoxic. *Enhydrina schistosa* (beaked sea snake) is encountered in the Arabian Sea, Bay of Bengal, Andaman Sea, and W. Indian Ocean. Adults are dull olive green or pale green, or grey with dark bands (**Fig 12.16**). The belly is cream to dirty white in colour. Head is greenish without markings, while the tail is mottled with black. Average length of these snakes is 3 to 4 feet. The shield of the lower jaw is small and buried in a cleft between the first pair of labials giving it a beaked profile, and hence the common name.

Hydrophis bituberculatus is seen in the Bay of Bengal, and coasts of Sri Lanka, while *Hydrophis caerulescens* is seen in the Arabian Sea, Bay of Bengal, and Andaman Sea. *Hydrophis cyanocinctus* is encountered in the Persian Gulf, Arabian Sea, Andaman Sea, and possibly also the Bay of Bengal. It is called annulated sea snake, and is whitish, pale green, or yellow in colour with blackish crossbands that may or may not encircle the body. *Hydrophis fasciatus* is seen in the Bay of Bengal, Andaman Sea, and possibly also the Arabian Sea. It is called

Fig 12.16: Beaked sea snake (*Enhydrina schistosa*)

banded small-headed sea snake, and has a small head with a long and slender neck. It is grey to dirty yellow in colour with dark crossbands that are widest on the vertebral surface and taper to points laterally. The neck is dark olive green to black in colour with yellow crossbars or spots. *Hydrophis ornatus* (reef sea snake) is seen in the Bay of Bengal, Andaman Sea, and the Arabian Sea. It is a large-headed, stout bodied snake, and is greenish-white, olive green, or yellow in colour with wide, dark crossbands or rhomboid spots.

■ Snake Venom

Snake venom is nothing but the toxic saliva secreted by modified parotid glands, and is a clear, amber-coloured fluid when fresh. It is the most complex of all poisons, containing more than 20 components. The concentration of venom shows diurnal and seasonal variation. Bites inflicted at night and immediately after hibernation are the most severe. Most of the dry weight of venom is constituted by protein, comprising a variety of enzymes, non-enzymatic polypeptide toxins, and non-toxic proteins. Non-protein ingredients of venom include carbohydrates and metals (often in the form of glycoprotein metalloprotein enzymes), lipids, free amino acids, nucleotides, and biogenic amines. The lethal and more deleterious fractions of snake venoms are certain peptides and proteins of relatively low molecular weight (6,000 to 30,000). The peptides appear to have very specific receptor sites, both chemically and physiologically.

The polypeptide toxins (often called neurotoxins) are found most abundantly in elapid and hydrophid venoms. Postsynaptic alpha neurotoxins such as alpha bungarotoxin and cobrotoxin contain about 60 to 70 amino acid residues, and bind to acetylcholine receptors on the motor end-plate. Presynaptic beta neurotoxins such as beta-bungarotoxin, cobrotoxin, and taipoxin contain about 120–140 amino acid residues, and a phospholipase A subunit, and prevent release of acetylcholine at the neuromuscular junction. Cobra's alpha bungarotoxin, binds to the acetylcholine receptors and inhibits neural transmission at the neuromuscular junction. Krait's beta bungarotoxin causes an initial release of acetylcholine, but then damages the nerve terminal and prevents any further release. It is for this reason that krait victims often take longer to recover than cobra victims. The acetylcholinesterase found in most elapid venoms is no longer thought to contribute to their neurotoxicity.

Enzyme function and patho-physiological disturbances are most clearly related in the case of viper venom pro-coagulants. For instance, Russell's viper venom contains at least two proteases, which activate the blood-clotting cascade. RVV-X, a glycoprotein, activates factor X by a calcium-dependant reaction, and also acts on factor IX and protein C. RVV-V, an arginine ester hydrolase, activates factor V. Echis venom contains a zinc metalloprotein "ecarin" which activates prothrombin. Russell's viper can induce neurotoxic symptoms in addition to haematological abnormalities. Many species of Russell's viper have this ability, and it is particularly evident in Southern India and Sri Lanka.

Hyaluronidase may serve to promote the spread of venom through tissues. Proteolytic enzymes (hydrolases) may be responsible for local changes in vascular permeability leading to oedema, blistering, and bruising, and to necrosis. Biological amines such as histamine and 5-hydroxytryptamine may contribute to local pain and permeability changes at the site of a snakebite.

Sea snake venom contains hyaluronidase, acetylcholinesterase, leucine aminopeptidase, 5-nucleotidase, phosphomonoesterase, phosphodiesterase, and phospholipase A. Sea snake venoms are highly toxic. Taking the minimal lethal dose of *E. schistosa* venom as 0.05 mg/kg for warm-blooded animals, it is estimated that the minimal lethal dosage for a 70 kg man would be 3.5 mg, or about one-third of the venom injected by a fresh adult sea snake.

SNAKEBITE

■ Epidemiology

Snakebites are reported from virtually every part of the world, except those countries where snakes (especially venomous snakes) are relatively rare (*page no. 137*). The incidence of serious bites is significantly higher in the tropics than in industrialised nations of the West. This is exemplified by the fact that while the USA records 6,000 to 8,000 venomous bites per year, with mortality ranging from 5 to 15 deaths, India records about 200,000 bites, of which nearly 15,000 end in death. In Britain, hardly 200 bites are reported each year, and only 14 deaths have occurred in the last 100 years!

Epidemics of snakebite have resulted from a sudden increase in snake population density, for example after flooding in Columbia, Pakistan, India, and Bangladesh. Invasion of the snake's habitat by large numbers of people may also be followed by an increased incidence of snakebite. This occurred during the construction of new roads through jungles in South America, and during the movement of farmers to newly immigrated areas in the former dry zone of Sri Lanka. Among the various states in India, Maharashtra records a high incidence of snakebites—more than 1,000 bites per year. Most of the bites are reported from rural parts of the state. Other states with significant reportage of snakebites include West Bengal, Uttar

Pradesh, Tamil Nadu, and Kerala. Most of the bites are said to be due to saw-scaled viper (almost two-thirds), while one-fourth of the number is due to Russell's viper; cobra, krait, pit viper, etc., account for only a small number of cases. A recent report from South India indicates that nearly 20% of poisoning cases admitted to hospitals could be due to envenomations.

■ Clinical Features

Non-Venomous Snakebite

A significant proportion of snakebites is said to be due to non-venomous snakes. Since the question of envenomation does not arise in such cases, systemic manifestations are non-existent, except those due to psychological shock. As a result of the fear and apprehension associated with snakes, every bite (venomous or otherwise) is attended by some degree of shock characterised by giddiness, syncope, sweating, palpitation, tachycardia, and hypotension. Consequent upon reassurance especially by a doctor, about the non-venomous nature of the bite, these symptoms usually resolve rapidly.

Venomous Snakebite

1. *Without Envenomation:*

a. It is well known that even when a highly venomous snake bites a human, serious envenomation may not occur. In fact, it has been suggested that 20 to 50% of venomous bites are not attended with serious toxicity.

b. Reasons for lack of envenomation in venomous bites include the following:

   ❖ *Dry bite:* A snake does not always inject venom at the time of biting.

   ❖ *Protective gear:* Envenomation may not occur in the case of bites inflicted on shod feet or heavily clothed parts.

   ❖ *Leakage of venom:* Head-on bites often result in efficient injection of venom, while sideswipes may cause some (or all) of the venom to escape outside the bitesite.

   ❖ *Superficial bite:* Since humans do not constitute normal prey for most venomous snakes, they bite only to defend themselves before making a quick get-away. In such instances, the snake often deliberately does not bite deeply, but instead only strikes superficially, thereby conserving precious venom for its genuine prey.

2. *With Envenomation:*

a. Colubrid bite

   ❖ Clinical effects of colubrid snakebite are generally localised, and comprise pain, oedema, erythema, ecchymosis and numbness, which resolve over one to two weeks.

   ❖ Excessive salivation with metallic taste, and headache have also been reported.

b. Elapid bite

   ❖ Local Effects: In general, elapid bites are associated with minimal local manifestations (**Fig 12.17**). Pain and swelling are relatively less intense, and often there is only a serosanguinous ooze from the bitesite with mild pain, tenderness, and blistering. However, cobras

Fig 12.17: Cobra bite – Minimal local effects
(*Pic:* Dr HS Bawaskar)

can occasionally cause significant local swelling, blistering, and regional lymphadenopathy. The lesion may emit a putrid smell, and break down with loss of skin and subcutaneous tissue (**Fig 12.18**). Elapid bites sometimes cause early onset of gangrene (of the wet type), while viperid bites progress more slowly, and the gangrene is usually of dry type. Secondary infections, e.g. tetanus, gas gangrene, etc. are relatively less common.

❖ Systemic Effects: Neurotoxicity is the dominant clinical feature of elapid bites. Symptoms usually occur earlier (within 15 minutes to ½ hour) in cobra bite, while they are often delayed (up to several hours) in krait bite.

– Preparalytic Stage—

   - Vomiting
   - Ptosis (preceded by contraction of frontalis muscle) (**Fig 12.19**)
   - Blurred vision, external ophthalmoplegia
   - Paraesthesiae around the mouth
   - Hyperacusis
   - Headache, myalgia
   - Vertigo
   - Hypersalivation (due to autonomic stimulation).

– Paralytic Stage—

   - The facial muscles, palate, jaws, tongue, vocal cords, neck muscles, and muscles of deglutition

Fig 12.18: Cobra bite – Local necrosis
(*Pic:* Dr DRK Prasad)

Fig 12.19: Cobra bite – Ptosis (killed snake on the left)
(*Pic:* Dr HS Bawaskar)

all become progressively flaccidly paralysed. Many patients find it difficult to open their mouths and speak.

- Respiratory arrest may occur due to obstruction of upper airway by the paralysed tongue or inhaled vomitus, or due to paralysis of intercostal muscles and diaphragm. Paradoxical respiration, as a result of the intercostal muscles becoming paralysed is said to be a frequent sign.
- Although a patient appears unconscious, most are able to follow simple commands as noted by purposeful movement of the fingers or toes. Loss of consciousness and convulsions are terminal phenomena resulting from hypoxaemia.
- Roughly half of patients bitten by *Naja kaouthia* (monocellate cobra) do not sustain envenomation. Local pain and swelling develops within 2 to 3 hours and becomes maximal in 24 to 48 hours. Blisters and skin discolouration may develop, and may be followed by necrosis of subcutaneous tissue with sloughing. Neurotoxicity, if it develops, generally begins 1 to 5 hours after envenomation, but may be delayed as long as 19 hours. Cranial nerve palsy is followed in some patients by generalised weakness and respiratory failure.
- Renal complications are rare in elapid bites.
- Although rarely reported in literature, disorders of platelet aggregation and coagulation-fibrinolysis system may occur after envenomation by cobras. Disseminated intravascular coagulation (DIC) may occur after bites by these snakes.
- Coral snakes usually cause milder manifestations as compared to other elapids. Even substantial envenomation is associated with full recovery, following timely intervention.

c. Viperid bite
  ❖ Local Effects:
    – Pitless as well as pit vipers cause marked local manifestations which develop rapidly, usually

within ½ hour, but may occasionally be delayed for several hours.
- Swelling first appears around the bitesite, and then spreads quickly to involve the whole limb (**Fig 12.20**) and adjacent trunk. There is associated pain, tenderness, and regional lymphadenopathy. Bruising is commonly seen over the path of superficial lymphatics and over regional lymph nodes. Persistent bleeding from bitesite is a constant feature.
- Blisters begin to appear in about 12 hours in and around the bitesite, progressing subsequently to involve the entire limb. They may contain either clear or bloodstained fluid. In about 10 to 15% of the cases, extensive necrosis of skin, subcutaneous tissues, and muscles may occur.
- Raised intracompartmental pressure adds to the problem in regions with tight fascial compartments such as anterior tibial compartment. This is characterised by severe pain, tense swelling, subcutaneous anaesthesia, and increased pain on stretching intra-compartmental muscles.

❖ Systemic Effects:
  – Haemostatic abnormalities are very characteristic of viperid bites. The first evidence of this is persistent bleeding from the bitesite. Haematuria may be seen within a few hours of the bite (**Fig 12.21**). Later gingival bleeding occurs (**Fig 12.22**), followed by epistaxis, haemoptysis (relatively rare), haematemesis (**Fig 12.23**), ecchymoses, intracranial and sub-conjuctival haemorrhages, and bleeding into the floor of the mouth, tympanic membrane, gastrointestinal tract, and genito-urinary tract. Bleeding into anterior pituitary (causing a Sheehan-like syndrome) has been reported. Subarachnoid haemorrhage manifests as severe headache and meningism, while intracerebral haemorrhage may cause hemiplegia, loss of consciousness, and convulsions. Retroperitoneal and intraperitoneal haemorrhages cause abdominal distension, tenderness, and peritonism, with signs of haemorrhagic shock.

Fig 12.20: Viper bite—Extensive swelling of lower limb
(*Pic:* Dr DRK Prasad)

Fig 12.21: Viper bite – Haematuria
(*Pic:* Dr HS Bawaskar)

Fig 12.22: Viper bite – Gingival bleeding
(*Pic:* Dr HS Bawaskar)

Fig 12.23: Viper bite – Haematemesis
(*Pic:* Dr HS Bawaskar)

– Viperid envenomation is almost synonymous with incoagulable blood, which results from defibrination. Intravascular haemolysis causing haemoglobinuria and renal failure is a frequent occurrence, especially in bites by Russell's viper. Acute renal failure is often associated with the presence of DIC which results in severe renal tubular and cortical necrosis with widespread microvascular fibrin deposition (microthrombi). It is suggested, however, that a direct toxic effect produced by the venom of Russell's viper may produce renal damage. The hump-nosed pit viper can also cause renal failure, but the saw-scaled viper usually does not.

– Hypotension is an important manifestation in all viper bites and is usually accompanied by tachycardia, unless the venom has affected the heart directly or reflexly, in which case the pulse may be slow or irregular.

– A study on saw-scaled viper bites has indicated that haemorrhagic manifestations could more commonly be due to primary pathological fibrinolysis (PPF) than disseminated intravascular coagulation (DIC). The significance of this assertion is that administration of heparin which is the treatment of choice for DIC, may actually worsen the condition if it is due to PPF.

– Cardiotoxicity (which may be seen in elapid bite also) produces a wide variety of ECG changes, as listed in **Table 12.2**.

– It is important to note that ptosis and neurological symptoms may occur in the case of Russell's viper bite (**Fig 12.24**), and every clinician must be alert to this possibility. Generalised flaccid paralysis can develop after envenomation. Neurotoxic effects are caused by the presence of phospholipases A2 with presynaptic neurotoxic activity. Conversely however, kraits and cobras **do not** cause coagulation abnormalities.

d. Hydrophid bite
  ❖ Local Effects: Sea snakebites are well-known to produce minimal local effects. The bite itself is often painless and the victim may not even realise he has been bitten. However teeth are often left behind in

Table 12.2: Common ECG Changes in Snake Envenomation

Sinus bradycardia

Sinus tachycardia

Sinus arrhythmia

Tall T waves

³ ST depression %1mm with flat or inverted T in all chest leads

³ ST depression %1mm with T inversion in inferior leads, or in anterior leads.

ST elevation in leads V_1 to V_6, I, aVL; Q wave V_1 to V_4 and ST depression in II, III, aVF

First degree or second degree heart block

Fig 12.24: Ptosis in Russell's viper bite
(*Pic:* Dr HS Bawaskar)

the wound. Local swelling is negligible, and regional lymphadenitis usually does not occur. Fang marks may appear as one, two or more small circular dots, as though made by a pin or hypodermic needle. It is important to note that in some cases, there may be no clear fang marks, but a vague scratch mark, and yet serious poisoning may occur.

❖ Systemic Effects:
  – The dominant clinical feature is myalgia with stiff-ness and tenderness of muscles, which become apparent in ½ hour to 2 hours. This is due to rhabdo-myolysis, since hydrophid venom is predominantly myotoxic. Myoglobinaemia and myoglobinuria occur, resulting in acute tubular necrosis and renal failure. A "fixed" specific gravity of 1.010–1.013, together with a low urine volume output, myoglo-binuria, and progressively rising blood urea are indicative of impending acute renal failure in the setting of sea snake envenomation.
  – Trismus is an early feature. Passive stretching of muscles is painful. Later, flaccid paralysis develops, beginning with ptosis (as in elapid bite).
  – Hyperkalaemia may be present due to release of potassium from damaged muscles. This may be severe enough to cause cardiac arrest. Tall, peaked T waves and QRS prolongation suggest severe hyperkalaemia.
  – Other effects may include dizziness, nausea, vomiting, headache, and diaphoresis.
  – Neurotoxicity may include ptosis, ophthalmo-plegia, dysarthria, blurred or double vision, mydri-asis, inability to sit unassisted, depressed muscle stretch reflexes, and flaccid paralysis. In some cases, paralysis of respiratory muscles causes death due to respiratory failure. Consciousness is usually retained till the end. The fatality rate is estimated to be about 3%. Failing vision is considered to be a terminal sign.

■ Diagnosis of Snakebite

1. Fang Marks:
   a. Classically, there should be two puncture wounds (**Fig 12.25**) which are separated from each other by a distance varying from 8 mm to 4 cm, depending on the species involved. However, a sideswipe may produce only a single puncture, while multiple bites could result in numerous fang marks. It is also important to remember that many venomous species possess more than one set of fangs and thus multiple fang marks may be present even in the normal course.
   b. In addition, many non-venomous species such as the Common Wolf Snake have large front teeth which inflict bites that look similar to fang marks.
   c. Occasionally, fang marks may not be clearly evident (**Fig 12.26**).
2. Identification of Snake:
   a. This is fraught with difficulties as mentioned earlier, though it can be attempted in those cases where the victim or his attendants bring with them the culprit (dead) snake.
   b. Extreme caution is imperative in this context: there are instances on record of killed snakes inflicting reflex bites on being handled! Even a completely severed head is not always innocuous in this regard.
3. Laboratory Investigations:
   a. Haematological—

Fig 12.25: Classical fang marks
(*Pic:* Dr DRK Prasad)

Fig 12.26: Indistinct fang mark (little toe of right foot)
(*Pic:* Dr HS Bawaskar)

– Anaemia
– Leucocytosis
– Thrombocytopenia
– High haematocrit initially; later it falls
– Evidence of haemolysis: fragmented RBC (schistocytes or helmet cells)
– Prolonged clotting time and prothrombin time
– Prolonged partial thromboplastin time
– Depressed fibrinogen levels
– Elevated FDP (Fibrin degradation products).
b. ECG—
– Common ECG changes include bradycardia with ST segment elevation or depression, T wave inversion, QT prolongation, and changes due to hyperkalaemia.
c. Metabolic—
– Hyperkalaemia
– Hypoxaemia with respiratory acidosis
– Metabolic acidosis or lactic acidosis (increased anion gap).
d. Urine—
– Haematuria
– Proteinuria
– Haemoglobinuria
– Myoglobinuria.
e. Renal—
– In acute renal failure, all features of azotaemia will be present.
f. Chest X-ray—
– Pulmonary oedema
– Intrapulmonary haemorrhages
– Pleural effusion.
g. X-ray of bitten part—
– For bitten areas that remain tender, plain radiographs may reveal the presence of embedded snake tooth/fang fragments.
h. Immunodiagnosis—
– Immunological detection of venom antigens in body fluids can be accomplished by ELISA. This is highly sensitive, but specificity may be inadequate to distinguish between different species of snakes.
– For forensic investigation of death due to snakebite, methods are being validated for immunoanalytical methods of detection of the venom of some venomous snakes such as cobra and krait from autopsy samples. Enzyme immunoassay methodology (IgY-based sandwich ELISA and indirect competitive inhibition ELISA) has been optimised for the detection of cobra and krait venom. A new preservant (70% ethanol, 2% glycerol, 28% [0.02 M] PBS, pH 7.4, and 0.05% thimerosal) is being recommended for preservation of forensic samples.

■ Treatment of Snakebite

1. First-Aid Measures
a. Verbal reassurance: Since most snakebites are either non-venomous or non-lethal, it is imperative to allay the anxiety that is inevitably experienced by a bitten victim, which can prove fatal (neurogenic shock).
b. Immobilisation: Since exertion can enhance systemic absorption of venom, there is universal consensus that the patient should be put at rest, and the bitten extremity immobilised by using a splint or sling. Encourage the patient to move as little as possible. Movement of the bitten part could speed the spread of venom. Remove rings and jewelry from the bitten limb.
– If available, firm binding of the splint with a crepe bandage is an effective form of immobilisation (*Sutherland wrap; Pressure Immobilisation Method*). The compression bandage should not be applied to an incised wound or bruise.
– *Local Compression Pads (Monash method):* These have been found to be useful in victims of bites by Russell's Viper. A firm rubber pad is applied with cotton bandaging over the site of the bite and the limb is then immobilised with a splint. However, there may be an increased risk of local tissue necrosis, bruising and pain at the site, which should be evaluated over the potential risk of systemic envenomation.
c. Beverages: Use of "stimulating" beverages such as coffee is inadvisable and ineffective. In some cases, it can provoke vomiting, the tendency for which is usually present in the early hours following a bite. Alcohol must never be administered, since it increases the absorption of venom.
d. Tourniquet: It is well known that systemic absorption of venom occurs mainly through superficial lymphatics, and therefore application of a tourniquet proximal to the bitesite of a bitten limb in order to prevent the spread has often been advocated (**Fig 12.27**). But there are serious risks associated with tourniquets and other similar occlusive methods, which include ischaemia and gangrene, damage to peripheral nerves (especially lateral popliteal nerve), increased fibrinolytic activity, congestion, swelling, increased bleeding, and increased local effect of venom. It has also been claimed that subsequent release of a tourniquet which has been retained for some time, leads to a flooding of

Fig 12.27: Tight tourniquet compromising blood circulation
(*Pic:* Dr DRK Prasad)

accumulated venom from the bitesite into the systemic circulation with life-threatening consequences. Because of the dangers associated with it, today the **general consensus is against application of a tourniquet**.

e. Incision and suction: There is much controversy surrounding the issue of incision and suction as a first-aid measure for snakebite. While there have been staunch advocates especially in the past, the current view is generally against such a practice. Some investigators have claimed that effective incision and suctioning (by breast pump or syringe) for a 30 minute period can extract about 90% of venom, even when done as long as 2 hours after the bite. However, some others vehemently deny this, and say that such a procedure can remove only about 20% of injected venom at the most. This is compounded by the serious risks associated with it, including uncontrolled bleeding in patients with incoagulable blood (viper bite), damage to nerves, blood vessels and tendons, and introduction of infection (**Fig 12.28**). Today, most authorities strongly condemn incision and suction as useless and hazardous. But some practitioners still advocate the method in selected cases, especially if it is done within the first 5 to 10 minutes following the bite. If it is decided to be done, cruciate incisions must be avoided. Parallel incisions may be made through the fang marks, about 1 cm long and no deeper than 3 mm, in the long axis of the limb.

f. Cyrotherapy: Local cooling (application of ice) in the region of the bitesite was previously recommended for minimising the absorption of venom. Today this is universally condemned because of serious risk of necrosis leading to gangrene, which may even necessitate amputation.

g. Electric shock: It has been suggested that if snake antivenom is not available to treat a venomous bite, local electric treatment may be done which is claimed to be life saving. The electric shock (25 kv, 1 ma) is to be applied direct to the bite by means of an insulated probe for a couple of seconds, and repeated 4 to 5 times at 5 to 10 second intervals, taking care to ground the area as closely to the site of the bite as possible. However,

doubts have been expressed as to the actual efficacy of this method. Today, the universal view is that it is a useless and dangerous method.

h. Drugs:
  – For mild to moderate pain, paracetamol can be given. If pain is severe, several authorities recommend judicious use of narcotic analgesics such as pentazocine or pethidine, even though in some cases this can be hazardous, e.g. elapid bites, where there may be CNS depression. Aspirin and non-steroidal anti-inflammatory drugs must not be used, since they commonly cause gastric erosions, and could lead to persistent gastric bleeding in patients with incoagulable blood, as in the case of viper bites.
  – Use of corticosteroids, which were formerly administered routinely, is no longer advocated except in allergic reactions to antivenom. The same applies to antihistamines.
  – Since vomiting is a common early symptom of systemic envenoming, patients should be made to lie on their side with the head down to avoid aspiration. Persistent vomiting can be treated with intravenous chlorpromazine. Intramuscular and subcutaneous injections should be avoided, especially in patients with incoagulable blood, since they can lead to haematoma formation. Pressure dressings should be applied to venepuncture sites to prevent oozing.
  – While some authorities recommend prophylactic antibiotics to prevent infection, others denounce this as unnecessary.
  – Though *Clostridium tetani* has not been isolated, its ubiquitous nature prompts most authorities to emphasise the importance of tetanus prophylaxis in the form of tetanus toxoid. If the patient has not been previously immunised, tetanus antiserum or tetanus human globulin must be given.

Table 12.3 lists measures which are harmful, and must not be undertaken. Rural folk in India resort to irrational and even bizarre methods (e.g. using the so-called "snake stone"), which must be condemned in unequivocal terms by doctors.

Fig 12.28: Unnecessary multiple deep incisions – viper bite
(*Pic:* Dr DRK Prasad)

Table 12.3: How Not to Treat a Snakebite
The following measures are potentially harmful, and must not be undertaken:
• Application of a tight tourniquet which occludes arterial supply
• Cauterisation of bitesite
• Multiple, deep incisions through bitesite
• Suction by mouth, vacuum pump, or syringe
• Application of injurious substances such as potassium permanganate, phenol, etc.
• Application of electric shock
• Application of ice (cryotherapy)
• Use of herbal, folk, or Ayurvedic medicines or remedies

2. **Hospital Measures**

a. Observe every case of alleged snakebite for a minimum period of 24 hours. Late onset envenoming is common in snakebite involving some species such as the hump-nosed pit viper.

b. Check for/monitor the following:
   – Pulse rate, respiratory rate, blood pressure, and WBC count every hour. Platelet counts are very useful in viper bites. A decrease is indicative of a potential coagulation abnormality.
   – Blood urea, creatinine.
   – Urine output.
   – Urinalysis can provide useful evidence of haemoglobinuria or myoglobinuria. Urinary NAG (N-acetyl-beta-delta-glucosaminidase) has been found to be useful in the early diagnosis of renal damage after Russell's viper bite. Elevations in urinary NAG levels are both sensitive and specific for detecting early renal damage.
   – Vomiting, diarrhoea.
   – Abnormal bleeds.
   – PT (prothrombin time), APTT (activated partial thromboplastin time), D-Dimer, and FDP (fibrin degradation products).
   – Extent of local swelling and necrosis. Obtain wound culture in necrotic wounds with suspected infection.
   – Peripheral smear: Often indicates irregularities in the RBC before the appearance of an abnormal clotting test. Helmet cells (keratocytes) and schistocytes (**Fig 12.29**) indicate the onset of micro angiopathic haemolysis (MAHA).
   – ECG, arterial blood gas (ABG) analysis. Oxygen saturation can be tested non-invasively with the use of a finger oxymeter, which is particularly important in the case of viper bites, where arterial or venepuncture are contraindicated.
   – Monitor pulmonary function tests (negative inspiratory force, vital capacity and FEV_1) to assess respiratory function and need for intubation.
   – Monitor serum cortisol levels in patients envenomed by Russell's viper. Alterations in pituitary and/or adrenal function have been reported.
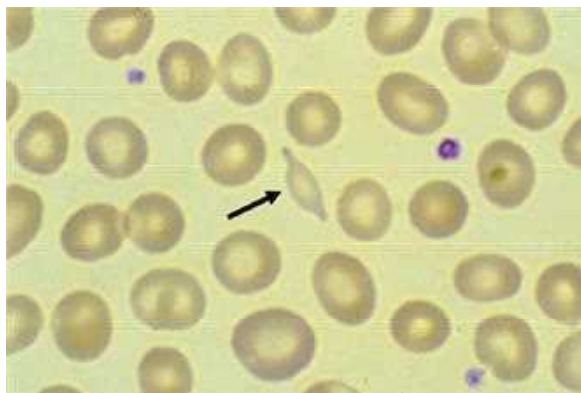
Fig 12.29: Schistocyte (*arrow*) – Peripheral smear

c. Antivenom (Antivenin) therapy:
   – Indications-
     - Never embark on antivenom therapy as a matter of routine. Apart from the risks and adverse effects involved (*vide infra*), such indiscriminate use is irrational because
       » Many cases of snakebite involve non-venomous snakes.
       » Envenomation is not the rule even in venomous bites.
       » Antivenoms available are usually effective against specific species of snakes, and are of no benefit against other species.
       » Antivenom is usually in short supply, and has limited shelf-life
     - Reid's criteria (modified by Persson) for antivenom therapy are as follows:
       » Prolonged or recurring hypotension
       » Persistent or recurring shock in spite of treatment
       » Pronounced leucocytosis
       » Protracted gastrointestinal symptoms
       » Acidosis
       » ECG changes
       » Raised serum creatine phosphokinase
       » Early extensive swelling in adults
       » Haemolysis
       » Pregnant women, small children.

The recommended indications have been summarised in **Table 12.4**. For Indian viper bites, the **20 WBCT** (20-minute whole blood clotting test) is recommended by some investigators, since it is a very reliable blood test to detect any coagulation abnormalities. It is also quick and simple, and can be carried out at the bedside with no specialist training. A few millilitres of freshly sampled venous blood are placed in a new, clean and dry glass bottle or tube. This is left undisturbed

Table 12.4: Indications for Antivenom Therapy

Systemic envenomation	Severe local envenomation
1. Haemostatic disturbances: Spontaneous systemic bleeding or caogulopathy	1. Local envenomation associated with neutrophil leukocytosis, elevated creatine phosphokinase and aminotransferases, haemoconcentration, uraemia, hypercreatinaemia, oliguria, hypoxaemia, acidosis, vomiting
2. CVS abnormalities: Shock, hypotension, abnormal ECG, arrhythmia, cardiac failure, pulmonary oedema	2. Local swelling involving more than half the bitten limb
3. Neurotoxicity	3. Extensive blistering or bruising
4. Generalised rhabdomyolysis	4. High-risk of necrosis
5. Impaired consciousness	

for 20 minutes, after which it is tipped, and if the blood is still flowing then the blood is incoagulable and ASV should be administered (**Fig 12.30**).

– Timing—Although antisnake venom must be administered as early as possible when signs of systemic or severe local envenomation develop, it is almost never too late to try antivenom therapy. Some investigators have reported beneficial effects even after a lapse of 1 week or more.

– Availability—
- In India, polyvalent antivenom is commonly available which is effective against the Big Four: common cobra, common krait, Russell's viper and saw-scaled viper. It can be procured from VINS Bioproducts, Hyderabad; Central Research Institute, Kasauli; Bharat Serums and Vaccines Ltd, Mumbai; Serum Institute of India, Pune; or Haffkine Biopharmaceutical Corporation, Mumbai. Sea snake antivenom is available from the Commonwealth Serum Laboratories (CSL), Melbourne, Australia (telephone: 619-389-1720; fax: 619-389-1887).
- The best form of antivenom is a lyophilised (freeze-dried) powder, which is produced by immunisation of horses with the venom of the snakes mentioned (*vide supra*). The powder must be reconstituted in distilled water or saline just before use. If the resulting solution is opaque (turbid) to any extent, it has lost its efficacy and should be discarded (**Fig 12.31**). The liquid form of antivenom has to be kept refrigerated, and is therefore subject to problems of power failure.
- The antivenom must always be administered intravenously. It should not be injected into the tissues in or around the bitesite. The only indication for intramuscular injection of antivenom is in the case of a remote field site involving a great many hours of transportation to a medical facility. If ASV is administered intramuscularly, a number of sites in the thigh should be used, and the area should be massaged to aid absorption. The problem with intramuscular administration is that antivenom has a large molecular

Fig 12.31: Turbid antivenom solution (left)
(*Pic:* Dr HS Bawaskar)

size and therefore bioavailability is very poor. Also, if a large amount of antivenom is required, finding a sufficiently large muscular site to inject the ASV will be problematic.

- Before beginning antivenom therapy, a skin test is conventionally advised for detecting hypersensitivity. But the current consensus is NOT to perform any test for hypersensitivity for the following reasons:
  » Most of the reactions to antivenom, i.e. anaphylactic and late serum reactions, are not IgE-mediated hypersensitivity reactions to horse or sheep protein. This has been confirmed by skin testing for IgE. In addition, radioallergosorbent tests have not found any evidence of IgE being present.
  » In fact, the very act of administering an ASV test dose may pre-sensitise the victim and therefore make an allergic reaction more likely.
  » There is also the logical argument which states that even if the patient shows some evidence of early sensitivity, antivenom is going to be required in any case, as it is the only known cure for envenomation. It therefore makes no sense to carry out the test when one then has to administer ASV as it is the only antidote available to the venom.

– Dose—
- There is no universal agreement on the exact dose of antivenom to be administered in snakebite. Unfortunately, despite widespread use, there are very few clinical trials to determine the ideal dose. Manufacturers base their

Fig 12.30: Incoaguable blood (*20-minute whole blood clotting test*)

recommendations on the mouse assay which may not correlate with clinical findings. The apparent serum half-lives of antivenoms in envenomed patients range from 26 to 95 hours, depending on their mode of preparation. The conventional practice is to base the initial dose on the severity of envenomation (**Table 12.5**).

- Pregnancy is not a contraindication. Children require the same dose of antivenom (or even more) as adults.
- Venepuncture sites must be dressed with pressure bandage.
- Repeat the initial dose of antivenom if severe CVS or CNS symptoms persist for more than ½ hour, or incoagulable blood persists for more than 6 hours after the first dose. It must be remembered that systemic envenoming can recur several days after an initial good response to antivenom. While some investigators claim that there is no fixed upper limit to the dose of antivenom to be administered, and enormous doses have been given in some cases, others insist that this is not advisable (*vide infra*).

– Storage of antivenom—Antivenom must be stored in a refrigerator. Lyophilised antivenoms stored at below 8ºC usually retain their activity up to 5 years or more. Reconstituted solutions remain stable up to 48 hours. Diluted solutions should be used within 12 hours of dilution.

– Reactions/Adverse Effects—
- Early (anaphylactic) reaction: Develops in 10 minutes to 1 hour of beginning the antivenom therapy. It begins with cough, urticaria, tachycardia, palpitations, nausea, vomiting, headache, and fever. The full-blown anaphylactic reaction is characterised by hypotension, bronchospasm, and angioedema. Treatment involves administration of adrenaline subcutaneously, 0.5 to 1 ml of 0.1% solution (1 in 1000) for adults; 0.01 mg/kg for children. This is followed by an antihistamine (e.g. chlorpheniramine maleate, 10 mg in adults; 0.3 mg/kg in children).
- Pyrogenic reaction: Develops in 1 to 2 hours of beginning the therapy. It is characterised by chills, goose fleshing, shivering, rise in temperature, sweating, vomiting, and diarrhoea. Treatment involves fanning, tepid sponging, hypothermia blankets, or antipyretic drugs such as paracetamol (5 mg/kg orally, as suppository, or via nasogastric tube).
- Late (serum sickness) reaction: Develops about 7 days after treatment. It usually responds to antihistamines and corticosteroids.

– Contraindications—There are no absolute contraindications to antivenom in life-threatening cases of snakebite. Caution may be exercised in atopic and previously sensitised individuals. The reappearance of signs of systemic envenomation after

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Table 12.5: Dose of Antivenom

1. Two methods of antivenom administration are recommended:

    IV injection: 2 ml/ minute

    IV infusion: 5–10ml of isotonic fluid/kg body weight

2. Haemotoxic/Neurotoxic Envenomation (< 3 hrs since bite):

    10 Vials ASV

3. Haemotoxic/Neurotoxic Envenomation (> 3 hrs since bite):

    7 Vials ASV

- No further antivenom is given over the next five hours
- Six hours after the first administration of antivenom a further clotting and blood analysis test is carried out in the case of haemotoxic envenomation to determine whether coagulability has been restored. If the blood test shows that coagulability has indeed been restored, no further antivenom is administered. In the event that coagulation has not been restored, a further dose of antivenom is administered over the next 30 to 60 minutes, and blood tests carried out again after six hours
- This six-hour period is crucial as it represents the time it takes the liver to restore clotting factors to normal levels
- Further clotting tests before six hours have elapsed will not give a useful reading and any further ASV may well be unnecessary as the liver may restore coagulation without it
- In the case of neurotoxic envenomation there is considerable confusion as to the regime to be adopted
- At the first sign of systemic neurotoxic symptoms such as ptosis or ophthalmoplegia, ASV should be administered to the patient, again over 30 to 60 minutes
- If the patient presents with respiratory failure at the hospital, ASV should be administered
- At this stage, assisted and mechanical ventilation are the primary means of treatment. In the case of post-synaptic envenomations, such as in the case of the cobra, there is some clinical evidence to suggest that antivenom can reverse neurotoxic symptoms in the early stages. If after 1–2 hours the symptoms have worsened, or have not reduced, a second dose of ASV should be administered
- If the patient undergoes respiratory failure or the symptoms have worsened to this extent, then ASV should be stopped after the second dose. At this stage assisted and mechanical ventilation are the primary means of treatment
- Once the respiratory muscles have been paralysed there is no good rationale for administering antivenom
- With regard to pre-synaptic neurotoxic envenomation such as in the case of the common krait, nerve terminals have been destroyed, and mechanical ventilation is required until these terminals can be rebuilt

the restoration of normal blood coagulation or the disappearance of neurotoxic symptoms is known as recurrence. It is a phenomenon that can appear in both viperine and cobra bites. Therefore, once coagulation has been restored, the victim should be kept under observation, blood monitoring should continue, and in the rare event that recurrence occurs, further antivenom must be administered. It is needless expense to the victim to routinely apply antivenom in the expectation that recurrence will arise.

– If antivenom is not available, the following conservative measures can be undertaken:
  - Haemostatic abnormalities: Give clotting factors and platelets (i.e. fresh frozen plasma and cryoprecipitate with platelet concentrates). Blood transfusion may be indicated.
  - Shock/Hypotension: give colloids/crystalloids as needed. Monitor central venous pressure and cardiac output. Dopamine and other pressor agents may be required. Blood transfusions may be indicated in the presence of systemic bleeding.
  - Myoglobinuria: correct hypovolaemia and acidosis.
  - Acute renal failure: supportive care or haemodialysis.

3. **Additional Measures**
   a. Clean bitesite with povidone-iodine, but do not apply dressings.
   b. Leave blisters alone. They will break spontaneously and heal. Alternatively they can be aspirated to dryness with a fine sterile needle. If there is local necrosis, excise the slough and apply saline dressings. It is preferable to cover denuded areas with split-skin grafts.
   c. Infection at the site of the bite can be prevented with erythromycin or penicillin. If the wound has been tampered with, an aminoglycoside such as gentamicin must be added. Secondary infections following improper "unclean" wound incisions (unclean knife or razor) may require broad spectrum antibiotic therapy (e.g. amoxicillin or cephalosporine along with gentamicin and metronidazole).
   d. Intracompartmental syndrome: This results from swelling of muscles within tight fascial compartments. It manifests as severe pain, weakness of compartmental muscles, resistance to passive stretching, hyperaesthesia of areas of skin supplied by local nerves, and tenseness of the compartment. An intracompartmental pressure, measured by either a Stryker intracompartmental pressure monitor (**Fig 12.32**) or a saline manometer, of more than 45 mmHg (60 cm of water) indicates risk of imminent necrosis. It is a strong indication for fasciotomy to relieve the pressure, but such a procedure must be embarked upon only after blood coagulability has been restored.
   e. Coagulability disorders caused by vipers are usually promptly reversed by antivenom administration.

Fig 12.32: Stryker intracompartmental pressure monitor

If coagulation abnormalities are not corrected by antivenom therapy it may be necessary to administer fresh whole blood, fresh frozen plasma, cryoprecipitates (containing fibrinogen, factor VII, fibronectin, and factors V and XIII), or platelet concentrates. Because of the risks involved, caution is advised when taking the decision to use blood products. Heparin and epsilon aminocaproic acid have not been found to be beneficial.

f. Hypotensive shock: This can be managed by antivenom therapy, foot end elevation, and vasopressors such as dopamine infusion (2.5–5 mcg/kg/min). It is necessary to constantly monitor central venous pressure or pulmonary arterial pressure (Swan-Ganz catheter).

g. Renal failure:
   – If urine output falls below 400 ml/24 hours, insert urethral and central venous catheters.
   – If urine flow fails to improve after rehydration, diuretics (e.g. frusemide upto 100 mg IV) and dopamine (2.5–5 mcg/kg/min) should be given, and the patient placed on strict fluid balance.
   – Acute renal failure is very common in the bites of Russell's viper and hump-nosed pit viper. It is essential that the vital signs are monitored carefully if renal failure is to be detected early. It is important to note that, whilst oliguria is a useful indication of renal failure, studies have shown that non-oliguric renal failure occurs in approximately 30% of cases.
   – Established renal failure will have to be managed by dialysis.
   – The onset of renal damage may begin within several hours of a bite with onset noted by the presence of proteinuria, and possible disruption of urine flow.
   – Administration of antivenom may not alter the course of severe renal damage, and therefore, the treatment of choice is dialysis which corrects the underlying pathology: acute reversible tubular necrosis.
   – Alkalinisation of urine is not recommended as it has not been shown to be effective in reducing nephrotoxicity, and may in fact cause complications such as alkalaemia, hypocalcaemia, and hypokalaemia.

h. Neurotoxicity:
  – All patients with neurotoxic symptoms should be administered the Tensilon (edrophonium) test, to judge whether anticholinesterase therapy can be beneficial. The following procedure can be adopted:
    - Give atropine (0.6 mg adults; 0.05 mg/kg children) IV to block muscarinic effects of edrophonium.
    - Administer edrophonium chloride (10 mg adults; 0.25 mg/kg children) IV—2mg at first, then 8 mg after 45 seconds. Estimate duration of lid retraction on upward gaze, maximum interdental distance on mouth opening, forced expiratory pressure, or vital capacity.
    - If there is convincing positive response, begin anticholinesterase therapy with neostigmine methylsulfate (50 to 100 mcg/kg) and atropine sulfate (15 mcg/kg) by subcutaneous injection every 4 hours, or by continuous IV infusion.
    - If the patient can swallow, give neostigmine orally (15 mg four times daily), or alternatively pyridostigmine (60 mg four times daily) with atropine (0.6 mg twice a day) or propantheline hydrochloride (15 mg twice daily).
    - In India, since edrophonium is not widely available, neostigmine methylsulphate is normally used. Therefore this test should be referred to as the "Anticholinesterase Test":
      » Instead of the fast acting edrophonium, the test period should be over 1 hour, and the patient observed for this period.
      » Useful measures are extent of iris (in mm) uncovered, length of time upward gaze can be maintained, inter-incisor width, and FEV.
      » The dosage recommended are 1.5 mg of neostigmine (IM), and 0.6 mg of atropine (IV). If the patient shows a positive response, a maintenance dose of 0.5 mg IM should be given with 0.6 mg atropine 8th hourly.
      » Neostigmine is highly effective in the case of post-synaptic bites such as in the case of the Cobra family. There are also some indications that neostigmine may produce good results in the case of pre-synaptic bites such as that of krait and the neurotoxic effects of the Russell's viper venom, which is also believed to be krait-like.

i. Respiratory failure: Keep airway clear. Head low. Semiprone. Jaw elevation. Oral airway, or tracheostomy, or cuffed endotracheal intubation. Mechanical ventilation. There are several cases on record of patients bitten by highly neurotoxic snakes, who have recovered completely without antivenom therapy after being mechanically ventilated for a number of days or weeks. Neurotoxic effects are completely reversible with time.

j. Rhabdomyolysis and myonecrosis: This is especially likely in the case of sea snakebites. Myoglobinuric nephropathy can be prevented by infusing mannitol 25 grams, and sodium bicarbonate 100 mEq in 1 litre 5% dextrose, over a period of 4 hours.* Urine output and CVP must be monitored.

k. A chronic phase that can occur months to years after a bite by a Russell's viper can produce weakness, loss of secondary sexual hair, amenorrhoea, testicular atrophy, and hypothyroidism. These result from hypopituitarism. Hypoglycaemia may also be present.

■ Prevention of Snakebite

1. Do wear shoes (or preferably leather boots and long trousers) when walking outdoors amid thick undergrowth or long grass.
2. Do carry an electric torch or flashlight when walking outdoors at night.
3. Do take care when collecting firewood, or moving logs, rocks, boxes, or debris which are likely hiding places for a snake.
4. Do take care when climbing rocks or trees with dense foliage, or swimming in lakes or rivers with lots of weeds.
5. Do use repellants in basements, attics and storerooms to ward off rodents and snakes (e.g. DDT, naphthalene, pyrethroids, formaldehyde fumigants, etc.).
6. Do not go near a snake even if it appears inactive or harmless. Slip away quietly. Do not make sudden movements.
7. Do not handle a snake even if it appears dead. Some snakes pretend to be dead to avoid attack.
8. Do not keep venomous snakes as pets or performing animals.
9. Do not sleep on the ground at night. You may wake up with a venomous snake lying cosily next to you, attracted by your body warmth.
10. Do not wade in the sea, especially in sand, or near coral reefs.

■ Forensic Issues in Snakebite

■ Snakes have been venerated and worshipped in India (especially by the aboriginal and Dravidian races) since ages. The mysterious power of inflicting death possessed by venomous snakes, their slithering movement, and periodic shedding of skin, inspired awe and dread among people of ancient civilisations, and led to their worship in idol form. Among all the snakes, the cobra has been the object of most attention in India. Even today it is worshipped by many Hindus. On Nag Panchami day (as per the Hindu calendar), milk is offered to cobras as a form of propitiation.** Hindus generally do not kill cobras on account of such veneration. Also, there is a popular belief that he who kills a cobra will be cursed for generations.

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* Watch out for hyponatraemia, hyperkalaemia, fluid overload, and hypocalcaemia.
** It is an ironical myth that snakes are fond of milk. In fact, the tongue of a snake is not adapted for lapping up fluids.

- Almost all cases of snakebite reported from around the world are accidental in origin, and the vast majority are due to inadvertent or deliberate provocation of a snake by a human. Snakes rarely if ever, attack human beings on their own. Several occupations are associated with increased risk of snakebite: grass-cutting, working in rubber, coconut, areca nut, and tea and coffee plantations.
- Perhaps, the only recorded case of suicide accomplished with the help of a venomous snake is that of Queen Cleopatra of Egypt (69–30 BC), who is said to have deliberately induced a snake (an asp) to bite her.
- While homicides can be accomplished by using a venomous snake as a tool, actual instances of murder committed by such an exotic method are rare.
- Deaths due to snakebite are regarded as medicolegal in nature, and a forensic autopsy is mandatory. Unfortunately, clear-cut signs of envenomation may be lacking in such cases, and even fang marks may not always be discernible.
- Today, immunodiagnosis with the help of ELISA makes it possible to conclusively diagnose death due to snakebite by analysing tissues around bitesite, or blister fluid, or even body fluids such as blood and urine for venom antigens.

Fig 12.33: Honey bee (*Apis mellifera*)

Fig 12.34: Paper wasp (*Polistes annularis*)

VENOMOUS INSECTS

There are 3 orders of toxicological importance in class insecta: hymenoptera, lepidoptera and coleoptera.

ORDER HYMENOPTERA

This order comprises mainly two-winged flies and ants. The common stinging hymenopterids include bees, wasps, yellow jackets, hornets, and fire ants. The term "hymenoptera" refers to membranous wings that characterise these insects.

■ Epidemiology

While snakebites are more common in tropical countries such as India, anaphylactic reaction to hymenoptera stings are much more common in temperate countries. This is despite the gross under-reporting of such stings. Hymenoptera stings are invariably caused by the honeybee* (*Apis mellifera*) (**Fig 12.33**), paper wasp (*Polistes annularis; Ropalidia gregaria*) (**Fig 12.34**), European wasp (*Vespula germanica*), hornets (*Vespa & Dolichovespula species*) (**Fig 12.35**), and yellow jackets (*Vespula pensylvanica*) (**Fig 12.36**). A few incidents result from stings of fire ants (*Solenopsis invicta*) (**Fig 12.37**), and rarely, jumper ants (*Myrmecia pilosula*).

The body of a bee is generally bright yellow with black triangular markings on the abdomen. It is usually 10 to 15 mm long, and folds its wings back at rest. Queen wasps have similar markings; however, they are larger and can grow up to 20 mm. Bees are attracted to sweet food and meat and can sting multiple times. They are found in large nests, located where shelter is available (e.g. under caves, hollows of trees, and wall cavities).

Fig 12.35: Hornet (*Vespa crabro*)

■ Venom

Venom is usually injected through a sting which may be barbed (e.g. bee), or smooth (e.g. wasp). Bees inject approximately 50 mcg of venom which is the total capacity of the venom sac, and leave behind the stings embedded in the skin, while wasps and hornets are capable of repeated stings. Ants generally bite firmly with their jaws and then sting or spray locally irritating venom. Fire ants have well developed abdominal stingers and inflict multiple stings.

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* Different from the bumble bee (*Bombus terrestis*) which is large, slow moving, and stings rarely.

Fig 12.36: Yellow jacket (*Vespula pensylvanica*)

Fig 12.37: Fire ants (*Solenopsis invicta*)

Hymenoptera venom is a mixture of biogenic amines (histamine, 5-hydroxytryptamine and acetylcholine), enzymes (phospholipase A and hyaluronidase), and toxic peptides (kinins in wasps; apamin, melittin, and mast cell degranulating peptides in bees).

A complete list of the components of hymenoptera venom is mentioned in **Table 12.6**.

■ Clinical Features

A. Local Reaction

1. In individuals not allergic to the venom, a single sting usually produces only mild effects such as local pain, redness, irritation, itching, and swelling, which resolve in a few hours. These reactions are not IgE-mediated, but represent a response to toxic and inflammatory venom components such as vasoactive amines and peptides.
2. Local reaction becomes dangerous only if the site of the sting is in a vital location, e.g. mouth or tongue (oedema leading to airway obstruction), or near the eye (cataract formation, glaucoma, etc.). External eye stings can cause pain, swelling, lacrimation, hyperaemia, and conjunctival chemosis. Corneal stings can cause corneal oedema, ulceration, hyperaemia, pain, scarring, and linear keratitis.
3. Severe cutaneous infection and cellulitis have occurred after stings from yellow jackets and wasps, which may pick up virulent bacteria while foraging on decaying animal and vegetable matter.

B. Allergic Reactions

1. Anaphylaxis
   a. About 4% of the human population is hypersensitive to hymenoptera venom. Yellow jackets and other wasps are the most serious offenders and cause twice as many allergic reactions as honeybees. In sensitive individuals, successive stings cause increasingly severe symptoms. Sensitisation to wasp venom is said to occur much more rapidly than to bee venom. It is pertinent to note that there is no association between bee or wasp sting allergy with atopy.
   b. Anaphylaxis is IgE-mediated, wherein the IgE antibodies attach to tissue mast cells and basophils in a previously sensitised individual. These cells are then

Table 12.6: Composition of Hymenoptera Venom

Vespids (*Wasps, hornets, yellow jackets*)	Apids (*Honey bees*)	Formicids (*Fire ants*)
Biogenic amines	Biogenic amines	Biogenic amines
Phospholipase A & B	Phospholipase A	Phospholipase
Hyaluronidase	Hyaluronidase	Hyaluronidase
Antigen 5	Acid phosphatase	Piperidines
Acid phosphatase	Minimine	
Kinin	Mellitin	
	Apamin	
	Mast cell degranulating peptide	

activated, resulting in the progression of the cascade reaction of increased vasoactive substances such as leukotrienes, eosinophil chemotactic factor-A (ECF-A), and histamine.

c. Clinical features develop within a few minutes of the sting, comprising tingling sensation of scalp, flushing, dizziness, visual disturbances, syncope, abdominal cramps, vomiting, diarrhoea, dry cough, wheezing, and tachycardia. In severe cases, the patient develops urticaria, angioedema, glottic oedema, profound hypotension, and coma. Hypertension has occurred in children with multiple bee stings, and in adults with multiple wasp stings. Apnoea, respiratory insufficiency and/or cardiopulmonary arrest have been reported in patients who became comatose after receiving multiple stings. Death may occur within minutes. Cardiorespiratory arrest has been reported after multiple stings from honey bees.

d. Individuals who have had an anaphylactic reaction to a Hymenoptera sting have a 35 to 60% chance of developing anaphylaxis from subsequent stings by an identical insect. Atopy does not necessarily increase the incidence of anaphylactic reactions to Hymenoptera stings, although asthmatic patients have more severe reactions to stings than nonatopic patients.

2. Delayed Reaction
   a. A few patients develop urticaria, skin rash, pedal oedema, and arthritis between 1 to 5 days after the sting.
   b. Sometimes, a serum sickness–like syndrome occurs a week or more after the sting. This is characterised by malaise, fever, headache, urticaria, lymphadenopathy, and polyarthritis. Renal failure may occur rarely.

C. Toxic Reactions

1. Multiple stings (especially involving a swarm of bees, wasps, or hornets) can cause massive envenoming characterised by vasodilation, hypotension, oedema, fatigue, vomiting, diarrhoea, headache, seizures, and coma. There have been reports of acute renal failure.
2. Delayed toxic reactions can occur, characterised by normal initial laboratory results, and subsequent evidence of haemolysis, coagulopathy, thrombocytopenia, rhabdomyolysis, liver dysfunction, and disseminated intravascular coagulation.
3. Fire ants can cause severe local reaction (**Fig 12.38**) and even fatal allergic reaction (especially in young children).

■ High-Risk Factors

Three or more of the following risk factors are more likely to have a major outcome or death:
1. Age 60 years or more
2. Prolonged attack time
3. High estimated number of stings
4. Medical history including cardiovascular problems
5. Early effects other than pain, such as vomiting, diarrhoea and hypotension/hypertension.

Fig 12.38: Local reaction—fire ant bites
(*Pic: Dr HS Bawaskar*)

■ Laboratory Diagnosis

1. Diagnostic procedures for sting allergy usually involve intradermal tests with various dilutions of Hymenoptera venoms. Most individuals with history of hypersensitivity to Hymenoptera stings have positive venom skin tests.
2. Intradermal skin tests are performed with venoms diluted to concentrations in the range of 0.001 mcg to 1 mcg/ml. A positive test is manifested by a specific wheal and flare reaction.
3. The radioallergoabsorbent test (RAST) is an "in vitro" method that measures the quantity of venom-specific antibodies in the patient's serum, and is used as an adjunct to the venom skin test. It is important to note that patients should not be skin tested until 2 to 4 weeks after a Hymenoptera sting.
4. Hymenoptera-sensitive patients should be referred to an allergist-immunologist trained in venom immunotherapy (VIT). This consists of periodic subcutaneous injections of the appropriate venom, starting with a low dose of about 0.01 mcg, and followed by progressively increased doses until a monthly maintenance dose of 100 mcg (300 mcg for mixed vespid venoms) is achieved.

■ Treatment

Any patient sustaining multiple stings should be observed for at least 6 hours with laboratory evaluation for haemolysis, thrombocytopenia, liver and renal function abnormalities, increased CK, and rhabdomyolysis. Patients with laboratory abnormalities, or signs and symptoms other than local pain should be admitted.

A. Local Reaction

1. Remove embedded stinger (common in the case of bees) by scraping with a blade or fingernail. Do not grasp the stinger with forceps which will cause further injection of venom due to squeezing.
2. Local infiltration with adrenaline 1:1000 (0.1–0.3 ml) near the sting site may help impede systemic absorption of venom.
3. Local cold compress: Local application of an ice pack at the sting site for 15 minutes every 30 minutes may decrease

intensity of swelling, reduce pain, and help retard absorption of venom.

4. Domestic meat tenderiser (papain) diluted 1 in 5 with tap water, is reputed to produce immediate relief of pain.

5. Several other local applications have been recommended, including topical application of 20% aluminum sulfate, soluble aspirin, and ammonia and Epsom salt soaks. None of these treatments has been evaluated by formal clinical trials.

6. Antihistamines: diphenhydramine (50 mg every 6 hours), chlorpheniramine (4 mg every 6 hours), or hydroxyzine (10 to 25 mg every 8 or 12 hours).

7. Local antiseptic cream.

8. Antibiotic may be administered only if there is evidence of infection.

B. Allergic Reactions

1. Anaphylaxis:
   a. 0.1% adrenaline (0.5 to 1 ml adult; 0.01 ml/kg child) by subcutaneous or intramuscular injection. It may be repeated in 20 minutes. Inhalation of adrenaline by a pressurised inhaler is effective in relieving bronchospasm, but not other effects of anaphylaxis. In life threatening anaphylaxis, intravenous adrenaline can be given with extreme caution (1 ml of 1:10,000 solution diluted in 10 ml of normal saline, given over 5–10 minutes). It can also be given as an infusion (1 mg in 250 ml of 5 % dextrose, infused at a rate of 1 to 4 mcg/min). The dangers of intravenous adrenaline include ventricular arrhythmias, myocardial infarction, and death.
   b. Antihistamine injection (e.g. chlorpheniramine maleate 10 mg IV or IM, or diphenhydramine 50 mg parenterally, then 25 to 50 mg orally every 4 to 6 hours for 24 to 72 hours) is useful in relieving urticarial symptoms. It can be continued for 24 to 48 hours.
   c. Airway management with adequate ventilation and oxygenation: Oxygen—5 to 10 L/min via high flow mask.
   d. Bronchodilators such as salbutamol to relieve dyspnoea and wheezing.
   e. Corticosteroids:
      – Methylprednisolone—1 to 2 mg/kg IV every 6 to 8 hours.
      – Prednisone—*Adults*: 40 to 60 mg/day. *Children*: 1 to 2 mg/kg/day (divided twice daily).
      – Large doses of hydrocortisone may be required to help the resolution of massive oedema.
   f. Correction of hypotension and shock: Dopamine and IV fluids.
   g. Continuous cardiac monitoring.
   h. Since rebound anaphylaxis can occur in some patients (up to 10 hours after a sting), observe every patient for 10 to 12 hours before discharging.

2. Delayed reaction:
   a. Antihistamines
   b. Analgesics
   c. Haemodialysis for renal failure.

C. Toxic Reactions

1. Parenteral antihistamines
2. Large doses of corticosteroids
3. Bronchodilators
4. Haemodialysis for renal failure.

■ Preventive Measures Against Hymenoptera Stings

1. Individuals who have recovered from anaphylaxis following an insect sting must be trained to self-administer adrenaline. They should carry a pre-loaded syringe of adrenaline when moving about in hymenoptera-infested areas.

2. Patients known to be hypersensitive should wear an identifying tag as they may be discovered unconscious after a sting.

3. Hymenoptera nests in areas around the living or working quarters of a sensitised patient should be destroyed.

4. When moving outdoors, tight, light-coloured, long-sleeved clothing should be worn.

5. Clothing with bright floral patterns should be avoided when moving about in gardens, or while working with plants.

6. Attractive scents, perfumes, soaps, and shampoos must not be used when moving in high-risk areas.

7. Materials or plants that attract hymenoptera (e.g. cloves, dandelions, open sweet drinks, etc) must be reduced.

8. Drinking juices or honey directly out of cans and bottles is a common cause of stings in the mouth and pharynx, and therefore should be avoided.

9. If individuals with venom sensitivity are taking beta-blockers or non-steroidal analgesic drugs, these should be withdrawn whenever possible, as both potentiate anaphylaxis.

10. Angiotensin-converting enzyme inhibitors and calcium channel antagonists may aggravate cardiovascular response to anaphylaxis, and should be substituted with other drugs if possible.

11. Adults with a history of significant allergic reactions to hymenoptera stings may benefit from desensitisation (immunotherapy).

VENOMOUS ARACHNIDS

Arachnids differ from insects mainly in the number of legs they possess: eight instead of six. There are two important orders from the toxicological point of view: Scorpionida and Aranea, both belonging to subphylum Chelicerata.

ORDER SCORPIONIDA

The members of this order comprise scorpions, which are capable of inflicting severe, and sometimes fatal stings. There are at least 650 different types of scorpions divided into 6 families. Most species are nocturnal, and seek areas that are cool and moist.

■ Anatomy

- The scorpion has a cephalothorax (fused head and chest), an abdomen, and a six segmented tail which terminates in a bulbous enlargement called telson. The telson contains the stinger and venom apparatus. In addition, the scorpion also has two claws (chelae or pedipalps) which help to grasp its prey. Scorpions differ in colour from straw yellow or light brown, to black.
- The commonest species seen in India is *Mesobuthus tamulus* (red scorpion) (**Fig 12.39**). It grows up to 3 inches in length. Larger scorpions are found in the outdoors (*Palamnaeus species*) which grow up to 7 inches (**Fig 12.40**).
- As a general rule, scorpions with thick and powerful claws are less toxic, while those with slender claws are more toxic.
- Scorpions sting; they do not bite.

■ Venom

Components of scorpion venom are complex and species-specific, those of the family Buthidae being the most potent. The main toxins include phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. The venom of *Buthus species* of India contains phospholipase A, which causes gastrointestinal and pulmonary haemorrhages, and disseminated intravascular coagulation.

Fig 12.39: Red scorpion (*Mesobuthus tamulus*)
(*Pic: Dr HS Bawaskar*)

Fig 12.40: Black scorpion (*Palamnaeus gravimanus*)
(*Pic: Dr HS Bawaskar*)

■ Mode of Action

1. Most scorpion venoms affect sodium channels with prolongation of action potentials, as well as spontaneous depolarisation of nerves of both adrenergic and parasympathetic nervous systems. Thus, both adrenergic and cholinergic symptoms occur.
2. Hyperkalaemia, hyperglycaemia (with reduction in insulin secretion), and increased secretion of renin and aldosterone are characteristic of stings by *Mesobuthus tamulus*.

■ Clinical Features

A. Local

1. Rapidly developing, excruciating local pain, swelling, redness, and regional lymphadenopathy.

B. Systemic

1. Signs of autonomic stimulation occur, comprising mydriasis, profuse sweating (**Fig 12.41**), urticaria, excessive salivation (**Fig 12.42**), vomiting, parasternal lift, priapism (**Fig 12.43**), hypertension, brady-/tachyarrhythmias, and ventricular premature contractions.
2. Pulmonary oedema may develop within 2 to 3 hours leading to death.

Fig 12.41: Scorpion sting—sweating, mydriasis
(*Pic: Dr HS Bawaskar*)

Fig 12.42: Salivation due to scorpion sting
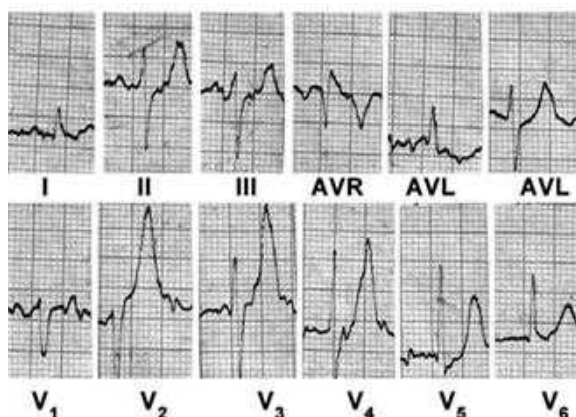(*Pic: Dr HS Bawaskar*)

Fig 12.43: Priapism due to scorpion sting
(*Pic: Dr HS Bawaskar*)

3. Intracerebral haemorrhage resulting in hemiparesis, from a scorpion sting, has been reported. Convulsions may occur.
4. ECG changes: Early changes suggestive of envenomation include peaked T waves in leads V_2 to V_6 (**Fig 12.44**), Q waves, ST-segment elevation in leads I and AVL, and left anterior hemiblock.
5. Hyperglycaemia is common with most species. Acute pancreatitis has been reported with some species.
6. Allergic reactions, including anaphylaxis has occurred.
7. Palamnaeus species causes local pain, paraesthesias, mild autonomic nervous system excitation, pulmonary infiltration, eosinophilia, salivation, nausea, sweating, and mild hypotension.
8. Children under the age of 10 are more likely to develop toxicity from most scorpion stings than older victims. Effects are most severe in infants and toddlers.

■ Treatment

Most victims (without hypertension or cardiac disease) and children over the age of 5 can usually be handled at home with local application of ice and other supportive measures for pain relief. Patients with cardiac problems/hypertension, elderly victims, and children under the age of 5 should be referred to a hospital for evaluation.

Fig 12.44: Scorpion sting—ECG showing peaked T waves
(*Pic: Dr HS Bawaskar*)

1. During transport to hospital
   a. Immobilise the affected extremity. Do NOT apply tourniquet (**Fig 12.45**).
   b. Local application of ice is beneficial in relieving pain. Prolonged cryotherapy is however contraindicated.
   c. A negative-pressure suction device may be used, if available, to extract venom at approximately 1 atm of negative pressure (it is doubtful whether this really works). Do <u>not</u> incise prior to suction.
2. On arrival at hospital
   a. Admit all patients with systemic manifestations (hypertension, hypovolaemia, pulmonary oedema) to intensive care unit under close electrocardiographic, echocardiographic, and if necessary, invasive haemodynamic monitoring.
   b. Patients with respiratory failure or with CNS disturbances should be mechanically ventilated; administer oxygen to all serious cases.
   c. Pain may be controlled by paracetamol or morphine tablets.
   d. Mild to moderate allergic reactions may be treated with antihistamines, with or without inhaled beta agonists, corticosteroids, or adrenaline. Treatment of severe anaphylaxis must include oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring, and IV fluids.
   e. Correct fluid and acid-base imbalance. However, avoid infusing large amounts of fluids due to the risk of pulmonary oedema. The pulmonary artery wedge pressure should be kept relatively low while maintaining adequate cardiac output, blood pressure, and urine output.
   f. Some investigators claim prazocin hydrochloride acts as an antagonist to scorpion venom, and is also cardioprotective. The recommended dose is 500 micrograms every 4 to 6 hours for adults, and 250 micrograms every 4 to 6 hours for children.
   g. Hypertension (>160/110 mmHg) is conventionally managed with nifedipine at a dose of 10 to 20 mg (adults) or 0.3 mg/kg (children) every 4 to 6 hours.
   h. Bawaskar & Bawaskar, renowned experts in the

Fig 12.45: Unnecessary tourniquet in scorpion sting
(*Pic: Dr HS Bawaskar*)

treatment of scorpion stings, recommend that hypertension (due to *Mesobuthus tamulus* envenomation) be controlled by sublingual nifedipine, with peripheral venom action antagonised by the post-synaptic alpha-blocker prazosin. Nifedipine reduces hypertension, and enhances myocardial contractility caused by increased catecholamine levels. Prazosin reduces preload and left ventricular impedence without heart rate or serum renin increases. It also inhibits the suppression of insulin caused by envenomation. Prazosin is also said to be useful in the treatment of pulmonary oedema from scorpion envenomation.

i. Hypotension is treated with dopamine infusion, beginning at a dose of 2 to 5 mcg/kg/min and increasing gradually to 20 mcg/kg/min, so as to achieve and maintain systolic reading of around 90 mmHg.

j. Pulmonary oedema is treated with prazocin or furosemide (1 to 2 mg/kg IV every 4 to 6 hours) and oxygen. Life-threatening pulmonary oedema may respond to a nitroprusside drip.

k. Agitation and convulsions can be controlled with IV diazepam (5 to 10 mg, adults; 0.2 to 0.3 mg/kg, children; repeated every 10 minutes as required). Alternatively, phenobarbitone can be given, 5 to 10 mg/kg IV.

l. Persistent vomiting usually responds to metoclopramide 5 to 10 mg IV (adults), or 0.5 mg/kg (children).

m. Cardiac rhythm disturbances are usually transient and resolve without specific treatment in most of the cases. Persistent tachyarrhythmias can be reversed with propranolol (1 mg/dose IV, administered no faster than 1 mg/min, repeated every 5 minutes until desired response is seen, or a maximum of 5 mg has been given).

n. Antivenom therapy—
   i. A goat serum-derived antivenom has been available in some countries since several years, but there is controversy as to its efficacy. Most patients develop serum sickness syndrome within 2 weeks of antivenom administration.
   ii. Scorpion antivenom effective against *Mesobuthus tamulus* has recently been introduced in India.* The recommended dose is 1 vial (reconstituted in 10 ml of injection water) initially, followed by further doses if required.

■ Prevention of Scorpion Sting

1. Clear debris and rubbish from all areas of work or rest.
2. Repellents may be used in areas of scorpion infestation:
   a. Spraying a mixture of 2% chlorine, 10% DDT and 0.2% pyrethroid in an oil base is quite effective.
   b. Alternatively, use a mixture of fuel oil, kerosene, and small amounts of creosote.
3. Inspect shoes, clothing, and bedding for scorpions.

4. Do not reach into dark corners, receptacles, or boxes. Use a flashlight first to check for scorpions.
5. As a rule, if one scorpion has been encountered in a particular area, there will be others around. Females generally give birth to 50 to 60 young, which remain close to where they were born. It is important to locate and kill them all.

ORDER ARANEA

All spiders, with the exception of two small groups, are venomous. There are over 100,000 species of spiders. However, only about 20 species cause serious envenoming in humans, while about 150 to 180 can cause significant toxicity.

The common Indian species that cause serious envenomation include Brown Recluse, Black Widow, Wolf Spider, and Tarantula. Other spiders such as Orb Weaver, Running Spider, Hackled-band Spider, Giant Crab Spider, Lynx Spider, Jumping Spider, and Tangleweb Weaver, which are also encountered in India, do not cause significant envenomation. Funnel Web Spider which can cause significant envenomation is found only in the Australian continent.

■ General Anatomy

■ Anatomically, a spider has a cephalothorax and an abdomen with 4 pairs of legs fanning out from the thorax. Two claw-like fangs called celicera protrude from the head and are connected to venom glands which are under voluntary control.

■ Although the venom is quite potent in many species, serious envenomation is rare because of inadequate injection mechanism, and small quantity injected with each bite.

■ During its normal life span of 1 to 2 years, a spider moults several times, as a result of which there may be periodic changes in colour and markings.

■ Spiders are extremely shortsighted, and depend mainly on sense of touch and vibration. The eyes are on the front part of the cephalothorax. Most spiders have 8 eyes. Their size and position varies by spider type.

■ Some large spiders (e.g. huntsman spider, wolf spider, orb weaving spider), possess large spines on their legs. The spines are raised from a prostrate to a vertical position when the spider is irritated. If the spider is grabbed, picked up, or brushed off, injuries (severe pain, erythema, pruritus) from the spines may occur. These injuries often occur in conjunction with a bite by the same spider, and splinters are usually found at bite sites.

■ Brown Recluse

Other Common Names

Fiddleback, Violin, or Brown Spider.

Species

Loxosceles reclusa, L. laeta, L. deserta, L. unicolor, L. arizonica, L. rufescens.

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* Scorpion venom antiserum (Haffkine Biopharmaceutical Corpn. Ltd., Mumbai).

Physical Appearance

- It is a small (6 to 20 mm long), orange or reddish brown or grey spider, with a brown violin shaped mark on its back (**Fig 12.46**). It infests dark areas such as basements, under rocks, and amid woodpiles. The female is more aggressive than the male and bites when provoked.
- Loxosceles spiders can be differentiated from most other "garden" brown spiders, of which there are many, by its set of six eyes (three pairs), rather than eight. Their webs are distinguished by a bluish hue.

Venom

- The venom is cytotoxic and consists of several toxic components including hyaluronidase, ribonuclease, deoxyribonuclease, alkaline phosphatase, lipase, and sphingomyelinase D. The last mentioned is the main constituent which is responsible for tissue destruction. It reacts with sphingomyelin in the RBC membrane causing the release of choline and N-acylsphingosine phosphate. This causes severe intravascular occlusion of micro-circulation leading to necrosis.
- Venom toxins may act as proteases upon molecular constituents of plasma extracellular matrix (fibronectin and fibrinogen), and basement membrane constituents (entactin and heparin sulfate proteoglycan). All of these degrading activities may be responsible for producing haemorrhage, delayed wound healing, and renal failure, as well as the spreading of other noxious toxins (e.g. dermonecrotic protein). By disrupting the subendothelial basement membrane, blood vessel wall instability and increased permeability can occur.

Clinical Features

1. Local
   a. The bite itself is usually painless, but later begins to bleed and ulcerate in 2 to 8 hours. The initial reaction often consists of erythema and pain or pruritus. A small

Fig 12.46: Brown recluse

vesicle may form at the bite area, and the lesion may take on a "bullseye" or "halo" appearance, having a central vesicle surrounded by an erythematous and ecchymotic area.
   b. Ulcerated lesions if untreated, usually enlarge until about a week when eschar formation takes place. Granulation and healing takes up to 2 months to be completed.
   c. In severe cases, cutaneous necrosis may occur and may extend to involve subcutaneous fat and muscle.
2. Systemic
   a. Systemic features (*"loxoscelism"*) include fever, chills, nausea, skin rash, myalgia, arthralgia, headache, vomiting, haemolysis, DIC, shock, renal failure, jaundice, convulsions and coma.
   b. Acute tubular necrosis with resulting oliguria or anuria may develop in patients with severe haemolysis.
   c. Fever is common in patients with systemic effects and may develop more often in children. Fever may be associated with chills and night sweats.

Diagnosis

1. Leucocytosis (20,000 to 30,000 per cubic mm).
2. Evidence of haemolysis and DIC: Decreased levels of fibrinogen, clotting factors, and platelets; increased levels of fibrin degradation products; prolonged PT and PTT; spherocytosis, positive D-dimer assay, and Coombs-positive haemolytic anaemia.
3. Abnormal renal and liver function tests.

Treatment

1. Local
   a. Wound cleansing.
   b. Immobilisation of bitten extremity.
   c. Tetanus prophylaxis.
   d. Analgesics: Persistent pain may necessitate lumbar sympathetic blocks. Application of cold compresses may help.
   e. Antipruritics: Diphenhydramine 5 mg/kg/day orally, with a maximum dose of 25 to 50 mg four times a day. Hydroxyzine may also be used: 25 to 50 mg every 6 to 8 hours; maximum dose 400 mg/day.
   f. Antibiotics, if wound gets infected.
2. Systemic
   a. Admit patient to hospital and monitor for evidence of haemolysis, coagulopathy and renal failure.
   b. If haemoglobinuria occurs, renal failure may be prevented by increasing IV fluids, and alkalinising urine.
   c. Significant haemolysis should be treated with transfusions.

■ Black Widow*

Widow (or hour-glass) spiders belong to the Latrodectus species of phylum Arthropoda.

Other Common Names

Hourglass Spider.

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* Other species encountered in India include the Red Back (*Latrodectus hasselti indicus*), while the following are not encountered in India: Western Black Widow (*Latrodectus hesperus*), Brown Widow (*L. geometricus*), and Red Widow (*L. bishopi*).

Species

Latrodectus mactans.

Physical Appearance

- The widow spiders are cosmopolitan and are found all over the world, except regions with extremes of climate (polar regions, hot deserts, and high mountains). They are easily identified because they are the only spiders with a black, globose abdomen.
- The female is much larger than the male with a leg span of 5 cm and body length of 1.5 cm. It has a characteristic red hourglass spot on the back of its shiny black body (**Fig 12.47**). The male has more colourful white markings and is less aggressive than the female. In fact, the popular name "Black Widow" is due to the female's practice of killing its partner after insemination.
- The preferred habitats of these spiders include outdoor toilets, stables, barns, woodpiles, and dark crevices. They usually spin a somewhat irregular web in various corners of undisturbed areas of homes or the outdoors.
- The red-back spider (*Latrodectus hasselti*) is best known from the adult female that usually has a black body and legs, with the following distinctive markings on the abdomen: the dorsal or top side has a distinct red stripe beginning in the mid portion, and on the underside is a red area in the shape of an hourglass or two triangles. However, variations on that pattern are common. The body may be light or dark brown; there may be red markings in front of and beside the main red band which may be light orange, or faded red. These spiders are found in open country areas, dark places, rubbish heaps, wood heaps, stacks of bags, or of scrap metal, under the bark of dead trees, empty tins, unused buckets, beneath or between stones, behind ferns, near gas or water metres, old boxes, etc.

Fig 12.47: Black widow

Venom

- The venom of black widow is neurotoxic, with six active components of molecular weight ranging from 5000–130,000 D. The main component is alpha latrotoxin which binds avidly to a specific presynaptic receptor.
- The venom affects the motor endplates of neuromuscular synaptic membranes by the binding of gangliosides and glycoproteins at the synapses. This causes the channels for sodium influx into neurons to remain open, as a result of which there is extensive release of acetylcholine and noradrenaline into the synapses, thereby inhibiting reuptake. The end result is massive stimulation of motor endplates as the venom travels through the lymphatic system.

Clinical Features (Latrodectism)

Grade 1
1. Sharp pain at bitesite, which may have one or two small puncture wounds, 1 to 2 mm apart. The immediate area may be warm, mildly indurated, and slightly reddened. Swelling of the affected part may occur after red-back spider bites.
2. No systemic features.

Grade 2
1. Muscular pain in bitten extremity.
2. Extension of pain to the trunk.
3. Local diaphoresis of bitten extremity.
4. Tender regional lymphadenopathy may be present.
5. No systemic features.

Grade 3
1. Generalised muscle pain and weakness, with difficulty in walking.
2. Generalised sweating.
3. Tachycardia and hypertension are quite common.
4. ECG changes have been reported in a few victims: slurring of the QRS with ST and T segments depression, prolonged QT interval, and changes consistent with inferolateral ischaemia.
5. Leucocytosis is a common finding.
6. Nausea, vomiting, and headache are also very common.
7. Priapism, urinary retention, pyuria, proteinuria, microscopic haematuria, and testicular pain have been reported in a few cases.
8. During this period the victim often displays a contorted, grimacing, sweating facial appearance, referred to as "*facies latrodectismica*".
9. In severe cases, the following manifestations occur: ptosis, salivation, hyperreflexia, tremor, convulsions, tachypnoea, and respiratory compromise. Board-like rigidity of the abdomen, shoulders, and back may develop. Although uncommon, acute renal failure has been reported following envenomation. Death is uncommon, but is more likely in the case of infants, old individuals, pregnant women, and chronic invalids.

Diagnosis

1. Leucocytosis
2. Elevated creatine kinase
3. Albuminuria.

Treatment

1. Calcium gluconate IV (10 ml of 10%) has been traditionally advocated for pain relief, but its actual efficacy is doubtful.
2. Pain is usually better controlled with a combination of IV morphine or pethidine and benzodiazepines (diazepam or lorazepam). Milder cases may be treated with aspirin, paracetamol, and/or codeine.
3. Application of cold or warm compresses (as guided by patient comfort) to bitten site is usually helpful.
4. Swelling responds to non-steroidal anti-inflammatory drugs.
5. Muscle relaxants such as diazepam, methocarbamol, or dantrolene may help relieve muscle spasm.
6. Tetanus prophylaxis is essential.
7. Wound care:
   a. Cleansing with antiseptics.
   b. Immobilisation, elevation, and serial observation.
   c. If infection sets in, antibiotics must be administered.
   d. Surgical intervention (excision) may be necessary if lesion exceeds 4 cm at 12 hours post-envenomation.

■ Wolf Spider

- Wolf spiders belong to Lycosa species.
- The bite of the wolf spider is generally not associated with serious manifestations. Occasionally it causes moderate pain, erythema, oedema, or pruritis. Rarely there is necrosis.
- Systemic manifestations may develop after 1 to 2 days, characterised by fever, chills, myalgia, and arthralgia. Very rarely there may be features of haemolysis, renal failure, and shock.
- Treatment involves supportive and symptomatic measures.

■ Tarantula

- The tarantula (*Lycosa tarantula*) is usually a variant of the wolf spider. Some authorities are of the opinion that it is an ancestor of true spiders, and belongs to family Theraphosidae.
- The commonest species involved in bites is *Dugesiella hentzi* (**Fig 12.48**). It is a large, hairy spider which caused panic in Europe in the 17th century, due to a large series of bites beginning from the Italian city of Taranto and spreading to several European countries. Mass hysteria led to the development of a special dance ("tarantella") which was supposed to protect the envenomed victim from serious effects.
- The hairs of the tarantula may cause urticaria and conjunctivitis on contact. A number of species have urticaria-inducing hairs on the back of the abdomen. The tarantulas may flick these hairs toward an aggressor as a defensive mechanism. Contact may cause itching and wheals that persist for weeks. Ophthalmia nodosa has been reported

Fig 12.48: Tarantula

after handling tarantula spiders. Allergic rhinitis may develop after inhalation of the hairs from pet tarantulas.
- Bites can be almost painless, or produce a deep, throbbing pain for an hour or so. Local swelling may develop.
- Treatment involves application of ice packs, wound cleansing, and antihistamines. Use of dapsone and steroids is controversial. Immobilisation of the affected part, elevation, systemic analgesics and supportive care usually suffice. Tetanus prophylaxis may be required.

MISCELLANEOUS VENOMOUS CREATURES

TICKS AND MITES

Ticks and mites belong to order Acari of class Arachnida. Adult females of about 30 species of hard tick (family Ixodidae) (**Fig 12.49**), and immature forms of 6 species of soft tick (family
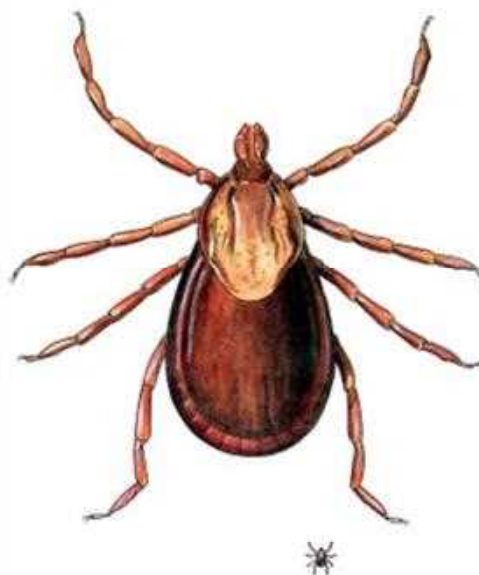
Fig 12.49: Hard tick

Argasidae) (**Fig 12.50**) are responsible for inducing **human tick paralysis**.

Ticks are often picked up from domestic animals, especially dogs, and they attach themselves in some hairy part of the body such as scalp, or in and around crevices or orifices. After attaching itself by means of a barbed hypostome, the tick introduces a salivary toxin and begins to engorge itself with the victim's blood. Five to six days later, a progressive, ascending lower motor neurone paralysis develops, with paraesthesiae. Most victims are children. The toxin acts by causing presynaptic neuromuscular block and decreased nerve conduction velocity.

Treatment involves locating the tick and detaching it without squeezing. For this purpose, it can be painted with ether, chloroform, petrol, kerosene, or turpentine, or prised out between the partially separated tips of a pair of small curved forceps. In most cases, detachment of the tick leads to complete recovery. But sometimes the condition keeps worsening and death results. Such cases respond to administration of specific antivenom.*

Gastrointestinal illness has been reported in children who handled the mite *Holothyrus coccinella* (**Fig 12.51**) and then placed their fingers in their mouths. Skin reactions and irritation in humans is seen from a number of different mites including *Dermanyssus gallinae* (chicken mite), *Ornithonyssus sylviarum* (northern fowl mite), *Ornithonyssus bacoti* (tropical rat mite), *Allodermanyssus sanguineus* (rodent mite), and *Rickettsia akari*. Respiratory allergies due to house dust mites are fairly common. Rhinitis and extrinsic asthma are caused by house dust mites (*Dermatophagoides species*) The scabies mite is antigenic and stimulates autoantibodies leading to a pemphigoid-like reaction. Scabies may mimic other skin

Fig 12.51: Mite

disorders also: contact dermatitis, scalp dermatitis, and generalised urticaria.

CENTIPEDES

Centipedes belong to Chilopoda. There are four orders: Scutigeromorpha, Lithobiomorpha, Geophilomorpha and Scolopendromorpha (the most venomous centipedes). Centipedes possess long, dorsoventrally flattened bodies with 15 to 181 somites (each of which has a pair of legs), a head bearing a pair of multijointed antennae, and three pairs of mouth parts (**Fig 12.52**). The number of segments is always odd, so there is really no 50-segment centipede with 100 legs.** Every segment, with the exception of the last one, has one pair of legs. Centipedes can grow up to 20 cm. The venom fangs are in the first segment. Three pairs of modified appendages which compose the mouth parts include the most important appendage, known as the venom claw, or "jaw". A neurotoxic venom is injected through venom ducts. Bites from the centipede are typically pointed in shape.

Centipedes are common in forests, but are also encountered near human habitations, infesting drains, kitchens, and bathrooms. They can inflict painful bites characterised by immediate local burning pain, erythema, swelling, inflammation, superficial necrosis, lymphadenopathy, and lymphangitis. The oedema

Fig 12.50: Soft tick

Fig 12.52: Centipede

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* Available in Australia, where most cases of fatal tick bite paralysis have occurred.
** "Centipede" means "one hundred legs".

may last for several hours. Local pain may be excruciating and the wound may bleed profusely. The commonest genus encountered in India is *Scolopendra*. Occasionally, systemic features are seen: anxiety, dizziness, vomiting, headache, convulsions, irregular pulse, and cardiac arrhythmias. Rhabdomyolysis, and renal failure have been reported with the Giant Desert Centipede (*Scolopendra species*).

Treatment is supportive. Bitesite is treated in the same manner as for a scorpion sting (*page no. 215*). Pain can be treated with application of ice over the injured area. Severe pain may require injection of local anaesthetic. A topical corticosteroid, antihistamine, local anaesthetic combination may be of value in controlling inflammation and itching. Tetanus prophylaxis should be considered.

MILLIPEDES

Millipedes belong to Diplopoda, and are commonly encountered in the countryside, especially during monsoon (**Fig 12.53**). They vary from a few centimeters to several centimeters in length, and have even more legs than centipedes (but *not* one thousand!).* Millipedes have two pairs of legs per segment and move slowly (in contrast to the centipedes which have one pair of legs per segment, but move quite fast). Also, millipedes have a cylindrical body, while centipedes are usually flattened.

Millipedes do not bite, and are not venomous, but have a glandular system that produces a foul-smelling, disagreeable fluid containing phenols and hydrocyanic acid. Some millipedes secrete or squirt these irritant liquids for defensive purposes, which can cause brown or purple skin lesions that blister after a few days and then peel. Sometimes these lesions take a long time to heal. Contact with the eye can result in severe conjunctivitis, corneal ulceration, and even blindness.

Treatment involves copious irrigation with water, and application of a topical anti-microbial agent. Eye injury necessitates expert ophthalmologic evaluation and treatment.

Fig 12.53: Millipede

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* "Multipede" means "one thousand legs".

MARINE VENOMOUS CREATURES

The sea is host to a wide variety of venomous creatures which sting or bite, and are a special threat to swimmers and divers. Marine envenomations have risen sharply in incidence over the last few decades owing to an increase in popularity of recreational diving and other water related sports.

■ Marine Vertebrates

Approximately 225 species of marine fish are known to be venomous. These include the stingray, scorpionfish, lion- or zebra-fish, stonefish, weeverfish, toadfish, stargazer, and certain catfish, sharks, ratfish, and surgeonfish. The most common marine envenomations are caused by fish belonging to family Scorpaenidae of class Osteichthyes and order Perciformes. Venomous fish produce envenomation by means of their spines, fins, or caudal stings.

In most cases, the stung victim experiences severe burning pain and swelling within seconds of the sting. Systemic symptoms include nausea, vomiting, hypotension, and rarely cardiac arrhythmias. Stings from a stingray can result in severe lacerations with tendency to necrosis. There is intense pain, associated with paraesthesias, nausea, vomiting, abdominal pain, cardiac arrhythmias, and convulsions. Limb paralysis may be seen with severe envenomations.

Treatment involves the following measures:
- Soaking the affected limb in hot water (110° to 115° F).
- Paracetamol, salicyclates, non-steroidal anti-inflammatory drugs, or opiate analgesic for pain, depending on the severity.
- Tetanus prophylaxis.
- Wound care.
- Supportive measures.

■ Marine Invertebrates

There are two important phyla of venomous marine invertebrates: Coelenterata and Echinodermata. Less common invertebrates which cause envenomation include molluscs such as cone shells and octopuses.

Coelenterates account for most of the reported cases of marine envenomations around the world, and comprise more than 9,000 species of which approximately 100 belonging to Cnidaria are venomous. The Cnidaria are subdivided into 3 classes: Hydrozoa, Schiphozoa, and Anthozoa:
- Hydrozoa
  - ❖ Portuguese man-o'-war (*Physalia sps*).
- Schiphozoa
  - ❖ Jellyfish ("box jelly", "fire medusa") (*Chironex fleckeri*)
  - ❖ Sea nettle.
- Anthozoa
  - ❖ Sea anemone
  - ❖ Coral.

Most of the Cnidaria possess stinging structures called nematocysts or cnidocytes, which are poisonous dart-like structures,

tightly coiled and enclosed within venom sacs. Following external contact, they are expelled from the sacs, injecting venom as they penetrate the flesh of their prey. The venom is a complex mixture of serotonin, histamine, bradykinin, haemolysin, prostaglandins, hyaluronidase, phosphodiesterases, fibrinolysin, RNAase, DNAase, adenosine triphosphatase, alkaline and acid proteases, as well as alkaline and acid phosphatases.

Envenomation usually results in local burning pain with erythematous or violaceous lesions, and regional lymphadenopathy. Erythema nodosum, arthralgias, and anaphylactoid reactions have also been reported. Delayed hypersensitivity reactions may occur, consisting of a pruritic erythematous maculopapular rash appearing at the initial tentacle contact points, usually in 7 to 14 days after envenomation. The reactions spontaneously resolve in some patients, while others recover following treatment with oral antihistamines and topical corticosteroids.

The box jellyfish, fire medusa, or sea wasp (*Chironex fleckeri*) (**Fig 12.54**) is the most venomous of all stinging marine creatures. It has a transparent box-like bell with four pedalia (feet). Each pedalia may have up to 15 tentacles attached. Because of its transparency, the box jellyfish is virtually invisible under natural conditions, including clear, sunlit seawater. When fully grown, the bell of *Chironex fleckeri* may measure up to 30 centimetres in diameter, weigh up to 6 kilograms, and the total length of its tentacles may be greater than 60 metres. *Chironex fleckeri* is predominantly found in northern Australian waters. Each box jellyfish carries enough venom to kill several adults. Features include profound muscle spasm, hypotension, acute respiratory distress, respiratory paralysis, cyanosis, haemolysis, arrhythmias, and cardiac arrest. Severe parasympathetic dysfunction (abdominal distension, urinary retention, dry eyes) is common. Death can occur in less than a minute. A few cases have been reported from India also. Neuromuscular paralysis leading to respiratory arrest may occur following *Chironex fleckeri* stings. The sting of a chirodropid is characteristic for leaving a "cross-hatched" or "frosted-ladder" tentacle imprint on the skin, as well as multiple wheals. The skin may become blackened, and permanent scarring may result.
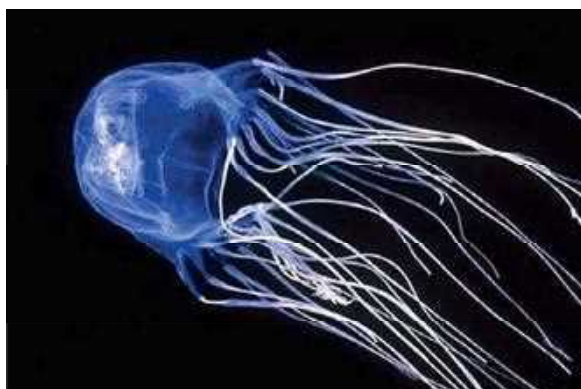

Fig 12.54: Box jellyfish (Sea wasp)

■ **General Treatment Measures for Cnidarian Stings**

- Anaphylaxis to jellyfish sting must be treated by maintaining airway and cardiovascular status. Adrenaline is administered in the usual way. Verapamil may be useful for arrhythmias. Antihistamines with or without inhaled beta agonists, and corticosteroids may be required. Topical corticosteroids and oral antihistamines are indicated in delayed hypersensitivity reactions.
- Remove any adhering tentacles carefully without too much tactile pressure which may cause additional nematocyst discharge. Do not rub the affected area.
- Inactivate unexploded nematocysts by topical application of any of the following solutions for at least half an hour:
  ❖ Vinegar (3 to 5% acetic acid). Altering pH below 6 inactivates the venom.
  ❖ A slurry (50% w/u) of sodium bicarbonate or baking soda. Altering pH above 8 dissolves tentacles.
  ❖ Aluminium subacetate 10 to 20% (Burow's solution). The aluminium ion denatures protein constituents of venom. Adding 5% detergent enhances efficacy.
  ❖ Meat tenderiser (papain). It causes denaturation of protein constituents, but is not as effective as aluminium subacetate.
- Apply dry baking soda, flour, sand, or shaving soap to the affected area.
- Scrape off remaining nematocysts from the wound with a knife.
- Wash the area with seawater: Bathe the affected part liberally with seawater. Do not use fresh or hot water, or alcohol. Fresh water/alcohol may discharge nematocysts and therefore should be avoided.
- Apply a steroid cream or lotion (e.g. triamcinolone 0.1%).
- If the lesion ulcerates, clean daily with Burow's solution and cover with dry dressings.
- Administer tetanus prophylaxis.
- For pain: Apply ice-packs for initial pain relief combined with IV or IM analgesics, if necessary (1 mg/kg of pethidine up to 50 mg, or morphine, 0.1 mg/kg up to 5 mg; can be repeated).
- Painful muscle spasms may be relieved by calcium gluconate 10% IV.
- For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Institute central venous pressure monitoring to guide further fluid therapy.
- For box jellyfish envenomation, specific antivenom is available (Commonwealth Serum Laboratories, Melbourne, Australia). It should be given in life-threatening stings, or severe stings where the pain is not controlled by other methods. The antivenom should preferably be given within 4 to 6 hours.

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Section

5

Neurotoxic Poisons

13

Somniferous Drugs

Neurotoxic poisons and drugs with predominant effects on the central nervous system are further sub-classified as follows:

1. **Somniferous Drugs (Narcotics)**
2. **Inebriants**
3. **Deliriants**
4. **Stimulants**
5. **Anticonvulsants and Antiparkinsonian Drugs**
6. **Anaesthetics, Antispasmodics and Muscle Relaxants**
7. **Drugs used in Psychiatry**
8. **Hallucinogens (Psychedelic Drugs)**

SOMNIFEROUS DRUGS (NARCOTICS)

■ Opium

Opium refers to the dried extract of the poppy plant (*Papaver somniferum*) which belongs to the family Papaveraceae. This plant grows well in India, but its cultivation is banned except on license obtained from the central government, for growing the plant strictly for the pharmaceutical industry. Such a license is issued only for the states of Rajasthan, Uttar Pradesh, and Maharashtra. India produces 70 to 80% of opium that is used worldwide by pharmaceutical companies to manufacture several vital drugs including morphine, codeine, and pethidine. Unfortunately, a significant quantity of opium is funnelled clandestinely into a global smuggling racket which feeds the illicit drug trade flourishing in Western countries.

Physical Appearance

- The poppy plant is a herb growing upto 1 metre in height (**Fig 13.1**). It is minimally branched with leaves clasping the glabrous stem by their cordate base.
- The leaves are oblong, irregularly toothed, and slightly sinuate or lobed.
- Flowers are large and may be bluish white, purple, or white in colour.
- Each plant bears 5 to 8 capsules which are incised in their unripe state (**Fig 13.2**) to extract a milky fluid that on drying yields opium.

- Crude opium is a dark brown or grey irregular mass (**Fig 13.3**) with a characteristic odour and bitter taste.

Fig 13.1: Poppy plants

Fig 13.2: Unripe poppy capsule with incisions

Fig 13.3: Crude opium

Toxic Part

Fruit capsule (unripe).

Toxic Principles

Opium obtained from the unripe fruit capsule contains a number of alkaloids which fall into two groups—

- *Phenanthrene group*: morphine, codeine, and thebaine.

- *Benzylisoquinoline group*: papaverine and noscapine (narcotine).

Apart from these natural derivatives there are several other drugs used in pharmacotherapeutics which are either semisynthetic or synthetic analogues. Examples of other derivatives include alfentanil hydrochloride, alphaprodine, anileridine hydrochloride, diprenorphine, ethoheptazine, ketobemidone, meptazinol hydrochloride, methylfentanyl, pholcodine, remifentanil hydrochloride, and sufentanil citrate. When referring to these derivatives, there has always been confusion in terminology. While strictly speaking, the term "opiate" refers to natural and semisynthetic derivatives, and the term "opioid" is a more inclusive term applying to all agonists and antagonists with morphine-like activity, for the sake of convenience (and to avoid confusion), the former term will be used in this book as an umbrella-expression to cover all derivatives of opium—natural, semisynthetic, and synthetic.

Uses

Opiates have tremendous pharmacological importance, and are used for various therapeutic purposes (**Table 13.1**).

Usual Fatal Dose

The usual fatal doses (as well as usual therapeutic doses) of common opiates are listed in **Table 13.2**.

Table 13.1: Pharmacological Uses of Opiates

Derivative	Nature	Classification	Use
Buprenorphine	Semisynthetic	Partial agonist	Analgesic, pre-anaesthetic medication
Butorphanol	Semisynthetic	Agonist-antagonist	Analgesic
Codeine	Natural	Agonist	Antitussive
Dextromethorphan	Semisynthetic	—	Antitussive
Diphenoxylate	Synthetic	Agonist	Antidiarrhoeal
Fentanyl	Synthetic	Agonist	Adjunct to anaesthesia
Heroin	Semisynthetic	Agonist	—
Hydrocodone	Semisynthetic	Agonist	—
Hydromorphone	Semisynthetic	Agonist	—
Levorphanol	Semisynthetic	Agonist	Analgesic
Loperamide	Synthetic	Agonist	Antidiarrhoeal
Methadone	Synthetic	Agonist	Analgesic, treatment of heroin abuse and opiate abstinence syndrome
Morphine	Natural	Agonist	Analgesic
Nalbuphine	Semisynthetic	Agonist-antagonist	Analgesic
Nalmefene	Semisynthetic	Antagonist	Treatment of opiate poisoning
Naloxone	Semisynthetic	Antagonist	Treatment of opiate poisoning
Naltrexone	Semisynthetic	Antagonist	Treatment of opiate poisoning and alcoholism
Oxycodone	Semisynthetic	Agonist	Analgesic
Oxymorphone	Semisynthetic	Agonist	—
Paregoric (tincture of opium)	Natural	Agonist	Analgesic
Pentazocine	Semisynthetic	Agonist-antagonist	Analgesic
Pethidine (meperidine)	Synthetic	Agonist	Analgesic
Propoxyphene	Synthetic	Agonist	Analgesic
Tramadol	Synthetic	Agonist	Analgesic

Table 13.2: Usual Fatal Dose and Usual Therapeutic Dose for Common Opiates

Opiate	Usual Fatal Dose	Usual Therapeutic Dose
Morphine	200 mg	10 to 15 mg
Codeine	800 mg (7 to 14 mg/kg)	10 to 60 mg
Etorphine	0.03 to 0.12 mg	—
Heroin	50 mg	—
Hydrocodone	100 mg	—
Crude Opium	500 mg	—
Pethidine	1 gm	50 to 150 mg
Methadone	100 mg	5 to 10 mg
Pentazocine	300 mg	30 to 60 mg
Propoxyphene	1 gm	100 to 150 mg
Diphenoxylate	200 mg	10 to 20 mg

Mode of Action

There are three major classes of opiate receptors to which different opiates bind with differing affinity.

- The μ (mu) receptor is also known as OP_3 and consists of 2 sub-types: $μ_1$ and $μ_2$ (OP_{3A} and OP_{3B}). Most of the clinically used opiates are relatively selective for μ receptors reflecting their similarity to morphine.
- The κ (kappa) receptor is also known as OP_2 and consists of 3 subtypes: $κ_1$, $κ_2$, and $κ_3$ (OP_{2A}, OP_{2B}, and OP_{2C}).
- The δ (delta) receptor is also known as OP_1, and is said to be important in spinal and supraspinal analgesia. Subtypes $δ_1$ and $δ_2$ have been postulated to exist, but not confirmed so far.
- The σ (sigma) receptor originally thought to be an opiate receptor is no longer considered to be opioid in nature since it is insensitive to naloxone, which is the most important characteristic of such receptors. However some opiates such as dextromethorphan and pentazocine are σ receptor agonists. Stimulation of σ receptor produces psychotomimetic effects and movement disorders (both of which have been reported with dextromethorphan and pentazocine).
- Two more receptors have been postulated to exist, but not demonstrated so far: ε (epsilon) and ζ (zeta).
- Mu and delta receptors appear to be involved in systems that influence mood, reinforcing effects, respiration, pain, blood pressure, and endocrine and gastrointestinal functions.
- Kappa receptors are able to produce endocrine changes and analgesia. In human subjects kappa agonists appear to produce dysphoria, rather than euphoria.
- Respiration, which is controlled mainly through medullary respiratory centres with peripheral input from chemoreceptors and other sources, is affected by opiates which produce inhibition at chemoreceptors via mu opiates receptors and in the medulla via mu and delta receptors. Tolerance develops more quickly to euphoria and other effects than to respiratory effects.

Toxicokinetics

- In general, most opiates are readily absorbed from the GI tract,* and also can be administered by subcutaneous, intramuscular or intravenous injection. However the effect of an oral dose is usually much less than that obtained on parenteral administratrion due to significant first-pass metabolism in the liver. For example, the bioavailability of oral morphine is only 25%.
- Extent of protein-binding is variable depending on the exact nature of the opiate, and varies from 7% for codeine to 96% for buprenorphine. Morphine displays protein-binding to the extent of 34%.
- The major metabolic pathway of morphine is conjugation with glucuronic acid to produce morphine-6-glucuronide which is also pharmacologically active. Excretion occurs in the urine as morphine-3-glucuronide.
- Duration of action of opiates varies from 2 hours (pentazocine, pethidine) to 4 hours (morphine, codeine, heroin), to 8 hours (methadone, buprenorphine). Fentanyl, alfentanil, and surfentanil are ultra-shortacting (few minutes to 1 hour).

Adverse Effects

- Respiratory depression, vomiting, vertigo, dysphoria, miosis, constipation, hypotension, urinary retention, and pruritis are commonly encountered.
- Pruritus is a common adverse event following the administration of opiates, particularly morphine sulfate.
- Priapism may be induced by opiates due to their sympatholytic actions which may induce an unopposed cholinergic state that could result in Ach-induced vasorelaxation involving NO pathways. Alpha-blockade has also been postulated as a mechanism. Autonomic system dysregulation appears not to be dose-specific.

Drug Interactions

- Depressant effect of opiates is enhanced by alcohol, phenothiazines, cyclic antidepressants and Monoamine oxidase inhibitors (MAOIs).
- Concomitant administration of cimetidine can result in mental confusion.

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. The triad of *coma, pinpoint pupils,* and *respiratory depression* is said to be almost pathognomonic for opiate poisoning. Such cases may be due to therapeutic overdose, accidental overdose (in addicts), or deliberate overdose (suicidal). The important clinical manifestations are summarised in **Table 13.3**.
   b. Pupils are usually pinpoint (**Fig 13.4**) but may be dilated in the presence of severe acidosis, hypoxia, or respiratory depression. Pethidine often causes mydriasis.

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* Some opiates (e.g. morphine) are even absorbed rectally and are available as rectal suppositories.

Table 13.3: Acute Opiate Poisoning

- Coma
- Pinpoint pupils (may be dilated if hypoxia is severe)
- Bradypnoea, cyanosis, non-cardiogenic pulmonary oedema
- Hypotension
- Hypothermia
- Convulsions
- Urinary retention

Fig 13.4: Pinpoint pupil—Opium overdose

c. Hypotension may be due to opiate-induced arteriolar and venous dilation. While bradycardia is said to be common, tachycardia and ECG readings of sinus tachycardia and nonspecific ST-T segment changes have been reported.

d. Bradypnoea is common in opiate poisoning. Respiratory rates of less than 8/minute are not unusual. Snoring prior to fatal opiate overdose has been reported and is likely due to a failure to maintain the patency of the upper airway. Gurgling may occur due to accumulation of pulmonary oedema fluid. Non-cardiogenic pulmonary oedema ("heroin-lung") is an infrequent, but severe, complication of heroin overdose and is generally abrupt in onset (immediate-2 hours) following intravenous heroin overdose. Manifestations include rales, pink frothy sputum, significant hypoxia, and bilateral fluffy infiltrates on chest X-ray. Some patients require mechanical ventilation. Resolution of symptoms usually occurs rapidly with supportive care alone, within hours to 1 to 2 days.

e. Morphine-induced seizures are primarily seen in neonates.

f. Cramping and constipation as well as sphincter of Oddi spasm may occur.

g. Hyperkalaemia may occur following an overdose, especially in the presence of rhabdomyolysis and acute renal failure.

h. Most opiates cross the human placenta. They have been shown to appear in the foetal circulation within 5 minutes following maternal IV injection. Morphine appears to act as a vasoconstrictor of the placental vasculature, causing a significant decrease in the biophysical profile score as a result of absent foetal breathing movements and a nonreactive nonstress test (NST). If delivery occurs quickly following an opiate dose to the mother, or after adequate time has passed to allow for maternal clearance, it is unlikely that the foetus would be affected. Foetuses demonstrating significant distress and acidosis and whose mothers received opiates 1 to 3 hours prior to delivery, or multiple doses, may be at increased risk for respiratory depression, which would most likely be multifactorial in origin.

2. **Chronic Poisoning:**

a. The American Psychiatric Association has laid out diagnostic criteria for opiate dependence and for categorising the severity of such dependence (**Table 13.4**).

b. The following are some useful pointers which indicate opiate addiction:
   – Unusual mood swings, periods of depression alternating with euphoria.
   – Withdrawal from family, friends, and social activities.
   – Frequent domestic strife.
   – Long hours of unexplained absence from home.

Table 13.4: Diagnostic Criteria for Opiate Dependence and Grading the Severity

I. Opiate Dependence (at least three of the following must be present)

- Opiates are taken in larger amounts, or over a longer period than the person intended
- Intense desire for the drug is present, or the person has made unsuccessful attempts to cut down intake
- Patient is frequently under the influence of the drug, or undergoing withdrawal when expected to be studying or working
- Social, occupational, or recreational activities are given up or reduced
- Demonstrates tolerance to the drug
- Demonstrates characteristic withdrawal syndrome
- Opiates are taken to relieve or avoid withdrawal reaction

II. Severity of Opiate Dependence

- Mild: few symptoms ; mild impairment of social and occupational activities
- Moderate: intermediate between mild and severe
- Severe: many symptoms ; marked impairment of occupational and social activities
- Partial remission: during past 6 months there has been some opiate use and some dependence symptoms
- Full remission: during past 6 months there has been no opiate use and no dependence symptoms

- Unexplained overspending.
- Frequent conflicts with law (e.g. driving offences).
- Dwindling sexual drive.
- Pills, syringes, etc. lying around the house.
- Bloody swabs or tissues lying around the home or in the woking place.
- Periodic disappearances into a locked room (bathroom, bedroom, etc.).
- Pinpoint pupils.
- Weight loss, pallor.
- Chronic constipation.
- Periodic withdrawal manifestations— sweating, tremors.

In addition, an addict may have dermal scars (from intravenous abuse) (**Fig 13.5**), and suffer from amnesia, confusion, and occasional hallucinations. Compartment syndrome may occur following abuse of narcotic injections, such as heroin. Abrupt cessation of opiate intake can cause a withdrawal reaction (*cold turkey*).* Common manifestations are mentioned in **Table 13.5**. Neonatal withdrawal may be seen in the infants of addicted mothers 12 to 72 hours after birth. Infants may be dehydrated, irritable, and experience tremors and cry continually and may have diarrhoea.

Fig 13.5: Skin lesions – Heroin addict

Diagnosis

1. Needle marks, dermal scars (suggestive of addiction).
2. Evidence of hypoglycaemia, hypoxia, and hypothermia.
3. Most opiates can be detected in urine or blood by RIA, GC, GC-MS, or HPLC.
4. Empirical administration of naloxone, (*can precipitate reaction in addicts*).

Treatment

1. **Acute Poisoning:****
   a. Supportive measures—
      - Maintenance of patent airway.
      - Endotracheal intubation, assisted ventilation: Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops. Crystalloid solutions must be administered judiciously. Pulmonary artery monitoring may help. In general the pulmonary artery wedge pressure should be kept relatively low while still maintaining adequate cardiac output, blood pressure and urine output.
      - Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.
      - Consider prehospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion.
   b. Naloxone is the antidote of choice for opiate poisoning, (**Box 13.1**).
   c. The use of physostigmine salicylate (0.04 mg/kg IV) has been suggested for reversing respiratory depression if the regular opiate antidotes are not available, since it increases the acetylcholine content of the reticular formation of the brainstem which is suppressed by opiates. However, there is controversy regarding such a measure since physostigmine (unlike regular opiate antagonists) is a dangerous antidote with serious adverse effects.

Table 13.5: Opiate Withdrawal*			
Anticipatory (3 to 4 hours)	*Early (8 to 10 hours)*	*Fully Developed (1 to 3 days)*	*Protracted Abstinence (upto 6 months)*
Anxiety, craving, drug-seeking behaviour	Restlessness, yawning, nausea, sweating, rhinorrhoea, lacrimation, mydriasis, stomach cramps, drug-seeking behaviour	Tremor, piloerection, vomiting, diarrhoea, muscle spasm, hypertension, tachycardia, fever, chills, impulse-driven drug-seeking behaviour	Hypotension, bradycardia, insomnia, anorexia, stimulus-driven opiate craving
Times mentioned in the table refer to heroin.			

* This expression is derived from the nodular appearance of skin of an addict withdrawing from opiate addiction, which is due to goose-fleshing and hypothermia.
** With particular reference to morphine, the archetypal opiate.

Box 13.1: Antidotes for opiates

Naloxone—

It is effective against all opiates including pentazocine, but is not very effective against buprenorphine. Dramatic reversal of the following features is achieved: miosis, respiratory depression, hypotension, coma.

Dose: The usual initial dose is 1.2 mg for an adult and 0.4 mg for a child. The best route of administration is IV, but if venous access is difficult, the drug can be injected sublingually or intramuscularly, or even instilled down an endotracheal tube. Since the effect of a single bolus dose of naloxone is usually short-lived, repeated doses are required. Repeat doses of 2 mg may be given to achieve a clinical effect. Generally, if no response is observed after 10 mg has been administered, the diagnosis of opiate-induced toxicity should be questioned. Very large doses of naloxone (10 mg or more) may be required to reverse the effects of buprenorphine overdose. Some investigators state that a naloxone infusion is better than repeated injections. The following steps are suggested:

- Determine the maintenance fluid requirement for 24 hours.
- To determine the amount of naloxone (in mg) to add to the maintenance fluid for a 24-hour period, take the bolus dose required for initial response (in mg) and multiply by 2/3 and 24 (hrs).
- To determine the desired rate of infusion (ml/hr), take the maintenance fluid, and divide by 24 (hrs)

This method is said to reduce the risk of possible fluid overload and pulmonary oedema. A continuous infusion of naloxone is especially useful in circumstances of opiate overdose with long acting opiates. Naloxone can be diluted in normal saline or 5% dextrose, but should not be added in alkaline solutions. Any prepared solution of naloxone should be used up in 24 hours. Caution should be exercised in reversing opiate toxicity in addicts because of the risk of precipitating withdrawal reaction. Observe patients for evidence of CNS or respiratory depression for at least 2 hours after discontinuing the naloxone infusion.

The American Academy of Pediatrics recommends a neonatal dose of 0.1 mg/kg intravenously or intratracheally from birth until age 5 years or 20 kg body weight.

Naltrexone—

Naltrexone is a long-acting opiate antagonist which can be administered orally. It is usually used for treating opiate addiction. However, it must not be given to an opiate-dependant patient who has not been detoxified. A challenge dose of naloxone to confirm the lack of opiate dependence is recommended before beginning naltrexone.

Dose: 50 mg/day orally, which may have to be continued for several weeks or months.

Nalmefene—

Nalmefene is a naltrexone derivative with pure opiate antagonistic effects, and has a longer duration of effect than naloxone in acute opiate poisoning. It is usually given intravenously beginning with 0.1 mg, and if withdrawal reaction does not occur, 0.5 mg is administered, followed by 1 mg in 2 to 5 minutes (if necessary). Nalmefene can also be given intramuscularly or subcutaneously.

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d. The use of drugs such as levorphanol and amiphenazole is no more recommended today.

e. Convulsions may be treated with benzodiazepines in the usual manner (5 to 10 mg initially, repeat every 5 to 10 minutes as needed), though this is frequently not necessary if naloxone is available. Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation. Evaluate for hypoxia, electrolyte disturbances, and hypoglycaemia (or treat with intravenous dextrose 50 ml IV in an adult, or 2 ml/kg in 25% dextrose for a child).

f. *For hypotension:* Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine (5 mcg per kg per min, progressing in 5 mcg per kg per min increments as needed), or noradrenaline (0.5 to 1 mcg per min, and titrate to maintain adequate blood pressure). Consider central venous pressure monitoring to guide further fluid therapy.

g. *Prevention of rhabdomyolysis:* Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is not routinely recommended.

2. **Chronic Poisoning:**

a. Gradual withdrawal of the opiate.

b. Substitution therapy with methadone begun at 30 to 40 mg/day and then gradually tapered off.

c. A beta adrenergic blocker like propranolol (80 mg) is said to be quite effective in relieving the anxiety and craving associated with opiate addiction, but has no effect on physical symptoms. Alternatively, drugs such as clonidine can be used. Buprenorphine or naltrexone can also be used. Recent reports suggest favourable outcome with gabapentin combined with clonidine and naltrexone. The regimen suggested is clonidine 0.1 mg thrice a day for 7 days, followed by naltrexone 50 mg twice a day for 14 days, along with gabapentin 600 mg twice a day on all the 21 days.

d. Antispamodics for abdominal cramps associated with vomiting and diarrhoea.

e. Tranquillisers or bed time sedation if necessary.

f. Psychiatric counselling.

Autopsy Features

1. Injection marks, dermal abscesses, scarring. Look for injection marks in the antecubital fossae, forearms, back of the hands, neck, groin, and ankles.

2. Tattooing, (a common feature of the drug sub-culture).

3. Emaciation, unkempt appearance.
4. Gross pulmonary oedema with froth exuding out of mouth and nostrils, especially in sudden heroin-related death. Another frequent autopsy finding in heroin fatalities is undiagnosed pneumonia.
5. Autopsy findings of heroin-induced spongiform leukoencephalopathy include spongiform degeneration of white matter, vacuolisation and fluid accumulation in myelin sheaths.
6. Cerebral oedema.
7. Congestion of liver with enlargement of hepatic lymph nodes. Chemical analysis of lymph nodes may reveal presence of morphine.*
8. Myocardial damage, with focal lesions formed by small mononuclear inflammatory cells and with degenerated, necrotic myocardial fibres and congestion, has been shown to occur as a result of prolonged hypoxic coma following opiate intoxication.
9. Samples of blood, urine, brain, liver, and bile must always be preserved for chemical analysis.

It is important to remember that infections such as serum hepatitis and AIDS are common among intravenous drug abusers, and hence autopsies conducted in drug-related deaths must be done cautiously with necessary precautions.

Forensic Issues

- Opiates are among the commonest of the drugs abused today in India. Heroin (*brown sugar*) is popular among all classes of addicts in metropolitan cities such as Mumbai, Delhi, Bangalore, etc. Opiates used for therapeutic purposes, e.g. morphine, pethidine, and pentazocine are more commonly abused by medical and paramedical personnel. Buprenorphine is emerging as a major drug of abuse even among non-medical personnel in recent times. Codeine which is easily available over the counter in the form of antitussive preparations is being increasingly abused especially by college-going youth.
- Accidental deaths are not infrequent from overdose, particularly among intravenous abusers of heroin ("death on the needle"). Wound botulism, which has been associated with subcutaneous or intramuscular black tar heroin injections, has caused potentially lethal, descending, flaccid paralysis when *Clostridium botulinum* spores germinated in wounds, releasing neurotoxins.
- "Cotton fever" is common among IV abusers, which is a febrile reaction that develops because these drugs are often filtered through cotton balls prior to being injected.
- Chronic parenteral opiate abuse can result in abscesses, acute transverse myelitis, anaphylaxis, AIDS, arrhythmias, wound botulism, cellulitis, endocarditis, faecal impaction, glomerulonephritis, hyper or hypoglycaemia, osteomyelitis, post-anoxic encephalopathy, tetanus, thrombophlebitis, nephropathy, hoarseness, hepatitis, pneumothorax, paraplegia, mycotic aneurysms, or leucoencephalopathy.

- Suicidal deaths are also reported from time to time since opiates are reputed to cause a painless death. Homicides are rare, but a few cases have been documented in medical literature.
- **Body Packer Syndrome**—Although this is more commonly associated with smuggling of cocaine, it has also been reported in the case of other drugs, especially heroin.
  - ❖ A "bodypacker" or "mule" is an individual who attempts to transport illicit drugs from one country to another by ingesting wrapped packages, or condoms (**Fig 13.6**), or balloons containing concentrated cocaine or heroin. After arrival at the destination, cathartics are self-administered and the packets are defaecated out. Sometimes rectal suppositories or disposable enemas are used.
  - ❖ Although generally asymptomatic, in a few cases serious toxicity may result due to rupture of packets. Death due to intestinal obstruction and perforation has been reported in heroin body packers.
  - ❖ Diagnosis of an asymptomatic body packer can be accomplished with the help of an abdominal X-ray (**Fig 13.7**), ultrasound, or CT scan. The last two methods should be resorted to only if X-ray is unclear. In some cases, faecal examination over a period of a few days may be necessary. Magnetic resonance does not visualise packets because of the lack of protons.
  - ❖ Asymptomatic patients should be treated by whole bowel irrigation with polythylene glycol solution. However some investigators do not approve of this method since the polythylene glycol can dissolve the heroin from a package, rupturing it and increasing absorption of heroin. Instead, a period of waiting is recommended so that all packages pass into the colon from the stomach, and then low-volume phosphosoda enemas or high-volume saline enemas are administered. Food ingestion must not be permitted until all packages have moved into the colon. Metoclopramide 10 mg, 8th hourly, may be administered to encourage gastric emptying. Bowel obstruction must be ruled out. It may

Fig 13.6: Plastic packets filled with cocaine (for bodypacking)

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* Even if heroin was being abused by the victim, it is metabolised into morphine in the body.

Fig 13.7: X-ray of Bodypacker

be advisable to empty the rectum first by a bisacodyl suppository.

❖ Symptomatic patients must be managed with continuous-infusion naloxone, activated charcoal, and whole bowel irrigation. Intestinal perforation or obstruction by packets requires surgical intervention.

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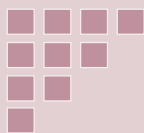
14

Inebriants

Inebriants are substances that induce intoxication or inebriation, and comprise mainly alcohols, barbiturates, benzodiazepines, and chloral hydrate.

ALCOHOLS

Alcohols are actually (hydroxy) derivatives of (aliphatic) hydrocarbons. There are 3 categories of alcohols—

1. **Monohydroxy alcohols :** They have only one hydroxyl (OH) group, e.g. ethanol, methanol, isopropanol, etc.
2. **Dihydroxy alcohols :** They possess two hydroxyl groups and are referred to as glycols, e.g. ethylene glycol, propylene glycol, etc.
3. **Trihydroxy alcohols :** They are not really alcohols, but only derivatives, e.g. propane derivative glycerol or glycerine.

■ Ethanol

Synonyms

Ethyl alcohol; Grain alcohol.

Physical Appearance

Clear, colourless liquid with a faint fruity odour, and sweetish burning taste. It is both water soluble and lipid soluble.

Sources

- Ethanol is produced mostly by synthetic production from ethylene. This is mainly by direct hydration process (replacing the earlier method of indirect hydration using sulfuric acid).
- Fermentation of sugar, cellulose, or starch: Such is the method used in the production of beverage alcohol.
- Enzymatic hydrolysis of cellulose.
- Ethanol can also be obtained by the reaction of methanol with synthesis gas at 185°C and under pressure.
- Anhydrous ethanol is manufactured by azeotropic distillation.
- Beverage ethanol is produced by fermentation of a sugar (from cereal, vegetable, or fruit) with yeast. If cereal is used as raw material, it has to be malted first to convert the starch to maltose, since yeast cannot ferment starch.

Malt is produced by moistening barley and allowing it to sprout which is then dried, ground, and added to the cereal in water resulting in the formation of *mash*. Beer is brewed by filtering *mash* and treating the filtered liquid (*wort*) with yeast. Whisky is made by adding yeast directly to the malted *mash*. Strong alcoholic beverages are distilled after fermentation.

- ❖ The ethanol content of various alcoholic beverages is expressed by volume percent or by proof, the latter being twice the percentage of alcohol by volume. Proof spirit refers to a standard mixture of alcohol and water of relative density 12/13 at 51°F, i.e. 49.28% of alcohol by weight (or 57.10% by volume). Proof strength of alcoholic beverages is expressed in degrees.
- ❖ **Table 14.1** lists the ethanol content of various alcoholic beverages.
- ❖ Apart from ethanol however, these beverages also contain several congeners to varying extent, e.g. low molecular weight alcohols such as methanol and butanol, as well as aldehydes, esters, phenols, tannins, and heavy metals (lead, cobalt, iron, etc.). Vodka is the purest form and contains no congeners. It is virtually odourless. White rum is also relatively pure.

Uses

- Beverage—Popular alcoholic beverages include beer, wine, whisky, gin, brandy, rum, and vodka (**Table 14.1**).

Table 14.1: Ethanol Content in Alcoholic Beverages	
Beverage	*Ethanol Content (percentage by volume)*
Light Beer (Lager and Pilsener)	4 to 6
Heavy Beer (Ale and Stout)	6 to 8
Natural Wine (Cider)	2 to 3
Fortified Wine (Sherry and Port)	10 to 20
Whisky, Gin, and Brandy	40 to 45
Rum	40 to 50
Liqueurs (e.g. Cognac, Crème de menthe, Schnapps, etc.)	17 to 50

In addition there are several indigenous preparations peculiar to particular regions, e.g. arrack, toddy, and feni in India, tequila in Mexico, sake in Japan, *eau de vie* or fruit brandy in France, etc.

- Solvent for after-shaves, colognes, mouthwashes, and perfumes. The alcohol content in these is variable (15 to 80 %).
- Medicinal—
  - ❖ Several antihistaminic, decongestant, multivitamin, and cough syrups contain varying percentage of alcohol (2 to 25 %).
  - ❖ Ethanol has been popular in the past as an antiseptic. Surgical spirit used even today is mostly ethanol with a small quantity of methanol (90 to 95% and 5 to 10 % respectively), along with traces of castor oil and methyl salicylate.
  - ❖ Ethanol sponging is an effective remedy for hyperthermia.
  - ❖ Injection of dehydrated alcohol (absolute alcohol) in close proximity of nerves or sympathetic ganglia is said to be effective for the relief of long lasting pain in conditions such as trigeminal neuralgia.
  - ❖ Antidote for methanol and ethylene glycol.
- Preservative—Rectified spirit (90 to 95 % ethanol) is used as a preservative for viscera, for chemical analysis.
- Fuel.
- Ethanol is used to extract nucleic acids from whole tissue or tissue culture in virtually all biotechnology processes.

Usual Fatal Dose

- One pint (approximately 550 ml) or quart (two pints or approximately 1100 ml) of a strong distilled spirit such as whisky taken in a short span of time can be lethal.
- The usual fatal dose corresponds to approximately 6 grams of ethanol/Kg body weight (adult); 3 gm/Kg (child).
- In terms of blood alcohol, a level in excess of 400 to 500 mg/100 ml is usually considered to be lethal. However there is a great deal of controversy regarding this since there are case reports of individuals succumbing to much lower blood alcohol concetration (BAC), while there have been reports of survival even with a BAC of over 1000 mg%.

Toxicokinetics

- Ethanol is toxic by oral, inhalation, subcutaneous, intravenous, intra-arterial, intraperitoneal, and dermal routes.
- Following oral administration, ethanol is rapidly absorbed from the stomach (20%) and small intestine (80%). Maximum or peak alcohol concentration in blood is reached in 30 to 90 minutes following the last drink. Many factors can delay absorption: undiluted ethanol (by provoking pylorospasm), presence of food, delayed gastric emptying due to any cause, and presence of congeners in alcohol. Vapourised ethanol can be rapidly absorbed by inhalation leading to intoxication. Following an equivalent dose of ethanol, women achieve a higher blood alcohol level than do men as a result of decreased gastric alcohol dehydrogenase activity. It is also a fact that liver damage occurs after

consumption of relatively smaller quantities of alcohol in women as compared to men.

- More than 90% of ethanol ingested is metabolised in the body, and only 5 to 10% is excreted unchanged by the kidneys, lungs, and sweat. Excretion of ethanol by the lungs obeys **Henry's Law** : *the ratio between the concentration of ethanol in the alveolar air and the blood is constant*. This alveolar air/blood constant (1 : 2100) forms the basis for reliably estimating blood alcohol concentration by breath analysis.
- Metabolism of alcohol is accomplished through 3 pathways in the liver—
  - ❖ 1. Alcohol dehydrogenase pathway (in the cell cytosol): This is the main pathway, by which hydrogen is transferred from ethanol to nicotine adenine dinucleotide (NAD), reducing it to NADH. The ratio of NAD to NADH (redox potential) is therefore dramatically altered which contributes to the development of metabolic abnormalities such as alcoholic ketoacidosis, impaired gluconeogenesis, and alterations in lipid metabolism. The acetaldehyde that is formed is converted to acetic acid by aldehyde dehydrogenase, which in turn is converted to acetylcoenzyme A and enters the Krebs (citric acid) cycle where it is metabolised to carbondioxide and water.
  - ❖ 2. Microsomal ethanol oxidising system (MEOS, located on the endoplasmic reticulum): This system becomes important when ethanol use becomes chronic. The ability of ethanol to stimulate the MEOS system forms the basis for interactions between ethanol and a number of other drugs metabolised by this system. Half-lives of several drugs are shortened in chronic alcoholics because of accelerated metabolism, e.g. phenytoin, methadone, tolbutamide, isoniazid, warfarin, etc. There are also indications that chronic ethanol abuse may potentiate paracetamol hepatotoxicity.
  - ❖ 3. Peroxidase-catalase system (in the hepatic peroxisomes).
  - ❖ In adults, the average rate of ethanol metabolism is 100 to 125 mg/kg/hr in occasional drinkers, and upto 175 mg/kg/hr in habitual drinkers. The blood alcohol level generally falls at a rate of 15 to 20 mg/100 ml/hr. This may be higher (upto 30 mg/100 ml/hr) in chronic alcoholics.

Mode of Action

- Till recently it was postulated that ethanol depresses the CNS by dissolving in the cell's lipid membrane and causing disorganisation of the lipid matrix (membrane fluidisation). However this mechanism has been challenged by studies which demonstrated that such membrane fluidisation occurred only at ethanol concentrations much above the pharmacologic range, and also that the same changes can be produced by minor temperature changes which produce no signs of intoxication.
- Now there are two theories which are gaining popularity.
  - ❖ According to one, ethanol acts by enhancing gamaaminobutyric acid (GABA)-nergic function through

interaction with GABA A receptors and associated chloride ion channels. However some investigators are not convinced by this theory.

- ❖ The second theory which appears to be more convincing has to do with N-methyl-d-aspartate (NMDA) ligand-gated, glutamate receptors. NMDA receptors mediate neurotoxicity by increasing permeability to calcium and regulate neuronal long-term potentiation. Studies demonstrate that in the acute form of ethanol use, NMDA receptor function is inhibited, while chronic ethanol use results in up-regulation of NMDA receptors.

- ■ Pharmacological effects of ethanol—
  - ❖ CNS: Ethanol is a CNS depressant but produces some apparently stimulating effects initially because of depression of inhibitory control mechanisms in the brain. First, those mental processes which depend on training and previous experience are affected (memory, concentration, and insight). Later the person becomes expansive, garrulous and may demonstrate emotional lability with mood swings. There are acompanying sensory and motor disturbances. With severe intoxication there is general impairment of CNS function, and finally coma supervenes. Acute ethanol use at bedtime interferes with normal sleep pattern, and with chronic use marked fragmentation of sleep occurs.
  - ❖ CVS: In moderate doses, ethanol produces tachycardia and vasodilation of cutaneous vessels with resultant warm and flushed skin. However no beneficial increase in coronary blood flow occurs; in fact there may be appreciable vasoconstriction which can aggravate existing angina. In spite of this fact, recent studies have indicated that regular use of moderate amounts of ethanol is associated with reduced risk for coronary heart disease (**Box 14.1**).
  - ❖ GIT: Ethanol normally stimulates salivary and gastric secretions, but if the concentration is too high (> 40%) they are inhibited, and the GI mucosa becomes congested and inflamed leading to erosive gastritis. Regular intake of excessive amounts of ethanol leads to chronic gastritis, pancreatitis, and cirrhosis of liver.
  - ❖ Genito-urinary: Ethanol induces diuresis by inhibition of antidiuretic hormone (ADH). There is a popular misconception (perpetuated in pulp fiction and films) that ethanol is an aphrodisiac. While it is true that there is often enhanced sexual inclination with (sometimes) aggressive behaviour, this is due to loss of inhibition and restraint rather than the result of sexual stimulation. Objective measurements in human beings of penile tumescence and vaginal pressure show that ethanol actually significantly decreases sexual responsiveness in both men and women. Chronic ethanol consumption can lead to impotence, sterility, testicular atrophy, and gynaecomastia (because of hyperestrogenisation, and reduced production as well as enhanced metabolic inactivation of testosterone). In women, there is increased predisposition to breast cancer.

Clinical Features

1. **Acute Poisoning** (Intoxication, Inebriation):
   a. Initially, ethanol produces excitement which progresses to loss of restraint, behavioural changes, garrulousness, slurred speech, ataxia, unsteady gait, drowsiness, stupor, and finally coma (**Table 14.2**).
   b. Rarely, alcohol induces allergic reactions (usually in the form of urticaria, nasal congestion, headache, etc.), which may be severe and may even result in death.
   c. There are also reports of cardiac dysrhythmias (especially atrial fibrillation) associated with binge drinking.
   d. Through all the 7 stages of ethanol intoxication, a distinct odour is perceptible in the breath of the individual. It is however not the alcohol itself which imparts this odour but other nonalcoholic constituents that give a particular flavour depending on the type of beverage consumed (wine, beer, whisky, etc.). It is important to remember that even after a person has completely sobered up from the effects of ethanol, the odour may persist in the breath for a considerable period of time.
   e. Ethanol is a mydriatic, but towards terminal stages (stages of stupor and coma), the pupils may become constricted, only to dilate once again at about the time of death. The **McEwan sign***(a perennial favourite of textbooks on toxicology) is highly **unreliable** and must not be depended upon for diagnosis of alcoholic coma.
   f. Hypothermia is common.
   g. Hypotension and tachycardia may be present. Atrial fibrillation and atrioventricular block have been reported with acute overdose. Cardiac output may be decreased in persons with pre-existing cardiac disease. After consuming recreational amounts of alcohol, persons suffering from variant angina may experience chest pain due to coronary artery spasm or myocardial ischaemia. Sudden cardiac failure, arrhythmias, subclinical left ventricular dysfunction, and other morphologic abnormalities of the heart can occur with chronic heavy abuse. Alcoholic cardiomyopathy has insidious onset and can be clinically inapparent. Symptoms of alcoholic cardiomyopathy are often present for an average of 10–12 months before diagnosis, but as much as 85% of cases have not been diagnosed through routine screening, unless angiography was performed.
   h. Bradypnoea may occur early, and tachypnoea may develop in cases of metabolic acidosis.
   i. Poor control of eye movements, with diplopia and nystagmus may occur and alter vision and performance. Acute overdoses of ethanol have caused spontaneous (not gaze-evoked) horizontal nystagmus. Amblyopia due to peripheral neuritis has been reported in chronic alcoholics. Bilaterally decreased vision occurs. Vitamin deficiencies correlate with the ocular defects and early administration of B vitamins causes recovery in some patients.

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* Pinching the skin of the face or neck, or light slapping, is supposed to dilate the constricted pupils of alcoholic coma momentarily.

Box 14.1: Ethanol and cardiac health

Recent attention in the medical press has focussed on the reported association between "moderate" alcohol consumption and decreased risk of sudden death, especially from cardiovascular causes. This has met with angry reactions from anti-liquor campaigners culminating in an emotional and sometimes bitter controversy. The following discussion is an attempt at presenting and analysing the facts available at present in a critical, unbiased manner.

To begin with, it must be admitted indubitably that alcohol is a vasodilator. But this is not the reason for alcohol's beneficial effects on the heart since the vasodilation is mostly confined to cutaneous vessels producing the warm, flushed skin of acute intoxication. There is virtually no increase in coronary blood flow in human beings. In fact, in individuals with existing coronary artery disease, ethanol decreases the time period of exercise required to precipitate angina and to produce changes in the ECG which are indicative of myocardial ischaemia. It has been proved conclusively that ethanol induces the release of catecholamines from the adrenal medulla, and while intoxicating doses can produce widespread vasodilation, moderate doses can cause appreciable vasoconstriction in such vital areas as the heart and the brain.

However, several studies in the recent past indicated a clear negative corelation between chronic ingestion of small amounts of ethanol and the incidence of coronary heart disease, beginning with the Kaiser-Permanente epidemiologic study done way back in 1974 which was at first received with scepticism by the scientific community. But it marked the beginning of a barrage of studies all around the globe over the next two decades establishing the clear association between moderate alcohol consumption and reduced risk of coronary heart disease. After much study and deliberation investigators have now come to the conclusion that the protective effect of ethanol on the heart is because it increases the concentration of high density lipoproteins (HDL) in the plasma, while at the same time decreasing that of low density lipoproteins (LDL). It is well known that the lower the concentration of HDL in the blood the greater is the risk for developing coronary heart disease (CHD). The reverse is true for LDL. Today several studies have established a convincing relationship between alcohol intake and the level of protective HDL, including both its HDL2 and HDL3 subfractions. Angiographic studies have also demonstrated that moderate alcohol consumers have less severe coronary atherosclerosis than teetotallers. Among the different types of alcoholic beverages there is evidence to suggest that wine (especially red wine) offers maximum protection.

It is now also clear that apart from its beneficial effect on cholesterol levels, alcohol has favourable effects on haemostatic factors such as plasma fibrinogen, fibrinolytic activity, and platelet adhesiveness. Investigations have demonstrated a clear-cut association between ethanol consumption and plasma levels of tissue plasminogen activator which is a major component of the fibrinolytic system. Increased fibrinolytic activity is very important in the prevention of coronary thrombosis and supplements the anti-atherosclerotic effect via the HDL-cholesterol levels. Even forensic autopsies have pointed towards a positive asociation between moderate drinking and cardiac health.

Having come to this conclusion, it must be emphasized that the purported beneficial effects rapidly evaporate as consumption is increased beyond desirable levels, and in fact the deleterious effects would then be much more than in those who don't drink at all. So the question arises: what is "moderate" alcohol consumption ? Unfortunately the definition of moderation varies from one study to another, but the balance of evidence is that the daily consumption must not exceed 2 to 3 drinks per day. A standard drink is roughly the equivalent of 45 ml of distilled spirits (15.1 gm alcohol) or 150 ml of wine (10.8 gm alcohol), or 350 ml of beer (13.2 gm alcohol).

In the final analysis, while physicians may use their discretion in advising patients about the beneficial effects of moderate ethanol consumption, it must be emphasized that safe drinking is not a panacea for sound cardiac health.

The benefits documented thus far need further study and irrefutable confirmation.

Table 14.2: Acute Alcohol Poisoning (Intoxication, Inebriation)

Blood Alcohol Concentration (mg/100 ml)	Stage of Intoxication	Clinical Features
0 – 50	Sobriety	Near normal behaviour
50 – 100	Euphoria	Feeling of well being, sociability, talkativeness, increased self confidence, decreased inhibitions, fine movements affected
100 – 150	Excitement	Emotional instability, impairment of memory and comprehension, increased reaction time, mild ataxia
150 – 200	Confusion	Disorientation, confusion, vertigo, diplopia, ataxia, slurred speech, staggering gait
200 – 300	Stupor	General inertia, diminished response to stimuli, inability to stand or walk, vomiting
300 – 500	Coma	Unconsciousness, abolished reflexes, subnormal temperature, incontinence of urine and faeces, respiratory compromise
> 500	Death	Death due to respiratory failure

The 7 stages can be remembered as a series of D's : Decent, Delighted, Delirious, Dazed, Dejected, Dead drunk, Dead.

j. Lactic or ketoacidosis may occur. Acidosis may occur due to metabolic disturbances, such as NADH over-production, oxidation of ethanol, decreased lactate utilisation, and inhibition of hepatic gluconeogenesis.

Hypoglycaemia which can result in seizures and coma is a serious complication of acute alcoholic intoxication, especially in children.

k. Medicolegally, stages 3 and 4 of alcoholic intoxication

(stages of excitement and confusion) are the most important, since most of the offences associated with drinking are committed during these two stages. It is pertinent to mention that stage 7 (death) is extremely rare in pure ethanol ingestion. In most cases there is recovery after prolonged sleep, with some residual after effects (*hangover*), consisting of headache, irritability, lethargy, nausea, and abdominal discomfort. While the last mentioned is mainly due to gastritis produced by ethanol, the other symptoms are actually the result of congeners and impurities present in alcoholic beverages which cause mild cerebral oedema. Part of the hangover may also be the result of hypoglycaemia induced by ethanol.

l.	While the subject of some professional dispute, some data indicate that a small number of people may be exceptionally sensitive to ethanol, exhibiting combative and irrational behaviour after ingesting non-intoxicating amounts. This has been termed pathological intoxication or ethanol idiosyncratic intoxication.

m.	Alcoholic intoxication (through all the stages) can mimic several conditions which can lead to errors in diagnosis. **Table 14.3** lists the differential diagnosis for acute ethanol intoxication.

Diagnosis

1.	*Bedside test*—Place 1 ml of unknown solution plus 1 ml of acetic acid and 1 drop of H_2SO_4 in a test tube and heat gently for 1 minute. A characteristic, strong fruity odour (due to ethyl acetate) is positive for ethanol.

2.	*Blood alcohol level*—The blood alcohol concentration (BAC) estimated by immunoassay or gas chromatography is the commonest method employed by laboratories in India. Although accurate, the results of these tests are often delayed several hours and are not really appropriate in the clinical scenario.

3.	Determine serum electrolytes, glucose, ethanol. Hypoglycaemia, hypokalaemia, and metabolic acidosis (lactic or ketoacidosis) may occur.

4.	BUN, creatinine, liver transaminases, and CPK may be useful in identifying secondary effects, such as hepatotoxicity (chronic ethanol use), respiratory depression, or rhabdomyolysis (if seizures are present).

5.	*Osmolality*: Serum or plasma osmolality allows estimation of blood ethanol level. A blood ethanol concentration of 150 mg% (32.5 mmol/L) increases osmolality by 21.6 milliosmoles/kg water. The following equation is said to give good correlation with blood ethanol concentration: BAL (g/L) = osmolal gap/27

6.	Qualitative determination of urinary ethanol is commonly included in a toxicology screen. However, urinary ethanol levels may be falsely elevated in patients with diabetes.

2.	**Chronic Poisoning** (Alcoholism, Ethanolism):

a.	Alcoholism is a condition in an individual who consumes large amounts of alcohol over a long period of time. It is characterised by
– a pathological desire for alcohol intake
– black-outs during intoxication
– withdrawal symptoms on ceasing alcohol intake.

b.	Unfortunately many patients are not diagnosed correctly as alcoholics by their doctors. A high index of suspicion is important, particularly in cases where there are repeated consultations for vague symptoms or minor accidents. If in doubt, a drinking history should be taken in which the patient is asked to describe a typical week's drinking.
– Consumption should be quantified in terms of units of alcohol. One unit* contains approximately 8 to 10 grams of alcohol and is the equivalent of half a pint of beer, a single measure (30 ml) of spirits, or a glass of table wine. Current opinion suggests that drinking becomes a problem at levels above 21 units/week for men and 14 units/week for women.

c.	Laboratory tests are useful in confirming alcohol abuse. Mean corpuscular volume (MCV) or gamma-glutamyl transpeptidase (gamma GT) is raised in approximately 50% of problem drinkers.

d.	Medical complications of alcoholism:
– *GIT*—gastritis, periodic diarrhoea, increased incidence of oropharyngeal and oesophageal cancer.
– *Liver*—fatty liver with portal hypertension, hepatitis (**Fig 14.1**), cirrhosis (**Fig 14.2**), increased incidence of hepatic carcinoma.

Table 14.3: Differential Diagnosis of Alcoholic Intoxication	
Pre-Coma	*Coma*
Barbiturate ingestion (and other similar drugs)	Hypoglycaemic or Diabetic coma
Carbon monoxide poisoning	Coma due to hypnotics, sedatives, and other drugs
Hypoglycaemia	
Head injury (post-concussional state)	
Cerebrovascular accident	
Psychotic states	
Disseminated sclerosis (and other similar neurological afflictions)	

* Not the same as "one drink". See page no 184

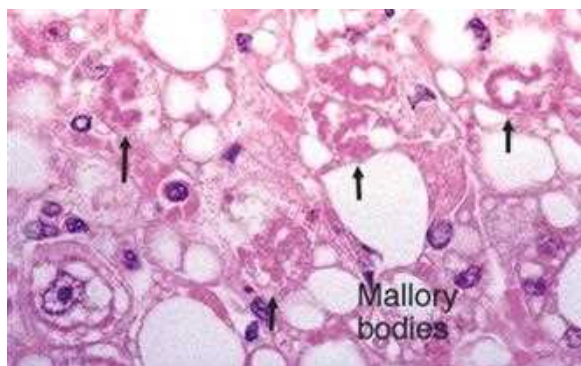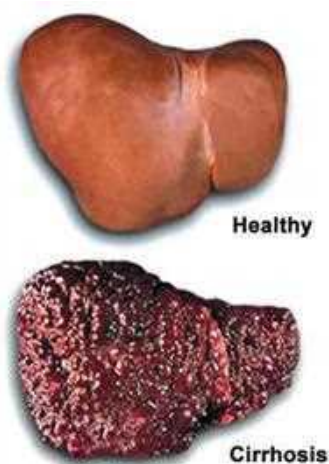**Fig 14.1:** Alcoholic hepatitis

Fig 14.2: Normal and cirrhotic liver

Fig 14.3: Mechanism of chronic alcoholic pancreatitis
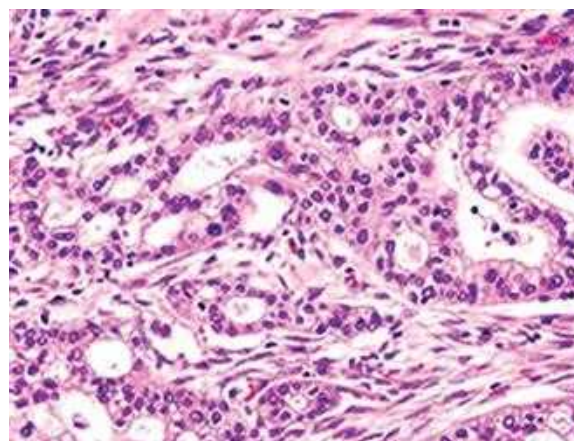
Fig 14.4: Pancreatic adenocarcinoma

Fig 14.5: Alcoholic cardiomyopathy

– *Pancreas*—acute or chronic pancreatitis (**Fig 14.3**), pancreatic cancer (**Fig 14.4**).
– *CVS*—cardiomyopathy (**Fig 14.5**), dysrhythmias, hypertension.
– *CNS*—polyneuropathy, cerebellar degeneration, demyelination of corpus callosum (Marchiafava-Bignami disease), amblyopia, stroke.
– *RS*—aspiration pneumonia, alcohol-induced asthma.
– *Endocrine*—hypogonadism and feminisation in males, amenorrhoea, menorrhagia, and infertility in females, pseudo-Cushing syndrome.
– *Blood*—anaemia, thrombocytopenia.
– *Skeletal muscle*—myopathy.
– *Neuropsychiatric*—memory disturbances (amnesia, blackout), delusions, delirium tremens, Wernicke's encephalopathy, Korsakoff's psychosis, dementia, alcoholic hallucinosis.
– *Teratogenecity*—Foetal Alcohol Syndrome (FAS)—this syndrome is characterised by facial dysmorphias (**Fig 14.6**) and other congenital abnormalities, prenatal growth retardation, and neurodevelopmental abnormalities, including developmental d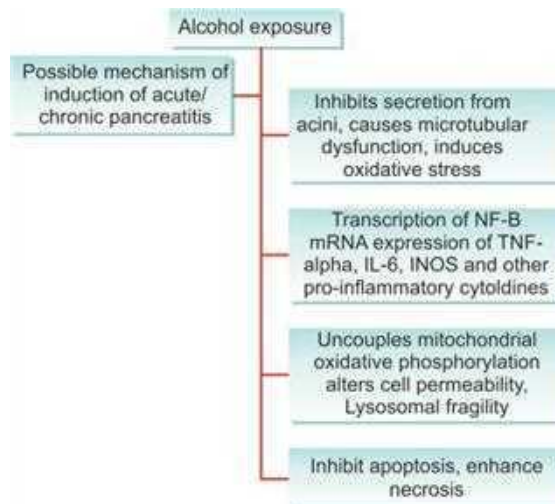elay or mental retardation, in some children o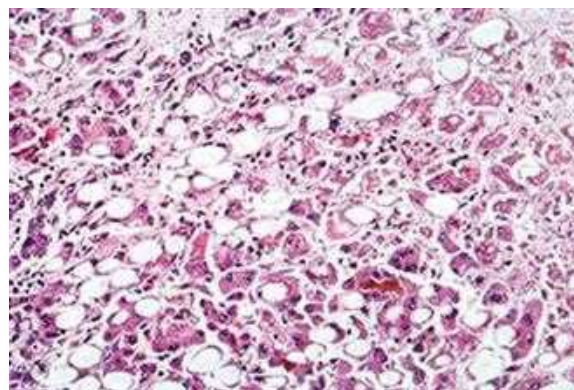f mothers who abused ethanol during pregnancy. Main abnormalities reported include cleft palate, spina bifida, ventricular and atrial septal defects, tetralogy of Fallot, pulmonary stenosis, and patent ductus arteriosus. Attention deficits, short-term memory, sequential processing deficits, and
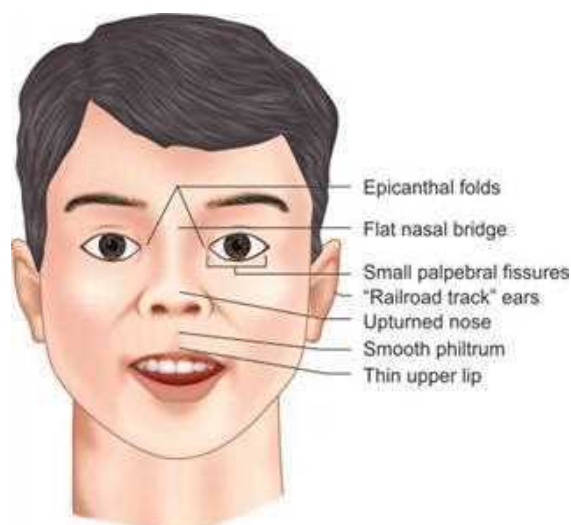
Fig 14.6: Foetal alcohol syndrome (facial features)

behavioural problems have been associated with FAS in school-age children.

– *Carcinogenicity*—alcohol consumption has been associated with various cancers, including liver cancer, oesophageal cancer, breast and prostate cancer, and colorectal cancer.

- Distilled liquors are more strongly linked with oesophageal cancers than wine or beer. This may be due to an irritative effect of alcohol on the digestive tract.
- Studies on the possible relationship between drinking and liver cancer have produced mixed results: some have shown an association while others have not.
- Ethanol consumption has been associated with a linear increase in breast cancer incidence in some studies.
- Ethanol has also been implicated in increasing the risk of cancer of the larynx, oesophagus, mouth, and pharynx in smokers. Ethanol should be regarded as a possible human co-carcinogen.
- Studies have also indicated a positive association between colorectal cancer and alcohol consumption, mainly at high levels of alcohol consumption.

e. Withdrawal syndromes: Sudden cessation of alcohol intake in a chronic alcoholic can provoke a withdrawal reaction which may manifest as one of the following:

– Common abstinence syndrome—
  - *Onset* : 6 to 8 hours after cessation of alcohol.
  - *Features*: Tremor affecting hands, legs, and trunk ("the shakes"), agitation, sweating, nausea, headache, insomnia.

– Alcoholic hallucinosis—
  - *Onset* : 24 to 36 hours.
  - *Features*: Objects appear distorted in shape, shadows seem to move, shouting or snatches of music may be heard.

- *Treatment*: Administration of phenothiazines (e.g. chlorpromazine 100 mg, 8th hourly).

– Seizures (Rum fits)—
  - *Onset* : 7 to 48 hours.
  - *Features*: Clonic-tonic movements, with or without loss of consciousness.

– Alcoholic ketoacidosis—
  - *Onset* : 24 to 72 hours.
  - *Features*: Occurs during withdrawal as well as after episodes of heavy drinking. In many cases there is a preceding history of GI disturbance such as gastritis or pancreatitis which has led to sudden diminution of alcohol intake. To compensate for the loss of carbohydrates and depleted glycogen stores, the body mobilises fat from adipose tissue as an alternative source of energy. There is a corresponding decrease in insulin and an increased secretion of glucagon, catecholamines, growth hormone, and cortisol. Fatty acids are oxidised and the final product, acetylcoenzyme A is converted to acetoacetate. This in turn is converted to beta-hydroxybutyrate because of ethanol-induced low redox state. Volume depletion in these patients interferes with the renal elimination of acetoacetate and beta-hydroxybutyrate and contributes to the acidosis. Paradoxically, the arterial pH may be normal due to a compensatory respiratory alkalosis and a primary metabolic alkalosis due to vomiting. Clinical features include drowsiness, confusion, tachycardia, and tachypnoea, progressing to Kussmaul breathing pattern and coma.
  - *Diagnosis*:
    » Blood alcohol concentration is typically not high.
    » Blood glucose may be slightly elevated.
    » Since the nitroprusside reaction detects only acetone and acetoacetate and not beta-hydroxybutyrate, the assay for ketones is likely to be only weakly positive.
    » There is an elevated anion-gap metabolic acidosis. Serum ketones are markedly elevated.
    » Hypokalaemia and hypochloraemia are often present.
  - *Treatment*:
    » Correction of volume depletion—infusion of solutions of normal saline with dextrose.
    » Potassium supplementation may be required.
    » Thiamine (50 to 100 mg) to prevent development of Wernicke-Korsakoff syndrome.

– Delirium tremens (DTs)—
  - *Onset* : 3 to 5 days.
  - *Features*: There is a dramatic onset of disordered mental activity characterised by clouding of consciousness, disorientation, and loss of

recent memory. There are vivid hallucinations which are usually visual, but sometimes auditory in nature. There is severe agitation with restlessness and shouting, tremor, and truncal ataxia. Insomnia is prolonged. Autonomic disturbances include sweating, fever, tachycardia, hypertension, and dilated pupils. Dehydration and electrolyte disturbances are characteristic. Blood testing shows leucocytosis and impaired liver function.

- *Treatment*:
  - » Well lit, reassuring environment.
  - » For agitation—diazepam 10 mg IV initially, and then 5 mg every 5 minutes until full control, followed by 5 to 10 mg orally 3 times daily.
  - » Thiamine in the usual dose.
  - » Correction of fluid and electrolyte imbalance.

– Wernicke-Korsakoff syndrome – This is very rare as a withdrawal phenomenon, and is actually the result of thiamine deficiency due to impoverished diet in an alcoholic.

- *Features*: Wernicke's encephalopathy is the acute form and is characterised by drowsiness, disorientation, amnesia, ataxia, peripheral neuropathy, horizontal nystagmus, and external ocular palsies. It results from damage to mammillary bodies, dorsomedial nuclei of thalamus, and adjacent areas of grey matter. When recovery from Wernicke's encephalopathy is incomplete, a chronic amnesic syndrome develops called Korsakoff's psychosis which is characterised by impairment of memory and confabulation (falsification of memory).
- *Treatment*:
  - » For Wernicke's encephalopathy— administration of thiamine 50 to 100 mg IV daily, infused slowly in 500 ml of fluid for 5 to 7 days, and fluid replacement.

Treatment

1. **Acute Poisoning** (Intoxication, Inebriation):
   a. Airway protection, ventilatory support.
   b. Activated charcoal is NOT useful.
   c. Stomach wash.
   d. Thiamine 100 mg IV
   e. Dextrose
      – *Indications*—If rapidly determined bedside glucose level is less than 60 mg/100ml, or if rapid determination is not available.
      – *Adult*—25 grams (50 ml of 50% dextrose solution) intravenously; may repeat as needed.
      – *Paediatric*—0.5 to 1 gram dextrose per kg as 25% dextrose solution or 10% dextrose solution (2 to 4 ml/kg).
      – *Precautions*—Glucose administration should

necessarily be preceded by 100 mg of thiamine IV or IM if chronic alcoholism or malnutrition is suspected, to prevent development of Wernicke's encephalopathy.

f. Intravenous fluids.

g. A variety of drugs have been tried to hasten the elimination of ethanol or reverse its intoxicating effects, including naloxone, physostigmine, and caffeine. None of them have been proved to be truly effective. Recently, flumazenil (3 mg IV) has been shown to be effective (in experimental studies) in reversing the respiratory depression associated with ethanol ingestion.

h. Haemodialysis can eliminate ethanol 3 to 4 times more rapidly than liver metabolism. May be useful in patients with excessive blood levels, impaired hepatic function and in those whose condition deteriorates in spite of maximal supportive measures. However, it is unusual for dialysis to be necessary to treat even severe ethanol intoxication.

2. **Chronic Poisoning:**

   a. Treatment of withdrawal—apart from the treatment measures outlined earlier (*vide supra*), the following drugs have also been tried with varying degrees of success:
      – Carbamazepine—It has been shown to be effective in treating alcohol withdrawal, including delirium tremens.
      – Chlormethiazole—It is one of the most popular drugs used for alcohol withdrawal abroad, and is administered in a rapidly reducing dosage over 6 to 7 days. However it is itself associated with a strong abuse potential.
      – Clonidine and gamma-hydroxybutyric acid have also shown promising results in the treatment of withdrawal symptoms. The former is given at a dose of 60 to 180 mcg/hr IV, and the latter 50 mg/kg, orally.
      – One of the most recent entrants is tiapride, an atypical neuroleptic agent which is a selective dopamine D2-receptor antagonist. But it should be given only as an adjunct while seizures, hallucinosis, etc., are being taken care of by other drugs. It is effective in ameliorating psychologic distress associated with alcohol abstinence. For delirium, the recommended dose is 400 to 1200 mg/day 6th hourly, while the maintenance dose subsequently to help abstain from alcohol should not exceed 300 mg/day.

   b. Aversion therapy—The main aim in the treatment of alcoholism is to gradually wean away the patient from the clutches of ethanol, once the acute manifestations of withdrawal have been taken care of. This process referred to quite loosely as de-addiction or detoxification, should be undertaken only after admission to a hospital over a period of several days, under close medical supervision. The insatiable craving for alcohol that is often present must be tackled effectively, and

usually requires strongly deterrent measures. Many methods have been tried in this connection, and one of the more succesful ways is to administer a drug called disulfiram. It is a disulfide molecule (tetraethylthiuram) which interferes with the oxidative metabolism of ethanol at the acetaldehyde stage, as a result of which acetaldehyde accumulates producing unpleasant symptoms* (**Table 14.4**).

  – *Principles of disulfiram therapy*—

    - Ensure that the patient is off alcohol for a minimum period of 12 hours before starting therapy.
    - Administer disulfiram only by the oral route.
    - Warn the patient explicitly that while he is on disulfiram, alcohol must not be consumed even in small quantity since it can provoke a severe (and sometimes fatal) reaction. He must also avoid taking medicinal preparations containing alcohol, including topical preparations.
    - The usual dose of disulfiram is 250 mg/day which may have to be taken for an indefinite period of time. Such chronic use unfortunately often produces side effects like halitosis (rotten egg odour due to sulfide metabolites), pruritis, headache, drowsiness, impotence, peripheral neuropathies, depression, mania, psychosis, and hepatotoxicity. The patient must be closely monitored and dosage reduced if necessary.
    - Other than disulfiram, there are numerous other substances which evoke a similar reaction with ethanol (**Table 14.5**).

  c. Supportive psychotherapy—More than individualised psychotherapy, it is group therapy which is effective in the long, term management of abstinence. Groups provide an opportunity for resocialisation and a sense of mutual commitment. Self-support organisations such as **Alcoholics Anonymous** (AA) play an important role. The AA which had its origins in the USA in 1935 now has more than 53,000 groups spread worldwide including India. The only requirement for membership is a "desire to stop drinking". There is no membership fee and the organisation functions on a self-supporting basis through contributions from the members. Local addresses of AA groups functioning in a given region can be located in the telephone directory of that area. Meetings are generally held once a week and are informal affairs conducted in a friendly atmosphere. Generally two or three speakers share their experiences during each session relating to their addiction and recovery.

Autopsy Features

1. Congested conjunctivae.
2. Characteristic odour in the vicinity of the mouth and nose, and in the gastric contents.
3. Congestion of GI tract.
4. Pulmonary and cerebral oedema.
5. Stigmata of chronic alcoholism may be present (fatty or cirrhotic liver, cardiomyopathy, and characteristic lesions in other organs).
6. Chemical analysis of viscera and body fluids:
   a. Apart from the routine viscera and body fluids, one half of brain (or one cerebral hemisphere), as well as samples of CSF and vitreous humor should be collected and preserved for chemical analysis.
   b. Blood should always be collected from a peripheral vein such as femoral vein and never directly from the heart. Caution must be exercised in interpreting the results of chemical analysis conducted on putrefying dead bodies since postmortem production of ethanol occurs in such

Table 14.4: Disulfiram-Ethanol Reaction

GIT	CNS	CVS	Skin	RS
Abdominal pain	Blurred vision	Syncope	Sweating	Tachypnoea
Nausea	Confusion	Hypotension	Flushing	
Vomiting	Vertigo	Tachycardia	Sensation of heat	
	Headache	Dysrhythmias	Pruritis	
	Weakness	Chest pain		
		Myocardial infarction		

Table 14.5: Substances Producing Disulfiram-like Reaction With Ethanol

Pharmaceuticals		Chemicals	Miscellaneous
Antimicrobials	Other Drugs	Calcium cyanamide	Activated charcoal
Cephalosporins	Chlorpropamide	Carbon di sulfide	Mushrooms
Chloramphenicol	Glipizide	Hydrogen sulfide	(Coprinus
Furazolidone	MAO Inhibitors	Tetra ethyl lead	Clitocybe)
Griseofulvin	Tolbutamide	Tri & Tetra chloro ethylene	
Metronidazole			
Nitrofurantoin			

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* There are several therapeutic drugs which react with disulfiram in diverse ways – amitryptiline, benzodiazepines, coumarin derivatives, isoniazid, metronidazole, paraldehyde, phenytoin, rifampicin, & theophylline.

cases due to the action of certain micro-organisms. This can result in a BAC of upto 20 to 30 mg/100 ml even when no alcohol had been consumed at all prior to death. Similar erroneous results may be obtained (in the case of a non-putrefied body) in a blood sample that has not been properly preserved. In all such cases the urine should be mandatorily tested, and if no alcohol is detected it can be safely presumed that the BAC is false due to postmortem production. In the absence of a urine sample, bacteriological examination of blood should be carried out before interpreting the results of chemical analysis.

c. As far as urine is concerned, a simple conversion factor was developed to convert urine alcohol concentration (UAC) to blood alcohol concentration (BAC):

BAC = – 5.6 + 0.811 UAC

This formula however cannot always predict the BAC accurately, and is more useful in corroborating rather than predicting BAC.

Forensic Issues

The use or abuse of ethanol is associated frequently with medicolegal implications and consequences. Alcohol abuse is prevalent worldwide. Efforts have been made to totally prohibit alcohol consumption in different countries without much success (with the possible exception of those countries where religious law is in force). Such attempts uaually lead to illicit brewing and consumption with even more serious consequences. At present in India, total prohibition is in force only in Gujarat. Efforts to implement the same in Tamilnadu, Andhra Pradesh, and Haryana met with dismal failure.

All over India (except Gujarat where prohibition is in force), the mere consumption of alcohol and consequent drunken behaviour in themselves do not constitute any offence. Only when the drunken individual behaves in such a manner as to become a public nuisance, or poses a threat, or actually commits an act endangering the life or property of another person (or even his own), will the law take cognisance of the fact.

1. **Drunkenness**
    a. A doctor is sometimes called upon by the police to examine an individual who has been taken into custody for creating public annoyance in a state of intoxication, or for driving a vehicle under the influence of alcohol, or for being involved in a criminal offence after drinking.
    b. In such a case, the doctor must exercise great caution before coming to a conclusion. He must first be familiar with the exact meaning of the term 'drunkenness". An individual can be certified to be drunk only when there is evidence that "he was so much under the influence of alcohol as to have lost control of his faculties to such an extent as to render him unable to execute safely the occupation in which he was engaged at the material time". The essence of this definition is that the doctor must search for evidence indicating that the individual concerned was *under the influence of alcohol.* The

smell of ethanol in the breath, the pulse rate, dilatation of pupils, colour of the face, etc., give no indication of the degree of intoxication. Conclusion regarding this must be arrived at after a detailed examination with special reference to the state of mind, co-ordination of movements, visual acuity, etc.

c. As in every medicolegal case, before embarking on the physical examination of the individual, the doctor must first obtain his written consent. This must be tempered by the fact that if an individual really is drunk then he is probably in no fit medical condition to give or refuse consent. In such cases, the doctor can proceed with the examination but should not divulge the results or his conclusions until the individual has sobered up and provides valid consent. However, if there is an explicit direction from a judicial court to divulge the results without delay, the doctor must comply with such direction. If an individual refuses consent and is uncooperative, the doctor can proceed with the examination without bothering about this formality if the former has been arrested for a criminal offence and is under the custody of the police (**S. 53 (1), CrPC**). But the requisition in such a case should have been issued by a police officer not below the rank of a Sub-Inspector. The doctor can conduct not only the physical examination of the accused, but can even collect samples of urine or blood for analysis.

d. Procedure of Examination: **Box 14.2**.

e. Sometimes the question is asked (when it is proved that a person had consumed alcohol), as to how much he could have drunk, i.e. the quantity of liquor consumed. To answer this question, two facts must be known: the BAC, and the nature of alcoholic beverage taken. If these are known an estimate can be made as to the minimum quantity of liquor consumed by consulting **Table 14.6**. A rule of thumb is that every ounce of an 800 proof liquor will raise the BAC by 25 mg% (i.e. one peg of distilled spirit, or one glass of wine, or a quarter to half bottle of beer). Average elimination rate is 15 to 20 mg% per hour. As an alternative or supplement to BAC, the level of alcohol can also be estimated in the urine (UAC).

To calculate the BAC from the UAC, multiply the latter by 0.66 which gives a rough estimate. For example, if the UAC is 100 mg%, the BAC would be $100 \times 0.66 = 66$ mg%. It is to be noted however that the first sample of urine voided after the individual was taken into custody by the police must not be used for analysis since there is a likelihood of erroneous interpretation. The urine sample will contain very low concentration of alcohol even after heavy drinking if the person had started consuming alcohol when his bladder was already containing urine. On the other hand, a very high concentration will be obtained if he had emptied his bladder and then commenced drinking heavily. Therefore the person should be asked to empty his bladder and then a second sample is collected after some time which is used for analysis.

Box 14.2: Scheme of examination for certification of drunkenness

Objective:
To decide whether
• The subject is under the influence of alcohol.
• His condition is due to illness or injury.
• It is safe for him to be detained in a police station, or he should be admitted to a hospital.

Consent:
Obtain informed, written consent.

Preliminary Particulars:
• Name, age, sex, occupation, and residential address.
• Identification marks: record at least two permanent marks of identification as for any medicolegal case.
• Time of commencement of examination.
• Escorts: record the name and number of escorting police constable, and the police station to which he is attached.
• History:
  – Has he consumed alcohol? If so, at what time, and what was the nature and quantity consumed?
  – Is he in the habit of consuming alcohol regularly ? If so, since how long and how frequently?
  – Does he suffer from any disease or disability?
  – Is he taking any medication or drugs? If so, what is the nature and dose?

Physical Examination:
• General appearance: state of clothing, behaviour, disposition, etc.
• Speech: normal or slurred or overprecise.
• Breath: odour of alcohol present or absent.
• Stance: does he sway when standing erect with his feet together and eyes closed ?
• Gait: ask him to walk across the room and observe whether the gait is normal or staggering, straight or irregular.
  Ask him to stop or turn around and observe whether there is a delay in response, as well as the manner of turning (tendency to fall).
• Writing: ask him to write or copy a few sentences in the language he is familiar with. Note the time taken, repitition/omission of words, etc.
• Eyes and visual acuity: note whether the eyes are reddened, presence or absence of nystagmus, status of pupils, and test for pupillary reaction to light.
• Vital data: record the pulse, temperature, and blood pressure.
• Reflexes: normal or depressed.
• Muscular coordination : test this by asking the individual to perform a few simple tests:
  – Finger-nose test
  – Buttoning/unbuttoning shirt
  – Picking up pencil/pen from the floor.
• Examine also the cardiovascular, pulmonary, and alimentary systems in the usual way.
• Look for the presence of injuries. Pay particular attention to evidence of head injury.

Mental Examination:
• Memory: test for ability to recall recent events.
• Orientation:
  – to time: ask him to state the approximate time of day, or the day of the week.
  – to space: ask him as to whether he is aware of his present location, the direction in which the entrance to the building lies, etc.

Laboratory Investigations:
• Collect blood and urine samples.
• With reference to the blood sample, about 5 ml drawn from a peripheral vein is usually sufficient.
• The site to be punctured should not be swabbed with surgical spirit since it can result in a false positive test for alcohol.
• Instead the area can be washed with soap and water prior to puncture, and swabbed with spirit after the blood sample has been withdrawn.
• The collected sample of blood must be preserved in a chemically clean container with sodium fluoride as preservative (50 mg for 5 ml).
• Some workers believe that it is desirable to add potassium oxalate (15 mg).
• Refrigeration of the sample or placing it in an icebox is a good alternative.
• For urine sample, the recommended preservative is phenyl mercuric nitrate. Alternatively, sodium fluoride (50 mg/10 ml) can be used.

Opinion :
This should be phrased in one of the following ways –
a. The individual examined has not consumed alcohol.
b. The individual examined has consumed alcohol, but is not under its influence.
c. The individual examined has consumed alcohol and is under its influence.
  Opinion (a) is given if there is no smell of alcohol in the breath and/or laboratory analysis is negative for alcohol; and all the clinical findings are normal.
  Opinion (b) is given if there is smell of alcohol in the breath and/or laboratory analysis reveals the presence of alcohol; but clinical examination reveals only normal findings.
  Opinion (c) is given if there is smell of alcohol in the breath and/or laboratory analysis reveals the presence of alcohol; and clinical examination reveals abnormal findings.

Authentication:
Signature of the medical officer, his name and designation, and the time of concluding the examination.

Table 14.6: Relationship Between Liquor Consumed & Blood Alcohol

Blood Alcohol Concentration (mg%)	Minimum Quantity of Liquor Consumed		
	Beer (litres)	Wine (litres)	Distilled Spirits (ml)
50	0.8	0.2	70
100	1.6	0.3	130
200	3.2	0.7	275
300	4.8	0.9	410
400	6.4	1.3	550
500	8	1.6	690
600	9.6	1.9	825

2. **Ethanol and Crime**

 a. Brawls, assaults (sexual and non-sexual), homicides, and suicides are commonly associated with intoxication.

Even if the assailant was so drunk that he had lost total control over his mental faculties and therefore was not in a position to judge whether his actions were right or wrong, he is still punishable for any criminal act committed by him (**S. 86, IPC**), unless the alcohol was administered to him without his knowledge or against his will (**S. 85, IPC**).

3. **Ethanol and Traffic Accidents**

 a. It is well known that consumption of ethanol and consequent intoxication has adverse effects on the driver of a vehicle in the form of visual blurring, motor incoordination, impairment of judgement, and increased reaction time. The Law Reform Commission Report No. 4 issued by the Australian government in 1976 succinctly correlates the BAC with driving impairment as follows:
    – *BAC upto 50 mg%*—driving ability of most individuals is unaffected, though there may be slight impairment in some individuals.
    – *BAC 50 to 100 mg%*—most people are affected to varying degree.
    – *BAC 100 to 200 mg%*—there is severe impairment of driving ability with increased liability to accident.
    – *BAC over 200 mg%*—there is a high likelihood of an accident.

 b. Driving a vehicle on a public thoroughfare under the influence of alcohol (or any other intoxicating drug) is an offence in almost every country of the world. In India, it is an offence punishable under Section 185 of the Motor Vehicle Act (1988, Amended 1994) in the form of a fine which can extend upto Rs. 2000, or imprisonment which can extend upto 6 months, or imposition of both. For a second offence committed within 3 years of the previous one, the punishment is enhanced to Rs. 3000, or 2 years, or both.

 c. Many countries permit mild degrees of intoxication, but beyond a certain statutory BAC, it becomes a culpable offence. For, e.g. the statutory limit is 20 mg% in Poland and Sweden, 50 mg% in Finland, Norway, Netherlands, Yugoslavia, Portugal, and Greece, 80 mg% in Denmark, Germany, Belgium, UK, France, Switzerland, Austria, Italy, and Spain, 100 mg% in Ireland, and 80 to 150 mg% in the different states of the USA. Some countries do not allow even traces of alcohol in the blood of a driver, e.g. Russia, Czechoslovakia, Hungary, Bulgaria, Romania, and Turkey. In India, the statutory limit has been fixed at 30 mg%. But the general practice is to convict only on the basis of a medical examination, i.e. when it is proved that the driver of the vehicle was under the influence.

 d. Breathalyser*—In many countries including India, traffic police carry special equipment in the form of breathalysers (**Fig 14.7**) to detect alcohol in the breath of a suspect driver. It serves as an "on the spot test". Estimates of BAC based on breath analysis are legally admissible as per S.185 of the Motor Vehicles Act, 1988 (amended 1994). The basic principle underlying a conventional breathalyser involves calculating the weight of alcohol which accompanies 190 mg of CO_2

Fig 14.7: Digital breathalyser

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* Also referred to as alcometer, intoximeter, or drunkometer.

in the subject's breath. This is converted to BAC using the observations that 1) alveolar air normally contains close to 5.5% (by vol) of CO_2 i.e. 190 mg of CO_2 in 2100 ml of alveolar air at 34°C, and 2) the weight of alcohol present in 1 ml of blood is equal to that present in 2100 ml of alveolar air. Proper breath sampling is essential to the correct analysis of breath alcohol. For correct sampling the operating procedure is performed so as to obtain what is described as alveolar air or deep-lung breath. This requires the collection of the end portion of a prolonged forced expiration, which is necessary to avoid too much mixing with dead space air, i.e. air that is not totally in equilibrium with the BAC. From numerous experiments conducted it is now well established that there is an excellent corelation between the breath and blood level, and the ratio is generally 2100 : 1. This is based on **Henry's law** which states that when a volatile chemical (ethanol) is dissolved in a liquid (blood) and is brought to equilibrium with air (alveolar breath), there is a fixed ratio between the concentration of the volatile compound (ethanol) in air (alveolar breath) and its concentration in the liquid (blood), and the ratio is constant at a given temperature, i.e. in this case 34°C which is the temperature at which the breath usually leaves the mouth.

4. Ethanol and Medical Practice

   a. The medical profession is generally considered to be one of the noble professions and it therefore behoves a doctor to conduct himself at all times with decency and decorum. Although he can use his discretion with reference to moderate consumption of alcohol when not on hospital duty, or when he is not dealing with patients, he can be held liable in the following situations:

   – A surgeon performing an operation under the influence of alcohol can be prosecuted under S.304-A of the IPC if the patient dies during the course of surgery. The fact that he was drunk at the time of the operation is likely to be considered as strong evidence of rashness.

   – A doctor may be sued for damages in the event of the patient suffering damage or death due to his negligent conduct. If he was intoxicated at the time he administered treatment it would only strengthen the evidence against him.

   – Patient management under the influence of alcohol will be considered as infamous conduct (professional misconduct), and the doctor is liable to be proceeded against by the State Medical Council. The drunken doctor runs the risk of his name being erased from the medical register.

■ Methanol

Synonyms

Methyl alcohol; Methyl hydroxide; Monohydroxymethane; Colonial spirit; Columbian spirit; Pyroxylic spirit; Wood alcohol; Wood naphtha; Wood spirit.

Physical Appearance

- Methanol is the simplest of the primary alcohols and is a colourless, highly polar, flammable liquid.
- Pure methanol has a faintly sweet odour at ambient temperatures; crude methanol may have a repulsive, pungent odour.
- It has a bitter taste.

Uses and Sources

1. Antifreeze *(10 to 50%)*
2. Carburettor cleaner (*20%*)
3. Denatured spirit (*5 to 10%*): While denatured spirit most often is a mixture of ethanol (90 to 95%) with methanol (5 to 10%), occasionally other substances may be used instead of the latter, e.g. acetone, aniline dyes, benzene, cadmium, camphor, castor oil, diethyl phthalate, ether, petrol, isopropanol, kerosene, nicotine, pyridine bases, sulfuric acid, or terpineol.
4. Embalming fluid (*20%*)
5. Leather dyes (*30%*)
6. Paint remover
7. Varnish and shellac (*5%*)
8. Windshield washing fluid (*35 to 95%*).

Usual Fatal Dose

- About 70 to 100 ml (range: 15 to 250 ml).
- Serious toxicity may occur from ingestion of 0.25 ml/kg of 100% methanol, and fatalities might occur from ingestion of 0.5 ml/kg of 100% methanol.

Mode of Action

- Methanol is rapidly absorbed through the skin, respiratory tract and gastrointestinal tract. Peak plasma levels are usually reached within 30 to 60 minutes following ingestion, although a long latent period (roughly 18 to 24 hours) usually is seen before toxic symptoms develop.
- In the liver, methanol is metabolised to formaldehyde (by alcohol dehydrogenase) and then to formic acid (by aldehyde dehydrogenase) which is responsible for retinal toxicity as well as metabolic acidosis.
- There are two pathways for metabolism of formic acid, oxidation via the catalase-peroxidase system, or metabolism by the tetrahydrofolic acid-dependant one-carbon pool which is catalysed by 10-formyl-tetrahydrofolate synthetase. Since metabolism is slow, significant levels of methanol can be found in the body for up to seven days after ingestion.

Clinical Features

1. Symptoms may be delayed for 12 to 24 hours (Range: 1 to 72 hours). The earliest manifestations include vertigo, headache with stiff neck (*meningismus*), nausea, vomiting, and abdominal pain.
2. Later there is ocular toxicity characterised by blurred or dimmed vision ("flashes" or "snowstorm"), and photophobia. Constricted visual fields, spots before the eyes, sharply reduced visual acuity, optic atrophy, blindness, and

nystagmus have all been described. Ophthalmologic examination usually reveals dilated pupils with sluggish light reaction. Fixed dilated pupils suggest severe poisoning. Fundoscopy (**Fig 14.8**) reveals hyperaemia of optic disc followed by retinal oedema. Irreversible sequelae include optic atrophy and visual field impairment.

3. Metabolic acidosis (high anion gap) is usually severe. A pH of less than 7.0 and bicarbonate less than 10 mEq/L are not uncommon following significant intoxication. The onset of acidosis may be delayed up to 18 to 48 hours, especially if ethanol has also been ingested. Therefore, the absence of acidosis does not rule out a significant methanol ingestion.

4. Other features include tachycardia, hypotension, and hypothermia. Convulsions are a late feature and may be followed by coma.

5. Hypomagnesaemia, hypokalaemia, and hypophosphataemia have been reported.

6. Occasionally a patient develops transient Fanconi syndrome (hypouricaemia, hypophosphataemia, glycosuria, and hyperchloraemic metabolic acidosis).

7. Acute necrotising pancreatitis may result from severe methanol poisoning.

8. Cause of death is usually respiratory failure, which may precede the cessation of heart beat by several minutes. In fatal methanol poisoning cases, marked sinus bradycardia may develop with widening of the pulse pressure. Further, severe hypotension, requiring fluid and vasopressor therapy, occurs terminally in severe methanol intoxications.

9. The most common permanent sequelae following recovery from severe poisoning are optic neuropathy, blindness,
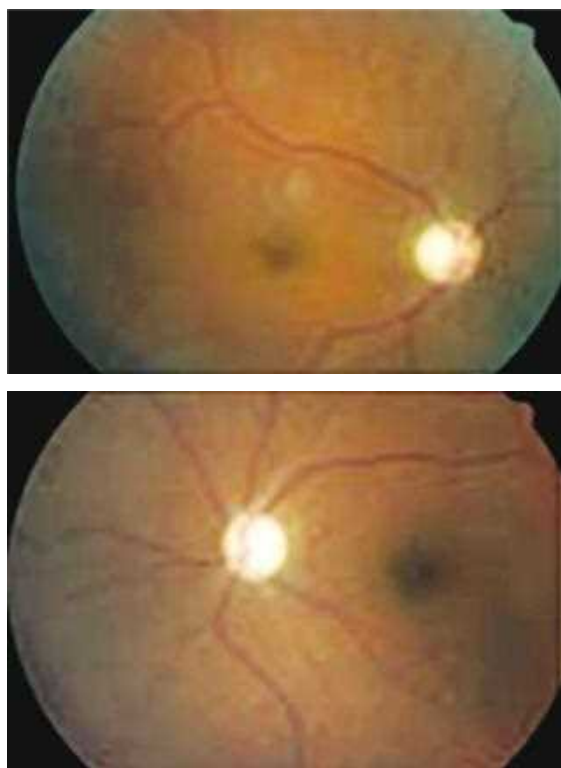
Parkinsonism, toxic encephalopathy, and polyneuropathy. Permanent ocular abnormalities may include pallor of the optic disc, attenuation and sheathing of retinal arterioles, a diminished pupillary light reaction, reduced visual acuity, central scotomata, and defects of optic nerve fibre bundles.

Diagnosis

Obtain CBC, electrolytes, urinalysis, and arterial blood gases in symptomatic patients or those with a history of significant exposure. Measure serum pH and electrolytes.

1. High anion gap acidosis.
2. Elevated osmolal gap.
3. Hypophosphataemia.
4. Elevated creatine phosphokinase.
5. Elevated amylase.
6. Blood methanol level: more than 50 mg/100 ml indicates serious poisoning. A detectable formic acid level may be consistent with methanol poisoning, as methanol is metabolised to formic acid.
7. CT Scan/MRI—Symmetrical areas of necrosis in the putamen of the brain are a classic finding in cases of acute lethal methanol toxicity. However, these findings are also present in other conditions, such as Wilson's disease and Leigh's disease, and are not pathognomonic for methanol poisoning.

Treatment

Patients with abnormal vital signs, visual disturbances, pulmonary oedema, evidence of renal dysfunction, high methanol levels, significant acidosis, or coma should be admitted to an intensive care unit.

1. Stomach wash with sodium bicarbonate.
2. Ipecac-induced emesis is not recommended because of the potential for CNS depression.
3. Activated charcoal does not adsorb significant amounts of methanol. Its use in the face of ingestion may be indicated to prevent absorption of co-ingested substances.
4. **Antidotes (Fig 14.9):**
   a. **Ethanol** is the specific antidote since it preferentially competes for the same enzyme (alcohol dehydrogenase) and prevents the metabolism of methanol which is then excreted unchanged in the urine. Ethanol has about 20 times the affinity for alcohol dehydrogenase compared
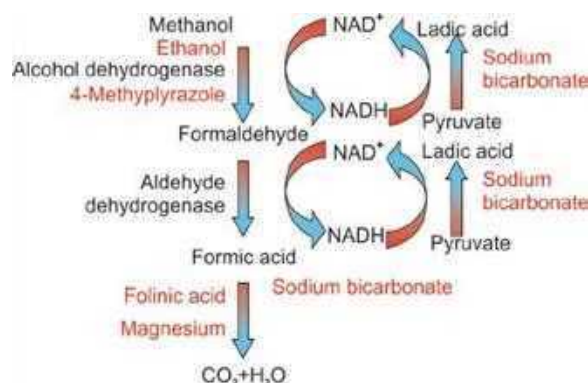

Fig 14.8: Fundoscopic picture—methanol poisoning
(*Pic: Dr. S Senthilkumaran*)

Fig 14.9: Methanol antidotes–mechanism of action

to methanol. This competitive effect of ethanol gains more time for excretion of unchanged methanol from the body, and it also inhibits the formation of methanol metabolites that produce severe acidosis. Formic acid is metabolised to carbon dioxide and water via a folate dependant system.

– *Mode of administration:*
  - 10% ethanol at a dose of 10 ml/kg administered IV over 30 minutes, followed by 1.5 ml/kg/hr, so as to produce and maintain a blood ethanol level of 100 mg/100 ml. Blood ethanol levels should be maintained at 100 to 130 mg/100 ml (21.7 to 28.2 mmol/L). It is safer to maintain a blood ethanol concentration greater than 130 mg/100 ml than to have it fall below 100 mg/100 ml.
    » Preparation from absolute ethanol: If single use vials of pyrogen free absolute ethanol are not available, tax-free bulk ethanol can be used, but it is not pyrogen free. A 0.22 micron filter should be used to minimise particulate matter. A 10% (V/V) solution can be prepared by any of the following methods:
      △ Remove 50 ml from 1 litre of 5% ethanol solution and replace with 50 ml of absolute alcohol.
      △ Replace 100 ml of fluid from one litre of dextrose 5% in water with 100 ml of absolute ethanol.
      △ Add 59 ml of absolute ethanol to one litre of 5% ethanol solution.
      △ Add 112 ml of absolute ethanol to one litre of dextrose 5% in water.
      △ Adding 59 ml of 95% ethanol solution to one litre of 5% ethanol solution (if absolute alcohol is not available).
      △ 59 ml of 95% ethanol provides 56 ml of ethanol (0.95×59 ml = 56 ml).
      △ One litre of 5% ethanol solution provides 50 ml of ethanol (0.05×1000 ml = 50 ml).
      △ 56 + 50 = 106 ml of ethanol divided by a total volume of 1059 ml = 10% (V/V).
    » Alternatively, 1 ml/kg of 95% ethanol in fruit juice (180 ml) can be given orally over 30 minutes. For maintenance, administer 0.17 to 0.28 ml/kg/hr as 50% ethanol in fruit juice.
    » If neither of these is practicable, give 125 ml of a distilled alcoholic beverage (gin, vodka, whisky, or rum) orally, diluted in glucose solution or juice, and repeat as required cautiously.
– Ethanol therapy should be continued until the following criteria are met:
  - Methanol blood concentration, measured by a reliable technique, is less than 10 mg/100 ml.

  - Formate blood concentration is less than 1.2 mg/100 ml.
  - Methanol-induced acidosis (pH, blood gases), clinical findings (CNS), electrolyte abnormalities (bicarbonate), serum amylase, and osmolal gap have resolved.
– Patients who concurrently ingested ethanol and methanol may have a normal acid-base profile despite a dangerously elevated blood methanol level. Consider implementing the ethanol treatment regimen in these patients until a methanol level can be determined. Determine blood ethanol level before beginning ethanol therapy and modify the loading dose accordingly.

b. In Western countries, a new antidote has been introduced viz., **4 methyl pyrazole** (**4MP**), or **fomepizole** which does not cause CNS depression (unlike ethanol). Upto 20 mg/kg of 4MP in divided doses have been given for 5 days without any demonstrable toxicity. The usual dose is 15 mg/kg, followed 12 hours later by 10 mg/kg 12th hourly for 4 doses, and then increased to 15 mg/kg 12th hourly for as long as necessary. Fomepizole is easier to use clinically, requires less monitoring, does not cause CNS depression or hypoglycaemia, and may obviate the need for dialysis in some patients.

c. **Sodium bicarbonate** IV : 500 to 800 ml of 7.5% solution, slowly.

d. **Folinic acid** IV: 1 to 2 mg/kg, 6th hourly. It hastens the elimination of formic acid. Folinic acid (5-formyltetrahydrofolic acid, i.e. 5-FTHF), or leucovorin or citrovorum factor is a biologically active form of folic acid (pteroylglutamic acid) which is an essential water soluble vitamin.

5. For convulsions: Attempt initial control with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.

6. Haemodialysis is very effective in removing methanol, formaldehyde, and formic acid. While ethanol treatment is also quite effective, it is extremely difficult to maintain therapeutic ethanol levels for long periods of time. Haemodialysis is strongly recommended in patients with acidosis or serum methanol levels of greater than 25 to 50 mg/100 ml. Haemoperfusion is not effective. Peritoneal dialysis and continuous venovenous haemofiltration are less effective.

Autopsy Features

1. Cyanosis is very prominent, especially in the upper parts of the body.
2. Liver and kidneys show toxic damage.
3. Lungs may reveal oedema, emphysematous changes, and desquammation of alveolar epithelium.
4. Eyes show evidence of retinal oedema.
5. Viscera must be preserved in saturated solution of sodium chloride and not rectified spirit, as in the case of all alcohols. In addition to the routine viscera, it is advisable to preserve one cerebral hemisphere.

Forensic Issues

Most of the cases of methanol poisoning are accidental arising out of either an alcoholic (deprived of ethanol for any reason) consuming methanol containing products, or because of intentional adulteration of ethanol (especially arrack) resulting in mass deaths. The latter are referred to quaintly as "liquor tragedies" and are reported in Indian newspapers at depressingly regular intervals from all parts of the country.

■ Isopropanol

Synonyms

Isopropyl alcohol, 2-propanol, Blue heaven.*

Physical Appearance

Colourless, volatile liquid with a faint odour of acetone and a slightly bitter taste.

Uses

1. Rubbing alcohol (70%), for massage.
2. Disinfectant.
3. Antifreeze.
4. Paint remover.
5. Window cleaning solution.
6. Toiletries (hair tonics, after-shave lotions).
7. Industrial solvent.

Usual Fatal Dose

- About 250 to 300 ml.
- In terms of blood level: > 300 mg%.

Toxicokinetics

Isopropanol can be absorbed through all routes. In the body it is rapidly metabolised by alcohol dehydrogenase. Approximately 80% is converted to acetone and the remainder is excreted unchanged in the urine. Acetone is excreted in the urine and breath, and also metabolised to acetate, formate, and carbon dioxide.

Mode of Action

Isopropanol is two to three times more potent than ethanol as a CNS depressant.

Clinical Features

- Lethargy, vertigo, headache, confusion, ataxia, dysarthria, nystagmus, miosis, abdominal pain, gastritis, haemorrhagic tracheobronchitis, hypotension, and apnoea. Isopropanol is generally believed to produce greater CNS depression than ethanol at comparable blood levels. Deep coma and areflexia are common following severe intoxication.
- Ketonaemia and ketonuria may be present, generally without metabolic acidosis.
- Emesis and haemorrhagic gastritis may occur following ingestion.

- It can also cause haemolytic anaemia, myopathy, and acute renal failure.
- A characteristic odour of acetone is usually perceptible in the breath.

Diagnosis

- Ketonuria.
- Determine serum isopropanol concentration and blood glucose. Blood isopropanol concentrations of 128 to 200 mg/100 ml, measured within hours after ingestion, have been associated with deep coma and death.
- The absence of hyperglycaemia or glucosuria when acetone is present helps differentiate between alcohol intoxication or diabetic ketoacidosis versus isopropanol intoxication
- Isopropanol is metabolised to acetone. As acetone may contribute to CNS depression, its blood level should also be routinely obtained and followed. Acetone may be detectable in the urine by 3 hours after ingestion, and in the blood by one-half to one hour after isopropanol ingestion. A high serum or urinary acetone without metabolic acidosis is strongly suggestive of isopropanol intoxication.
- Increased osmolal gap.
- High anion gap metabolic acidosis.

Treatment

- Skin decontamination in the case of dermal exposure.
- Stomach wash and activated charcoal in the case of ingestion. However, many investigators are of the opinion that activated charcoal does not adsorb isopropanol efficiently.
- Haemodialysis: Useful in patients demonstrating marked symptoms (persistent hypotension, coma) unresponsive to standard therapy.
- Supportive measures, including correction of hypotension, metabolic acidosis, etc.

Forensic Issues

Isopropanol may be generated spontaneously in a dead body, presumably due to bacterial or other putrefaction processes. This fact must be borne in mind when subjecting viscera to chemical analysis.

■ Ethylene Glycol

Synonyms

1,2-Ethanediol; Glycol alcohol.

Physical Appearance

Colourless, syrupy, odourless, non-volatile liquid, with a bitter-sweet taste.

Uses

1. *Antifreeze:* Ethylene glycol lowers the freezing point of water. More than 25% of the ethylene glycol produced is used in antifreeze and coolant mixtures for motor vehicles.

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* In hospitals, isopropanol is often coloured blue to distinguish it from other colourless liquids, which has led to the designation "blue heaven" by abusers.

It is also used widely for aircraft deicing, and used in condensers and heat exchangers.

2. Solvent.
3. Hydraulic brake fluid.
4. As a glycerine substitute in commercial products such as paints, lacquers, detergents, and cosmetics.

Usual Fatal Dose

About 70 to 100 ml (1.4 ml/kg or 1.56 gm/kg).

Mode of Action

Ethylene glycol is not absorbed through skin, and because of its low vapour pressure does not produce toxicity upon inhalation. It is however rapidly absorbed through the GI tract and is metabolised (more than 80%) to glycoaldehyde, glycolic acid, and oxalic acid which inhibit diverse metabolic pathways in the body, including oxidative phosphorylation. Other metabolites include glyoxylic acid, glyoxal, formic acid, glycine, oxalomalate, malate, benzoic acid, and hippuric acid.

Clinical Features

1. **First Phase** (*CNS stage*): upto 12 hours post-ingestion.
   a. This stage is mainly due to the parent compound itself and is characterised by vomiting, inebriation, lethargy, nystagmus, ataxia, convulsions, and coma.
   b. Facial paralysis, strabismus, ophthalmoplegias, papilloedema, mydriasis, retinal injury, and eye and throat irritation may occur.
2. **Second Phase** (*CVS stage*): 12 to 24 hours post-ingestion.
   a. This stage is characterised by tachycardia hypertension (sometimes hypotension), tachypnoea, congestive heart failure, and circulatory collapse.
   b. Severe metabolic acidosis with compensatory hyperventilation can develop with multiple organ failure in significant poisonings. Tachypnoea and Kussmaul's respiration may be the first clinical signs of developing metabolic acidosis which, if untreated, can progress and become life-threatening.
   c. Cardiogenic pulmonary oedema may occur with severe poisoning.
3. **Third Phase** (*Renal stage*): 24 to 72 hours post-ingestion.
   a. There is oliguria, flank pain, acute tubular necrosis and renal failure. Urine contains calcium oxalate or hippurate crystals. Calcium oxalate crystals are found as monohydrates (prism or needle-like) or dihydrates (tent or envelope-shaped). The former may resemble sodium urate crystals. Hippurate crystals are produced by the transamination of glyoxalate to glycine. It is important to note that absence of calcium oxalate crystals does not rule out the diagnosis. Haematuria and proteinuria are common. In surviving cases, renal function usually returns to normal, but in some cases permanent renal damage has occurred.
   b. Hypocalcaemia results in manifestations of tetany.
   c. Delayed onset of adult respiratory distress syndrome (ARDS) has been described after ingestion of ethylene glycol.

Diagnosis

1. High anion gap acidosis: Increased anion gap metabolic acidosis results from the metabolism of ethylene glycol to acidic metabolites, predominantly glycolic acid.
2. Osmolal gap: Normal anion gap is 12 to 16 using the formula $AG = (Na + K) - (Cl + HCO3)$, but may vary from laboratory to laboratory. The osmolal gap may be used to estimate the serum ethylene glycol level (in mg/100 ml) by simply multiplying the gap by 6.2 (the molecular weight of ethylene glycol/10). This method assumes that the patient's serum contains only ethylene glycol (and no other osmotically active substances such as ethanol).
3. Calcium oxalate crystals in urine (**Fig 14.10**).
4. Xanthochromic CSF with pleocytosis.
5. Determine blood ethylene glycol concentration in all patients. Ethylene glycol concentrations must be interpreted with regard to the time of ingestion and the acid/base status of the patient. Shortly after ingestion ethylene glycol concentrations greater than 30 to 50 mg/100 ml (8.06 mmol/L) are frequently associated with severe intoxication. In severely acidotic or acidaemic patients lower ethylene glycol concentrations may be associated with severe toxicity.
6. If antifreeze has been ingested, the urine will fluoresce from the fluorescent dye in the product, when examined under Wood's lamp. A fluorescent dye, sodium fluorescein, is present in many commercial antifreeze products. However, fluorescent urine is not a reliable indicator of ethylene glycol ingestion, due to variations in interpretation of urine fluorescence among observers and the fact that most normal urine specimens exhibit some degree of fluorescence.
   a. *Method:*
      - If the fluorescein content is not listed on the container, a sample of the product should also be examined for fluorescence.
      - Urine samples should be collected as soon as possible after ingestion, preferably within 2 hours and absolutely within 4 hours. A spectrofluorophotometer is more sensitive than visual inspection.
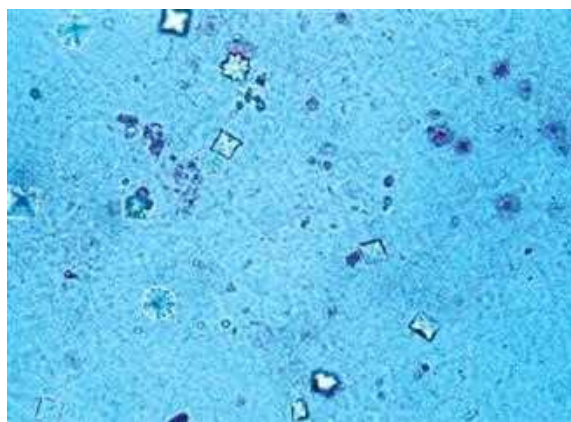
Fig 14.10: Calcium oxalate crystals in urine—Methanol poisoning (*Pic: Dr. S Senthilkumaran*)

– Urine must be collected using non-fluorescent containers (i.e. borosilicate glass test tubes). Plastic specimen containers are fluorescent.
– The pH of the urine should be checked and adjusted to 4.5 or greater before examination.

Treatment

DO NOT WAIT FOR SYMPTOMS TO APPEAR.

1. Stomach wash and activated charcoal. However, the utility of activated charcoal is limited due to ethylene glycol's rapid absorption from the GI tract and its poor binding affinity for activated charcoal. Unless there is concern for coingestants, there is little benefit from activated charcoal administration in ethylene glycol ingestions.
2. Ethanol is the antidote and must be given IV, (same as for methanol poisoning). It inhibits the metabolism of ethylene glycol. 4-methyl pyrazole (fomepizole) is a better alternative.
   a. *Indications:* The following criteria have been proposed by the American Academy of Clinical Toxicology as indications for treatment of ethylene glycol poisoning with an antidote (either ethanol or fomepizole):
   – Documented plasma ethylene glycol concentration greater than 20 mg/100 ml
   Or
   – Documented recent (hrs.) history of ingesting toxic amounts of ethylene glycol and osmolal gap greater than 10 mOsm/L
   Or
   – History or strong clinical suspicion of ethylene glycol poisoning and at least 2 of the following criteria:
     - Arterial pH less than 7.3
     - Serum bicarbonate less than 20 mEq/L
     - Osmolal gap greater than 10 mOsm/L
     - Urinary oxalate crystals present.
   b. *Loading Dose (ethanol):*
   – Intravenous Loading Dose
     - Administer 7.6 ml/kg IV of 10% ethanol (V/V) in dextrose 5% in water over 30 minutes to achieve a blood ethanol concentration of above 100 mg/100 ml (21.7 to 28.2 mmol/L). Some authors recommend a loading dose of 10 ml/kg to ensure an adequate initial level despite variability in ethanol distribution and ongoing metabolism during the infusion.
   – Oral Loading Dose
     - 95% ethanol: Administer 0.8 to 1 ml/kg orally in 6 ounces of orange juice over 30 minutes.
     - 40% ethanol: Administer 1.8 to 2 ml/kg orally in 6 ounces of orange juice over 30 minutes (80° proof spirits contain 40% ethanol; for 20% (40° proof) spirits administer 4 ml/kg).

   c. *Maintenance Dose (ethanol):*
   – Dosing to maintain a blood ethanol level of 100 mg/100 ml (21.7 millimoles/litre). Begin maintenance infusion as soon as the loading dose is infused.
   – Determine blood ethanol concentrations at the end of the loading dose and hourly thereafter until stable levels of 100 to 120 mg/100 ml have been achieved. Monitor blood ethanol concentrations at least three times daily once a stable ethanol infusion has been achieved.
   – Patients who have concurrently ingested ethanol and ethylene glycol may have a normal acid-base profile and urinalysis despite a dangerously elevated blood ethylene glycol concentration. Consider implementing the ethanol treatment regimen in these patients until an ethylene glycol concentration can be determined. Determine blood ethanol concentration before beginning antidotal therapy and modify the loading dose accordingly.
   d. *Dose (fomepizole):* An initial loading dose of 15 mg/kg is intravenously infused over 30 minutes followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until ethylene glycol concentrations are below 20 mg/100 ml.
3. Haemodialysis*:
   a. *Indications* –
   – Severe metabolic acidosis (< 7.25-7.3) unresponsive to therapy
   – Renal failure
   – Blood ethylene glycol 50 mg/100 ml (8.06 millimoles/L) unless fomepizole is being given and patient is asymptomatic with normal arterial pH
   – Deteriorating vital signs despite intensive supportive therapy
   – Electrolyte imbalances unresponsive to conventional therapy
   – Serum glycolic acid level > 8 mmol/L.
4. Sodium bicarbonate IV.
5. Pyridoxine 50 mg and thiamine 100 mg IM, 6th hourly for 2 days. Thiamine is recommended to stimulate the conversion of glyoxylate to alpha-hydroxy-beta-ketoadipate, a non-toxic metabolite. Pyridoxine is recommended to allow adequate stores of cofactor necessary for the conversion of glyoxylate to nontoxic glycine.
6. Monitor serum calcium level and replace as indicated, with 10% calcium gluconate IV.
7. Maintenance of good urine volume enhances urinary elimination of ethylene glycol.

Autopsy Features

■ Cerebral oedema, chemical meningoencephalitis.
■ Toxic damage of liver and kidneys.
■ Oxalate crystals in brain, spinal cord, and kidneys.

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* Addition of 95 % ethanol to dialysate is necessary to replace the ethanol lost during the procedure.

■ Barbiturates

The barbiturates are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine) and were extensively used as sedative-hypnotics till the 1960s when the benzodiazepines arrived and quickly displaced them.

Examples

1. Long acting (duration of action 6–12 hrs)
   a. Mephobarbitone
   b. Phenobarbitone.
2. Intermediate acting (duration of action 3–6 hrs)
   a. Amobarbitone
   b. Aprobarbitone
   c. Butobarbitone.
3. Short acting (duration of action < 3 hrs)
   a. Hexobarbitone
   b. Pentobarbitone
   c. Secobarbitone.
4. Ultra-short acting (duration of action <15–20 min)
   a. Thiopentone
   b. Methohexitone.

Uses

1. Sedative-hypnotic.
2. Pre-operative sedation.
3. Treatment of seizure disorders.

Usual Fatal Dose

- Phenobarbitone: 6 to 10 grams.
- Amobarbitone, pentobarbitone, secobarbitone: 2 to 3 grams.
- Lethal blood level for short- and intermediate-acting barbiturates varies from 3 to 4 mg/100 ml, while for phenobarbitone it ranges from 8 to 15 mg/100 ml.

Toxicokinetics

- Most barbiturates which are used as sedative-hypnotics are administered orally. Intravenous route is usually reserved for management of status epilepticus or induction/maintenance of general anaesthesia.
- Following absorption, barbiturates are distributed widely. The long acting barbiturates have a plasma half-life of about 80 hours.
- Metabolism of most of these drugs occurs by oxidation in the liver resulting in the formation of alcohols, ketones, phenols, or carboxylic acids which are excreted in the urine as such or in the form of glucuronic acid conjugates. Metabolism of barbiturates is more rapid in children and is slower in the elderly.

Adverse Effects

- Residual depression after the main effect of the drug has passed off.
- Paradoxical excitement (especially in the elderly).
- Hypersensitivity reaction—localised swelling of eyelid, cheek, or lip, erythematous or exfoliative dermatitis.
- Synergistic action with ethanol and antihistamines.
- Barbiturates are contraindicated in patients with acute intermittent porphyria since they enhance porphyrin synthesis.

Clinical (Toxic) Features

1. Slurred speech, ataxia, lethargy, confusion, headache, nystagmus.
2. CNS depression, coma, shock.
3. Pupils are at first constricted, but later dilate because of hypoxia.
4. Hypothermia.
5. Cutaneous bullae (*"barb burns", barbiturate blisters*): These are clear, erythematous or haemorrhagic blisters, and occur in various areas of the body, most typically on the hands, buttocks, and between the ankles and knees, usually over pressure points. These lesions have also been reported over non-pressure points, such as dorsal surfaces of fingers and toes, and ocular conjunctiva.
6. Death may occur from respiratory arrest or cardiovascular collapse. Delayed death may be due to acute renal failure, pneumonia, pulmonary oedema, or cerebral oedema.
7. Chronic barbiturate (ab)use is associated with the development of tolerance which is responsible for decreasing the therapeutic to toxic index. An addict may obtain therapeutic benefit only with 5 to 6 times the normal dose. Abrupt withdrawal results in anorexia, tremor, insomnia, cramps, seizures, delirium, and orthostatic hypotension.

Diagnosis

1. Serial plasma levels may be useful in the management of phenobarbitone overdose. Plasma levels exceeding 8 mg/dL (80 mcg/mL) (344 mcmol/L) are generally associated with some degree of coma. In the absence of tolerance, plasma levels exceeding 2 to 3 mg/dL may be associated with CNS depression.
2. EEG: alpha coma* indicates poor prognosis.

Treatment

Monitor CBC, serum electrolytes, glucose, blood urea nitrogen, creatinine, and urine myoglobin in patients with significant intoxication. The onset of toxic effects is usually within 2 hours, but peak toxicity may not occur for 18 or more hours. All patients with a detectable phenobarbitone level require a repeat serum phenobarbitone level at approximately 6 hours after the initial level. If the repeat serum phenobarbitone level is within the therapeutic range, the patient has been decontaminated, and is asymptomatic, the patient is not at risk of toxicity. If the repeat serum phenobarbitone level is greater than the initial level, additional levels are needed to follow the course of overdose.

- Gastric lavage (preferably with a large-bore, double-lumen tube), can be done with benefit upto 12 to 24 hours post-ingestion.

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* Normally, alpha activity in the EEG is associated with wakefulness. When it occurs in coma, it is referred to as alpha coma.

- Activated charcoal in the usual dose. Multiple dose activated charcoal has been shown to greatly increase phenobarbitone elimination in animal studies, volunteers, and overdose patients.
- Forced alkaline diuresis is said to be particularly useful in phenobarbitone poisoning (see *page no* 23 for details of the procedure). However, it should be considered only in severe barbiturate toxicity with life-threatening signs and symptoms. It appears to be less effective than multiple dose activated charcoal, and is generally not the preferred method of elimination enhancement. Forced diuresis is of no value in the treatment of short acting barbiturate intoxication.
- Haemodialysis or haemoperfusion: Barbiturate elimination can be increased by haemodialysis or charcoal haemoperfusion. However, these techniques are rarely needed when managing even severe barbiturate intoxication, and should be reserved for patients with haemodynamic compromise refractory to aggressive supportive care. Even though haemoperfusion can clear barbiturates two to four times more rapidly than dialysis, haemoperfusion will not correct electrolyte imbalances, and has been associated with platelet consumption, hypothermia, hypotension, and decreased serum calcium.
- Exchange transfusion may be beneficial in severe cases.
- For hypotension: First administer 10 to 20 ml/kg of isotonic intravenous fluids and place in Trendelenburg position. Repeat boluses of isotonic intravenous fluids should be administered prior to initiating vasopressor therapy. If the patient is unresponsive to isotonic fluid therapy administer a vasopressor. Dopamine or noradrenaline should be titrated to desired response.
- Supportive measures: supplemental oxygen, intubation, assisted ventilation, IV fluids.
- Withdrawal may be treated by reinstitution of phenobarbitone, and a programme of gradual reduction over three weeks. A tapering schedule of 10 percent every 3 days has been used successfully.

Autopsy Features

- Peripheral cyanosis.
- Froth at the mouth and nose.
- *Barbiturate blisters* on the dependant parts of skin surface*: buttocks, inner aspects or back of thighs, calves, and forearms.
- Intensely congested lungs.
- Congestion or even erosion of the stomach.

Forensic Issues

- The incidence of poisoning with barbiturates has declined dramatically in recent years as a direct result of decline in their use as sedative-hypnotics. However cases do get reported even today, mostly the result of deliberate self-ingestion. This type of (suicidal) poisoning was rampant in the 1960s when these drugs were widely prescribed and consequently abused. One of the most famous cases during this period concerned immortal Hollywood actress **Marilyn Monroe (Fig 14.11)** who at the end of her short, tempestuous career became hopelessly addicted to alcohol and barbiturates. In 1962, at the age of 36, Marilyn Monroe was found dead at home following an overdose of barbiturates.
- In most parts of the world today, the few barbiturates still used in therapeutics comprise phenobarbitone and thiopentone. The latter being available only as an injectable preparation has never been popular for committing suicide. Nevertheless there have been reported cases.
- In India, as per some studies, barbiturates used to account for the maximum number of poison-related fatalities every year right upto the early 1970s, but after that the incidence has plummeted rapidly, and today they account for only a negligible proportion of deaths.
- Accidental barbiturate poisoning due to inadvertent overdose is not uncommon among addicts because of their phenomenon of tolerance. But earlier hypotheses that a patient could overdose himself to death by so-called *automatic behaviour* brought on by sleepy confusion have not withstood scientific analysis.
- Intravenous thiopentone has been used as *truth serum* to extract confessions during interrogation by inducing a state of drowsy disorientation in the course of which the person may reveal the truth. This controversial practice is closely related to the legitimate psychiatric practice of *narcoanalysis* used to diagnose certain mental ailments by placing the patient in a reclining position and administering amylobarbitone or some other short-acting barbiturate intravenously until lateral nystagmus is induced or drowsiness is noted, when the interview is begun and sustained in a gentle fashion with periodic maintenance doses of the drug. This is sometimes referred to as the "Amytal interview", Amytal being a popular trade name for amylobarbitone in some Western countries.

Fig 14.11: Marilyn Monroe

■ Benzodiazepines

Examples

Alprazolam, brotizolam, chlordiazepoxide, chlorazepate, clobazam, clonazepam, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazepam, triazolam and zolazepam.

Uses

1. Anxiety disorders
2. Seizure disorders
3. Insomnia
4. Movement disorders (adjunctive therapy)
5. Mania (adjunctive therapy)
6. Some of these drugs are also used for inducing skeletal muscle relaxation, as pre-anaesthetic medication, and for the treatment of alcohol withdrawal.

Usual Fatal Dose

Uncertain for most benzodiazepines. Even ingestion of up to 2000 mg diazepam has not resulted in death, or for that matter, even serious morbidity. However, several cases of fatality due to triazolam and flunitrazepam overdose have been described.

In general, benzodiazepine metabolism appears to be inhibited by ethanol when given concurrently. Clinically, concomitant administration of high doses of ethanol and benzodiazepines act to synergistically depress respiration.

Mode of Action

Benzodiazepines act by stimulating the GABAb (gamma aminobutyric acid b) receptors, thereby opening up the chloride ion channel in the receptor complex, resulting in the increased conductance of chloride ion across the nerve cell membrane. This lowers the potential difference between the interior and exterior of the cell, blocking the ability of the cell to conduct nerve impulses.

Toxicokinetics

Most benzodiazepines are administered orally or by IV injection. Intramuscular injection may lead to erratic absorption.1 However, lorazepam and midazolam are exceptions to this and can be given IM. Following absorption, all benzodiazepines are bound to plasma proteins to the extent of 70 to 99%, and are metabolised extensively by different microsomal enzyme systems in the liver. Metabolites are invariably as active as the parent compound.

Adverse Effects

- Weakness, headache, amnesia, vertigo, diplopia, nausea, diarrhoea, and rarely chest pain.
- Paradoxical effects (*disinhibition* or *dyscontrol reaction*) may sometimes occur characterised by restlessness, agitation, and hallucinations.
- Flurazepam has been associated with nightmares and hallucinations.
- Allergic, hepatotoxic, and haematological reactions are rare.

Drug Interactions

- Ethanol has a synergistic effect with benzodiazepines and increases both the rate of absorption as well as associated CNS depression. Similar effect is also seen with concomitant administration of phenothiazines and barbiturates.
- Sodium valproate may cause psychotic reactions when given along with benzodiazepines.

Clinical (Toxic) Features

Benzodiazepines are remarkably safe drugs and rarely produce serious toxic effects even with substantial ingestion. Death is uncommon unless other synergistic drugs have also been ingested. However, newer benzodiazepines such as alprazolam, triazolam, and temazepam are associated with fatalities.

1. **Acute Poisoning:**
   a. *Mild*—Drowsiness, ataxia, weakness.
   b. *Moderate* to *Severe*—
      – Vertigo, slurred speech, nystagmus, partial ptosis, lethargy, coma.
      – Hypotension and respiratory depression supervene in potentially lethal ingestions: Respiratory depression is the primary clinical concern in benzodiazepine overdose. Overdose may depress respiratory rate and tidal volume and airway protective reflexes.
      – Both miosis and mydriasis have been reported. Nystagmus may also occur.
      – Analysis of acute benzodiazepine overdoses in relation to the incidence of coma indicate that short acting benzodiazepines (midazolam and triazolam) and intermediate acting (flunitrazepam) have a higher acute toxicity, as compared to diazepam, lorazepam and nitrazepam. Flurazepam and temazepam may also have greater toxicity.
      – Triazolam, as well as other benzodiazepines, have been implicated in next-day memory impairment/amnesia in a significant number of patients.
      – Administration of benzodiazepines to a pregnant woman prior to delivery may produce signs of poisoning in the neonate. A condition called "floppy infant syndrome", characterised by hypotonia that may last several days, may occur following maternal diazepam use.
2. **Chronic Poisoning:**
   Long-term use of benzodiazepines is associated with the development of tolerance. Abrupt cessation provokes a mild withdrawal reaction characterised by anxiety, insomnia, headache, tremor, and paraesthesia. Restlessness, encephalopathy, and hallucinations may occur after abrupt withdrawal from high daily doses. Convulsions may occur after a lapse of 3 to 10 days.

Diagnosis

Estimation of plasma levels of benzodiazepines is usually not necessary. Qualitative testing for presence of benzodiazepine is helpful to confirm presence, especially when overdose history

is sketchy. Quantitative levels are not usually clinically useful. Blisters of skin (bullae) can occur following overdose with nitrazepam, oxazepam, and temazepam.

Treatment

1. **Acute Poisoning:**
   a. *Decontamination*—Ipecac-induced emesis is not recommended because of the potential for CNS depression. Stomach wash may be helpful if the patient is seen within 6 to 12 hours after the ingestion. Cuffed endotracheal intubation is a prerequisite in comatose patients. Activated charcoal adsorbs benzodiazepines and can be administered in the usual manner.
   b. Establish clear airway. Oxygen and assisted ventilation are often necessary.
   c. IV fluids (Ringer's lactate at a rate of 150 ml/hr for adults).
   d. Correction of hypotension: Begin by infusing 10 to 20 ml/kg of isotonic fluid, and place patient in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
   e. Forced diuresis and haemodialysis are ineffective.
   f. *Antidote*—
      – Flumazenil is effective in reversing the coma induced by benzodiazepines as well as zolpidem. The effect is however usually short-lived, and flumazenil also has the tendency to induce a withdrawal reaction in benzodiazepine-dependant patients. The mode of action is competitive antagonism.
      – In practice, most patients achieve complete reversal of benzodiazepine effect with a total slow IV dose of just 1 mg. Some investigators suggest that flumazenil is better administered in a series of smaller doses in an incremental manner beginning with 0.2 mg and progressively increasing by 0.1 to 0.2 mg every minute until a cumulative total dose of 3.5 mg is reached. However, resedation occurs within ½ hour to 2 hours (depending on the nature and dose of benzodiazepine ingested), and therefore patients must be carefully monitored and subsequent doses of flumazenil should be administered as needed. The use of continuous flumazenil maintenance infusion over 5 to 24 hours seems of therapeutic value in the event of resedation after initial response.
      – Flumazenil has also been reported to reverse cardiovascular depression secondary to benzodiazepine use.
      – Flumazenil does not reverse respiratory depression very well and hence fundamental procedures such as supplemental oxygen, endotracheal intubation, and ventilation must not be neglected.
      – Flumazenil is contraindicated in mixed ingestions involving tricyclic antidepressants and drugs which induce seizures, e.g. theophylline, carbamazepine, chloroquine, etc. But there are indications that it may be beneficial in hepatic encephalopathy and ethanol overdose.
      – Flumazenil may cause the following adverse effects: fatigue, nausea, vomiting, hypertension, tachycardia, anxiety, confusion, restlessness, aggression, and rarely convulsions and cardiac arrhythmias.

2. **Chronic Poisoning:**
   a. Phenobarbitone-substitution technique is recommended for benzodiazepine withdrawal which employs propranolol for acute somatic symptoms, while phenobarbitone is used for detoxification.
   b. However the most frequently used method among clinicians is the replacement of a short half-life benzodiazepine (such as alprazolam) with a long half-life benzodiazepine (such as clonazepam), before initiating a taper and final discontinuation.

Forensic Issues

■ Ever since the introduction of benzodiazepines in the 1960s, they have become progressively more popular as anxiolytic agents and sedatives, displacing the barbiturates from their previously held top spot. In spite of extensive use worldwide, there have been only a few cases reported involving fatalities, demonstrating the wide margin of safety of benzodiazepines. But complacency must be avoided and the safety profile of these drugs should not be taken for granted, as deaths have been reported in some recent cases even from unexpectedly low doses of certain benzodiazepines. There are also indications that some of the newer benzodiazepines have a slightly smaller margin of safety. This is particularly true with reference to paediatric and geriatric patients who are more susceptible to the toxicity of these drugs.

■ An area of concern with long-term benzodiazepine use is the possibility of *behavioural disinhibition* which may induce a person to hostile acts, aggressive behaviour, and verbal indecency.

■ Yet another important issue is with reference to the use of benzodiazepines to deliberately induce amnesia in certain individuals in order to accomplish an immoral act (e.g. date rape). Many of these drugs, particularly flunitrazepam, are capable of causing retrograde amnesia. Flunitrazepam (Rohypnol®; "Roofies") has become popular as a drug of abuse, often combined with alcohol, marijuana, or cocaine to produce an intense "high". It has been used as a "date rape" drug, both for its properties of lowering inhibitions and because it can cause retrograde amnesia.

■ While addiction to benzodiazepines is an undeniable possibility among patients on long-term therapy, the abuse potential is much less when compared to most other sedative-hypnotics such as the barbiturates. Withdrawal reactions are also generally less severe and more easily managed. However, abrupt cessation after prolonged use

may precipitate tachycardia, hypertension, agitation, hallucinations, delirium, and convulsions. Withdrawal syndrome is more likely if the drug has been taken at therapeutic dose for more than four months, higher dosage has been used, the drug is stopped suddenly, or a short acting benzodiazepine has been taken.

- Severe dysmorphism, malformations, intrauterine and extrauterine growth retardation, and central nervous system dysfunction have been described in infants born of mothers who used benzodiazepines during pregnancy.

■ Chloral Hydrate

Chloral hydrate (2,2,2,-trichloroacetaldehyde) is rarely used as a hypnotic today, but is a common adulterant of illicit liquor to enhance its intoxicating effect (*Mickey Finn* or *Knock-out drops*). It is a white crystalline substance soluble in water or alcohol with a pungent, pear-like odour and bitter taste.

Chloral hydrate is well absorbed on oral administration and is quickly metabolised to trichloroethanol in the liver by alcohol dehydrogenase. This is the active form which is later conjugated with glucuronic acid and excreted in the urine as urochloralic acid. Chlorobutanol is structurally related to trichloroethanol, and is used as a sedative/hypnotic in doses of 300 to 1200 mg/day.

Chloral hydrate overdose manifests as nausea, vomiting, gastric irritation, miosis, hypotension, renal and hepatic damage, and cardiac arrhythmias (ventricular fibrillation, ventricular tachycardia, and torsades de pointes), cardiac arrest, respiratory depression, and coma. Non-cardiogenic pulmonary oedema and aspiration pneumonitis have been reported after massive overdose. Renal tubular toxicity may occur between 2 and 5 days following ingestion. Pupils are usually miotic initially, but later may be dilated. Breath may have a pear-like odour.

The usual fatal dose is around 10 grams, but deaths have occured with doses as low as 4 grams.

Chronic use of chloral hydratecan lead to a dependency syndrome with a withdrawal state similar to delirium tremens (convulsions and psychosis).

Chloral hydrate tablets and capsules may be visualised by X-ray. A simple diagnostic test involves the instillation of a small amount of the suspected liquid in 10 ml of water, to which 2 ml of purified aniline and 4 ml of 20% sodium hydroxide are added and heated gently. The evolution of a foul odour (*skunk odour*) is indicative of a positive result, which also occurs with chloroform and carbon tetrachloride. The test can also be done on 10 ml of distillate. Chloral hydrate and trichloroethanol in plasma can be analysed by gas chromatography.

Institute continuous cardiac monitoring and obtain an ECG after significant overdose. Monitor pulse oximetry and/or arterial blood gases in patients with CNS or respiratory depression. Emesis is not recommended. Chloral hydrate is rapidly absorbed, particularly after ingestion of liquid formulations. Gastric lavage is also unlikely to be of benefit in most cases. If performed, lavage should be done carefully because of the risk of perforation. In the case of liquid ingestions a small flexible tube may be indicated to prevent oesophageal damage.

Treatment should be mainly directed at the management of cardiac arrhythmias which are potentially life- threatening. Unfortunately the arrhythmias are usually non-responsive to conventional anti-arrhythmic drugs, and a beta-adrenergic antagonist (non-cardioselective or beta1-specific), or adrenergic neurone blocking drug such as bretylium may have to be administered. Propranolol has been the most commonly used beta adrenergic blocker for chloral hydrate-induced arrhythmias. *Dose:* 1 mg/dose intravenously, administered no faster than 1 mg/min repeated every 5 minutes until desired response is seen, or a maximum of 5 mg has been given. Esmolol, a short-acting beta-blocker, may be preferable to propranolol since it has rapid onset and short duration of action, enabling rapid attenuation of adverse effects if the patient's status deteriorates. *Dose:* Infuse 500 mcg/kg for one minute. Follow loading dose with infusion of 50 mcg/kg per minute for 4 minutes. If inadequate response to initial loading dose and 4 minute maintenance dose, repeat loading dose (infuse 500 mcg/kg for one minute), followed by a maintenance infusion of 100 mcg/kg /min for 4 minutes. Re-evaluate therapeutic effect. If response is inadequate, repeat loading dose, and increase the maintenance dose by increments of 50 mcg/kg/min, administered as above. Arrhythmias refractory to propranolol or esmolol may respond to lignocaine. Torsades de pointes usually responds to magnesium sulfate or isoproterenol or amiodarone.

For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. Consider central venous pressure monitoring to guide further fluid therapy. If hypotension persists consider administering dopamine or noradrenaline. *Caution:* Catecholamines may precipitate ventricular arrhythmias in patients with chloral hydrate overdose.

Flumazenil (200 micrograms followed by three additional 100-microgram doses, at one minute intervals) may produce dramatic improvement in chloral hydrate poisoning according to some investigators.

Haemodialysis and haemoperfusion have been advocated as beneficial, and may be useful in a patient unresponsive to normal supportive care, or in whom acid-base or fluid and electrolyte problems may become uncontrollable.

Sudden withdrawal from chronic chloral hydrate use can result in delirium and convulsions, which may have to be managed with barbiturates or other sedative-hypnotic drugs.

There are indications that chloral hydrate may be carcinogenic.

OTHER SEDATIVE-HYPNOTICS

■ Paraldehyde

Paraldehyde is a polymer of acetaldehyde and occurs as a colourless liquid with a pungent odour and disagreeable taste.

It was previously popular as a hypnotic, but is today used only for the treatment of alcoholic withdrawal (*delirium tremens*), or certain other psychotic states in hospitalised patients.

Paraldehyde is irritating to the alimentary tract and hence is never given orally. Oral administration has produced severe corrosion of the stomach. Parenteral use is associated with serious problems (narrow safety margin on IV administration; skin sloughing, sciatic nerve damage, sterile abscess formation, etc. on IM injection). For these reasons, paraldehyde is usually only given rectally.

Proper storage of paraldehyde is essential—below 30° C—in small, light resistant, well filled, tightly covered containers, or else it is likely to depolymerise to acetaldehyde which then gradually metabolises to acetic acid. Severe poisonings and fatalities have been reported following administration of partially decomposed paraldehyde.

Metabolites in man have not been determined but based on animal studies, it is thought that up to 80% of paraldehyde is converted to acetaldehyde in the liver which is then converted to acetic acid. Acetic acid is thought to be further metabolised via the Krebs cycle to carbon dioxide and water. Approximately 28% is excreted by way of the lungs, and 3% is excreted unchanged in the urine.

Continued use of large doses of paraldehyde may cause visual and acoustic hallucinations, delusions, impairment of memory, intellect, and speech, unsteady gait, tremors, anorexia, and weight loss.

Signs and symptoms of poisoning include pungent odour on breath, irritation of mouth and throat, bleeding gastritis, muscular irritability, vertigo, hypotension, tachycardia, miosis (or mydriasis), pulmonary haemorrhages and oedema, dilatation of the right heart, oliguria, albuminuria, fatty changes in the liver and kidney with toxic hepatitis and nephrosis, azotaemia, and coma. A high anion-gap metabolic acidosis is characteristically encountered. Leucocytosis is also said to be a common finding. Cough is a common early symptom, and intense coughing for 2 to 5 minutes is often seen with IV administration of low doses.

Deaths have been reported with ingestion of as little as 25 ml of paraldehyde. Other deaths have been reported from ingestion of 31 to 120 ml, and rectal administration of 12 to 31 ml. Intravenous paraldehyde has been fatal at doses of 35 ml.

Treatment involves mainly supportive measures with particular emphasis on maintenance of airway, breathing, and circulation. Therapeutic levels of paraldehyde vary considerably due to individual susceptibility, but the estimated concentration to prevent convulsions is 100 to 200 mg/L. Check for possible acidosis. Correction of metabolic acidosis is imperative. Although hypotension is usually not severe, support with pressor drugs may be necessary. For acute lung injury, maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FiO_2 is required to maintain adequate oxygenation, mechanical ventilation, and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.

■ Methaqualone

Methaqualone is a non-barbiturate sedative-hypnotic with anticonvulsant, anaesthetic, antihistaminic and antispasmodic properties. It was extensively abused in the past (*Mandrax, Quaalude, Sopor*), which led to its withdrawal from the market. Combination of methaqualone with wine ("luding out") is said to produce powerful euphoria with feelings of invincibility.

Absorption of this drug after oral administration is rapid and metabolism occurs in the liver leading to the formation of numerous hydroxy metabolites. Methaqualone is completely metabolised by the hepatic microsomal enzyme system, primarily by hydroxylation. Methaqualone is highly lipid soluble, and also has a slow biotransformation, leading to a long half-life.

Dizziness, ataxia, slurred speech, and drowsiness are common in mild intoxication with methaqualone. Overdose is characterised by ataxia, lethargy, coma (sometimes preceded by delirium), hyperreflexia, and respiratory arrest. In severe poisoning, pyramidal signs such as hypertonicity, limb hyperreflexia, clonus, flailing limb motions, myoclonia and upgoing Babinski responses are common. Hypotension, absence of EEG activity, muscular hyperactivity, and respiratory depression are also common phenomena. Tachycardia, hypotension, and myocardial infarction have been reported in severe cases. Reversible ECG changes may occur. Pupils may be somewhat mydriatic and sluggishly responsive, or may be miotic.

Usual fatal dose is around 8 grams. Acute ingestion of greater than 800 mg in an adult is usually considered toxic. Ingestion of as little as one tablet in a child can cause toxicity.

In severely intoxicated patients monitor CBC, liver and renal function tests, platelets, coagulation tests, electrolytes, arterial blood gases, and ECG. Consider prehospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion. Early gastric lavage is also beneficial. Treatment is essentially supportive, with emphasis on control of convulsions and hypotension. Although haemodialysis and haemoperfusion are effective in removing methaqualone, they should be reserved for life-threatening situations. Many patients have been successfully treated without the aid of dialysis. Forced diuresis is contraindicated because of the possibility of precipitating pulmonary oedema.

Abrupt withdrawal following chronic use causes nausea, vomiting, abdominal cramps, weakness, anxiety, restlessness, tachycardia, hyperreflexia, agitation, convulsions, and delirium. Death may occur if severe withdrawal is not treated.

■ Buspirone

Buspirone is an azaspirodecanedione agent (*azapirone*) which is mainly employed as an anxiolytic agent. It is chemically and pharmacologically unrelated to benzodiazepines, barbiturates, and other sedative/anxiolytic drugs. Buspirone has a high affinity for serotonin (5-HT1a) receptors with no significant affinity for benzodiazepine receptors, and does not affect gamma-aminobutyric acid (GABA) binding. Ipsapirone is a related compound.

Buspirone is rapidly absorbed, highly protein-bound, and metabolised in the liver. Despite complete absorption after oral dosing, extensive first-pass metabolism limits the bioavailability of buspirone to approximately 4 percent. The presence of food in the stomach decreases the rate of absorption and increases the amount of unchanged (unmetabolised) drug in the system. 20 to 40% of the drug is excreted in faeces.

While the exact mode of action is not clear, the heteroarylpiperazine moiety of buspirone may be responsible for its anxiolytic and serotonergic activity. Buspirone suppresses serotonergic activity while enhancing dopaminergic and noradrenergic cell firing. It also acts on the dopaminergic system in the CNS.

Central nervous system (CNS) depression is the primary toxic manifestation, based on animal data and clinical trials. Other common adverse effects include dizziness, headache, nervousness, lightheadedness, and excitement. Dysphoria, motor impairment, paraesthesias, and toxic psychosis have been reported with buspirone use. Dysuria, enuresis, nocturia, and priapism have been associated with therapeutic use. Withdrawal or rebound anxiety has not been reported with abrupt discontinuation of therapy. There have been rare reports of serotonin syndrome associated with the concomitant use of buspirone and some antidepressant agents.

Overdose manifests as GI distress, vertigo, miosis, bradycardia, and sometimes hypotension. Convulsions have been reported.

Treatment is supportive. Most cases require just decontamination (stomach wash), or administration of activated charcoal. Hypotension can be corrected by the usual methods. Serotonin syndrome must be managed on recommended lines (*page no 326*).

■ Zolpidem

Zolpidem is an imidazopyridine derivative which is a sedative-hypnotic with rapid onset of action and short half-life. It binds selectively to the benzodiazepine w-1 receptor subtype in the central nervous system.

Therapeutic doses have produced the following side effects: dizziness or light-headedness, somnolence, headache, and gastrointestinal upset. Several reports of somnambulism have occurred. Visual and tactile hallucinations, confusion, nightmares, delirium and agitation have been reported in some individuals with symptoms beginning within 30 minutes of a single 10 mg dose.

Overdose is characterised by coma and pinpoint pupils, preceded by vertigo, vomiting, tremor, myoclonic jerks, and diplopia. Pulmonary oedema has been reported.

One patient developed slurred speech, confusion, loss of co-ordination, and sleepiness after ingesting an unknown amount of zaleplon (a related drug). He was amnestic for the events after recovering from the overdose.

Chronic use of zolpidem can cause tremors, sweats, chills, and headache. Sudden withdrawal has been reported to cause convulsions.

Treatment of acute overdose involves stomach wash, activated charcoal, and supportive measures. Flumazenil (repeated doses) is said to be effective in reversing the coma.

■ Zopiclone

Zopiclone is a member of cyclopyrrolones, and is a new-generation sedative-hypnotic with anticonvulsant and muscle relaxant properties. Zopiclone and related drugs such as eszopiclone and suriclone are non-benzodiazepine hypnotic/anxiolytic agents. Even though these drugs are chemically unrelated to benzodiazepines, they nevertheless potentiate gamma-aminobutyric acid (A)-mediated neuronal inhibition.

Overdose leads to rapid loss of consciousness. Chronic use is associated with metallic or bitter taste, dry mouth or sialorrhoea, GI distress, drowsiness, rebound insomnia, and confusion. Other common adverse effects include asthenia, dizziness, memory impairment, feeling of drunkenness, euphoria, anxiety, depression, impaired co-ordination, hypotonia, and speech disorder. Severe overdoses may result in hypoxia, pulmonary oedema, and respiratory failure. The potential for physical dependence has been reported; psychiatric reactions, including hallucinations, have also been described. Abrupt withdrawal of zopiclone, particularly following higher dosages and longer usage, may result in convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances, and insomnia.

Treatment of overdose is on general lines. Provide general supportive therapy as indicated, including administering intravenous fluids and maintaining adequate airway. Monitor respiratory, cardiac, and haemodynamic status of all patients following significant overdose. Flumazenil may be beneficial.

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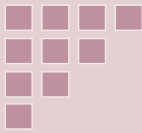
Deliriants

Deliriants are substances that induce delirium (acute confusional state with disorientation, delusions and hallucinations), and comprise mainly datura and cannabis. Datura has prominent anticholinergic effects and can cause full-fledged anticholinergic syndrome, while cannabis does not. **Table 15.1** lists important examples of agents that can cause anticholinergic syndrome.

■ Datura

Other Common Names

Jamestown weed; Jimson weed; Thorn apple; Stinkweed; Devil's weed; Angel's trumpet.

Botanical Name

Datura stramonium, D. metel, D. fastuosa

Physical Appearance

- This is a small coarse shrub with a strong and rather unpleasant smell, belonging to family Solanaceae which grows wild all over the Indian countryside.

- It grows to a height of 3 to 5 feet, and has a handsome foliage of dark green ovate, pointed leaves, and large tubular (trumpet-shaped) flowers which may be white (*alba*) or purple (*niger*) (**Fig 15.1**).
- The fruit capsule is spherical with soft spines (**Fig 15.2**) and contains 50 to 100 dark brown reniform (kidney-shaped) seeds (**Fig 15.3**) which bear a superficial resemblance to chilly seeds.*

Uses

The active principles have various uses in modern medicine (**Table 15.2**).

Toxic Part

All parts, especially seeds.

Toxic Principles

Hyoscine (scopolamine), hyoscyamine, and traces of atropine, together referred to commonly as *belladonna alkaloids*.

Table 15.1: Anticholinergic Agents

Category	Examples
Antidepressants (tricyclic)	Amitriptyiline, desipramine, doxepin, imipramine, nortriptyline, etc.
Antipsychotic drugs	Phenothiazines, butyrophenones
Antihistamines	Chlorpheniramine, diphenhydramine, orphenadrine, promethazine
Antiparkinsonian drugs	Benztropine mesylate, biperiden, ethopropazine, procyclidine, trihexyphenidyl
Antispasmodic drugs	Methantheline bromide, propantheline bromide
Ophthalmic preparations	Atropine ophthalmic solution, cyclopentolate, tropicamide
Other drugs	Methapyrilene
Belladonna alkaloids	Atropine, scopolamine, hyoscyamine
Plant alkaloids	Bittersweet *(Solanum dulcamara)* Black henbane *(Hyoscyamus niger)* Deadly nightshade *(Atropa belladonna)* Jimson weed *(Datura species)* Jerusalem cherry *(Solanum pseudocapsicum)* Potato leaves, tuber *(Solanum tuberosum)*

* See page no 127 differentiating points.

Fig 15.1: Datura Plant (*Pic: Dr. Shashidhar C Mestri*)

Fig 15.2: Datura fruit capsule (*Pic: Dr. Shashidhar C Mestri*)

Fig 15.3: Datura capsule and seeds

Table 15.2: Medicinal Uses of Datura Alkaloids	
Alkaloid	*Uses*
Atropine	1. Treatment of bradycardia, vagal syncope
	2. Preanaesthetic medication (for reducing salivation and bronchial secretions)
	3. Antidote for organophosphates, carbamates, and certain mushrooms
	4. Treatment of iridocyclitis, and for facilitating refractory procedures in children (local application as eye drops or ointment)
Hyoscine	1. Antispasmodic
	2. Aid to radiological and endoscopic examination of GI tract
	3. Preanaesthetic medication
	4. Treatment of motion sickness (transdermal patch)

Mode of Action

Belladonna alkaloids competitively inhibit the muscarinic effects of acetylcholine. Sites of action are at the autonomic effectors innervated by postganglionic cholinergic nerves or on smooth muscles that do not contain cholinergic innervation. Central nervous system effects result from their central antimuscarinic actions, i.e. vagal stimulation and decrease in heart rate.

Toxicokinetics

The toxicokinetics of atropine are mentioned in **Table 15.3**.

Clinical (Toxic) Features

Summarised in the classic phrase: *blind as a bat, hot as a hare, dry as a bone, red as a beetroot, and mad as a wet hen.*
The important manifestations can be better remembered as a series of D's:
1. Dryness of mouth, thirst, slurred speech.
2. Dysphagia.
3. Dilated pupils (with no reaction to light or accommodation).

Table 15.3: Toxicokinetics of Atropine	
Bioavailability	About 95%
Presystemic metabolism	860 ng/ml (after 40 mg 1% atropine in eye)
Pharmacologic effects	2 to 3 ng/ml onwards
Time to peak plasma level	13 minutes (IM)
	1 hour (oral)
	1.5 to 4 hours (aerosol)
Volume of distribution	2 to 4 L/kg
Plasma protein binding	50%
Elimination half-life	2 to 4 hours
Excreted unchanged	20 to 50%

4. Diplopia.
5. Dry hot skin, with flushing, hyperpyrexia.
6. Drunken gait (ataxia), hyperreflexia, convulsions.
7. Delirium with hallucinations, agitation, amnesia, incoherence.
8. Dysuria, urinary retention, bladder distension.
9. Death, preceded by tachycardia, arrhythmias, coma, and respiratory depression.

Usual Fatal Dose

- About 50 to 100 datura seeds.
- About 10 to 100 mg of atropine (usually 60 to 75 mg). However, recovery has been recorded with 1000 mg of atropine.

Diagnosis

1. Even minute traces of atropine in blood (as low as 10 ng/ml) can be detected by GC-MS (gas chromatography-mass spectrometry). However, there is little or no correlation between dose of atropine, plasma concentration, and observed clinical effects.
2. Neutrophil leucocytosis is often encountered.
3. *Dilated pupils*: If the pupils do not constrict within 15 to 30 minutes after instillation of 2–3 drops of 1% pilocarpine, it is indicative of atropine or anticholinergic poisoning.
4. *Cat's eye test:* Instillation of a few drops of the patient's urine into the eyes of a cat results in rapid mydriasis.

Treatment

1. Treat the patient in a quiet and dark environment.
2. Treat respiratory failure with endotracheal intubation and assisted ventilation. Tidal volume should be at least 10 to 15 ml/kg.
3. Monitor ECG, pulse, and temperature continuously.
4. *Gut decontamination*: Gastric lavage (after intubation), activated charcoal.
5. Dialysis and haemoperfusion do not appear to be effective.
6. Catheterise bladder.
7. Administer IV fluids, keeping a close watch on intake and output and renal function.
8. Agitation can be controlled with judicious use of diazepam. Do not use phenothiazines or antihistamines, since they can aggravate the anticholinergic effects.
9. Hyperthermia can be managed by hydration and cooling measures.
10. *Antidote:* Physostigmine is the antidote of choice, and should be administered if the following indications are present:
    a. Coma
    b. Arrhythmias
    c. Hallucinations
    d. Severe hypertension
    e. Convulsions.
    The adult dose is 2 mg IV, slowly, repeated if required, in 20 minutes. Do not give it as a continuous infusion. Continuous cardiac monitoring is mandatory. The paediatric dose is 0.5 mg IV, slowly, repeating if required, at 5 minute intervals till a maximum of 2 mg.

Physostigmine is an effective but dangerous antidote, and can give rise to convulsions, asystole, hypotension, hypersalivation, and bradyarrhythmias, if administered without caution. Neostigmine and pyridostigmine being quaternary ammonium compounds do not traverse the blood-brain barrier, and therefore are not effective in countering atropine-induced CNS toxicity. Pilocarpine is also ineffective. Physostigmine is a tertiary amine that easily passes the blood-brain barrier.

11. Drugs to be avoided in the treatment of datura poisoning: antihistamines, phenothiazines, tricyclics, quinidine, disopyramide, procainamide, and morphine.

Forensic Issues

- *Accidental*—Accidental poisoning may result from any one of the following ways:
  - ❖ Mistaken identity involving capsicum seeds (**Fig 15.4**).
  - ❖ Foraging children in the countryside chewing on the seeds (or other parts of the plant) out of curiosity.
  - ❖ Therapeutic misadventures.
  - ❖ Overenthusiastic use of atropine as an antidote for organophosphate or carbamate poisoning.
- *Suicidal*—Owing to easy accessibility, datura is not infrequently reported in suicidal ingestions, especially in rural parts of India.
- *Homicidal*—There have been rare instances of murder being accomplished with one or the other belladonna alkaloids.
- *Stupefaction*—The term "stupefaction" is loosely applied to the process of rendering a victim suddenly incapacitated by exposing him to a deliriant poison such as datura, in order to facilitate robbery or rape. An extract of the seeds is usually employed, which is mixed with food or drink and administered to the unsuspecting victim. Sometimes, stupefaction is induced by exposing the person to fumes of incense, by mixing datura with other constituents of an incense or joss stick (*agarbathi*). Even cigarettes may be adulterated in a similar fashion. Gullible railway or bus passengers are the usual victims who fall into the trap of accepting food, drink, or tobacco from "friendly" strangers.

Fig 15.4: Chilly (capsicum) seeds (*Pic:* Dr. Shashidhar C Mestri)

■ *Datura abuse*—The hypnotic and hallucinogenic properties of datura have been known since ages.

■ Cannabis

Cannabis is among the earliest mind-altering drugs known to man and has been around for at least 4000 years. Today, it is the world's most commonly used illicit drug, with more than 300 million regular users. In terms of popularity ratings, it stands 4th among psychoactive drugs (after caffeine, nicotine, and alcohol).

Source

Cannabis preparations (*vide infra*) are derived from Indian hemp plant (*Cannabis sativa*) (**Fig 15.5**), which is a hardy, aromatic annual herb that grows wild under most climatic conditions. The plant grows to a height of 5 to 15 feet, and is characterised by an odd number of leaflets on each leaf (varying from 5 to 9), all having serrated or saw-tooth edges. The male and female flowers are borne on separate plants. After pollination, the male plants die back.

Toxic Principles

The main active principle is δ^9 (delta-9) tetrahydrocannabinol (THC) which is a cannabinoid found in both the male and female plants. The concentration of THC is highest in the bracts, flowers, and leaves, while it is practically non-existent in the stem, root, and seeds. The THC content of the plant varies greatly, and is probably controlled more by the type of seed than by the soil or climatic conditions. Apart from THC, *Cannabis sativa* contains a number of other cannabinoids, including cannabidiol, cannabinol, cannabidolic acid, cannabicyclol, and cannabigerol. So far, more than 60 of these cannabinoids have been identified.

Uses

1. The durable fibres of the woody trunk of cannabis, referred to collectively as Indian hemp, has been used for centuries to produce rope and twine, as well as fine or rough cloth. The cannabis plant is possibly the most efficient source of paper pulp, producing up to 5 times as much cellulose per acre per year, as trees.
2. Cannabis seeds are used as food by man, poultry, and other birds, as well as furnishing hemp-seed oil for paint and soap.
3. Therapeutic uses:
   a. THC in the form of a synthetic oral cannabinoid ("dronabinol") has been shown to be effective in controlling the nausea and diarrhoea associated with AIDS, as well as the nausea and vomiting caused by chemotherapy for cancer or AIDS. It also increases appetite and produces weight gain in both AIDS and cancer patients.
   b. Since smoked cannabis lowers intraocular pressure, it has been suggested that this effect though short-lived (3 to 4 hours), can be utilised for treating glaucoma.
   c. Some studies suggest a possible role for cannabis in the treatment of multiple sclerosis, epilepsy, and dystonic states, though convincing scientific evidence is lacking.
   d. THC possesses analgesic properties and has been tried in the treatment of pain due to cancer.

Mode of Poisoning

Toxic effects arise mainly from the abuse of various cannabis preparations for their mind-altering properties.
1. *Marijuana*: The term "marijuana" refers to any part of the plant or its extract that is used to induce psychotomimetic or therapeutic effects. Synonyms include Mary Jane, MJ, maconha, pot, weed, grass, puff and dagga.
2. *Ganja*: Although some texts refer to ganja as being synonymous with marijuana, while others consider it to be a resinous mass composed of leaves and bracts, in India (where the term actually originated), it is used to refer to crushed leaves and inflorescences of female plants (**Fig 15.6**). It is usually smoked in a pipe ("chillum") or in the form of cigarettes ("reefer" or "joint"). Ganja is said to contain 1 to 2% THC.
3. *Bhang*: Bhang consists of dried mature leaves and flower stems that are ground with water and mixed with milk (**Fig 15.7**) or fruit juice. It is consumed by Hindus in India during festivals such as Holi and Shiv Ratri.

Fig 15.5: Cannabis sativa (*Pic:* Dr. S Sivasuthan)

Fig 15.6: Ganja

Fig 15.7: Bhang (mixed with milk)

4. *Hashish (Charas)*: This preparation is made out of dried resin collected from flower tops, and contains varying concentrations of THC up to 10% (**Fig 15.8**). It is popular in the Middle East and North Africa. Hashish oil or "liquid hashish" is an alcohol or petrol extract which occurs as a dark green viscous liquid with the consistency of tar. It is the most potent of all cannabis preparations and contains 20 to 30% (or more) THC.
5. *Sinsemilla*: It is the most popular form of cannabis in the USA, and refers to seedless (unpollinated female) plant which averages 5% of THC.
6. *Marijuana "Blunts"*: This is nothing but cheap cigars sliced open, packed with cannabis, and resealed. The harsh stench of the cigar masks the characteristic sweet smell of cannabis. Blunts are very popular among the youth in some parts of the USA.

Mode of Action

- Recently a receptor site has been identified in rat brain that binds reversibly and selectively with cannabinoids. Receptor binding was also found in the peripheral B lymphocyte-rich areas such as the marginal zone of the spleen, nodular corona of Peyer's patches, and cortex of lymph nodes.
- Another recent development has been the isolation of an endogenous cannabinoid-like ligand within the brain, named "anandamide".*

Fig 15.8: Charas

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* Derived from Sanskrit "ananda" which means "bliss".

- A cannabinoid antagonist was also discovered that antagonises cannabinoid-induced inhibition of adenylcyclase and smooth muscle contraction.
- All this suggests the presence of a cannabinoid neurochemical pathway.
    - It appears that cannabinoids exert many of their actions by influencing several neurotransmitter systems and their modulators. These include GABA, dopamine, acetylcholine, histamine, serotonin, noradrenaline, and prostaglandins.
    - Cannabinoid receptor location and density in animal models has correlated well with clinical effects in humans. The highest density of receptors occurs in the basal ganglia and molecular layer of cerebellum, which correlates with its interference in motor coordination. Intermediate levels of binding were found in the hippocampus, dentate gyrus, and layers I and IV of cortex, consistent with effects on short-term memory and cognition. Low receptor density is noted in the brainstem areas controlling cardiovascular and respiratory functions, which correlates with the cannabinoids' known lack of lethality.
    - After binding to receptors, cannabinoids also produce effects through second-messenger systems including inhibition of adenylcyclase and calcium channels, and also probably by enhancing potassium channels activity.

Toxicokinetics

Smoking cannabis generally produces immediate effects, while ingestion results in slow and unpredictable effects due to the instability induced by the acidic environment of the stomach. The most important factor in determining the bioavailability of THC happens to be the smoking dynamics (manner in which the cannabis is smoked). It takes about 15 seconds for the lungs to absorb the THC and transport it to the brain. Peak effects are seen in 10 to 30 minutes and may last for 1 to 4 hours. The mean terminal half-life of THC in plasma of frequent cannabis smokers is 4.3 days (range: 2.6–12.6 days).

Drug Interactions

- Concomitant use of cannabis and ethanol produces additive effects on psychomotor performance.
- Concomitant use of cannabis and cocaine can greatly increase the heart rate.
- Concomitant use of cannabis and phencyclidine ("supergrass" or "superweed") produces an intensely vivid hallucinogenic experience.

Clinical (Toxic) Features

1. **Acute Poisoning:**
    a. Euphoria with increased garrulity and hilarity, especially when smoked in a social group setting.
    b. Temporal and spatial disorientation with intensification of sensation (colours become brighter, sounds become more distinct, music is heard with heightened fidelity) and increased clarity of perception.

c. At high doses, the user experiences hallucinations, sedation, and sometimes dysphoria characterised by unpleasant sensations, fear, and panic.

d. Sometimes an acute toxic psychosis is precipitated with suicidal ideation, anxiety, and paranoia. Occasionally, schizophrenic symptoms occur. Flashback phenomena have been reported.

e. Tachycardia, palpitations, hypotension (high doses).

f. Stimulation of appetite.

g. Bloodshot eyes due to conjunctival congestion.

h. Pupils are usually not affected.

2. Chronic Poisoning:

Chronic users of cannabis demonstrate tolerance to most of the physical effects, while this is not very apparent in the case of mood and behavioural changes.

a. Amotivational Syndrome: Chronic indulgence is said to induce an amotivational syndrome characterised by apathy, poor concentration, social withdrawal, and lack of motivation to study or work. However, the actual existence of such a syndrome is being questioned by some investigators today who state that previous studies had not attempted to adequately distinguish between the effects of cannabis and pre-existing psychological status. In other words, it is difficult to determine which came first, the drug or the amotivation.

b. Heavy cannabis users demonstrate an increased tendency to develop manic, schizophreniform, and confusional psychoses over a period of time. The development of acute psychosis after chronic use is controversial because of questions about the contribution of premorbid personalities and multiple-drug use.

c. Medical Complications:
   – Chronic lung disease and carcinogenesis. Experiments have revealed that cannabis smoking can cause a five-fold increase in blood CoHb level and three-fold increase in the amount of tar inhaled when compared with tobacco.
   – Cancers of mouth and larynx.
   – Aspergillosis: Studies have shown that cannabis is often contaminated with Aspergillus spores which can cause aspergillosis in immunocompromised individuals.
   – Digital clubbing has been reported in chronic hashish users.

Usual Fatal Dose

There are no authentically documented cases of lethality from cannabis intoxication alone. The few cases of fatality that have been reported have not adequately ruled out the possibility of multiple-drug intoxication. In spite of such lack of documented fatalities, some authors have suggested that the fatal dose for IV cannabis is about 1 to 2 grams, while it is 700 grams for ingestion (of bhang).

Diagnosis

1. **Clinical:**
   a. Symptomatology
   b. Characteristic 'burnt rope' odour in the breath of a recent smoker.

2. **Identification of suspected specimen:** Suspend leaf or stem fragments in several drops of chloral hydrate (10%) on a microscope slide and examine under low power for characteristic "cystolith hairs". These hairs look like bear claws or elephant tusks. At the base of these claws is a wart-like cluster composed of calcium carbonate deposit. Add a drop of 20% HCl and note the gentle effervescent release of carbon dioxide gas in tiny bubbles.

3. **Urine levels of cannabinoids:**
   a. THC is hydrophobic and accumulates in adipose tissue. Screening tests may be positive for up to 70 or more days, depending on the cut-off levels used and the individual's lipid stores of THC. Some investigators state that after using three or more joints per day, an individual who then stops smoking cannabis completely and adopts an excessive fitness programme mobilising body fat, will test positive for urinary THC (at 50 to 100 ng/ml) for more than 2 months. An individual who smokes an occasional joint will test positive (at 500 to 1000 ng/ml) for 3 to 4 days.
   b. False positive results may occur with therapeutic use of ibuprofen, fenoprofen, and naproxen. False negatives may result from dilution, diuretic use, common salt, or other contaminants. Concomitant testing of urine specific gravity, pH, temperature, and creatinine could help in eliminating these confounders.

Treatment

1. **Acute Poisoning:**
   a. Decontamination measures in cases of ingestion.
   b. Acute psychotic reactions respond to benzodiazepines.
   c. Supportive measures.

2. **Chronic Poisoning:**
   a. Psychosocial therapy consisting of attempts to promote realistic and rewarding alternatives to the drug and associated life styles, along with a commitment to abstinence from self-administered or unprescribed psychotropic drugs. A combination of interventions is recommended, including urine testing, participation in multi-step programmes, education about drug effects, drug counselling, psychotherapy, and family therapy.
   b. Drug-focussed group therapy comprising strategies such as social pressure to reinforce abstinence, teaching socialisation and problem solving skills, reducing stress and the sense of isolation common with drug abuse, relapse prevention exercises, and varying degrees of confrontation.

c. Short-term use of anxiolytic agents such as benzodiazepines may be necessary in some cases when anxiety symptoms are severe.

d. Short-term use of antipsychotic medication may be required if there are persistent delusional ideas or frightening flash backs.

Medicosocial and Forensic Issues

- Cannabis has been around for thousands of years, initially touted for its "medical" uses, and later condemned for its abuse potential. The first reference to the medical use of cannabis is in a pharmacy book written about 2737 BC by the Chinese Emperor Shen Nung, who recommended it for "absent-mindedness, female weakness, gout, rheumatism, malaria, beri beri, and constipation".

- The mind-altering properties of cannabis probably did not receive wide attention until about 1000 BC when it became an integral part of Hindu culture in India. After AD 500, cannabis began creeping westward, and references to it began appearing in Persian and Arabic literature.

- Cannabis was brought to Europe by Napoleon's soldiers returning from Egypt in the early part of 19th century. It made its entry into the USA at about 1920 when Mexican labourers smuggled the weed across the border into Texas. Its popularity spread quickly, and by 1937 most of the American states had enacted laws prohibiting the use or possession of marijuana. Today, inspite of all efforts at minimising the abuse of cannabis, the drug is the most commonly used illicit substance in the USA.

- The use of cannabis among youth reached its peak in the 1960s when the drug became associated with social protest. The hippie generation ("flower people") was particularly fond of cannabis, to whom it was a "gateway drug" opening the doors to more potent "hard drugs" such as opiates and hallucinogens.

- Recent reports of medical uses of cannabis have led to the resurgence of "pot culture" beginning with the 1990s.

- Consumption of cannabis in various forms has always been popular in India. Sanyasis and temple poojaris use it to induce a trance-like state for the purpose of religious meditation. There are several festivals such as Holi and Shiva Ratri when widespread consumption occurs even among the general populace.

- While long-term cannabis use can cause serious health problems (*vide supra*), acute intoxication sometimes leads to medicolegal complications. The danger lies in the capacity of cannabis to interfere with motor skills and judgement. Operating a motor vehicle or other machinery under the influence of the drug could lead to potential loss of life or limb.

- Occasional acute psychotic reactions precipitated by long-term heavy cannabis use can cause the user to "run amok" in homicidal frenzy. This became well known during the Vietnam war when several American soldiers began suffering from acute toxic psychosis arising out of heavy abuse. Cannabis is also known to induce suicidal ideation brought on by anxiety and paranoia.

- While cannabis does not appear to have teratogenic effects on the foetus, some studies have indicated that infants whose mothers had used the drug during pregnancy exhibited impaired foetal growth.

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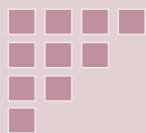
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Stimulants

There are several drugs and chemicals that stimulate the central nervous system, among which the most important are the following: amphetamines (including designer amphetamines), and cocaine.

Amphetamines

The original amphetamine, racemic beta-phenylisopropylamine was first synthesised in 1887, and was marketed in 1932 as a nasal decongestant (*Benzedrine* inhaler). Widespread abuse led to its ban in 1959.

Source

- Amphetamine belongs to the phenylethylamine family with a methyl group substitution in the alpha carbon position. Numerous substitutions of the phenylethylamine structure are possible, resulting in several amphetamine-like compounds. These compounds have now collectively come to be known as "amphetamines", and include amphetamine phosphate, amphetamine sulfate, benzphetamine, chlorphentermine, clobenzorex hydrochloride, dextroamphetamine, diethylpropion, mazindol, methamphetamine, 4-methylthioamphetamine, methylphenidate, pemoline, phendimetrazine, phenmetrazine, and phentermine.
- Methamphetamine abuse began in the 1950s and reached a peak in the 1970s. It used to be referred to as "speed" or "go" (**Fig 16.1**). In the late 1980s, a pure preparation of methamphetamine hydrochloride made its appearance for the first time in Hawaii where it was referred to as "batu". It quickly made its way across to the United Kingdom, Australia, Western Europe, and USA, where it became popular by the slang name "ice" (or "glass") (**Fig 16.2**). While ice is produced by the ephedrine reduction method and is very pure, occurring as large translucent crystals, a variant produced by an oil-based method is called "crystal" (or "crank"), and is a white to yellow crystal product.
- Methamphetamine powder can be inhaled, smoked, ingested, or injected. Ice and crystal are almost always smoked.

Uses

Some amphetamines have therapeutic uses and are still available as prescription drugs in Western countries (**Table 16.1**). They are not available in India (except for mephentermine).

Fig 16.1: Methamphetamine ("Speed") pills

Fig 16.2: Methamphetamine ("Ice") crystals

Mode of Action

- The major mechanism of acion of amphetamines involves the release of monoamines from storage sites in axon terminals, which leads to increased monoamine concentration in the synaptic cleft. The release of dopamine in the nucleus

Table 16.1: Therapeutic Uses of Amphetamines

Drug	Use
Amphetamine	Attention-deficit /hyperactivity disorder, weight reduction
Dextroamphetamine	Attention-deficit /hyperactivity disorder, narcolepsy
Methamphetamine	Attention-deficit /hyperactivity disorder, weight reduction
Methylphenidate	Attention-deficit /hyperactivity disorder, narcolepsy
Benzphetamine	Weight reduction
Fenfluramine*	
Dexfenfluramine*	Weight reduction
Diethylpropion	Weight reduction
Pemoline**	Attention-deficit /hyperactivity disorder
Phendimetrazine	Weight reduction
Phentermine	
Chlorphentermine*	Weight reduction
Mephentermine	Hypotension
Clobenzorex hydrochloride	Weight reduction

*Banned since 1997 in most countries

**No longer considered as first-line therapy for ADHD based on reports of severe hepatotoxicity in some patients

accumbens and related structures is responsible for the reinforcing and mood elevating effects of amphetamines.

- Methylphenidate has a different mechanism of action. Like cocaine, it produces CNS action by blocking the dopamine transporters responsible for the reuptake of dopamine from synapses following its release. The relatively low abuse potential of orally administered methylphenidate is due to slow occupation of dopamine transporters in the brain. Also, unlike cocaine, methylphenidate occupies the transporter sites for a much longer time.
- The most prominent effects of amphetamines are the catecholamine effects as a result of stimulation of peripheral alpha and beta adrenergic receptors. Enhanced concentration of noradrenaline at the locus coeruleus is responsible for the anorexic and stimulating effects, as well as to some extent, for the motor-stimulating effects.
- Cardiovascular effects result from the stimulation of release of noradrenaline.

Toxicokinetics

- In general, peak plasma levels are seen in about 30 minutes after intravenous or intramuscular injection, and about 2 to 3 hours after oral amphetamine ingestion.
- Amphetamines are extensively metabolised in the liver, but much of what is ingested is excreted unchanged in the urine. The excretion of unchanged amphetamine is dependent on pH, and at urine pH less than 6.6, a range of 67 to 73% of unchanged drug is excreted in the urine. At urine pH greater than 6.7, the percent excreted unchanged in the urine is reported to be 17 to 43%.

Clinical Features

1. **Acute Poisoning:**
   a. *CNS:*
      i Euphoria
      ii Agitation
      iii Headache
      iv Paranoia
      v Anorexia
      vi Hyperthermia: can be severe, and may result from hypothalamic dysfunction, metabolic and muscle hyperactivity, or prolonged seizures.
      vii Hyperreflexia
      viii Choreoathetoid movements: In one case, a young child who ingested fourteen 5-mg tablets of methylphenidate (along with a cough and cold medication containing antihistamine and dextromethorphan), developed choreoathetoid movements within five hours of overdose. The symptoms resolved several hours later without any specific treatment.
      ix Convulsions: Seizures are associated with a high mortality rate.
      x Intracerebral haemorrhage: Abuse of amphetamine and related drugs can increase the risk for cerebrovascular incidents in young adults.
      xi Coma: If it occurs, is associated with a high mortality rate.
   b. *CVS:*
      i Tachycardia: Tachycardia is common, however, reflex bradycardia secondary to hypertension can occur.
      ii Hypertension: Hypertension is common following amphetamine use and may result in end organ damage. Pulmonary hypertension has been associated with methamphetamine use. Hypotension and cardiovascular collapse may result from severe toxicity, and is associated with a high fatality rate.
      iii Arrhythmias.
      iv Vasospasm.
      v Myocardial ischaemia: Infarction can occur (*vide infra*).
      vi Cardiomyopathy: Acute and chronic cardiomyopathy can result from hypertension, necrosis, or ischaemia.

c. *Sympathetic Effects:*
   i Mydriasis
   ii Sweating
   iii Tremor
   iv Tachypnoea
   v Nausea.
d. *Other Effects:*
   i Muscle rigidity.
   ii Pulmonary oedema.
   iii Ischaemic colitis: More common in chronic poisoning.
   iv Rhabdomyolysis: Develops in patients with severe agitation, muscular hyperactivity, hyperthermia, or seizures.
   v Metabolic acidosis: This occurs with severe poisoning, and has even been reported after smoking crystal methamphetamine.
e. *Complications:*
   i Psychosis with visual and tactile hallucinations.
   ii Cerebral infarction.
   iii Myocardial infarction.
   iv Aortic dissection: Several cases of fatal aortic dissection associated with chronic amphetamine use have been reported.
   v Ventricular fibrillation.
   vi Acute renal failure: Renal failure may develop secondary to dehydration or rhabdomyolysis in patients with severe amphetamine poisoning.
   vii Use of "ice" is associated with unique neuropsychiatric toxicity. Auditory hallucinations, severe paranoia, and violent behaviour have been reported.
   viii Amphetamines and methamphetamines can induce spontaneous recurrences of paranoid hallucinatory states known as "flashbacks".

2. **Chronic Poisoning:**

   a. Amphetamines can be taken orally, by injection, by absorption through nasal and buccal membranes; or by heating, inhalation of the vapours, and absorption through the pulmonary alveoli. Inhaled amphetamine is almost immediately absorbed with a rapid onset of effects. Unlike cocaine, amphetamines can be vapourised without much destruction of the molecule, thus obviating the need for preparing a free-base form for smoking. As with opiates, the rapid onset of effects from amphetamine injection or inhalation produces an intensely pleasurable sensation referred to as "rush".
   b. Manifestations of heavy chronic amphetamine use:
      i Hyperactivity, hyperexcitability.
      ii Anorexia, loss of weight, emaciation: Weight loss is one of the most characteristic findings with chronic use of amphetamine or its derivatives, and is said to be the most striking effect in chronic "ice" smoking.
      iii Vomiting and diarrhoea are common. Ischaemic colitis may occur.
      iv Stereotyped behaviour (skin picking, pacing, interminable chattering).
      v Dyskinesias: bruxism, tics.

vi Paranoid psychosis, unpredictable violence: The most common symptoms in patients with methamphetamine-induced psychosis were auditory and visual hallucinations, persecutory delusions, and delusions of reference.
vii Heightened sexual activity initially, follo-wed by impotence and sexual dysfunction.
viii Occasionally, very rapid IV injection of a large dose produces a condition called "overamped", characterised by inability to speak or move even though consciousness is fully retained. Blood pressure and temperature are usually elevated. There may be respiratory distress.
ix Deterioration of *social* (family problems), *physical* (slovenly, unkempt appearance), and *economic* (loss of job, bankruptcy) status.
x Adverse psychological reactions—anxiety reactions, amphetamine psychosis, exhaustion syndrome, depression and hallucinosis.

c. Medical complications—cardiomyopathy, vasculitis, pulmonary hypertension, permanent neurological deficits, HIV infection, hepatitis, endocarditis, osteomyelitis and pulmonary abscesses.
d. Obstetric complications (in pregnant users) — eclampsia, intrauterine growth retardation, prematurity, etc. Amphetamine use during pregnancy has also been associated with birth defects, increased risk of cardiac malformations and cleft palate.
e. Intravenous injection abusers may display skin lesions, such as "tracks", abscesses, ulcers, cellulitis, or necrotising angitis.
f. Withdrawal syndrome: Withdrawal after prolonged amphetamine abuse may precipitate severe depression and suicide attempts. Anxiety, abdominal cramps, gastroenteritis, headache, diaphoresis, lethargy and dyspnoea may result. Increased appetite is common.

Drug Interactions

- Sympathomimetics, monoamine oxidase inhibitors, and tricyclic antidepressants cause potentiation of effects, while antihistamines cause diminution of effects.
- Amphetamines may increase anticonvulsant levels.

Usual Fatal Dose

- The fatal dose of amphetamines is highly variable, and while death can occur with as little as 1.5 mg/kg of methamphetamine, survival has been recorded with 28 mg/kg. This in fact represents the usual range of amphetamine's lethal dose—150 mg to 2 grams. However, because of tolerance, addicts can tolerate up to 5 grams (single IV dose), or 15 gm/day (smokable methamphetamine).
- Lethal blood level is said to be around 0.2 mg per 100 ml, though addicts can tolerate much higher levels with hardly any toxic effects.
- Death due to amphetamine toxicity most commonly results from arrhythmias, hyperthermia, or intracerebral

haemorrhage. In cases of survival, symptoms gradually resolve as the drug is excreted over a period of 24 to 48 hours.

Diagnosis

1. Urine is the specimen of choice. Levels above 2 mg/100 ml indicate acute toxicity. Methods of analysis include TLC, RIA, HPLC, and GC-MS. The first three methods often give false positive results, and hence confirmation of a positive test must always be done by GC-MS.
2. A new method (electron-impact mass fragmentography) enables detection and even quantitation of methamphetamine in hair, nails, sweat, and saliva.
3. Hair analysis may provide documentation of methamphetamine or other drug exposure for several months or longer. To obtain hair samples, a new disposable scissors should be used to cut a very small amount of hair (100 mg total, about the width of a pencil) from about 10 different places. The hair must be cut as close to the scalp as possible.

Treatment

1. **Acute Poisoning:**
   a. *Stabilisation*:
      i IV line, cardiac monitoring.
      ii Oxygen.
      iii Evaluate blood glucose, BUN, and electrolyte levels.
      iv Consider the necessity of a CBC, urinalysis, coagulation profile, chest X-ray, CT scan of head, and lumbar puncture, depending on the presentation.
      v Measure core temperature.
      vi Shock is a poor prognostic sign and needs to be managed effectively. Consider the need for right-sided heart catheterisation to measure right-sided filling pressure and cardiac output.
   b. *Supportive Measures:*
      i Airway management, ventilatory support.
      ii Rapid rehydration.
      iii Mannitol diuresis promotes myoglobin clearance to prevent renal failure.
      iv Assess psychological and neurological status.
      v Gastric decontamination (in cases of ingestion) with appropriate tracheal protection. Activated charcoal is beneficial.
   c. *Specific Measures:*
      i. Anxiety, agitation, and hyperactivity can usually be controlled with benzodiazepines. Diazepam is the drug of choice, and is administered in a dose of 10 mg IV at intervals (up to a maximum of 100 mg). Much larger doses (hundreds of milligrams) may be required to obtain adequate sedation. Titrate dose to clinical response. Control of agitation is an important aspect to the treatment of amphetamine overdose, since it often leads to hyperthermia, a common cause of mortality in amphetamine overdose. Neuroleptics are generally not preferred since they may aggravate hyperthermia, convulsions, and cardiac arrhythmias. Physical restraint is inadvisable, since resistance against such measures will aggravate rhabdomyolysis and hyperthermia. Extreme agitation and hallucinations may require the administration of IV droperidol (up to 0.1 mg/kg). Since haloperidol lowers the seizures threshold, and is associated with neuroleptic malignant syndrome, it is not advisable.
      ii. Convulsions can be managed with benzodiazepines (IV diazepam), phenytoin, or barbiturates. Refractory cases may require curarisation.
      iii. Hyperthermia should be tackled aggressively with hypothermic blankets, ice baths, and dantrolene infusions. Large IV doses of benzodiazepines can help. Refractory cases must be subjected to neuromuscular paralysis and mechanical ventilation.
      iv. Tachycardia can be managed with beta blockers (atenolol). Labetolol which has combined alpha and beta blocking effects, may be preferable if tachycardia is associated with hypertension. Sedation with intravenous benzodiazepines (diazepam 5 to 10 mg IV repeated every 5 to 10 minutes as needed) is usually sufficient for treating hypertension. A short acting, titratable agent such as sodium nitroprusside should be considered if unresponsive to benzodiazepines.
      v. For ventricular arrhythmias: Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia. Sotalol is a good alternative. Amiodarone and sotalol should be used with caution if the QT interval is prolonged, or if torsades de pointes is involved in the overdose. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present, and PVCs are thought to represent an escape complex.
      vi. For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy, and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is not routinely recommended.
      vii. Diazepam and chlorpromazine have been effective in treating amphetamine-induced chorea.
      viii. Although peritoneal dialysis and haemodialysis have been demonstrated to enhance elimination of amphetamine, the clinical efficacy of these procedures in human overdose has not been proven and they are rarely if ever clinically indicated. Acidification of urine enhances amphetamine excretion, but may precipitate acute renal failure in patients with myoglobinuria and is therefore contraindicated.

2. **Chronic Poisoning:**
   a. Most casual users of amphetamines do not need treatment. Those with moderately severe dependence can be treated on an outpatient basis without using drugs. Strategies range from residential and ambulatory detoxification to day treatment, multistep activities, and case

management. It is preferable to provide a structured and manualised cognitive behavioural treatment, making use of a combination of group and individual counselling.

b. A wide variety of pharmacological agents have been tried as adjuncts to (or major elements in) the treatment of amphetamine dependence. These include drugs such as imipramine and fluoxetine, but results have been disappointing.

■ Designer Amphetamines

Designer drugs are congeners of active compounds that have been modified from legitimate pharmaceutical agents, and are used for recreational purposes. Apart from amphetamines, there are several other groups of designer drugs **(Table 16.2)**, which have been discussed in detail elsewhere. Designer drugs are usually stronger and cheaper than the parent compound, and can be easily synthesised in clandestine laboratories. The term "designer drug" does not include new forms or new dosing routes of old drugs (e.g. cocaine used in freebase form, i.e. "crack"). It also does not include legal drugs which are abused (e.g. ephedrine, caffeine, phenylpropanolamine, etc.).

The first designer amphetamine to be developed was methylenedioxymethamphetamine, which was introduced by E Merck and Company in Germany in 1914. However, it was never marketed. It was only in the 1970s and early 1980s that it made its appearance as an "underground" drug.* Since 1983 it has become increasingly popular among adolescents and college students as a recreational drug to be used during "rave parties" which are extended dance parties often lasting all night long. The other designer amphetamines (**Table 16.2**) quickly followed and are mostly available as gelatin capsules or loose powder for ingestion. They have made their way into India in the late 1990s, and are quite openly abused by college students from affluent families.

Mode of Action

- While designer amphetamines share a number of properties with the original amphetamines, unlike the latter, they are potent releasers of serotonin.
- Chronic administration can result in permanent damage to serotonergic neurons.

Uses

Methylenedioxymethamphetamine (MDMA) was used in the early years following its synthesis, by psychologists to enhance psychotherapy. Today, there are no legal uses for any of the designer amphetamines.

Clinical Features

1. Designer amphetamines are abused by teenagers and young adults for inducing euphoria, facilitating intimacy and verbosity, and heightening sexuality. Users of MDMA report that it "expands consciousness" without making them lose control. Sometimes these drugs are labeled "entactogens" for their alleged ability to increase sensitivity to touch, or "empathicogens", for their alleged ability to create empathy, especially before sexual encounters. MDMA is considered an "entheogen" which means "to become divine from within". Entheogen refers to a state of shamanic or ecstatic possession induced by ingestion of mind-altering drugs.

2. "*Candyflipping*" refers to the intentional combination of ecstasy with LSD. Another method of use is called "*stacking*" in which 3 or more tablets of MDMA are taken at once; or MDMA is mixed with alcohol, cannabis or some other drug (ketamine, GHB, cocaine, etc.) in order to modify the "high". Stacking can increase the risk of overdose, since MDMA, acting as a stimulant, can mask the sedative effects of alcohol or any other drug. There is current vogue for combining ecstasy with sildenafil to enhance sexual pleasure (*"sexstasy"*).

3. Effects are seen 30 to 45 seconds after ingestion (on an empty stomach) in the form of a 'rush', which lasts 15 to 30 minutes. This is followed by a sense of clarity and joy. A booster dose may be taken at this point, to prolong these feelings. About ½ hour to 3 hours after the initial ingestion, a "plateau" phase occurs in which repetitive or trance-like movements become extremely pleasurable. The "coming down" phase occurs 3 to 6 hours after the initial ingestion, and can lead to negative feelings or emotions (depression, anxiety). Symptoms may persist for several days.

Table 16.2: Designer Drugs				
Amphetamines	*Opiate Derivatives*	*Methaqualone Derivatives*	*Arylhexyl-amines*	*Phenylethyl-amines*
Methamphetamine ("Speed" "Crystal" "Ice") Methylenedioxymethamphetamine or MDMA ("Adam", "Ecstasy", "XTC" "MDM", "M&M") Methylenedioxyamphetamine (MDA) Methylenedioxyethamphetamine (MDEA) ("Eve") Dimethoxymethylamphetamine or DOM Bromodimethoxyamphetamine or Bromo-DMA or DOB Bromomethoxyloxyphenylethylamine or 2-CB/ MFT ("Afterburner") Trifluoromethylphenyl-piperazine ("Molly")	1. Fentanyl derivatives: Alpha-methylfentanyl ("China white") Methylfentanyl 2. Pethidine derivatives: Methylphenylpropionox-ypiperidine or MPPP Methylphenyltetrahy-dropyridine or MPTP	Mecloqualone Nitromethaqualone	Phencyclidine	Mescaline

* Any drug of abuse that is not certified as having therapeutic uses by the Food and Drug Administration of USA is termed an "underground drug".

4. Acute toxicity results in nausea, anorexia, anxiety, mydriasis, hyperthermia, muscle rigidity, trismus, sinus tachycardia, sweating, tachypnoea, cardiac arrhythmias, cardiac arrest, metabolic acidosis, rhabdomyolysis, myoglobinuria, acute renal failure, and disseminated intravascular coagulation. The following have also been reported: convulsions, cerebral infarcts, hallucinations, paranoia, chest pain, hyperkalaemia, and fulminant hepatic failure. Pulmonary oedema and ARDS may occur in severe intoxications. Coma may develop in severe cases.

5. Chronic use results in anorexia, weight loss, exhaustion, jaundice, irritability, flashbacks, paranoia, depression, or psychosis. However, since frequent use diminishes the pleasurable effects of these drugs, users often taken them only at intervals of 2 to 3 weeks, and then gradually lose interest and stop intake altogether over a period of time.* There appear to be no reports of individuals who take excessive doses of these drugs frequently over an extended period of time.

6. Ecstasy has been associated with cardiovascular and musculoskeletal malformations in babies exposed *in utero*.

Treatment

Treatment measures are essentially the same as for all amphetamine poisonings.

Medicosocial and Forensic Issues

- Amphetamines are the most widely used illicit drugs (second only to cannabis) in the United Kingdom, Australia, and many parts of Europe. Significant abuse also occurs in the USA. After the introduction of amphetamines into clinical use in the early 1930s, they were available as prescription drugs for various indications (obesity, narcolepsy, attention deficit disorder, psychotherapy), and even sold over the counter in the form of nasal inhalers till the early 1970s. Since then their pharmaceutical use has been greatly curtailed, though many of these drugs are still available (under restriction) in Western countries. They are virtually banned in India.

- Japan experienced an epidemic of intravenous methamphetamine abuse in the years following the Second World War. Crystalline methamphetamine ("ice") was introduced in the 1980s in Hawaii, and quickly became popular in other countries.

- Today, designer amphetamines are a rage among adolescent party-goers, and are used extensively in the course of "rave parties". This fad has now gripped several metropolitan Indian cities where tablets of Ecstasy are available freely among elite circles (**Fig 16.3**). Much of this popularity has to do with the copious amount of information existing on these drugs on the Internet, and the fact that unlike certain other drugs like heroin and cannabis, designer drugs are considered "hep" and "cool". Also, unlike many other hard drugs, designer drugs can be easily consumed (ingested) without the messiness of nasal insufflations, smoking, or injection.

Fig 16.3: "Ecstasy" pills

- Adulteration of MDMA tablets may be done with oriental herbal ephedrine (*Ma Huang*) or ketamine.
- Paramethoxyamphetamine (PMA, "death") a ring-substituted amphetamine (methoxylated phenethylamine derivative) has been fraudulently marketed as MDMA, and has caused several deaths.

■ Cocaine

Source

- Cocaine (*"coke"* or *"snow"*) is a natural alkaloid present in the leaves of the coca plant (**Fig 16.4**), i.e. *Erythroxylon coca*,** a shrub that grows well in South America, Mexico, Indonesia, and West Indies.
- Chemically, cocaine is benzoylmethylecgonine, and belongs to the tropane family of natural alkaloids, other members of which include atropine and scopolamine.

Fig 16.4: Coca plant

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* Freshmen love it, sophomores like it, juniors are ambivalent, and seniors dislike it!
** Not to be confused with cocoa plant, i.e., *Theobroma cacao*, from which cocoa is obtained, one of the sources of caffeine.

- It occurs as colourless to white crystals, or white crystalline powder.

Mode of Intake

- Cocaine is usually abused by either chewing coca leaves, smoking coca paste, or "snorting" cocaine hydrochloride (**Fig 16.5**). The last mentioned is the most popular form of cocaine intake, i.e. the drug is inhaled in powder form through the nostrils (**Fig 16.6**). Occasionally, cocaine hydrochloride is injected intravenously.
- Today, a smokable form of cocaine ("*crack*" or *"rock"*) has virtually become a rage in the West. Pure alkaloidal cocaine ("*free-base*" or *"baseball"*) can also be smoked. Occasionally coca paste or cocaine sulfate (cocaine base, "*pasta*", "*bazooka*") is smoked.
- Cocaine freebase is prepared from cocaine hydrochloride by extracting the cocaine with an alkaline solution (buffered ammonia) and adding a solvent such as ether or acetone. The mixture separates into two layers, the top solvent layer containing the dissolved cocaine. The solvent is then evaporated leaving almost pure cocaine crystals.
  - ❖ "*Free-base*" is a colourless, odourless, transparent, crystalline substance that makes a popping or cracking sound when heated (hence the term "*crack*").
  - ❖ Both free-base and crack are more stable to pyrolysis than the hydrochloride salt, and therefore can be smoked either using a "coke pipe" or mixed into a cigarette ("*joint*").

Fig 16.5: Cocaine powder

Fig 16.6: "Snorting" cocaine

- ❖ A solution of cocaine hydrochloride can also be heated in a pan with baking soda added until a solid "*rock*" is formed, pieces of which can be smoked directly.
- Street cocaine is often impure. The content of pure cocaine ranges from 10 to 50 percent (most commonly 15 to 20 percent). Cocaine which is available on the street is often adulterated with one or more of the following compounds: talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, lignocaine, strychnine, amphetamine, or heroin ("*speed ball*").

Uses

1. Topical anaesthetic (4 to 10% solution) for intranasal and bronchoscopic procedures.
2. Ophthalmologic anaesthesia.
3. Relief of severe (oncologic) pain: Cocaine is one component of Brompton's cocktail, (the others being morphine, chlorpromazine, and alcohol), which is popular in Europe for the control of intractable pain associated with some forms of cancer.
4. Cocaine is one of the components of TAC (the others being tetracaine and adrenaline) which is sometimes used as a topical anaesthetic in children with scalp and facial lacerations.

Mode of Action

- CNS:
  - ❖ Cocaine is the most powerful naturally derived CNS stimulant known to man. Stimulation of the brain occurs in a rostral-to-caudal fashion. The cortex is stimulated first resulting in excitement, restlessness, and increased motor activity. Subsequent stimulation of lower motor centres produces tonic-clonic convulsions. The medulla is at first stimulated resulting in an initial increased respiratory rate, followed by depression with resultant respiratory failure.
  - ❖ The CNS stimulant effects of cocaine are mediated through inhibition of dopamine reuptake in the nucleus accumbens. The dopamine-reuptake transporter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release. Cocaine, which binds strongly to the dopamine-reuptake transporter, is a classic blocker of such reuptake after normal neuronal activity. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons producing the characteristic cocaine "high".
  - ❖ Cocaine also increases the concentrations of the excitatory amino acids, aspartate and glutamate in the nucleus accumbens. These excitatory amino acids increase the extracellular concentrations of dopamine. Excitatory amino acid antagonists attenuate the effects of cocaine induced convulsions and death. Dopamine$_2$ (D$_2$) receptor agonists accentuate cocaine craving, while dopmanie$_1$ (D$_1$) agonists diminish such craving.

- ❖ Cocaine also inhibits reuptake of noradrenaline and serotonin. Increase in the concentrations of the former plays an important role in the toxic effects of cocaine.
- ■ Peripheral nerves:
  - ❖ Through direct blockade of fast sodium channels, cocaine stabilises the axonal membrane, producing a local anaesthetic effect. Cocaine is the only local anaesthetic that interferes with the uptake of neurotransmitter by the nerve terminals and simultaneously functions as a vasoconstrictor.
- ■ CVS:
  - ❖ Initial effect of cocaine on the CVS is bradycardia, secondary to stimulation of vagal nuclei. However, the bradycardia is too transient to be clinically evident, and tachycardia becomes the prominent effect resulting from central sympathetic stimulation. The cardiostimulatory effect of cocaine is due in large part to sensitisation to adrenaline and noradrenaline, preventing neuronal reuptake of these catecholamines, as well as due to increased release of noradrenaline from adrenergic nerve terminals. The increased concentrations and persistence of catecholamines near the receptors of the effecter organ lead to exaggerated sympathetic effects.
  - ❖ The sympathomimetic effects of cocaine increase myocardial oxygen demand and the alpha-adrenergic mediated coronary vasoconstriction limits coronary artery blood flow.
  - ❖ Cocaine inhibits endogenous fibrinolysis, increases thrombogenicity, and enhances platelet aggregation.

Toxicokinetics

- ■ Absorption—
  - ❖ *Ingestion and insufflation*: Cocaine is well-absorbed from oral, nasal, and pulmonary routes. Onset of action on insufflation is within 1 to 3 minutes, and peak effects are seen in 20 to 30 minutes.
  - ❖ *Intravenous injection*: Onset of action is within seconds, and peak action occurs in 3 to 5 minutes.
  - ❖ *Inhalation*: Smoking produces effects as rapidly as IV injection.
- ■ Metabolism—
  - ❖ Cocaine is metabolised by liver esterases and plasma cholinesterase to ecgonine methylester (EME), one of the major metabolites, while non-enzymatic hydrolysis results in the formation of the other major metabolite, benzoylecgonine (BE). Minor metabolites include norcocaine ecgonine, ecgonidine, norecgonidine methyl ester, norecgonine methyl ester, and *m*-hydroxybenzoylecgonine.
  - ❖ Patients with lower plasma cholinesterase levels may be predisposed to more severe cocaine toxicity. Since children have lower plasma cholinesterase levels, they may be affected by smaller amounts of cocaine. In addition, the metabolic half-life of cocaine may be increased by lower plasma cholinesterase concentrations.

- ■ Excretion—
  - ❖ Excretion is mainly through urine. Due to the long elimination half-life of BE, assays for its detection in urine may be successful up to 2 to 3 days following cocaine use. In rare cases, it has been detected even after 3 weeks.

Clinical Features

1. **Acute Poisoning:**
   a. Hyperthermia—This results from:
      i. Augmentation of heat production due to increased psychomotor activity.
      ii. Diminution of heat dissipation due to vasoconstriction.
      iii. Direct pyrogenic effect due to action on thermoregulatory centres in the hypothalamus.
      iv. Stimulation of calorigenic activity of liver. Body temperature often soars to 108 to 112°F, and does not respond to conventional antipyretics. It is often associated with rhabdomyolysis, seizures, and renal failure.
   b. CNS effects—
      i. Headache: Three patterns of cocaine-induced headaches have been identified –
         - *Pattern 1*—Develops within minutes, and lasts for 2 to 48 hours. The headache is usually occipital or bilateral, with associated throbbing, photophobia, nausea, and vomiting.
         - *Pattern 2*—Occurs during a cocaine "binge", (4 to 14 days of abuse, 1 to 3 g/day), with onset after a few days, which increases in severity progressively. It is mostly frontal, with associated throbbing, nausea, and sometimes diplopia and dizziness.
         - *Pattern 3*—Occurs 1 to 4 days after the last dose of cocaine, and worsens over the next 1 week with continued abstinence. It is also frontal, with associated throbbing, nausea, vomiting, photophobia, and occasionally neck stiffness.
      ii. Anxiety, agitation.
      iii. Hyperactivity, restlessness.
      iv. Tremor, hyperreflexia
      v. Convulsions: Generalised tonic-clonic, partial motor, and partial complex seizure have all been reported. Seizures may be recurrent and status epilepticus has been reported, particularly in children. Sometimes there is lethargy and decreased level of consciousness which can persist up to 24 hours ("*cocaine washed out syndrome*").
      vi. Cerebrovascular accidents are not uncommon, and include subarachnoid haemorrhage, intracerebral haemorrhage, cerebral infarction, transient ischaemic attacks, migraine-type headache syndrome, cerebral vasculitis, and anterior spinal artery syndrome. Infarction of the brainstem/spinal cord has also occurred.

c. Psychiatric effects—
   i. Paranoid state with suspiciousness, hypervigilance, anxiety.
   ii. Stereotypy.
   iii. Hallucinations.
   iv. Toxic delirium.
d. Ophthalmologic effects—
   i. Mydriasis and/or loss of eyebrow and eyelash hair from smoking crack cocaine may occur.
   ii. Corneal abrasions/ulcerations due to particulate matter in smoke ("*crack eye*").
   iii. Central retinal artery occlusion and bilateral blindness due to diffuse vasospasm. Retinal foreign body granuloma may occur with IV abuse.
e. CVS effects—
   i. Tachycardia.
   ii. Systemic arterial hypertension.
   iii. Coronary artery vasoconstriction with myocardial ischaemia and infarction.
   iv. Tachyarrhythmias of all types can occur, including sinus tachycardia, atrial fibrillation or flutter, other supraventricular tachycardias, ventricular premature contractions, ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Sinus tachycardia is the most common finding. If hypertension is significant, a reflex bradycardia may occur.
   v. Chronic dilated cardiomyopathy has been reported.
   vi. Aortic dissection and rupture.
   vii. Coronary artery dissection.
   viii. Sudden cardiac death can occur.
f. Pulmonary effects—
   i. Thermal injuries to the upper airway leading to epiglottitis, laryngeal injury, and mucosal necrosis have been reported after smoking "crack" or free base cocaine.
   ii. Exacerbation of asthma.
   iii. Noncardiogenic pulmonary oedema.
   iv. Pneumothorax, pneumomediastinum.
   v. Diffuse alveolar haemorrhage.
   vi. Bronchiolitis obliterans with organising pneumonia.
g. Musculoskeletal effects—
   i. Rhabdomyolysis with hyperthermia, massive elevation of creatine phosphokinase, and acute renal failure: Although the mechanism of cocaine-associated rhabdomyolysis is unclear, it is postulated that it may result from ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure activity.
h. GI effects—
   i. Acute mucosal ischaemia.
   ii. Colitis.
   iii. Intestinal perforation: It is postulated that cocaine blocks the reuptake of noradrenaline leading to mesenteric vasoconstriction and focal tissue ischaemia and perforation.
   iv. Pneumoperitoneum has been reported after smoking crack cocaine.
   v. Hepatic necrosis (centrilobular, midzonal, and panlobar) has been reported in overdose.
i. Renal effects—
   i. Renal failure, usually secondary to myoglobinuria and rhabdomyolysis, has been reported after intravenous or intranasal cocaine use.
   ii. Renal infarction has occurred following intravenous cocaine use.
j. Uteroplacental effects—
   i. Increased incidence of spontaneous abortion, low birthweight, and abruptio placentae.
   ii. Neonatal intoxication may also occur. Infants exposed to cocaine in utero may display tremulousness, impaired orientation, increased startle response, irritability, muscular rigidity, arousal deficits, impaired motor ability, and lower scores on the Brazelton Neonatal Behavioral Assessment Scale (measuring interactive behaviour and response to environmental stimuli).
   iii. There are indications that cocaine may be teratogenic.
k. Miscellaneous effects—
   i. Priapism has been observed after topical application of cocaine to the glans penis.
   ii. Severe metabolic acidosis has been reported due to seizures, agitation, and hypotension.
l. Drug combination effects—
   i. Cocaine is often combined with other drugs such as ethanol and heroin.
      - Concurrent use of cocaine and ethanol produces additive effects on the brain. It results in the formation of the metabolite, cocaethylene which is more cardiotoxic, and is associated with enhanced mortality.
      - Combination of cocaine with heroin is referred to as "s*peed ball*" and is reputed to produce a double effect of initial high "kick" of cocaine, followed by subsequent euphoric "rush" of heroin. "*Speed ball*" is usually injected.

2. **Chronic Poisoning:**
   a. Cocaine dependence—
      i. Cocaine dependence is defined as a cluster of physiological, behavioural, and cognitive symptoms that, taken together, indicate that the person continues to use cocaine despite significant problems related to such use.
      ii. Some cocaine users can use cocaine intermittently without becoming dependant, though it is not clear how long such intermittent, nondependant use can continue. Intermittent use consists of episodes or binges of use, often starting on weekends and paydays, and lasting until the drug supply is exhausted or toxicity develops.
      iii. Such binges, during which the drug may be used every 15 to 30 minutes, can last 7 or more

consecutive days (though usually this extends to only 3 or 4 days). When the binge comes to an end, a "*cocaine crash*" occurs.

b. Cocaine abuse—

   i. Some cocaine abusers develop problems or adverse effects related to their drug use (i.e. their use is maladaptive). Examples of such recurrent maladaptive patterns include use that leads to multiple legal problems, failure to meet major social, school, or work-related obligations, and continued use despite social or vocational difficulties caused by, or aggravated by cocaine use. When one or more such substance-related problems occur in a 12-month period, the diagnosis of cocaine abuse is made.

   ii. Chronic use of cocaine leads to CNS dopamine depletion and increases in the number and sensitivity of dopamine receptors. The dysphoric state associated with cocaine withdrawal (*vide infra*) and craving for cocaine appears to be a result of the dopamine-depleted condition.

   iii. Features of chronic cocaine use:
- Anorexia, emaciation.
- Mydriasis
- Agitation, restlessness: A cocaine-associated *agitated delirium syndrome* has been identified, comprising the following in sequence: hyperthermia, delirium with agitation, respiratory arrest, and death.
- Hallucinations, especially tactile, characterised by a crawling sensation under the skin ("*cocaine bugs*") with resultant excoriation, leading to irregular scratches and ulcers (Magnan's sign). Perceptual disturbances or pseudo-hallucinations involving vision ("snow lights", geometric patterns), smell, hearing, and taste have also been reported.
- Tremor.
- Recurrent chest pain.
- Cardiomyopathy
- Psychiatric changes: Depression, psychosis, panic disorders, attention deficit disorders, and eating disorders.
- Decreased libido, impotence, gynaecomastia, galactorrhoea, amenorrhoea, and sexual dysfunction are common with chronic cocaine abuse.
- *"Crack hands"*: A syndrome of multiple, blackened, hyperkeratotic lesions (linear or circular), of the fingers and palms has been described in crack cocaine smokers. These lesions probably result from the heat of the glass cocaine pipe.
- Maternal chronic cocaine use during pregnancy has been suggested as a possible factor in Sudden Infant Death Syndrome. Cocaine readily passes into breast milk and can cause adverse effects in the nursing infant.
- Evidence of medical complications (**Table 16.3**):

Table 16.3: Medical Complications of Cocaine

CNS—

Tremors, convulsions, "sympathomimetic storm", migraine headaches, cerebral vasculitis, cerebral infarction, intracranial haemorrhages

CVS—

Hypertension, cardiac arrhythmias, myocardial ischaemia, myocardial infarction, cardiomyopathies, myocarditis, endocarditis, aortic rupture

RS—

Alveolar haemorrhage, ARDS, pneumomediastinum, pneumothorax, pulmonary thrombosis

GI—

Mesenteric ischaemia, malnutrition

ENT—

Rhinitis, nasal septal necrosis, sinusitis, laryngitis

Metabolic—

Hyperthermia, hypoglycaemia, lactic acidosis, hypo/hyperkalaemia

Renal—

Rhabdomyolysis-induced renal failure

Psychiatric—

Depression, paranoia, violent behaviour

Obstetric and Paediatric—

Abruptio placentae, abortion, prematurity, growth retardation

Infections (IV use)—

Hepatitis B, AIDS, endocarditis

    » Extensive bony destruction of the orbital walls with associated orbital cellulitis may occur in patients with a history of chronic intranasal cocaine abuse.

    » Intestinal ischaemia following cocaine ingestion, injection, or crack use has been described.

    » Hepatic damage with elevation of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase is common.

    » Cocaine withdrawal—Conventionally, cocaine withdrawal is said to occur in 3 phases:

   iv. *Phase I*—("Crash"):
- The total duration of this phase lasts for anywhere between 9 hours and 4 days, and is subdivided further into the following stages –
    » Early: Agitation, depression, anorexia, intense craving for cocaine.
    » Intermediate: Fatigue, tendency to sleep, decreased craving.
    » Late: Exhaustion, hypersomnia, hyperphagia, absence of craving.

   v. *Phase II*—Normalised sleep, improved mood, followed subsequently by return of anergia, anhedonia, anxiety, and increased craving.

   vi. *Phase III*—("Extinction"): Increased tendency to relapse. The extinction phase may be prolonged

and consists of brief, episodically evoked cravings that occur months to years after withdrawal.

Usual Fatal Dose

- About 500 mg (*oral*)
- About 100 mg (*mucosal contact*)
- Lethal blood level: 0.2 mg/100 ml
  Chronic users of cocaine can tolerate much higher doses.

Diagnosis

1. Blood or plasma cocaine levels are not clinically useful, although they may be advisable to be done in medicolegal cases. Qualitative urine tests using kits may be helpful in clinical diagnosis (by utilising chromatography, radioimmunoassay, enzyme immunoassay, fluorescence polarisation immunoassay, and enzyme-multiplied immunoassay technique). Cocaine metabolites can be identified in the urine and provide a method for qualitatively identifying suspected cocaine poisoning or abuse. Benzoylecgonine, the major metabolite of cocaine, can usually be detected in urine for 48 to 72 hours after cocaine use.

2. Other Diagnostic Clues—
   a. *Hair analysis*: Cocaine benzoylecgonine and ecgonine methyl ester can be analysed in hair samples by GC-MS and RIA. This can be done in adults, as well as in any infant whose mother was a cocaine user. It must be noted that external contamination of hair can occur from crack smoke, but that can be washed off, whereas systemic exposure is not affected by washing the hair.
   b. *ECG*: Non-Q-wave myocardial infarction, with the presence of a Twave infarct ECG pattern is often seen in cocaine users. During acute cocaine use abnormalities are more prevalent, and the QT interval is prolonged. Two-dimensional echocardiography may be useful in detecting the presence of new regional wall-motion abnormalities in patients experiencing cocaine-induced chest pain. Troponin levels may be more useful in evaluating potential myocardial injury than creatinine kinase.
   c. *Acid-base abnormalities*: Arterial blood gases in cocaine abusers show a pH varying from 7.35 to 7.5. Alkalosis (pH > 7.45) is caused by hyperventilation, and is manifested by tachypnoea and low $PaCO_2$. About one third of patients show evidence of acidosis which may be the result of hypoventilation secondary to depressed mental status or chest trauma. Metabolic acidosis is not uncommon, and usually results from convulsions, agitation, or trauma.
   d. Estimate serum creatine kinase for evidence of rhabdomyolysis. Monitor renal function and urine output in patients with elevated CPK.
   e. *X-ray*: Body packer syndrome (*page no 179*) can be diagnosed by plain films of the abdomen in the supine and upright positions. However, false negatives have been reported. Radiography may not detect cellophane-wrapped packets or crack vials. Even false-negative abdominal CT scans have been reported. It is therefore advisable to perform a contrast study of the bowel with follow-up X-rays 5 hours after the oral ingestion of a water-soluble contrast compound such as meglumine amidotrizoate (50 ml). Daily views are performed thereafter until negative views coincide with the passage of two drug packet-free stools.

Treatment

1. **Acute Poisoning:**
   a. Activated charcoal adsorbs cocaine in vitro under both acidic and alkaline conditions, and can be administered in cases of ingestion.
   b. Hyperthermia—
      i. Minimise physical activity and sedate with benzodiazepines.
      ii. Ice baths, packs, cool water with fans, etc.
      iii. Oxygen $D_{50}W$ (as necessary).
      iv. Diazepam 5 mg IV or lorazepam 2–4 mg IV titrated to effect.
      v. Paracetamol 2000 mg (in the form of 500 mg rectal suppositories).
      vi. Severe, intractable cases may respond to dantrolene (1 mg/kg) every 6 hours. Alternatively, bromocriptine can be administered orally in a nasogastric tube.
   c. Anxiety and agitation—
      i. Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect.
      ii. Physical restraints.
      iii. Antipsychotics such as haloperidol or droperidol, and phenothiazines are not recommended since they can induce malignant hyperthermia and convulsions.
   d. Convulsions—
      i. Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect.
      ii. Phenobarbitone 25–50 mg/min up to 10–20 mg/kg.
      iii. If seizures are not controlled by the above measures, consider continuous infusion of midazolam (0.2 mg/kg slow bolus, or 0.75 to 10 mcg/kg/min as infusion), or propofol (1 to 2 mg/kg, followed by 2 to 10 mg/kg/hr) or pentobarbitone (10 to 15 mg/kg at a rate of 50 mg/min, followed by 0.5 to 1 mg/kg/hr).
      iv. Intractable convulsions may require neuromuscular paralysis with intubation and mechanical ventilation.
   e. Cerebrovascular accidents—Neurosurgical consultation is mandatory.
   f. Hypertension—
      i. Without tachycardia:
         - Phentolamine 0.02 to 0.1 mg/kg IV
         - Nifedipine 0.1 to 0.2 mg/kg IV
         - Nitroprusside 2 to 10 mcg/kg/min IV.
      ii. With tachycardia:
         - Labetolol 10 to 20 mg IV, repeated every 10 minutes (max: 300 mg). Labetolol must be used with caution (**Table 16.4**).
         - Nitroglycerine IV titrated to effect.

Table 16.4: Drugs to be Avioded in the Treatment of Cocaine Poisoning

Drug	Adverse Effects
Beta blockers (especially propranolol)	Coronary artery spasm (Paradoxical hypertension)
Lignocaine, procainamide, quinidine	Convulsions Arrhythmias
Haloperidol, droperidol, phenothiazines	Hyperpyrexia Convulsions
Dantrolene	Cardiac insufficiency
Bromocriptine	Coronary artery constriction
Aspirin	Thyrotoxicosis (thyroid storm)

iii. With chest pain:
- Nitroglycerine drip.
- Oxygen by nasal cannula (5 L/min).
- Monitor cardiac status.
- If systolic BP is higher than 120 mmHg, administer nitroglycerine sublingually (up to 3 tablets or 3 sprays of 0.4 mg each).
- If pain does not respond to nitroglycerine, use morphine (2 mg IV titrated to pain relief).
- Obtain ECG.
- If chest pain is strongly suggestive of a myocardial infarction, consider thrombolytic therapy.
- Diazepam 5 mg IV, or lorazepam 2–4 mg IV titrated to effect can prevent excess production of catecholamines by the CNS.
- Mechanical reperfusion (angioplasty).

g. Arrhythmias—
i. Sinus tachycardia:
- Observation.
- Oxygen.
- $D_{50}W$ (as necessary).
- Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect (if indicated).
ii. Supraventricular tachycardia:
- Observation
- Oxygen
- $D_{50}W$ (as neccesary).
- Diltiazem 20 mg IV, or verapamil 5 mg IV.
- Adenosine 6–12 mg IV for AV node re-entry.
- Cardioversion (if necessary).
iii. Ventricular arrhythmias:
- Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia).
- Oxygen.
- $D_{50}W$ (as necessary).
- Hypertonic sodium bicarbonate: Sodium bicarbonate may be useful in the treatment of QRS widening and ventricular arrhythmias associated with acute cocaine use. A reasonable

starting dose is 1 to 2 mEq/kg repeated as needed. Monitor arterial blood gases, maintain pH 7.45 to 7.55.
- Diazepam 5 mg IV, or lorazepam 2–4 mg IV.
- Lignocaine 1.5 mg/kg IV bolus, followed by 2 mg/min infusion. Watch out for adverse effects (**Table 16.4**). Procainamide may also be used with caution.
- Defibrillation (if haemodynamically unstable).

h. Myocardial infarction—
i. IV line.
ii. Oxygen.
iii. Aspirin to inhibit platelet aggregation. Watch out for increased thyroxine levels (**Table 16.4**).
iv. For systolic BP higher than 100 mmHg, administer sublingual nitroglycerine or nifedipine 10 mg orally, or phentolamine 1 to 5 mg IV (followed by a drip of 10 mg in 1 litre of D_5W at 10 ml/min).
v. For life-threatening arrhythmias, use of type IA antiarrhythmic agents may be considered (with caution).
vi. Thrombolytic therapy may be necessary if myocardial infarction is not amenable to relief by nitrates, calcium channel blockers, or phentolamine. Caution about the use of thrombolytics in cocaine-associated acute myocardial infarction (AMI) is generally advocated. Thrombolytics should be avoided in patients with cocaine-induced myocardial infarction and uncontrolled hypertension, because of the increased risk of intracranial haemorrhage.

i. Aortic dissection—The hypertension that precipitated aortic dissection must be controlled immediately with nitroprusside and calcium channel blockers.

j. Pulmonary oedema—
i. Frusemide 20–40 mg IV.
ii. Morphine sulfate 2 mg IV titrated to pain relief.
iii. Nitroglycerine drip titrated to blood pressure or respiratory status.
iv. Phentolamine or nitroprusside (if necessary).
v. Incubate and ventilate.
vi. Monitor fluids with pulmonary artery catheter.

k. Rhabdomyolysis—
i. Cardiac monitoring.
ii. Serial potassium determinations.
iii. Serial serum creatine kinase and urine myoglobin studies.
iv. IV hydration (urine output must be maintained at 3 ml/kg/hr).
v. Dopamine and frusemide (60 mg three times a day) may reduce renal vascular resistance and help in reducing the number of haemodialyses required to reverse oliguria.

l. Acidosis—Correction of acidaemia through supportive care measures such as hyperventilation, sedation, active cooling, and sodium bicarbonate infusion can have beneficial effects on conduction defects.

m. Elimination enhancement measures—

i. Cocaine is rapidly metabolised. Forced diuresis, urine acidification, dialysis, and haemoperfusion are ineffective in significantly altering elimination.

ii. Increasing the level of butyrylcholinesterase in the blood (which metabolises cocaine to inactive compounds) could help in rapidly inactivating cocaine in acute intoxications.

2. Chronic Poisoning:

a. Psychotherapy—This involves cognitive-behavioural, psychodynamic, and general supportive techniques. One example of a cognitive-behavioural method uses contingency contracting, in which it is agreed in advance that for a specified period of time (e.g. 3 months), if the patient uses cocaine (as detected by supervised urine testing), the therapist will initiate action that will result in serious adverse consequences for the patient, such as informing the employer.

b. Group psychotherapy—

   i. Interpersonal group therapy focuses on relationships, and uses the group interactions to illustrate the interpersonal causes of individual distress, and to offer alternative behaviours.

   ii. Modified dynamic group therapy is concerned with emphasising character as it manifests itself individually and intrapsychically, and in the context of interpersonal relationships with a focus on affect, self-esteem, and self-care.

c. Group counselling—The most widely used form of psychosocial treatment for cocaine dependence is group counselling, in which the group is open-ended with rolling admissions; the group leaders are drug counsellors, many of whom are recovering from addiction, and the emphasis is on providing a supportive atmosphere, discussing problems in recovery, and encouraging participation in multistep programmes.

d. Pharmacotherapy—

   i. Several drugs have been tried to help ameliorate the manifestations of cocaine withdrawal. Many of these (fenfluramine, trazodone, neuroleptic agents, etc.) have either not demonstrated clinical efficacy, or have produced serious side effects.

   ii. Bromocriptine has successfully reduced cocaine craving and decreased withdrawal symptoms in several studies. Oral doses of 0.625 mg given 4 times daily may produce a rapid decrease in psychiatric symptoms. Dose can be decreased in patients experiencing adverse effects.

   iii. Amantadine, a dopamimetic agent, increases dopaminergic transmission and has been found to be useful in the treatment of early withdrawal symptoms and short-term abstinence. The usual dose recommended is 200 mg to 400 mg orally, daily, for up to 12 days. It is probably as effective as bromocriptine, and less toxic.

   iv. Tricyclic antidepressants may be useful for selected cocaine users with comorbid depression or intranasal use.

   v. Initial studies with fluoxetine promised good results, but craving actually worsened in some patients. Several studies indicated better efficacy with carbamazepine for controlling craving. Carbamazepine at doses of 200 to 800 mg orally, 2 to 4 times daily has benefited some patients. Phenytoin also shows promise in helping to sustain abstinence from cocaine in some patients.

Autopsy Features

- There are no specific findings at autopsy, except for nasal septal ulceration and perforation if the deceased had been a long-term abuser of cocaine. Histological study of nasal septal mucosa in such cases may reveal characteristic changes including arteriolar thickening, increased perivascular deposition of collagen and glycoprotein, and chronic inflammatory cellular infiltration.

- Histopathology of heart may demonstrate microfocal lymphocytic infiltrates, acute coronary thrombosis, early coagulation necrosis of myocardial fibres, and non-atherosclerotic coronary obstruction due to intimal proliferation.

- Cocaine can be recovered by sampling from recent injection sites, or by swabs from the nasal mucosa. It can also be recovered from the liver and especially brain, where cocaine may be found not only in dopamine-rich areas such as caudate, putamen, and nucleus accumbens, but also in other extra-striatal regions.

- Specimens obtained postmortem should be preserved with sodium fluoride, refrigerated, and analysed quickly. Tissue specimens should be frozen.

Mediocosocial and Forensic Issues

- Cocaine has been abused for centuries, but its toxic properties have been studied extensively only in the last couple of decades. In the current drug subculture, cocaine has become the "*champagne drug*" because of its cost and relative scarcity. The situation is not much different in India with cocaine abuse restricted mainly to the affluent classes of society.

- Cocaine has always been popular with musicians (especially jazz and rock), other artistes, and film personalities. Today cocaine has made inroads into the general population, especially adolescents. After the cocaine epidemic of the 1970s ("snorting seventies") in the West, there had been a relative lull in the 1980s and early 1990s. A recent survey shows the cocaine resurgence of the 21st century has not only affected Western countries, but even poorer countries such as India. In fact a sizeable chunk of youth (including girls) from well-to-do families in metropolitan cities such as Mumbai, Delhi, and Bangalore have no qualms about drug abuse, and even openly admit to using "party drugs" such as cocaine as a "cool" mode of recreation. Since cocaine has a reputation of enhancing sexual pleasure, such widespread abuse has also led to increased spread of sexually transmitted diseases such as AIDS because of high-risk sexual practices among the users.

- Cocaine abuse by pregnant mothers can lead to devastating effects on the foetus and the new-born (**Table 16.5**). There is convincing evidence that cocaine is teratogenic and can play an important role in the causation of several serious congenital anomalies (**Table 16.6**).
- Cocaine abuse is well-known for its propensity to cause sudden death not only due to its deleterious effects on health (cerebrovascular accidents, myocardial infarction, malignant hyperthermia, renal failure), but also due to its capacity to provoke the user to commit acts of aggression and violence. Deaths due to massive overdose are especially common among those who smuggle the drug within their bodies ("cocaine packers").
  - ❖ **Bodypacker Syndrome**:
    - The practice of swallowing balloons, condoms, or plastic packets filled with illegal drugs for the purpose of smuggling is called "body packing", (**Fig 16.7**), and the individual who does this is referred to as a "mule".
    - This must be differentiated from "body stuffing" in which an individual who is on the verge of being arrested for possession of illegal drugs, swallows his illicit contraband to conceal the evidence. Leaking from these poorly wrapped packets can produce cocaine toxicity.
    - Sudden death due to massive overdose can occur in either a bodypacker or a bodystuffer, if one or

Fig 16.7: CT Scan – Cocaine Packets in a Bodypacker

more of the ingested packages burst within the gastrointestinal tract.
- Diagnosis: Mentioned on *page no. 180*
- Treatment:
  - Emesis, lavage, charcoal, as applicable.
  - Cathartic/whole bowel irrigation to flush the packages out of the intestines.
  - Symptomatic patients should be considered a medical emergency, and be evaluated for surgical removal of the packets.
  - Asymptomatic patients should be monitored in an intensive care unit until the cocaine packs have been eliminated. This must be confirmed by follow-up plain radiography and barium swallows.
  - Bowel obstruction in asymptomatic patients may necessitate surgery. Endoscopic removal has been successful in some cases.

Table 16.5: Complications of Cocaine Abuse during Pregnancy

Spontaneous abortion
Placenta praevia
Abruptio placentae
Prematurity
Placental infarction
Intrauterine growth retardation
Low-birth-weight
Congenital anomalies
Foetal death

Table 16.6: Some Teratogenic Effects of Cocaine

Body Area	Anomaly
Cranio-spinal	Exencephaly, hydrocephaly, cephalomalacia, encephalocoele, myelomeningocoele
Facial	Cleft lip, cleft palate, facial diplegia, ptosis, cutis aplasia
CVS	Atrial septal defect, ventricular septal defect, transposition of great vessels, pulmonary artery stenosis, cardiomegaly
GI and GU tracts	Ileal atresia, inguinal hernia, renal agenesis, multicystic kidneys, hydronephrosis, hypospadias, hydrocoele, undescended testis
Extremities	Phocomelia, polydactyly, syndactyly

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17 Anticonvulsants and Antiparkinsonian Drugs

ANTICONVULSANTS (ANTI-EPILEPTICS)

Anticonvulsants are drugs which fight convulsions (seizures) of both the epileptic and non-epileptic variety.

■ Classification

1. Hydantoins: phenytoin, mephenytoin, ethotoin
2. Barbiturates: phenobarbitone, mephobarbitone
3. Deoxybarbiturates: primidone
4. Iminostilbenes: carbamazepine
5. Succinimides: ethosuximide
6. Oxazolidinediones: trimethadione, paramethadione
7. Benzodiazepines: clonazepam, clorazepate, diazepam, lorazepam
8. Other Anticonvulsants: valproic acid, gabapentin, lamotrigine, vigabatrin, acetazolamide, felbamate, topiramate, zonisamide

The toxicity of barbiturates and benzodiazepines has already been discussed in earlier chapters. Of the remaining anticonvulsants, the more important ones will be dealt with in this chapter.

■ Phenytoin

Synonym

Diphenylhydantoin.

Uses

- Phenytoin is effective against all types of partial and tonic-clonic seizures, but not absence seizures. It is NOT indicated as first line therapy of febrile, hypoglycaemic, or other metabolic seizures.
- Phenytoin is also used in the treatment of ventricular arrhythmias (especially digitalis-induced).
- It may be effective in treating paroxysmal choreoathetosis, especially the kinesigenic type.
- It is used alone or with other anticonvulsants to control paroxysmal pain in some patients with trigeminal neuralgia (tic douloureux).

- Fosphenytoin, mephenytoin, and ethotoin are other hydantoin anticonvulsants which are chemically related to phenytoin. The latter two are rarely used on account of serious adverse effects. Intravenous fosphenytoin loading has been used to treat quinidine-like conduction defects, bradyarrhythmias, or heart block, in tricyclic antidepressant overdose.

Toxicokinetics

- Phenytoin is reasonably well absorbed on oral administration. It is given intravenously in status epilepticus.* Intramuscular injection is not advisable since the drug gets precipitated at the site, and absorption is slow as well as erratic.
- Phenytoin is rapidly distributed into all tissues. The volume of distribution is 0.5 to 0.8 L/kg. It is extensively bound to albumin (more than 90%).
- The major metabolite resulting from breakdown in the hepatic endoplasmic reticulum is a parahydroxyphenyl derivative which is inactive and is excreted initially in the bile, and later in the urine, after conjugation with glucuronide. Metabolism occurs primarily in the liver by para-hydroxylation to 5-(p-hydroxyphenyl)-5-phenyl-hydantoin (HPPH).
- In acute overdose, peak levels are frequently delayed for 24 to 48 hours, and occasionally as long as 7 days.
- Protein-binding of phenytoin is impaired in the following situations : neonatal and elderly patients, late stages of pregnancy, hyperbilirubinaemia, liver disease, uraemia, burns, surgery, malnutrition (and other conditions causing hypoalbuminaemia), as well as combination therapy with salicylates, sulfonamides, valproic acid, and tolbutamide. In these settings, the total plasma concentration of phenytoin may result in underestimation of the free fraction and inadvertent phenytoin toxicity. Therefore the exact determination of the free phenytoin fraction is essential, which can be accomplished by serum ultrafiltration followed by gas chromatography or EMIT technology.
- At therapeutic levels, elimination follows first-order kinetics. Elimination half-life has been reported to be 7 to 60 hours. In overdose settings, saturation of the hepatic hydroxylation system occurs, and zero order kinetics

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* Intravenous phenytoin should be administered only with saline and not with glucose as it precipitates in the latter.

predominate. Elimination follows a Michaelis-Menten model, with a prolonged t(1/2). As phenytoin is continually excreted, elimination changes from zero-order to first-order kinetics and drug levels decrease more rapidly. Toxicity may persist for 7 to 10 days.

Mode of Action

- Phenytoin acts on the motor cortex preventing the spread of seizure activity. It stabilises the threshold for hyperexcitability and reduces post-tetanic potentiation at synapses.
- Further, phenytoin reduces brainstem activity which is responsible for the tonic phase of tonic-clonic convulsion.
- The toxic cardiovascular effects of phenytoin injection are related to the diluent, propylene glycol. Propylene glycol is not a diluent in the current fosphenytoin injectable forms.

Adverse Effects

- Therapeutic doses (especially when administered over a prolonged period of time) can result in dyskinesia, peripheral neuropathy, hirsutism, hypokalaemia, macrocytic anaemia, hepatitis, thyroiditis, skin rashes, vertigo, mild sedation and CNS depression, mental status changes, hallucinations, ataxia, dysarthria, hyperreflexia, nystagmus, and diplopia.
- Chronic high blood levels may cause a "phenytoin encephalopathy" with increase in seizure frequency and the development of more tonic or opisthotonic components. Transient focal neurologic signs such as hemiparesis may be seen, especially in brain-damaged patients.
- Gingival hypertrophy occurs in about 20% of patients (mostly children or adolescents) (**Fig 17.1**), and is due to altered collagen metabolism.
- Subcapsular cataract formation has been reported in chronic use with phenytoin.
- Toxic hepatitis may occur leading to liver necrosis and chronic inflammation along with cholangitis, with chronic phenytoin use.
- Renal dysfunction, possibly a hypersensitivity reaction to phenytoin, has also been reported with therapeutic use.
- Hypersensitivity reactions are known to occur with phenytoin and usually manifest as fever, rash, lymphadenopathy, and hepatosplenomegaly, 3 weeks to 3 months after initiation of therapy. Such a reaction (*phenytoin hypersensitivity syndrome*) can be potentially fatal.

- *Purple glove syndrome* has been reported following intravenous phenytoin. It is a progressive development of limb oedema, discolouration, and pain after phenytoin administration (**Fig 17.2**), with some patients developing skin ulceration. Elderly patients and patients receiving large, multiple IV doses appear to be at greatest risk.
- Injectable phenytoin is very alkaline in nature with a pH of 12, and is therefore quite irritating to soft tissues if it extravasates during IV infusion. Cyanosis and oedema have occurred in some patients. Necrosis necessitating amputation has also occurred from extravasation of undiluted intravenous phenytoin.
- Arrhythmias and hypotension are associated with rapid intravenous infusions of phenytoin, and appear to be due to the diluent, propylene glycol.
- Phenytoin is a known teratogen and can cause a number of defects in the newborn, together referred to as *foetal hydantoin syndrome*, (**Table 17.1**) (**Fig 17.3**). Several studies have reported a possible risk of birth defects with phenytoin, when used during the first trimester of pregnancy. Increased risk of neural-tube defects, cardiovascular defects, oral clefts, and urinary tract defects have been reported. Phenytoin has also been linked with transplacental tumorigenesis of the kidney, ureter, and bladder, and neuroblastoma.

Drug Interactions

- When valproic acid is administered with phenytoin, the concentration of free phenytoin may decrease, remain constant, or increase from pre-valproic acid levels.
- Disulfiram has been reported to rapidly increase serum phenytoin concentration within four hours of the administration of the first dose of disulfiram.
- Phenytoin serum concentration has been reported to increase to a toxic level following the addition of fluvoxamine to the treatment regimen.
- Ethanol can increase phenytoin serum levels.
- Phenobarbitone may increase or decrease phenytoin levels.

Fig 17.1: Gingival hyperplasia–phenytoin

Fig 17.2: Purple glove syndrome—phenytoin

Table 17.1: Foetal Hydantoin Syndrome

Chest Anomalies	Cranio-facial Anomalies	Limb Anomalies	Other Anomalies
Congenital breast disease	Mental retardation	Small or absent nails	Pilonidal sinus
Widespread hypoplastic nipples	Broad nasal bridge	Hypoplasia of distal phalanges	Hernia
Chest wall deformities	Low-set hairline	Altered palmar crease	Abnormal genitals
	Short neck	Digital thumb	Neuroblastoma
	Ocular hypertelorism	Dislocated hip	Acne vulgaris
	Microcephaly		Hirsutism
	Cleft lip/palate		Optic nerve hypoplasia
	Low-set ears		Haemorrhagic disease
	Epicanthic folds		
	Ptosis		

Fig 17.3: Foetal hydantoin syndrome

- Phenytoin serum levels have been reported to decrease significantly when ciprofloxacin was added to the therapy regimen.
- Phenytoin increases the metabolism of oestrogen and the production of sex hormone-binding globulin, via hydroxylation, thus decreasing the effectiveness of the contraceptives.
- Fluconazole, tolbutamide, cimetidine, ranitidine, INH, and amiodarone have been implicated in inducing phenytoin toxicity.

Clinical (Toxic) Features

1. Overdose with phenytoin causes at first lateral gaze nystagmus, ataxia, and drowsiness, followed by vertical or horizontal nystagmus, oscillopsia (a very fine vertical or horizontal periodic dancing of the eyes), slurred speech, lurching gait, coarse tremor of the extremities, mental confusion, and disorientation. Hypothermia can occur. True coma is uncommon.
2. Hypotension appears to be common following intravenous phenytoin, and is concentration- and dose-related. Atrial and ventricular conduction depression and ventricular fibrillation have been reported following high-dose infusions

of phenytoin. These effects are more typically reported in elderly or gravely ill patients.
3. Severe poisonings may rarely result in respiratory depression. Sometimes, paradoxical intoxication occurs characterised by increased seizure activity.
4. Death is rare, and if it does occur it is invariably due to cardiac arrest or ventricular fibrillation.

Usual Fatal Dose

- Toxic effects are rare at plasma levels less than 20 mcg/ml (80 mcmol/L), but are common in patients with plasma levels greater than 30 mcg/ml (120 mcmol/L).
- Estimates of the minimal lethal dose are unreliable. Deaths are very rare even with massive acute oral overdosage and have been reported mostly with the relatively serious hypersensitivity reactions seen with chronic use. The lowest published lethal dose in a human child is 100 mg/kg.

Treatment

1. *Decontamination*: Stomach wash and activated charcoal are beneficial.
2. *Stabilisation*:
   a. Cardiac monitoring is advisable following parenteral overdose or rapid infusions.
   b. Treat hypotension by Trendelenberg position, fluid infusion, and pressor amines (dopamine or noradrenaline).
   c. Treat heart block with atropine or pacemaker.
   d. For seizures (paradoxical intoxication), use diazepam. If seizures persist or recur, administer phenobarbitone.
3. *Supportive measures*:
   a. Hypersensitivity reactions may respond to corticosteroids.
   b. Forced diuresis, peritoneal dialysis, and haemodialysis are generally ineffective. However, there are some reports on the successful use of charcoal haemoperfusion in the treatment of phenytoin overdose.

■ Primidone

Primidone is a congener of phenobarbitone and is similar in action to it, but is much less potent. One of the two active metabolites of primidone is in fact phenobarbitone, the other being phenylethylmalonamide (PEMA).

Common adverse effects include sedation, vertigo, nausea, ataxia, diplopia, and nystagmus. Serious adverse effects are rare

and comprise leukopenia, thrombocytopenia, SLE, lymphadenopathy, and psychotic reactions.

Primidone overdose usually presents with coma and loss of deep tendon reflexes, nystagmus, strabismus, ankle and knee clonus, and positive Babinski, Hoffman, and Chaddock signs. In severe toxicity, massive crystalluria occurs with passage of hexagonal crystals in urine.

Primidone levels of 5 to 15 mcg/ml may be considered therapeutic. Levels greater than 15 mcg/ml are associated with toxicity, and levels of 70 to 80 mcg/ml are associated with the development of crystalluria.

Treatment is on the same lines as for phenobarbitone poisoning.

■ Carbamazepine

Carbamazepine (5H-dibenzazepine-5-carboxamide) is a carbamylated derivative of iminostilbene and is chemically as well as stereospatially related to the tricyclic antidepressants.

Uses

- Carbamazepine is very useful in the treatment of partial and tonic-clonic seizures.
- It is also employed in the management of trigeminal neuralgia and bipolar affective disorder (manic-depressive psychosis).
- Other uses include unipolar depression, schizoaffective illness, resistant schizophrenia, dyscontrol syndrome associated with limbic system dysfunction, intermittent explosive disorder, post-traumatic stress disorder and atypical psychosis.
- There are also reports of beneficial effects in the management of alcohol, cocaine and benzodiazepine withdrawal, restless legs syndrome, nonneuritic pain syndromes, neurogenic or central diabetes insipidus, and hereditary and nonhereditary chorea in children.

Toxicokinetics

- Absorption following oral administration is erratic, and it may take upto 24 hours for peak levels to occur. Most of the absorbed carbamazepine is metabolised to an epoxide, conjugated with glucuronic acid and excreted in the urine.
- Carbamazepine is 75% protein bound and its epoxide metabolite is approximately 50% protein bound.
- Following an oral dose of carbamazepine, about 72% is excreted in urine; 1 to 2% is unmetabolised drug. Approximately 15 to 30% of an oral dose of carbamazepine is excreted in faeces.

Drug Interactions

- Erythromycin interferes with carbamazepine metabolism; concurrent administration of the two drugs has caused carbamazepine toxicity.
- Isoniazid will slow the metabolism of carbamazepine and increase serum levels.
- Drugs expected to increase carbamazepine half-life and plasma concentration by inhibition of its metabolism include the following: cimetidine, clarithromycin, desipramine, dextropropoxyphene (propoxyphene), diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, isoniazid, ketorolac, lamotrigine, metronidazole, nefazodone, niacinamide, omeprazole, rifampicin, sertraline, terfenadine, ticlopidine, trazodone, valproic acid, and verapamil.
- The combination of lithium and carbamazepine has been reported to result in an interaction consisting of neurotoxic manifestations of tiredness, tremors, abnormal gait, and unsteadiness.

Clinical (Toxic) Features

1. Acute carbamazepine toxicity manifests as nausea, vomiting, hypotension, tachycardia, cardiac conduction anomalies (sinus tachycardia, bradyarrhythmia, a-v conduction delay), mydriasis, nystagmus, ataxia, dysarthria, dystonia, myoclonus, choreoathetosis, encephalopathy, hallucinations, drowsiness, respiratory depression, and coma which may be preceded by convulsions. Cyclic coma may occur, possibly due to delayed absorption. Delayed onset of coma may occur following overdose of controlled-release carbamazepine.
   a. Bullous lesions resembling barbiturate-induced bullous eruption has been reported.
   b. Urinary retention may occur as an anticholinergic effect.
   c. Cardiovascular effects are inconsistent and may not be clinically significant. Severe hypotension has been reported following overdose; it is not common, but is indicative of severe poisoning.
   d. Hypothermia may occur following acute overdose and last up to 10 hours. Hyperthermia is a less common occurrence.
   e. Death may result from cardiovascular toxicity, aspiration pneumonitis, hepatitis, or aplastic anaemia.
2. Chronic poisoning is characterised by recurrent headache, diplopia, ataxia, vertigo, haematological disturbances (neutropenia, pancytopenia, thrombocytopenia, aplastic anaemia, agranulocytosis), and hypersensitivity reactions (dermatitis, eosinophilia, lymphadenopathy, splenomegaly).
   a. Progressive ataxia, resulting in difficulty in walking, is common following carbamazepine toxicity.
   b. Hepatitis has been reported after chronic therapy.
   c. Short-term therapy with carbamazepine has been associated with Stevens Johnson Syndrome and toxic epidermal necrolysis in a case-control study and appears to be a risk factor. The risk is largely confined to the start of carbamazepine therapy.
   d. Therapeutic doses of carbamazepine in men appears to decrease the bioactivity of androgens, thus possibly affecting reproduction.
   e. Carbamazepine has been reported to cause an unusual idiosyncratic reaction of antiepileptic hypersensitivity syndrome in some patients. Manifestations include fever, rash, lymphadenopathy, eosinophilia, lymphocytosis, elevated ESR, coagulopathy and hepatotoxicity. If unrecognised and untreated, this syndrome can be fatal.

f. There are indications that carbamazepine is teratogenic and can cause spina bifida, congenital heart disease, diaphragmatic hernia, digital hypoplasia, and hydronephrosis. Facial abnormalities and growth retardation have also been reported. Other reported abnormalities include anal atresia, meningomyelocele, ambiguous genitalia, hypertelorism, cleft lip, congenital hip dislocation, and inguinal hernia.

Diagnosis

- Diagnosis of carbamazepine poisoning is based on blood levels of the drug. Therapeutic concentrations vary between 4 and 12 mcg/ml (17 and 51 micromol/L). Ataxia and nystagmus may occur at levels greater than 12 mcg/ml. Levels above 40 mcg/ml are potentially fatal. Children are susceptible at lower levels.
- Seizures, coma, and severe respiratory depression following large ingestions independently predict a poor prognosis.
- Ingestion of greater than 24 grams is also a predictor of poor prognosis in adults.
- Patients with rising serum levels have been reported to have a coagulum of undigested tablets, which may be visualised on abdominal X-ray with contrast media

Treatment

1. Multiple-dose activated charcoal.
2. Stomach wash.
3. Cardiac monitoring: hypertonic sodium bicarbonate may help in reversing some of the electrocardiographic anomalies.
4. Endotracheal intubation and assisted ventilation.
5. Correction of hypotension, electrolyte abnormalities, and oliguria. For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
6. For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is NOT routinely recommended.
7. Treatment of convulsions. Attempt initial control with a benzodiazepine (diazepam or lorazepam). If convulsions persist or recur administer phenobarbitone.
8. Hypothermia should be managed by gradual rewarming.
9. Charcoal haemoperfusion is said to be effective in eliminating the drug. However, forced diuresis, haemodialysis, and peritoneal dialysis are not benefiial.
10. Flumazenil may help in reversing the coma (temporarily).

Forensic Issues

Like many other drugs in its category, carbamazepine is not infrequently involved in deliberate suicidal overdose.

Munchausen syndrome by proxy has also been reported with this drug.

■ Valproic Acid

Uses

- Valproic acid (n-dipropylacetic acid) is a branched-chain carboxylic acid that is used in the treatment of tonic-clonic, myoclonic and absence seizures.
- It is also useful in the management of the manic phase of bipolar affective disorder.

Toxicokinetics

- Valproic acid (related compounds: sodium valproate, divalproex, valpromide) is rapidly and completely absorbed on oral administration, and peak concentrations usually occur in 1 to 4 hours.
- Peak levels occur 4 to 5 hours after ingestion of divalproex tablets.
- Valproic acid is 88 to 91% protein bound in healthy patients but decreased in uraemia. Following a massive overdose however, saturated protein binding results in increased fraction of unbound valproic acid.
- The half-life in patients receiving chronic doses of valproic acid usually ranges from 10 to 14 hours. The serum half-life appears to be prolonged in the overdose situation and may be up to 30 hours.
- Most of the drug is metabolised to the conjugated ester of glucuronic acid, while mitochondrial metabolism accounts for the remainder.

Clinical (Toxic) Features

1. Acute poisoning is characterised by lethargy, somnolence, confusion, gastrointestinal upset (mainly vomiting), tachycardia, hypotension, encephalopathy, respiratory depression, coma, liver damage (with elevation of liver enzymes and hyperammonaemia), metabolic acidosis, thrombocytopenia, leukopenia, pancytopenia, aplastic anaemia, and acute pancreatitis.
   a. Hypotension is often refractory to fluid resuscitation and vasopressor therapy.
   b. Significant QT interval prolongation appears to be a common effect of acute valproic acid poisoning.
   c. The manufacturer of valproic acid has issued a warning concerning the development of life-threatening pancreatitis in children and adults following therapeutic dosing. Some cases of haemorrhagic pancreatitis with rapid progression from initial symptoms to death have been described. Onset of pancreatitis may be shortly after initiation of valproic acid therapy or following several years of use.
   d. Miosis and nystagmus have been reported.
   e. Cerebral oedema and coma have been reported in fatal cases.
   f. Onset of toxicity and peak levels may be delayed more than 8 hours after ingestion of divalproex, enteric coated formulations, or coingestion with drugs that slow gastrointestinal absorption.

2. Chronic poisoning is strongly associated with hepatotoxicity which may terminate fatally. Jaundice, drug-induced hepatitis, hepatocellular necrosis, transient elevated liver enzymes (SGPT/ALT, SGOT/AST), and fatal cholestatic hepatitis have been associated with chronic valproate administration. Fatal hepatotoxicity is reported in 1 out of every 800 children under the age of 2 years following antiepileptic therapy with valproic acid. It is suggested that valproic acid may induce a carnitine deficiency in young children and result in non-specific symptoms of deficiency, hepatotoxicity, and hyperammonaemia. Carnitine supplementation (100 mg/kg/day or 2 gm/day, divided into 3 or 4 doses) may help prevent the onset of hepatotoxicity.

   a. Apnoea, pulmonary haemorrhage, and bronchopneumonia have been reported with chronic valproate administration.

   b. Seizures, behavioural changes (irritability, longer and deeper sleep, superficial sleep, hyperactivity, increased alertness, lassitude, drowsiness, increased sociability, calmness, increased sadness, happiness, aggression), multiple system atrophy, extrapyramidal disorder, and cerebellar syndrome have also been seen as adverse effects of chronic therapeutic use.

   c. Severe hyperammonaemic encephalopathy has been reported following chronic therapy, and as a synergistic effect of other anticonvulsants (phenobarbitone, phenytoin, and topiramate) administered with valproic acid.

   d. Renal failure has also occurred in some cases.

   e. Hypothermia has been reported in children following short-term therapeutic dosing.

   f. Parkinson's syndrome has been associated with chronic valproate therapy.

   g. Valproic acid may be teratogenic and is suspected to cause spina bifida and facial malformations (*foetal valproate syndrome*) **(Fig 17.4)**. The risk of congenital anomalies is greater in infants whose mothers were treated with multiple anti-epileptic drugs at the same time. Valproic acid in combination with other primary anti-epileptic drugs may be more teratogenic than other combinations of anti-epileptic drugs.

Foetal valproate syndrome – Facial features

- Tall forehead
- Medial eyebrow deficiency
- Flat nasal bridge
- Broad nasal root
- Shallow philtrum
- Long upper lip
- Thin vermillion border

Fig 17.4: Foetal valproate syndrome

Usual Fatal Dose

- Therapeutic levels of valproate vary between 50 and 100 mcg/ml. Serum concentrations are not reliable for predicting severity of CNS depression in valproic acid poisoning cases; however, more serious effects (coma, acidosis, aspiration, respiratory depression) are generally seen at concentrations > 850 mcg/ml.

- Patients ingesting less than 400 mg/kg of valproate are not likely to develop severe toxicity. Severe toxicity has been associated with ingestions of 19 to 45 grams in adults.

Treatment

1. Treatment of acute valproate poisoning involves the usual measures of stabilisation, administration of activated charcoal, and supportive measures.

2. Haemodialysis or charcoal haemoperfusion appear to be beneficial.

3. Several cases have been reported concerning the use of combinations of multiple-dose activated charcoal, forced diuresis and continuous arteriovenous haemofiltration (CAVH) following severe valproic acid intoxications. CAVH is recommended when imminent haemodynamic instability is present.

4. Orthoptic liver transplantation could help patients with fulminant hepatic failure.

5. While carnitine supplementation has been suggested to counter hyperammonaemia, its actual utility is doubtful. Carnitine has also been used in cases of valproic acid overdose, though conclusive beneficial effects have not been demonstrated.

■ Gabapentin

Gabapentin is an amino acid structurally related to gamma-aminobutyric acid (GABA), the major endogenous inhibitory neurotransmitter in the brain, and is used in the treatment of partial seizures by combining with other anticonvulsants. It acts by enhancing the promoted release of GABA, though the exact mechanism is unclear. It does not interact with GABA receptors and it is not an inhibitor of GABA uptake or degradation.

Gabapentin is used as an add-on anticonvulsant agent in the treatment of refractory partial seizures. It also appears effective in generalised seizures.

Gabapentin is well-absorbed after oral administration and is not metabolised at all. It is excreted unchanged in the urine.

Common adverse effects include drowsiness, vertigo, ataxia, nystagmus, hypertension, and fatigue. Hypertension has been reported following therapeutic doses, as also alopecia. Serious leukopenia has been reported rarely. Impotence has occurred following therapeutic doses. Weight gain and painful gynaecomastia have also been reported. Abrupt cessation of gabapentin after prolonged use can cause withdrawal (seizures or catatonia).

Therapeutic serum levels have not been established. Some investigators report a reference range for therapeutic gabapentin serum level of 2 to 15 mcg/ml.

Overdose results in slurred speech, diplopia, ataxia,

dizziness, somnolence, and sedation. Other effects have included gastrointestinal effects, especially diarrhoea. Symptoms usually resolve in 18 to 24 hours without specific therapy. Overdoses as high as 108 grams have been reported with full recovery following symptomatic therapy.

Gastric lavage may be done if the patient is seen within 3 hours. Monitor vital signs regularly. For mild/moderate asymptomatic hypertension, pharmacologic intervention is generally not necessary. Sedative agents such as benzodiazepines may be helpful in treating hypertension and tachycardia in agitated patients, especially if a sympathomimetic agent is involved in the poisoning. For hypertensive emergencies (severe hypertension with evidence of end organ injury (CNS, cardiac, renal), or emergent need to lower mean arterial pressure within one hour, nitroprusside is preferred.

Gabapentin can be removed by haemodialysis; however, since toxicity after acute overdose is generally mild it is unlikely to be necessary. Haemodialysis may be indicated by the patient's clinical status or in patients with significant renal impairment.

■ Topiramate

Topiramate is a recent entrant and is recommended as adjunctive therapy for adults with partial seizures. It is a sulfamate-substituted monosaccharide, and blocks action potentials and increases the frequency with which GABA activates GABA(A) receptors. Topiramate also antagonises the ability of kainate to activate the kainate/AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; non-NMDA) subtype of excitatory amino acid (glutamate) receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) receptor subtype.

Adverse effects include lethargy, confusion, anxiety, depression, vertigo, tremor, ataxia, diplopia, nystagmus, paraesthesia, speech disorders, anorexia, fatigue, weight loss, and nephrolithiasis.

The recommended total daily dose of topiramate as adjunctive therapy is 400 mg/day in two divided doses. It is recommended that therapy be initiated at 50 mg/day and titrated to an effective dose.

The oral absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours. Topiramate is only minimally bound to plasma proteins (approximately 13 to 17%). Volume of distribution is 0.6 to 0.8 L/kg. Topiramate is not metabolised to a significant extent. Most of an oral dose appears in the urine unchanged (approximately 70%). The plasma elimination half-life is 18 to 24 hours after oral administration, and is not dose dependant.

Overdose information is limited. Generalised seizures, metabolic acidosis, and coma have been reported following topiramate overdose ingestions.

Topiramate has demonstrated teratogenicity in experimental animal studies. Embryotoxicity and foetotoxicity have also been observed. No long-term carcinogenicity studies have been carried out in humans. Mice have developed bladder tumours at doses of 300 mg/kg topiramate for 21 months.

Treatment of overdose is symptomatic and supportive.

Topiramate is cleared by haemodialysis. However, there is little experience in the use of haemodialysis for patients with topiramate poisoning, and clinical indications for its use in patient management are unclear.

Autopsy findings in one case of overdose fatality revealed pulmonary oedema, mucous plugging of the small airways, and cerebral oedema.

■ Zonisamide

Zonisamide (a sulfonamide derivative) is a substituted 1,2-benzisoxazole anticonvulsant, and is indicated in the treatment of partial, generalised, and mixed seizures, especially in those patients whose seizures are refractory to other anti-epileptics inhibition of the spread of seizure activity with zonisamide therapy may be explained by zonisamide's reduction of the T-type calcium current. The degree of current inhibition is concentration-dependant and allows fewer channels to be open during depolarisation, thereby suppressing the inward current. These effects occur without evoking a change in inactivation kinetics or voltage-dependant action. Zonisamide also has a biphasic effect on dopamine function that is dependant on the dose.

Therapeutic doses of 20 to 50 mg/kg enhance dopamine function while supratherapeutic doses of 100 mg/kg inhibit dopamine function. This biphasic effect on dopamine function may explain the anticonvulsant and mood stabilising effects at therapeutic doses and the sedative side effects at supratherapeutic doses.

Zonisamide is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. Zonisamide binds to erythrocytes extensively because of its affinity for binding to carbonic anhydrase and other red cell protein components. The peak plasma concentrations range from 2 to 5 mcg/ml after an oral zonisamide dose of 200 to 400 mg, and will generally occur within 2 to 6 hours. At concentrations of 1.0 to 7.0 mcg/ml, zonisamide is approximately 40% bound to plasma proteins. Zonisamide is hepatically metabolised to acetyl and glucuronide conjugate metabolites The plasma elimination half-life is approximately 63 hours.

Therapeutic zonisamide plasma concentration ranges from 10 to 30 mg/L. Adverse effects have occurred with plasma concentrations of greater than 30 mg/L. Adverse effects include anorexia, nausea, vertigo, somnolence, ataxia, headache, tremor, and increased incidence of renal calculi. Hyperthermia and oligohidrosis, often resulting in heat stroke, have been reported among paediatric patients, following therapeutic administration of zonisamide. Seizures have been reported following abrupt withdrawal of zonisamide therapy. Psychosis, including auditory hallucinations, mania, delusions, paranoia, and violent behaviour, have been reported in adults and children following therapeutic administration of zonisamide. The patients' psychiatric symptoms gradually disappeared following discontinuation of zonisamide therapy. Severe skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, were also reported with a few fatalities.

Human overdose information is limited. Bradycardia, hypotension, respiratory depression, and coma have been reported

following overdose. Multiple generalised tonic-clonic seizures and cardiac arrest have also occurred.

Treatment is symptomatic and supportive. Monitor for evidence of decreased sweating and increased temperature in paediatric patients following zonisamide ingestion. Paediatric patients appear to be at increased risk for zonisamide-associated oligohidrosis and hyperthermia.

Anencephaly and atrial septal defects occurred after first trimester exposure to zonisamide and other anticonvulsant agents, although it is not clear if zonisamide is the direct cause.

ANTIPARKINSONIAN DRUGS

The commonest form of Parkinsonism is idiopathic Parkinsonism or paralysis agitans (*shaking palsy*), the cause for which is unclear even today, though the pathognomonic feature is loss of pigmented, dopaminergic neurones of substantia nigra and appearance of intracellular inclusions (Lewy bodies).

Parkinsonism can also result from established causes such as toxicity (dopamine receptor-blocking drugs), adverse drug effects (antipsychotics such as haloperidol, antiemetics such as prochlorperazine and metoclopramide), and cerebral stroke.

It is important to remember that anti-parkinsonian drugs are effective mainly in the treatment of idiopathic Parkinsonism, while in the other cases drugs usually do not produce much relief. These drugs include levodopa-carbidopa, levodopa-benserazide, dopamine receptor agonists such as bromocriptine and pergolide, MAOIs such as selegiline, muscarinic receptor antagonists such as trihexyphenidyl, benzotropine mesylate and diphenhydramine, and an anti-viral agent, amantidine.

Only those drugs which have not been discussed elsewhere will be discussed in this section.

■ Levodopa

Synonyms

L-dopa; Larodopa; Dopar; L-3,4-dihydroxyphenylalanine.

Uses

Levodopa is the metabolic precursor of dopamine* and is one of the most effective agents in the treatment of Parkinsonism.

Toxicokinetics

- On oral administration, levodopa is rapidly absorbed and peak plasma levels are usually achieved in ½ hour to 2 hours. Over one-half of the oral dose is decarboxylated in the gastrointestinal wall. Absorption of intact levodopa is via a saturable transport system. Erratic gastric emptying may account for multiple peak levels after single oral doses.
- In the brain, levodopa is converted to dopamine by decarboxylation, mainly within the presynaptic terminals of dopaminergic neurons in the striatum, subsequently, the action of dopamine is terminated by the sequential actions of the enzymes catechol-O-methyl-transferase (COMT) and

monoamine oxidase (MOA), or by reuptake of dopamine into the terminal.

- Levodopa is metabolised by decarboxylation (via levodopa decarboxylase) to dopamine in the gut, liver, and kidney and by o-methylation, transamination, and oxidation. 70 to 80% of levodopa is excreted in the urine in the form of metabolites (dopamine, norepinephrine, vanillinemandelic acid, homovanillic acid, dihydroxyphenylacetic acid, vanillpyruvate, vanillactate, etc.) within 24 hours.
- To prevent decarboxylation of levodopa after administration, it is always combined with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase such as carbidopa or benzeraside. This enables a large amount of levodopa to remain unmetabolised and therefore available to cross the blood-brain barrier, and also minimises the incidence of gastrointestinal side effects.

Adverse Effects

- Postural hypotension (especially severe in the elderly), anorexia, nausea, vomiting, cardiac arrhythmias, delirium, hallucinations, depression, leukopenia, and thrombocytopenia. GI bleeding can occur in patients with peptic ulcer.
- Dyskinesias (facial tics, grimacing, head bobbing, torticollis and choreoathetosis) have been reported following chronic therapy.
- Hallucinations were reported in 5.6% of patients given levodopa in one study, and insomnia was reported in 23.6%.
- Sudden withdrawal after prolonged use may precipitate neuroleptic malignant syndrome, convulsions, agitation, paranoia, mania, hypoventilation and myoglobinuria.

Drug Interactions

- Effects are enhanced by amantadine, anticholinergics, and amphetamines.
- Effects are reduced by phenothiazines, haloperidol, reserpine, benzodiazepines, and phenobarbitone.
- Hypertensive crisis can be precipitated by concomitant administration of furazolidone or MAOIs.

Clinical (Toxic) Features

- Clinically, the most prominent signs/symptoms seen following acute overdose include confusion, agitation, insomnia, and excessive motor activity.
- Other effects reported after acute overdose have included nausea, vomiting, sinus tachycardia, postural hypotension, restlessness, hypertension and dyskinesias.
- Bilateral maximally dilated pupils, with absent light reaction, were reported in one case.
- Respiratory dyskinesias have been reported following therapeutic use and include dyspnoea, hypoventilation, diaphragm myoclonic jerks, and respiratory alkalosis.

Diagnosis

Elevation of urinary levodopa (free and total), dopamine, dihydroxyphenylacetic acid, noradrenaline and homovanilic acid.

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* In fact, its therapeutic effect results solely from its decarboxylation to dopamine in the body.

Treatment

1. Supportive measures.
2. Pancuronium may have to be administered in severe cases.
3. Specific treatment for dyskinesias has primarily included reduction of dosage and supportive care.
4. Other treatments which have been tried, but have not been proven clinically efficacious, include deanol (100 mg three times daily) and pyridoxine (10 to 15 mg IV).
5. Hypertension is usually transient and frequently followed by hypotension, and, therefore, should not be treated with medications unless severe or symptomatic.
   a. *For hypotension:* infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
6. Neuroleptic malignant syndrome due to levodopa withdrawal may be successfully managed with oral dantrolene sodium (*Adult and child:* 1 mg/kg orally every 12 hours up to 50 mg/dose), oral bromocriptine mesylate 5 mg 3 times a day, or reinstitution of levodopa.

■ Bromocriptine

Bromocriptine is an ergot derivative with potent dopaminergic agonist action (high affinity for the D_2 receptor site).

Uses

Bromocriptine is indicated for treatment of dysfunctions associated with hyperprolactinaemia, acromegaly to reduce serum growth hormone, and for idiopathic or postencephalitic Parkinson's disease.

It is no longer indicated for the treatment of suppression of physiological post-partum lactation; the FDA (USA) is of the opinion that bromocriptine may cause a serious adverse effect in post-partum women.

Toxicokinetics

The drug is well absorbed on oral administration and peak plasma levels are reached in about 2 hours. The plasma half-life of bromocriptine is approximately 6 to 8 hours. The volume of distribution is 1 to 4 L/kg, and plasma protein binding is to the extent of 96%. Liver is the main site of metabolism and the main route of excretion is biliary. Less than 0.1% is excreted unchanged.

Mode of Action

Bromocriptine is a synthetic ergoline and a direct dopamine D_2 agonist stimulant. Some of its activity includes inhibition of the release of prolactin by the pituitary, resulting in decreased plasma prolactin concentrations. Bromocriptine, as a dopamine agonist, occupies dopaminergic receptors in the pituitary gland to inhibit prolactin secretion. The D_2 receptor sites show properties related to dopaminergic behavioural and endocrine responses.

Adverse Effects

- Nausea, vomiting, vertigo, postural hypotension, nasal congestion, constipation, and mood disturbances.
- Less common problems include headache, dryness of mouth, mydriasis, hallucinations, digital vasospasm, erythromelalgia,* and bladder disturbances.
- Diplopia, dyskinesia, anginal pain, and ergotism have also been reported.
- Long-term therapy may result in pleural effusion, pleural and pulmonary fibrosis, retroperitoneal fibrosis, and pleuritic chest pain.
- Hypothermia, hypertension, myocardial infarction, stroke, and seizures have been reported in postpartum women who were given bromocriptine for lactation suppression.
- Sudden discontinuation can result in hyperpyrexia.

Drug Interactions

- Bioavailability of bromocriptine is increased if it is given along with erythromycin.
- Alcohol reduces tolerance to bromocriptine and vice versa.
- Bromocriptine has been reported to sensitise patients to acute dystonic crisis following administration of a neuroleptic. Dopamine antagonists, such as the neuroleptics or metoclopramide, may diminish the effectiveness of the dopamine agonists when given concurrently.
- Life-threatening symptoms of seizures, cerebral vasospasm, ventricular tachycardia and cardiac dysfunction have been reported when bromocriptine was combined with sympathomimetics.

Clinical (Toxic) Features

Drowsiness, vertigo, postural hypotension, sweating, hallucinations, agitation, convulsions, nausea, and vomiting. Dyskinesias may occur.

Treatment

1. Gastric lavage can be done if the patient is seen within a short time post-ingestion (upto 2 to 3 hours). Activated charcoal may not be beneficial.
2. Rest of the treatment involves supportive and symptomatic measures. Most cases of overdose with bromocriptine appear minimal and treatable with supportive care.
3. Monitor CNS changes for possible dyskinesias or seizures. Specific treatment for dyskinesias primarily includes reduction of dosage and supportive care.
4. If the patient is hyperactive, administer diazepam 10 to 20 mg orally to adults, (no more than 0.1 mg/kg in children).
5. Blood pressure and ECG must be followed up in symptomatic patients.
6. Because of the significant protein binding of bromocriptine, haemodialysis is not expected to be of benefit.

■ Pergolide

Pergolide mesylate is a synthetic ergot derivative and is used in the treatment of Parkinsonism as well as hyperprolactinaemia.

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* Also referred to as tender red foot, it is characterised by burning and throbbing sensation of feet which comes and goes.

It is an ergoline derivative, and a selective dopamine agonist with a high affinity for the D_2 receptor site, and a lesser affinity for the D_1 receptor site.

Pergolide is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 2 hours. At least 10 metabolites of pergolide have been detected in the urine and faeces, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone.

Adverse effects include somnolence, dyskinesias, nausea, dry mouth, constipation, and hallucinations. Profound somnolence resulting in unplanned daytime sleep episodes has occurred in an increasing number of patients receiving pergolide as treatment of Parkinson's disease. Dyskinesias were reported in 62.4% of patients who received pergolide during a clinical trial, as compared with 24.6% of patients who received placebo. Retroperitoneal fibrosis has been reported in several patients following long-term pergolide therapy. There are some reports of erythromelalgia of the lower extremities in Parkinsonian patients on pergolide therapy. Pleuropulmonary fibrosis was reported in several patients following long-term pergolide therapy.

Overdose with pergolide may result in vomiting, sweating, dizziness, agitation, dyskinesias, hallucinations, involuntary movements, palpitations, and hypotension.

Treatment is symptomatic.

■ Trihexiphenidyl

It is also referred to as benzhexol hydrochloride and is used in the treatment of Parkinsonism, extrapyramidal syndromes, and nerve gas poisoning. Trihexiphenidyl is a synthetic tertiary amine antimuscarinic agent.

Chronic use results in memory and cognitive impairments. Sudden withdrawal can cause anxiety, irritability, insomnia, headache, sweating, and tachycardia.

Overdose causes anticholinergic manifestations such as confusion, hallucinations, dry mouth, dilated pupils, diplopia, tachycardia, and hyperthermia.

Treatment involves supportive measures, and continuous ECG and cardiac monitoring,

■ Benztropine

Benztropine mesylate (or benzatropine methanesulfonate) is a synthetic tertiary amine antimuscarinic antiparkinsonian drug possessing anticholinergic, antihistaminic, and local anaesthetic effects.

It can be administered orally, intramuscularly, or intravenously. Adverse effects include skin rash, dry mouth, mydriasis, diplopia, nausea, and tachycardia. Risk of anticholinergic side effects is greatly increased when administered with other anticholinergic drugs, and may result in paralytic ileus or hyperthermia which can be fatal.

Overdose produces weakness, confusion, depression, vomiting, urinary retention, constipation, paralytic ileus, hyperthermia, heat stroke, and hallucinations. ECG changes include sinus tachycardia without QRS or QTc prolongation. Acute psychosis characterised by bizarre behaviour has been reported. Death can occur.

Serum benztropine levels over 100 ng/ml are associated with serious toxicity.

Treatment involves ECG monitoring, gastric lavage, and activated charcoal. Physostigmine can be considered in the presence of serious toxicity. Supportive measures include catheterisation of bladder, treatment of hyperthermia, hypertension, etc.

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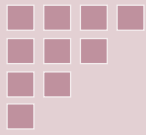
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Anaesthetics and Muscle Relaxants

ANAESTHETICS

Anaesthetic agents can be classified into two groups:
1. General Anaesthetics—
   a. Inhalational Agents: nitrous oxide, halothane, isoflurane, enflurane, sevoflurane, and desflurane.
   b. Intravenous Agents*: thiopentone, methohexitone, thiamylal, diazepam, lorazepam, midazolam, etomidate, ketamine, fentanyl and its derivatives, morphine, pethidine, butorphanol, and propofol.
2. Local Anaesthetics—Cocaine, lignocaine, bupivacaine, chloroprocaine, etidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine, dibucaine, dyclonine, pramoxine, benzocaine, proparacaine, etc.

INHALATIONAL ANAESTHETICS

■ Nitrous Oxide

Synonyms

Dinitrogen monoxide; Laughing gas; Hyponitrous acid anhydride; Factitious air.

Physical Appearance

- Nitrous oxide is a colourless gas with a slightly sweetish odour and taste.
- May also exist in the form of a liquid or cubic crystals.
- Nitrous oxide is abundant in the atmosphere as a result of bacterial decomposition of organic nitrogen compounds in soil.

Uses

- As a sole agent, nitrous oxide is used intermittently to provide analgesia for dental and obstetric procedures.
- In combination with other agents, nitrous oxide is used as a general anaesthetic.
- It is also used as a foaming agent for whipped cream, to make nitrates from alkali metals, as an oxidant for organic compounds, and in some rocket fuel combinations. Consumer cans of whipped cream have been reported to release up to 1.5 L of nitrous oxide. High concentrations of carbon dioxide and fluorocarbons may also be released.

Mode of Action

- Nitrous oxide is a gas that acts as a central nervous system depressant and can cause asphyxiation by oxygen displacement.
- It oxidizes cobalt in vitamin B_{12}, rendering it biologically inactive. This produces a deficiency in available active B_{12} and the results mimic B_{12} deprivation states.
- Nitrous oxide has been demonstrated to be a partial agonist at mu, kappa, and sigma receptors of the endogenous opioid system. This may explain the emetic and addictive properties of nitrous oxide. Naloxone appears to partially reverse nitrous oxide-induced analgesia.

Adverse Effects

- Nitrous oxide is 35 times more soluble in blood than nitrogen. When it is inhaled, compliant air-containing spaces such as the bowel will increase in size, while non-compliant spaces such as eustachian tubes will increase in pressure. This can lead to bowel distension, tympanic membrane rupture, etc.
- Nitrous oxide has been reported to cause mild hypertension when used as an anaesthetic. Cardiac arrhythmias may occur, and may be the result of hypoxia. Nausea and vomiting may occur.
- Acute neurologic effects of intoxication are primarily due to asphyxia. Signs and symptoms may include headache, dizziness, and excitation that may progress to CNS depression, seizures, and death. Respiratory irritation may be noted. Interstitial emphysema and pneumomediastinum have been reported following inhalation from whipped cream dispensers.
- Nitrous oxide is thought to be a potential carcinogen based on animal studies.

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* Also referred to as Induction agents.

Clinical (Toxic) Features

1. Respiratory depression, increased muscle tone, hypertension, mydriasis, cardiovascular failure.
2. Chronic use (or abuse, especially by hospital and dental personnel) can lead to bone marrow depression, polyneuropathy, megaloblastic changes, and death. Chronic abuse can also cause myeloneuropathy. Findings include ataxia, peripheral sensory neuropathy, and weakness. Impotence has been reported as an early sensory complaint associated with nitrous oxide-induced myeloneuropathy Many of the neurological and haematopoietic effects of nitrous oxide are believed to be due to the selective inactivation of vitamin B_{12}.
3. Bone marrow depression with resultant leukopenia, thrombocytopenia and severe megaloblastic anaemia has been noted following chronic or intermittent inhalation of nitrous oxide.

Usual Fatal Dose

- Exposure to 50 to 70% nitrous oxide for 3 hours can result in aplastic anaemia and death.
- Inhalation of 40% nitrous oxide in air can cause confusion and sedation, while an 80% level causes unconsciousness in most individuals.

Treatment

1. Removal from source of exposure. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.
2. Cerebral oedema and elevated intracranial pressure (ICP) may occur. Emergent management includes head elevation and administration of mannitol; hyperventilation should be performed if there is evidence of impending herniation.
3. Plasma nitrous oxide levels are not clinically useful.
4. Case reports suggest that administration of folate and vitamin B_{12} supplements may help reverse myeloneuropathy associated with chronic nitrous oxide abuse, although this has not been well studied.
5. Folinic acid, 30 mg, IV, for bone marrow abnormalities.
6. Methionine-supplemented diet to minimise neurologic damage.
7. Arrhythmias are generally secondary to hypoxia and usually resolve with oxygenation. Therapy with antiarrhythmics should be reserved for patients with arrhythmias that persist after adequate oxygenation.
8. Monitor patient for signs of bleeding and infection. Treatment is symptomatic and supportive. Folate supplementation may reverse the bone marrow abnormalities associated with nitrous oxide toxicity.
9. Supportive measures:
   a. Treatment of hypoxia.
   b. Control of seizures.
   c. Treatment of pulmonary oedema.
   d. Continuous cardiac monitoring.

■ Halothane

Synonyms

Bromochlorotrifluoroethane.

Physical Appearance

Halothane is a non-flammable, volatile liquid. It is colourless and has a sweetish odour. It is light-sensitive.

Uses

Halothane can be used in combination with oxygen, or other gas mixtures such as nitrous oxide and oxygen for general anaesthesia. During such use, the arterial blood levels of halothane usually range from 80 to 260 mg/L.

Halothane is known for its abuse potential among hospital personnel since inhalation of small amounts produces pleasurable effects. A popular method of halothane abuse is to drip the liquid onto a pad held over the face.

Toxicokinetics

- Approximately 60 to 80% of absorbed halothane is eliminated unchanged in the exhaled gas in the first 24 hours, and smaller amounts continue to be exhaled over the subsequent days or even weeks.
- Of the non-exhaled fraction, 50% undergoes biotransformation by the hepatic P450 system, while the remaining is eliminated unchanged by other routes, especially urine which contains organic fluorine-containing compounds such as trifluoroacetic acid.
- Metabolites include apart from trifluoroacetie acid, bromide and chloride salts, chlorotrifluoroethane, and chlorodifluoroethylene.

Adverse Effects

Hypotension, cardiac rhythm disturbances, malignant hyperthermia (*page no. 252*). Malignant hyperthermia has been reported in patients given halothane with and without suxamethonium (succinylcholine).

Drug Interactions

- Concomitant administration of adrenaline increases the risk of ventricular arrhythmias and acute pulmonary oedema.
- Halothane potentiates the effect of neuromuscular blocking agents.
- Chlorpromazine and morphine enhance the respiratory depressant properties of halothane.

Clinical (Toxic) Features

1. The most important toxic effect is hepatitis. Two types of hepatitis have been observed.
   a. The first is a mild dysfunction which develops in about 20% of exposed patients, is characterised by moderate elevation of serum aminotransferase level, and is associated with complete recovery.
   b. The second is a life-threatening hepatitis occurring in about 1 in 10,000 exposed patients which can terminate

in massive hepatic necrosis in approximately 1 in 35,000 patients. Chills and fever are often associated with the hepatitis reaction seen with halothane. The histopathological findings in such a case are identical to those seen in viral hepatitis.

c. Predisposing factors to halothane hepatitis include multiple exposures, obesity, female sex, and old age. Genetic factors may also play a role as some races (e.g. Mexican-Indian or Mexican-Spanish) are more susceptible.

2. Pulmonary oedema and seizures occur if halothane is administered intravenously, while inhalation is not associated with such effects.

3. On ingestion, there is vomiting, depression of consciousness, hypotension, shallow breathing, bradycardia with extrasystoles, and pulmonary oedema. Asystole has occurred with therapeutic use.

4. Sinus tachycardia occurs often in early phases of halothane overdose.

5. There is a characteristic fruity or sweet odour to the breath.

Treatment

1. Full recovery is usual with supportive care, endotracheal intubation, and gastric lavage. Ingestion of this inhalational anaesthetic is unlikely, but has occurred. Absorption is rapid and gastric lavage is not routinely recommended as it is unlikely to be useful unless performed very soon after ingestion. Consider administration of activated charcoal after a potentially toxic ingestion.

2. For bradycardia, give 0.5 mg to 1 mg of atropine intravenously; repeat every five minutes if bradycardia persists. 3 mg (0.04 mg/kg) intravenously is a fully vagolytic dose in most adults. Doses less than 0.5 mg may cause paradoxical bradycardia in adults.

3. Dantrolene may be used for malignant hyperthermia. The dose is 1 mg/kg by rapid intravenous infusion until symptoms subside (maximum dose 10 mg/kg in a single dose).

4. N-acetylcysteine has been an effective pre-treatment in protecting against halothane-induced hepatotoxicity in animals. The importance of this finding is unknown in human overdoses, as hepatitis is not a commonly occurring effect with acute overdose.

■ Other Inhalational Anaesthetics

Isoflurane and its isomer **enflurane** are non-flammable, but possess high vapour pressure and hence necessitate the use of a precision vapouriser. Isoflurane is a clear, colourless, volatile liquid, and has a pungent odour. Enflurane is a volatile fluorinated methyl ethyl ether, and is a clear, colourless, volatile and stable liquid with a mild sweet odour; it is non-flammable. Isoflurane has also been used as a solvent and dispersant for fluorinated compounds.

Isoflurane produces hypotension, coma, seizures, respiratory depression, and apnoea in overdose, but has a wide safety margin. The minimum lethal human dose to this agent has not been delineated. At normal anaesthetic doses isoflurane has been associated with hypotension, arrhythmias, miosis, seizures, nephrotoxicity, hepatotoxicity, neuroleptic malignant syndrome, and respiratory depression. Rarely it may induce malignant hyperthermia. The diagnosis of malignant hyperthermia can be confirmed by muscle biopsy.

Enflurane may cause CNS and respiratory depression, coughing, laryngospasm, hypotension, hepatotoxicity, renal toxicity, and seizures. Up to 80% of patients who experience seizures will have them within the first 24 hours following surgery. Fatalities have been reported following the inhalational abuse of one entire bottle of enflurane. Enflurane has been reported to induce cerebral hyperexcitability which appears as a burst-suppression pattern on an EEG and may progress to seizures. Tricyclic antidepressants taken concurrently with enflurane may result in a lowered seizure threshold with resultant seizures. Shivering may occur in the postoperative period. ECG changes, nausea and vomiting, and malignant hyperthermia have occurred with enflurane anaesthesia. Rhabdomyolysis with acute renal failure is a rare effect. Malignant hyperthermia has occurred in a few cases.

Cardiac rhythm during isoflurane anaesthesia is generally stable, and isoflurane does not sensitise the heart to the effect of exogenous adrenaline. The hypercapnia associated with spontaneous ventilation during isoflurane anaesthesia increases heart rate. Blurred or double vision may be a temporary effect of both isoflurane and enflurane. Both agents lower intraocular pressure. Coughing, nausea, and vomiting are common to both.

Serum fluoride concentrations should be monitored in overdose cases involving either isoflurane or enflurane. Monitor vital signs in all patients. Follow temperature and monitor for signs of fever possibly leading to malignant hyperthermia. Monitoring complete blood count, urinalysis, and liver and kidney function tests is suggested for patients with significant exposure. Continuous cardiac monitoring is recommended.

Because of rapid absorption and onset of CNS depression, induced emesis is not recommended. Consider prehospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Gastric lavage may be useful in significant ingestions. Enflurane ingestions have rarely been reported, while isoflurane ingestions have occurred more commonly. Carefully observe patients with inhalation exposure for the development of any systemic signs or symptoms and administer symptomatic treatment as necessary. Administer 100% humidified supplemental oxygen, perform endotracheal intubation and provide assisted ventilation as required. Administer inhaled beta adrenergic agonists if bronchospasm develops. Exposed skin and eyes should be flushed with copious amounts of water. Dantrolene and ice may be of use in malignant hyperthermia. Seizures can be successfully treated with barbiturates, phenytoin, or diazepam.

Decrease depth of anaesthesia if hypotension occurs. Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.

Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia). Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia,

particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present and PVCs are thought to represent an escape complex.

Isoflurane has been implicated in causing myocardial ischaemia, but this effect appears to be limited to patients with coronary artery disease.

Electromyographic studies suggest that patients with myasthenia gravis are more sensitive to the neuromuscular depressant effects of isoflurane than are normal patients.

Although isolated reports of liver dysfunction with isoflurane have appeared, a causal relationship has not been established; it is felt that isoflurane is highly unlikely to be even rarely responsible for postoperative hepatotoxicity. Hepatotoxicity develops infrequently following enflurane anaesthesia, but may be severe. However, most patients recover in 3 to 4 weeks with malaise being the only persistent effect.

Self-limited production of carbon monoxide (CO) via the degradation of enflurane in the presence of desiccated soda lime has been demonstrated under some situations. It was found that total CO production was linearly dependant on the amount of desiccated soda lime, and that if very large absorber systems are used, there may be increased potential to produce particularly large amounts of CO. This could cause carbon monoxide poisoning, particularly in children, after mask induction, or initial wash-in with enflurane.

Isoflurane produces bronchodilation and may be useful in the management of refractory status asthmaticus. However, acute asthma has been reported with enflurane use.

Desflurane is produced by substitution of chlorine of isoflurane with fluorine. While cardiac output is well maintained with controlled ventilation, desflurane has a tendency to induce cardiovascular depression.

Servoflurane is a non-flammable, non-irritating agent that may be nephrotoxic when carbon dioxide absorbers are used, since it gets degraded to produce an olefin.

INTRAVENOUS ANAESTHETICS

The toxic profile of barbiturates, benzodiazepines, and opiates has been discussed elsewhere and hence will not be dealt with here.

■ Etomidate

Etomidate is a synthetic carboxylate imidazole and is a potent ultra-short acting hypnotic agent without analgesic properties. Overdose may result in prolonged unconsciousness. Etomidate inhibits adrenal steroidogenesis which may be the reason for increased mortality when it was used for prolonged sedation of critically ill patients.

■ Ketamine

Ketamine is a phencyclidine derivative chemically related to cyclohexamine.

Uses

- Ketamine is a general anaesthetic that is rapid acting, producing profound analgesia with normal laryngeal-pharyngeal reflexes, skeletal muscle tone, and cardiovascular and respiratory stimulation. When given intravenously, it induces sedation associated with immobility, amnesia, and analgesia (*dissociative anaesthesia*).
- Ketamine is popular as an anaesthetic in cases of trauma and emergency surgical procedures.
- It is also frequently used for short-term sedation during clinical procedures; most frequently in the paediatric population.

Toxicokinetics

- Onset of effects after IV administration is 30 to 40 seconds, and after IM administration, 3 to 8 minutes.
- The duration of unconsciousness following the usual anaesthetic dose (*vide infra*) is about 40 to 60 minutes.
- Ketamine undergoes first-pass metabolism by the liver necessitating higher doses when taken by the oral or rectal route. It undergoes N-demethylation by the cytochrome P450 system to form norketamine. Norketamine is an active metabolite with an anaesthetic potency one-third that of ketamine.

Adverse Effects

- During the period of unconsciousness, patients are usually noncommunicative though the eyes may be open and they appear to be awake. Skeletal muscle spasm is often present.
- Following usual anaesthetic doses, side effects include significant transient increases in blood pressure and heart rate, respiratory depression, airway obstruction, apnoea, muscular hypertonus, psychomotor, psychomimetic, and acute dystonic reactions.
- Ketamine elevates intracranial and intraocular pressure.
- Mydriasis and nystagmus may occur.
- Emergence phenomena are also commonly reported characterised by vivid dreams, nightmares, hallucinations, screaming, crying, disorientation, and delirium. They can be minimised by concomitant administration of a benzodiazepine. Nightmares following ketamine use sometimes last for several days to weeks. Children and the elderly seem less sensitive to these effects.
- Ketamine must not be used for anaesthetic purposes in alcoholics since exaggerated psychotomimetic effects are commonly precipitated in such individuals during the recovery phase.

Clinical (Toxic) Features

Overdose is associated with convulsions, hypertension, tachycardia, and respiratory depression. The usual anaesthetic dose of ketamine is 2 mg/kg IV or 5 to 10 mg/kg IM.

Usual Fatal Dose

The minimal toxic or lethal dose is not well established in the literature. Deaths have been reported in adults following doses of 900 to 1000 mg.

Treatment

1. Treatment of the adverse and toxic effects of ketamine involves mainly symptomatic and supportive measures. Plasma ketamine levels are not clinically useful. Airway control and ventilatory support are essential.
2. Seizures and panic attacks must be treated with benzodiazepines; dystonic reactions respond to diphenhydramine (5 to 50 mg IV over 2 minutes) or benztropine.
3. Droperidol intravenous administration as a pre-anaesthetic agent in doses of 75 mcg/kg has been reported to be effective in reducing the incidence of psychotomimetic and circulatory side effects of ketamine. However, based on cases of QT prolongation and/or torsades de pointes in patients receiving droperidol at doses at or below recommended dosing, it should be reserved for use in patients who fail to show an acceptable response to other agents.
4. Alpha and beta blocking agents, benzodiazepines, and verapamil have been shown to block cardiovascular stimulation. Pulmonary hypertension and pulmonary oedema may be reversed by fentanyl.
5. There is evidence to suggest that 4-aminopyridine reverses most of the effects of ketamine toxicity.
6. Atropine or glycopyrrolate can help in reducing tracheobronchial secretions.
7. Physostigmine has been suggested in the management of phencyclidine overdose, but there is little evidence that indicates physostigmine is of value in the treatment of ketamine overdose and it is NOT recommended.

Forensic Issues

- Ketamine is increasingly gaining popularity as a recreational drug and is employed in "rave" parties for its dissociative hallucinatory effects. It is usually taken intranasally or by inhalation, but may also be injected (IM or IV). It is most commonly taken in powdered form and either mixed in a drink or snorted.
- Slang names: *K, Kay, K-amine, Special K, Vitamin K, Ketaset, Green, Jet, Mauve, Purple, Special LA coke, Super acid, Super C.*
- Ketamine has become popular in the teen and young adult culture because of its unique combination of hypnotic, analgesic and amnesic effects with limited respiratory depression. It can produce a "dissociative" effect which is characterised by analgesia and amnesia without causing a loss of consciousness. Users describe the effects of ketamine as an "out of body" experience or "near death", characterised by exhilarating sensations of immobility and a disregard for death.
- Other common effects include tachycardia, altered mental status, anxiety, palpitations, slurred speech, hallucinations, nystagmus, mydriasis, mild hypertension, and chest pain.

Ketamine may produce bronchodilation and increased salivary and tracheobronchial secretions. Confusion, vomiting and memory loss are less common. Rarely seizures, polyneuropathy, or respiratory arrest may occur. Epistaxis and anosmia (loss of sense of smell) have been reported following chronic snorting of ketamine. Death is rare following ketamine abuse or overdose.

- Ketamine crosses the placenta. Severe adverse effects on the infant, including respiratory depression, have been reported following ketamine use for obstetric analgesia.

■ Fentanyl and Droperidol

When fentanyl citrate (an opiate) is combined with droperidol (a neuroleptic), a state of *neuroleptanalgesia* is produced during which a number of diagnostic or minor surgical procedures can be performed. A common precomposed mixture contains 0.05 mg of fentanyl and 2.5 mg of droperidol per millilitre. This is given as an IV infusion. Neuroleptanalgesia can be converted to *neuroleptanaesthesia* by the concurrent administration of 65% nitrous oxide in oxygen.

Adverse effects of neuroleptanalgesia include respiratory depression (which can be treated with naloxone), extrapyramidal reactions (which respond to atropine or benztropine), and hypotension.

■ Propofol

Propofol (2,6-diisopropylphenol) is a synthetic intravenous anaesthetic which is an oil at room temperature and is supplied as a 1% emulsion (in 10% soyabean oil, 2.25% glycerol, and 1.2% purified egg phosphatide).

Uses

- Propofol is useful in the induction and maintenance of general anaesthesia as part of inpatient or outpatient surgery in adults and children over 3 years of age.
- The exact mechanism of action is unclear but is probably related to its ability to enhance GABA-mediated synaptic inhibition.

Adverse and Toxic Effects

1. Propofol is known to cause hypotension, bradycardia, and even cardiac arrest.
2. In children, it may induce choreiform movements, rigidity, and ataxia if the usual dose is exceeded.
3. Some paediatric cases have demonstrated high morbidity associated with lipaemic serum and elevated levels of very-low-density lipoproteins and triglycerides. Whether this has any relationship to the lipid carrier of propofol is not clear.
4. Several paediatric case reports of "propofol infusion syndrome" following prolonged propofol use for intensive care sedation have been described. The syndrome, which may be fatal, is characterised by metabolic acidosis, bradyarrhythmias, rhabdomyolysis, hyperkalaemia, hyperlipaemia, acute renal failure, massive ketonuria, elevated liver enzymes, fatty liver and myocardial failure. Biochemical findings are consistent with impaired

fatty-acid oxidation; the resultant lack of substrates and the build-up of intermediaries in the metabolism of long-chain, medium-chain, and short-chain fatty acids could theoretically account for the clinical features present. Although children are said to be more likely to develop this condition, adults have also been affected. Fatalities have occurred in both groups.

5. Fever has been associated with prolonged propofol infusion in children.
6. Anaphylactic reactions have occurred during propofol administration.
7. Discoloured urine (olive green, rusty brown, tea-coloured) has been reported in several paediatric exposures to prolonged propofol infusions used for intensive care sedation (**Fig 18.1**).
8. Complex external ophthalmoplegia has been reported in patients recovering from propofol anaesthesia.
9. It appears that propofol has both anti-convulsant and pro-convulsant activity. There have been several reports of seizure activity following the use of propofol. Seizures or excitatory effects have been reported during induction, immediately after anaesthesia and delayed (sometimes for up to several days after surgery) following the use of propofol. Several possible mechanisms have been suggested:
   – Propofol has a primary action at or close to the GABA receptor with a much lower level of glycine antagonism responsible for the excitatory effects
   – Antidopaminergic action
   – Imbalance between cortical and subcortical effects with propofol is involved with the symptoms observed.
10. Propofol is susceptible to contamination with micro-organisms (*S.aureus, E.coli, P.aeruginosa, C.albicans,* etc.), and cases have been recorded where bacteraemia has resulted from its use in patients. It is recommended that propofol ampoules should be wiped with alcohol

Fig 18.1: Discolouration of urine-propofol
(*Pic:* Dr S Senthilkumaran)

before use, and strict aseptic techniques should be followed when preparing infusions.

Treatment

1. Monitor arterial blood gases in all patients following a significant exposure.
2. Monitor ABGs routinely in children receiving propofol infusions for a prolonged period or in patients as indicated.
3. Obtain baseline electrolyte levels and monitor fluid status.
4. Monitor ECG and blood pressure in patients following overdose or prolonged exposure.
5. Establish respiration and create an artificial airway if necessary. Check adequacy of tidal volume.
6. Aggressively treat and evaluate coma. Intubate and ventilate as needed.
7. Physostigmine may help in central anticholinergic syndrome (especially if it is asociated with hypotension and arrhythmias), but must be used with caution.
8. Atropine is useful in bradycardia. For ventricular arrhythmias, obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia). Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Unstable rhythms require cardioversion.
9. If there is evidence of metabolic acidosis, with a pH of less than 7.1 administer sodium bicarbonate at 1 to 2 mEq/kg every 1 to 2 hours. Repeat ABGs to evaluate response.
10. For rhabdomyolysis, early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is NOT routinely recommended.

LOCAL ANAESTHETICS

■ Cocaine*

Cocaine is present in the leaves of the coca plant (*Erythroxylon coca*) and is an ester of benzoic acid and methylecgonine. Local anaesthetic effect is due to blockade of nerve impulses. It also has local vasoconstrictive effect secondary to inhibition of norepinephrine re-uptake. Cocaine hydrochloride is used as a 1%, 4%, or 10% solution for topical application. Its use is greatly restricted because of its toxicity and abuse potential. Cocaine is mainly used as a local anaesthetic for the upper respiratory tract.

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* For a detailed description on the toxic profile of cocaine, see page no 219.

■ Other Local Anaesthetics

Procaine, introduced in 1905, was the first synthetic local anaesthetic and is an amino ester. The other amino esters include amylocaine, benzocaine, butacaine, chloroprocaine, cyclomethycaine, hexylacaine, isobucaine, meprylcaine, oxybuprocaine, piperocaine, proparacaine (proxymetacaine), propoxycaine, tetracaine (amethocaine), and of course cocaine.

A second group of local anaesthetics comprise the amino amides—articaine, bupivacaine, butanilicaine, carticaine, dibucaine (cinchocaine), etidocaine, lignocaine (lidocaine), mepivacaine, oxethazaine, prilocaine (propitocaine), and ropivacaine.

A third group of miscellaneous agents include diperidon, dyclonine, and pramoxine.

The most commonly used local anaesthetics are lignocaine and bupivacaine. A mixture of lignocaine (500 to 1000 mg/L), adrenaline (0.25 to 1 mg/L) and sodium bicarbonate (12.5 mmol/L) in 0.9% saline is usually infused into the surgical site for local anaesthesia, and to minimise blood loss during tumescent liposuction. Doses of lignocaine during this procedure can reach 55 mg/kg. Death can result from severe bradycardia and hypotension during such a procedure.

Mode of Action

- Local anaesthetics reversibly block the generation and conduction of nerve impulses. The blockade progresses as follows: peripheral vasodilation, rise in skin temperature, loss of pain sensation, loss of temperature sensation, loss of proprioception, loss of touch and pressure sensation, and finally motor paralysis.
- Local anaesthetics produce a conduction block at the cell membrane of the involved nerve. All nerves (sensory, motor, and autonomic) are affected, but small diameter pain/temperature (AS fibres) and autonomic ones (B and C fibres) are most susceptible. This conduction block is eventually reversible and is produced by a transient increase in sodium permeability, which would normally produce the action potential and permit its propagation.
- Anaesthetics prevent the increase of sodium pump permeability which occurs during normal impulse transmission. They also interfere with permeability of potassium in the resting nerve. The permeability of both sodium and potassium are calcium dependant and it is believed that local anaesthetics compete with calcium for membrane binding sites.
- Local anaesthetics also have intrinsic vasodilator activity.

Toxicokinetics

- Local anaesthetics are absorbed from mucosal surfaces as well as from parenteral sites. They are rapidly absorbed from the GI tract with peak plasma levels occurring within 30 to 60 minutes.
- Peak blood concentrations occur within 10 to 15 minutes of intramuscular lignocaine administration. Peak blood levels occur within 30 to 45 minutes of caudal, epidural, peripheral nerve block, or infiltration anaesthesia. Absorption is retarded by co-administration of a vasoconstrictor (e.g.

adrenaline). There is significant first-pass hepatic metabolism of amide-type agents (65% for lignocaine).

- *Protein binding:* bupivacaine—82 to 96%; etidocaine—96%; lignocaine—51 to 80%; mepivacaine—60 to 85%; prilocaine—55%; tetracaine—76%.
- *Volume of distribution:* bupivacaine—0.4 to 1 L/kg; etidocaine—1.9 L/kg; lignocaine—1.1 L/kg; mepivacaine—1.2 L/kg; procaine—0.3 to 0.8 L/kg.
- Agents of the ester type are rapidly metabolized mainly in the plasma by pseudocholinesterases yielding para—aminobenzoic acid derivatives. They are also metabolised to a small degree by liver esterases. Agents with an amide linkage are metabolised by hepatic microsomal enzymes.
- Metabolites of both types of compounds are excreted in the urine. Only small amounts of parent drug are excreted unchanged.
- *Elimination half—life:* articaine—20 to 120 minutes; bupivacaine—1.3 to 5.5 hours; etidocaine—1 to 2.7 hours; lignocaine—1.5 to 2 hours; mepivacaine—1.9 hours; prilocaine—1.5 hours; procaine—7 to 8 minutes.

Adverse Effects

Toxicity is due to an exaggerated pharmacological activity, primarily involving the cardiovascular and central nervous systems. High drug levels result in depressed membrane function of all excitable tissues eventually resulting in membrane instability.

Dyclonine has a different chemical structure than "caine" type anaesthetics. Hypotension is due to reduced cardiac output and peripheral vasodilation. At high doses, respiratory stimulation, followed by respiratory depression occurs. Unlike other local anaesthetics, dyclonine has anticonvulsant activity.

Clinical (Toxic) Features

1. Allergic Reactions: Generally rare and usually associated with ester compounds.
   a. Idiosyncrasy—Vasovagal attack or hysterical reactions. Anxiety, panic attacks, hallucinations, and psychotic reactions have occurred.
   b. Local Effects—Accidental subarachnoid injection of chloroprocaine may cause adhesive arachnoiditis or cauda equina syndrome. Intravenous use is associated with venous thrombosis.
   c. Systemic Effects – Usually result from inadvertent intravascular injection of local anaesthetics. The following manifestations occur: perioral numbness, tingling, auditory and visual disturbances, twitching, convulsions, cardiac arrhythmias, coma, and death. Sometimes there is flaccidity, apnoea, coma, and circulatory collapse. Urticaria and angioedema may accompany systemic allergic reactions. Other dermatological effects include contact dermatitis, generalised burning and numbness and pruritus. Vasodilation, with pink skin, has been reported.
2. Systemic Toxicity: Toxicity may occur after ingestion, topical use, or parenteral administration. It may result from an excessive dose, mistaken drug identity, enhanced

drug absorption, inadvertent intravascular injection, altered protein binding, slowed redistribution and/or elimination.

a. Cardiac arrhythmias, myocardial depression, and cardiovascular collapse due to profound vasodilation. Toxic doses of local anaesthetics depress cardiac conduction and contractility, causing arrhythmias (sinus bradycardia, AV junctional or ventricular bradycardia, second or third degree heart block, asystole; rarely ventricular tachycardia or fibrillation due to re-entrant mechanisms). A transient period of tachycardia and hypertension may precede bradycardia, hypotension, and asystole. Heart block occurs more readily in patients with concomitant therapy with calcium channel blockers and beta blockers. ECG manifestations include sinus bradycardia, atrioventricular block, increased PR and QRS intervals and asystole.

b. CNS effects invariably precede significant cardiovascular toxicity, except following massive IV injection. Subjective effects after therapeutic doses or in mild toxicity include drowsiness, impending doom, headache, dizziness, paraesthesias, euphoria, numbness of the mouth, light-headedness, tinnitus, anxiety, confusion, tremors, agitation, disorientation, hallucinations and lethargy. While there is often a progression of symptoms after IM, SC, or continuous IV infusion, seizures and coma may occur suddenly after rapid IV administration. Most of the local anaesthetics are anticonvulsants at low doses and convulsants at high doses. Seizures can occur regardless of route of administration, though they are more common with IV use.

c. Nausea and vomiting.

3. Miscellaneous Effects:

a. Lignocaine IV may cause sudden apnoea and asystole.

b. Bupivacaine is known to cause QRS prolongation even with proper administration of therapeutic dose. It is more cardiotoxic than lignocaine.

c. Prilocaine can cause methaemoglobinaemia since it is an aniline derivative.

d. Structurally different from the benzoate esters or the amides, pramoxine is reported to have relatively "low systemic toxicity". It also does not cause sensitisation as frequently as benzocaine, yet is an equally effective anaesthetic.

e. Exposure to prilocaine, benzocaine, lignocaine, tetracaine, or cetacaine may result in methaemoglobinaemia. The aetiology is metabolism to o-toluidine and 4-hydroxy-2- methylaniline, both known methaemoglobin inducers.

f. Ring keratitis, corneal oedema, Descemet's membrane folds, and a subtotal corneal epithelial defect have been described after abuse of topical ocular anaesthetics.

g. Local anaesthetics readily cross the placenta. Foetal or neonatal poisoning may occur as a result of spinal or regional nerve blocks, systemic maternal poisoning, or inadvertent intracranial injection of local anaesthetics into the foetus during labour and delivery. Bupivacaine is contraindicated in obstetrical paracervical block anaesthesia. Use of bupivacaine in obstetrical paracervical block has resulted in foetal bradycardia and death.

Usual Fatal Dose

The minimum IV toxic doses of some local anaesthetics are listed in **Table 18.1**. The single dose limit for lignocaine is 2 mg/kg for IV doses and 3 to 4.5 mg/kg for infiltration, nerve block, or regional anaesthesia. When administered with adrenaline for local anaesthesia, the total dose should not exceed 7 mg/kg. Fatalities can occur upon intravascular injection of therapeutic (infiltration/nerve block) doses.

Diagnosis

■ Therapeutic levels of lignocaine vary between 1 to 5 mcg/ml. Serious poisoning may occur at levels above 5 mcg/ml for lignocaine, mepivacaine, or procaine. For bupivacaine, therapeutic plasma concentrations are less than 3 mcg/ml. Bupivacaine is more toxic than lignocaine when given intravenously. For etidocaine, peak plasma concentrations following therapeutic doses range from 0.5 to 1.5 mcg/ml.

■ Serum protein (alphal-acid glycoprotein) concentrations must be considered when interpreting lignocaine levels, since assays generally measure total drug concentration. Free drug levels may be relatively higher in patients with low protein concentrations.

Treatment

1. Maintain airway; ventilate with 100% oxygen.

2. Treat acidosis (presence of acidosis increases toxicity). Consider sodium bicarbonate in patients with severe metabolic acidosis. A reasonable starting dose is 1 to 2 mEq/kg. Monitor serum electrolytes and arterial blood gases. Respiratory acidosis should be corrected by assisted ventilation.

3. Treat convulsions with thiopentone IV (50 to 100 mg), diazepam (10 mg), or midazolam (2 mg). Attempt initial control with a benzodiazepine. If seizures persist or recur administer barbiturates. Phenytoin may worsen cardiac arrhythmias and should be avoided.

4. Treat hypotension with IV fluids, pressors (e.g. dopamine), Trendelenberg position.

5. Treat bradycardia with atropine, tachycardia or ventricular fibrillation with electrical cardioversion, or bretylium (5 mg/kg IV).

Table 18.1: Minimum IV Toxic Doses of Local Anaesthetics

Drug	Toxic Dose (mg/kg)
Bupivacaine	1.6
Chloroprocaine	22.8
Etidocaine	3.4
Lignocaine	6.4
Mepivacaine	9.8
Procaine	19.2
Tetracaine	2.5

6. Acute lignocaine toxicity can usually be managed with supportive measures. Massive overdose may necessitate atrioventricular cardiac pacing, or extracorporeal pump assistance.

7. Bupivacaine-induced cardiac arrest may respond to cardio-pulmonary bypass.

8. Methaemoglobinaemia resulting from lignocaine and prilo-caine can be treated with methylene blue (1 to 2 mg/kg/dose or 0.1 to 0.2 ml/kg/dose IV over 5 minutes as needed every 4 hours).

9. Haemodialysis, exchange transfusion, AV haemofiltration and forced diuresis have not been shown to substantially increase clearance. Urinary acidification is not recom-mended. Although acidification of the urine will enhance the excretion of local anaesthetics, the contribution to overall elimination is small, and the risk of such therapy outweighs the benefit.

Forensic Issues (Anaesthetics)

■ In contrast to earlier years, anaesthesia is asociated with low mortality today and is estimated to be just 1 in 10,000 with proper care in administration.

■ Low blood volume, underventilation, aspiration and vomiting, and collapse following intravenous block are the main factors in the few deaths reported.

■ Increased susceptibility to mortality is associated with heart disease, advanced age, and high-risk surgery (cardiovas-cular, thoracic, abdominal, or neurologic).

■ **Table 18.2** mentions important causes of death during anaesthesia.

■ Pregnancy is not associated with significant enhancement of mortality. However some studies suggests an increased risk for congenital anomalies (hydrocephalus and eye defects) in babies born to mothers who had been administred general anaesthetics in the first trimester.

■ There is evidence to suggest that operating room workers may suffer from the results of occupational exposure to general (inhalational) anaesthetics if precautions are not taken – proper connection of scavenging equipment, turning the gas off when breathing system is discon-nected from patient, and use of properly fitting masks on patients.

■ Anaesthetic agents are not uncommonly employed for suicide. Homicides are rare.

■ Anaesthetic drug abuse is a significant problem among

Table 18.2: Common Causes of Anaesthetic Deaths

• Aspiration of gastric contents
• Overdose of anaesthetic agents
• Hypoxia
• Airway problems
• Polypharmacy
• Errors in choice of anaesthetic or technique
• Errors in evaluation or preparation of patient
• Inadequate monitoring of patient's status during anaesthesia
• Inadequate ventilation

anaesthesia personnel in the Western countries, while similar data are not available in the Indian context.

❖ Common agents abused include alcohol, narcotic drugs, barbiturates, tranquillisers, and nitrous oxide. Halothane and ketamine are also being increasingly abused. Even topical ocular anaesthetics may be abused by hospital personnel which may lead to keratitis, corneal damage, and visual loss.

❖ Ketamine, as well as fentanyl and its derivatives are known for their abuse potential even among the general population (*discussed in earlier sections*). Ketamine, like phencyclidine, has become a popular drug of abuse in several Western countries. Users apparently desire the hallucinogenic side effects. Chronic use can result in tolerance requiring increasing dosages of ketamine to produce the same effects. The following long-term adverse effects have been associated with ketamine abuse: flashbacks, hallucinations, attentional dysfunction, memory impairment, tolerance, and a high degree of dependence. Signs and symptoms of ketamine withdrawal may include chills, autonomic arousal, lacrimation, restlessness, visual, olfactory, and tactile hallucinations, nightmares and psycho-logical cravings.

❖ Nitrous oxide is used as a propellant gas in food aerosols (i.e. foaming agent for whipped cream). "Whippet" is a slang term for a cylinder or cartridge designed to charge whipped cream dispensers. The term "nanging" has also been used to describe the recreational use of this agent via cartridges of nitrous oxide. Widespread abuse of this agent has been reported in the United States. These cartridges may be commercially available in supermarkets (Australia), adult bookstores, bar supply shops, and by mail order. Individuals abusing this agent may also purchase it in a can of cooking oil preparation or whipping cream, where it is used as a propellant. The can is inverted and sprayed for a short time until no further oil or whipping cream comes out and only the gas is being emitted from the nozzle. The gas is sprayed into a plastic bag and breathed or sniffed directly. Fatalities are usually due to suffocation and a plastic bag may be found near the victim's head.

❖ Propofol is increasingly being used as an intravenous drug of abuse. In one report, several young males employed at health care centers were arrested for erratic driving behaviour and were found to be injecting themselves with propofol. The famous pop star Michael Jackson (**Fig 18.2**) is alleged to have died due to an overdose of propofol that was being administered to him by his personal physician to help him sleep, since he suffered from severe insomnia.

❖ Procaine may produce a stimulant effect, similar to cocaine, when inhaled and is sometimes called "synthetic cocaine". Powdered procaine is commonly used to "cut" cocaine and has been sold as cocaine when mixed with mannitol or lactose.

Fig 18.2: Michael Jackson—Alleged to have died from propofol overdose

MUSCLE RELAXANTS

1. Central Skeletal Muscle Relaxants—
   Baclofen, carisoprodol, chlormezanone, chlorzoxazone, metaxalone, methocarbamol, tizanidine.
2. Neuromuscular Blocking Agents—
   a. Depolarisers: Succinylcholine, decamethonium.
   b. Non-depolarisers:
      i. Benzylisoquinolines: Atracurium, cis-atracurium, doxacurium, metocurine, mivacurium, tubocurarine.
      ii. Ammoniosteroids: Pancuronium, pipecuronium, rocuronium, vecuronium.
      iii. Gallamine is a synthetic drug that is no more used today.
3. Miscellaneous Drugs—
   Orphenadrine, dantrolene, cyclobenzaprine.

CENTRAL SKELETAL MUSCLE RELAXANTS

■ Baclofen

Uses

- Baclofen is used to treat muscle spasticity, clonus, flexor spasms, spinal disorders and multiple sclerosis.

Mode of Action

- Baclofen is a derivative of the inhibitory neurotransmitter GABA (*gamma amino butyric acid*).
- It inhibits both monosynaptic and polysynaptic reflexes at spinal level and also has CNS depressant effects.
- Baclofen appears to act as a presynaptic GABA-B receptor agonist, and reduces the tonic activity of spinal gamma-motor-neurons, probably by acting at a novel receptor site.

Adverse Effects

- At therapeutic doses (40 to 80 mg/day), baclofen is relatively free of adverse effects, and toxicity usually manifests only at daily doses exceeding 150 to 200 mg/day.

Toxicokinetics

- Baclofen is well absorbed orally and bioavailability is around 70 to 80%.
- Peak plasma levels (usually 0.3 to 0.6 µg/ml) are achieved in about 2 hours.
- Plasma protein binding is to the extent of 30%, while the apparent volume of distribution is 0.8 L/kg.
- About 15% is metabolised by the liver.
- Approximately 85 to 90% of baclofen is excreted unchanged in the urine, and about 10% in the faeces.
- Elimination half-life ranges from 2 to 6 hours, though in overdose this may rise to more than 30 hours.

Drug Interactions

- Baclofen can potentiate the effects of other CNS depressants and alcohol, as well as that of antihypertensives.
- Concomitant administration of levodopa (in Parkinsonism) may sometimes cause confusion, agitation, and hallucinations.

Clinical (Toxic) Features

1. Overdose is characterised by agitation, involuntary movements, twitching, convulsions, delirium, flaccidity, coma, and respiratory depression.
2. Nausea and vomiting are common.
3. There may also be hypo- or hypertension, cardiac arrhythmias, and hypothermia.
   a. Hypotension and bradycardia are the most common cardiovascular complications.
   b. Mild hypertension, tachycardia, first and second degree AV block, QTc prolongation, atrial fibrillation, and PVCs have also been reported.
4. Pupils are often dilated with sluggish or no reaction to light. Less commonly, pupils may be normal or miotic.
5. Symptoms can occur very suddenly in intrathecal injection overdose of baclofen, which may in fact present as coma. Other effects include bradycardia, hypothermia, itching, dysphoria, drowsiness, light-headedness, dizziness, somnolence, respiratory depression, seizures, and hypotonia.
6. Baclofen has been associated with encephalopathy. EEG changes in baclofen-induced encephalopathy include periodic sharp waves, bursts of triphasic waves, trains of delta activity, intermittent rhythmical delta waves, burst suppression pattern without reactivity to stimulation, and diffuse background slowing.
7. Long-term administration of therapeutic doses of baclofen may cause fatigue, vertigo, nausea, confusion, depression, headache, and muscle weakness. Movement disorders and memory impairment have been described at therapeutic doses. Dystonia, chorea, akinetic mutism, dyskinesia, and flapping tremor have also been reported at therapeutic

doses. Depression, confusion, mania, psychosis, amnesia, catatonia and mood disorders can also occur. Abrupt withdrawal results in convulsions, hallucinations, insomnia, confusion, and agitation. Withdrawal after chronic intrathecal infusion may be more severe including severe rebound spasticity, hyperthermia, hypotension, tachycardia, conduction disturbances (including atrial fibrillation), rhabdomyolysis, disseminated intravascular coagulation, hepatic injury, neuropsychiatric changes (i.e. mental status depression) and in some cases multiorgan failure and death.

Usual Fatal Dose

- Blood baclofen levels of over 1.5 to 2 mcg/ml are indicative of toxicity.
- Ingestion of 300 mg has caused serious intoxication in healthy adults; elderly patients may develop CNS and respiratory depression after 50 mg.

Treatment

1. Admission to an intensive care facility, with gastric lavage and activated charcoal, has been recommended for adults ingesting over 100 mg and children ingesting over 5 mg/kg of baclofen.
2. Treatment of overdose involves oxygen administration, assisted ventilation, gastric lavage (if patient is conscious and seen within 2 to 3 hours of ingestion), activated charcoal, IV diazepam for convulsions and trendelenberg position, IV fluids and pressor amines (dopamine or noradrenaline) for hypotension.
3. Atropine has been reported to be useful in treating bradycardia and hypotension associated with baclofen overdose.
4. Institute continuous cardiac monitoring and assess adequacy of respirations using pulse oximetry and/or arterial blood gases.
5. Physostigmine is said to be effective in reversing respiratory depression, arreflexia, and coma. The usual dose is 1 to 2 mg by slow IV infusion, repeated cautiously if required, all the while watching out for adverse effects (*page no 209*). The use of physostigmine is contraindicated in the presence of cardiac depression. Since the vast majority of patients respond well to supportive care, physostigmine is not recommended except for severe toxicity not responsive to supportive measures.
6. Forced diuresis may be helpful in enhancing the elimination of baclofen. The method advocated is NaCl 0.45% in 5% dextrose-in-water, with furosemide 1 mg/kg (maximum 40 mg), to obtain a urine flow of 3 to 6 ml/kg/hour.
7. Haemodialysis has shortened the duration of toxic effects of baclofen in several patients with severely impaired renal function.
8. Withdrawal symptoms respond to reinstitution of baclofen with subsequent gradual tapering of the dose if indicated. Treatment of intrathecal baclofen withdrawal should include the restoration of intrathecal baclofen (ITB) (i.e. refill pump, change battery, etc.); after ITB dosing clinical improvement should be noted within 30 minutes with maximal benefit in 4 to 6 hours. If intrathecal restoration is

not immediately possible, begin oral baclofen and/or oral or intravenous benzodiazepines may prevent potential fatal sequelae. Oral baclofen is not anticipated to relieve all the symptoms related to intrathecal baclofen withdrawal.

■ Carisoprodol

Synonyms

Carisoprodate; Isobamate; Isopropyl meprobamate.

Uses

- Carisoprodol is related structurally and pharmacologically to meprobamate and is a CNS depressant with muscle relaxant properties.
- It is usually used as an adjunct to analgesics in the relief of acute musculoskeletal pain.

Clinical (Toxic) Features

1. Blood levels of over 30 mcg/ml are associated with toxicity.
2. Overdose results in drowsiness, lethargy, vertigo, diplopia, nystagmus, headache, ataxia, tachycardia, convulsions, and coma.
3. Horizontal and vertical nystagmus, mydriasis and blurred vision may occur.
4. Sinus tachycardia with a prolonged QT interval has been reported.
5. Death can occur. Survival may be associated with amnesia relating to events during the course of toxicity.
6. Chronic therapeutic use may cause skin rash, drowsiness, nausea, vertigo, ataxia, tremor and headache.
7. Sudden cessation of chronic therapy can cause a withdrawal reaction: anxiety, tremors, muscle twitching, insomnia, auditory and visual hallucinations, bizarre behaviour.

Treatment

1. Stomach wash if the patient is seen within 3 to 4 hours, activated charcoal, and cathartics.
2. Supportive measures usually suffice to reverse the toxic effects.
3. Flumazenil has been used with beneficial effects (0.2 mg IV, repeated as required).

■ Other Central Muscle Relaxants

Chlormezanone use is associated with drowsiness, weakness, nausea, vertigo, skin rash, confusion, and dry mouth. Anticholinergic effects (mydriasis, hot, dry skin), coma, flaccidity, and absent reflexes have been reported. Rarely it may cause Stevens-Johnson syndrome, erythema multiforme, and cholestatic jaundice. Several cases of hepatitis associated with therapeutic use of chlormezanone have been reported. As of November, 1996, Sanofi Winthrop manufacturers worldwide have voluntarily instituted a recall of all products which contain chlormezanone, due to toxic epidermal necrolytic reactions.

Chlorzoxazone may induce anaphylactoid reactions, drowsiness, vertigo, GI disturbances, headache, skin rash, and jaundice.

Tizanidine use may result in drowsiness, vertigo, nausea, dry mouth, insomnia, headache, mild hypotension, and bradycardia. It is a centrally acting (alpha$_2$-adrenergic agonist) muscle relaxant structurally related to clonidine, and is a short-acting drug used to treat spasticity. In a retrospective study, hypotension was observed in 8 of 45 patients following tizanidine overdose, while bradycardia was observed in 14 patients. Palpitations, ventricular extrasystoles, rash, sweating, skin ulcer, pruritus, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, elevated liver enzymes, back pain, lethargy, anxiety, syncope, tremor, depression, weakness, paraesthesia, miosis, visual hallucinations, and fever are uncommon adverse effects. Dryness of the mouth has been observed relatively frequently during tizanidine therapy, particularly during initiation of therapy. This effect generally subsides with continued administration. Concurrent administration of tizanidine and ethanol may result in additive central nervous system depression.

Methocarbamol is a carbamate derivative used for the symptomatic relief of muscle spasm. Toxicity results when blood levels exceed 40 mcg/ml. Symptomatology manifests as hypotension, bradycardia, convulsions, diplopia, headache, and vomiting.

Metaxalone can cause muscle rigidity and CNS depression.

■ Neuromuscular Blocking Agents

Uses

- Adjuvant in surgical anaesthesia to obtain skeletal muscle relaxation.
- Facilitation of orthopaedic procedures such as correction of dislocations and alignment of fractures.
- Facilitation of endotracheal intubation, laryngoscopy, bronchoscopy, oesophagoscopy, etc.
- Prevention of trauma during electroconvulsive therapy.

Mode of Action

- The essential mechanism of action of all NMBs is inhibition of the effects of acetylcholine (ACH) on nicotinic receptors at the neuromuscular junction (NMJ).
- The depolarising NMBs (or DNMBs) such as succinylcholine (suxamethonium) produce muscle depolarisation in the same way as ACH. The action of succinylcholine is prolonged because it is relatively resistant to hydrolysis by true acetylcholinesterase.
- The nondepolarising NMBs (or NDNMBs) act by competitive inhibition of ACH at nicotinic receptors, and their action is in general of shorter duration.

Toxicokinetics

- The toxicokinetics of commonly used NMBs is summarised in **Table 18.3**.
- Succinylcholine is rapidly hydrolysed by plasma pseudocholinesterase to an intermediate metabolite succinylmonocholine. This metabolite is weaker in action than succinylcholine, but because of its slower rate of hydrolysis may accumulate and cause prolonged paralysis of the patient.
- Succinylmonocholine is hydrolysed to succinic acid and choline, neither of which has pharmacologic action.
- Therapeutic doses produce the following sequence of skeletal muscle depression: heaviness to the eyelids, difficulty in swallowing and talking, diplopia, progressive weakness of the extremities, the neck, trunk, spine, intercostals, and diaphragm. The paralysis recedes in the reverse.

Adverse Effects

- Prolonged apnoea and respiratory paralysis.
- Rapacuronium has been voluntarily withdrawn from the market by the manufacturer, due to reports of an association with rapacuronium administration and the occurrence

Table 18.3: Classification and Properties of NMBs

Agent	Classification	Nature	Time of Onset (min)	Duration (min)	Mode of Elimination
Atracurium	Benzylisoquinoline	Intermediate-acting	2 – 5	30 – 40	Hofman degradation; hydrolysis by plasma cholinesterases
Doxacurium	Benzylisoquinoline	Long-acting	5 – 6	90 – 120	Renal elimination; liver metabolism
Mivacurium	Benzylisoquinoline	Short-acting	2 – 5	12 – 15	Hydrolysis by plasma cholinesterases
Pancuronium	Ammoniosteroid	Long-acting	5 – 6	120 – 180	Renal elimination; liver metabolism
Pipecuronium	Ammoniosteroid	Long-acting	2 – 5	80 – 100	Renal elimination; liver metabolism
Rocuronium	Ammoniosteroid	Intermediate-acting	1 – 2	30 – 40	Renal elimination; liver metabolism
Succinylcholine	Dicholine ester	Ultrashort-acting	1 – 2	6 – 8	Hydrolysis by plasma cholinesterases
D-tubocurarine	Cyclic benzyl-isoquinoline	Long-acting	5 – 6	80 – 120	Renal elimination; liver metabolism
Vecuronium	Ammoniosteroid	Intermediate-acting	2 – 4	30 – 40	Renal elimination; liver metabolism

Other examples of NDNMBs: Alcuronium, Cisatracurium, Dimethyl tubocurarine iodide, Gallamine, Rapacuronium

of bronchospastic events, including the occurrence of unexplained fatalities.

- Cardiovascular collapse preceded by tachy- or bradycardia, and hypo- or hypertension. Gallamine has a shorter duration of action than tubocurarine and, due to its blocking of the cardiac vagus, it may cause sinus tachycardia and, occasionally, arrhythmias and hypertension.

- Histamine-release effects: bronchospasm, hypotension, excessive airway secretions.

- Hyperkalaemia (with succinylcholine): The potassium may originate from skeletal muscle, released by depolarisation at the neuromuscular junction or from damaged muscle fibres caused by incoordinate contractions The rise in potassium usually occurs 3 to 5 minutes after IV administration of succinylcholine, and is usually 0.5 to 1 mmol/L. The increase usually lasts less than 10 to 15 minutes.

- Bradycardia may occur secondary to severe hyperkalaemia and may progress rapidly to asystole or ventricular fibrillation in this setting. Use in patients with extensive burns, traumatic muscle injury, paraplegia, hemiplegia, muscular dystrophy, multiple sclerosis, prolonged pharmacologic neuromuscular blockade, upper motor neuron injury or extensive denervation of skeletal muscle can predispose to severe hyperkalaemia and ventricular arrhythmias.

- Malignant hyperthermia: Malignant hyperthermia (MH) is a rare, genetically influenced, potentially lethal complication associated with the use of inhalational anaesthetics, amino-amide local anaesthetics, and some muscle relaxants (succinylcholine, decamethonium, d-tubocurarine, and gallamine). It can also be precipitated in susceptible individuals by stress, hot environment, emotional excitement, physical exertion, and infection. The genetic susceptibility to MH is due to a mutation of the ryanodine receptor gene located in the region of 12–13.2 of chromosome 19. This is responsible for decreased calcium uptake by the sarcoplasmic reticulum of muscle cells leading to increase in myoplasmic calcium, which is triggered by a nmber of agents. A number of aerobic and anaerobic metabolic processes are set in motion resulting in excessive heat and CO_2 and lactic acid production. Indications of MH during anaesthesia include the following:
  - ❖ Tachycardia (unexplained).
  - ❖ Tachypnoea, cyanosis (unexplained).
  - ❖ Rigidity (masseters fail to relax for intubation).
  - ❖ Marked hyperthermia (late sign).
  - ❖ Hypotension, arrhythmias.
  - ❖ Metabolic acidosis.
  - ❖ Hyperkalaemia, hypercalcaemia.
  - ❖ Electrolyte disturbances.
  - ❖ Rhabdomyolysis, disseminated intravascular coagulation (DIC), renal failure.
  - ❖ Pulmonary oedema.

Early diagnosis can be aided by arterial blood gas analysis (hypoxaemia), electrolyte level estimation, oximetry, and end-tidal CO_2 measurement (increased). Death in MH may be due to ventricular fibrillation, DIC, renal failure, cerebral oedema, or pulmonary oedema.

- Succinylcholine-induced rhabdomyolysis from prolonged fasciculations or malignant hyperthermia can lead to renal failure. Elevated serum levels of creatine phosphokinase (CPK) and myoglobin commonly follow IV administration of succinylcholine.

- Persistent weakness (especially in critically ill patients subjected to prolonged ventilation) referred to as *ICU neuromuscular syndrome*. Recovery may take upto 6 months. Precautionary measures are necessary to minimise the possibility of this distressing complication.

Drug Interactions

Some of the important drug interactions with NMBs are listed in **Table 18.4**.

Clinical (Toxic) Features

1. Succinylcholine (succinyldicholine, diacetylcholine, or suxamethonium) is a bis-quaternary ammonium ion composed of two acetylcholine molecules connected by their acetate groups. The dose necessary to produce neuromuscular blockade and respiratory paralysis in adults ranges from 0.3 to 1.1 mg/kg in adults (mean 0.6 mg/kg). Succinylcholine use is sometimes associated with prolonged apnoea which may be due to genetically determined atypical pseudocholinesterase (incidence 1 : 2500), or due to exposure to cholinesterase inhibitors such as organophosphates.

   a. Adverse effects of succinylcholine include cardiac arrhythmias, hyperkalaemia, increased intracranial pressure, increased intraocular pressure, increased intragastric pressure, myalgia, muscle fasciculation, muscle rigidity (especially masseters), malignant hyperthermia, rhabdomyolysis and myoglobinuria.

   b. In children with unsuspected myopathies (especially *Duchenne's muscular dystrophy*), acute rhabdomyolysis, severe hyperkalaemia, and cardiac arrest can occur, and hence it is advisable not to use succinylcholine in the paediatric age group (particularly boys under the age of 8 years) except for emergency intubation.

   c. Succinylcholine is also well known for causing anaphylaxis in susceptible individuals (mostly women) which manifests as rapid circulatory collapse without other conventional signs such as skin rash or wheezing.

2. Tubocurarine and all other curariform blocking agents are derived from curare (**Fig 18.3**), a large vine, found in the canopy of the South American rainforest. Overdose causes complete skeletal muscle paralysis without affecting consciousness. Initially the small muscles of the eyes, ears, fingers, and toes are paralysed, followed by face and neck, upper and lower limbs, and finally the diaphragm and intercostal muscles, leading to respiratory failure.

   a. Metocurine produced by methylation of tubocurarine is twice as potent while doxacurium is a long-acting NMB without histamine-releasing effects. Unlike the others, it is metabolised rapidly at first to laudanosine, and later to an acrylate moiety both of which do not possess NMB property.

Table 18.4: Drugs That Interact With NMBs

Drug	Interaction With Succinylcholine	Interaction With Nondepolarisers
Antibiotics—tetracyclines, clinda-mycin, aminoglycosides, lincomycin, polymyxins, metronidazole	Potentiation	Potentiation
Anticonvulsants—phenytoin	Unclear	Inhibition
carbamazepine	Unclear	Inhibition
Cardiac drugs—nifedipine, verapamil	Potentiation	Potentiation
digitalis	More tendency for arrhythmias	More tendency for arrhythmias
propranolol	Potentiation	Potentiation
procainamide	Unclear	Potentiation
quinidine	Potentiation	Potentiation
Cholinergic drugs	Unclear	Inhibition
Organophosphates	Potentiation	Unclear
Cimetidine	Potentiation	Unclear
Glucocorticoids	Unclear	Inhibition
Inhalation anaesthetics—halothane, isoflurane, enflurane, desflurane, sevoflurane	Potentiation	Potentiation
Intravenous anaesthetics— barbiturates, etomidate, fentanyl	None	Potentiation
benzodiazepines	Diazepam accentuates block	Midazolam potentiates vecuronium
ketamine	Unclear	Potentiation
Local anaesthetics—lidocaine	Potentiation	Low-dose causes potentiation
procaine	Potentiation	Potentiation
Lithium	Prolongs onset and duration	Prolongs effect of pancuronium
MAOIs	Prolongation	Unclear
Tricyclics	Unclear	Cardiac arrhythmias with pancuronium
Theophylline	Unclear	Inhibition. Cardiac arrhythmias with pancuronium

Fig 18.3: Curare vine

b. cis-Atracurium is a purified atracurium isomer which is much more potent, and unlike its parent compound is not associated with histamine release.

c. Mivacurium is a short-acting drug composed of a mixture of 3 stereo-isomers, but may sometimes cause prolonged block.

d. Pancuronium is a synthetic bis-quaternary aminosteroid which has a selective cardiac antimuscarinic (atropine-like) action resulting in increased heart rate and blood pressure. It is partly metabolised and undergoes some degree of deacetylation in the liver, which is responsible for prolonged effects in the presence of hepatic insufficiency.

e. Vecuronium is a derivative of pancuronium with similar potency, but is less prone to induce tachycardia and hypertension.

f. Pipecuronium is a long-acting analogue producing a block of long duration.

g. Rocuronium is known for its rapid onset of action and does not produce histamine release or significant cardiac effects.

Treatment

1. Reversal of NDNMB block can be achieved by anti-cholinesterases such as neostigmine (0.040–0.080 mg/kg), pyridostigmine (0.2–0.4 mg/kg), or edrophonium (0.5–1.0 mg/kg), in combination with antimuscarinic agents such as glycopyrrolate (0.01–0.02 mg/kg) or atropine (0.02–0.03 mg/kg).

2. Overdose with depolarising agents such as succinylcholine cannot be reversed pharmacologically, and must be managed with prolonged assisted ventilation.

3. Physostigmine, neostigmine and other anticholinesterase drugs, including edrophonium, are contraindicated as antidotes to succinylcholine because they actually prolong its action by interfering with metabolism by cholinesterase. Determine pseudocholinesterase activity in patients with unexpectedly prolonged effects. However, many of the patients who react abnormally to succinylcholine have qualitative rather than quantitative defects in plasma pseudocholinesterase.

4. Maintain patent airway and supply 100% oxygen. Assisted ventilation is usually required. Most patients will recover if adequate airway, ventilation and oxygenation are established rapidly.

5. Treatment of malignant hyperthermia:
   a. Discontinue all triggering agents.
   b. Hyperventilate with 100% oxygen (10 L/min).
   c. Give dantrolene sodium 2 to 3 mg/kg IV bolus, followed by increments upto a maximum of 10 mg/kg. Stop dantrolene when the signs of MH are controlled, and administer it subsequently at 1 mg/kg IV 6th hourly for 1 to 2 days, and then the same dose orally for 1 more day.
   d. Give sodium bicarbonate to correct metabolic acidosis (1 to 2 mEq/kg).
   e. Treat hyperthermia with
      i. IV iced saline, 15 ml/kg, q15 min × 3.
      ii. Lavage of stomach, bladder and rectum with iced saline.
      iii. Skin surface cooling with ice.
   f. Treat persistent arrhythmias with standard anti-arrhythmic drugs (except calcium channel blockers which can cause or aggravate hyperkalaemia).
   g. Treat hyperkalaemia with hyperventilation, sodium bicarbonate, IV glucose, and insulin. Dangerous hyperkalaemia may necessitate calcium administration (2 to 5 mg/kg of calcium chloride).
   h. Ensure adequate urine output (more than 2 ml/kg/hr).
   i. Monitor
      i. End-tidal CO_2.
      ii. Arterial and venous blood gases.
      iii. Serum potassium and calcium.
      iv. Clotting studies.
      v. Urine output.

6. Treat cardiovascular failure in the usual way.

7. Treat severe hyperkalaemia (associated arrhythmias, QRS widening) aggressively. Monitor ECG continuously during and after therapy.
   a. *Calcium chloride:* Adult: 5 ml IV bolus of a 10% solution over 5 minutes; Child: 0.2 to 0.3 ml/kg of a 10% solution over 5 to 10 minutes (20 to 30 ml/kg /dose).
   b. *Sodium bicarbonate:* Adult or Child: 1–2 mEq/kg IV bolus.
   c. *Insulin/dextrose:* Adult: 5 to 10 units regular insulin IV bolus with 100 ml of D50 IV immediately; monitor serum glucose every 30 minutes; Child: 0.5 to 1 gm/kg dextrose as D25 or D10 IV followed by 1 unit of regular insulin for every 4 grams of dextrose infused; monitor serum glucose every 30 minutes.
   d. *Sodium polystyrene sulfonate:* Adult 15 to 60 grams by nasogastric tube or rectal enema; Child: 1 gm/kg by nasogastric tube or rectal enema.

8. Pretreatment with 0.125 mg/kg IV succinylcholine followed in 60 seconds by 1 mg/kg IV may reduce postoperative muscle fasciculations and pain in adults. Pretreatment with d-tubocurarine (0.05 mg/kg) may decrease myoglobinaemia.

9. For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is NOT routinely recommended.

10. In susceptible patients, succinylcholine can produce a rise in ICP that may lead to herniation. Pretreatment with a low dose of a nondepolarising agent such as pancuronium 0.01 mg/kg IV or low dose succinylcholine 0.1 mg/kg IV 3 to 5 minutes prior to administration of full dose succinylcholine, may blunt the rise in ICP.

11. In patients with renal failure, haemodialysis may be effective in reversing prolonged neuromuscular blockade due to tubocurarine or pancuronium. However, dialysis will not be effective for overdose of atracurium or vecuronium since these agents are not renally excreted.

MISCELLANEOUS MUSCLE RELAXANTS

■ Orphenadrine

Orphenadrine is a tertiary amine antimuscarinic agent closely related to diphenhydramine.

Uses

■ Orphenadrine is used in the treatment of painful skeletal muscle disorders.
■ It is also used to treat drug induced extrapyramidal reactions and Parkinson's disease.

Toxicokinetics

■ Orphenadrine is rapidly and completely absorbed from the stomach and intestines, peak plasma levels are reached in 2 to 4 hours, and after undergoing an enterohepatic cycle is almost entirely metabolised by first-order kinetics to eight metabolites, the most important among which is N-demethylorphenadrine (NDO). Absorption may be delayed due to the drug's anticholinergic effects on gastric motility.
■ Approximately 50 to 60% is excreted as metabolites in the urine, about 8% is excreted unchanged, while the remainder gets eliminated in the faeces. Elimination half-life is 14 hours after therapeutic doses.

Mode of Action

Orphenadrine has certain central effects on muscle tone, and is anticholinergic and antihistamininc, with some local anaesthetic effects.

The usual oral dose of orphenadrine is 100 mg twice a day, while the usual parenteral dose is 60 mg IV or IM twice a day.

Adverse Effects

- Dry mouth, nausea, blurred vision, mydriasis, tachycardia, urinary retention, headache, vertigo, agitation, tremors, and mental confusion. Constipation is a common anticholinergic side effect.
- Rarely aplastic anaemia or anaphylactic reactions may occur.

Drug Interactions

- Potentiation of the effects of alcohol, anticholinergics, antidepressants, MAOIs, and CNS depressants.
- Propoxyphene may aggravate tremors and confusion.
- There is synergistic effect with levodopa.

Clinical (Toxic) Features

1. Overdose results in mydriasis, tachycardia, dry hot skin, decreased gastrointestinal motility, athetoid movements, agitation, confusion, hallucinations, convulsions, urinary retention, hypokalaemia, hypoglycaemia, hypotension, ventricular arrhythmias, respiratory depression, and cardiac arrest.
2. Bradycardia has been reported with severe overdose.

Usual Fatal Dose

- Therapeutic blood levels should be below 0.2 mg/L. Blood levels of over this are associated with toxicity, and levels over 4 to 8 mg/L may be fatal.
- In a review of orphenadrine toxicity, the minimum lethal dose was between 2 to 3 grams for adults.
- Death has been reported in children ingesting as little as 400 mg of orphenadrine.

Treatment

1. Continuous ECG monitoring, pulse, respiration, and temperature measurements.
2. Monitor blood glucose; follow serum electrolytes, renal function and CPK levels in patients with prolonged seizures or hypotension.
3. Stomach wash can be beneficial upto 4–6 hours of ingestion.
4. Activated charcoal is said to help in the prevention of absorption of orphenadrine, and is administered in the usual dose.
5. Correct hypoglycaemia with intravenous dextrose, 50 ml of 50% dextrose in adults; 2 to 4 ml/kg of 25% or 10% dextrose in children. Follow blood glucose carefully and repeat as needed.
6. Physostigmine is the antidote and effectively reverses the anticholinergic manifestations. However it should be used with caution, since its cardiotoxic effects can aggravate the cardiac depressant property of orphenadrine. The dose recommended is 2 mg IV for an adult and 0.5 mg for a child. Dilute the dose of physostigmine in 10 ml of dextrose 5% in water or normal saline. Give over 5 minutes. This can be repeated after 15–20 minutes if required. Atropine at a dose of 0.5 mg per 1 mg of physostigmine (of the last dose administered) should be available to reverse life-threatening physostigmine induced, toxic cholinergic effects such as bronchoconstriction.
7. Attempt initial control of convulsions with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.
8. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
9. Lignocaine, phenytoin, esmolol, isoproterenol, amiodarone, or magnesium sulfate may be used to treat cardiac conduction disorders. Quinidine, disopyramide, and procainamide are contraindicated as their effects on myocardial conduction are similar to that of other sodium blocking drugs. Because orphenadrine has sodium blocking properties arrhythmias may respond to administration of sodium bicarbonate. An initial dose of 1 mEq/kg is appropriate, repeated as needed with careful monitoring of blood pH.
10. Convulsions usually respond to IV diazepam. Barbiturates are best avoided.
11. Hypokalaemia may require potassium replacement under strict ECG monitoring.

Forensic Issues

- Orphenadrine has mood elevating effects at therapeutic doses, and has been chronically abused for its euphoric effects.

■ Dantrolene

Dantrolene is a hydantoin derivative which is structurally similar to both anticonvulsants and local anaesthetics, but does not possess their properties. It inhibits the release of calcium from skeletal muscle sarcoplasmic reticulum, dissociating excitation-contraction coupling. It has no effect on either smooth or cardiac muscle.

The most important use of dantrolene is to treat malignant hyperthemia. It is also sometimes employed in the control of fever in thyrotoxicosis. Dantrolene has also been used in the treatment of the following conditions with varying degrees of success: heatstroke, neuroleptic malignant syndrome, MAOI overdose, amphetamine overdose, and organophosphate poisoning. It has also been tried as an antispastic agent for skeletal muscle.

Dantrolene can be administered orally or intravenously. About 70% of the oral dose is absorbed, and the peak blood level is reached around 5 hours postingestion. It is metabolised

in the liver to 5-hydroxydantrolene, and upto 25% is excreted in the urine as the hydroxy metabolite.

Overdose results in muscle weakness, visual disturbances, lethargy, nausea, vertigo, pulmonary oedema, convulsions, hepatic toxicity (hepatitis), aplastic anaemia and leukopenia. Pericarditis has been reported in patients on chronic dantrolene therapy. Hepatotoxicity has been reported as an idiosyncratic reaction to therapeutic doses of dantrolene.

Treatment involves symptomatic and supportive measures.

■ Cyclobenzaprine

Cyclobenzaprine (proheptatriene, dimethylpropylamine) is a synthetic chemical, and is a tricyclic amine similar in structure and action to amitriptyline. It is sometimes used in the treatment of acute skeletal muscle spasm. Therapeutic doses range from 30 to 60 mg/day in adults. It should only be used for short periods (up to two or three weeks). The major metabolites of cyclobenzaprine include amitriptyline, norcyclobenzaprine and nortriptyline.

Adverse effects are anticholinergic in nature comprising mydriasis, warm, dry, flushed skin, dry mouth, urinary retention, constipation, decreased bowel sounds, vertigo, nausea, ataxia, disorientation, and sometimes convulsions. These symptoms become more pronounced in overdose, and in addition, the following manifestations are seen : urinary retention, tachycardia, delirium, hallucinations, hypotension (rarely hypertension), respiratory depression, and cardiac arrhythmias.

The CNS depressant effects of cyclobenzaprine are enhanced when it is coingested with other CNS depressant drugs (benzodiazepines, opioids, barbiturates, ethanol, sedative hypnotics, etc.). Concomitant cyclobenzaprine and anticholinergic therapy may result in additive anticholinergic effects. Concomitant monoamine oxidase (MAO) inhibitor and cyclobenzaprine therapy may result in hyperpyrexia, excitation, and seizures.

Treatment is on similar lines as for tricyclic overdose (*page no.324*). Gastric lavage is said to be beneficial upto several hours after ingestion. Serious symptoms may necessitate the use of physostigmine (1 to 4 mg IV slowly, over 5 to 10 minutes). If the heart rate exceeds 160 beats/minute and/or the patient demonstrates evidence of haemodynamic instability with central anticholinergic symptoms, treatment with physostigmine may be necessary.

Teratogenicity has been reported following first trimester maternal exposure to cyclobenzaprine. A syndrome of imperforate oropharynx with costovertebral and auricular anomalies was reported in a child of 32-week gestation following first trimester maternal ingestion of cyclobenzaprine and zomepirac.

Forensic Issues (Muscle Relaxants)

- Accidental overdose involving these drugs is not uncommon.
- Suicides have been reported with many of these drugs, and most of them have involved medical or paramedical personnel.
- Homicides are increasingly being reported, especially with reference to neuromuscular blocking agents. There is even a report of a serial murder involving multiple victims with succinylcholine.

- Some of these drugs are subject to being abused, e.g. orphenadrine, baclofen.

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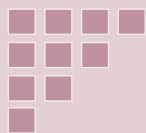
Drugs Used in Psychiatry

The principal drugs used in psychiatry comprise those indicated for the treatment of anxiety, psychosis, depression, and mania. The toxicity of drugs used in the treatment of migraine and Alzheimer's disease will also be discussed in this chapter. **Anti-anxiety drugs** include benzodiazepines, barbiturates, meprobamate, and buspirone, all of which have been discussed in preceding sections.

ANTIPSYCHOTICS

Most antipsychotics used today induce sedation as well as suppress extrapyramidal movement disorders encompassing spontaneous and complex patterns of behaviour. They are also referred to as *major tranquillisers* or *classical neuroleptics*. Many of these drugs act as dopamine receptor antagonists, though a few of them do not (e.g. clozapine).

1. **Phenothiazines**
    a. *Aliphatic* : chlorpromazine, triflupromazine.
    b. *Piperazine* : trifluoperazine, prochlorperazine, perphenazine, fluphenazine.
    c. *Piperidine* : thioridazine, mesoridazine.
2. **Thioxanthines**
    Chlorprothixene, clopenthixol, flupenthixol, pifluthixol, thiothixene, zuclopenthixol.
3. **Butyrophenones**
    Droperidol, haloperidol, benperidol.
4. **Indoles**
    Molindone.
5. **Dibenzoxapines**
    Clothiapine, metiapine, zotapine, loxapine, amoxapine.
6. **Diphenylbutylpiperidines**
    Pimozide, fluspirilene, penfluridol.
7. **Dibenzodiazepines**
    Clozapine, fluperlapine, olanzapine.
8. **Benzisoxazoles**
    Risperidone.

The toxicity of all classical neuroleptic drugs will be discussed together, while a few other antipsychotics which possess a slightly different toxicological profile will be discussed separately.

■ Classical Neuroleptics

Uses

1. Neuroleptics are used in the treatment of schizophrenia, manic phase of manic-depressive illness, severe depression associated with psychosis, and organic psychotic states.
2. Phenothiazines are particularly useful in the treatment of amphetamine intoxication, anxiety, dysreflexia, behaviour problems, depression, chemotherapy-induced emesis, mania, porphyria and schizophrenia.
3. Phenothiazine itself is used as an insecticide, in the manufacture of dyes, as a polymerisation inhibitor, antioxidant, chain transfer agent in rubber production, as a parent compound for chlorpromazine as well as related antipsychotic drugs, as a urinary antiseptic, and as an anthelmintic drug.
4. Thioxanthenes are also used for the treatment of psychosis and schizophrenia. Flupenthixol is primarily used for the treatment of acute and chronic psychoses. Although it has been studied in depressive illnesses and cocaine withdrawal, further research is needed.
5. Haloperidol and benperidol are used to treat schizophrenia and acute psychosis; schizoaffective disorders; paranoid syndrome; and Tourette's syndrome. Haloperidol is frequently used for agitation or aggressive behaviour, especially in elderly patients. Droperidol is used as an antiemetic and sedative.
6. Molindone is a dihydroindolone antipsychotic agent. It is not structurally related to the phenothiazines, the butyrophenones or the thioxanthenes. It is indicated for the management of the manifestations of psychotic conditions (e.g. chronic schizophrenia, brief reactive psychosis, or schizophreniform disorders).
7. Pimozide is a drug that belongs to the diphenylbutylpiperidine group of neuroleptics, and is an orally active antipsychotic drug, which shares with other antipsychotics the ability to block dopaminergic receptors on neurons in the central nervous system. It is indicated for the suppression of motor and phonic tics in patients with Tourette's disorder

who have failed to respond satisfactorily to standard treatment. The ability of pimozide to suppress motor and phonic tics in Tourette's Disorder is thought to be a function of its dopaminergic blocking activity. Pimozide has also been used in the treatment of schizophrenia.

Mode of Action

- Neuroleptics inhibit the activity of a variety of receptors—dopaminergic, cholinergic, $alpha_1$ and $alpha_2$ adrenergic, histaminic, and serotonergic ($5HT_2$). Neuroleptic activity is thought to be related to the dopamine-receptor blocking activity in the limbic system. There are 6 sub-types of dopamine receptor – D_1, D_{2A}, D_{2b}, D_3, D_4, and D_5. Most neuroleptics have a high affinity for D_2 and D_3 receptors. Some neuroleptics (thioxanthenes and phenothiazines) bind with great affinity to D_1, D_2, D_3, and D_4 sub-types, while haloperidol and pimozide have high selectivity at D_2 and D_3 receptors and less D_4 affinity.
- Phenothiazines are neuroleptic agents which affect four anatomical sites of action, specifically the reticular activating system of the midbrain, the limbic system, the hypothalamus, and the globus pallidus and corpus striatum. Antipsychotic effects of phenothiazines are still not understood completely but suggested mechanisms include post-synaptic block of adrenergic or dopaminergic receptor sites, metabolic inhibition of oxidative phosphorylation, or decrease in the excitability of the neuronal membranes. They possess significant anticholinergic, alpha-adrenergic blocking, quinidine-like and extrapyramidal effects. Since the phenothiazines also lower the seizure threshold, large doses may produce seizures.
- Like other neuroleptics, flupenthixol is an antagonist at postsynaptic D_1 and D_2 dopamine receptors. Low doses of flupenthixol may exert selective effects on inhibitory presynaptic dopamine autoreceptors. This may partially explain its activating and antidepressant properties.
- Thiothixene has some pharmacological properties in common with the piperazine phenothiazines; mode of action has not been clearly established.
- Similar to other neuroleptics, haloperidol centrally blocks the action of dopamine by binding previously to D_{2A} receptors, and to a lesser extent, D_{1A} receptors. The potency of all antipsychotic drugs correlates well with their affinity for D_{2A} receptors.
- Pimozide is a neuroleptic which is thought to act by decreasing the permeability of membranes covering dopaminergic receptors. This prevents released neurotransmitters from reaching these sites. Pimozide binds preferentially to dopamine-2 receptors (as do the butyrophenones), whereas phenothiazines bind more selectively to dopamine-1 receptors. This may explain pimozides's efficacy in the treatment of Gilles de la Tourette and other tic disorders, as well as its unique side effect profile (*vide infra*).

Toxicokinetics

- All dopamine receptor antagonists are generally well absorbed on oral or parenteral administration. Haloperidol is readily absorbed (60 to 70%) from the gastrointestinal tract. Plasma concentrations usually peak 1 to 4 hours after ingestion and ½ to 1 hour after intramuscular injection. Following oral administration, haloperidol is detectable in the plasma within 1 hour with peak values occurring at 3 to 6 hours. A number of factors interfere with GI absorption—antacids, caffeine, smoking, and food.
- Most antipsychotics are highly lipophilic and accumulate in fat, lungs, and brain. They are generally highly protein-bound. Protein binding is over 90% for haloperidol.
- Metabolism is largely hepatic and occurs through conjugation with glucuronic acid, hydroxylation, oxidation, demethylation, and sulfoxide formation, by cytochrome P450 (CYP)2D6 and CYP3A isoenzymes. Systemic clearance is high because of a high hepatic extraction ratio, and only negligible amounts of the unchanged drug are excreted in the urine.
- The toxicokinetics of long-acting (injectable) antipsychotics differ greatly from those of short-acting (oral and injectable) drugs. Long-acting compounds take much longer to reach steady state and are eliminated very slowly.
- Pimozide is slowly absorbed, and peak plasma levels are noted around 8 hours. Protein binding is reported to be 99%. Pimozide is metabolised in the liver by oxidative N-dealkylation to at least two metabolites thought to be inactive. The kidney is the major route of elimination.
- Elderly patients should be prescribed lower than usual dosages of antipsychotics owing to decreased renal clearance, diminished cardiac output, decreased liver size, and weaker P450 activity.

Adverse and Toxic Effects

1. Neurological:
   a. *Neuroleptic malignant syndrome (NMS)*: This was first described in 1968 and is a rare complication occurring in about 0.02 to 2.4% of patients taking antipsychotic medication. However, NMS can be caused by other drugs also (**Table 19.1**). Among the neuroleptics, NMS is most frequently associated with phenothiazines, butyrophenones, and thioxanthines. Several cases have been reported with therapeutic doses of haloperidol. Among the phenothiazines, NMS appears most commonly following fluphenazine decanoate administration or withdrawal.
      i. NMS is believed to be an idiosyncratic reaction and carries with it a high mortality (20 to 40%).
      ii. The syndrome is twice as common in males as in females, and is more likely to occur in younger patients.
      iii. The pathophysiology is thought to be central dopamine blockade, and symptoms usually begin 3 to 9 days after neuroleptic treatment, lasting for about 5 to 10 days even after discontinuing the drug.
      iv. In essence, NMS is a severe form of extrapyramidal reaction and is manifested by hyperthermia (39° C to 42°C), muscular hypertonicity (generalised "lead pipe" rigidity, akinesia, tremor, choreoathetosis),

Table 19.1: Aetiology of Neuroleptic Malignant Syndrome

Neuroleptic Drugs	Non-Neuroleptic Drugs
Phenothiazines	Tricyclic Antidepressants: *desipramine, amoxapine, maprotiline, trimipramine, dothiepin, amitryptiline, fluoxetine*
Butyrophenones	Monoamine Oxidase Inhibitors: *phenelzine*
Thioxanthenes	Anticonvulsants: *carbamazepine, phenytoin*
Other Dopamine Antagonists: *metoclopramide, sulpride, sultopride, zuclopenthixol, tetrabenazine*	Withdrawal Parkinsonian Medication: *ethopropazine, levodopa, carbidopa, amantidine, bromocriptine*
	Lithium with clozapine, or carbamazepine, or phenelzine, or chlorpromazine, or doxepin, or antiparkinsonian agents
	Oestrogen: trigger for patients on neuroleptics

fluctuating mental status (confusion, agitation, stupor), and autonomic irregularities (tachycardia, labile blood pressure, tachypnoea, urinary incontinence, respiratory stridor, sweating, cardiac arrest).

v. Complications include rhabdomyolysis, aspiration pneumonia, pulmonary embolism, pulmonary oedema, ARDS, DIC, seizures, myocardial infarction, peripheral neuropathy and death.

vi. Laboratory investigations indicate the presence of metabolic acidosis, liver enzyme abnormalities, leukocytosis, and elevation of creatinine as well as creatine phosphokinase.

vii. Differential diagnosis includes all causes of fever, leukocytosis, and rigidity (**Table 19.2**).

b. *Acute extrapyramidal syndromes*: These syndromes result from decreased dopamine activity in the basal ganglia and have their onset soon after initiation of antipsychotic drug therapy, but disappear once the drug use is discontinued.

i. Akathisia—It is the most common and most distressing of the acute extrapyramidal syndromes resulting from antipsychotic therapy and is characterised by a sensation of restlessness manifesting as agitation, fidgeting, restless legs, hostility, and belligerence. This may mislead the clinician into believing that the patient requires an increased dosage of the drug which will only worsen the condition. Akathisia is more frequently encountered in elderly patients.

ii. Acute dystonia—This is more common in children and male adults administered butyrophenones and piperazines and is characterised by oculogyric crisis (upward gaze paralysis), spasms of jaw and throat, tongue protrusion, torticollis (neck twisting), retrocollis (spasm of back of neck), opisthotonus, facial grimacing, tortipelvis (abdominal wall spasm), and laryngeal dystonia which can be life threatening.

iii. Parkinsonism—This is more common in elderly patients and manifests classically as akinesia, rigidity, shuffling gait, mask-like facies, and tremor. Examination often reveals a positive glabella tap.

c. *Chronic extrapyramidal syndromes*:

i. Tardive dyskinesia—This is the most serious side effect of long term phenothiazine and haloperidol treatment. Elderly women are most susceptible. Manifestations are quite disabling and comprise facial gimacing, eye blinking, furrowing of eyebrows, lip smacking, tongue protrusion, jaw deviation, and choreoathetoid-like movements of the limbs. These features are completely absent in sleep. Once established, tardive dyskinesia may take a long time to disappear, and sometimes becomes permanent.

ii. Rabbit syndrome—This is characterised by rhythmic involuntary movements of the oral and masticatory musculature mimicking the chewing movements of a rabbit. It may be irreversible.

2. Cardiovascular:

a. Common cardiovascular adverse effects include orthostatic (or postural) hypotension, cardiac arrhythmias, and ECG anomalies (prolongation of PR, QRS, and QTc intervals, blunt T waves, and depressed ST segments).

b. Cardiac arrest and sudden death have been reported in overdose patients.

c. Ventricular tachycardia may progress to torsades de pointes or ventricular fibrillation and can be difficult to treat.

Table 19.2: Differential Diagnosis of Neuroleptic Malignant Syndrome

CNS Disorders	Systemic Disorders	Autoimmune Diseases
Infections	Infections	Heat stroke
Tumours	Metabolic conditions	Toxins (carbon monoxide, strychnine, tetanus)
Cerebrovascular accidents	Endocrinopathies (thyroid storm, phaechromocytoma)	Drugs (salicylates, dopamine inhibitors and antagonists, psychedelics, MAOIs, anaesthetics, anticholinergics, alcohol withdrawal)
Trauma		
Seizures		
Major psychoses (lethal catatonia)		

d. Among the phenothiazines, thioridazine and mesoridazine are associated with maximum cardiotoxicity.

3. Gastrointestinal: Gastrointestinal toxic effects manifest as dry mouth and constipation; less commonly there may be vomiting or diarrhoea.

4. Other Systems:
   a. Urinary retention may result from the anticholinergic effect of many of these drugs.
   b. Leukopenia, thrombocytopenia, agranulocytosis, and pancytopenia are rare complications.
   c. Skin rash occasionally occurs. Photosensitivity reactions are not uncommon, and therefore patients should be instructed to avoid direct sunlight.
   d. High-dose thioridazine therapy can cause retinal pigmentation and blindness. Presumably, other phenothiazines can also cause this effect.
   e. Female patients may experience galactorrhoea, breast enlargement, and irregular menses while on antipsychotic medication owing to increased circulating prolactin concentrations. In males there may be decreased libido, erectile disurbances, and ejaculatory problems. Priapism associated with the therapeutic use of chlorpromazine, thioridazine, mesoridazine, and fluphenazine has been reported.
   f. An absent gag reflex and swallowing difficulties have been associated with phenothiazine therapy. Sudden death due to asphyxiation and/or aspiration of gastric content has occurred secondary to the absent gag reflex.
   g. Hepatic disease has been associated with almost all of the phenothiazines. Cholestatic jaundice or mixed cholestatic and hepatocellular jaundice, not necessarily related to either dose or duration of therapy, are the most common hepatic problems associated with therapeutic use and overdose.
   h. Acute overdoses of antipsychotic drugs result in the exaggeration of the usual adverse effects already described, and summarised in **Table 19.3**.
      i. Phenothiazines may interfere with the body's ability to thermoregulate, and cause hyperthermia or hypothermia. Hypothermia may occur with therapeutic use and overdose of phenothiazines and related agents; the elderly are especially vulnerable.
      ii. Hypotension and hypertension have both been reported; hypotension is the more common serious effect. Patients who overdose on thioridazine may experience late onset atrioventricular block.

Table 19.3: Neuroleptic Drug Overdose

- Severe rigidity, dystonia
- Sedation, delirium, restlessness
- Convulsions
- Fever
- Hypotension, ECG changes, cardiac arrhythmias
- Mydriasis
- Anticholinergic effects : dry mouth, ileus, urinary retention
- Coma, respiratory depression

Cardiac disorders may be most pronounced 10 to 15 hours after ingestion.

iii. Chlorpromazine has been reported to cause coma with pulmonary oedema with ingestion of overdose.

iv. Patients who have overdosed on phenothiazines and related agents may develop rhabdomyolysis secondary to episodes of neuroleptic malignant syndrome, seizures or prolonged immobility. Rhabdomyolysis is often followed by acute renal insufficiency.

v. Mydriasis is common with ingestion of chlorpromazine and thioridazine.

vi. Most common manifestations of acute intoxication with chlorprothixene include somnolence, coma, miosis, seizures, hypotension, cardiac arrhythmias, and respiratory depression. Possible sequelae include acute reversible renal failure.

vii. Flupenthixol overdose results in extrapyramidal movements, somnolence, and tardive dyskinesia, while thiothixene causes hypotension, somnolence, extrapyramidal signs, and tardive dyskinesia.

viii. Most common major signs of acute intoxication with haloperidol include somnolence, coma, respiratory depression, extrapyramidal signs, cardiac arrhythmias, and hypotension. Premature ventricular contractions, ventricular arrhythmias, torsades de pointes, and bradycardia have been reported with overdose. Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal. Possible sequelae with haloperidol include neuroleptic malignant syndrome and acute renal failure. Extrapyramidal effects are common with both droperidol and haloperidol therapy. Potentially irreversible, involuntary dyskinetic movements may develop in some patients treated therapeutically with haloperidol. Elderly women appear at greatest risk. These signs may also occur with overdose. Sudden death has been reported in young, otherwise healthy adults given large therapeutic doses of haloperidol or droperidol.

ix. Molindone is somewhat less likely than other neuroleptics to cause hypotension, but may cause sedation. It can however facilitate the onset of neuroleptic malignant syndrome. Extrapyramidal effects (rigidity, tremor, akathisia, major tonic spasms and tardive dyskinesia) are likely with large doses. Especially in patients who have previous exposure to neuroleptics, therapeutic administration and overdose may facilitate rhabdomyolysis with high CPK levels, myoglobinuria, hyperkalaemia, acid-base derangements and subsequent acute renal failure. Although most neuroleptic drugs are associated with weight gain, molindone appears to be more often associated with weight loss. Menstrual

abnormalities can occur with molindone therapy (heavy menstrual flow, amenorrhoea.).

x. Intoxication with dibenzoxapines can result in respiratory depression, hypotension, prolonged seizures, coma, hyperthermia, rhabdomyolysis and renal failure. Cardiac arrhythmias and conduction delays are not a prominent feature of overdose, but have been reported, usually in patients with severe neurologic toxicity: supraventricular tachycardia, atrial flutter, premature ventricular contractions, nonspecific ST segment and T wave changes, QRS prolongation, bradycardia, and myocardial failure. Anticholinergic effects are not prominent. Pupils may be dilated but usually respond to light; blurred vision may occur secondary to loss of accommodation reflexes. Miosis has also been reported, usually in patients with seizures or CNS depression. Mortality is most often due to complications of intractable seizures or brain death.

xi. Loxapine overdose complicated by multiple seizures, rhabdomyolysis, and acute renal failure has been reported. Mild overdoses only result in drowsiness, lethargy and confusion. Parkinsonism, akathisia, dystonic reactions, tardive dyskinesia, choreoathetosis, cogwheel rigidity, tardive myoclonus, and lingual dyskinesia have been described at therapeutic doses in patients treated with loxapine and amoxapine.

xii. With pimozide therapy, adverse effects occur in about 10 to 15% of patients and are dose related, occurring most frequently when the daily dose exceeds 10 mg/day. Hypotension, cardiac arrhythmias including QT prolongation and torsade de pointes, extrapyramidal effects, anorexia, nausea, diarrhoea or constipation, sedation, mydriasis, facial swelling, amenorrhoea with galactorrhoea, xerostomia, anxiety, agitation, dysphoria, lethargy, and depression may occur. Prolongation of the QT interval occurs commonly after an overdose. Hypotension, cardiac arrhythmias including QT prolongation and torsade de pointes, and seizures may occur following an overdose with pimozide. Extrapyramidal and anticholinergic effects also occur following overdoses.

Diagnosis

1. Monitor acid-base status, fluid and electrolyte balance, hepatic enzyme levels (serum ALP, SGOT, and SGPT), renal function and urine output.
2. Patients with clinical signs of neuroleptic malignant syndrome should be monitored for rising serum CPK levels and leukocyte count.
3. Institute continuous cardiac monitoring and follow serial ECGs.
4. Unabsorbed phenothiazines are radiopaque in the gastrointestinal tract, and the diagnosis of phenothiazine ingestion can be made radiographically. Absence of radiopacity does not rule out phenothiazine overdose.

5. Phenothiazines have been reported to impart a pink to red, purple, orange, or rust colour to the urine. This change in urine colour is variable among patients.

Treatment

1. *Neuroleptic malignant syndrome:*
   a. Discontinue neuroleptic therapy.
   b. Management of hyperthermia by rapid external cooling with ice. Do not use antipyretics; they are useless in this setting.
   c. Dantrolene sodium, 1 to 3 mg/kg/day IV in 4 divided doses (maximum 10 mg/kg/day). Maintenance dose (oral): 50 to 200 mg/day.
   d. Bromocriptine, 2.5 to 10 mg orally, 3 times a day (maximum 20 mg, 4 times a day). Continue with dantrolene or bromocriptine (rarely both together), until patient's condition improves, or until creatine kinase levels return to normal. It is important to note that dantrolene or bromocriptine (or even amantidine) may not produce immediate improvement, which usually takes 24 to 72 hours to be evident. Bromocriptine and amantidine act by inducing central dopamine agonist effects, while dantrolene inhibits the release of calcium from sarcoplasmic reticulum.
   e. Pancuronium and sodium nitroprusside have been used with success in some cases of neuroleptic malignant syndrome.
   f. Supportive measures—correction of fluid and electrolyte imbalance, management of hypo/hypertension, maintaining pulmonary, cardiovascular, and renal functions, and sedation.
   g. Electroconvulsive therapy may be required in some cases.
2. *Acute extrapyramidal syndromes:*
   a. Akathisia—
      i. Reduce dose of neuroleptic drug.
      ii. Administer antiparkinsonian drugs or benzodiazepines, or both.
      iii. Propranolol (20 to 50 mg daily) may help to reduce hyperactivity associated with haloperidol.
   b. Acute dystonia—
      i. Diphenhydramine, 1 to 2 mg/kg, IV, (maximum 100 mg), **or** benztropine mesylate, 1 to 2 mg, IV.
      ii. Maintenance: benztropine mesylate orally, 1 to 2 mg twice a day, **or** trihexyphenidyl 2 mg three times a day, **or** diphenhydramine 1 mg/kg (upto 50 mg), four times a day.
      iii. Parkinsonism—Administration of antiparkinsonian drugs, (*page no 236*).
3. *Chronic extrapyramidal syndromes:*
   a. Tardive dyskinesia—It is the most recalcitrant of the adverse effects of neuroleptic medication, and once established is extremely resistant to treatment. Therefore preventing this complication is more important, which can be achieved by avoidance of high-dose, long-term daily therapy as well as observing "drug holidays" i.e. periods of abstinence from drugs.

    i. Treatment of tardive dyskinesia has been attempted with a wide variety of drugs with little or no success. They include the following: serotonergic drugs (tryptophan, cyproheptadine), noradrenergic drugs (lithium), β-adrenergic receptor antagonists (propranolol), and α-adrenergic agonists (clonidine).

    ii. Newer approaches with morphine, naloxone, oestrogen, pyridoxine, manganese, phenytoin, and papaverine have also not been encouraging.

    iii. Anticholinergic agents usually aggravate existing tardive dyskinesia, while cholinergic drugs are only marginally beneficial.

    iv. Benzodiazepines may give temporary relief, but sometimes there is exacerbation.

  b. Rabbit syndrome—

    i. Discontinue neuroleptic therapy.

    ii. Administer antiparkinsonian drugs.

4. *Cardiovascular toxicity:*

  a. Arrhythmias can be managed effectively by temporary cardiac pacing which should preferably last for 10 days, especially in patients who have presented with ventricular tachycardia associated with AV block I or II. Drugs such as quinidine, procainamide, disopyramide, and isoproterenol are contraindicated. Lignocaine-like drugs are only sometimes effective. Lignocaine is indicated in patients with frequent PVCs (greater than 5 per minute), coupled, multifocal, or R on T phenomenon associated with ingestion. Cardioversion is often required for ventricular tachycardia, and is the initial treatment for ventricular fibrillation, but the arrhythmias are often resistant. A pacing wire may be the only effective treatment, especially if atrioventricular block is present.

  b. For torsade de pointes: Withdraw the causative agent. Haemodynamically unstable patients require electrical cardioversion. Emergent treatment with magnesium, isoproterenol, or atrial overdrive pacing is indicated. Detect and correct underlying electrolyte abnormalities (hypomagnesaemia, hypokalaemia, hypocalcaemia).

  c. All patients with neuroleptic-induced cardiac toxicity should be subjected to careful cardiac monitoring.

  d. Hypotension usually responds to Trendelenberg position and Ringer's lactate. If vasopressors are considered necessary, α-adrenergic agonists such as noradrenaline are the drugs of choice. Use of adrenaline in hypotensive patients who have overdosed on neuroleptics is generally NOT recommended, since these drugs may reverse adrenaline's usual pressor action and aggravate hypotension. Because dopamine is more easily administered and can often be instituted more readily, it is recommended by some investigators as the agent of choice. According to them, if hypotension does not respond to dopamine, an agent with more selective alpha agonist activity is a logical second choice (noradrenaline, metaraminol).

5. *Gastrointestinal symptoms:*

  a. Patients who experience a severely dry mouth should be advised to rinse their mouth frequently, and to chew gum (preferably sugar-less) or candy. Over-indulgence of the latter can however predispose to oral fungal infections and dental caries.

  b. Constipation can be managed with stool softeners or laxatives.

6. *Acute neuroleptic overdose:*

  a. Activated charcoal and stomach wash can help if the patient is seen in a short time after the ingestion. Sustained-release formulations of thioridazine, chlorpromazine, and possibly other phenothiazines may require extended treatment. Whole bowel irrigation or extended administration of activated charcoal may reduce absorption.

  b. Stabilisation—intubation, assisted ventilation, IV line, cardiac monitoring.

  c. Decontamination—gastric lavage, activated charcoal.

  d. Elimination enhancement – haemodialysis, haemoperfusion, etc. do not appear to be beneficial. Plasmapheresis may be beneficial in haloperidol-induced NMS.

  e. Management of convulsions with diazepam or phenytoin. Seizures are a particular problem with dibenzoxapines such as amoxapine and loxapine. If seizures cannot be controlled with diazepam or lorazepam, or recur, administer phenobarbitone. If phenobarbitone is ineffective, consider propofol, barbiturate coma and/or neuromuscular paralysis with continuous EEG monitoring.

  f. Management of hypotension: Fluid challenge is sufficient for correction of hypotension in most patients. If it is not effective, dopamine is recommended as the drug of choice. If hypotension does not respond to dopamine, an agent with more selective alpha agonist activity is a logical second choice (noradrenaline, metaraminol).

  g. Cardiac monitoring: Since the phenothiazines produce "quinidine-like" effects on the myocardium, quinidine, procainamide, and disopyramide should be avoided. Lignocaine is usually effective for ventricular arrhythmias. Sodium bicarbonate may also be effective in treating arrhythmias and QRS widening. Cardioversion is often required for ventricular tachycardia, and is the initial treatment for ventricular fibrillation, but the dysrhythmias are often resistant. A pacing wire may be the only effective treatment, especially if atrioventricular block is present. With reference to torsades des pointes, haemodynamically unstable patients require electrical cardioversion. Emergent treatment with magnesium, isoproterenol, or atrial overdrive pacing is indicated.

  h. Detect and correct underlying electrolyte abnormalities.

  i. Management of rhabdomyolysis:

    i. Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is NOT routinely recommended.

ii. Initial treatment should be directed towards controlling acute metabolic disturbances such as hyperkalaemia, hyperthermia, and hypovolaemia. Control seizures, agitation, and muscle contractions.

iii. Vigorous fluid replacement with 0.9% saline is necessary even if there is no evidence of dehydration. Hypovolaemia, increased insensible losses, and third spacing of fluid commonly increase fluid requirements. Strive to maintain a urine output of at least 2 to 3 ml/kg/hr. In severe cases 500 ml of fluid per hour may be required for the first several days. Monitor fluid input and urine output, plus insensible losses. Monitor for evidence of fluid overload and compartment syndrome; monitor serum electrolytes, CK, and renal function tests.

ATYPICAL NEUROLEPTICS

■ Dibenzodiazepines

Clozapine is an atypical neuroleptic, antipsychotic drug with a tricyclic dibenzodiazepine structure. It is the most important member of this group and is known for its low-risk of producing extrapyramidal reactions. It has low affinity for D_2 receptors, but is an active alpha-adrenergic antagonist.

Uses

- Treatment of schizophrenia not responding to other antipsychotic agents.
- Treatment of psychosis in patients who cannot tolerate extrapyramidal adverse effects.

Toxicokinetics

- Clozapine is rapidly absorbed on oral administration and peak plasma levels are reached in 2 hours. Elimination half-life is about 12 hours, while the mean volume of distribution is 2.0 to 5.1 L/kg. Binding to plasma proteins is to the extent of 95%.
- Clozapine undergoes extensive first-pass metabolism in the liver and gut, and about 80% appears in the urine or faeces as metabolites. 2 to 5% of the dose is excreted unchanged in the urine; 49% of a dose is excreted as metabolites in the urine. 38% of a dose is excreted as metabolites in the faeces.

Mode of Action

- Clozapine differs from classical neuroleptics in that it blocks D_1 more than D_2 receptors, raises plasma prolactin levels only slightly, and does not induce supersensitivity in striatal dopamine systems. The actual mode of action may be differential modulation of D_1 and D_2 receptors in the extrapyramidal, limbic and cortical systems.
- Clozapine causes greater antagonism of serotonin S_2 receptors than conventional neuroleptics.
- It also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors.

Adverse Effects

- Common effects following long-term use include nausea, vomiting, weight gain, vertigo, hypotension, salivation, constipation, tachycardia, and sedation. Hypertension sometimes occurs. Seizures are not infrequent.
- In 2 to 3% of patients, clozapine can cause haematological problems including leukopenia, eosinophilia, and agranulocytosis.
- Neuroleptic malignant syndrome is uncommon, as also serious extrapyramidal manifestations.
- Hyperglycaemia, glucose intolerance and new-onset diabetes have been reported with clozapine therapy.
- Sudden cessation of clozapine therapy can cause a withdrawal reaction. In one case series, withdrawal of clozapine resulted in delirium and psychosis which rapidly resolved when low dose clozapine was resumed.

Drug Interactions

- Benztropine—Concurrent use may result in excessive anticholinergic effects.
- Carbamazepine—Concurrent use may result in bone marrow suppression.
- Cimetidine—Concurrent use may result in increased clozapine serum levels and risk of clozapine toxicity.
- Erythromycin—Concurrent use may result in increased clozapine serum levels and risk of clozapine toxicity.
- Lithium—Concurrent use may result in neuromotor effects or myelosuppression.
- Ritonavir—Concurrent use may result in increased risk of haematologic abnormalities, excessive sedation, dizziness, and hypotension.
- Venlafaxine—Concurrent use may result in increased serum concentrations of both drugs.
- Benzodiazepines—Concurrent use may result in elevated clozapine serum levels and toxic clozapine effects such as sedation, cognitive impairment, respiratory depression and cardiovascular complications.
- Fluoxetine—Increased clozapine levels with possible clozapine toxicity may occur when these two drugs are administered concomitantly.
- Fluvoxamine—Concurrent use may result in elevated serum clozapine levels and toxic clozapine effects (dizziness and hypotension).
- Zidovudine—Concurrent use with clozapine may result in additive bone marrow toxicity, with subsequent decrease in WBC and possible agranulocytosis.
- Risperidone—Concurrent use of risperidone and clozapine can result in neuroleptic malignant syndrome.
- Tobacco—Tobacco products may induce CYP1A2 activity in patients on clozapine. Therefore, smoking cessation can increase clozapine levels leading to toxic symptoms.

Clinical (Toxic) Features

1. Overdose with clozapine results in antimuscarinic or anticholinergic effects: restlessness, lethargy, disorientation, confusion, agitation, delirium, mydriasis, blurred vision,

convulsions, hypo- or hypertension, tachycardia, arrhythmias (atrio-ventricular block, extrasystoles, ventricular fibrillation, ST prolongation), hypothermia, salivation,* dry skin, urinary retention, constipation, ARDS, and myocarditis.

2. Other features include agranulocytosis, fasciculations, tremor, myoclonus, and coma. Sudden death can occur.
3. Effects of overdose in children comprise tachycardia, ataxia, confusion, myoclonus, drooling, nystagmus, muscle rigidity, lethargy, and decreased muscle tone. Children may develop severe symptoms of intoxication with a relatively small exposure (>100 mg).
4. Postmarketing safety data suggested that clozapine is associated with increased risk of fatal myocarditis. This is of greatest concern during the first month of therapy.

Usual Fatal Dose

Fatal dose is usually above 2500 mg, though intake of even 300 to 400 mg can be lethal.

Treatment

1. Decontamination: Gastric lavage may be beneficial in the first 1 or 2 hours post-ingestion. Activated charcoal may also be beneficial.
2. Diazepam or phenytoin for convulsions. Valproic acid may also be given, but carbamazepine is contraindicated (enhances risk of agranulocytosis).
3. Treatment of hypotension by Trendelenberg position, IV fluids, plama expanders, and vasopressors (dopamine or noradrenaline). Adrenaline is contraindicated.
4. Treatment of arrhythmias with lignocaine, phenytoin, or pacing. Quinidine, procainamide, and disopyramide are contraindicated.
5. Treatment of agranulocytosis with granulocyte colony-stimulating factor (G-CSF). Filgrastim should be considered in selected patients with severe granulocytopenia. Starting dose is usually 5 mcg/kg/day in adults by subcutaneous injection or intravenous infusion. Monitor CBC and absolute granulocyte count. An initial leukocyte count with differential should be obtained at admission following a potential clozapine overdose. The leukocyte and granulocyte count should then be monitored once or twice weekly for four weeks following overdose.
6. Physostigmine may reverse clozapine-induced delirium.
7. Clozapine has been associated with a rise in liver enzymes. Monitoring is advisable.
8. Renal function must also be monitored during therapeutic use and overdose with clozapine.
9. Metabolic acidosis has been reported in a few cases, and will require the usual treatment measures.
10. Haemodialysis, haemoperfusion, forced diuresis, and exchange transfusion are unlikely to be useful in clozapine overdose because of the relatively large volume of distribution and high degree of protein binding.

■ Benzisoxazoles

The most important (and virtually the sole) member of this group is risperidone.

Uses

- Risperidone is a useful antipsychotic drug for the treatment of schizophrenia with specific benefit on "negative" symptoms—affective blunting, paucity of speech, and emotional apathy.
- It is also said to be useful in the treatment of psychotic depression.
- Risperidone is considered to be the treatment of choice for Pervasive Developmental Disorders (PDD) of childhood.

Toxicokinetics

- Risperidone is rapidly absorbed on oral administration and peak plasma levels are seen in 2 hours. After oral dosing, mean peak plasma concentrations of the active 9-hydroxyrisperidone metabolite generally occur after 3 hours in extensive metabolisers and after 17 hours in poor metabolisers. Because of moderate first pass metabolism, bioavailability of the parent compound is 66% in extensive metabolisers compared with 82% in poor metabolisers.
- Risperidone is metabolised in the liver by hydroxylation and oxidative n-dealkylation to the active moiety 9-hydroxy-risperidone. It has an apparent volume of distribution of 1 to 2 L/kg and is 88% bound to plama proteins.
- Upto 30% of the drug is excreted unchanged in the urine, while 15 to 30% of an administered dose is excreted in the faeces.
- Elimination half-life of risperidone is 2.8 hours in extensive metabolisers and 16 hours in poor metabolisers, while the half life of 9-hydroxy-risperidone is 20 to 22 hours in both groups.

Mode of Action

- Risperidone exhibits weak dopamine D_2 antagonism, but is a potent centrally acting serotonin 5-HT_2 and catecholamine antagonist. In vitro studies have shown that risperidone acts primarily as a serotonin (5-HT_2) and dopamine (D_2) antagonist. It binds with highest affinity to serotonergic receptors.
- Risperidone also binds to alpha-1 and alpha-2 adrenergic and histamine H_1 receptors, although with much less affinity. Dissociation from 5-HT_2 and H_1 receptors is slow; however, the drug rapidly dissociates from dopaminergic and alpha adrenergic receptors.

Adverse Effects

- Blurred vision, vertigo, confusion, anorexia, asthenia, orthostatic hypotension, increase in plasma prolactin levels, and sedation.
- Males may experience erectile and ejaculatory disturbances. Priapism, although rare, has been reported in association with risperidone use.

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* Paradoxical sialorrhoea in the midst of anticholinergic manifestations.

- Constipation, diarrhoea, nausea, and dyspepsia have been reported following therapeutic administration of risperidone.
- Hyperglycaemia has also been reported, and may be associated with ketoacidosis or hyperosmolar coma and death. Patients with diabetes mellitus, or who have predisposing risk factors for the development of diabetes mellitus, may experience a worsening of glucose control during risperidone therapy.

Drug Interactions

- Concurrent administration of clozapine with risperidone decreases the clearance of risperidone.
- Coadministered ritonavir increases serum concentrations of risperidone, potentially resulting in toxicity.
- Increased risperidone levels may occur when it is combined with fluoxetine. Severe extrapyramidal side-effects have been reported with fluoxetine-risperidone combination.

Clinical (Toxic) Features

1. Tachycardia, drowsiness, CNS depression, miosis, slurred speech, hypotension, tremor, agitation, extrapyramidal effects, auditory hallucinations, hyponatraemia, hypokalaemia and ECG changes (QRS and QTc prolongation).
2. Chorea and tardive dyskinesia occurred in some reported cases.
3. A few cases of mania developing after starting risperidone therapy have been reported. Sexual disinhibition was one of the most predominant symptoms.

Treatment

1. Early gastric lavage, followed by activated charcoal and a cathartic may minimise the severity of poisoning.
2. Monitor serum electrolytes including sodium, potassium and magnesium after significant overdose. Cardiac and electrolyte monitoring is advisable for at least 12 to 24 hours in an intensive care unit.
3. Sodium bicarbonate is generally first line therapy for QRS widening and ventricular arrhythmias. In patients unresponsive to bicarbonate, consider lignocaine or amiodarone.
4. Treat hypotension and circulatory collapse with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Adrenaline and dopamine are best avoided, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade. Because dopamine is more easily administered and can often be instituted more readily, it is recommended as the agent of choice. If hypotension does not respond to dopamine, an agent with more selective alpha adrenergic activity is a logical second choice (noradrenaline, metaraminol).
5. If extrapyramidal symptoms develop, anticholinergic agents can be administered.
6. In the case of seizures, attempt initial control with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.

7. Neuroleptic malignant syndrome can be successfully managed with diphenhydramine, oral bromocriptine, benzodiazepines, or intravenous or oral dantrolene sodium in conjunction with cooling and other supportive care.
8. Haemodialysis and haemoperfusion are unlikely to be useful in risperidone overdose because of high degree of protein binding.

ANTIDEPRESSANTS

Major depression is one of the affective disorders, and is perhaps the commonest mental illness worldwide. It is characterised by feelings of intense sadness and despair, slowing of thought process, impaired concentration, constant worry, agitation, and self-deprecation.

1. **Norepinephrine (or noradrenaline) reuptake inhibitors**
   a. *Tertiary amine tricyclics*: amitryptiline, clomipramine, doxepin, imipramine, trimipramine.
   b. *Secondary amine tricyclics*: amoxapine,* desipramine, maprotiline,* nortriptyline, protriptyline.
2. **Selective serotonin reuptake inhibitors**
   Citalopram, duloxetine, fluoxetine, fluvoxamine, milnacipran, oxaflozane, paroxetine, pizotifen, sertraline, venlafaxine.
3. **Monoamine oxidase inhibitors**
   Isocarboxacid, iproniazid, moclobemide, pargyline, phenelzine, pimozide, selegiline, toloxatone, tranylcypromine.
4. **Atypical antidepressants**
   Bupropion, mirtazepine, nefazodone, trazodone.
   The toxicity of the important antidepressants among these groups will be discussed in the following sections.

■ Cyclic Antidepressants

Tricyclic antidepressants possess a 3-ring molecular structure. Examples include amitriptyline, clomipramine, desipramine, dibenzepin, doxepin, dothiepin, imipramine, lofepramine, nortriptyline, protriptyline and trimipramine.

Uses

- Tricyclic antidepressants are used to treat a wide range of disorders such as depression, panic disorder, social phobia, bulimia, narcolepsy, attention deficit disorder, obsessive compulsive disorder, childhood enuresis, and chronic pain syndromes.

Toxicokinetics

- All cyclic antidepressants are rapidly absorbed from the GI tract and have large volumes of distribution (10 to 50 L/kg). Most of them bind to plasma protein alpha$_1$-glycoprotein with varying affinity.
- They are all highly lipophilic, sparingly water soluble, and substantially metabolised by first-pass in the liver. The metabolites retain significant pharmacologic activity until hydroxylation occurs by microsomal enzyme system.

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* Also referred to as tetracyclic antidepressants.

- The half-lives of these compounds are highly variable (4 hrs to 93 hrs).
- Approximately 30% of the absorbed dose is eliminated by gastric and biliary secretion, while renal clearance accounts for 3 to 10% of the parent compound. It is however important to remember that cyclic antidepressants taken in large quantities (overdose) exhibit significantly altered toxicokinetics.
  - ❖ Absorption may be delayed by inhibition of gastric emptying and peristalsis.
  - ❖ Enterohepatic recirculation delays final elimination of a large amount of the drug.
  - ❖ Enzymes responsible for hydroxylation can become saturated.
  - ❖ The amount of drug unbound to plasma proteins may increase (because of acidaemia).

Mode of Action

- Cyclic antidepressants, notably the tricyclics, are structurally similar to the phenothiazines with similar anticholinergic, adrenergic, and alpha-blocking properties of the phenothiazines.
- Following absorption, these agents are extensively bound to plasma proteins and also bind to tissue and cellular sites, including the mitochondria.
- Cyclic antidepressants act by inhibiting voltage-gated sodium channels in myocardial cells, blocking of H_1, H_2, and D_2 receptors, as well as muscarinic receptors, inhibiting alpha-adrenergic receptors, interacting with GABA receptors, and inhibiting the transport and reuptake of biogenic amines at nerve terminals.
- The toxicity of cyclic antidepressants is mainly due to effects on myocardium, CNS, and peripheral vasculature. There is prolongation of action potential duration in most myocardial cells, decreased peripheral vascular resistance, and induction of anticholinergic effects. Convulsions resulting from overdose are caused by complicated interactions within the brain due to altered concentrations of GABA, dopamine, noradrenaline and acetylcholine.

Adverse Effects

- Postural hypotension, cardiac arrhythmias, vertigo, weakness, tremor, confusion, weight gain, agranulocytosis and thrombocytopenia.
- Anticholinergic effects are common: tachycardia, hypertension, mydriasis, dry and flushed skin, visual blurring, decreased GI motility (constipation), urinary retention, and delirium with hallucinations and convulsions.
- Abrupt withdrawal of a chronically administered cyclic antidepressant can cause a *cholinergic rebound syndrome*: anorexia, nausea, vomiting, diarrhoea, sweating, myalgia, headache, fatigue, anxiety, insomnia, mania, akithisia or Parkinsonism.

Drug Interactions

- Cyclic antidepressants potentiate the sedative effect of alcohol, and the hypertensive effect of sympathomimetics.
- They aggravate the anticholinergic effect of antiparkinsonian and antipsychotic drugs, and cause marked hyperpyrexia with convulsions and coma when combined with MAOIs.
- The effect of antihypertensive drugs is reduced.
- Serotonin reuptake inhibitors inhibit cytochrome P450-2D6 and can cause elevations in serum tricyclic antidepressant levels.
- While tricyclic antidepressants and MAOIs have been used concomitantly to treat severe depression, the combination has occasionally been associated with the development of serotonin syndrome. Overdose with the combination of tricyclic antidepressants and MAOI appears to cause severe effects and has a high fatality rate.

Clinical (Toxic) Features

1. Overdose results in seizures (especially common with maprotiline and amoxapine), which are generally brief in duration, tachycardia,* hypotension, agitation, hallucinations, confusion including anticholinergic delirium, hyperthermia, ataxia, urinary retention, and coma. Coma is usually short-lived, and most patients waken within 24 hours.
2. Anticholinergic effects (mydriasis, tachycardia, urinary retention, decreased gastrointestinal motility) are common, but may be masked in severe overdose.
3. Miosis may be present in deeply comatose patients. Nystagmus may occur.
4. Rhabdomyolysis and renal failure may result from prolonged seizures or coma.
5. Significant metabolic acidosis may develop in patients with prolonged seizures or hypotension.
6. Neuroleptic malignant syndrome (NMS) has been reported.
7. Respiratory depression is common with significant overdoses and may develop rapidly. Adult respiratory distress syndrome may occur after severe overdose.
8. Cardiovascular toxicity results in myocardial depression, ventricular tachycardia, and fibrillation. A variety of ECG findings have been described (**Table 19.4**). Severe cardiac toxicity generally develops within six hours, although ECG changes may persist beyond 48 hours.
9. Myocardial infarction has been reported following overdose and with therapeutic use.
10. The duration of coma with cyclic antidepressant overdose is generally less than 6 to 12 hours. If this is prolonged beyond 24 hours, it indicates development of complications or concomitant ingestion of CNS depressants.

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* Combination of seizures with tachycardia should always arouse the suspicion of poisoning with any of the following: **cyclic antidepressants, amphetamines, datura, cocaine, xanthines, sympathomimetics,** and **anticholinergics**.

Table 19.4: ECG Findings in Cyclic Antidepressant Overdose

• Sinus tachycardia
• Prolonged PR, QRS, QTc intervals
• ST-T wave changes
• Bundle branch block
• II or III degree A-V block
• Supraventricular arrhythmias : atrial fibrillation, flutter, bradycardia
• Ventricular arrhythmias: premature ventricular beats, idioventricular rhythm, ventricular tachycardia, fibrillation, torsade de pointes

11. Amitryptiline overdose may be associated with peripheral neuropathy, polyradiculoneuropathy, and extrapyramidal manifestations.
12. Radiological evidence of pulmonary oedema is present in 10 to 15% of patients with cyclic antidepressant overdose: diffuse bilateral pulmonary infiltrates and other features characteristic of ARDS.
13. Uncommon manifestations include fulminant hepatic failure, bowel ischaemia, and acute intestinal pseudo-obstruction. Pruritic erythematous rash, vesicular eruption, blistering and skin discolouration have also been reported.
14. Withdrawal syndromes may occur after discontinuation of tricyclic antidepressants. Symptoms associated with tricyclic antidepressant withdrawal may include nausea, diarrhoea, malaise, myalgias, headache, rhinorrhoea, anxiety, agitation, mania, insomnia, nightmares, arrhythmias and ventricular ectopy.
15. A suggested toxicity rating for various cyclic antidepressants in overdose is outlined in **Table 19.5**.

Usual Fatal Dose

■ Death is not uncommon in severe cyclic antidepressant overdose, and is more likely in the presence of the following factors:
   ❖ Age > 30 years.
   ❖ Serum drug level > 800 ng/ml (2880 mmol/L).
   ❖ Ingestion of amitryptiline.
   ❖ Heart rate > 120.
   ❖ QRS duration > 100 ms.
   ❖ QRS axis > 90°.
   ❖ Terminal 40-ms axis > 135°.
   ❖ QTc interval > 480 ms.

■ Serum drug level of more than 1000 ng/ml (10 to 20 mg/kg PO) is usually fatal. The therapeutic range for most tricyclic antidepressants is 100 to 260 ng/ml.
■ Ten times the therapeutic daily dose of a cyclic antidepressant is potentially fatal.
■ Fatal poisonings have occurred in children following the ingestion of as little as 250 mg of imipramine or amoxapine.

Diagnosis

■ Monitor serum electrolytes, renal and hepatic function in patients with significant toxicity.
■ Follow CPK levels in patients with prolonged seizures or coma.
■ Serum tricyclic levels are useful in initial assessment since they may serve to confirm a history of ingestion.
■ ECG changes (*vide supra*). Monitor serial ECGs and institute continuous cardiac monitoring in all patients with suspected tricyclic overdose. ECG changes may include sinus tachycardia, prolonged PR interval, widening of the QRS complex, QTc prolongation, rightward shift in the axis of the terminal 40 milliseconds of the QRS complex, T-wave flattening or inversion, ST segment depression, right bundle branch block, junctional rhythm and atrioventricular block.
■ Elevation of creatine kinase and lactic acid dehydrogenase levels.
■ Chest X-ray to detect pulmonary oedema.

Treatment

1. Patients with ECG changes should be monitored in the ICU until the mental status is baseline, the patient is asymptomatic, and the ECG has returned to normal for 24 hours. Monitor cardiac rhythm and serial ECGs. Maximal limb-lead QRS duration of 0.10 seconds or longer has been associated with an increased incidence of seizures, while a QRS of 0.16 seconds or longer has been associated with an increased incidence of ventricular dysrhythmias. A terminal 40 ms QRS axis of >120 degrees or an R wave in lead aVR of > 3 mm are thought to be a more sensitive indicator of tricyclic antidepressant toxicity than QRS interval, although they have not been correlated with outcome or complications.
2. *Supportive measures*:
   a. Maintain airway; intubate if indicated.
   b. Monitor arterial blood gases.
   c. Administer oxygen if necessary.
   d. Treat hypotension with IV crystalloids, inotropes

Table 19.5: Toxicity Rating of Cyclic Antidepressants

Relatively Safe	Potentially Dangerous	Dangerous	Very Dangerous	Extremely Dangerous
Lofepramine	Clomipramine	Phenelzine	Maprotiline	Dothiepin
Mianserin	Protryptiline	Imipramine		Amitryptiline
Fluvoxamine	Trazodone			Tranylcypromine
Fluoxetine				
Viloxazine				

(dopamine), vasopressors (noradrenaline), etc., as necessary. Intra-aortic balloons have been used successfully when pressors have failed.

3. *Reduce drug absorption:*
   a. Stomach wash (within the first 6 hours).
   b. Activated charcoal (1 gm/kg).

4. *Enhance drug elimination:*
   a. Multiple-dose activated charcoal.
   b. Diuresis and haemodialysis are not effective.
   c. Haemoperfusion is not routinely recommended, but has been used in patients with severe intoxication.

5. *Treat convulsions:*
   a. Diazepam 0.1 mg/kg IV
   b. Phenytoin 15 mg/kg IV infusion.
   c. If seizures cannot be controlled with diazepam or phenytoin, or recur, administer phenobarbitone. If phenobarbitone is ineffective, consider paralysis and/or barbiturate coma.

6. *Treat arrhythmias:*
   a. Serum alkalinisation to a pH of 7.45 to 7.55 using intravenous boluses of sodium bicarbonate is recommended for patients with arrhythmias or QRS widening.
   b. Intubation and hyperventilation may be used as an adjunct to sodium bicarbonate to achieve serum alkalinisation, with careful monitoring of blood gases to avoid profound alkalaemia.
   c. Conventional antiarrhythmics may also be necessary. Quinidine, disopyramide, and procainamide are type 1a and are contraindicated, as their effects on myocardial conduction are similar to that of the tricyclic antidepressants.
   d. Increased QRS duration may be the best indication of severity of overdose and risk of serious complications, and should be treated aggressively.
   e. Sinus tachycardia—supportive measures only.
   f. Supraventricular arrhythmias—alkalinise (to 7.40 – 7.45 pH); synchronised cardioversion if alkalinisation is ineffective. 1 to 2 mEq/kg of sodium bicarbonate is administered as needed to achieve a physiologic pH, or slightly above (7.45 to 7.55). A pH greater than 7.60 or a pCO_2 less than 20 mmHg is probably undesirable. Effective alkalinisation may not be achievable by using intravenous continuous infusion of sodium bicarbonate with conventional doses (2 ampoules per litre).
   g. Ventricular tachycardia—alkalinise (to 7.40 – 7.45 pH); lignocaine 1mg/kg IV, bolus, followed by infusion of 2 to 4 mg/min; synchronised cardioversion if these measures are ineffective; isoprenaline infusion 0.5 to 5.0 mcg/min and overdrive pacing for torsade de pointes.
   h. Ventricular fibrillation—defibrillate; sodium bicarbonate 1 to 3 mmol/kg, and hyperventilation for achieving a pH of 7.45 – 7.50; 1: 1000 adrenaline, 0.5 to 1.0 mg IV; lignocaine 1 mg/kg IV bolus, followed by 2 to 4 mg/min infusion; beta blockers if these measures are ineffective.
   i. Bradycardia or heart block—alkalinise to 7.40 to 7.45 pH; isoprenaline; pacemaker.
   j. Refractory cardiac arrest—basic and advance life support for a minimum of 1 hour; alkalinise to 7.5 pH.
   k. Hypertonic saline has been found to be useful in some cases.
   l. Use of physostigmine in the setting of tricyclic antidepressant overdose is controversial and has been associated with the development of seizures and fatal dysrhythmias. It is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies.
   m. Flumazenil is contraindicated even if benzodiazepines are known coingestants; use of flumazenil in the setting of tricyclic antidepressant overdose has been associated with the onset of seizures and ventricular arrhythmias.

■ Selective Serotonin Reuptake Inhibitors (SSRI)

These drugs constitute the second generation of antidepressant drugs and are much safer and better tolerated than the first generation drugs (*cyclics* and *monoamine-oxidase inhibitors*). Important examples include citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, oxaflozane, paroxetine, pizotifen, sertraline, venlafaxine. A related group of drugs comprises the **selective serotonin-noradrenaline reuptake inhibitors** (**SNRIs**), mainly represented by venlafaxine, milnacipram, and duloxetine. For the sake of convenience, both groups are discussed together under one heading.

Uses

Treatment of
- Depression
- Panic disorder
- Obsessive-compulsive disorder
- Sleep disorders
- Migraine
- Substance abuse.

Toxicokinetics

- All SSRIs (except paroxetine) are rapidly absorbed on oral administration. Because of slower absorption in the case of paroxetine, symptoms of toxicity can be delayed. Peak plasma concentrations are generally reached in about 2 to 8 hours depending on the drug. Sertraline is also slowly absorbed; peak plasma concentrations are reached approximately 5 to 8 hours after oral dosing.
- Protein binding ranges from 50% (for citalopam) to 99% (for sertraline). Fluoxetine binds to plasma proteins to the extent of 94%.
- The primary route of elimination of most of these drugs appears to be renal. Elimination half-lives range from 15 to 26 hours.

Mode of Action

- The SSRIs specifically inhibit the reuptake of serotonin, thereby potentiating the activity of neuronally released serotonin.
- They also alter the sensitivity of serotonin subtype $5HT_{1A}$ or $5HT_{1C}$ receptors.

- Sertraline has a greater selectivity for inhibiting 5-HT uptake relative to noradrenaline than any other drug in this class of therapeutic agent.

Adverse Effects

- Anorexia, dry mouth, nausea, vertigo, blurred vision, tremor, drowsiness, sexual dysfunction, seizures; suicidal ideation, mania, and paranoia; extrapyramidal effects; cardiac arrhythmias; hyponatraemia and SIADH; and serum sickness or flu-like symptoms.
- **Serotonin syndrome:** The serotonin syndrome is a disorder that can be caused by use of drugs or combinations of drugs which increase serotonin availability. It most often occurs when two or more drugs which increase serotonin availability by different mechanisms are used simultaneously. Similarly, the more severe cases tend to result from drug interactions, especially when a monoamine oxidase inhibitor is involved. It may develop after therapeutic use or overdose. The SSRIs may cause the development of this syndrome when used alone, or (more commonly) when administered along with other serotonergic agents especially monoamine oxidase inhibitors (MAOIs).
  - ❖ Main features include agitation, restlessness, confusion, disorientation, hallucinations, drowsiness or insomnia, tachypnoea, flushing, abdominal pain, ataxia, tremor, hypomania, myoclonus, muscle rigidity, opisthotonus, trismus, hyperactivity, convulsions, sweating, salivation, tachycardia, mydriasis, nystagmus, teeth chattering, hyper- or hypotension, hyperpyrexia, coma and diarrhoea.
  - ❖ *Sternbach's diagnostic criteria* for serotonin syndrome include at least three of the following features: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, incoordination and fever.
  - ❖ *Hunter serotonin toxicity criteria*: Hunter serotonin toxicity criteria was developed by using the Hunter Area Toxicology Service (HATS) dataset of overdoses with any serotonergic drug. Following the use/overdose of a serotonergic agent, a diagnosis of serotonin toxicity can be made if the patient meets any of the following 5 criteria:

- – If the patient has spontaneous clonus.
- – If the patient has inducible clonus, and agitation or diaphoresis.
- – If the patient has ocular clonus, and agitation or diaphoresis.
- – If the patient has tremor and hyperreflexia.
- – If the patient is hypertonic, and has a temperature greater than 38°C and ocular clonus or inducible clonus.

Any 'yes' decision on any of the decision rules suggests definite or significant serotonin toxicity of sufficient clinical significance to require consideration of treatment with specific 5-HT$_{2A}$ antagonists. It was found that the presence of a temperature equal or greater than 38.5°C and/or marked hypertonia or rigidity (particularly truncal) indicated severe serotonin toxicity with a high risk of progression to respiratory compromise. These new criteria are simpler, more sensitive (84% vs 75%) and more specific (97% vs 96%) than Sternbach's criteria.

- ❖ The syndrome usually occurs in the first 2 hours of the first dose of the drug and usually resolves within 6 to 24 hours of stoppage of the medication. Some cases resolve even without discontinuation of the drug. Sometimes however, complications ensue including metabolic acidosis, lactic acidosis, rhabdomyolysis, myoglobinuria, renal and hepatic dysfunction, DIC, or ARDS.
- ❖ Hyperthermia is characteristic of serotonin syndrome. In severe cases core temperature may exceed 42°C.
- ❖ Apart from the SSRIs, there are several other drugs which can cause the serotonin syndrome (**Table 19.6**).
- ❖ Serum electrolytes, glucose, renal function tests, CK and an ECG are recommended in all patients with suspected serotonin syndrome. Obtain liver function tests, PT/PTT or INR, platelets, and arterial blood gases in patients with severe hyperthermia, hypotension or other severe effects.
- ❖ It is important to note that the serotonin syndrome has many similarities with neuroleptic malignant syndrome (NMS) (*page no. 258*). However, NMS tends to have a slower onset and more prolonged duration of

Table 19.6: Causes of Serotonin Syndrome

Serotonin Reuptake Inhibitors	Serotonin Breakdown Inhibitors	Serotonin Release Enhancers	Serotonin Agonists or Precursors
SSRIs, amitriptyline, nortriptyline, imipramine, clomipramine, doxepin, trazodone, nefazodone, tramadol, dextromethorphan	MAOIs, cocaine	Amphetamine, MDMA (Ecstacy), phentermine, reserpine	LSD, lithium, L-tryptophan, buspirone sumatriptan, rizatriptan, zolmitriptan

Other Drugs

Amantadine, bromocriptine, brompheniramine, bupropion, carbamazepine, codeine, dextropropoxyphene, dihydroergotamine, droperidol, fentanyl, levodopa, metoclopramide, pentazocine, phenylpropanolamine

symptoms. Also, it is more frequently associated with fever and muscle rigidity than serotonin syndrome. On the other hand, serotonin syndrome is more likely to have myoclonus and hyperreflexia.

❖ Treatment of serotonin syndrome:
  – Benzodiazepines for agitation.
  – Rapid external cooling.
  – Benzodiazepines or barbiturates for convulsions. Neuromuscular blockade (with non-depolarising paralytics) in severe cases.
  – Nitroprusside for severe hypertension; noradrenaline, adrenaline, or phentolamine (NOT dopamine) for severe hypotension.
  – Benefit may be obtained in some cases with cyproheptadine (4 mg/hr), methysergide (2 mg twice daily), or propranolol. Chlorpromazine has also been used to treat cases of serotonin syndrome.

Drug Interactions

- *Diazepam*—Concurrent administration of diazepam, with fluoxetine, may result in increased serum diazepam levels due to inhibition of diazepam metabolism by fluoxetine.
- *MAO inhibitors*—The combined use of fluoxetine (and other SSRIs) with MAO inhibitors may induce serotonin syndrome.
- *Tricyclics*—Plasma levels of tricyclics may be greatly increased when coadministered with fluoxetine and other SSRIs. Sertraline is a weak inhibitor of several hepatic enzymes. Inhibition appears to be dose-dependant, with higher doses, such as in overdoses, resulting in possible clinical relevance of drug interactions, particularly with tricyclic antidepressants (resulting in increased serum levels of TCA and toxicity).

Clinical (Toxic) Features

1. Acute SSRI overdose results in abdominal pain, nausea, vomiting, diarrhoea, vertigo, lethargy, insomnia, diplopia, CNS depression, tremors, and rarely convulsions.
2. There is also likelihood of ECG abnormalities (junctional rhythm, bigeminy and ventricular tachycardia, and QTc prolongation associated with ventricular tachycardia). Left bundle branch block has been reported with citalopram. Hypotension has also been reported.
3. Abrupt withdrawal of an SSRI after prolonged therapeutic use may cause vertigo, nausea, vomiting, fatigue, and myalgia. A discontinuation syndrome of dizziness, lightheadedness, insomnia, fatigue, anxiety, agitation, nausea, headache, and sensory disturbances has been described after abrupt discontinuation of therapy with fluoxetine. A constellation of symptoms have been reported following discontinuation of sertraline therapy. Symptoms have included: fatigue, nausea, abdominal cramps, diarrhoea, shortness of breath, memory impairment, dizziness, insomnia, chills, headache, eye discomfort, tinnitus, ataxia, abnormal sensations ("electric shocks", skin tingling sensations, and involuntary movements). Symptoms typically resolve spontaneously, generally within 3 weeks, or with reinstatement of sertraline therapy.

4. Paroxetine exposure in utero, with maternal doses ranging from 20 to 120 mg/day, has resulted in a neonatal syndrome with effects including jitteriness, vomiting, irritability, hypoglycaemia, and necrotising enterocolitis. Withdrawal is also common in adults; the FDA (USA) has published a new product warning concerning severe paroxetine withdrawal effects, which could lead to drug dependency.

Treatment

1. Treatment involves supportive measures. Syrup of ipecac is contraindicated, while stomach wash is usually not necessary.
2. Serum levels are not clinically useful in managing overdose.
3. Monitor for evidence of serotonin syndrome.
4. Admit those with significant clinical effects including seizures or persistent lethargy or arrhythmias.
5. Sodium bicarbonate may be useful in treating QRS prolongation or arrhythmias. A reasonable starting dose is 1 to 2 mEq/kg intravenous bolus, repeated as necessary. Monitor arterial blood gases to maintain a pH of 7.45 to 7.55.
6. Because of the large volume of distribution and high degree of protein binding of SSRIs, haemodialysis, forced diuresis, haemoperfusion and exchange transfusion would not be expected to be useful in overdose.

■ Monoamine Oxidase Inhibitors (MAOIs)

Today MAOIs have been largely replaced by the cyclic antidepressants for the treatment of a variety of psychiatric disorders, but continue to be used in certain types of anxiety and phobias as well as treatment-resistant depression.

Examples of MAOIs include clorgyline, isocarboxacid, iproniazid, lazabemide, moclobemide, pargyline, phenelzine, pimozide, selegiline, toloxatone, and tranylcypromine. Irreversible MAOIs such as clorgyline, isocarboxacid, phenelzine, tranylcypromine, and selegiline are used in the treatment of Parkinsonism (*page no. 236*). Procarbazine, an antineoplastic agent used in Hodgkin's disease has weak MAOI activity.

Uses

Monoamine oxidase inhibitors (MAOIs) are useful in the treatment of depression, agoraphobia, anxiety disorders, bulimia, migraine, panic disorders, obsessive-compulsive disorders, phobic disorders, narcolepsy and Parkinson's disease.

Toxicokinetics

Monoamine oxidase inhibitors (MAOIs) are rapidly absorbed on oral administration and are metabolised by acetylation, followed by urinary excretion.

Mode of Action

- The MAOIs act (obviously) by inhibiting monoamine oxidase which is a flavin-containing enzyme located in the mitochondrial membrane of liver and central as well as peripheral sympathetic nerve terminals. Monoamine oxidase oxidatively deaminates and inactivates monoamines, some of which are essential as neurotransmitters or modulators of nervous system transmission, e.g.

noradrenaline, dopamine, adrenaline, and serotonin. As a result of MAO inhibition, the pool of noradrenaline in the presynaptic sympathetic nerve terminal is expanded which causes the elevation of CNS noradrenaline and dopamine. This is presumed to be the reason for the antidepressant effect of MAOIs.

- Some MAOIs are selective for the monoamine oxidase-A enzyme, located primarily in the placenta, intestines and liver. Others are selective for the monoamine oxidase enzyme B, located primarily in the platelets, brain and liver. Others are non-selective. Selectivity is lost in overdose.
  - ❖ Meclobemide (reversible) and clorgyline (irreversible) are selective MAO-A inhibitors.
  - ❖ Lazabemide, pargyline and selegiline are selective MAO B inhibitors.
  - ❖ Phenelzine, tranylcypromine and isocarboxazid are non-selective MAOIs.

Adverse Effects and Drug Interactions

- Patients taking MAOIs are prone for multiple food and drug interactions some of which are life-threatening. Many such reported instances involve the concomitant intake of sympathomimetic agents such as ephedrine and phenylpro-panolamine, or the ingestion of foods containing tyramine.* Sympathomimetic agents act by causing the release of noradrenaline stored in the peripheral sympathetic nerve terminals. The already expanded pool of noradrenaline arising out of MAO inhibition is greatly aggravated by this release, resulting in hypertension, tachycardia, (sometimes bradycardia), severe occipital headache, hyperthermia, altered mental status, convulsions, and even intracranial haemorrhage and death.
- While most sympathomimetic agents are capable of producing this reaction, there are exceptions, e.g. adrenaline, noradrenaline and isoproterenol, which do not release a stored pool of noradrenaline, but instead bind directly with postsynaptic alpha- and beta-adrenergic receptors. Apart from sympathomimetic drugs, there are a number of other drugs with which the MAOIs interact adversely (**Table 19.7**).

- Combination of MAOIs with indirect acting sympatho-mimetic drugs can cause severe hypertension. Drugs with the potential to cause this reaction include amphetamines, dopamine, cocaine, phentermine, ephedrine, metaraminol, and phenylpropanolamine.

- With reference to the reaction with tyramine, a similar mechanism is postulated. Pharmacologically active dietary monoamines are found in substantial quantities in protein foods which contain decarboxylating bacteria. Amino acids are converted to monoamines (tyramines, histamine, phenylethylamine) which are normally degraded in the GI tract and liver by MAO, but in the setting of MAO inhibition large amounts of these mono-amines enter the systemic circulation, release stored noradrenaline, and cause a severe hypertensive crisis. Foods capable of producing this tyramine reaction are listed in **Table 19.8.**

- It must be mentioned that the tyramine reaction is mainly associated with irreversible MAOIs, while reversible MAOIs do not normally induce such a reaction, e.g. brofaromine, cimoxatone and moclobemide.

- The MAOIs are also capable of causing the serotonin syndrome (*page no. 270*), especially when combined with selective serotonin reuptake inhibitors (SSRIs). At least 14 days should elapse between the discontinu-ation of an MAOI and the initiation of SSRI therapy. In some cases, e.g. fluoxetine, this interval may have to be prolonged upto 4 to 5 weeks. Combination of MAOIs

Table 19.7: Monoamine Oxidase Inhibitor—Drug Interactions

Drug	Reaction
Sympathomimetic agents (amphetamines, phenylpropanolamine, fenfluramine, phentermine, tyramine, dopamine, metaraminol, ephedrine, mephentermine)	Hypertension, tachy (or brady)cardia, severe occipital headache, hyper-thermia, convulsions, intracranial haemorrhages, death
CNS depressants (pethidine, dextromethorphan)	Hyperpyrexia, convulsions, coma
Other CNS depressants, i.e. sedatives (anaesthetics, alcohol, antihistamines, barbiturates, benzodiazepines, neuroleptics, anticonvulsants)	Potentiation of CNS depression
Antihypertensives (reserpine, methyldopa, guanethidine)	Paradoxical hypertension and excitation
Other antihypertensives (clonidine, hydralazine, diuretics)	Potentiation of hypotension
Anticholinergics (atropine, scopolamine, L-dopa)	Potentiation of anticholinergic effects, CNS excitation
Antibiotics (nitrofurans)	CNS excitation, hyperpyrexia
Anticoagulants (coumarins)	Potentiation of effects
Antidiabetics (insulin, oral hypoglycaemics)	Potentiation of hypoglycaemia
Tricyclic antidepressants	Additive toxicity
SSRIs (fluoxetine)	Additive toxicity

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* A pharmacologically active dietary monoamine.

Table 19.8: Monoamine Oxidase Inhibitor—Food Interactions

Food	Induction of Toxicity
Foods containing tyramine—	
Avocados	Overripe
Bananas	Peels, large amount of fruit itself
Bean curd	Fermented bean curd, soya bean, soya sauce, etc.
Beer	Some brands
Caviar	Refrigerated or stale
Cheese	Most types (except cottage cheese)
Fish	Dried varieties
Liver	Safe only if fresh
Meat	Safe only if fresh
Sausage	Some varieties (bologna, salami, pepperoni)
Soups	Usually contain protein extracts
Wines	Chianti, champagne
Foods not containing tyramine—	
Caffeine	Large amounts (pressor effect)
Chocolate	Large amounts (pressor effect)
Fava beans	Overripe (pressor effect)
Ginseng	May cause headache, tremor, manic symptoms
Whisky	Cause unknown

with tricyclics can also produce serious (even fatal) reactions, though the practice of combined therapy is actually quite common.

■ Addicts who abuse cocaine are at special risk of suffering a severe reaction when they are on MAOI medication. Features include severe headache, hyperthermia, tremor, convulsions, and death.

Clinical (Toxic) Features

1. Overdose is characterised by an initial delay in presentation of upto 12 hours or more.
2. Symptoms include anxiety, flushing, headache, nausea, tachycardia/bradycardia, hypertension/hypotension, agitation, delirium, hallucinations, nystagmus, tremors, muscle rigidity, trismus, opisthotonus, convulsions, hyperthermia, profuse sweating, tachypnoea, respiratory depression, and cardiovascular collapse.
3. Pupils may be dilated and minimally reactive to light after MAOI overdose or MAOI-induced serotonin syndrome. Ping pong gaze (rhythmic and pendular, conjugate horizontal eye movements) has been described in some cases of MAOI overdose.
4. Death occurs in some cases from complications such as ARDS, DIC, and myoglobinuric renal failure.
5. Overdose complicated by rhabdomyolysis or hypotension often leads to myoglobinuria, acute tubular necrosis and renal failure.
6. Coagulopathy, haemolysis and thrombocytopenia may develop with MAOI overdose.
7. The newer reversible, selective inhibitors of MAO-A (e.g. moclobemide) appear to have a less severe toxicity profile when used in overdose. They have also been suggested to interact less with tyramine than traditional MAOIs and thus may have less potential to cause hypertensive crisis when tyramine-containing foods are ingested.
8. Chronic use of these drugs (especially phenelzine and tranylcypromine) can lead to withdrawal reaction on abrupt cessation, characterised by anxiety, depression, confusion, hallucinations, nausea, vomiting, diarrhoea and chills.

Usual Fatal Dose

Ingestion of greater than 2 to 3 mg/kg of an MAOI should be considered potentially life-threatening, and 4 to 6 mg/kg or greater is consistent with reported fatalities.

Treatment

Due to the potential for delayed and severe toxicity, any patient with a history of acute MAOI overdose, even in the absence of symptoms in the first 4 to 6 hours, should be admitted for ICU monitoring and remain until stable for 24 hours. The following measures are suggested for the treatment of adverse as well as toxic effects of MAOIs:

1. Maintenance of airway, oxygen, assisted ventilation, etc. (as needed).
2. Cardiac monitoring.
3. Electrolytes should be monitored closely, particularly for hyperkalaemia.
4. Monitor liver and renal function, and CPK level.
5. Severe hypertension should be treated with IV sodium nitroprusside or phentolamine. Methyldopa and guanethidine are contraindicated as they may potentiate hypertensive crises.
6. Hypotension (or shock) can be managed by IV fluids, and vasopressors such as noradrenaline or dopamine, i.e. direct-acting alpha-adrenergic agonists.

7. Ventricular tachyarrhythmias usually respond to lignocaine, phenytoin, or procainamide.

8. If the patient is seen within a short time of overdosing, gut decontamination must be carried out—lavage, activated charcoal, cathartics.

9. Acidic diuresis and haemodialysis have been tried with varying degree of success but are probably best avoided. Although MAO inhibitor excretion is enhanced by forced acid diuresis, there is no evidence that it is effective in reducing the severity of an overdose. In fact, such a procedure may be dangerous in this situation because of the instability of the cardiovascular system.

10. Muscle rigidity and agitation may respond to phenothiazines such as chlorpromazine. Diazepam is however safer, and phenytoin is a good alternative. In the presence of intractable muscle rigidity, neuromuscular paralysis with pancuronium may be necessary.*

11. Seizures are best treated with benzodiazepines or barbiturates.

12. Hyperthermia can be managed with paracetamol and external cooling. In severe cases (malignant hyperthermia-type), IV dantrolene is given at a dose of 2.5 mg/kg, every 6 hours, for 24 hours. As an alternative, bromocriptine can be administered.

13. For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is not routinely recommended. Initial treatment should be directed towards controlling acute metabolic disturbances such as hyperkalaemia, hyperthermia, and hypovolaemia. Control seizures, agitation, and muscle contractions.

14. Serotonin syndrome must be treated on the recommended lines outlined under SSRIs (*page no 271*).

15. Patients should be placed on special diets low in tyramine-containing foods for at least 2 weeks post-exposure.

■ Atypical Antidepressants

Bupropion is a unicyclic antidepressant which acts by selectively inhibiting neuronal reuptake of dopamine, noradrenaline, and serotonin. It also has moderate anticholinergic activity. The chemical structure of this propiophenone is similar to amphetamine and diethylpropion, although its pharmacologic effects and adverse effects are distinctive. Apart from its use as an antidepressant, bupropion is also said to be effective in the treatment of attention deficit disorder, reduction of cocaine use, and even in diminishing the craving for chocolates. It has also been used as an aid in smoking cessation. Owing to the risk of seizure induction, bupropion must never be combined with other drugs which can lower the seizure threshold.

Bupropion is well-absorbed orally, with peak plasma levels within 2 hours. It is protein bound to the extent of 85%, has a volume of distribution of 19.8 to 47 L/kg, and a half-life ranging from 3.8 to 23 hours. 99% of the dose is metabolised to M-chlorohippuric acid, hydroxybupropion, erythrohydrobupropion, and threohydrobupropion. 87% of the dose is excreted in the urine, mostly as metabolites.

Overdose results in vertigo, vomiting, miosis, tachycardia, hypokalaemia, and convulsions. In most cases, seizures are of short duration and may not require ongoing treatment. Sometimes, the onset of convulsions may be delayed; one patient developed seizures 19 hours after ingestion of sustained release bupropion. Massive overdose has resulted in cardiac arrest, severe hypoxia, and mixed respiratory and metabolic acidosis. Auditory and visual hallucinations have been described frequently following bupropion overdose. Psychosis may result. Cardiovascular overdose effects include primarily tachycardia and rarely hypotension.

Serotonin syndrome following bupropion therapy or overdoses has not been reported to date. Bupropion has dopamine agonist properties, but does not affect serotonin and does not inhibit monoamine oxidase.

Chronic use can cause rash, nocturia, ataxia, convulsions, dystonia, hallucinations, and hypomania. Tremor is a common effect in higher therapeutic doses (400 to 600 mg/day). Use of bupropion during pregnancy has been associated with an increased incidence of spontaneous abortion. Bupropion and its metabolites are excreted into human breast milk.

Treatment of overdose involves control of convulsions with IV diazepam, phenytoin, or barbiturates, and if necessary neuromuscular blockade (with a non-depolarising agent). Obtain serum electrolytes. Cardiac monitoring may be necessary. Monitor for seizures and mental status changes. Urine myoglobin, serum creatinine and creatine kinase levels, etc., should be monitored for detecting rhabdomyolysis. Hypokalaemia must be corrected. If the patient has been seen within a short time of the overdose, activated charcoal can be administered. Emesis and gastric lavage are known to aggravate convulsive tendency.

Life-threatening toxicity is unusual. Survival has ben recorded even after overdoses of 9 gm in adults. Deaths that have been reported are preceded by multiple uncontrolled seizures, bradycardia, cardiac failure and cardiac arrest.

Mirtazepine is a tetracyclic antidepressant belonging to the piperazinoazepine group of compounds. It is a 5-HT$_2$ and 5-HT$_3$ receptor antagonist, a histamine-1 receptor antagonist, a moderate peripheral alpha-1 adrenergic antagonist, and a moderate muscarinic receptor antagonist. It is a noradrenergic and specific serotonergic antidepressant (NaSSA). Mirtazepine acts by increasing neuronal serotonin and noradrenaline through alpha$_2$-adrenergic antagonism. It is a very recent entrant and is said to hold great promise as an antidepressant. Mirtazapine is recommended for the short-term treatment (less than 6 weeks) of major depressive disorders.

Adverse effects are fewer as compared to other drugs, and even in overdose mirtazepine is said to be more benign. Reported adverse effects include tachycardia, hypertension/hypotension, CNS depression, including somnolence and confusion, arthralgia, myalgia, dry mouth, constipation, and rarely, liver dysfunction.

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* Succinylcholine must not be administered because of enhanced risk of malignant hyperthermia.

Overdose experience is limited. The main features include CNS depression and tachycardia. Miosis has been reported following overdose with mirtazapine. Seizures have only been reported in one patient out of 2,796 in premarketing clinical trials, and in none of the 8 overdose cases reported so far. Overdoses of 10 to 30 times the maximum recommended dose produced no serious adverse effects in one series of patients. Overdoses of 30 and 50 times the normal daily dose produced no complications in some patients.

Treatment is mainly supportive. Monitor CBC, urinalysis, and liver and kidney function tests in patients with significant exposures. It is also advisable to monitor vital signs and institute continuous cardiac monitoring. Support respiratory and cardiovascular function. Since mirtazapine is 85% bound to plasma protein, it is unlikely that haemodialysis or peritoneal dialysis would be effective in enhancing elimination.

Nefazodone is also a recent entrant and is approved for use in the treatment of major depression. It is a phenylpiperazine with some similarity to trazodone (*vide infra*). Nefazodone has pharmacologic actions in both the serotonergic and noradrenergic systems, and is indicated for the treatment of depression.

Following oral administration, nefazodone is almost completely absorbed. It is subject to extensive first-pass metabolism, resulting in approximately 20% variable bioavailability. Food delays absorption and decreases bioavailability by about 20%, which is believed to be clinically insignificant. Nefazodone appears to be highly and loosely protein-bound (> 99%). The volume of distribution ranges from 0.22 to 0.87 litres. Nefazodone is metabolised in the liver to three active metabolites: hydroxy-nefazodone (OH-nefazodone), desethyl hydroxynefazodone (triazole dione), and m-chlorophenylpiperazine (mCPP).

Adverse effects are less common. Common adverse effects at therapeutic doses include headache, dizziness, light-headedness, somnolence, dry mouth, diaphoresis, nausea, confusion and blurred vision. Liver failure has been reported following chronic therapy.

Serotonin syndrome has resulted following therapeutic doses of nefazodone and mirtazapine (both partial serotonin antagonists) in some patients. Nefazodone should not be used with a MAOI, or within 14 days of discontinuing use of a MAOI because of the risk of precipitating serotonin syndrome. A period of at least 1 week should be awaited after discontinuing nefazodone before starting a MAOI. Nefazodone may cause increased serum levels of drugs which are metabolised by cytochrome P450IIIA4 or P450 3A4 isoenzyme. Nefazodone is a weak inhibitor of cytochrome P450 2D6. Some of the drugs affected by nefazodone include terfenadine, astemizole, alprazolam, and triazolam. Concomitant intake of ethanol and nefazodone is not advisable.

Overdose results in nausea, vomiting, hypotension, bradycardia, prolonged QT interval, seizures, sedation, and somnolence. Hepatitis has been reported following overdoses with nefazodone.

Treatment is symptomatic and supportive. Following nefazodone overdose, monitor heart rate, ECG, blood pressure, liver function tests, neurologic and respiratory status.

Nefazodone overdose alone has not prolonged QRS duration and there is no evidence that therapies used in tricyclic antidepressant overdose (hyperventilation, sodium bicarbonate) are useful. There is only a small risk for seizures in overdose, thus prophylactic treatment with anticonvulsants is not recommended. Hypotension usually responds to intravenous fluids. Atropine is indicated if significant bradycardia or heart block occur. Give 1 mg IV and repeat in three to five minutes if asystolic cardiac arrest persists.

Nefazodone is highly protein bound and largely excreted as metabolites. Although one metabolite is active, it is unknown if forced diuresis will be beneficial, and it is generally not recommended.

Trazodone is a triazalopyridine derivative and acts by 5-HT$_2$ antagonism as well as serotonin reuptake blocking activity. It is chemically and structurally unrelated to tricyclic and tetracyclic antidepressants, but related to nefazodone; it is an "atypical" tetracyclic antidepressant since it has antidepressant and also anxiolytic and hypnotic activities.

Trazodone is rapidly and completely absorbed, with peak levels occurring in 1/2 to 2 hours. In vitro, trazodone is reportedly 89 to 95% protein bound. It is extensively metabolised in the liver by N-oxidation and hydroxylation. Seventy-five percent is excreted renally, mostly as metabolites. Less than 1% is excreted unchanged in the urine.

Trazodone is particularly suited for the treatment of major depression in elderly patients, because it lacks anticholinergic and cardiac adverse effects. However it causes orthostatic hypotension. Myoclonus and convulsions can also occur. Cholestasis has been reported in a few cases. Peripheral oedema has been reported in 10% of patients receiving therapeutic doses.

Since therapeutic use is associated with priapism, there may be a role for trazodone in the treatment of male impotence. Surgery was required in 26 of 84 cases of priapism reported to the manufacturer, and subsequent impotence may be permanent. Prolonged or inappropriate erections should be referred to a physician after immediately discontinuing the drug.

A trazodone withdrawal syndrome has been reported following the gradual discontinuation of therapeutic doses of trazodone. It has been suggested that development of this syndrome may be due to serotonergic effects and short half-lives of trazodone and its metabolite, m-chlorophenylpiperazine, which may result in noradrenergic rebound following discontinuation. Withdrawal signs/symptoms have consisted of insomnia, vivid dreams, lassitude, nausea, diarrhoea, abdominal pain, anxiety, palpitations, hypomania, headache, myalgia, restless legs and formication. Rapid withdrawal has been reported to result in predominantly gastrointestinal symptoms which respond to administration of atropine. It has been suggested that a cholinergic rebound may occur following rapid withdrawal.

Overdose is associated with CNS depression and hypotension. Lethargy, drowsiness, and ataxia are frequent symptoms. Coma is rare, but can be prolonged. Nausea and vomiting are also frequent. Mydriasis and tinnitus have occurred in some cases. Although seizures and mild cardiovascular abnormalities have been described, these are relatively rare. Hypotension, bradycardia and transient first degree heart block have been the

most frequently reported cardiovascular effects. Hyponatraemia and marked hypokalaemia have been reported following overdose.

Treatment consists of symptomatic and supportive measures. There is no specific treatment for trazodone overdose other than supportive care. Trazodone overdose alone has not produced prolonged QRS duration and there is no evidence that therapies used in tricyclic depressant overdose (bicarbonate, phenytoin) are useful. Phenytoin should actually be avoided due to the potential effect of trazodone on the QTc interval. There are only a few cases of seizures in overdose, thus prophylactic treatment with anticonvulsants is not recommended. Hypotension has responded to intravenous fluids. Atropine is indicated if significant bradycardia or heart block occurs. Give 1 mg IV and repeat in three to five minutes if asystolic cardiac arrest persists. Control convulsions with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.

Priapism is an emergency requiring immediate consult with a urologist. It has been suggested that administration of anticholinergics (e.g. benztropine) or beta-blockers may be effective in reversing trazodone-induced priapism, but clinical studies will be needed to verify efficacy.

ANTI-MANIC DRUGS

■ Lithium

Lithium, the lightest of all metals is the drug of choice even today (more than 50 years after its introduction) for the treatment of manic-depressive psychosis i.e. bipolar affective disorder. It is also useful as adjunctive therapy for depression, mania in children and young adults, alcoholism, and as a prophylaxis for cluster headaches.

Lithium is a naturally occurring alkali metal, present in the earth's crust at concentrations of 0.005%. Lithium is used in industry as a coolant in nuclear reactor, in alkaline storage batteries, and in the manufacture of alloys. Occupational toxicity is however uncommon. Lithium bromide, lithium chloride, lithium hydroxide, and lithium silicate are synthesised from lithium carbonate which acts as a chemical intermediate.

Toxicokinetics

- Lithium is rapidly absorbed on oral administration and peak levels are achieved in 2 to 4 hours. Soluble lithium compounds are rapidly and completely absorbed from the gastrointestinal tract, besides subcutaneous, intramuscular, and intraperitoneal areas.
- The volume of distribution is 0.6 L/kg, and plasma protein binding is to the extent of only 10%. Lithium is evenly distributed among the tissue compartments. Sustained release formulations require 25 to 30 hours for complete distribution.
- The therapeutic elimination half-life is about 20 to 24 hours, and 95% of the drug is excreted by the kidney of which 80% is reabsorbed, while the remaining 20% appears in the urine unchanged.

Mode of Action

- The exact mechanism of action is so unclear that there have been innumerable theories propounded to explain the therapeutic efficacy of lithium in bipolar disorders none of which have been conclusively demonstrated to be correct.
- The main premise is as follows: since lithium crosses cell membranes by various methods including the sodium pump, the sodium leak canal, a lithium-bicarbonate exchange, and the sodium-lithium counter exchange system, it is believed that the chemical exerts its therapeutic effect by substituting for sodium in these transmembranal ion exchanges.
- A monovalent cation, chemically similar to Na+ and K+, lithium is thought to act by
  - ❖ imperfect substitution for other cations in ionic processes and
  - ❖ alteration of the critical microenvironment required for humoral or metabolic processes.
- By these mechanisms in the CNS, lithium affects nerve excitation, synaptic transmission and neuronal metabolism.

Adverse Effects

- Thirst, polyuria, tremor (even at rest), acne, hypothyroidism, impaired concentration, ataxia, and dysarthria.
- Less commonly there may be alopecia, psoriasis of fingernails, and restless legs syndrome.
- Sudden cessation of lithium treatment after a prolonged course can sometimes precipitate asthma.

Drug Interactions

- Diuretics and NSAIDs (except aspirin) reduce lithium excretion. Combination of these drugs increases the steady-state plasma lithium concentration by 39 to 50%. Observation for toxicity and frequent monitoring is recommended.
- Synergistic effect is noted with pancuronium and suxamethonium.
- Combination with neuroleptics may result in encephalitis.
- The effect of antidepressants in general may be augmented by lithium.
- Lithium is frequently combined with haloperidol for acute manic episodes during the first and second week of treatment. Irreversible neurological toxicity and brain damage have occurred in some of these patients.
- In a review of lithium drug interactions, treatment of breakthrough depression with tricyclic antidepressants in patients taking lithium was associated with worsening of lithium-induced tremor. There were also case reports of extrapyramidal symptoms and seizures with the combination.
- ACE inhibitors have been reported to enhance the toxic effects of lithium. They increase the tubular reabsorption of lithium.
- Thiazide diuretics also, via their action on distal tubules, cause sodium depletion with a subsequent decrease in lithium clearance; lithium toxicity is thus likely to result.

Clinical (Toxic) Features

1. There are 3 types of lithium poisoning:
   * Acute poisoning in patients *not* under lithium treatment: mild or moderately severe manifestations.
   * Acute poisoning in patients under lithium treatment: severe manifestations.
   * Chronic poisoning in patients under lithium treatment.
2. **Table 19.9** lists the manifestations of lithium toxicity. Nausea and vomiting are common effects. Headache can occur.
3. There are indications that lithium intake during pregnancy may be associated with cardiovascular and other congenital malformations. Congenital malformations, including cardiac defects have been reported in infants of mothers receiving lithium therapy in the first trimester. Lithium toxicity may be one of the causes of *Floppy baby syndrome*.
4. In patients treated with lithium chronically, T wave flattening is the most common EKG abnormality found in 20 to 100%, occurring within 5 days of starting treatment and disappearing within 3 to 5 days after discontinuing treatment. Sinus node dysfunction is the most frequently reported conduction defect.
5. Hypercalcaemia and hyperkalaemia with cardiac rhythm disturbances have been reported as a side effect of lithium treatment.
6. Neutrophilia is a reported side effect of treatment with lithium, and significant leukocytosis may develop with lithium toxicity.
7. Tremor, hyperreflexia, ataxia, slurred speech, lethargy, confusion, and cogwheel rigidity occur with mild to moderate intoxications. Agitation is common. Seizures and coma may develop with severe poisoning. Fine tremor of the hands is usually seen in 45 to 50% of patients starting lithium therapy. Less than 10% of patients experience tremor after one year of therapy.
8. Severe neurologic effects are much more common in patients with chronic poisoning than in those with acute overdose. Since lithium clears from the plasma much faster than from the brain, patients with chronic lithium toxicity may still have neurological toxicity when lithium levels have fallen into or below the therapeutic range.
9. Dehydration is a common finding in patients with chronic lithium intoxication. Dehydration may precipitate chronic lithium toxicity secondary to increased renal tubular resorption of lithium ion, and lithium toxicity may cause dehydration secondary to nausea and vomiting, polyuria and decreased water drinking from mental status changes.
10. Long-term lithium therapy has been shown to result in decreased renal glomerular function. Nephrogenic diabetes insipidus and resulting hypernatraemia may develop, particularly with chronic overdose. Acute overdose can lead to renal failure.
11. Only 1% of lithium therapy patients experience dermatologic effects. Acne, folliculitis, psoriasis, alopecia, cutaneous ulcers, xerosis cutis, anaesthesia of the skin, and exfoliate dermatitis can all occur, which usually resolve when therapy is discontinued.
12. Hypothyroidism has been associated with chronic lithium intoxication. In systematic studies, the incidence has been consistently elevated (10.4% of cases), especially in females (14%) and in older individuals. There is a substantially increased risk of hypothyroidism in female patients age greater than 60, and in patients with a family history of thyroid disease. The symptoms of Graves' disease may be masked by lithium therapy.

Diagnosis

1. Blood lithium level (BLL): Toxicity is associated with levels over 2 mEq/L. Death is likely if the BLL crosses 5 mEq/L. Therapeutic levels generally range from 0.6 to 1.2 mEq/L. However, serum levels do not necessarily correlate with toxicity after acute ingestion.
2. Evidence of hypernatraemia, hypocalcaemia, and hypoparathyroidism.
3. Perform urinalysis and determine serum creatinine to rule out impaired renal function.

Table 19.9: Lithium Poisoning

System	Acute	Chronic
GIT	Nausea, vomiting	Nausea
CNS	Weakness, vertigo, tremor, twitching, hypertonia, hyperreflexia, muscle rigidity, ataxia, agitation, tinnitus, drowsiness, slurred speech, confusion, myoclonus, convulsions, extrapyramidal symptoms, headache, CNS depression, coma	Parkinsonism, psychosis, amnesia, photophobia, blurred vision
CVS	Prolonged QT interval, ST and T wave anomalies, hypotension	Myocarditis, T wave changes, bundle branch blocks, bradycardia, junctional rhythm, hypotension
Blood	Leukocytosis	Aplastic anaemia
Renal	Polyuria	Nephrogenic diabetes insipidus, interstitial nephritis, renal failure
Endocrine	—	Hypothyroidism
Skin	—	Dermatitis, ulcers, localised oedema

Treatment

1. *Stabilisation*: Maintenance of airway, breathing, and circulation. Cardiac monitoring is desirable. In the case of hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy. For mild/moderate asymptomatic hypertension, pharmacologic intervention is seldom necessary and 4 to 6 hours of observation is usually adequate. For severe hypertension, use nitroprusside or esmolol.

2. *Decontamination* : Activated charcoal is ineffective. Stomach wash may help if the patient is seen early. Whole-bowel irrigation with a balanced polyethylene-electrolyte solution (PEG-ELS) is said to be quite beneficial. The recommended rates of administration are 2 L/hr (adult), and 500 ml/hr (child). Bentonite has been shown to reduce lithium absorption in vitro. In one study, bentonite reduced the lithium concentration by 20.5% in deionised water (pH 7) and by 48.1% in simulated gastric fluid (pH 1.2) at a bentonite lithium ratio of 30.1 (p value 0.0001).

3. *Elimination enhancement*: Haemodialysis is indicated in the following situations—
   i. Severe intoxication with coma, convulsions, or respiratory failure.
   ii. > Grade 3 coma.
   iii. Progressive deterioration.
   iv. Rising serum concentration.
   v. > 4 mEq/L of serum concentration.

On an average, 4 hours of haemodialysis will reduce plasma lithium concentration by 1.0 mEq/L, and a total dialysis time of 10 to 12 hours may be required. Lithium clearance during haemodialysis is approximately 100–120 ml/min; thus four hours of haemodialysis is equivalent to 24-hour clearance of 16–20 ml/min. Renal lithium clearance is 20 to 30% of creatinine clearance; thus those with renal impairment (calculated creatinine clearance less than 60 ml/min) are generally good candidates for haemodialysis. Serum lithium levels should not be considered a major criterion in acute intoxications. The decision to institute dialysis in acute intoxications should be based on a combination of clinical toxicity, the duration of exposure, and a serial profile of serum lithium levels.

However, patients who have been dialysed sometimes develop a "rebound" lithium level after treatment because of subsequent leakage of intracellular lithium into the plasma. Hence a repeat level should always be performed 6 hours post-dialysis, and if this is high, a second round of dialysis may be needed.

If haemodialysis cannot be done, some investigators suggest that sodium polystyrene sulfonate can be administered which is beneficial in decreasing lithium absorption. It can however cause sodium overload and hypokalaemia.

Recent studies indicate that continuous arteriovenous haemodiafiltration (CAVH) can be very effective in lithium poisoning. Successful use of veno-venous filtration has also been reported in some isolated case reports.

ANTI-MIGRAINE DRUGS

Migraine is treated pharmacologically using either an acute, or prophylactic, or combined medication programme utilising one or more of several drugs available for the purpose. These drugs include analgesics (aspirin or paracetamol), anti-emetics (diphenhydramine, prochlorperazine, promethazine, meto-clopramide), combination analgesics (aspirin or paracetamol with a mild vasoconstrictor, e.g. isometheptene,* or a sedative, e.g. butalbital), ergot alkaloids, and sumatriptan. Prophylactic treatment mainly involves beta-blockers, calcium channel inhibitors, serotonin antagonists, or antidepressants.

A detailed discussion on ergot alkaloids and sumatriptan follows, while all the other drugs have been discussed elsewhere (*see Index*).

■ Ergot Alkaloids

Ergot is produced by a fungus, *Claviceps purpurea*, which infests certain types of grain, especially rye. The spores of the fungus are carried by insects or wind to young rye where they germinate into hyphae (filaments). The hyphae penetrate deep into the grain and harden into a purplish structure called sclerotium, which elaborates a number of ergot alkaloids, (*vide infra*). During wet seasons, *C. purpura* can infest wheat, barley, rye (most common), oats, wheatgrass, quackgrass, smooth bromegrass, wild rye and bluegrasses.

Examples of ergot alkaloids include dihydroergocornine, dihydroergocristine, dihydroergosine, dihydroergotamine, dihydroergotaxime, ergobasine, ergocornine, ergocristine, ergocryptine, ergosine, ergometrine or ergonovine, ergotamine, ergotaxime, methylergonovine, bromocriptine, lergotrile, lisuride, lysergol, metergoline, methylergonovine, and methysergide. All these are derivatives of 6-methylergoline, a tetracyclic compound. There have been more than 350 chemicals identified, but less than 10 are used therapeutically. The primary clinical uses have been to relieve the pain of migraine and to contract the post-partum uterus. Natural ergot is also the source of the potent hallucinogen lysergic acid diethylamide or LSD (discussed in greater detail under **Hallucinogens**, *page no 284*).

Uses

- Treatment of migraine and cluster headaches.
- Prophylaxis and treatment of postpartum or post-abortion bleeding.
- Treatment of uterine atony, menorrhagia, and menopausal bleeding.
- Bromocriptine is used in the treatment of Parkinsonism, suppression of lactation, hypogonadism, galactorrhoea, and mastalgia. It is also indicated for acromegaly.

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* Isometheptene is a synthetic sympathomimetic amine, which possesses alpha and beta adrenergic properties. It is contraindicated in patients with glaucoma, renal disease, hypertension, heart disease, liver disease, and concomitant use of MAOIs.

- Ergot derivatives (e.g. bromocriptine pergolide) have been used for the treatment of prolactin-secreting pituitary tumours and hyperprolactinaemic infertility.
- Dihydrogenated ergot alkaloids (dihydroergocornine, dihydroergocristine and dihydroergocryptine) in combination, (ergoloid mesylates) in equal amounts are available in numerous products for the relief of senility symptoms.

Toxicokinetics

- Oral administration of ergot alkaloids is associated in general with poor absorption and extensive first-pass hepatic metabolism.
- Ergotamine is absorbed erratically, incompletely, and slowly from the GI tract following therapeutic oral doses. Rectal doses seem to be absorbed more predictably.
- Ergometrine is rapidly absorbed after oral and intramuscular injection; onset of uterine contractions occur in about 5 to 15 minutes after an oral dose, and 2 or 3 minutes after an intramuscular dose.
- Intramuscular absorption is unpredictable but is approximately 10 times more when compared to oral administration.
- Suppositories may increase bioavailability by as much as 20 times.
- Peak plasma levels are generally achieved in 1/2 hour to 2 hours, volume of distribution is about 2 L/kg and half-life varies from 1.4 to 6.2 hours.
- Ergotamine is metabolised by the liver by largely undefined pathways; 90% of the metabolites are excreted in the bile. Less than 10% is excreted in the urine.

Mode of Action

- The ergot alkaloids act as partial agonists and/or antagonists at adrenergic, dopaminergic, and tryptaminergic (serotonin) receptors. The degree of activity of each alkaloid at these receptor sites varies greatly and determines the pharmacological activity of the different agents.
- The major pharmacological effects include smooth muscle stimulation, resulting in vasoconstriction, hypertension, increased uterine muscle activity, peripheral adrenergic blockade, and central sympatholytic activity, resulting in hypotension.

Adverse Effects

- Nausea, vomiting, weakness in legs, myalgia, tingling and numbness of fingers and toes, precordial distress, tachy- or bradycardia, and localised itching and oedema.
- Severe and sometimes fatal bronchospasm may occur following therapeutic doses of ergotamine in patients with a history of asthma.
- A rare complication of methysergide use is pleuropulmonary fibrosis which resolves when the drug is discontinued.
- Seizures may occur within a few hours of administration of ergot alkaloid uterotonics to neonates.
- Foetal mortality and hypoxic-type anomalies along with other multiple deformities have been observed in humans and experimental animals. Foetal distress, stillbirths and abortion have also occurred.

- Ergotamine is secreted into human milk and can exert its pharmacological effects to an infant by this route; cautious use is advised. Prolonged administration can inhibit lactation.
- The American Academy of Pediatrics considers the use of ergotamine during breastfeeding to be contraindicated based on a study in which vomiting, diarrhoea, and convulsions were observed in most nursing infants.

Clinical (Toxic) Features

1. Excessive use of ergot preparations leads to a condition called *ergotism* which is characterised by burning of extremities, haemorrhagic vesiculations, pruritis, formication, nausea, vomiting, bradycardia, and peripheral ischaemia of lower extremities sometimes leading to gangrene. Prolonged vasospasm and vasoconstriction are responsible for pain, pallor, coolness, paraesthesias, absence of pulse, and gangrene in the extremities.
2. Other features of toxicity due to ergot include headache, miosis, delirium, hallucinations, and convulsions.
3. Vomiting, diarrhoea, and abdominal cramps may occur.
4. Ischaemic pancreatitis and hepatitis have been reported following acute ergotamine poisoning.
5. Ischaemia of cerebral, mesenteric, coronary, and renal vasculature have also been reported.
6. Renal failure may develop in patients with renal arterial spasm or prolonged hypotension.
7. There are some studies indicating the predisposition to mitral and/or aortic valve disease (regurgitant as well as stenotic) in patients administered ergot alkaloids for prolonged periods.
8. Hypertension, hypotension, peripheral cyanosis, tachycardia, bradycardia, and myocardial infarction have occurred with both therapeutic doses and overdose.
9. Cerebral, coronary, mesenteric, ophthalmic and renal artery vasospasm may produce ischaemia or infarction in the corresponding end organ.
10. Toxicity of bromocriptine is dealt with in detail under **Antiparkinsonian Drugs** (*page no 236*).

Drug Interactions

- Serious, life-threatening peripheral ischaemia has been associated with the coadministration of ergotamine with potent CYP 3A4 inhibitors. The latter include protease inhibitors (ritonavir, nelfinavir, indinavir) and macrolide antibiotics (erythromycin, clarithromycin, and troleandomycin).
- Based on an increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these agents.

Treatment

1. Acute Poisoning:
   a. Since even a small dose can lead to toxicity in hypersensitive individuals, all unintentional or intentional ingestions should be considered potentially toxic. Therapeutic doses may be fatal in those with underlying

cardiovascular disease or other predisposing conditions. Toxicity has occurred following as little as 0.5 mg (IM, IV, or SC) of ergotamine, 0.2 mg of IV ergonovine or methylergonovine, less than 5 mg SL ergotamine, and 2 mg of rectal ergotamine. Conditions known to increase susceptibility to ergot toxicity include febrile states, sepsis, malnutrition, thyrotoxicosis, pregnancy, hepatic disease, renal disease, hypertension, coronary artery disease, and peripheral vascular disease.

b. Decontamination is usually not necessary because of spontaneous vomiting.

c. Activated charcoal is beneficial.

d. Hypertension or cerebral/mesenteric/cardiac ischaemia: IV nitroglycerine (10 to 20 mcg/min and increased by 5 or 10 mcg/min every 5 to 10 min) or nitroprusside (1 to 5 mcg/kg/min intravenously) titrated to adequate blood pressure and perfusion. Phentolamine has also been suggested for treatment of severe hypertension or cerebral, myocardial or mesenteric ischaemia. In less severe cases, oral prazosin (1 to 3 mg/day), or captopril (50 mg three times a day), or nifedipine (10 mg three times a day) may be used as an alternative to parenteral agents. Diazoxide, niacin, papaverine, phenoxybenzamine, reserpine, and tolazoline have been used in the past but are no longer recommended.

e. Peripheral ischaemia: oral prazosin, captopril, or nifedipine titrated to adequate perfusion. Administration of sodium nitroprusside in doses of 1 to 5 mcg/kg/min intravenously has been shown to dramatically reduce systemic vascular resistance with accompanying improvement of ischaemia. Doppler ultrasound studies and plethysmography may support the diagnosis of peripheral vascular ischaemia and be useful in assessing the efficacy of treatment. Angiography is often used when the history and clinical features are inadequate to confirm diagnosis of vascular insufficiency. It will also differentiate vascular spasm from thrombosis.

f. Anticoagulant (heparin in combination with sodium nitroprusside or nitroglycerin) therapy should be instituted in all patients with evidence of vascular insufficiency.

g. Hyperbaric oxygen treatment has been successful in reversing ergotamine-induced peripheral ischaemia when other measures (including nitroprusside) had failed.

h. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.

i. Bradycardia: Give atropine (0.5 mg to 1 mg IV, repeated every five minutes if bradycardia persists).

j. Convulsions and hallucinations: diazepam or lorazepam titrated until these manifestations cease.

k. Hypercoagulable states: heparin or dextran titrated until anticoagulated.

2. **Chronic Poisoning:**
   a. Withdraw drug.
   b. Surgery (if gangrene is advanced).
   c. **Sympathetic block, epidural block, or sympathectomy which were all advocated in the past are no more recommended today.** These methods may relieve vasoconstriction mediated via the CNS, but do not antagonise the direct action of ergot on arteriolar smooth muscle.

Forensic Issues

A relationship between puerperal psychosis and ergot administration (especially ergonovine) has been postulated.

■ Sumatriptan

Sumatriptan resembles 5-hydroxytryptamine in structure and is usually given subcutaneously in the treatment of migraine and cluster headaches. It can also be administered orally. Other members of the group include almotriptan, avitriptan fumarate, eletriptan, frovatriptan, naratriptan hydrochloride, rizatriptan, and zolmitriptan.

Mode of Action

Sumatriptan is a highly selective agonist at 5-HT receptors of the 5-HT_{1D} or 5-HT_1-like subtype, but is almost devoid of activity at 5-HT_2 and 5-HT_3 receptors. The resultant vasoconstriction can relieve the severity of migraine which is due to vasodilation in the cerebral circulation.

Adverse Effects

- Unpleasant taste (oral use), injection site reaction, tingling, warm sensation, vertigo, fatigue, chest tightness, rarely myocardial ischaemia and infarction, and even asthma and ventricular arrhythmias.
- Acute myocardial infarction, ventricular arrhythmias, and coronary vasospasm have occurred with therapeutic doses of subcutaneous and oral sumatriptan. Cardiac arrest has been reported. Chest tightness or pressure with therapeutic doses occurred in 5% of patients after subcutaneous sumatriptan and 3% of patients after oral sumatriptan.
- A temporal association between subcutaneous dosing with sumatriptan for migraine and subsequent episodes of intracranial bleeding has been reported in some patients.

Drug Interactions

Sumatriptan should not be combined with 5-HT reuptake inhibitor antidepressants, MAOIs, or lithium. Caution should also be exercised with ergotamine and catecholamines.

Clinical (Toxic) Features

A few cases of overdose have so far been reported with manifestations such as dysphoria, burning sensation over face, and sedation. Increased blood pressure may occur following overdoses.

Sumatriptan should never be given intravenously because of the potential for coronary vasospasm.

Treatment

1. Symptomatic and supportive measures. ECG and blood pressure should be monitored for at least 12 hours. For mild/moderate asymptomatic hypertension, pharmacologic intervention is generally not necessary.
2. Sedative agents such as benzodiazepines may be helpful in treating hypertension and tachycardia in agitated patients, especially if a sympathomimetic agent is involved in the poisoning. Vasodilation therapy may be required.
3. For hypertensive emergencies (severe hypertension with evidence of end organ injury (CNS, cardiac, renal), or emergent need to lower mean arterial pressure 20 to 25% within one hour), nitroprusside is preferred. Nitroglycerin and phentolamine are possible alternatives. In the event of anginal pain, nitrites must be given.
4. Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Amiodarone and sotalol should be used with caution if a substance that prolongs the QT interval and/or causes torsades de pointes is involved in the overdose. Unstable rhythms require cardioversion.
5. In the event of serotonin syndrome being precipitated, the recommended measures for its treatment must be undertaken (*page no 270*).

DRUGS USED IN ALZHEIMER'S DISEASE

Alzheimer's disease is a degenerative disorder characterised by marked atrophy of cerebral cortex resulting in progressive impairment of cognitive abilities with a relentless course to death in 6 to 10 years.

Various drugs have been tried, to halt or slow the progress of the disease including choline chloride, phosphatidyl choline (lecithin), and physostigmine. But the most promising is tacrine hydrochloride.

◼ Tacrine

Tacrine and related drugs are centrally-acting, non-competitive reversible cholinesterase inhibitors, currently approved for treatment of Alzheimer's disease. They also act as partial agonists at muscarinic receptors, block reuptake of dopamine, serotonin and noradrenaline, inhibit monoamine oxidase activity, and may block sodium and potassium channels. Tacrine is an acridine derivative (1,2,3,4-tetrahydro-9-aminoacridine), and is a potent centrally acting inhibitor of acetylcholinesterase. It can be combined with lecithin.

Apart from Alzheimer's disease, tacrine has also been tried in the treatment of acute antidepressant drug overdose, myasthenia gravis, and tardive dyskinesia.

Echothiophate is a long-acting, irreversible cholinesterase inhibitor used in the treatment of glaucoma. **Metrifonate** is the prodrug of dichlorvos (DDVP), an organophosphate insecticide, and has itself been used as an insecticide. Worldwide research

and development of **velnacrine** for Alzheimer's disease was halted by Hoechst-Roussel in 1994.

Tacrine was actually developed originally as a partial antagonist of morphine, and has been used along with it in the treatment of terminal cancer pain.

When tacrine is taken concurrently with food, bioavailability is reduced by 30 to 40%. Administration of tacrine at least 1 hour before meals has no effect on absorption. Tacrine is well absorbed following an oral dose due to its lipid solubility. The oral bioavailability of tacrine ranged from 2.4% to 36% in patients with either Alzheimer's disease or amyotrophic lateral sclerosis. Absolute bioavailability is approximately 17%. Tacrine readily penetrates the blood-brain barrier. Protein binding is approximately 55%. Metabolism is extensive and occurs primarily in liver; the aromatic ring is hydroxylated at one or more positions primarily by cytochrome P-450 IA2 isozymes. At least 3 hydroxylated metabolites of tacrine have been identified in the urine, which may be biologically active. Up to 80% of a systemic dose is eliminated via the urine.

Chronic use of tacrine is associated with vomiting, diarrhoea, headache, myalgia, and ataxia. Gastroenteritis appears to be a dose-dependant effect. Patients receiving metrifonate (15 mg/kg) experienced adverse effects of nausea, vomiting and diarrhoea, which were not seen at lower doses. Significant dose-related elevations in liver function tests, primarily SGPT (ALT), have been observed in 20 to 40% of Alzheimer's patients within 6 to 8 weeks after beginning oral tacrine. This appears to be a reversible effect. Liver biopsies in several patients with elevated hepatic function tests have demonstrated granulomatous hepatitis and liver cell necrosis. An immunologic mechanism has been suggested. Urinary frequency, stimulation of ureters and urinary bladder may occur, with resultant involuntary urination as a result of cholinergic effects of tacrine, especially at higher doses or overdoses.

Tacrine may be carcinogenic since it belongs to the chemical class, acridines, of which some members are animal carcinogens.

Drugs that may interact with tacrine include bethanechol, cimetidine, succinylcholine, and theophylline. Because bethanechol is a cholinergic agonist and tacrine is a cholinesterase inhibitor, additive or possibly synergistic cholinergic adverse effects (such as diarrhoea or vomiting) may result with concurrent use. Concurrent administration of tacrine with cimetidine may result in an increase in the AUC of tacrine of 64% and an increase in peak tacrine levels of 54%. Concomitant tacrine and succinylcholine therapy can result in prolongation of the action of succinylcholine. This is due to inhibition of plasma pseudocholinesterase, the enzyme responsible for metabolism of succinylcholine. Concurrent administration of tacrine with theophylline has doubled the half-life of theophylline and doubled the average plasma theophylline levels.

Overdose results in a cholinergic crisis characterised by muscarinic effects such as severe vomiting, salivation, sweating, bradycardia, hypotension, miosis, flushing, bronchospasm, increased bronchial secretions, involuntary urination and/or defaecation, lacrimation, and convulsions. Decreased cardiac

contractility, shock, cardiac arrest, atrial fibrillation, and heart block may occur as a result of cholinergic crisis. In severe cases, nicotinic effects such as muscle weakness and fasciculations might develop. Death may result from respiratory failure.

It is estimated that the human lethal dose of tacrine is approximately 30 mg/kg when unopposed by anticholinergic agents. This is based on LD50 studies in animals and prelethal toxicity. Therapeutic serum concentrations range from 7 to 16 ng/ml.

Treatment of overdose involves mainly symptomatic and supportive measures. Liver function tests should be closely monitored in any patient presenting with overdose. Monitor arterial blood gases and/or pulse oximetry, pulmonary function tests, and chest X-ray in patients with significant exposure. Depression of blood cholinesterase may occur following overdoses with these drugs. Decreases seen in plasma cholinesterase are immediate, while there is a gradual decline in erythrocyte cholinesterase levels. Atropine can be used as an antidote (initial dose of 1 to 2 mg IV, repeated every 3 to 60 minutes as needed to control muscarinic symptoms, then as needed for 24 to 48 hours). Glycopyrrolate and methscopolamine bromide have been suggested as alternatives to atropine in treating the peripheral cholinergic symptoms induced by cholinergic, muscarinic agonists. However, controversy exists on the effectiveness of glycopyrrolate to reverse the cholinergic effects of tacrine.

For bronchospasm, administer beta$_2$ adrenergic agonists. Consider the use of inhaled ipratropium and systemic corticosteroids. Monitor peak expiratory flow rate; monitor for hypoxia and respiratory failure, and administer oxygen as necessary. For seizures, administer benzodiazepines or barbiturates.

Pralidoxime should be considered in patients with severe nicotinic effects after large, acute, recent exposures. The WHO currently recommends an initial bolus of at least 30 mg/kg, followed by an infusion of more than 8 mg/kg/hr. It is estimated that a plasma concentration of at least 4 mg/L may be necessary for pralidoxime to be effective. An alternative dose for adults is 1 to 2 grams diluted in 100 ml of normal saline infused over 15 to 30 minutes.

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20

Hallucinogens (Psychedelic Drugs)

Hallucinogens (also called psychedelics or psychotomimetic agents) are substances that induce changes in thought, perception, and mood, without causing major disturbances in the autonomic nervous system. Perceptual alterations can take the form of illusions, synaesthesias, or hallucinations. An *illusion* is the result of misinterpretation of an actual experience, while *synaesthesias* are sensory misperceptions (e.g. hearing colour or seeing sounds). Both require external stimuli for their institution. *Hallucinations* differ from them in this important respect, since they are perceptual alterations without any external stimulation whatsoever.

Hallucinations may be visual, auditory, olfactory, gustatory, or tactile in nature. Most hallucinogens induce visual or auditory hallucinations; a few cause tactile or olfactory manifestations. While a number of therapeutic drugs can cause hallucinations in overdose, they are not classified as hallucinogens. A true hallucinogen is a drug that induces hallucinations in small doses (sometimes, as in the case of LSD, in microgram doses). Most genuine hallucinogens cause vivid visual hallucinations, while the other types of hallucinations are relatively uncommon. **Table 20.1** lists common hallucinogens, some of which will be discussed in detail in this section, while the others have been discussed in appropriate sections elsewhere (*see Index*).

LYSERGIC ACID DIETHYLAMIDE (LSD)

Source

- Lysergic acid diethylamide (LSD)* is the synthetic diethylamide derivative of ergot alkaloids, and was originally synthesised exclusively from these alkaloids produced by the fungus *Claviceps purpurea*, which is a contaminant of rye and certain other grains.
- Today, most LSD is synthesised entirely in the laboratory, and typically sold to addicts as liquid-impregnated blotting paper (**Fig 20.1**) or sugar cubes, tiny tablets ("microdots"), gelatin squares ("window panes"), liquid, or powder.
- LSD is said to be the most powerful of all hallucinogens, and is active in doses of 50 to 100 mcg. It occurs as a water-soluble, colourless, tasteless, and odourless powder.
- Drugs related to LSD (lysergamides) also occur naturally in plants such as "Morning glory" (*Rivea corymbosa*) (**Fig 20.2**) and "Hawaiian baby woodrose" (*Ipomoea violacea*). Seeds of morning glory contain lysergic acid hydroxyethylamide, which is 1/10th as powerful as LSD. At least 200 to 300 seeds have to be pulverised—intact seed coat resists digestion—and ingested, for inducing hallucinogenic effects.

Mode of Intake

Lysergic acid diethylamide (LSD) is almost always ingested. Other less common routes of intake include intranasal, sublingual, smoking, conjuctival instillation, and very rarely injection.

Mode of Action

- LSD is structurally related to serotonin (5-hydroxytryptamine) and is an agonist at the 5-HT$_1$ receptor. Serotonin modulates many psychological and physiological processes including mood, personality, affect, appetite,

Table 20.1: True Hallucinogens

Indole Alkaloid Derivatives	Piperidine Derivatives	Phenylethylamine Derivatives	Cannabinoids
LSD	Datura	Mescaline	Tetrahydro cannabinol
Psilocin, psilocybin	Cocaine	Designer amphetamines	
Ibogaine	Phencyclidine		
Harmine	Ketamine		
DMT, DET, DPT, etc.			
Bufotenine			

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* LSD actually stands for the drug's German name: Lyserge Saure Diethylamid.

Fig 20.1: LSD-impregnated paper

Fig 20.2: Morning glory flowers

sexual desire, motor function, temperature regulation, pain perception, and sleep induction.

- LSD inhibits central raphe neurons of brainstem through stimulation of $5\text{-}HT_{1A}$ receptors, which are coupled to adenylcyclase.
- LSD is also an agonist at $5\text{-}HT_{2A, 2C}$ receptors, which are not located presynaptically on serotonergic cell bodies but on certain subpopulations of neurons in postsynaptic regions. The majority of $5\text{-}HT_2$ receptors in the brain are located in the cerebral cortex. Animal experiments have shown that LSD is anatomically distributed maximally in the visual and auditory cortex, and the limbic cortex (besides the pituitary, pineal, and hypothalamic areas), which parallels the finding of high concentration of $5\text{-}HT_2$ receptors in human cerebral cortex.
- Recent studies also suggest that activation of D_1 (dopamine) receptors may contribute to the neurochemical effects of LSD.

Toxicokinetics

- LSD has a half-life of 2.5 hours, while the duration of effects lasts for up to 8 hours. But psychotropic effects can occur for several days, and urine-screen is usually positive for 100 to 120 hours.

- The route of metabolism is hepatic hydroxylation.
- The usual dose of abuse is 100 to 300 micrograms. Doses over 0.2 mg/kg are potentially lethal.

Clinical (Toxic) Features

1. **Acute Poisoning**
   a. Physical
      i. Mydriasis, hippus*.
      ii. Vertigo.
      iii. Tachycardia, hypertension.
      iv. Sweating, piloerection.
      v. Hyperthermia.
      vi. Tachypnoea.
      vii. Muscle weakness, ataxia.
      viii. Hyperactivity.
      ix. Coma.
   b. Psychological
      i. Euphoria or dysphoria.
      ii. Vivid hallucinations, synaesthesias.
      iii. *Bizarre perceptual changes:* People's faces and body parts appear distorted, objects undulate, sounds may be magnified and distorted, colours seem brighter with halos around objects. Occasionally there is depersonalisation, and the hallucinating person may feel as if he is observing an event instead of being involved in it.

2. **Chronic Poisoning**
   a. Prolonged psychotic reactions which are mainly schizophrenic in nature.
   b. Severe depression.
   c. *Flashback phenomena:* The person re-lives the LSD experience periodically in the absence of drug intake for months or years.
   d. *Post-hallucinogen perception disorder:* A persistent perceptual disorder often described by the person as if he is residing in a bubble under water in a "purple haze" with trailing of lights and images. Associated anxiety, panic, and depression are common. The following unusual phenomena have also been reported:
      i. Pareidolias—images of faces on floor and walls, floating faces hovering in space.
      ii. Aeropsia—visualisation of air in the form of numerous vibrating pinpoint-sized dots ("molecules").

Diagnosis

1. Radioimmunoassay of serum or urine (limit of detection 0.1ng/ml).
2. HPTLC (high performance thin layer chromatography) can detect LSD in urine in concentrations less than 1 mcg/litre.
3. HPLC (high pressure/performance liquid chromatography) of serum and urine.
4. GC-MS (gas chromatography-mass spectrometry) can confirm positive LSD urine levels to a lower limit of 5 pg/ml.

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* Spasmodic, involuntary contraction and dilation of pupils.

Treatment

1. Avoid gut decontamination as LSD is ingested in micro-quantities and rapidly absorbed, rendering decontamination procedures totally redundant.
2. Do not use restraints in agitated patients; it will only exacerbate the condition.
3. Because of the short half-life and few serious medical reactions, elimination enhancement procedures such as haemodialysis, haemoperfusion, etc., are not warranted.
4. Treat acute panic attacks with quiet environment, reassurance, supportive care, and administration of diazepam (5–10 mg IV) or haloperidol (in severe cases).
5. Treat acute psychotic reactions with cautious administration of neuroleptics such as haloperidol. Avoid phenothiazines which can cause hypotension, sedation, extrapyramidal reactions, lowered seizure threshold, and potentiation of anticholinergic effects.
6. Treat flashbacks with psychotherapy, anti-anxiety agents, and neuroleptics.
7. Treat post-hallucinogen perception disorder with long-lasting benzodiazepines such as clonazepam, and to a lesser extent anticonvulsants such as valproic acid and carbamazepine. This approach must be combined with behavioural therapy. The patient must be instructed not to consume alcohol, cannabis, caffeine, and other drugs which can intensify the disorder.

PHENCYCLIDINE

Chemically, phencyclidine is 1-(1-phenylcyclohexyl)piperidine, and is commonly referred to by addicts as "angel dust" or "PCP". It was developed in the 1950s as a potential general anaesthetic by Parke-Davis under the brand name Sernyl. It was termed a "dissociative anaesthetic" because unlike conventional anaesthetics which induced a state of relaxed sleep, PCP induced a state of catatonia with flat facies, open mouth, fixed staring, rigid posturing, and waxy flexibility. Patients seemed dissociated from the environment without classical coma. However, a significant proportion of patients showed severe adverse reactions during emergence, including agitation and hallucinations. Some suffered from psychosis for up to 10 days. PCP was therefore quickly withdrawn. Today, **ketamine** a less potent PCP derivative is quite popular as an anaesthetic.

Source

PCP, a phenylcyclohexylamine, is easily synthesised from piperazine, cyclohexanone, and potassium cyanide.

Mode of Intake

- PCP is abused by smoking, insufflation, ingestion, or rarely IV injection.
- It is commonly sold on the street as tablets (about 5 mg), capsules, powder, aqueous or alcoholic solution, or as "rock salt" crystal. It is often mixed with parsley, mint, oregano, or marijuana.

- Sometimes "crack" is dipped in PCP and smoked ("tragic magic"), or cannabis is dipped in PCP ("love boat").

Mode of Action

- Phencyclidine antagonizes the action of glutamate at the NMDA (N-methyl-d-aspartate) receptor. It binds within the ion channel (PCP binding site) to block Ca^{++} influx which results from glutamate binding. Unlike the other types of glutamate receptor channels, NMDA channels are permeable to both Ca^{++} and Na^+.
- Following NMDA receptor activation, NMDA-mediated Ca^{++} flux may lead to stimulation of calmodulin-dependant kinases with activation of postsynaptic second-messenger pathways. Opening the NMDA channel facilitates access of PCP to its receptor, accelerating the rate at which PCP-induced blockade of NMDA receptor-mediated neurotransmission takes place.
- At doses much higher than at which it exerts its unique behavioural effects by blocking NMDA receptor-mediated neurotransmission, PCP also blocks presynaptic monoamine reuptake, thus directly increasing synaptic levels of dopamine and noradrenaline.
- At even higher doses, PCP blocks neuronal Na^+ and K^+ channels, as well as muscarinic cholinergic receptors. This may explain the occurrence of convulsions in PCP overdose.

Toxicokinetics

- The volume of distribution of phencyclidine is 6.2 L/kg.
- Plasma protein binding is about 65%.
- Since it is highly lipid soluble, it accumulates in brain and adipose tissue. Metabolism of the latter causes release of PCP which contributes to the recurrence of symptoms.
- PCP can be detected in urine up to 20 to 30 days (usually 2 weeks).

Clinical (Toxic) Features

1. CNS:
   a. Level of consciouness ranges from fully alert to comatose. The coma is usually preceded as well as followed (upon recovery) by agitation and psychosis.
   b. Confusion, disorientation, amnesia.
   c. Catatonia with unusual posturing, mutism and staring.
   d. Myoclonic and dystonic movements, opisthotonus, torticollis.
   e. Acute toxic psychosis with bizarre behaviour, agitation, and violence.
   f. Cholinergic (sweating, miosis, salivation, bronchospasm), or anticholingeric (mydriasis, tachycardia, urinary retention) signs may be present.
   g. Hallucinations (auditory and visual).
   h. Convulsions.
   i. Hyperthermia.
2. Eye:
   a. Blank stare.
   b. Dysconjugate gaze.
   c. Nystagmus (horizontal, vertical, or rotatory).

d. Blurred vision.
e. Miosis (occasionally mydriasis).
3. CVS:
   a. Sinus tachycardia.
   b. Hypertension.
4. GIT:
   a. Vomiting.
5. RS:
   a. Tachypnoea.
6. Renal:
   a. Myoglobinuria.
   b. Acute renal failure.

Usual Fatal Dose

- Approximately 100 mg or more.
- Lethal blood level: 0.1 mg/100 ml.

Diagnosis

Serum PCP levels usually do not correlate well with clinical picture. Therefore, a qualitative test is adequate in most cases.
1. Laboratory findings:
   a. Leucocytosis
   b. Hypoglycaemia
   c. Hyperkalaemia
   d. Elevated muscle enzymes.
2. EEG: Diffuse slowing with theta and delta waves.

Treatment

1. The need for gastric lavage should be assessed carefully. Often such measures may exacerbate agitation and violence.
2. Activated charcoal is highly beneficial and can be administered at a dose of 1 gm/kg every 4 hours for several doses.
3. A single dose of a suitable cathartic such as sorbitol can be given (unless there are specific contraindications).
4. Some authors recommend urinary acidification to enhance excretion of PCP (which is a weak base). But only 10% of the drug is excreted in the urine, while the remaining 90% is metabolised in the liver. Hence the practical utility of urinary acidification is negligible.
5. Haemodialysis and haemoperfusion are not beneficial.
6. As of now there is no antidote for PCP, though efforts are on to develop PCP-specific antigen binding fragmens (Fab) which can prove to be very useful.
7. Agitated patients should be restrained, at first physically and later pharmaceutically. Hypoglycaemia, if present, must be treated with 50% dextrose in water. Subsequently if agitation persists, administer titrated doses of diazepam 5 to 10 mg IV, every 10 minutes, until the patient is calmed. Phenothiazines should be avoided since they can worsen dystonic reactions, hypotension, hyperthermia, and lower the seizure threshold.
8. Specific antihypertensive therapy should be instituted in patients with very high blood pressure.
9. Myoglobinuria should be treated with IV infusion of 1 litre of 5% dextrose in water (containing 25 grams of mannitol and 100 mEq of sodium bicarbonate), at a rate of 250 ml/hour. Monitor the patient for hypokalaemia. If renal failure has occurred, haemodialysis should be undertaken.

DIMETHYLTRYPTAMINE (DMT)

N,N-Dimethyltryptamine (DMT) is a hallucinogen obtained from the seeds and leaves of certain South American plants such as *Piptadenia pergyina* and *Virola calophylla*, as well as in the tropical legume *Mucuna pruriens*.

Dimethltryptamine (DMT) is not absorbed from the gastrointestinal tract, and so is typically snorted, smoked, or injected. This elicits a virtually instantaneous onset of visual hallucinations, bodily dissociation, extreme shifts in mood, and auditory phenomena. Effects peak within 2 minutes after injection, and resolve in 20 to 30 minutes. This has earned it the name "businessman's trip". Physical effects include mydriasis, raised body temperature, tachycaria and hypertension.

Treatment involves "talking the patient down" in a quiet, dark room, and institution of symptomatic measures. Phenothiazines should be avoided to minimise the danger of convulsions.

MESCALINE

Mescaline is the principal hallucinogenic agent among several alkaloids present in peyote, a small bluish green spineless cactus that grows in dry and rocky areas of southwestern United States and northern Mexico. The scientific name of the cactus is *Lophophora williamsii* (**Fig 20.3**). The terms "peyote buttons" and "mescal buttons" refer to the round fleshy tops of the cactus which have been sliced off and dried. Some Native American churches use these buttons in their religious ceremonies. Each button contains the equivalent of 45 mg of mescaline. It is rapidly absorbed on ingestion.

Clinical (Toxic) Features

Ingestion of 6 to 12 mescal buttons is required to induce a hallucinatory experience. Symptoms usually resolve in about 12 hours after ingestion.
1. Phase of GI distress: (30 to 60 minutes)—Nausea, vomiting, diarrhoea (rare).

Fig 20.3: Peyote (*Lophophora williamsii*)

2. Phase of sympathomimetic effects: (1 to 2 hours) — Mydriasis, tachycardia, hypertension, sweating, tremor.
3. Phase of sensory manifestations: (4 to 6 hours) —Vivid visual hallucinations, emotional lability, anxiety, panic reactions.

Treatment

Involves provision of a quiet dark environment, and calm reassurance. Diazepam may be given orally or intravenously.

INHALANTS (GLUE SNIFFING; VOLATILE SUBSTANCE ABUSE)

Inhalant drugs (volatile substances) are widely available and frequently abused, especially by adolescents from poor socio-economic background. These substances are mostly volatile hydrocarbons which are used as solvents, propellants, thinners, and fuels (**Table 20.2**). The hydrocarbon is typically inhaled by pouring into a container for "sniffing", a rag or sock for "huffing", or a plastic/paper bag for "bagging" (**Fig 20.4**). Abusers often begin with "sniffing" (lower concentrations), and progress subsequently to "huffing" and "bagging" (higher levels of exposure).

The most commonly abused inhalants include toluene from paints and glues; petrol; butane from cigarette lighter fluids; butyl and isobutyl nitrite; and halogenated hydrocarbons from typewriter correction fluids, propellants, and dry cleaning fluids.

Inhalation of volatile substances produces intoxicating effects rapidly. They are well absorbed through the lungs and distributed quickly to the CNS. One or two huffs will begin to intoxicate the user within seconds, and the effects usually last for several hours. Chronic users can maintain a prolonged high with periodic inhalations every few hours.

Fig 20.4: Glue sniffing ("Bagging") (*Pic:* Dr Rais Vohra)

Clinical (Toxic) Features

1. Acute
   a. *CNS*—Excitation, agitation, hallucinations, headache, vertigo, nystagmus, ataxia, convulsions, lethargy, stupor, respiratory depression.
   b. *CVS*—Arrhythmias and sudden death ("*sudden sniffing death*").
   c. *Other Effects*—
      i. Methaemoglobinaemia (butyl and isobutyl nitrites).
      ii. Carbon monoxide poisoning (methylene chloride).
      iii. Hepatitis (chlorinated hydrocarbons).
      iv. Metabolic acidosis, rhabdomyolysis, renal failure, hypokalaemia (toluene).
2. Chronic
   a. *Chronic painter syndrome*—A neurobehavioural syndrome due to solvent-induced encephalopathy,

Table 20.2: Common Inhalants of Abuse

Inhalant	Constituent
Acrylic paint	Toluene
Aerosol propellant	Fluorocarbons, nitrous oxide
Anaesthetics	Enflurane, halothane, isoflurane, nitrous oxide
Dyes	Acetone, methylene chloride
Fire extinguisher	Bromochlorodifluoromethane (BCF)
Bottled gas, torches	Propane, butane
Glues/adhesives	Toluene, benzene, xylene, acetone, naphtha, n-hexane, trichloroethylene, ethylacetate, tetrachloroethylene, trichloroethane, carbon tetrachloride, methylethyl ketone
Lighter fluid	Butane
Nail polish remover	Acetone, amyl acetate, isopropanol
Paint stripper	Methylene chloride
Paint varnish/lacquer	Trichloroethylene, toluene, mineral spirits
Petrol (gasoline)	Hydrocarbons
Polystyrene cements	Acetone, toluene, trichloroethylene, n-hexane
Refrigerants	Fluorochloromethanes
Rubber cement	Benzene, n-hexane, trichloroethylene
Shoe polish	Chlorinated hydrocarbons, toluene
Solvent (laboratory)	Carbon tetrachloride, chloroform, diethylether, n-hexane, methyl isobutylketone
Spot remover	Trichloroethane, trichloroethylene, carbon tetrachloride
Typewriter correction fluid	Trichloroethane, trichloroethylene, perchloroethylene

characterised by memory loss, anxiety, depression, sleep disorders, neurasthenia, and personality changes. CT scan often reveals areas of atrophy, and EEG readings are usually abnormal.

b. Cerebellar dysfunction with chorea (petrol).
c. Peripheral neuropathy (n-hexane).
d. Increased incidence of leukaemia, aplastic anaemia, and multiple myeloma (benzene).
e. Abdominal pain, nausea, vomiting, haematemesis.
f. Cardiomyopathy.
g. Hepatotoxicity.
h. Pulmonary disorders—pulmonary hypertension, acute respiratory distress.
i. Dementia (leaded petrol, toluene).

Medicosocial and Forensic Issues

Hallucinogen abuse has been traditionally a Western phenomenon, and drugs of abuse such as LSD and phencyclidine have always been popular only in countries such as the USA, UK, Australia, and parts of Europe. The popularity of such drugs has been fuelled by their glamorous representation in films and rock music. The 1960s saw an explosion of hallucinogen use almost in the form of an epidemic, and though it declined steeply in the 1970s and 1980s, there has been an alarming resurgence over the last decade.

The dangers of hallucinogen use do not have as much to do with acute toxicity, as with long-term psychological damage. The inevitable fallout is violent crime manifesting as assaultative behaviour, homicides, and suicides. Several horrific crimes have been committed by drug-crazed individuals acting out their bizarre fantasies.

Volatile substance abuse (VSA) is a uniquely adolescent phenomenon, and is particularly common among lower socio-economic classes, mainly because these substances are cheap, easily available, and legal to possess. Also, the mode of intake is relatively simple. VSA is quite common among street urchins of major Indian cities, probably because these inexpensive substances offer a rare exciting experience to escape from the daily misery of poverty. Persons with adolescent conduct disorder and adult antisocial personality disorder are especially prone to VSA.

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21

Spinal and Peripheral Neurotoxic Agents

The most important drugs and poisons which act either on the spinal cord or on the peripheral nerve endings include strychnine, hemlock and neuromuscular blocking agents. The latter has been discussed in **Chapter 18.**

STRYCHNINE

Strychnine is the principal alkaloid in the strychnos plant (seeds), and is a powerful spinal stimulant.

Botanical Name

Strychnos nux vomica.

Other Common Names

Dog button, Poison nut.

Physical Appearance

- This is a tree belonging to family Logianaceae which grows well in South India, as well as in certain other parts of the country (**Fig 21.1**).
- Leaves are oval, dark or variegated green.
- Fruits are globular (**Fig 21.2**) and contain greyish brown disc-shaped seeds about an inch in diameter and ¼ inch thick, which are slightly concave on one side and convex on the other (**Fig 21.3**). The pericarp is very tough. The outer surface is satin-like due to innumerable fine, silky hairs. While the seeds are odourless, they are extremely bitter to taste.*

Uses

- The main alkaloid strychnine has been in use as a rodenticide since the 16th century. It is sometimes used for killing stray dogs (hence the name "dog buttons").
- Strychnine was first used medically in 1540, and continued to be used in many stimulants, tonics, and cathartics until as recently as the 1960s.
- Even today, strychnine is popular in folk medicine.

Fig 21.1: *Strychnos nux vomica* tree

Toxic Part

Leaves, fruits, and seeds (in increasing order of toxicity).

Toxic Principle

Strychnine and brucine are the principal alkaloids, of which the former is much more powerful. It is a basic alkaloid and can be extracted from the seeds as an odourless, bitter-tasting, white crystalline material.

Mode of Action

Strychnine prevents the uptake of glycine at inhibitory synapses, especially in the ventral horns (anterior horn cells) of the spinal cord. It results in the competitive antagonism of the inhibitory neurotransmitter at the post-synaptic spinal cord motor neuron. There is a net excitatory effect, and minimal sensory stimulation can set off powerful muscle contractions.

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* In fact, the alkaloid responsible, i.e. strychnine is said to be the most bitter substance in the world. The taste is detectable even in a dilution of 1/100,000 or more.

Fig 21.2: Nux vomica fruits

Fig 21.3: Nux vomica seeds

Fig 21.4: Opisthotonus

Fig 21.5: Risus sardonicus

Clinical Features

1. A feeling of apprehension and anxiety is a common prodromal manifestation.
2. Muscle twitching, spasms, followed by overwhelming convulsions (each lasting from 30 seconds to 2 minutes) which are precipitated by minimal external stimuli.
3. Opisthotonus is a characteristic feature. It is due to powerful extensor spasm causing the body to be hyperextended with arching of the back (**Fig 21.4**). Less commonly, emprosthotonus (forward bending) and pleurosthotonus (lateral bending) are seen.
4. Trismus (*lockjaw*), risus sardonicus (*sardonic smile* due to grimacing that results from facial muscle spasm) (**Fig 21.5**). There may be frothing from the mouth. Pupils are usually dilated.
5. An important diagnostic feature is that there is complete muscle relaxation in between spasms and convulsions.
6. Another feature of significance is that the patient maintains a clear sensorium during and between convulsive episodes.
7. Complications include hypoxia, hyperthermia, cardiac arrest, rhabdomyolysis, metabolic acidosis, and acute renal failure.
8. The usual fatal event is respiratory failure consequent to spasm of respiratory muscles. Prognosis for recovery improves if the patient survives beyond 5 hours.

Differential Diagnosis

Mentioned in **Table 21.1**.

Usual Fatal Dose

- About 30 to 50 mg for strychnine.
- About 1 to 3 grams for strychnos seeds.

Diagnosis

1. TLC gives reliable qualitative results on gastric aspirate, urine, blood, or tissues. The best specimens are urine and gastric aspirate.
2. HPLC provides accurate quantitative data.
3. Blood levels in the range of 0.1 to 0.3 mg/100 ml are generally lethal.

Table 21.1: Differential Diagnosis of Strychnine Poisoning

Disease	Toxic Ingestion	Others
Tetanus	Cocaine	Hysteria
Rabies	Phenothiazines	
Meningitis	Phencyclidine	
	Chlorinated hydrocarbons	
	Isoniazid	

Treatment

1. Induction of emesis is contraindicated, since vomiting may precipitate severe convulsive episodes.
2. Cautious stomach wash with full protection of airway may be done in the absence of convulsions. Activated charcoal should be administered both prior to and following gastric lavage, and is said to be very beneficial.
3. Forced diuresis and dialysis are not advisable.
4. External stimuli should be reduced to the barest minimum. Treatment should preferably be carried out in a quiet, dark environment.
5. The key to successful management involves aggressive control of convulsions. Diazepam can be tried first, and may have to be administered in large doses (up to, or more than 1 mg/kg). Lorazepam is a good alternative. If benzodiazepines are ineffective, barbiturates can be administered (e.g. pentobarbitone). Intractable convulsions may necessitate neuromuscular blockade with pancuronium (0.04 to 0.1 mg/kg).
6. Intubation and mechanical ventilation are invariably necessary.

Autopsy Features

- Early onset and disappearance of rigor mortis.
- Postmortem caloricity.
- Signs of asphyxia.
- Frothing at mouth.
- Dilated pupils.

Forensic Issues

- Strychnine has always had (a mostly unjustified) reputation of being the homicidal poisoner's choice for murder. This myth has been propagated in popular detective fiction by writers such as Agatha Christie. In reality, strychnine has been uncommonly employed in murder owing to various obvious reasons: bitter taste, dramatic nature of symptoms (that will always arouse suspicion of foul play), and easy detectability in body fluids and tissues. However, occasional cases do get reported from time to time.
- Accidental poisoning can result in children who chew on the seeds out of curiosity while playing or foraging in the countryside.
- Previously, therapeutic misadventures used to be fairly common when strychnine was an approved constituent of various over-the-counter tonics and cathartics. Even today, certain indigenous medicinal preparations (including Ayurvedic preparations) do contain significant concentrations of strychnine or brucine.
- Accidental poisoning can also result from inadvertent consumption of strychnine-containing rodenticides.
- Owing to the agonising nature of death, strychnine is rarely employed in suicide.

POISON HEMLOCK

Botanical Name

Conium maculatum.

Physical Appearance

- Hemlock belongs to the family Umbelliferae of genus Cicuta, and is a biennial herb that grows erect to an average height of 1 to 3 metres (**Fig 21.6**).
- The larger stems are hollow and bear numerous purple spots that are very distinctive.
- Leaves are fine, light-green, and fern-like. When crushed, they give off an unpleasant "mousy" smell.
- Fruits are smooth skinned with crenate ribs, and are binoculated, measuring about 9 mm long, and 6 mm across.

Toxic Part

All parts.

Toxic Principles

The toxins of poison hemlock are simple piperidine alkaloids: coniine and gamma-coniceine. They are structurally similar to nicotine and possess similar clinical features in toxicity.

Mode of Action

The mode of action is two-fold. The most serious effect occurs at the neuromuscular junction where these alkaloids act as non-depolarising blockers causing respiratory failure due to flaccid paralysis. The second effect at the autonomic ganglia is nicotinic in nature resulting in salivation, mydriasis, and tachycardia, followed by bradycardia. Less commonly, rhabdomyolysis and acute tubular necrosis can occur.

Clinical Features

1. Nausea, vomiting, abdominal pain.
2. *Stimulant phase*: tachycardia, tremors, sweating, mydriasis, convulsions.
3. *Depressive phase:* bradycardia, ascending motor paralysis, and coma.

Fig 21.6: Poison hemlock

Treatment

1. *Aggressive GI decontamination*: lavage and activated charcoal.
2. Benzodiazepines for convulsions.
3. Respiratory support.
4. Forced diuresis may help in preventing renal failure.

Forensic Issues

Hemlock was popular in ancient times as a means of execution. The most famous personality executed in this fashion was **Socrates**, who was condemned to death for his "crime" of introducing new divinities.

Today, most cases of hemlock poisoning result from accidental circumstances due to mistaken identity with edible vegetables such as wild carrot, parsley, or anise seeds.

WATER HEMLOCK

Botanical Name

Cicuta maculata.

Physical Appearance

- Like poison hemlock, this plant also belongs to family Umbelliferae, and is a weed that grows along the banks of lakes, streams, and marshes (**Fig 21.7**).
- It is characterised by its thick, hollow, tuberous roots, but is often mistaken for several wild edible plants such as *Daucus carota* (Queen Anne's lace).

Toxic Part

All parts, particularly the root.

Toxic Principle

Cicutoxin, which is among the most potent biotoxins. It causes over-stimulation of central cholinergic pathways.

Clinical Features

1. Nausea, vomiting, abdominal pain.
2. Powerful convulsions often leading to lethal status epilepticus

Treatment

1. *Gastric decontamination*: stomach wash, activated charcoal.

Fig 21.7: Water hemlock

2. Diazepam or barbiturates for convulsions. Refractory cases may necessitate administration of general anaesthesia.
3. Haemodialysis may be helpful.
4. Aggressive supportive measures.

Forensic Issues

Most cases of poisoning result from mistaken identity with edible plants (*vide supra*).

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Section

6

Cardiovascular Poisons

Diuretics, Antihypertensives and Antiarrhythmics

DIURETICS

Diuretics are generally classified as follows:
1. Carbonic anhydrase inhibitors
2. Osmotic diuretics
3. Loop diuretics
4. Thiazide diuretics
5. Potassium sparing diuretics.

■ Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors are non-bacteriostatic sulfonamides that inhibit carbonic anhydrase, thereby reducing the rate of aqueous humour formation in the eye and resulting in decreased intraocular pressure. Acetazolamide is the prototype of this group, which also includes brinzolamide, dichlorphenamide, dorzolamide, ethoxzolamide, methazolamide, and sulthiame. These drugs act by inhibiting the membrane-bound as well as cytoplasmic forms of carbonic anhydrase, resulting in total abolition of sodium bicarbonate reabsorption in the proximal renal tubule. This results in rapid rise of urinary bicarbonate excretion, raising urinary pH to 8 and causing metabolic acidosis.

Uses

1. Acetazolamide, dichlorphenamide, and methazolamide are primarily used for the treatment of glaucoma.
2. Acetazolamide is used for the treatment of oedema resulting from congestive heart failure, as well as that which is drug-induced. Its main indication however is open angle glaucoma.
3. Brinzolamide and dorzolamide are topical ophthalmic agents that are indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.
4. Sulthiame has been used as an antiepileptic in most forms of epilepsy.

Toxicokinetics

Acetazolamide is almost completely absorbed on oral administration and demonstrates a plasma half-life of 6 to 9 hours. Dichlorphenamide acts within 1 hour, with a maximal effect usually observed in 2 to 4 hours. Methazolamide is absorbed from the gastrointestinal tract more slowly than acetazolamide; the duration of action is 10 to 18 hours. These drugs are bound to the carbonic anhydrase II enzyme, and high concentrations are generally found in tissues containing this enzyme, including red blood cells and the renal cortex. Protein binding is to the extent of 94% for acetazolamide, 60% for brinzolamide, 33% for dorzolamide, and 55% for methazolamide. Acetazolamide, brinzolamide, and dorzolamide are primarily excreted unchanged in the urine.

Adverse Effects and Toxic Features

1. Bone marrow depression (aplastic anaemia, leukopenia, thrombocytopenia, agranulocytosis), skin toxicity, urinary alkalinisation, confusion, lethargy, and metabolic acidosis are common adverse effects.
2. There is increased tendency for renal calculi.
3. Rare adverse effects may include taste disturbances, ataxia, gastritis, cholestatic hepatitis, and renal failure. Impotence has been reported with carbonic anhydrase inhibitors.
4. Overdose causes drowsiness, lethargy, metabolic acidosis, tachycardia, tachypnoea, electrolyte imbalances, and paraesthesias. Paraesthesias of the extremities, of the tongue, and at the mucocutaneous junction of the lips are common occurrences following acetazolamide therapy, and will generally resolve upon discontinuation of the medication.

Contraindications

- Hypersensitivity to sulfonamides
- Hepatic cirrhosis
- Addison's disease
- Hyperchloraemic acidosis.

Treatment

1. In cases of carbonic anhydrase inhibitor overdose ingestions, treatment is usually symptomatic and supportive.
2. Consider prehospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion.
3. Fluid and electrolyte levels should be monitored closely and replaced if needed.

4. Monitor arterial blood gases in symptomatic patients for possible metabolic acidosis. Treat severe acidosis (less than pH 7.1) with IV sodium bicarbonate. Begin with 1 mEq/kg in adults and children. Repeat doses of no more than one-half the original amount may be given no more often than every 10 minutes if required. Monitor blood gases to adjust dose.

Haemodialysis may be effective, especially in the presence of renal failure.

■ Osmotic Diuretics

Osmotic diuretics act (primarily in the loop of Henle and secondarily in the proximal tubule), as non-reabsorbable solutes thereby limiting the osmosis of water into the interstitial space. By extracting water from intracellular compartments, they expand extracellular fluid volume, decrease blood viscocity, and inhibit renin release. They increase the urinary excretion of nearly all electrolytes—sodium, potassium, calcium, magnesium, chloride, bicarbonate, and phosphate.

Commonly used osmotic diuretics include mannitol, glycerine, isosorbide, laevulose, and urea. Of these, glycerine and isosorbide are active orally, while the others are not and must be given intravenously.

Uses

Treatment of
- Acute tubular necrosis
- Dialysis disequilibrium syndrome
- Glaucoma
- Cerebral oedema.

Adverse Effects and Toxic Features

1. Pulmonary oedema may be precipitated in patients with heart failure or pulmonary congestion.
2. Other adverse effects include hyper- or hyponatraemia, headache, nausea, vomiting, and dehydration.
3. Glycerine can cause hyperglycaemia.
4. Mannitol has caused fatal colonic perforation when used orally as a purgative. It has also been implicated in the development of renal failure in several case reports.

■ Loop Diuretics

These agents are inhibitors of sodium-potassium-chloride symport in the ascending limb of the loop of Henle, and are highly efficient diuretics. Therefore they are also referred to as high-ceiling diuretics. Examples include **furosemide, bumetanide, azosemide, piretanide, tripamide, muzolimine, torasemide, etozolin, ozolinone,** and **ethacrynic acid.**

Uses

Treatment of
- Acute pulmonary oedema
- Chronic congestive heart failure
- Hypertension
- Nephrotic syndrome
- Cirrhosis of liver
- Poisoning (to increase renal elimination by forced diuresis).

Drug Interactions

1. Increased ototoxicity with aminoglycosides
2. Increased incidence of arrhythmias with digitalis
3. Increased incidence of hyperglycaemia with sulfonylureas
4. Blunted diuretic response with NSAIDs
5. Synergism with thiazides.

Adverse Effects and Toxic Features

1. Overdose causes hyponatraemia (with or without extacellular fluid volume depletion), hypotension, and circulatory collapse. In addition, there may be hypochloraemic alkalosis, hypokalaemia, and hypomagnesaemia (with cardiac arrhythmias), and hypocalcaemia (with tetanic manifestations).
2. Ventricular arrhythmias and syncope have been reported following high-dose intravenous therapy with furosemide.
3. GI bleeding may occur during therapy with ethacrynic acid and furosemide, particularly in patients with renal failure.
4. Other effects include hyperuricaemia, hyperglycaemia, and ototoxicity manifesting as tinnitus, vertigo, and deafness.

Treatment

Treatment comprises supportive and symptomatic measures. Diuretic blood levels are not clinically useful. Monitor fluid and electrolyte balance carefully and provide replacement therapy as needed.

■ Thiazide Diuretics

These agents are inhibitors of sodium chloride symport, acting mainly in the distal convoluted tubule, with secondary action in the proximal tubule. Excretion of sodium and chloride is increased, but thiazides are only moderately effective in practice, since 90% of the filtered load is reabsorbed before reaching the distal convoluted tubule.

Common thiazides and thiazide-like drugs include bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide, chlorthalidone, indapamide, metozalone, clopamide, clorexolone, cyclothiazide, cyclopenthiazide, fenquizone, mefruside, metolazone, xipamide and quinethazone.

Uses

Treatment of
- Oedema (cardiac, hepatic, or renal causes)
- Hypertension
- Nephrogenic diabetes insipidus
- Calcium nephrolithiasis
- Bromide poisoning.

Drug Interactions

1. Increased ototoxicity with aminoglycosides
2. While interactions with several drugs are common, thiazides can produce life-threatening ventricular tachycardia and fibrillation with quinidine.

Adverse Effects and Toxic Features

1. *Fluid and electrolyte disturbances:* Extracellular volume depletion, hypotension, hypokalaemia, hyponatraemia, hypochloraemia, metabolic alkalosis, hypomagnesaemia, hypercalcaemia, hyperuricaemia. Hypochloraemic metabolic alkalosis has occurred following chronic therapeutic use and abuse of thiazide diuretics.
2. *GIT:* Vomiting, diarrhoea/constipation, cramps. Rarely cholecystitis and pancreatitis. Hyperglycaemia has been reported with thiazide use.
3. *CNS:* Headache, vertigo, paraesthesias.
4. *CVS:* Atrioventricular block with premature atrial complexes has been reported following high-dose hydrochlorothiazide therapy.
5. *RS:* Pulmonary oedema has been reported in several cases after therapeutic ingestion of hydrochlorothiazide.
6. *Blood:* Dyscrasias.
7. *Skin:* Rashes.
8. *Sexual:* Impotence, decreased libido.
9. *Other:* Hyperuricaemia and hyperlipidaemia may occur following chronic use of thiazides.

Treatment

1. Treatment comprises supportive and symptomatic measures. Diuretic overdoses are generally benign, with the greatest risk being dehydration. Emesis or gastric lavage may potentiate fluid and electrolyte disturbances and are unnecessary.
2. If the ingestion is recent and substantial, administer activated charcoal (in aqueous solution without cathartic).
3. Diuretic blood levels are not clinically useful.
4. Monitor fluid and electrolyte balance carefully and provide replacement therapy as needed.
5. Haemodialysis may be useful.

■ Potassium Sparing Diuretics

Potassium sparing diuretics interfere with reabsorption of sodium at the distal tubule, thereby decreasing potassium secretion. Examples include amiloride, eplerenone, triamterene, and spironolactone. Amiloride and triamterene act by blocking sodium channels in the luminal membrane of principal cells in the late distal tubule and collecting duct, while spironolactone competitively inhibits the binding of aldosterone to mineralocorticoid receptors.

The major therapeutic use of potassium sparing diuretics is in the treatment of oedema or hypertension, *in combination* with other diuretics so as to offset the latters' kaluretic (or potassium excreting) effect. Spironolactone is particularly useful in the treatment of primary hyperaldosteronism.

Drug Interactions

1. Co-administration of potassium sparing diuretics with ACE inhibitors is associated with an increased risk of severe hyperkalaemia.
2. Amiloride used with other diuretics may produce hyponatraemia and hypochloraemia.
3. Severe hyponatraemia may occur when triamterene and chlorpropamide are concomitantly administered.

Adverse Effects and Toxic Features

1. The most dangerous adverse effect is hyperkalaemia.
2. Cardiovascular abnormalities secondary to hyperkalaemia include bradycardia, conduction defects, sinus arrest, and hypotension. Cardiovascular symptoms have only been reported after chronic therapy and not from an acute ingestion. Tall, peaked T waves or T-wave elevations compared with previous tracings, lowered R waves, increased depth of the S wave, widening or absence of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and/or depression of ST segment have been associated with ECG changes of hyperkalaemia.
3. Weakness, areflexia, and fatigue may be noted secondary to hyperkalaemia from chronic therapy.
4. There can also be effects related to the gastrointestinal (vomiting, diarrhoea), CNS (headache, drowsiness, confusion, vertigo), musculoskeletal (leg cramps), and dermatological (skin rashes), systems. Metabolic acidosis can occur with hyperkalaemia.
5. Spironolactone can cause peptic ulceration, gynaecomastia, impotence, and hirsutism, and menstrual irregularities and breast soreness in females. There are indications that it may be carcinogenic.
6. Angina pectoris and myocardial infarction have occurred in patients treated with eplerenone.

Treatment

1. Patients should be monitored for fluid status and serum electrolytes (particularly sodium and potassium). Administer 0.9% saline as needed.
2. Monitor vital signs and ECG in symptomatic patients, particularly in patients with significant electrolyte abnormalities.
3. Consider administration of activated charcoal after a potentially toxic ingestion.
4. Treat severe hyperkalaemia (associated arrhythmias, QRS widening) aggressively. Monitor ECG continuously during and after therapy.
   a. *Calcium chloride:* Adult: 5 ml IV bolus of a 10% solution over 5 minutes; Child: 0.2 to 0.3 ml/kg of a 10% solution over 5 to 10 minutes (20 to 30 mg/kg/dose).
   b. *Sodium bicarbonate:* Adult or Child: 1–2 mEq/kg IV bolus.
   c. *Insulin/dextrose:* Adult: 5 to 10 units regular insulin IV bolus with 100 ml of D50 IV immediately; monitor serum glucose every 30 minutes. Child: 0.5 to 1 gm/kg dextrose as D25 or D10 IV followed by 1 unit of regular insulin for every 4 grams of dextrose infused; monitor serum glucose every 30 minutes.
   d. *Sodium polystyrene sulfonate:* Adult 15 to 60 ml by nasogastric tube or rectal enema; Child: 1 gm/kg by nasogastric tube or rectal enema.
5. If hypotension is not corrected by treatment of hyperkalaemia, infuse 10 to 20 mg/kg of isotonic fluid and place

in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.

Forensic Issues (All Diuretics)

Despite the widespread use of diuretics in medical practice, acute overdoses involving these agents are fortunately quite rare. Most reported cases of toxicity are actually related to chronic use. Long-term diuretic use to treat hypertension has recently been associated with the development of type 2 diabetes.

ANTIHYPERTENSIVES

Antihypertensives are generally classified as follows:
1. Diuretics
2. Sympatholytic drugs
    a. Centrally acting agents
    b. Ganglionic blocking agents.
    c. Adrenergic neuron blocking agents
    d. Beta adrenergic antagonists (Beta blockers)
    e. Alpha adrenergic antagonists (Alpha blockers).
3. Vasodilators
    a. Arterial
    b. Arterial and venous
4. Calcium channel blockers
5. Angiotensin converting enzyme inhibitors
6. Angiotensin II receptor antagonists.
    Diuretics have already been discussed in the foregoing sections.

SYMPATHOLYTIC DRUGS

■ Centrally Acting Agents

■ Methyldopa

Methyldopa acts centrally via an active metabolite, alpha-methyl-noradrenaline, to lower blood pressure. It is an antihypertensive, whose specific mechanism of action is uncertain. Although methyldopa is an inhibitor of dopa-decarboxylase, this effect does not appear to be responsible for its antihypertensive effect. The major antihypertensive action appears to be on the CNS by alpha adrenergic agonist activity in the medulla and the anterior hypothalamus, in a manner similar to clonidine.

The usual dose of methyldopa as an antihypertensive is 250 mg two to three times daily. This can be gradually increased to 500 mg to 2 grams daily, up to a maximum daily dose of 3 grams. It is well absorbed orally and peak plasma levels are seen after 2 to 3 hours. Mean bioavailability is about 50%. Methyldopa crosses the blood-brain barrier where it is decarboxylated in the CNS to active alpha-methylnoradrenaline. Protein binding is less than 15%. Approximately 50% of an oral dose is metabolised by the liver. Elimination is biphasic with a

reported half-life of approximately 1.7 hours in the initial phase, with the second phase being more prolonged. It is excreted in the urine as the sulfate conjugate (50 to 70%), and as the parent drug (25%). Urinary excretion is essentially complete in 36 hours following oral doses. Plasma half-life is reported to be 105 minutes. Terminal half-life is about 7 to 16 hours.

Patients receiving therapeutic doses of methyldopa (250 to 750 mg/day) demonstrate serum methyldopa concentrations of 2 mcg/ml.

Adverse Effects and Toxic Features

1. Methyldopa may induce life-threatening effects such as haemolytic anaemia, hepatitis, pancreatitis, and myocarditis, apart from a myriad other lesser effects including headache, drowsiness, depression, oedema, bradycardia, nasal stuffiness, nightmares, disorders of sexual function, gynaecomastia, galactorrhoea, dryness of mouth, and nightmares. Around 20% of patients develop a positive Coombs' test.*
2. Acute overdosage of methyldopa may result in severe hypothermia, dry mouth, nausea, vomiting, hypotension, dizziness, weakness, lethargy, coma and bradycardia. Paraesthesias, headache, weakness, involuntary movements, and psychic disturbances have been reported.

Treatment

1. All cases of symptomatic methyldopa overdose should be admitted to the intensive care unit and monitored for cardiovascular complications. No specific lab work (CBC, urinalysis, electrolytes) is needed unless otherwise indicated. Monitoring of blood pressure, central venous or pulmonary wedge pressure may be necessary.
2. For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
3. Atropine can be used to treat bradycardia.
4. Although there are no published data regarding use of haemodialysis or haemoperfusion following methyldopa overdoses, data following therapeutic use suggest that these procedures may be of value following severe intoxication refractory to conventional therapy.

■ Clonidine

Clonidine is an imidazoline compound with potent alpha2-adrenergic agonist effects. At high doses, it has been shown to act as a peripheral partial alpha-adrenergic receptor agonist, resulting in stimulation of the peripheral post-synaptic alpha2-receptors, thus temporarily increasing blood pressure and pulse rate.

Apart from its utility in hypertension, clonidine is also used in the treatment of attention deficit disorder, prophylaxis of migraine, and management of ethanol, opiate, and nicotine withdrawal. It is well absorbed orally and demonstrates peak

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* A test for antiglobulins in RBC: used in diagnosing haemolytic anaemia.

effects at 2 to 3 hours. Excretion as unchanged drug is mostly via the kidneys. Apraclonidine is a related drug which is used as 0.5% or 1.0% ophthalmic solution in a sterile isotonic solution for topical application to the eye. **Guanfacine** and **guanabenz** are not popular in India, but share the same mode of action as clonidine.

Adverse Effects

1. Dry mouth, drowsiness, orthostatic hypotension, insomnia, agitation, myalgia, arrhythmias, and GI upset. Paralytic ileus occurs rarely.
2. Abrupt withdrawal of clonidine can be life-threatening. Withdrawal effects include agitation, tremor, palpitations, insomnia, severe hypertension, nausea, and vomiting. Even otherwise, rebound hypertension is common.

Clinical (Toxic) Features

1. Usual therapeutic plasma level of clonidine has been reported as less than or equal to 4 mcg/L. Toxic effects generally occur within 30 minutes to 4 hours after overdose and usually resolve within 24 to 72 hours.
2. Overdose results in bradycardia progressing to heart block, hypotension, hypothermia, CNS depression, miosis, and periodic apnoea. Sometimes there is paradoxical hypertension. Clonidine poisoning is much more severe in children as compared to adults.
3. Central adrenergic inhibitory effects following clonidine overdose include impaired consciousness, hypotonia and hyporeflexia, miosis, bradycardia, hypotension, respiratory depression and apnoea, and hypothermia. Partial peripheral adrenergic stimulatory effects include mild to moderate hypertension and tachycardia, which is usually short-lived, and most often followed by hypotension and bradycardia.
4. Large overdoses may result in reversible cardiac conduction defects or arrhythmias.
5. Hypothermia may occur within 1 hour of the ingestion and may last as long as 48 hours, but is usually mild and resolves spontaneously within 6 to 8 hours.
6. Drowsiness, somnolence, ataxia, impaired consciousness and coma are frequently seen. Seizures may rarely occur following large overdoses.
7. Toxic effects following ingestion of apraclonidine ophthalmic drops are similar to those of clonidine overdose.

Treatment

1. Clonidine levels are not readily available or useful for guiding therapy.
2. No specific lab work (CBC, electrolytes, urinalysis) is needed unless otherwise indicated.
3. Monitor for CNS and respiratory depression. Monitor vital signs, continuous ECG, and pulse oximetry in symptomatic patients.
4. Endotracheal intubation and ventilation may be indicated in the presence of apnoea, coma, depressed respirations, or hypotonia during the first 24 hours following ingestion of clonidine.
5. All patients with an altered mental status, bradycardia, hypo or hypertension require observation (frequent monitoring of vital signs and ECG) for a minimum of 6 to 12 hours or until the patient remains asymptomatic for a period of 4 hours.
6. Activated charcoal is beneficial if administered early. Induction of vomiting and gastric lavage are contraindicated.
7. Naloxone reverses the deleterious effects on respiration and CVS function. Large doses may have to be administered (upto 8 to 10 mg). Naloxone is most effective at reversing respiratory depression, somewhat helpful at lessening the "paradoxical hypertensive" effect, and least effective against hypotension. The most frequently recommended initial naloxone dose for opiate overdose is as follows: 0.4 to 2 mg intravenous bolus in both children and adults, and may be repeated at 2 to 3 minutes intervals according to desired patient response. Caution should be exercised when administering naloxone to the paediatric patient. Severe hypertension requiring management with phentolamine has followed the administration of naloxone in several paediatric clonidine overdoses.
8. Atropine counteracts bradycardia. Bradycardia and hypotension may respond to atropine alone in patients with heart rates below 60. Give 1 mg intravenously, and repeat in three to five minutes if asystolic cardiac arrest persists. Three milligrams (0.04 mg/kg) intravenously is a fully vagolytic dose in most adults.
9. For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position.If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy. Dopamine is effective for hypotension. Paradoxical hypertension responds well to sodium nitroprusside (intravenous infusion at a rate between 0.5 and 10 mcg/kg/min, and adjusted based on the patient's response).
10. Cardiac arrhythmias should be treated with standard antiarrhythmic drugs, if necessary.
11. Alpha-adrenergic antagonists such as tolazoline may have antidotal action in clonidine poisoning. The recommended dose is 5 to 10 mg as IV infusion every 15 minutes (upto a maximum of 40 mg).
12. Yohimbine, a CNS alpha2-adrenergic antagonist, has been used for treatment of clonidine overdose.
13. Haemodialysis, haemoperfusion and forced diuresis are not likely to significantly enhance the elimination of this drug.

■ Ganglionic Blocking Agents

Ganglionic blocking agents such as **hexamethonium, mecamylamine, pempidine, pentolinium,** and **trimethaphan** are effective antihypertensive drugs, but their use is now curtailed to the treatment of hypertension associated with dissecting aneurysm of aorta. They interfere with neurotransmission in sympathetic and parasympathetic ganglia.

Adverse Effects

1. Constipation (sometimes diarrhoea), paralytic ileus, urinary retention, impotence, dry mouth, postural hypotension, tachycardia, drowsiness, and blurred vision.

2. Various arrhythmias (AV block, left bundle branch block, ventricular fibrillation) have been reported with trimethaphan therapy. Respiratory arrest has also been reported following high doses. Chronic therapy has led to coughing, dyspnoea, and intra-alveolar and interstitial pulmonary fibrosis.

Clinical (Toxic) Features

1. Respiratory arrest can occur.
2. Mydriasis, urinary retention, and seizures may occur, especially following large doses of mecamylamine. Tremor, hallucinations, and confusion may also follow high dose mecamylamine.

Treatment

1. Intravenous crystalloid boluses.
2. Direct-acting vasopressors such as noradrenaline.
3. Attempt initial control of seizures with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.
4. Physostigmine or neostigmine (0.5 to 1 mg IV, slowly) have proved useful in some cases.
5. Gastrointestinal function may be restored with cholinergic agents such as bethanechol.

■ Adrenergic Neuron Blocking Agents

Guanethidine and **guanedrel** interfere with the action potential that triggers the release of noradrenaline, while **reserpine** depletes noradrenaline and other catecholamines from the nerve end terminals. Guanadrel is a sympatholytic agent with similar pharmacologic properties as guanethidine. It is one-third as potent as guanethidine on a weight basis, has a shorter onset, longer duration of action, and may be less likely to produce orthostatic hypotension.

Guanethidine is a potent antihypertensive agent for moderate to severe hypertension. It is also used in the treatment of renal hypertension, including that secondary to pyelonephritis, renal amyloidosis, and renal artery stenosis. Guanadrel is used to treat mild to severe hypertension. Both are however not popular in India.

■ Reserpine

Reserpine, an alkaloid present in the root of the Indian plant *Rauwolfia serpentina* **(Fig 22.1)**, has been used for treating hypertension for decades, and is also indicated in the treatment of Raynaud's phenomenon. Related alkaloids include alseroxylon, deserpidine, raubasine, and rescinnamine.

Reserpine is readily absorbed following oral and intramuscular dosing. Peak plasma level is reached 1 to 3 hours postingestion. Six percent is excreted in the urine in the first 24 hours, and about 8% in the first four days, mainly as the metabolite trimethoxybenzoic acid. Up to 15 to 60% of the dose is eliminated in the faeces. Reserpine and its congeners deplete catecholamines and serotonin peripherally and centrally from nerve terminal fibers. The resulting responses exhibit as CNS depression and peripheral sympatholysis.

Fig 22.1: *Rauwolfia serpentina*

Rescinnamine, also isolated from the root of *Rauwolfia serpentina* is used to treat some types of hypertension. In India, a crude extract of *Rauwolfia serpentina* (e.g. Sarpagandha) has been used for centuries to treat insomnia and certain forms of mental illness.

The adverse effects of reserpine include orthostatic hypotension, dizziness, blurred vision, bradycardia, nausea, vomiting, diarrhoea, and impotence. In addition, it often induces depression, drowsiness, hallucinations, nightmares, nasal stuffiness, and exacerbation of peptic ulcer disease. It is contraindicated in patients with a history of depression because of the risk of precipitating suicidal behaviour. Overdose produces profound CNS depression. Patients may initially demonstrate hypertension and tachycardia for up to one day followed by hypotension and bradycardia. Non-reactive and pinpoint pupils occur frequently after overdose. Higher doses may produce cardiac arrhythmias and an angina-like syndrome. CNS depression occurs, ranging from drowsiness, lethargy, and mental depression through stupor and coma. Coma may be long-term, but mild, often allowing the patient to be aroused when needed. Peripheral responses are biphasic: initially they may demonstrate catecholamine release, then depletion. Diarrhoea and intense gastric acid secretion may occur.

Parkinsonism may develop in patients being treated with reserpine, particularly at higher dosages. Endocrine disorders causing breast engorgement, galactorrhoea, and gynaecomastia have been reported.

Severe stuffy nose, lethargy, and respiratory depression may occur in infants of mothers ingesting reserpine during pregnancy. Since it is excreted in breast milk, serious adverse reactions are possible in nursing infants.

Adrenaline and noradrenaline urine levels may be elevated one to two days after an acute ingestion. It has been recommended that overdosed patients should be observed for a minimum of 72 hours, due to the long duration of action. For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy. Alprazolam may help counter reserpine-induced depression.

■ Beta Adrenergic Antagonists (Beta Blockers)

Beta-adrenergic blocking agents compete with endogenous and/or exogenous beta-adrenergic agonists for receptor sites. Depending upon the agent and its relative selectivity for beta1 (located primarily in the heart) and beta2 receptors (located chiefly in bronchial smooth muscle and blood vessels), principal pharmacologic effects include a lowering of blood pressure, negative inotropic and chronotropic effects, and depressed AV conduction.

Examples

Acebutolol, adimolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilolol, carazolol, carteolol, carvediolol, celiprolol, cetamolol, coloranolol, cycloprolol, dilevalol, divelalol, draquinolol, esmolol, espanolol, flestolol, indenolol, labetalol, landiolol, levobetaxolol, levobunolol, levomoprolol, medroxalol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, propranolol, sotalol, teratolol, tilisolol, and timolol.

First generation beta blockers (nadolol, propranolol, pindolol, labetalol, sotalol, timolol, etc.) are antagonists at both beta1 and beta2 adrenoceptors and are known to aggravate asthma, obstructive airway disease, peripheral artery disease, and diabetes mellitus. Second generation drugs such as acebutolol, atenolol, and metoprolol are selective for beta1 adrenoceptors, and therefore relatively safer. Recently, a new beta-adrenergic receptor referred to as beta3 adrenoceptor has been discovered. Classic beta blockers are all agonists (not antagonists) at this receptor.*

Uses

Beta-blockers are used in the treatment of hypertension, angina, arrhythmias, cardiomyopathy, migraine headaches, and thyrotoxicosis. Ophthalmic products are used in the treatment of glaucoma.

Adverse Effects

1. Bradycardia, dizziness, fatigue, diarrhoea, sleepiness, confusion, depression, and headache. While CNS effects at therapeutic doses are more often associated with more lipid soluble agents (propranolol, metoprolol), in overdose all agents may cause significant CNS depression. Effects range from drowsiness and lethargy to obtundation and coma. Therapeutic doses of beta adrenergic blocking agents may cause bronchospasm in susceptible patients. Worsening angina may develop in patients after withdrawal from chronic beta blocker therapy.
2. Drug-induced retroperitoneal fibrosis has been reported following treatment with practolol, atenolol, and oxprenolol.
3. Propranolol can cause hypoglycaemia and resultant seizures in diabetics treated with oral hypoglycaemics or insulin and in non-diabetics who are dieting, fasting and exercising. The clinical effects of hypoglycaemia (tachycardia and sweating) may be absent due to beta-blockade in such cases.
4. Propranolol appears to cross the placenta and may result in intrauterine growth retardation, bradycardia, hypoglycaemia, respiratory depression and impaired response to anoxic stress. Acebutolol, atenolol, betaxolol, labetalol, metoprolol, nadolol, propranolol and timolol are excreted in human breast milk.

Drug Interactions

- Severe bradycardia, conduction blocks and hypotension have been reported in patients taking calcium antagonists and beta blockers at therapeutic doses.
- Complete atrioventricular block, bradycardia, hypotension and biventricular failure have been reported after therapeutic use of digoxin and propranolol.
- Quinidine inhibits metabolism of timolol and increases the degree of beta blockade experienced after use of timolol eye drops.
- Dystonia may develop if propranolol and gabapentin are given together, due to synergistic effect.

Clinical (Toxic) Features

1. Lipid soluble beta blockers such as propranolol, oxprenolol, labetalol, metoprolol, pindolol, and timolol are capable of producing serious toxicity. Fatalities have been reported with propranolol, metoprolol, acebutolol, and oxprenolol. Co-ingestion of alcohol is nearly always catastrophic. Labetalol and atenolol are said to be safest in overdose and rarely cause death.
2. Manifestations of overdose include hypotension, bradycardia, arrhythmias, delirium, seizures, mydriasis, coma, and respiratory failure. Hypoglycaemia is common in children. Bradycardia and hypotension are the most common effects in beta blocker overdose. Complications of profound hypotension may include acute renal failure, respiratory failure and non-cardiogenic pulmonary oedema.
3. Other cardiovascular effects may include atrioventricular blocks, intraventricular conduction delays, ventricular arrhythmias, pulmonary oedema and cardiac arrest. An irregular pulse may be a sign of conduction defects or arrhythmias. Asystole has also been reported.
4. Pindolol has greater beta-agonist properties and overdoses have been associated with hypertension and tachycardia.
5. CNS depression is common in patients with significant cardiovascular toxicity. Seizures have been frequently reported with propranolol overdose. Sotalol is notorious for causing delayed toxicity, and for inducing a prolonged QT interval and ventricular arrhythmias. Fatalities are common.
6. Metabolic acidosis may develop in patients with profound hypotension or seizures.
7. Ophthalmic preparations containing beta-blockers may cause systemic manifestations. Increased airway resistance

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* Isoproterenol is an agonist at all three beta receptors.

(usually in asthmatics), hypoglycaemia, fatigue, behavioural abnormalities, and diplopia may be noted.

8. Abrupt stoppage of beta blockers after chronic use may result in rebound hypertension, tachycardia, palpitations, tremor, headache, and sweating. Patients with angina may develop myocardial infarction.

Diagnosis

Plasma levels of these agents are not clinically useful and are not routinely available.

Treatment

1. Outlined in **Table 22.1.**
2. Glucagon is said to have antidotal action. It produces a positive chronotropic and inotropic cardiac effect, which occurs despite beta-blockage. The drug has been reported to increase myocardial contractility in patients refractive to isoproterenol. Glucagon is thought to activate the adenylate cyclase system at a different site than isoproterenol. If the patient responds at a particular dose of glucagon, start an hourly infusion at the response dose (e.g. if a patient responds to 10 mg, then start an infusion at 10 mg per hour).
3. Monitor electrolytes and renal function in patients with hypotension.
4. Monitor blood glucose in symptomatic children and diabetics.
5. Institute continuous cardiac monitoring, monitor blood pressure, and obtain an ECG.
6. Obtain a chest X-ray in patients with respiratory depression, significant hypotension or evidence of pulmonary oedema.
7. Patients, who at presentation show evidence of significant cardiovascular (bradycardia, heart failure, heart block, hypotension, electromechanical dissociation, asystole, new bundle branch block or widened QRS complex) respiratory (respiratory depression, bronchospasm, or pulmonary oedema) or neurologic toxicity (CNS depression or seizures), independent of the dose ingested, should be admitted to a monitored setting for at least 24 hours of observation and treatment.

8. Hypotension usually responds to intravenous glucagon, atropine, isoproterenol or pacing. Atropine reduces vagal stimulation and subsequently increases heart rate. Isoproterenol is a beta agonist which competitively antagonises the effect of the beta-blocker. It is used for temporary control of haemodynamically significant bradycardia; generally other modalities (atropine, dobutamine, pacing) should be used first because of the tendency to develop ischaemia and arrhythmias with isoproterenol. 1 mg of isoproterenol is added to 250 ml of dextrose 5% in water, for a final concentration of 4 mcg/ml. Infuse 2 mcg/min, gradually titrating to 10 mcg/min as needed, to desired response. If hypotension persists, administer dopamine or noradrenaline. Refractory cardiotoxicity may respond to calcium chloride. Intra-aortic balloon pump has been used successfully after pharmacologic therapy failed, in cases of severe propranolol and atenolol poisoning.

9. Extracorporeal membrane oxygenation may be useful in providing haemodynamic support for arrhythmias, hypotension, and heart failure unresponsive to glucagon, dopamine, noradrenaline, adrenaline, or pacemaker.

10. Hypoglycaemia should be managed with intravenous dextrose. Bronchospasm responds to salbutamol (0.25 to 0.5 ml in 2 to 4.5 ml of normal saline delivered every 4 to 6 hours per nebuliser).

11. Nadolol, sotalol, acebutolol, and atenolol are haemodialysable. Propranolol, metoprolol, and timolol are not removed by haemodialysis. Haemoperfusion is said to be effective in nadolol, atenolol, and sotalol overdose. However, it should be considered only when treatment with glucagon and other pharmacotherapy fails.

■ Alpha Adrenergic Antagonists (Alpha Blockers)

These drugs selectively block alpha1-adrenergic receptors without affecting alpha2-adrenergic receptors. Examples of agents used in the treatment of hypertension include prazosin, terazosin, indoramin, phenoxybenzamine, phentolamine, tamsulosin, tolazoline, urapidil and doxazosin. Terazosin is

Table 22.1: Treatment of Beta Blocker Overdose

Mild Poisoning		Moderate Poisoning		Severe Poisoning
		As for **mild poisoning,**		As for **moderate poisoning,**
		Plus		Plus
1. Activated charcoal	1	Endotracheal intubation	1	Intra-arterial and pulmonary artery pressure monitoring
2. Stomach wash	2	Glucagon 2–5 mg IV push, followed by 2–5 mg/hr, upto a maximum of 10 mg/hr	2	Catecholamine infusion : Isoproterenol—start at 0.1 mcg/kg/min, titrate rapidly to effect. OR Dobutamine—start at 2.5 mcg/kg/min
3. Whole-bowel irrigation (for sustained-release preparations)	3	Atropine upto 3 mg IV	3.	Phosphodiesterase inhibitors e.g. milrinone 50 mcg/kg IV bolus over 2 min, then 0.25–1.0 mcg/kg/min
4. Atropine 1 mg IV for bradycardia			4.	Ventricular pacing
5 Fluid boluses for hypotension			5.	Extracorporeal circulation or intra-aortic balloon pump

also used for treating urinary symptoms from benign prostatic hypertrophy.

Adverse effects include *first-dose phenomenon,** dizziness, tachycardia and palpitations. Peptic ulcer is frequently exacerbated by these agents. Headache and asthenia have been reported with therapeutic use of terazosin. Therapeutic use of prazosin has been associated with several cases of paranoia, hallucinations, and confusion. Based on observations from one study, it has been suggested that doxazosin should not be used as monotherapy for management of stage 1 or stage 2 hypertension, because of an increase in the incidence of congestive heart failure. Vomiting, abdominal pain, and diarrhoea may occur following large oral doses.

Overdose results in hypotension and CNS depression. Hypotension and reflex tachycardia are the most common manifestations. However, tachycardia may not always occur. Phentolamine may cause acute and prolonged hypotension. Death has occurred following IV administration of phentolamine when used in the diagnosis of pheochromocytoma. Seizures have been reported with indoramin overdose. Phenoxybenzamine produces miosis, while phentolamine and tolazoline produce mydriasis. Priapism may occur.

Treatment involves administration of IV fluid boluses, and vasopressors such as dopamine. However, dopamine being primarily a beta-adrenergic agent, has produced fatal cardiac arrest secondary to hypotension, when given with tolazoline. Adrenaline stimulates both alpha and beta receptors. In the presence of alpha blockade, the net effect may be vasodilation and worsening of hypotension. Noradrenaline primarily stimulates alpha receptors and is preferable. Priapism is a surgical emergency requiring immediate consultation with a urologist.

■ Vasodilators

Vasodilators are used in the management of hypertension and peripheral vascular disease. Examples include buflomedil, cadralazine, diazoxide, dihydralazine, fenoldopam, hydralazine, isoxsuprine, minoxidil, molsidomine, nicotinyl alcohol, sodium nitroprusside, and todralazine.

Hydralazine, dihydralazine, cadralazine, minoxidil, diazoxide and buflomedil are all peripheral vasodilators; their dilatory effect is greater on arterioles than on veins. Diastolic blood pressure is frequently lowered more than systolic. An increase in heart rate, stroke volume and cardiac output is commonly seen.

■ Hydralazine

Hydralazine causes direct relaxation of arteriolar smooth muscle, but is not a dilator of capacitance vessels such as the coronary arteries. Because of preferential dilatation of arterioles over veins, postural hypotension is not a significant problem. Hydralazine is usually combined with a sympatholytic agent or a diuretic and is effective orally. Parenteral use is recommended for the treatment of hypertensive emergencies in pregnancy.

Toxicokinetics

About 50 to 90% bioavailability; peaks in plasma in about 1 hour; protein binding is about 88 to 90%; volume of distribution is 1.6 L/kg; metabolised by hydroxylation, followed by glucuronidation and N-acetylation; 3 to 14% is excreted unchanged in the urine; elimination half-life is about 2 to 8 hours.

Adverse Effects

1. *Pharmacological*: headache, dizziness, lacrimation, blurred vision, oedema of the eyelids, nausea, flushing, hypotension, palpitations, and tachycardia. Myocardial ischaemia is not unlikely.
2. *Immunological*: lupus syndrome, serum sickness, glomerulonephritis. About 10 to 20% of patients on long-term hydralazine therapy with doses exceeding 400 mg daily develop a lupus-like syndrome. The syndrome occurs most commonly in Caucasians who are slow acetylators. Peripheral neuropathies have also been noted following chronic hydralazine therapy.

Clinical (Toxic) Features

Dizziness, syncope, palpitations and nausea.

Treatment

Decontamination, followed by IV fluid boluses, and peripherally acting vasopressors such as noradrenaline.** Calcium channel blockers or beta blockers may be considered in patients with persistent tachycardia or myocardial ischaemia. Peripheral neuropathies may be corrected with pyridoxine.

■ Minoxidil

Minoxidil is an efficacious antihypertensive in patients with drug-resistant, severe hypertension. It acts through an active metabolite minoxidil N-O sulfate, which produces arteriolar vasodilatation (without effect on capacitance vessels). Minoxidil increases blood flow to skin, skeletal muscle, GI tract, and heart. Apart from its use in hypertension, minoxidil is also used topically to promote hair growth in patients with male pattern baldness.

Toxicokinetics

About 95% bioavailability; protein binding is not significant; volume of distribution is 2 to 3 L/kg; elimination half-life varies from 2.3 to 28.9 hours.

Adverse Effects

1. Pericardial effusion, pulmonary hypertension, dermatitis, breast tenderness or gynaecomastia, oedema, pulse and BP changes, shortness of breath, dizziness, headache, redness of conjunctivae, and increased growth of facial, and (later) body hair. Some of these effects appear even on topical application.
2. Several cases of allergic contact dermatitis have been reported when minoxidil has been used in the treatment of baldness.

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* Orthostatic hypotension occurring within 90 minutes of the initial dose of the drug, or when the dosage is increased.

** Catecholamines such as adrenaline and dopamine are not recommended, since there is a risk of tachycardia and exaggerated myocardial response.

3. There have also been several case reports of women applying 5% topical minoxidil, over a period of 2 to 3 months, to treat androgenetic alopecia and subsequently developing severe hypertrichosis of the face and extremities. The excessive hair growth on the face and limbs gradually disappeared over a period of several months after discontinuation of minoxidil.

Clinical (Toxic) Features

1. Moderate to severe hypotension.
2. Angina pectoris and haemorrhagic pericarditis have also been reported after minoxidil overdose.
3. Coma can occur.

Treatment

In treating hypotension due to minoxidil, avoid cardiac stimulating sympathomimetics such as adrenaline and noradrenaline. When a vital organ is underperfused, use phenylephrine, vasopressin, dopamine, or angiotensin II. Haemodialysis may be useful in minoxidil overdose.

■ Sodium Nitroprusside

Sodium nitroprusside (sodium nitroferricyanide) exerts its vasodilatory effects after being metabolised in the RBC, and releasing nitric oxide. It also releases five atoms of cyanide which can cause significant toxicity in the presence of renal insufficiency or low thiosulfate stores (infants, malnourished individuals, critically ill patients).

Uses

Sodium nitroprusside* is used intravenously mainly for the treatment of hypertensive emergencies, and also to induce controlled hypotension during anaesthesia in order to reduce bleeding in surgical procedures. It is also used to control acute congestive heart failure (CHF). Sodium nitroprusside reacts with haemoglobin and is then nonenzymatically decomposed to cyanide in the blood. Following IV administration, nitroprusside is rapidly metabolised to cyanogen (cyanide radical). Like cyanide, it inhibits electron transport in mitochondrial cytochrome oxidase, thus inhibiting cellular respiration. The mitochondrial enzyme, rhodanase, located primarily in the liver, converts cyanide to thiocyanate, which is then cleared renally.

Adverse Effects

Acute onset of anxiety, restlessness, muscle twitching, and diaphoresis has been observed following excessive nitroprusside infusion rates. Toxic accumulation of cyanide with severe lactic acidosis can also occur if sodium nitroprusside is infused at a rate greater than 5 mcg/kg/min. This can be prevented by concomitant administration of sodium thiosulfate. The overall incidence of cyanide toxicity associated with nitroprusside appears to be infrequent. Risk factors for development of nitroprusside-induced cyanide toxicity include hypoalbuminaemia, cardiopulmonary bypass procedures, renal impairment, or the administration of moderate to high doses of nitroprusside.

Clinical (Toxic) Features

1. Blood cyanide concentrations may be the most useful parameter to monitor nitroprusside toxicity, especially for those infusions less than 7 days in duration, at normal rates. Thiocyanate levels may be appropriate to monitor during prolonged nitroprusside use or at unusually high infusion rates. Generally, blood cyanide and serum thiocyanate concentrations are toxic if they are greater than 500 mcg/L and greater than 100 mg/L, respectively; however, patients do not consistently display signs or symptoms at these levels.
2. Acute toxicity following therapeutic use is characterised by vasodilation and hypotension, possibly complicated by nausea, vomiting, sweating, headache, palpitations, and substernal distress.
3. Development of severe acidosis has been reported with increasing blood cyanide levels.
4. Thiocyanate may cause a neurotoxic syndrome manifested by toxic psychosis, hyperreflexia, confusion, weakness, tinnitus, seizures and coma.

Treatment

1. Administer 100% oxygen to maintain an elevated PO_2. Oxygen may reverse the cyanide-cytochrome oxidase complex and facilitate the conversion to thiocyanate following thiosulfate administration.
2. Patients exhibiting dyspnoea, headache, and impaired mental status should be treated with sodium nitrite and sodium thiosulfate.
3. Hypotension secondary to excessive infusion rates of nitroprusside typically responds to discontinuation of infusion (within minutes). Fluid replacement and pressors may be necessary if hypotension persists.
4. Administer sodium bicarbonate, 1 mEq/kg IV to acidotic patients. Base further sodium bicarbonate administration on serial arterial blood gas determinations.
5. Haemodialysis may be an effective adjunct by correcting resistant acidaemia, and by increasing thiocyanate clearance, thereby favouring thiosulfate-cyanide reaction to thiocyanate.

■ Calcium Channel Blockers

Calcium channel blockers (calcium antagonists; slow channel blockers) block the influx of calcium into various cells, primarily vascular, cardiac, and smooth muscle tissue. They are used primarily for treatment of supraventricular tachycardia, angina, and hypertension. Examples include **amlodipine, bepridil, diltiazem, felodipine, isradipine, lacidipine, mibefradil, nicardipine, nifedipine, nimodipine, nisoldipine, perhexiline, verapamil,** etc. (See **Table 22.2** for classification). Newer agents include **aranidipine, lercanidipine, nilvadipine, nitrendipine, tiapamil.**

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* Because it decomposes in light, only fresh solution should be used, and the infusion bottle should be covered with opaque wrapping.

Table 22.2: Classification and Uses of Calcium Channel Blockers

Drug	Class	Therapeutic Use
Verapamil	Phenylalkylamine	Hypertension, atrial flutter/fibrillation, supraventricular re-entry tachycardias
Diltiazem	Benzothiazepine	- Do -
Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine	Dihydropyridines	Hypertension, Raynaud's phenomenon, Prinzmetal's angina, oesophageal spasm, vascular headaches, post-subarachnoid haemorrhage vasospasm
Bepridil	Diarylaminopropylamine ether	Class I antiarrhythmic agent

Mode of Action

- Calcium antagonists selectively inhibit membrane transport of calcium during the slow inward excitation-contraction coupling phase in cardiac and vascular smooth muscle. Intracellular calcium ion outflow may also be speeded through stimulation of ATP dependant Ca and Na-K pumps.
- All calcium channel blockers (CCBs) act by antagonising L-type voltage-sensitive slow calcium channels, except mibefradil which blocks T channels. L-channel blockade impairs calcium influx into cardiac and smooth muscle cells, resulting in decreased force of myocardial contraction, negative inotropy, inhibition of SA and AV nodes, and peripheral arteriolar vasodilatation.
- Calcium antagonists selectively inhibit membrane transport of calcium during the slow inward excitation-contraction coupling phase in smooth muscle leading to coronary and peripheral vasodilation. In general, they have a negative inotropic (contractility) effect on the myocardium not usually manifested with therapeutic doses due to compensation of the sympathetic nervous system.
- Verapamil has the most powerful myocardial depressant effect, while diltiazem has much less effect, and nifedipine is a weak myocardial depressant but exerts very significant effects on peripheral vascular smooth muscle. Therefore verapamil is the most potent at lowering heart rate, cardiac output, and blood pressure, while nifedipine produces maximum decrease in systemic vascular resistance.

Toxicokinetics

All CCBs are absorbed well orally and are highly protein-bound. Verapamil, diltiazem, and nifedipine undergo extensive hepatic metabolism. Volumes of distribution are large for the former two (about 5.5 L/kg), but much smaller for nifedipine (0.8 L/kg). Amlodipine differs from the other members of its class (dihydropyridines) in that it has a very long plasma half-life (35 to 45 hours), and prolonged duration of action.

Adverse Effects

Dizziness, flushing, headache, oedema, palpitations, hypotension, GI upsets. Gingival hyperplasia has been noted with amlodipine.

Drug Interactions

- Severe bradycardia, conduction blocks and hypotension have been reported in patients taking calcium antagonists and beta blockers at therapeutic doses and in overdose.
- Mibefradil appears to interfere with the body's metabolism of lovastatin and simvastatin (and also possibly atorvastatin and cerivastatin), and increase the risk of muscle injury. Fluvastatin and pravastatin do not have similar metabolism and mibefradil would not be expected to increase the risk of muscle injury with these agents.
- QT interval prolongation has been associated with concurrent administration of cisapride and diltiazem.
- Complete AV block and QTc prolongation were reported following concurrent administration of high-dose verapamil and erythromycin, which may be due to a pharmacokinetic interaction between the two drugs as a result of both drugs being potent CYP3A4 and P-glycoprotein inhibitors.

Clinical (Toxic) Features

1. Early manifestations may be mild such as dizziness and lethargy. GI manifestations such as vomiting and diarrhoea are relatively uncommon.
2. Bradycardia, hypotension, A-V conduction anomalies, idioventricular rhythms, complete heart-block. Heart rates below 60 beats/min with accompanying hypotension at presentation are common. It is important to remember that patients who are asymptomatic on admission may subsequently suddenly deteriorate into profound cardiogenic shock.
3. Nifedipine and amlodipine lack the effects of other structural classes of CCBs on AV nodal conduction. Therefore, these agents are more likely to result in reflex tachycardia secondary to diminished perfusion; bradycardia is twice as likely with verapamil and diltiazem.
4. AV block, especially greater than first degree, is predominately a finding with verapamil. ECG manifestations following verapamil intoxication include heart block, first, second and third degree AV block, junctional rhythm, QT interval prolongation, moderate S-T segment depression, low amplitude T-waves, prominent U-waves, and atrial fibrillation. Cardiac disturbances commonly persist for 9 to 48 hours, but have been reported to last as long as 7 days.
5. Symptoms may be delayed and of prolonged duration following ingestion of sustained-release dosage forms. Gastric concretions from sustained-release dosage forms have been found at autopsy. Gastroscopy may be required for confirmation if suspected in the living patient, since these masses have not been apparent on abdominal films.
6. In severe poisoning, altered mental status, convulsions, stroke, renal failure, non-cardiogenic pulmonary oedema,

and coma can occur. Noncardiogenic pulmonary oedema has been reported following diltiazem, verapamil, and amlodipine overdose.

7. Hyperglycaemia has been reported in several cases, probably because normal calcium influx is impaired by CCBs which affects insulin release from beta cells in the pancreas.

8. Acute renal failure has been reported, usually in patients who develop prolonged hypotension and/or rhabdomyolysis after severe poisoning.

9. Profound hypocalcaemia (with tetany) can occur.

10. CNS depression, secondary to haemodynamic instability occurs following significant overdose. Effects may include drowsiness, confusion, and coma. Cerebral infarction has been reported. Seizure activity may result from acidosis, anoxia, or an existing predisposition.

11. Toxicity is likely to be more severe in elderly patients, young children, patients with underlying CVS disease, and co-ingestions with beta-adrenergic antagonists, digoxin, or other drugs with cardiovascular activity. Sustained-release preparations are associated with delayed presentation (sometimes upto 15 hours), and much longer duration of toxicity.

Treatment

1. Intravenous access; continuous ECG monitoring. Monitor haemodynamic status closely including heart rate, blood pressure, continuous cardiac monitoring and serial ECG, and urinary output. Obtain 12-lead ECG demonstrating the rhythm and intervals; repeat every 2 hours for the first 8 hours, and then at longer intervals subsequently.

2. Monitor electrolytes, renal function tests and glucose; monitor respiratory function with arterial blood gases.

3. CCBs are generally radiolucent. Concretions of sustained-release preparations may be apparent on abdominal radiographs.

4. Airway protection; oxygenation.

5. GI decontamination: stomach wash and activated charcoal. For overdoses involving sustained-release preparations, whole bowel irrigation with polyethylene glycol is said to be beneficial. Repeat charcoal following whole bowel irrigation since the PEG/electrolyte solution may desorb drug from charcoal. If continued absorption is suspected in a symptomatic patient after these procedures, consider abdominal X-ray (if brand is radiopaque), ultrasound, or gastroscopy.

6. Patients who show the following signs of toxicity, (or any patient with a history of ingestion of sustained release dosage forms) should be admitted to a monitored setting for at least 24 hours of observation and treatment, independent of the dose ingested:
   a. CVS—Hypotension or bradycardia (or tachycardia with nifedipine); heart block; A-V dissociation; asystole; congestive heart failure
   b. RS—Pulmonary oedema
   c. GI—Nausea or vomiting
   d. CNS—Seizures; altered mental status

7. Bradycardia usually responds to atropine, the efficacy of which may be enhanced by initial treatment with calcium. Dosage recommended is 0.5 to 1 mg IV every 2 to 3 minutes to a maximum of 3 mg. In children: 0.02 mg/kg.

8. Calcium therapy: 10% calcium chloride, 10 to 20 ml, IV, or calcium gluconate, 30 to 60 ml, IV, and repeated every 15 to 20 minutes, upto 4 doses. Alternatively, calcium can be administered as an infusion: 0.2 to 0.4 ml/kg/hr of 10% Calcium chloride, or 0.6 to 1.2 ml/kg/hr of 10% Calcium gluconate. While calcium therapy is beneficial in CCB overdose, serum Calcium should be monitored to prevent hypercalcaemia. However, some degree of hypercalcaemia may be necessary before severely intoxicated patients respond to aggressive calcium therapy. Hence, some authors advocate administering 1 gram of calcium salts every 2 to 3 minutes until conduction block is reversed or clinical evidence of hypercalcaemia develops. Use of calcium chloride may aggravate existing acidosis. Calcium therapy is contraindicated in ingestions involving digoxin.

9. Hypotension secondary to reduced systemic resistance and lowered cardiac output may require both fluid replacement, Trendelenburg positioning and vasoconstriction with noradrenaline or high dose dopamine. Calcium may also help, especially when depressed cardiac contractility is contributory. Glucagon may improve perfusion pressure by stimulating cardiac output. Pacing may be required. Catecholamines and sympathomimetics such as adrenaline, noradrenaline, dopamine, isoproterenol, and dobutamine have been used with varying degrees of success in CCB poisoning.

10. Glucagon has been reported to be beneficial by several investigators. It exerts chronotropic and inotropic effects and can help reverse hypotension, but may not improve heart rate. Dose: 2 to 5 mg IV over 1 minute, followed by 4 to 10 mg over 5 minute (*adults*); 50 mcg/kg (*children*). Because of the short half-life of glucagon, a maintenance infusion is subsequently necessary at the "response dose", i.e. the initial effective dose. Continuous infusion of up to 5 mg/hr has been used with benefit.

11. Conduction deficits and bradyarrhythmias do not need specific treatment if they are not felt to be contributing to continuing hypotension. Antidotal therapy should include calcium (as the chloride) and/or atropine initially, followed by isoproterenol and/or pacing for resistant or nonresponsive cases.

12. Inamrinone, a non-catecholamine inotropic agent has also been used in CCB poisoning with encouraging results. It is usually combined with glucagon or some other inotropic agent such as isoproterenol. Dose : 1 mg/kg IV over 2 minutes, followed by infusion of 5 to 20 mcg/kg/min.

13. Other drugs which are being tried include 4-aminopyridine, and insulin-plus-glucose. The latter can be administered as bolus doses, 10 IU and 25 grams respectively, with the subsequent administration of insulin infusion, the dose ranging from 0.1 IU/kg/hr to 1.0 IU/kg/hr, and

dextrose (50% w/v) infusion, the dose ranging from 5 gm/hr to 15 gm/hr, via a central venous catheter. Insulin infusions, with or without dextrose given concurrently, have been administered with beneficial effects to several haemodynamically unstable patients following calcium antagonist intoxication who were refractory to conventional therapy.

14. Patients not responding to pharmacologic therapy may require transthoracic or intravenous cardiac pacing. Newer methods include intra-aortic balloon counterpulsation and emergent cardiopulmonary bypass.

15. Seizures should be treated with diazepam initially, progressing to phenobarbitone for nonresponsive cases. Correction of underlying metabolic acidosis, hypoxia, and hypotension should also be pursued.

16. In general, the large volumes of distribution and high protein binding of all calcium channel blocking agents would suggest haemodialysis or haemoperfusion would have limited usefulness in removal of significant quantities of these drugs.

■ Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)

Angiotensin converting enzyme (ACE) inhibitors are highly popular drugs in the treatment of hypertension. Examples include benazepril, captopril, cilazepril, delapril, enalapril, fosinopril, lisinopril, moexipril, pentopril, perindopril, quinapril, ramipril, spirapril, trandolapril.

Mode of Action

These agents are specific inhibitors of peptidyldipeptide carboxyhydrolase, the enzyme which converts angiotensin I to angiotensin II; thus preventing vasoconstriction. They may also inhibit bradykinin degradation resulting in a decrease in blood pressure. ACE inhibitors act by inhibiting the conversion of angiotensin I to angiotensin II in the lung and vascular endothelium. This results in vasodilation, decreased peripheral vascular resistance, decreased blood pressure, increased cardiac output, and a slight increase in renal, cerebral, and coronary blood flow.

Toxicokinetics

These drugs are generally well absorbed orally and have highly variable half-lives, volumes of distribution, and protein binding.

Adverse Effects

■ Skin rash, dysgeusia, chronic cough, bronchospasm, neutropenia, hyperkalaemia, hypotension, proteinuria, renal insufficiency, pancreatitis, hepatotoxicity, leukopenia, and occasionally angioneurotic oedema. Hyperkalaemia has been a reported side effect of captopril, enalapril, lisinopril, or perindopril therapy, and may be exacerbated when used in combination with potassium-sparing diuretics and is more common in patients with chronic renal failure.

■ Pancreatitis has only been reported with chronic therapeutic use of lisinopril and enalapril. Hepatotoxicity has been associated with captopril therapy. Renal failure may develop after therapeutic use in patients in whom renal perfusion is dependant on angiotensin II. This includes patients with renal artery stenosis, volume depletion, and severe CHF.

■ ACE inhibitors must not be used in pregnancy since they are teratogenic and can cause a number of foetal anomalies including defects in skull ossification, pulmonary hypoplasia, neonatal hypertension, and renal failure. Hypotension, neonatal anaemia, hyperkalemia, neonatal skull hypoplasia, anuria, and renal failure have occurred in foetuses and neonates. Oligohydramnios has also occurred, possibly due to decreased foetal renal function, and has been associated with limb contractures, craniofacial deformities, hypoplastic lung development.

■ Angioneurotic oedema occurs in about 0.1% of patients receiving ACE inhibitors and commonly involves periorbital, perioral, and oropharyngeal tissues. It may develop after months or years of uneventful therapy with these agents. In severe cases dyspnoea, chest pain, and airway compromise may develop. Elevation of bradykinin levels induced by ACE inhibitors is said to be the main cause. Treatment involves maintenance of airway (with nasopharyngeal airway, intubation, or surgical intervention, depending on the case), and standard antiallergic drug therapy (adrenaline, diphenhydramine, and corticosteroids). However, there is no evidence to suggest that ACE inhibitor-induced angioneurotic oedema is an allergic phenomenon.

■ Cough associated with ACE inhibitor therapy is well documented. Although the exact mechanism is unknown, increased sensitivity of the cough reflex may be due to accumulation or persistence of inflammatory mediators such as bradykinins, substance P, or prostaglandins within the airway. This troublesome side effect occurs with a variable incidence ranging up to 39%. Cough induced by chronic ACE inhibitor therapy responds well to sodium cromoglycate. Women are affected 3:1 compared to men. Drug discontinuation and substitution of an alternative antihypertensive agent may have to be resorted to if the condition is severe and does not respond to any treatment measures.

■ Various types of dermatitis have been reported with chronic use of ACE inhibitors. With therapeutic use, the overall incidence of rashes ranges from 6.1 to 10.9% and is dose-dependant.

Drug Interactions

■ Concomitant use of captopril and allopurinol has rarely been associated with a serum sickness or Stevens-Johnson syndrome.

■ Hypoglycaemia has been reported with simultaneous use of ACE inhibitors and insulin or oral hypoglycaemic agents.

■ The combination of cyclosporin and ACE inhibitors may cause acute renal failure, although this is rare.

■ The combination of ACE inhibitors and potassium sparing diuretics may cause hyperkalaemia.

- The combination of NSAIDs and ACE inhibitors may cause renal insufficiency.
- Several cases of life-threatening anaphylactoid reactions have been reported in patients receiving ACE inhibitors and haemodialysis with a polyacrylonitrile membrane dialyzer (AN69).

Clinical (Toxic) Features

1. In many cases of overdose, patients remain asymptomatic.
2. Hypotension, hyperkalaemia, and renal failure: while hypotension is generally not very severe, occasional cases have been reported of profound hypotension.
3. Fatalities are rare, but have been reported.

Treatment

1. Monitor BUN and serum creatinine if there is evidence of significant hypotension or if there is pre-existing renal disease. Monitor vital signs, particularly blood pressure.
2. Administration of activated charcoal in the usual manner.
3. Correction of hypotension with IV colloids and/or crystalloids. If this fails, dopamine or adrenaline or noradrenaline may be used with caution. Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
4. Angiotensin infusion at doses ranging from 8.5 to 18 mcg/minute has been successful in reversing hypotension in patients who did not respond to volume and pressor infusions.
5. Naloxone is said to be effective in reversing hypotension induced by ACE inhibitor overdose.
6. Early endotracheal intubation should be considered in patients with ACE inhibitor induced angioedema. Orotracheal intubation may be technically difficult in patients with severe tongue swelling; be prepared to obtain a surgical airway.
7. Haemodialysis may be beneficial.

■ Angiotensin II Receptor Antagonists

These drugs are similar to ACE inhibitors in that they inhibit the effects of angiotensin II, but instead of blocking the formation of angiotensin II, they act as antagonists at its receptors. Angiotensin II receptor antagonists selectively bind and, therefore, block the AT(1) receptor subtype. This class of drug blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II on smooth muscle and the adrenal gland. The benefit of this different mode of action is that the bradykinin system is unaffected, and hence cough and angioneurotic oedema do not occur.

Examples include **losartan, tasosartan,** and **valsartan.**

Adverse Effects

- Dizziness, insomnia, headache, muscle cramps, and leg pain occurred during clinical studies. Hyperkalaemia (greater than 20% increase in serum potassium) occurred during clinical trials with valsartan.

- These drugs can potentially cause oliguria and azotaemia in patients whose renal function may depend on function of the renin-angiotensin-aldosterone system (e.g. severe CHF or renal artery stenosis).
- Reversible hepatotoxicity has been reported.
- Angioedema has also been reported.
- Angiotensin II receptor antagonists should be discontinued as soon as possible when pregnancy is detected. Severe foetal deformity has been reported in humans and animal models. Foetal death has been reported in one case following exposure to losartan during weeks 20 to 31 of pregnancy. Oligohydramnios was present along with a pattern of foetal abnormalities associated with angiotensin II antagonists.

Clinical (Toxic) Features

Hypotension, tachy-/bradycardia, hyperkalaemia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment

1. Symptomatic and supportive measures.
2. Monitor renal and liver function tests in symptomatic patients or following significant overdose.
3. Monitor blood pressure and heart rate frequently following a significant ingestion. Consider cardiac monitoring.
4. If hypotensive, give 500 to 2000 ml crystalloid initially (20 ml/kg in children) and titrate to desired effect (stabilisation of vital signs, mentation, urine output); adults may require up to 6 to 10 L/24 hours. Central venous or pulmonary artery pressure monitoring is recommended in patients with persistent hypotension. Vasopressors should be used in refractory cases unresponsive to repeated doses of noradrenaline and after vigorous intravenous crystalloid rehydration.
5. Based on the high degree of protein binding of most of these agents, haemodialysis would not be effective.

Forensic Issues (Antihypertensives)

- Most cases of antihypertensive drug overdose are accidental (for e.g. in children), or suicidal. Paediatric poisoning arises out of parental negligence rendering these and other dangerous pharmaceutical preparations easily accessible to toddlers. Tragically, deaths have occurred in some cases.
- Among the various antihypertensives, the beta blockers have frequently been implicated in serious poisoning, with propranolol being the commonest agent implicated.
- Reserpine increases suicidal tendency among patients.
- Extended (or sustained) release antihypertensives are generally associated with prolonged and more profound effects in overdose.
- Calcium channel blockers are increasingly being reported in serious overdoses, while the safest drugs appear to be ACE inhibitors.
- An abuse potential for clonidine has been identified in treatment-seeking opiate abusers, particularly those with concurrent cocaine use. Chewing of clonidine patches has been reported as a mechanism of abuse in drug-seeking

individuals. Two patterns of clonidine use included: illicit use to decrease opiate withdrawal as well as for its sedating effect, and, illicit use for its psychoactive effects, including the interaction with methadone, in addition to decreasing opiate withdrawal. Physical withdrawal symptoms were reported in 57% of 30 patients abusing clonidine when the drug was stopped.

- Hypoxic-ischaemic encephalopathy with permanent mental regression has been reported in a 3-year-old boy following clonidine poisoning in a case of Munchausen by proxy. Prior to this event, the boy had several lethargic episodes during hospitalisations when the mother was present. Hypothermia, respiratory depression and arterial hypotension also occurred during some of these episodes.

ANTIARRHYTHMICS

Cardiac arrhythmias can be benign or malignant, and a wide array of drugs exist for their treatment or control.

Vaughan Williams' classification of antiarrhy-thmic drugs—

1. **Class I: Sodium channel blockers**
   a. *Moderate to marked sodium channel blockade* —disopyramide, procainamide, quinidine.
   b. *Mild to moderate sodium channel blockade*—lignocaine, phenytoin, mexiletine, tocainide.
   c. *Marked sodium channel blockade*—encainide, flecainide, moricizine, propafenone.
2. **Class II: Beta adrenergic blockers:** atenolol, esmolol, metoprolol, propranolol, and timolol.
3. **Class III: Potassium channel blockers**: acecainide, amiodarone, bretylium, sotalol.
4. **Class IV: Calcium channel blockers**: diltiazem, nicardipine, nifedipine, verapamil.
5. **Unclassified:** adenosine.

Several of these drugs and their toxicities have been discussed elsewhere (see *Index*), and the toxicities of only those drugs which have not been adequately dealt with in other sections, will be discussed here.

■ Disopyramide

Disopyramide is a quinidine-like class IA antiarrhy-thmic, cardiac depressant drug. It has negative inotropic and anticholinergic properties, and is effective in the treatment of various supraventricular and ventricular arrhythmias. It depresses myocardial excitability and conduction velocity.

Uses

1. Maintenance of sinus rhythm in patients with atrial flutter or fibrillation.
2. Prevention of recurrence of ventricular tachycardia or fibrillation.
3. Treatment of neurally mediated hypotension

Toxicokinetics

Disopyramide is 85% bioavailable. Protein binding varies with drug concentration (decreasing as concentration

increases) from 5 to 65%, averaging 40%. The kidney excretes 40 to 60% of the drug, while the liver metabolises the parent compound and its metabolite mono-N-dealkylated disopyramide. The latter is responsible for most of the anticholinergic effects of the drug. The major route of excretion occurs predominately via the urine with about 50% excreted unchanged, approximately 20% excreted as the N-dealkylated metabolite, and 10% as other metabolites. The half-life of disopyramide is 6 to 8 hours, and that of its principal metabolite 3 to 4 hours.

Adverse Effects

Hypotension, dry mouth, blurred vision, angle-closure glaucoma, vomiting, diarrhoea, colic, difficulty in micturition. Rarely, blood dyscrasias and psychosis. Therapeutic doses have occasionally been associated with cholestatic jaundice with elevated serum liver enzyme levels. Laboratory values generally return to normal following discontinuance of the drug, but may remain elevated for several months.

Drug Interactions

Reduced efficacy with phenytoin. Potentiates some of the effects of beta blockers, verapamil, digitalis, and amiodarone. Because of the serious risk of potentiating arrhythmias, disopyramide must not be combined with any other antiarrhythmics.

Clinical (Toxic) Features

1. Usual adult dosage is 400 to 800 mg per day in divided doses. The toxic dose is said to be 1.5 grams. Therapeutic plasma range is reported to be 2 to 6 mcg/ml.
2. In overdose, cardiovascular and anti-muscarinic effects are pronounced.
   a. Similar cardiovascular toxicities occur as with quinidine and procainamide: depression of atrial, atrioventricular and ventricular conduction, arrhythmias, hypotension, heart failure, syncope, cinchonism, paraesthesia, and coma; but anticholinergic effects are more pronounced, and heart failure is more frequent. Syncope is usually related to transient torsade de pointes ventricular tachycardia.
   b. Hypotension occurs from alpha receptor blockade and depressed myocardial contractility.
   c. ECG manifestations, in addition to the aforementioned arrhythmias, include significant QRS and QT interval prolongation, PR prolongation, ST depression, and T inversion.
3. Early loss of consciousness with subsequent respiratory arrest, tachy- or bradyarrhythmias and cardiac arrest is characteristic of severe disopyramide overdoses.
4. Pulmonary oedema, probably secondary to compromised cardiac function, may occur.

Treatment

1. Obtain serial ECGs and institute continuous cardiac monitoring following overdoses. ECG should be monitored for cardiac arrhythmias, including torsade

de pointes, QRS widening, QT prolongation, and AV dissociation.

2. Monitor oxygen saturation and respiratory function in all disopyramide overdose cases. Severe overdoses may result in respiratory failure.

3. Activated charcoal is beneficial.

4. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypo-magnesaemia).

5. Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Amiodarone and sotalol should be used with caution (since disopyramide prolongs the QT interval and/or causes torsades de pointes). Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present and PVCs are thought to represent an escape complex.

6. Do not use procainamide or quinidine. Bretylium has not been studied for these overdoses, but its alpha blocking properties may cause severe hypotension and cardio-vascular collapse when combined with the negative inotropism of disopyramide.

7. Treatment of ventricular tachycardia (especially torsades de pointes variant) may require DC cardioversion, over-drive pacing, isoproterenol infusion to decrease temporal dispersion of refractoriness, and/or sodium bicarbonate IV bolus therapy.

8. High doses of calcium chloride (0.5 grams every 5 minutes upto a maximum of 3 grams) in combination with conventional supportive measures and cardiopulmo-nary resuscitation are quite effective in reversing some of the cardiac effects.

9. For hypotension: infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.

10. Onset of acute lung injury after toxic exposure may be delayed up to 24 to 72 hours after exposure in some cases. Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FiO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.

11. Forced diuresis is potentially dangerous, has not been shown to increase disopyramide excretion or improve outcome after overdose, and is not recommended. Attempt to maintain normal urine output, since 40 to 70 percent is excreted unchanged in the urine irrespective of pH.

12. Haemodialysis or haemoperfusion is effective in enhancing the elimination of the drug. The former is preferable.

■ Procainamide

Procainamide is classified as a Vaughn Williams' Class IA antiarrhythmic agent. In contrast, its active metabolite, N-acetylprocainamide (NAPA; acecainide) has been described as a Class III antiarrhythmic drug. Procainamide is an antiarrhythmic agent with electrophysiologic properties similar to that of quinidine. Its primary effects on the heart are to decrease electrical impulse conduction velocity through atrial and ventricular tissue manifested by a widened QRS and PR interval in the ECG, and to prolong the effective refractory period. While N-acetylprocainamide retains some of the same clinical effects as procainamide, it has a slightly different electrophysiologic profile. It increases the effective refractory period with a selective lengthening of the action potential by prolonging repolarisation. There is no effect on depolarisation, which is thought to result from its inability to block fast sodium channels and depress phase 4 depolarisation. Thus, the drug has been described as a Class III antiarrhythmic.

Uses

■ To suppress ventricular ectopy.
■ To suppress atrial and ventricular tachyarrhythmias.

Toxicokinetics

Procainamide can be given orally but absorption is often delayed in overdose situations. The apparent volume of distri-bution is 1.7 to 2.22 L/kg. Peak plasma level: 1 to 2 hours; protein binding: 15%. It is metabolised by the liver and under-goes biotransformation by acetylation to N-acetylprocainamide (NAPA) which is pharmacologically active. Excretion occurs in the urine (approximately 40 to 60% procainamide and 84% NAPA are excreted unchanged in the urine). Elimination half-life is approximately 8 hours.

Adverse Effects and Clinical (Toxic) Features

1. The usual oral adult dose of procainamide is 1 gram initially, followed by 50 mg/kg/day in divided doses every 3 hours. Therapeutic range for procainamide serum levels varies from 6 to 14 mcg/ml (25.5 to 59.5 mmol/L).

2. Adverse Effects:
   a. Nausea, vomiting, diarrhoea, anorexia.
   b. Drowsiness, blurred vision, paraesthesias, hallucina-tions. Toxic psychosis has been reported.
   c. *Proarrhythmic events* : torsade de pointes, ventricular tachycardia, and fibrillation.
   d. Skin rash.
   e. Thrombocytopenia.
   f. Drug-induced systemic lupus erythematosus (SLE), characterised by fever, arthralgias, myalgias, pleural effusion and pain, and serositis.
   g. Elevated liver enzyme and serum bilirubin levels have been reported.

3. Overdose results in arrhythmias (ventricular tachycardia, junctional tachycardia), conduction abnormalities (QRS and QTc prolongation), torsade de pointes, hypotension,

mental status depression, seizures, anticholinergic effects, respiratory depression, nausea, vomiting and diarrhoea.

Treatment

1. Monitoring drug levels of procainamide and its active metabolite, N-acetyl procainamide, may be helpful in diagnosis of procainamide toxicity.
2. *Decontamination* : stomach wash and activated charcoal.
3. *Elimination enhancement*: haemoperfusion, continuous arteriovenous haemofiltration, or continuous arteriovenous haemodiafiltration. Resin haemoperfusion or haemodialysis are the methods of choice for removal of procainamide and N-acetylprocainamide.
4. Continuous ECG monitoring, airway and circulatory support, and IV access.
5. Sodium bicarbonate or sodium lactate may help in reversing the sodium blockade. Cardiac toxicity often responds to intravenous sodium bicarbonate. A reasonable starting dose is 1 to 2 mEq/kg as an intravenous bolus repeated as needed to reverse QRS widening and arrhythmias and maintain an arterial pH of 7.45 to 7.55. Monitor serial ECGs, arterial blood gases and serum potassium.
6. Lignocaine: 1 to 1.5 mg/kg IV push. For refractory VT/VF an additional bolus of 0.5 to 0.75 mg/kg can be given over 3 to 5 minutes. Total dose should not exceed 3 mg/kg or more than 200 to 300 mg during a one hour period. Only bolus therapy is recommended during cardiac arrest. Once circulation has been restored begin maintenance infusion of 1 to 4 mg/min. If arrhythmias recur during infusion, repeat 0.5 mg/kg bolus, and increase the infusion rate incrementally (maximal infusion rate is 4 mg/min). For a child: 1 mg/kg initial bolus intravenously; followed by a continuous infusion of 20 to 50 mcg/kg/min.

■ Lignocaine (Lidocaine)*

Lignocaine is an aminoacyl amide, and is a synthetic derivative of cocaine. It is used as an anaesthetic agent as well as antiarrhythmic agent. It is effective in controlling ventricular arrhythmias.

Toxicokinetics

Lignocaine is generally given intravenously, and is 50% bound to protein with an apparent volume of distribution of 1.3 L/kg in adults. It is metabolised in the liver to monoethylglycinexylidide (MEGX) which is active pharmacologically, and subsequently to inactive compounds which are excreted mainly in the urine.

Adverse Effects and Clinical (Toxic) Features

1. Blood levels of more than 5 mcg/ml are associated with serious toxicity, and more than 15 mcg/ml with death.
2. Vertigo, drowsiness, confusion, ataxia, dysarthria, hearing loss, visual disturbances, agitation, fasciculations, convulsions, cardiovascular collapse, and coma.
3. Massive overdose can produce rapid onset of hypotonia,

apnoea, and asystole. Even after recovery, symptoms can persist for a prolonged period because of persistent metabolites.

Treatment

1. Diazepam for convulsions.
2. Fluids, dopamine, adrenaline, atropine, and cardiac pacing as necessary.
3. Extracorporeal pump may help in severe overdose.

■ Mexiletine and Tocainide

Mexiletine (mexiletene) and tocainide are analogues of lignocaine with modified structures (to enable them to be administered orally for long periods). Both drugs have been used for ventricular arrhythmias with varying degree of success. They can be combined with quinidine. Mexiletine is a primary amine similar to lignocaine, but orally active. Its primary use is as a Class 1B antiarrhythmic drug with electrophysiologic properties in man similar to lignocaine, but dissimilar from quinidine, procainamide, and disopyramide. Tocainide is an orally bioavailable derivative of lignocaine. Tocainide is rarely employed in practice because of the potential risk of bone marrow aplasia and pulmonary fibrosis. Mexiletine was originally introduced as an anorectic agent but is no more used for that purpose today.

Mexiletine is rapidly and well absorbed (greater than 90%) when administered orally. Peak levels are obtained 2 to 3 hours after ingestion. The half-life is 12 to 13 hours. Mexiletine is highly protein-bound (70%), and also has a high volume of distribution (5.5–12 L/kg). Metabolism of this drug is accelerated by phenobarbitone, rifampicin, and phenytoin, but slowed by cimetidine, INH, and disulfiram. 7.5 to 15% is excreted unchanged in the urine within 72 hours. Elimination is increased by acid urine and decreased by alkaline urine.

Adverse Effects and Clinical (Toxic) Features (Mexiletine)

1. Therapeutic serum level is 1 to 2 mcg/ml.
2. *Chronic effects:*
   a. Bradycardia, hypotension (*IV*), hepatotoxicity, GI distress, vertigo, tremor, ataxia.
   b. Skin eruptions may occur as a result of hypersensitivity syndrome.
   c. Rare cases of severe hepatic necrosis have been reported during therapeutic use of mexiletine.
3. *Acute overdose*:
   a Vertigo, paraesthesias, hypotension, nausea, drowsiness, disorientation, bradycardia, heart block, torsades de pointes, asystole, convulsions, hypokalaemia. Paraesthesias of the tongue often occur as an early symptom of overdose.
   b. ECG changes may include those related to heart block (increased PR interval) or conduction delay (increased QRS interval).
   c Agitation and hallucinations have been reported.

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* See also page no. 246

Treatment (Mexiletine)

1. Stomach wash, activated charcoal.
2. Atropine (1 mg intravenously and repeat in 3 to 5 minutes if asystolic cardiac arrest persists) for bradycardia. Insertion of a temporary pacemaker is the treatment of choice for bradyarrhythmias induced by drugs of this class.
3. Benzodiazpines for convulsions. If seizures persist or recur administer phenobarbitone.
4. IV fluids.
5. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
6. Although urinary acidification will enhance the renal clearance of mexiletine, it is unlikely to be of clinical significance, and risks aggravating acidaemia and other adverse renal effects in convulsing patients outweigh theoretical benefit.

■ Propafenone (Fenopraine)

Propafenone is a class IC antiarrhythmic drug which blocks the fast sodium channel of the myocardial cell. It has some negative inotropic and beta-adrenoceptor blocking activity. Propafenone is structurally related to propranolol and is administered orally for the treatment of life-threatening ventricular arrhythmias. It is indicated in patients without structural heart disease to treat paroxysmal atrial fibrillation/flutter (PAF) or paroxysmal supraventricular tachycardia (PSVT) associated with disabling or life-threatening symptoms. It can have proarrhythmic effects and its use is not recommended in lesser ventricular arrhythmias.

It is 95% absorbed, peaks in 2 to 3 hours, has a plasma half-life varying from 2 to 32 hours, and less than 1% is excreted unchanged in the urine. Apparent volume of distribution is 1.1 to 3.6 L/kg and protein binding is to the extent of 97%. Therapeutic plasma levels should preferably not exceed 2 mcg/ml. Propafenone is metabolised by the cytochrome P-450 pathway which produces the major metabolites 5-hydroxy propafenone and N-desalkyl propafenone.

Adverse Effects

- Bradycardia, cardiac conduction anomalies, hypotension, proarrhythmias, worsening of heart failure, vertigo, headache, GI distress, alteration of taste (metallic or bitter taste), visual blurring. Constipation and nausea have been commonly reported side effects with propafenone therapy.
- Liver damage has been reported rarely with therapeutic use.

Drug Interactions

- Potentiation of effects with local anaesthetics, beta blockers.
- Increases digoxin plasma levels.
- Poentiates anticoagulant effects of warfarin.

Clinical (Toxic) Features

1. The adult therapeutic dose range is 600 to 900 mg/day. Therapeutic levels range from 90 to 3,000 ng/ml.

2. Toxicity is usually most severe within 3 hours of ingestion. Effects of overdose can include gastrointestinal upset, blurred vision, hypotension, drowsiness, prolongation of the QRS interval, atrioventricular blocks, bradycardia, A-V dissociation and conduction disturbances, ventricular arrhythmias, asystole, convulsions, acidosis and coma.
3. Neurologic disturbances are relatively common with propafenone overdose, and several types of convulsions have been described including minor motor and tonic-clonic seizures. Dizziness, amnesia, disorientation, neuropathy, paraesthesias, coma and mania have also been reported.

Treatment

1. Admit to intensive care and monitor cardiac function and tidal volume. Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia).
2. Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Amiodarone and sotalol should be used with caution. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present and PVCs are thought to represent an escape complex.
3. The class IC agents have been shown to be moderately refractory to conventional antiarrhythmic drug therapy, cardioversion, and ventricular pacing. Because of crossover in electrophysiologic properties, class IA agents (quinidine, procainamide, disopyramide) are relatively contraindicated. Class IB agents (lignocaine, phenytoin, mexiletine, tocainide) may be the best alternative based on electrophysiologic properties, but could also exacerbate toxicity.
4. Stomach wash and/or activated charcoal, upto 4 to 6 hours post-ingestion.
5. Sodium loading : molar sodium lactate, sodium bicarbonate, or hypertonic saline may be administered. Serum alkalinisation with sodium bicarbonate may be useful in treating arrhythmias. A reasonable starting dose is 1 to 2 mEq/kg as an intravenous bolus, repeated as needed to maintain arterial pH 7.45 to 7.55. Monitor ECG, arterial blood gases and electrolytes.
6. Diazepam for convulsions. If seizures persist or recur administer phenobarbitone.
7. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy. Atropine and pressor amines (dopamine, dobutamine) may be used as necessary.
8. There are a few cases reported of beneficial effects following the use of infused adrenaline and temporary internal pacemaker.

▪ Amiodarone

Amiodarone (3,5-Diiodophenyl ketone hydrochloride) is an iodinated benzofuran derivative with a structural similarity to thyroxine. Each 200 mg contains 75 mg of iodine. Amiodarone is a class III antiarrhythmic agent that primarily prolongs cardiac action potential duration. It also possesses vasodilatory and non-competitive antiadrenergic activity.

Uses

Treatment of
1. Resistant, life-threatening supraventricular and ventricular arrhythmias.
2. Intractable congestive heart failure.

Toxicokinetics

Amiodarone can be given orally or intravenously. Bioavailability on oral administration is low (28 to 50%), with peak plasma levels achieved 3 to 8 (range 2 to 12) hours after therapeutic doses. Absorption is slow and variable (22 to 86%). First pass metabolism in the gut wall or liver may be the cause. Amiodarone is extensively distributed, with concentrations in the skin, skeletal muscle, adipose tissue, lung, liver, and myocardium. Tissue concentrations generally exceed that of plasma. The volume of distribution is large (9–17 L/kg), protein binding is to the extent of 98%, and the elimination half-life varies from 3 to 21 hours. Its major metabolite is desethylamiodarone, and the principal route of elimination is by hepatic excretion into the bile where it may get concentrated upto 50 times that of the serum. Less than 1% is excreted by the kidneys.

Mode of Action

- Prolongs the action potential duration of myocardial cells without altering the resting membrane potential.
- Non-competitive alpha and beta sympathetic receptor blockade resulting in vasodilation.

Adverse Effects and Clinical (Toxic) Features

- Rapidly progressive adult respiratory distress syndrome. Symptoms develop either acutely, resembling an infectious pneumonitis, or slowly with cough, dyspnoea, and weight loss. Pulmonary toxicity (interstitial pneumonitis or pulmonary fibrosis) may manifest as dyspnoea, cough, fever, chest pain, malaise, weakness, anorexia, weight loss, and abnormal pulmonary function tests following amiodarone therapy. Clinical and radiologic findings have included exertional or progressive dyspnoea, tachypnoea, cough, pleuritic chest pain, fever, malaise, elevated ESR, leukocytosis, hypoxaemia, decreased total lung capacity, diffuse interstitial or alveolar infiltrates, and pleural thickening. Pulmonary function studies have shown a decrease in carbon monoxide diffusing capacity (DCO). Haemoptysis, an unusual adverse effect of amiodarone therapy, is associated with amiodarone-induced pulmonary toxicity.
- Proarrhythmias, ventricular arrhythmias, bradycardia, heart block.

- Hypotension has been reported with rapid IV infusion.
- A metallic or salty taste may occur with chronic therapy.
- Hypo- or hyperthyroidism: Both hypo-and hyperthyroidism have been reported during chronic therapy. Amiodarone has been demonstrated to cause congenital myxoedema in infants born of amiodarone-treated women.
- Hepatotoxicity: Transient liver enzyme elevations may occur with chronic use, but are often asymptomatic. Signs and symptoms may include hepatomegaly, ascites, abdominal pain, nausea, vomiting, anorexia, and weight loss. Chronic amiodarone therapy may induce alcohol-like cirrhotic liver changes.
- Acute pancreatitis has been reported following therapeutic use of amiodarone.
- Epididymitis has occurred in some male patients.
- Blue-green discolouration of skin and nails, alopecia. Prolonged exposure to sunlight after 6 to 39 months of chronic amiodarone therapy may result in blue or purple skin discolouration (pseudocyanosis). Cutaneous hyperpigmentation occurs in 1 to 5% of patients taking therapeutic doses of amiodarone. Photosensitivity reactions consisting of burning, flushing, urticaria, maculopapular eruptions, alopecia, erythema and skin blisters have been reported after brief exposure to sunlight in patients receiving amiodarone for as little as one week.
- Peripheral neuropathy: Proximal muscle weakness, myopathy, and myalgias have been noted in conjunction with neuropathies.
- Malaise, fatigue, tremors, lack of co-ordination, abnormal gait, ataxia, dizziness, and/or paraesthesia can occur in up to 4 to 9% of patients receiving amiodarone.
- Corneal microdeposits: Benign pigmented corneal micro-deposits occur in 76 to 100% of patients receiving chronic therapy. Visual disturbances such as blurred vision, coloured halos or photophobia may accompany these changes. Optic neuropathy has also been reported. Severity is related to dosage and duration of treatment. A typical symptom is described as blue-green coloured rings or halos around surrounding light sources. Optic examination shows opacities of the cornea, retina, lens and optic nerves. Blue-white opacities can occur in the anterior subcapsular region of the lens following amiodarone therapy. These changes may develop in 50 to 60% of the patients receiving therapy and are not reversible with drug cessation. The opacities, however, rarely interfere with visual acuity.
- Bone marrow granulomas may develop after months of therapy with amiodarone. Initial symptoms include: intermittent fever, night sweats and fatigue.
- Overdose experience with amiodarone is limited. Adults ingesting 2.6 to 8 grams developed asymptomatic slight bradycardia and QT prolongation with a delayed onset of 1 to 3 days post-ingestion. No other toxic effects have been noted in overdose. In substantial overdose, bradycardia and/or heart block, torsades de pointes and hypotension should be anticipated.

Drug Interactions

- Potentiates the effect of oral anticoagulants and other antiarrhythmics.
- Increases digoxin concentration by 70 to 100%.
- Additive effect with beta blockers and Calcium channel blockers.
- Amiodarone administration in pregnancy may result in neonatal hypothyroidism and prematurity.

Treatment (overdose)

1. Although a therapeutic range is approximately 1 to 2.5 mcg/ml, several authors question the usefulness of serum levels to predict either clinical efficacy or toxicity.
2. Decontamination measures may be effective upto several hours post-ingestion. Perform stomach wash only while cardiac monitoring is done, since profound bradycardia can occur.
3. Oral cholestyramine (4 grams every hour for 4 hours) may help in reducing the half-life of amiodarone.
4. Pulmonary toxicity responds to corticosteroids, but rapid withdrawal may lead to recurrence. Chest X-ray findings in patients with amiodarone-induced pulmonary toxicity are nonspecific, including areas of consolidation, infiltrates, and interstitial disease. Chest CT may be helpful in evaluating patients with suspected amiodarone-induced pulmonary toxicity.
5. Monitoring of ECG is essential and may need to be continued for several days postingestion. Severe cardio-vascular collapse is treated with isoprenaline and DC cardioversion.
6. Bradycardia responds to beta-adrenergic agonists or pacemaker. With chronic therapy, bradycardia has been unresponsive to atropine, presumably due to the noncom-petitive nature of amiodarone's antiadrenergic effects. Beta-adrenergic agonists such as isoproterenol or ephedrine may be helpful in cases of sinus arrest.
7. Intravenous magnesium sulfate has been successfully used to treat nonsustained polymorphous ventricular tachycardia with prolonged QT interval due to amiodarone therapy.
8. Hypotension responds to vasopressors. Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrena-line. Consider central venous pressure monitoring to guide further fluid therapy.
9. Haemodialysis and haemoperfusion do not appear to be beneficial.

Adenosine

Adenosine (9-beta-D-ribofuranosyladenine) is a nucleotide found in all cells, and is released from myocardial cells under various physiological and pathological conditions. It is primarily formed as a degradation product of adenosine triphosphate (ATP). As an intermediate metabolite in several biochemical pathways, adenosine contributes to the regula-tion of numerous physiologic processes, including platelet function, coronary and systemic vascular tone, and lipolysis in adipocytes.

Adenosine, an endogenous coronary vasodilator, is used in a continuous infusion (0.140 mg/kg/min for 6 minutes) as a pharmacologic agent for thallium stress testing. Adenosine causes more vasodilation in normal coronary arteries, leading to increased thallium uptake in normal myocardium versus ischaemic areas. It is effective in the treatment of re-entrant supraventricular tachycardia when administered as a rapid IV bolus. Adenosine has a half-life of just a few seconds and is metabolised to inosine.

Adenosine acts by decreasing spontaneous depolarisation in the sinus node and conduction velocity in the A-V node. Its direct negative chronotropic and dromotropic properties are the basis for its wide therapeutic application in patients with supraventricular tachycardia.

The duration of electrophysiologic and clinical effects with adenosine is extremely short, usually less than 10 seconds, due to rapid cellular uptake and metabolism. Total clearance from plasma occurs in less than 30 seconds following intravenous administration. Adenosine is rapidly cleared from the plasma by cellular uptakes, particularly by erythrocytes, vascular endothelial cells, and cardiomyocytes. Within cells, adenosine is rapidly degraded to inosine by adenosine deaminase and subsequently to hypoxanthine. It is also metabolised to adenosine monophosphate (AMP) by adenosine kinase.

Adverse Effects and Clinical (Toxic) Features

1. Cutaneous flushing, dyspnoea, chest pain, nausea, vomiting, vertigo, headache, hypotension, and proarrhythmias. Occasionally there may be minimal cardiac adverse effects including atrial fibrillation, atrial flutter, bradycardia, and angina-like chest pain at doses as high as 23 milligrams. Sometimes adenosine may induce prolonged bradysystole and convulsions.
2. Infusion of adenosine causes angina-like chest pain in susceptible persons without ECG signs of ischaemia. In controlled US trials, some patients developed dyspnoea following intravenous adenosine administration. It is thought that adenosine can produce bronchoconstric-tion by enhancing IgE-dependant release of pre-formed mediators from mast cells. Until further data are avail-able, adenosine should be used with caution in asthmatic patients.
3. **Adenosine triphosphate:** May be associated with a higher incidence of adverse effects than adenosine. A high frequency of cardiac adverse effects have been observed, including sinus bradycardia, sinus arrest, sinus tachycardia, and varying degrees of atrioventricular (AV) block upon termination of the tachycardia. Noncardiac adverse effects include flushing, malaise, hyperpnoea, headaches, retching, vomiting, seizures (rare), and coughing.

Drug Interactions

- Dipyridamole is a competitive inhibitor of adenosine's transport into cells and can potentiate the effects of the

drug. Significantly lower doses of adenosine should be administered to patients receiving dipyridamole.

- Adenosine may not be effective in patients receiving methylxanthines; methylxanthines are competitive antagonists of adenosine and can completely block the electrophysiologic effects of the drug.
- If adenosine is used to treat patients with toxic concentrations of calcium channel blockers, prolonged bradycardia may occur.

Treatment

1. Continuous electrocardiogram monitoring is recommended, especially in patients capable of rapid atrioventricular (AV) conduction.
2. The duration of electrophysiologic and clinical effects with adenosine is extremely short, usually less than 10 seconds, due to rapid cellular uptake and metabolism. Laboratory measures are not likely to be useful in an intoxication.
3. External pacing.
4. Theophylline for prolonged chest pain (in patients with ischaemic heart disease).
5. Symptomatic and supportive measures.
6. The incidence of adverse effects with adenosine triphosphate can be reduced with the use of smaller initial doses (10 mg). Pretreatment with inosine may also alleviate the adverse effects of ATP.

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23 Cardiac Drugs and Lipid Lowering Agents

CARDIAC DRUGS

1. **Drugs used in heart failure**
2. **Anti-anginal Drugs**
3 **Lipoprotein Lowering Drugs**

Drugs Used in Heart Failure

1. Cardiac Glycosides
2. Diuretics
3. Vasodilators
4. Beta Adrenergic Receptor and Dopaminergic Receptor Agonists
6. Phosphodiesterase Inhibitors
7. Beta Adrenergic Receptor Antagonists (Beta Blockers).

Some of these drugs have been discussed in earlier chapters. The following discussion is restricted only to those drugs which have not been dealt with so far.

CARDIAC GLYCOSIDES

The history of cardiac glycosides in relation to the treatment of congestive heart failure begins with the classic **1785** monograph by **William Withering**, who wrote about the therapeutic and toxic properties of *Digitalis purpurea*. The common name of this plant is *foxglove*, and it grows well in the hilly regions of Darjeeling, Nilgiris, and Kashmir. It is a biennial or perennial herb belonging to family Scrophulariaceae, growing upto 1 to 1.5 metres in height (**Fig 23.1**). Leaves are hairy, ovate, toothed, and grey-green in colour, while the flowers are tubular and pink or white in colour (**Fig 23.2**). There is a related species, *Digitalis lanata*, which is also rich in cardiac glycosides. Leaves constitute the main source of glycosides in both plants.

The following discussion will be mainly with reference to the digitalis glycosides digoxin and digitoxin, which are the most widely used cardiac glycosides. Other less commonly

Fig 23.1: Foxglove plant

Fig 23.2: Foxglove flowers

used glycosides include gitoxin, gitalin, digitonin, digitin (all from *D.purpurea*), lanatoside C, and deslanoside (both from *D.lanata*).

Uses

- Treatment of mild to moderate heart failure
- Control of ventricular response rate in patients with chronic atrial fibrillation.

Digoxin increases left ventricular ejection fraction resulting in improvement of heart failure symptoms. Digoxin is often used in conjunction with a diuretic and an angiotensin-converting enzyme inhibitor for the treatment of heart failure.

Toxicokinetics

- Both digoxin and digitoxin are well absorbed orally, but while the former is only moderately protein bound (25%), and has a large apparent volume of distribution (*adults* : 7 to 8 L/kg, *neonates* : 10 L/kg, *infants* : 16 L/kg), digitoxin is highly protein bound (97%), and has a low apparent volume of distribution.
- Peak serum concentrations of digoxin occur within 1.5 to 6 hours after an oral dose. For digitoxin and digitalis leaf, the peak of cardiac toxicity is 4 to 12 hours.
- Digoxin is metabolised to a very minor extent (about 16%) via hydrolysis, oxidation, and conjugation. Metabolism is not dependant on the cytochrome P450 system.
- After a single dose, digoxin is the major serum and urine metabolite of digitoxin. 60 to 80% of digoxin is excreted unchanged in the urine and the terminal half-life is about 36 hours. Digitoxin has a much longer elimination half-life (about 100 hours).
- Most of an administered dose of digoxin is distributed to skeletal muscle after absorption (about 65%). The myocardium : plasma ratio is about 30 : 1.

Mode of Action

- Digitalis glycosides inhibit active transport of Na$^+$ and K$^+$ across cell membranes by binding onto a specific site on the extracytoplasmic face of the alpha subunit of Na$^+$-K$^+$-ATPase. The force of contraction of the heart (positive inotropic effect) is increased due to increase in cytosolic Ca^{++} during systole. Both Na$^+$ and Ca^{++} enter the myocardial cells during each cycle of depolarisation, contraction, and repolarisation. During repolarisation and relaxation, Ca^{++} is pumped back into the sarcoplasmic reticulum by Ca^{++}-ATPase and is removed intracellularly by a Na$^+$Ca^{++} exchanger, and a sarcolemmal Ca^{++}-ATPase.

- Massive acute cardiac glycoside overdose differs significantly from chronic toxicity. In acute overdose, the sodium-potassium pump is poisoned, producing a fall in intracellular potassium and a rise in extracellular potassium, which may be marked. The normal membrane resting potential is reduced, and electrical conduction is slowed, with eventual complete loss of myocardial electrical function. Clinically this results in high grade heart block, and eventually in asystole, which may not respond to electrical pacing.

Adverse Effects

- CVS: Arrhythmias are induced, the more common types comprising non-paroxysmal atrial tachycardia, premature ventricular extrasystoles, premature atrial and junctional extrasystoles, and all grades of A-V block. The most serious arrhythmias are ventricular tachycardia and ventricular fibrillation. The toxic cardiac effects of digitalis glycosides are summarised in **Table 23.1**.
- GIT: Anorexia, nausea, vomiting, weakness.
- CNS: Confusion, disorientation, headache, and hallucinations (digitalis delirium).
- Eye: Transient amblyopia, blurred vision, scotomata, photophobia, and chromatopsia.
- Miscellaneous: Gynaecomastia, restlessness, diarrhoea in elderly.

Drug Interactions

- Toxicity is increased by diuretics (except potassium-sparing) and corticosteroids, because of hypokalaemia.
- Common drugs that may reduce the elimination of cardiac glycosides and result in digitalis intoxication include: amiodarone, propafenone, quinidine, and verapamil.
- Blood levels increased by Calcium channel blockers, spironolactone, quinidine and Calcium salts.
- Effectiveness reduced by phenytoin, neomycin, sulfasalazine, kaolin, pectin, and some antacids.
- Metoclopramide interferes with absorption.
- Erythromycin, tetracycline, and omeprazole increase absorption.

Clinical (Toxic) Features

1. Manifestations of digitalis overdose are mentioned separately for adults and children in **Table 23.2**.
2. Poisoning may be acute or chronic.
   a. In an acute ingestion, nausea and vomiting are prominent as well as evidence of cardiotoxicity.

Table 23.1: Toxic Cardiac Effects of Digitalis Glycosides

Property	Cardiac Chambers	AV Node	ECG
Excitability	Increased	No effect	Extrasystoles, tachyarrhythmias
Automaticity	Increased	No effect	Extrasystoles, tachyarrhythmias
Conduction velocity	Decreased	Decreased	Increased PR interval, AV block
Refractoriness	Decreased	Increased	Increased PR interval, AV block, decreased QTc interval

Table 23.2: Acute Digitalis Poisoning

Adults		Children	
Cardiac	*Non-Cardiac*	*Cardiac*	*Non-Cardiac*
• AV block (high degree)	• Anorexia, nausea, vomiting	• Often not severe.	• Vomiting
• Ventricular ectopy, tachy-cardia, fibrillation	• Confusion	• Bradycardia, AV block (I or II degree)	• Lethargy
• Non-paroxysmal atrial tachy-cardia	• Hyperkalaemia	• ST segment depression	
		• Junctional rhythm	
• Sinus bradycardia		In severe cases—	
		• AV junctional tachycardia alternating with slow ventric-ular rate	
		• Ventricular fibrillation	

b. In chronic poisoning, non-specific symptoms, such as malaise and weakness predominate, as well as the classic, but rare, visual disturbances.

3. Lethargy, drowsiness, weakness, paraesthesias, and headache may occur with digoxin toxicity. Signs of toxic psychosis, including hallucinations, paranoia, agitation, confusion, and delirium, may also occur. Often, CNS signs will be the only presentation of digitalis toxicity, before cardiac or gastrointestinal symptoms.

4. In many patients, though, the sole evidence for digitalis toxicity is the appearance of a cardiac arrhythmia. Nonparoxysmal nodal tachycardia, atrial tachycardia with AV dissociation and bidirectional ventricular tachycardia are common. Poor prognosis is associated with old age, plasma digoxin level exceeding 15 ng/ml, and presence of AV block (high degree), hyperkalaemia, or ventricular tachycardia.

5. The hallmark of digitalis poisoning is increased automaticity coupled with concomitant conduction delay. Every known type of arrhythmia has been associated with digitalis intoxication, including bradycardia, all degrees of heart block, PAT with block, bundle branch block, nodal tachycardia with AV dissociation, atrial and ventricular ectopy, and ventricular tachycardia and fibrillation; any or all may occur in the same patient. Although no single arrhythmia is always present, commonly appearing aberrations include frequent premature ventricular beats, bradyarrhythmias, paroxysmal atrial tachycardia with block, junctional tachycardia, and bidirectional ventricular tachycardia.

6. Nausea, vomiting and abdominal pain are early manifestations of acute and chronic toxicity. The most common presenting symptoms in a paediatric patient are gastrointestinal complaints, sinus bradycardia, or first-degree AV block.

7. Hypotension and cardiac arrest may occur. Peak cardiac effects generally occur 3 to 6 hours following digoxin overdosage and may persist for the ensuing 24 hours or longer. Profound hyperkalaemia after acute ingestion is common.

8. Non-occlusive mesenteric infarction and refractory shock resulting in death have been reported following digoxin toxicity.

9. Photophobia, amblyopia, miosis, and aberrations of colour (predominance of yellow-green), are associated primarily with chronic toxicity. Cones are 50-fold more sensitive than rods. Inhibition of light response by photoreceptors is concentration-dependant and reversible.

Usual Fatal Dose

▪ Digitalis leaf: 2 grams
▪ Gitalin: 15 mg
▪ Digoxin: 10 mg
▪ Digitoxin: 3 mg.

Acute digoxin ingestion of greater than 10 mg in a previously healthy adult, or 4 mg in a child may produce serious toxicity, including cardiac arrest.

Therapeutic plasma concentration of digoxin should not exceed 2 ng/ml. Concentrations exceeding 15 ng/ml are potentially fatal. Usual therapeutic range: 0.5 to 2 ng/ml (0.64 to 2.56 nmol/L). Paediatric patients appear to be more resistant to the cardiotoxic effects of digoxin than adults at comparable serum levels. Children excrete digoxin more rapidly than older patients. In overdose, the distribution phase may be prolonged, therefore, serum digoxin levels may not be meaningful until approximately 6 hours post-ingestion. Due to digoxin pharmacokinetics, serum samples should not be drawn within 6 hours of the previous dose, unless toxicity or overdose is strongly suspected.

Treatment

A summary of the important treatment measures is given in **Table 23.3**.

1. Initial Treatment
   a *Decontamination*: Emesis, lavage, activated charcoal,* cathartic (as applicable). Emesis and stomach wash may enhance vagal stimulation and exacerbate bradycardia

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* In place of **activated charcoal,** steroid-binding resins such as **cholestyramine** (12 to 16 gm/day orally), or **colestipol** may be used to equally good effect.

Table 23.3: Treatment of Digitalis Poisoning

Low-Risk Patients	Intermediate-Risk Patients	High-Risk Patients
No evidence of ECG rhythm disturbances Serum digoxin mildly elevated Left ventricular function is good No history of severe cardiac disease	ECG reveals cardiac toxicity No life-threatening complications	Serum digoxin markedly elevated Presence of life-threatening arrhythmias
Treatment :	*Treatment :*	*Treatment :*
• Withhold digitalis	• Observe in monitored setting	• Admit to coronary care unit
• Repeat ECG	• Obtain K and Mg levels. If the levels are low, begin replacement therapy	• Decontamination measures
• Watch out for digitalis withdrawal		• Use atropine for sinus bradycardia, sinoatrial arrest, and II or III degree heart block
	• If haemodynamically significant arrhythmias or high-grade ectopy exists, administer antiarrhythmic drugs	• Insert temporary pacemaker if patient is haemodynamically unstable
		• Use Fab fragment therapy

or heart block. While digoxin immune Fab fragments are the preferred treatment for severe or life-threatening cardiac glycoside intoxication, multiple dose activated charcoal may be useful in situations in which Fab fragments are not available. Whole bowel irrigation may be useful after large ingestions.

b. Forced diuresis, haemodialysis and haemoperfusion are generally ineffective.

c. Monitor serum glycoside and potassium levels frequently. Hyper- or hypokalaemia may occur.

d. All patients with a history of cardiac glycoside ingestion should have a baseline electrocardiogram, and serial serum levels and electrolytes. Patients who remain asymptomatic with normal (or unchanged from previous) baseline and follow-up electrocardiogram, declining serum levels, and normal electrolytes, may be discharged after 6 hours of observation, following psychiatric consultation if indicated.

2. Advanced Treatment:

a. ***Antidote:*** Digoxin-specific antibody fragments (Fab) - Fab therapy is of proven efficacy in not only digitalis overdose, but also in oleander poisoning. Fab fragments are administered intravenously. They bind intravascular free digoxin and then diffuse into the interstitial space and bind free digoxin there. Digoxin and potassium levels should be followed; continuous ECG monitoring is also indicated. Therapy should be guided by the occurrence of life-threatening arrhythmia, significant cardiac compromise or severe hyperkalaemia rather than by digoxin concentration alone. In the absence of major clinical signs/symptoms, an absolute digoxin concentration of greater than 10 nmol/L (6 hours after last dose) is an indication for the use of digoxin Fab fragments.

  – Indications for antidotal treatment include—
  - Ingestion of greater than 10 mg digoxin by an adult (4 mg by a child).
  - Potassium concentration exceeding 5 mEq/L.
  - Serum digoxin level of more than 15 ng/ml.
  - Progressive bradyarrhythmias or severe ventricular arrhythmias.
  - Rapidly progressing clinical symptomatology.

  – Dose—Each vial (**Digibind**) contains 38 mg of Fab fragments.
  - Dose depends on total body load (TBL) of digoxin which can be calculated in 3 ways:
    » Estimate amount of digoxin ingested and asume 80% bioavailability, i.e., **x** mg ingested × 0.8 = TBL. (For digitoxin, bioavailability is taken as 100%).
    » Estimate serum digoxin (or digitoxin) level and use the following formula - Serum level (ng/ml) x volume of distribution (Vd) × weight (kg), where Vd is 5.6 L/kg for digoxin, and 0.56 L/kg for digitoxin.
    » Use an empiric dose based on average requirements for an acute or chronic overdose in an adult or child: Adult = 10 to 20 vials (*acute poisoning*), 3 to 6 vials (*chronic poisoning*); Child = 10 to 20 vials (*acute poisoning*), ¼ to ½ vial (*chronic poisoning*).

  – Mode of Administration—Intravenous, over 30 minutes, via a 0.22 micron membrane filter. Reconstitute each vial with 4 ml of sterile water and use immediately (or within 4 hours if refrigerated).
  – Adverse Effects—Allergic reactions (rare).
  – Disadvantages—Not yet available in India. Can be procured from abroad, but is extremely expensive. A full course of antidotal therapy with Fab fragments can cost several thousand dollars.

b. In the absence of Fab fragments, ventricular irritability can be treated with phenytoin or lignocaine. Antiarrhythmics that may be useful include atropine, phenytoin and lignocaine.

Dose –
– *Phenytoin:* 50 mg/min, slow IV (maximum 1000 mg in adult, 15 to 20 mg/kg in child). Maintenance oral dose : 300 to 400 mg/day in adult, 6 to 10 mg/kg/day in child.
– *Lignocaine:* 1 mg/kg IV bolus, followed by continuous infusion at 1 to 4 mg/min in adult, or 20 to 50 mcg/kg/min in child. 15 minutes after initial bolus, an additional 1 mg/kg IV bolus should be administered (both adult and child).

c. Atropine is useful in the management of bradycardia, and varying degrees of heart block due to the digitalis-induced effects of enhanced vagal tone on SA node rhythmicity and on conduction through the AV node. In patients with severe supraventricular bradyarrhythmias, or high degrees of AV block, 0.5 mg of atropine is given IV in an adult, (0.02 mg/kg in child, minimum being 0.1 mg). This dose can be repeated every 5 minutes as necessary.

d. Magnesium (20 ml of 20% solution over 20 minutes by slow infusion) has been reported to reverse digoxin induced arrhythmias. It should be used extremely cautiously if at all in the presence of renal failure.

e External or transvenous pacemaker: Pacemaker use should be considered in severe bradycardia and/or slow ventricular rate due to second or high-degree AV block that fails to respond to atropine and/or phenytoin when digoxin Fab are not available.

f Percutaneous cardiopulmonary bypass has been used for therapy resistant cardiac arrest due to digoxin overdose. Catecholamines may be needed during bypass to maintain arterial pressure. This method may provide haemodynamic support and sufficient tissue perfusion to allow neutralisation by digoxin immune FAB in patients with cardiac arrest due to massive cardiac glycoside overdoses.

g. Haemodialysis is ineffective in removing cardiac glycosides but may assist in restoring serum potassium to normal levels. Plain, charcoal, and immobilised antidigoxin antibody haemoperfusion have all been used in digoxin and digitoxin overdose. None of these techniques have proven utility in these ingestions.

h. Treatment of hypo-/hyperkalaemia, and hypomagnesaemia, as follows—
– *Hypokalaemia*: IV potassium chloride in 0.9 or 0.45 % sodium chloride, at a rate of 0.5 to 1.0 mEq/min (1 mEq/kg/hour in a child).
– *Hyperkalaemia*: IV insulin, dextrose, sodium bicarbonate, and oral ion-exchange resins (sodium polystyrene sulfonate). Digoxin immune Fab is first-line treatment. Fab fragments and bicarbonate/insulin/glucose should not be used simultaneously because severe hypokalaemia may result. **Do not administer calcium salts**. Calcium increases cardiac effects of glycosides, and may precipitate arrhythmias. Hyperkalaemia is caused by poisoning of Na-K pump by glycoside, so that intracellular

potassium becomes extracellular; there is not increased total body potassium.
– *Hypermagnesaemia*: 2 grams magnesium sulfate (10%) IV over 20 minutes (25 mg/kg/dose in a child). Maintenance : 1 to 2 gm/hr (adult), 25 to 50 mg/kg/hr (child).

BETA ADRENERGIC RECEPTOR AND DOPAMINERGIC RECEPTOR AGONISTS

Out of the several examples of these two groups, only two drugs used in heart failure (**dopamine** and **dobutamine**) will be discussed here.

■ Dopamine

Uses

Treatment of haemodynamic imbalances in shock syndrome due to:
■ Congestive heart failure
■ Myocardial infarction
■ Endotoxic septicaemia
■ Open heart surgery
■ Renal failure
■ Trauma.

Toxicokinetics

Dopamine hydrochloride is an endogenous catecholamine, and is a direct precursor of noradrenaline. It accounts for about one-half of all catecholamines in the brain, and is present in greater quantities than noradrenaline or 5-hydroxytryptamine. Dopaminergic neurons and receptors are highly organised and concentrated in several areas, especially in the basal ganglia and limbic system.

Dopamine is administered only by the intravenous route since it is inactivated when given orally. Volume of distribution is approximately 0.89 L/kg, and steady-state plasma concentrations are achieved in 5 to 10 minutes. Elimination half-life of infused dopamine is about 9 minutes, while that of a bolus IV dose is about 2 minutes. Dopamine is extensively metabolised in the liver, and less than 10% of a dose is excreted unchanged in the urine. It is metabolised in liver, kidney, and plasma by monoamine oxidase and catechol-O-methyltransferase to inactive metabolites. About 20% is cleared by the lungs, especially when plasma dopamine levels are high.

Mode of Action

The usual dose is given as an initial intravenous infusion rate of 2 to 5 mcg/kg/min, then titrated up to a maximum of 50 mcg/kg/min is recommended for maintaining blood pressure control.
■ At low dosages (0.5–2 mcg/kg/min), D_1 and D_2 receptors are activated. D_1 receptor activation leads to renal, mesenteric, cerebral, and coronary vascular dilation. D_2 receptor activation causes the blood pressure to remain stable or decrease, while renal plasma flow, glomerular filtration rate, and sodium excretion increase.
■ At higher dosages (2–5 mcg/kg/min), beta adrenoceptors

are activated leading to increased cardiac contractility, heart rate, and atrioventricular conduction. Beta$_1$ receptor activation leads to increased cardiac output and systolic blood pressure.

- At much higher dosages (> 5 mcg/kg/min), alpha$_1$ and alpha$_2$ receptors are activated leading to vasoconstriction. Systolic and diastolic blood pressures increase.

Adverse Effects

- Tachy-/bradycardia, ectopic beats, palpitations, anginal pain, dyspnoea, hypo-/hypertension, vasoconstriction, mydriasis, vomiting.
- The following are commonly seen: hypertension (sometimes followed by hypotension), myocardial ischaemia or infarction, supraventricular tachyarrhythmias, bradycardia, or ventricular arrhythmias, pulmonary oedema with rales, rhonchi, dyspnoea, and frothy or bloody sputum.
- Systemic symptoms have occurred following ocular exposure to undiluted parenteral dopamine solution; ocular exposures should be treated as parenteral exposures.
- Dopamine is contraindicated in phaeochromocytoma, uncorrected tachyarrhythmias, and ventricular fibrillation.

Drug Interactions

- Halogenated anaesthetics and cyclopropane can precipitate severe arrhythmias.
- MAOIs potentiate dopamine's effects.
- Ergot derivatives and tricyclics increase vasoconstriction.
- Cardiac effects are antagonised by beta blockers.

Toxic (Clinical) Features

Patients with pre-existing vascular disease may be subject to excess ischaemic effects which usually begin after 24 hours of dopamine use and may progress to gangrene of an extremity. Doses of over 10 mcg/kg/min are always risky. Hypertension is invariably induced when large doses of dopamine are administered. Deaths have occurred.

Treatment

1. Admit patient in coronary care unit with cardiac monitoring and electrocardiographic surveillance.
2. If ischaemia occurs in an extremity, infiltrate the area immediately with 10 to 15 ml of a saline solution containing 5 to 10 mg of phentolamine mesylate. Alternatively, 50 mg of phentolamine diluted to 1 mg/ml with 0.9% sodium chloride can be administered in multiple subcutaneous injections of 0.5 mg each to cover the entire area of extravasation. The possible risk of phentolamine-induced hypotension can be minimised by giving these doses over 1 to 2 hours.
3. Intravenous chlorpromazine, 10 mg as a loading dose, and 0.6 mg/min drip has been used for digital ischaemia induced by dopamine.
4. Correct hypovolaemia with adequate fluid replacement.
5. For mild/moderate asymptomatic hypertension, pharmacologic intervention is generally not necessary. Sedative agents such as benzodiazepines may be helpful in treating

hypertension and tachycardia in agitated patients. For hypertensive emergencies (severe hypertension with evidence of end organ injury (CNS, cardiac, renal), or emergent need to lower mean arterial pressure 20 to 25% within one hour), nitroprusside is preferred.

■ Dobutamine

Dobutamine hydrochloride is a synthetic catecholamine structurally related to dopamine, and is primarily an inotropic agent with secondary peripheral vasodilating properties.

Toxicokinetics

Dobutamine is inactive orally, and is invariably administered intravenously. The duration of action is less than 10 minutes. Apparent volume of distribution varies between 0.20 to 0.08 L/kg in patients with low output cardiac failure. Dobutamine is metabolised in the liver and other tissues, and excreted in the urine. Elimination half life is 2.4 ± 0.7 minutes.

Mode of Action

Dobutamine exerts its cardiovascular action through its beta$_1$-adrenergic agonist activity, and also induces alpha$_1$-adrenoceptor-mediated vasoconstriction as well as beta$_2$-adrenoceptor-mediated vasodilation. It has no action on dopamine receptors.

The usual therapeutic regimen is an intravenous infusion dose of 2.5 to 10 mcg/kg/min up to a maximum of 40 mcg/kg/min.

Adverse Effects

- Cardiac arrhythmias, myocardial ischaemia, hypotension, palpitations, headache, dyspnoea, nausea.
- Extravasation can lead to tissue necrosis at the site.

Drug Interactions

- Additive effect with nitroprusside.
- Antagonistic to phentolamine and prazocin.

Toxic (Clinical) Features

1. Hypotension (sometimes hypertension), oliguria, tachyarrhythmias, myocardial ischaemia, tachypnoea, paraesthesias, stuffy nose, mydriasis, and warm and flushed skin. These manifestations usually clear in 2 to 3 hours.
2. In rare cases, the sodium bisulfite component of commercial dobutamine solution can induce allergic-type reactions including anaphylaxis.
3. Local erythema and pruritis are often reported 4 to 12 days subsequent to dobutamine use, at the site of IV administration.
4. Withdrawal of dobutamine therapy sometimes leads to worsening of dyspnoea, hypertension, and renal dysfunction.

Treatment

1. Stop dobutamine administration.
2. Monitor respiration, blood pressure, arterial blood gases, and if possible central venous pressure and pulmonary wedge pressure.
3. Supportive measures.

4. Do not discharge until serial electrocardiograms and cardiac enzymes show no evidence of myocardial damage.
5. Dobutamine withdrawal manifestations can be treated with 25 mg hydralazine before the first reduction in dobutamine infusion, and every 4 hours subsequently (upto a maximum of 150 mg).

PHOSPHODIESTERASE INHIBITORS*

Inamrinone, dipyridamole, enoximone, milrinone, pimobendan, vesnarinone. The important examples are discussed here.

■ Amrinone (Inamrinone)

As of April 2000, the name of amrinone was changed to "inamrinone" to reduce the number of accidental injuries and deaths associated with the cardiac drug names inamrinone and amiodarone.

Inamrinone, a bipyridine derivative is a noncatecholamine cardiotonic agent with positive inotropic effects and vasodilatory properties.

Uses

Treatment of
- Refractory congestive heart failure.
- Pulmonary hypertension.
- Post-operative heart failure.

Toxicokinetics

Inamrinone is usually administered intravenously. Oral inamrinone was discontinued due to reports of a higher incidence of gastrointestinal adverse effects when compared to the intravenous form. Plasma half-life varies from 2.6 to 3.6 hours. Volume of distribution is 1.2 litres/kg. 10 to 40% of the drug is excreted unchanged. Several metabolites have been identified in the urine, and include N-glycolate (8%), N-acetate (5%), and O-glucuronide and N-glucuronide (less than 5% each). Elimination half-life is 3.6 hours in normal subjects; 5.8 hours in patients with congestive heart failure.

Mode of Action

The inotropic action of inamrinone is due to selective inhibition of phosphodiesterase III, with subsequent increase in cardiac cyclic AMP concentration.

Inamrinone does not inhibit the cardiac Na^+-K^+-dependant ATP.

The recommended adult dosage for inamrinone is an initial intravenous loading dose of 0.75 ml/kg over 2 to 3 minutes followed by a continuous infusion of 5 to 10 mcg/kg/min, with the total daily dosage not to exceed 10 ml/kg/day.

Adverse Effects

- Headache, nausea, vomiting, diarrhoea, and abdominal pain occur occasionally.

- Reduced tear secretion and dysosmia have been reported with inamrinone.

- Bright yellow discolouration of nails has been described following therapeutic use.
- Thrombocytopenia can occur in upto 34% of patients taking the drug on a long-term basis. Pancytopenia has been reported following short-term, high-dose IV therapy.
- Intravenous use is also associated with hypotension, ventricular arrhythmias, hepatotoxicity, metabolic acidosis, and GIT disturbances (vomiting, diarrhoea, abdominal pain).
- The commercial preparation of inamrinone contains sodium metabisulfite which can cause allergic reactions in susceptible patients (e.g. asthmatics).

Drug Interactions

- Additive inotropic effects are seen with cardiac glycosides.
- Severe hypotension may occur when disopyramide is administered together with inamrinone.
- Dextrose must not be used when administering inamrinone, since chemical interaction and precipitation can occur.

Toxic (Clinical) Features

The following manifestations have been reported in inamrinone overdose: severe hypotension, ventricular arrhythmias, thrombocytopenia, hepatotoxicity, metabolic acidosis, oliguria, and cardiac arrest.

Treatment

1. Admit patient to cardiac intensive care unit. Monitor vital signs and cardiac parameters continuously.
2. Treat hypotension with IV fluids and pressor agents as required. Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
3. For arrhythmias: Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia). Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Amiodarone and sotalol should be used with caution. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present and PVCs are thought to represent an escape complex.
4. Particular attention must be paid to ventilatory support, oxygen administration, electrolyte studies (especially potassium levels), complete blood count, and hepatic and renal function tests.

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* Other examples such as **caffeine** and **theophylline** have been discussed elsewhere (page no 488).

■ Dipyridamole

While dipyridamole has no role in congestive heart failure, it is being discussed here for the sake of convenience. Dipyridamole is a coronary vasodilator. It is an antithrombotic agent most often used to modify platelet function. It is also used intravenously as a non-nitrate coronary vasodilator for non-invasive stress thallium cardiac imaging.

Uses

- Long-term prevention of coronary insufficiency.
- For coronary dilatation, and to improve collateral circulation following myocardial infarction.
- For inhibition of platelet aggregation.

Toxicokinetics

Dipyridamole is well absorbed orally, and peak plasma concentrations are achieved in 70 to 75 minutes. Oral absorption is from 30 to 70% of the dose ingested. It is extensively protein-bound (99%), and the volume of distribution is approximately 2 L/kg. After undergoing an enterohepatic recirculation, dipyridamole is mainly excreted in the faeces. 86 to 92% of the dose is recovered in the faeces. Elimination half-life is 10 to 16 hours.

Mode of Action

Dipyridamole acts by inhibiting adenosine transport with consequent accumulation in plasma, inhibiting cyclic AMP and phosphodiesterase, and stimulating prostaglandin I_2 synthesis.

Adverse Effects

- Gastrointestinal disturbances, headache, vertigo, facial flushing, and skin rash are common.
- In some cases there may be significant hypotension.
- Intravenous use can cause cardiac arrhythmias and worsening of angina.
- Intravenous dipyridamole can induce severe bronchospasm in asthmatic patients.
- Allergic reactions are rare, but have occurred.

Drug Interactions

- Dipyridamole can be combined with aspirin in the prevention of thromboembolic phenomena.
- It potentiates the effects of oral anticoagulants and anti-arrhythmic agents.
- Heparin given concomitantly can induce bleeding.
- Aminophylline may reverse its vasodilating effect.

Toxic (Clinical) Features

Symptoms and signs of overdose include headache, facial flushing, drowsiness, weakness, fainting, nausea with GI distress, hypotension, and brady- or tachycardia. Fatalities are rare. Angina has been reported as a side effect and may occur following overdose in patients with underlying myocardial ischaemia.

Treatment

Blood pressure should be monitored for at least 3 to 4 hours. Patients with uderlying cardiac disease or a history of asthma may require more intensive monitoring.

1. Activated charcoal may be beneficial.
2. Haemodialysis and haemoperfusion are ineffective, since dipyridamole is highly protein-bound.
3. Supportive measures:
   a. Atropine for bradycardia.
   b. Anginal symptoms usually respond to sublingual nitroglycerine therapy. If this is ineffective, IV theophylline can be tried.
   c. Severe chest pain following dipyridamole administration responds to aminophylline and anti-anginal medication. Thrombolysis may be required.
   d. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
   e. Dipyridamole produces vasodilation via inhibition of adenosine reuptake, leading to accumulation in plasma and tissues. Adenosine-mediated adverse effects, such as bronchoconstriction and angina, can be reversed with intravenous aminophylline administration.

■ Anti-anginal Drugs

Drugs used in the treatment of myocardial ischaemia manifesting as angina pectoris include the following:

1. Organic nitrates
2. Calcium channel blockers
3. Beta-adrenergic receptor antagonists.

The toxicities of calcium channel blockers and beta-adrenergic receptor antagonists have been discussed elsewhere (*refer Index*).

ORGANIC NITRATES

■ Examples

Nitroglycerine, amyl nitrite, isosorbide dinitrate, isosorbide-5-mononitrate, erythrityl tetranitrate, pentaerythritol tetranitrate.

Physical Appearance

Organic nitrates are polyol esters of nitric acid.* Amyl nitrite is a highly volatile liquid, while low molecular mass nitrates such as nitroglycerine** are moderately volatile, oily liquids, and high molecular mass nitrate esters such as erythrityl tetranitrate are solids.

All organic nitrates are capable of denitration (i.e. they release nitric oxide), and are collectively termed nitrovasodilators.

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* On the other hand, organic nitrites are esters of nitrous acid, e.g. amyl nitrite which is generally classed as a nitrate only for the sake of convenience
** In the pure form (without an inert carrier such as lactose), nitroglycerine is highly explosive.

Uses

Treatment of
- Angina pectoris (and some cases of myocardial infarction).
- Prinzmetal's angina.
- Congestive heart failure.

Toxicokinetics

- Glyceryl trinitrate can be administered orally, sublingually, transdermally (ointment or patch), or as IV infusion. Erythrityl tetranitrate is usually administered only sublingually, while pentaerythritol tetranitrate is given orally. Isosorbide-5-mononitrate is also given orally, while isosorbide dinitrate can be administered orally and sublingually.
- Metabolism is effected by the hepatic enzyme glutathione-organic nitrate reductase which converts the lipid soluble nitrate esters into more water soluble denitrated metabolites and inorganic nitrite.
- Peak plasma concentrations of glyceryl trinitrate and isosorbide dinitrate (sublingually) are achieved in 4 minutes and 6 minutes respectively. Plasma half-life is 1 to 3 minutes for the former and 45 minutes for the latter. Isosorbide-5-mononitrate (which is actually a metabolite of isosorbide dinitrate) has a half-life of 2 to 5 hours.
- Sublingual organic nitrates as well as those which are administered orally or transdermally, exhibit the unfortunate phenomenon of tolerance which attenuates their pharmacologic effects on repeated administration.

Mode of Action

Organic nitrates exhibit the following actions:
- Relaxation of smooth muscle (especially of blood vessels).
- Reduction of pre-load (due to reduced venous return).
- Relief of coronary vasospasm.
- Reduction of after-load (due to dilatation of arterioles).

Adverse Effects

- Nitrite-induced peripheral vasodilatation may occur after nitrates have been converted to nitrites in vivo. Headache is common. Vertigo and weakness may occur due to postural hypotension, and can be severe in concomitant alcohol ingestion.
- Other effects include tachycardia, decreased peripheral vascular resistance, and cardiovascular collapse. Bradycardia occurs less often.
- Drug rash can occur especially in the case of pentaerythritol tetranitrate.

Drug Interactions

Combined use with calcium channel blockers, antihypertensives, phenothiazines, and tricyclics can cause severe orthostatic hypotension.

Patients on organic nitrate therapy must not consume alcohol (*vide supra*).

Toxic (Clinical) Features

1. Nausea and vomiting are the first signs to be noted following ingestion.
2. Methaemoglobinaemia is induced in overdose which can be life-threatening. Once nitrates have been converted to nitrites, cyanosis and dyspnoea may develop due to methaemoglobin formation. Suspect methaemoglobinaemia in all cyanotic patients, who do not improve with supplemental oxygen.
3. There is also headache, vertigo, flushing and hypotension.
4. Arrhythmias including atrial fibrillation, frequent ventricular premature beats, and bigeminy may occur with severe poisoning.

Diagnosis

1. *Cooking test*: Clotted blood sample is placed in a boiling water bath. After "cooking" and cooling, the sample turns salmon pink. Normal blood sample will be chocolate brown.
2. Commercial urine reagent strips for detection of urinary tract infections will turn intensely pink in organic nitrate poisoning.

Treatment

1. Ensure airway. Administer 100% oxygen. Assisted ventilation may be required.
2. Determine methaemoglobin concentration and measure arterial blood gases in all cyanotic patients or patients with dyspnoea or other signs of respiratory distress. Normal methaemoglobin level is less than 3%. A G-6-PD assay is indicated in patients who develop methaemoglobinaemia and/or haemolysis. Blood with methaemoglobinaemia that has been exposed to oxygen has a characteristic chocolate brown colour. Initial bedside determination can be made by placing a drop of blood on filter paper with a control drop of blood nearby. If there is greater than 15% methaemoglobinaemia, the affected blood will have a chocolate brown colour in comparison with the control blood.
3. Obtain an ECG and institute continuous cardiac monitoring if the patient has ischaemic symptoms or significant methaemoglobin concentration.
4. Treat hypotension with Trendelenburg position, IV fluids, pressors (dopamine).
5. *Decontamination* : activated charcoal, stomach wash, etc., in oral ingestions.
6. Nitrate salts are irritating to mucous membranes; dilution with milk or water is appropriate following ingestion. Treatment should focus on hypotension and methaemoglobinaemia. Give supportive care, appropriate airway management, and administration of 100% oxygen. Cardiac and haemodynamic parameters should be monitored continuously.
7. **Antidote**: Methylene blue is the antidote of choice in severe poisoning (methaemoglobin level more than 30%).
   a. Dose*: 1 to 2 mg/kg (25 to 50 mg/m^2) of 1% solution (10 mg/ml), IV, over 5 minutes. This can be repeated once after 1 hour if symptoms do not subside.

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* Do not exceed recommended dose, since excessive methylene blue administration will induce paradoxical methaemoglobin formation.

b. Adverse effects: dyspnoea, chest pain, anxiety, tremor, dysuria, increased frequency of micturition, bluish skin discolouration. Overdose can cause haemolysis. Patients with G6PD deficiency are especially susceptible.

c. Failure of methylene blue therapy suggests one of the following: inadequate dose of methylene blue, inadequate decontamination, NADPH dependant methaemoglobin reductase deficiency, haemoglobin M, sulfhaemoglobinaemia, or G6PD deficiency.

8. Blood transfusion may have to be considered in the event of severe anaemia produced by haemolysis. Hyperbaric oxygen (HBO) may be used as a supportive measure while preparations for exchange transfusion are being made. HBO therapy can provide sufficient oxygen to maintain life as dissolved oxygen in blood, and obviates temporarily the need for functional haemoglobin.

Forensic Issues

■ Adverse reactions to organic nitrates are not uncommon. Toxicity is usually the result of therapeutic errors in dosage. Occasionally accidental poisoning occurs (especially in children).

■ It is important to remember that nitrates not used in cardiovascular therapeutics can cause poisoning in other situations. For example, ammonium nitrate is widely used in disposable cold packs, and cases have been recorded of deliberate self-ingestion resulting in gastritis, hypotension, and methaemoglobinaemia. Anion gap was reduced in some patients.

■ Sodium nitrate is said to be a frequent cause of nitrate poisoning in China, where 1 to 2 grams are often ingested at each meal.

■ Lipoprotein Lowering Drugs

■ HMG CoA Reductase Inhibitors: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.

■ Bile Acid-binding Resins: cholestyramine, colestipol hydrochloride.

■ Nicotinic Acid (Niacin).

■ Probucol.

■ Fibric Acid Derivatives: clofibrate, gemfibrozil, bezafibrate.

HMG COA REDUCTASE INHIBITORS

These drugs block synthesis of cholesterol in the liver by competitively inhibiting HMG CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase activity. They are capable of lowering LDL cholesterol levels by 25 to 45%. All of them are absorbed well orally, are generally extensively protein-bound, and excreted mainly in the bile.

Mode of Action

■ The active beta-hydroxy acid form of the HMG CoA reductase inhibitors are competitive inhibitors of the enzyme (HMG CoA reductase). Atorvastatin, cerivastatin,

fluvastatin and pravastatin are active drugs, whereas lovastatin and simvastatin are prodrugs. The liver is the primary site of action of these drugs.

■ Inhibition of HMG CoA reductase prevents conversion of HMG CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. However, at therapeutic doses, the enzyme is not completely inhibited, thereby allowing biologically necessary amounts of mevalonate to be available.

■ When cholesterol synthesis is inhibited in the liver, an upregulation of LDL receptors and an increase in catabolism of LDL cholesterol occurs. Some reduction in LDL production as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL, may also result. Thus, HMG CoA reductase inhibitors reduce LDL cholesterol, VLDL, cholesterol, and to a lesser extent, plasma triglyceride concentrations. They slightly increase high-density lipoprotein (HDL) concentrations.

Adverse and Toxic (Clinical) Features

1. Myalgia, hepatic function impairment, headache, peripheral neuropathy, insomnia, behavioural changes, extrapyramidal symptoms, hyperkalaemia, flatulence, dyspepsia, diarrhoea, rash, pulmonary fibrosis, acute renal failure, and rhabdomyolysis.

2. Chronic use may cause cataract, especially with lovastatin. The manufacturer recommends slit-lamp examination as a precaution, before or shortly after starting treatment with lovastatin, and annually thereafter.

3. Severe proximal muscle weakness in upper and lower extremities has been described in patients given HMG CoA reductase inhibitor therapy. Creatine phosphokinase was elevated in all cases. Histologic examinations of the skeletal muscle showed myopathic changes, such as atrophy and muscle fibre necrosis.

4. In August, 2001, Bayer Pharmaceutical Division announced a voluntary withdrawal of cerivastatin (Baycol®) from the market due to several reports of fatal rhabdomyolysis following cerivastatin therapy. Cholestin, formerly promoted as a dietary supplement to lower cholesterol levels, has been reclassified by the FDA as an unapproved drug based on the fact that cholestin contains lovastatin.

5. Elevated liver enzyme levels, progressing to clinical hepatitis, have been reported following lovastatin therapy. Minor and sporadic elevations of liver enzymes developed during clinical trials with atorvastatin.

6. Pancreatitis has been reported with gemfibrozil-lovastatin combined therapy.

7. Dermatitis, photosensitivity, and dermatomyositis may occur following therapy with HMG CoA reductase inhibitors.

8. Case reports suggest that these agents can cause thrombocytopenia and haemolytic anaemia following short-term therapeutic dosing.

9. Poisoning with HMG CoA reductase inhibitors is uncommon. Ingestion of up to 6 grams of lovastatin has been reported without specific effects or sequelae. Severe toxicity is not expected, unless a coingestant is present.

Drug Interactions

- Decreased plasma levels may occur if antacids or colestipol are given simultaneously.
- Decreased activity is associated with concomitant use of propranolol.
- Statins may enhance the anticoagulant effect of warfarin.
- Pectin and oat bran have been reported to reduce the absorption of lovastatin in the body, thereby decreasing lovastatin's effect on low-density lipoprotein (LDL) cholesterol.
- Myopathy and rhabdomyolysis are rare side effects of HMG CoA reductase inhibitor monotherapy and appear to be dose-related. The risk of development of rhabdomyolysis is considerably increased with concurrent administration of all CYP3A inhibitors, such as cyclosporine with lovastatin or simvastatin, or cerivastatin with gemfibrozil.
- Alcohol use should be curbed when these drugs are being consumed regularly.
- These drugs are contraindicated in pregnancy since congenital anomalies may occur.

Treatment

1. Treatment of toxicity is symptomatic and supportive. Significant toxicity has not been reported after acute overdose of these agents.
2. Pre-hospital decontamination is generally not necessary unless coingestants are involved.
3. Monitor serum creatinine, BUN, creatine phosphokinase, and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis in symptomatic patients. For rhabdomyolysis: early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency; diuretics such as mannitol or furosemide may be needed to maintain urine output; urinary alkalinisation is not routinely recommended.
4. Haemodialysis is not expected to significantly enhance the clearance of these drugs due to extensive protein binding and large volumes of distribution.

BILE ACID BINDING RESINS

These drugs are the safest agents available for lowering plasma lipoproteins. Both cholestyramine and colestipol hydrochloride are anion-exchange resins and are not absorbed for the most part, acting by promoting bile acid excretion. Inhibition of the return of bile acids to the liver results in an increase in conversion of cholesterol to bile acids. Triglyceride synthesis is enhanced which promotes very low density lipoprotein (VLDL) removal, contributing to the low density lipoprotein (LDL), lowering effect.

Colestipol is indicated as adjunctive therapy for the reduction of elevated serum total and LDL-C in patients with primary hypercholesterolaemia (elevated LDL-C) who do not respond adequately to diet.

Adverse and Toxic (Clinical) Features

1. Anorexia, bloating, abdominal discomfort, vomiting, flatulence, perianal pruritis, and constipation. Rarely there may be faecal impaction.
2. Transient and modest elevations of aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) and alkaline phosphatase have been observed with colestipol.
3. Mild increases in serum calcium and decreases in serum phosphorus and 25-hydroxy-vitamin D levels have been reported in children on long-term therapy.
4. Headache, chest pain, angina, tachycardia, and shortness of breath have been reported infrequently during therapeutic use.
5. Since colestipol hydrochloride is a chloride form of an anion exchange resin, there is a possibility that prolonged use may lead to the development of hyperchloraemic acidosis.
6. Since colestipol hydrochloride is an anion exchange resin, it may have a strong affinity for anions other than the bile acids. It is recommended by the manufacturer that patients should take other drugs one hour before or 4 hours after colestipol to prevent absorption problems of concomitant therapy. Colestipol can interfere with normal fat absorption and prevent the absorption of some fat soluble vitamins such as vitamin K.

Treatment

1. These agents are largely not absorbed in the gastrointestinal tract. Attempts at gastrointestinal decontamination are generally not warranted.
2. In minimal to moderate ingestions, increased fluid intake, fibre, and a stool softener should be instituted.
3. If obstruction is ruled out, a polyethylene glycol electrolyte oral solution (PEG-ES) may be used to expedite the evacuation of these resins (2 litres initially followed by 1.5 to 2 litres per hour).

PROBUCOL

Probucol is rarely used as a hypolipidaemic agent because of its unreliability in lowering LDL levels, and also because of its tendency to persistently lower HDL levels. However it is remarkably efficacious in lowering cholesterol levels in patients with homozygous familial hypercholesterolaemia.

Adverse effects include flatulence, nausea, diarrhoea, headache, vertigo. Diarrhoea can be minimised or prevented by combining with cholestyramine.

FIBRIC ACID DERIVATIVES

Fibric acid derivatives, including clofibrate, fenofibrate, bezafibrate, ciprofibrate, and simfibrate, are antilipidaemic agents which decrease serum lipids by reducing the very-low-density lipoprotein fraction (Sf 20 to 400) rich in triglycerides. These

drugs reduce triglycerides (TG) and VLDL, while increasing HDL levels. They act by increasing the activity of lipoprotein lipase and other enzymes. Clofibrate also decreases serum cholesterol levels, primarily the low-density lipoprotein fraction (Sf 0 to 20).

Uses

- Clofibrate is indicated as adjunctive therapy to diet for the treatment of type III hyperlipidaemia. It may also be helpful in some patients with severe hypertriglyceridaemia due to Type IIb, Type IV, and Type V hyperlipidaemias.
- Fenofibrate is indicated as adjunctive therapy to diet for the treatment of Type IV and V hyperlipidaemia in patients who are at risk for pancreatitis.
- Ciprofibrate is being investigated as a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate.

Adverse and Toxic (Clinical) Features

1. Myalgia, GI upset, rash, alopecia (rare). Muscular syndrome may be dose-dependant; the most frequent effect is myalgia, with the most commonly affected muscles being those of the lower extremities. Arthralgia and flu-like symptoms have also been reported.
2. Nausea, vomiting, constipation, dyspepsia, diarrhoea, and flatulence occur transiently in approximately 10% of patients. Epigastric pain has been reported as a frequent side effect, and cholelithiasis is increased.
3. Impotence and decreased libido have been reported.
4. Clofibrate therapy has been associated with multiple cardiovascular side effects (peripheral vascular disease, pulmonary embolism, thrombophlebitis, angina pectoris, cardiac arrhythmias, cardiomegaly) of varying severity, fever, hepatotoxicity, myopathies, and gastrointestinal irritation. Fatigue, weakness, drowsiness, dizziness, and headache have also been reported. Renal effects of clofibrate have included dysuria, haematuria, proteinuria and oliguria. Hepatomegaly, jaundice, hepatitis, and transient increases in serum transaminase levels have occurred.
5. Increases of serum transaminase levels greater than 3 times the upper limit of normal were reported following fenofibrate therapy.
6. Concomitant administration of clofibrate with anticoagulants may cause hypoprothrombinaemia. When anticoagulants are given concurrently with clofibrate, the dosage of the anticoagulant should usually be reduced by one-half (depending on the individual case) to maintain the prothrombin time at the desired level in order to prevent bleeding complications.

7. Co-administration of clofibrate with phenytoin may cause an increase in phenytoin serum levels due to displacement of phenytoin from its protein binding site.
8. An increased hypoglycaemic effect has been reported following concurrent administration of clofibrate and tolbutamide.

Treatment

1. Patients should be observed for potential CNS depression, musculoskeletal, cardiovascular, and hepatic or renal damage, as these are the primary manifestations of toxicity due to therapeutic use.
2. Periodic examinations for muscle tenderness and dysfunction are mandatory to detect the muscular syndrome, and determinations of CPK and AST should be performed during therapy.
3. Parameters that may increase—serum aldolase, BSP retention, thymol turbidity, glutamic-oxaloacetic transaminase.
4. Parameters that may decrease—fibrinogen, gamma-glutamyl transpeptidase, serum alkaline phosphatase.
5. Therapeutic plasma levels of p-chlorophenoxyisobutyric acid (CPIB) have been reported to be 80 to 150 mcg/ml. The average maximum plasma level after a 500 mg oral dose was 44.0 mcg/ml.
6. Gastric decontamination is probably usually not necessary and should be considered only if several times the daily therapeutic dose was ingested.

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Anticoagulants and Related Drugs

The following drugs will be discussed in this chapter: anticoagulants, antifibrinolytics, thrombolytics and antiplatelet drugs.

ANTICOAGULANTS

1. Heparin and Low-Molecular-Weight Heparins: dalteparin, enoxaparin, nadroparin, pamaparin, parnaparin, reviparin, tedelparin, tinzaparin.
2. Oral Anticoagulants:
   a. Coumarins—warfarin (coumadin), panwarfarin, warficide, coumachlor, coumafuryl, coumatetralyl,* fumasol, prolin, ethyl biscoumacetate (tromexan), phenprocoumon, dicoumarol, acenocoumarol, diphenacoum,* brodifacoum,* bromadiolone.*
   b. Indandiones—diphacinone, anisindione, phenindione, pivalyn, diphenadione,* chlorophacinone,* pindone,* valone.

HEPARINS AND LOW MOLECULAR WEIGHT HEPARINS

Heparin was discovered by McLean, a medical student, in 1916, and isolated by Howell (who owned the laboratory in which McLean worked), in 1922. The name heparin derives from the fact that it is abundantly present in the liver. Heparin is an anionic sulfated glycosaminoglycan mucopolysaccharide with anticoagulant activity and normally found in mast cells. It is a heterogenous mixture of proteins of various sizes. There is no exact molecular weight for standard heparin; molecular weights have ranged from 4000 to 40,000 daltons.

Low Molecular Weight Heparins (LMWH) are fragments of heparin with anticoagulant activity, and are isolated from standard heparin by gel filtration chromatography or differential precipitation with ethanol.

Uses

- Heparin is used in the prophylaxis and treatment of deep vein thrombosis, embolism, and post-surgical arterial embolism.

- Other uses include diagnosis and treatment of disseminated intravascular coagulation, and prevention of coagulation through an extracorporeal circuit, in dialysis, in blood transfusions, and in blood drawn for laboratory use, and lipid reduction in idiopathic hyperlipaemia.

Toxicokinetics

- Heparin and LMW heparins are not absorbed through the GI tract and must always be administered parenterally (usually subcutaneously or intravenously). Intramuscular heparin often causes large haematomas at the site of injection. Low doses can be administered subcutaneously or into a fat depot; larger doses can be administered by the continuous or intermittent intravenous infusion.

- Absorption of heparin from the gastrointestinal tract does occur in experimental animals when it is complexed with amino acids, given with adjuvants such as sodium ethylenediamine-tetra-acetate, or encapsulated in liposomes. Onset of action is immediate (*IV*), or delayed by 1 to 2 hours (*SC*).

- Low molecular weight heparins have a bioavailability of more than 85% compared to normal heparin, which has a bioavailability of 15 to 20%, when given subcutaneously. Heparin is primarily distributed into the blood and therapeutic plasma levels range from 0.2 to 0.6 U/ml. Half-life of heparin varies from 1 to 5 hours, and it is cleared and degraded mainly by the reticuloendothelial system. It is cleaved by heparinase into oligosaccharides in the liver and spleen, after undergoing N and O-desulfation by desulfatase in the reticuloendothelial system. A small amount of undegraded heparin appears in the urine.

- Low molecular weight (LMW) heparins have longer half-lives than heparin. They are metabolized more slowly than normal heparin, and are partially metabolized by desulfation and depolymerization.

Mode of Action

- Heparin inhibits thrombosis by accelerating the binding of the protease inhibitor antithrombin III to thrombin and other

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* Long-acting preparations

serine proteases involved in coagulation. Thus factors IX to XII, kallikrein, and thrombin are inhibited.

- Heparin also inhibits the activation of factor XIII (fibrin stabilising factor) and prevents the formation of a stable fibrin clot.
- Heparin also affects plasminogen activator inhibitor, protein C inhibitor, and other components of coagulation.

Adverse Effects

- The primary adverse effect associated with heparin therapy or overdosage is over-anticoagulation and haemorrhage. Common sites of bleeding may include the GI tract, skin, urinary tract, and the pulmonary and cardiovascular systems. The risk of haemorrhage increases with the duration of heparin therapy, but may be reduced by careful control of dosage. Factors associated with an increased risk of minor bleeding while receiving heparin include aspirin use, underlying morbid condition, alcohol consumption, renal failure and female sex.
- Heparin-induced thrombosis-thrombocytopenia syndrome (HITTS)—may manifest as *thrombotic phenomena*: deep venous thrombosis, pulmonary emboli, myocardial infarction, cerebral thrombosis, digital vasculitis, adrenal infarction, renal artery embolism, priapism, skin necrosis, aortic and limb arterial thrombosis, or as *haemorrhagic phenomena*: cerebral haemorrhage, GI bleeding, adrenal haemorrhage, skin bruising, epistaxis, haematuria, intramuscular haematoma, etc. HITTS carries a 30% death rate.
- Mild thrombocytopenia (100,000 to 150,000/mcl) may be noted in up to 30% of patients on heparin therapy and is generally transient. Clinically significant thrombocytopenia occurs in less than 10% of patients on heparin therapy, and this too is generally transient.
- Vasospastic reactions may develop 6 to 10 days after initiation of heparin therapy. Vasospasm may present as painful, ischaemic, cyanotic extremities, or with tachypnoea, headache, chest pain, arthralgia, or hypertension depending on the site of arterial spasm. The duration of vasospasm is typically 4 to 6 hours
- Delayed, transient alopecia may occur.
- Chemosis and subconjunctival injection as well as hyphaema have been reported with intravenous heparin.
- Epistaxis has been reported with therapeutic doses.
- Occasionally, cardiovascular collapse may occur with significant haemorrhage or cardiac tamponade.
- Hypersensitivity reactions are occasionally reported: urticaria, conjunctivitis, rhinitis, asthma, and anaphylaxis.
- Hallucinations and distorted perceptions have been reported among humans given heparin sodium by subcutaneous route.
- Minor reversible elevations in serum transaminases have been reported in up to 95% of patients receiving heparin.
- Priapism has been noted after discontinuation of heparin therapy.
- Heparin use during pregnancy may be associated with increased susceptibility to premature delivery, foetal loss, neonatal death, and maternal death.
- Skin necrosis has been reported following heparin and

low molecular-weight heparin (LMWH) therapy. Skin necrosis and tender erythematous nodules (panniculitis) at the sites of subcutaneous heparin injections have been ascribed to the complications of heparin-induced thrombocytopenia. Given its association with thrombosis and increased mortality, the onset of skin reactions warrants prompt discontinuation of heparin and close monitoring for thrombocytopenia and platelet-aggregating antibodies.

- Hyperkalaemia and secondary hypoaldosteronism have been reported following either unfractionated heparin therapy or low-molecular-weight heparin therapy, especially in patients with diabetes mellitus or renal insufficiency. Osteoporosis and spontaneous fractures may be noted with long-term heparin therapy with heparin (15,000 units daily for over 6 months).

Drug Interactions

- Potentiation of oral anticoagulants, methotrexate, and oral hypoglycaemics.
- Salicylates and dipyridamole enhance activity of heparin.
- Bleeding tendency enhanced with NSAIDs and aspirin.
- Incompatible with aminoglycoside antibiotics.
- The combination of heparin and dihydroergotamine carries a risk of vasospasm and ischaemia.

Toxic (Clinical) Features

1. Overdose of heparin results in rapid prolongation of coagulation time and active bleeding.
2. Hypotension and respiratory distress develop.
3. Chronic heparin therapy is associated with hyperkalaemia due to aldosterone suppression.
4. Abrupt withdrawal of heparin can put the patient at increased risk for transient ischaemic attack or cerebral stroke.

Treatment

1. Admit patient to intensive care and monitor blood clotting parameters. Orally ingested heparin is not absorbed from the gastrointestinal tract and will not result in toxicity.
2. Evaluate airway, breathing, and circulatory status.
3. Undertake complete blood count, platelet count, coagulation profile (bleeding time, clotting time), and activated partial thromboplastin time. The most reproducible and frequently used monitoring tool for assessment of anticoagulation with heparin is the activated partial thromboplastin time (aPTT). Thromboembolism is prevented by "therapeutic" values of 1.5 to 2.5 times baseline. There is a large interpatient variability in anticoagulant response to heparin as evaluated by the aPTT. Similar doses of heparin may lead to 12-fold variations in aPTT. The baseline aPTT accounts for most of the variability and should be determined prior to initiating therapy. Blood samples for aPTT should be collected as close to the steady state of heparin infusion as possible (i.e. at least 6 and preferably 8 hours after initiating or changing infusion rates).
4. Other coagulation tests (PT, TT, and aCT) may be used for monitoring heparin effects. Thrombin time (TT) measures

Factor IIa conversion of fibrinogen to fibrin. Normal adult values range from 13 to 20 seconds. Therapeutic heparin therapy results in a thrombin time of 50 to 100 seconds at a 1:4 dilution. The activated coagulation time (aCT) is less sensitive to effects of low heparin concentrations, but is a global test that can be performed rapidly at the bedside. Normal adult values are 80 to 130 seconds, with therapeutic heparinisation at 150 to 190 seconds.

5. Urinalysis should be obtained for detection of haematuria. Examine sputum and stool for the presence of blood.

6. Because of the short duration of action of aqueous heparin after therapeutic doses, treatment of extremely prolonged clotting time or minor bleeding during therapy is usually managed simply by decreasing or stopping the heparin dose or frequency of injections. In the event of significant hemorrhage, a heparin antagonist should be used to reverse the effects of heparin on coagulation (*vide infra*). Replace blood loss with whole blood or plasma. Exchange transfusion has been successful in neonates.

7. Antidote: **Protamine sulfate** is used in severe overdose involving heparin or LMW heparins. Protamine is a low-molecular-weight protein found in the sperm and testis of salmon, and forms ionic bonds with heparin rendering it devoid of anticoagulant activity. Protamine reacts with heparin to form a stable salt, resulting in neutralisation of heparin's anticoagulant activity (within 30 to 60 seconds). Each milligram of protamine (given IV) inactivates 100 U of heparin.

   a. Dose: 2 mg/kg (maximum 50 mg), slow IV over 10 minutes. Alternatively, protamine can be given in a ratio of 0.75 to 2.1 : 1 times the total operative heparin dose. Since the half-life of heparin is very short (about 1½ hours), protamine administration should take into account the time elapsed since overdose. Paradoxically, protamine sulfate has weak anticoagulant activity when given in the absence of heparin. Therefore, the maximum recommended dose is 100 mg over a short period. After an initial dose, further protamine therapy should be guided by monitoring aPTT or aCT every 5 to 15 minutes. Protamine is associated with a low (0.2%), but clinically significant, incidence of complications which have a high mortality (30%). It should therefore only be reserved for patients with evidence of severe haemorrhage.

   b. Adverse effects:
      – Hypotension, bradycardia, dyspnoea, pulmonary oedema, vomiting, lassitude.
      – Protamine interacts with platelets, fibrinogen, and other plasma proteins and may cause an anticoagulant effect of its own.
      – There is a significant risk of anaphylaxis which is enhanced in patients with a history of allergy to fish. Diabetic patients receiving protamine-containing insulin (NPH) are also at increased risk.
      – Sometimes neutralisation of blood heparin with protamine may be followed by a resurgence of anticoagulant activity ("heparin rebound").

8. Treatment of HITTS:
   a. Withdraw heparin.
   b. Substitute with LMW heparins. However, current opinion is that low-molecular weight heparins are not recommended to be used as alternative anticoagulant therapy in patients with heparin-induced thrombocytopenia. Immunological cross-reactivity may occur resulting in a recurrence of the thrombocytopenia.
   c. Warfarin as sole therapy may be risky, because in some patients, a thrombus may grow or embolise before warfarin becomes effective. This is not a problem with ancrod or other alternative thromboembolic therapy. If oral anticoagulation is used, it should initially be given in conjunction with danaparoid or a direct thrombin inhibitor. Warfarin has also reportedly been associated with the development of skin necrosis and venous limb gangrene in HIT patients who received warfarin as sole alternative anticoagulant therapy.
   d. Dextran therapy.
   e. Administer antiplatelet drugs (aspirin, dipyridamole). When re-exposure to heparin is essential and platelet-aggregating antibodies are still present, aspirin, dipyridamole, sulfinpyrazone, and iloprost have been used with variable success to prevent recurrence of thrombocytopenia and thrombosis. Because the concurrent use of heparin and aspirin carries a risk for hemorrhagic complications, shorter-acting nonsteroidal anti-inflammatory agents have been recommended, such as ibuprofen, instead of aspirin.
   f. Incidence of venous thrombosis can be minimised with IV streptokinase.
   g. Heparin-associated thrombocytopenia has been treated successfully with IV immunoglobulin (0.4 gm/kg), followed by platelet transfusion.
   h. Lepirudin (rDNA) is indicated specifically for anticoagulation in patients with heparin-induced thrombocytopenia and associated thromboembolic disease, in order to prevent further thromboembolic complications. It is a synthetic recombinant hirudin derived from yeast cells. Lepirudin should be administered as a slow (15 to 20 seconds) intravenous bolus dose of 0.4 mg/kg body weight (up to 110 kg), followed by 0.15 mg/kg body weight (up to 110 kg) as a continuous intravenous infusion for 2 to 10 days or longer as needed. The infusion rate should be adjusted according to the aPTT ratio. The target range for the aPTT ratio during treatment should be 1.5 to 2.5.
   i. Recently, argatroban, a synthetic direct thrombin inhibitor derived from L-arginine has been approved as an alternative anticoagulant for the prevention and treatment of thromboembolism in patients with heparin-induced thrombocytopenia. Elimination is primarily by the liver, making its use preferable over lepirudin in patients with renal insufficiency. The recommended initial dose is 2 mcg/kg/min administered as a continuous infusion. Dose can be adjusted as clinically indicated, not exceeding 10 mcg/kg/min, until the

steady-state aPTT is 1.5 to 3 times the initial baseline value (not to exceed an aPTT of 100 seconds).

■ Oral Anticoagulants

The commonest agent involved in overdose (or rodenticide-related poisoning) is warfarin (coumafene). Brodifacoum, difenacoum, and bromadiolone are 4-hydroxycoumarin derivatives with a 4-bromo (1-1 biphenyl) side chain. Coumatetralyl is a 4-hydroxy coumarin derivative rodenticide which most likely produces a long acting anticoagulant effect. It differs from brodifacoum in having a 2H-1-benzopyran-2-one group in place of the 4-bromo (1-1 biphenyl) group found in brodifacoum. Chlorophacinone, diphacinone and pindone are indandione anticoagulants with a long duration of action. All these agents produce a more potent and persistent anticoagulant effect than warfarin or other coumarin compounds.

Mode of Action

- All oral anticoagulants act by inhibiting vitamin K (which is a cofactor in the post-ribosomal synthesis of clotting factors II, VII, IX, and X), by interfering with the activity of vitamin K 2,3-epoxide reductase and vitamin K quinone reductase.
- Platelet count, fibrinogen level, and the concentrations of other clotting factors remain unaffected. Fibrin split products may be elevated.
- In overdose with long acting anticoagulants, PT prolongation and clinical bleeding have persisted for 45 days to 8 months.

Toxicokinetics

- Following oral administration, warfarin is bioavailable to the extent of 100%, peaking in the plasma in about 1 hour, with a volume of distribution of 0.126 L/kg and protein-binding of 98 to 99%.
- It is metabolised by oxidation to 6-hydroxywarfarin and 7-hydroxywarfarin (inactive), and by reduction to diastereoisomeric alcohols.
- Elimination half-life is about 40 hours. Duration of action may extend upto 5 days.

Adverse Effects

- Haemorrhage, drop in haematocrit, vomiting, diarrhoea, hepatic dysfunction, jaundice, pancreatitis, and cutaneous reactions—skin eruptions (papular, vesicular, urticarial, or purpuric), ecchymosis, purpura, *purple toe syndrome* (**Fig. 24.1**), and skin necrosis.
  - ❖ Purple toe syndrome is due to small atheroemboli which are no longer adherent to their plaques by clot.
  - ❖ Patients with protein C, protein S, and antithrombin III deficiencies are at increased risk for skin necrosis. The common sites for necrosis include breasts, thighs, and buttocks.
- The gastrointestinal tract is the site of bleeding in most of the patients. Upper airway bleeding may result in pain, dysphonia, dysphagia, dyspnoea and inability to clear secretions. Intracranial haemorrhage and haematomyelia may occur following warfarin therapy.

Fig 24.1: Purple toe syndrome

- Haematomyelia, an uncommon occurrence, has been reported following warfarin therapy. Symptoms include paresis, back or neck pain, and urinary incontinence. A CT scan or magnetic resonance imaging (MRI) usually confirms the diagnosis.
- Hypotension occurs as a result of hemorrhage due to warfarin therapy, particularly in patients who are over anticoagulated.
- Alopecia is reported to occur after both acute and chronic use. The response is directly related to the highest dose given and not to the duration of treatment. Hair is shed diffusely two or three months after an adequate dose of the drug.
- Warfarin or other coumarins, if administered during pregnancy (especially the first trimester) can cause a malformation syndrome—*warfarin embryopathy*.
  - ❖ Craniofacial, musculoskeletal, skin, eye, gastrointestinal, and cardiovascular developmental abnormalities have been observed in the offspring of women administered warfarin during pregnancy (**Fig 24.2**). It causes characteristic skeletal anomalies when given in the first trimester, and central nervous system defects when given later in pregnancy.
  - ❖ When warfarin is given during the first trimester, nasal hypoplasia, respiratory deficiency secondary to nasal obstruction, dextrocardia, abdominal situs inversus, retardation, calcified stippling of secondary epiphyses, reduced birth weight, rhizomelia (short proximal limbs), scoliosis, and short phalanges have been reported.
  - ❖ In addition to teratogenicity due to first trimester exposure, second and third trimester exposure has been associated with microcephaly, retardation, and optic atrophy. A variety of ophthalmic disorders have been reported, including optic atrophy, large eyes, microphthalmos, and opacified lenses.

Fig 24.2: Foetal warfarin syndrome

❖ Heparin does not cross the placental barrier and therefore can be given during pregnancy.

Drug Interactions

Table 24.1 represents a summary of important drug interactions involving coumarins.

Toxic (Clinical) Features

1. Overdose with coumarins leads to bleeding in multiple organ sites that can prove life-threatening. In massive overdose, these agents have produced rapid and persistent hypoprothrombinaemia and associated bleeding diathesis. **Table 24.2** lists some of the laboratory (and other investigative) findings.
2. Warfarin may lead to toxic effects by ingestion, inhalation, and intravenous administration. It is moderately toxic by dermal, subcutaneous, and intraperitoneal routes.
3. The primary effect of warfarin overdose is prolongation of prothrombin time, and subsequent risk of haemorrhage. The onset of prolonged PT correlates with the half-life of factor VII, usually appears within 24 hours of ingestion, and peaks between 36 to 72 hours. Clinical manifestations begin a few days or weeks after ingestion, and include epistaxis, gingival bleeding, pallor, haematuria, haematochezia, melaena, and haematomas around joints and on buttocks. Other symptoms include back pain, bleeding lips, mucous membrane haemorrhage, abdominal pain, vomiting, and petechial rash. Later, paralysis due to cerebral haemorrhage, and finally haemorrhagic shock and death may occur.
4. Long-acting anticoagulants are about 100 times more potent than warfarin on a mole for mole basis. In addition, they have a much longer duration of action which can sometimes last for weeks or months. While the onset of prolonged prothrombin times occurs generally within 48 hours, the first clinical signs of bleeding may be delayed until one to four weeks after ingestion. Common manifestations in such cases include purpura, GI bleeding, haematemesis, haemoptysis, epistaxis, haematuria, melaena, menorrhagia, and CNS bleeds. Multiple ecchymoses and haematomas may be evident on physical examination. Chest pain and tachycardia may develop secondary to blood loss.

Treatment

1. *Investigations:*
   a. Plasma levels of warfarin can be measured by a variety of techniques, but are not generally obtained to monitor the clinical course in poisoning cases.
   b. The international normalised ratio (INR) or prothrombin time (PT) are the best values to monitor. The onset of INR elevation or PT prolongation is between 12 and 24 hours post-ingestion. Any increase in INR or prolongation of prothrombin time when compared to normal controls, indicates toxicity. The risk of bleeding is minimal with a PT of 1.3 to 1.5 times control. At PT of 2 times control or greater there is an exponentially increased risk of bleeding. In the case of long acting anticoagulants, INR or prothrombin times may be normal 24 hours post-ingestion, and become prolonged at 48 hours or later, therefore 24 and 48 hour PT (or INR) has been recommended.
   c. Determination of blood clotting factors II, VII, IX, and X may be helpful in guiding therapy in symptomatic patients. Since clotting factors may be abnormal with a normal INR or PT, they are a more sensitive measure of toxicity and may be more useful in guiding vitamin K_1 therapy.

Table 24.1: Drug Interactions Involving Coumarins

Increased Anticoagulant Effect	Decreased Anticoagulant Effect
Alcohol, allopurinol, NSAIDs, anabolic steroids, amiodarone, propafenone, quinidine, chloramphenicol, ciprofloxacin, cotrimoxazole, erythromycin, metronidazole, ofloxacin, sulfonamides, azithromycin, clarithromycin, norfloxacin, tetracyclines, SSRI antidepressants, fluconazole, itraconazole, ketoconazole, proguanil, cisapride, disulfiram, danazol, flutamide tamoxifen, clofibrate, simvastatin, thyroxine, cimetidine, omeprazole, sulfinpyrazone, rifampicin	Carbamazepine, phenobarbitone, valproate, primidone, griseofulvin, oral contraceptives, vitamin K, disopyramide, vitamin C

Table 24.2: Laboratory Findings in Warfarin Overdose

Normal		Abnormal	
	Decreased	Increased	Other Findings
Blood calcium	Haemoglobin	WBC	Stool for occult
Capillary fragility	RBC	Prothrombin time	blood : Positive
Fibrinogen	Factors II, VII, IX, and X	Coagulation time	Cystoscopy :
Platelets		Bleeding time	"meat juice" at
Liver function tests		Activated partial	ureteral ostia
Kidney function tests		thromboplastin time	
Electrolytes			

d. Monitor haemoglobin and haematocrit if bleeding occurs. Monitor urine and stool for occult blood. Various imaging studies may be helpful in diagnosing spontaneous haemorrhage into various tissues or body compartments.

2. *Stabilisation:*
   a. Admit to intensive care facility and monitor clotting parameters. Watch out for signs of bleeding or bruising. Coagulopathy may persist for 6 weeks or longer in patients who ingest large amounts of long acting anticoagulants in suicidal attempts. Premature discharge of such patients at 3 to 4 weeks postingestion prior to full normalisation of factor levels has resulted in fatalities.
   b. Frequent outpatient monitoring should be done on patients discharged on oral vitamin K_1 to ensure compliance and adequacy of treatment. Factor assays should be normal prior to discontinuation of vitamin K_1.
   c. Administer whole blood or plasma if bleeding is severe.

3. *Decontamination:*
   a. Emesis and gastric lavage are contraindicated due to the potential risk of inducing bleeding.
   b. Activated charcoal can be administered. Patients on chronic anticoagulation therapy should receive activated charcoal after an acute overdose unless contraindicated.

4. *Antidote:* **Vitamin K_1** (phytomenadione, phytonadione, phylloquinone).
   a. Mode of action: Since oral anticoagulants are vitamin K antagonists, administration of vitamin K_1 sets right the anomaly. Vitamins K_2 (menaquinones), K_3 (menadione), and K_4 (menadiol sodium diphosphate) are not recommended, since they can induce haemolysis, hyperbilirubinaemia, and kernicterus in neonates, and haemolysis in G6PD deficient patients.
   b. Indications: Prophylactic treatment for a suspected large ingestion of warfarin is not recommended. PT or INR should be checked 24 hours after ingestion. If results are normal, PT and INR should be repeated at 48 hours after ingestion. If PT or INR is elevated, then Vitamin K_1 may be given.
   c. Dose:
      – Oral—50 to 100 mg, 3 to 4 times a day, for 1 to 2 days, (adults); 10 to 25 mg/day, (children).
      – Subcutaneous—25 to 50 mg, 2 to 4 times a day.
      – Intravenous—25 to 50 mg (diluted in normal saline or glucose), given slowly, 2 to 4 times a day. Rapid IV administration can cause facial flushing, sweating, chest pain, hypotension, dyspnoea.
      – Intramuscular use can result in haematoma formation.
      – Anaphylactoid reactions have been reported with vitamin K_1.

5. *Supportive measures:*
   a. Administer fresh frozen plasma and/or prothrombin complex concentrate and packed red blood cells as needed for significant active bleeding. The usual dose of fresh frozen plasma given to correct coagulation factor deficiency is 15 ml/kg, but the recommended dose required to reverse over anticoagulation due to warfarin has not been established.
   b. Since long-acting anticoagulants are metabolised by the hepatic mixed-function oxidase system (cytochrome P450), phenobarbitone 100 to 200 mg/day, may be helpful in reducing the duration of coagulopathy by inducing the hepatic microsomal metabolism of these compounds.

Forensic Issues (Anticoagulants)

- Anticoagulant poisoning may result from accidental, suicidal or homicidal causes.
  ❖ Accidental incidents are mostly the result of therapeutic errors. Occasionally, childhood poisoning may result from inadvertent consumption of products containing these agents, especially rat poisons.
  ❖ Suicidal intake of such rodenticides is also quite commonly reported in India.
- Covert use of long acting anticoagulants may be a manifestation of child abuse or Munchausen syndrome.

ANTIFIBRINOLYTICS

Examples

Aprotinin, epsilon-aminocaproic acid, ancrod, hirudin, tranexamic acid.

■ Aprotinin

Aprotinin is a basic proteinase inhibitor obtained from bovine organs, and is given intravenously to reduce peri-operative

blood loss in open heart surgeries. It is also useful in the management of traumatic, haemorrhagic, pancreatogenic, and endotoxic shock. Aprotinin acts as an inhibitor of multiple mediators (e.g. kallikrein, plasmin). It is able to modulate the systemic inflammatory response associated with cardiopulmonary bypass surgery, thus decreasing the risk of bleeding.

Aprotinin is also combined with other components to be applied topically as a fibrin glue for wound haemostasis, suture support, and tissue adhesion or sealing. In May 1998, the United States FDA approved the use of fibrin sealants containing aprotinin in multi-ingredient products. These sealants are freeze-dried concentrates which are reconstituted separately as solutions of fibrinogen and thrombin. Because sealants contain ingredients derived from pooled human plasma, procedures are in place to reduce possible viral transmission (donor screening and product pasteurisation). Up until the present time, no cases of viral infection have been reported.

Aprotinin has been withdrawn from the Italian market based on concerns that it may transmit a bovine spongiform encephalopathy and/or a new variant Creutzfeldt-Jakob disease.

During therapeutic use with aprotinin, the following have occurred infrequently: anaphylactic or anaphylactoid reactions which can range from mild to life-threatening symptoms and may not appear until the second or third dose. However, severe symptoms have been reported in a few individuals following a test dose. Anaphylaxis is not considered an uncommon response to intravenous therapy, but is a relatively rare response following fibrin sealant use.

Haematologic and lymphatic disorders have been reported during therapy: thrombosis (which may include the central nervous system, cardiovascular and pulmonary occlusions and/or emboli), leukocytosis, thrombocytopenia, and coagulation disorders. In controlled US trials with aprotinin, an incidence between 1% and 2% was reported for the following: thrombocytopenia, leukocytosis, coagulation disorders (including disseminated intravascular coagulation). High IV doses can lead to decrease in arterial pressure and metabolic acidosis.

Coronary and arterial thrombosis have been reported in patients following the use of aprotinin during cardiac surgery, as well as, other types of surgery and/or disease processes. Sudden episodes of hypotension have been (rarely) reported in trauma victims following the use of fibrin glue containing bovine thrombin and cryoprecipitate. This may be secondary to bovine impurities or relatively high concentrations of glue.

Treatment involves the use of noradrenaline, steroids, and sodium bicarbonate. Obtain a CBC with differential following a significant exposure or as indicated in symptomatic patients. Monitor for signs or symptoms of bleeding. Monitor CBC, PT or INR, PTT, bleeding time in patients with evidence of bleeding. In the immediate hours following surgery, elevations in the partial thromboplastin time (PTT) and celite activated Clotting Time (celite aCT) are anticipated due to circulating aprotin. The celite aCT is considered a more accurate determination of whole blood clotting time in the presence of aprotinin. Monitor blood pressure and respiratory function. Airway management may be indicated in patients with symptoms of anaphylaxis.

Decontamination is NOT indicated; aprotinin is inactivated in the gastrointestinal tract. Mild to moderate allergic reactions may be treated with antihistamines with or without inhaled beta agonists, corticosteroids or adrenaline. Treatment of severe anaphylaxis also includes oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring, and IV fluids. If hypotensive, give 500 to 2000 ml crystalloid initially (20 ml/kg in children), and titrate to desired effect (stabilisation of vital signs, mentation, urine output); adults may require up to 6 to 10 L/24 hours. Central venous or pulmonary artery pressure monitoring is recommended in patients with persistent hypotension. Dopamine may be used in refractory cases unresponsive to repeated doses of adrenaline, and after vigorous intravenous crystalloid rehydration.

■ Epsilon Aminocaproic Acid

ε-Aminocaproic acid is an inhibitor of fibrinolysis, which is useful in the management of post-partum haemorrhage, haematuria, hereditary angioedema, subarachnoid haemorrhage, prevention of haemorrhage after dental extraction in haemophiliacs, and prevention of rebleeding following traumatic hyphaema. It is a synthetic amino acid which is similar in structure to lysine and ornithine.

Aminocaproic acid is readily absorbed from the gastrointestinal tract. Peak plasma levels are reached within 2 hours of a single oral dose. After prolonged administration, it distributes throughout both the intravascular and extravascular compartments. It readily penetrates red blood cells. It does not appear to be bound to plasma proteins. Aminocaproic acid is readily excreted in the urine. 80% of a single dose is excreted in 12 hours.

Side effects include nausea, vomiting, diarrhoea, conjunctival hyperaemia, and delirium. Hypotension and bradycardia may be seen after too rapid intravenous administration. Overdose results in rash, vomiting, diarrhoea, myopathy, prolongation of bleeding time, seizures, thrombosis formation, hepatic failure, and acute renal failure. Severe cases of myopathy may be associated with muscle necrosis, myoglobinuria, rhabdomyolysis, and prolonged elevations of muscle enzymes.

Treatment involves stabilisation and supportive measures. Bleeding time, hepatic function, and renal function should be monitored. Serial bleeding time tests are indicated for patients receiving aminocaproic acid. Myopathy may occur, producing high plasma creatine kinase levels, and mild hyperbilirubinaemia. Serial creatinine phosphokinase (CPK) levels are important in monitoring a patient using aminocaproic acid. This is especially true if the therapy is in excess of 2 weeks and a total dose greater than 500 grams. In general, aminocaproic acid-associated renal failure and myopathy have improved with discontinuation of therapy. Aminocaproic acid can be removed by dialysis.

■ Hirudin

Hirudin is a polypeptide, present in leeches (*Hirudo medicinalis*) (**Fig 24.3**), and is a highly selective thrombin inhibitor. It is a naturally occurring 65-amino acid polypeptide that is produced from the saliva of the medicinal leech. It is now being produced in other forms as a recombinant molecule.

Fig 24.3: Leech (*Hirudo medicinalis*)

Recombinant derivatives of hirudin include argatroban, biva-lirudin, desirudin, efegatran, inogatran, lepirudin, napsagatran, and ximelagatran.

Direct thrombin inhibitors target sites on the thrombin molecule responsible for substrate recognition and/or cleavage. The substrate recognition site (exosite 1) binds thrombin to fibrinogen prior to its enzymatic actions. The catalytic (active) site is responsible for activating platelets and the cleavage of fibrinogen to fibrin for thrombus formation. Direct thrombin inhibitors can block both the active site and exosite 1 or the active site alone, specifically inhibiting thrombin activity. Heparin is unable to inactivate thrombin because the heparin-activated antithrombin binds to the active site and blocks the fibrin-binding site. Because direct thrombin inhibitors do not bind to the fibrin-binding site, they can bind both unbound and fibrin-bound thrombin. They are also not inhibited by platelet factor 4.

The most common complication observed with selective thrombin inhibitor therapy is haemorrhage, although the incidence of major bleeding is less when compared with other anticoagulants. Bleeding from puncture wound sites, anaemia, haematomas, haematuria, gastrointestinal and rectal bleeding, epistaxis, intracranial bleeding and haemothorax have been reported. Concurrent treatment with thrombolytics (e.g. rt-PA, streptokinase), coumarin derivatives (e.g. Vitamin K antago-nists), and drugs that affect platelet function may increase the risk of bleeding complications. Thrombolytics may enhance the effect on aPTT prolongation. Other non-haemorrhagic effects seen in clinical trials include hypotension, cardiac arrest, dyspnoea, fever, nausea, vomiting, diarrhoea, cardiac arrhythmias, and abnormal hepatic and renal function. Some of these complications are likely related to underlying disease processes. Acute allergic reactions and formation of antihirudin antibodies have also been reported.

Overdose results in significant haemorrhage which responds well to prothrombin complex concentrate.

Treatment involves symptomatic and supportive measures. If bleeding is suspected, monitor patient's haematocrit, haemo-globin, activated partial thromboplastin time, INR, platelet count and fibrinogen. Monitor vital signs, ECG, renal and hepatic function in symptomatic patients. No specific antidotes are available for the direct thrombin inhibitors. If excessive anticoagulation occurs, discontinue the drug or decrease the infusion dosage. If necessary, blood loss and reversal of bleeding tendency can be managed with packed red blood cells and cryoprecipitate or fresh frozen plasma.

◼ Thrombolytics

Thrombolytic agents are plasminogen activators which cleave the Arg-Val bond of plasminogen resulting in the formation of plasmin. They are used in the treatment of thromboembolic disorders such as myocardial infarction, peripheral arterial thromboembolism, and venous thromboembolism (deep-vein thrombosis and pulmonary embolism). They are also used to clear blocked cannulas and shunts. Common examples include alteplase, anistreplase, reteplase, streptokinase, tenectoplase, urokinase, and tissue plasminogen activator.

Streptokinase is a 47-kDa protein produced by beta haemolytic streptococci, which forms a stable non-covalent 1 : 1 complex with plasminogen, leading to its conversion to plasmin. It is given intravenously. Plasma half-life varies from 18 to 23 minutes. The effectiveness may be decreased if given within 5 days to 12 months after prior use of strep-tokinase or anistreplase, or after streptococcal infection. This is due to the formation of antistreptokinase antibodies which may result in resistance to thrombolysis. Patients with high antibody titres who are nevertheless given streptokinase are more prone to experience adverse reactions (hypotension; serum sickness).

Urokinase is a two-chain serine protease isolated from cultured human kidney cells. It is metabolised in the liver and has a half-life of 15 to 20 minutes. Mode of administration is intravenous.

Tissue plasminogen activator (t-PA) is a serine protease also referred to as alteplase. Following IV administration it is metabolised in the liver and has a half-life of 3 to 5 minutes.

Bleeding is the most common adverse effect of throm-bolytic therapy. The bleeding associated with thrombolytic therapy can be categorised into 2 groups. The first category is superficial or surface bleeding (primarily observed at disturbed sites including venous cutdowns, and arterial punctures). The second category is the internal bleeding involving the gastrointestinal tract, genitourinary tract, retro-peritoneal sites, or intracranial sites. Minor bleeds include haematuria, haematemesis, haematomas, and oozing from IV puncture sites. Strokes and intracerebral bleeding occur occasionally. Other adverse effects include hypotension, headache, backache, renal dysfunction, hepatic dysfunction, leukocytosis, platelet activation, emboli, arterial occlusions, reperfusion arrhythmias, nausea, vomiting, haemoperi-cardium, hallucinations, agitation, confusion, depression, bronchospasm, cutaneous or allergic reactions, chills, and fever. Streptokinase can cause hypersensitivity reactions,

haemolysis, and Guillain-Barre syndrome. A few cases of alteplase-induced anaphylactoid reaction with angioedema have been reported.

Reperfusion arrhythmias are common after the use of thrombolytics in the setting of acute myocardial infarction. A wide variety of atrial and ventricular arhythmias have been documented, including bradycardia, idioventricular rhythm, pre-mature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. These are related to the reperfusion of ischaemic myocardium, rather than a direct arrhythmogenic effect of thrombolytic therapies per se. Haemopericardium causing cardiac tamponade has been observed following intravenous streptokinase for the treatment of pulmonary embolism.

The possible association of streptokinase therapy and Guillain-Barre syndrome has been reported in several patients. Neuralgic amyotrophy with severe pain and pareses in the upper extremities (Parsonage-Turner syndrome) has also been reported.

Concurrent administration of thrombolytic agents with oral anticoagulants is contraindicated when the prothrombin time is greater than 15 seconds. Concurrent use of thrombolytic agents with drugs known to significantly affect platelet integrity (e.g. aspirin, indomethacin, dipyridamole, phenylbutazone) should also be avoided.

Treatment of toxic effects arising from the use of these agents involves the following measures:

- If bleeding is suspected, monitor patient's haematocrit, haemoglobin, partial thromboplastin time, prothrombin time/INR, platelet count, and fibrinogen. Monitor vital signs, renal and hepatic functions in symptomatic patients.
- Discontinue the drug.
- Replace volume as required.
- Apply (normal) pressure to (compressible) bleeding sites for 15 to 20 minutes.
- If bleeding continues, administer transfusion products. Cryoprecipitate (10 U) can be given.
- If patient continues to bleed, 2 to 6 U of fresh-frozen plasma may be necessary.
- If the bleeding is persistent in spite of the above measures, 10 U of platelets and antifibrinolytic drugs (ε-aminocaproic acid or tranexamic acid) must be given. The use of aminocaproic acid as an antidote for streptokinase has not been documented, but it may be considered in an emergency situation.
- Aprotinin has been effective in reversing streptokinase-induced bleeding in some patients with acute myocardial infarction who underwent emergency cardiac surgery.

Antiplatelet Drugs

Common examples include aspirin, dipyridamole, and ticlopidine. While the former two have been discussed in detail elsewhere (*refer Index*), ticlopidine will be discussed here.

Ticlopidine is a thienopyridine which inhibits platelet function by inducing a thrombasthenia-like state. It is used for prevention of thrombosis in cerebral vascular and coronary artery disease that can lead to myocardial infarction, peripheral arterial disease, and stroke. It is also used to prevent thromboembolic occlusion of newly implanted coronary stents.

The oral bioavailability of ticlopidine is 80 to 90 per cent, with peak concentrations occurring at approximately 2 hours. It is reported to reversibly (98%) bind to plasma proteins, mainly to serum albumin and lipoproteins, and is extensively metabolised by the liver. Approximately 60 per cent of a radiolabeled dose is recoverable in the urine, mainly as metabolites; about 23 per cent is excreted in the faeces. The elimination half-life of ticlopidine ranges from 24 to 33 hours.

Adverse effects include bleeding, nausea, vomiting, abdominal pain, diarrhoea, cholestatic jaundice, elevated liver enzyme levels, agranulocytosis, anaemia, and thrombocytopenia. Neutropenia has also been reported. Aplastic anaemia has occurred. Skin rashes are a common side effect with this agent. They are usually either urticarial or maculopapular.

Cases of fatal thrombotic thrombocytopenia purpura (TTP) have occurred following ticlopidine therapy. Chronic diarrhoea resulting in weight loss has been reported in patients taking ticlopidine therapeutically. Reversible cholestatic jaundice (occurring at a reported incidence of 1%) may also occur with therapeutic use of this drug. Elevated hepatic serum enzymes can occur following therapeutic doses, usually noted between 10 days and 12 weeks after starting therapy. These patients develop jaundice, generally without fever, with laboratory tests revealing elevation of transaminase concentrations and/or cholestasis.

Agranulocytosis may occur alone, or with thrombocytopenia and/or anaemia. Thrombotic thrombocytopenic purpura (TTP), a potentially life-threatening condition, has been reported as an adverse event in approximately one case per 2000 to 4000 patients exposed. Clinical symptoms include changes in mental status, mild renal dysfunction, and fever. Laboratory findings include severe thrombocytopenia and microangiopathic haemolytic anaemia. Thrombotic Thrombocytopenic Purpura-Haemolytic Uraemic Syndrome (TTP-HUS) has uncommonly been associated with therapeutic use of ticlopidine. It is suggested that this is an immune-mediated reaction. High mortality and morbidity is associated with this condition. Plasma exchange therapy appears to be beneficial.

Ticlopidine has been rarely implicated in overdoses. Agitation, tachycardia, hypotension, hypoxia, metabolic acidosis, and bleeding have been reported. Treatment is symptomatic and supportive. Granulocyte colony-stimulating factor (G-CSF) has been used to treat severe neutropenia/leukopenia associated with ticlopidine therapy. The mortality from ticlopidine induced thrombotic thrombocytopenic purpura may be reduced by plasma exchange or plasmapheresis.

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Cardiotoxic Plants

Common cardiotoxic plants include the following: aconite, azalea, death camas, false hellebore, foxglove, lily of the valley, meadow saffron, mountain laurel, common oleander, yellow oleander, rhododendron, suicide tree, and yew.

Several of the cardiotoxic plants contain various cardiac glycosides which act in similar fashion. Some of these glycosides are useful in pharmacotherapeutics (e.g. digitalis derived from foxglove). **Table 25.1** lists common plants which contain cardiac glycosides. Some cardiotoxic plants do not contain glycosides (e.g. aconite).

Foxglove (digitalis) has been dealt with in detail under cardiac glycosides (*page no 318*).

■ Aconite

Other Common Names

Monkshood, Wolfsbane, Mousebane, Helmet flower, Soldier's cap, Old wife's hood, Friar's cap, Bear's foot.

Botanical Name

Aconitum species, of which there are 350 worldwide. *Aconitum napellus* is the European variety, *A. columbianum, A. reclinatum,* and *A. uncinatum* are encountered in America, *A. japonicum,* and *A. carmichaelii* are Oriental varieties, while Indian species include *A. ferox, A. chasmanthum, A. cordatum,* and *A. balfouri.*

Physical Appearance

This plant belongs to family Ranunculaceae and grows well in the hilly regions of Northern and Eastern parts of India, extending from Assam to Kashmir. It is a perennial herb with distinctive helmet shaped flowers, which may be blue, purple, or pinkish white in colour (**Fig 25.1**). The root is stout and dark (**Fig 25.2**), and has a superficial resemblance to horseradish (**Fig 25.3**).

Table 25.1: Plants Containing Cardiac Glycosides

Family	Representative Example	
	Botanical Name	*Common Name*
Apocynaceae	*Cerbera thevetia*	Yellow oleander
	Nerium oleander	Common or Pink oleander
	Strophanthus	Dogbane
Asclepiadaceae	*Asclepias*	Milkweed
	Calotropis	Crown flower
Celastraceae	*Euonymus europaeus*	Spindle tree
Cruciferae	*Cheiranthus*	Wall flower
	Erysimum	Wall flower
Liliaceae	*Convallaria majalis*	Lily of the valley
	Urginea maritima	Squill
	Urginea indica	Squill
Ranunculaceae	*Helleborus niger*	Henbane
Scrophulariaceae	*Digitalis purpurea*	Foxglove
	Digitalis lanata	Woolly foxglove

Fig 25.1: Aconite plant

Fig 25.2: Aconite roots

Fig 25.3: Horseradish roots

Toxic Part

All parts, but the root is most toxic. It is said to have a bitter-sweet taste.*

Toxic Principles

- European and American species contain aconitine, mesaconitine, and jesaconitine.

- Indian species contain hypoaconitine and mesoaconitine which are less potent.

Aconite species contain diterpene (C20) and norditerpene (C19) alkaloids, the nitrogen molecule of which is usually ethylated or methylated to make them alkamines. C20 diterpenes are relatively low in toxicity, but the esterified, norditerpene bases have high toxicity. If the ester functions are hydrolysed, toxicity is reduced to that of ordinary diterpenes.

Uses

- The tuber is very popular in Chinese medicine for the treatment of various ailments. The root is usually processed by drying, soaking, or boiling, which significantly reduces its toxicity. Raw aconite roots are highly toxic. Herbal decoctions of aconite are generally prepared by soaking the roots in water or saturated lime water and then boiling. This causes hydrolysis of aconite alkaloids to less toxic benzylaconine and aconine derivatives.
- Aconite is also used in Indian folk remedies. It is also used as an antipyretic in Ayurvedic medicine, after "detoxification".
- Formerly, aconite found mention in the British Pharmacopoeia (until 1953), but today it is only used in allopathic medicine as a proarrhythmic agent in animal studies to test the efficacy of antiarrhythmic agents.
- Aconite is sometimes used as an abortifacient.

Usual Fatal Dose

- About 9 to 18 grams of root.
- About 3 to 5 mg of aconitine.
- About 10 to 15 ml of tincture.

However, deaths have been reported with as little as 1 grams of root, 0.2 mg of aconitine, and 5 ml of aconite tincture. It has been estimated that an adult lethal dose is generally about 1 grams of plant part (root), 5 ml of a prepared tincture, or 2 mg of pure aconite.

Drying and storing these plants could result in changes in the composition and even transformation of the alkaloidal content, thus altering toxicity of individual exposures.

Mode of Action

Aconitine acts on nerve axons by opening sodium channels, as well as by inhibiting complete repolarisation of the membrane of myocardial tissue, causing repetitive firing.

Aconitine also stimulates the vagal medullary centre.

Clinical Features

Symptoms generally begin within 10 to 20 minutes of ingestion. A tingling or burning sensation in the fingers and toes is usually seen first, followed by sweats and chills, a generalised paraesthesia, dryness of mouth, and numbness. The following are seen:

1. *GIT*: Nausea, hypersalivation, vomiting, diarrhoea. Chewing on a root may cause swelling of the lips, tongue, and mouth, making speech difficult.
2. *CVS:* Palpitations, hypotension, ventricular ectopics, arrhythmias, AV block.

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* That is why aconite is referred to as "mitha zahar" in Hindi, which means "sweet poison".

3. *CNS:* Tingling and numbness of mouth and lips which may extend to the limbs, followed by convulsions. Initial feelings of numbness may progress to paralysis of the skeletal muscles. Vertigo is often present. The following have been reported: severe headache, restlessness, and confusion. Muscular fasciculations may lead to tonic or clonic seizures. Ataxia is often present.
4. *RS:* A few patients have reported breathing difficulty after ingesting aconite-containing herbals. Pulmonary oedema often occurs in the terminal stages.
5. *Eye:* Visual blurring, fluctuant pupils (*hippus*), mydriasis. Miosis may be seen until the patient develops hypoxia. Xanthopsia (yellow halos around objects) has been reported.
6. Metabolic acidosis has developed in a few patients.
7. Death usually occurs from ventricular arrhythmias or respiratory paralysis, and this may happen in just a few minutes, or take several days.

Treatment

1. Gastric decontamination (lavage, charcoal).
2. Perform an arterial blood gas, serum electrolytes, creatine phosphokinase (fractionated), and an ECG.
3. Provide airway support, and establish vascular access.
4. Extensive vomiting and diarrhoea often necessitate fluid and electrolytes to be given in substantial doses.
5. There is no specific antidote. Treatment is symptomatic and supportive after decontamination.
6. Treat convulsions with benzodiazepines, followed by phenytoin, if required.
7. Treat metabolic acidosis and hypokalaemia.
8. Bradyarrhythmia and hypersalivation respond to atropine.
9. Institute continuous cardiac monitoring. Arrhythmias are unfortunately often refractory to drug management. No single antiarrhythmic agent has been found to be uniformly effective for controlling tachyarrhythmias. DC cardioversion is not effective. Calcium gluconate or chloride may help reverse arrhythmias in some cases. They must be followed up with magnesium sulfate.
10. In one animal study, flecainide, a sodium-channel blocker, as well as a beta blocker, was an effective antiarrhythmic for aconite poisoning.
11. In one patient with severe aconite-induced cardiotoxicity, cardiopulmonary bypass and a left ventricular assist device were found to be beneficial.

Forensic Issues

■ Poisoning with aconite has never been common. Most reported cases are accidental in nature, resulting from therapeutic misadventures. Aconite is used in herbal medicines (cold preparation, antipyretic, digestive and general tonic, etc.), or to increase the intoxicating effect of alcoholic beverages. Fatalities have been reported with the use of tincture aconite added to liquor.

■ A few cases result from mistaken identity with horse-radish.* Rarely, suicides and homicides have been reported.

■ Common Oleander

Other Common Names

White oleander, Pink oleander, Rose laurel, Rose bay, Rosa francesca, Laurier rose, Adelfa.

Botanical Name

Nerium oleander

Physical Appearance

This plant belonging to family Apocynaceae is a large evergreen ornamental shrub with long lanceolate leaves and clusters of whitish or pinkish flowers (**Fig 25.4** and **Fig 25.5**). The leaves produce a clear, thick sap.

Toxic Part

All parts, especially the root.

Toxic Principles

The seeds, stem, and root are rich in the following cardiac glycosides: oleandrin, neriin, folinerin, rosagenin, and digitoxigenin.

Fig 25.4: *Nerium oleander* trees – on a street in Nice, France
(*Pic*: Dr Shashidhar C Mestri)

Fig 25.5: *Nerium oleander* flowers
(*Pic*: Dr Shashidhar C Mestri)

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* One way of distinguishing the two is to cut the root. Aconite will turn pinkish on exposure to air. Horseradish will show no change.

Uses

- Decoction of the leaves and root are used in Indian traditional medicine as local applications for various skin ailments.
- Root is used by rural folk as abortifacient.
- Common oleander is a popular ornamental garden plant.

Usual Fatal Dose

- About 5 to 15 leaves
- About 15 grams of root.

Serious poisoning rarely develops after "taste" ingestions of whole plant material by children. Taste/exploratory ingestions of *Nerium oleander* are unlikely to result in toxicity.

Mode of Action

All the glycosides have digoxin-like effects; they inhibit sodium-potassium ATPase.

Clinical Features

Symptoms generally begin within 10 to 20 minutes of ingestion. A tingling or burning sensation in the fingers and toes is usually seen first, followed by sweats and chills, a generalised paraesthesia, dryness of mouth, and numbness. The following are seen:

1. *GIT:* Nausea, vomiting, diarrhoea. Numbness of tongue occurs sometimes.
2. *CVS:* Increased ectopy and conduction delay (bradycardia, supraventricular tachycardia with AV block), electrolyte imbalances (especially hyperkalaemia) and hypotension/hypertension. Ventricular fibrillation is potentially lethal. Decreased QRS-T interval, T wave flattening/inversion, irregular ventricular rate, and increased PR interval, etc., have also been reported. Smoke from a burning oleander plant can cause dizziness, vomiting, and cardiac arrhythmias.
3. *CNS:* Delirium, lethargy, dizziness, drowsiness. Occasionally there may be seizures, and coma.

Diagnosis

1. Because oleander-derived cardiac glycosides are cross-reactive with the frequently used radio-immunoassays for digoxin, an elevated level may help confirm suspicion of oleander poisoning.
2. Thin-layer chromatography and fluorescence spectrophotometry can also be used to identify oleander glycosides.
3. Reverse-phase HPLC and HPLC/MS are more specific.

Treatment

All patients with a history of cardiac glycoside-containing plant ingestion should have a baseline ECG and electrolytes. Patients who at presentation show signs of toxicity, independent of the dose ingested, should be admitted to the ICU for at least 24 hours of observation and treatment.

1. Gastric lavage, activated charcoal: Gastric lavage is of limited benefit in patients ingesting plant parts, particularly children, because of the size of the plant parts relative to the lavage tube. Also, the procedure may worsen bradycardia secondary to vagal stimulation. Whole gut lavage may be more useful in such situations.
2. IV fluids.
3. Careful measurement of serum potassium is one of the most important laboratory tests to be done, since hyperkalaemia is quite common. The emergency management of life-threatening hyperkalaemia (potassium levels greater than 6.5 mEq/L) includes IV bicarbonate, glucose, and insulin (administer 0.2 unit/kg of regular insulin with 200 to 400 mg/kg glucose). Concurrent administration of IV sodium bicarbonate (about 1 mEq/kg) is of additive value in rapidly lowering serum potassium levels.
4. Atropine for sinus bradycardia and AV block: 1 mg IV; repeat in 3 to 5 minutes if asystolic cardiac arrest persists. 3 mg (0.04 mg/kg) IV is generally considered to be a fully vagolytic dose in most adults. Insertion of a pacemaker should be considered in those patients with severe bradycardia, and/or slow ventricular rate due to second degree AV block who fail to respond to atropine (and/or phenytoin).
5. Antiarrhythmics (e.g. lignocaine): Lignocaine is useful in the management of ventricular tachy-arrhythmias, PVCs, and bigeminy.
6. Digoxin-specific Fab fragment therapy is said to be effective (*page no 321*). Treatment with Fab fragments should be considered in those severely intoxicated patients who fail to respond to immediately available conventional therapy.
7. Haemodialysis is ineffective in removing cardiac glycosides, but may assist in restoring serum potassium to normal levels.

Forensic Issues

- Accidental poisoning from its use in traditional medicine.
- Suicidal ingestion of decoction prepared from leaves or root is fairly common in rural areas.
- Homicidal cases are rare, but have been reported. In one attempted case of murder, a middle-aged male presented to the ED with a two-month history of nausea, anorexia, colicky abdominal pain, vomiting, diarrhoea, lethargy, confusion, dry mouth, dizziness, paraesthesias, tremor, and episodes of slurred speech with blurred, yellowish vision. Subsequent police investigation revealed that the wife was attempting to poison him by using water boiled with roots of *Nerium oleander* for making coffee over an eight-week period.

■ Yellow Oleander

Other Common Names

Bastard oleander, Exile oleander, Be-still tree, Lucky nut, Tiger apple.

Botanical Name

Thevetia peruviana, T.neriifolia, Cerbera thevetia.

Physical Appearance

It is an ornamental shrub (that grows to about 30 feet height) belonging to family Apocynaceae with longish (about 15

cm long) leaves yielding a milky sap, and yellowish funnel-shaped flowers (**Fig 25.6**). The leaves are pointed, with dark green upper surface, and lighter green undersides. The edges are often rolled. Fruit is diamond shaped or clam shaped, and has 2 to 4 seeds in its stony inner section. It is about ½ inch in size, greenish at first, and turning yellow when ripe, and may even appear blackish in the later stages. The kernel (seed) is very toxic (**Fig 25.7**). All parts of the plant contain a milky juice or sap.

Toxic Part

All parts, particularly seeds and root. Yellow oleander plant parts are generally more toxic than *Nerium oleander*.

Toxic Principles

- Cerberin
- Nerifolin
- Peruvoside
- Ruvoside
- Thevetin A and B.

In decreasing order of toxicity, the most toxic glycosides in yellow oleander are: peruvoside, ruvoside, thevetin A, nerifolin, cerberin, and thevetin B.

Fig 25.6: Yellow oleander
(*Pic*: Dr Shashidhar C Mestri)

Fig 25.7: Yellow oleander—Seed
(*Pic*: Dr Shashidhar C Mestri)

Uses

- Like common oleander, yellow oleander is also used in traditional Indian medicine for the treatment of various ailments.
- Bark extracts containing cardenolides have been investigated as cytotoxic agents in cancer research.

Usual Fatal Dose

- About 8 to 10 seeds.
- About 15 to 20 grams of root.

The rest of the information is essentially the same as that for common oleander (*vide supra*), though toxicity is likely to be more severe.

The commonest manifestations associated with yellow oleander poisoning include bradycardia with AV block, hypotension, lethargy, dizziness, and GI distress. Convulsions, electrolyte disturbances, hypertension, and coma have also been reported. Mydriasis may occur. Numbness and burning sensation of the mouth may develop.

The sap of yellow oleander tree may cause blistering or dermatitis on contact.

Subendocardial and perivascular haemorrhage with focal myocardial oedema have been found during autopsies of some of the patients who died.

Cardiac glycosides of this plant are best identified by radioimmunoassay.

As far as specific treatment is concerned, it has been shown that anti-digoxin Fab fragments are effective in the management of yellow oleander-induced arrhythmias. They rapidly restore sinus rhythm, and revert bradycardia and hyperkalaemia back to normalcy. Digoxin Fab fragments are indicated if the potassium concentration exceeds the upper limit of the normal range (5 mEq/L), in association with other severe symptoms. Even if the exact cause is uncertain as to whether yellow oleander is the culprit in a given case, some investigators recommend the empiric administration of 10 vials of digoxin-specific Fab. However, serum potassium can drop steeply, and must be monitored frequently for several hours post-administration. This is especially likely to occur if Fab fragments have been given along with glucose, insulin, and bicarbonate. The latter combination therapy (glucose, insulin, and bicarbonate) must be tried only if Fab fragments are not available.

Atropine is useful in the management of bradycardia, and varying degrees of heart block. Lignocaine is useful in the management of ventricular tachy-arrhythmias, PVCs, and bigeminy.

Certain steroid compounds such as spironolactone and pregnenolone-16alpha-carbonitrile have been shown to decrease glycoside toxicity by increasing biliary excretion. Although not yet tried in humans, these agents could be tried as a treatment modality.

■ Suicide Tree

Other Common Names

Ordeal tree, Tangena nut, Pong-pong.

Botanical Name

Cerbera odallum

Physical Appearance

It is a small tree that grows well in South India, especially Kerala. It bears fruits which resemble unripe (green) mangoes (**Fig 25.8**). The fruit contains generally two hemispherical seeds with a tough, horny, granular envelope (kernel). The kernel is rounded on the outside, and flattened or depressed about the centre on the internal side. It is formed of two unequal cotyledons, the external surrounding the internal and a short ascending radicle. The seeds are employed in folk medicine as an emeto-cathartic, while the bark, the latex (rich in caoutchouc) and the leaves are used as purgatives, but all are dangerous.

Toxic Part

Kernel of fruit.

Toxic Principle

Cerberin: The seeds of *Cerbera Odallum* contain a colourless crystallisable glucoside *Cerberin*. It yields with dilute acids *Cerberetine,* which is equally toxic and of a handsome yellow colour. The seeds contain 77% fixed oil. Cerberin is very toxic, especially on the heart. It blocks the calcium ion channels in heart muscle, causing disruption of the heartbeat.

Manifestations of poisoning as well as treatment are the same as that for oleander.

Forensic Issues

Cerberin is difficult to detect in autopsies and its taste can be masked with strong spices. Therefore it is a common method

Fig 25.8: *Cerbera odallum* (*Pic*: Dr S Sivasuthan)

Fig 25.9: Mango and Odallum
(*Pic*: Dr S Sivasuthan)

in both homicide and suicide in India (especially in states like Kerala). Accidental poisoning may result from mistaken identity (with unripe mango) (**Fig 25.9**).

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Section

7

Asphyxiant Poisons

Toxic Gases

Toxic gases may be classified as follows:

1. **Simple Asphyxiants**—These gases displace oxygen from the ambient air and reduce the partial pressure of available oxygen. Examples include carbon dioxide, nitrogen, aliphatic hydrocarbon gases (butane, ethane, methane, and propane), and noble gases (argon, helium, neon, radon, and xenon).

2. **Respiratory Irritants**—These gases damage the respiratory tract by destroying the integrity of the mucosal barrier. Examples include acrolein, ammonia, chloramine, chlorine, formaldehyde, hydrogen sulfide, methyl bromide, methyl isocyanate, oxides of nitrogen, osmium tetroxide, ozone, phosgene, and sulfur dioxide. Heavy metal-related gases also come under this category (cadmium fumes, copper fumes, mercury vapour, zinc chloride and zinc oxide).

3. **Systemic Asphyxiants**—These gases produce significant systemic toxicity by specialised mechanisms. Examples include carbon monoxide, cyanide, and smoke. It must be noted that systemic toxicity may also be observed in the case of some simple asphyxiants and respiratory irritants, though it is not the predominant feature.

Discussion of toxicity of the examples mentioned under the various categories now follows, while pointing out that some of them have been discussed elsewhere (consult *Index*).

SIMPLE ASPHYXIANTS

■ Carbon Dioxide (CO_2)

Physical Appearance

Colourless, odourless, non-flammable gas which is heavier than air. In its solid form (*dry ice*) it is whitish in colour and acts as a corrosive.

Uses

1. Fire extinguisher.
2. Carbonation of soft drinks.
3. Shielding gas during welding processes.
4. Synthesis of urea, for dry ice, and organic synthesis.

Clinical Features

Four stages have been described, depending on the arterial oxygen saturation:

- ❖ *Indifferent Stage:*
  - – $\%O_2$ Saturation: 90%
  - – Night vision: decreased.
- ❖ *Compensatory Stage:*
  - – $\%O_2$ Saturation: 82 to 90%
  - – Respiratory rate: compensatory increase
  - – Pulse: compensatory increase
  - – Night vision: decreased further
  - – Performance ability: somewhat reduced
  - – Alertness: somewhat reduced
  - – Symptoms may begin in those with significant pre-existing cardiac, pulmonary, or haematologic diseases.
- ❖ *Disturbance Stage:*
  - – $\%O_2$ Saturation: 64 to 82%
  - – Compensatory mechanisms become inadequate
  - – Air hunger
  - – Fatigue
  - – Tunnel vision
  - – Dizziness
  - – Headache
  - – Belligerence
  - – Euphoria
  - – Visual acuity: reduced
  - – Numbness and tingling of extremities
  - – Hyperventilation
  - – Poor judgement
  - – Memory loss
  - – Cyanosis
  - – Decreased ability for escape from toxic environment.
- ❖ *Critical Stage:*
  - – $\%O_2$ Saturation: 60 to 70% or less
  - – Deterioration in judgement and co-ordination may occur in 3 to 5 minutes or less
  - – Total incapacitation and unconsciousness follow rapidly.

Unconsciousness leading to death will occur when the atmospheric oxygen concentration is reduced to 6 to 8% or less. Concentrations up to 35% CO_2 have an exciting effect upon both circulation and respiration. Concentrations above 35% have a depressing effect upon both circulation and respiration. Bradycardia progressing to asystole may occur in the absence of signs of cyanosis following inhalation exposure to 99.97% carbon dioxide. Investigators suggest hypercapnia and acidosis may contribute to the cause of cardiac arrest.

Dermal exposure to solid carbon dioxide ("dry ice") may cause frostbite injury. Severe tissue burns have been reported.

Diagnosis

Arterial blood gases are useful to assess the degree of hypoxaemia.

Treatment

1. Move patient from the toxic environment to fresh air. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.
2. Administer 100% humidified supplemental oxygen, perform endotracheal intubation, and provide assisted ventilation as required.
3. If hypoxia has been severe or prolonged, carefully evaluate for neurologic sequelae and provide supportive treatment as indicated.
4. Treatment of frostbite:
   a. Freeze injury associated with dermal exposure to "dry ice" is unlike frostbite in that the damage occurs within seconds and rewarming is not beneficial.
   b. Some investigators suggest that freeze injuries of this nature should be managed much like a thermal burn.
   c. Burn surgeons should be consulted in the more severe cases.
   d. Do not institute rewarming unless complete rewarming can be assured; refreezing thawed tissue increases tissue damage. Place affected area in a water bath with a temperature of 40 to 42^{0}C for 15 to 30 minutes until thawing is complete. Some authors suggest that an antibacterial (hexachlorophene or povidone-iodine) be added to the bath water.
   e. Correct systemic hypothermia.
   f. Rewarming may be associated with increasing pain, requiring narcotic analgesics.
      – Digits should be separated by sterile absorbent cotton; no constrictive dressings should be used. Protective dressings should be changed twice per day.
      – Perform daily hydrotherapy for 30 to 45 minutes in warm water 40^{0}C. This helps debride devitalised tissue and maintain range of motion.
      – The injured extremities should be elevated and should not be allowed to bear weight.
      – Prophylactic antibiotics are recommended by some investigators.
      – Topical aloe vera may decrease tissue destruction and should be applied every 6 hours.
      – Ibuprofen is a thromboxane inhibitor and may help reduce tissue loss. Adult dose of 200 mg every 12 hours is recommended.

Forensic Issues

- Most cases are accidental resulting from inadvertent build-up of CO_2 in a confined space.
- Dry ice can generate toxic concentrations of CO_2.
- Release of carbon dioxide from rising colder, deep water producing a deadly cloud of gas has been postulated to explain the deaths associated with the Lake Nyos disaster of August 21, 1986, Lake Monoun disaster of August 1984, and Dieng Plateau, Indonesia disaster of February 20, 1979. Survivors of the Lake Nyos disaster in August, 1986 were noted to have superficial blisters which healed rapidly. Characteristics of the blisters suggested that they were the result of depriving the skin of oxygen. Hospitalised and outpatient survivors had symptoms compatible with exposure to a suffocating gas. Many survivors had lost consciousness for hours (6 to 36 hours) after the incident. Cough, headache, fever, weakness or malaise, and limb swelling were frequently noted (10% or more incidence) among the victims. Evidence after the incident suggested a slow build-up of carbon dioxide deep in the lake, followed by its release as a cold, suffocating aerosol. Dogs, cats, cattle, goats, chickens, snakes, and frogs were also found dead in their tracks. Insect life was noted to be absent for approximately 24 hours following the incident.
- Excess levels of carbon dioxide, ammonia, and other asphyxiant gases have been theorised to accumulate at the face of a sleeping infant. If the infant is unable to change its position or breathing pattern, sudden infant death syndrome (SIDS) may result from asphyxiation. Asphyxia may be due to an excess of CO_2 and abnormal reflex actions connected with breathing and swallowing.

■ Aliphatic Hydrocarbon Gases

Ethane is an odourless gas which is used as a refrigerant and as a component of natural gas. It is methane (*swamp gas*), however, which is the major component of natural gas. Both are odourless gases and produce simple asphyxiation at high concentrations. Conversion of domestic gas from coal gas (mostly carbon monoxide) to natural gas (mostly methane) has significantly reduced mortality from domestic gas leaks, since methane is much less toxic as compared to carbon monoxide. Methane being odourless, a stenching agent (alkyl mercaptan) is deliberately added to domestic gas so that leaks can be immediately recognised. It is important to remember that a build-up of methane resulting in 4.8 to 13.5% concentration in air constitutes an explosive mixture which can be ignited by a flame or even a tiny spark. Most explosions in mines (as well as homes using natural gas as fuel) occur because of this reason.

Butane, liquefied petroleum gas, propane, and propylene have a faint petroleum-like odour and may be stenched with

mercaptans for transport and storage. Butane is used as a raw material for automobile fuels, in organic synthesis, and as a solvent, refrigerant, and aerosol. Propane is used as a raw material in organic synthesis, as a component of industrial and domestic fuels, as an extractant, a solvent, and a refrigerant, and in the manufacture of ethylene. Incomplete combustion of these agents can release carbon monoxide into the ambient air. Butane is often abused by adolescents in the form of inhalation (*see "glue sniffing", page no* 576).

Liquefied petroleum gas is used as a domestic, industrial, and automotive fuel. Propylene is a raw material in polypropylene, isopropyl alcohol, isopropylbenzene, acetone, and propylene oxide manufacturing.

Most of the aliphatic hydrocarbon gases act as simple asphyxiants (*vide supra*), in addition to additional specific toxicities.

RESPIRATORY IRRITANTS

■ Ammonia

Physical Appearance

- Extremely irritant gas with a penetrating odour.
- It is highly water soluble (forming ammonium hydroxide which is an alkaline corrosive).
- Aqueous ammonia is a colourless liquid with a strong alkaline reaction (pH 11.6) and a penetrating pungent odour. When heated to decomposition, it emits toxic fumes of ammonia and oxides of nitrogen.

Uses

- Agriculture (fertiliser)
- Mining
- Manufacture of plastics and explosives
- Refrigerant
- Cleaning and bleaching agent
- Treatment of syncope in the form of smelling salts (*page no 57*).
- Household ammonia is 5 to 10%. Strong ammonia solution is 28% (sold in pharmacies).

Clinical Features

1. Inhalation produces such severe upper airway irritation that the victim seldom remains exposed for more than an instant, unless he is trapped. Symptoms include lacrimation, cough, dyspnoea, convulsions, coma, and death. There is glottic and laryngeal oedema, sloughing of bronchial mucosa, and chemical pneumonitis with pulmonary oedema.
2. If recovery from the acute event is incomplete, a chronic condition may set in called *reactive airways dysfunction syndrome* or *RADS.* This is a persistent, asthma-like syndrome and is also referred to as *irritant induced asthma.* It is different from *occupational asthma* since there is no evidence of atopy in individuals suffering from RADS, and the agents involved are generally not considered to be immunologically sensitising. However it is true that RADS can occur as a chronic occupational condition in people who work with chemicals. The inflammatory response of the airways in RADS most probably has a neurogenic aetiology involving the release of substance P from unmyelinated sensory neurons or C fibres. Substance P is a well-known culprit in neurogenic inflammation. Management is best effected by immediate (and permanent) exclusion from the source of exposure and symptomatic measures, though the response to beta₂ adrenergic agonist therapy is not as good as in occupational asthma.

3. Ingestion of ammonia solution produces corrosion of the alimentary tract and aspiration pneumonia. Nausea and vomiting occur frequently following ingestion. Swelling of the lips, mouth, and larynx, and oral or oesophageal burns may occur if concentrated ammonia solutions are ingested.
4. Dermal contact can result in deep, penetrating burns. Exposure to anhydrous ammonia stored at minus 28⁰ F may produce frostbite injury with thrombosis of surface vessels and subsequent ischaemia and necrosis.
5. Ocular exposure can result in immediate and serious chemical burn with rapid penetration into the interior of the eye. Conjunctivitis, lacrimation, corneal irritation, and temporary or permanent blindness can result. Total corneal epithelial loss may occur. Ammonia has greater tendency than other alkalies to penetrate and damage the iris, and to cause burns and cataracts in cases of severe exposure. Iritis may be accompanied by hypopyon or haemorrhages, extensive loss of pigment, and severe glaucoma.
6. Chronic exposure in workers may lead to initial complaints of chronic cough, dyspnoea on effort, bilateral infiltrates on chest X-ray, and lung function indices reflecting ventilatory and diffusion abnormalities Asthma and laryngitis have been reported in workers chronically exposed to ammonia.

Usual Fatal Dose

- About 5 to 10 ml of liquid ammonia.
- Inhalation of the gas at concentrations above 5000 ppm can be rapidly fatal. Fatalities may also occur from exposure to ammonia concentrations of 2500 to 4500 ppm if inhaled for 30 minutes.
- Mixing of ammonia with hypochlorite bleach results in the formation of chloramine, which causes a toxic pneumonitis (pulmonary oedema) following inhalation, and may produce residual pulmonary function abnormalities.

Diagnosis

1. Chest X-ray in dyspnoeic patients.
2. Early endoscopy to determine the extent of injury.
3. Barium swallow after 1 to 2 weeks to rule out oesophageal strictures.
4. Presence of ammonia in an unknown solution, stomach contents, or vomitus can be confirmed by placing an open bottle of concentrate HCl in the vicinity. This will produce copious white fumes of ammonium chloride. The determination of ammonia in air may be done using an ammonia-specific electrode, second derivatives spectroscopy, ion chromatography, or colourimetrically.

Treatment

Ammonia blood levels are generally not useful indicators of exogenous ammonia exposure or toxicity. It is normally found in human blood at a concentration of 80 to 110 mcg/100 ml. There can be a four-fold or greater rise in blood ammonia in some toxic liver diseases because the urease needed to convert ammonia to urea is found only in the liver. A serum concentration of 1,000 to 10,000 mcg/100 ml is considered toxic.

1. Ocular exposure should be treated with prolonged irrigation with water (30 minutes or more) until the eye reaches neutral pH as tested with a litmus paper in the conjunctival sac.
2. Dermal exposure requires washing with soap and water, followed by copious irrigation with water alone. Frostbite should be treated in the standard manner (*page no 350*).
3. Inhalation should be treated with oxygen, PEEP (positive end expiratory pressure), intubation, and bronchodilators. Intubation or tracheostomy may be life-saving following severe exposure if stridor, indicating laryngeal oedema, is present. Partial liquid ventilation has shown promise in preliminary studies.
4. If bronchospasm and wheezing occur, consider treatment with inhaled sympathomimetic agents.
5. In the case of ingestion, a small quantity of water or milk can be administered as a first-aid measure to dilute the chemical. Neutralisation with vinegar or weak acids is not recommended. Demulcents can be given. Do NOT attempt dilution in patients with respiratory distress, altered mental status, severe abdominal pain, nausea or vomiting, or patients who are unable to swallow or protect their airway. Diluents should not be force fed to any patient who refuses to swallow. Activated charcoal is of no benefit, and may induce vomiting and obscure endoscopy findings. **Stomach wash and emetics are contraindicated**. Obtain consultation concerning endoscopy as soon as possible, and perform endoscopy within the first 24 hours when indicated.
6. Antibiotics are indicated only when there is evidence of infection.
7. The use of corticosteroids for the treatment of caustic ingestion is controversial.

Forensic Issues

1. While poisoning with ammonia is not very common, most of the cases reported are suicidal in nature. Since the solution or gas even when weak has a distinct irritant smell, accidental poisoning is unlikely. Obviously, its properties preclude its choice for murder.
2. However, of late ammonia is being used as a spray to incapacitate victims of robbery. Serious eye injuries can result.

■ Formaldehyde

Synonyms

Dormol, fannoform, formalin, formalith, formic aldehyde, formol, lysoform, methanal, methyl aldehyde, methylene oxide, morbicid, oxomethane, oxymethylene.

Physical Appearance

1. Colourless gas with strong pungent smell.
2. Formalin is an aqueous solution of formaldehyde containing 37 to 40% formaldehyde and 10 to 15% methanol.* This is however generally referred to as 100% formalin. Therefore 10% formalin would actually mean a 1: 10 dilution of such a commercial preparation and contains 3.7% formaldehyde. Formalin is a clear, colourless liquid with a pungent odour. Some formaldehyde aqueous solutions can be amber to dark brown or even reddish in colour.
3. Formaldehyde is also available as a solid polymer, paraformaldehyde, in a powder or flaked form containing from 90 to 93% formaldehyde, and as its cyclic trimer, trioxane.

Uses and Sources

1. Industrial/Household: Formaldehyde is used in fertilisers, pesticides, sewage treatment, paper-making, preservatives, embalming fluids, disinfectants, foam insulation, urea and melamine resins, artificial silk and cellulose esters, explosives, particle board, plywood, air fresheners, cosmetics, fingernail polishes, water-based paints, tanning and preserving hides, and as a chemical intermediate. It is also used as a preservative and coagulant in latex rubber, and in photograph developing processes and chrome printing.
2. Medical/Veterinary: Therapeutically, formaldehyde has been used to treat massive haemorrhagic cystitis and hydatid cysts of the liver. It has also been used in veterinary medicine. Formaldehyde is sometimes used to sterilise dialysis machines. Dialysis patients using dialyser machines sterilised with formaldehyde receive a small dose with each treatment. The most frequent sequelae is a type of autoimmune haemolytic anaemia; rarely, peripheral eosinophilia may occur. Severe hypersensitivity reactions have been observed in a few of these dialysis patients, though the exact relationship of this to formaldehyde-sterilised equipment is unclear. Currently other sterilisers are in use such as a mixture of hydrogen peroxide and peracetic acid.
3. Formaldehyde is a common contaminant of smoke and is even present to a significant extent in tobacco smoke. Burning wood, cigarette smoking, and other forms of incomplete combustion emit formaldehyde. Addicts sometimes dip cigarettes of tobacco or cannabis in formaldehyde ("amp" or "dank") before smoking, in the belief that this produces a hallucinogenic effect and "body numbness". It is a dangerous practice and can result in encephalopathy, pulmonary oedema, rhabdomyolysis and coma.

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* Methanol prevents polymerisation of formaldehyde to paraformaldehyde which precipitates and settles to the bottom as a sediment. Other inhibitors of polymerisation used with formaldehyde include ethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, and isophthalobisguanamine.

Mode of Action

Formaldehyde is a protoplasmic poison and potent caustic. It causes coagulation necrosis, protein precipitation, and tissue fixation. Due to conversion in the body to formic acid there is usually profound metabolic acidosis, and this is aggravated by the concomitant presence of methanol (a common additive in formalin solutions) which is also broken down to formic acid. Delayed absorption of methanol might occur following ingestion of formalin if the formaldehyde causes fixation of the stomach.

Clinical Features

1. **Acute Poisoning:**
   a. Inhalation—cough, lacrimation, dyspnoea, chest pain, wheezing, rhinitis, anosmia, tracheitis, bronchitis, laryngospasm, pulmonary oedema, headache, weakness, dizziness, and palpitations.
   b. Ingestion—severe abdominal pain, vomiting, diarrhoea, haematemesis, tachypnoea, hypotension, cyanosis, altered mental status, and coma. Seizures, jaundice, albuminuria, haematuria, anuria, and metabolic acidosis have also been reported. Ulceration of mouth, oesophagus, and stomach is common. Strictures and perforation are possible delayed complications. Renal failure is a frequent complication in severe poisoning. Hepatotoxicity has been reported. Skin and mucous membrane may appear whitened. If the patient survives for more than 48 hours, the prognosis is good.
   c. Dermal exposure—dermatitis, brownish discolouration of the skin, urticaria, and pustulovesicular eruptions, may develop from dermal exposure. Concentrated solutions can cause coagulation necrosis.
   d. Ocular exposure—irritation, lacrimation, and conjunctivitis may develop with exposure to vapours. Eye exposure to solutions with high formaldehyde concentrations may produce severe corneal opacification and loss of vision. Inhalation or ingestion of formaldehyde has not been found to affect vision in humans or animals.

2. **Chronic Poisoning:**
   a. Formaldehyde is a known carcinogen in animals, and epidemiologic data among humans are mounting in implicating the chemical in human carcinogenesis. There are reports of increased incidence of nasopharyngeal cancers in individuals occupationally exposed to formaldehyde. Some epidemiologic studies have found a slightly elevated risk for lung cancer mortality with formaldehyde exposure. Suggestive association between occupational exposure to formaldehyde and deaths from breast cancer was seen in one case-control study.
   b. Asthma and dermatitis in sensitive individuals.
   c. Possible disturbances in memory, mood, and sleep; headache, and fatigue. Seizures may also be induced.
   d. Occupational exposure at recommended limits is not thought to present a reproductive risk. Formaldehyde exposure among female hospital workers did not correlate with an increase in spontaneous abortion in one study, but did correlate in another.
   e. Formaldehyde is a potent genotoxin and has been reported to be active in many short-term genetic tests, including the Ames Salmonella assay and other assays for mutation using bacteria, chromosome aberrations and sister chromatid exchanges in vitro and in vivo, and many assays detecting direct effects on DNA.

Usual Fatal Dose

About 30 to 50 ml of 100% formalin (*liquid*) ; more than 100 ppm (*gas*). Ingestion of as little as 30 ml of 37% (approximately 2 tablespoons) formaldehyde solution (formalin) has been reported to cause death in an adult. Exposure to air concentrations as low as 2 ppm can cause eye and upper respiratory irritation. Dermal exposure to formalin can result in irritation (*acute*), or allergic dermatitis (*chronic*) in susceptible individuals. Exposure to solutions of 2 to 10% may result in blisters, fissures, and urticaria.

Diagnosis

1. Formaldehyde plasma levels are not widely available, but may help in dialysis monitoring.
2. Monitor acid base status in symptomatic patients.
3. Monitor liver function tests.
4. Monitor haematocrit and haemoglobin concentration in dialysis patients repeatedly exposed parenterally to formaldehyde.
5. Monitor blood methanol levels after significant formalin ingestion.
6. Pulmonary function testing and nasal and bronchial provocation tests may be recommended in patients with signs and symptoms of reactive airways dysfunction following inhalation of formaldehyde.
7. The presence of a small amount of endogenously derived formate in human urine is normal; however, formate derived from the metabolism of formaldehyde, several other industrial compounds (methanol, halomethanes, acetone) and some pharmaceutical compounds may elevate the urine formate concentration above the normally expected values.
8. Urinary formic acid levels were shown to be subject to a great deal of individual variation and did not correlate with known exposures to formaldehyde. Formic acid is not a suitable biomarker for formaldehyde exposure.

Treatment

1. **Acute Poisoning:**
   a. Dilution with milk or water as a first-aid measure may help reduce corrosive effects. Emesis is contraindicated. Activated charcoal may be of benefit.
   b. Gentle gastric aspiration with a soft nasogastric tube (if the victim is seen within 1 hour of ingestion).
   c. Sodium bicarbonate IV.
   d. Haemodialysis.
   e. Ethanol infusion will help counteract methanol toxicity.
   f. Monitor electrolytes, fluids, acid-base, and renal function.

g. Dopamine or noradrenaline for hypotension
h. Watch for signs of gastrointestinal haemorrhage and perforation.
i. Early endoscopy to assess the degree of injury.
j. *Inhalation exposure:* Administer 100% humidified supplemental oxygen, perform endotracheal intubation, and provide assisted ventilation as required. Administer inhaled beta adrenergic agonists if bronchospasm develops. Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
k. Exposed skin and eyes should be flushed with copious amounts of water. Patients with ocular exposure to significant concentrations of formaldehyde should be evaluated by an ophthalmologist.

2. Chronic Poisoning:
a. Removal of patient from exposure.
b. Symptomatic measures.
c. Preventive measures include exhaust ventilation at place of work, use of goggles, face shields, gloves, and aprons.

Autopsy Features

1. Odour of formalin around the mouth and nostrils, and in the stomach contents.
2. Inflammatory oedema of oesophagus, larynx, and lungs.
3. Stomach (and sometimes the proximal small intestine) may show signs of "fixation" of tissues. Histological details may be well preserved.
4. Kidneys may reveal microscopic evidence of tubular necrosis.
5. **Autopsy Diagnosis:** To confirm the presence of formaldehyde in the gastric contents, a small quantity of the latter is dissolved in resorcinol in a test tube and sulfuric acid is gently poured along the sides of the tube. A red to violet coloured ring will develop at the junction of the two solutions.

Forensic Issues

Most reported cases of acute poisoning are either accidental or suicidal in nature. Chronic poisoning is invariably due to occupational exposure.

Some Indian studies conducted in embalming rooms of medical colleges revealed fairly high formaldehyde concentration of ambient air, stressing the need for fixing standard limits of exposure in work places in India like in the West.

■ Hydrogen Sulfide

Synonyms

Dihydrogen monosulfide, Dihydrogen sulfide, Hydrosulfide, Sulfur hydride, Hydrogen sulfuric acid, Hydrosulfuric acid, Sulfureted hydrogen.

Physical Appearance

Colourless gas, heavier than air, with a strong "rotten egg" odour. Because it rapidly paralyses olfactory nerve endings in high concentrations, odour is not a dependable means of detecting this gas. Natural gas containing hydrogen sulfide is termed "sour gas". Hydrogen sulfide is a liquid at high pressures and low temperatures, and is shipped as the liquefied material under its own vapour pressure.

Uses and Sources

1. Decay of organic sulfur-containing products such as fish, manure, sewage, septic tank contents, etc. It is produced by bacterial action on sewage effluents containing sulfur compounds when oxygen has been consumed by excessive organic loading of surface water ("sewer gas").
2. Industrial sources—pulp paper mills, leather industry, petroleum distillation and refining, vulcanising of rubber, heavy-water production, viscose-rayon production and coke manufacture from coal.
3. Natural sources—volcanoes, caves, sulfur springs, and subterranean emissions.
4. Other sources—burning of wool, hair, and hides can release hydrogen sulfide.
5. Hydrogen sulfide is used or encountered in farming (usually as agricultural disinfectants), brewing, tanning, glue making, rubber vulcanising, metal recovery processes, heavy water production (for nuclear reactors), in oil ("sour crude" refinery) and gas exploration and processing, in rayon or artificial silk manufacture, lithography and photo-engraving, fur-dressing and felt-making plants, slaughter houses, fertiliser cookers, beet sugar factories, analytical chemistry and dye production.

Usual Fatal Dose

- Exposure to concentrations approaching 250 ppm causes irritation of mucous membranes, conjunctivitis, photophobia, lacrimation, corneal opacity, rhinitis, bronchitis, cyanosis, and acute lung injury.
- At concentrations of 250 to 500 ppm, signs and symptoms include headache, nausea, vomiting, diarrhoea, vertigo, amnesia, dizziness, apnoea, palpitations, tachycardia, hypotension, muscle cramps, weakness, disorientation, and coma.
- At concentrations of 750 to 1000 ppm, victims may experience abrupt physical collapse or "knock down". Higher concentrations may also result in respiratory paralysis, asphyxial seizures, and death. The mortality rate is in the range of six per cent.

Toxicokinetics

After absorption, H_2S is detoxified in the body to thiosulfate and polysulfides by enzymatic and non-enzymatic oxidation of sulfides and sulfur. This reaction is catalysed by oxyhaemoglobin. As per recent studies, hydrogen sulfide is metabolised by oxidation to sulfate, methylation, and reaction with metalloproteins (responsible for the most serious toxic effects).

Mode of Action

Like cyanide (*vide infra*), H_2S is a cellular poison and inhibits cytochrome oxidase by disrupting electron transport. In fact it is said to be a more powerful inhibitor of cytochrome oxidase than cyanide. The resulting inhibition of oxidative phosphorylation produces cellular hypoxia and anaerobic metabolism. Anaerobic metabolism further causes lactic acidosis. H_2S is also a strong respiratory irritant and reacts with the moisture on the surface of the mucous membrane to form sodium sulfide.

Clinical Features

1. **Acute Exposure:**
   a. Low-level exposure: keratoconjunctivitis, corneal ulceration (*gas eye*), rhinitis, bronchitis, pulmonary oedema. Injection of the conjunctivae, seeing coloured halos, ocular pain, corneal bullae, blurred vision and blepharospasm may be noted following exposure to 150 to 300 ppm. Olfactory fatigue may occur after 2 to 15 minutes of exposure at 100 ppm. Recovery of smell is slow, depends on the extent of exposure, and may require weeks to months.
   b. High-level exposure: headache, vertigo, nystagmus, vomiting, dyspnoea, convulsions, sore throat, cardiac dysrhythmias, and conduction defects. Inhalation exposure to 500 ppm for 30 minutes produces sweating, somnolence, weakness, amnesia, malaise, confusion, delirium, hallucinations, nystagmus and coma.
   c. Pure gas exposure: Death can result in seconds due to respiratory failure if the gas is inhaled in its pure form. Characteristics of a fatal exposure are rapid collapse, respiratory depression, tremors, blurred vision, cyanosis, seizures and tachycardia.
   d. Skin exposure: may result in severe pain, itching, burning, and erythema, especially in moist areas. Cyanosis may be noted.

   Recovery may be associated with neurological sequelae such as memory failure (*amnestic syndrome*), disorientation, delirium, and dementia. There may also be impairment of hearing, vision, and olfaction. Basal ganglia damage results in tremor, ataxia, and muscle rigidity. Some of these effects are irreversible.

2. **Chronic Exposure:**
   a. Results in headache, weakness, nausea, and weight loss.
   b. One report suggests basal ganglia abnormalities—ataxia, dystonia and choreoathetosis.
   c. An epidemiological study of Chinese female workers found an increased risk of spontaneous abortions associated with exposure to benzene, gasoline and hydrogen sulfide.

Diagnosis

1. Rotten egg odour in the vicinity of the patient.
2. Blackening of copper and silver coins in the patient's pockets, or darkening of jewellery.
3. Measurement of sulfide ion level in the blood by ion-selective electrode in combination with Conway microdiffusion cells. Levels higher than 0.05 mg/L are associated with toxic effects. Reliable results are obtained only if the analysis is done within 2 hours of exposure, and the sample had been tested without delay, because sulfide concentrations rise with tissue decomposition.

4. Presence of H_2S in the air at a scene of poisoning can be detected by exposing a strip of filter paper moistened with lead acetate. It will get blackened.
5. Monitor vital signs. Monitor pulse oximetry and/or arterial blood gases and chest radiograph in patients with respiratory signs or symptoms.
6. Measuring blood sulfide and thiosulfate levels or urinary thiosulfate levels may be performed to document the exposure but are not useful for emergency treatment. Whole blood sulfide concentration in normal subjects is less than 0.05 mg/L.
7. In fatal cases, confirmation of hydrogen sulfide poisoning can be done by measuring both sulfide and thiosulfate levels in blood.

Clinical (Toxic) Features

1. Respiratory arrest can occur.
2. Mydriasis, urinary retention, and seizures may occur, especially following large doses of mecamylamine. Tremor, hallucinations, and confusion may also follow high dose mecamylamine.

Treatment

Immediate removal of victim from contaminated area to fresh-air area. Rescuers must use self-contained breathing apparatus. Immediate supportive care should be given as most fatalities occur at the scene. Maximum oxygen flow and supportive care may be sufficient treatment without the need to use nitrites. Seizures may have to be controlled with muscle relaxants (i.e. succinylcholine) to complete intubation. Symptomatic patients must be kept under observation for an average of 48 hours, and monitored closely for acute lung injury, dysrhythmias, peripheral neuritis, or some degree of neurological disturbance.

1. High-flow oxygen. Hyperbaric oxygen is said to be beneficial.
2. Nitrites are antidotal in action in H_2S poisoning. They induce methaemoglobinaemia. Since H_2S has greater affinity for methaemoglobin than for cytochrome oxidase, it dissociates from the latter and binds preferentially to the former resulting in the formation of sulfmethaemoglobin. Dose:
   a. An amyl nitrite perle is broken and inhaled for 30 seconds every minute until intravenous sodium nitrite can be begun.
   b Sodium nitrite, 10 ml of 3% solution (amounting to 300 mg), is given IV over 4 minutes.
   c. Unlike in the case of cyanide poisoning, sodium thiosulfate is not necessary in hydrogen sulfide poisoning because the body spontaneously detoxifies sulfmethaemoglobin.
3. Many cases of H_2S poisoning have been treated successfully with supportive care and oxygen, without resorting to nitrites.

a   Use **maximum** oxygen flow.

b   Monitor fluid and electrolyte balance.

c.   Watch for development of aspiration pneumonia and pulmonary oedema.

d.   Treat convulsions with conventional anticonvulsants. Refractory seizures may have to be managed by succinylcholine (with ventilatory support).

e.   Treat metabolic acidosis in the usual way.

Autopsy Features

1.   Greenish discolouration of grey matter of brain, viscera, and bronchial secretions.

2.   Characteristic odour.

3.   Pulmonary oedema.

4.   Generalised visceral congestion with scattered petechiae.

5.   Decomposition is said to be faster in hydrogen sulfide-related death.

Forensic Issues

Most cases of poisoning are accidental in nature arising out of industrial or occupational mishaps. Cleaning out sewers replete with hydrogen sulfide can pose an occupational risk, which can sometimes be potentially life-threatening.

■ Methyl Isocyanate (MIC)

Methyl isocyanate (MIC) is one of a group of isocyanates, the others being toluene di-isocyanate (TDI) and diphenylmethane di-isocyanate (MDI).

Physical Appearance

Colourless liquid with a sharp odour, which becomes gaseous at 39^0C. It is an extremely reactive chemical and needs to be stored carefully. Contact with water results in an exothermic reaction.

Methyl isocyanate is produced by heating metal cyanates or by heating N,N-diphenyl-N'-methylurea.

Uses

■   Manufacture of carbaryl (a carbamate pesticide).

■   Manufacture of polyurethane articles (plastics, urethane foam, adhesives, etc.).

Mode of Action

Methyl isocyanate (MIC) is a powerful respiratory irritant. Even brief exposure at high concentrations may cause severe injury, burns, or death.

Usual Fatal Dose

At 2 ppm, no odour is generally discernible, but irritation and lacrimation may be noted. Symptoms become more marked at 4 ppm and unbearable at 21 ppm.

Exposures to breathing zone concentrations of 0.5 ppm are likely to produce a respiratory response.

Clinical Features

1.   Inhalation of MIC gas produces immediate lacrimation, photophobia, lid swelling, and corneal ulceration; cough, choking sensation, dyspnoea, chest pain, haemoptysis, pink frothy discharge from nose, and pulmonary oedema; less commonly vomiting, convulsions, and coma. Metabolic acidosis has been reported.

2.   Dermal exposure results in erythema and vesiculation.

3.   Ocular exposure can cause permanent damage. A 40% increased incidence of trachoma, 36% increased risk of other lid infection and 45% increased incidence of irritant symptoms were noted in the exposed population of Bhopal resulting in a "Bhopal eye syndrome". A follow-up study three years after the Bhopal methyl isocyanate exposure demonstrated an excess of eyelid infection, decreased visual acuity, cataracts, and eye irritation among survivors as compared to controls.

4.   There is conflicting data as to whether methyl isocyanate is foetotoxic; however, it crosses the placental barrier. Reports from Bhopal, and animal studies suggest a high degree of adverse reproductive effects and teratogenicity. Long-term effects after survival include RADS (*reactive airways dysfunction syndrome, page no 351*), and pregnancy-related problems: high incidence of spontaneous abortions, and increased perinatal mortality.

5.   Respiratory function and visual acuity has remained abnormal among the persons exposed in the Bhopal incident for at least two years, and longer in those of close proximity to the 1984 accident. Lung function showed mainly restrictive changes with small airway obstruction and interstitial deposits. Pulmonary function testing performed 1–7 years after the Bhopal accident demonstrated that deterioration in respiratory function occurred in gas-exposed patients as a consequence of accumulation of inflammatory cells (macrophagus and lymphocytes). The intensity of the inflammatory response was greatest in the most severely exposed patients.

Treatment

Monitor ECG, chest X-ray, pulse oximetry, peak air flows, arterial blood gases, serum electrolytes, and renal and hepatic function in symptomatic patients. High-performance liquid chromatography (HPLC) is specific and sensitive for the detection of MIC in blood.

1.   Decontamination of skin and eyes with saline. Remove contact lenses and irrigate exposed eyes with copious amounts of room temperature 0.9% saline or water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist after 15 minutes of irrigation, an ophthalmologic examination should be performed. Topical antibiotics may be useful in secondary infection. Severe iritis may be treated with topical atropine or homatropine.

2.   Ingestion: emesis, activated charcoal.

3.   Inhalation: covering the face with a wet cloth immediately during exposure may minimise toxicity. Move patient from the toxic environment to fresh air. Monitor for respiratory distress. Observation for 72 hours is advisable to detect delayed onset of acute lung injury. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.

4. Oxygen, endotracheal intubation, assisted ventilation as required
5. Bronchodilators and corticosteroids may be beneficial. Administer beta$_2$ adrenergic agonists, inhaled ipratropium, and systemic corticosteroids (e.g. prednisone 1 to 2 mg/kg/day).
6. Antibiotics are indicated only when there is evidence of infection.
7. Supportive measures.
8. Isocyanates are **not** the same as cyanides and antidotes for the latter such as nitrites and sodium thiosulfate must **not** be used for the former. Effects of cyanide poisoning have been noted but this is most likely due to impurities.

Autopsy Features

1. Haemorrhages and cerebral oedema, cherry red colour of blood, fatty infiltration of the liver, and renal tubular necrosis were the principal autopsy findings of Bhopal victims.
2. Signs of asphyxia.
3. Pulmonary and cerebral oedema.
4. Generalised visceral congestion.

Forensic Issues

Methyl isocyanate (MIC) was involved in one of the most devastating gas disasters, which occurred in Bhopal, Madhya Pradesh in 1984, leaving more than 2000 people dead (unofficial estimates put the figure at more than 10,000), and more than 200,000 injured. The incident occurred in a small pesticides division of Union Carbide Company (**Fig 26.1**) manufacturing carbaryl (a carbamate), for which methyl isocyanate is required. This deadly chemical was stored in huge, double-walled stainless steel tanks, one of which burst on the night of December 2, 1984. More than 24,000 kg of MIC gas escaped over the next several hours into the atmosphere forming an ominous white cloud that drifted rapidly over the surrounding heavily populated neighbourhood killing thousands in their sleep and incapacitating several thousands more.

■ Phosgene

Synonyms

Carbonyl chloride, Carbon oxychloride, Chloroformyl chloride.

Fig 26.1: Remains of the Union Carbide Company at Bhopal

Physical Appearance

Colourless gas, heavier than air, with an odour of freshly-cut hay. At high concentrations, the gas has an odour described as suffocating, strong, stifling, or pungent. Below 0–8.3^{0}C or when compressed, phosgene condenses to a colourless to light yellow, non-combustible, highly toxic, fuming/volatile liquid that produces poisonous vapour and sinks in water.

Uses and Sources

- High temperature decomposition of chlorinated hydrocarbons such as carbon tetrachloride, chloroform, and methylene chloride yields phosgene.
- Phosgene and chlorine may be formed by burning polystyrene.
- Solvents, paint removers (when exposed to heat) yield phosgene.
- Phosgene is used as an intermediate in the manufacture of industrial chemicals such as isocyanates (e.g. toluene diisocyanate, polymethylene polyphenylisocyanate, etc.) and their derivatives (polyurethane and polycarbonate resins), carbamates, and chloroformates.
- Phosgene is used in the manufacture of insecticides, herbicides, and pharmaceuticals (especially barbiturates).

Usual Fatal Dose

In concentrations of 3 to 5 ppm, irritation of the eyes, throat and upper respiratory tract are noted. Total dose (concentration in ppm multiplied by time of exposure in minutes) determines the risk of pulmonary oedema. A cumulative dose of 50 ppm × min can result in delayed pulmonary oedema; a dose of 150 ppm × min will probably result in pulmonary oedema, and a dose of 300 ppm × min is likely to be fatal. Exposure to 25 ppm is extremely dangerous and greater than 50 ppm may be rapidly fatal.

Mode of Action

Phosgene is hydrolysed in the body to hydrochloric acid which produces a systemic inflamatory response. It also stimulates the synthesis of lipoxygenase-derived leukotrienes causing pulmonary oedema. Further, phosgene increases pulmonary vascular permeability, leading to increased fluid accumulation in the interstitial and alveolar compartments. The ability of the lymphatics to clear the excess fluid is exceeded, resulting in gas diffusion abnormalities and pulmonary oedema.

Clinical Features

Phosgene gas has low water solubility and thus can be deeply inhaled into the lung before an individual is aware of significant exposure.

1. **Stage I:** Coughing, choking, lacrimation, nausea, vomiting, headache, conjunctivitis, rhinitis, pharyngitis, bronchitis, and upper respiratory tract irritation may occur after exposure to concentrations exceeding 3 to 5 ppm. Brief exposure to 50 ppm or greater may be rapidly fatal. Eye irritation is not a significant warning property. Exposures to 2 ppm may not cause eye irritation, but can result in significant, delayed respiratory effects.

2. **Stage II:** Symptom-free interval lasting from half an hour upto 1 to 2 days.
3. **Stage III:** Progressive pulmonary oedema sets in with rapid, shallow respiration, cyanosis, and painful, paroxysmal cough producing frothy whitish or yellowish liquid. Hypoxia, hypovolaemia, and circulatory failure may lead to death. It is generally felt that if the victim survives 24 to 48 hours, the prognosis will be favourable. However, patients who survive exposure with pulmonary oedema may have persistent complaints of exertional dyspnoea and reduced exercise capacity and abnormal pulmonary function tests for months.
4. Severe dermal burns or frostbite may develop following skin exposure to the liquefied material.
5. Pulmonary fibrosis and emphysema may develop after chronic exposure.

Diagnosis

There is no specific method of diagnosis. Chest X-ray may reveal incipient toxic pulmonary oedema much earlier than overt clinical manifestations.
1. Plasma phosgene levels are not clinically useful.
2. Monitor arterial blood gases and/or pulse oximetry, pulmonary function tests, and chest X-ray in patients with significant exposure.
3. Serial chest X-rays are recommended if significant exposure is suspected as effects may be delayed.
4. Monitor fluid balance if pulmonary oedema is developing.

Treatment

1. Rest and warmth (especially important during the latent stage).
2. Humidified oxygen, intermittent positive pressure ventilation (IPPV), positive end-expiratory pressure (PEEP), etc.
3. Codeine phosphate for cough (30 to 60 mg).
4. Diuretics in combination with PEEP may help to ameliorate interstitial oedema.
5. **Steroid therapy:** Steroids used soon after exposure may lessen the severity of pulmonary oedema. Betamethasone valerate, beclomethasone dipropionate, or dexamethasone sodium phosphate is generally recommended. The initial dose is five times that conventionally used in asthma, followed by about half the dose for 12 hours, and then standard asthma dosages for the subsequent 72 hours. Systemic therapy can be started simultaneously with methyl prednisolone 2 grams IV or IM., followed by the same dose 12th hourly for upto 5 days. Alternatively, 1000 mg prednisolone can be given IV on the first day followed by 800 mg/day for the next 2 days, 700 mg/day for 2 more days, and then progressively reducing the dosage quickly.
6. One proposed regimen for preventing pulmonary oedema in adults is as follows:
   a. Ibuprofen 800 mg (at least one dose).
   b. Methylprednisolone 1 gram intravenously (or equivalent corticosteroid), or dexamethasone phosphate 10 mg aerosol (may be less effective than IV administration).
   c. Aminophylline 5 mg/kg loading dose followed by 1 mg/kg every 8 to 12 hours to maintain a serum level of 10 to 20 mcg/ml.
   d. Terbutaline 0.25 mg subcutaneously.
   e. N-acetylcysteine 10 ml of a 20% solution aerosolised.
   f. Oxygen as needed.
7. Antibiotic and antifungal treatment may be necessary if steroids are used.
8. Adrenaline can be used for the relief of acute bronchial spasm.

Autopsy Features

Massive pulmonary oedema is the most striking feature.

Forensic Issues

Phosgene was used as part of chemical warfare during World War I. Prepared for the first time in 1812, phosgene had a large scale presence in World War I as an asphyxiant war gas. The first chemical agent of warfare in modern times was chlorine, used by the German army at Ypres in 1915 against the Allies. Shortly thereafter, the Germans began mixing the chlorine with phosgene, or deployed phosgene alone as a weapon. Phosgene, together with arsenicals, blister agents, and mustard gas (also introduced during World War I) have been estimated to be responsible for approximately 1.3 million casualties during the war, including at least 90,000 fatalities. By the time World War I concluded, mustard gas was the most widely used, but phosgene caused the most deaths.

Today most cases are due to accidental occupational exposure.

SYSTEMIC ASPHYXIANTS

■ Carbon Monoxide

Synonyms

Carbonic oxide, Carbon oxide, Exhaust gas, Flue gas.

Physical Appearance

Pure carbon monoxide is an odourless, colourless, non-irritating gas, which is lighter than air.

Sources

1. Incomplete combustion of almost any form of fuel (wood, charcoal, gas, kerosene).
2. Automobile exhaust.
3. Fires.
4. Paint remover (especially methylene chloride).
5. Tobacco smoke.
6. Endogenous CO resulting from haeme degradation can never reach toxic levels on its own. Normal CO level in plasma is in the range of 1 to 5 % and may rise upto 7 to 8 % in smokers.

Usual Fatal Dose

This is usually expressed in terms of plasma concentration of the gas (carboxyhaemoglobin or COHb). COHb level exceeding 50 to 60 % is potentially lethal.

A carbon monoxide concentration of 5000 ppm in air is lethal to humans after five minutes of exposure.

Toxicokinetics

The lungs avidly absorb CO which combines with haemoglobin (85%) and myoglobin (15%). Elimination occurs exclusively through the lungs.

Mode of Action

- Carbon monoxide has an affinity for haemoglobin which is 230 to 270 times greater than that of oxygen. Therefore, in spite of adequate partial pressure of oxygen (PO_2) in blood, there is reduced arterial oxygen content. Further, CO causes a leftward shift of the oxyhaemoglobin dissociation curve,* thus affecting the offloading of oxygen from haemoglobin to the tissues. The net result of all this is the decreased ability of oxygen to be carried by the blood and released to tissues.
- Apart from the COHb-mediated hypoxia described, it is postulated that CO may also interfere with cellular respiration by inactivating mitochondrial cytochrome oxidase.
- CO poisoning in experimental animals has been associated with brain lipid peroxidation, and thus a free radical peroxynitrate is produced which causes cellular toxicity. In the brain this can cause further mitochondrial dysfunction, capillary leakage, leukocyte sequestration and apoptosis. This change primarily occurs during the recovery phase when lipid peroxidation occurs, which produces an overall reversible demyelination in the brain. Common sites for CO-induced brain injury are the basal ganglia, the cerebral white matter, hippocampus and cerebellum.
- Cardiac damage resulting in dysrhythmias is mainly because of reduced oxygen carrying capacity of the blood due to COHb formation, and partially due to the binding of CO with myoglobin.
- The profound hypotension encountered in severe CO poisoning is due to 2 reasons: activation of guanyl cyclase which relaxes smooth muscle, and displacement of nitric oxide from platelets resulting in vasodilation.
- In a study on rats, the delayed effects of neuropathology following carbon monoxide poisoning were studied. The authors hypothesised that acute CO-mediated oxidative stress can cause alterations in myelin basic protein (a major myelin protein of the CNS), and that the immune response to these modified proteins can precipitate delayed neurological dysfunction. The results suggested that following CO poisoning adduct formation between MBP and malonylaldehyde, a reactive product of lipid peroxidation, causes an immunological cascade resulting in part in a loss of antibody recognition of MBP. Thus, the neuropathology observed following acute CO exposure may be linked to an adaptive immunological response to chemically modified MBP. The authors suggested that these findings may have clinical application in the treatment of delayed neurotoxicity with anti-inflammatory agents.

Clinical Features

1. **Acute Exposure:**
   a Mentioned in relation to severity of exposure in **Table 26.1**. The earliest manifestations are often non-specific and may be confused with other conditions. In fact misdiagnosis is quite common unfortunately with CO exposure, especially in India where awareness about poisoning is generally low. **Table 26.2** outlines the important conditions in the differential diagnosis.
   b. Two of the "classical" features of CO poisoning mentioned in several textbooks on toxicolgy are actually quite rarely encountered in clinical practice:
   – Cherry red colour of blood and tissues (including skin) is seen only in 2 to 3 % of cases.
   – Development of cutaneous bullae (blisters) is another uncommon finding in clinical practice.
   c. It has been suggested that a more thorough examination of the eye (i.e. electrodiagnostic tests) would reveal that retinal haemorrhage may occur frequently, and that it can occur superficially or deeper in the nerve fibre layer (flame haemorrhage), and is often peripapillary. The venous changes that develop include engorgement and tortuosity, while oedema of the optic disc may be observed. All these changes reflect the hypoxic injury to the retina due to CO poisoning. Paracentral scotomata, homonymous hemianopia, tunnel vision, temporary blindness, and permanent blindness are known sequelae.

Table 26.1: Acute Carbon Monoxide Poisoning	
Severity	*Symptoms and Signs*
Mild (COHb < 30%)	Headache, nausea, vomiting, dizziness, exertional dyspnoea
Moderate (COHb 30 to 40%)	Chest pain, blurred vision, confusion, weakness, increasing dyspnoea, tachycardia, tachypnoea, ataxia, severe headache, syncope, flushing, cyanosis, perspiration, decreased vigilance, diminished manual dexterity, impaired sensorimotor task performance, prolonged reaction time, difficulty thinking, impaired judgement, loss of muscular control, tinnitus or roaring in the ears, drowsiness, hallucinations and cardiovascular toxicity
Severe (COHb > 40%)	Trismus, muscle spasms, convulsions, palpitations, disorientation, ventricular dysrhythmias, hypotension, myocardial ischaemia, skin blisters, pulmonary oedema, respiratory failure, involuntary evacuations, coma, collapse, and death

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* This is probably due to reduction in the erythrocyte 2,3-diphosphoglycerate concentration.

Table 26.2: Differential Diagnosis of Carbon Monoxide Poisoning

Alcoholic intoxication	Hyperventilation syndrome
Cardiac arrhythmias	Influenza
Cerebrovascular accident	Meningitis, encephalitis
Depression	Migraine
Epilepsy	Myocardial infarction
Food poisoning	Pneumonia

d. Although sensorineural hearing loss is associated with acute CO poisoning, chronic low dose exposure to CO may result in similar toxicity.

e. Myocardial ischaemia may be precipitated or aggravated by CO; reported even with low CO levels in patients with pre-existing coronary artery disease. Electrocardiographic changes of CO poisoning include S-T segment depression or elevation, T wave abnormalities, atrial fibrillation, and intraventricular conduction block.

f. Muscle necrosis, rhabdomyolysis, compartment syndrome and elevated CPK have been reported following toxic exposures. Elevated CPK and myoglobinuria are characteristic. Delayed movement disorders have been reported following CO poisoning. Haematuria, albuminuria, renal failure, myoglobinuria, and acute tubular necrosis have developed with severe poisoning. Lactic acidosis may occur.

g. Bullous lesions associated with carbon monoxide poisoning generally appear within 24 hours of exposure and are usually located on the palms and soles. They are not a common occurrence.

h. High susceptibility groups to CO poisoning include infants (high respiratory and metabolic rates), pregnant women, the elderly, individuals with anaemia, haematologic disorders and patients with a history of ischaemic heart disease or chronic obstructive lung disease. Children may be more susceptible than adults to the neurological effects of CO, but no statistical comparisons exist to support this claim.

i A "post CO syndrome", including headache, nausea, and weakness may persist for 2 to 3 weeks following exposure to carbon monoxide. Severe residual or delayed neurologic effects ("interval" form of CO poisoning) may also occur after acute CO poisoning. Demyelination in the central nervous system and other effects may occur 48 to 72 hours after exposure. The patient should be observed carefully for CNS and other post-exposure hypoxic effects. The most commonly involved regions of the brain include the globus pallidus and the deep white matter. Signs and symptoms include mental deterioration, irritability, aggressive behaviour, apathy, disorientation, hypokinesia, akinetic mutism, distractibility, confusion, severe memory loss, delayed loss of consciousness, coma, gait disturbances, faecal and urinary incontinence, speech disturbances, tremor, bizarre behaviour, visual loss, movement disorders, chorea, peripheral neuropathy, Tourette's syndrome, and a Parkinsonian syndrome. Physical findings include masked face, glabella sign, grasp reflex, increased muscle tone, short stepped gait, retropulsion, intention tremor, hyperreflexia, clonus, flaccid paresis, Babinski's sign, ataxia, and choreoathetosis.

j. Another syndrome of delayed subtle neuropsychologic effects has been described. Effects include headache, anorexia, nausea, apathy, lethargy, forgetfulness, subtle personality changes and memory problems, irritability and dizziness. These patients generally do not have gross abnormalities on physical or neurologic exam. Neuropsychometric testing is usually required to identify abnormalities.

k. Recovery from the acute episode may be followed by permanent neurological sequelae such as dementia, amnesia, psychosis, Parkinsonism, paralysis, chorea, blindness, apraxia, agnosia, amnestic/confabulatory state, depression, peripheral neuropathy, urinary/faecal incontinence, vegetative state, and akinetic mutism. Personality changes may also occur, with increased irritability, verbal aggression, violence, impulsivity and moodiness.

2. **Chronic Exposure:** The following features are seen in chronically poisoned patients—
   a. Headache, dizziness, confusion, intellectual deterioration.
   b. Weakness, nausea, vomiting, abdominal pain.
   c. Paraesthesias
   d. Visual disturbances: homonymous hemianopia, papilloedema, scotomata, retinal haemorrhages.
   e. Hypertension, hyperthermia.
   f. Cherry red skin.
   g. Palpitations, aggravation of angina, intermittent claudication.
   h. Elevated RBC and WBC count.
   i. Albuminuria, glycosuria.
   j. Permanent neurological sequelae are common and include amnesia, agnosia, apraxia, rigidity, personality changes, psychosis, blindness, and hearing impairment.
   k. CO exposure during pregnancy is teratogenic, depending upon the stage of pregnancy. The foetus is more vulnerable to CO poisoning than the mother. Exposure to the foetus can result in permanent brain damage, including mental retardation, limb malformation, hypotonia, areflexia, basal ganglia damage, neuronal loss in the cerebral cortex, microcephalus, low infant birth weight, telencephalic dysgenesis, seizures, and stillbirth.

Diagnosis

Summary—Determine COHb level when the patient is first seen and repeat every 2 to 4 hours until patient is asymptomatic, or level is within the normal range. Monitor ECG, electrolytes, CPK, urinalysis, arterial blood gases if symptomatic, or if the COHb level is greater than 20%. Pulse oximetry may not provide a reliable estimate of oxyhaemoglobin saturation.

1. Estimation of carboxyhaemoglobin level (COHb): Normal levels range from 0 to 5%, but in heavy smokers it may be as high as 10%. The usual method of estimation is a co-oximeter, which spectrophotometrically reads the percentage of total haemoglobin saturated with CO. Either arterial blood or venous blood (in lithium heparin tube) can be used. It must be borne in mind that COHb levels do not always correlate with clinical manifestations or the final outcome.

2. Pulse oximetry: It is a non-invasive method of measuring oxygen saturation and is relatively easy to perform, painless, rapid, and accurate. A special sensor is placed on a patient's finger, toe, or nose. The sensor consists of a light-emitting diode that projects two discrete wavelengths of light corresponding to saturated and unsaturated haemoglobin (660 and 940 nm) together with a photodetector.

   a. **Caution**: In CO poisoning, pulse oximetry gives higher readings than the true HbO_2 (oxyhaemoglobin) levels and may fail to alert the physician to potentially lethal hypoxia. COHb absorbs light almost identically to HbO_2 at 660 nm. The oximeter responds to COHb as if it were HbO_2. Similarly the oximeter overestimates oxygen saturation with increasing methaemoglobinaemia. A disparity between the oxygen saturation calculated from PaO_2 values and pulse oximetry readings in fact should alert the physician to the presence of methaemoglobinaemia.

3. Arterial blood gases: Partial pressure of oxygen is usually normal, but the oxygen saturation expressed as a percentage is decreased. A gap between the measured percentage HbO_2 and the calculated percentage HbO_2 indicates the necessity for measuring COHb. PCO_2 may be normal or slightly decreased. Metabolic acidosis is invariably present.

4. ECG: This may reveal myocardial damage in the form of ST depression or elevation, T wave flattening or inversion and dysrhythmias.

5. Chest X-ray: This may reveal ground-glass appearance, perihilar haze, peribronchial cuffing and intra-alveolar oedema.

6. CAT Scan: This may reveal low-density globus pallidus lesions which are predictive of neurological sequelae. Lucencies of the basal ganglia, particularly the globus pallidus is characteristic of severe carbon monoxide poisoning. Low density lesions of subcortical white matter, representing demyelination or necrosis, may also be seen.

7. MRI: Cytotoxic oedema and demyelination, as well as damage to white matter and basal ganglia are often detected accurately by MRI. In a study of CO-poisoned patients, MRI scans performed 6 months after exposure detected a 15 mm loss in the cross-sectional surface area of the corpus callosum, compared with MRI images obtained on the day of CO exposure. The effects appeared to be generalised atrophy, rather than sub-region specific alterations. The authors suggested that long-term brain effects of CO poisoning may be underestimated. T-2 weighted MRI may demonstrate abnormalities of the basal ganglia, particularly the globus pallidus. Diffusion MRI has been used as a more specific diagnostic aid following CO poisoning in some adults and children following exposure.

8. Positron Emission Tomography (PET Scan): In a study of two adults a few years after CO poisoning, PET scan imaging (findings indicated significant metabolic decreases in the orbitofrontal and dorsolateral prefrontal cortex as well as areas of the temporal lobe) was consistent with the residual neurological deficits observed in each patient. The authors suggested that PET imaging may be helpful in detecting the neuropathologic sequelae associated with chronic nonlethal CO poisoning.

9. Ancillary Investigations:

   a. Routine laboratory investigations often reveal elevated serum creatine kinase and lactate dehydrogenase levels, as well as creatinine. Hypokalaemia and hyperglycaemia are also usually present.

   b. Neuropsychometric testing is indicated following moderate-to-severe poisoning. Evaluated parameters included general orientation, digit span, trailmaking, digit symbols, aphasia screening, and block design. Equipment for doing this test include the WAIS set of nine blocks for block design testing (8991-135).

   c. Retinal haemorrhage is a common finding in CO poisoning. It has been suggested that careful eye exam may provide useful diagnostic information. Findings include superficial or deep retinal haemorrhage, venous changes (i.e. engorgement and tortuosity) and oedema of the optic disc.

10. Bedside Tests:

    a. Take 1 drop of blood and dilute with 10 to 15 ml of water. Compare with normal blood diluted in the same manner. Blood containing carbon monoxide is pink.

    b. Add 0.1 ml of blood to 2 ml of ammonium hydroxide solution (0.01 mol/L), and vortex-mix for 5 seconds. A pink tint in comparison with the colour obtained from a normal blood specimen suggests the presence of COHb.

    c. Dilute 1 ml of the patient's blood with 10 ml of water in a test tube and add to it 1 ml of a 5% solution of sodium hydroxide. If COHb is present, the solution will turn straw yellow (< 20% COHb) or pink (> 20% COHb). In the case of normal blood (HbO_2) the solution turns brown in colour.

    d. All the bedside tests are only screening tests and the results must be confirmed by other methods mentioned earlier, especially spectrophotometric estimation of COHb level.

Treatment

Admit all patients with neurologic signs or symptoms, chest pain, abnormal EKG, metabolic acidosis, and carboxyhaemoglobin level greater than 20%.

1. Immediate removal from the contaminated environment.
2. Oxygen (100%) through a tight-fitting mask or endo-tracheal tube, until COHb falls to 15 to 20%. Onset of acute lung injury after toxic exposure may be delayed up to 24 to 72 hours after exposure in some cases. Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
3. Monitor cardiac and respiratory status.
4. Patients who only develop minor symptoms such as headache, nausea and transient vomiting, who have normal mental status examinations and neuropsychometric tests, and who are not pregnant may be treated with 100% oxygen by non-rebreather mask and discharged when asymptomatic. Make sure patients are not returning to a carbon monoxide contaminated environment.
5. Watch for the development of cerebral oedema with serial neurologic exams, CAT scans, and fundoscopic examination. Hyperventilation (PCO_2 25 to 30 mmHg), head elevation (35^0), and mannitol (0.25 to 1 gm/Kg of 20% solution over 30 minutes) are recommended as initial management of raised intracranial pressure. The role of corticosteroids is controversial. Refractory cerebral oedema is due to cell death, and although mannitol, urea, glycerol, or other methods to reduce life-threatening cerebral oedema may be employed, they are unlikely to affect the outcome.
6. Metabolic acidosis must not be treated aggressively. Severe acidosis should be treated. However, a slight acidosis may be beneficial by shifting the oxygen-dissociation curve to the right, allowing more oxygen to be released to the tissues. Therefore alkalaemia should be avoided. Sodium bicarbonate is not recommended.
7. Administer supplemental glucose to prevent hypoglycaemia.
8. Convulsions can be controlled with IV diazepam or phenytoin in the usual manner.
9. Physical activity should be restricted for at least 1 month after the exposure to minimise the incidence of cerebral demyelination.
10. **Antidote:** Hyperbaric oxygen.
    a   Several authorities consider administration of hyperbaric oxygen (HBO) to be antidotal in its effects in carbon monoxide poisoning. It involves inhalation of oxygen at a pressure greater than 1 atmosphere absolute (ATA). 100% oxygen at ambient pressure reduces the half-life of COHb to 40 minutes, while at 2.5 atmospheres absolute it is reduced to just 20 minutes. Hyperbaric oxygen should be instituted with 30 minutes of 100% oxygen at 3 ATA, followed by 2 ATA for 60 minutes or until a COHb level less than 10% is achieved.

b. HBO also increases the amount of dissolved oxygen by about 10 times which is an additional benefit. Further, animal studies indicate that HBO prevents lipid peroxidation in the brain after loss of consciousness from CO exposure, thereby minimising the incidence of neurologic damage. Studies among human victims of CO poisoning indicate significantly reduced incidence of neuropsychiatric symptoms in those treated with HBO as compared with those who receive normobaric oxygen.
c. Normally a dramatic recovery of consciousness is seen during hyperbaric treatment. Patients remaining unconscious may be given further hyperbaric oxygen treatments.
d. It must be borne in mind however, that HBO therapy is associated with serious risks such as cerebral gas embolism, rupture of tympanic membranes, visual deficits, reversible myopia, sweating, palpitations, syncope, claustrophobia, and oxygen toxicity (convulsions and pulmonary oedema). So the routine administration of HBO is not recommended in every case of CO poisoning.
e. Severely ill patients should NOT be transferred to a facility with a hyperbaric chamber until they have been stabilised: an airway should be secured, ventilation should be adequate, convulsions should be controlled, and blood pressure and perfusion should be acceptable.
f. The decision to use hyperbaric oxygen during pregnancy must be based on several factors: The maternal need for HBO, the proven foetotoxicity of CO, the theoretical foetotoxicity of HBO, and the absence of demonstrated efficacy of HBO to prevent the foetotoxicity of CO.
g. **Table 26.3** lists the important indications for HBO therapy.
h. Hyperbaric oxygen is also used in the treatment of poisoning due to cyanide, hydrogen sulfide, smoke, methylene chloride, and carbon tetrachloride.

Table 26.3: Indications for Hyperbaric Oxygen Therapy in Carbon Monoxide Poisoning

1. Coma
2. Seizures
3. Focal neurological deficits
4. COHb > 25% (> 15% in children and pregnant women)
5. Ischaemic chest pain or ECG abnormalities
6. Persistent neurological symptoms (headache, ataxia, confusion)
7. Abnormal neuropsychiatric examination*
8. Presence of hypoxia, myoglobinuria, or abnormal renal function*
9. Abnormal chest X-ray*

*Controversial indications

Autopsy Features

1. Cherry red (pink) colour of skin (**Fig 26.2**), especially noticeable in the areas of postmortem lividity. In dark complexioned individuals, the colour can be made out more easily in the inner aspects of lips, nail beds, tongue, and palms and soles.
2. Cutaneous bullae (skin blisters) are sometimes seen in the regions of the calves, buttocks, wrists, and knees.
3. Cherry pink colour of blood and tissues. If blood is diluted with water in a test tube and held against light or a white background, the pink colour will be more easily made out.
4. Pulmonary oedema.
5. The white matter of the brain is said to be firmer than usual in CO poisoning, and the brain as a whole retains its shape better after removal from the skull cavity.
6. In a prospective study of residential fire victims, soot deposits were monitored and were not found to be predictive of CO poisoning. Although the absence of soot makes carboxyhemoglobinaemia less likely, this study indicated that specificity was low in determining actual CO poisoning.
7. In delayed deaths, necrosis and cavitation of basal ganglia, especially globus pallidus and putamen are commonly described features. Petechiae and ring shaped haemorrhages may be seen in the white matter. Heart may show focal areas of necrosis.
8. It is mandatory to collect blood for chemical analysis preferably from a peripheral vein. But unlike in other cases of poisoning, if blood is difficult to obtain from a vein, heart blood or blood from body cavities or even bone marrow can be used for analysis. Sodium fluoride may be added as a preservative (see *page no 35*).

Forensic Issues

- Next to carbon dioxide, carbon monoxide is the most abundant atmospheric pollutant and is progressively increasing in concentration. Apart from its role as an environmental contaminant, CO is responsible for a significant number of deaths encountered in forensic practice. Once upon a time

Fig 26.2: Cherry pink colour—carbon monoxide poisoning

when domestic gas consisted of *coal gas* (which contained upto 7% CO), suicides accomplished with it at home were very common in Western countries. "Putting the head in the gas oven" was the most common form of self-destruction in countries such as the UK. Now that *coal gas* has been replaced by *natural gas* (which contains little or no CO), a major means of domestic suicide has been removed. But incomplete combustion of *natural gas* can release CO which can cause accidental poisoning in ill-ventilated areas.

- Today the suicidal use of CO is utilised in a different way. The victim utilises the exhaust fumes of a motor car either by merely sitting in a closed garage with a window of the car open while the fumes build-up in the enclosed area, or a device is fitted (e.g. a hose) to pipe the gas into the interior of the car with all windows rolled up. Such cases are however less common in India and other Asian countries while they are quite frequently reported in Western countries. The use of catalytic converters in automobiles has lessened the likelihood of death resulting from a suicide attempt via inhalation of exhaust fumes.
- Accidental CO poisoning can occur in several other situations apart from domestic exposure. Internal combustion engine exhaust fumes, malfunctioning home heating systems, gas hot water heaters, gas clothes dryers, charcoal and poorly vented wood/coal stoves, space heaters, gas and kerosene lanterns, and fires in buildings are common sources of carbon monoxide poisoning. Defective exhaust system of an automobile can allow gas to percolate through the floor or engine bulkhead into the interior. Sometimes the driver may become so affected that he loses control of the vehicle resulting in a crash. The same applies to leakage of gas into the cockpit of a plane (especially light aircraft) leading to the disablement of the pilot.
- Tobacco smoke is an important source of carbon monoxide contamination of environment. Mainstream cigarette smoke, that which is inhaled into the smoker's lungs, can contain as much as 5% carbon monoxide by volume. Sidestream smoke, the source of environmental exposures, contains between 70 and 90% of the total CO per cigarette. In indoor areas where smoking is permitted, carbon monoxide levels can exceed 11 ppm; this compares to less than 2 ppm in most non-smoking areas.
- A common cause of accidental CO poisoning resulting in mass deaths is a conflagration where-in a large building (hotel, theatre, block of flats, etc.) goes up in flames. The majority of deaths in such cases are caused by inhalation of smoke (containing CO) rather than by burns. A high-risk of CO poisoning exists for fire fighters who often enter enclosed spaces in structural fires. Use of respiratory protective gear can prevent lethal CO exposure, but are not routinely used in all phases of fire fighting.
- Homicidal poisoning with CO is rare, but cases have been reported (and continue to be reported) from time to time.
- Sudden infant death syndrome (SIDS) may be a misdiagnosis of carbon monoxide toxicity in some cases.

■ Cyanide

Physical Appearance

- Cyanide occurs as a gas or liquid or solid. In its gaseous state it is referred to as hydrogen cyanide (HCN); the liquid form is referred to as hydrocyanic acid or Prussic acid; salts of cyanide occur as solids (white, crystalline powder).
- The odour of cyanide, especially the gas, is described as "bitter almond" in nature. However, it cannot be perceived by everybody. About 20 to 40 % of the human population (mostly males) do not possess this capacity which is inherited as a sex-linked recessive trait. Some sources put this at 40 to 60%.
- Hydrogen cyanide is a colourless flammable gas with a faint bitter almond odour. Hydrocyanic acid is the liquefied form of hydrogen cyanide, and is a bluish-white liquid with a faint, bitter almond odour.
- Cyanogen is a colourless, flammable gas with a pungent, almond-like odour. Cyanogen bromide is a colourless or white crystalline solid with a penetrating odour. Cyanogen chloride is either a colourless irritant gas or liquid with a pungent odour. Cyanogen azide is a clear, colourless, oily liquid, while cyanogen iodide is a colourless, solid poison.
- Potassium, sodium, and calcium cyanides are white, deliquescent, non-combustible solids with a faint bitter almond odour. Zinc cyanide is an odourless, greyish-white to white solid-powder.
- Calcium cyanamide is a white crystalline solid. Dimethyl cyanamide is a colourless liquid.
- Related compounds include cyanuric acid, cyanuric chloride, cyanoacetamide, cyanoacetonitrile, cyanoacetic acid, cyanodiethylamide, and cyanide compounds of phosphorus and mercury.
- The taste of cyanide has been described as bitter and burning in nature.

Uses

1. *Industrial*: Electroplating, metal processing, extraction of ores, photographic processes, production of synthetic rubber, and manufacture of plastics.
2. *Agriculture*: Insecticide and rodenticide.
3. *Medicinal*:
   a. Laetrile (synthetic amygdalin) is used as a chemotherapeutic agent for cancer in the USA though studies have shown it is not efficacious, and in fact can be hazardous.

   b. Sodium nitroprusside is an effective antihypertensive and is especially useful in treating hypertensive crisis as an intravenous infusion. But it is metabolised in the body to cyanide and infusions exceeding the recommended dose can lead to cyanide toxicity.
4. *Laboratory*: Cyanide is used in various laboratory processes.
5. *Household*: Household uses of cyanide include fumigation, silver-polishing, and as fertilisers, rodenticides, and insecticides.
6. *Warfare*: Cyanogen and cyanogen halides (cyanogen bromide, cyanogen chloride, cyanogen iodide) release hydrogen cyanide and have been used as military chemical warfare agents.

Sources

1. *Plants*: Cyanide is present in the form of cyanogenic glycosides in a wide variety of plants and plant parts (**Table 26.4**). Hydrolysis of these glycosides by digestive enzymes can release cyanide in the GI tract.
2. *Combustion*:
   a Burning of plastic furniture (polyurethane or polyacrylonitrile).
   b. Burning of silk or wool.
3. Cigarette smoking—Each cigarette liberates 150 to 200 mcg of HCN.

Cyanide can be released by hepatic metabolism from various nitrile compounds, such as malononitrile, succinonitrile, acetonitrile, propionitrile and allynitrile following absorption into the body.

Usual Fatal Dose

- **Hydrogen cyanide:** Inhalation of 1 part in 2000 can kill instantaneously, 1 part in 10,000 within a few minutes, 1 part in 50,000 within a few hours. The upper limit of safety is 1 part in 100,000. As per American Conference of Governmental Industrial Hygienists (ACGIH), 1986, air concentrations of 0.2 to 0.3 mg/m^3 (200 to 300 parts per million) are rapidly fatal.
- **Hydrocyanic acid:** 50 to 100 mg.
- **Cyanide salts** (of sodium, potassium, or calcium)**:** 100 to 200 mg. Specifically for potassium or sodium cyanide, the minimum lethal dose has been estimated to be about 3 mg/kg.
- **Bitter almonds** (derived from *Prunus amygalis varamara*, a plant which grows in Kashmir)**:** 50 to 80 in number. Bitter almonds must not be confused with normal almonds, which are not only non-toxic, but actually delicious and nutritious (**Fig 26.3**).

Table 26.4: Cyanogenic Plants

Plant	Toxic Part	Cyanogenic Glycoside
Prunus species : cherry laurel, chokeberry, mountain mahogany, bitter almond, peach, apricot, plum and wild black cherry	Leaf, bark, seed	Prunasin or amygdalin
Sorghum species : sorghum, sudan grass, johnson grass, and arrow grass	Grain, shoot	Dhurrin
Apple, pear, crab apple	Seed	Amygdalin
Cassava, lima beans	Bean, root	Linamarin
Miscellaneous : christmas berry, velvet grass, jet berry bush, elderberry, bamboo, cycad nut	Bead, leaf, shoot, sprout	Unclear

Fig 26.3: Normal almonds (top) and bitter almonds (below)

Toxicokinetics

Absorption is rapid across both skin and mucous membrane. Ingestion of cyanide salts results in the release of HCN through the action of hydrochloric acid in the stomach, and is subsequently absorbed as the cyanide ion (CN^-). Cyanide is distributed to all organs and tissues via the blood, where its concentration in red cells is greater than that in plasma by a factor of 2 or 3. Toxicokinetics estimation in acute potassium cyanide poisoning treated with sodium nitrite-thiosulfate showed a volume of distribution (Vd) of approximately 0.41 L/kg.

Metabolism occurs mainly in the form of conversion to thiocyanate by the enzyme *rhodanese* (present in the mitochondria of liver and kidneys), which needs sodium thiosulfate for effective functioning. Half-life for the conversion of cyanide to thiocyanate from a nonlethal dose in man is between 20 minutes and 1 hour. Once the relatively nontoxic metabolite thiocyanate is formed it is excreted mainly in the urine. However, thiocyanate may accumulate in a patient with renal impairment resulting in thiocyanate toxicity.

Some of the cyanide is converted to cyanacobalamin (vitamin B_{12}) in the presence of hydroxocobalamin (vitamin B_{12a}).

Small amounts of cyanide are excreted in the breath and sweat producing the characteristic bitter almond odour.

Mode of Action

- The toxic effect of cyanide is mainly attributed to its production of a histotoxic anoxia by inhibition of cytochrome oxidase. This is a metalloenzyme essential for oxidative phosphorylation which is responsible for aerobic energy production. Cytochrome oxidase functions in the electron transport chain within mitochondria converting catabolic products of glucose into adenosine triphosphate (ATP). Cyanide inhibits cytochrome oxidase at the cytochrome aa_3 portion of the enzyme. As a result of the consequent reduced ATP production, tissues resort to anaerobic energy production which is a less efficient alternative pathway for formation of ATP. Pyruvic acid no longer enters the krebs cycle, but is converted to lactic acid which accumulates and results in metabolic acidosis.

- Apart from cytochrome oxidase, cyanide also inhibits succinic dehydrogenase, superoxide dismutase, carbonic anhydrase, and several other enzymes.
- Cyanide causes direct neurotoxicity through lipid peroxidation due to inhibition of antioxidant enzymes such as catalase, glutathione dehydrogenase, glutathione reductase, and superoxide dismutase. In vitro studies with rat hippocampal cell cultures suggest that KCN-mediated neurotoxicity is also partly mediated via endogenous glutamate receptor activation.

Clinical Features

1. **Acute Poisoning:**
   a. Inhalation produces the most rapid and serious exposures resulting in almost immediate coma, while ingestion causes less rapid onset because of slower entry into the circulation, and passage of cyanide through the portal system where the liver metabolises some of it by the first-pass effect.
   b. CNS: Headache, anxiety, agitation, confusion, convulsions, and coma. Pupils are often dilated and sluggish in reaction.
   c. CVS: Initial tachycardia and hypertension, followed by bradycardia and hypotension and ventricular dysrhythmias.
   d. RS: Tachypnoea followed by bradypnoea, and cardiogenic or non-cardiogenic pulmonary oedema. Cyanosis is generally a late finding and usually does not occur until circulatory collapse and tachycardia are evident, particularly at the premorbid stage of cyanide toxicity.
   e. GIT: Ingestion of cyanide salts frequently results in nausea, vomiting, and abdominal pain. Some salts cause corrosion.
   f. Skin: Brick-red colour of skin and mucous membranes is said to be characteristic (**Fig 26.4**). It is due to increased haemoglobin oxygen saturation in venous blood because of decreased utilisation of oxygen by tissues. This phenomenon can be made out better in retinal vessels on fundoscopic examination.
   g. Acid-base: Anion gap metabolic acidosis and lactic acidosis are common following cyanide toxicity. Blood gases may show a decreased A-V (arterial-venous) oxygen saturation difference (i.e. an increased mixed venous oxygen saturation).
   h. The skin feels cold and clammy to the touch. Cyanosis is a late feature.
2. **Chronic Poisoning:**
   a. Survivors of serious acute poisoning may develop delayed neurologic sequelae, especially in the form of Parkinsonian symptoms—akinesia, rigidity (*cog wheel type*), dystonia, dysarthria, and tremor. CAT scan or MRI often reveals basal ganglia damage. Cases of patients developing sequelae such as personality changes, paranoid psychosis, and memory deficits have also been reported.
   b. Chronic exposure is associated with headache, vertigo, tremors, weakness, fatigue, dizziness, confusion,

Fig 26.4: Cyanide poisoning—brick red colour of blood
(*Pic*: Dr S Senthilkumaran)

Fig 26.5: Cassava tubers

– Chronically cyanide-exposed workers have developed enlarged thyroid glands and decreased iodine uptake, presumably because of interference from the presence of the thiocyanate natural cyanide detoxification product. Abnormal thyroid function tests have been reported following chronic cyanide exposure in the occupational setting.

functional changes in hearing, motor aphasia, optic neuropathy, seizures, paresis/hemiparesis, myelopathy, and permanent mental impairment.

c. Chronic, low-level exposure may result in any of the following—

– Tobacco amblyopia: Progressive loss of visual function seen almost exclusively in heavy smokers. Cessation of smoking and administration of hydroxocobalamin reverses the visual impairment in some individuals.

– Leber's hereditary optic atrophy: Congenital deficiency of rhodanese is suspected in this condition which exclusively affects males and results in acute visual failure due to the sensitivity of optic nerve to cyanide. Hydroxocobalamin may be beneficial.

– Tropical ataxic neuropathy (Nigerian nutritional ataxic neuropathy) : It is prevalent among populations consuming large quantities of cassava or tapioca (*manihot*) (**Fig 26.5**). This tuber contains two cyanogens —linamarin and lotaustralin which can be removed only by proper fermentation techniques. Symptoms include peripheral sensory neuropathy, optic atrophy, ataxia, deafness, glossitis, stomatitis, and scrotal dermatitis. A related condition resulting from chronic consumption of improperly processed bitter cassava is "Konzo" which produces spastic paraparesis.

– Frequent nosebleeds have been described in workers chronically exposed to cyanide.

– Workers, such as electroplaters and picklers, who are exposed daily to cyanide solutions may develop a "cyanide rash", characterised by itching, and by macular, papular, and vesicular eruptions.

Diagnosis

1 Characteristic odour in the vicinity of the patient.

2. Lee-Jones test:

a. Add a few crystals of ferrous sulfate to 5 ml of gastric aspirate.

b. Add 5 drops of 2% sodium hydroxide.

c. Boil and cool.

d. Add 10 drops of 10% hydrochloric acid.

e. Interpret: Greenish-blue colour indicates cyanide, while purplish colour indicates salicylates.

3. A variation of the Lee-Jones test involves the following steps:

a. Add 2 ml aqueous sodium hydroxide solution (100 gm/L) to 1 ml of sample.

b. Add 2 ml aqueous ferrous sulfate solution (100 gm/L).

c. Add sufficient aqueous hydrochloric acid (100 ml/L) to dissolve the ferrous hydroxide precipitate.

d. Interpret: Blue colour indicates cyanide.

4. Quantitative assays : microdiffusion techniques using the Conway cell generally require 2 to 3 hours (*p-Nitrobenzaldehyde/o-dinitrobenzene method*), but a modification of the procedure (*pyridine/barbituric acid method*) allows a semiquantitative reading after 10 minutes of diffusion which can be done in emergency situations.

5. Serum cyanide level: This is confirmatory, but difficult to accomplish in practice. Normal serum level is less than 0.004 mcg/ml for non-smokers, and 0.006 mcg/ml for smokers. Whole-blood levels are higher than serum levels—0.016 mcg/ml for non-smokers and 0.041 mcg/ml for smokers.

a. Blood cyanide levels and associated symptoms:

– No symptoms: Less than 0.2 mg/L (mcg/ml) (SI = 7.7 mcmol/L)

- Flushing and tachycardia: 0.5–1.0 mg/L (mcg/ml) (SI = 19.2 to 38.5 mcmol/L)
- Obtundation: 1.0–2.5 mg/L (mcg/ml) (SI = 38.5 to 96.1 mcmol/L)
- Coma and respiratory depression: Greater than 2.5 mg/L (mcg/ml) (SI = 96.1 mcmol/L)
- Death: Greater than 3 mg/L (mcg/ml) (SI = 115.4 mcmol/L).

6. Laboratory findings: Laboratory tests should include CBC, arterial and venous blood gases, serum electrolytes and lactate, assessment of renal function, chest X-ray (following inhalation exposure or if the patient has abnormal respiratory signs and symptoms),and whole blood cyanide levels.
   a. Serum lactate level more than 10 mmol/L.
   b. Elevated serum anion gap.
   c. Arterial blood gas analysis.
   d. Elevated venous oxygen saturation.

7. Cyanide and thiocyanate levels can also be measured in timed urine collections which may yield useful information on cyanide clearance. However, such testing is seldom done clinically; it is more a research tool.

8. ECG: Erratic atrial and ventricular cardiac rhythms with varying degrees of atrioventricular block, followed by asystole may be seen in severe cyanide poisoning. ST-T segment elevation or depression may occur.

9. Fundoscopic examination: retinal arteries and veins that appear equally red on fundoscopic examination is suggestive of cyanide poisoning.

Treatment

1. **Stabilisation:** Assisted ventilation, 100% oxygen, cardiac monitoring, IV access, treatment of metabolic acidosis, vasopressors for hypotension.

2. **Decontamination:**
   a. Cutaneous exposure—remove clothing and wash skin with soap and water.
   b. Ingestion—stomach wash (preferably with 5% sodium thiosulfate solution), activated charcoal, and cathartics, after antidotal therapy has been instituted. Emesis is not recommended due to rapid progression of the clinical course and potential for early development of seizures, coma, or apnoea. Absorption of cyanide is rapid and charcoal may only be beneficial if administered immediately after ingestion.
   c. Haemodialysis and haemoperfusion are NOT effective. However, haemodialysis as adjunct treatment to supportive care, intravenous sodium nitrite, and sodium thiosulfate has been reported in the successful management of some patients with cyanide toxicity. Charcoal haemoperfusion as adjunct treatment to supportive care, intravenous sodium nitrite, and sodium thiosulfate has also been reported in the successful management of a few patients.

3. **Antidotal therapy:**
   a. The 3-step Eli Lilly cyanide kit approach—
      - First step: Amyl nitrite (one perle of 0.2 ml is crushed and inhaled for 30 seconds) every minute until the 2nd step is begun.

- *Alternative administration methods*:
   - Administer amyl nitrite via a nebuliser or
   - Give amyl nitrite via an inhaler device; may be particularly useful if there are many victims.
   - Advantages to either of these methods is that oxygen can be administered along with amyl nitrite, rapid delivery of the drug, accurate dose delivery, less risk of inhalation by first aid or medical personnel, and less risk of injury due to glass fragments. A disadvantage to this method of drug delivery is the increased risk of amyl nitrite toxicity. Further studies to determine the optimal safe dose with these methods are suggested.

- Second step: Sodium nitrite (3% solution) slow IV, i.e. over 5 to 10 minutes.
   - Adult dose—10 ml (300 mg).
   - Paediatric dose—0.33 ml/kg, upto a maximum of 10 ml.
   - Exceeding the recommended dose can result in fatal methaemoglobinaemia. It is highly recommended that total haemoglobin and methaemoglobin concentrations be rapidly measured (30 minutes after dose), when possible, before repeating a dose of sodium nitrite to be sure that dangerous methaemoglobinaemia will not occur, especially in the paediatric patient. It has been suggested to dilute the sodium nitrite dose in 50–100 ml of normal saline, begin the infusion slowly, and increase the infusion rate to as rapid as possible without decreasing blood pressure.

- Third step: Sodium thiosulfate (25% solution), 3 to 5 ml/min, IV.
   - Adult dose—50 ml (12.5 gm).
   - Paediatric dose—1.65 ml/kg (412.5 mg/kg), upto a maximum of 50 ml.
   - Both sodium nitrite and sodium thiosulfate can be repeated at half the initial dose at the end of 1 hour if symptoms persist or reappear. It has been suggested that a continuous infusion of sodium thiosulfate be given after the initial bolus to maintain high thiosulfate levels. Low sodium intravenous fluids are required to avoid sodium overload. If large amounts of sodium thiosulfate are required, haemodialysis may be necessary to maintain a physiologic serum sodium level. There are very few cases reported where continuous infusion has been tried, but it may be considered if deterioration occurs following a bolus dose.
   - Sodium thiosulfate can be administered without sodium nitrite in patients who deteriorate after the initial administration of the antidote kit, provided that the patient is stable and the clinical condition does not warrant more aggressive therapy.

– **Mechanism of action of nitrites:** Nitrites induce methaemoglobinaemia which causes the detachment of cyanide from the haeme group of cytochrome oxidase. Amyl nitrite perles are meant to be a temporising measure until sodium nitrite can be administered intravenously. Amyl nitrite perles should be used when intravenous access is delayed or not possible. If vascular access is available and the patient is severely poisoned, amyl nitrite may be omitted and intravenous sodium nitrite and sodium thiosulfate should be administered.

– **Mechanism of action of sodium thiosulfate:** It enables the enzyme rhodanese to catabolise cyanide to non-toxic thiocyanate which is excreted in the urine.

b. Other Antidotes—

– 4-dimethylaminophenol (4-DMAP): It is the agent of choice to induce methaemoglobinaemia in Europe (as opposed to the USA where nitrites are more popular). Sweden has however deleted it from treatment guidelines for cyanide poisoning since 1990. 4-DMAP can sometimes produce unexpectedly high levels of methaemoglobin which can be life-threatening. Dose: 3 mg/kg, IV.

– Dicobalt edetate (Cobalt-EDTA): It acts by chelating cyanide without inducing methaemoglobinaemia. Cobalt-EDTA is used in Britain and France under the brand name *Kelocyanor*. It is unfortunately associated with serious adverse effects including hypotension, cardiac arrhythmias, decreased cerebral blood flow, and angioedema. In fact the edetate (ethylene diamine tetra acetate) part of the antidote is included only because it is hoped that it will minimise the toxicity of cobalt. Dose: 20 ml, IV, (300 to 600 mg).

– Hydroxocobalamin (Vitamin B_{12} precursor): It combines with cyanide to form cyanacobalamin (vitamin B_{12}), which is excreted in the urine. Dose: 50 mg/kg of commercial solution (1000 mcg/ml). This may require the IV infusion of upto 3.5 litres in an adult.

– Alpha-ketoglutaric acid: It is presently only in the experimental stage, but shows a great deal of promise since it binds with cyanide to render it non-toxic without inducing methaemoglobinaemia.

– Pyruvate, mercaptopyruvate, sulfur sulfanes, and stroma-free methaemoglobin solutions have been tried in animal studies, but are not yet recommended for human use.

– Hyperbaric oxygen: The Undersea Medical Society has classified cyanide poisoning as a disorder for which hyperbaric oxygen therapy is mandatory (Category 1: approved for third party reimbursement and known effective as treatment). Category 1, a category intended for disorders in which the efficacy of hyperbaric oxygen has been established in extensive clinical trials. The placement of cyanide poisoning in Category 1 stands in contrast to the existing literature, which indicates that the role of hyperbaric oxygen as an adjunct to the chemical antidote treatment of the cyanide poisoned patient has not been clearly established. The literature seems to indicate that the role of hyperbaric oxygen as an adjunct to the chemical antidote treatment of the cyanide poisoned patient has not been clearly established. Further research in this area is necessary. Because cyanide is among the most lethal poisons, and intoxication is rapid, "standard antidotal therapy" for isolated cyanide poisoning should be of primary importance. Hyperbaric oxygen may be an adjunct to be considered in patients who are not responding to supportive care and antidotal therapy, and for those patients poisoned by both cyanide and carbon monoxide.

– Methylene blue is NOT an antidote for cyanide and must NOT be used.

4. **Other measures –**
   a. For severe acidosis (pH < 7.1): Administer sodium bicarbonate, 1 mEq/kg intravenously. Base further sodium bicarbonate administration on serial arterial blood gas determinations.
   b. For convulsions: Attempt initial control with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.
   c. For hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
   d. For acute lung injury: Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
   e. Asymptomatic patients with a history of significant cyanide exposure should be observed closely in the hospital. Vascular access should be established, laboratory evaluations performed, and the cyanide antidote kit ready at the bedside. If laboratory evaluations are normal and the patient remains asymptomatic for at least 8 hours, they may be discharged from the hospital with appropriate follow-up instructions.

Autopsy Features

1. External:
   a. Odour of bitter almonds.
   b. Brick red colour of skin and mucous membranes. It is especially evident in areas of postmortem lividity.
   c. Cyanosis of extremities.
   d. Froth at mouth and nostrils (may be blood-stained).
2. Internal:
   a. Haemorrhagic gastritis (ingestion death). Stomach wall may appear hardened. The lining is usually badly damaged presenting a blackened, eroded surface.

b. Pulmonary and cerebral oedema.

c. Disseminated petechiae in brain, meninges, pleura, lungs, and pericardium.

The most appropriate fluids and tissues to remove for chemical analysis are blood, stomach contents, lung, liver, kidney, brain, heart, and spleen. Lung should be sent intact, sealed in a nylon bag. Spleen is said to be the best specimen for cyanide analysis since it generally has the highest concentration of the poison owing to a strong presence of RBC.

There appears to be some evidence that cyanide can be generated in decomposing body tissues and fluids as a result of microbial action. As to whether this is significant enough to vitiate results of chemical analysis is unresolved, though it does not appear likely.

Forensic Issues

1. **Homicide:**

   a. The very mention of cyanide to a lay person would make him think of murder. Like arsenic and strychnine, cyanide has a reputation (quite unfounded) of being a homicidal poisoner's favourite, probably because of the perpetuation of such a notion in popular detective fiction. But the reality is that except for certain exceptional situations, its employment in murder has been quite rare. There are two features which go against the concept of cyanide being an ideal homicidal poison—its possible detection by smell, and the suspicion likely to be aroused by the dramatic nature of death. Cyanide in fact has been more commonly involved in the commission of mass murder, e.g. the genocide of Jews perpetrated by the Nazis during the second world war. Initially the Nazis used carbon monoxide, but later in order to expedite their gory task they began employing hydrogen cyanide (*zyklon B*). Upto 10,000 innocent people per day were butchered by this "efficient" gas and the final tally ran into millions (**Fig 26.6**). Earlier during the first world war, HCN was used as a war gas but was quickly replaced by other more effective war gases such as nitrogen mustard.

   b. More recently, mass homicide (albeit on a much smaller scale) was accomplished with the help of cyanide by Jim Jones (**Fig 26.7**), a self-styled preacher who founded a cult called the People's Temple in 1974, in California, USA. This "religious" sect comprising mainly mentally afflicted individuals, cripples, drug addicts, and ex-convicts, soon moved to Guyana due to local public disapproval. In November 1978, most of them (numbering around 900) died after drinking a cyanide solution prepared by Dr L Schat, a medical officer of the cult on instructions issued by Jones (**Fig 26.8**). The latter shot himself to death. The reason for such an abrupt and bizarre end to this cult is unclear, though it may have been triggered off by rumours of imminent investigations into the sect's activities by a group of relatives of some cult members.

   c. Cyanide has been (and continues to be) used legitimately to kill convicted criminals in some of the states of the

Fig 26.6: Mass grave of exterminated prisoners— Belsen concentration camp, Germany

Fig 26.7: Jim Jones

Fig 26.8: Victims of the Peoples Temple massacre

USA, gassing with it being the official mode of execution in these states.

d. While cyanide has always been touted as a rapidly acting, sure-fire killer, there have been some notable instances where it failed to live up to its reputation. One such celebrated case involved the murder of the Russian monk Grigori Rasputin (**Fig 26.9**) by Prince Yussoupov, who resented the former's increasing power and influence. The Prince invited Rasputin one day to his mansion for dinner and plied him with cyanide-laced cakes. The monk ate two of the cakes with great relish which should have been sufficient in the normal course to have killed several men, and yet he suffered no ill effects. Subsequently, Prince Yussoupov and his fellow conspirators had to shoot him, club him, and drown him in ice cold water of a nearby river before Rasputin finally succumbed.

2. **Suicide:**
   a. The use of cyanide for suicide is relatively uncommon in the general population, but in certain occupational groups having ready access to cyanide it may be employed more frequently, e.g. pharmacists, chemists, and medical or paramedical personnel.
   b. One of the myths associated with cyanide is that it kills with lightning speed, and while this may be true to a certain extent in some cases of inhalation of the poison in its gaseous form, there is ample evidence to show that in many instances death is delayed for several minutes or even hours.

3. **Accident:**
   a. Accidental exposure to cyanide can occur in a number of ways.
      – Since hydrogen cyanide is occasionally used for fumigation (ships, greenhouses), deaths can occur from negligence. Industrial and laboratory mishaps involving this chemical are also not infrequent.
      – The significant presence of cyanide in smoke emitted by the combustion of polyurethane articles, silk and

Fig 26.9: Grigori Rasputin

woollen clothing, as well as celluloid film is now a well established fact. This undoubtedly contributes to the mortality in conflagrations.
      – A comparatively lesser known danger is that associated with the seeds and kernels of cyanogenic fruits. Serious poisoning and even deaths have been reported (especially in children) from the ingestion of apricot kernels which is considered a delicacy in some countries of the Middle East. The most toxic of all cyanogenic fruits is bitter almond, the oil of which is sometimes used as a flavouring agent and can occasionally cause serious poisoning. Sweet almonds are non-toxic.
      – Chronic consumption of certain kinds of foods rich in cyanogenic glycosides (e.g. cassava or tapioca) can cause debilitating neurological ailments.

■ Smoke

Smoke is defined as a solid aerosol resulting from the incomplete combustion (pyrolysis) of any organic matter, and should be differentiated from "fumes" which refer to a suspension of fine solid particles in a gas resulting from condensation (e.g. metal oxides generated during smelting, welding, etc.). The exact composition of smoke depends on the material burnt (**Table 26.5**).

Diagnosis

1. Arterial blood gas analysis.
2. Carboxyhaemoglobin and methaemoglobin concentrations.
3. Chest X-ray (may be normal in the early stages). Xenon ventilation studies can detect small airway and alveolar injury before radiographic changes become apparent.
4. Spirometry: with special reference to FEV_1.
5. Other tests of value include EKG, SMA-6, slit lamp exam of the eyes, indirect laryngoscopy and pulmonary function tests (Xenon 133 lung scan, bronchoscopy, and 99mTc DTPA clearance).

Treatment

An evaluation of the exposure setting may help the physician determine the amount and type of toxic substances to which the victim has been exposed. Factors of potential importance include open vs closed space, estimated length of exposure, presence or absence of steam, explosion, nature of burning material and packaging, status of other victims and the amount, colour, and odour of smoke.

Remove victim from environment, decontaminate, secure airway, ventilate, establish intravenous access, monitor cardiac rhythm, treat pulmonary oedema and commence burn care if required.

1. Oxygen.
2. Aspirate tracheal secretions.
3. Bronchodilators (parenteral or nebulised inhalation). Use aminophylline for bronchospasm.
4. Mechanical ventilation, PEEP for pulmonary oedema.
5. Management of CO or cyanide toxicity if present, on conventional lines.
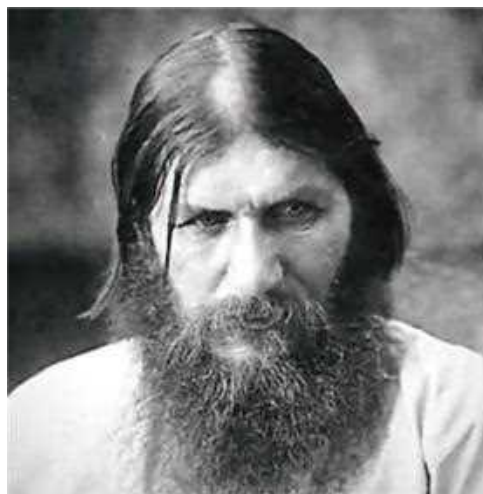
Table 26.5: Composition of Smoke

Material Burnt	Combustion Products
Wood, cotton, paper	Carbon monoxide, acrolein, acetaldehyde, formaldehyde, methane
Plastics	Cyanide, aldehydes, ammonia, nitrogen oxides, phosgene, chlorine
Rubber	Hydrogen sulfide, sulfur dioxide
Wool	Carbon monoxide, hydrogen chloride, phosgene, cyanide, chlorine
Silk	Sulfur dioxide, hydrogen sulfide, cyanide, ammonia
Nylon	Ammonia, cyanide
PVC (polyvinyl chloride)	Carbon monoxide, phosgene, chlorine
Polyurethane	Cyanide, isocyanates
Nitrocellulose	Nitrogen oxides, acetic acid, formic acid
Acrylic material	Acrolein, hydrogen chloride
Petroleum products	Carbon monoxide, acrolein, acetic acid, formic acid

6. Methaemoglobinaemia (more than 20 to 30%) can be treated with methylene blue. The usual adult dose is 1 to 2 mg/kg IV over 5 minutes, followed by a 15 to 30 ml fluid flush to minimise local pain. For children, the usual recommended dose is 0.3 to 1 mg/kg.
7. Use dexamethasone, mannitol, furosemide for cerebral oedema.
8. Consider the use of hyperbaric oxygen, especially in those cases where carbon monoxide and hydrogen cyanide are thought to be present.

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Section

8

Hydrocarbons and Pesticides

27

Hydrocarbons

Traditionally, the term *hydrocarbons* has been used to represent compounds derived from petroleum distillation, and hence were considered synonymous with *petroleum distillates*. But this is incorrect since the term should (logically) cover all organic compounds made of predominantly carbon and hydrogen molecules. The number of carbon molecules can vary from 1 to 60. In general, compounds which contain 1 to 4 carbon molecules are gaseous, while those which have 5 to 19 are liquids, and compounds with more than 20 are solids.

1. **Aliphatic Hydrocarbons (Paraffins)**
    These comprise compounds with saturated molecules (containing **no** carbon-carbon double or triple bonds) which have straight or branched-chain arrangements. Common examples include butane, ethane, methane, and propane (*gaseous*) ; benzine, gasoline or petrol, diesel oil, kerosene, mineral seal oil, lubricating oil or mineral oil, and turpentine or pine oil (*liquids*) ; paraffin wax, petroleum jelly or vaseline, grease, tar, and asphalt (*semi-liquids* or *solids*).

2. **Aromatic Hydrocarbons**
    They contain at least one benzene ring and are unsaturated compounds. Common examples include benzene, toluene, xylene, styrene and naphthalene.

3. **Halogenated Hydrocarbons**
    Most of these are clear, colourless liquids which have a chloroform-like odour. Common examples include carbon tetrachloride, ethylene dibromide, ethylene dichloride, dichloroethylene, trichloroethylene, methylene chloride, propylene chloride, chloroform, methyl chloroform, methyl bromide, fluorocarbons and organochlorine insecticides.

4. **Cycloparaffins (Naphthenes)**
    They are saturated hydrogen compounds which are arranged in closed rings. Common examples include cyclohexane and methylcyclopentane.

5. **Alkenes (Olefins)**
    These compounds contain one carbon-carbon double bond in the molecule. They are mostly used in the manufacture of other hydrocarbon products such as halogenated hydrocarbons.

ALIPHATIC HYDROCARBONS

Uses

Listed in **Table 27.1.**

Mode of Action

■ Ingestion of aliphatic hydocarbons with high molecular weight such as paraffin wax, vaseline, grease, etc. is associated with little or no toxicity.

■ Liquid hydrocarbons are the most toxic, but symptoms generally are the result of aspiration into the airways rather than absorption from the GI tract.

■ The aspiration potential of a hydrocarbon depends on 3 properties—*viscocity, surface tension,* and *volatility*. *Viscocity* is the tendency of a substance to resist flow ("the ability to resist stirring") which is measured in Saybolt Seconds Universal (SSU). The lower the viscocity (i.e. below 60 SSU), the higher the tendency for aspiration. *Surface tension* refers to the adherence of a liquid compound along its surface ("the ability to creep"). It is the result of cohesive forces generated by the attraction between molecules (van der Waals forces). The lower the surface tension, the higher the tendency for aspiration. *Volatility* refers to the ability of a liquid to become a gas. The higher the volatility, the higher the tendency for aspiration.

■ Aliphatic hydrocarbons possessing high aspiration potential include gasoline, kerosene, mineral seal oil, and turpentine.

Clinical Features

1. RS: Respiratory distress from aspiration usually begins within 30 minutes of exposure, and is manifested mainly by gasping, coughing, and choking. There are 3 grades:
    a. *Mild* : coughing, choking, tachypnoea, drowsiness, rales, rhonchi.
    b. *Moderate* : grunting, lethargy, flaccidity, bronchospasm.
    c. *Severe* : cyanosis, coma, seizures.
    Moderate fever is often present but does not correlate with severity. Haemoptysis and pulmonary oedema may occur after significant aspiration or inhalation.

Table 27.1: Uses of Aliphatic Hydrocarbons

Compound	Use
I. Gases —	
Butane, propane	Fuel
II. Liquids —	
Benzine	Solvent
Diesel oil	Fuel
Gasoline (Petrol)*	Fuel
Kerosene	Fuel, curing of tobacco, lighter fluid
Mineral seal oil	Furniture polish
Turpentine (Pine oil)**	Paint thinner, paint remover
III. Semiliquids, Solids —	
Paraffin wax	Candles
Petroleum jelly (Vaseline)	Lubricant
Tar, asphalt	Road surfacing

* May also contain small quantities of aromatic hydrocarbons such as xylene and benzene, as well as tetraethyl lead and cresyl phosphates.
** It is actually an aromatic hydrocarbon, but possesses properties of aliphatic hydrocarbons, and is not a petroleum distillate. It is derived by steam distillation of pine resin.

2. CNS: Lethargy with depressed sensorium. Coma and convulsions are rare. Aniline, heavy metals, camphor, pesticides and other additives or contaminants in hydrocarbon preparations may produce additional CNS toxicity. For instance, chronic cerebellar degeneration may be associated with lead additives of gasoline.
3. GIT: Burning of mouth, sore throat, nausea, and vomiting. Haematemesis may occur. Diarrhoea is rare.
4. CVS: Arrhythmias are seen in solvent abuse (*page no 576*), but are rare in ingestions.
5. Skin: Acute exposure can cause dermatitis, and if this is prolonged it may result in full thickness burns. Chronic exposure to kerosene can cause severe acne. Contact with liquefied petroleum gases (e.g. propane, butane, propylene, isobutane, butenes, n-butane), ethane, etc. can result in frostbite or effects resembling frostbite.
6. Haematologic: Disseminated intravascular coagulation, haemolytic anaemia and pancytopenia have occasionally been reported following vapour inhalation, aspiration, or ingestion of hydrocarbons.
7. Other effects:
   a. Elevated liver enzyme levels and hepatosplenomegaly can occur with petroleum distillate ingestion.
   b. Renal effects (acute renal tubular necrosis, proteinuria, or haematuria) occur infrequently following acute exposure to petroleum distillates and other unsubstituted hydrocarbons.
   c. Straight chain hydrocarbons with few carbon atoms (e.g. methane, ethane, propane gases) can cause asphyxiation if exposure occurs in poorly ventilated spaces.

d. Injection of kerosene, naphtha, turpentine, gasoline, or hydrocarbon insecticides has resulted in febrile reactions, local tissue inflammation and systemic effects, including pulmonary oedema, pneumonia and mild CNS depression. Injection of pressurised hydrocarbons has caused severe tissue damage. Subcutaneous injection of paint, lacquer or other material via high pressure spray guns is a surgical emergency. High-pressure injection injuries can result in necrosis and thrombosis with amputation required in 60 to 80% of cases.
e Exposure to hydrocarbons may result in the loss of colour vision, with the risk of impaired colour vision increasing with increasing exposure.
f. Poisoning due to inhalation of butane and other similar gaseous hydrocarbons is dealt with under "Glue sniffing" (*page no 576*).

Diagnosis

1. X-Ray—Changes may be evident as early as 30 minutes after exposure and peak at about 72 hours, after which there is gradual resolution. Common radiologic findings include perihilar densities, bronchovascular markings, bibasilar infiltrates, and pneumonic consolidation. Early upright X-rays may reveal two liquid densities in the stomach (*double bubble sign*) (**Fig 27.1**), which represents two interfaces: air-hydrocarbon, and hydrocarbon-fluid, since hydrocarbons are not miscible with water and are usually lighter. Two important points are to be noted in connection with radiographic changes in hydrocarbon ingestion—
   a. They correlate poorly with clinical symptoms.
   b. They lag behind clinical improvement.
2. Arterial blood gases—There is hypoxaemia.
3. Blood—Leucocytosis is common during the first 48 hours.
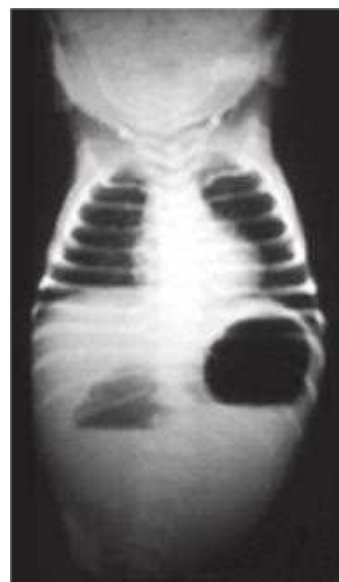
Fig 27.1: Double bubble sign

Treatment

1. The following signs and symptoms present upon initial examination of patients after hydrocarbon ingestion have 80% or better predictive value for pneumonitis:
   a. Lethargy, rhonchi, rales, retractions, cyanosis, and the development of leukocytosis and fever within 4 hours.
   b. The only parameter with an 80% or greater predictive value for NO toxicity was the absence of tachypnoea.
   c. Early chest X-rays were not useful in predicting pneumonitis in symptomatic or asymptomatic patients.
2. The immediate concern is the threat of respiratory failure. A chest X-ray should be taken after stabilisation to confirm or rule out aspiration. The following measures are necessary if respiration is compromised:
   a. Endotracheal intubation.
   b. Oxygen.
   c. Continuous positive airway pressure or positive end-expiratory pressure. A recent innovation is high frequency jet ventilation (HFJV), utilising high respiratory rates (220 to 260) with small tidal volumes. Extracorporeal membrane oxygenaion (ECMO) is an effective option in severe pulmonary toxicity when all other meaures have failed.
   d. Bronchodilators—preferably inhaled cardioselective drugs such as salbutamol.
3. Decontamination:
   a. If there is suspicion of dermal exposure, all clothing should be removed and the skin washed with copious amounts of soap and water, since significant toxicity can result from cutaneous absorption.
   b. Induction of vomiting is not recommended.
   c. Stomach wash may be done cautiously after intubation, especially in those cases where a large quantity of hydrocarbon has been ingested. However, several investigators are against this practice and assert that it only enhances the risk of pulmonary toxicity.
   d. Activated charcoal is generally considered to be ineffective in adsorbing petroleum distillates, though there are experimental studies suggesting the opposite.
4. While prophylactic administration of corticosteroids was advocated in the past, it is not advocated today, since studies have not demonstrated any beneficial effects. On the other hand it can increase the chances of bacterial superinfection.
5. Similarly, prophylactic administration of antibiotics which was the norm in the past is also discouraged today, since it can alter the bacterial flora and lead to subsequent infection by resistant gram-negative bacteria. Pulmonary cultures should be done to decide on antibiotic administration, though this may not be practicable in critically ill patients. In such cases, prophylactic antibiotic therapy may be justified.
6. Crystalloid solutions must be administered judiciously. Pulmonary artery monitoring may help. In general, the pulmonary artery wedge pressure should be kept relatively low while still maintaining adequate cardiac output, blood pressure and urine output.
7. Treatment of frostbite:
   a. *Rewarming—*
      – Do not institute rewarming unless complete rewarming can be assured; refreezing thawed tissue increases tissue damage. Place affected area in a water bath with a temperature of 40 to 42^0 Celsius for 15 to 30 minutes until thawing is complete. The bath should be large enough to permit complete immersion of the injured part, avoiding contact with the sides of the bath. A whirlpool bath would be ideal. Some authors suggest that an antibacterial (hexachlorophene or povidone-iodine) be added to the bath water.
      – Correct systemic hypothermia.
      – Rewarming may be associated with increasing pain, requiring narcotic analgesics.
   b. *Wound Care—*
      – Digits should be separated by sterile absorbent cotton; no constrictive dressings should be used. Protective dressings should be changed twice per day.
      – Perform daily hydrotherapy for 30 to 45 minutes in warm water 40^0 Celsius. This helps debride devitalised tissue and maintain range of motion.
      – The injured extremities should be elevated and should not be allowed to bear weight.
      – Clear blisters should be debrided but haemorrhagic blisters left intact.
      – Further surgical debridement should be delayed until mummification demarcation has occurred (60 to 90 days). Spontaneous amputation may occur.
      – Analgesics may be required during the rewarming phase; however, patients with severe pain should be evaluated for vasospasm. Arteriography and noninvasive vascular techniques (e.g. Doppler ultrasound, digital plethysmography, isotope scanning), have been useful in evaluating the extent of vasospasm after thawing.
      – Tetanus prophylaxis as indicated.
      – Topical aloe vera may decrease tissue destruction and should be applied every 6 hours.
      – Ibuprofen is a thromboxane inhibitor and may help reduce tissue loss. Adult dose of 200–400 mg every 12 hours is recommended.
8. The following treatment measures/drugs are contraindicated in hydrocarbon poisoning:
   a. Emetics
   b. Activated charcoal
   c. Olive oil/mineral oil
   d. Cathartics
   e. Catecholamines (dopamine, adrenaline, noradrenaline, isoproterenol, etc.).
9. Tar and asphalt can cause distressing problems of a different sort. These hot hydrocarbon mixtures can produce

severe burns on dermal contact. The material hardens quickly and becomes extremely difficult to remove. Thermal injury can be minimised by immediate cooling with cold water. Removal of hardened tar can be attempted after application of mineral oil, petroleum jelly, or antibacterial ointment. Recent reports suggest that surface-acting agents in combination with a hydrocarbon ointment may be more effective.

Autopsy Features

1. Pulmonary oedema and varying degree of lung pathology (*page no 376*) are prominent features.
2. There may also be evidence of gastrointestinal congestion and (rarely) corrosion.
3. There is often characteristic odour depending on the type of hydrocarbon ingested.

Forensic Issues

- Most cases of poisoning result from accidental exposure. In India, accidental kerosene poisoning is quite common in the paediatric age group, since it is a popular household fuel and is often negligently left around in the kitchen in bottles or cans.
- Suicidal ingestion of hydrocarbon products is not uncommon because of easy availability of many of these agents.
- Experimental animal studies and some studies on cancer incidence and mortality in human occupational groups suggest that hydrocarbon exposure is associated with renal neoplasia.

AROMATIC HYDROCARBONS

■ Benzene

Synonyms

Benzol, Benzole, Benzolene, Coal naphtha, Phenyl hydride, Annulene, Carbon oil, Cyclohexatriene, Mineral naphtha, Motor benzol, Phene, Pyrobenzol, Pyrobenzole.

Physical Appearance

Colourless, volatile, inflammable liquid, with a strong, pleasant odour.

Sources

- Natural sources of benzene include volcanoes and forest fires. Benzene is also a natural constituent of crude oil.
- Benzene can be recovered from coal tar and produced from the hydrodemethylation of toluene under catalytic or thermal conditions.
- A chief source of benzene is catalytic reformat, wherein the naphthenes and paraffins contained in naphtha are converted to aromatic hydrocarbons. Solvent extraction is then used to recover the benzene.
- Most of the benzene produced is generally derived from the petrochemical and petroleum-refining industries.
- Cigarette smoke also is said to contain benzene.

Uses

- Benzene is extensively used in industry for the manufacture of drugs, chemicals, insecticides, glues, varnishes, paints, polishes, explosives, batteries, shoes, and rubber tyres.
- It is also used in printing, photography, and dry cleaning.
- It is a popular solvent in laboratories.
- Petrol often has significant concentrations of benzene (as an octane booster).

Clinical Features

1. **Acute Exposure:**
   a. Benzene can be absorbed through all routes.
   b. Most individuals can begin to smell benzene in air at 1.5 to 4.7 parts per million (ppm) and detect the odour of benzene in water at 2 ppm.
   c. Brief exposure (5 to 10 minutes) to very high benzene air concentrations (10,000 to 20,000 ppm) can result in death.
   d. On inhalation (of lower concentrations), principal manifestations include vertigo, tinnitus, vomiting, dyspnoea, convulsions, coma, and death. Cardiac arrhythmias are possible.
   e. On ingestion, symptoms include burning pain in the mouth and pharynx, epigastric pain, vomiting, vertigo, tachycardia, hypotension, dyspnoea, convulsions and coma.
   f. Aspiration produces similar manifestations as in the case of aliphatic hydrocarbons.
   g. Locally (on skin), benzene has a strong irritating effect, producing erythema, burning and, in more severe cases, oedema and blistering.

2. **Chronic Exposure:**
   a. Benzene has been classified as a human carcinogen by various international monitoring agencies. The causal relationship between chronic exposure and a variety of haematologic disorders has been known for the last 50 years or more. These include aplastic anaemia, acute myeloblastic leukaemia, haemolytic anaemia, and pancytopenia. Benzene exposure is associated with translocations between chromosomes 8 and 21, and hyperploidy of 8 and 21 in the circulating lymphocytes of workers exposed to benzene. These aberrations may be involved in benzene-induced leukaemia.
   b. Headache, dizziness, irritability, nervousness, fatigue, anorexia and epistaxis may also occur with chronic benzene poisoning.
   c. Paroxysmal nocturnal haemoglobinuria (PNH) has been reported in patients occupationally exposed to benzene. PNH is often associated with aplastic anaemia and rarely with acute leukaemia.
   d. Insulin-dependant diabetes mellitus has been reported with benzene exposure.
   e. An epidemiological study of pregnant women in a large petrochemical industry showed a positive correlation between reduced birth weight and exposure to benzene and work stress.

Diagnosis

1. Benzene is metabolised extensively in the liver and excreted in the urine, with 51 to 87% excreted as phenol, 6% as catechol, and 2% as hydroquinone. Other metabolites include phenylmercapturic acid (0.5%), benzene dihydrodiol (0.3%), and trans, trans-muconic acid (1.3%). Monitoring benzene in expired air and urine phenol levels may be useful for observing workers exposed to benzene. Urine phenol levels in unexposed individuals are less than 10 mg/L. Urine phenol levels after chronic exposure to airborne concentrations of 0.5 to 4 ppm are less than 30 mg/L. Urine phenol levels after exposure to 25 ppm average 200 mg/L.
2. Analysis of urinary t, t-muconic acid appears to be a better indicator than phenol for assessment of exposure to low levels of benzene.
3. Gas chromatography head-space analysis is the preferred method for determining benzene in blood or urine. The lower limit of detection is 0.64 nmol/L for benzene in blood and 0.51 nmol/L in urine.
4. Obtain baseline CBC.
5. Monitor ECG for cardiac arrhythmias.

Treatment

Acute exposure is treated on the same lines as in the case of aliphatic hydrocarbons.
1. Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.
2. Consider pre-hospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway.
3. Consider gastric lavage with a large-bore orogastric tube after a potentially life-threatening ingestion if it can be performed soon after ingestion (generally within 60 minutes).
4. Remove contaminated clothing and wash exposed area extremely thoroughly with soap and water.
5. Administer 100% humidified supplemental oxygen, perform endotracheal intubation and provide assisted ventilation as required. Administer inhaled beta adrenergic agonists if bronchospasm develops. Exposed skin and eyes should be flushed with copious amounts of water.
6. Treat convulsions in the usual manner.

Autopsy Features

1. Marked congestion of brain.
2. Pulmonary oedema. On sectioning the lungs there is exudation of blackish, frothy liquid.
3. Multiorgan congestion.

Forensic Issues

Most cases of exposure (acute and chronic) are occupational in nature.

Toluene and Xylene produce similar (though milder) manifestations on acute exposure and are managed by supportive measures, with the same precautions in decontamination as for other hydrocarbons.

■ Naphthalene

Synonyms

Moth flake, Tar camphor, White tar.

Physical Appearance

White scaly powder which volatilises at room temperature.

Sources

- Naphthalene occurs naturally in the essential oils of the roots of *Radix* and *Herba ononidis*, and crude oil.
- It can be manufactured by crystallising and separating the naphthalene fraction.
- Naphthalene can also be produced by boiling coal tar oils at temperatures between 200–250⁰ C, followed by crystallisation and distillation.
- It can also be derived from catalytic processing of petroleum, or isolated from cracked petroleum.
- Naphthalene is formed in cigarette smoke by pyrolysis, and is also a photodecomposition product of carbaryl, an agricultural pesticide.

Uses

- Moth repellent (in the form of moth balls) (**Fig 27.2**)*
- Deodorant cakes
- Scintillation counters.

Fig 27.2: Moth balls

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* While naphthalene is the commonest constituent of moth balls, other agents are also used as moth repellents, e.g. camphor, paradichlorobenzene, etc.

Toxicokinetics and Mode of Action

Naphthalene itself is not responsible for the toxic effects. Its metabolites alpha and beta naphthol as well as naphthoquinone are powerful haemolytic agents. Individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency are especially vulnerable to the toxicity of these metabolites. Naphthalene is first metabolised by hepatic mixed function oxidases to the epoxide, naphthalene-1,2-oxide. The epoxide is enzymatically converted into the dihydrodiol, 1, 2-dihydroxy-1,2-dihydronaphthalene or conjugated with glutathione. The dihydrodiol is then conjugated to form a polar compound with glucuronic acid or sulfate, or further dehydrogenated to form highly reactive 1,2-dihydroxynaphthalene. Dihydroxynaphthalene can be enzymatically conjugated with sulfate or glucuronic acid or spontaneously oxidised to form 1,2-naphthoquinone. Naphthalene is also metabolised to mercapturic acid derivatives.

Naphthalene metabolites (naphthols and naphthylglycuronates) are excreted in the urine as 1-naphthylmercapturic acid (15% of absorbed dose), as conjugates of 1,2-dihydronaphthalene-1,2-diol (10% of absorbed dose), and as 1- and 2-naphthols and 1,2-dihydroxynaphthalene. Conjugates of glutathione (cysteinylglycine, and cysteine; intermediates in formation of mercapturic acids) are excreted mainly in the bile as metabolites of naphthalene.

Naphthalene can be absorbed via oral, inhalation, and dermal routes.

Clinical Features

1. *Non-haemolytic manifestations*: Vomiting, abdominal pain, diarrhoea, headache, diaphoresis, optic neuritis, restlessness, lethargy, fever, convulsions, hepatomegaly, splenomegaly. Hyperbilirubinaemia and fatal kernicterus may occur in newborns with significant haemolysis. Centrilobular necrosis occurred in one paediatric poisoning case. Coma and acute lung injury may develop in severe toxicity. Naphthalene skin exposure may cause hypersensitivity dermatitis. Repeated exposure may cause corneal ulceration, lenticular opacities, cataracts, headache, malaise and vomiting.
2. *Haemolytic manifestations*: Pallor, weakness, jaundice, cyanosis, haemolysis, haemolytic anaemia, methaemoglobinaemia (**Fig 27.3**), hyperkalaemia, dysuria, haematuria, and dark urine (haemoglobinuria), albuminuria, oliguria, and acute renal failure. Cardiovascular shock can occur in patients with severe haemolytic anaemia. Metabolic acidosis may develop in patients with acute renal failure secondary to haemolysis.
   a. Haematological Findings: Increased WBC count, fragmented RBC, anisocytosis, Heinz bodies, and poikilocytosis.
   b. Infants and patients with G6PD deficiency, sickle cell anaemia, or sickle cell trait are more likely to develop haemolysis and/or methaemoglobinaemia.

Fig 27.3: Methaemoglobinaemia
(*Pic*: Dr S Senthilkumaran)

3. Chronic exposure to naphthalene can result in aplastic anaemia, hepatic necrosis, and jaundice. Naphthalene and coal tar exposure have been associated with laryngeal and intestinal carcinoma.

Diagnosis

1. Obtain baseline CBC, electrolytes, glucose-6-phosphate dehydrogenase level, liver enzymes and renal function tests, urinalysis and urine dipstick test for haemoglobinuria.
2. Measurement of urinary metabolites (1-naphthol or mercapturic acid) may help to confirm the diagnosis. Urinary naphthol levels may be utilised to monitor industrial creosote exposure (naphthalene is the most abundant compound found in creosote vapour).
3. X-ray: Abdominal radiographs may help differentiate between mothballs or other products which contain paradichlorobenzene (densely radiopaque) from those which contain naphthalene (radiolucent or faintly radiopaque).

Treatment

Acute exposure is treated on the same lines as in the case of aliphatic hydrocarbons.

1. Ingestion of one mothball may produce toxicity; patients with ingestion of more than this amount should be referred to a health care facility for gastric decontamination and observation. If laboratory findings are negative and the patient is asymptomatic during a 4 to 6-hour observation period, the patient may be discharged with instructions to return for a follow-up CBC and urinalysis for up to 5 days post-ingestion. Patients should be instructed to return if any gastrointestinal symptoms, pallor, dark or diminished urine output, or CNS symptoms develop.

2. Decontamination—
   a. Induced emesis is more useful for mothballs because of their size. Do not induce vomiting if the patient has any evidence of lethargy or CNS depression.
   b. Gastric lavage may be useful for ingestion of flakes, but its effectiveness may be limited by naphthalene's poor water solubility. Mothballs dissolve slowly; gastric decontamination should be considered even in patients presenting late after ingestion.
   c. Information on the benefit of activated charcoal is scant, but adsorption is thought to occur. Consider administration of activated charcoal after a potentially toxic ingestion (up to 1 hour).
   d. Dermal Decontamination—Remove contaminated clothing and wash exposed area thoroughly with soap and water. Consider discarding contaminated clothing, as washing does not easily remove naphthalene.
3. Avoid oral administration of oil or fatty substances.
4. Control seizures.
5. Alkaline Diuresis—
   a. Should be performed if there is evidence of haemolysis. This may prevent renal deposition of red blood cell break down products in the renal tubules and resultant renal failure.
   b. Administer 1 to 2 mEq/kg of sodium bicarbonate as an intravenous bolus. Add 132 mEq (3 ampoules) sodium bicarbonate and 20 to 40 mEq potassium chloride (as needed) to one litre of dextrose 5% in water and infuse at approximately 1.5 times the maintenance fluid rate.
   c. In patients with underlying dehydration additional administration of 0.9% saline may be needed to maintain adequate urine output (1 to 2 ml/kg/hour).
   d. Manipulate bicarbonate infusion to maintain a urine pH of at least 7.5. Additional sodium bicarbonate (1 to 2 mEq/kg) and potassium chloride (20 to 40 mEq/L) may be needed to achieve an alkaline urine. Do not administer potassium to an oliguric or anuric patient.
   e. Obtain hourly intake/output and urine pH. Assure adequate hydration and renal function prior to alkalinisation. Monitor fluid and electrolyte balance carefully. Monitor blood pH, especially in intubated patients, to avoid severe alkalaemia. Administer furosemide as needed to maintain urine output.
6. Treat haemolysis with blood transfusion, packed red cell transfusions, or exchange transfusion.
7. Monitor methaemoglobin level and treat if symptomatic, or if methaemoglobin levels are greater than 30%. Treat with methylene blue 1 to 2 mg/kg/dose (0.1 to 0.2 ml/kg/dose) IV over 5 minutes as needed every 4 hours. It is important to remember that large doses of methylene blue may itself cause methaemoglobinaemia or haemolysis. Also, methylene blue must not be administered if the patient has G6PD deficiency.
8. Haemodialysis may help enhance elimination, though it is not routinely recommended.

Forensic Issues

- Most cases of exposure are accidental in nature.
- A few are suicidal.
- In the case of mothball ingestion (suicidal or accidental), sometimes there is confusion as to whether the active ingredient is naphthalene, camphor or paradichlorobenzene.
  ❖ Differentiating between mothballs containing paradichlorobenzene (PDB), naphthalene and camphor:
    – *Physical appearance*—Naphthalene is dry, while PDB has a wet and oily appearance.
    – *Specific gravity*—Distinguishing between camphor, naphthalene, and PDB mothballs can be done by testing whether they float or sink in a saturated solution of salt water (4 ounces of tepid water to which 3 heaping tablespoons of table salt has been added and stirred vigorously until the salt will not dissolve any more). Camphor mothballs float in both water and salt solution. Naphthalene mothballs sink in water but float in saturated salt solution. PDB mothballs sink in both water and salt solution.
    – *Solubility*—PDB is more soluble in turpentine than naphthalene. A mothball of PDB will usually dissolve within 30 to 60 minutes whereas at least one fourth of the naphthalene will be left.
    – *Heat*—PDB produces a bright green colour in a bunsen burner flame; Naphthalene does not.
    – *Melting point*—PDB: 53^0 C; Naphthalene: 80^0 C. Placing a small piece of the mothball in a test tube heated to 60^0 C in water bath may simplify the melting point test. PDB will liquefy within several minutes; naphthalene will remain intact.
    – *Chemical test*—If chloroform and ammonium chloride powder are added to PDB no colour change occurs; naphthalene turns blue.

■ Polycyclic Aromatic Hydrocarbons

These compounds (also called polynuclear aromatic hydrocarbons) contain three or more fused benzene rings in varying arrangements that consist of carbon and hydrogen, e.g. benzoanthracene, benzopyrene, anthracene, phenanthrene, benzofluoranthene, chrysene, coronene, dibenzacridine, dibenzanthracene, dibenzocarbazole, dimethylbenzanthracene, 3-methylcholanthrene and pyrene.

Sources

Polycyclic aromatic hydrocarbons (PAHs) are components of most fossil fuels and are ubiquitous in the natural environment.
- Forest fires.
- Sea food and agricultural products.
- Charring, barbecuing, smoking of foods; foodstuffs such as coffee, roasted peanuts; refined vegetable oils, crude coconut oil, heavily smoked ham.
- Emissions sources:
  ❖ Cigarette smoke

- ❖ Coal tar pitch
- ❖ Coke production
- ❖ Engine exhaust
- ❖ Engine oil, used
- ❖ Fuel burning, and open burning of refuse
- ❖ Restaurants and smokehouses
- ❖ Roof tarring
- ❖ Sidewalk tarring
- ❖ Wood-burning fireplaces.

Clinical Features

1. Acute poisoning is rare.
2. Chronic exposure in the form of inhalation or dermal contact can predispose to lung and skin cancer. Increased incidence of cancers of the skin, bladder, lung and gastrointestinal tract have been described in PAH-exposed workers. Apart from such carcinogenic potential, PAHs are also responsible for eye irritation and photosensitivity, skin erythema, cough and bronchitis, and haematuria.
   - ❖ Chronic effects include:
     - – Photosensitivity and irritation.
     - – *Respiratory*—Irritation with cough and bronchitis.
     - – *Mouth*—Leukoplakia.
     - – *Dermal*—"Coal tar warts" (precancerous lesions enhanced by UV light exposure), erythema, dermal burns, photosensitivity, acneiform lesions, irritation.
     - – *Hepatic/Renal*—Mild hepatotoxicity or mild nephrotoxicity.
     - – *Genitourinary*—Haematuria.

Routine monitoring and physical assessments (e.g. complete blood count, hepatic and renal function tests, chest X-ray and pulmonary function tests, dermal assessments) of individuals with significant exposure is recommended, even in the absence of symptoms.

HALOGENATED HYDROCARBONS

■ Examples

Listed in **Table 27.2**.

Physical Appearance

Most halogenated hydrocarbons are clear, colourless, non-inflammable liquids with sweetish, chloroform-like odour. Many of them also exist as gases. For instance, methyl bromide is a toxic inhalant, and an intense vesicant, with dermal exposures resulting in burns. It is a colourless, transparent, volatile liquid or gas with a burning taste. It is nearly odourless, though chloropicrin is typically added to commercial forms of methyl bromide to give it an intense odour.

Toxicokinetics

- The usual route of exposure is either inhalation or ingestion. Many halogenated hydrocarbons can be absorbed through skin, albeit slowly.
- After absorption they are distributed mainly in the blood, brain, and adipose tissue.
- Metabolism occurs in the liver by cytochrome P450 oxidation. There is partial glutathione conjugation.

Table 27.2: Halogenated Hydrocarbons

Compound	Use
Acetylene tetrabromide (Tetrabromoethane)	Gauge fluid, solvent, refractive index liquid in microscopy
Carbon tetrachloride* (Tetrachloromethane)	Manufacture of fluorocarbon propellants (Freon), solvent, cleansing and degreasing agent, grain fumigant, dry cleaning, fire extinguisher
Chloroform	Anaesthetic agent
Dichloroethylene (1,2-Dichloroethane)	Degreaser, solvent, fumigant, manufacture of nylon, rayon, etc.
Ethylene dibromide (1,2-Dibromoethane)	Soil fumigant
Ethylene dichloride (1,1-Dichloroethane)	Cleansing and degreasing agent, solvent, grain fumigant
Fluorocarbon , Freon	Solvent for cleaning electronic equipment, degreaser, refrigerant, fire extinguisher, dry cleaning
Methyl bromide	Fire extinguisher, fumigant insecticide, refrigerant
Methyl chloride	Refrigerant (now obsolete)
Methylene chloride (Dichloromethane)	Solvent, paint remover, degreaser, manufacture of aerosol propellants and urethane foam
Propylene dichloride (Dichloropropane)	Degreaser, dry cleaning, stain remover, manufacture of cellulose plastics
Tetrachloroethane	Feed stock, cleanser, degreaser
Tetrachloroethylene	Solvent, dry cleaning, pesticide, metal cleaner
Trichloroethane	Solvent, degreaser, pesticide
Trichloroethylene	Solvent, degreaser, refrigerant, typewriter cleaning fluid, paint remover, adhesive, anaesthetic

*Banned from most commercial uses in Western countries

Mode of Action

- Most of these agents are powerful hepatorenal toxins, producing centrilobular liver necrosis and renal tubular degeneration.
- In the case of carbon tetrachloride, the hepatic mixed-function oxidase system metabolises it to the trichloro-methyl radical (CCl3.). This initiates lipid peroxidation, protein-lipid cross links, and trichloromethyl adducts with DNA, protein and lipid. The trichloromethyl radical may poison the cytochrome P 450. It may be released from the cytochrome P 450 or may be converted to chloroform via a one-electron reduction and abstraction of a proton. Further reduction may release hydrochloric acid and carbon monoxide. The trichloromethyl radical may alternatively react with oxygen to form a trichloromethyl peroxy free radical, which may react to form phosgene. This may play a significant role in mediation of carbon tetrachloride hepatotoxicity.
- Recent studies have focused on intracellular calcium homoeostasis. The metabolism of carbon tetrachloride disrupts the hepatocyte ATP dependant Ca++ pump. This results in a rise of intracellular cytoplasmic Ca++. The latter may be a toxic second messenger that activates mechanisms which destroy cellular membranes resulting in cell death.
- Methyl bromide, and possibly some other hydrocarbons, behave as alkylating agents and sulfhydryl enzyme inhibitors in mammalian tissues. It has been speculated that hexokinase and pyruvate oxidase may be especially susceptible to inactivation by methylation of SH-groups in the CNS. The similarity of neuropathological manifestations of methyl bromide toxicity to those seen in thiamine deficiency may be related to effects of methyl bromide interference with metabolism of pyruvate, where thiamine acts as a co-factor.

Clinical Features

1. **Acute Poisoning:**
   a. Vomiting, diarrhoea, abdominal pain, headache, lethargy, vertigo and stupor.
   b. Headache, fatigue, confusion, altered mental status, delirium, amnesia, incoherent speech, ataxia, intention tremor, and positive Rhomberg sign may occur. Behavioural disturbances resembling psychosis may be noted as an early manifestation of methyl bromide toxicity.

c. Liver damage results in hepatitis, jaundice, and hepatic encephalopathy (**Table 27.3**).
d. Renal involvement is manifested by oliguria or anuria, haematuria and renal failure.
e. Additional features include acidosis, hypertension, convulsions and respiratory failure. Hypotension, ventricular arrhythmias, depressed cardiac muscles, fatty degeneration, and a slowed or irregular pulse may occur.
f. If alcohol has been consumed along with a halogenated hydrocarbon, particularly carbon tetrachloride, there is rapid onset and progression of symptoms.
g. Methyl bromide intoxication is characterised by myoclonic convulsions and permanent brain damage. Signs and symptoms may include blurred or double vision, nystagmus, hypotension, cough, tachypnoea, cyanosis, lethargy, profound weakness, dizziness, slurring of speech, hyperreflexia, albuminuria, haematuria, oliguria, anuria, and impaired liver function.
h. Dermal exposure (especially by methyl bromide) may result in second degree burns. Methyl bromide is an intense vesicant with the capacity to penetrate protective clothing. Skin blisters are produced, but are rarely deep enough to destroy entire skin layer. Spillage of liquid fumigant on the skin is likely to result in injury ranging from erythema to vesiculation. The inflammation and blistering can be delayed for 15 to 20 hours. Healing is gradual, often taking several weeks. Skin contact with many halogenated hydrocarbons, especially carbon tetrachloride can lead to dermatitis through defatting action. Erythema, hyperaemia, wheals, and vesiculations may be seen. Gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhoea) and renal or hepatic damage can occur even from dermal exposure.

2. **Chronic Poisoning:**
   a. Trichloroethylene (together with ethanol) when used as a degreaser results in intermittent skin contact producing flushing (*Degreaser's flush*) due to vasodilation of superficial skin vessels.
   b. Chronic exposure to halogenated hydrocarbon solvents can cause *Painter's syndrome*: headache, fatigue, memory lapses, irritability, depression, and intolerance to alcohol.
   c. Occurrence of a protracted extrapyramidal syndrome following low-level methyl bromide exposure has been documented in several cases. Depression, slow mentation, poor memory, neurosis, muscle paralysis,

Table 27.3: Hepatic Encephalopathy

Stage	Mental Status	Neuromuscular Changes	EEG
I	Euphoria/depression, slowing of thought, slurred speech, restlessness	Slight tremor, ataxia	Usually normal; sometimes slow (5 to 6 cycles/sec)
II	Drowsiness, inappropriate behaviour, lethargy, disorientation	Tremor, asterixis, dysarthria, abnormal reflexes	Generalised symmetric slowing, triphasic waves
III	Somnolence, stupor, delirium, confusion	Tremor, asterixis, muscle rigidity, abnormal reflexes, incontinence of urine, faeces	Symmetric slowing, triphasic waves
IV	Coma	Plantar extension, decerebrate	Very slow (2 to 3 cycles/sec), delta activity

and ataxia may be long-term or permanent disabilities associated with methyl bromide poisoning. Other long-term effects include myoclonus, difficult speech, cognitive impairment, muscular atrophy, peripheral neuropathy and seizure disorders.

d. Chronic exposure to carbon tetrachloride has been possibly associated with myasthenic reaction, a defect in neuromuscular transmission.

e. There are reports suggesting that some halogenated hydrocarbons are carcinogenic and may cause renal cancer (especially carbon tetrachloride, tetrachloro-ethylene, and trichloromethane). Effects of chronic exposure to carbon tetrachloride include liver cancer in persons with acute poisoning, which might occur with prior chronic exposure, even in the absence of cirrhosis, and a possible association with brain tumours, lymphatic leukaemias and lymphosarcomas.

Usual Fatal Dose

About 4 to 5 ml for most halogenated hydrocabons; 20 to 25 ml for a few others. With reference to methyl bromide, airborne concentrations as low as 100 ppm have been reported to be harmful, while concentrations of 8,000 to 60,000 ppm may be fatal.

Diagnosis

1. Characteristic odour in the breath.
2. Positive Fehling's test (for sugar in the urine).
3. **Isonitrile Test:** 10 ml of distillate or a small amount of the suspected liquid in 10 ml of water is placed in a test tube. To this, 1 ml of purified aniline and 2 ml of 20% sodium hydroxide are added and gently heated. A positive result is indicated by the development of a foul skunk-like odour due to formation of phenyl isonitrile.
4. Gas chromatography can be used to quantitate halogenated hydrocarbons in biological samples.
5. Carbon tetrachloride blood levels in acutely poisoned patients ranged from 0.1 to 31.5 mg/L. 2 to 5 mg/dL are generally considered toxic blood levels.
6. Serum inorganic bromide levels may be useful in confirming exposure to methyl bromide and may correlate with the clinical severity of poisoning. Values in excess of 5 mg/100 ml bromide are generally toxic. However, this is not always the case.
7. Hepatorenal toxicity is indicated by elevated serum hepatic aminotransferase, bilirubin, alkaline phosphatase, and creatinine.
8. Individual serum bile acids appear to be very sensitive indicators of liver damage and may be used as early indicators of carbon tetrachloride-induced liver injury as measured by high performance liquid chromatography. This appears to be much more sensitive than measuring liver enzyme or bilirubin levels.
9. A chest radiograph should be considered in patients with respiratory symptoms. Carbon tetrachloride is radiopaque, and some ingestions may be able to be confirmed with an abdominal radiograph.

Treatment

1. Decontamination—dermal exposure should be treated by stripping the patient and washing copiously with soap and water. Eye involvement must be treated by irrigation for at least 15 to 20 minutes. Consider administration of activated charcoal after a potentially toxic ingestion. Gastric lavage can also be done cautiously in potentially lethal ingestions.
2. Administer oxygen if there is evidence of altered mental status or respiratory failure.
3. Watch out for cardiac arrhythmias, aspiration pneumonitis, and hepatorenal failure.
4. Carbon tetrachloride-induced liver cirrhosis results in bile acids not being detoxified in the enterohepatic circulation. In rat studies administration of cholestyramine, which has a strong affinity for bile acids in the intestine, prevents their enteral resorption and decreases the induction of cirrhosis.
5. N-acetylcysteine given within 8 to 10 hours after exposure has been reported to prevent hepatic damage from acute poisoning by CCl_4 in humans. It is probably most effective if given within 16 hours following ingestion of carbon tetrachloride. Further studies are needed before this therapy can be routinely recommended. Estimated dose of NAC: Loading dose of 140 mg/kg orally as a 5% solution in cola followed by a maintenance dose of 70 mg/kg orally every 4 hours for 17 doses. Alternatively, the **Prescott protocol** can be followed: gastric lavage followed by intravenous infusion of N-acetylcysteine at 150 mg/kg over 15 minutes, then 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours.
6. Intravenous administration of N-acetylcysteine has been suggested as a treatment for methyl bromide poisoning also, possibly based on the hypothesis that methyl bromide preferentially reacts with dermal SH-groups. N-acetylcysteine would serve as a source of SH-groups to react with unbound methyl bromide. However, this treatment cannot be recommended until further studies are done to confirm efficacy.
7. Treat renal failure with dialysis and hepatic failure with fresh frozen plasma, vitamin K, low-protein diet, neomycin and lactulose.
8. Hyperbaric oxygen significantly improved survival and decreased the degree of SGPT elevation in rats poisoned with carbon tetrachloride. A review of subsequent literature suggests that hyperbaric oxygen treatment is appropriate treatment for carbon tetrachloride intoxication.
9. Haemodialysis is generally not effective, though an anecdotal report suggests it may be useful in methyl bromide poisoning. Haemodialysis or haemoperfusion may be necessary to support patients in renal or hepatic failure, respectively.
10. Treatment of dermal burns (methyl bromide):

a. After initial flushing with large volumes of water to remove any residual chemical material, clean wounds with a mild disinfectant soap and water.

b. Loose, nonviable tissue should be removed by gentle cleansing with surgical soap or formal skin debridement. Intravenous analgesia may be required.

c. Removal and debridement of closed blisters is controversial. Current consensus is that intact blisters prevent pain and dehydration, promote healing, and allow motion; therefore, blisters should be left intact until they rupture spontaneously or healing is well underway, unless they are extremely large or inhibit motion.

d. Prophylactic topical antibiotic therapy with silver sulfadiazine is recommended for all burns except superficial partial thickness (first-degree) burns. Systemic antibiotics are generally not indicated unless infection is present or the burn involves the hands, feet, or perineum.

e. Depending on the site and area, the burn may be treated open (face, ears, or perineum) or covered with sterile nonstick porous gauze. The gauze dressing should be fluffy and thick enough to absorb all drainage. Alternatively, a petrolatum fine-mesh gauze dressing may be used alone on partial-thickness burns.

f. Analgesics such as paracetamol with codeine may be used for pain relief if needed.

g. Tetanus toxoid 0.5 ml intramuscularly (or other indicated tetanus prophylaxis) should be administered if required.

Autopsy Features

1. Characteristic odour.
2. Petechiae in the brain, airways, and lungs.
3. Pulmonary oedema.
4. Fatty degeneration, cardiomegaly
5. Renal and hepatic necrosis. Large foci of centrilobular necrosis of the liver with normal portal vasculature was reported at autopsy of a 36-year-old female following a fatal methyl bromide exposure.

Forensic Issues

Most cases are accidental in nature arising out of occupational exposure. There have been cases of suicidal ingestion involving one or other of these compounds.

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Chapter 27 ◆ Hydrocarbons
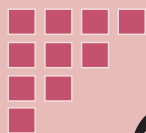
Pesticides

Pesticides are compounds that are used to kill pests which may be insects, rodents, fungi, nematodes, mites, ticks, molluscs, and unwanted weeds or herbs.

1. Insecticides
2. Rodenticides
3. Fungicides
4. Nematicides
5. Acaricides
6. Molluscicides
7. Herbicides
8. Miscellaneous Pesticides.

INSECTICIDES

These are compounds which kill or repel insects and related species. For example, organophosphates, carbamates, organochlorines, pyrethrum and its derivatives (pyrethroids).

■ Organophosphates (Organophosphorus Compounds)

It is true that calling these compounds "organophosphates" is not correct, and they should be referred to as "organophosphorus compounds". But, "organophosphates" is such an irresistibly compact expression. So, with apologies to the purists, this term will be used for the sake of convenience in this book, even if it raises some hackles.

Organophosphates are among the most popular and most widely used insecticides in India. **Table 28.1** lists common varieties along with respective brand names.

Physical Appearance

These compounds are available as dusts, granules, or liquids. Some products need to be diluted with water before use, and some are burnt to make smoke that kills insects.

Usual Fatal Dose

Toxicity Rating*:

The following compounds are extremely toxic (*LD50: 1 to 50 mg/kg*), or highly toxic (*LD50: 51 to 500 mg/kg*)—

Chlorfenvinphos, Chlorpyriphos, Demeton, Diazinon, Dichlorvos, Dimethoate, Disulfoton, Ediphenphos, Ethion, Fenitrothion, Fensulfothion, Fenthion, Fonophos, Formothion, Methyl Parathion, Mevinphos, Monocrotophos, Oxydemeton Methyl, Phenthoate, Phorate, Phosphamidon, Quinalphos, TEPP, and Thiometon.

The following compounds are moderately toxic (*LD50: 501 to 5000 mg/kg*), or slightly toxic (*LD50: more than 5000 mg/kg*)—

Abate, Acephate, Coumaphos, Crufomate, Famphur, Glyphosate, Malathion, Phenthoate, Primiphos Methyl, Ronnel, Temephos, Triazophos, and Trichlorphon.

Even in cases where treatment was begun early with atropine and oximes, mortality in organophosphate poisoning is generally to the extent of 7 to 12%.

Mode of Action

- Organophosphates are powerful inhibitors of acetylcholinesterase which is responsible for hydrolysing acetylcholine to choline and acetic acid after its release and completion of function (i.e. propagation of action potential). As a result, there is accumulation of acetylcholine with continued stimulation of local receptors and eventual paralysis of nerve or muscle.
- Although organophosphates differ structurally from acetylcholine, they can bind to the acetylcholinesterase molecule at the active site and phosphorylate the serine moiety. When this occurs, the resultant conjugate is infinitely more stable than the acetylcholine-acetylcholinesterase conjugate, although endogenous hydrolysis does occur. Depending on the amount of stability and charge distribution, the time to hydrolysis is increased. Phosphorylated enzymes degrade very slowly over days to weeks, making the acetylcholinesterase essentially inactive.
- Once the acetylcholinesterase is phosphorylated, over the next 24 to 48 hours an alkyl group is eventually lost from the conjugate, further exacerbating the situation. As this occurs, the enzyme can no longer spontaneously hydrolyse and becomes permanently inactivated.

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* Partly as per the **Insecticide Rules, 1971.**

Table 28.1: Common Organophosphate Pesticides

Generic Name	Brand Name
Acephate	Acemil, Acet, Acetaf, Agrophate, Asataf, Dhanraj, Hilfate, Hythane, Orthene, Ortran, Sicothene, Starthene, Torpedo
Anilofos	Aniloguard, Arozin, Dhanudan
Chlorfenvinphos	Birlane, Chlorfenvinphos
Chlorpyriphos	Agrofas 20, Calban, Chlorofos 20, Classic, Coroban 20, Cyfos, Daspan, Dermite, Dermot, Dhanuchlor, Dhanvan, Dursban, Force, Gilphos, Hildan, Hyban 20, Lasso, Lethal, Nuchlor, Phors 20, Primaban, Radar, Roban, Ruban 20, Sicobon, Strike, Suchlor, Tafaban, Tefaban, Tricel
Cyclopyriphos	Duramet
Demeton methyl	Metasostox
Diazinon	Agroziron, Basudin, Bazanon, Ditaf, Suzinon, Tik 20, Zionosul 50
Dichlorvos	Agrovan 76, Agro 76 EC, Bangvas, Cockroach killer, Dash, DDVP, Divap, Divisol, Madhuvun, Nuvan, Nuvasul 76, Paradeep, Savious,Vapona, Vapox, Vegfru
Dimethoate	Agrodimet 30, Agromet 30EC, Bangor 30EC, Corothate, Cropgor 30, Cycothate, Cygon, Devigor, Dimethoate, Dimex, Entogor, Hexagor, Hygro 30, Klex Dimethoate, Krogar, Methovip, Milgor, NB Dimethoate, Paragor, Parrydimate, Primogor, Ramgor, Rogor, Tagor, Tara 909, Tara Dimex Sulgor, Tka 30, Unigor, Vijaygor, Vikagor
Ediphenphos	Hinosan, Nukil
Ethion	Challenge, Demite, Dhanumit, Dhan-unit, Ethion, Ethione, Ethiosul 50, Fosmit, Mit 505, Mitex, Miticil, Mitvip, Phostech, RP-thion, Tafethion, VegFru Fosmite, Volathin
Fenitrothion	Accothion, Agrothion, Danathion, Fenicol, Fenitrosul 50, Folithion, Sicothoin, Sumithion, Vikathion
Fenthion	Agrocidin, Baytex, Fenthiosul, Labaycid, Lebaycid, Lebazate
Formothion	Anthio
Iprobenfos	Tagkite
Malathion	Agromal, Bharat, Celthion, Cython, Dhuthione, Finit, Himalaya, Kathion, Licel, Madhuthione, Maladan, Maladol, Malafil, Malathione, Malazene, Primothion, Sulmathion, VegFru Malatox
Methyl Parathion	Ant repellant,* Agropara, Agrotex, Ekatox, Folidol, Folidol-M, Harvest Kempar, Kilex-M, Metacid, Metapar, Metpar, Milphor, Paracrop, Paradol, Parahit, Parataf, VegFru Paratox
Monocrotophos	Atom, Azodrin, Balwan, Corophos, Entophos, Hilcrone, Luphos, Macrophos, Microphos, Monocil, Monochrovin, Monocrome, Monocron, Monocrown, Monocyl, Monodhan, Monokem, Monostar, Monovip, Nuvacron, Sicocil, Sufos, Unicron
Oxydemeton Methyl	Dhanuciytax, Hexasystox, Hymox, Knock Out, Metaciyta, Metasystox
Phenthoate	Agrofen, Delsan, Elsan, Guard, Phentox
Phorate	Anuphorate, Croton, Dhan, Dhang, Dragnet, Fortan, Glorat, Luphate, Phorachem, Phoratox, Phrotax, Thimate 10G, Thimet, VegFru Foratox, Vijayphor, Volphor
Phosalone	Zolone
Phosmet	Phosmite
Phosphamidon	Agromidon 85, Bangdon 85, Bilcran 85, Cildon, Delphamidon, Demacron, Demecron, Dimecron, Directon, Eagle, Entecron 85, Hildon, JK Midon, Midon, Phamidon, Phosul, Rilon, Sudon, Sumidon, Vimidon
Phoxim	Phoxin
Primiphos Methyl	Acetellic
Profenfos	Carina, Curacrone, Polytrine, Profex
Quinalphos	Agroquin, Agroquinol, Bayrusil, Chemlox, Coroqueen, Dhanulux, Dyalux, Ekalux, Fact, Flash, Kilex, Quenguard, Quick, Quinal, Quinaltof, Quinseed 25, Silofos, Solux, Vazara, Vikalux
Temephos	Abate 50EC, Farmico's
Thiometon (Morphothion)	Agrothimeton, Ekatin
Triazophos	Hostathion, Sutathion, Triphos, Truso
Trichlorphon	Dipterex

* Caution : The same brand name may refer to lindane

- Apart from acetylcholinesterase, organophosphates exert powerful inhibitory action over other carboxylic ester hydrolases such as chymotrypsin, butyrlcholinesterase (pseudocholinesterase), plasma and hepatic carboxylesterases, paraoxonases, and other non-specific proteases.
- It has been proposed that delayed peripheral neuropathy caused by organophosphates is due to phosphorylation of some esterase(s) other than acetylcholinesterase, such as neurotoxic esterase, also known as neuropathy target esterase (NTE). Neuropathy caused by inhibition of NTE may develop 2 to 5 weeks after an acute poisoning.

Toxicokinetics

- Organophosphates can be absorbed by any route including transdermal, transconjunctival, inhalational, across the GI and GU mucosa, and through direct injection.
- Manifestations usually begin within a few minutes to few hours, but may be delayed upto 12 hours or more in the case of certain compounds (e.g. fenthion, parathion).

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. Cholinergic Excess—
      – *Musscarinic Effects* (hollow organ parasympathetic manifestations): Common manifestations include bronchoconstriction with wheezing and dyspnoea, cough, pulmonary oedema, vomiting, diarrhoea, abdominal cramps, increased salivation, lacrimation, and sweating, bradycardia, hypotension, miosis, and urinary incontinence. Some of these can be remembered by the acronym SLUDGE —**S**alivation, **L**acrimation, **U**rination, **D**iarrhoea, **G**astrointestinal distress and **E**mesis. Excessive salivation, nausea, vomiting, abdominal cramps, and diarrhoea are common muscarinic effects, and have been reported even following the cutaneous absorption of organophosphate. Bradycardia and hypotension occur following moderate to severe poisoning.
      – *Nicotinic Effects* (autonomic ganglionic and somatic motor effects): Fasciculations, weakness, hypertension, tachycardia, and paralysis. Muscle weakness, fatiguability, and fasciculations are very common. Hypertension can occur in up to 20 per cent of patients. Tachycardia is also common. Cardiac arrhythmias and conduction defects have been reported in severely poisoned patients. ECG abnormalities may include sinus bradycardia or tachycardia, atrioventricular and/or intraventricular conduction delays, idioventricular rhythm, multiform premature ventricular extrasystoles, ventricular tachycardia or fibrillations, torsades de pointes, prolongation of the PR, QRS, and/or QT intervals, ST-T wave changes, and atrial fibrillation.
   b. CNS Effects—Restlessness, headache, tremor, drowsiness, delirium, slurred speech, ataxia, and convulsions. Coma supervenes in the later stages. In a review of 16

cases of paediatric organophosphate poisoning, all 16 children developed stupor and/or coma. Death usually results from respiratory failure due to weakness of respiratory muscles, as well as depression of central respiratory drive. Acute lung injury (non-cardiogenic pulmonary oedema) is a common manifestation of severe poisoning. Acute respiratory insufficiency, due to any combination of CNS depression, respiratory paralysis, bronchospasm, ARDS, or increased bronchial secretions, is the main cause of death in acute organophosphate poisonings. Metabolic acidosis has occurred in severe poisonings. A characteristic kerosene-like odour is often perceptible in the vicinity of the patient since the solvent used in many organophosphate insecticides is some petroleum derivative such as aromax.
   c. Other points of importance—
      – The Peradeniya Organophosphorus Poisoning (POP) Scale is predictive of death, necessity for mechanical ventilation, and the required total atropine dose over the first 24 hours. This scale rates 5 clinical variables, each on a 0 to 2 scale: miosis, muscle fasciculations, respirations, bradycardia, and level of consciousness.
      – In a given case, there may be either tachy- or brady-cardia; hypo- or hypertension.
      – Miosis while being a characteristic feature, may not be apparent in the early stages. In fact mydriasis is very often present, and hence treatment should not be delayed if there is absence of pupillary constriction. Blurred vision may persist for several months.
      – Ocular exposure can result in systemic toxicity. It can cause persistent miosis in spite of appropriate systemic therapy, and may necessitate topical atropine (or scopolamine) instillation.
      – Exposure to organophosphate vapours rapidly produces symptoms of mucous membrane and upper airway irritation and bronchospasm, followed by systemic symptoms if patients are exposed to significant concentrations.
      – While respiratory failure is the commonest cause of death, other causes may contribute including hypoxia due to seizures, hyperthermia, renal failure, and hepatic failure.
      – Patients with OP poisoning and QTc prolongation are more likely to develop respiratory failure and have a worse prognosis than patients with normal QTc intervals. Patients with OP poisoning who develop PVCs (premature ventricular contractions) are more likely to develop respiratory failure and have a higher mortality rate than patients without PVCs.
      – Aspiration of preparations containing hydrocarbon solvents may cause potentially fatal lipoid pneumonitis.
      – An *Intermediate Syndrome* sometimes occurs one to four days after poisoning due to long-lasting cholinesterase inhibition and muscle necrosis. It is more

common with chlorpyrifos, dimethoate, monocrotophos, parathion, sumithion, fenthion, fenitrothion, ethyl parathion, methyl parathion, diazinon, malathion, and trichlorfon. Main features include muscle weakness and paralysis characterised by motor cranial nerve palsies, weakness of neck flexor and proximal limb muscles, and acute respiratory paresis. Paralytic signs include inability to lift the neck or sit up, ophthalmoparesis, slow eye movements, facial weakness, difficulty swallowing, limb weakness (primarily proximal), areflexia, respiratory paralysis, and death. It may be due to inadequate treatment of the acute episode especially involving subtherapeutic administration of oximes or inadequate assisted ventilation. Several investigators have proposed that intermediate syndrome may develop as a result of several factors: inadequate oxime therapy, the dose and route of exposure, the chemical structure of the organophosphates, the time to initiation of therapy, and possibly efforts to decrease absorption or enhance elimination of the organophosphates. Once it sets in, the intermediate syndrome will have to be managed by supportive measures, since it does not respond to oximes or atropine.

– A *Delayed Syndrome* sometimes occurs 1 to 4 weeks after poisoning due to nerve demyelination, and is characterised by flaccid weakness and atrophy of distal limb muscles, or spasticity and ataxia. A mixed sensory-motor neuropathy usually begins in the legs, causing burning or tingling, then weakness. This syndrome also does not respond to either oximes or atropine. Severe cases progress to complete paralysis, impaired respiration and death. The nerve damage of organophosphate-induced delayed neuropathy is frequently permanent. The mechanism appears to involve phosphorylation of esterases in peripheral nervous tissue and results in a "dying back" pattern of axonal degeneration. Organophosphates that have been associated with delayed neuropathy in humans include chlorophos, chlorpyrifos, dichlorvos, dipterex, ethyl parathion, fenthion, isofenphos, leptophos, malathion, mecarbam, merphos, methamidophos, mipafox, trichlorofon, trichloronate, and TOCP (tri-ortho-cresyl phosphate).

– Parathion ingestion is sometimes associated with haemorrhagic pancreatitis which can terminate fatally. Diazinon has also been implicated. Haemoperfusion is said to be beneficial if this occurs.

– Patients poisoned with highly lipid soluble OPs such as fenthion have rarely developed extrapyramidal effects including dystonia, resting tremor, cog-wheel rigidity, and choreoathetosis. These effects began 4 to 40 days after acute OP poisoning and spontaneously resolved over 1 to 4 weeks in survivors.

– It is important to note that children may have different predominant signs of organophosphate poisoning than adults. In one study of children poisoned by organophosphate or carbamate compounds, the major signs and symptoms were CNS depression, stupor, flaccidity, dyspnoea, and coma. Other classical signs of organophosphate poisoning such as miosis, fasciculations, bradycardia, excessive salivation and lacrimation, and gastrointestinal symptoms were infrequent.

– Bradypnoea sometimes occurs. Respiratory rates of less than 8/minute are not unusual. Snoring prior to fatal overdose has been reported and is likely due to a failure to maintain the patency of the upper airway. Gurgling may occur due to accumulation of pulmonary oedema fluid. Non-cardiogenic pulmonary oedema is an infrequent, but severe, complication of overdose and is generally abrupt in onset (immediate-2 hours). Manifestations include rales, pink frothy sputum, significant hypoxia, and bilateral fluffy infiltrates on chest X-ray. Some patients require mechanical ventilation. Resolution of symptoms usually occurs rapidly with supportive care alone, within hours to 1 to 2 days.

2. **Chronic Poisoning:**

It usually occurs as an occupational hazard in agriculturists, especially those who are engaged in pesticide spraying of crops. Route of exposure is usually inhalation or contamination of skin. The following are the main features—

a. *Polyneuropathy*: paraesthesias, muscle cramps, weakness, gait disorders.

b. *CNS Effects* : drowsiness, confusion, irritability, anxiety.

c. *Sheep Farmer's Disease* : psychiatric manifestations encountered in sheep farmers involved in long-term sheep-dip operations.

d. Organophosphate poisoning has been associated with a variety of subacute or delayed onset chronic neurological, neurobehavioural, or psychiatric syndromes. One author has termed these "chronic organophosphate-induced neuropsychiatric disorder; (COPND) and noted that the standard hen neurotoxic esterase test is not sufficient to detect which OPs can cause this condition.

Diagnosis

1. Depression of cholinesterase activity:

a. If the RBC cholinesterase level is less than 50% of normal, it indicates organophosphate toxicity. RBC cholinesterase levels are more reliable in diagnosing organophosphate poisoning than serum cholinesterase.

– Disadvantages—

- Normal cholinesterase level is based on population estimates and there is a wide distribution in the definition of normal. A person with a "high normal" level may become symptomatic with a "low normal" activity.

- Several individuals do not seem to possess a known baseline level.
- A very low cholinesterase level does not always correlate with clinical illness.
- False depression of RBC cholinesterase level is seen in pernicious anaemia, haemoglobinopathies, anti-malarial treatment, and blood collected in oxalate tubes. Elevated levels may be seen with reticulocytosis due to anaemias, haemorrhage, or treatment of megaloblastic or pernicious anaemias.

b. Depression of plasma cholinesterase level (to less than 50%) is a less reliable indicator of organophosphate toxicity, but is easier to assay and more commonly done. Depressions in excess of 90% may occur in severe poisonings, and is usually associated with mortality.
   - Because it is a liver protein, plasma cholinesterase activity is depressed in cirrhosis, neoplasia, malnutrition, and infections, some anaemias, myocardial infarction, and chronic debilitating conditions.
   - Certain drugs such as sucinyl choline, lignocaine, codeine, and morphine, thiamine, ether, and chloroquine can also depress its activity.
   - Studies have demonstrated that RBC cholinesterase levels may be significantly higher in pregnant women than in nonpregnant controls, while plasma cholinesterase levels are generally lower during pregnancy. These levels revert to normal by six weeks postpartum.
   - The organophosphates phosdrin and chlorpyrifos may selectively inhibit plasma pseudocholinesterase, while phosmet and dimethoate may selectively inhibit red blood cell cholinesterase.

c. For the purpose of estimation of cholinesterase level, blood should be collected only in heparinised tubes. Alternatively, samples can be frozen. Plasma cholinesterase usually recovers in a few days or weeks; red blood cell cholinesterase recovers in several days to 4 months depending on severity of depression.

2. *P-Nitrophenol Test:* P-nitrophenol is a metabolite of some organophosphates (e.g. parathion, ethion), and is excreted in the urine. Steam distill 10 ml of urine and collect the distillate. Add sodium hydroxide (2 pellets) and heat on a water bath for 10 minutes. Production of yellow colour indicates the presence of p-nitrophenol. The test can also be done on vomitus or stomach contents.

3. *Thin Layer Chromatography* (*TLC*): The presence of an organophosphate in a lavage, or vomit, or gastric aspirate sample can also be determined by TLC. The sample is extracted twice with 5 ml of petroleum ether, and the extract is washed with distilled water. It is then dried in steam compressed air, reconstituted in methanol, and spotted on silica gel-coated TLC plate along with the standard and run in a mixture of petroleum ether and methanol (25 : 1). After the solvent has travelled a considerable distance, the plate is dried and exposed to iodine vapour. The RF is compared with that of the standard.

4. *Ancillary Investigations:*
   a. There may be evidence of leukocytosis (with relatively normal differential count), high haematocrit, anion gap acidosis, hyperglycaemia.
   b. In every case, monitor electrolytes, ECG and serum pancreatic isoamylase levels in patients with significant poisoning. Patients who have increased serum amylase levels and those who develop a prolonged QTc interval or PVCs are more likely to develop respiratory insufficiency and have a worse prognosis. If pancreatitis is suspected, an abdominal CT-scan can be performed to evaluate diffuse pancreatic swelling.
   c. If respiratory tract irritation is present, monitor chest X-ray. Many organophosphate compounds are found in solution with a variety of hydrocarbon-based solvents. Aspiration pneumonitis may occur if these products are aspirated into the lungs. Bronchopneumonia may develop as a complication of organophosphate-induced pulmonary oedema.
   d. High performance thin layer chromatography (HPLC) technique can be used to identify several organophosphate compounds in human serum.

Treatment

Determine plasma or red blood cell cholinesterase activities. Depression in excess of 50 per cent of baseline is generally associated with severe symptoms (*vide supra*).

1. **Acute Poisoning:**
   a. *Decontamination*:
      - If skin spillage has occurred, it is imperative that the patient be stripped and washed thoroughly with soap and water.
         - Shower is preferable. Make the patient stand (if he is able to) under the shower, or seated in a chair.
         - Wash with cold water for 5 minutes from head to toe using non-germicidal soap. Rinse hair well.
         - Repeat the wash and rinse procedure with warm water.
         - Repeat the wash and rinse procedure with hot water.
         - Treating personnel should protect themselves with water-impermeable gowns, masks with eye shields, and shoe covers. Latex and vinyl gloves provide inadequate protection, unless a double pair is used.
      - If ocular exposure has occurred, copious eye irrigation should be done with normal saline or Ringer's solution. If these are not immediately available, tap water can be used.
      - In the case of ingestion, stomach wash can be done, though this is often unnecessary because the patient would have usually vomited several times by the time he is brought to hospital. Activated charcoal can be administered in the usual way.

b. *Antidotes:*
- Atropine—It is a competitive antagonist of acetyl-choline at the muscarinic postsynaptic membrane and in the CNS, and blocks the muscarinic manifestations of organophosphate poisoning.
- Oximes—The commonest is pralidoxime (pyridine-2-aldoxime methiodide), which is a nucleophilic oxime that helps to regenerate acetylcholinesterase at muscarinic, nicotinic, and CNS sites. Actually, human studies have not conclusively substantiated the benefit of oxime therapy in acute organophosphate poisoning, but they are widely used. Most authors advocate the continued use of pralidoxime in the clinical setting of severe organophosphate poisoning.

The antidotes for organophosphates have been discussed together in detail in **Table 28.2**.

c. *Supportive Measures:*
- Administer IV fluids to replace losses.
- Maintain airway patency and oxygenation. Suction secretions. Endotracheal intubation and mechanical ventilation may be necessary. Monitor pulse oximetry or arterial blood gases to determine need for supplemental oxygen.
- Oxygenation/intubation/positive pressure ventilation: To minimise barotrauma and other complications, use the lowest amount of PEEP possible while maintaining adequate oxygenation. Use of smaller tidal volumes (6 ml/kg) and lower plateau pressures (30 cm water or less) has been associated with decreased mortality and more rapid weaning from mechanical ventilation in patients with ARDS.
- The following drugs are contraindicated: parasympathomimetics, phenothiazines, antihistamines,

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Table 28.2: Antidotes for Organophosphates

Atropine

Mode of action : Blocks the muscarinic manifestations of organophosphates. However, since atropine affects only the postsynaptic muscarinic receptors, it has no effect on muscle weakness or paralysis

Diagnostic dose: Organophosphate-poisoned patients are generally tolerant to the toxic effects of atropine (dry mouth, rapid pulse, dilated pupils, etc.)

If these findings occur following a diagnostic atropine dose, the patient is probably not seriously poisoned

Diagnostic dose—Adult: 1 mg intravenously or intramuscularly; Child—0.25 mg (about 0.01 mg/kg) intravenously or intramuscularly

Therapeutic dose: 1 to 2 mg IV or IM (adult); 0.05 mg/kg IV (child); every 15 minutes until the endpoint is reached, i.e. drying up of tracheobronchial secretions. Pupillary dilatation and tachycardia are not reliable indicators of the endpoint

Atropine can also be administered as an IV infusion after the initial bolus dose, at a rate of 0.02 to 0.08 mg/kg/hr. Once the endpoint has been reached, the dose should be adjusted to maintain the effect for at least 24 hours

Atropinisation must be maintained until all of the absorbed organophosphate has been metabolised. This may require administration of 2 to 2,000 milligrams of atropine over several hours to weeks

Atropine therapy must be withdrawn slowly to prevent recurrence or rebounding of symptoms, often in the form of pulmonary oedema. This is especially true of poisonings from lipophilic organophosphates such as fenthion

Precautions:
- Many parenteral atropine preparations contain benzyl alcohol or chlorobutanol as preservatives. High-dose therapy with these preparations may result in benzyl alcohol or chlorobutanol toxicity. Preservative-free atropine preparations are available, and should be used if large doses are required
- The half-life of atropine is significantly longer in children under 2 years and adults over 60; the rate of administration in these patients should be adjusted accordingly
- Effects of overdosing with atropine include fever, warm dry skin, inspiratory stridor, irritability, and dilated and unresponsive pupils

Adverse effects : Atrial arrhythmias, AV dissociation, multiple ventricular ectopics, photophobia, raised intraocular pressure, hyperpyrexia, hallucinations, and delirium

Pralidoxime (Pyridine-2-aldoxime methiodide; 2-PAM)

Structurally, pralidoxime is 2-hydroxyiminomethyl-1-methyl pyridinium chloride

Mode of action: It is usually given along with atropine. Pralidoxime competes for the phosphate moiety of the organophosphorus compound and releases it from the acetylcholinesterase enzyme, thereby liberating the latter and reactivating it

While it is advisable to begin pralidoxime therapy within 48 hours of poisoning, it can be administered even much later with beneficial effects

Till recently, pralidoxime was said to be contraindicated in carbamate poisoning because experiments with carbaryl (*Sevin*) suggested a worsening of symptoms when it was administered. However, recent studies have pointed out that while pralidoxime is not a necessary adjunct to atropine in carbamate overdose, it may be beneficial in some cases

Dose: *For adults*—1 to 2 gm in 100 to 150 ml of 0.9% sodium chloride, given IV over 30 minutes

This can be repeated after 1 hour, and subsequently every 6 to 12 hours, for 24 to 48 hours

Contd...

Contd...

Alternatively, a 2.5% concentration of pralidoxime can be given as a loading dose followed by a maintenance dose

Serious intoxication may require continuous infusion of 500 mg/hr in adults. Many workers feel that this high dose therapy minimises the incidence of complications such as the Intermediate Syndrome

Maximum dose should not exceed 12 gm in a 24 hour period. Infusion over a period of several days may be necessary and is generally well tolerated

The WHO currently recommends an initial bolus of at least 30 mg/kg, followed by an infusion of more than 8 mg/kg /hr

It is estimated that a plasma concentration of at least 4 mg/L may be necessary for pralidoxime to be effective

For children—20 to 40 mg/kg to a maximum of 1 gm/dose given IV, and repeated every 6 to 12 hours for 24 to 48 hours

Alternatively, iv infusion can be resorted to, at a rate of 9 to 19 mg/kg/hr

Adverse effects: Rapid administration can cause tachycardia, laryngospasm, and even cardiac or respiratory arrest

Other adverse effects include drowsiness, vertigo, headache, and muscle weakness

It is generally not advised for the treatment of carbamate overdose, especially carbaryl

In cases where intravenous administration is not possible, pralidoxime can be given intramuscularly as an initial dose of 1 gram or up to 2 grams in cases of very severe poisoning

In some countries obidoxime is used instead of pralidoxime, though it does not appear to be superior to the latter

It is apparently favoured over pralidoxime in clinical practice in Belgium, Israel, The Netherlands, Scandinavia, and Germany, and is the only oxime available in Portugal

A few investigators suggest that oximes have only a limited role in organophosphate poisoning, and successful management is possible without employing them at all, though this view is not shared by most other workers in the field

Diazepam

Some studies indicate that the addition of diazepam to atropine and 2-PAM improves survival. It reduces the risk of seizure-induced brain and cardiac damage

Dose: *For adults*—5 to 10 mg IV slowly, every 15 minutes, upto a maximum of 30 mg

For children—0.25 to 0.4 mg/kg IV slowly, every 5 to 10 minutes, upto a maximum of 10 mg

If diazepam is ineffective, phenytoin or phenobarbitone can be used instead

and opiates. Do not administer succinylcholine (suxamethonium) or other cholinergic medications. Prolonged neuromuscular blockade may result when succinylcholine is administered after organophosphate exposure.
– Treat convulsions with benzodiazepines or barbiturates.
– Antibiotics are indicated only when there is evidence of infection.
– Haemoperfusion, haemodialysis, and exchange transfusion have not been shown to affect outcome or duration of toxicity in controlled trials of organophosphate poisoning.
d. *Prevention of Further Exposure:* After the patient has recovered, he should not be re-exposed to organophosphates for at least a few weeks since he is likely to suffer serious harm from a dose that normally would be harmless, owing to alteration of body chemistry. Following acute poisoning, patients should be precluded from further organophosphate exposure until sequential RBC cholinesterase (AChE) levels have been obtained and confirm that AChE activity has reached a plateau. Plateau has been obtained when sequential determinations differ by no more than 10%. This may take 3 to 4 months following severe poisoning.

e. *Treatment of Pregnant Victim:* Therapeutic choices during pregnancy depend upon specific circumstances such as stage of gestation, severity of poisoning, and clinical signs of mother and foetus. The mother must be treated adequately to treat the foetus. A severely poisoned patient with a late gestation viable foetus may be a candidate for emergency Caesarean section. The foetus may require intensive care after birth.
– Pralidoxime chloride is recommended for use in the pregnant patient to counteract muscle weakness.
– Glycopyrrolate: Unlike atropine, glycopyrrolate usually does not readily cross the placenta and would not directly affect foetal poisoning. However, the foetus may be best served by treating the mother to retain good respiratory function and foetal oxygenation.
2. **Chronic Poisoning:**
a. Removal of the patient from the source of exposure.
b. Supportive and symptomatic measures.

Autopsy Features

1. *External*—
a. Characteristic odour (garlicky or kerosene-like).
b. Frothing at mouth and nose.

c. Cyanosis of extremities.
d. Constricted pupils.
2. *Internal—*
   a. Congestion of GI tract; garlicky or kerosene-like odour of contents.
   b. Pulmonary and cerebral oedema.
   c. Generalised visceral congestion.

Forensic Issues

Discussed at the end of the chapter, together with all the other pesticides.

■ Carbamates

Carbamates are as popular as organophosphates in their role as insecticides (and fungicides) and share a number of similarities. Only the differentiating features will be discussed. Indian brands are listed in **Table 28.3**.

Usual Fatal Dose

Toxicity Rating*:
The following are extremely toxic (*LD50: 1 to 50 mg/kg*), or highly toxic (*LD50: 51 to 500 mg/kg*)—
Aminocarb, Bendiocarb, Benfuracarb, Carbaryl, Carbofuran, Dimetan, Dimetilan, Dioxacarb, Formetanate, Methiocarb, Methomyl, Oxamyl, Propoxur.
The following are moderately toxic (*LD50: 501 to 5000 mg/kg*), or slightly toxic (*LD50: more than 5000 mg/kg*)—
Aldicarb, Bufencarb, Isoprocarb, MPMC, MTMC, Pirimicarb.

Mode of Action and Clinical Features

Carbamates (like organophosphates) are inhibitors of acetylcholinesterase, but carbamylate the serine moiety at the active site instead of phosphorylation. This is a reversible type of binding and hence symptoms are less severe and of shorter duration. As a result both morbidity and mortality are limited when compared to organophosphate poisoning. Also, since carbamates do not penetrate the CNS to the same extent as organophosphates, CNS toxicity is likewise much less. With respect to all other clinical manifestations, there is general similarity between carbamates and organophosphates.

Carbamates are rapidly metabolised. They are rapidly hydrolysed by liver enzymes to methyl carbamic acid and a variety of low toxicity phenolic substances. These metabolites may sometimes be measured in urine as long as 2 to 3 days after significant pesticide absorption.

Miosis, a muscarinic effect, is characteristic of severe and moderately severe poisonings, but may appear late. Pupil dilation may occur as a nicotinic effect and may be present in up to 10% of patients.

Sinus tachycardia with ST segment depression may occur early in the course of poisoning. Repolarisation abnormalities may occur and are generally transient.

Dyspnoea is a common manifestation of carbamate exposure.

Chest tightness, bronchospasm, increased pulmonary secretions, and rales may develop secondary to muscarinic effects. Acute lung injury (pulmonary oedema) is a potential clinical manifestation of severe carbamate poisoning and is attributed to the muscarinic action of the insecticide. Contributing factors to the development of pulmonary oedema include bradycardia and weakened cardiac contraction from an accumulation of acetylcholine on the cardiovascular system. Hypoxia may develop due to increasing capillary permeability.

Headache, dizziness, blurred vision, tremor, paresis, mental depression, coma, delayed neuropathies, various dystonias, weakness, muscle twitching, and convulsions have all been reported with carbamate poisoning. Children may be more likely to develop CNS depression, convulsions, and hypotonia than the typical cholinergic syndrome. Absence of classic muscarinic effects has been reported in several children intoxicated with carbamate insecticides. The presence of either a cardiac arrhythmia or respiratory failure is associated with a higher incidence of fatal poisoning.

Various peripheral neuropathies have been reported after carbamate use. The symptoms are similar to those seen with organophosphates. Acute pancreatitis has been reported with propoxur.

Table 28.3: Common Carbamates

Generic Name	Brand Name
Aldicarb	Aldrin, Temik
Carbaryl	Agrovin, Agroyl, Bangvin 50, Caravet, Corovin, Hexavin, Kevin 50, Kilex Carbaryl, Sevidal, Sevin 50, Sujacarb, Sulfarl 50
Carbaryl + Gamma BHC	Sevidol
Carbofuran	Agrofuron 3G, Carbocil 3, Carburan, Crane, Furadan 3G, Hexafuran, VegFru Diafuran
Carbosulfan	Marshal
Fenobucarb	Merlino
Methomyl	Astra, Dunet, Lannate, Lannet, Mathoyl
MPMC (Xylylcarb)	Bipuin
MTMC (Metolcarb)	Emisan
Propoxur	Baygon, Isocarb, Protox Bait
Thiodicarb	Larvin

* Partly as per the **Insecticide Rules, 1971.**

Diagnosis

In the case of carbamate poisoning, measurement of cholinesterase activity in blood may be misleading due to in vitro reactivation of carbamylated enzyme. In vitro decarbamylation has been found to be promoted by dilution of the sample. The carbamylated sample should be stored undiluted and refrigerated or frozen. Carbamylated cholinesterase activity follows a non-linear kinetic pattern over time, whereas phosphorylated enzyme activity is linear. At inhibition of greater than 40%, the non-linear pattern characteristic of carbamates is easily mapped.

One technique for assessing absorption of the principal N-methyl carbamate compounds is measurement of specific phenolic metabolites in urine, e.g. carbaryl (alpha-naphthol), carbofuran (carbofuranphenol) propoxur (isopropoxyphenol).

Chest X-ray should be obtained in all symptomatic patients. The major cause of morbidity and mortality in carbamate insecticide poisonings is respiratory failure and associated pulmonary oedema.

Treatment

An important differentiating point from organophosphates is that oximes are generally not recommended, while atropine can be given. Especially in carbaryl poisoning, oxime therapy can lead to the production of a carbamylated oxime which may be a more potent acetylcholinesterase inhibitor than carbaryl itself. With other carbamate insecticides (particularly aldicarb), oximes may be a useful adjunct to atropine therapy. In 1986, a consensus of international experts concluded that pralidoxime can be used in conjunction with atropine for specific indications as follows:

- Life-threatening symptoms such as severe muscle weakness, fasciculations, paralysis, or decreased respiratory effort.
- Continued excessive requirements of atropine.
- Concomitant organophosphate and carbamate exposure.

In all cases, administer atropine in repeated doses intravenously until atropinisation is achieved (indicated by drying of pulmonary secretions). *Adult dose*—2 to 4 mg IV every 10 to 15 minutes. *Paediatric dose*—0.05 mg/kg IV every 10 to 15 minutes.

Convulsions can be controlled with a benzodiazepine (diazepam or lorazepam). If they persist or recur, administer phenobarbitone.

■ Organochlorines

Organochlorine pesticides are one variety of chlorinated hydrocarbons. There are 4 distinct categories of these pesticides:
1. *DDT and analogues*—for example, DDT (dichlorodiphenyltrichloroethane), and methoxychlor.
2. *Benzene hexachloride group*—for example, benzene hexachloride (BHC), and gamma-hexachlorocyclohexane (lindane).
3. *Cyclodienes and related compounds*—for example, aldrin, dieldrin, endosulfan (thiodan), endrin, isobenzan, chlordane, chlordecone (kepone), heptachlor, mirex (dechlorane).
4. *Toxaphene and related compounds*—for example, toxaphene. **Table 28.4** lists Indian brand names of organochlorine pesticides.

Physical Appearance

These compounds are available as dusting powders, wettable powders, emulsions, granules and solutions.

Uses

- Insecticide.
- Gamma benzene hexachloride is used as a scabicide (treatment of scabies), and a pediculocide (eradication of head lice). It is available as topical ointment, cream, or lotion. Some Indian brand names include *Bexarid* (Shalaks), *Gab* (Gufic), *Gamaric* (Euphonic), *Scaboma* (Glenmark), and *Ultrascab* (Perch).

Usual Fatal Dose

- DDT, lindane: 15 to 30 grams.
- Aldrin, dieldrin, endrin : 2 to 6 grams.

Toxicity Rating: Dieldrin is placed in the "extremely toxic" category (*LD50: 1 to 50 mg/kg*), while DDT, endosulfan, and lindane are considered "highly toxic"(*LD50: 51 to 500 mg/kg*), as per the ***Insecticide Rules, 1971***.

In addition, the following are extremely toxic: endrin, aldrin, chlordane, and toxaphene, while these are highly toxic: kepone, heptachlor, mirex. The following are least toxic:

Table 28.4: Common Organochlorine Pesticides

Generic Name	Brand Name
Aldrin	Agroaldrin, Alcrop, Alditon, Aldrex, Aldrin 30, Mildrin 30, Tarmahit 30
BHC	Agrobenz D10, Agro BHC, Gamazene, Gammexane, Haxaman, Hexidole Hilbleach 50WP, Kargo BHC, Premodole 10EC, Sevidol (with carbaryl), Solchlor, Sudarshan, Sulbenz 50, Sunbrand
Chlordane	Agrodane 20EC, Chlordane, Mitox 20EC, Sudarshan 5EC, Termex, VegFru Chlortox
DDT	DDT Sudarshan 50, Didinex 25EC, Ramdit, Ranodit, Soltax, Suldit 50, Sunbrand, Tafarol, Tafidex
Dicofol	Kelthane, Klin
Endosulfan	Agrosulfan, Chemusulfan, Endohit, Endoseed, Endosol, Endosulfan, Endoxin, Endotaf, Endovip, Ethsulfan, Hexasulfan, Hildane, Hildon, Kenrilfan, Kesulfan, Marvel, Speed, Thiodan, Thiodon, Unidhan
Heptachlor	Agrochlor D5, Agrodono, Heptachlor, Heptaf 50, Heptar, Heptox, VegFru Heptex
Lindane	Agrodane, Bexarid, Canodane, Emscab, Gab, Gamaric, Gamascab, Kenodan, Lindane 20, Lindex, Linsuline, Lintaf, Rasayan Lindane, Scabex, Scaboma, Scarab, Starbrand Lindane, Ultrascab

methoxychlor, perthane, kelthane, chlorobenzilate, and hexa-chlorobenzene.

Acute hazard potential may be ranked (highest to lowest) approximately as: endrin, aldrin, dieldrin, chlordane, toxaphene, kepone, heptachlor, DDT and methoxychlor.

Toxicokinetics

Commercial preparations of organochlorines are commonly dissolved in petroleum distillates which form emulsions when added to water. All the organochlorines can be absorbed transdermally, orally, and by inhalation. Gastrointestinal absorption of these agents is generally efficient, particularly in the presence of absorbable lipid (animal or vegetable) fat. DDT is the least well absorbed transdermally, while dieldrin is very well absorbed. Many of these compounds are metabolised slowly and persist in tissues (especially fat) for prolonged periods. High residue levels from organochlorine insecticide poisonings are found in adipose tissue. However, unlike other organochlorine pesticides, methoxychlor does not substantially accumulate in fatty tissues of humans.

Excretion of organochlorine compounds does not follow first order kinetics. As body stores get lower, the half-life for the remaining store increases dramatically. This is probably due to complex lipoprotein binding, wherein different bound forms exhibit different dissociation characteristics. It is still possible to classify the organochlorines roughly in terms of the rapidity of excretion from storage levels that represent an acute toxic threat:

- Excreted or metabolised within hours to a few days:
  - ❖ chlordane (except the heptachlor component)
  - ❖ chlorobenzilate
  - ❖ endosulfan
  - ❖ endrin
  - ❖ kelthane
  - ❖ methoxychlor
  - ❖ perthane
  - ❖ toxaphene.
- Excreted within several weeks to a few months:
  - ❖ aldrin
  - ❖ dieldrin
  - ❖ heptachlor
  - ❖ hexachlorobenzene.
- Excreted only over several months or years:
  - ❖ beta isomer of benzene hexachloride
  - ❖ DDT
  - ❖ kepone
  - ❖ mirex.

Mode of Action

Organochlorines do not depress cholinesterase enzymes. These compounds act by various other mechanisms.

- DDT and analogues affect the sodium channel and sodium conductance across the neuronal membrane especially of the axon. They also alter the metabolism of serotonin, noradrenaline and acetylcholine.
- The cyclodienes and lindane appear to inhibit the GABA-mediated chloride channels in the CNS.

- The neurotoxic mechanism of endosulfan involves inhibition of the calmodulin-dependant Ca_2+ -ATPase activity, alterations in the serotoninergic system, and inhibition of GABA receptors.
- An important property of the chlorinated hydrocarbons, particularly toxaphene, chlordane, DDT, and lindane is their capacity to induce the drug-metabolising enzymes of the liver. Most of these agents cause liver necrosis and they are potent enzyme inducers. Evidence suggests an important role of benzoquinones in the hepatotoxicity of chlorinated hydrocarbons as opposed to traditional epoxides. Cytochrome P450 appears to be associated with covalent protein binding of reactive metabolites.

Clinical Features

1. **Acute Poisoning:**
   a. *GIT*: nausea, vomiting, abdominal pain, hyperaesthesia or paraesthesia of the mouth and face.
   b. *CNS*: headache, vertigo, myoclonus, tremor, ataxia, nervousness, amnesia, rapid and dysrhythmic eye movements, mydriasis, weakness, agitation, confusion, and convulsions. Occasional reports have associated peripheral neuropathy with exposure to organochlorines.
   c. *Other systems*: fever, aspiration pneumonitis, renal failure. Coronary spasm, hypotension, and sinus tachycardia may occur following exposure. Dieldrin, endrin, chlordane, toxaphene, and DDT are direct respiratory depressants. Severe metabolic acidosis has been reported.
   d. Organochlorine pesticides such as DDT pass through the placenta, with an average level in the newborn blood reaching around a third of that in maternal blood. They can also be found in breast milk.

2. **Chronic Poisoning:**
Long-term exposure to some of these compounds (chlordecone, chlordane, heptachlor) results in cumulative toxicity with manifestations such as weight loss, tremor, weakness, opsoclonus, ataxia, pseudotumour cerebri, abnormal mental changes, oligospermia, and increased tendency to leukaemias, thrombocytopenic purpura, aplastic anaemia, hepatomegaly, centrilobular hepatic necrosis and liver cancer.

The International Agency for Research on Cancer (IARC) has listed some of these agents (e.g. DDT) as "possibly carcinogenic to humans", although it also categorises them as being inadequately assessed for human carcinogenic potential. For other agents (e.g. aldrin), carcinogenicity has been demonstrated in animal studies, but insufficient data has accrued from human studies.

Diagnosis

1. Abdominal radiograph may reveal the presence of certain organochlorines which are radiopaque.
2. Organochlorines can be detected in serum, adipose tissue, and urine by gas chromatography.
3. Blood chlorinated hydrocarbon levels are not clinically useful following acute exposure. For most compounds

they reflect cumulative exposure over a period of months or years rather than recent exposure.

4. Measurement of organic halogen compounds in urine is suggested as an indicator of exposure. Sensitivity is as low as 1 mcg of organic halogen per 100 ml of urine.

Treatment

1. Decontamination—the same measures as detailed under organophosphate poisoning must be undertaken.
    a. Move patient from the toxic environment to fresh air.
    b. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis. Administer 100% humidified supplemental oxygen, perform endotracheal intubation and provide assisted ventilation as required. Administer inhaled beta adrenergic agonists if bronchospasm develops.
    c. Exposed skin and eyes should be flushed with copious amounts of water. Remove contaminated clothing and jewelry; wash skin, hair and nails vigorously with repeated soap washings. Leather absorbs pesticides; all contaminated leather should be discarded. Rescue personnel and bystanders should avoid direct contact with contaminated skin, clothing, or other objects.
2. Do NOT give oils by mouth. They tend to increase intestinal absorption of these lipophilic toxicants.
3. Seizures should be controlled with benzodiazepines, phenytoin, or phenobarbitone in the usual way. If they are not effective enough, sodium thiopentone can be administered IV, or neuromuscular blockade is done.
4. Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation. Evaluate for hypoxia, electrolyte disturbances, and hypoglycaemia (if present, treat with intravenous dextrose: 50 ml IV (adult), or 2 ml/kg (child) of 25% dextrose).
5. Cholestyramine, a non-absorbable bile acid binding anion exchange resin is effective in enhancing the faecal excretion of organochlorine compounds, particularly chlordecone. It is administered at a dose of 16 gm/day for several days. It can be mixed with fruit juice and given orally (4 gm, 6th hourly). It can interfere with absorption of other therapeutic drugs which must therefore be administered either 1 hour before, or 4 hours after each dose of cholestyramine.
6. Hyperthermia should be managed aggressively with cooling.
7. Supportive measures—special attention must be paid to the airway and breathing, and adequate circulation should be maintained.
8. The following are contraindicated—oil-based cathartics, adrenaline, and atropine. Do NOT administer adrenergic amines, which further increase myocardial irritability and produce refractory ventricular arrhythmias.
9. Haemodialysis and haemoperfusion have not been proven effective.

■ Pyrethrins and Pyrethroids

Pyrethrins are active extracts of the chrysanthemum plant (*Chrysanthemum cinerariaefolium*), and include pyrethrum and piperonyl butoxide. They are esters of pyrethric and chrysanthemic acids formed by the keto alcohols pyrethrolone, cinerolone, and jasmololone. Pyrethrin I and pyrethrin II are two of the most insecticidally potent pyrethric and chrysanthemic esters. Pyrethroids are synthetic analogues and number over 1000 varieties which are used as insecticides to incapacitate or "knock out" insects. Most mammals are resistant since they can rapidly metabolise and detoxify these agents. Common pyrethrins and pyrethroids available commercially in India are mentioned in **Table 28.5**.

Uses

- These compounds are used as household insect repellants and insecticides. They are sold as liquids, sprays, dusts, powders, mats, and coils.
- They are also used to prevent pest infestation in granaries, and in agriculture as pesticides.
- Pyrethrum extract is effective for treating pediculosis of the head, body and pubic area.

Usual Fatal Dose

Pyrethrum has an LD50 of over 1 gm/kg. However, the minimal lethal dose of pyrethrum is not clearly established, though it is probably in the range of 10 to 100 grams. Most cases of toxicity are actually the result of allergic reactions.

Mode of Action

Structurally, pyrethroids are of 2 types—

Type I pyrethroids do not contain a cyano group, e.g. permethrin.

Type II pyrethroids contain a cyano group, e.g. deltamethrin, cypermethrin, fenpropathrin, fenvalerate, etc.

Like DDT, pyrethroids prolong the inactivation of the sodium channel by binding to it in the open state. Type II agents are more potent in this regard, and also act by inhibiting GABA-mediated inhibitory chloride channels. Low toxicity in mammals is probably due to rapid metabolic breakdown in the liver: pyrethrum is broken down mainly by oxidation of the isobutenyl side chain of the acid moiety and of the unsaturated side chain of the alcohol moiety with ester hydrolysis playing a role. Some organophosphates may enhance pyrethrin toxicity due to competition for carboxyesterases responsible for rapid detoxification of pyrethrins via ester hydrolysis. Very young children are perhaps more susceptible to poisoning by pyrethroids because they may not hydrolyse the pyrethrum esters efficiently.

Two types of allergens present in crude pyrethrum oleoresin have been identified: glycoproteins or glycopeptides ranging in molecular weight from 60,000 to 200,000 (most important) and the sesquiterpene lactones, principally pyrethrosin (minor

Table 28.5: Pyrethrins and Pyrethroids

Generic Name	Brand Name
Allethrin	Baygon mats, Good Knight, Pynamin Forte
Alphamethrin	Alfaguard, Farsa, Farward, Stop
Alphamethrin + Chlorpyriphos	Anuphan, Fenit-20, Twister
D-allethrin	Baygon Knock-out aerosol, Baygon Power mats, Good Knight mats, Hit insect repellant
Barthrin	Basothrin
Cyfluthrin	Bulldock
Cyhalothrin	Karate, Reeva
Cypermethrin	Agrocyper, Arjun, Basathrin, Bilcyp, Bilsif, Challenger, Cilcord, Colt, Cybil, Cymber, Cymbush, Cymet, Cymper, Cymperm, Cyper, Cyperguard, Cyperhit, Cyperin, Cypermethrin-Sandoz, Cypermil, Cypersul, Cypertech, Cypervip, Cyrux, Fury, Gilcyp Tech, Hilcyperin, Hypowder, Hycper, Java, Megacypher, Megathrine, Motal, Parathrin, Pest-seal, Raksha, Ralathin, Ralo, Ralothrin, Ramceper, Retolin, Ripcord, Riptan, Shakti, Sicerin, Sicorin, Starcyprin, Superkiller, Suraksha, Tackle, Vegfrucott, Unicyper, Ustad
Cypermethrin + Chlorpyriphos	Anaconda, Cannon, Nurelle-D, Neurocombi, Shelter, Super-D
Cypermethrin + Quinalphos	Prasanth
Decamethrin	Decathrin
Deltamethrin	Butox, Decaguard, Decis, Deltex, Hexit (*with allethrin*), K-Othrine
Deltamethrin + Triazophos	Crove, Shekari, Spark
Fenvalerate	Agrofen, Anchor, Anusan, Capvalerate, Dhanusan, Fencidin, Fenfen, Fenhit, Fenkill, Fenlid, Fenny, Fenval, Fenvil, Fenvip, Fighter, Gilfen, Hilten, Parafen, Primovel, Silofen, Starfen, Sumicidin, Sumitox, Triumpheard, Trumpcard, Vijayfen
Fluvalinate	Marvik
Permethrin	Ambush, Lee, Permasect, Permethrin, Pounce
Pyrethrum	Tortoise mosquito coil

importance). Refined pyrethrins and synthetic pyrethroids are said to have little or no allergenic effect.

Clinical Features

1. *Skin contact*: dermatitis, blistering. The usual lesion is a mild erythematous dermatitis with vesicles, papules in moist areas, and intense pruritus; a bulbous dermatitis may also occur. Skin contamination with pyrethrins can cause localised paraesthesia.
2. *Eye contact*: Eye exposures may result in mild to severe corneal damage that generally resolves with conservative care. Corneal denudation and decreased visual acuity have been reported following ocular contact exposure during normal use of pediculicide shampoos containing pyrethrin. Chemical conjunctivitis was diagnosed in a patient after a pyrethrin-containing mist was inadvertently sprayed into the eyes.
3. *Inhalation*: rhinorrhoea, sore throat, wheezing, dyspnoea. Asthma or reactive airways disease syndrome can occur following inhalation exposures, as also hypersensitivity pneumonitis with chest pain, cough, dyspnoea and bronchospasm. Eosinophilia may accompany an acute allergic reaction. Dizziness and headache have been reported following exposure to pesticide mists.
4. *Ingestion* (large doses): paraesthesias, nausea, vomiting, vertigo, fasciculations, hyperthermia, altered mental status, seizures, pulmonary oedema, coma. Nausea, vomiting and abdominal pain commonly occur and develop within 10 to 60 minutes following ingestion. Hypotension and tachycardia, associated with anaphylaxis, may occur. Severe poisoning may result in marked adrenal activation, with increases in adrenaline and noradrenaline accompanying motor signs.

Diagnosis

1. Serum cholinesterase levels are normal.
2. ECG may demonstrate ST-T changes, sinus tachycardia, and ventricular premature beats.
3. A colour test with 2-2 (2-aminoethylamine) ethanol produces red to violet colour in the presence of pyrethroidal substances. It is however not suitable for analysis of pyrethrins in body fluids, except, possibly at very high concentrations.

Treatment

1. *Skin contact*—decontaminate with soap and water.
2. *Eye contact*—irrigate with normal saline or water for 10 to 15 minutes.
3. *Systemic poisoning*—
   a. Mild to moderate allergic reactions may be treated with antihistamines (e.g. diphenhydramine 50 mg orally, intravenously, or intramuscularly initially, then 25 to 50 mg orally every 4 to 6 hours for 24 to 72 hours) with or without inhaled beta agonists, corticosteroids (e.g.

methyl prednisolone 1 to 2 mg/kg intravenously every 6 to 8 hours) or adrenaline (1:10,000 solution, 3 to 5 ml diluted in 10 ml 0.9% saline slow intravenous push over 5 to 10 minutes). Treatment of severe anaphylaxis also includes oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring and IV fluids.

b. In massive ingestions, stomach wash can be done after making sure that there are no petroleum distillate additives.

c. Activated charcoal is beneficial. However, if the pyrethrin is formulated in an organic solvent, activated charcoal is unlikely to be of benefit. If the pyrethrin is formulated in a petroleum base, the risk of hydrocarbon pneumonitis may exceed the toxic hazard of the insecticide. Gastric decontamination is therefore, generally not recommended.

d. Oils and fats (including milk) promote the intestinal absorption of pyrethroids and should be avoided.

e. Oxygen and ventilatory asistance must be administered as indicated.

f. Bronchospasm is treated with standard bronchodilators. Administer beta$_2$ adrenergic agonists. Consider use of inhaled ipratropium and systemic corticosteroids. Monitor peak expiratory flow rate, monitor for hypoxia and respiratory failure, and administer oxygen as necessary. Consider systemic corticosteroids in patients with significant bronchospasm, e.g. prednisone 60 mg/day (adult), or 1 to 2 mg/kg/day (child).

g. Seizures can be controlled with diazepam. Consider phenobarbitone if seizures recur after diazepam 30 mg (adults) or 10 mg (children > 5 years).

h. If hypotensive give 500 to 2000 ml crystalloid initially (20 ml/kg in children) and titrate to desired effect (stabilisation of vital signs, mentation, urine output); adults may require up to 6 to 10 litres/24 hours. Central venous or pulmonary artery pressure monitoring is recommended in patients with persistent hypotension. Vasopressors such as dopamine should be used in refractory cases unresponsive to repeated doses of adrenaline, and after vigorous intravenous crystalloid rehydration

i. Atropine and oximes are contraindicated, but some investigators recommend the former for drying up secretions.

j. Cutaneous paraesthesias are said to respond to topical applications of vitamin E.

RODENTICIDES

These are compounds which kill rats, mice, moles, and other rodents. Examples, anticoagulants, thallium, vacor, phosphorus, zinc and aluminium phosphide, alpha-naphthyl-thiourea, cholecalciferol, arsenic, barium carbonate, bromethalin,

fluoroacetamide, sodium monofluoroacetamide, red squill, strychnine.

Some of these are very commonly involved in human poisoning, e.g. phosphorus, zinc and aluminium phosphide, long acting anticoagulants (especially bromadiolone), etc., but they have been discussed elsewhere (consult *Index*).

HERBICIDES (WEEDICIDES)

These are compounds which kill weeds. Examples acrolein, dalaphon, paraquat, diquat, glyphosate, atrazine, propazine, simazine, nitrofen, trichloroacetic acid, and chlorophenoxy compounds.

■ Paraquat and Diquat

Paraquat and diquat are widely used herbicides which belong to the bipyridyl group.* Paraquat is 1,1-dimethyl-4,4-bipyridylium dichloride, and was first synthesized in 1882, but began to be used as a herbicide only since the 1960s. It is available either in granular form (25–80 gm/kg) or as water soluble concentrate which is an odourless brown liquid (100–200 gm/L). The granular form is available as colourless crystals (dichloride salt) or a yellow solid (bis(methyl sulfate) salt). In India, most of the concentrates of paraquat are available as 10–20% solutions, and therefore 10 ml of a 20% solution can contain about 2 grams of paraquat. Common brand names include *Weedol*, *Gramoxone* and *Uniquat*.

Diquat is 1,1-ethylene-2,2-dipyridylium dibromide, and is less commonly used than paraquat. It has the same indications and mode of action as paraquat but produces much less severe pulmonary lesions.

Toxicokinetics

Absorption through inhalation, skin contact, or eye contact is minimal, though prolonged contact can be hazardous. On ingestion, paraquat solution is much more rapidly absorbed than the granular form. After absorption it tends to accumulate in the lungs and kidneys. Paraquat has a large volume of distribution (1.2 to 1.6 L/kg). More than 90% of an absorbed dose is excreted by the kidneys as the parent compound within 12 to 24 hours. Paraquat is distributed into all organs. Highest concentrations are found in kidney and lung; paraquat also accumulates in muscle tissue, which may represent a reservoir, explaining prolonged detection of plasma or urine paraquat weeks or months following ingestion.

Mode of Action

■ Paraquat is a rapidly-acting herbicide. It kills the tissues of green plants by contact action with foliage and by some amount of translocation to the xylem.

■ Corneal injury and protracted opacification of the cornea may result following eye exposure to paraquat. Extensive loss of superficial areas of the corneal and conjunctival

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* Other bipyridyl herbicides which are rarely encountered include **chlormequat, difenzoquat** and **morfamquat.**

epithelium may occur. Healing, although slow, is usually complete if given prompt medical care.

- Irritation of the skin and mucous membranes may be severe following paraquat exposure.
- After ingestion, sore throat and difficulty in swallowing can occur. Irritation of the gut including abdominal pain, nausea, vomiting, and diarrhoea may occur immediately following ingestion. Concentrated solutions of paraquat corrode the GI mucosa. Tachycardia, hypotension, and cardiorespiratory arrest can occur with large ingestions. Cerebral oedema may occur. Pancreatitis may develop in some cases of acute paraquat poisoning, and can cause severe abdominal pain.
- The maximum damage is seen in the lungs where cellular injury is initiated by the NADPH-dependant reduction of paraquat to the monocation radical (PQ^+). Reaction with molecular oxygen yields the superoxide radical (O_2^-) and reforms the paraquat dication, ready to be reduced again. This process known as redox cycling is sustained by the extensive supply of electrons and oxygen in the lungs. This and the subsequent reactions explain why oxygen enhances the toxicity of paraquat, and paraquat enhances the toxicity of oxygen. Two superoxide species form hydrogen peroxide in a reaction catalysed by superoxide dismutase. Superoxide and hydrogen peroxide undergo a series of iron-catalysed reactions to yield the hydroxyl radical (OH) which is thought to be the ultimate toxic element. The hydroxyl radical causes degradation of cell membranes through lipid peroxidation resulting in cellular death.

Usual Fatal Dose

Estimated lethal dose is 10 to 15 ml of the concentrate. Ingestion of 20 to 40 mg of paraquat ion per kg body weight (7.5–15.0 ml of 20% (w/v) paraquat concentrate) results in death in most cases. Prudence requires that all cases of paraquat ingestion be treated as potentially fatal poisonings.

Clinical Features

1. **Typical Form:** (*ingestion of 30 to 50 mg/kg of paraquat*)
   a. Initial Phase—pain in the mouth, oesophagus, and stomach due to corrosion, vomiting, diarrhoea, dysphagia, aphonia. There may be gastric perforation/ GI haemorrhage.
   b. Second Phase—begins after 2 to 5 days and is characterised by renal and hepatic toxicity, i.e. renal tubulopathy and centrilobular hepatic necrosis respectively. Although hepatic injury from exposure to paraquat may be quite severe, clinical outcome is generally not determined by hepatotoxic effects.
   c. Third Phase—begins after 5 days and is characterised by pulmonary fibrosis which leads to progressive respiratory failure.
2. **Hyperacute Form:** (*ingestion of more than 50 mg/kg of paraquat*)

There is rapid development of cardiogenic shock ending in death in 3 to 4 days. Renal and hepatic lesions are also common.
3. **Subacute Form:** (*ingestion of less than 30 mg/kg of paraquat*)

This is characterised only by gastrointestinal manifestations.

Mortality in paraquat poisoning can be high and is related to two factors—concentration and quantity. Ingestion of 20% solution is associated with high mortality. Swallowing more than a mouthful can cause death in 72 hours because it corresponds to ingestion of more than 50 mg/kg. If it is less than a mouthful, death may be delayed upto 70 days and is usually due to pulmonary fibrosis. Pneumothorax, pneumopericardium and subcutaneous emphysema may develop in patients with paraquat induced lung injury.

Survivors of severe paraquat poisoning often develop progressive pulmonary fibrosis within 5 to 10 days or longer after exposure. Continued survival is dependant on the extent of lung involvement.

Occupational exposure to paraquat can cause a dry, cracking dermatitis and nail atrophy.

Diagnosis

1. X-ray of the chest may reveal patchy infiltration in the early stages, and opacification of one or both lung fields in later stages. However, if death is due to the hyperacute form of presentation, no abnormalities may be noted on the chest X-ray.
2. Plasma paraquat level can be assayed by spectroscopy, radioimmunoassay, or HPLC. Serum levels greater than 0.2 mcg/ml at 24 hours, and 0.1mcg/ml at 48 hours are associated with high mortality.
3. Urine can be tested for gross amounts of paraquat by alkalising 3 to 5 ml with a few mg of sodium bicarbonate, then adding a few mg of sodium dithionite. An intense blue-green colour is a positive test.
4. Urine paraquat level can be assayed by spectrophotometry. Survival is usually associated with levels less than 1mcg/ml, while mortality is high when the level exceeds 10 mcg/ml.
5. When submitting samples for chemical analysis it must be ensured that only plastic containers are used, since paraquat binds to glass.
6. Monitor renal and liver function tests carefully. Obtain baseline urinalysis and monitor urine output.
7. Obtain baseline pulmonary function tests, chest X-ray, and ABGs and monitor serially for several days.

Treatment

All cases of paraquat ingestions should be considered as medical emergencies even if the patient is asymptomatic.
1. Perform upper gastrointestinal endoscopy to identify the extent and severity of corrosion.
2. Stomach wash may be beneficial only if done within 1 hour of ingestion. Emesis and cathartics are contraindicated. Activated charcoal is of doubtful value.

3. Pain due to corrosion may be relieved by ice-cold fluids (e.g. ice cream), mouthwashes, local anaesthetic sprays, and lozenges. Opiates may be required in some cases.

4. Haemodialysis or haemoperfusion may be beneficial if undertaken within the first 10 to 12 hours.

5. Supportive measures form the mainstay of treatment : protection of airway, maintenance of circulation, treatment of secondary infection, prevention or treament of renal failure, and treatment of complications. **Oxygen must not be administered as far as possible since it enhances lung damage**. Allow additional oxygen only in victims considered beyond rescue to relieve air hunger and terminal disease.

6. N-acetylcysteine may be of value. There are indications that if intravenous n-acetylcysteine and early haemodialysis (within 4 hours of ingestion) are undertaken, survival rate may improve.

7. The combination of corticosteroids and cyclophospha-mide has shown promise in reducing paraquat mortality, although efficacy has not been proven in prospective controlled clinical trials. In one prospective, randomised study, patients received gastric lavage followed by activated charcoal instillation, two 8-hour haemoper-fusion sessions against activated charcoal, and 10 mg intravenous dexamethasone every 8 hours for 14 days. The patients randomised into the treatment group also received at the end of haemoperfusion 1 gram of intra-venous methylprednisolone daily for days 1, 2, and 3, and cyclophosphamide 15 mg/kg daily for days 2 and 3 of pulse therapy. In a single case reported separately, recovery was achieved in a severely poisoned paraquat patient by a second pulse of methylprednisolone on day 30 when pulmonary inflammation and hypoxaemia emerged despite steady daily therapy of dexamethasone after the first pulse therapy. More study of a larger number of severely poisoned patients must be performed to confirm or refute benefit of this approach before it can be recommended as a standard treatment.

8. Non-steroidal anti-inflammatory agents, colchicine, collagen synthesis inhibitors, desferrioxamine, or total exclusion from external respiration may prevent lung fibrosis. However, the efficacy of these treatments has yet to be established in the treatment of human paraquat poisonings.

9. Pulmonary damage may be ameliorated by radiotherapy. However the current consensus is NOT to undertake radio-therapy because of lack of clinical evidence of efficacy. Lung transplantation has not met with success in most cases where it was attempted, though some recent reports indicate that it could be beneficial. Nitric oxide inhalation to maintain tissue oxygenation in anticipation of lung trans-plantation once all absorbed paraquat has been eliminated, is recommended by some investigators.

Autopsy Features

1. Ulceration around lips and mouth, reddened or desquamated oral and oesophageal mucosa (**Fig 28.1**), erosion and patchy haemorrhages in the stomach.
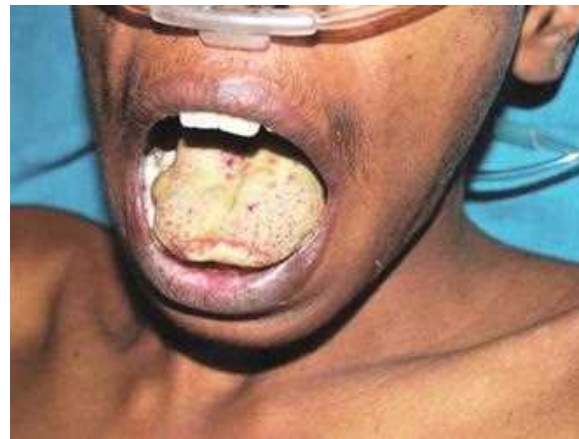
Fig 28.1: Oral corrosion—Paraquat ingestion (*Pic*: Dr N Ganapathy)

2. Liver may show pallor or mottled fatty change; centri-lobular necrosis.

3. Lungs often appear stiffened. There may be evidence of proliferative pulmonary fibrosis, fibrinous pleurisy, or scanty blood-stained pleural effusion. Cut surface reveals oedema.

4. Kidneys may reveal evidence of tubular damage.

■ Chlorophenoxy Compounds

Chlorophenoxyacetate herbicides include the following:
- MCPA (4-chloro-2-methylphenoxyacetic acid)
- MCPP (2-methyl-4-chlorophenoxypropionic acid)
- DCPP (2,4-dichlorophenoxypropionic acid)
- 2,4D (2,4-dichlorophenoxyacetic acid)
- 2,4,5-T (2,4,5-trichlorophenoxyacetic acid)

These herbicides are used to kill broad-leaved weeds in cereal crops, grassland parks and gardens, and weeds in ponds, lakes, and irrigation canals.

Brands

2,4D: Fennoxone, Weednash.

Toxicokinetics

Rapid and complete absorption of chlorophenoxy compounds from the GI tract has been reported. Dermal absorption is limited. Chief organs of deposition are kidneys, liver, central and peripheral nervous systems, and the gastrointestinal tract. They are highly protein bound. Phenoxy acid esters and salts are primarily metabolised by acid hydrolysis; a minor amount is conjugated. They are primarily eliminated unchanged (90%) by the kidneys via the renal organic anion secretory system.

Clinical Features

1. *Ingestion:*
   a. Nausea, vomiting, diarrhoea, miosis, fever, hypotension, emesis, tachycardia, bradycardia, ECG abnormalities, pulmonary oedema, muscle rigidity, rhabdomyolysis, muscle weakness, peripheral neuropathy, hyperthermia, acidaemia and coma.

b. Hypocalcaemia, hyperkalaemia, and hypophosphataemia.
c. Ingestions involving high concentrations, or exposures of long duration may produce burning in the mouth, oesophagus and stomach.
d. Vertigo, headache, malaise and paraesthesias can occur.
e. Thrombocytopenia and leukopenia have also been reported.

2. Allegations of human birth defects related to 2,4-D and/or 2,4,5-T have not been confirmed. However, some evidence from a report on Vietnam veteran's children shows a limited or suggestive level of evidence between exposure to 2,4-D and/or 2,4,5-T and spina bifida. A major limitation of the report was the inability to quantify levels of herbicide exposure in individual troops.
3. The causal relationship between chlorophenoxy herbicides and cancer remains controversial. Some studies have suggested a relationship between chlorophenoxy herbicides and both soft tissue sarcoma and non-Hodgkin's lymphoma, while others have not.
4. A mixture of 2,4-D and 2,4,5-T (Agent Orange) has been alleged to have caused cancer, birth defects, and many other illnesses in Vietnam veterans. It is however more likely that a contaminant (2,3,7,8-tetrachlorodibenzodioxin or TCDD) caused these effects.

Diagnosis

1. *Serum/Blood:*
   a. Monitor CPK levels and serum myoglobin levels.
   b. Monitor liver and kidney function tests.
   c. Monitor CBC and platelet count.
2. *Urine:*
   a. Monitor urine for pH, protein, RBC's, myoglobin, and urine output.
   b. Chlorophenoxy compound urine analysis may be useful as a confirmatory test. Limited data suggest that urinary 2,4-D levels may be useful in monitoring workers with industrial and commercial exposure.
3. *Radiographic Studies:* Monitor the chest X-ray in patients with significant exposure.
4. *Laboratory Methods:*
   a. GC/MS—A method using acid hydrolysis, diazoethane derivatisation, and silica gel column chromatography for sample preparation followed by combined capillary gas chromatography and mass spectrometry in the selective ionisation modes of positive and negative chemical ionisation was successful in improving the detection limit to 1 ppb for urine samples. This method is designed for use in large epidemiologic studies to document exposure to chlorophenoxy herbicides.
   b. HPLC—Can be used by utilising methanolic hydrochloric acid extraction and resolution with a phenylsilyl-modified silica column/aqueous buffer acetonitrile eluent, to partially quantify a variety of chlorophenoxy compounds in biological samples of acutely poisoned patients. The limit of detection is said to be 20 mg/L.
   c. 2,4-D can be quantitated in human autopsy material. Visceral samples are acidified, and blood and plasma deproteinised with methanol, followed by acidification, extraction with diethyl ether, and analysis using HPLC.
   d. Urinary levels of 2,4-D can be detected with gas chromatography with mass selective detection (GC/MSD) with a lower limit of detection of 5 ppb.
   e. Ultraviolet Spectrometry—This is an older and non-selective method which does not differentiate between chlorophenoxy and benzonitrile herbicides. These two herbicide types are often combined in commercial products. Published values using this method are of dubious value.
   f. A direct enzyme immunoassay can detect urinary levels as low as 19 ppm and has been validated in 2,4-D-exposed workers.

Treatment

1. *Decontamination:* Activated charcoal, gastric lavage, etc., can be considered if no more than 4 hours have elapsed since ingestion.
2. Manage respiratory depression if present. Assisted ventilation may be required.
3. Hypotension: Infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline. Consider central venous pressure monitoring to guide further fluid therapy.
4. Maintain adequate urine flow with intravenous fluids if the victim is dehydrated. Monitor fluid and electrolyte balance and replace as required.
5. Manage hyperthermia with sponge baths.
6. Induce alkaline diuresis if myoglobinuria, coma, or severe metabolic acidosis is present.
7. Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disturbances (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia). Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is a good alternative. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present.
8. *For inhalation exposure:*
   a. Move patient from the toxic environment to fresh air. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.
   b. Administer 100% humidified supplemental oxygen, perform endotracheal intubation and provide assisted ventilation as required.
   c. Administer inhaled beta adrenergic agonists if bronchospasm develops.
   d. Onset of acute lung injury after toxic exposure may be delayed up to 24 to 72 hours after exposure in some cases. Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to

maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops. The pulmonary artery wedge pressure should be kept relatively low while still maintaining adequate cardiac output, blood pressure and urine output.

9. *For dermal exposure:*
   a. Remove contaminated clothing and jewellery; wash skin, hair and nails vigorously with repeated soap washings. Leather absorbs pesticides; all contaminated leather should be discarded.
   b. Treat dermal irritation or burns with standard topical therapy. Patients developing dermal hypersensitivity reactions may require treatment with systemic or topical corticosteroids or antihistamines.
10. Haemodialysis is not effective; alkaline diuresis may be useful, particularly if begun soon (*vide supra*). Plasmapheresis may be effective for late treatment of poisoning.

Autopsy Features

1. Apart from non-specific signs, evidence of disseminated muscle cell necrosis was discovered in myocardial fibres, focal with reactive cellular infiltration, in one case of fatal ingestion. The man died within 12 hours of the ingestion. Significant erosion of the stomach lining was also observed. There was in addition, massive haemostasis of the lungs in all capillaries, and severe alveolar oedema
2. Fluid filled lungs with large quantities of oedema fluid expressible from cut surfaces were described at autopsy in another fatal ingestion case. In this case, the abdominal and thoracic cavities contained a thin reddish watery fluid.

■ Glyphosate

Glyphosate, an aminophosphonate (non-cholinesterase inhibitor-organophosphate compound), is used as a herbicide. It has a low order of toxicity in mammals, but the surfactant or other components contained in many preparations may contribute to toxic effects. It is an odourless, colourless to white crystalline powder and is weakly acidic.

Glyphosate herbicides are commonly applied in spray form and primarily formulated as either a water-soluble liquid or concentrate solution, or a solution made with a water-soluble powder and other ingredients. The following preparations are also available: pressurised liquids, aerosols, emulsions, pellets/tablets, granules, powders, and microencapsulated products.

Glyphosate formulations and their toxicity differ depending on the type and concentration of the active ingredient and/or the added surfactants. The polyoxyethylene tallowamines (e.g. polyoxyethylene amine or POEA) is a class of surfactants most commonly used in glyphosate formulations. Other glyphosate herbicide additives include sulfuric and phosphoric acid and a variety of inert materials.

Brands

Glycel, Glyphos, Roundup, Sampoo.

Mode of Action

The surfactant present in commercial solution, polyoxyethyleneamine, an anionic surfactant, may be responsible for many of the toxic effects of glyphosate. Surfactants alone may cause circulatory failure, respiratory failure, seizures, generalised oedema and gastric erosion.

Glyphosate appears to undergo minimal metabolism. Results from animal studies indicate that essentially no toxic metabolites are produced and nearly 100% of the body burden is parent compound.

Usual Fatal Dose

Ingestion of > 200 ml is likely to produce severe toxicity.

Clinical Features

While instances of glyphosate poisoning have not been very common in India, cases are beginning to be reported.
1. Common features include pain in the mouth and throat, mucosal erosion/ulceration, vomiting, mild hepatotoxicity, and leukocytosis. Endoscopy in patients with ulceration showed gastritis, oesophagitis, and mucosal oedema, but no full thickness injury.
2. Less commonly, the patient may suffer from diarrhoea, abnormal mental status, oliguria/anuria, metabolic acidosis; hyperthermia, pulmonary oedema and shock.
3. Various cardiac arrhythmias, including ventricular arrhythmias, bradycardia, and cardiac arrest have been reported.
4. Poor prognosis is associated with the combination of pulmonary oedema, acidosis and hyperkalaemia.
5. Dermatitis resembling sunburn has been seen when the material has been in contact with skin for more than 30 minutes. No systemic symptoms have been seen due to absorption via intact or abraded skin.

Treatment

1. Serum levels of glyphosate are not clinically useful in assessing the severity of exposure or poisoning.
2. Monitor CBC, serum creatinine, BUN, liver function tests, serum electrolytes, arterial blood gases, urinalysis, and chest radiograph in symptomatic patients. Monitor cardiovascular function; including blood pressure frequently. Obtain baseline ECG; repeat as indicated.
3. Emesis is not recommended. Instead, rinse the mouth and dilute with milk or water.
4. Activated charcoal can be administered in the usual manner.
5. Obtain consultation concerning endoscopy as soon as possible, and perform endoscopy within the first 24 hours when indicated. If burns are found, follow 10 to 20 days later with barium swallow or oesophagram.
6. Scintigraphy: Scans utilising radioisotope labelled sucralfate (technetium 99m) may represent an alternative to endoscopy, particularly in young children, as no sedation is required for this procedure.
7. The use of corticosteroids for the treatment of caustic ingestion is controversial.

8. The use of antibiotics is suggested if corticosteroids are used, or if perforation or infection is suspected. Agents that cover anaerobes and oral flora such as penicillin, ampicillin, or clindamycin are to be preferred.
9. For acute lung injury, maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
10. For hypotension, infuse 10 to 20 ml/kg of isotonic fluid and place in Trendelenburg position. If hypotension persists, administer dopamine or noradrenaline.
11. Treat severe acidosis (less than pH 7.1) with IV sodium bicarbonate. Begin with 1 mEq/kg in adults and in children. Repeat doses of no more than half the original amount may be given, no more often than every 10 minutes if required.
12. Glyphosate is excreted rapidly in the urine. Maintaining an adequate urine output is important as the clearance of glyphosate by the kidney (52.9 ml/min) was as good as by haemodialysis (52.5 ml/min); both of which were superior to haemoperfusion (6.4 ml/min).

FUNGICIDES

These are compounds which kill fungi and moulds. Examples, thiocarbamates, captan, captafol, bavistin, vitavax, hexachlorobenzene and sodium azide.

■ Thiocarbamates

Examples include benomyl, benthiocarb (or thiobenzcarb), cycloate, diallate, ferbam, molinate, thiram, thiophanate, triallate, zineb and ziram.

Carbendazim (carbendazole), ETU, mancozeb, maneb, and vondozeb are benzimidazole (ethylenebisdithiocarbamate or ethylenethiourea) compounds that are also used as fungicides.

Brands

Propineb: *Antracol*
Carbendazim: *Bavistine, Benguard, Benfil, Dhanustin, Derosal, Fungi guard, JK Stein, Kilex, Paedistin*
Benomyl: *Benlate, Benofit*
Benthiocarb: *Saturn*
Mancozeb: *Bayleton, Captofol, Captaf, Dithane M-45, Dhanuka M-45, Hilthane, Indofil M-45, Kavach, Krilaxlyl, Luzem, Manzate, Ridomil, Sparsh, Uthane, Vijay M-45, Zeb M, Zeb 75, Zebatane*
Carbendazim + Mancozeb: *CM-75*
Carbendazim + Iprodione: *Quindal*
Mancozeb + Metalaxyl: *Master, Matca, Pestmil*
Mancozeb + Thiophanate methyl: *Roko*
Thiophanate methyl: *Cover*
Zineb: *Indofil*
Ziram: *Cumun-L, Zinax, Ziram*

These compounds are used as fungicides and have relatively low toxicity. They do not inhibit acetylcholinesterase (unlike carbamates).

Sources and Uses

1. Most of these compounds are used as fungicides. Formulations are widely used for pest control in home gardens and in commercial agriculture.
2. Some are found in suntan and antiseptic sprays, and some medicated cleansing agents. Some are also used in the plastic industry as an antioxidant, and as a rubber accelerator.
3. Carbendazim is also used as a preservative in the paint, textile, papermaking and leather industries. Carbendazim is also currently undergoing clinical trials in adult patients with advanced malignancies (i.e. breast cancer, melanoma, colon cancer).

Usual Fatal Dose

Ingestion of > 200 ml is likely to produce severe toxicity.

Clinical Features

1. Absorption of these agents across the skin and GI lining is probably slower than absorption of the organochlorine and ester insecticides. Exposure results in vomiting, diarrhoea, abdominal pain, weakness, conjunctivitis, vertigo, seizures, and rarely renal failure.
2. Other manifestations have included CNS depression, extrapyramidal effects, and neuropathy.
3. These agents are often compounded with hydrocarbon-based solvents, which may be responsible for toxicity. Some agricultural workers experience upper respiratory congestion, hoarseness, and cough if they breathe sprays or dusts containing these compounds.
4. To some degree, all of these chemicals, the sulfur-containing in particular, are irritating to the skin and mucous membranes. Thiram is related to disulfiram and produces a similar reaction with ethanol.
5. Although detailed pharmacokinetic studies of these compounds are not available, there is indirect evidence (minimal tissue storage after dosing) that these chemicals are rapidly metabolised and/or excreted by humans, usually within hours or days of absorption.
6. *Teratogenecity and carcinogenecity:*
   a. In female rats exposed to carbendazim during gestation, significant maternal toxicity, embryonal lethality, teratogenic effects, and retarded foetal development were reported.
   b. Ethylene thiourea (ETU): A contaminant and breakdown product of ethylene bisdithiocarbamate fungicides (maneb, nabam, zineb) is a recognised carcinogen in animals. Hepatomas, lymphomas, and thyroid carcinomas have been described.

Treatment

1 Activated charcoal can be administered.
2. Gastric lavage is recommended if done early and cautiously.

3 Intravenous fluids may be useful in restoring extracellular fluid volume if this has been depleted by vomiting and diarrhoea.

4. For convulsions: Attempt initial control with a benzodiazepine (diazepam or lorazepam). If seizures persist or recur administer phenobarbitone.

NEMATICIDES

These are compounds which kill nematodes (i.e. worms). For example, ethylene dibromide.

■ Ethylene Dibromide

Fumigants are applied to control rodents, nematodes, insects, weed seeds, and fungi anywhere in the soil, structures, crop, grains, and commodities. Many different chemical classes have been used historically as fumigants, but only a few remain in use today. Most fumigants were abandoned because of their toxicity, many of which were halogenated solvents. The list of discontinued halogenated hydrocarbons includes carbon tetrachloride, chloroform, dibromochloropropane, 1,2-dichloropropane, ethylene dibromide, and ethylene dichloride.

Ethylene dibromide was previously approved for use as a fumigant to protect against insects, pests, and nematodes in citrus, vegetable, and grain crops, and as a fumigant for turf, particularly on golf courses. In 1984, the Environment Protection Agency (EPA) banned its use as a soil and grain fumigant. Unfortunately, in India, it continues to be used widely, causing human poisoning not infrequently.

Mode of Action

Ethylene dibromide alkylates macromolecules causing cellular disruption and reduced glutathione levels. Cellular disruption in tissues and organs, such as liver and kidneys, results in progressive dysfunction. Manifestation of some of the effects of acute high exposure may be delayed a few days.

Clinical Features

Ethylene dibromide is a severe skin irritant in liquid form, and inhaling or ingesting it can cause death.

1. Inhalation/Ingestion: Burning sensation, cough, bronchitis, dyspnoea, pulmonary oedema, hepatotoxicity with liver necrosis, acute renal failure, metabolic acidosis, CNS depression, coma and death. Abdominal pain, vomiting, and diarrhoea, are common early manifestations in cases of ingestion.

2. Dermal Exposure: Erythema, pain, blistering.

3. Ocular Exposure: Conjunctivitis has been reported after exposure to ethylene dibromide. Temporary loss of vision may occur.

4. Chronic Exposure: There is inconclusive but suggestive evidence that ethylene dibromide may reduce fertility in men. Antispermatogenic effects have been demonstrated in various animal species.

Diagnosis

1. Serum bromide levels can be used to document that exposure did occur. However, bromide levels do not accurately predict the clinical course.

2. Routine laboratory studies include CBC, glucose, and electrolyte determinations.

3. Additional studies for patients exposed to ethylene dibromide include liver-function tests and renal-function tests.

4. In cases of inhalation exposure, chest radiography and arterial blood gas measurements may be helpful.

Treatment

1. Establish a patent airway, ensure adequate respiration and pulse. Administer supplemental oxygen as required and establish intravenous access if necessary. Place on a cardiac monitor.

2. Irrigate exposed skin and eyes as appropriate. Remove contaminated clothing.
    a. Flush exposed skin and hair with water for at least 15 minutes, then wash twice with mild soap. Rinse thoroughly with water. Use caution to avoid hypothermia when decontaminating patients, particularly children or the elderly. Use blankets or warmers after decontamination as needed.
    b. Irrigate exposed or irritated eyes with tap water or saline for 15 to 20 minutes. Remove contact lenses if easily removable without additional trauma to the eye. An ophthalmic anaesthetic, such as 0.5% tetracaine, may be necessary to alleviate blepharospasm, and lid retractors may be required to allow adequate irrigation under the eyelids.

3. Activated charcoal is helpful in cases of ingestion.

4. Treat patients who have bronchospasm with an aerosolised bronchodilator such as salbutamol.

5. If evidence of shock or hypotension is observed, begin fluid administration. For adults with systolic pressure less than 80 mmHg, bolus perfusion of 1,000 ml/hour intravenous saline or lactated Ringer's solution may be appropriate. Higher adult systolic pressures may necessitate lower perfusion rates. For children with compromised perfusion administer a 20 ml/kg bolus of normal saline over 10 to 20 minutes, then infuse at 2 to 3 ml/kg/hour.

6. There is no proven antidote for ethylene dibromide poisoning. Dimercaprol (BAL) or N-acetylcysteine have been suggested as antidotes based on the postulated mechanism of ethylene dibromide's toxicity. However, no adequate studies have tested the efficacy of these therapies, and they are not recommended for routine use.

7. Supportive and symptomatic measures.

8. Patients who survive should be monitored over a period of time for late neuropsychiatric sequelae.

ACARICIDES

These are compounds which kill mites, ticks and spiders. Examples, azobenzene, chlorobenzilate, tedion, and kelthane. They are infrequently encountered in human poisoning.

MOLLUSCICIDES

Compounds which kill molluscs such as snails and slugs. For example, metaldehyde.

■ Metaldehyde

It is a tetramer compound with an 8 member ring containing aldehyde molecules, and is a cyclic polymer of acetaldehyde. Metaldehyde is a popular molluscicide being effective against snails and slugs. It is a tasteless substance with a mild characteristic odour. It is available in some countries in tablet form for the purpose of producing coloured flames used in entertaining.

Instances of poisoning are however rare. It is a local irritant on skin and mucous membrane and a systemic convulsant. Metaldehyde overdosage results in lethargy, severe abdominal pain, nausea, vomiting, diarrhoea, hyperthermia, seizures, coma, and death. Profound hyperthermia may occur in association with seizures. Metabolic acidosis and respiratory alkalosis have been reported. Other effects have included renal tubular injury and liver necrosis. Increased tracheobronchial secretions are prominent. Respiratory failure may occur 24 to 40 hours after ingestion. Mydriasis has been reported. Inhalation of metaldehyde fumes may cause CNS depression.

The probable lethal dose is in the range of 100 mg/kg for adults.

Bait that contains metaldehyde can be detected by placing the substance in a test tube and gently warming. Metaldehyde sublimes to form copious "artificial snow".

Treatment is mainly directed at decontamination and management of convulsions. Activated charcoal may be beneficial. Dialysis is ineffective. Unproved antidotes which have been tested in animals or suggested include: calcium gluconate for seizures; D-penicillamine; N-acetylcysteine; thiamine; and ascorbic acid. None of these have been tested in humans.

MISCELLANEOUS PESTICIDES

These include compounds of lead, copper, and mercury, nicotine, rotenone, sabadilla, hydrogen cyanide, methyl bromide, naphthalene, tetrachloroethylene, trichloroethane, dinitrophenol, dinitrocresol, dinitrobutylphenol, pentachlorophenol, chlorfenson and chloralose. Dioxins which are present as contaminants of some herbicides also can produce toxicity. Many of these compounds have been discussed in other sections elsewhere, and the reader is advised to consult the *Index* for locating them.

FORENSIC ISSUES (ALL PESTICIDES)

Acute pesticide poisoning is a serious global problem accounting for an estimated 3 million cases of severe poisoning worldwide each year, with approximately 220,000 deaths. More than 90% of these cases are reported from developing countries such as India. In the UK, pesticides are responsible for only about 1% of deaths from poisoning while various studies in India indicate that the figures range from 20% to a staggering 70%. In the paediatric age group domestic pesticides can account for a substantial number of poisoning cases. Among the various pesticides, organophosphates and carbamates account for most of the reported cases of poisoning, though aluminium phosphide is making relentless inroads, especially in Northern and Central India. Suicidal exposure to these pesticides is invariably via the oral route, though a few cases have involved self-injection (**Fig 28.2**).

The terrible potential for pesticides to cause mass poisoning was not realised in India till the Kerala food poisoning tragedy in 1958. Wheat flour and sugar had been inadvertently stored in the same cabin on a ship as parathion, which leaked into the packages containing the former. Over a thousand people were poisoned subsequently due to consumption of the contaminated material and more than a hundred died. More recently (late 1970s), a severe convulsive epidemic broke out among several hundred people in Uttar Pradesh due to shocking ignorance on the part of farmers who were preserving food grains with BHC. Another (even more recent) incident involved accidental spraying of BHC in concentrated form in a thickly populated area leading to similar mass morbidity.

Unfortunately, lessons are not learnt from history and even today instances of negligent storage of food grains, sugar, vegetables, and fruits along with toxic pesticides leading to large scale contamination are not uncommon. Pesticide contamination of vegetables is an even bigger problem in India as compared to many other countries. In fact the contamination of food with pesticides resulting from excessive crop spraying or improper storage is so widespread in India, that blood samples and milk samples (from lactating mothers) collected randomly from several people in one study demonstrated residual insecticide levels in most of the samples.

Exposure to pesticides can occur in other ways. A study of offices sprayed with diazinon, chlorpyrifos, or bendiocarb revealed in many cases that surface concentrations were higher at 24 or 48 hours than at 1 hour after spraying. Occupants should be warned of treatment times and steps taken to minimise exposure. Health care professionals may be exposed to

Fig 28.2: Subcutaneous injection of OP pesticide with discolouration and myonecrosis (*Pic*: Dr S Senthilkumaran)

cholinesterase inhibitors while caring for patients. Hospitals need to plan for such emergencies by having access to large stores of atropine, toxic waste disposal, and individual ventilation systems. Organophosphates found in veterinary products may be a source of poisoning for veterinarians, veterinary technicians, groomers, pet owners, and domestic pets.

Vietnam veterans potentially exposed to chlorophenoxy herbicides were noted to have chronic liver abnormalities. However, a study of 350 patients suggested that viral and alcoholic complications, rather than herbicides, were the causative factors.

Organophosphates which are very rapid-acting, such as tabun, sarin, soman, and VX, have been developed as "nerve gases" for chemical warfare. Human exposure secondary to terrorist activity has occurred. The most notable case of sarin use by a terrorist group occurred in March, 1995, where sarin was released in a subway system of Tokyo, Japan. Estimates are that 1,000 people were affected by the attack with 12 deaths.

Organophosphates may be deliberately ingested by cocaine abusers in an attempt to prolong cocaine effects by decreasing cholinesterase activity. Symptomatic organophosphate poisoning has been reported in this setting.

In order to curb the incidence of accidental poisoning resulting from occupational exposure, negligent handling, as well as contamination of water, milk, and food stuff, several clauses have been incorporated in the **Insecticides Act** of **1968**, and the **Insecticides Rules** of **1971**.

Since several organochlorine pesticides have been banned (including DDT and BHC) from 1997 onwards, the incidence of poisoning involving these compounds has been declining. However, cases are still reported owing to surreptitious use.

Today, many household insecticides consist of carbamates and pyrethroids and hence poisoning involving them are on the rise, particularly among children.

Poisoning due to other pesticides is relatively uncommon except among individuals who are occupationally exposed.

Owing to easy availability, pesticides such as organophosphates and carbamates have always been extremely popular in India for the purpose of committing suicide. In recent times, aluminium phosphide has begun to find increasing favour and has in fact edged out the other insecticides from the top spot in some states.

Homicidal poisoning involving pesticides has always been rare owing to disagreeable odour/taste, which most of these chemicals possess. Significant exceptions include thallium and arsenical compounds. However, cases have been reported even with other pesticides. One case report documents two child murders accomplished with paraquat.

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Section

9

Miscellaneous Drugs and Poisons

Analgesics and Antihistamines

Drugs used to reduce fever are referred to as antipyretics, while those that relieve pain are called analgesics. Anti-inflammatory drugs are (obviously) those which reduce inflammation. There is however considerable overlap and a given drug may possess any or all of these properties. Classification and nomenclature are therefore based on the **predominant** property, e.g. while a drug such as acetylsalicylic acid may also possess anti-inflammatory property, it is its capacity to reduce fever and relieve pain which are the dominant effects. Hence it is generally referred to and classified as an analgesic-antipyretic. This precept will be applied in the following discussion.*

ANALGESIC-ANTIPYRETICS

The analgesic-antipyretics of paramount importance are salicylates and paracetamol. Phenacetin is no more used today. Analgin has serious adverse effects but is still available in India. Nefopam is a new entrant.

■ Salicylates

These compounds are derivatives of salicylic acid and include acetyl salicylic acid, sodium salicylate, and methyl salicylate. Salicin, a naturally occurring salicylate is a constituent of several plants but is present in highest concentration in the willow tree (*Salix alba vulgaris*) (**Fig 29.1**), which grows near lakes and rivers in temperate climates and whose branches are used to make cricket bats and baskets. Other plants include Acacia (flower oil), Aspens, Birches, Calycanthus (leaves), Camellia (leaves), Chenopodium (leaves), Hyacinth, Marigold, Milkwort, Poplars, Spiraea, Teaberry, Tulips and Violets.

Salicylic acid (orthohydroxy benzoic acid) is so irritating that it can only be used as an external application. **Hoffman**, a chemist at Bayer Company first synthesised acetyl salicylic acid in the laboratory in **1897**, and together with his chief pharmacologist **Heinrich Dreser**, he performed a number of pharmacological and toxicological tests to evaluate its therapeutic benefits and safety profile. The name "aspirin" was coined in **1899**, and since then the drug has marched through time displaying a rare and astonishing staying power. In fact, in recent times aspirin has surprised the medical profession with newer and far more exciting applications (*vide infra*).

Fig 29.1: Willow tree

Examples

Acetaminosalol, Aloxiprin, Aluminium aspirin, Ammonium salicylate, Antipyrine salicylate, Aspirin, Benorylate, Bismuth subsalicylate, Bromosalicylic acid acetate, Calcium aminosalicylate, Calcium carbaspirin, Carbamoylphenoxyacetic acid, Choline salicylate, Diethylamine salicylate, Ethyl salicylate, Fendosal, Glycol salicylate, Homomenthyl salicylate, Lithium salicylate, Magnesium salicylate, Menthyl salicylate, Octyl salicylate, Phenazone salicylate, Phenyl aminosalicylate, Phenyl salicylate, Physostigmine salicylate, Potassium aminosalicylate, Potassium salicylate, Salicylamide, Salicylic acid, Salsalate, Silver salicylate, Sodium aminosalicylate, Sodium salicylate, Sodium thiosalicylate, Thurfyl salicylate, Triethanolamine salicylate, Trolamine salicylate

Physical Appearance

Acetyl salicylic acid is an odourless, white, crystalline powder with an unpleasant saline taste. Sodium salicylate occurs as odourless, white scaly crystals with the same unpleasant saline taste. Methyl salicylate is a colourless liquid with aromatic odour and sweetish taste.

Salicylates for therapeutic use are available as tablets, capsules, powders, effervescent tablets and liquid preparations for ingestion; rectal suppositories; and as liniments, creams and lotions for topical application.

* **Narcotic analgesics** being a distinct entity are discussed elsewhere (page no. 230).

Uses

1. **Sodium salicylate and acetyl salicylic acid:**
   a. Antipyretic.
   b. Analgesic.
   c. Treatment of rheumatoid arthritis.
   d. Low-dose aspirin is used in the prophylaxis of cerebrovascular ischaemic events, angina pectoris, and is also recommended by some authorities for the prevention of colon cancer, and migraine. Accumulating data suggests that aspirin may prevent or protect against the development of colon and possibly other types of gastrointestinal cancers. Combination of warfarin with aspirin may improve efficacy in preventing ischaemic heart disease, but may ironically increase the chances of a haemorrhagic fatal stroke.

2. **Sodium aminosalicylate:**
   It is used sometimes as a second-line drug in the management of tuberculosis.

3. **Bismuth subsalicylate:**
   It is used to treat diarrhoea, and as prophylaxis for travellers diarrhoea.

4. **New derivatives of salicylic acid:**
   a. Mesalamine (5-aminosalicylic acid) is used as a suppository or rectal suspension enema for its local effects in the treatment of inflammatory bowel disease (proctosigmoiditis). Olsalazine (sodium azodisalicylate) is said to be effective in relieving manifestations of ulcerative colitis, and can be administered orally. Sulfasalazine (salicylazosulfapyridine) is also beneficial.
   b. Diflunisal, a difluorophenyl derivative of salicylic acid is said to be much more potent than aspirin in the treatment of musculoskeletal sprains and osteoarthritis.
   c. Benorylate (4-acetamidophenyl-o-acetylsalicylate) is an ester of aspirin and paracetamol. It causes less gastric irritation and bleeding. The usual therapeutic dose in adults is 4 gm/day. Toxicity can result if this is exceeded. Manifestations are a combination of those seen in aspirin and paracetamol poisoning with particular tendency toward centrilobular hepatic necrosis.

5. **Locally acting salicylates:**
   a. Salicylic acid is a keratolytic agent.
   b. Methyl salicylate (*oil of wintergreen, sweet birch oil, gautheria oil*), is used for the local treatment of musculoskeletal pain and inflammation. Commercial preparations are not less than 98% w/w. One ml of 98% methyl salicylate is equivalent to 1.4 grams ASA in salicylate potency, and its action is the same as salicylates; or one teaspoonful of oil of wintergreen (5 ml) is equivalent to approximately 7000 mg of salicylate or 21.7 adult aspirin tablets.
   c. Methyl salicylate is also used as a flavouring agent for candy.
   d. Homomenthyl salicylate (homosalate) is a sunscreen agent found in many sunscreen products and contains 46% salicylic acid. Homosalate could be hydrolysed in vivo to free salicylic acid and homomenthol.
   e. Trolamine salicylate cream (10 grams of cream contains 500 mg of salicylic acid) is used in the management of osteoarthritis.
   f. Salicylates are often combined with antihistamines and decongestants, or caffeine in cold and allergy preparations. Several products contain combinations of paracetamol and salicylate, while others combine salicylate with opioids.

Toxicokinetics

Salicylates are rapidly absorbed from the stomach, and to a slightly lesser extent from the small intestine. Delayed absorption is seen in the following situations: enteric coated preparations, pylorospasm, pyloric stenosis, and bezoar formation. Therapeutic serum salicylate levels should not exceed 30 mg/100 ml. Salicylic acid and methyl salicylate are readily absorbed through intact skin. Salicylates distribute well into plasma; saliva; milk; and spinal, peritoneal and synovial fluid and into body tissues including kidney, liver, lung and heart.

Metabolism occurs chiefly in the liver, where salicylates are broken down into salicyluric acid, ether glucoronide, ester glucoronide, and gentisic acid. Excretion is mainly through urine.

The half-life of salicylates is 2 to 4 hours at therapeutic levels, but may increase to 20 hours at toxic levels. Plasma salicylate is 50 to 80% protein bound, especially to albumin, with salicylic acid being more highly bound than aspirin. As salicylate doses are increased, the proportion bound to plasma protein decreases, and the volume of distribution increases. There is also a decrease in protein binding from 90% at therapeutic levels to less than 75% at toxic levels. The apparent volume of distribution increases from 0.2 L/kg to more than 0.3 L/kg. The half-life of plasma salicylate elimination increases with dose. The reported half-lives in adults range from 2.4 to 19 hours with doses of 0.25 gram, and about 10 to 20 grams of sodium salicylate, respectively. In poisoned children, the half-life ranged from 15 to 29 hours.

Sustained release preparations of aspirin contain aspirin released over a 12-hour or longer period of time. Prolonged absorption and persistently elevated salicylate levels may occur following overdose. Enteric-coated formulations are designed to dissolve in the alkaline medium of the small intestine, and are likely to cause bezoars and prolonged drug absorption.

Mode of Action

■ Salicylates stimulate the respiratory centre in the brainstem leading to hyperventilation and respiratory alkalosis. They also interfere with Krebs cycle, inhibit production of ATP, and increase lactate production, leading to ketosis and a wide anion-gap metabolic acidosis. In children, respiratory alkalosis is quite transient, and metabolic acidosis is the predominant feature. Respiratory acidosis in salicylate overdose indicates grave prognosis and is seen in salicylate-induced pulmonary oedema, CNS depression from mixed overdose,* or severe fatigue due to prolonged hyperventilation.

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* Especially involving salicylates and one or more of the following : **benzodiazepines, alcohol, barbiturates** and **tricyclics.**

- Salicylates are extremely irritating to the GI mucosa, and overdose often results in haemorrhagic gastritis. In the US, the FDA requires an alcohol warning on all over-the-counter pain relievers, which includes aspirin, other salicylates, paracetamol, ibuprofen, ketoprofen, and naproxen sodium, due to a potential drug interaction resulting in upper GI bleed or liver damage.
- Aspirin is commonly involved in allergic reactions, ranging in severity from urticaria or angioedema to acute anaphylaxis.

Drug Interactions

- Salicylate and/or acetazolamide toxicity may occur in patients taking salicylates chronically when acetazolamide is added to drug regimen. The syndrome of effects reported are confusion, fatigue, hyperchloraemic metabolic acidosis, incontinence, lethargy, and somnolence shortly after the introduction of acetazolamide in patients chronically receiving aspirin.
- Effective October, 1998, the US FDA mandated that products containing aspirin or other salicylates display the following warning regarding chronic consumption of alcohol and salicylate use, "Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take this medication or other pain relievers/fever reducers. This medication may cause stomach bleeding".

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. *Early*—Nausea, vomiting, sweating, tinnitus (ringing or hissing), vertigo, and hyperventilation due to respiratory alkalosis. Irritability, confusion, disorientation, hyperactivity, slurred speech, agitation, combativeness, hallucinations, ataxia, and restlessness may be early findings in patients with severe toxicity.
   b. *Late*—Deafness, hyperactivity, agitation, delirium, convulsions, hallucinations, hyperpyrexia. Coma is unusual.
   c. *Complications*—Metabolic acidosis, pulmonary oedema, rhabdomyolysis, cardiac depression, thrombocytopenic purpura. Gastrointestinal bleeding, perforation and pancreatitis are less common complications. Salicylates must **not** be therapeutically administered to children under 15 years of age, especially if they are suffering from chicken pox or influenza. There is a serious risk of precipitating *Reye's syndrome* which

can be fatal (**Table 29.1**). The main features are acute onset of hepatic failure and encephalopathy. It probably results from damage to mitochondria in liver cells. Patients with Reye's syndrome generally have elevated serum ammonia levels, elevated LFT's and an absent or low CSF salicylate level, while salicylate intoxicated patients have higher serum and CSF salicylate levels. Recovery is associated usually with permanent neurological sequelae.

d. Respiratory alkalosis develops early in the course of intoxication and may be the only acid base disturbance with mild salicylism. Respiratory alkalosis with compensatory metabolic acidosis develops in most adults with moderate intoxication. Metabolic acidosis with acidaemia and compensatory respiratory alkalosis develops in severe overdose and is associated with a higher rate of complications and death.

e. The three most common auditory alterations described by individuals after large doses of salicylates include tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sounds. Symptoms can occur gradually within the initial few days of therapy or within hours of an extremely large dose.

f. Dehydration and hypokalaemia are common. QT prolongation, U waves and flattened T waves have been described in several patients with hypokalaemia after acute salicylate overdose.

g. Significant toxicity has been reported after chronic topical use of creams and ointments containing salicylates. Salicylic acid found in topical wart removal products at concentrations up to 17% (w/w) can cause mucosal burns if ingested.

2. **Chronic Poisoning (*Salicylism*):**
   a. This is characterised by slow onset of confusion, agitation, lethargy, disorientation, slurred speech, hallucinations, convulsions, and coma. There may also be tinnitus, hearing loss, nausea, dyspnoea, tachycardia and fever.
   b. Sometimes "salicylism" presents as *pseudosepsis syndrome* characterised by fever, leukocytosis, hypotension, and multi-organ system failure: ARDS, acute renal failure and coagulopathy (DIC).
   c. Prolongation of PT and PTT, thrombocytopenia, hypofibrinogenaemia, elevation of fibrin degradation products, and red blood cell fragmentation has developed in some patients with multiorgan system failure associated with chronic salicylate toxicity.

Table 29.1: Reye's Syndrome

Stage	Manifestations
I	Lethargic
II	Stuporous, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
III	Comatose, decorticate posture, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
IV	Comatose, decerebrate posture, sluggish pupillary reaction, inconsistent response (oculocephalic reflex)
V	Comatose, flaccid posture, no pupillary reaction, no response to painful stimuli, no response to oculocephalic reflex

d. Chronic maternal ingestion is associated with an increased incidence of stillbirths, antepartum/post-partum bleeding, prolonged pregnancy/labour, and lower birth weight. The American Academy of Pediatrics recommends that salicylates should be used cautiously during breastfeeding; some studies also suggest that bismuth subsalicylates consumed during lactation can lead to problems.

Treatment

1. In patients with severe poisoning, examine the urine for calcium oxalate crystals. Also, monitor calcium and renal function (BUN, creatinine).
2. Local treatment with cold milk or ice cream as a demulcent is sufficient in most cases. Cold water or sucking on crushed ice will also relieve oral pain. Remove all visible evidence of plant debris from the oropharynx.
3. In severe cases, parenteral opioids, corticosteroids, IV fluids, and endotracheal intubation may be required. Tetany should be treated with intravenous calcium gluconate.
4. Ocular exposure to sap resulting in chemical conjuncti-vitis and corneal abrasions must be treated with copious irrigation, systemic analgesics, and expert ophthalmologic consultation.

Diagnosis

1. Monitor serum salicylate level, glucose and electrolytes every 2 hours until the salicylate level is consistently falling and acid base abnormalities are improving. Peak salicylate levels develop rapidly after methyl salicylate ingestion, but may be delayed 6 hours or more following ingestion of tablets, and more than 12 hours after ingestion of enteric coated or sustained release products. Obtain an arterial blood gas in symptomatic patients and follow until acid base abnormalities are improving.
2. Obtain a CBC, renal and hepatic function tests and INR or PT and PTT in patients with clinical evidence of moderate to severe toxicity.
3. In patients with pyloric stenosis, enteric coated aspirin has been shown to remain in the stomach for prolonged periods of time. This can be shown by instillation of contrast media into the stomach followed by an abdominal X-ray. This procedure should be considered in patients with serum salicylate levels that do not decline or continue to rise. Concretions of bismuth subsalicylate or enteric coated aspirin may be radiopaque on plain abdominal radiographs.
4. **Laboratory Findings:**
   a. Anion-gap acidosis.
   b. Hypokalaemia (acidosis may mask it).
   c. Hypocalcaemia.
   d. Hypoglycaemia.
5. **Bed-side Tests:**
   a. Ferric chloride test—
      – Add a few drops of 10% ferric chloride solution to 1 ml of urine. A purple colour indicates the presence of salicylates.

– However it is not conclusive, since a positive result is also obtained in phenol, phenothiazines, phenyl-butazone, and oxyphenbutazone.
   – A method using ferric chloride on methanolic extract of haemolysed whole blood has been described. The minimum salicylate level this method can detect is 5 mg/100 ml.
   b. Trinder's test—
      – Reagent: Trinder's reagent is used which is obtained by mixing 40 grams of mercuric chloride (dissolved in 850 ml of purified water), with 120 ml of aqueous HCl (1 mol/L) and 40 grams of hydrated ferric nitrate, followed by dilution to 1 litre with purified water.
      – Method: The test can be done on urine, stomach contents, or scene residue. Add 0.1 ml of Trinder's reagent to 2 ml of sample and mix for 5 seconds. A strong violet colour indicates the presence of salicylates. Mere darkening is not significant. If the sample to be tested is stomach contents or scene residue, it is better to first boil 1 ml of the sample with 1 ml of aqueous HCl (0.1 mol/L) for 10 minutes, cool, filter, and then neutralise with 1 ml of aqueous sodium hydoxide (0.1 mol/L).
   c. Confirmatory test—
      – The only confirmatory test is to estimate the serum salicylate level. Unfortunately, the seriousness of poisoning correlates poorly with serum levels. Previously, the ***Done nomogram*** (first published in **1960**) was highly recommended to correlate serum salicylate level with the degree of intoxica-tion at varying intervals after acute ingestion of aspirin. But there are severe limitations to its use and is now not generally considered to be reliable. It has been shown to underestimate or overestimate toxicity after salicylate ingestion, and is of no use in evaluating toxicity after ingestion of enteric coated or sustained release products, or in patients with subacute or chronic salicylism. Studies have indicated that it has poor predictive value.
      – Whenever a serum salicylate level is obtained, it is essential to determine the concurrent arterial blood pH, since in the presence of acidaemia more salicylic acid leaves the blood and enters the CSF and other tissues, with consequent worsening of symptoms. Therefore, a falling serum salicylate level may be difficult to interpret as it can reflect either an increased tissue distribution with increased toxicity, or an increased clearance with decreased toxicity. A falling serum salicylate level accompanied by a falling or low blood pH should be presumed to reflect a serious or worsening situation, not a benign or improving one.

Treatment

1. Patients with major signs or symptoms (metabolic acidosis, dehydration, mental status changes, seizures, pulmonary oedema) should be admitted to the Intensive Care Unit regardless of serum salicylate level. Patients with minor

symptoms only (i.e. nausea, tinnitus) following acute overdose may be managed in the emergency department with decontamination and alkaline diuresis if the salicylate level is shown to be declining. Admission should be strongly considered regardless of the salicylate level or symptoms in infants, children less than 2, the elderly, in chronic overdose, or when the ingested tablets are enteric coated or sustained release.

2. Stomach wash may be beneficial upto 12 hours after ingestion, since toxic doses of salicylates often cause pylorospasm and delayed gastric emptying. Whole bowel irrigation might be useful in patients with bezoars, or patients who have ingested enteric coated or sustained release products.

3 Activated charcoal (AC): It is said to be very efficacious in the treatment of salicylate poisoning since each gram of AC can adsorb 550 mg of the drug. A 10:1 ratio of AC to salicylate ingested appears to result in maximum efficiency. The initial dose of AC can be combined with a cathartic to enhance elimination. Some investigators recommend multiple dosing of AC (i.e. MDAC), while others do not consider it to be more beneficial.

4. Urinary alkalinisation: This should not be confused with *forced diuresis* which was recommended in the past, where the accent was on increasing urinary flow rate in order to increase salicylate clearance. It carries with it the risk of fluid overload with attendant complications. Alkalinisation of both blood and urine can be achieved with intravenous sodium bicarbonate.* Acetazolamide must not be used since it produces a systemic metabolic acidosis.

   a. Dose of $NaHCO_3$
   – *For mild poisoning*: 1 mEq/kg of $NaHCO_3$ is added to the first bottle of 5% dextrose. If alkalinisation (i.e. urinary pH between 7.5 and 8.5) is not achieved in a few hours, it can be repeated.
   – *For severe poisoning*: Additional bolus therapy of 50 to 100 mEq of $NaHCO_3$ over 1 to 2 hours may be necessary.
   – Monitor serum electrolytes and urine pH every 1 to 2 hours. Adjust potassium and bicarbonate administration as needed to maintain a urine pH of 7.5 to 8. It is important to correct hypokalaemia while alkalinising the urine. Alkalinisation should be stopped when serum salicylate level falls below 35 mg/100 ml.

5. Haemodialysis: It is very effective in salicylate poisoning and must always be considered in the presence of cardiac or renal failure, intractable acidosis, convulsions, severe fluid imbalance, or a serum salicylate level more than 100 mg/100 ml. Patients with evidence of cerebral oedema require immediate dialysis. Charcoal haemoperfusion produces better salicylate clearance than haemodialysis, but does not correct fluid and electrolyte balance like haemodialysis.

6. Supportive measures:
   a. Correction of fluid and electrolyte imbalance (*watch out for fluid overload!*).
   b. Correct dehydration with 0.9% saline 10 to 20 ml/kg/hr over 1 to 2 hours until a good urine flow is obtained (at least 3 to 6 ml/kg/hr). In patients, in whom urinary alkalinisation is being considered, initial hydration may be with 10 to 20 ml/kg of D5W with 88 to 132 milliequivalents of bicarbonate added. Patients in shock may require more rapid fluid administration.
   c. Hypoprothrombinaemia can be corrected by 2.5 to 5 mg of vitamin K IV every day.
   d. Hyperpyrexia must be tackled by cooling measures (e.g. ice in the axilla and groin).
   e. Correction of metabolic acidosis with $NaHCO_3$.
   f. Correction of hypocalcaemia with calcium gluconate IV (5 to 10 ml in adults).
   g. Correct hypokalaemia as needed. Patients undergoing forced or alkaline diuresis may require large amounts of potassium supplementation due to renal potassium wasting. Institute continuous cardiac monitoring in patients with hypokalaemia, and those requiring high doses of potassium.
   h. Correction of hypoglycaemia with glucose IV (50 ml of 5% dextrose or 1 ml/kg).
   i Treatment of convulsions with benzodiazepines.
   j. Mild cerebral oedema and elevated intracranial pressure (ICP) can be managed by head elevation and administration of mannitol; hyperventilation should be performed if there is evidence of impending herniation. Haemodialysis may be necessary.
   k. Salicylates can interfere with coagulation mechanisms, therefore, patients with evidence of active bleeding or coagulation disorders require laboratory monitoring to include prothrombin time (PT) and INR. Give blood or blood products (fresh frozen plasma) if bleeding is excessive. Vitamin K may be beneficial in the presence of a prolonged PT or INR.

7. Treatment of Reye's syndrome:
   a. Admit the patient to an intensive care unit.
   b. Raise the head-end of bed (40⁰).
   c. Mannitol IV (0.2 to 1.0 gm/kg).
   d. Acute hyperventilation may be helpful.
   e. Short acting barbiturates in resistant cases.

Autopsy Features

1. Petechiae in the skin (occasionally).
2. Erosions of gastric mucosa. Black, altered blood may lie in the stomach. Sometimes massed concretions of tablets are present.
3. Petechiae in various organs and serous membranes (parietal pleura, pericardium).
4. Pulmonary and cerebral oedema.

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* Do not give sodium bicarbonate orally since it can enhance salicylate absorption from the GI tract by facilitating dissolution.

Forensic Issues

- Most of the cases of overdose are suicidal in nature; a few may be accidental.
- In some individuals, a small dose of aspirin can provoke a fatal hypersensitivity reaction. The patient is usually (curiously) a middle-aged female, and often has nasal polyps. Within minutes of ingestion there is an acute vasomotor rhinitis, angioneurotic oedema, and urticaria. Death results from laryngeal oedema, hypotension, or shock.
- Salicylate poisoning can also result from extensive application of salicylate-containing ointments, keratolytic agents, or other agents containing methyl salicylate.

■ Paracetamol

Synonyms

Acetaminophen; N-acetyl-p-aminophenol; 4-hydroxyacetanilide.

Physical Appearance

Paracetamol exists as white, odourless, bitter tasting crystals or crystalline powder.

Uses

1. Antipyretic: The search for an effective and safe antipyretic began in the 19th century when **Cahn** and **Hepp** accidentally discovered the fever-reducing property of acetanilide and introduced it into pharmacotherapeutics as "antifebrin" in **1886**. However its unacceptable toxicity led to a search for less toxic compounds, and a related compound namely, phenacetin was synthesised and introduced in **1887**. This was extensively used till recently when its role in *analgesic nephropathy** became clear and led to its withdrawal. In **1893**, **von Mering** introduced paracetamol, and a hundred years later it is still going strong. In fact, paracetamol is the active metabolite of both acetanilide and phenacetin.
2. Analgesic.

Toxicokinetics and Mode of Action

- Paracetamol is rapidly and completely absorbed from the GI tract. Peak plasma levels are reached in ½ to 1 hour, while the plasma half-life is about 2 hours. Following an overdose, the peak plasma level is not usually reached for 4 hours. Absorption may be delayed by other drugs and high carbohydrate foods which delay gastric emptying.
- Protein binding for paracetamol is 5 to 20%. Volume of distribution is 0.8 to 1 L/kg (adult). The half-life of paracetamol may exceed 12 hours in acute overdose.
- Normally about 90% of the drug undergoes hepatic conjugation with glucuronide and sulfuric acid to form inactive and harmless metabolites, while 10% is oxidised (through P450 mediation) to N-acetyl-p-benzoquinoneimine (NAPQI) which is a highly reactive intermediate. NAPQI is capable of covalent binding and arylating critical cell proteins inducing a series of events that result in cell death. In the normal course, glutathione rapidly detoxifies this intermediate to cysteine and mercapturate conjugates. In the overdose situation, glutathione stores become depleted and the toxic NAPQI binds covalently with hepatocytes of the liver causing centrilobular hepatic necrosis. However there is significant individual susceptibility to the toxic effects of paracetamol and upto 20% of seriously poisoned patients do not develop hepatotoxicity.
- Concomitant intake of drugs which induce P450 enzyme (e.g. phenobarbitone) can enhance the chances of hepatotoxicity. Alcoholism and chronic therapy with drugs such as isoniazid and anticonvulsants also predispose to hepatic failure.

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. *Stage I* (1/2 hr to 24 hrs): Anorexia, vomiting, sweating, malaise.
   b. *Stage II* (24 to 72 hrs): Relatively symptom-free. There may be right upper quadrant pain. Liver function tests may be abnormal.
   c. *Stage III* (72 to 96 hrs): Hepatic necrosis sets in with coagulation defects, jaundice, and encephalopathy. Nausea and vomiting reappear. Renal failure and myocardial damage are frequently present. Death is usually due to hepatic failure and is preceded by coma. Elevated blood levels of liver enzymes (SGOT/ALT, SGPT/AST) may begin to develop within 24 hours after overdose, and peak 2 to 3 days post-ingestion. Increased total bilirubin and prolonged PT may also occur in some patients within 24 hours of paracetamol ingestion. Decreased serum interleukin-6 (IL-6) has been found to be associated with hepatic injury following acute paracetamol overdose in a prospective study. It is suggested that measuring serum IL-6 or C-reactive protein (a surrogate for IL-6) levels may serve as a prognostic factor in predicting hepatic injury following an acute overdose.
   d. *Stage IV* (4 days to 2 wks): If the patient survives the IIIrd stage, complete resolution of hepatic damage is the rule rather than the exception. There are no reported cases of chronic hepatic dysfunction from paracetamol.
   e. *Additional Manifestations*:
   – Hypotension and shock with hypothermia, in the absence of hepatic dysfunction, have been reported following acute paracetamol overdose. The mechanism of paracetamol-induced hypotension is unclear.
   – Myocardial injury (with ECG changes and CPK MB elevations) has occasionally been reported in severe overdose. It is unclear if paracetamol is a direct myocardial toxin, or if these effects are secondary to metabolic or cardiopulmonary abnormalities induced by severe paracetamol toxicity.

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* Prolonged duration of phenacetin therapy causes chronic interstitial nephritis and renal failure.

- – Coma and metabolic acidosis within 3 to 4 hours of ingestion have been described rarely.
- – Acute pancreatitis with hyperamylasaemia has been reported following paracetamol overdose.
- – Acute alcohol ingestion in chronic alcohol abusers had a protective effect against hepatic encephalopathy. In patients who were not alcohol abusers and either took an acute alcohol ingestion or did not take any alcohol, only a non-significant trend toward a protective effect of acute alcohol ingestion was shown. Therapeutic doses of paracetamol do not appear to cause hepatotoxicity in chronic alcoholics.
- – Adolescents are 6 times more likely to develop liver damage and 2 times more likely to develop potentially toxic levels than children less than 6 years old.
- – Transient renal damage may occur. Nephrotoxic effects include acute tubular necrosis, flank pain, haematuria, proteinuria, and an antidiuretic hormone effect.
- – Metabolic acidosis and high blood lactate levels may be seen early (12 hours), especially in severe overdoses. Metabolic acidosis is common 3 to 4 days after ingestion in patients developing hepatic failure.
- – Hyperphosphataemia (>1.2 mmol/L) appears to be an early predictor of nonsurvival in severe paracetamol-induced hepatotoxicity (ALT >1000 U/L; hepatic encephalopathy; liver transplantation) at 48 to 96 hours post-ingestion. The degree of hyperphosphataemia in fatalities has correlated with renal function. It is proposed that hyperphosphataemia is due to renal dysfunction in the absence of hepatic regeneration (which is associated with lowering of serum phosphate). Hypophosphataemia has been reported, may occur in the absence of hepatic encephalopathy, and may be suggestive of a subclinical renal effect.

2. **Chronic Poisoning:**
   a. This is uncommon, but cases have been reported where-in an individual has consumed large doses of paracetamol over a period of time for relief of chronic pain which resulted in toxic hepatitis. This is more common in alcoholics, AIDS patients (in whom there is depletion of glutathione), and patients receiving other medications which are cytochrome P450 inducers, e.g. isoniazid, rifampicin, phenytoin, carbamazepine, and barbiturates.
   b. Chronic overdose among children is more common than in adults mainly because of dose miscalculation by parents. Features include anorexia, vomiting, lethargy, low body temperature, hepatomegaly, and oliguria.
   c. There is no clear evidence that either paracetamol or N-acetylcysteine is teratogenic. Paracetamol overdose does not appear to increase the risk for birth defects or adverse pregnancy outcome unless severe maternal toxicity results.

   d. There is no evidence that paracetamol is carcinogenic. In fact, in a case control study, patients who ingested paracetamol were at decreased risk of developing ovarian cancer.

Usual Fatal Dose

- About 20 to 25 grams. However doses as low as 10 grams can cause serious hepatotoxicity. Ingestion of even 150 mg/kg or 7.5 grams has caused liver injury.
- Children under the age of 10 years appear to be more resistant to the toxic effects of paracetamol. It has been suggested that the toxic dose for a 5-year-old child, based on liver size ratio compared to an adult, is 187.5 mg/kg. Predicted toxic dose for a younger child would be even higher.
- In a prospective, observational study of acute paediatric overdose ingestions of paracetamol (excluding extended-release preparations) of up to 200 mg/kg, some investigators found that with home monitoring alone these patients do not develop signs or symptoms of hepatic injury at 72-hour follow-up.

Diagnosis

1. *Evidence of hypoglycaemia, metabolic acidosis*.
2. *Evidence of hepatocellular injury*:
   a. Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and prothrombin time. ALT and AST may rise within 24 hours after ingestion, and peak within 48 to 72 hours. Levels over 10,000 units/L are common.
   b. Hypophosphataemia is often present. Hyperphosphataemia (greater than 1.2 mmol/L), occurring 48 to 96 hours after the overdose, and in the presence of both renal and hepatic dysfunction, is a poor prognostic indicator.
   c. Decreased serum interleukin-6 (IL-6) or C-reactive protein (a surrogate for IL-6) levels following acute paracetamol overdose have been found to be statistically associated with hepatic injury and may serve as prognostic factors for predicting impending hepatic injury.
   d. Fatal cases of paracetamol overdose usually have a bilirubin level greater than 4 mg/100 ml and a prothrombin time greater than twice the control or a prothrombin time ratio of 2.2 or greater on the third to the fifth day.
   e. Serum prealbumin concentrations decrease significantly after 36 hours and continue to decrease during liver failure, providing a true index of liver function.
3. *Evidence of renal damage*: Proteinuria, phosphaturia.
4. *Evidence of myocardial damage*: ECG changes indicative of arrhythmias.
5. *Serum paracetamol level*: The lowest acute dose of paracetamol capable of toxicity is generally regarded as 7.5 grams in an adult and 150 mg/kg in a child, though it is more likely that the actual figures may be 15 grams and 250 mg/kg respectively.

a. Interpretation of serum paracetamol (acetaminophen) levels is usually done on the basis of the **Rumack-Matthew nomogram** (**Fig 29.2**). The original nomogram was based on the fact that patients in whom the AST or ALT values would rise (more than 1000 IU/L) could be separated from those in whom this would not happen on the basis of initial paracetamol level (PL). The nomogram line was constructed on a plot of PL versus time since ingestion. The line chosen started at a PL of 200 mcg/ml, 4 hours post-ingestion; declined with a 4-hour half-life through 50 mcg/ml, 12 hours post-ingestion; and ended at 6.25 mcg/ml, 24 hours post-ingestion. The line is based solely on ALT elevation rather than hepatic failure and is very sensitive though not very specific. Without antidotal therapy (*vide infra*), 60% of the patients with initial PL above this line would develop ALT values above 1000IU/L.

– While the original line is still widely in use, the line used in USA has been lowered by 25% in order to enhance sensitivity. By using this modified nomogram it is said that nomogram failures in the USA are virtually non-existent.

– The purpose of the Rumack-Matthew nomogram is to predict the risk of hepatic injury at the outset and begin antidotal therapy well in time. Levels obtained before 4 hours or after 24 hours cannot be interpreted, nor can levels obtained after chronic overdose. Though the risk cannot be predicted earlier than 4 hours post-ingestion, this does not matter at all since there seems to be no added efficacy in antidotal therapy when begun earlier than 4 hours after the overdose.

– In those cases where the time of ingestion is unknown and cannot be determined, it is advisable to determine both PL and AST. If the AST is elevated regardless of PL, begin antidotal therapy. If the PL is less than 10 mcg/ml and AST level is normal, the antidote (N-acetylcysteine) can be withheld.

– If it is not possible for any reason to estimate the paracetamol level at all, then the risk of hepatic
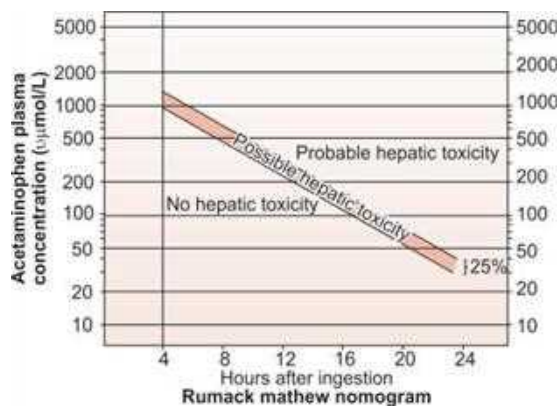
Fig 29.2: Rumack Matthew nomogram

injury should be predicted on the basis of the history. Do not delay antidotal therapy for lack of a paracetamol level. Administer loading dose, then discontinue if level comes back below the nomogram treatment line.

– Conflicting reports are found in the literature regarding whether or not a lower treatment line on the Rumack-Matthew nomogram should be used for treating acute paracetamol overdoses in chronic alcoholics. On the one hand, a review of the literature has shown in animal studies that a lower dose of paracetamol is required to produce hepatotoxicity following chronic alcohol use due to induction of CYP enzymes and glutathione depletion. It is suggested that the animal results may apply to human cases, and some authors suggest a conservative guess of halving the dose/concentration for treatment. On the other hand, due to species differences in CYP expression, activity and induction, results cannot always be extrapolated from animals to human cases. Also, a literature review does not conclusively substantiate that exposure to chronic excessive amounts of alcohol will predispose paracetamol overdose patients to hepatotoxicity.

– After 24 hours postingestion, the presence of paracetamol in the plasma may be documented, but interpretation of these levels is difficult. Because of increasing evidence of the beneficial effect of N-acetylcysteine instituted more than 24 hours after overdose, its use is recommended in patients presenting 24 hours or more post-ingestion who have measurable paracetamol levels or biochemical evidence of hepatic injury.

6. One study compared a qualitative urine paracetamol screen (thin-layer chromatography) to a qualitative serum paracetamol screen in several patients following intentional ingestions. It was found that a negative urine paracetamol was highly predictive of negative serum paracetamol levels. This suggests that a negative urine screen may obviate the need for 4-hour quantitative serum levels.

7. Concomitantly ingested drugs which change the rate of gastric emptying (codeine, other opiates, antimuscarinic drugs, antihistamines), may delay absorption of paracetamol. Additional levels may be needed to determine the peak and the need for antidote.

8. Assessment of prognosis—Poor prognosis is characteristic of

a. pH < 7.30 in spite of fluid and haemodynamic resuscitation.

b. PT > 100 seconds, creatinine > 3.3 mg/100 ml, and grade III or IV encephalopathy.

c. Abnormal PT which continues to rise on the 4th day. In late presenters following paracetamol overdose, the best prognostic marker in established hepatotoxicity is the prothrombin time. Extended courses of

N-acetylcysteine may be given until the prothrombin time improves.

Treatment (Table 29.2)

Children who have an unobtainable history or in whom a large amount of paracetamol is suspected to have been ingested (>200 mg/kg) should be referred to a health care facility for a 4-hour paracetamol serum level determination, and consideration for administration of activated charcoal.

1. *Stomach wash*: useful only in cases of very early presentation (<1 hour), or in concomitant ingestion of other drugs which delay GI absorption.
2. *Activated charcoal* can adsorb paracetamol, but it can also adsorb the antidote (N-acetylcysteine) and hence must be administered earlier to 4 hours post-ingestion. It is most effective if given within one hour of ingestion of a liquid formulation or a tablet formulation.
3. *Anti-emetic*, if the patient is vomiting repeatedly.
4. *Supportive measures*:
   a. 10 to 20% dextrose for hypoglycaemia.
   b. Vitamin K_1 if PT is elevated.
   c. Fresh-frozen plasma if there is overt bleeding.
   d. Mannitol (0.5 gm/kg given over 10 minutes) for cerebral oedema.
   e. Broad spectrum antibiotics IV (ceftazidime or fluoxacillin) if necessary.

   f. H_2 antagonists to prevent upper GI haemorrhage.
   g. Do **not** give sedatives, benzodiazepines, or NSAIDs.
5. *Antidotal therapy:*
   a. Methionine—This is an oral antidote that is popular in the UK and some other countries, but is presently not available in India. It is a glutathione precursor and protects against paracetamol-induced hepatic and renal damage, provided it is administered within 8 to 10 hours of ingestion. Dose: 2.5 grams, 4 doses, at 4-hour intervals.
   b. N-acetylcysteine (NAC)—It is a derivative of L-cysteine, a naturally occuring amino acid. NAC is the antidote of choice for paracetamol poisoning in the USA, and is gaining in popularity elsewhere including India. It gives maximum protection against hepatotoxicity when administered within 10 hours of paracetamol overdose, but can be given with (lesser) benefit upto 36 hours.
      – Indications:
        - NAC is indicated in paracetamol overdose if PL estimated between 4 and 12 hours post-ingestion lies above the nomogram line (**Fig 29.2**).
        - Paracetamol ingested is more than 100 mg/kg.
        - Likelihood exists of paracetamol-induced hepatic failure.

Table 29.2: Guidelines for the Treatment of Paracetamol Poisoning

< 8 hrs After Overdose
- Estimate PL
- Administer activated charcoal
- Begin IV NAC if PL is above nomogram line
- If PL is not available by 8 hrs, begin NAC if > 150 mg/kg PCM has been ingested
- Discontinue NAC if PL is below nomogram line
- On completion of NAC therapy, check PT, ALT/AST and PL
- If patient is asymptomatic, and investigations are normal, patient can be discharged

8–15 hrs After Overdose
- Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid-base status, and blood count
- Begin NAC if > 150 mg/kg PCM has been ingested
- Discontinue NAC if PL is below nomogram line
- On completion of NAC therapy, repeat investigations (except PL)
- If patient is asymptomatic, and investigations are normal, patient can be discharged

15–24 hrs After Overdose
- Begin NAC if > 150 mg/kg PCM has been ingested
- Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid-base status, and blood count
- Repeat investigations at the end of NAC course
- If the investigations are abnormal, or if the patient is symptomatic, continue NAC therapy until recovery

> 24 hrs After Overdose
- Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid-base status and blood count
- If the patient has ingested > 150 mg/kg PCM, or is symptomatic, or has abnormal investigations, begin NAC therapy
- Repeat investigations at the end of NAC course, and consider continuing the course if the patient has or is at risk of developing hepatic failure

PL = plasma paracetamol level; NAC = N-acetylcysteine; PCM = paracetamol; PT = prothrombin time;

ALT = alanine aminotransferase; AST = aspartate aminotransferase

– Dose—
- Oral: 5% solution given as loading dose of 140 mg/kg. This is followed by 17 more doses at 70 mg/kg, 4th hourly, total making upto 1330 mg/kg over 72 hours. The calculated dose can be administered mixed with water, or flavoured or carbonated drink. *For a child:* Initial - 140 mg/kg for one dose, followed by 70 mg/kg/dose every 4 hours for 68 hours, beginning within 10 hours of the ingestion. A shorter duration of oral NAC has been recommended by some investigators for acute paracetamol overdoses presenting within 24 hours of ingestion: loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours until the serum paracetamol level is no longer detectable and aminotransferase levels are normal, instead of the standard 72-hour treatment protocol. These investigators found this method safe and effective in patients not demonstrating hepatotoxicity within 36 hours of an acute overdose.

– Intravenous—
- 20 hour regimen (**Prescott protocol**) → 150 mg/kg made up in 200 ml of 5% dextrose is given IV over 15 minutes, followed by 50 mg/kg in 500 ml of 5% dextrose over 4 hours, and 100 mg/kg in 1 litre of 5% dextrose over 16 hours. The total dose works out to 300 mg/kg given over 20 hours. *For a child:* Standard intravenous dosing can cause hyponatraemia and seizures secondary to large amounts of free water. To avoid this complication, NAC should be diluted to a final concentration of 40 mg/ml. 150 mg/kg infused over 15 minutes (infuse 3.75 ml/kg over 15 minutes), followed by 50 mg/kg infused over 4 hours (infuse 1.25 ml/kg over 4 hours, i.e., 0.31 ml/kg/hr), and 100 mg/kg infused over 16 hours (infuse 2.5 ml/kg over 16 hours, i.e. 0.16 ml/kg/hr).
- 48 hour regimen → useful in delayed admissions and massive ingestion. A loading dose of 140 mg IV is given over 1 hour, followed 4 hours later by the first of 12 maintenance doses of 70 mg/kg, each administered over 1 hour. The total dose of NAC works out to 980 mg/kg in just over 48 hours.

– Adverse effects:
- Oral—drinking NAC through a straw minimises its unpleasant odour. The main problem with oral NAC is induction of vomiting. Metoclopramide or ondansetron may have to be administered.
- Intravenous—anaphylactoid reaction. If it occurs, it should be managed in the usual way with antihistamines, epinephrine, etc.
- Isolated effects include pruritus, angioedema, nausea and vomiting, bronchospasm, tachycardia, hypotension, and hypertension. Facial or chest flushing is common, beginning 15 to 75 minutes after initiation of infusion, and is associated with peak NAC plasma concentrations of 100 to 600 mcg/L.
- A decrease in the prothrombin index (which corresponds to an increase in prothrombin time or INR) has been reported following administration of IV NAC for treatment of patients with paracetamol poisoning who did not exhibit signs of hepatocellular injury. The time of the decrease appeared to be associated with the start of the NAC infusion instead of with the ingestion of paracetamol. Because prothrombin time is measured as a prognostic indicator in patients with paracetamol poisoning, the concern is that the decrease in prothrombin index may be misinterpreted as a sign of liver failure. It is suggested that patient management decisions should not be based solely on the measurement of this value.

6. *Liver transplantation*: When fulminant liver failure develops after a massive paracetamol overdose, virtually the only treatment modality available is liver transplantation.
   a. Indications—
      – pH < 7.3.
      – PT > 100 seconds, and serum creatinine > 3.4 mg/100 ml in patients with grade III or IV encephalopathy.
      – **Schiodt et al (1999)** developed a model, based on a prospective and validated study, to predict hepatic encephalopathy (HE) in paracetamol overdose, and to identify high-risk patients for early transfer to a liver intensive care unit/transplantation facility. The most accurate model for HE included: log10 (hours from overdose to antidote treatment), log10 (plasma coagulation factors on admission), and platelet count × hours from overdose (chi-square = 41.2, P<0.00001). HE was not seen in patients treated within 18 hours after overdose. A good predictor of later hepatic encephalopathy also includes a total Gc-globulin level less than 120 mg/L on day 2 following paracetamol overdose. This value was based on a prospective longitudinal study including 84 patients with acute paracetamol overdose.
      – The **O'Grady criteria** is a multivariate prognostic scoring system for predicting the need for listing a patient for liver transplantation. The criteria include: arterial blood pH < 7.3 or H+ >50 mmol/L; or, PTR >100 seconds and serum creatinine >300 mcmol/L in patients with Grade III or IV encephalopathy. A **modified O'Grady criteria** states that if serum lactate is >3 at 4 hours, or >3.5 at 12 hours (after initial fluid resuscitation), the positive predictive value

of the O'Grady criteria is increased. A high APACHE (Acute Physiologic and Chronic Health Evaluation) II or III score may also predict the need for liver transplantation.

– The use of arterial lactate concentration may allow for earlier identification of patients at high-risk of fatal paracetamol induced liver failure and likely to benefit from listing early for liver transplantation. Some investigators have found that an early arterial lactate 4 hours after transfer (median of 43 hours after ingestion) above 3.5 mmol/L correlated with an increased risk of fatal outcome. An arterial lactate concentration 12 hours after transfer and after adequate fluid resuscitation (guided by invasive haemodynamic monitoring) above 3.0 mmol/L also correlated with an increased risk of fatality. All patients had ICP monitoring as appropriate, noradrenaline was used as the primary vasopressor, NAC was infused at 150 mg/kg for 24 hours, and continuous venovenous haemofiltration with lactate-free fluid was used for renal replacement.

– **Bernal et al** have proposed criteria for liver transplantation in paracetamol-induced acute liver failure as follows:

   - strongly consider listing for transplantation if arterial lactate concentration >3.5 mmol/L after early fluid resuscitation
   - list for transplantation if arterial pH <7.3 mmol/L, or arterial lactate concentration >3.0 mmol/L after adequate fluid resuscitation.
   - or concurrently serum creatinine >300 mcmol/L, INR >6.5 and there is encephalopathy of grade 3 or greater.

7. *Forced diuresis, haemodialysis*, and *charcoal haemoperfusion* are of little value in preventing paracetamol induced hepatotoxicity.

8. *Albumin dialysis*: A molecular adsorbent recirculating system (MARS), which is a modified dialysis method using an albumin-containing dialysate that is recirculated and perfused online through charcoal and anion-exchange columns, has been used following a massive paracetamol overdose with hepatic encephalopathy (grade II), severe acidosis, INR of 7, and hepatorenal syndrome. Albumin dialysis allowed time for hepatic regeneration during conventional supportive care in this case. A course of 5 consecutive 8-hour treatments was performed.

9. *Continuous haemofiltration*: This may be preferable to intermittent haemodialysis in patients with paracetamol-induced hepatic and renal failure. Use of intermittent haemodialysis is associated with increases in intracranial pressure in these patients due to both cytotoxic and vasogenic cerebral oedema.

10. *Extracorporeal sorbent-based devices*: Paracetamol-induced hepatitis or hepatic failure have been treated at 16 to 68 hours after an overdose for 4 to 6 hours with the Liver Dialysis System (a single-access haemodiab-sorption system for treatment of serious drug overdose, and for treatment of hepatic encephalopathy). During this treatment, paracetamol levels dropped an average of 73%. If paracetamol levels were still measurable in plasma, treatment was repeated 24 or 48 hours later. In this group, liver enzymes normalised 24 hours after the last treatment and no patient required a liver transplant. No adverse effects due to this treatment were noted.

Autopsy Features

1. Liver may be enlarged and yellowish in colour. Microscopy reveals centrilobular necrosis.
2. Histological evidence of renal damage.
3. Cerebral oedema.
4. Cardiac findings in fatal overdoses have included subendocardial haemorrhages, fatty degeneration, and focal necrosis.

Forensic Issues

- Attempted suicide with paracetamol accounts for a staggering 15 to 30% of cases of poisoning in the UK; a similar scenario exists in the USA where paracetamol overdose accounts for more hospitalisations than any other pharmaceutical agent. While the situation is at present not as bad in India, there are alarming indications of rising incidence.
- Accidental poisoning most often results from inadvertent therapeutic overdose either as an acute or as a chronic phenomenon. A few cases result from hypersensitivity reactions which (though rare) may sometimes produce serious manifestations ranging from dermal to respiratory to anaphylactoid reactions.
- As of November 1997, the FDA (USA) requires an alcohol warning on all over-the-counter pain relievers, which includes paracetamol, aspirin, other salicylates, ibuprofen, ketoprofen, and naproxen sodium due to a potential drug interaction resulting in upper GI bleeding or liver damage.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID)

Classification

- **Pyrazolones**—oxyphenbutazone, phenylbutazone.
- **Propionic acids**—benoxaprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, pirprofen, suprofen, tiaprofenic acid.
- **Fenamic acids**—flufenamic acid, meclofenamic acid, mefenamic acid.
- **Heterocyclic acetic acids**—etodolac, indomethacin, ketorolac, sulindac, tolmetin, zomepirac.
- **Aryl acetic acids**—diclofenac, alclofenac.
- **Oxicams**—isoxicam, piroxicam, tenoxicam.
- **Sulfonanilide**—nimesulide.

Mode of Action

The mode of action of all NSAIDs is similar—inhibition of synthesis of prostaglandins, prostacyclins, and thromboxane, by

binding to cyclo-oxygenase. Most NSAIDs can cause nephro-toxicity on long-term administration (*analgesic nephropathy*). Regular monitoring of serum creatinine in patients receiving such drug therapy is advisable.

■ Pyrazolones

Phenylbutazone was introduced in 1949, followed soon thereafter by its metabolite oxyphenbutazone. Both are potent anti-inflammatory drugs, but are associated with significant adverse effects, and hence have been withdrawn from routine use in several countries. They are still available in India. Their use should be restricted to acute gout and acute exacerbations of rheumatoid arthritis and ankylosing spondylitis.

Related drugs include aminopyrine, antipyrine, amidopyrine, azapropazone, dipyrone, noramidoprine, phenazone, and sulfinpyrazone.

Mode of Action

Phenylbutazone interferes with prostaglandin synthesis via inhibition of the cyclo-oxygenase pathway. It is irritating to the mucosa of the gastrointestinal tract.

Clinical Features

1. Main features of overdose with phenylbutazone/oxyphenbuta-zone include vomiting, abdominal pain, acid-base and electrolyte disturbances, pulmonary oedema, vertigo, seizures, hypotension, coma, and respiratory and cardiac arrest.
2. Salicylate-like symptoms including stimulation of the respiratory center, respiratory alkalosis, and metabolic acidosis have been reported.
3. Other reported effects include hyperglycaemia, hypocalcaemia, cyanosis, paraesthesias, tinnitus, erythematous rash, profuse sweating, and dyspnoea.
4. Renal, hepatic, and haematological complications soon follow. Renal dysfunction is common, including proteinuria, haematuria, anuria, oliguria and in one fatal case, acute nephritis. Urine may be red due to a pyrazolone metabolite.
5. Blood dyscrasias (agranulocytosis, thrombocytopenia, aplastic anaemia) are more common with dipyrone. Methaemoglobinemia has been reported with antipyrine. Pancytopenia has been reported after overdose with phenylbutazone and oxyphenbutazone.
6. Moderate to marked hepatocellular injury has been reported with chronic ingestion (less than 6 weeks) of therapeutic doses. Gastric ulceration was reported in a few patients.
7. Fatal dose is highly variable (4 to 40 gm).
8. Phenylbutazone enhances the effects of tolbutamide and other sulphonylurea antidiabetic agents, and coumarin anticoagulants, and may enhance the effects of phenytoin and some sulfonamides.

Diagnosis

1. Ferric chloride test (*page no 583*).
2. Obtain a baseline CBC, renal and liver function tests, and urinalysis in symptomatic patients.
3. After 24 hours, a red discolouration of the urine may be seen, due to rubazonic acid, a pyrazolone metabolite.

Mode of Action

1. Stomach wash, activated charcoal. Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.
2. Treat convulsions in the usual manner.
3. It is postulated that the excretion of phenylbutazone, like salicylate, may be enhanced in an alkaline urine. This may be considered in very severely intoxicated patients. However, alkaline diuresis is of questionable value since pyrazoles are extensively metabolised, and only 1 to 5% of the drug is eliminated unchanged by the kidneys.
4. Haemoperfusion in life-threatening cases. Because of the low water solubility and high protein binding, haemodialysis is not likely to be effective.
5. Plasmapheresis is claimed to be beneficial in severe poisoning, and has been tried successfully in a case of phenylbutazone overdose.

■ Propionic Acids

The first member of this group to be introduced into pharmacotherapeutics was ibuprofen in 1969. All propionic acids inhibit PG synthesis as well as platelet aggregation (thereby increasing bleeding time). They are widely used today in the relief of musculoskeletal disorders, fractures, sprains, and dysmenorrhoea. Examples include benoxaprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, ketorolac, loxoprofen, oxaprozin, pirprofen, suprofen, and tiaprofenic acid.

Angioedema, hives, itching, rash, and swelling have been reported with therapeutic use. GI distress, nausea, and epigastric pain are the most common adverse effects with therapeutic doses; upper GI bleeding may occur after acute or chronic ingestion. Oesophageal stricture may occur with minimal liquid intake. Enteropathy may occur with chronic ingestion. Effective October 1999, the FDA requires an alcohol warning on all over-the-counter pain relievers, which includes aspirin, other salicylates, paracetamol, ibuprofen, ketoprofen, and naproxen sodium. The statement is as follows: If you drink 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Isolated cases of thrombocytopenia, agranulocytosis, haemolysis, lymphopenia, and pancytopenia have been reported after therapeutic use of propionic acids.

Ibuprofen overdoses have been commonly reported in the literature, while the other members of this group are less commonly mentioned. Children ingesting less than 200 mg/kg generally are asymptomatic or have mild effects. Ingestions of 400 mg/kg in children have been associated with severe toxicity. Therapeutic plasma levels should be between 20 to 30 mcg/ml.

Main symptoms include vomiting, abdominal pain, diarrhoea, seizures, apnoea, hypotension, bradycardia, metabolic acidosis, and renal and hepatic dysfunction. Lethargy, drowsiness, headache, nystagmus, diplopia, tinnitus, ataxia, apnoea (particularly in infants), adult respiratory distress syndrome, and hypothermia may develop. Miosis has been reported in acute

overdose. Hypokalaemia, hypophosphataemia, hyponatraemia, and hyperkalaemia (associated with renal failure) can occur.

Overdose of ketoprofen produces only mild symptoms, based upon reports from Great Britain. Symptoms include vomiting and drowsiness; ingestion of 5 grams in an elderly male produced no symptoms.

Treatment involves gastric lavage, activated charcoal, and supportive measures. Monitor for signs and symptoms of gastrointestinal ulceration and/or haemorrhage, i.e. stool guaiac test. Antacids may be of some value in patients with GI symptoms. Patients with severe epigastric pain, dysphagia or drooling should be evaluated for possible oesophageal stricture. Management of hypotension, acidosis, and gastrointestinal bleeding may be necessary. Enhanced elimination using urine alkalinisation or haemodialysis has not been shown to be of benefit.

Possible complications of use during pregnancy include delayed labour, complications during delivery, postpartum bleeding, and respiratory depression in the newborn.

■ Fenamic Acids

Also referred to as anthranilic acids, these compounds are occasionally involved in overdose producing muscle twitching, and seizures, apart from gastrointestinal distress. Management is supportive, following decontamination (gastric lavage, activated charcoal). Monitor renal function and acid base status in symptomatic patients. Control of convulsions can be achieved with benzodiazepines or barbiturates. Haemodialysis is not expected to be effective in treating acute intoxication, but charcoal haemoperfusion might be effective.

Mefenamic acid is used in mild to moderate pain (e.g. headache, dental pain, post-operative and postpartum pain, and dysmenorrhoea, musculoskeletal and joint disorders). Safety and effectiveness in paediatric patients under the age of 14 years have not been established. Adverse effects from therapeutic use include GI irritation or ulceration, GI bleeding, headache, dizziness, drowsiness, skin rashes, acute renal failure, elevated liver enzymes, increased bleeding time and tinnitus. Rare effects include anaphylactoid reactions, cardiovascular effects, hyperglycaemia, hallucinations, coma, meningitis, seizures, respiratory depression, pneumonia, dermal reactions, and haematologic abnormalities (e.g. haemolytic anaemia, agranulocytosis, pancytopenia, thrombocytopenic purpura, bone marrow aplasia).

In overdose, muscle twitching and seizures are most common. The lowest dose to cause coma and seizures in an adult was 3.5 grams. Vomiting, diarrhoea, abdominal pain, lethargy, drowsiness, and acidaemia can occur. Less frequent symptoms include respiratory depression, hypertension, coma, dyskinesias, agitation and restlessness, GI bleeding, and acute renal failure. Anaphylaxis can also occur in overdose.

It has been suggested that therapeutic serum levels must not exceed 20 mcg/ml.

■ Heterocyclic Acetic Acids

Frontal headache is the most common adverse effect following therapeutic dosing with these compounds. Other reported effects include gastritis, epigastric distress, lightheadedness, vertigo, dizziness, mental confusion, and occasionally somnolence, stupor, or hallucinations. Neutropenia, thrombocytopenia, and rarely aplastic anaemia may occur following chronic ingestion of therapeutic doses.

Intoxication with indomethacin is generally not associated with serious effects, though occasionally it may cause convulsions. Nausea, vomiting, gastritis, gastrointestinal ulceration with perforation, and haemorrhage may occur. Disorientation, mental confusion, and lethargy have been reported. Sulindac overdose can cause renal failure. It has also been implicated in development of psychosis, especially in the elderly patient. Ketorolac has been withdrawn from use in some countries and restrictions imposed in other countries because of its severe adverse effects relating to GI tract and kidneys, while zomepirac has been withdrawn in the USA because of its tendeny to induce anaphylaxis.

Treatment of overdosage is symptomatic and supportive. Patients should be monitored for possible gastrointestinal ulceration and/or haemorrhage. Monitor renal function and haematocrit in symptomatic patients. Antacids may be of some value for relief of symptoms in patients with gastrointestinal symptoms.

■ Aryl Acetic Acids

Diclofenac toxicity is relatively benign resulting in nausea, abdominal pain, drowsiness, headache, and tinnitus. Treatment is supportive following decontamination. Rare instances of anaphylaxis have also been reported.

■ Oxicams

Intoxication with piroxicam or tenoxicam results in dizziness, blurred vision, and sometimes coma. Most cases of overdose develop no effects or mild effects consisting of lethargy and gastrointestinal upset. Severe overdose may cause hypotension, coma, respiratory depression, gastrointestinal bleeding or acute renal insufficiency. Seizures can occur. Treatment is on symptomatic and supportive lines.

■ Nimesulide

Nimesulide belongs to the sulfonanilide class of NSAIDs, and has rapidly gained in popularity as an anti-inflammatory drug with analgesic-antipyretic properties. It is said to have a good safety profile, and overdoses have so far rarely been reported. However, a few rare cases document fulminant hepatic failure in patients who were taking nimesulide regularly. These patients had increasing jaundice over a 7 to 10-day period, in addition to confusion, nausea, and vomiting. Despite liver transplantation, some patients died due to multi-organ failure. Today there are emerging concerns about the real safety profile of nimesulide.

■ Cox-2 Inhibitors

The cyclo-oxygenase-2 (COX-2) inhibitors decrease the synthesis of prostaglandins through the selective inhibition of COX-2, with little or no inhibition of COX-1, resulting in anti-inflammatory and analgesic properties. Although similar to traditional non-steroidal anti-inflammatory drugs (NSAIDs), selective inhibition of COX-2 is claimed to result in fewer adverse effects traditionally associated with NSAIDs.

Examples

Celecoxib, parecoxib rofecoxib, valdecoxib and etoricoxib.

As of September 30, 2004, Merck voluntarily withdrew rofecoxib from the market after drug safety monitoring of a long-term study indicated that the drug may increase the risk of serious cardiovascular events, including myocardial infarctions and strokes among patients receiving rofecoxib, as compared to patients receiving placebo. Although the risk appeared small among individual users, the overall risk of a heart attack was twice the risk, as compared to placebo-treated patients. The Acting Commissioner of the FDA, reported that other drugs in this class would be closely monitored for similar side effects (FDA, 2004).

Several Indian doctors are also of the opinion that COX-2 inhibitors must be restricted in use. The role of fatty acids in modifying the cardiovascular hazards of COX-2 inhibitors is being investigated. Possible future (safer) alternatives to these drugs include nitric oxide (NO) NSAIDs, which have a nitric oxide moiety linked to a conventional NSAID, and show promise of a high safety profile.

Uses

Treatment of osteoarthritis and rheumatoid arthritis, management of acute pain in adults, and for treatment of primary dysmenorrhoea.

Mode of Action

The cyclo-oxygenase enzyme (prostaglandin synthase H) consists of 2 isoforms, COX-1 and COX-2. The cyclo-oxygenase-2 (COX-2) inhibitors decrease the synthesis of prostaglandin H2 through the selective inhibition of COX-2, with little or no inhibition of COX-1, resulting in anti-inflammatory and analgesic properties. Although similar to traditional non-steroidal anti-inflammatory drugs (NSAIDs), selective inhibition of COX-2 may result in fewer gastrointestinal adverse effects traditionally associated with NSAIDs.

Clinical Features

1. In various controlled trials, COX-2 inhibitors have been associated with a decreased incidence of gastrointestinal side effects and increased GI tolerability compared to traditional non-steroidal anti-inflammatory drugs. However, the COX-2 inhibitors are not without gastric side effects, and the amount of safety afforded by selective inhibition of COX-2 has been questioned. Several authors have reported cases of acute renal failure with therapeutic dosing of COX-2 inhibitors. In fact the COX-2 inhibitors are said to be as nephrotoxic as conventional NSAIDs.
2. Celecoxib is contraindicated in patients with a hypersensitivity to sulfonamides. The relative reporting rate of sulfonamide-type adverse drug reactions with celecoxib was 80% higher than with rofecoxib.
3. Overdose information with COX-2 inhibitors is limited. Significant poisonings may be expected to result in symptoms similar to those observed with typical non-steroidal anti-inflammatory agents, such as gastrointestinal upset or lethargy. Significant poisoning may result in rare effects

of hypertension, acute renal failure, respiratory depression and coma.

4. In a large, randomised study of patients receiving long-term, daily treatment for rheumatoid arthritis with either rofecoxib 50 mg/day, or naproxen 1000 mg/day (Vioxx Gastrointestinal Outcomes Research Study (VIGOR); aspirin not permitted), patients receiving rofecoxib had a relative risk of 2.38 (95% confidence interval, 1.39 to 4.0; p less than 0.001) for developing serious, thrombotic, cardiovascular adverse events (MI, ischaemic stroke, unstable angina, cardiac thrombus, sudden or unexplained death, transient ischaemic attack, resuscitated cardiac arrest) compared with patients treated with naproxen. These results may be due to prothrombotic effects of rofecoxib or antithrombotic effects of naproxen.

Treatment

1. Monitor serum electrolytes, renal function and urinalysis after significant overdose.
2. Management consists of controlling possible gastrointestinal bleeding and providing supportive care.
3. No data are available regarding the utility of extracorporeal elimination techniques to remove celecoxib or other COX-2 inhibitors from the body. However, based upon celecoxib's high degree of protein binding (97%) and large volume of distribution (400 L), dialysis is unlikely to be clinically useful.

ANTIHISTAMINES

Antihistamines or histamine antagonists are of three types:
1. H_1-receptor antagonists (classical antihistamines) lessen histamine-mediated symptoms of allergic reaction.
2. H_2-receptor antagonists reduce gastric acidity.
3. H_3-receptor antagonists have no therapeutic indication, and hence will not be discussed at all.

Examples (of drugs with antihistaminic properties)

Brompheniramine, chlorpheniramine, dexbrompheniramine, dexchlorpheniramine, dimethindene, pheniramine, pyrrobutamine, triprolidine, carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, diphenylpyraline, doxylamine, phenyltoloxamine, antazoline, methapyrilene, pyrilamine, thenyldiamine, tripelennamine, methdilazine, promethazine, trimeprazine, astemizole, azatadine, azelastine, cyproheptadine, desloratadine, diphenylpyraline, ebastine, emedastine, loratadine, mebhydrolin, olopatadine, phenindamine, terfenadine, buclizine, cetirizine, chlorcyclizine, cyclizine, hydroxyzine, meclizine, niaprazine.

Some of these have been discussed elsewhere (Consult Index).

■ H₁ Receptor Antagonists (Classical Antihistamines)

- **Highly sedating**—diphenhydramine, dimenhydrinate, doxylamine, embramine, promethazine and hydroxyzine.
- **Moderately sedating**—pheniramine, antazoline, trimeprazine, meclizine and buclizine.

- **Mildly sedating**—chlorpheniramine, methdilazine, mepyramine, dimethindene, triprolidine, mebhydroline, cyclizine and clemastine.
- **Non-sedating**—terfenadine, astemizole, cetirizine and loratidine.
- **Anti-vertiginous**—cinnarizine.

Two related groups of drugs comprising the following, will also be discussed in this section:

- **5-Hydroxytryptamine Antagonists**—cyproheptadine,* methysergide, pizotifen, ketanserin, and ondansetron.
- **Decongestants**—pseudoephedrine, ephedrine, and phenyl-propanolamine.

Uses

- Treatment of allergic reactions and allergic disorders.
- Symptomatic relief of common cold.
- Treatment of vertigo, travel sickness.
- Anti-emetic.
- Sleeping aid.

Adverse Effects (Therapeutic Doses)

- Drowsiness, tachycardia, dilated pupils, decreased bowel sounds, and urinary retention are the most common adverse effects following therapeutic administration.
- Other adverse effects may include nausea and vomiting, dystonic reactions, and hepatotoxicity.
- Pneumonitis, chest tightness, and wheezing have also been reported.
- Anticholinergic effects such as mydriasis visual disturbances, diplopia, nasal dryness and stuffiness, and mouth and throat dryness, can occur with overdose or therapeutic use.

Toxicokinetics

Antihistamines are generally well-absorbed after ingestion. Following oral administration, effects start within 15 to 30 minutes and are fully developed within one hour. Oral bioavailability is incomplete, ranging from 25 to 50%. Antihistamines are widely distributed throughout the body including the CNS, and are metabolised in the liver. Unchanged drug and metabolites are excreted in the urine.

Clinical (Toxic) Features

1. The toxicity of antihistamines is related to their anticholinergic (antimuscarinic) activity with the exception of toxic exposure to loratadine, terfenadine, and astemizole. The action of acetylcholine at muscarinic receptors is blocked.
2. Most patients will present with CNS depression and anticholinergic manifestations (except those who have ingested cetirizine, loratidine, terfenadine, or astemizole). Main symptoms include somnolence, lethargy, mydriasis, blurred vision, convulsions, hallucinations, extra-pyramidal movement disorders and psychosis.

3. Nystagmus and catatonic stupor have been described in relation to diphenhydramine overdose.
4. Other features include sinus tachycardia with hypo- or hypertension, dryness of skin and mucous membranes, cutaneous flushing, anhydrosis, hyperthermia, urinary retention, vomiting and diarrhoea/constipation.
5. Skin is usually flushed, warm and dry after overdose.
6. Hypertension is more commonly reported than hypotension. Tachycardia is also very common.
7. Rhabdomyolysis can occur. Acute renal failure has been reported in patients who developed rhabdomyolysis after overdose.
8. Terfenadine and astemizole are known to cause ventricular dysrhythmias and cardiac conduction defects. Several cases of prolonged QTc and QRS intervals and non-specific ST and T-wave changes were reported following antihistamine overdoses.
9. Children are more likely to suffer from CNS stimulation, convulsions, and ARDS. Hallucinations, anxiety, restlessness, and agitation have been reported following overdoses of carbinoxamine, cetirizine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, and tripelennamine.
10. Cetirizine, loratidine, terfenadine, and astemizole cause much less CNS depression and anticholinergic effects.

Treatment

If less than four times the maximum daily dose has been ingested by an asymptomatic patient, he may be observed at home. If symptoms are present (other than mild somnolence), or if greater than four times the maximum daily dose has been ingested, the patient should be referred to a health care facility for evaluation.

1. Monitor vital signs, and watch for development of seizures, hyperthermia, and dysrhythmias.
2. Stomach wash, activated charcoal.
3. Whole bowel irrigation with polyethylene glycol electrolyte lavage solution should be considered in patients with extremely large ingestions and those involving sustained release preparations. However, cautious assessment of bowel motility is recommended prior to and during whole bowel irrigation. Antihistamine overdose is frequently complicated by decreased bowel sounds, reduced gastrointestinal motility, or intestinal ileus.
4. Physostigmine for anticholinergic effects.
   a. Dose: 2 mg (adults); 0.5 mg (children), by slow IV push. It can be repeated at 5–10 minute intervals if there is no significant improvement.** Reversal within minutes of coma, arrhythmias, hallucinations, and other findings can be expected if the diagnosis is correct, and the patient has not suffered anoxia or other insult, or ingested a combination preparation.

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* Also has H_1 antihistamine properties.
** Watch out for cholinergic toxicity! Keep atropine ready.

    b. *Note:* Physostigmine should not be used in patients with suspected tricyclic antidepressant overdose, or an ECG suggestive of tricyclic antidepressant overdose (QRS widening, R wave in aVR). It can precipitate seizures and intractable cardiac arrest.

5. Diazepam IV for agitation/psychosis, or convulsions. If seizures persist or recur administer phenobarbitone. Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation.

6. Acute dystonic reactions to antihistamines may be treated with oral or intravenous diazepam.

7. Cooling measures for hyperthermia. Sponge patient with tepid water, and use fans to maximise evaporative heat loss. Avoid phenothiazines.

8. Sinus tachyarrhythmias rarely require treatment. In agitated patients, sedation with benzodiazepines will generally control tachycardia. If severe tachycardia results in haemodynamic compromise or ischaemia, beta blocking agents may be used as a temporising measure. A short-acting cardioselective agent such as esmolol is preferred. Use with caution in patients with asthma or COPD.

9. For mild/moderate asymptomatic hypertension, pharmacologic intervention is generally not necessary. Sedative agents such as benzodiazepines may be helpful in treating hypertension and tachycardia in agitated patients, especially if a sympathomimetic agent is involved in the poisoning. For hypertensive emergencies (severe hypertension with evidence of end organ injury (CNS, cardiac, renal), or emergent need to lower mean arterial pressure 20 to 25% within one hour), nitroprusside is preferred. Nitroglycerine and phentolamine are possible alternatives.

10. Cardiotoxicity necessitates careful cardiac monitoring. Dysrhythmias can be corrected with IV magnesium sulfate (2 to 6 gm in adults ; 25 to 50 mg/kg in children), or lignocaine. Cardioversion can be tried.

Forensic Issues

- Apart from the fact that these agents are not uncommonly involved in accidental or deliberate overdose, several investigators have evaluated performance while under the influence of therapeutic doses of antihistamines and found that these agents decreased skills. They are therefore not recommended for individuals who drive motor vehicles or operate machinery.

- Antihistamine (especially cyclizine) abuse has been reported among teenagers in the West. Hallucinations, confusion/disorientation, tachycardia, and systolic hypertension appeared to be the most commonly occurring effects.

H$_2$ RECEPTOR ANTAGONISTS

Histamine-$_2$ receptor antagonists competitively inhibit the interaction of histamine with H$_2$ receptors. They are highly selective and have little or minimal effect on H$_1$ or other receptors. H$_2$ antagonists mainly interfere with gastric secretion, although they exert inhibitory effects on cardiovascular and other systems affected by H$_2$ receptors. They do not exhibit anticholinergic properties.

Important examples of this group of drugs used widely in the treatment of peptic and duodenal ulcer, include cimetidine, ranitidine, famotidine, nizatidine and roxatidine.

Cimetidine has been implicated in causing significant drug interactions with a number of other therapeutic drugs because of its ability to inhibit cytochrome P450 mixed function oxidase activity— amitryptiline, benzodiazepines, carbamazepine, imipramine, lignocaine, nifedipine, phenytoin, quinidine, terfenadine, theophylline, verapamil and warfarin.

H$_2$ blockers can produce the following effects during therapeutic use: cardiovascular (bradycardia, hypotension, AV block and sinus arrest (especially with rapid IV administration); haematologic (agranulocytosis, pancytopenia, aplastic anaemia, and thrombocytopenia), and dermatologic (including Stevens-Johnson syndrome, toxic epidermal necrolysis). Cimetidine, ranitidine, and famotidine have been associated with drug-induced fever, which typically resolves within 48 to 72 hours after discontinuation of the drug. The most consistent adverse reaction reported with famotidine is a severe, throbbing headache, with an incidence of up to 4.7%. This has also been reported for ranitidine. There are also case reports which suggest an association between ranitidine use and hepatotoxicity. Gynaecomastia and increased prolactin levels may be seen following therapeutic doses of cimetidine.

Acute toxicity is rare with these compounds. There is one report of cimetidine overdose producing tachycardia, mydriasis, and slurred speech. Other effects reported include bradycardia, confusion, and vomiting. Bradycardia, hypotension, and cardiac arrest may occur if cimetidine is given rapidly intravenously. Cimetidine has caused complete atrioventricular block, wide-complex tachycardia, and cardiac arrest after both oral and intravenous doses. Sinus bradycardia is the most frequently reported cardiovascular effect. Dry mouth, mild drowsiness, epigastric discomfort with diarrhoea, muscle pain, headache, dizziness, delirium, psychosis, elevated liver or kidney function tests, leukopenia, and thrombocytopenia have also been reported. Visual hallucinations, CNS depression, seizures, dystonia and coma have occurred.

Chronic administration can cause confusion, restlessness, extrapyramidal effects, seizures, and peripheral neuropathies.

Treatment of acute toxicity involves administration of activated charcoal, and supportive measures. Convulsions can be controlled with benzodiazepines or barbiturates. Bradycardia usually responds to atropine. Haemodialysis may be useful. However, according to some investigators, less than 20% of a single dose is recoverable in the dialysate of patients undergoing haemodialysis.

While it appears safe to manage most accidental ingestions at home, the maximum tolerated dose has not been defined. Patients have survived ingestions of 12 to 24 grams. Ranitidine which is much more potent than cimetidine has also been very rarely implicated in overdose. There is one case report of accidental overdose in a 3 month old child producing a dystonic reaction. So far, there are no documented fatalities following an acute oral overdose of cimetidine alone or any of its related agents.

5-HYDROXYTRYPTAMINE (5-HT) ANTAGONISTS

■ Cyproheptadine

Uses

1. Anti-allergic.
2. Appetite stimulant.
3. Treatment of migraine, hyperlactinaemia, and Cushing's syndrome.

Clinical (Toxic) Features

1. Toxicity results in hallucinations, ataxia, seizures, tachycardia, mydriasis, and staggering gait. Fatalities can occur.
2. Cyproheptadine has been reported to cause toxic psychosis following overdose ingestions in children. Toxic psychosis is characterised by agitation, disorientation, and hallucinations.
3. Acute hepatitis has also occurred after therapeutic administration of cyproheptadine.
4. Weight gain has been reported as a side effect of cyproheptadine therapy. The increase in weight is directly proportional to the amount of cyproheptadine ingested.
5. Cyproheptadine has also been reported to interact with fluoxetine in two patients being treated for bulimia nervosa. The bulimia was in remission after fluoxetine therapy and reappeared after cyproheptadine was added.

Treatment

1. Stomach wash.
2. Control of seizures with diazepam or phenytoin.
3. Supportive measures.

■ Ketanserin

Uses

1. Hypertension.
2. Peripheral vascular disease, Raynaud's disease.

Clinical Features

Hypotension, bradycardia, drowsiness, vertigo, nausea.

Treatment

Symptomatic measures: stomach wash, elevation of legs, pressor amines, IV normal saline.

■ Ondansetron and Related Drugs

Ondansetron is a selective serotonin 5-HT$_3$ receptor antagonist. Newer derivatives include alosetron, dolasetron, granisetron, and tropisetron

Uses

1. Prevention of emesis during cytotoxic chemotherapy.
2. Reduction in the severity of radiation-induced emesis, and terminal cancer emesis.
3. Ondansetron and dolasetron are indicated also for the treatment or prevention of post-operative nausea and vomiting.

Clinical (Toxic) Features

1. Adverse effects of therapeutic doses include constipation or diarrhoea, headache, dry mouth, and hiccup, and asymptomatic elevation of liver enzymes. Rash and injection site reactions have occurred; ondansetron is not a vesicant. Injection site reactions include redness, swelling, burning. Burning sensations and hot flashes have been reported. There is also a report of shock with cardiac arrest and apnoea, a few minutes following ondansetron injection.
2. Toxicity has so far been rarely reported. Accidental intravenous administration of ondansetron at 10 times the normal dose has occurred with no serious adverse reaction. However, one patient who received 72 mg of ondansetron as a single intravenous dose developed sudden blindness of 2 to 3 minutes duration. Some studies mention the following manifestations in overdose : fever, rash, restlessness, diarrhoea, seizures. Mild transient elevation of serum lactate dehydrogenase has been reported. Headache, dizziness, sedation, and extrapyramidal reactions have occurred.
3. Overdose of intravenous administration of dolasetron has resulted in hypotension, dizziness and abnormal ECG intervals. Co-administration of dolasetron with anti-arrhythmic drugs may increase the chances for QT prolongation.
4. Glaxo Wellcome voluntarily withdrew alosetron from the United States market on November 28, 2000. Several deaths and many cases of serious adverse events, including ischaemic colitis and severely obstructed or ruptured bowels due to complications of severe constipation, were reported in patients taking alosetron. In June 2002, the US Food and Drug Administration has decided to allow alosetron back on to the US market under heavy restrictions for use only in women with refractory, diarrhoea-predominant irritable bowel syndrome.

Treatment

1. Supportive and symptomatic.
2. Activated charcoal is beneficial.
3. Haemodialysis/haemoperfusion is not expected to be of benefit due to the large volume of distribution (160 L for ondansetron).

■ Decongestants

Uses

- Decongestants reduce nasal congestion by stimulating the alpha-adrenergic receptor sites on vascular smooth muscles which causes the dilated arterioles to constrict and thereby reduce the blood flow to engorged nasal vascular beds.
- Pseudoephedrine is the d-isomer of ephedrine and has only 25% of the adrenergic receptor activity of ephedrine. While both ephedrine and pseudoephedrine are stimulants of alpha as well as beta adrenergic receptors, phelylpropanolamine is devoid of beta-adrenergic receptor activity. Phenylpropanolamine is a sympathomimetic agent with primarily direct alpha-adrenergic agonist effects, but also

indirect stimulation of noradrenaline release. It also has weak beta-1 agonist effects but lacks beta-2 agonist properties. It is used as an oral and topical decongestant and an anorexiant.

- Locally instilled nasal decongestants comprise imidazoline compounds such as naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, which are powerful alpha$_2$-adrenergic receptor stimulants.

Clinical (Toxic) Features

1. Toxicity usually manifests as CNS stimulation, hypertension, and tachycardia (bradycardia with phenylpropanolamine). Headache is common. Serious manifestations include seizures, dysrhythmias, cerebral haemorrhage, and psychosis.

2. Imidazoline decongestants cause CNS depression, hypotension, bradycardia, and respiratory depression. Imidazolines may also be used in combination with other sympathomimetics (e.g. phenylephrine or ephedrine), in which case, hypertension may be seen. Miosis may be present. Mydriasis has also occurred.

3. Imidazolines have presynaptic alpha-2 stimulant effects, like clonidine. Overdose or intoxication from oral ingestion or excessive topical administration can result in severe drowsiness with diaphoresis, hypotension or shock, bradycardia, respiratory depression, and coma. These manifestations may occur in both adults and children; however, young children (especially infants) are more susceptible to toxicity. Recovery may be expected in 12 to 36 hours. CNS depression ranging from sleepiness, hypotonia, and hyporeflexia to coma is common in children. Lucidity upon arousal from a depressed mental state by vigorous verbal or tactile stimuli following imidazoline overdose is an important differential diagnostic finding. Headache, nervousness, tremors, and insomnia are frequently reported.

4. Chronic overuse may result in reactive vasodilation of the nasal mucosa. Acute psychosis and hypertension have been reported with chronic abuse.

5. Signs and symptoms of phenylpropanolamine overdose comprise hypertension, mydriasis, arrhythmias, anxiety, chest pain, auditory and visual hallucinations, paranoid ideation, occasionally delirium and psychosis, seizures, haemorrhagic and non-haemorrhagic cerebral infarctions, rhabdomyolysis, urinary retention, and renal failure. In fact, phenylpropanolamine has a propensity to cause significant hypertension, and may result in reflex bradycardia, extensive myocardial ischaemia, cerebral haemorrhage, or renal toxicity. Tachycardia can also occur. Peak blood pressure effects of phenylpropanolamine occur at about 2.5 hours after PPA ingestion with individual times ranging from 0.5 to 4.5 hours.

6. Psychiatric disturbances, particularly in children, have been reported after ingestion of phenylpropanolamine including restlessness, irritability, aggressiveness, sleep disturbances, psychotic episodes, confusion, acute mania and hallucinations.

Treatment

Because drowsiness and coma may occur rapidly, emesis is not indicated even when nasal decongestants have been ingested. Emesis is contraindicated in patients with hypertension, since protracted vomiting may increase intracranial pressure. Activated charcoal and gastric lavage are also not routinely recommended, though they may be of value in phenylpropanolamine ingestions. Monitor serum CPK and renal function in severely symptomatic patients, and those with prolonged seizures or coma. A CT scan is indicated in patients with severe headache, neurologic deficits, or abnormal mental status (especially in the case of phenylpropanolamine).

1. Seizures, agitation, and psychosis should be treated with IV diazepam. Refractory cases should be managed with barbiturates or neuromuscular blocking agents. Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation. Evaluate for hypoxia, electrolyte disturbances and hypoglycaemia.

2. Severe symptomatic palpitations, tremor, and associated anxiety may respond to propranolol, particularly in patients with combination overdose of phenylpropanolamine and other sympathomimetic agents. However, propranolol may worsen hypertension in patients with single-ingredient phenylpropanolamine overdose.

3. Persistent or highly elevated hypertension should be treated with nitroprusside or nifedipine. Nitroglycerin and phentolamine are possible alternatives.

4. Hypotension can be managed with isotonic fluids, Trendelenberg position, and dopamine infusions.

5. Dysrhythmias usually respond to standard doses of lignocaine or bretylium. Propranolol can also be used. Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative for stable monomorphic ventricular tachycardia. Sinus tachycardia does not generally require treatment unless haemodynamic compromise develops. If therapy is required, a short acting, cardioselective agent such as esmolol is generally preferred. Bradycardia generally does not require treatment. Since the bradycardia is a reflex response, atropine should theoretically be avoided as it may worsen hypertension.

6. Because the imidazoline decongestants produce sedation, hypotension, and bradycardia via a central alpha-adrenoreceptor stimulation, similar to clonidine, the administration of naloxone may theoretically be beneficial.

7. Dialysis may be beneficial in phenylpropanolamine overdose.

Forensic Issues

- Caffeine was formerly available in combination with phenylpropanolamine and ephedrine in formulations designed to mimic controlled stimulants. This combination was declared irrational by the FDA (USA) in August 1982, and removed from the market. Combinations of caffeine with phenylpropanolamine are illegal regardless of labelling. In fact in 2000, the FDA has requested the

discontinuation of phenylpropanolamine from all pharmaceutical products and has issued a public health warning concerning the risk of haemorrhagic stroke associated with phenylpropanolamine use, particularly among women. The dose of PPA used for appetite suppression is greater than the dose used in cough and cold preparations. The association between use of PPA in cough and cold preparations and increased risk of haemorrhagic stroke is less clear.

- Some patients developed acute hepatitis, characterised by abdominal pain, jaundice, and elevated liver enzyme levels, within 2 to 12 weeks after beginning daily use of a dietary supplement containing 25 mg norephedrine (phenylpropanolamine), 100 mg sodium usniate, 100 mcg 3,5-diiodothyronine, 3 mg yohimbine, and 100 mg caffeine. One of the patients developed fulminant hepatic failure with cerebral oedema despite discontinuation of the product. However, with supportive care, all patients gradually recovered without sequelae.

- Phenylpropanolamine is an FDA Pregnancy Category C drug. There is a recognised association between 1st trimester use and foetal malformations (hypospadias, gastroschisis, polydactyly, cataract, pectus escavatum, congenital dislocation of the hip, etc.).

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Anti-Infectives

Anti-infective drugs are those which fight infections caused by bacteria, viruses, fungi, and protozoa, as well as infestations resulting from parasites such as helminths.

■ Antimicrobial Agents

1. **Antibacterial Drugs**
   a. Sulfonamides
   b. Quinolones
   c. Penicillins
   d. Cephalosporines
   e. Aminoglycosides
   f. Tetracycline
   g. Chloramphenicol
   h. Macrolides
   i. Antituberculous drugs
   j. Antileprotic drugs
2. **Other Antibacterial Drugs**
   a. Antiviral drugs
   b. Antiherpesvirus drugs
   c. Antiretrovirus drugs
   d. Other Antiviral drugs
3. **Antifungal Drugs**
   a. Polyene antifungal group—amphotericin B, natamycin, and nystatin.
   b. Synthetic nucleoside analogues—flucytosine
   c. Imidazoles—clotrimazole, econazole, isoconazole, itraconazole, ketoconazole, miconazole, and tioconazole.
   d. Miscellaneous—griseofulvin, undecylenic acid, benzoic and salicylic acids, propionic and caprylic acids, and potassium iodide.

■ Antiprotozoal Agents

1. **Antimalarial Drugs**
   a. Tissue Schizontocides—chloroguanide (proguanil).
   b. Blood Schizontocides—
   – Rapid acting—quinine, chloroquine, amodiaquine, quinidine, mefloquine, halofantrine, and endoperoxides (qinghaosu).
   – Slow acting—antifolate (pyrimethamine and sulfadoxine), and antibiotic compounds (tetracyclines).
   c. Gametocytocides—chloroquine, quinine, and primaquine.
   d. Sporontocides—chloroquine.

2. **Antiamoebic Drugs**
   a Luminal amoebicides—diloxanide furoate, quinidochlor, and clioquinol (iodochlorhydroxyquin).
   b. Systemic amoebicides—emetine, dehydroemetine, and chloroquine.
   c. Mixed amoebicides—5-nitroimidazoles.
   – **Other Antiprotozoal Drugs:** sodium stibogluconate.
3. **Antihelminthic Agents**
   1. Benzimidazoles
   2. Diethylcarbamazine
   3. Niclosamide
   4. Piperazine
   5. Praziquantel
   6. Pyrantel pamoate
   7. Levamisole.

The toxicity of some of the important drugs will be discussed here.

ANTIMICROBIALS

■ Antibacterials

Sulfonamides

Sulfonamide drugs are derivatives of para-aminobenzenesulfonic acid. The sulfonamides were the first ever drugs used systemically for treatment of bacterial infections. Prontosil was the earliest such compound proved to have chemotherapeutic value, the discovery of which in **1935** led to the Nobel prize being awarded (in **1938**) to **Domagk**, a German scientist. This was followed by the development of a profusion of similar compounds which were used extensively in therapeutics till the advent of penicillin in the 1940s.

Examples

Sulfadiazine, sulfacetamide, sulfamethoxazole, sulfanilamide, sulfisoxazole, sulfadoxine, sulfasalazine, sulfacytine, silver sulfadiazine, sulfaguanidine, sulfamethizole, sulfapyridine, sulfisoxazole and mafenide.

Today the only systemic sulfonamide that is still popular as an antibacterial is sulfamethoxazole which is usually combined with trimethoprim (for synergistic effect) in a ratio of 5:1, the combined product being referred to as co-trimoxazole.

Sulfacetamide is used as a topical preparation, as also silver sulfadiazine and mafenide.

Sulfadoxine is a long-acting sulfonamide which is usually used in combination with pyrimethamine in the prophylaxis and treatment of malaria (*page no 460*).

Sulfasalazine is a poorly absorbed sulfonamide which is used in the therapy of ulcerative colitis.

Uses

Micro-organisms susceptible to sulfonamides include *Streptococcus pyogenes, Strep. pneumoniae, Haemophilus influenzae, H.ducreyi, Nocardia, Actinomyces, Calymmatobacterium granulomatis,* and *Chlamydia trachomatis.*

Toxicokinetics

Except for locally acting preparations, all sulfonamides are rapidly absorbed from the GI tract. Peak plasma levels are achieved in 2 to 6 hours. Binding to plasma proteins (especially albumin) is notable, though variable, depending on the exact compound. Sulfonamides are distributed throughout all tissues and body fluids, and readily pass through placenta. Metabolism occurs by acetylation in the liver, and excretion is mainly through the urine (upto 20% as unchanged parent compound).

Mode of Action

- Sulfonamides are bacteriostatic in normal doses and bacteriocidal in extremely high concentrations.
- They act therapeutically by inhibiting para-aminobenzoic acid or para-aminoglutamic acid required for the biosynthesis of folic acid.

Adverse Effects

1. *Crystalluria*: This is particularly common with older sulfonamides (such as sulfadiazine) which are insoluble and get precipitated in acid urine, producing crystalline deposits that can cause urinary obstruction. The risk can be minimised by ensuring a minimum daily urine flow of 1200 ml (in adults), and alkalinisation. **Table 30.1** provides a list of agents that can cause crystalluria.
2. Acute haemolytic anaemia, aplastic anaemia, and agranulocytosis.
3. Hypersensitivity reactions are not infrequent and may take the form of dermal or mucous membrane manifestations such as skin rash, erythema nodosum, Stevens-Johnson

syndrome (**Fig 30.1**),* Behcet's syndrome,** and exfoliative dermatitis. Stevens-Johnson and Lyell's Syndromes are usually associated with the use of a long-acting sulfonamide, although other sulfonamides have been reported to cause these reactions. This serious reaction has been reported even with the use of ophthalmic preparations. Transient myopia, conjunctivitis, and keratitis may occur in association with hypersensitivity reaction. **Table 30.2** lists some common drug-related causes of skin allergy.

4. Headache, depression, and hallucinations have been reported with therapeutic use of sulfonamides. Tremor occurred in one patient following a fixed-dose combination of trimethoprim/sulfamethoxazole.
5. Hepatocellular, cholestatic, or mixed types of hepatitis have been reported with therapeutic doses of sulfonamides.
6. Administration of sulfonamides to premature infants leads to kernicterus.
7. A higher rate of adverse reactions are reported with AIDS patients who receive sulfonamides, which may be because of increased sensitivity to reactive sulfonamide metabolites.

Clinical (Toxic) Features

Cases of overdose involving sulfonamides have rarely been reported. Toxicity is associated with nausea, vomiting,

Fig 30.1: Stevens-Johnson syndrome – Skin of trunk

Table 30.1: Drugs Inducing Crystalluria

Overdose	Therapeutic Dose
Amoxycillin	Antihistamines
Ampicillin	Ciprofloxacin
Cephalexin	Ethylene Glycol
Methotrexate	Phenacetin
Primidone	Salicylates
Sulfonamides	Sulfonamides

Table 30.2: Drug-related Allergic Skin Reactions

Skin Reaction	Drug
Pruritis, urticaria, maculo-papular rash	Most drugs
Fixed drug eruption	Metronidazole, penicillin
Toxic epidermal necrosis	Allopurinol, barbiturates, carbamazepine, phenytoin, sulfonamides
Contact dermatitis	Antibiotics
Photodermatitis	Griseofulvin, sulfonamides

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* Also referred to as **erythema multiforme,** it is characterised by a macular eruption with dark red papules or tubercles in ring-shaped or disc-shaped patches.
** Ulceration of mouth and genitalia, iritis and joint pains.

diarrhoea, facial swelling headache, mental confusion, convulsions, and bone marrow depression. Methaemoglobinaemia can occur. Renal failure has been reported with trimethoprim. Coma and seizures were reported following a large overdose of sulfasalazine in one patient.

Diagnosis

The hepatotoxicity and nephrotoxicity associated with these pharmaceuticals may alter lab tests of liver function and kidney function including alkaline phosphatase, bilirubin, transaminase, cephalin flocculation, BUN, creatinine, urine protein, etc. Monitor the haematopoietic system in long-term treatment, even at normal doses.

1. *Bedside test*: Place 1 drop of patient's urine on wood pulp (lignin) or pulp paper (newspaper), and add to it 1 drop of concentrate HCl. Normal urine stains yellow, sulfa derivatives stain orange. The test can also be done on pulverised sulfa tablet directly.
2. Quantitation in serum can be done with HPLC.

Treatment

1. Stomach wash.
2. Haematologic evaluation.
3. Diazepam for convulsions.
4. Determine the methaemoglobin concentration, and evaluate the patient for clinical effects of methaemoglobinaemia (dyspnoea, headache, fatigue, CNS depression, tachycardia, acidosis, etc.). Treat patients with symptomatic methaemoglobinaemia with methylene blue (this usually occurs at methaemoglobin levels above 20 to 30%, but may occur at lower methaemoglobin levels in patients with anaemia, or underlying pulmonary or cardiovascular disorders). *Dose:* 1 to 2 mg/kg/dose (0.1 to 0.2 ml/kg/dose) IV over 5 minutes, as needed every 4 hours.
5. If kidney function is normal, administer 0.45% sodium chloride in D5W, and a diuretic such as furosemide 1 mg/kg to a maximum of 40 mg/dose to obtain a urine flow of 3 to 6 ml/kg/hr to increase renal excretion. For anuria or agranulocytosis, dialysis and/or isolation should be considered.
6. Supportive measures.
7. *For acute allergic reaction:* The drug should be immediately discontinued and the patient observed for the possibility of anaphylactic shock. In this situation the normal treatment for anaphylaxis is carried out with the establishment of an open airway, adrenaline, and diphenhydramine.
8. Intravenous N-acetylcysteine (24 g over 3 days) was reported to be effective in treating hepatitis cause by sulfasalazine in one reported case.
9. Haemodialysis may be beneficial.

■ Quinolones

Among the very few members of the classic quinolones used today is nalidixic acid, while there are several fluorinated 4-quinolones (fluoroquinolones) which are very popular as broad spectrum antibacterials. Examples include amifloxacin, balofloxacin, ciprofloxacin, enoxacin, enrofloxacin, fleroxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, sparfloxacin and trovafloxacin.

Fluoroquinolones are used mainly for urinary tract infections, lower respiratory tract infections and skin structure infections.

Uses

1. Nalidixic acid is used only for urinary tract infections against gram-negative organisms. It is not related to sulfonamides, antibiotics, or nitrofurans.
2. Cinoxacin is an antibacterial closely related (structurally) to nalidixic acid. It differs in that its activity is reduced only slightly in the presence of serum, has a lower incidence of side effects, less resistance development, and less CNS and neuromuscular toxicity.
3. Rosoxacin is a 4-quinolone antibacterial agent, active against *Neisseria gonorrhoea.*
4. Fluoroquinolones are effective in the treatment of infections caused by *E.coli, Salmonella, Shigella, Enterobacter, Campylobacter,* and *Neisseria.* Some of them (e.g. ciprofloxacin) are also effective against *Staphylococci, Chlamydia, Mycoplasma, Pseudomonas, Legionella, Brucella,* and *Mycobacterium.*

Toxicokinetics

These drugs are well absorbed after oral administration (except nalidixic acid), and are widely distributed in body tissues. Peak serum levels are usually obtained in 1 to 3 hours and the volume of distribution is high. Excretion may be renal (e.g. lomefloxacin, ofloxacin), or non-renal (e.g. nalidixic acid, pefloxacin). The estimated half-life of nalidixic acid is 3.2 hours in overdose, and could be as short as 85 minutes and as long as 6 to 7 hours therapeutically.

Mode of Action

These drugs inhibit DNA topoisomerase and DNA gyrase in susceptible cells.

Adverse Effects

1. While the quinolones and fluoroquinolones are generally well tolerated, the following adverse effects have been reported: skin rash, nausea, abdominal discomfort, headache, vertigo, and rarely, delirium with hallucinations. Crystalluria and nephrolithiasis have been reported with therapeutic use. Haemolytic anaemia has been reported in therapeutic and occupational exposures, primarily in patients exposed to nalidixic acid, and with erythrocyte G6PD deficiency. Arthralgias, myalgias, and polyarthritis have been reported.
2. Fluoroquinolones are not recommended for children (under 15 years) because of the risk of inducing arthralgia and joint swelling. Rare adverse effects of fluoroquinolones include rhabdomyolysis, tendonitis, tendon rupture, delirium, altered mental status, QT prolongation and ventricular arrhythmias. Tendinopathy (a rare effect)

appears to be a class-related adverse effect of fluoroquinolones and includes first and second generation drugs.

3. Disturbances of blood glucose have been reported with levofloxacin therapy, usually in diabetic patients receiving an oral hypoglycaemic agent or insulin. Both hyperglycaemia and hypoglycaemia have been reported in these patients.

4. Cerebellar dysfunction and an extrapyramidal syndrome, characterised by confusion, irregular asymmetrical involuntary movements, and slurred speech have been reported after therapeutic use of pefloxacin.

5. In June 1999, the USFDA issued a health advisory regarding the possible risk of liver toxicity associated with trovafloxacin.

6. In October 1999, the manufacturer announced the voluntary withdrawal of grepafloxacin due to severe cardiovascular events that were observed in a small number of patients. According to the company, the benefits did not outweigh the potential risks to patients based on the availability of alternative antibiotics.

7. Due to observed quinolone toxicity on growing cartilage in animals, use of all fluoroquinolone antibiotics during pregnancy is contraindicated.

Drug Interactions

Concomitant administration of theophylline or NSAIDs with fluoroquinolones is associated with a risk of CNS excitation resulting in delirium and convulsions. Drug interactions involving caffeine, cimetidine, and antacids have also been reported with these agents.

Clinical (Toxic) Features

1. Therapeutic nalidixic acid levels are thought to be 20 to 50 mcg/ml. Serious symptoms have occurred at nalidixic acid serum levels between 146 to 185 mcg/ml, but symptoms have been noted with as little as 25 mcg/ml.
   a. Acute toxicity with nalidixic acid is relatively common, resulting in vomiting, convulsions, hyperglycaemia, benign intracranial hypertension, behaviour disorders, lethargy, toxic psychosis, and metabolic acidosis.
   b. Visual disturbances (hazy vision, halos, inability to focus, colour perception changes, diplopia, visual hallucinations) and photophobia have also been reported.
   c. The CNS effects of cinoxacin are primarily those of CNS depression, with seizures not reported in animal studies. Mydriasis and musculoskeletal changes were reported.

2. Overdose with fluoroquinolones has caused dizziness, drowsiness, disorientation, slurred speech, nausea, vomiting, and tremors.
   a. Overdose with ciprofloxacin has been occasionally reported with manifestations such as nausea, arthralgias, crystalluria, convulsions, and renal and hepatic failure.
   b. Ofloxacin overdose has also been reported, and is said to cause vomiting, convulsions, vertigo, psychosis, dysgeusia and anosmia.

3. Chronic use of quinolones and fluoroquinolones can cause hypersensitivity reactions (rashes, pneumonitis, anaphylaxis), haematologic effects (thrombocytopenia, haemolytic anaemia, leukopenia), GI effects (nausea, vomiting, abdominal pain, diarrhoea), CNS effects (convulsions, psychosis), nephrotoxicity, lactic acidosis, arthropathy and myopathy.
   a. One report indicates that ciprofloxacin can cause fatal bone marrow suppression.
   b. Hepatic injury including hepatitis, acute liver failure and subfulminant hepatic failure have been reported with the use of fluoroquinolones in both short and long-term use.
   c. At therapeutic doses haematuria, crystalluria, and interstitial nephritis have been associated with ciprofloxacin therapy in humans. No permanent renal impairment has resulted from ciprofloxacin therapy.
   d. Vaginitis has been associated with the therapeutic use of ciprofloxacin.

Diagnosis

1. HPLC quantitation of the drug in plasma.
2. Urine levels can be estimated by GC/MS.
3. Blood picture: eosinophilia, neutropenia.
4. Elevated serum transaminase.
5. Haematuria.

Treatment

1. Stomach wash (within 2 hours of ingestion).
2. Activated charcoal may be helpful.
3. Treatment of seizures with benzodiazepines or phenytoin.
4. Periodic evaluation of renal function: urinalysis for crystalluria, serum creatinine, blood urea nitrogen.
5. Adequate hydration (to prevent crystalluria).
6. Supportive care including replacement of fluid and electrolytes lost during prolonged vomiting remains the cornerstone of treatment.
7. Alkaline diuresis is thought to increase the rate of excretion of the quinolone antibiotics. It has never been shown to affect outcome after overdose and is not routinely recommended.
8. Haemodialysis and haemoperfusion are not very effective owing to the high volume of distribution of most of these drugs. It may be of some benefit in fluoroquinolones (especially ciprofloxacin).
9. Steroids may help in ameliorating arthralgias and interstitial nephritis, if present.

■ Penicillins

In **1928**, **Sir Alexander Fleming** (**Fig 30.2**) made an epoch making discovery at St.Mary's Hospital, London, when he observed that a mould containing one of his cultures caused bacteria in its vicinity to perish. Since the mould belonged to the genus *penicillium*, Fleming named the antibacterial substance "penicillin". Subsequent work by **Florey**, **Chain**, and **Abraham** at Oxford university led to the production of crude penicillin which was tested on patients with dramatic

Fig 30.2: Sir Alexander Fleming

results. Since then (the 1940s), penicillin has retained its hold as an antibiotic par excellence, and is even today (in the new millennium) used widely, with newer derivatives continuing to be developed every other year.

There are four classes of penicillins:

1. **Aminopenicillins**
   a. Amoxycillin
   b. Amoxycillin/potassium clavulanate
   c. Ampicillin
   d. Ampicillin/sulbactam
   e. Bacampicillin.
2. **Extended Spectrum**
   a. Carbenicillin
   b. Mezlocillin
   c. Piperacillin
   d. Piperacillin/tazobactam sodium
   e. Ticarcillin
   f. Ticarcillin/potassium clavulanate.
3. **Natural Penicillins**
   a. Penicillin G
   b. Penicillin V.
4. **Penicillinase-resistant**
   a. Cloxacillin
   b. Dicloxacillin
   c. Methicillin
   d. Nafcillin
   e. Oxacillin.

Uses

Penicillins are effective against infections caused by *Streptococcus, Neisseria, Listeria, Proteus, E.coli, Pseudomonas, Enterobacter, Spirochaetes,* and *Klebsiella*. Some of the penicillins are also active against *Staphylococcus aureus*.

Toxicokinetics

After absorption, parenteral penicillins are generally eliminated from the blood rapidly since the half-life is low (about 30 minutes). Therefore repository preparations have been developed to prolong their presence in the blood: procaine penicillin G, and benzathine penicillin G. Probenecid which blocks the renal tubular secretion of penicillin can also be used for the same purpose. Excretion of penicillin is mainly through urine (10% by glomerular filtration, and 90% by tubular secretion). Non-renal elimination includes hepatic inactivation and to some extent excretion in the bile. The latter two means of inactivation and excretion respectively, assume the greater importance for all penicillins in patients with renal impairment.

Mode of Action

- All penicillins contain 6-aminopenicillanic acid (6-APA), which is composed of a thiazolidine ring and a beta-lactam ring as a part of their chemical structure. Addition of various chains by acylation of the 6-amino group of 6-APA yields semi-synthetic penicillins, (e.g. amoxycillin, ampicillin, carbenicillin, cloxacillin, dicloxacillin, hetacillin, methicillin, nafcillin, oxacillin and phenethicillin).
- Penicillins and cephalosporins are together referred to as beta-lactam antibiotics,* and share the same mechanism of action, i.e. they inhibit the synthesis of bacterial peptidoglycan cell wall. Since there are several micro-organisms which produce beta-lactamase, the spectrum of activity of penicillins can be broadened by beta-lactamase inhibitors such as clavulanate.
- In general, the penicillins are active against most grampositive cocci and bacilli, and some gram-negative cocci. Staphylococci produce an enzyme penicillinase which can render most of the penicillins ineffective, except the following which are resistant to hydrolysis by the enzyme — methicillin, oxacillin, cloxacillin, dicloxacillin and nafcillin.

Adverse Effects

1. **Hypersensitivity Reactions:** Penicillins are the most common agents implicated in drug allergy, (**Table 30.3**). In decreasing order of frequency, allergic reactions to penicillins include maculopapular rash, urticarial rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Stevens-Johnson syndrome, and anaphylaxis. The most common adverse effects occurring after administration of intramuscular procaine penicillin G are the Hoigne syndrome and the Jarisch-Herxheimer reaction. Hypersensitivity reactions may occur with any type of penicillin, with any dosage, and with any mode of administration, though generally the most severe reactions are observed with injection of procaine penicillin. The occurrence of a reaction on one occasion does not necessarily imply repetition on subsequent exposures, though this is very likely to happen. On the other hand, hypersensitivity reactions can appear in the absence of a previous known exposure to the drug. Dermal manifestations of allergy are most commonly seen with ampicillin.

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* Other β-lactam antibiotics include the **carbapenems** : imipenem, meropenem, and aztreonam. The last name is actually a monobactam.

Table 30.3: Non-Dermal Allergic Drug Reactions

Reaction	Presentation	Causes
Anaphylaxis	Urticaria, angioedema, rhinitis, asthma, abdominal pain, cardiovascular collapse	Penicillins, neuromuscular blocking drugs
Pulmonary	Interstitial pneumonia, asthma	Amiodarone, nitrofurantoin, NSAIDs, beta blockers
Hepatic	Acute or chronic hepatitis	Halothane, chlorpromazine, carbamazepine
Haematological	Haemolytic anaemia	Penicillins, methyldopa, mefenamic acid
	Thrombocytopenia	Furosemide, thiazides, gold
	Neutropenia	Penicillins
	Agranulocytosis	Chloramphenicol, phenylbutazone
	Aplastic anaemia	NSAIDs, sulfonamides
Renal	Interstitial nephritis, nephrotic syndrome	Cimetidine
Cardiac	Eosinophilic myocarditis	Methyldopa
Other	Serum sickness, vasculitis, lymphadenopathy	Anticonvulsants, diuretics, antibiotics, hydralazine, procainamide, penicillamine

a. **Anaphylaxis**—It has been estimated that the over-all risk for a serious anaphylactic reaction with penicillins is 2/100,000 (or 0.002%). The reaction results from the local and systemic release of endogenous vasoactive substances including leukotrienes C_4 and D_4, histamine, eosinophilic chemotactic factor, and vasoactive substances such as bradykinin, kallikrein, prostaglandin D_2, and platelet-activating factor.
  – Grades of anaphylaxis:
    I. Local cutaneous reaction (> 15 cm).
    II. Generalised urticaria.
    III. Asthma, angioedema
    IV. *Airway type*—asthma, swelling of tongue, dysphagia, laryngeal oedema. *Cardiovascular type*—hypotension, cardiovascular collapse.
  – Treatment: (for Grade II, III, or IV)
    - Adrenaline: 0.01 ml / kg (upto 0.5 ml) of 1: 1000 solution, subcutaneously, every 15 minutes.
    - Oxygen: 40 to 100 %.
    - Beta$_2$-adrenergic stimulants: preferably by nebulisation (0.3 to 0.5 ml in 2.5 ml of 0.9% NaCl).
    - Corticosteroids: preferably methylprednisolone 125 to 250 mg, 6th hourly, for 2 to 4 doses.
    - Antihistamines: preferably diphenhydramine (1 mg/kg).
    - Aminophylline: 6 mg/kg , IV infusion.
    - IV fluids: 10 to 30 ml/kg (titrated to effect).
    - Activated charcoal: 1 gm/kg (if reaction has occurred to oral penicillin).
b. **Jarisch-Herxheimer Reaction**—Abut 70 to 90% of patients with secondary syphilis suffer this self-limited reaction when penicillin is administered. It begins several hours after injection of the first dose and is characterised by fever, chills, headache, myalgia, and arthralgia. Cutaneous syphilitic lesions may become more prominent. The pathogenesis of this reaction is believed to be an acute antigen response to lysed bacteria. Treatment involves administration of aspirin. Penicillin therapy should be continued as the reaction does not recur after the first dose.
c. **Hoigne Syndrome**—It is invariably associated with injection of procaine penicillin and is more common in males. It has also occurred with oral administration of amoxycillin. Main features include anxiety, fear, illusions, hallucinations, tachycardia, hypertension, vertigo, tinnitus, abnormal taste, neuromuscular twitching, confusion, agitation, depression, and seizures. The cause is unknown, though it is generally attributed to a sudden increase in free procaine levels in the CNS, and also postulated by some to be related to microemboli formed from penicillin G procaine crystals. Onset is immediate, and may last for up to 60 minutes.

2. Other Adverse Effects:
  a. Orally administered penicillins can alter the composition of microflora by eliminating sensitive micro-organisms, which can result in superinfection by resistant microbes. Occasionally, **pseudomembranous colitis** may develop due to overgrowth and production of toxin by *Clostridium difficile*. There is formation of a pseudo-membrane on the mucosa of the colon (**Fig 30.3**) with diarrhoea (mixed with blood and mucus), abdominal cramps, fever and leucocytosis. Treatment involves immediate cessation of penicillin and administration of vancomycin or metronidazole.
  b. Diarrhoea, nausea, vomiting, and abdominal pain often occur.
  c. Cardiac conduction defects have occurred following rapid IV administration of potassium penicillin G. Cardiorespiratory arrest may follow procaine penicillin G administration.
  d. Drowsiness, myoclonus, seizures, and coma may occur following IV administration of large doses of penicillins. Neurological side effects may be more common

Fig 30.3: Pseudomembranous colitis

in patients with impaired renal function. Seizures may occur in very-low-birth-weight (VLBW) neonates (neonates weighing less than 750 grams) who receive ampicillin at doses of 25 to 100 mg/kg/dose every 8 to 12 hours. Other factors in these patients that may contribute to the development of seizures include renal impairment and increased permeability of the blood-brain barrier.

e. Hepatotoxicity, including elevated liver enzymes, cholestatic hepatitis, granulomatous hepatitis, and acute vanishing bile duct syndrome, may occur.

f. Renal failure, crystalluria, interstitial nephritis, and haemorrhagic cystitis have been reported following the use of penicillin derivatives.

g. Electrolyte imbalances may occur when large doses of potassium or sodium penicillin G or carbenicillin disodium are administered intravenously.

h. Thrombocytopenia, neutropenia, and agranulocytosis have been reported following administration of the semi-synthetic penicillins.

i. Dermatologic reactions vary greatly in severity, character, and distribution. Amoxycillin and ampicillin appear to cause skin rashes more frequently than other penicillins.

Clinical (Toxic) Features

1. Overdose with penicillins is rare and almost never life-threatening. Manifestations include nausea, vomiting, diarrhoea, and occasionally electrolyte abnormalities.

2. Large intravenous doses of penicillins can produce convulsions due to interaction with picrotoxin-binding site on gamma amino butyric acid (GABA), which results in the inhibition of GABA from binding to its receptor. This causes a lack of inhibitory tone giving rise to seizures. Treatment involves the use of benzodiazepines and barbiturates.

3. Intrathecal injection of penicillin G may produce arachnoiditis or severe encephalopathy. Intravenous administration often results in phlebitis and thrombophlebitis.

4. Accidental injection of penicillin into sciatic nerve during deep intramuscular administration of the drug in the region of the buttock can cause severe pain and nerve dysfunction which can persist for weeks.

5. Overdoses of oxacillin and nafcillin have been reported to result in hepatitis.

6. Chronic toxicity with penicillins can manifest as bone marrow suppression, interstitial nephritis, vasculitis, and cholestatic hepatitis. Methicillin in the long run may induce corneal damage. Ampicillin has been reported to aggravate weakness in myasthenia gravis.

Treatment

1. Urinalysis should be monitored following very large doses of penicillins, or when such drugs are used in large doses for prolonged periods of time.

2. There are limited data regarding the acutely toxic amount of penicillin. The minimum oral amount reported in the literature to produce systemic effects is 11 times the maximum daily therapeutic dose (574 mg/kg). Toxicity is unlikely with doses of 250 mg/kg or less. Patients without a history of penicillin allergy and with ingestion of small to moderate doses of penicillin can almost always be managed at home. Patients ingesting large doses of penicillin (e.g. over 15 times the usual single therapeutic dose or over 250 mg/kg of amoxycillin) should probably receive gastric decontamination and should definitely be evaluated in a hospital.

3. Gastric decontamination is rarely indicated but may be considered following an extremely large overdose of ingested penicillin.

4. Manage seizures in the usual manner with benzodiazepines or barbiturates. CSF penicillin levels greater than 8 units (5 mcg/ml) could result in seizures.

5. Cardiac arrhythmias should be treated with standard antiarrhythmic drugs, if necessary.

6. Haemodialysis: In severe overdosage where increased absorption may have occurred and there exists severe renal impairment, dialysis may be considered for correction of acidosis and electrolytes, rather than for removal of penicillins. Combined charcoal haemoperfusion and haemodialysis has been effective in removal of penicillin in a few cases.

■ Cephalosporines

Cephalosporines made their debut in **1948** when **Brotzu** isolated an antibacterial agent from the cultures of a fungus *Cephalosporium acremonium*. Since then, there has been a gradual growing of interest in the production of these drugs, culminating over the last decade in frenetic activity on the part of scientists to develop newer cephalosporines, so much so that a systematic classification has become necessary.

Classification

1. *First generation cephalosporines*—cephalothin, cefazolin, cephalexin, cephapirin, cephradine, and cefadroxil. These drugs are active mainly against gram-positive bacteria, and are less effective against gram-negative micro-organisms.

2. *Second generation cephalosporines*—cefamandole, cefoxitin, cefaclor, cefuroxime, cefuroxime axetil, loracarbef, cefonicid, cefmetazole, cefotiam, cefprozil, and cefotetan. These drugs have better efficacy against gram-negative bacteria.

3. *Third generation cephalosporines*—cefotaxime, cefpodoxime proxetil, ceftizoxime, ceftriaxone, cefoperazone, cefdinir, cefditoren, cefixime, ceftibuten, and ceftazidime. These drugs are highly active against the *Enterobacteriaceae* (including β-lactamase producing strains), but are less effective against gram-positive cocci as compared to the first generation cephalosporines.

4. *Fourth generation cephalosporines*—cefepime is the prominent example of this group, which is very useful in the treatment of infections due to aerobic gram-negative bacilli resistant to third generation cephalosporines.

5. *Oxacephalosporines*—flomoxef, latamoxef.

Toxicokinetics

The following cephalosporines are well absorbed orally: cephalexin, cefaclor, cefadroxil, loracarbef, cefprozil, cefixime, cefpodoxime proxetil, ceftibuten, and cefuroxime axetil. The remaining cephalosporines are administered intramuscularly or intravenously.

Excretion is mainly renal. Many cephalosporines are concentrated in the bile and can also penetrate into CSF easily.

Mode of Action

Cephalosporines inhibit bacterial cell wall synthesis in the same way as penicillins (*vide supra*).

Adverse Effects

- The most important adverse effects arise out of hypersensitivity in the same manner as penicillins. The similarity is because of the shared beta-lactam structure of the two groups of antibiotics, which also accounts for the cross-reactivity that is not uncommonly observed. Manifestations of allergy include skin rashes, bronchospasm, fever, and anaphylaxis. However, the incidence of anaphylactic reactions to cephalosporines is said to be less than 0.02%, (0.04% in those patients with previous penicillin allergy).
- Seizures have been reported following therapeutic administration.
- Vomiting, diarrhoea and pancreatitis may occur.
- Pseudocholelithiasis may follow intravenous administration of ceftriaxone.
- A disulfiram-like reaction can develop following the use of cefoperazone, moxalactam, cefotetan, or cefamandole followed by ethanol ingestion.
- Blurred vision, deviation of the eyes, rapid eye movements, and bilateral mydriasis have been reported in patients who developed CNS toxicity (seizures, encephalopathy) following parenteral administration of cefazolin and ceftazidime.
- Rare effects reported with cephalosporin administration include renal failure, interstitial nephritis, nephrolithiasis and crystalluria.
- Coagulopathies may occur following IV moxalactam, cefazolin, cefoperazone, cefmetazole and cefamandole.
- Leukopenia, thrombocytopenia, anaemia, and agranulocytosis may occur following cephalosporin therapy.

- Skin rashes may occur with cephalosporin administration.
- Stevens-Johnson syndrome has been reported with cephalexin ingestion, and toxic epidermal necrolysis occurred following cefazolin administration.

Clinical (Toxic) Features

1. Acute overdose produces manifestations similar to those seen with penicillin, including the possibility of convulsions. Treatment is supportive.

2. Cephalosporines containing an *n-methylthiotetrazole* (nMTT) side chain, such as cefamandole, cefazolin, cefmetazole, cefotetan, cefperazone, and moxalactam, can dissociate in the body after administration and release free nMTT which results in acute toxicity. Further, nMTT inhibits the enzyme aldehyde dehydrogenase (in the same manner as disulfiram), and in conjunction with alcohol can cause a disulfiram-like reaction. It is also postulated that the nMTT side chain is responsible for producing hypoprothrombinaemia, since it depletes vitamin K-dependant clotting factors by inhibition of vitamin K epoxide reductase. If this occurs, fresh frozen plasma and vitamin K_1 should be administered.

3. Chronic effects of cephalosporine therapy include serum sickness, interstitial nephritis, hepatitis, and immune-mediated haemolytic crisis.

Treatment

1. Urinalysis should be monitored following very large doses of cephalosporines, or when such drugs are used in large doses for prolonged periods of time.

2. Activated charcoal may be indicated in patients with underlying renal insufficiency, following an extremely large overdose (greater than 15 times the usual single therapeutic dose).

3. Treament of allergic reactions in the usual manner.

4. The coagulopathies associated with intravenous cephalosporine therapy can be corrected with the administration of exogenous vitamin K and fresh frozen plasma.

5. Supportive measures.

6. In severe overdosage where increased absorption may have occurred and there exists severe renal impairment, dialysis may be considered.

■ Aminoglycosides

Aminoglycoside antibiotics contain amino sugars linked to an aminocyclitol ring by glycosidic bonds.

Examples*

Amikacin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paramomycin, streptomycin, , and trospectomycin.

The first of these compounds to be discovered was streptomycin which was isolated from the actinomycete *Streptomyces griseus*, in **1943** by **Schatz, Bugie,** and **Waksman**. This was soon followed by the isolation of other members of the group in rapid succession.

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* The difference in spelling (-micin) of amikacin, gentamicin, and netilmicin, as compared to the other aminoglycosides (-mycin) is because the former are all derived from **Micromonospora,** while the latter are obtained from **Streptomyces.**

Uses

These antibiotics are mainly active against infections caused by aerobic, gram-negative bacilli— *Citrobacter, Enterobacter, Escherichia, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia,* and *Staphylococcus*. Kanamycin and streptomycin have a more limited spectrum compared to the other aminoglycosides.

In conjunction with penicillin or vancomycin, some of these agents (streptomycin, gentamicin), are also active against strains of *Enterococci* and *Streptococci*. Streptomycin is sometimes used for the treatment of drug-resistant tuberculosis.

Toxicokinetics

The aminoglycosides being highly polar cations are poorly absorbed from the GI tract and hence are administered parenterally (IM). Peak plasma concentrations are achieved in 30 to 90 minutes. Binding to plasma albumin is negligible (except in the case of streptomycin), and the apparent volume of distribution is 25% of body weight. Concentrations of these drugs in tissues and secretions is generally low. However they can cross the placental barrier, and streptomycin in particular is known to produce toxic effects (hearing loss) in children born to mothers who have received the drug during pregnancy.

Excretion is mainly through the urine by glomerular filtration. In the presence of renal impairment, these drugs must be used with great caution owing to the risk of accumulation and resultant toxicity.

Mode of Action

- Aminoglycosides are bactericidal antibiotics which inhibit protein synthesis by interfering with the 30s ribosomal subunit of RNA.
- In toxic doses, these drugs produce renal damage by binding to phospholipids on brush border membranes in the proximal renal tubules resulting in cellular dysfunction. Risk factors include genetic predisposition, advanced age, renal disease, female sex, previous aminoglycoside therapy, liver dysfunction, large doses, long duration of therapy, frequent doses, concomitant administration of other nephrotoxic drugs and presence of shock.
- Ototoxicity of aminoglycosides is related to high cochlear and vestibular trough concentrations resulting in damage to sensory hair cells.
- Rare instances of neuromuscular blockade produced by aminoglycosides is due to inhibition of acetylcholine release from presynaptic nerve terminals, as well as blockade of acetylcholine receptors.

Adverse Effects and Clinical (Toxic) Features

1. *Ototoxicity*—
   a. Administration of any of the aminoglycosides can cause both vestibular and auditory dysfunction which may be irreversible, owing to destruction of vestibular and cochlear sensory cells.
   b. Symptoms include tinnitus (high pitched and continuous), deafness, and dysequilibrium characterised by ataxic gait, stumbling, and loss of balance on turning. Onset may be sudden and severe, but is usually progressive over 6 to 10 months. Vertigo is a rare symptom.
   c. With neomycin, ototoxicity is characterised by a latency of 2 to 6 weeks after onset of therapy, hearing loss often being noticed days to weeks after the drug has been discontinued.
   d. Ototoxicity after acute single overdose is not well documented.
   e. Streptomycin is predominantly vestibulotoxic; kanamycin, neomycin, and amikacin are predominantly cochleotoxic; gentamicin and tobramycin are both vestibulo- and cochleotoxic.
   f. Ototoxicity (deafness and vertigo) has been reported following use of topical neomycin and otic solutions containing gentamicin.
2. *Nephrotoxicity*—
   a. About 8 to 26 % of patients receiving any aminoglycoside for several days develop nephrotoxicity, which is fortunately usually reversible. Typically, acute tubular necrosis sets in after 7 to 10 days of therapy. Recovery on stoppage occurs over 4 to 6 weeks.
   b. The following rank order of decreasing toxicity is generally accepted for aminoglycosides: neomycin > gentamicin > tobramycin > amikacin > netilmicin > streptomycin.
3. *Neuromuscular blockade*—
   a. All aminoglycosides are capable (rarely) of causing neuromuscular blockade with consequent paralysis. The order of decreasing potency for blockade is neomycin > kanamycin > amikacin > gentamicin > tobramycin.
   b. Risk factors for inducing neuromuscular blockade include concurrent use of curare-like drugs, succinylcholine, and magnesium, as well as presence of botulinum toxin and disease entities such as myasthenia gravis.
4. *Other effects*—
   a. Optic nerve toxicity has been reported with streptomycin, as also peripheral neuritis and paraesthesia. Intramuscular injections involving this drug are extremely painful.
   b. Less common adverse effects associated with chronic aminoglycoside use include electrolyte abnormalities, allergic reactions, hepatotoxicity, anaemia, granulocytopenia, thrombocytopenia, eosinophilia, reproductive dysfunction and toxic psychosis.
   c. Acute ischaemic retinopathy has occurred from intraocular administration of gentamicin.
   d. Hypersensitivity reactions have been reported most frequently with neomycin, including skin rashes, eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis and anaphylaxis.

Diagnosis

1. Ototoxicity can be detected in the early stages by full-tone audiometric testing which is capable of revealing high-frequency hearing loss. Vestibular dysfunction can be diagnosed at its inception by electronystagmography.

2. Monitor serum aminoglycoside concentration.
   a. *Gentamicin:* Toxicity (primarily nephrotoxicity) may occur with persistent peak serum levels more than 12 mcg/ml, and/or trough levels more than 2 mcg/ml.
   b. *Amikacin:* Toxicity (primarily nephrotoxicity) may occur with persistent peak serum levels more than 20 to 35 mcg/ml, and trough levels more than 8 mcg/ml.
   c. *Netilmicin:* Toxicity (primarily nephrotoxicity) is associated with persistent peak serum levels greater than 16 mcg/ml, and trough levels greater than 4 mcg/ml.
   d. *Tobramycin:* Toxicity (primarily nephrotoxicity) is associated with persistent peak serum levels greater than 10 to 15 mcg/ml, and trough levels greater than 2 to 4 mcg/ml.
   e. *Streptomycin:* Toxicity is associated with peak serum levels greater than 50 mcg/ml.
   f. The amounts of neomycin present in topical ointments, otic and ophthalmic preparations (3.5 to 5 mg/gm or ml) do not present a hazard even if the entire package contents were orally ingested (10 to 30 gm or ml).
3. Monitor renal function carefully. Laboratory abnormalities indicative of nephrotoxicity include proteinuria, granular casts, elevated urinary sodium, and increased fractional excretion of sodium. Elevation of serum creatinine occurs in the later stages.

Treatment

1. Acute overdoses of aminoglycoside antibiotics are almost invariably the result of dosage errors (especially in infants). Fortunately these overdoses are rarely life-threatening, and most patients can be successfully managed with supportive measures. Charcoal administration can be considered if the patient is seen within a short time following ingestion.
2. Maintain good urine output (3 to 6 ml/kg/hr) with intravenous fluids. This appears to be the treatment of choice for a single acute overdose of aminoglycosides.
3. Some cases of renal toxicity induced by aminoglycosides can be tackled by the administration of ticarcillin or carbenicillin which forms a complex with the aminoglycoside thereby inactivating its effects.
4. Peritoneal or haemodialysis is effective in eliminating aminoglycosides from the blood, the latter being preferable. In patients with compromised renal function and toxic levels of gentamicin or tobramycin, administration of ticarcillin to bind the aminoglycoside may be as effective as hemodialysis. The complex has been shown to be excreted renally and decreases the aminoglycoside half-life to 12 hours in renal failure patients. *Dose* - 2 to 5 grams intravenously every 4 to 6 hours until serum aminoglycoside levels are less than 0.2 mcg/ml.
5. In a guinea pig model of gentamicin ototoxicity, concurrent treatment with vitamin E 100 mg/kg day IM slowed the progression of high frequency hearing loss, and reduced the loss of outer hair cells in the cochlea of animals treated with intramuscular gentamicin 100 mg/kg daily for 14 days. It was postulated that vitamin E interfered with gentamicin-induced free radical formation.
6. Mild to moderate allergic reactions may be treated with antihistamines with or without inhaled beta agonists, corticosteroids or adrenaline. Treatment of severe anaphylaxis also includes oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring, and IV fluids.

■ Tetracyclines

Tetracyclines are generally considered to be "broad spectrum" antibiotics owing to their efficacy against a wide range of micro-organisms. They are close congeners of polycyclic naphthacenecarboxamide.

Examples

Chlortetracycline and oxytetracycline are obtained from *Streptomyces aureofaciens* and *S. rimosus* respectively. Demeclocycline is the product of a mutant strain of *S.aurofaciens*, while tetracycline, methacycline, doxycycline, and minocycline are all semisynthetic derivatives.

Uses

The tetracyclines have a wide range of antimicrobial activity against aerobic and anaerobic gram-positive and gram-negative bacteria, as well as several microorganisms which are generally resistant to antibiotics, such as *Rickettsia, Coxiella burnetti, Mycoplasma pneumoniae, Chlamydia, Legionella,* atypical mycobacteria, and *Plasmodium* species.

Toxicokinetics

Most of the tetracyclines are absorbed from the GI tract. The percentage of an oral dose that is absorbed is lowest for chlortetracycline (30%), followed by oxytetracycline, demeclocycline (95%), and highest for minocycline (100%). Absorption is adversely affected by concurrent ingestion of milk and milk products, iron salts, and several types of antacids.

Following absorption, tetracyclines are distributed widely in tissues and secretions. There is a tendency to accumulate in the reticuloendothelial cells of liver, spleen, and bone marrow, and in bone, dentine, and enamel (of unerupted teeth).* They cross the placenta and enter the foetal circulation and amniotic fluid.

The primary route of excretion is the kidney, though a small quantity is excreted by way of bile into the intestines from where part of it enters the enterohepatic cycle. Doxycycline is not eliminated via the same pathways as other tetracyclines, and does not accumulate significantly in patients with renal failure, making it the safest of the group.

Mode of Action

Tetracyclines are bacteriostatic agents and act by inhibiting protein synthesis, the 30s ribosomal subunit, binding to aminoacyl transfer RNA, and binding to the 50s ribosomal unit.

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* Children administered tetracycline develop permanent brown discolouration of teeth due to formation of a tetracycline-calcium-orthophosphate complex **(Fig 30.4)**. The same applies to children of mothers who had received the drug during pregnancy. The period of greatest danger is from mid-pregnancy to 6 months of postnatal period for deciduous teeth, and from a few months to 5 to 8 years of age for permanent teeth. Enamel hypoplasia is common in permanent teeth. Tetracyclines also get deposited in the skeleton during gestation and childhood resulting in depression of bone growth.

Fig 30.4: Tetracycline stained teeth

Adverse and Clinical (Toxic) Features

1. Acute overdose of tetracyclines is generally not attended with serious toxicity. Gastro-intestinal distress is common, manifested by nausea, vomiting, epigastric pain, and occasionally diarrhoea. Rarely, there is development of oesophagitis, oesophageal ulcers, and even pancreatitis.

2. Pancreatitis, characterised by moderate to severe epigastric pain with elevated serum amylase and lipase levels, has been reported with minocycline therapy.

3. Hepatic damage results from large doses, and is characterised by jaundice, azotaemia, acidosis, and shock. Autoimmune hepatitis and fulminant hepatic failure, requiring liver transplantation, have been associated with long-term minocycline therapy.

4. Renal toxicity has also been reported. Ingestion of outdated or degraded tetracycline can result in the development of a variant of *Fanconi syndrome* characterised by vomiting, polydipsia, polyuria, proteinuria, acidosis, glycosuria, and aminoaciduria.

5. Patients administered tetracyclines (especially doxycycline and demeclocycline) should avoid exposure to sunlight, or else photosensitivity reactions may occur in the skin, as also onycholysis and pigmentation of nails. Skin hyperpigmentation consisting of either focal blue-grey pigmentation at sites of prior cutaneous inflammation or normal skin of the legs, or diffuse dark-grey discolouration of sun-exposed areas has been reported.

6. Tetracyclines should not be administered to pregnant women and also to children under the age of 8 years (see footnote on *page no 439*). Hepatotoxicity, pancreatitis, and renal failure may occur in pregnant women following ingestion of tetracyclines during pregnancy. Maternal ingestion of tetracyclines during pregnancy, particularly during the first trimester, may cause various congenital defects, including cardiovascular defects, oral clefts, polydactyly, hypospadias, limb hypoplasias and inguinal hernias.

7. Intravenous administration of tetracyclines can result in severe thrombophlebitis.

8. Long-term therapy with tetracyclines is associated with leukocytosis, atypical lymphocytes, toxic granulation of granulocytes and thrombocytopenic purpura.

9. Administration of tetracyclines to infants and elderly patients can cause increased intracranial pressure (*pseudotumour cerebri*).

10. Hypersensitivity reactions including skin rash, angioedema and anaphylaxis have been reported in sensitive individuals.

11. Minocycline sometimes produces vestibular toxicity manifested by vertigo, ataxia, nausea, and vomiting. A lupus-like syndrome, consisting of fevers, fatigue, and diffuse arthralgias, has also been reported during long-term minocycline therapy for treatment of acne.

12. Demeclocycline has been reported to cause nephrogenic diabetes insipidus.

Treatment

1. Withdrawal of the drug and institution of supportive measures.

2. Renal and hepatic monitoring steps should be instituted when prolonged use of large doses of tetracyclines has occurred.

3. Severe toxicity is unlikely after ingestion. Gastrointestinal decontamination is generally not required. Antacids may be useful in treating gastric irritation.

■ Chloramphenicol

Chloramphenicol is a derivative of dichloroacetic acid, and was first isolated from *Streptomyces venezuelae* in **1947**.

Uses

Though chloramphenicol is one of the "broad spectrum" antibiotics, its serious adverse effects restricts its use only for certain cases of meningitis, typhus, and typhoid fever, as well as Rocky Mountain spotted fever.

Toxicokinetics

Chloramphenicol is rapidly absorbed orally, and peak plasma concentrations are achieved within 3 hours. It can also be administered parenterally (usually IV) for serious infections, in the form of a succinate preparation. Chloramphenicol is well distributed in tissues and body fluids (including CSF), and crosses the placental barrier readily. Reported values (Vd) range from 0.57 L/kg to 1.55 L/kg. The major route of elimination is by hepatic metabolism to the inactive glucuronide which is excreted in the urine by filtration and secretion. About 50% of chloramphenicol is bound to plasma proteins.

Mode of Action

1. Chloramphenicol inhibits the 50s ribosomal subunit and protein synthesis in rapidly proliferating cells. Inhibition of mitochondrial enzymes, oxidative phosphorylation, and mitochondrial biogenesis, all contribute to the development of metabolic acidosis produced by this drug in overdose.

2. Bone marrow suppression results from ultrastructural microsomal changes induced by chloramphenicol, resulting in the decreased production of essential proteins and enzymes. Inhibition of DNA synthesis in marrow stem cells by the p-nitrosulfathiazole group of this antibiotic is

said to be responsible for the potentially fatal induction of aplastic anaemia.

Adverse Effects

- Skin rashes, fever, and angioedema are uncommonly reported hypersensitivity reactions to chloramphenicol.
- Jarisch-Herxheimer reaction has been observed during therapy for syphilis, brucellosis, and typhoid fever.
- Serious adverse reactions to chloramphenicol (usually but not always dose-related) include anaemia, leukopenia, and thrombocytopenia. Aplastic anaemia is not dose-related, but is instead an idiosyncratic reaction. The risk while being low (approximately 1 in 30,000), is potentially fatal if it does materialise. Even if recovery occurs, there is a subsequent increased predisposition to acute leukaemia.

Clinical (Toxic) Features

1. Oral administration of large doses causes nausea, vomiting, unpleasant taste, and diarrhoea. Glossitis, stomatitis, or enterocolitis may occur.
2. Blurring of vision, optic neuritis, and digital paraesthesias.
3. Metabolic acidosis (an early sign, more common with chronic toxicity).
4. Hypotension, hypothermia, sudden cardiovascular collapse.
5. **Chronic toxicity:** Anaemia and leukopenia (reversible after discontinuation), metabolic acidosis, optic neuritis, and peripheral neuritis.
6. Overdose in neonates can result in *Grey baby syndrome*,* characterised by vomiting, refusal to feed, tachypnoea, abdominal distension, cyanosis, and loose, greenish stools. Within 24 hours the baby becomes flaccid, hypothermic, and turns ashen-grey in colour. Mortality is around 40%. Autopsy has shown both left and right ventricular dilation. Serum concentrations associated with this syndrome usually exceed 50 mcg/ml. A reduced dose (25 mg/kg) should be used in this age group (premature infants and newborns), and serum levels should not exceed 10 mcg/ml. Two factors are responsible for this syndrome: a) deficiency of glucuronyl transferase in the neonate, and b) inadequate renal excretion of unconjugated drug. Grey baby syndrome has also been observed in toddlers 6 to 25 months of age.
7. **Idiosyncratic reaction:** Aplastic anaemia, which does not appear to be dose-related (incidence 1:30,000 to 1:50,000), and may occur weeks or months after therapy has been discontinued; it has occurred after IV, oral, and ocular routes. It carries high mortality (>50% mortality).
8. Hypersensitivity reactions are rare, but contact dermatitis, rashes, drug fever, angioedema, urticaria, and occasional cases of anaphylaxis have been reported.
9. **Carcinogenecity:** A population based case-control interview study in Shanghai suggests an 11-fold increased risk of acute lymphocytic leukaemia (ALL) and acute non-lymphocytic leukaemia (ANLL) following the use of chloramphenicol.

Treatment

Obtain plasma chloramphenicol levels (therapeutic levels vary from 10 to 25 mcg/ml), baseline CBC, and arterial blood gas (to monitor for metabolic acidosis). Monitoring of leukocyte and reticulocyte counts during therapy is advisable. Following large overdoses (doses exceeding 100 mg/kg/dose, or single doses of 10 gm or more), observation in a medical facility for a minimum of 12 hours after the event is necessary, since manifestations may begin only 5 to 12 hours following ingestion.

1. Gastric lavage may be helpful for recent ingestions. Activated charcoal can be administered subsequently (1 gm/kg).
2. For optic neuritis, with or without peripheral neuritis: administration of vitamins B_6 and B_{12} has been recommended. Doses used by these authors were 500 mg orally twice a day of vitamin B_6, and 0.5 mg orally once a day of vitamin B_{12}.
3. Chloramphenicol is not well dialyzed. With a half-life of 1.6 to 4 hours in the setting of normal hepatic and renal function, it is unlikely that dialysis would remove the drug sufficiently and rapidly to prevent toxicity. However, in patients with impaired renal function, clearance is moderately increased by haemodialysis.
4. Charcoal haemoperfusion is said to be beneficial.
5. Exchange transfusion has been used successfully in neonates.

■ Macrolides

Macrolide antibiotics possess a many-membered lactone ring to which are attached one or more deoxy sugars.

Examples

Azithromycin, clarithromycin, dirithromycin, erythromycin, miocamycin, roxithromycin and troleandomycin.

Uses

Erythromycin was first isolated in **1952** from *Streptomyces erythreus*. The other members of the group are semisynthetic derivatives.

The macrolides are effective mainly against aerobic gram-positive cocci and bacilli, and to a lesser extent, against gram-negative organisms such as *H. Influenzae, N. meningitidis, N. gonorrhoeae, Campylobacter species, Pateurella multocida, Mycoplasma pneumoniae,* and *Legionella pneumophila*. The macrolide antibiotics act as bacteriostatic agents at low concentrations, and (less frequently) bactericidal agents at high concentrations.

Toxicokinetics

Though erythromycin base is adequately absorbed on ingestion, it is inactivated by gastric acids, and so it is usually administered as enteric-coated tablets or as capsules containing enteric-coated pellets. Esters of erythromycin (estolate, stearate, and ethyl succinate) improve acid stability and facilitate better

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* **Grey syndrome** with similar manifestations can occur rarely in adults.

absorption. Semi-synthetic macrolides are rapidly absorbed from the GI tract, though food can considerably delay absorption.

The macrolides are widely distributed in all tissues and body fluids (except brain and CSF), and can also cross the placental barrier easily. Excretion is renal as well non-renal.

Mode of Action

Macrolides are bacteriostatic agents which inhibit protein synthesis by binding reversibly to 50s ribosomal subunits of sensitive micro-organisms.

Adverse and Clinical (Toxic) Features

1. In general, macrolide antibiotics are considered to have fewer, less severe toxic effects than most other antimicrobial agents.
   a. Allergic reactions are uncommon (fever, eosinophilia, and skin eruptions).
   b. The most striking side-effect, especially associated with erytrhromycin estolate is cholestatic hepatitis, which is probably immune-mediated. Cholestasis is characterised by elevated liver enzymes, fever, abdominal pain, and jaundice. Patients without previous exposure to erythromycin generally develop symptoms after an average of 16 days of therapy. Patients who have received the drug previously may develop symptoms within less than 24 hours, and occasionally after a single dose. Discontinuation of the drug usually results in resolution of hepatotoxic effects.
   c. Other effects include gastrointestinal irritation, ototoxicity, and thrombophlebitis (after IV administration). Candidal oesophagitis and gingival hyperplasia are uncommon adverse effects of treatment with various macrolides. Large doses of macrolides are also associated with (reversible) high-frequency sensorineural hearing loss.
   d. Rare instances of acute pancreatitis have been reported.
   e. Exacerbation of myasthenia gravis may occur infrequently following erythromycin administration.
   f. Interstitial nephritis and glomerulonephritis have been reported with the administration of erythromycin, but are uncommon.
   g. Rarely, erythromycin has been reported to cause cardiac arrhythmias (QT prolongation and torsades de pointes). In general, the risk of arrhythmias is increased when erythromycin is administered in combination with other drugs that prolong the QT interval.
   h. Contact dermatitis, fixed drug eruptions, toxic pustuloderma, and toxic epidermal necrolysis are uncommon side effects which may occur with macrolide use.
2. Acute oral overdoses of macrolide antibiotics are usually not life-threatening, and comprise mainly gastrointestinal manifestations. Seizures may occur. Treatment is the same as for penicillin overdose.

Drug Interactions

Macrolides (especially erythromycin) potentiate the effects of astemizole, carbamazepine, corticosteroids, cyclosporine, digoxin, ergot alkaloids, terfenadine, theophylline, triazolam, valproate, and warfarin, by interfering with P450-mediated metabolism of these drugs.

Treatment

1. Severe toxicity is unusual after ingestion; prehospital decontamination is generally not necessary. Discontinuation of the drug usually results in the resolution of the toxic effects.
2. Food, milk or an antacid may be administered for treatment of gastrointestinal distress.
3. CBC, electrolytes, and urinalysis are not generally needed unless the development of haematological disturbances (rare) or nephritis (rare) is suspected, or if the patient has experienced prolonged vomiting and diarrhoea.
4. Monitor ECG, vital signs, and fluid and electrolyte balances in massive overdoses.
5. Arrhythmias respond to magnesium sulphate, isoproterenol, phenytoin, or overdrive pacing.
6. Liver enzyme levels may aid in diagnosing or following a patient with evidence of cholestasis or hepatitis.

■ Anti-tubercular Drugs

Millions of people worldwide are infected with tuberculosis, with at least 10 million new cases and 1 million deaths reported each year. India is one of the countries with a high incidence of this disease which is rising alarmingly with the advent of AIDS.

Drugs used in the treatment of tuberculosis belong to two categories:
1. *First-line drugs*—These drugs combine the greatest level of efficacy with a relatively low level of toxicity. Examples: isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide.
2. *Second-line drugs*—Microbial resistance or other reasons (e.g. concomitant AIDS) may necessitate the addition of these drugs. Examples: ciprofloxacin, ofloxacin, ethionamide, aminosalicylic acid, cycloserine, amikacin, kanamycin, capreomycin, and thioacetazone.

Some of these drugs have been discussed elsewhere (*see Index*), and only the important examples from the remaining will be discussed here.

1. Isoniazid (Isonicotinic Acid Hydrazide; INH)

Isoniazid or INH represents the cornerstone of the treatment of tuberculosis, and is also the drug of choice for prophylaxis in case of positive tuberculosis skin test reaction. INH is the hydrazide of isonicotinic acid, and its isopropyl derivative iproniazid is a monoamine oxidase inhibitor used in the treatment of depression (*page no 271*). INH is bactericidal for both extracellular and intracellular organisms. It is usually used with other antituberculous drugs such as rifampin and

pyrazinamide. Isoniazid as sole therapy is only acceptable when used prophylactically.

Isoniazid is readily absorbed on oral or parenteral administration, and diffuses easily into all body fluids and tissues. Upto 95% of the drug is excreted in the urine within 24 hours, mostly as metabolites. The main metabolic pathway involves acetylation followed by hydrolysis, the rate of acetylation being genetically and racially determined. Fast acetylation is characteristic of Japanese, Chinese, Eskimos, and Negroes, while slow acetylation is seen mainly among Scandinavians, Jews, and North African Caucasians. Fast acetylation is inherited as an autosomal trait. The plasma half-life is 0.7 hours in rapid acetylators and 2 to 4 hours in slow acetylators. In the presence of renal or hepatic dysfunction, slow acetylators can accumulate substantial amounts of INH in the plasma.

The principal metabolites of INH include acetyl isoniazid, isonicotinic acid, isonicotinyl glycine, isonicotinyl hydrazones, and traces of methylisoniazid.

The normal therapeutic dose of INH is 5 mg/kg/day to a maximum of 300 mg/day. Up to 10 mg/kg/day (600 mg/day) is occasionally used in severely ill patients. The incidence of adverse effects is about 5.4%. Main features include rash, fever, jaundice, and peripheral neuritis. Haematological effects include eosinophilia, agranulocytosis, anaemia, and thrombocytopenia. Vasculitis has also been reported. The neurotoxicity of INH is due to vitamin B_6 (pyridoxine) depletion. In the normal course, pyridoxine is phosphorylated by a specific kinase in the liver and then oxidised to pyridoxal phosphate by a flavoprotein. The availability of pyridoxine is affected by INH in the following ways: INH combines directly with pyridoxine and forms an isonicotinyl-hydrazide complex which is excreted in the urine; it forms hydrazones which inhibit pyridoxine phosphokinase, the enzyme that converts pyridoxine to its active form; INH hydrazides inactivate pyridoxal 5'-phosphate, rendering it ineffective. The net effect is that there is a decrease in the availability of gamma-aminobutyric acid (GABA) which is the main inhibitory neurotransmitter of the CNS, since pyridoxine is necessary for the synthesis of GABA. The resultant loss of inhibitory influence of GABA on the CNS is the presumed aetiology of INH-induced convulsions. The hepatotoxicity of INH is mediated directly by its toxic metabolites.

Acute INH overdose is characterised by the clinical triad of convulsions, metabolic acidosis, and coma. Other features include vomiting, vertigo, hyperthermia, hypotension, hyperglycaemia, glucosuria, and ketonuria. INH-induced convulsions are often severe and do not respond to anticonvulsant therapy. They may develop abruptly within 30 minutes to 3 hours after overdose. Status epilepticus may ensue with convulsions lasting for hours and requiring aggressive treatment. Rhabdomyolysis may develop in patients with protracted convulsions. The metabolic acidosis is asociated with a high anion gap, and is mainly due to build-up of lactate secondary to seizures. Severe anion gap metabolic acidosis (pH < 7.0) is common in patients who develop convulsions after INH overdose. The acidosis is frequently refractory to IV sodium bicarbonate therapy alone, but generally reverses after pyridoxine therapy. Mild hepatic dysfunction has been reported following acute overdoses of isoniazid. Clinical hepatitis with nausea, vomiting, fatigue, fever, abdominal pain, malaise, pruritus, and elevated liver function tests is less common, occurring in 0.3 to 1.3% of patients in most studies.

Chronic effects include hepatitis, peripheral neuropathy, optic neuritis, encephalopathy, psychosis, insomnia, vertigo, arthritis, backache, anorexia, constipation, vomiting, and haematological effects (anaemia, haemolysis, agranulocytosis, eosinophilia, and methaemoglobinaemia). Peripheral neuritis occurs in about 20% of patients receiving 6 mg/kg/day of INH without supplemental pyridoxine. It occurs most often in patients who are slow acetylators, and those who are malnourished, alcoholic, uraemic or diabetic. It is also dose related, occurring in 44% of patients receiving more than 16 mg/kg/day. A pellagra-like syndrome may also occur with chronic INH therapy, characterised by dermatitis, diarrhoea, and dementia. Psychosis has been reported with isoniazid therapy.

Doses as low as 1.5 grams can induce toxicity. In relation to body weight, 10 to 30 mg/kg can cause seizures, while doses in excess of 50 mg/kg can cause death.

Treatment

- *Decontamination*: Stomach wash can be done if the patient is seen within 1 to 2 hours post-ingestion and is asymptomatic. If the patient is convulsing, seizures must be controlled and the airway secured before gastric lavage. Activated charcoal has been shown to be beneficial and should be administered in the usual manner.

- *Control of convulsions*: Actively convulsing patients should be given diazepam 5 to 10 mg IV at a rate of 5 mg/min, which can be repeated after 10 to 20 minutes if convulsions persist. There are however several reported cases of INH-induced convulsions not responding to diazepam even though it is a GABA-enhancing agent and should (theoretically) be effective. Phenytoin has been proven to be useless in this setting and must not be tried at all. If convulsions are not controlled by the above measures, consider continuous infusions of midazolam (*loading dose*: 0.2 mg/kg slow bolus; *infusion*: 0.75 to 10 mcg/kg/min), propofol (*initial*: 1 to 2 mg/kg, *maintenance*: 2 to 10 mg/kg/hr), or pentobarbitone (*loading dose*: 10 to 15 mg/kg at a rate of 50 mg/min until burst suppression, or electrocerebral inactivity on EEG; *maintenance*: 0.5 to 1 mg/kg/hr). Endotracheal intubation, mechanical ventilation, and vasopressors will be required, and consultation with a neurologist is strongly advised. Occasionally, neuromuscular paralysis may be required to avoid hyperthermia, severe acidosis, and rhabdomyolysis; continuous EEG monitoring is mandatory if neuromuscular paralysis is used.

- *Antidote*: Pyridoxine should be given to all patients (symptomatic or asymptomatic) who are suspected to have ingested a large amount of INH (>80 mg/kg). The recommended dose is 1 gram IV for every gram of INH ingested to a maximum of 5 grams, at a rate of 1 gram every 2 to 3 minutes. If the amount of INH ingested is unknown, a dose of 5 grams may be administered to an adult, or 70 mg/kg in a child (upto a maximum of 5 gm). This can be repeated

after 30 minutes if seizures persist. Combining pyridoxine with diazepam is said to be synergistic and therefore recommended. But while pyridoxine is a relatively safe antidote, there is some indication that it may cause severe sensory neuropathy if given in very large doses, and so caution should not be thrown to the winds while administering it.

- *Management of acidosis*: If acidosis does not respond to pyridoxine, diazepam, or IV fluids, sodium bicarbonate can be given at a dose of 44 to 88 mEq/L by IV bolus. But care should be taken to see that it is not mixed with pyridoxine solution.
- *Supportive measures* : If aspiration pneumonitis develops, endotracheal intubation must be done and intermittent positive pressure breathing undertaken. Hypotension can be managed by IV fluids.
- *Elimination enhancement*: INH is dialysable since it has a low volume of distribution and is not much protein-bound. Haemodialysis is preferable to peritoneal dialysis. In the case of the latter, pyridoxine may be added to each litre of fluid used for dialysis. Haemoperfusion and exchange transfusion have also been successfully employed in INH overdose.

2. **Rifampicin (Rifampin; Rifamycin)**

Rifampicin is a semisynthetic derivative of rifamycin B which is one of a group of structurally similar, complex macrocyclic antibiotics produced by *Streptomyces mediterranei*. Rifampicin and INH (given together) are the most effective drugs available for the treatment of tuberculosis. The former is also used in the prophylaxis of meningococcal disease and *H.influenzae meningitis*.

A related drug, rifabutin (derived from rifamycin S) is used in the prophylaxis of mycobacterium avium complex-mediated infection in AIDS patients and shares some of the toxic manifestations of rifampicin.

Adverse effects of rifampicin include rash, fever, nausea and vomiting, and jaundice. In some patients a flu-like syndrome develops, characterised by fever, chills, and myalgia. There may also be interstitial nephritis, acute tubular necrosis, and haematological disturbances (thrombocytopenia, haemolytic anaemia, eosinophilia).

Rifampicin is a potent inducer of hepatic microsomal enzymes and therefore reduces the half-life of a number of drugs including anticoagulants, barbiturates, clofibrate, contraceptives (oral), corticosteroids, cyclosporine, digitoxin, fluconazole, halothane, ketoconazole, methadone, metoprolol, propranolol, quinidine, sulfonylureas, theophylline and verapamil.

Rifampicin is a hepatotoxic poison. Toxic hepatitis appears more frequently and with greater severity during combination therapy with INH. This is noted most frequently in children. Apart from liver failure, overdose of this drug produces vomiting, flushing, angioedema, periorbital and facial oedema, mental changes, and pulmonary oedema. Patients typically present with nausea, vomiting, mental status changes, and reddish discolouration of the skin. Renal failure occurs less frequently. Thrombocytopenia, haemolytic anaemia, methaemoglobinaemia, hypothrombinaemia, transient leukopenia,

and anaemia have been reported following chronic ingestion of therapeutic doses. Hypersensitivity reactions include fever, pruritus, urticaria, various skin eruptions, polyarthropathy, and soreness of the mouth and tongue.

Overdosage can rarely result in convulsions, arrhythmias, pulmonary oedema, and death. Ingestion of more than 14 grams is potentially lethal. Since rifampicin and its metabolites are red in colour, overdose results in a characteristic orange-red staining of tissues, urine, faeces, saliva, tears, and sweat (*Red man syndrome*). Sclerae may also appear yellow-orange in colour. Cutaneous staining can be partially removed by washing or scrubbing.

Treatment

- Monitor CBC, renal and hepatic function tests in symptomatic patients. Elevated total bilirubin level is the most common finding, and may be due to interference of rifampicin with the bilirubin assay. Liver function tests and renal tests should be closely followed.
- Activated charcoal can be administered.
- Convulsions must be treated with benzodiazepines in the usual maner.
- Onset of acute lung injury after toxic exposure may be delayed up to 24 to 72 hours after exposure in some cases. Maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
- Since rifampicin has an extensive volume of distribution and is significantly protein-bound, it is not eliminated well by haemodialysis or haemoperfusion.

3. **Ethambutol**

Ethambutol is a synthetic bacteriostatic antituberculous drug which is effective only in actively growing cells. Ethambutol is effective as adjunctive therapy for the treatment of tuberculosis, but is not indicated as monotherapy for this disease. It is also used in combination to treat other mycobacterial infections including Mycobacterium avium-complex. It is usually given in combination with INH.

The most important adverse effects are related to the eyes: optic neuritis (resulting in diminished visual acuity and red-green discrimination), constriction in visual fields, and even blindness. These effects may be unilateral or bilateral, and are usually reversible. Optic neuritis is the principal side effect of ethambutol therapy, but usually manifests at doses in excess of 15 mg/kg. Other effects include GI upset, pruritis, arthralgia, vertigo, confusion, and peripheral neuritis. Gouty arthritis has been reported after therapeutic administration of ethambutol.

Acute overdose results in nausea, vomiting, abdominal pain, fever, confusion, hallucinations, and retrobulbar neuritis (if the dose exceeds 10 gm). Acute overdose involving both ethambutol and isoniazid may result in synergistic nervous system toxicity.

Treatment involves supportive measures. Haemodialysis or peritoneal dialysis may be beneficial. Patients with optic neuritis can benefit from parenteral hydroxycobalamine 40 mg/day for 10 to 28 weeks followed by a reduced dose of 20 mg/day. Deaths have so far not been reported in ethambutol overdose.

4. Pyrazinamide

It is an analogue of nicotinamide and is bactericidal to actively dividing tubercle bacilli. Pyrazinamide is well absorbed orally and is widely distributed throughout the body. It is partly hydrolysed to pyrazinoic acid and then hydroxylated to 5-hydroxypyrazinoic acid and excreted.

The most serious adverse effect is hepatitis with jaundice, and even death may occur from hepatic necrosis. Pyrazinamide is therefore contraindicated in individuals suffering from hepatic dysfunction or disease.

Acute overdose involving this drug has rarely been reported.

5. Ethionamide

It is a bacteriostatic anti-TB drug which is associated with the following adverse effects: nausea, vomiting, metallic taste, postural hypotension, mental depression, blurred vision, headache, tremor, skin rashes, impotence, menorrhagia, alopecia, and hepatitis. Concomitant administration of pyridoxine is advisable. Monitor liver enzyme levels after significant overdose. Monitor electrolytes in patients with severe vomiting or diarrhoea. Monitor for evidence of encephalopathy after significant overdose. Case reports suggest that pyridoxine, nicotinamide and parenteral multiple vitamins may be useful in the treatment of ethionamide-induced encephalopathy.

Use of ethionamide should be avoided during pregnancy or in women of childbearing age, unless the benefits outweigh its potential hazards: developmental anomalies (congenital heart disease, spina bifida, spinal anomalies, Down's syndrome and possible hydrocephalus).

6. Cycloserine

It is a broad-spectrum antibiotic elaborated by *Strep. orchidaceus*, which acts by interfering with bacterial cell wall synthesis. Adverse effects include drowsiness, headache, tremor, dysarthria, vertigo, confusion, psychosis, and convulsions. Other effects include megaloblastic anaemia, polyarthritis, and a pellagra-like syndrome. Concomitant administration of pyridoxine is advisable.

7. Capreomycin

It is an antimycobacterial agent elaborated by *Strep. capreolus*, and must be given only by intramuscular or intravenous injection. Capreomycin is used concomitantly as part of a multidrug regimen to treat tuberculosis that is resistant to other therapy. It may also be used to treat infections due to other Mycobacterial species. Electrolyte abnormalities and metabolic alkalosis may occur with therapeutic use. Leukocytosis, eosinophilia, and various skin rashes may occur. Adverse effects include

ototoxicity similar to streptomycin (*page no 437*), and renal tubular damage. Severe renal tubular dysfunction and tubular necrosis have occurred. Loss of visual acuity has been rarely reported with capreomycin therapy. The ototoxicity, nephrotoxicity, and neuromuscular blocking effects of aminoglycoside antibiotics may be increased by concomitant administration of capreomycin. Capreomycin is a possible inducer of *Bartter's syndrome*.*

There is no antidote for capreomycin overdose. Treatment is symptomatic and supportive. Haemodialysis may be helpful in overdose.

8. Thioacetazone

It was formerly widely employed in India (in combination with INH) because of its low cost. However it is extremely toxic, and death can result even from therapeutic doses (150 mg). Patients with AIDS (or HIV seropositivity) are particularly susceptible, and therefore the drug is contraindicated. When given along with streptomycin, thioacetazone can potentiate the former's tendency to cause ototoxicity. Adverse effects include vomiting, anorexia, conjunctivitis, mild to severe skin eruptions, vertigo, convulsions and cerebral oedema.

■ Antileprotic Drugs

While leprosy (*Hansen's disease*) is a rare entity in Western countries, it is a significant public health problem in Third World nations such as India.

Chaulmoogra oil (with weak antileprotic property) had been used extensively in the olden days before the advent of sulfones which constitute the sheet anchor of antileprotic therapy today. Clofazimine is used in resistant cases, while drugs such as rifampicin, ethionamide, thalidomide, thiacetazone, and sulfadoxine have also been used with varying degree of success. Newer drugs which appear promising in the treatment of leprosy include minocycline, clarithromycin, pefloxacin, and ofloxacin.

1. Sulfones

The sulfones are chemically related to sulfonamides and are derivatives of 4,4´-diaminodiphenylsulfone or dapsone, which is in fact the most widely used antileprotic even today, more than 50 years after it was first introduced. Sulfoxone sodium (not yet available in India) is used when dapsone produces severe gastric distress.

Dapsone is marketed in India by Burroughs Wellcome as 25 mg, 50 mg, and 100 mg tablets for oral administration. It is a bacteriostatic antileprotic and anti-inflammatory drug used in the treatment of leprosy, dermatitis herpetiformis, vasculitis, pemphigus, and generalised pustular psoriasis. It is also widely used in AIDS patients for the treatment and prophylaxis of PCP (*Pneumocystis carinii* pneumonia), and prophylaxis against toxoplasmosis.

Following absorption, dapsone is widely distributed to tissues. The concentrations in most organs approximate the plasma concentration. Dapsone readily penetrates into nerve

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* Hyperplasia of juxtaglomerular cells of kidney, hypokalaemic alkalosis, and hyperaldosteronism without associated hypertension.

tissue with a nerve tissue concentration approximately the same as the plasma concentration. Peak serum concentrations are found at 2 to 8 hours after oral dosing. The mean elimination half-life of dapsone is about 30 hours, which may be prolonged to 2 to 4 days after overdose. Dapsone is acetylated by N-acetyltransferase found in the liver and jejunal mucosa primarily to monoacetyldapsone (MADDS). It is also hydroxylated by the mixed function oxidase system in the presence of oxygen and NADPH. The hydroxylated metabolite, N-hydroxydapsone (NOH-dapsone), may be responsible for the haematologic manifestations (methaemoglobinaemia and haemolysis) seen in overdose. Dapsone and monoacetyldapsone may be excreted in the urine as glucuronide or sulfate conjugates.

Adverse effects of dapsone therapy include haemolysis (with reticulocytosis and Heinz body formation), methaemoglobinaemia, nausea, vomiting, headache, insomnia, blurred vision, and peripheral neuropathy. Occasionally *Sulfone syndrome* may develop in some malnourished patients 5 to 6 weeks after beginning the therapy, which is characterised by fever, exfoliative dermatitis, hepatic necrosis with jaundice, lymphadenopathy, methaemoglobinaemia, and anaemia. Dapsone has been associated with clinical exacerbation of porphyria and is NOT indicated in porphyric patients.

Cases of dapsone overdose have been reported, usually due to calculation errors resulting in vomiting, abdominal pain, haemolysis, methaemoglobinaemia, sulfhaemoglobinaemia, deep cyanosis, restlessness, blurred vision, and convulsions. Giddiness, hallucinations, dizziness, agitation, and confusion have been reported following overdoses. Methaemoglobinaemia, haemolysis, and CNS stimulation are the most common manifestations. Death may occur. A glucose-6-phosphate dehydrogenase deficient individual has about a 2-fold increase in sensitivity toward dapsone-induced haemolytic anaemia. Animal studies have shown a decrease in methaemoglobin formation when cimetidine was given concurrently with a once a day dosing. When tested in humans given 400 mg of cimetidine three times daily for 3 days before and 4 days after dapsone, drug concentrations increased 30% (less metabolism). This has not been tried in the overdose situation.

Dapsone is contraindicated in pregnancy due to its ability to produce anaemia or methaemoglobinaemia.

Drug-induced psychosis has been reported during both therapeutic use and following intentional ingestion (2.5 gm) resulting in extreme agitation and violence.

The usual fatal dose is 2 to 5 grams for an adult. Plasma levels of over 10 mg/L are associated with serious toxicity. Studies of haemolysis such as haptoglobin and free haemoglobin, and reticulocyte counts may be useful to monitor haemolysis. Other tests that could help aid the diagnosis of latent methaemoglobinaemia and haemolytic anaemia include red cell fragility, Heinz bodies, and lactic acid dehydrogenase. Monitor urine for haemoglobinuria. Dapsone and its metabolite monoacetyldapsone (MADDS) levels can be measured in urine, and if available may be useful to follow urinary excretion.

Treatment involves gastric decontamination and administration of methylene blue (to correct methaemoglobinaemia),

at a dose of 1 to 2 mg/kg IV, given over 5 to 10 minutes. This may have to be repeated several times over every 4 hours for a number of days. *Caution:* Large doses of methylene blue iself may cause methaemoglobinaemia or haemolysis. Infusion of packed red blood cells may be required. If cyanosis fails to clear after treatment of presumed methaemoglobinaemia with methylene blue, or recurs late in the clinical course, sulfhaemoglobinaemia may be present. Convulsions can be controlled by diazepam or phenytoin IV in the usual doses. Blurred vision sometimes responds to prednisolone (75 mg/day for 1 week, and then tapered off). However, corticosteroids are of no use in the management of haemolysis. Ascorbic acid has been tried, but there is no clear-cut indication as to its efficacy. Oxygen inhalation therapy is not beneficial.

Decontamination with activated charcoal is useful in the early stages of dapsone overdose. Extracorporeal methods of eliminating the drug from the blood stream can be tried, but they have no proven value. However there are reports of beneficial effects with charcoal haemoperfusion and haemodialysis.

2. **Clofazimine**

It is a phenazine dye which is used in dapsone-resistant leprosy and lepra reactions (*erythema nodosum leprosum*).

Adverse effects include a reddish or brownish skin discolouration, diarrhoea, abdominal pain, loss of weight, and bull's eye retinopathy. There may be deposition of clofazimine crystals in gut wall tissue, mesenteric lymph nodes, and cytoplasm of alveolar macrophages. Clofazimine crosses the placenta and is present in breast milk. Infants may be pigmented at birth, or subsequently from ingesting breast milk.

Diagnosis can be established by thin layer chromatography, and X-ray abnormalities of small bowel (alternating segments of constriction and dilation, cogency of mucosal folds, and circumscribed "polypoid" areas).

Treatment is symptomatic and supportive. Periodic fundoscopy (every 4 months) is advised in all patients receiving clofazimine.

■ Other Antibacterial Drugs *(in random order)*

1. **Clindamycin**

Clindamycin is a congener of lincomycin, and though it is not structurally related to erythromycin and chloramphenicol, it has a similar mode of action, i.e. binding to the 50s subunit of bacterial ribosomes and suppression of protein synthesis. It is administered mainly for anaerobic infections either orally or parenterally. It is especially effective in infections due to *Bacteroides fragilis*, and in some staphylococcal and streptococcal infections. Clindamycin has antiprotozoal actions also, and is administered systemically in combination with other antiprotozoal agents for the treatment of babesiosis, malaria, and toxoplasmosis. Clindamycin is also used for the topical treatment of acne vulgaris as a gel or cream.

Adverse effects include diarrhoea which may sometimes be due to a serious complication—pseudomembranous colitis (*page no 435*). This is in fact a widely reported adverse effect of lincomycin and clindamycin therapy when administered orally

and/or parenterally. The colitis usually presents with loose stools or diarrhoea that may be bloody. In cases of more severe disease, patients may have fever, leucocytosis, nausea and vomiting, tenesmus, and abdominal tenderness or cramping. Diagnosis can be established by proctoscopy, sigmoidoscopy, or by a barium contrast study. If pseudomembranous colitis is present, these procedures may reveal erythematous, friable mucosa covered with small, raised, yellowish-white plaques, and the formation of pseudomembranes. Symptoms usually appear after 5 to 10 days of antibiotic therapy, although this can be variable. Protein-losing enteropathy, toxic megacolon, and perforation of the colon occur occasionally, and are serious complications that may lead to shock and death. Even topical clindamycin, used to treat facial acne, has caused pseudomembranous colitis.

The symptoms of non-specific colitis are very similar to pseudomembranous colitis including bloody diarrhoea, tenesmus, abdominal pain, and fever. The difference with non-specific colitis is that there are no pseudomembranes present during proctoscopic examinations, and rectal biopsies show non-specific inflammatory changes.

Cardiac arrhythmias, dermatitis, nephrotoxicity, hepatotoxicity, skin rashes, erythema multiforme, anaphylaxis, and haematological abnormalities have also been reported with clindamycin. Rapid administration of large doses has resulted in ventricular arrhythmias, hypotension and cardiac arrest.

Lincomycin and clindamycin may augment pancuronium-induced neuromuscular blockade as well as produce neuromuscular blockade when administered alone.

Clindamycin has been reported to cause hepatotoxicity, including elevated liver enzyme levels and cholestatic liver disease with reduced numbers of bile ducts. Acute renal failure has occurred following combination therapy of gentamicin and clindamycin.

Acute ingestion of lincomycin and clindamycin has not been associated with significant toxicity. Gastrointestinal decontamination is generally NOT necessary. The use of diphenoxylate hydrochloride-atropine sulfate is NOT recommended for the treatment of lincomycin- or clindamycin-induced diarrhoea. Discontinuation of the drug usually results in improvement of the diarrhoea.

For pseudomembranous colitis: Metronidazole 750 mg orally every 6 hours for 7 days can rapidly eliminate *C. difficile* toxin from the stools and shorten the course of illnessis. Vancomycin therapy, 500 mg orally every 6 hours for 7 to 10 days is an alternative therapy. In debilitated patients with recurrent *C. difficile* colitis, parenteral gamma-globulin (400 mg/kg intravenously every 3 weeks), and replacement of colonic bacteria with *Saccharomyces boulardii*, a non-pathogenic yeast, have been advocated.

Neither haemodialysis nor peritoneal dialysis appear to be effective in reducing lincomycin or clindamycin levels significantly.

2. Vancomycin

Vancomycin is a chromatographically purified, tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). It is very useful in the treatment of serious infections caused by methicillin-resistant staphylococci and penicillin-resistant pneumococcal infections. It is also effective against *Clostridium difficile* which causes pseudomembranous colitis (*page no 435*). Vancomycin is usually only administered intravenously. It may be administered orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration is not effective for the above indications.

Adverse effects include skin rashes, anaphylaxis, fever, ototoxicity (sensorineural hearing loss), and nephrotoxicity. The actual number of cases of ototoxicity associated with vancomycin use is small, and most cases of permanent hearing loss have been associated with the co-administration of an aminoglycoside. Severe lacrimation and conjunctivitis have been seen with therapeutic use. Nephrotoxicity can occur with excessive serum levels but is usually reversible upon discontinuation of the drug. Reversible neutropenia which usually develops within the first week or more after the start of therapy or after a total dose of 25 grams or more has been reported in several dozen individuals. The effects promptly reverse when therapy is withdrawn.

Rapid IV infusion can cause tachycardia and hypotension. Occasionally, this results in the *Red man syndrome* (**Fig 30.5**)* or *Red neck syndrome*, which is characterised by hypotension, pruritis, cutaneous flushing (face, neck, chest, and arms), chest pain, and dyspnoea. Earlier it was thought to be caused by impurities in the drug formulation, but now it is postulated that the syndrome occurs because of vancomycin-induced release of endogenous histamine. Reactions generally resolve within 20 minutes, but may persist for several hours. The incidence and severity can be minimised by antihistamine prophylaxis, lower and more frequent vancomycin dosing, and 2-hour infusions.

Acute vancomycin overdose results in oliguria and renal failure. Toxicity is reported at levels sustained above 80 to 100 mcg/ml. Hypotension, apnoea, deafness, and flushed skin have been reported after overdose. Treatment involves multi-dose activated charcoal (even if vancomycin has been given IV), and institution of supportive measures. Gastrointestinal absorption of vancomycin is negligible; decontamination is rarely indicated unless coingestants are involved. Monitor the patient for development of possible ototoxicity, nephrotoxicity, haematopoietic, or cardiac abnormalities. While haemodialysis and charcoal haemoperfusion are not effective, continuous arteriovenous haemofiltration may be beneficial. However there are some reports of efficacy with haemodialysis also.

3. Teicoplanin

Teicoplanin obtained from *Actinoplanes teichomyetius* is a new antibiotic with a spectrum of activity similar to vancomycin.

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* A similar entity is seen with reference to **rifampicin** use which causes reddish discolouration of skin, other tissues, and body fluids, due to its red coloured metabolites **(page no 444).**

Fig 30.5: Red man syndrome – Rifampicin

However, unlike the latter, it can be given by intramuscular injection. Once-daily dosing is sufficient for the treatment of most infections since it has a prolonged serum elimination half-life. Adverse effects include skin rash, fever, neutropenia, and ototoxicity (rare).

4. Spectinomycin

It is an antibiotic produced by *Strep. spectabilis*, and is used mainly for the treatment of gonorrhoea in patients who are intolerant or allergic to beta-lactam antibiotics and quinolones. Spectinomycin is given by intramuscular injection, and in rare instances can cause urticaria, fever, chills, vertigo and insomnia.

5. Polymyxin B and Colistin (Polymyxin E)

These antibiotics obtained from *Bacillus* species of micro-organisms are highly nephrotoxic and hence not advised to be administered systemically. Polymyxin B sulfate is available in India for ophthalmic, otic, and topical use, as well as for systemic use.

6. Bacitracin

It is an antibiotic produced by *Bacillus subtilis*, and is actually a group of polypeptides, the most active of which is Bacitracin A. It is mainly employed for ophthalmic and topical use in combination with other drugs such as neomycin, polymyxin, and hydrocortisone. The major use of bacitracin is topical treatment of gram-positive infections on the skin or in the eye. The drug is also used prophylactically to prevent dermal infections. Intramuscular bacitracin is available to treat infants with pneumonia and empyema caused by susceptible staphylococci; however, it is rarely used because of the availability of more effective and less toxic agents. Parenteral use is associated with serious nephrotoxicity and ototoxicity. Transient epigastric distress, including nausea, vomiting, diarrhoea, or anal itching or burning may occur with therapeutic use. Several cases of anaphylaxis have been reported with the use of bacitracin ointment.

ANTIVIRALS

■ Antiherpesvirus Agents

1. Acyclovir

Acyclovir is a synthetic purine nucleoside analogue which was first approved for use in 1982. Valacyclovir is the L-valyl ester prodrug of acyclovir. The latter acts (after being converted to acyclovir triphosphate by intracellular phosphorylation mediated by thymidine kinase), by inhibiting viral reverse transcriptase, thereby terminating viral DNA synthesis. Valacyclovir is converted to acyclovir in the body after oral administration. It serves to increase relative oral bioavailability of acyclovir. Penciclovir and famciclovir are related drugs which are similar to acyclovir in action and toxicity.

Acyclovir and related drugs are antiviral agents indicated for the treatment of herpes simplex-1 and -2, herpes simplex encephalitis, herpes zoster, varicella zoster, and prophylaxis of cytomegalovirus.

Acyclovir is generally well tolerated at recommended doses. Oral administration sometimes causes vomiting and headache. Intravenous use may result in phlebitis, renal dysfunction (due to precipitation of acyclovir crystals in renal tubules), and encephalopathy. The latter is associated with high-dose administration and manifests as lethargy, confusion, hallucinations, delirium, and convulsions. Hallucinations may occur. Topical use may cause occasional burning on application, with erythema on drying.

A few cases of acute overdose have been reported with acyclovir in adults as well as infants, but serious toxicity was not evident in any of them, though renal dysfunction occurred in one which was rectified by appropriate treatment. The risk of nephrotoxicity is primarily related to high serum levels following bolus IV injections or overdose and is usually reversible. The incidence of renal toxicity may be greatly decreased by administering acyclovir slowly in a concentration less than 7 mg/ml. Adequate hydration and high urine output should be maintained throughout treatment to minimise nephrotoxicity. Myoclonus, agitation, tremor, and convulsions have also been reported in overdose.

Treatment: Any patient suspected of a toxic oral or intravenous exposure to acyclovir, famciclovir or penciclovir should be monitored in a controlled setting until all signs and symptoms of toxicity have subsided. The amount contained in a 15-gram tube of ointment (750 mg) of acyclovir is unlikely to produce toxicity and is within the daily recommended oral dose in adults. Penciclovir is poorly absorbed after oral administration, so ingestion is unlikely to cause significant toxicity. Monitoring hepatic enzymes, renal function and urinalysis may be of value in evaluating the seriousness of acyclovir overdose.

- *Decontamination*: Gastric lavage can be done if the patient is seen within 2 hours of ingestion. Acyclovir is adsorbed well by activated charcoal.
- Intravenous fluid hydration may aid in solubilising crystals and therefore prevent or minimise crystal deposits in renal tubules and collecting ducts.

- Haemodialysis has been shown to be beneficial in acyclovir overdose. Due to the low molecular weight, water solubility, and low protein binding of acyclovir, it is anticipated that continuous haemodialysis would be effective in removal of acyclovir from plasma. Famciclovir and penciclovir are also removed by haemodialysis. Exchange transfusion, haemoperfusion, and peritoneal dialysis are not efficacious.
- *Supportive measures*: Patients should be carefully monitored for signs of neurotoxicity (encephalopathy) and renal dysfunction, and appropriate measures instituted if they are evident.

2. Foscarnet

Foscarnet is trisodium phosphonoformate, and acts by inhibiting viral nucleic acid synthesis through direct interaction with herpesvirus DNA polymerase or HIV reverse transcriptase. It is effective against HSV, VZV, HIV, and CMV (cytomegalovirus) infections. Foscarnet is administered intravenously, but has serious potential for nephrotoxicity and hypocalcaemia. Other toxic effects include convulsions, paraesthesias, hallucinosis, vomiting, hepatic damage and painful genital ulcerations.

Treatment involves haemodialysis and supportive measures.

3. Ganciclovir

Ganciclovir is a nucleoside analogue which is structurally similar to acyclovir but is 50 times more active against CMV. It utilises cellular kinases for conversion to its active triphosphate form which inhibits viral DNA replication. Ganciclovir is a synthetic guanine derivative and acts as an acyclic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses (sensitive viruses include cytomegalovirus). It is however quite toxic and produces haematologic abnormalities (leukopenia, anaemia and thrombocytopenia), and chronic renal failure. Other adverse effects include vomiting, diarrhoea, liver damage, convulsions, vertigo, torsades de pointes, cardiac arrest, cardiac conduction abnormalities, ventricular tachycardia, gastrointestinal perforation, multiple organ failure, pancreatitis, and sepsis. Pneumonia, dyspnoea, and cough have also been reported. Pruritus, rash, and sweating were the most frequent dermatologic complaints associated with intravenous or oral ganciclovir.

Since ganciclovir has been almost exclusively evaluated in immunocompromised patients with infections, the adverse events reported may be confounded by underlying disease processes and concomitant drug therapies. Irreversible pancytopenia, persistent bone marrow suppression, hepatitis, haematuria, elevated creatinine, convulsions, neutropenia, anaemia, leukopenia, and thrombocytopenia have been reported after intravenous overdose as well as with intravenous or oral therapeutic doses. Retinal damage and permanent visual loss have been reported after overdose by intravitreal injection.

Valganciclovir is the l-valyl ester of ganciclovir. It is a prodrug, being rapidly hydrolysed to ganciclovir in plasma following oral administration; it was developed to improve the bioavailability of oral ganciclovir.

Ganciclovir has been shown to be carcinogenic and teratogenic in animal studies. Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use.

Treatment of overdose involves gut decontamination (induction of emesis is contraindicated because of the potential for convulsions, cardiovascular instability, and CNS depression), and institution of elimination procedures such as haemodialysis or CAVH (continuous arteriovenous haemodialysis). Treatment of convulsions and cardiac arrhythmias require special attention.

4. Idoxuridine

It is an iodinated thymidine analogue which inhibits the *in vitro* replication of various DNA viruses such as herpes viruses and pox viruses. Idoxuridine is however only recommended for topical treatment (HSV keratitis), and may occasionally cause allergic reactions resulting in pruritis and inflammation.

5. Vidarabine

Vidaribine is an adenosine analogue which is recommended for use in HSV encephalitis, neonatal herpes, and zoster or varicella in immunocompromised patients. It is administered intravenously. Toxic effects include vomiting, diarrhoea, weakness, hypokalaemia, haematological abnormalities, and CNS disturbances.

Antiretroviral Agents

These drugs are used mainly in the treatment of AIDS and T-cell leukaemias. They have a similar mechanism of action i.e. they are first converted by cellular kinases into their active triphosphate form, which inhibits viral reverse transcriptase, thereby terminating viral DNA chain formation.

1. Zidovudine (AZT, ZDV)

Zidovudine (azidothymidine) was the first drug approved for use in the treatment of HIV infection, and has been around since 1987. It is usually given orally, but can also be administered as an intravenous infusion.

Adverse effects include serious anaemia, leucopenia, nausea, headache, myalgia, vomiting, diarrhoea, taste perversion, sweating, vertigo, dyspnoea, chest pain, and increased urinary frequency. Nausea and vomiting are common side effects of zidovudine therapy, occurring in 66 of 145 (46%) of AIDS patients during clinical trials. Dark blue or brownish transverse fingernail and toenail discolouration may occur after weeks of zidovudine therapy.

Several cases of acute overdose with zidovudine have been reported in the literature with minimal effects. Following acute overdoses of up to 50 grams in both adults and children, with no fatalities, some patients experienced non-specific CNS symptoms. Acute overdose may cause seizures, nystagmus, ataxia, nausea, and headache. Based on the adverse drug reaction profile, bone marrow suppression might be expected to occur after overdosage.

Chronic effects of zidovudine therapy may include a syndrome of fatal lactic acidosis and hepatic failure. Granulocytopenia has been the most frequently reported adverse effect following therapeutic use, and is directly related to dose and duration of therapy. Anaemia has been the second most common adverse reaction during therapy. Polymyositis-like syndrome has been reported in several patients on months of therapy.

Treatment involves symptomatic and supportive measures. Complete blood counts (CBC's) should be monitored intensively in patients who overdose on zidovudine. Arterial blood gases and hepatic function should be monitored in symptomatic patients. Intensive monitoring for bone marrow suppression is recommended following overdosage. In the presence of bone marrow suppression, transfusions and protective measures for granulocytopenia may be needed until recovery of bone marrow function.

Severe metabolic acidosis (arterial pH less than 7.1) should be corrected with IV sodium bicarbonate (a reasonable starting dose is 1 to 2 mEq/kg). Monitor blood gases to guide bicarbonate therapy. Monitor serum sodium to avoid overload. Some investigators suggest that there could be a riboflavin deficiency in AIDS patients taking these drugs, resulting in lactic acidosis and hepatic steatosis. These authors have treated patients with this syndrome with riboflavin 50 mg and reported clinical recovery and return of serum lactate levels to normal.

Haemodialysis and haemoperfusion do not appear to be beneficial.

2. **Didanosine (Dideoxynosine, DDI)**

Didanosine is a purine nucleoside which is recommended for the treatment of zidovudine-resistant/intolerant cases of HIV infection. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5-triphosphate (ddATP). The active metabolite inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5-triphosphate (dATP), and by its incorporation into viral DNA. Viral DNA growth is terminated. It can be administered orally (though food decreases absorption significantly), or intravenously.

Adverse effects include painful peripheral neuropathy and pancreatitis. Painful distal symmetrical peripheral neuropathy is a major dose-limiting toxicity of didanosine. It often progresses to severe, opioid-requiring pain. It generally has an abrupt onset and rapid progression. Histologically, axonal degeneration is evident. The frequency is related to didanosine dose and stage of disease. The painful neuropathic syndrome consists of tingling, burning, or aching in the lower extremities, particularly at night-time but gradually progressing to interfere with walking, sleep, and routine daily activities. There are no associated neurologic deficits except for occasional diminished vibratory sensation and decreased ankle reflexes.

The major toxicity of didanosine is pancreatitis, which has been fatal in some cases, and has been posted as a warning in the product insert. Pancreatitis is often accompanied by severe lactic acidosis. Frequency of pancreatitis is dose-related, with an incidence in phase 3 adult studies ranging from 1 to 10%, and in paediatric studies up to 13%. Other nucleoside reverse transcriptase inhibitors have been reported to cause pancreatitis, however, it appears most often following didanosine or stavudine therapy.

Less common effects comprise rhinitis, epistaxis, rhinorrhoea, sinusitis, pharyngitis, abdominal pain, diarrhoea, rash, heart failure, hepatitis and hepatic failure, CNS disturbances (convulsions), and retinal depigmentation and optic neuritis (in children). Hepatomegaly with steatosis, which may be fatal, has been reported with the therapeutic use of didanosine, especially in women. Arrhythmias were reported in 6% of paediatric patients in phase I trials. Dermatologic effects include the development of skin rashes, eczema, impetigo, pruritus, excoriation, sweating, erythema, and Stevens-Johnson syndrome.

Overdose experience is limited. The major toxicity of didanosine is pancreatitis. Possible effects of overdose (based on extrapolation from adverse effects) include pancreatitis, convulsions, peripheral neuropathy, diarrhoea, hyperuricaemia, hepatic dysfunction, and lactic acidosis. Treatment is mainly supportive. Monitor the following laboratory tests in symptomatic patients after an overdose: cardiac monitoring, aminotransferases, complete blood count, and levels of electrolytes, platelets, creatine kinase, and amylase, acid base status. Convulsions may rarely occur and should be treated aggressively. Cardiac failure, pancreatitis, hepatic dysfunction, and peripheral neuropathy must be anticipated, and treated on conventional lines as and when they arise. Haemodialysis may be beneficial.

3. **Stavudine**

Stavudine is a thymidine nucleoside analogue which is used in HIV patients who are intolerant to other drugs. It is well absorbed on oral administration, and is metabolised in the liver, and probably also via degradation and salvage by other pyrimidine pathways which may contribute to its elimination.

The main adverse effect is painful sensory neuropathy. The most serious presentation of nucleoside analogue toxicity with chronic therapeutic administration is mitochondrial toxicity leading to lactic acidosis, with or without hepatic microsteatosis. Pancreatitis, neuropathy and myopathy often accompany the syndrome. Lactic acidosis has been reported in patients receiving both single and dual nucleoside analogue (NRTI) regimens for HIV infection and may lead to multiorgan failure. This most commonly occurs in persons on prolonged (> 6 months) therapy. The manufacturers of lamivudine and stavudine have issued warnings concerning lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, with the therapeutic use of these drugs. The syndrome of lactic acidosis and hepatic steatosis, a complication of nucleoside reverse-transcriptase inhibitors, may be associated with riboflavin deficiency in these patients.

Peripheral lipoatrophy or lipomata, histologically seen as apoptosis, has been reported in up to 50% of NRTI treated patients, with stavudine causing more reported cases than the other NRTIs.

Overdose experience is limited. Based on toxicities seen with chronic (therapeutic) administration, acute overdose may be associated with peripheral neuropathies and hepatotoxicity.

Treatment is mostly supportive. Complete blood counts (CBCs) should be monitored frequently in patients who overdose on nucleoside analogs. Monitor serum electrolytes, renal and liver function tests, pancreatic enzymes and CPK.

Convulsions may occur and should be treated aggressively. Cardiac failure has been reported and cardiac monitoring is recommended. Hepatic failure may occur and liver function should be monitored. Peripheral neuropathies, which are generally reversible on drug withdrawal, may occur and should be treated with pain management as needed.

4. Zalcitabine

It is a cytosine nucleoside analogue which has a potency similar to zidovudine, but suffers from the same adverse effect (painful sensory neuropathy) as didanosine and stavudine. Severe peripheral neuropathy necessitating discontinuation of therapy occurs in about 10% of patients. After stopping zalcitabine, some patients experience a period of symptom intensification, referred to as "coasting", lasting for several weeks to months. Pancreatitis has also been reported. Lactic acidosis, with or without hepatic microsteatosis can also occur. Ototoxicity, mouth ulcers, oesophageal ulceration, hepatomegaly, cardiac arrhythmias, neutropenia, cutaneous eruptions, arthralgia, dizziness, confusion, amnesia, and depression are the other adverse effects reported.

Overdose experience is limited. Based on toxicities seen with chronic (therapeutic) administration, acute overdoses may be expected to result in peripheral neuropathies, hepatic dysfunction, gastrointestinal effects, elevated pancreatic enzymes, and possibly convulsions.

Treatment is on the same lines as for stavudine (*vide supra*).

5. Lamivudine

It is a nucleoside analogue in which the $3^/$ carbon of the ribose of zalcitabine has been replaced by sulfur, and shows promise as a new anti-AIDS drug with relatively low toxicity. However, diarrhoea, which does not appear to be dose-dependant, may be severe enough to necessitate discontinuance of medication, and may be accompanied by nausea and vomiting. Skin rashes and/or pruritus, hair loss, oral ulcerations/lesions, anaemia, thrombocytopenia, and neutropenia have also occurred. Drowsiness and convulsions are a rare occurrence but have been reported following therapy with lamivudine. Based on toxicities seen with chronic (therapeutic) administration, acute overdoses may be expected to result in bone marrow suppression, peripheral neuropathies and gastrointestinal effects.

■ Other Antiviral Agents

1. Amantadine

Amantadine and its alpha-methyl derivative rimantadine are mainly used in the prophylaxis and treatment of influenza A virus infections. Amantadine is also used in the treatment of Parkinsonism and drug-induced (carbon monoxide, antipsychotics) extrapyramidal effects, as well as herpes zoster. There are indications that it may also be useful in treating cocaine withdrawal symptoms.

Amantadine is well absorbed orally (55 to 90%). Peak blood levels are reached in 1 to 4 hours after an oral dose. Adverse effects include anticholinergic symptoms of dry mouth, tachycardia and difficulty in focusing, while the two most serious areas of toxicity are cardiac arrhythmias and CNS stimulation. Chronic use of amantadine (especially in the elderly, and in the

renally compromised) can produce delirium, hallucinations, disorientation, and weakness. These can be greatly aggravated if anticholinergic drugs are given concomitantly. Ocular toxicity may occasionally occur, characterised by blurred vision, corneal irritation, oculogyric crises, and mydriasis. There are also reports of peripheral oedema, congestive heart failure, and urinary retention.

Amantadine, a dopamine agonist, is considered as a serotonergic drug. Theoretically, any drug or combination of drugs, that has the ability to increase serotonin activity can produce serotonin syndrome. At the present time, there are few reports in the literature of this adverse event with amantadine.

A study of elderly patients receiving antiviral treatment revealed a lower incidence of adverse effects related to the CNS in patients receiving rimantadine compared with amantadine.

Acute overdose causes dry mouth, mydriasis, psychosis, and urinary retention. Psychosis is characterised by agitation, disorientation, and hallucinations. Convulsions can occur. Cardiovascular manifestations include ventricular fibrillation, prolonged QT interval, torsade de pointes, and cardiopulmonary arrest. There are also reported cases of ARDS and pulmonary oedema. While survival has been reported with an acute ingestion of 2.8 grams, doses more than 2 grams are potentially fatal. Levels over 4 mcg/ml are associated with severe toxicity.

■ Treatment:

- Gastric emptying may be beneficial upto 4 hours post-ingestion. Activated charcoal is said to be useful.
- Chest X-rays should be obtained in significant ingestions. Death due to pulmonary oedema, in the absence of preceding signs or symptoms, has been described. If pulmonary oedema is developing, maintain adequate ventilation and oxygenation with frequent monitoring of arterial blood gases and/or pulse oximetry. If a high FIO_2 is required to maintain adequate oxygenation, mechanical ventilation and positive-end-expiratory pressure (PEEP) may be required; ventilation with small tidal volumes (6 ml/kg) is preferred if ARDS develops.
- Because of the large volume of distribution, amantadine is generally not well removed by peritoneal dialysis, haemodialysis, or forced diuresis.
- Physostigmine (0.5 mg IV) is helpful in countering agitation, tremors, hallucinations, and delirium. Caution must be exercised with this drug since it can induce seizures, bradycardia, and asystole. Physostigmine should not be used in patients with suspected tricyclic antidepressant overdose, or an ECG suggestive of tricyclic antidepressant overdose (QRS widening, R wave in aVR). In the setting of tricyclic antidepressant overdose, use of physostigmine has precipitated convulsions and intractable cardiac arrest.
- Convulsions can be controlled with benzodiazepines or barbiturates.
- Continuous ECG monitoring is essential to watch out for signs of cardiovascular toxicity. Since ventricular arrhythmias and pulmonary changes can have an onset of up to 48 hours post-ingestion, cardiac and pulmonary monitoring

is recommended for at least 48 hours in patients with significant ingestions. Lignocaine is the drug of choice for cardiac arrhythmias. Amiodarone, phenytoin, or over-drive transvenous pacing can also be effective. Sodium bicarbonate may be effective for ventricular arrhythmias, particularly in association with QRS widening. Administer sodium bicarbonate 1 to 2 mEq/kg intravenously. Repeat as needed to achieve an arterial pH of 7.4 to 7.5. Monitor frequent blood gases and ECGs. For torsades de pointes, emergent treatment with magnesium, isoproterenol, or atrial overdrive pacing is indicated. Avoid class Ia antiarrhythmics (quinidine, disopyramide, procainamide, aprindine) and most class III antiarrhythmics (N- acetylprocainamide, sotalol) since they may further prolong the QT interval and have been associated with torsades de pointes.

2. Interferons

Interferons are naturally occurring, species specific, proteins or glycoproteins that are "biological response mediators" that are produced by cells in response to an event. They are powerful cytokines which possess immunomodulating, antiproliferative, and antiviral actions. There are 3 major classes—alpha, beta, and gamma. The different kinds of interferons include Human leukocyte interferon, Alpha-A-interferon, Alpha-2-interferon, Interferon alfa-2c, Human lymphoblastoid interferon, Interferon alfa-n3, Interferon-beta, T Lymphocyte interferon, and Interferon gamma-1b. Alpha interferons are approved for use in India for the treatment of condyloma acuminata, chronic hepatitis B, and AIDS-related Kaposi's sarcoma. They have also been recommended for the treatment of certain types of leukaemia (e.g. hairy cell leukaemia), as well as renal cell carcinoma, malignant melanoma, and bladder cancer.

Interferons inhibit viral transcription, translation, assembly, and release. They do not directly destroy tumour cells or viruses; they stimulate existing host defenses. They induce T-cell mediated cytotoxicity, natural killer cell activity, macrophage activity, and antibody production.

Interferons are poorly absorbed on oral administration. Following IM or SC injection, absorption exceeds 80%, plasma levels generally peaking at 4 to 8 hours and returning to baseline by 18 to 36 hours. Elimination from the blood relates to the tissues, cellular uptake, and metabolism primarily in the liver and kidney. Insignificant excretion occurs in the urine.

Adverse effects include an influenza-like syndrome (usually self-limiting), characterised by fever, headache, malaise, chills, tachycardia, myalgia, anorexia, vomiting, and diarrhoea. Dizziness, lightheadedness, nasal congestion, sinus drainage, and urinary urgency are reported less frequently. A salty or metallic taste has been described at the start of interferon therapy and at high doses. Excessive growth of eyelashes has been reported.

More serious effects include bone marrow suppression, mental confusion, convulsions, neurasthenia, thyroid dysfunction, pulmonary oedema, respiratory insufficiency, pneumonitis, and cardiotoxicity (cardiac arrhythmias, cardiomyopathy, myocardial ischaemia and infarction, and hypo/hypertension). Somnolence, lethargy, confusion, mental laziness, and extreme fatigue have been reported with doses greater than 100 million units. Spastic paraplegias have also been reported in paediatric patients. Hyperkalaemia and hypocalcaemia may occur with high doses. A decrease may be seen in erythrocytes, leucocytes, granulocytes, lymphocytes and platelets.

Most of these toxic effects induced by interferons are reversible on discontinuation of therapy. The acute syndrome of fever, chills, malaise, and myalgias can be managed by paracetamol or non-steroidal anti-inflammatory drugs.

3. Ribavirin

Ribavirin is a purine nucleoside analogue which has a broad-spectrum antiviral activity against many RNA and DNA viruses. It is recommended for use in the treatment of influenza, respiratory syncytial viral infections, herpes viral infections, and acute viral hepatitis. In India, ribavirin is available as an oral preparation, while abroad it is available in an aerosolised form (for respiratory syncytial viral infections). Oral bioavailability is only 40 to 45%.

Adverse effects of oral ribavirin include anaemia and bone marrow suppression, apart from headache, fatigue, dizziness, insomnia, irritability, dyspnoea, pharyngitis, skin rashes, and gastrointestinal disturbances (anorexia, dyspepsia, vomiting). Intravenous infusion can cause rigors. Aerosolised ribavirin is well tolerated, but may occasionally cause rash, conjunctival irritation, and transient wheezing. Infrequent reports of cardiac abnormalities have developed in patients following aerosolised ribavirin.

There are indications that ribavirin may be teratogenic and oncogenic. Ribavirin was teratogenic in all rodent species tested. Cleft palate was a common effect. Pregnant women should not directly care for patients receiving the aerosolised form of the drug.

Treatment is mostly symptomatic and supportive. Monitor haemoglobin and liver function tests. These changes have been seen with chronic therapeutic administration, and have been reversible upon discontinuation. Patients may have decreased haemoglobin and in a few instances transfusions have been given. Although there may be an increase in indirect bilirubin, ribavirin does not appear to be hepatotoxic. Haemodialysis is ineffective.

ANTIFUNGALS

■ Amphotericin B

Amphotericin B is a polyene macrolide antibiotic obtained from *Streptomyces nodosus*, and is one of the earliest systemic antifungals to be introduced into clinical practice.

Uses

Amphotericin B is administered as an IV infusion for the treatment of systemic fungal infections caused by *Candida, Aspergillus, Cryptococcus, Neoformans,* and *Mucor* species. In other words, it is effective for the treatment of serious infections including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, paracoccidioidomycosis and sporotrichosis. Due to

its significant toxicity, amphotericin B is reserved for life-threatening infections. Intrathecal administration can be done for fungal meningitis (especially due to *Coccidioides*). Bladder irrigation with amphotericin B in sterile water is effective for candida cystitis.

Less toxic formulations of amphotericin B have been introduced recently: amphotericin B lipid complex, amphotericin B cholesteryl sulfate complex, and amphotericin B liposome.

Mode of Action

Amphotericin B acts by combining with the ergosterol of the cytoplasmic membrane of the fungus, thereby creating porous cell membranes. This is followed by leakage of cellular organelles and cell lysis. Since human cells have cholesterol instead of sterols in their cell membranes, they are less affected.

Toxicokinetics

Amphotericin B is absorbed very poorly from the GI tract. After IV administration, more than 90% of the drug is bound to proteins. Approximately 2 to 5% of each dose is excreted in the urine.

Adverse Effects

- Common adverse effects include fever, chills, arthralgia, myalgia, and tachypnoea, which are usually self-limiting.
- Cardiovascular effects comprise tachycardia, hypo/hypertension, and ventricular fibrillation.
- Other reported effects include renal impairment, red man syndrome rash (erythema of the hands, soles, face, and neck), hepatic damage, haematologic abnormalities (anaemia, leukopenia, thrombocytopenia), phlebitis, pulmonary distress, hyperkalaemia, vomiting, and diarrhoea.
- Intrathecal administration has caused paraesthesia, delirium, temporary psychosis, and parkinsonism.
- A few cases of painful cyanotic Raynaud's phenomenon after intravenous administration or inhalation of amphotericin B have been reported.

Drug Interactions

Amphotericin B potentiates potassium loss by corticosteroids, enhances digitalis toxicity, and aggravates renal toxicity when given concomitantly with other nephrotoxic drugs. It is antagonistic to ketoconazole.

Toxic (Clinical) Features

Several cases of overdose with amphotericin B have been reported, and even a few fatalities. Main features include vomiting, diarrhoea, abdominal distension, hypokalaemia, and cardiac arrest. Overdose cases have resulted in mild renal damage, thrombocytopenia, fever, and chills. Children and infants tolerate comparable dosages of amphotericin B better than adults.

Treatment

Overdose patients should be monitored for altered renal function (BUN, creatinine, creatinine clearance), altered electrolytes (especially hyperkalaemia), and have a complete blood count.

Ingestions of large amounts of ointment, creams, or lozenges may necessitate gastrointestinal decontamination.

1. Admit acutely overdosed patients to intensive care unit and monitor cardiac function. Supportive measures are indicated. Haemodialysis is not beneficial.
2. Amphotericin-induced fever and chills can be prevented/managed by ibuprofen, hydrocortisone, or pethidine.
3. Amiloride (5 mg twice daily) can help minimise hypokalaemia.
4. Nephrotoxicity can be minimised by infusing 1 litre of normal saline every day.
5. Amphotericin B is highly protein bound. Therefore, exchange transfusion in infants has been recommended as a treatment for overdose.

■ Flucytosine

Flucytosine is a fluorinated pyrimidine related to fluorouracil. It is sometimes used (orally) in combination with amphotericin B for systemic fungal infections. Its use as a single drug is greatly restricted owing to rapid emergence of resistant strains. It is used today mainly to treat serious systemic fungal infections due to *Candida* and *Cryptococcus* species.

Flucytosine is known for causing bone marrow suppression, and also GI toxicity manifesting as vomiting, diarrhoea, abdominal distension, and even bowel perforation. Patients with a history of haematological disorders, symptomatic HIV infection, radiation, or myelosuppressive therapy are more likely to develop bone-marrow depression following flucytosine treatment. Hepatotoxicity has been reported during therapeutic use of flucytosine. Infrequent problems that have occurred during therapeutic use include neurological effects (convulsions, headache, sedation, vertigo), psychological effects (confusion, hallucinations), allergic reactions, rash, pruritus, urticaria, toxic epidermal necrolysis and cardiac toxicity.

Treatment involves stomach wash, stabilisation, and supportive measures. Monitor CBC with differential and platelet count, as well as, hepatic and renal function tests in symptomatic patients or following exposure as indicated. Serum flucytosine levels may be useful following an acute or an acute-on-chronic exposure. There is an increased risk of toxicity with prolonged serum levels of 100 mcg/mL or higher. Haemodialysis is said to be beneficial, since flucytosine is minimally protein bound (4% or less) and the volume of distribution is similar to total body water.

Since flucytosine is metabolised to 5-fluorouracil (a cytotoxic drug), a detailed follow-up is necessary in cases of overdose. Flucytosine has been shown to be teratogenic.

■ Imidazoles

All imidazoles act by inhibiting the conversion of lanosterol to ergosterol, the main sterol of fungal cell membranes.

Clotrimazole is usually not associated with serious toxicity. Nausea, vomiting, and diarrhoea are frequent side effects following oral administration of clotrimazole. Depression, drowsiness, disorientation, visual alterations, abnormal liver function tests have occurred.

Fluconazole can be given orally or parenterally for a number of systemic fungal infections. It causes nausea, abdominal

discomfort, headache, vertigo, delirium, convulsions, skin rash, and hepatic damage sometimes progressing to fatal hepatic necrosis. Long-term use is associated with alopecia. Hypokalaemia is common. Treatment involves symptomatic and supportive measures. Haemodialysis may be of value.

Ketoconazole was the first synthetic broad-spectrum oral antifungal drug to be introduced into practice and has been around since 1981. It is effective in the treatment of a number of systemic fungal infections. Adverse reactions include hepatitis, anaphylaxis, vomiting, rashes, headache, fever, photophobia, and gynaecomastia. Concomitant alcohol intake can cause nausea and flushing. Deaths have been reported even from therapeutic doses (due to hepatotoxicity). Incidentally, one of the many metabolites of ketoconazole is paracetamol, which is itself a hepatotoxic drug. Treatment involves symptomatic and supportive measures. Extracorporeal methods of elimination are not likely to be useful since much of the parent drug is metabolised. Though paracetamol is one of its metabolites, the use of N-acetylcysteine is not recommended at present.

Miconazole was formerly used intravenously and occasionally induced arrhythmias, hyponatraemia, and seizures. Today it is only used as a local application. Less commonly used imidazole antifungals include bifonazole, butoconazole, croconazole hydrochloride, econazole nitrate, fenticonazole nitrate, omoconazole nitrate, oxiconazole nitrate, sertaconazole nitrate, sulconazole nitrate, and tioconazole. Overdose experience is limited with these agents. Due to minimal oral absorption and limited systemic toxicity, severe toxic effects following oral overdose is not anticipated. Ingestion of even large quantities should produce only minor GI symptoms. Treatment is usually unnecessary. Dermal application, however, may produce local irritation. Patients treated with imidazole antifungal vaginal products have reported (rarely): dysuria, slight urinary frequency, lower abdominal cramping, and dyspareunia. An objectionable odour has been reported in up to 20% of patients using butoconazole. Some of these agents are teratogenic.

■ Griseofulvin

Griseofulvin is a fungistatic antibiotic which can be administered orally. It is derived from *Penicillium griseofulvin* and *Penicillium janczewskii*, and is effective in the treatment of a variety of dermatophytoses, (especially against various species of Microsporum, Epidermophyton, and Trichophyton). It is presumed to act by disrupting the fungal mitotic spindle structure and arrest fungal growth in the M phase of the life cycle.

Griseofulvin is also said to be beneficial in the treatment of Raynaud's disease, systemic sclerosis, lichen planus, herpes zoster, and molluscum contagious. The recommended daily dose for children is 10 mg/kg and for adults 500 mg to 1 gram daily. Peak plasma levels are noted about 4 to 6 hours following a therapeutic dose, and the plasma half-life is about 24 hours. Griseofulvin is metabolised in the liver and excreted in the urine. A major portion of orally administered griseofulvin is eliminated unchanged in the faeces.

Adverse effects include confusion, fatigue, dry mouth, headache, anorexia, vomiting, abdominal cramps, diarrhoea,

vertigo, blurred vision, lethargy, insomnia, albuminuria and cylindruria without evidence of renal insufficiency, and haematological disturbances (leukopenia, neutropenia). Hepatotoxicity has also been reported. Hypersensitivity reactions include urticaria, angioedema, and erythema multiforme. Cross-reactivity with penicillin is a possibility.

There is insufficient information in the literature to accurately characterise the syndrome following griseofulvin overdosage. However, limited toxicity can be expected. Hyperamylasaemia and elevated liver enzymes have been reported following griseofulvin overdose. Griseofulvin is a microsomal enzyme inducer, produces an alcohol intolerance reaction, and has been associated with development of porphyria. Concomitant intake of alcohol along with griseofulvin can induce a disulfiram-like reaction.

Efficacy of oral contraceptives may be affected and there can be amenorrhoea or intermenstrual bleeding. Griseofulvin is said to be foetotoxic and should not be administered to pregnant women. There have been reports of mongolism and conjoined twins.

Treatment of overdose is symptomatic and supportive. Activated charcoal, cathartics, or extracorporeal methods of elimination do not appear to be beneficial, though early stomach wash may help. Intensive care therapy is desirable in serious overdose with constant respiratory and cardiac monitoring. Mild to moderate allergic reactions may be treated with antihistamines with or without inhaled beta agonists, corticosteroids or adrenaline.

■ ANTIPROTOZOAL AGENTS

Since protozoal infections such as trypanosomiasis (*Sleeping sickness*) and leishmaniasis (*Kala azar*) are uncommon in India, the toxicity of drugs used in their treatment will not be discussed here.

■ Antimalarials

While malaria is considered a global disease accounting for around 500 million cases with about 3 million deaths each year, many of these cases are actually reported from tropical countries such as India.

■ Chloroguanide (Proguanil)

Chloroguanide is a biguanide derivative and is usually used in combination with chloroquine or atovaquone, for the prophylaxis and treatment of acute, uncomplicated falciparum malaria, particularly in areas where chloroquine resistance has been reported. It is a prodrug that metabolises to cycloguanil, the active dihydrofolate reductase inhibitor antimalarial agent, and is administered orally.

Adverse effects are uncommon and manifest as occasional nausea and diarrhoea. Mouth ulceration, headaches, dizziness, and skin rash have also been reported. Total alopecia was reported in several patients following chronic proguanil therapy. The severity of alopecia was directly proportional to the duration of proguanil use and appeared to be reversible upon discontinuation of the medication.

Overdose (more than 1 gm) may cause vomiting, abdominal pain, diarrhoea and haematuria. Large doses of proguanil may result in the transient appearance of epithelial cells and casts in

the urine. Megaloblastic anaemia and pancytopenia have been reported in patients with severe renal impairment. Fatalities have not been reported.

Treatment is symptomatic and supportive. Monitor CBC as indicated in symptomatic patients. Monitor fluid and electrolyte status in patients with significant vomiting and/or diarrhoea.

■ Primaquine

Primaquine is an 8-aminoquinoline which is given orally for the terminal prophylaxis and radical cure of vivax and ovale malaria. It is invariably given together with chloroquine. Primaquine causes haemolysis in susceptible individuals who suffer from glucose-6-phosphate dehydrogenase deficiency. Severe haemolytic reactions are seen among blacks and dark-skinned Caucasians such as Greeks, Sardinians, Sephardic Jews, and Iranians. Methaemoglobinaemia is fairly common with high doses of primaquine and can be severe in individuals with NADH-methaemoglobin-reductase deficiency. Less serious adverse effects include abdominal distress, mild anaemia and leucocytosis.

Overdose is associated with granulocytopenia, agranulocytosis, hypertension, and arrhythmias. During the course of primaquine therapy, it is desirable to perform regular blood counts and urinalysis for haemoglobinuria.

■ Quinine and Quinidine

The bark of the Cinchona tree (**Fig 30.6**) yields both quinine and quinidine which have been around for more than 350 years. Quinidine is a more powerful antimalarial than quinine, but is unfortunately also much more toxic. Hydroquinidine is a related drug with actions and uses similar to those of quinidine. Quinine is very bitter (the bitterness threshold of quinine hydrochloride is 1:30,000).

Uses

1. Quinine is mainly indicated in the treatment of chloroquine-resistant and multidrug-resistant falciparum malaria.
2. Quinine is also reportedly beneficial for relieving nocturnal leg cramps, and for the symptomatic relief of myotonia congenita.
3. Quinidine is a potent antiarrhythmic agent and is used for the maintenance of sinus rhythm (in atrial flutter/fibrillation), as well as for the prevention of ventricular tachycardia/fibrillation. It is a class 1A antiarrhythmic agent.
4. Tonic water is reported to contain 30 to 80 mg quinine per 1000 ml. Blurring of vision has been reported in individuals consuming 100 to 200 mg quinine via tonic water, and is a potentially serious effect if driving or flying.
5. Quinine has been found as an adulterant in illicit heroin samples.

Toxicokinetics

Cinchona alkaloids are rapidly absorbed when given orally or intramuscularly, but the latter mode of administration often leads to tissue necrosis. Peak plasma levels are achieved in 3

Fig 30.6: Cinchona tree

hours (2 to 7 hours for quinidine). Both quinine and quinidine are highly protein-bound. The liver, kidneys, and muscles metabolise 80% of the ingested dose, while 20% is excreted unchanged in the urine. Quinine is oxidised to form several polar hydroxy metabolites. About 17% is excreted unchanged, 17% as 3-hydroxyquinine and 34% as 2-hydroxyquinine. A nonphenolic dihydroxy derivative has also been identified. Renal excretion is greatly enhanced in acidic urine.

Clinical (Toxic) Features

1. Repeated therapeutic doses as well as overdose result in a cluster of manifestations referred to as *Cinchonism* which is characterised by the following:
   a. Mild: Tinnitus, headache, nausea, disturbed vision.
   b. Severe: Vertigo, deafness,* mydriasis, photophobia, diplopia, constricted visual fields, scotomata, blindness (*quinine amblyopia*), vomiting, diarrhoea, abdominal pain, sweating, skin rash, hypoglycaemia, and cardiac arrhythmias. Rapid infusion can cause severe hypotension.
   c. Potentially lethal: delirium, coma, seizures, myocardial depression.
2. Fixed dilated pupils are seen frequently in children following quinine overdose. Following an overdose, onset of symptoms of oculotoxicity may vary from a few hours to a day or more. In addition to cinchonism, quinine is thought to have either an ischaemic action on the retinal vasculature or a direct toxic effect on the retina, causing constricted visual fields that can progress to blindness with dilated nonreactive pupils. Central vision usually recovers first. Complete recovery of vision may take several months; pupils may remain dilated after recovery of vision. Permanent visual deficits may remain.

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* Due to micromechanical changes on the contactile structure of the outer hair cells of the organ of Corti. It is usually temporary.

3. Cardiovascular effects typically occur within 8 hours of ingestion. Cardiotoxicity which may be delayed until 25 hours after ingestion has been reported. ECG changes closely reflect relative tissue levels. Sinoatrial, atrioventricular, and His-ventricular conduction delays may occur resulting in significant QRS and QT interval prolongation, PR prolongation, ST depression and T wave inversion on ECG. Ventricular fibrillation and ventricular tachycardia, may also occur. Torsade de pointes may lead to syncope. Hypotension occurs frequently following severe overdose. Torsade de pointes has been reported following therapy with quinidine and hydroquinidine. Hypokalaemia may occur secondary to quinine-induced electrolyte fluxes. Aggressive treatment is not always recommended since a mild degree of hypokalaemia may protect against cardiotoxicity.

4. In one case series of 96 patients with quinine intoxication, tinnitus and other auditory complaints developed in 17% of the patients with reported ingestions of less than 1 gram compared with 80% of the patients with reported ingestions of more than 5 grams. Hearing loss is typically reversible at therapeutic doses and occurs in 20% of patients taking prolonged courses of 200 to 300 mg daily. Sensorineural hearing loss affects high frequencies initially. By the time losses at conversational frequencies are noted, the hearing loss may be irreversible.

5. Central nervous system toxicity seems to be more marked in children than adults; children frequently present with convulsions following an overdose.

6. Hepatotoxicity with therapeutic quinine use has been reported, and has occurred within 24 hours of initiation of a quinine dose, although onset generally occurs after 2 weeks of therapy. On discontinuance of quinine, liver enzyme values usually return to normal.

7. Hypoglycaemia has also been reported. Special care is necessary in diabetics, since the hypoglycaemic effect of antidiabetic drugs can get aggravated.

8. Haemolytic uraemic syndrome (HUS) has occasionally been reported as an adverse effect of quinine therapy. In these cases, the immune-mediated nature of the blood dyscrasia is specific to quinine. The presence of quinine-dependant antibodies to red cells, granulocytes or platelets has been demonstrated in some cases. There appears to be no correlation between the type and specificity of antibody and severity of renal failure. Quinine-induced haemolysis and renal failure, due to acute interstitial nephritis, has been reported.

9. Haemolytic anaemia may occur in patients with G6PD deficiency. Immune-mediated pancytopenia and coagulopathy may occur at therapeutic doses of quinine. This may be associated with renal failure and the haemolytic uraemic syndrome.

10. Quinine and quinidine are contraindicated in myasthenia gravis (can aggravate muscle weakness), and in pregnancy (can induce abortion due to oxytocic action). Quinine crosses the placental barrier. Numerous malformations and foetal anomalies have been reported. Quinine has often been used as a home abortifacient, resulting in a 59% incidence of congenital anomalies and 16% of maternal deaths.

11. Quinine can sometimes produce a hypersensitivity reaction characterised by massive haemolysis, haemoglobinuria with passage of dark urine, anuria, and renal failure (*black water fever*). It occurs usually during the course of treatment of falciparum malaria. A variant form of quinine toxicity, with hypersensitivity mimicking septic shock, has been reported.

12. Quinidine has been implicated as a cause of a variety of dermatologic effects including thrombocytopenic purpura, angioedema, exfoliative dermatitis, livedo reticularis, photodermatitis, urticaria, scarlatiniform or morbilliform eruptions, acneiform eruptions, flushing, pruritus, contact dermatitis, lichenoid and bullous reactions, psoriasis, erythroderma and erythema multiforme.

13. Chronic therapeutic use of quinidine has been associated with a variety of immune mediated disorders including haemolytic anaemia, thrombocytopenia, an SLE-like syndrome, sicca syndrome (keratoconjunctivitis, arthritis, fever), and lymphadenopathy.

Usual Fatal Dose

- Quinine: 4 to 8 grams (adult); 1 to 2 grams (child).
- Quinidine: 4 to 6 grams.
- There are however reports of survival following ingestion of upto 20 grams of quinidine.
- In both quinine as well as quinidine, plasma concentrations over 5 mcg/ml have been associated with cinchonism. Levels above 10 mcg/ml are associated with visual impairment, and levels above 16 mcg/ml are associated with cardiac arrhythmias.
- In the case of quinidine, convulsions have been reported after overdoses of 4.5 grams or more.

Diagnosis

1. Measurement of serum levels of these drugs by high pressure liquid chromatography. Quinine levels higher than 15 mcg/ml, and quinidine levels higher than 10 mcg/ml are indicative of serious toxicity.

2. Early recognition of visual damage is essential. Eye changes (photophobia, misty vision) usually begin in ½ to 1 hour after overdose and may progress to partial or complete blindness in 6 to 12 hours. While such blindness may resolve over a period of time (1 to 3 weeks), it sometimes becomes permanent.
   a. Ophthalmoscopic findings**:**
      – Pallor of optic disc.
      – Constriction of retinal arteries and veins.
      – Cherry spot at the macula.
      – Retinal oedema.

Treatment

The overdosed patient should be hospitalised in an intensive

care facility with immediate attention given to vital signs (blood pressure, pulse, respiration) and careful monitoring of ECG and respiratory status. Patients should be warned of possible blindness but reassured that some recovery of sight frequently occurs.

1. Stomach wash (with prior endotracheal intubation) should be undertaken only if the patient is seen within 1 to 2 hours of ingestion.

2. Activated charcoal has been proved to be beneficial and can be administered in the usual manner (1 gm/kg). Despite quinine's relatively large volume of distribution, high protein binding, and poor in vitro adsorption by charcoal, studies have shown enhanced elimination with multiple-dose-charcoal regimens in therapeutic doses and overdoses. It should be considered in patients with potentially life-threatening overdose.

3. While acid diuresis promotes clearance of quinine and quinidine, it is associated with cardiotoxicity and hence is not recommended. On the other hand, serum alkalinisation with sodium bicarbonate can be beneficial. It is desirable to achieve and maintain a serum pH of 7.45 to 7.50.

4. *For hypotension:* Pure or predominant alpha agonists may be more effective in managing hypotension. These include noradrenaline and metaraminol.

5. Continuous cardiac monitoring is essential. Alkalinisation of serum usually prevents conduction abnormalities and arrhythmias. Treat QRS widening and/or ventricular arrhythmias with intravenous bicarbonate. A reasonable starting dose is 1 to 2 mEq/kg as an intravenous bolus. Repeat as necessary to maintain arterial pH 7.45 to 7.55. Administration of Class I, II, and III antiarrhythmic agents is contraindicated. Ventricular tachycardia/fibrillation can be corrected by direct-current cardioversion. Torsade de pointes can be tackled with magnesium sulfate, isoproterenol or overdrive pacing, while transvenous pacing is useful for complete heart block.

6. Refractory bradycardia or heart block that compromises blood pressure, requires temporary pacemaker insertion. Markedly prolonged conduction, Mobitz II block, or third degree heart block should be considered indications for prophylactic pacemaker insertion.

7. Correction of acidosis, electrolyte imbalance, and hypoxia are imperative for the successful management of cardiotoxicity.

8. For convulsions, attempt initial control with a benzodiazepine (diazepam or lorazepam). If convulsions persist or recur administer phenobarbitone. Evaluate for hypoxia, electrolyte disturbances and hypoglycaemia.

   a. Visual damage may be minimised by stellate ganglion block, but there appears to be some controversy regarding this. Specific treatment for quinine retinal toxicity has so far not been evolved. Vision usually improves with appropriate prompt reversal of systemic toxicity, though pupils may remain dilated for a long time even after complete restoration of eyesight.

   b. There is a report of a case of blindness (an infant who ingested 600 mg) which was treated with intravenous isosorbide dinitrate. An ophthalmological review 6 weeks post-discharge showed full restoration of sight.

9. In another case of quinine poisoning resulting in bilateral visual loss with retinal arteriolar constriction, fluctuating visual loss suggested an element of vasospasm. The authors chose to use IV nimodipine (0.01 mg/kg/hr) for vasospasm, and IV hydration with 0.9% saline to maintain a central venous pressure of at least 9 mmHg. In addition, IV noradrenaline was administered to maintain a systolic blood pressure of 140–180 mmHg. Over the next 24 hours, the patient's vision improved to 6/9 bilaterally and did not deteriorate again. Within 12 hours of the therapy, retinal blood flow was noted to be improved on direct fundoscopy.

10. Haemodialysis combined with resin haemoperfusion may help in eliminating quinine from the blood. Exchange transfusion does not appear to be beneficial.

11. Hyperbaric oxygen therapy has been recommended by some investigators but its actual efficacy is in doubt.

◼ Chloroquine and Amodiaquine

Chloroquine and amodiaquine are 4-aminoquinolines which were products of American research during World War II, though there are reliable indications that chloroquine had been synthesised by the Germans several years earlier as *Resochin,* which is incidentally a very popular brand name for chloroquine even today. Other members of the group of 4-aminoquinolones include broxyquinoline, cycloquine, di-iodohydroxyquine, hydroxychloroquine, mepacrine, pamaquine, pentaquine, and plasmocid.

Amodiaquine is actually a congener of chloroquine and is no longer used abroad owing to its propensity for causing hepatic damage and agranulocytosis. Another related compound, hydroxychloroquine is preferred in the treatment of rheumatoid arthritis and SLE in place of chloroquine since it is less oculotoxic in the long run.

Toxicokinetics

Chloroquine is well absorbed orally and parenterally (intramuscular and subcutaneous injection). It has a large volume of distribution, and is moderately protein-bound (50%). Peak plasma levels are achieved in 2 to 3 hours. There is a large amount of tissue storage with chloroquine. Chloroquine accumulates especially in heart, kidney, liver, pancreas, lung and spleen, and is strongly bound in melanin-containing cells (eye and skin). Excretion occurs in the urine, upto 20% of the drug being unchanged. The main metabolite is monodesethyl chloroquine. Renal excretion of chloroquine and its major metabolite is enhanced by acidification of the urine.

Adverse Effects and Clinical (Toxic) Features

1. Long-term effects of prolonged chloroquine therapy include malaise, anorexia, pruritus, urticaria, haemolytic anaemia, methaemoglobinaemia, retinopathy, psychosis, seizures, convulsions, vertigo, headache, and convulsions. Sudden respiratory apnoea can occur. CVS manifestations comprise hypotension, atrioventricular conduction defects, and cardiac arrhythmias. Hypokalaemia is often present. Cardiomyopathy has also been reported in several cases.

2. In a retrospective chart review, chronic therapy with hydroxychloroquine was found to be less toxic to the retina than chloroquine therapy. Effects of chloroquine retinopathy include pigmentary stippling, mottling, a "bull's eye" pattern of macular hyperpigmentation, attenuation of the retinal arteries, pale optic discs, disturbance of colour vision, loss of central vision scotoma and visual field defects.

3. Psychosis as the sole adverse effect has been reported often with therapeutic use of chloroquine, especially in children. Capgras' syndrome (the misguided belief that a familiar person has been replaced by an imposter), was reported in the case of an 8-year-old girl who was treated with therapeutic chloroquine for three days. Psychiatric disturbances may appear as early as within 24 hours of the first dose, or as late as several days after the final dose. A retrospective review of chloroquine-induced psychiatric complications (organic psychoses, schizophrenia, depression, and anxiety) found that symptoms appeared after intake of 2.4 to 6 grams of chloroquine between 4 and 40 days after onset of therapy. The exact mechanism remains unknown.

4. Acute overdose with chloroquine can cause nausea, vomiting, diarrhoea, haemorrhagic gastritis, hyperexcitability, agitation, convulsions, coma, QRS widening, ventricular arrhythmias, hypotension, shock, cardiac arrest, respiratory arrest and death.
   a. The following are indications of severe toxicity: systolic BP < 90 mmHg, QRS duration >110 milliseconds, and hypokalaemia (K^+ < 3.0 mEq).
   b. Chloroquine overdose has resulted in life-threatening cardiotoxic effects. The primary effects include hypotension, vasodilation, ECG abnormalities (prolonged PR, QRS, and QT interval), ventricular arrhythmias and cardiovascular collapse. Cardiac arrest may occur rapidly, within 1 to 2 hours following ingestion. Hypotension is frequent and may progress rapidly to cardiogenic shock with increased central venous pressure following chloroquine or hydroxychloroquine overdose. Severe hypokalaemia (1 to 2 mmol/L) is frequent in severe intoxication.

5. Amodiaquine toxicity results in spasticity, seizures, convulsions, dysarthria, syncope, hepatitis and agranulocytosis.

6. Hydroxychloroquine poisoning produces vomiting, seizures, arrhythmias (less common), myocarditis and myopathy and hepatic failure.

7. Chloroquine is wrongly believed to be an effective abortifacient by the lay public. It is true that stillbirths and spontaneous abortions have occurred after taking chloroquine or hydroxychloroquine, but these drugs are by no means reliable abortifacients.

Usual Fatal Dose

- Chloroquine: 3 to 6 grams. As little as 2.25 to 3 grams of chloroquine may be fatal in an adult. About 2 to 3 times the therapeutic dose may be fatal in children. Estimated fatal dose is 30 to 50 mg chloroquine base/kg.
- Hydroxychloroquine: 10 to 20 grams. Adults have developed hypotension and ventricular arrhythmias after ingesting 12 to 22 grams.
- Chloroquine toxicity is dose dependant. The following has been observed in adults:
  - ❖ Dose ingested greater than 4 grams - neurological, cardiovascular and ECG disturbances; serum chloroquine level greater than 5 mg/L at the 4th hour.
  - ❖ Dose ingested 2 to 4 grams - neurological symptoms and ECG abnormalities, serum chloroquine level of 2.5 to 5 mg/L.
  - ❖ Dose ingested less than 2 grams - no clinical symptoms, serum chloroquine level less than 2.5 mg/L.
  - ❖ The occurrence of side effects in patients under chloroquine therapy is related to chloroquine serum levels. No side effects occurred in patients with serum levels less than 0.4 mg/L, whereas 80% of the patients with a level higher than 0.8 mg/L had side effects.

Diagnosis

1. Serum level estimation by high pressure liquid chromatography. Chloroquine levels higher than 5 mcg/ml are associated with serious toxicity.

2. Like quinine, chloroquine fluoresces under UV light (254 nm and 366 nm), and this property can be used to identify the substance in urine. For this purpose, first add 0.1 ml of dilute HCl to 1 ml of urine and then vortex-mix for 10 seconds. If there is fluorescence, add 1 gram of sodium chloride, vortex-mix for 10 seconds and examine under UV light again. The urine will not fluoresce any more.

Treatment

Patients with suspected chloroquine overdose should receive gastric decontamination, have an ECG performed and continuous cardiac monitoring for a minimum of 6 hours after ingestion. Patients who are asymptomatic during this period may be discharged after psychiatric evaluation (if indicated). Monitor serum electrolytes and arterial blood gases in symptomatic patients.

1. *Stabilisation*: The patient should be treated in an intensive care unit and continuous cardiac monitoring must be done. Preparations should be made for airway protection (endotracheal intubation) and mechanical ventilation. Defibrillator and cardiac pacemaker may be required.

2. *Treatment of convulsions*:
   a. Correct anoxia by administering 100% oxygen.
   b. Give diazepam (upto 10 mg IV slowly in adults; 0.1 to 0.3 mg/kg IV slowly in children).
   c. If convulsions do not respond to diazepam, administer phenytoin (15 mg/kg IV at 0.25 to 0.5 mg/kg/min). In severe cases, neuromuscular paralysis may be required to avoid hyperthermia, severe acidosis, and rhabdomyolysis; continuous EEG monitoring is mandatory if neuromuscular paralysis is used.
   d Correct hypotension by IV fluids, Trendelenberg position, and dopamine or noradrenaline.

3. *Cardioprotection:*
   a. Adrenaline (1: 10,000) at a dose of 0.25 mcg/kg/min, until systolic pressure is at least 100 mmHg.

b. Diazepam 2 mg/kg over 30 minutes (preferably through motor-driven syringe type pump). The role of diazepam in chloroquine poisoning has long been under study. It is believed that diazepam apparently competes for cardiac chloroquine fixation sites.

c. Indications for noradrenaline therapy include massive ingestion (> 5 gm chloroquine), very low systolic pressure (< 80 mmHg), and prolonged QRS interval (> 120 milliseconds). Diazepam is indicated in patients with convulsions, arrhythmias, QRS widening, hypotension, or circulatory collapse.

4. *Decontamination*: Gastric lavage may be done if the patient is seen within 2 hours of ingestion. Activated charcoal (1 gm/kg) is highly recommended.

5. *Elimination*: Acid diuresis though advocated by some investigators is best avoided. Exchange transfusion may be useful. Peritoneal dialysis and haemodialysis are of little value in removing chloroquine from the body. Chloroquine is well adsorbed by charcoal. However it has a large volume of distribution and is rapidly distributed intracellularly; therefore the amount removed by haemoperfusion is not large.

6. *Supportive measures*:

a. Correct hypokalaemia with potassium (0.25 mEq/kg/hr, upto a maximum of 10 mEq/hr in 2 hours). Initial hypokalaemia should be corrected cautiously because potassium and quinidine-like drugs have a synergistic cardiotoxic effect, and intensive administration of potassium may lead to a sudden hyperkalaemia.

b. Arrhythmias may require lignocaine. Ventricular tachycardia/fibrillation can be corrected by direct current cardioversion. Recurrence can be prevented by rapid pacemaker stimulation. Avoid class Ia antiarrhythmics (quinidine, disopyramide, procainamide, aprindine), and most class III antiarrhythmics (N- acetylprocainamide, sotalol).

c. Monitor liver and renal function.

■ Other Antimalarial Drugs

1. Mefloquine

It is an antimalarial agent which is a blood schizontocide. It is a 4-quinolone-methanol developed in the 1960s to combat drug-resistant strains of *Plasmodium falciparum*. It is administered orally, and plama levels rise in a biphasic manner to reach their peak in about 15 to 17 hours. Mefloquine is widely distributed and highly protein-bound (98%). Excretion is mainly by faecal route.

Therapeutic doses are usually well tolerated, but may occasionally cause abdominal pain, vomiting, diarrhoea, and vertigo. Higher doses result in ataxia, headache, bradycardia, prolongation of the QTc interval, hypoglycaemia, psychosis, anxiety, depression, agitation, nightmares, hallucinations, paranoia and audiovisual disturbances. Women may be more susceptible to mefloquine-induced neuropsychiatric effects. Other effects reported include skin rashes, pruritus and urticaria, hair loss, muscle weakness, myalgia, liver function disturbances, and occasionally thrombocytopenia and leucopenia. Rare complications include encephalopathy and seizures. Concomitant administration of quinine or chloroquine enhances the risk of convulsions as well as cardiotoxicity. Since mefloquine has a long elimination half-life (13 to 24 days), adverse effects may persist for several weeks after drug cessation. A post-malaria neurological syndrome has been reported, consisting of confusion, psychosis, seizures, or tremor developing after treatment for malaria.

Treatment of acute toxicity is on general lines with special attention directed towards control of seizures. All patients with mefloquine overdose should be admitted and observed with continuous cardiac monitoring, along with neurologic and psychiatric assessment, for at least 24 hours. Activated charcoal can be administered or stomach wash done, if decontamination is applicable in a given case. Atropine, dobutamine, or pacing can control bradycardia. Phenytoin, lignocaine, or amiodarone may be required for ventricular arrhythmias. Methods of extracorporeal elimination are unlikely to be of benefit because of the large volume of distribution and extensive protein binding of mefloquine.

Spontaneous abortions and an increased number of stillbirths were seen in women who received mefloquine for malaria prophylaxis early in pregnancy. Animal experiments suggest that mefloquine is teratogenic.

2. Halofantrine

It is a phenanthrene methanol which is sometimes used as an alternative to quinine and mefloquine for the treatment of drug-resistant falciparum malaria. It is a blood schizontocide with no apparent activity against the sporocyte, gametocyte, or hepatic stages of the infection.

Side effects include vomiting, diarrhoea, and abdominal pain. Syncope, dizziness, pruritus, and convulsions may also occur. High doses induce cardiotoxicity (QTc interval prolongation and ventricular arrhythmias). Halofantrine should be taken on an empty stomach. Food, especially food high in fat content, increases the absorption of halofantrine, which may increase its toxicity.

Although not reported, overdose of halofantrine might also be expected to cause cardiotoxicity (ECG abnormalities and ventricular arrhythmias) and gastrointestinal toxicity (nausea, vomiting, diarrhoea, and abdominal pain).

Treatment of halofantrine overdose is mainly symptomatic and supportive. Activated charcoal and/or gastric lavage may be of help in the initial stages. Monitor fluid and electrolytes in cases of severe vomiting and diarrhoea, and ECG for ventricular arrhythmias. Antiarrhythmic agents (lignocaine, phenytoin, amiodarone, etc.) may be required. Convulsions can be controlled with benzodiazepines. Liver function tests should be monitored in symptomatic patients.

3. Endoperoxidases

They are recent entrants in the field of antimalarial therapy, and are represented mainly by **qinghaosu** (a sesquiterpene lactone discovered in China), and its derivatives **artemether** and **artesunate**. They are used in the treatment of drug-resistant falciparum malaria. They are generally well tolerated, but can occasionally cause gastrointestinal distress and cardiotoxicity.

4. Pyrimethamine

It is a dihydrofolate reductase inhibitor, and is used in combination with **sulfadoxine** (a long-acting sulfonamide), **or trimethoprim,** for the treatment of chloroquine-resistant falciparum malaria. This drug combination is also recommended for the therapy of toxoplasmosis. Adverse reactions include severe cutaneous eruptions, DIC, blood dyscrasias, anaphylactoid reactions, peripheral neuritis, ataxia, vertigo, and renal/hepatic damage. Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anaemia.

Most serious cases of pyrimethamine overdose have been reported in children under three years old. Symptoms include vomiting, rashes, CNS depression, convulsions, hyperpyrexia, tachycardia, respiratory rate changes, and jaundice. Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more and include nausea, vomiting, dizziness, headaches, mental depression, confusion, and bone marrow depression.

Treatment of overdose with either agent is supportive in nature. Haemodialysis is moderately effective in eliminating trimethoprim. Due to higher protein binding, it is not likely that haemodialysis will be very effective for the elimination of pyrimethamine.

5. Mepacrine (Quinacrine)

It is an acridine derivative which was formerly used widely as an antimalarial drug, but is unpopular today owing to severe side effects including vertigo, headache, ataxia, vomiting, yellowish discolouration of skin and urine, bluish-black discolouration of palate and nails, psychosis, convulsions, ocular toxicity, exfoliative dermatitis, liver damage, and aplastic anaemia. It is incompatible with alcohol and can produce a disulfiram-like reaction. Mepacrine has been banned in the USA and most other Western countries since the early 1990s. That it is still available in India is a sad reflection of governmental apathy towards the sale of dangerous and obsolete drugs.

ANTIAMOEBICS

Amoebiasis, like malaria, is a scourge of tropical countries such as India while it is relatively rare in the West. Infection is particularly common among lower socio-economic groups and institutionalised individuals.

■ Diloxanide Furoate

It is the furoate ester of a dichloroacetamide derivative which is given alone in asymptomatic cyst passers, and in combination with metronidazole or tinidazole for patients with active amoebiasis. It is administered orally. Side effects are rare: flatulence, vomiting, urticaria.

■ Quinidochlor and Clioquinol

These are halogenated 8-hydroxyquinolines which are used as luminal amoebicides to treat asymptomatic cyst passers. High doses can cause *Subacute myelo-optic neuropathy* (*SMON*).* A delayed onset retrograde amnesia is seen in some patients. More commonly they cause gastrointestinal upset, diarrhoea, allergic reactions, and thyroid enlargement. Optic neuropathies and optic atrophy have occurred in some patients who have taken large doses. These changes have resulted in visual impairment and in some cases, permanent blindness. An iron chelate of clioquinol may result in a green colour or green "fur" on the tongue in some patients. The urine may also be green coloured. The halogenated hydroxyquinolines have produced frequent allergic reactions in humans, and have included both sensitisation (1.4 to 1.9%) and cross-sensitisation to such agents as quinoline-based antimalarial drugs, and in a few cases, potassium iodide.

Because of the neurotoxicity seen between 1955 and 1970, clioquinol and similar halogenated hydroxyquinolines have been taken off the market in many countries.

Patients on these agents chronically, or who take large overdoses may require monitoring of visual fields, neurologic status, and folic acid and vitamin B_{12} levels. No specific treatment has been effective, other than discontinuation of the drug. In some cases, there has been improvement of vision over the several months immediately following discontinuation of the clioquinol.

■ Emetine and Dehydroemetine

Emetine is an alkaloid obtained from *Cephaelis ipecacuanha* (Brazil root), the syrup prepared from which is a popular emetic today (*page no 18*). Emetine and its derivative dehydroemetine were previously popular as systemic amoebicides. Both are rarely used today owing to cardiotoxicity as well as other adverse effects such as vomiting, hypotension, and myoneuralgia. The usual fatal dose of emetine is around 200 mg for an adult.

■ 5-Nitroimidazoles

The 5-nitroimidazoles comprise metronidazole, nimorazole, ornidazole, secnidazole, and tinidazole. Much of the following discussion is centred around metronidazole which is the most important member of the group, and has an extremely broad spectrum of antiprotozoal and antimicrobial activity.

Uses

1. Drug of choice for the treatment of all symptomatic forms of amoebiasis.
2. Drug of choice for the treatment of giardiasis.
3. Treatment of genital infections with *Trichomonas vaginalis*.
4. Treatment of serious anaerobic infections.
5. Treatment of peptic ulcer due to *Helicobacter pylori*.
6. Treatment of pseudomembranous colitis.
7. Secnidazole is used in the treatment of giardiasis, intestinal amoebiasis, vaginal trichomoniasis, and bacterial vaginitis.

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* Neurological disease characterised by ataxia, impaired vision, convulsions, and coma. The drug affects the long fibres of the spinal cord, and the optic nerve. Most cases have been reported from Japan and a few from Australia. There may be permanent neurological disability.

8. Tinidazole is effective in the treatment of susceptible protozoal infections and prophylactic treatment of anaerobic bacterial infections. It is primarily used in the treatment of trichomoniasis, giardiasis, and amoebiasis or amoebic liver abscess.

Toxicokinetics

Metronidazole is completely absorbed on oral administration. Peak plasma level is generally achieved in 1 to 3 hours. It penetrates into all tissues and fluids. Metronidazole and related drugs are widely distributed in many body fluids including bile, breast milk, CSF, saliva; they can also cross the placenta readily, and be found in a variety of body tissues. Liver is the main site of metabolism, while excretion occurs mainly in the urine which may turn reddish brown. Most of these drugs are only minimally protein bound.

Adverse and Clinical (Toxic) Features

1. Adverse effects include headache, nausea, metallic taste, anorexia, and occasionally vomiting and diarrhoea. Glossitis and stomatitis may occur. Rare side effects include vertigo, insomnia, CNS depression, sensory neuropathies, encephalopathy, convulsions, and ataxia. Urticaria, dysuria, darkening of the urine, and cystitis have also been reported. Tinidazole is generally much better tolerated than metronidazole.
2. Dark urine (green/black) has been reported in some cases.
3. Concomitant intake of metronidazole with alcohol induces a disulfiram-like reaction. Psychotic responses have also been reported with concurrent ethanol and metronidazole therapy. Alcoholic beverages or products containing ethanol or propylene glycol should not be used during tinidazole therapy also (and for 3 days after the cessation of therapy), because nausea, vomiting, abdominal cramps, headaches and flushing may occur.
4. Animal experiments suggest that metronidazole is carcinogenic.

Treatment

Acute toxicity has rarely been reported with this drug. Single oral doses of metronidazole of 15 grams have been tolerated with only minimal clinical effects. However, standard treatment measures may be indicated in ingestions of greater than 1 to 2 grams. A baseline CBC and renal and hepatic function tests should be obtained. Treatment is symptomatic and supportive. Metronidazole is rapidly removed by haemodialysis.

ANTIHELMINTHICS (ANTHELMINTICS)

Infection with parasitic worms (*helminthiasis*) is a global problem with more than 2 billion people estimated to be affected, though tropical countries demonstrate the maximum prevalence. Common worms encountered include nematodes (round worms), trematodes (flukes), and cestodes (tapeworms).

Hookworms, threadworms, whipworms, and guineaworms are also common culprits in India. In some parts of the country filariasis (due to the nematode *Wuchereria bancrofti*), echinococcosis or hydatid disease (due to the tapeworm *Echinococcus granulosis*), and cysticercosis (due to the larval form of the tapeworm *Cysticercus*) are occasionally reported.

The following discussion is centred around the common antihelminthic drugs available in India.

■ Benzimidazoles

These are broad-spectrum antihelminthic agents, the most popular of which include albendazole, cambendazole, mebendazole, and thiobendazole.

Uses

Benzimidazoles are effective in the treatment of cutaneous larva migrans (creeping eruption), strongyloidiasis (threadworm infestation), hydatid disease, and infestation due to *Enterobius* (pinworm), *Ancylostoma* and *Necator* (hookworms), *Ascaris* (roundworm), *Trichuris* (whipworm) and *Taenia solium* (tapeworm).

Mebendazole has also been used as a fungicide for controlling spoilage in citrus fruits and Dutch Elm disease. Thiabendazole has also been used as a fungicidal food preservative.

Adverse and Clinical (Toxic) Features

1. Common side effects include nausea, vomiting, and vertigo, while ocasionally there may be diarrhoea, headache, rash, fever, haematuria, and intrahepatic cholestasis. Elevated SGOT, SGPT, alkaline phosphatase, and BUN have been reported during therapeutic treatment with mebendazole. Colour vision disturbances and tinnitus have been reported during therapeutic use of thiabendazole. Sicca complex occurs rarely during thiabendazole therapy; symptoms include reduced tear production and dry mouth. Neutropenia and leukopenia are rare side effects with high-dose therapy. Mebendazole and albendazole are less toxic than thiobendazole.
2. Animal experiments suggest that these drugs are teratogenic and hence should not be administered to pregnant women.

Treatment

1. Symptomatic and supportive measures.
2. Activated charcoal/stomach wash may be helpful in the early stages of an overdose.
3. Hepatic injury generally responds to supportive care.
4. Monitor for fluid and electrolyte replacement.

■ Diethylcarbamazine

It is a piperazine derivative and remains the drug of choice for filariasis and tropical pulmonary eosinophilia, more than 50 years after it was introduced into therapeutics. Diethylcarbamazine is also used in the treatment of loiasis,* onchocerciasis, and ascariasis.

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* Caused by the African eye worm (a filarial worm) which infests the subcutaneous tissues and conjunctiva of man, sometimes producing itchy oedematous areas called calabar swellings.

Absorption is rapid after oral administration and toxic effects are uncommon with usual therapeutic doses. Peak plasma concentrations are reached in 1 to 2 hours, followed by a rapid decline, then a secondary rise 3 to 6 hours after dosing. The drug does not distribute in the fat and consequently has a volume of distribution, close to that of body water. It is primarily excreted in the urine as unchanged drug, but a relatively small amount is excreted as the N-oxide metabolite.

Most of the severe clinical effects following diethylcarbamazine ingestion are due to allergic reactions to the protein substance elaborated by the dying microfilariae and not to diethylcarbamazine alone. The most disturbing adverse effect is the *Mazotti reaction* which is a result of the host response to destruction of parasites, and is characterised by rash, itching, tender lymphadenopathy, fever, arthralgia, and headache. It usually occurs with the first dose and disappears in 3 to 7 days. Rare toxic effects include encephalitis and retinal haemorrhages (invariably during the course of treatment of loiasis). Corneal opacities, anterior uveitis, visual field restriction, optic atrophy, punctate keratitis, and chorioretinal changes have been observed when diethylcarbamazine has been administered as eye drops (or even orally) in onchocerciasis. Dose-related responses to diethylcarbamazine, when used for therapy of filariasis, include weakness, dizziness, lethargy, anorexia, and nausea. These effects generally occur within 1 to 2 hours following a dose and may persist for several hours.

In a study of almost 300,000 therapeutic administrations of the drug, approximately 29% of the patients experienced adverse reactions. The WHO no longer recommends the use of diethylcarbamazine for onchocerciasis.

There is no antidote for diethylcarbamazine poisoning. Treatment is symptomatic and supportive.

■ Niclosamide

Niclosamide is a halogenated salicylanilide derivative which is mainly used in the treatment of tapeworm infestation. Unfortunately, while the drug may kill adult worms, ova are usually unaffected, which may result in cysticercosis due to liberation of viable ova into the lumen of the gut following digestion of dead worm segments. However, niclosamide is a very safe drug and is virtually free from serious side effects.

■ Piperazine

Piperazine is a cyclic secondary amine which is very effective against roundworm, pinworm, and threadworm infestations. It is also used as a corrosion inhibitor, insecticide, and accelerator for curing polychloroprene.

Piperazine is given orally and acts by inducing flaccid muscle paralysis in the worms facilitating their expulsion by peristalsis. In therapeutic doses piperazine is safe, but overdose results in convulsions, hallucinations, and respiratory failure. The problem is that the margin between therapeutic and toxic dose is very narrow. Toxicity has been reported to develop at doses as low as 30 mg/kg/day in patients with renal failure, and 50 to 75 mg/kg/day in patients with normal renal function. Common effects include nausea, vomiting, confusion, muscular weakness, and ataxia. Treatment involves administration of anticonvulsants and symptomatic measures.

■ Praziquantel

It is a pyrazinoisoquinoline derivative and is effective against tapeworms, liver flukes, and schistosomiasis. Praziquantel displays two major effects: it causes spastic paralysis of worms, and (at higher doses) induces tegumental damage which activates host defence mechanisms resulting in the destruction of the worms.

Side effects include abdominal pain, headache, drowsiness, vertigo, urticaria, rash, fever, and arthralgia. They usually respond to symptomatic measures such as administration of analgesics. Praziquantel is contraindicated in ocular cysticercosis since the host response can cause irreversible damage to the eye. Concomitant intake of alcohol can aggravate vertigo that is often associated with this drug.

■ Pyrantel Pamoate

It is a depolarising neuromuscular blocking agent and causes spastic paralysis of pinworm, roundworm, and hookworm. Adverse effects are mild and comprise headache, drowsiness, insomnia, anorexia, nausea, abdominal cramps, diarrhoea, rash, and occasional dizziness. Transient elevations of serum transaminase levels have been reported in a small percentage of patients. It must not be given along with piperazine because both are mutually antagonistic.

■ Levamisole

This drug is not in use in Western countries because of the risk of agranulocytosis, but still finds a place in India. Levamisole is effective against roundworms and hookworms. Apart from blood dyscrasias, it can cause hepatic damage, GI distress, and olfactory disturbances. Haematologic toxicity has included neutropenia, anaemia, thrombocytopenia, and fatal cases of agranulocytosis have occurred with therapy. Levamisole also has nicotinic and muscarinic effects at cholinergic receptors. Initially there may be stimulation of the ganglionic and skeletal muscle transmission, followed by blockade. CNS depression, clonic convulsions, and dizziness may occur. An encephalopathy-like syndrome has developed in some patients during chronic therapy; onset of symptoms is variable. Taste perversion, salivation, lip licking, and head shaking have occurred with therapeutic doses. Frequent urination and defaecation have been reported.

Treatment is symptomatic and supportive. Do not administer antacids since levamisole may be better absorbed in an alkaline medium. Atropine may help in some cases of levamisole toxicity.

AUTOPSY FEATURES *(ANTI-INFECTIVE OVERDOSE DEATHS)*

The autopsy investigation of a therapeutic drug-related fatality is always difficult for the following reasons:

- The exact nature of the drug ingested may be unclear.
- More than one type of pharmaceutical preparation may have been ingested.
- There may have been considerable time elapsed between the time of ingestion and death as a result of which the

offending drug may have been metabolised and excreted completely.

- Analysis of therapeutic drugs in body fluids and tissues is usually difficult because of lack of facilities.
- Sufficient postmortem data do not exist for most of the therapeutic drug-related fatalities.
- Most pharmaceutical drugs do not leave behind characteristic or specific features in a dead body, and this is especially true of anti-infective drugs.

Because of these reasons, often the forensic pathologist is left with no alternative except to look for vague, non-specific signs of drug overdose such as congestion of the GI tract, pulmonary or cerebral oedema, scattered petechiae on serous membranes, and generalised visceral congestion. Sometimes residues of the drug involved may be obtainable from the stomach or intestine in the form of powder particles, concretions, or distinctively coloured fluid material. These can be submitted for toxicological analysis which in any case is the only authentic method of confirming a drug-related death (if it can be successfully accomplished!). Even this slender possibility may be rendered impracticable in injection deaths.

Apart from toxicological analysis, one other investigation which can sometimes help is histopathological analysis of viscera, and this must always be undertaken especially with reference to target organs.

FORENSIC ISSUES (ANTI-INFECTIVES)

- Poisoning resulting from pharmaceutical preparations is usually accidental in nature arising out of therapeutic overdose, allergic reactions, or inadvertent ingestion (mistaken identity, paediatric poisoning, etc.). The usual culprits include analgesic-antipyretics, NSAIDs, benzodiazepines, sedative-hypnotics, antidepressants, and anticonvulsants.
- Poisoning from anti-infective drugs is relatively uncommon, though adverse (side) effects especially at high therapeutic doses frequently occur, which is all the more likely if the duration of therapy is prolonged. However as the incidence of poisoning relentlessly rises in India, the agents employed for deliberate self-ingestion have undergone a subtle but definite change over a period of time. While chemicals and plant products were overwhelmingly common in the past, today pharmaceutical preparations are making significant inroads.
- But though this may be true, the contribution of anti-infective drugs to this grim scenario still remains negligible as demonstrated by studies in which therapeutic drugs accounted for upto 20 to 30 % of suicidal poisoning, and

yet anti-infective preparations hardly figured in the list of culprits. That is of course no reason to be complacent since these drugs are so frequently prescribed, and therefore the incidence of accidental overdose is probably not insignificant inspite of a paucity of studies substantiating this assumption.

- In Western countries with advanced economies and relatively sophisticated medical services, suicidal poisoning with pharmaceutical preparations has always been more common than toxic agents. This is due to easy accessibility, since these drugs are either obtainable from a doctor on prescription, or on demand across the counter of a pharmacy.
- In the Indian context, the following examples represent some common situations producing anti-infective drug morbidity and mortality:
  - ❖ Idiosyncratic reactions to drugs, e.g. quinine.
  - ❖ Allergic reactions including anaphylaxis, e.g. penicillins.
  - ❖ G6PD deficiency in some individuals which can predispose to toxicity even with therapeutic doses of some drugs, e.g. primaquine, dapsone.
  - ❖ Inadvertent intake of alcohol along with incompatible anti-infectives, e.g. metronidazole, cephalosporines, griseofulvin, etc. However, well controlled studies have not substantiated this disulfiram-like reaction with regard to metronidazole and alcohol. The likelihood of this drug interaction is not considered clinically significant, since in some studies it has occurred with placebo. Several reports have anecdotally described deliberate abuse of the metronidazole-alcohol combination to produce pleasurable CNS effects: a sudden onset or "rush" of excitement, giddiness, and flushing. Nausea was denied or reported as a transient effect by these subjects.
  - ❖ Tetracycline ingestion (usually on the advice of quacks) by children and pregnant women, resulting in dental and skeletal problems.
  - ❖ Ignorant patients ingesting outdated anti-infectives (especially tetracycline) which can cause renal problems.
  - ❖ Administration of chloramphenicol to neonates by quacks.
  - ❖ Accidental paediatric poisoning involving attractively coloured or flavoured medicines.
  - ❖ Use of quinine as abortifacient in rural areas.
  - ❖ Chronic toxicity resulting from inadequately supervised treatment regimens involving the use of drugs such as INH,* dapsone, chloroquine, aminoglycosides, penicillins, macrolides, and streptomycin.

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* Studies have indicated that 10% of all patients administered INH for a prolonged period develop liver toxicity, of whom 10% progress to hepatitis, and of these 10% die from related complications. It would do well for physicians prescribing INH to remember this **Ten percent Toxicity Rule!**

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Gastrointestinal and Endocrinal Drugs

1. **Gastrointestinal Drugs**
   a. Antacids and Anti-ulcer drugs
   b. Laxatives
   c. Antidiarrhoeals
   d. Antiemetics and Prokinetics
   e. Bile Acids and Pancreatic Enzymes
2. **Endocrinal Drugs**
   a. Antipituitary Hormones
   b. Thyroid and Anti-thyroid Drugs
   c. Oestrogens, Progestins, Androgens and Antagonists
   d. Adrenocorticotropic Hormone and Corticosteroids
   e. Insulin and Oral Hypoglycaemics

The toxicity of some of the important drugs will be discussed here.

GASTROINTESTINAL DRUGS

■ Antacids and Anti-ulcer Drugs

Antacids

One of the commonest ailments plaguing mankind throughout history has been indigestion or dyspepsia, the causes for which are many: hepatic, gastric, cardiac, alcoholic, and even hysterical. By far the most prevalent form appears to be gastric (or more properly gastrointestinal), resulting from dysfunction of stomach and intestines, and the vast majority of such cases are related to excessive acidity—acid dyspepsia. It is no wonder then that a plethora of drugs exist for the prevention or treatment of this "ubiquitous" condition, never mind the fact that many a case may merely be the result of over-eating. For centuries, acid dyspepsia has been tackled by countering the acidity in the stomach with antacids, a classic example of therapeutic neutralisation.

Classification of Antacids

1. *Aluminium*
   a. Aluminium carbonate
   b. Aluminium hydroxide
   c. Aluminium phosphate
   d. Dihydroxyaluminium aminoacetate.
2. *Calcium*
   a. Calcium carbonate.

3. *Magnesium*
   a. Magnesium carbonate
   b. Magnesium hydroxide
   c. Magnesium oxide
   d. Magnesium trisilicate.
4. *Combination preparations*
   a. Dihydroxyaluminium sodium carbonate
   b. Magaldrate.

Formulations

- Chewing gums
- Liquids
- Lozenges
- Powders
- Tablets.

Uses

- Peptic ulcer
- Acute gastritis and stress ulceration
- Non-ulcer dyspepsia
- Zollinger-Ellison syndrome
- Gastroesophageal reflux
- Gastrointestinal bleeding
- Oesophagitis
- Magnesium oxide: Hypomagnesaemia resulting from malnutrition, restricted diet, alcoholism, or magnesium-depleting drugs.

Toxicokinetics

Antacids are generally poorly soluble and are cleared from the empty stomach in 15 to 30 minutes. Except for aluminium phosphate, aluminium-containing antacids combine with dietary phosphate to form insoluble, nonabsorbable aluminium phosphate. Calcium chloride formed in the reaction of hydrochloric acid and calcium carbonate is converted to insoluble calcium salts and soaps in the small intestine where absorption rate in therapeutic doses ranged from 9 to 37%. Magnesium chloride formed after neutralisation of hydrochloric acid is partly (15 to 30%) absorbed. Sodium citrate is completely absorbed.

While in most cases, almost all the ingested antacid is eliminated in the faeces, some cations (especially aluminium and magnesium) may be absorbed to a lesser or greater extent

from the intestine. Small amounts of the cations from the insoluble aluminium and calcium-containing antacids and 97% of the magnesium-containing antacids are eliminated as soaps, phosphates, and sundry other insoluble compounds such as magnesium chloride. While this usually poses no problems, renal insufficiency can cause absorbed aluminium to predispose to osteoporosis, encephalopathy, and proximal myopathy. Calcium salts can produce hypercalcaemia. Overingestion of bismuth salts can raise the plasma bismuth level significantly.

Calcium reacts with carbonate in the intestines to form calcium carbonate which is excreted primarily in the faeces. Aluminium may be excreted as carbonates and hydroxides. Biliary excretion is an important route of elimination of orally absorbed aluminium thus requiring close monitoring of long-term antacid therapy in patients with liver disease.

Simethicone is included in many antacid preparations, and acts as a surfactant to decrease foaming.

Mode of Action

- The primary action of antacid is to neutralise gastric acid (90% at gastric pH of 1.3 to 2.3 and 99% at pH of 3.3), thereby increasing the pH in the stomach and duodenal bulb. Antacids react with hydrochloric acid to form chlorides, water, and carbon dioxide. Acidity is thereby neutralised. Elevation of the pH in the gastric antrum increases the secretion of gastrin and causes a compensatory secretion of acid and pepsin. This rebound secretion is brief and of a low degree with aluminium hydroxide, magnesium hydroxide, or sodium bicarbonate, but is prolonged and intense with calcium carbonate.
- The anti-pepsin effect of antacids has been attributed to the following mechanisms:
  - ❖ An increase in the pH to above 4 resulting in inhibition of pepsinogen conversion to pepsin.
  - ❖ Absorption of pepsin by the antacid.
  - ❖ Possible stimulation of endorphin release or prostaglandin formation.

Adverse Effects and Clinical (Toxic) Features

1. Acute ingestion of antacids rarely leads to toxicity. Magnesium and aluminium hydroxide are of low-order toxicity, while calcium carbonate and sodium bicarbonate must be used with extreme caution because of their potential for systemic toxicity.
2. With prolonged administration and/or excessively large doses, arrhythmias, hypo- and hypertension, encephalopathy, renal failure, diarrhoea, constipation, gastrointestinal obstruction and/or perforation, alkalosis, fluid, electrolyte, and mineral derangements, and myopathies and osteodystrophies have been reported.
3. Alkalosis (especially with unneutralised sodium bicarbonate).
4. *Milk-alkali syndrome*: Common in the past when large doses of sodium bicarbonate or calcium carbonate were advocated along with milk for the treatment of peptic ulcer. Problems associated with such a regimen include

hypercalcaemia (with nausea, vomiting, anorexia, weakness, headache, dizziness, and change in mental status), reduced parathormone secretion, phosphate retention, precipitation of calcium salts in the kidney, metabolic alkalosis and renal insufficiency.
5. Nephrolithiasis: has been reported with long-term use of calcium- and magnesium-containing antacids.
6. *Side effects*: Belching, abdominal distension, nausea, flatulence. Bismuth salts can cause blackish discolouration of oral mcosa (and stools). Constipation is the main side effect of aluminium antacids.
7. Bismuth salts in excess can cause ataxia, encephalopathy, and osteodystrophy.
8. Prophylactic antacid therapy in paediatric intensive care units (to prevent stress ulcers) can cause hypotonia, difficulty in arousing, hypermagnesaemia, hypercalcaemia, and aluminium hydroxide bezoar formaton.
9. Dialysis encephalopathy syndrome, characterised by dysarthria, apraxia, asterixis, myoclonus, dementia, focal seizures, and vitamin D-resistant osteomalacia, has been reported in patients with elevated aluminium levels in bone, brain and muscle.
10. Phosphate depletion syndrome—hypophosphataemia may occur as early as the second week of therapy with aluminium hydroxide given in doses of 30 ml three times a day. Manifestations include anorexia, bone pain, muscle weakness, paraesthesias and seizures.
11. Alzheimer's disease and its possible association with antacids has been inferred in a few inconclusive case-control studies.

Drug Interactions

Antacids alter the rate of dissolution, absorption, and elimination of several drugs, especially theophylline, iron, tetracycline, quinolones, isoniazid, ketoconazole, ethambutol, benzodiazepines, phenothiazines, ranitidine, phenytoin, prednisone, procainamide, etc., where bioavailability is decreased, and sulfonamides, levodopa, and valproate, where bioavailability is increased.

Treatment

1. Supportive and symptomatic measures. Decontamination with activated charcoal is not necessary because of the poor absorption from the gastrointestinal tract and lack of systemic toxicity after overdose.
2. Monitor electrolytes, pH, serum aluminium, calcium, and/or magnesium levels, EKG, and renal function tests in patients with renal impairment, especially if symptomatic.
3. Normal serum aluminium levels are less than 15 mg/L.
4. Normal total serum calcium levels are 9 to 10.4 mg/dL (4.5 to 5.2 mEq/L).
5. Normal serum magnesium levels range from 1.3 to 2.6 mEq/L.
6. Excessive aluminium tissue deposits can be mobilised with desferrioxamine prior to haemodialysis.
7. Symptomatic hypercalcaemia in chronic ingestion may require fluids and diuretic therapy. Mithramycin is indicated

in severe hypercalcaemia unresponsive to 12 to 24 hours of saline diuresis.

8. Haemodialysis and peritoneal dialysis can reduce serum aluminium, calcium, and magnesium levels but are rarely necessary after acute ingestion.

Anti-ulcer Drugs

1. H$_2$ receptor antagonists
2. Inhibitors of H$^+$, K$^+$-ATPase
3. Agents effective against *Helicobacter pylori*.

H$_2$ Receptor Antagonists

Examples include burimamide, cimetidine, famotidine, nizatidine, ranitidine, roxatidine, zolentidine. These drugs are used in the treatment of duodenal ulcer, gastric ulcer, Zollinger-Ellison syndrome, gastroesophageal reflux disease, stress ulcers and hypersecretory states.

H$_2$ receptor antagonists are well absorbed after oral administration and peak plasma concentrations are attained in 1 to 2 hours. Although subject to hepatic metabolism, these drugs are excreted unmetabolised in large part in the urine.

H$_2$ receptor antagonists competitively inhibit the interaction of histamine with H$_2$ receptors, which results in inhibition of gastric acid secretion. The output of pepsin also falls correspondingly. It is postulated that by blocking H$_2$ receptors on the parietal cell, the ability of histamine, gastrin, and acetylcholine to stimulate acid secretion is blocked. However, there is no effect on rate of gastric emptying, pressure of lower oesophageal sphincter, and pancreatic secretion. Ranitidine is 5 to 12 times better than cimetidine, and famotidine is 30 to 60 times better than cimetidine on a molar basis in controlling gastric acid hypersecretion.

Adverse effects include somnolence, confusion, slurred speech, restlessness, hallucinations, and seizures. Rarely there may be facial twitching, Parkinsonism, chorea, and dystonia. There have been reports of gynaecomastia. Cardiovascular effects include bradycardia, hypotension, AV block, and cardiac arrest. They are more common with intravenous use. Famotidine and ranitidine can cause thrombocytopenia. The following have also been reported: agranulocytosis, pancytopenia, and aplastic anaemia. Hepatic hypersensitivity reactions are more common with ranitidine. Hyperprolactinaemia occurs with the use of all H$_2$ receptor antagonists. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Cimetidine, ranitidine, and famotidine have been associated with drug-induced fever, which typically resolves within 48 to 72 hours after discontinuation of the drug. The mechanism is thought to be CNS histamine receptor blockade. Cardiac arrest has occurred following therapeutic IV administration of cimetidine.

CNS disturbances may occur with therapeutic or overdoses of all the H$_2$ receptor antagonists, but is reported to a greater degree with cimetidine, which crosses the blood-brain barrier more readily than the other drugs in this class. The most common symptom reported has been confusion. The most consistent adverse reaction reported with famotidine is a severe, throbbing headache, with an incidence of up to 4.7%. This has also been reported for ranitidine.

Liver enzyme elevation is the most frequently reported hepatic effect of H$_2$ receptor antagonists. The LFT's typically normalise following discontinuation of the drug, and may be due to a hypersensitivity reaction. Acute interstitial nephritis has also been reported. Gynaecomastia and increased prolactin levels may be seen following therapeutic doses of cimetidine.

Cimetidine has an imidazole ring and therefore inhibits the cytochrome P450 mixed-function oxidase involved in the hepatic metabolism of several drugs. It also reduces hepatic blood flow and impedes the elimination of drugs like propranolol which are metabolised in the liver. Absorption of cimetidine is significantly reduced by antacids, and hence there is need for adequate spacing between the two (of at least 1 hour). Cimetidine potentiates the effect of anticoagulants, phenytoin, theophylline, benzodiazepines, beta blockers, metronidazole, lignocaine, procainamide, verapamil, and quinidine. Potentially lethal interactions have been reported with morphine. There is also potentiation of effects of ethyl alcohol. Ranitidine has a furan ring instead of an imidazole ring, and does not inhibit the cytochrome P450 mixed-function oxidase enzyme system. However it may interact adversely with warfarin, benzodiazepines, metoprolol, nifedipine and paracetamol.

Overdose is associated with dry mouth, mild drowsiness, epigastric discomfort with diarrhoea, muscle pain, elevated liver or kidney function tests, leukopenia, thrombocytopenia, vertigo, slurred speech, mydriasis, confusion, drowsiness, headache, delirium, psychosis, mild bradycardia, hypotension, and other CVS effects (*vide supra*). Fatalities are rare.

Treatment: In significant overdoses it may be advisable to monitor cardiac function, liver function and renal function tests, as well as endocrine and CNS effects. Stomach wash may be done (within 4 hours). Convulsions constitute an absolute contraindication. Activated charcoal may be beneficial. Benzodiazepines can be given for convulsions. If seizures persist or recur, administer phenobarbitone. Cimetidine-induced agitation and delirium have been reversed by physostigmine in several reported cases. However, the use of physostigmine for this purpose is still very questionable. Doses used in adults were 1 mg IV, repeated once if needed. Patients demonstrating cardiac abnormalities should have continuous ECG monitoring. Arrhythmias must be managed in the usual way, e.g. atropine for bradycardia, lignocaine for ventricular arrhythmias. Haemodialysis may be effective.

Inhibitors of H$^+$, K$^+$-ATPase (Proton Pump Inhibitors)

The proton pump inhibitors act by inhibiting the H$^+$,K$^+$-ATPase system which acts as the ultimate mediator of acid secretion, and is located in the apical membrane of the gastric parietal cell. Examples include esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. They are used in the treatment of patients with ulcers in the stomach, duodenum, or oesophagus, when there is inadequate response to H$_2$ receptor antagonists (especially in Zollinger-Ellison syndrome). They are also beneficial in the treatment of gastroesophageal reflux disease (GERD). In addition, they are used in combination with amoxycillin and clarithromycin in the treatment of *H. pylori* infection and duodenal ulcer disease (active or past history within 5 years).

Because it is acid-labile, omeprazole is marketed in capsules containing enteric-coated granules. The absolute oral bioavailability is approximately 30 to 60% at doses of 20 to 40 mg which may be due in part to presystemic metabolism. Omeprazole is extensively metabolised in the liver. About 80% of a dose is eliminated in the urine as at least six metabolites, predominantly hydroxyomeprazole and its corresponding carboxylic acid. The remainder is excreted in the bile.

Chronic use of proton pump inhibitors can cause headache, nausea, abdominal pain, diarrhoea, peripheral neuropathy, gynaecomastia, haemolytic anaemia, subacute myopathy, hepatic failure, and gastric polyposis. Hyperhydrosis can be a troublesome recurrent feature. Diarrhoea is frequently reported with therapeutic use of proton pump inhibitors. Ocular damage has been associated with the use of proton pump inhibitors. In several case reports, individuals reported the following after therapeutic use of omeprazole or pantoprazole: papillary oedema and papillitis which progressed to anterior ischaemic optic neuropathy with persistent visual field defects, ocular pain and irreversible visual impairment. Acute interstitial nephritis has been reported in a few cases. Isolated cases of neutropenia and agranulocytosis have been reported following therapeutic use of omeprazole. There are indications that tendency to carcinogenicity may be enhanced during long-term use.

Proton pump inhibitors can interfere with the absorption of some drugs (e.g. ketoconazole, iron salts, and digoxin) by inhibiting gastric acid secretion. Omeprazole inhibits cytochrome P450, and may interfere with metabolic clearance of concomitantly administered drugs. Elimination of the following drugs may be prolonged: diazepam, warfarin, phenytoin and aminophylline.

Overdose results in mild tachycardia, vasodilation, confusion, abdominal pain, nausea, vomiting, drowsiness, sweating, headache, dry mouth, and blurred vision. Individuals have survived doses ranging from 320 mg to 900 mg (16 to 45 times the usual therapeutic dose). Treatment consists of supportive and symptomatic measures. Stomach wash may be beneficial if done within 4 hours of ingestion. Activated charcoal can be administered. Haemodialysis was shown to be effective.

Agents Effective Against Helicobacter pylori

Helicobacter pylori is a gram-negative bacillus which can colonise the gastric epithelium and cause an inflammatory gastritis leading to peptic ulceration, gastric lymphoma, and adenocarcinoma. 70 to 90% of patients with gastric and duodenal ulcers have *H.pylori* that can be identified in antral samples. Eradication of *H.pylori* correlates well with amelioration of peptic ulcer disease.

The usual method recommended today is triple therapy involving metronidazole, a bismuth compound, and either tetracycline or amoxycillin. Adverse effects include vertigo, nausea, vomiting, and diarrhoea. Alternatively, omeprazole is used in combination with amoxycillin and tinidazole. The incidence of adverse effects is less with this regimen.

■ Laxatives

Laxatives are drugs which promote defaecation, and are widely employed in the treatment of constipation. Constipation can result not only from diseases of large intestine, nervous system, and endocrine system, but also from exposure to a number of drugs and toxins (**Table 31.1**). Laxatives only treat the symptom (constipation) but not the underlying cause. Hence every effort must be made to identify and treat the cause, rather than resort to the indiscriminate use of laxatives which can lead to serious repercussions (*vide infra*).

Classification

1. Bulk-forming laxatives
2. Saline and osmotic laxatives
3. Stimulant laxatives
4. Surfactant laxatives
5. Other laxatives : mineral oil, cisapride.

Bulk-forming Laxatives

Functional constipation is best treated by a diet rich in plant fibre. Bulk-forming laxatives act as supplements to dietary fibre and include wheat bran, psyllium (*Plantago afra* or *Plantago indica*), methylcellulose, carboxymethylcellulose, guar gum (*Cyanopsis psoraloides*), gum tragacanth (*Astraplus gummifer*)**,** karaya (*Sterculia species*), glucomannan (*Konjac mannan*), malt soup extract, flaxseed (*Linum usitatissimum*), isapghula (*Plantago ovata*), and polycarbophil. These laxatives generally swell in water to form a gel that serves to maintain soft, well-hydrated faeces. They also reflexively stimulate peristalsis. The laxative effect is usually apparent within 12 to 24 hours and may not become fully apparent for as long as 72 hours.

Glucomannan is a polysaccharide composed of glucose and mannose. Capsules of the fibre absorb up to 60 times their weight in water to form a gel.

Systemic toxicity is unlikely since these agents are unabsorbed from the gastrointestinal tract and excreted in the faeces. Adverse effects are rare and usually mild: flatulence, borborygmi, intestinal impaction. Intestinal obstruction has been occasionally observed. It can be prevented by taking enough water concurrently with the laxative. Obstruction and impactions are usually associated with intestinal pathology or lack of adequate hydration. Glucomannan has resulted in decreased blood glucose and serum insulin levels when given in single doses to diabetic patients. Diabetics should be cautioned that decreased insulin or oral hypoglycaemic requirements may occur.

Anaphylactoid reactions have been reported following exposure to psyllium containing products. Moderate-to-severe

Table 31.1: Toxic Causes of Constipation	
Analgesics	Diuretics
Antacids	Heavy metals (iron, lead)
Anticholinergics	MAOIs
Antidiarrhoeals	Muscle relaxants
Antihistamines	Opiates
Antiparkinsonian drugs	Phenothiazines
Botulinum toxin	Propranolol
Corticosteroids	Tricyclics
Clonidine	Verapamil

wheezing, tightness in the chest or throat, urticaria, and angi-oedema have been reported in some patients. The seed husk of psyllium mucilloid contains a protein that appears to be the source of the allergic reactions. Highly purified psyllium mucilloid may decrease the allergenicity to psyllium-containing products.

Treatment

- Immediately dilute with 4 to 8 ounces (120 to 240 ml) of water or milk (not to exceed 4 ounces or 120 ml in a child).
- Monitor fluid and electrolyte status carefully in sympto-matic patients.
- Emesis and activated charcoal are usually not necessary following ingestions.
- Restrict solid food and maintain high fluid intake until diarrhoea resolves. Oral fluid should consist of hypotonic solutions containing appropriate electrolytes.
- Rigid oesophagoscopy has been used to relieve oesophageal obstruction.
- Mild to moderate allergic reactions may be treated with antihistamines with or without inhaled beta agonists, corti-costeroids or adrenaline. Treatment of severe anaphylaxis also includes oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring and IV fluids.

Saline and Osmotic Laxatives

Saline laxatives are generally given by mouth producing catharsis with soft or fluid stools. The citrates, sulfates, and tartrates of sodium or potassium are the usual agents used: magnesium sulfate (*epsom salt*), magnesium hydroxide (*milk of magnesia*), magnesium citrate, sodium phosphate, potas-sium bitartrate, potassium sodium tartrate, potassium sulfate, sodium citrate, sodium sulfate, lactulose, glycerine, sorbitol, mannitol, and polyethylene glycol electrolyte solution. These agents act by their osmotic properties in the luminal fluid and are poorly absorbed. However, many of the ions found in saline cathartics may be absorbed from the gastrointestinal tract. Some of them are utilised as cathartics in the treatment of poisoning (*page no 20*).

Saline cathartics are poorly absorbed from the gastrointes-tinal tract, hence systemic toxicity is unlikely unless massive amounts have been ingested. Nausea, vomiting, abdominal pain, and diarrhoea are frequent findings. Severe diarrhoea may result in excessive fluid and electrolyte loss. Fluid and electrolyte abnormalities (dehydration and hypokalaemia) occur secondary to excessive diarrhoea. A mild diuresis may occur following excessive absorption of these compounds. Magnesium and sodium salts can cause electrolyte distur-bances and must be used with caution in the presence of renal impairment. Excessive absorption of sodium may aggravate congestive heart failure. Seizures may occur with elevated serum sodium levels. Lactulose can cause flatulence, cramps, nausea, hypernatraemia and hypokalaemia.

Oedema following saline laxative withdrawal is not uncommon. The presumed mechanism is persistent hyperal-dosteronism resulting in sodium retention.

Treatment

- Monitor serum potassium and sodium concentrations in symptomatic patients following exposure to one of the saline cathartics.
- Fluid and electrolyte status should be monitored at regular intervals.
- Emesis is usually not necessary and may worsen dehydra-tion and electrolyte imbalances after large ingestions; it is not recommended.
- Due to molecular size and ionic dissociation, charcoal is not likely to be beneficial.
- Restrict solid food and maintain high fluid intake until diarrhoea resolves. Oral fluids should consist of hypotonic solution containing appropriate electrolytes.
- Patients developing congestive heart failure from sodium intoxication may be treated with fluid restriction and/or diuretic therapy, furosemide 1 mg/kg IV to a maximum of 40 mg.

Stimulant Laxatives

These may be either diphenylmethane derivatives (phenol-phthalein, bisacodyl), or anthraquinones (danthron, i.e. dihy-droxyanthraquinone, and its derivatives contained in senna, cascara, rhubarb, and aloe). Senna is obtained from the dried pods or leaflets of *Cassia acutifolia* or *Cassia angustifolia* (**Fig 31.1**). Cascara sagrada ('sacred bark') is obtained from the bark of the buckthorn tree *Rhamnus purshiana* (**Fig 31.2**). Danthron was removed from the market in the United States in 1987 because of fears of carcinogenicity. As of August 1997, the FDA has also proposed a ban on phenolphthalein, based on animal carcinogen data and its potential risk to humans.

All these drugs stimulate intestinal motility by promoting the accumulation of water and electrolytes in the colonic lumen.

Fig 31.1: *Cassia angustifolia*

Fig 31.2: *Rhamnus purshiana* (Cascara sagrada)

Adverse and Toxic Effects

The therapeutic dose of diphenylmethane derivatives varies widely between different individuals, and therefore a particular dose can be ineffective in one, while being excessive in another.

- Phenolphthalein discolours urine (and even faeces) pink or red.
- Gastric irritation is common with diphenylmethane derivatives.
- Phenolphthalein use is associated with allergic reactions (including Stevens-Johnson syndrome), osteomalacia, and protein-losing gastro-enteropathy. Hypersensitivity reactions may lead to death. Hypotension and pulmonary oedema, although rare and probably secondary to an allergic response, have been reported following phenolphthalein intoxication.
- All stimulant laxatives suffer from a delayed onset of action (6 to 10 hours).
- Anthraquinones can cause yellowish or brownish coloured urine. Large doses induce nephritis. Melanosis coli (pigmentation of colonic mucosa) has been observed on long-term use.
- Hepatitis and jaundice have been seen with various stimulant laxatives. Chronic abuse of senna has caused toxic hepatitis.
- Orange vaginal secretions have been reported after use of large amounts of danthron.

Treatment

- Monitor fluid and electrolyte balance in severely symptomatic patients.
- All persons with significant toxicity, dehydration, abnormal electrolyte levels, or a history of poor compliance should be admitted for intravenous therapy and consideration of antibiotic therapy.
- Activated charcoal has been shown to reduce the absorption of phenolphthalein in humans and to decrease the purgative effect.

- Restrict solid food and maintain high fluid intake until diarrhoea resolves. Oral fluid should consist of polyionic hypotonic solution containing appropriate electrolytes. Patients with moderate to severe dehydration must be treated with IV fluids.

Surfactant Laxatives

Examples include docusates (docusate sodium, calcium, and potassium)*, poloxamers (polyoxyethylene-polyoxy-propylene polymers), bile acids (dehydrocholic acid), and castor oil. Surfactant laxatives act as stool-wetting and stool-softening agents, allowing the mixing of water, fats, and faecal material. Docusates elevate alveolar surface tension by displacement of pulmonary surfactant from the alveolar hypophase. There is then a marked fall in arterial oxygen tension, an increase in airway pressure, and an increased alveolar epithelial permeability. Stool softener laxatives are indicated prophylactically in patients who should not strain during defaecation, such as those with an episiotomy wound, those with thrombosed haemorrhoids, fissures, or perianal abscesses, body wall and diaphragmatic hernias, anorectal stenosis, or postmyocardial infarction.

Docusates while being minimally effective laxatives, produce only mild side effects—cramps, nausea, skin rash.

Castor oil obtained from the seeds of the castor plant (*Ricinus communis*) contains ricin, a very potent toxalbumen, and ricinoleic acid. The oil is a very powerful and dangerous laxative capable of inducing copious evacuation which can result in dehydration and electrolyte disturbances. It can reflexly stimulate uterine musculature and hence is contraindicated in pregnant women.

Mineral Oil

Mineral oil is a petroleum product and consists of a mixture of aliphatic hydrocarbons. It is categorised as a lubricant laxative. While being an effective laxative (penetrating and softening stools), routine use is not advocated owing to the following adverse effects:

- Foreign body reaction in intestinal mucosa.
- Leakage of oil past the anal sphincter with rectal irritation.
- Malabsorption of fat soluble vitamins (chronic use). Mineral oil acts as a lipid solvent and administration with meals may interfere with absorption of essential fat-soluble substances.
- Aspiration can lead to lipid pneumonitis.
- A human teratogen by inhalation, mineral oil has caused testicular tumours in the foetus.

Treatment

- Monitor for respiratory distress after ingestion of mineral oil. Monitor ABGs/pulse oximetry and chest radiographs in patients with respiratory distress.
- Due to aspiration hazard and generally low toxicity of these compounds, gastric decontamination is contraindicated.
- Fluid and electrolyte status should be monitored in patients demonstrating severe vomiting and diarrhoea.

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* Being respectively dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate and dioctyl potassium sulfosuccinate.

- Extracorporeal membrane oxygenation (ECMO) (a pulmonary bypass procedure used in cases of reversible acute pulmonary and cardiovascular failure) has been successful in the therapy of paediatric aspiration involving mineral oil or mineral seal oil found initially unresponsive to standard therapy for hydrocarbon aspiration.

Cisapride

Cisapride and renzapride (a related drug) are oral gastrointestinal prokinetic agents that stimulate gastrointestinal motility and are used in the treatment of gastroesophageal reflux disease. Cisapride is a benzamide, and is mainly employed in the treatment of gastric retention and other gastroparetic conditions. Since it also increases colonic motility, it is sometimes recommended as a laxative, especially for chronic constipation. Renzapride has been shown in clinical trials to be useful in the treatment of diabetic gastroparesis and constipation-predominant irritable bowel syndrome. In 2000, cisapride was withdrawn from the market in both the United States and the United Kingdom due to increasing numbers of reported adverse events of heart rhythm abnormalities.

Cisapride increases the release of acetylcholine at the myenteric plexus level of the gastrointestinal tract, increases the lower oesophageal resting tone, and increases the amplitude of lower oesophageal contractions. Gastrointestinal motility is then stimulated, gastric emptying is accelerated, and colonic peristalsis is increased. Renzapride is a type 3 serotonin antagonist and a type 4 serotonin agonist. Following a therapeutic dose, renzapride blocks serotonin 3 receptors and stimulates serotonin 4 receptors; it does not exhibit dopamine D(2) receptor antagonism. It also has been shown to stimulate gastric acid secretion during low-dose pentagastrin infusion, and block secretion during high-dose pentagastrin stimulation. Due to this interchange of mechanisms, this drug lowers oesophageal sphincter pressure and increases gastric emptying.

Cisapride should be taken prior to a meal, since food increases its absorption. Adverse effects include headache, vertigo, abdominal cramps, borborygmi, gastrointestinal distress, urinary frequency. Tachycardia has been reported. ECG abnormalities, QT prolongation, and arrhythmias including torsades de pointes have also been reported. Akathisias have also occurred rarely. Urinary incontinence and vaginitis have developed in a few patients.

Overdose experience with cisapride and renzapride are limited. Retching, borborygmi, flatulence, stool frequency, and urinary frequency have been reported. Drugs that inhibit the cytochrome P450 3A4 enzymes may increase blood levels of cisapride, resulting in cardiac arrhythmias. Concurrent use of erythromycin, clarithromycin, troleandomycin, nefazodone, indinavir, ritonavir, and azole antifungals can induce cardiac arrhythmias. Drugs known to prolong the QT interval and increase the risk of arrhythmia should also not be taken concurrently with cisapride. Since cisapride increases gastric emptying and rate of absorption, the effect of sedative drugs and alcohol may be significantly pronounced.

Treatment

- Monitor electrolyte levels if the patient experiences severe and prolonged diarrhoea.
- Obtain an ECG and institute continuous cardiac monitoring for possible QT prolongation and arrhythmias.
- Activated charcoal may be administered.
- For torsades de pointes: Withdraw the causative agent. Haemodynamically unstable patients require electrical cardioversion. Emergent treatment with magnesium sulfate, isoproterenol, or atrial overdrive pacing is indicated. Detect and correct underlying electrolyte abnormalities (hypomagnesaemia, hypokalaemia, hypocalcaemia).
- Despite its prolongation of the QT interval, amiodarone has been reported to be effective in treating both acute episodes of torsades de pointes, as well as preventing recurrences.
- Avoid class Ia antiarrhythmics (quinidine, disopyramide, procainamide, aprindine) and most class III antiarrhythmics (N- acetylprocainamide, sotalol) since they may further prolong the QT interval, and have been associated with torsades de pointes.
- Mexiletine may be useful in the treatment of cisapride-induced long QT syndrome. Caution should however be observed in the presence of pre-existing impaired cardiac function, since mexiletine could suppress the ventricular contraction together with a decrease of cardiac output, leading to potential cardiovascular collapse.
- Sinus tachyarrhythmias do not need to be routinely treated unless the patient demonstrates signs and/or symptoms of haemodynamic instability. In those cases, tachyarrhythmias may respond to IV esmolol.

ANTIDIARRHOEALS

Most antidiarrhoeals (like laxatives) tackle the symptom but not the underlying cause which is usually infectious in nature. Therefore antimicrobial therapy is mandatory most of the time. However, there are several types of diarrhoea (secretory diarrhoeas) which have a non-infectious cause and must be treated differently, e.g. diarrhoea due to carcinoid syndrome, drug-related diarrhoea, etc. **Table 31.2** lists some common drugs associated with diarrhoea.

Table 31.2: Drugs Causing Diarrhoea

Adrenergic neurone blocking agents

Antimicrobials (especially broad-spectrum)

Cholinergics and Anticholinesterases

Laxatives

Prokinetic drugs

Prostaglandins

Quinidine

Classification

- Opiates – diphenoxylate, difenoxin, loperamide
- Bismuth subsalicylate
- Octreotide.
  The opiates and bismuth salts have been discussed in detail elsewhere (consult *Index*).

Octreotide

Octreotide, the acetate salt of a cyclic octapeptide, is the synthetic analogue of somatostatin, a hormone which inhibits the release of somatotropin (human growth hormone), and insulin secretion. It has to be administered parenterally, and is usually injected subcutaneously. It is used in the treatment of refractory diarrhoea (e.g. AIDS-related diarrhoea), Zollinger-Ellison syndrome, endocrine tumours related to the GI tract (carcinoid, gastrinoma, insulinoma, etc.) and acromegaly. Additional uses include treatment of congenital hyperinsulinism (nesidioblastosis), chylothorax, prolonged recurrent hypoglycaemia after sulfonylurea overdose, severe rheumatoid arthritis, hepatic hydrothorax, severe pancreatitis, diabetic retinopathy and variceal bleeding.

Adverse effects include anorexia, nausea, GI upset (diarrhoea/steatorrhoea, constipation, abdominal discomfort, flatulence), cholelithiasis, hypoglycaemia/hyperglycaemia, pancreatitis, hypothyroidism, sinus bradycardia, conduction abnormalities and arrhythmias.

Overdose data is limited; hypoglycaemia, flushing, dizziness and nausea have been reported.

Treatment

1. Monitor blood glucose, CBC, ECG, and liver function in symptomatic patients.
2. Monitor fluid and electrolyte status in patients with significant nausea and vomiting.
3. Significant toxicity is not anticipated after ingestion because of limited bioavailability. Consider gastric decontamination only after very large ingestions.
4. There is no antidote for octreotide overdose. Overdose treatment is symptomatic and supportive.

ANTIEMETICS AND PROKINETIC DRUGS

■ Antiemetics

Emesis or vomiting is a common manifestation of infections, gastrointestinal disorders, anaesthesia, motion sickness, and drug toxicity.

Classification

- $5\text{-}HT_3$ Antagonists
- D_2 Antagonists
- Corticosteroids
- Cannabinoids
- Antihistamines.

While D_2 antagonists* such as phenothiazines and butyrophenones, corticosteroids, cannabinoids, and antihistamines have been discussed elsewhere (consult *Index*), only the $5\text{-}HT_3$ antagonists will be dealt with here. Benzamides and related compounds (which are also D_2 antagonists) are discussed in the subsequent section on **prokinetic drugs** (*vide infra*).

$5\text{-}HT_3$ Antagonists

Examples include alosetron, dolasetron, granisetron, ondansetron, and tropisetron. These drugs antagonise the $5\text{-}HT_3$ receptors located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone. They are used in the management of chemotherapy-induced emesis, radiation-induced emesis and postoperative nausea.

Adverse effects include constipation, vertigo, headache, blurred vision, asymptomatic elevation of liver enzymes, dystonic reactions, and allergic reactions. Cases of anaphylactoid-anaphylactic reactions have been reported. Reactions consisted of urticaria, angioedema, hypotension, bronchospasm, and dyspnoea. Several cases of chest pain associated with therapeutic use of ondansetron have been reported. Bronchospasm has occurred with intravenous infusion, rarely.

Suspected cases of overdose with ondansetron have presented with the development of fever, rashes, pruritus and restlessness. Mild transient elevation of serum lactate dehydrogenase and temporary blindness of 2 to 3 minutes duration have occurred. Overdose of intravenous administration of dolasetron has resulted in hypotension, dizziness and abnormal ECG intervals. Monitoring complete blood count and liver and kidney function tests is suggested for patients with significant exposure. Activated charcoal may be considered. There is no specific antidote for ondansetron. Treatment is symptomatic and supportive. Haemodialysis/haemoperfusion is not expected to be of benefit due to the large volume of distribution. Diphenhydramine has been used to manage adverse effects of therapeutic use including fever, rashes, pruritus and restlessness.

■ Prokinetic Drugs

Classification

- Benzamides: metoclopramide, trimethobenzamide, cisapride.
- Benzimidazole derivatives: domperidone.
- Motilin, erythromycin, and other macrolide antibiotics.

Metoclopramide

Metoclopramide is a benzamide analogue, and is structurally related to procainamide, but lacks local anaesthetic and antiarrhythmic actions. It is a central and peripheral acting dopamine antagonist. Because of dopaminergic blockade, it can cause significant CNS effects and hyperprolactinaemia. As a cholinergic agonist, it enhances the action of acetylcholine at

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* D_2 antagonists are drugs which are antagonistic to D_2 dopamine receptors and include substituted benzamides, benzamide derivatives, and neuroleptic drugs.

muscarinic receptors. Metoclopramide also possesses oxidant activity. Bromopride is the bromo-analogue of metoclopramide.

Metoclopramide enhances the motility of smooth muscle of oesophagus, stomach, and upper small intestine, leading to an acceleration of gastric emptying and intestinal transit. Lower oesophageal sphincter pressure is increased preventing oesophageal reflux. Central dopamine inhibition leads to abolition of nausea and vomiting.

Metoclopramide is used in the treatment of gastroesophageal reflux, gastric stasis, vascular headache (adjunct treatment) and persistent hiccups. It is also useful for managing diabetic gastroparesis, oesophageal reflux, and vomiting, including that due to postoperative- and cancer chemotherapy-related. Bromopride is used as an antiemetic, and for the treatment of various gastrointestinal disorders, similar to metoclopramide.

Adverse effects include drowsiness, vertigo, anxiety, extrapyramidal effects (tremors, agitation, parkinsonian syndrome). Hyperaldosteronism and hyperprolactinaemia with amenorrhoea may occur. Neuroleptic malignant syndrome has been reported.

Overdose results in increased muscle tone, opisthotonus, torticollis, trismus, cog-wheel rigidity, grimacing, extrapyramidal reactions, confusion, irritability, panic-like reactions, agitation, nystagmus, strabismus, conjugate deviation of eyes, and convulsions. Bradycardia and heart block have been reported. Methaemoglobinaemia has also been reported, as well as rare reports of sulfhaemoglobinaemia. Acute dystonic reactions are more common in children and young adults, whereas prolonged reactions such as tardive dyskinesia, and parkinsonism are more common in elderly patients.

Treatment

1. Stabilisation—maintenance of airway, cardiovascular and respiratory function, intravenous line, cardiac monitoring, brain scan, and EEG.
2. Consider administration of activated charcoal after a potentially toxic ingestion. Administer charcoal as an aqueous slurry; most effective when administered within one hour of ingestion.
3. Treatment of convulsions with diazepam.
4. Treatment of hypokalaemia.
5. Diphenhydramine (25 to 50 mg IV over 2 min) or benztropine (1 to 4 mg IV or IM) for extrapyramidal effects. If the patient does not respond administer diazepam.
6. For bradycardia: Give 1 mg IV, and repeat in 3 to 5 minutes if asystolic cardiac arrest persists. 3 mg (0.04 mg/kg) IV is a fully vagolytic dose in most adults.
7. Methylene blue (1 to 2 mg/kg of a 1% solution given IV over 5 minutes) has been used successfully to reverse methaemoglobinaemia in premature and full term infants who had received metoclopramide.
8. Haemodialysis or peritoneal dialysis are reported to be ineffective in removing metoclopramide, probably due to the drug's high volume of distribution.

■ Bile Acids and Pancreatic Enzymes

Bile Acids

Bile acids are constituents of bile and are synthesised from cholesterol. After being secreted, they are largely reabsorbed in the ileum and recycled via an enterohepatic cycle. Examples include cholic acid, deoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid. They are used in the treatment of gallstones and primary biliary cirrhosis.

Adverse effects include diarrhoea, pruritis, dry skin, sweating, hair thinning, nausea, dyspepsia, myalgia, rhinitis, insomnia.

Pancreatic Enzymes

Pancreatic enzymes are standardised preparations of pancreas which contain protease, amylase, and lipase. They are used in cases of pancreatic enzyme insufficiency, such as that found in cystic fibrosis. Examples include pancreatin and pancrelipase, which contain amylase, lipase, and protease. They are used in the treatment of chronic pancreatitis and pancreatic insufficiency. Adverse effects include nausea, diarrhoea, and hyperuricaemia. Perianal irritation, particularly in infants, has been reported with therapeutic use. Many of these products are made from hog pancrease, and hence, individuals sensitive to pork protein may experience allergic reactions. Pancreatic alpha amylase and trypsin have been determined to be two of the causative allergens. There have been several cases of these enzymes being contaminated by Salmonella. Folate absorption is inhibited by use of pancreatic extracts. These extracts form complexes with folates which reduce absorption. Patients on chronic therapy should have folate monitored.

Toxicity is uncommon, but there have been cases of hypersensitivity after inhalation, anal irritation, and oral irritation when the tablets are held in the mouth. Asthma, bronchial hypersensitivity, and pulmonary hypersensitivity have been reported after exposure to the powder in both home and occupational settings. These symptoms may occur in parents of children with cystic fibrosis. Fibrosing colonopathy have been reported in children with cystic fibrosis following long-term pancreatin therapy, with the majority of patients receiving high-dose preparations. It has been theorised that delayed gastrointestinal transit time and prolonged exposure of the colon to high-strength pancreatic enzymes in cystic fibrosis patients may be associated with the development of fibrosing colonopathy in these patients.

In general, pancreatic enzyme tablets are low in toxicity and are not expected to produce serious overdose effects. Treatment should be symptomatic and supportive. Patients should be monitored for irritation of the gastrointestinal tract, possible hypersensitivity reactions, and increased uric acid in the blood and urine. Dilution may be indicated following ingestion of large amounts in order to reduce irritation. Immediately

dilute with 4 to 8 ounces (120 to 240 ml) of water or milk (not to exceed 4 ounces or 120 ml in a child). Activated charcoal is generally not indicated because of low toxicity. Mild to moderate allergic reactions may be treated with antihistamines with or without inhaled beta agonists, corticosteroids or adrenaline. Treatment of severe anaphylaxis also includes oxygen supplementation, aggressive airway management, adrenaline, ECG monitoring and IV fluids.

ENDOCRINAL DRUGS

■ Anterior Pituitary Hormones*

Human Growth Hormone

It is used in the treatment of growth hormone-deficient children. Today, recombinant DNA technology is used to produce growth hormone (recombinant **somatropin**, **somatrem**, etc.). The usual mode of administration is subcutaneous injection, though it can also be given intramuscularly. Somatropin is a biosynthetic polypeptide hormone with an amino acid sequence identical to that of human growth hormone. Somatrem is a polypeptide hormone derived from recombinant DNA technology. It has the identical sequence of 191 amino acids constituting pituitary-derived human growth hormone and an additional amino acid, methionine, on the N-terminus of the molecule. The commercial preparation is administered after reconstitution with bacteriostatic water for injection, containing benzyl alcohol as an antimicrobial preservative. Benzyl alcohol has been associated with toxicity in newborns.

Recombinant growth hormone is used in adults to treat growth failure caused by growth hormone deficiency of either childhood- or adult-onset aetiology, chronic renal insufficiency in childhood, and Prader-Willi syndrome; for long-term treatment of short stature associated with Turner's syndrome; and to treat AIDS-associated cachexia or weight loss.

Adverse Effects

- Pain at the injection site.
- Local lipoatrophy (subcutaneous injection).
- Predisposition to diabetes mellitus, pancreatitis, hypo- and hyperglycaemia.
- Peripheral oedema.
- Hypothyroidism.
- Intracranial hypertension: Benign intracranial hypertension with papilloedema (visual changes, headache, nausea and vomiting) has been reported in several patients treated with growth hormone products. Symptoms usually occurred within the first 8 weeks of therapy and resolved upon discontinuation of the therapy, or a reduction of the growth hormone dose.
- Carpal tunnel syndrome.
- Gynaecomastia.
- Increased alkaline phosphatase.
- Local reactions at injection site including pain, numbness,

redness, and swelling have occurred with somatropin and somatrem. Hyperglycaemia may occur with an acute overdose. Symptoms of gigantism and/or acromegaly may be observed following long-term overdosage.

Prolactin

Prolactin is synthesised and secreted not only by the pituitary, but also by decidual cells in the terminal luteal phase of the menstrual cycle. It has no therapeutic value. On the other hand, excessive secretion of prolactin (hyperprolactinaemia) can cause problems such as galactorrhoea, amenorrhoea, and infertility in women, and impotence, gynaecomastia, and infertility in men. Causes of hyperprolactinaemia include disorders of hypothalamus or pituitary, renal failure, primary hypothyroidism, and the use of dopaminergic antagonists. Treatment is accomplished by administering dopaminergic drugs such as bromocriptine. The toxicity of bromocriptine is discussed on

Gonadotrophic Hormones (Glycoprotein Hormones)

These include luteinising hormone (LH), follicle stimulating hormone (FSH), and chorionic gonadotropin (CG). They are used in the treament of infertility and cryptorchidism. CG is helpful in the diagnosis of pregnancy, since the plasma and urine concentrations go up during this period.

Adverse effects include hyperstimulation of ovaries, increased tendency to abortion, and precocious puberty when CG therapy is undertaken in young boys for the treatment of cryptorchidism.

■ Thyroid and Antithyroid Drugs

Thyroid Hormone

Major therapeutic use of **thyroxine** is as hormone replacement therapy for hypothyroidism and cretinism. Natural (desiccated thyroid and thyroglobulin) thyroid hormone is available to treat hypothyroid disease states and thyroid cancer. Synthetic preparations of thyroid hormone include Levothyroxine sodium (T4) and Liothyronine sodium (T3). Liotrix is a mixture of thyroxine and tri-iodothyronine (4 parts T4 to 1 part T3). Thyrotropin, or recombinant human thyroid stimulating hormone, is available in the US as Thyrogen®. It is indicated for thyroid cancer diagnostic/monitoring.

Both hormones (T3 and T4) are metabolised primarily by deiodination with only 20% of the hormone excreted in the faeces intact or conjugated. Approximately 40% of T4 is converted in peripheral tissues to T3.

Adverse effects include exacerbation of angina, arrhythmias, and provocation of myocardial infarction. Tremor, sweating, headache, flushing, tachycardia, and palpitations have been reported. Loss of weight is common.

Toxicity following massive overdosage may occur within 12 to 24 hours if a tri-iodothyronine (T3) containing product has been ingested. Acute ingestions of levothyroxine result in

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* **Adrenocorticotropic hormone** is discussed in a subsequent section (page no 481).

only mild symptoms, usually days after ingestion. Adults rarely experience symptoms with one-time ingestions of at least 6 grains desiccated thyroid (usual adult dose is 1.5 to 2.5 grains/day), or 3 mg of levothyroxine. Similar amounts are probably required to produce symptoms in young children. Fatalities are extremely unlikely with acute thyroid hormone overdose.

The following signs and symptoms have occurred in overdose cases: vomiting, diarrhoea, abdominal pain, fever, tachycardia, palpitations, hypertension, increased sweating, congestive heart failure, and cardiac arrhythmias. Pulmonary oedema, presenting as sudden dyspnoea several days after overdose, requiring endotracheal intubation, has been reported after tri-iodothyronine overdose. Headache, confusion, agitation, mydriasis, and tremor are common. Psychosis has been reported. Seizures may occur following massive acute overdoses.

Symptoms may be delayed up to 10 to 15 days, and hence keeping the patient under observation is important. Mild hypertension may occur due to adrenergic discharge resulting in hyperthyroidism. Angina and ventricular dysrhythmias have been reported. T3 is more likely to cause angina than T4.

Chronic intake causes weight loss, myocarditis, angina, and ventricular arrhythmias. Thyrotoxicosis is fairly common after chronic overdoses of T3 and T4, but is generally unusual following acute ingestions. Thyroid compounds may induce myocarditis in chronic overdoses and can be associated with sudden death in the presence of coronary artery disease.

Treatment

- It is advisable to monitor patients through follow-up telephone calls for 5 days at home if initially asymptomatic or minimal symptoms, due to the prolonged onset of action of levothyroxine. Levels of T3, T4 and protein-bound iodine (PBI) may be markedly elevated both with and without clinical signs of toxicity; these values are virtually no help in treatment or prognosis of the overdose. Gastric decontamination is probably not warranted in most cases. However, consider administration of activated charcoal after a potentially toxic ingestion. Propranolol may be administered (1 mg/dose IV, administered no faster than 1 mg/min, repeated every 5 minutes up to a maximum of 5 mg) to treat the adrenergic findings associated with hyperthyroidism. Alternatives to propranolol include labetalol or sotalol.
- Institute continuous cardiac monitoring and obtain an ECG in patients with moderate or severe symptoms.
- Prednisolone and propranolol to block the peripheral effects of thyroxine.
- Cholestyramine (4 grams orally every 6 to 8 hours) to block the enterohepatic circulation of thyroid hormone.
- Propylthiouracil (*vide infra*) to block endogenous thyroxine production.
- Sodium ipodate and iopanoic acid have been advocated as effective and safe alternatives for the treatment of hyperthyroidism.
- Charcoal haemoperfusion or plasmapheresis to enhance elimination. Diuresis and haemodialysis are ineffective due to high protein binding.

■ Antithyroid Drugs

Thioureylenes

The thioureylenes are compounds belonging to the family of thioamides, and the most important representative of the group is propylthiouracil (PTU). Other examples include methimazole and carbimazole, which are organic thiourea antithyroid drugs included in the chemical class of mercaptoimidazolines. Carbimazole is a prodrug of methimazole. Carbimazole is rapidly and completely metabolised to methimazole in the body, with the antithyroid activity of carbimazole dependant upon this conversion to methimazole.

Antithyroid drugs inhibit the formation of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residues of thyroglobulin. They also inhibit the coupling of these iodotyrosyl residues to form iodothyronines by inhibiting the peroxidase enzyme.

In addition to blocking hormone synthesis, propylthiouracil (unlike other antithyroid drugs) inhibits the peripheral deiodination of thyroxine to tri-iodothyronine.

Propylthiouracil, carbimazole, and methimazole are used in the management of hyperthyroidism including the treatment of Graves' disease, thyroid storm, and in preparing individuals for thyroidectomy and as an adjunct to radioiodine therapy.

Adverse Effects

- Agranulocytosis: Chronic ingestion of PTU, carbimazole, or methimazole has been reported to cause leukopenia, agranulocytosis, aplastic anaemia, eosinophilia, leukaemia, thrombocytopenia and hypoprothrombinaemia.
- Hepatotoxicity: Chronic ingestion of PTU produces a characteristic hepatocellular or mixed cytotoxic-cholestatic hepatitis, believed to be a hypersensitivity reaction.
- Arthralgia: Arthritis syndrome, which is rare, is generally transient, occurring within 2 months of initiation of therapy and resolving within 4 weeks of stopping therapy.
- Following therapeutic use of carbimazole or methimazole, dizziness, paresthesias, and headache have been described occasionally.
- Skin rashes may occur secondary to haematologic toxicity during chronic therapy.
- Gastric upsets.
- Methimazole therapy has uncommonly been reported to be related to the occurrence of T-lymphotropic virus type I-associated uveitis, with vitreous opacities and retinal vasculitis. The exact mechanism of this adverse reaction is unknown.
- Reversible nephrotic syndrome has been observed in a very few patients during therapy with methimazole or carbimazole. It is likely that this is the result of a direct toxic effect on the glomerular basement membrane and epithelial podocytes.
- Carbimazole hypersensitivity resulting in the development of antibodies to connective tissue or neural antigens in the cochlea has been reported. Hearing loss and tinnitus resulted.

Toxic Effects

- Vomiting, headache, fever, arthralgia, pruritis and pancytopenia.
- Clinical signs/symptoms of overdose with carbimazole or methimazole may include manifestations of hypothyroidism, including nausea and vomiting, constipation, headache, drowsiness, coldness, dry and puffy skin, muscle aches, and goitre. CNS depression and/or stimulation may occur. Hypothyroidism is unlikely to develop after a single acute overdose ingestion. Less frequently, overdose may result in hepatic enzyme changes or neuropathies.
- Very little data are available on the effects of acute overdose with propylthiouracil. Decreased T3 and elevated alkaline phosphatase levels were the only effects seen after a massive overdose in a young girl.
- Chronic overdose may result in clinical hypothyroidism (nausea and vomiting, constipation, headache, drowsiness, coldness, dry and puffy skin, muscle aches). Propylthiouracil is transferred across the placenta and can induce goitre and hypothyroidism in the unborn. Hyperthyroidism may also occur as a compensatory mechanism. Infants of women with Graves' disease who were treated with propylthiouracil may be either hypothyroid or hyperthyroid.
- The administration of propylthiouracil to the mother from the 14th week of pregnancy or later has been of concern because of the possible development of goitre and mental retardation in the infant. Incidence of birth defects was not significantly higher in children of women who had been treated with propylthiouracil during pregnancy.
- Methimazole crosses the placental membrane readily and can induce goitre and cretinism in the developing foetus. Congenital defects such as aplasia cutis (manifested by scalp defects), oesophageal atresia with tracheoesophageal fistula, and choanal atresia with absent/hypoplastic nipples have occurred rarely in infants exposed to methimazole in utero.
- Chronic ingestion of PTU, carbimazole or methimazole can result in a variety of immunologic-mediated adverse effects which are not expected to occur in overdose, including agranulocytosis, aplastic anaemia, vasculitis, lupus-like syndrome, and hepatitis. Fatal hepatic necrosis has been reported. Most adverse effects are dose-related and occur within the first 4 to 8 weeks of therapy.
- Chronic propylthiouracil use has been linked with acute myeloblastic leukaemia in isolated cases.

Treatment

- Symptomatic and supportive measures.
- Alkaline phosphatase levels have been elevated in overdose cases involving PTU. Isoenzyme determination is recommended. Elevations in alkaline phosphatase do not necessarily reflect liver toxicity and may be related to increased bone or bile isoenzyme.
- Monitor thyroid function tests and liver function in symptomatic patients.
- Total and differential leukocyte counts should be performed in patients with suspected haematologic reactions.

Agranulocytosis is usually reversible on discontinuation of therapy. Administration of recombinant human granulocyte colony-stimulating factor may hasten recovery. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), or filgrastim, may be effective in accelerating bone marrow recovery after carbimazole or methimazole therapy. Erythrocyte and platelet transfusions may be necessary. Treatment with these drugs has been shown to significantly shorten recovery time in patients with methimazole-induced agranulocytosis.

- Infection or fever in neutropenic patients should be treated aggressively with antibiotics. Cultures and sensitivities should be done. Appropriate broad-spectrum antibiotics should probably be initiated before culture results are known. Adjust antibiotic regimen based on culture results.
- Haemodialysis, peritoneal dialysis, forced diuresis, or charcoal haemoperfusion have not been shown to be beneficial in overdose with these agents.

■ Oestrogens, Progestins, and their Antagonists

Oestrogens

Oestrogens are hormones secreted primarily by the ovarian follicles and also by the adrenals, corpus luteum, placenta and testes, or they are synthetic steroidal and non-steroidal compounds. Oestrogens are readily absorbed through the skin and mucous membranes. Following intramuscular administration of aqueous suspensions or oil solutions, absorption begins promptly and continues for several days. Natural, unconjugated oestrogens are inactivated in the gastrointestinal tract and liver following oral administration. Conjugated oestrogens, some synthetic derivatives and the non-steroidal oestrogens can be administered orally.

Oestrogens are widely distributed throughout most body tissues with the greatest concentrations in fat deposits. Steroidal oestrogens are metabolised primarily in the liver. Metabolism also occurs in the kidneys, gonads, and muscle tissues. Endogenous oestrogens appear in the urine as glucuronides and sulfates of oestradiol, oestrone, and oestriol. Diethylstilbestrol (DES) is metabolised to active intermediates such as DES semiquinone and DES quinone. The steroids and their metabolites are conjugated which increases their water solubility and facilitates excretion into the urine, which is the primary route of excretion.

Classification

- *Steroidal oestrogens*—oestradiol, ethinyl oestradiol, polyestradiol mestranol, quinestrol, estrone, equilin, equilenin.
- *Non-steroidal oestrogens*—diethylstilbestrol, dienestrol, bisphenol A, genistein.

Uses:

- Oral contraceptive.
- Hormone replacement therapy (in post-menopausal women).
- Treatment of ovarian dysgenesis (Turner's syndrome).

Adverse Effects

- *Carcinogenicity*: Oral contraceptives can increase the risk of breast cancer, (controversial). Post-menopausal women taking unopposed oestrogen or taking oestrogen combined with progestin have an increased risk of breast cancer compared with post-menopausal women taking no hormone replacement therapy. Older women (60–64 years) had the greatest increase in risk. Oestrogen (without progestins) in post-menopausal women increases the risk of endometrial carcinoma. Increased relative risk of endometrial carcinoma has been associated with prolonged continuous administration of oestrogens for relief of menopausal symptoms in several retrospective case-control studies. There is a lower risk of endometrial cancer associated with use of a combined oestrogen-progestagen regimen in post-menopausal women than with unopposed oestrogens. However, long-term (5 years or more) use of combined therapy, even when the progestagen is added for more than 10 days per month, is associated with an increased risk of endometrial cancer. There is increased incidence of vaginal and cervical adenocarcinoma in female offspring of mothers administered diethylstilbestrol (DES) during the first trimester of pregnancy. Maternal ingestion of DES during early pregnancy increases the risk of vaginal adenocarcinoma and the incidence of epididymal cysts, maldescended testes, hypoplastic testes, varicocoeles, spermatozoal defects and perhaps seminoma in the exposed offspring many years later. Masculinisation of the female foetus may occur during the first trimester. Due to the potential risk to the infant, breast-feeding is not recommended when the mother is receiving hormone therapy.
- Increased susceptibility to gall bladder disease. Oestrogen is thought to promote the formation of gallstones by increasing cholesterol saturation of bile, altering bile acid composition, and decreasing bile flow.
- Chronic use has also been associated with an increased risk of thromboembolic disease. Risk for thromboembolic disorders and consequent pulmonary embolism is increased by current oral contraceptive oestrogen use or post-menopausal oestrogen use, but past use of post-menopausal hormones or oral contraceptives does not increase risk for thromboembolic disorders.
- Fullness and tenderness of breasts, with development of oedema. Therapeutic, chronic doses may produce decreased glucose tolerance, changes in the menstrual cycle (breakthrough bleeding, spotting, missed menses, amenorrhoea, changes in menstrual flow), and breast changes. Chronic exposure to oestrogenic substances often causes breast tenderness, enlargement and secretion
- Increased tendency to suffer migraine. The occurrence of persistent severe headaches may be a sign of impending cerebrovascular occlusion.
- Leg cramps.
- Gynaecomastia.
- Porphyria cutanea tarda, and chloasma.
- Hypertension.
- Older contraceptives containing high doses of oestrogens were associated with increased risk for myocardial infarction.
- Hepatotoxicity. Elevated liver function tests, cholestatic jaundice, and liver tumours have occurred in patients receiving therapeutic doses of oestrogen.
- Contact lens intolerance and visual disturbances may occur in patients receiving oestrogens therapeutically. Contact dermatitis has been reported with oestradiol transdermal patch.
- Hirsutism/alopecia has been reported with oestrogen therapy.

Toxic Effects

- Oral contraceptives taken orally in overdose usually do not produce serious toxicity. Toxicity, other than gastrointestinal effects, is unlikely following acute exposure to oestrogens.
- Nausea, vomiting, abdominal cramps, diarrhoea and biliary calculi may occur following an acute overdose.
- Oestradiol implant overdose has resulted in facial swelling, pitting oedema, and hypertension.

Treatment

- Symptomatic and supportive measures.
- Oestrogen blood levels are not clinically useful after overdose.
- No specific lab work (CBC, electrolytes, urinalysis) is needed unless otherwise indicated.
- Gastric decontamination is rarely necessary. Treatment to ease gastrointestinal irritation is all that is required.
- In chronic toxicity, discontinue medication and monitor for severe signs of toxicity and treat symptomatically.

Anti-oestrogens

The selective oestrogen receptor modulators (SERMs) are non-steroidal anti-oestrogenic agents. Their anti-oestrogenic effects may be related to their ability to compete with oestrogen for binding sites in target tissues such as breast tissue. These agents block oestrogen effects in breast tissue, inhibit bone resorption, produce an oestrogen-like effect on the cardiovascular system, and barely, if at all, stimulate tissue in the breast or the uterus. The two common examples of anti-oestrogens are **tamoxifen** and **clomiphene**, though both possess oestrogenic as well as anti-oestrogenic effects. Clomiphene citrate is a non-steroidal ovulatory stimulant. Other examples of SERMs include droloxifene, levormeloxifene, raloxifene and toremifene.

Tamoxifen is mainly used in the treatment of breast cancer, while clomiphene is useful in treating female infertility. The approved indication for tamoxifen is for the treatment of node-positive breast cancer in post-menopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. Tamoxifen is the first-line therapy in advanced breast cancer for post-menopausal women. It is used as an alternative to oophorectomy or ovarian irradiation in pre-menopausal women with metastatic breast cancer. Toremifene

is indicated for the treatment of metastatic breast cancer in post-menopausal women with oestrogen-receptor positive or unknown tumours. It binds to oestrogen receptors and may have oestrogenic, anti-oestrogenic, or both properties, depending upon the duration of treatment. Clomiphene is indicated for the treatment of ovulatory failure in patients desiring pregnancy.

Clomiphene can cause the following adverse effects: ovarian enlargement, abdominal pain, nausea and vomiting, vasomotor flushing, blurred vision, breast discomfort, depression, nervousness, insomnia, dizziness, and headache. Elevated transaminases, as well as occasional reports of hepatitis, have been reported. Additionally, various liver neoplasms have been reported, but the causal relationship remains uncertain. Ovarian hyperstimulation syndrome has been reported after therapeutic use of clomiphene. Early effects may include nausea, vomiting, diarrhoea and weight gain. In severe cases, effects may include gross ovarian enlargement, ascites, dyspnoea, oliguria, pleural effusion, pericardial effusion, anasarca, acute abdomen, hypotension, renal failure, pulmonary oedema, intraperitoneal and ovarian haemorrhage, ovarian torsion, deep venous thrombosis, respiratory distress, electrolyte imbalances, hypovolaemia, hypoproteinaemia, haemoconcentration, and shock. Symptoms of overdose (e.g. nausea, vomiting, vasomotor flashes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain) following inadvertent use of more than the recommended dose appear to be an extension of adverse effects. Treatment consists of supportive and symptomatic measures. Due to the large molecular weight of clomiphene (approximately 580), dialysis and similar techniques are not anticipated to be beneficial.

Tamoxifen can cause the following adverse effects: hot flushes, oedema, GI upset, vertigo, rash, pruritis vulvae, vaginal bleeding, thromboembolic phenomena, leucopenia, thrombocytopenia,. In patients with bone metastases, tamoxifen can cause dangerous hypercalcaemia. Corneal changes, cataracts, glaucoma, abnormal vision/diplopia, and retinopathy have been observed in patients receiving therapeutic tamoxifen or toremifene. Myocardial infarction has been reported with chronic therapeutic use. Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, more severe liver damage including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included deaths. A causal relationship is unclear. Steatohepatitis progressing to cirrhosis has been reported in some women with breast cancer following long-term (3 to 5 years) adjunctive therapy with tamoxifen. In some clinical studies, toremifene administration was associated with angina and arrhythmias during therapeutic use. Thromboembolic events, including pulmonary embolism, thrombosis and thrombophlebitis, have been associated with tamoxifen and toremifene. Tamoxifen may cause developmental abnormalities of the genital tract in humans and an interval of many years between *in utero* exposure and clinical manifestations could exist. Results from animal studies using tamoxifen are similar to those using diethylstilbestrol (DES) under similar conditions. Based on a literature review, the incidence of endometrial cancer is increased in women after receiving tamoxifen therapy.

Although a small risk, data suggests it may act as a tumour promoter in human endometrium. There is little information regarding overdose in humans. At doses at least 6 times (400 mg/m^2) the recommended dose (20 to 40 mg daily), neurotoxicity (seizures, tremor, hyperreflexia, unsteady gait and dizziness) and electrocardiographic changes (prolonged QT interval) were noted. Treatment consists of symptomatic and supportive measures. Monitor liver function tests following acute overdose. Consider administration of activated charcoal after a potentially toxic ingestion. Gastric lavage may be done with a large-bore orogastric tube after a potentially life-threatening ingestion if it can be performed soon after ingestion (generally within 60 minutes). Monitor ECG for QT prolongation and arrhythmias. Obtain periodic complete blood counts, including platelet counts. Monitor for signs of tremor, hyperreflexia, unsteady gait, dizziness and seizures.

Progestins

Progestins are hormones naturally secreted by the ovary mainly from the corpus luteum during the second half of the menstrual cycle, from the placenta during pregnancy, and from adrenal glands in both sexes. Progestins are also available as synthetic steroidal compounds. Natural progesterone is a crystalline substance similar to androsterone. It induces extensive progestational development necessary for implantation of the ovum. Agents similar to progesterone include hydroxyprogesterone caproate, medrogestone, and medroxyprogesterone acetate. Agents similar to 19-nortestosterone include norethandrolone, norethindrone, norethynodrel, norgestrel, desogestrel, and norgestimate. Other examples of progestins include allyloestrenol, dydrogesterone and norethisterone.

Progestins are used for a number of purposes, including treatment of amenorrhoea, abnormal uterine bleeding, hypoventilation, contraception (routine, as well as emergency contraception) and management of bleeding during post-menopausal therapy. Progestins are used (with oestrogens) for hormone replacement therapy in post-menopausal women, and (with or without oestrogens) for contraception.

Chronic toxicity can result in headache, irregular menses, mastalgia, bloating, decreased libido, GI upsets, weight gain, oedema, acne, rash, urticaria, breast discomfort, mental depression, hypertension, insomnia, vertigo, alopecia, thromboembolic phenomena, hepatotoxicity.

Acute attacks of porphyria can be precipitated by progesterone. Common signs and symptoms of an acute attack may include abdominal pain, nausea, vomiting, constipation, tachycardia, hypertension, depression, anxiety, irritability, fatigue or other mood changes, restlessness, fine tremors, excessive sweating, pain in the limbs, head, neck, or chest, muscle weakness, or sensory loss. Diagnosis is based on the increased urinary excretion of porphyrin precursors delta-aminolevulinic acid and porphobilinogen.

Ingestion of progestins during early pregnancy may cause virilisation of the female foetus, chromosomal abnormalities, or congenital malformations. Congenital malformations such as Tetralogy of Fallot or chromosomal anomalies such as genitourinary abnormalities, may also occur.

Single acute overdoses will seldom result in toxicity. Gastric decontamination should be considered after large or mixed ingestions. Supportive treatment will be adequate in most situations.

Anti-progestins

The most important example is **mifepristone** which is used to induce abortion (in the first trimester). Mifepristone is indicated for the medical termination of intrauterine pregnancy for pregnancies up to 49 days in duration. It has also been used successfully as an emergency contraceptive agent, in the treatment of inoperable meningiomas, as a cervical ripening and labour induction agent, and has significantly decreased the tumour volume in patients with uterine leiomyomas. Mifepristone is a substituted 19-nor steroid compound, derived from norethisterone, with potent anti-progestogenic activity, anti-glucocorticoid activity, and weak anti-androgenic activity.

Adverse effects include nausea, anorexia, abdominal pain, fatigue, and menorrhagia. Severe uterine bleeding, necessitating blood transfusions and curettage in some instances, may occur following therapeutic administration of mifepristone as sole therapy or in combination therapy with prostaglandin or misoprostol administration. Other adverse effects of mifepristone include dizziness, skin rashes, and elevated liver enzyme levels.

Due to mifepristone's antiglucocorticoid activity, it is speculated that mifepristone overdose ingestions may result in adrenal failure, though this has not yet occurred. In case of mifepristone intoxication, treatment is symptomatic and supportive. In cases of severe uterine bleeding after elective abortion, curettage and transfusion of packed red blood cells may be necessary.

Androgens (Anabolic Steroids)

Examples include testosterone, testosterone esters (propionate, enanthoate, and cypionate), danazol, fluoxymesterone, methyltestosterone, oxandrolone, nandrolone, stanozolol, ethylestrenol, oxymetholone, methandrostenolone, mesterolone, and boldenone. Testosterone is secreted by the testis and is the main androgen in the plasma of men. In women, testosterone (in small amounts) is secreted by the ovary and adrenal glands. Many of the androgens are modified forms of testosterone (to circumvent rapid degradation in the body) or synthetic testosterone-like drugs.

Anabolic steroids cause a retention of nitrogen which may result in weight gain and a feeling of well-being. There is also retention of potassium, sodium, phosphorus and chloride associated with a gain in weight, which could be accounted for by the water held in association with the retained salts and protein. Anabolic steroids are thought to promote the improved use of proteins by contributing to the reversal of catabolic processes. Increased protein synthesis has been noted in skeletal muscle cells. They have been used in the treatment of hypogonadism, hereditary angioneurotic oedema, osteoporosis due to androgen deficiency, and also for enhancement of athletic performance, for stimulation of erythropoiesis in refractory anaemias, and enhancement of stature (controversial).

Testosterone is readily absorbed on oral administration, but is virtually ineffective since it is absorbed into the portal circulation and metabolised by the liver before reaching the systemic circulation. Injected testosterone also is metabolised and excreted too quickly for the androgenic effect to manifest. In order to retard the rate of absorption, testosterone esters in oil are used which are less polar than the free steroid, and when injected intramuscularly are slowly absorbed. Testosterone is metabolised mainly in the liver, at first to androstenedione, and later to androsterone or etiocholanolone. Dihydrotestosterone is metabolised to androsterone, androstenedione and androstanediol. Esters of testosterone are hydrolysed to free testosterone and subsequently metabolised in the manner described. Excretion occurs principally in the urine and minimally in the faeces.

Adverse Effects

- *Virilising effects*—Results in masculinisation when taken by women, characterised by hirsutism, acne, deepening of the voice, menstrual irregularities, male pattern baldness, prominent musculature, and hypertrophy of clitoris.
- *Feminising effects*—Seen in men who receive androgens,* and is characterised by gynaecomastia. This is because of conversion (by aromatisation) of the androgen to oestrogen in extraglandular tissues.
- Administration of anabolic steroids during gestation may result in masculinisation of the urogenital sinus and clitoral hypertrophy. Premature bone maturation and decreased birthweight have been reported.
- Growing children may develop pre-mature fusion of the epiphyses of long bones, leading to permanent short stature.
- Cystic acne, sebaceous cysts, furunculosis, and seborrheic dermatitis have occurred in persons using anabolic steroids.

Toxic Effects

- *Oedema*—Retention of water and sodium chloride leads to weight gain and oedema.
- *Jaundice*—Results from stasis and accumulation of bile in biliary capillaries of the central portion of hepatic lobules without obstruction in the larger ducts. Peliosis hepatis is common: formation of blood-filled sacks in the peripheral zones of hepatic lobules. There is elevation of plasma levels of bilirubin, aspartate aminotransferase, and alkaline phosphatase. An increased predisposition to hepatic carcinoma has been reported. Hepatotoxicity is however rare with testosterone esters.
- *CVS effects*—Hypertension and thrombotic complications (stroke, myocardial infarction).
- *Endocrine effects*—Testicular atrophy, low sperm count, sterility, gynaecomastia. In women, masculinising effects occur (*vide supra*). Decreased testicular size is a common complaint among users, and a common finding in chronic users at autopsy.
- *Behavioural changes*—Increased aggressiveness, iritability, psychosis. Increased aggression known as "roid rage", delusional grandiosity, and acts of violent crime including

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* Except 19-nortestosterone and fluoxymesterone.

homicide have been described as a result of anabolic steroid abuse by athletes. Psychotic symptoms have been described in bodybuilders and football players during periods of anabolic steroid abuse. Patients who chronically misuse anabolic steroids may experience a withdrawal reaction. Anorexia, depression, fatigue, insomnia, decreased sex drive, and dissatisfaction with body image have all been reported.

- Anabolic steroid use parallel with exercise may lead to dysplasia of collagen fibrils, decreased tendon strength, and increased likelihood of rupture under stress. Several cases of unusual tendon rupture have been reported among steroid users, including that of triceps, extensor pollicis longus, and rectus femoris.

Treatment

- Blood anabolic steroid levels are not clinically useful.
- Withdrawal of androgen. Steroid withdrawal needs to be treated as other drug withdrawals, including detoxification, support in denial phase, short-term rehabilitation/recovery therapy, and long-term aftercare recovery.
- Natriuresis for treatment of oedema.
- Supportive and symptomatic measures. In acute single overdosage, toxicity is unlikely. Gastrointestinal decontamination is generally not needed after acute ingestion unless another toxic coingestant is involved.
- Liver-specific isoenzymes (alkaline phosphatase, lactate dehydrogenase) should be used to monitor liver function in athletes.
- Some of the effects resulting from long-term administration are irreversible.

Forensic Issues: Abuse of anabolic steroids by athletes to enhance performance has attained epidemic proportions in recent times. Athletes often take doses of androgens in 100 to 1000-fold excess over physiologic doses. In spite of such widespread conviction about the "beneficial" effects of anabolic steroids in relation to athletic performance, it is not yet clear as to whether these agents really do work (except for increasing muscle mass). The tragic part is that several athletes have died in their prime due to the adverse effects of such abuse. Testing for anabolic steroids in athletes is now mandatory during the course of competitive athletic events. Testosterone abuse may be detected by checking the ratio of testosterone to epitestosterone. If this ratio exceeds 6 to 1, it is an indication of exogenous testosterone use. The International Olympic Committee has issued strict guidelines in this regard, and suggests that gas chromatography-mass spectrometry (GC-MS) is the best method for drug testing in urine samples. Oral products can be detected for 2 to 14 days after the last use, and injectables for up to a month. Nandrolone decanoate injections can be detected up to 12 months.

Anti-androgens

Examples include onadorelin, leuprolide (both agonists of gonadotropin releasing hormone), cyproterone acetate, and flutamide (both specific androgen receptor antagonists). Other non-specific anti-androgens include the antifungal drugs ketoconazole and liarozole, the aldosterone antagonist spironolactone and 5α-reductase inhibitors such as finasteride.

Cyproterone is a synthetic progestogen which competes with dihydrotestosterone for binding to the androgen receptor, and has been used in the treatment of acne, hirsutism, male pattern baldness, virilising syndromes, and prostate cancer. There are indications that cyproterone is hepatotoxic, and may even cause hepatocellular carcinoma.

Flutamide (niftolide) is a non-steroidal anti-androgen which is sometimes used in the treatment of prostatic cancer. It has been demonstrated to block the action of dihydrotestosterone (DHT) on prostatic tissue androgen receptors resulting in involution of the prostate gland. It does not possess androgenic, adrenocortical, antiestrogenic, oestrogenic, progestational, antilibido, antifertility, or gonadotropin-inhibiting actions. Flutamide is used in the treatment of metastatic prostatic adenocarcinoma as a single drug therapy, or in combination with either a luteinising hormone-releasing hormone analogue or orchidectomy. Flutamide, in combination with oral contraceptives, has also been used for the treatment of hirsutism and benign prostatic hyperplasia.

Adverse effects of flutamide include breast tenderness, gynaecomastia, and possible hepatotoxicity. Other effects include hypertension, drowsiness, confusion, depression, anorexia, nausea, vomiting, and diarrhoea/constipation. Anaemia, leukopenia, and thrombocytopenia have also been reported following therapeutic doses of flutamide in humans. Teratogenic data is lacking for humans, but animal data indicate that a decreased survival time for offspring, feminisation of male foetuses, cryptorchidism, and a slight increase in minor skeletal malformations occur when high doses are given.

Primary signs of overdose may include hypoactivity, decreased respirations, ataxia, lacrimation, somnolence, emesis, and methaemoglobinaemia. It is logical to conclude that an overdose may also result in hypertension, as this is reported in approximately 1% of patients following therapeutic doses of flutamide. Hepatotoxicity is also likely.

Treatment

- Flutamide blood levels are not clinically useful.
- Monitor liver and renal function tests and ECG in overdose.
- In acute single overdosage, toxicity is unlikely and supportive treatment to ease gastrointestinal irritation and CNS depression may be all that is required.
- Consider pre-hospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion.
- Consider gastric lavage with a large-bore orogastric tube after a substantial ingestion if it can be performed soon after ingestion (generally within 60 minutes).
- Determine the methaemoglobin concentration and evaluate the patient for clinical effects of methaemoglobinaemia (dyspnoea, headache, fatigue, CNS depression, tachycardia, acidosis, etc.). Treat patients with symptomatic methaemoglobinaemia with methylene blue (1 to 2 mg/kg/dose,

i.e. 0.1 to 0.2 ml/kg/dose, intravenously over 5 minutes as needed every 4 hours). Administer oxygen while preparing for methylene blue therapy.

- Because flutamide is so highly protein-bound, it is unlikely that haemodialysis would be of any clinical benefit in removal of drug in overdose cases.

- In chronic toxicity, patients should be monitored for the development of gynaecomastia and galactorrhoea.

■ Adrenocorticotropic Hormone and Corticosteroids

Adrenocorticotropic Hormone (ACTH, Corticotropin)

Adrenocorticotropic hormone or ACTH is secreted by the anterior lobe of the pituitary and stimulates the adrenal cortex to produce corticosteroids, i.e. glucocorticoids and mineralocorticoids, as well as androgens. ACTH release itself is controlled and regulated by corticotropin-releasing hormone or CRH which is secreted by the hypothalamus. It has very limited therapeutic applications and is at present used only for testing the integrity of the hypothalamic-pituitary-adrenal axis (HPA axis) in those patients needing supplemental steroids in stressful situations. For this purpose, a synthetic form of ACTH called cosyntropin is administered intramuscularly or intravenously at a dose of 0.25 mg, and the plasma cortisol level is measured before and (30 minutes) after the test. An increase in cortisol level to greater than 20 μg/100 ml indicates normal response. This is referred to as the *cosyntropin stimulation test.*

The ACTH can cause hypersensitivity reactions and hyponatraemia.* Cosyntropin is much safer in this regard, and so is generally preferred. Administration of ACTH can induce fatal adrenal haemorrhage.

Corticosteroids

Classically, two types of corticosteroids are described: *glucocorticoids* which regulate carbohydrate metabolism, and *mineralocorticoids* which regulate electrolyte balance. The main glucocorticoid in humans is cortisol or hydrocortisone, while the main mineralocorticoid is aldosterone. Over a period of time since the 1950s, several corticosteroids have been identified as well as synthesised: cortisone, desoxycorticosterone, hydrocortisone, fludrocortisone, prednisone, prednisolone, methyl prednisolone, triamcinolone, beclomethasone, betamethasone, budesonide, paramethasone, rimexolone and dexamethasone.

Topical corticosteroids comprise alclometasone, amcinonide, betamethasone, budesonide, clobetasol, clocortolone, cortisol, desonide, desoximetasone, dexamethasone, diflorasone, fluocinolone, fluocinonide, flurandrenolide, halcinonide, hydrocortisone, loteprednol, methyl prednisolone, mometasone, rimexolone and triamcinolone.

Ophthalmic steroids comprise dexamethasone, fluorometholone, medrysone and prednisolone.

Inhalational steroids comprise beclomethasone, flunisolide and triamcinolone.

Corticosteroids are used as *replacement therapy* for acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, and congenital adrenal hyperplasia. They are also used in the treatment of non-endocrine diseases such as rheumatic disorders, nephrotic syndrome and some forms of glomerulonephritis, allergies, bronchial asthma, ocular diseases, skin diseases and cerebral oedema.

Adverse Effects (chronic therapy)

- Abrupt withdrawal after prolonged high-dose therapy results in flare up of the underlying disease, acute adrenal insufficiency (*Addisonian crisis*), and glucocorticoid withdrawal syndrome: fever, myalgia, arthralgia. Pseudotumour cerebri, dysphoria, irritability, emotional lability, depression, fatigue, anxiety, and depersonalisation can also occur. Symptoms may persist for 2 to 8 weeks after discontinuation.

- Fluid and electrolyte abnormalities.

- Hypertension.

- Hyperglycaemia.

- Increased susceptibility to infections and peptic ulceration.

- Osteoporosis (especially ribs and vertebrae). Chronic ingestion results in cushingoid appearance, muscle weakness, and osteoporosis.

- Myopathy (especially weakness of proximal limb muscles).

- Behavioural disturbances: nervousness, mood changes, insomnia, psychosis. Chronic toxicity may produce psychosis. Higher doses over shorter periods of time, as seen with prednisone and pulse methylprednisolone therapies, has produced psychosis and hallucinations. Mania has been documented during high-dose corticosteroid therapy.

- Cataract (especially in children). Chronic exposure may cause posterior subcapsulary cataracts and glaucoma; this risk appears to be greater in patients with probable rheumatoid arthritis.

- Fat redistribution, acne, hirsutism, striae, ecchymosis.

- Oral candidiasis has been reported following chronic inhalations of beclomethasone dipropionate.

- In one study, conducted to determine the influence of postnatal systemic dexamethasone treatment for neonatal chronic lung disease on subsequent brain growth and development in premature infants, it was determined that systemic dexamethasone administration caused a 22% reduction in total cerebral tissue volume as compared with total cerebral tissue volume in infants not treated with dexamethasone. Cerebral cortical grey matter volume was also reduced by 35% in pre-mature infants treated with dexamethasone as compared with infants not treated with dexamethasone. These findings suggest an impairment in brain growth which may subsequently have a deleterious effect on neurodevelopmental outcome following neonatal administration of dexamethasone. The use of corticosteroids has been found to increase the incidence of cerebral palsy and neurodevelopmental impairment.

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* Commercial ACTH is isolated from animal pituitaries and can contain significant concentrations of vasopressin (antidiuretic hormone).

Toxic Effects:

- Steroid overdose is rarely reported. A single massive dose of corticosteroid is unlikely to cause serious effects, unless there are specific contraindications.
- One case of suspected acute adrenal insufficiency has been reported after acute overdose.
- High-dose intravenous "pulse" therapy has a fairly high incidence of adverse effects. Most reactions are neuropsychiatric, but cardiac arrhythmias, seizures, and anaphylaxis have been reported.

Treatment

- Corticosteroid levels are not clinically useful. Emesis and activated charcoal are generally not necessary following corticosteroid overdose. However, they should be considered in the setting of a polypharmacy ingestion. Consider activated charcoal if co-ingestants with the potential for significant toxicity are involved. In chronic toxicity fluids and electrolytes should be monitored closely.
- *Acute adrenal insufficiency*: Administration of water, sodium chloride, glucose, and cortisol.
- *Chronic primary adrenal insufficiency*: Administration of hydrocortisone, liberal salt intake. Fludrocortisone may have to be added.
- *Secondary adrenal insufficiency*: Administration of hydrocortisone.
- *Psychiatric manifestations*: Tapered withdrawal and administration of neuroleptic drugs. Antidepressants may worsen the symptoms.
- Avoid chronic daily dosage of corticosteroids for durations greater than 3 weeks when possible. When chronic doses for periods greater than 3 weeks are essential, attempts should be made to manage the underlying disease with alternate day dosage. Single daily doses of shorter-acting preparations such as prednisone, prednisolone, or methylprednisolone on alternate mornings may be used. Adverse effects appear to be more common and more severe with the preparations having longer duration of effect, or when shorter-acting preparations are administered in multiple daily doses. The diet should have adequate protein content but caloric restrictions should be considered because of the apparent appetite stimulation properties of corticosteroids.

INSULIN AND ORAL HYPOGLYCAEMICS

■ Insulin

Insulin is a hormone that facilitates the penetration of glucose and amino acids through cell membranes of skeletal and heart muscle. Insulin was first extracted successfully from the pancreatic islets by a young Canadian surgeon **Frederick G Banting**, together with a medical student **Charles H Best**, in **1921**. They were helped in their quest by **JRR Macleod**, a professor of physiology, and **JB Collip**, a chemist. Therefore when the Nobel prize in Medicine (Physiology) was awarded to Banting and Macleod in 1923, there was a furore prompting Banting to share his prize with Best, while Macleod shared his with Collip.

Preparations

The various preparations of insulin currently available are mentioned (along with some relevant properties) in **Table 31.3.**

Uses

Subcutaneous administration of insulin is the primary treatment for all patients with IDDM (*insulin-dependant diabetes mellitus* or *Type I DM*), and for patients with NIDDM (*non-insulin-dependant diabetes mellitus* or *Type II DM*), that is not adequately controlled by diet or oral hypoglycaemics, and for patients with post-pancreactectomy diabetes or gestational diabetes.

Toxicokinetics

Insulin is usually administered by subcutaneous injection. Commercial preparations are available for either subcutaneous or intravenous injection which differ in respect to onset and duration of action. The onset and duration of action vary considerably depending on the preparation (**Table 31.3**). Insulin is not absorbed from the GI tract. Metabolism to the extent of 50% of the administered dose occurs in the liver. The half-life of insulin is about 20 minutes if it has been injected IV, while it is 2 hours by the subcutaneous or intramuscular route. Insulin is 5% protein bound.

Insulin is reabsorbed in the proximal renal tubule (upto 98%), and 60% is returned to the venous blood. Less than 2% is excreted unchanged.

Adverse Effects

Hypoglycaemia: This remains one of the potential hazards of insulin therapy, and is invariably the result of inadvertent overdose. Symptoms will depend on the extent of overdose and the time elapsed since administration (**Table 31.4**). Prolonged hypoglycaemia can produce behaviour disturbances, convulsions, coma, and death. Irreversible neurologic sequelae are likely to occur when the duration of untreated hypoglycaemia approaches 7 hours following overdose. Sequelae may include amnesia, dementia, and confusion. While there is little correlation between insulin dose and severity of hypoglycaemia, serious sequelae are common when insulin is combined with other agents such as barbiturates.

Sensitivity reactions: These are more common with bovine preparations than with porcine insulin, while human insulin is associated with negligible incidence of allergic reactions. Cutaneous manifestations are most common, while in some cases there may be systemic effects. In a few cases, insulin resistance may be encountered due to IgG antibodies.

Lipoatrophy and lipohypertrophy: The former is said to be a variant of an immune response to insulin, while the latter is because of lipogenic action of high local concentrations of insulin. Both are rare with purified insulin preparations. It is advisable to rotate the site of injection frequently to avoid these effects.

Insulin oedema: Sodium retention consequent to insulin administration can result in oedema, abdominal bloating, weight gain, and blurred vision.

Table 31.3: Insulin Preparations

Preparation	Appearance	Added Protein	Zinc Content (mg/100 U)	Buffer	Onset of Action (hrs)	Duration of Action (hrs)
RAPID –						
Regular (crystalline)	Clear	None	0.01 – 0.04	None	0.3 – 0.7	5 – 8
Semilente	Cloudy	None	0.2 – 0.25	Acetate	0.5 – 1	12 – 16
INTERMEDIATE –						
NPH (isophane)	Cloudy	Protamine	0.016 – 0.04	Phosphate	1 – 2	18 – 24
Lente	Cloudy	None	0.2 – 0.25	Acetate	1 – 2	18 – 24
SLOW –						
Ultralente	Cloudy	None	0.2 – 0.25	Acetate	4 – 6	20 – 36
Protamine zinc	Cloudy	Protamine	0.2 – 0.25	Phosphate	4 – 6	24 – 36

Table 31.4: Hypoglycaemia Due To Insulin

Time after insulin administration	Symptoms
30 minutes	Sweating, salivation, drowsiness, restlessness, tachycardia (when stimulated), bradycardia (when somnolent)
2 to 4 hours	Loss of contact with environment, myoclonus, primitive reflexes (grasping, sucking), mydriasis
4 to 5 hours	Comatose, roving eye movements, tonic and torsion muscular spasms, extensor plantar response
5 to 6 hours	Decerebrate rigidity
6 to 7 hours	Miosis, bradycardia, flaccid tone, depressed reflexes

Drug Interactions

The hypoglycaemic action of insulin is enhanced by fasting, alcohol, barbiturates, salicylates, MAOIs, beta blockers, ACE inhibitors, and benzodiazepines. It is depressed by glucagon, adrenaline, oestrogens, adrenocortical hormones, INH, chlorpromazine and thyroxine.

Clinical (Toxic) Features

Acute Poisoning:

General—

- Patients with intermediate or extended insulin overdose may not develop symptoms for 18 to 36 hours except for vomiting and lethargy. With long acting insulin, there is a compensatory mechanism in the first 24 hours which helps to maintain normoglycaemia. Later this is exhausted, leading to irreversible brain and myocardial damage due to severe hypoglycaemia.
- After an insulin overdose, upto 12 days of treatment may be required before insulin needs return to normal. Non-diabetic patients are found to be more likely to present with hypoglycaemia, and develop recurrent hypoglycaemia despite oral intake and IV glucose infusion following intentional misuse.
- Hypoglycaemia can occur with therapeutic doses of insulin in diabetics on an uncontrolled diet, with too much exercise, or in patients with brittle diabetes. It is difficult to predict the minimum toxic or lethal dose of insulin and severity of intoxication must be based on clinical findings.

Specific—

- Eyes: Mydriasis, sluggish external ocular movements.
- CNS: Drowsiness, confusion, headache, restlessness, extensor spasms, extensor plantar reflexes, absent gag reflex. Deep tendon reflexes may be normal, depressed or exaggerated. Generalised seizures may accompany severe hypoglycaemia following overdose. Aphasia, maniacal behaviour, and other personality changes secondary to hypoglycaemia can also occur.
- Skin: Cold, clammy, pale, with profuse sweating.
- Respiratory system: Breathing is deep and heavy, with periods of apnoea. Pulmonary oedema may occur.
- CVS: Tachycardia.
- Extremities: Pain, cramps, twitching.
- Hypokalaemia may occur along with other electrolyte abnormalities following massive insulin overdose. See also **Table 31.4**.

Chronic Poisoning

- This is usually the result of chronic overtreatment with insulin.
- There is recurrent, episodic hypoglycaemia characterised by
  - ❖ Pallor, restlessness, stertorous respiration, depression, inattentiveness.
  - ❖ Sweating.
- Nightmares, night sweats, difficulty in awakening.
- Glycogen-laden hepatomegaly.
- Morning hypothermia.

Diagnosis

- Monitor blood sugar levels regularly. Plasma glucose levels of 30 mg/dL or lower are common following large overdosage. Urinary glucose and acetone determination are also diagnostic for diabetic ketoacidosis. Immediate differentiation between hypoglycaemia and ketoacidosis is accomplished by the use of a bedside blood glucose testing strip.

- Plasma insulin levels do not correlate well with severity of hypoglycaemia.
- Leukocytosis is commonly observed.
- Potassium levels may be depressed.
- *ECG*: Sinus tachycardia, occasional premature ventricular beats, elevated ST segments.
- *EEG*: Slow diffuse waves without lateralising discharges.
- *Urinalysis*: Albuminuria, hyaline casts.
- Chronic insulin-induced hypoglycaemia is often associated with the presence of insulin-binding antibodies and low C-peptide levels.

Treatment

- *Stabilisation*: Airway, breathing and circulation must be established and maintained. Endotracheal intubation and assisted ventilation may be necessary.
- *Antidote*: **Glucose** is the specific antidote and must be administered without delay.
- Give 50 ml 50% dextrose as IV bolus upon admission.
- Follow this up with continuous glucose infusion of 5% or 10% dextrose in water, sufficient to maintain slight hyperglycaemia.
- Alternatively, if a patient is symptomatic, or has blood glucose level <60 mg/dL administer an IV bolus (50 ml) of 50% dextrose over a period of 2 to 3 minutes. Improvement will usually be seen in 5 to 10 minutes. A continuous IV infusion of 10 percent dextrose in water should be started following overdosage of longer acting insulin preparations given subcutaneously. Monitor blood glucose levels regularly to maintain a blood glucose level of 100 mg/dL.
- Oral glucose cannot be relied upon to maintain euglycaemia.
- **Glucagon** 1 to 2 mg, IM, may help in mobilising hepatic glycogen stores, but is not effective in the presence of prolonged hypoglycaemia, fasting, or alcohol abuse. Glucagon is only effective when the patient has adequate liver glycogen stores.
- Adrenaline (1 : 1000), 1 mg, SC, can be beneficial in some cases.
- Some investigators have achieved success by surgically excising visible injection sites down to the muscle layer.
- Cerebral oedema is treated with mannitol and dexamethasone.
- Hypokalaemia is managed by potassium supplements. Administer intravenous potassium chloride (20 to 60 mEq/L of fluid) to correct cardiac arrhythmias, muscle paralysis, or EKG changes secondary to hypokalaemia.
- Administer 300 grams daily or more of carbohydrates when the patient awakens, to supplement intravenous glucose and prevent secondary hypoglycaemia.
- Excision of the skin and fat down to the muscle wall of an insulin injection site using local anaesthetic has been utilised in the management of injected insulin overdoses.
- Haemodialysis does not appear to enhance elimination of insulin.
- Permanent brain damage has been reported following injection of 800 and 3200 units of insulin in diabetic patients.

At the same time, recovery has occurred following up to 3200 units in adults.

■ Oral Hypoglycaemics

Classification

Sulfonylureas—
- First generation analogues: tolbutamide, chlorpropamide, tolazamide, acetohexamide.
- Second generation analogues: glibenclamide (glyburide), glimepiride, glipizide, gliclazide.
  Biguanides—metformin, phenformin,* and buformin.
  Alpha-glucosidase inhibitor—acarbose.
  Thiazolidinedione derivatives—troglitazone.

■ Sulfonylureas

Sulfonylureas are antidiabetic agents that lower blood glucose in non-insulin dependant diabetics by directly stimulating the acute release of insulin from functioning beta cells of pancreatic islet tissue.

Uses

- Treatment of NIDDM patients who cannot achieve appropriate control with changes in diet alone.
- Sulfonylureas are contraindicated in IDDM, pregnancy, lactation, and liver and kidney disease.

Toxicokinetics

Sulfonylureas are rapidly absorbed on oral administration, are highly protein-bound, and are subjected to extensive hepatic metabolism

Adverse Effects

- Severe hypoglycaemia, especially in elderly patients and those with hepatic or renal impairment.
- Cholestatic jaundice.
- Agranulocytosis, thrombocytopenic purpura, aplastic anaemia, haemolytic anaemia.
- Vomiting, epigastric pain.
- Sensitivity reactions.

Drug Interactions

- Hypoglycaemic effect of sulfonylureas is **increased** by salicylates, coumarin anticoagulants, phenylbutazone, sulfonamides, MAOIs, chloramphenicol, cimetidine, and beta blockers.
- Hypoglycaemic effect is **reduced** by barbiturates, phenytoin, rifampicin, oestrogens, corticosteroids, furosemide, thiazides, and sympathomimetic drugs.
- Alcohol can cause a disulfiram-like reaction with first generation sulfonylureas. Some investigators claim that such a reaction can also occur with second generation drugs such as glipizide and glibenclamide.
- There are indications that long-term use of tolbutamide may be associated with increased susceptibility to myocardial infarction.

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* Phenformin has been withdrawn from use in several countries since the 1970s, owing to high incidence of lactic acidosis.

Clinical (Toxic) Features

- *CNS*: Confusion, lethargy, slurred speech, restlessness, dizziness, delirium, convulsions, opisthotonus. The following have been reported —monoplegia, hemiplegia, ataxia, extensor plantar response, absent deep tendon reflexes, and athetoid movements. Decerebrate posture, coma, and death may supervene.
- *Eye*: Normal or dilated.
- *Skin*: Hot, sweaty, sensitivity reactions.
- *GIT*: Vomiting, abdominal pain.
- *RS*: Dyspnoea, pulmonary oedema, apnoea.
- *CVS*: Tachycardia, hypotension.
- *Renal*: Proteinuria, oliguria.
- *Hepatic*: Cholestatic jaundice.
- *Blood*: Agranulocytosis, pancytopenia, aplastic anaemia, thrombocytopenia.
- Though sulfonylureas are generally not recommended to be given in pregnancy, some reports indicate that drugs such as glyburide may be relatively safe.

Diagnosis

- Blood levels of sulfonylureas do not correlate well with severity of poisoning.
- Frequent measurement of blood sugar levels is important.
- Arterial blood gases and serum potassium levels may reveal a hypokalaemic metabolic acidosis.
- Leukocytosis is often present.
- ECG: may show sinus tachycardia, T-wave inversion or ST elevation.

Treatment

- *Stabilisation*: Endotracheal intubation and assisted ventilation may be required.
- *Treatment of hypoglycaemia*: Hypoglycaemic episodes may last for several days; prolonged treatment may be required.
  - ❖ Glucose: 50 ml, 50% glucose as IV bolus, followed by IV infusion of 10% glucose in water (for upto 24 to 48 hours).
  - ❖ Glucagon: 1 to 2 mg, IM (or SC or IV), can help in raising blood sugar. It may have to be repeated every few hours.
  - ❖ Diazoxide: It is an inhibitor of insulin secretion, and can be given orally (200 mg every 4 hours), for several days.
  - ❖ Dexamethasone: Some reports suggest beneficial effects with dexamethasone when administered early.
- *Alkaline diuresis*: Sodium bicarbonate has been shown to enhance elimination of chlorpropamide.
- *Decontamination*: Emesis can be induced in the alert patient if seen within 4 to 8 hours. In the convulsive or comatose patient, gastric lavage can be done (after endotracheal intubation). Activated charcoal is beneficial.
- *Treatment of hypotension*: Trendelenberg position, IV fluids, pressor amines.
- *Treatment of convulsions*: Benzodiazepines or phenytoin.

- *Treatment of cerebral oedema*: Mannitol and dexamethasone.
- *Other measures*: Octreotide has been shown to be beneficial in suppressing plasma insulin. Dose – 50 mcg, every 12 hours, subcutaneously.

■ Biguanides

Metformin and phenformin are derivatives of guanidine, and are active components of the French lilac (*Galega officinalis*). While both drugs are used widely in India, phenformin has been withdrawn from several countries in the West because of the serious risk of lactic acidosis (64 cases/100,000 patient years). Metformin has a risk of only 3 cases/100,000 patient years.

Uses

- Biguanides are used orally in the management of mild to moderate NIDDM, especially if the patient is elderly and obese.
- Metformin is said to be relatively safe in pregnancy

Toxicokinetics

These drugs are absorbed from the small intestine, do not bind to plasma proteins, and are excreted unchanged in the urine. Oral bioavailability is 50 to 60%. The half-life of metformin varies from 1.3 to 4.5 hours.

Mode of Action

Biguanides induce increase in peripheral glucose utilisation, decrease in hepatic gluconeogenesis, and decrease in intestinal absorption of glucose, vitamin B and bile acids. They usually do not lower the blood sugar in normal individuals (unless other hypoglycaemic agents or ethanol has been concomitantly ingested).

Adverse Effects

- Diarrhoea, abdominal discomfort, metallic taste.
- **Lactic acidosis**: While phenformin is associated with a greater risk of lactic acidosis, the other biguanides can also cause it in the presence of renal or hepatic impairment, cardiac failure, or chronic hypoxic lung disease.
  - ❖ Manifestations: Acute onset of diarrhoea, vomiting, hyperventilation, and alteration of consciousness.
  - ❖ Diagnosis: Anion gap metabolic acidosis, low serum pH and bicarbonate, elevated serum potassium, normal or depressed serum chloride, increased blood lactate and lactate/pyruvate.
  - ❖ Treatment: Sodium bicarbonate IV (1 to 2 mEq/kg). Upto 50 mEq every 15 minutes may be required. Total dose should not exceed 400 mEq.

Clinical (Toxic) Features

- GIT: Nausea, vomiting, diarrhoea, abdominal cramps, haematemesis.
- CNS: Agitation, confusion, convulsions, coma.
- RS: Rapid, deep breathing, pulmonary hypertension.

- CVS: Tachycardia, hypotension.
- Others: Lactic acidosis.

Diagnosis

- Elevation of lactate/pyruvate ratio.*
- Elevation of 3-β-hydroxybutyrate concentration.
- Blood glucose may be depressed, normal, or elevated.
- Leucocytosis, thrombocytopenia.
- Elevated serum creatinine, albuminuria.
- Lactic acidosis is characterised by a number of abnormal laboratory values (*vide supra*).

Treatment

- *Stabilisation*—Establish airway, undertake endotracheal intubation, and perform assisted ventilation (if necessary).
- Stomach wash, activated chacoal.
- Treatment of hypoglycaemia with 50 ml of 50% glucose IV (0.5 gm/kg/dose in children).
- Treatment of acidosis with IV sodium bicarbonate (1 to 2 mEq/kg). Upto 200 to 400 mEq may be required.
- Treatment of hypotension with Trendelenberg position and IV fluids. Pressor amines such as dopamine must be used with caution, since they can aggravate lactic acidosis.
- Haemodialysis.

■ Other Hypoglycaemics

Acarbose

Acarbose is an alpha-glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of intestinal brush-border alpha-glucosidase. This results in depressed absorption of carbohydrates with blunting of postprandial rise of plasma glucose. Adverse effects include flatulence, gastritis, abdominal pain, nausea, anorexia, stool discolouration, hepatitis, and dermal reactions (urticaria, exanthema).

The action of acarbose is potentiated by concomitant intake of other oral hypoglycaemics, while thiazides, furosemide, steroids, phenothiazines, oral contraceptives, phenytoin, nicotinic acid, INH, and sympathomimetics interfere with its effects.

Troglitazone, Ciglitazone, Pioglitazone

These drugs are thiazolidinediones and have been recently introduced in the treatment of insulin-resistant diabetes. They do not cause hypoglycaemia in diabetic or normal persons, but may produce hepatotoxicity.

Forensic Issues

Most cases of toxicity are iatrogenic due to inadvertent overdoses. However there have been several cases of intentional insulin overdose among depressed patients intent on committing suicide. A few of these cases may represent factitious administration. Surreptitious insulin administration may be a symptom of serious underlying psychiatric disorder (especially in adolescents with insulin-dependant diabetes mellitus). Insulin has been used as a performance-enhancing drug by body builders. It can often be obtained on the "black market" by users identified as anabolic androgenic steroid injectors to promote anabolic processes and inhibit catabolism.

Oral hypoglycaemics are also often involved in accidental and suicidal overdose. In fact deliberate overdose with these agents in diabetics appears to occur more often than self-poisoning with insulin. Sometimes inadvertent name confusion leads to unpredicted and unwanted hypoglycaemic effects. Indigenous medicines reputed to be effective in diabetes can contain one of these compounds.

While homicidal poisoning with insulin and oral hypoglycaemics is quite rare, a few notable cases have been reported from around the world.

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* Normal ratio is 10 :1.

32

Other Drugs

In this chapter, the following classes of drugs which defy easy slotting, will be discussed:
1. Anti-asthmatic Drugs
2. Catecholamines
3. Immunomodulators
4. Antineoplastic Agents
5. Drugs Acting on Uterus
6. Radiocontrast Agents
7. Drugs Used in the Treatment of Impotence.

ANTI-ASTHMATIC DRUGS

■ Classification

1. Bronchodilators:
   a. Beta-adrenergic agonists
   b. Beta$_2$-selective adrenergic agonists
   c. Methylxanthines
   d. Anticholinergics
2. Anti-inflammatory Drugs:
   a. Glucocorticoids
   b. Cromolyn sodium and Nedocromil

■ Bronchodilators

■ Beta-Adrenergic Agonists

Beta-adrenergic agonists have an important role as cardiac stimulants owing to both chronotropic and inotropic effects on the heart, and are (relatively) rarely used as bronchodilators today, so their inclusion here may appear incongruous.

Isoproterenol (Isopropylarterenol, Isoprenaline, Isopropylnoradrenaline)

This drug is used to stimulate heart rate in bradycardia or heart block as an emergency measure, and occasionally for the treatment of asthma. It is readily absorbed by inhalation and by parenteral administration. It is metabolised in the liver by catechol-o-methyltransferase (COMT). It acts by lowering peripheral vascular resistance and mean arterial pressure, while increasing cardiac output and relaxing smooth muscles.

Adverse effects include tachycardia, palpitations, headache, and flushing. Sometimes arrhythmias or cardiac ischaemia may occur.

Dobutamine

Dobutamine resembles dopamine in its structure, but possesses an aromatic substitute on the amino group. It is used for short-term treatment of cardiac decompensation due to depressed contractility. Infusion of dobutamine in combination with echocardiography is useful in the non-invasive assessment of patients with coronary artery disease.

Dobutamine is ineffective orally, since it is inactivated by extensive presystemic metabolism in the GI mucosa and liver. The duration of action on IV administration is just 8 to 10 minutes. It has an apparent volume of distribution of 0.20 to 0.80 L/kg. Dobutamine is metabolised in the liver by COMT, and by conjugation with glucuronic acid, and excreted in the urine. Dobutamine is a beta$_1$-adrenergic agonist, and also induces alpha$_1$-adrenoceptor-mediated vasoconstriction, as well as beta$_2$-adrenoceptor-mediated vasodilation. This results in an increase in cardiac output without significantly changing the blood pressure. Unlike dopamine, it does not cause release of endogenous noradrenaline.

Adverse effects include nausea, tachycardia, palpitations, angina, dyspnoea, headache, and hypotension. Overdose results in hypotension, oliguria, supraventricular tachycardia, stuffy nose, hoarseness, flushing of skin, tachypnoea, palpitations, anginal pain, paraesthesias, and urinary incontinence. Signs and symptoms usually clear within 2 hours.

Treatment consists of symptomatic and supportive measures. The patient must not be discharged until serial ECGs and cardiac enzymes show no evidence of myocardial damage.

■ Beta$_2$-Selective Adrenergic Agonists

Beta$_2$-selective adrenergic agonists are much more useful in the treatment of asthma than beta-adrenergic agonists, because unlike the latter, they do not stimulate beta$_1$-adrenergic receptors in the heart that can result in serious cardiac effects. But in conditions of overdose, such selectivity may be lost. Another advantage is that these drugs have enhanced oral bioavailability, and hence can be given orally. However, inhalation of small doses in aerosol form affords best protection against adverse effects.

Examples

Metaproterenol (orciprenaline), terbutaline, albuterol (salbutamol), isoetharine, isoxsuprine, pirbuterol, bitolterol, fenoterol, formoterol, procaterol, salmeterol and ritodrine.

Ritodrine is more commonly used for inhibition of uterine contractions (in premature labour*)*. Isoxsuprine is used to relieve the symptoms of central and peripheral vascular diseases such as arteriosclerosis, Buerger's disease and Raynaud's disease.

Toxicokinetics

Beta$_2$ agonists can be given orally, by inhalation, or by injection (SC, IM, IV). Following oral administration, most beta agonists (especially salbutamol and bitolterol) are well absorbed, with the exception of terbutaline and orciprenaline. Despite adequate absorption however, the systemic bioavailability of these drugs is generally low, because of extensive sulfation in the liver and the small intestinal wall. As a result, the oral dose of beta$_2$ agonists needs to be 5 to 10 times greater than the parenteral dose.

Mode of Action.

- Bronchodilation.
- Relaxation of uterine muscle.
- Peripheral vasodilation.
- Anti-allergic effect on mast cells causing inhibition of release of bronchoconstriction mediators (histamine, prostaglandin D$_2$, etc.).
- Promotion of intracellular shift of potassium from serum, leading to a decrease in serum potassium concentration.
- Stimulation of non-pulmonary beta$_2$ receptors, resulting in tachycardia, prolongation of QTc interval, T wave changes, tremor, and increase in blood glucose.

Adverse Effects

- Tremor, restlessness, anxiety.
- Tachycardia, palpitations, hypotension, myocardial ischaemia (especially on systemic administration).
- Headache.
- Hypokalaemia.

Drug Interactions

- Beta blockers inhibit bronchodilator effect.
- Diuretics and xanthines augment hypokalaemia.
- Synergistic effect with theophylline and beclomethasone.
- Potentiation of vascular effects with MAOIs and tricyclics.

Clinical (Toxic) Features

1. CNS: Tremor, agitation, vertigo, headache, mydriasis.
2. CVS: Chest pain, angina, hypotension. ECG changes—Prolongation of QTc interval, atrial fibrillation, right bundle branch block, and ST-T wave changes. Sinus tachycardia is said to be the most frequent ECG change seen.
3. General: Nausea, hyperglycaemia, hypokalaemia, and flushed sweaty skin. Rarely there may be lactic acidosis, rhabdomyolysis, and acute renal failure.

4. Chronic overdose with salbutamol has led to the development of psychosis.

Treatment

1. *Decontamination*—Stomach wash may be done if the patient is seen within 4 to 6 hours.
2. *Stabilisation*—
   a. Admission to intensive care unit and observation for at least 4 to 6 hours. The patient can be discharged if there is normal heart rate, absence of tremor, and presence of normal blood sugar and serum potassium.
   b. For serious cases, cardiac monitoring and oxygen administration are necessary.
   c. Haemodialysis may be useful if there is evidence of acute renal failure.
3. *Antidote*—Some investigators have suggested the use of beta blockers (e.g. propranolol 0.01 mg/kg) for symptomatic improvement of tremor, tachycardia, and hypokalaemia. More cardioselective drugs such as metoprolol may be preferable in order to avoid precipitation of wheezing in asthmatic patients. However, actual efficacy of such beta blockers is controversial.
4. *Special Measures*—
   a. For serious hypokalaemia, administer potassium chloride cautiously, while repeating serum potassium levels and serial ECGs. In most cases, hypokalaemia reverts to normal spontaneously. Beta blockers may help in speeding the return to normalcy, but must be used with caution in asthmatic patients.
   b. In children, it is important to monitor blood glucose levels for several hours to rule out hyperglycaemia.
   c. Pulmonary oedema may be precipitated if an overdose of β$_2$ agonists has been taken by a pregnant woman in labour. This should be managed by oxygen, IV diuretics, and fluid restriction.

Forensic Issues

- Deliberate overdose with beta agonists is not uncommon in some Western countries, but is relatively rare in India.
- A disturbing (and unexpected) aspect of beta agonist use in the form of inhalation, has been an increase in mortality from asthma. This was first noticed with isoproterenol in the 1960s, and subsequently with salbutamol and fenoterol. Possible causes for such increased mortality may be related to the following factors:
  - Unnecessarily frequent use.
  - Unsupervised use.
  - Induction of paradoxical bronchospasm by propellants, preservatives, emulsifying agents, or contaminants.
  - Fenoterol mortality may be due to its unique formulation as a bromide.

■ Methylxanthines

Xanthine is a dioxypurine structurally related to uric acid. **Theophylline**, **caffeine**, and **theobromine** are methylated

xanthines. All these three alkaloids occur naturally in various plants. The leaves of *Thea sinensis* constitute the source of the hugely popular beverage "tea" that is drunk by half the population of the world (**Fig 32.1**). Tea contains caffeine and small amounts of theophylline and theobromine. The seeds of *Theobroma cacao* are used in the preparation of cocoa and chocolate which contain theobromine and some caffeine (**Fig 32.2**). Coffee is extracted from the beans of *Coffea arabica* and contains mainly caffeine (**Fig 32.3**). Cola-flavoured drinks containing considerable amounts of caffeine are prepared from the nuts of *Cola acuminata* (**Fig 32.4**).

Important derivatives of methylxanthines (with increased water solubility) include **aminophylline** (combination of theophylline and ethylenediamine), and choline theophyllinate (or

Fig 32.1: Tea plantation

Fig 32.2: Cocoa tree

Fig 32.3: Coffee plant

Fig 32.4: Cola tree

oxtriphylline). Diphylline is a covalently modified derivative. Other important xanthine derivatives include enprofylline, and pentoxifylline.

Theophylline and Aminophylline

They are used in the treatment of asthma, chronic obstructive pulmonary disease (relief of dyspnoea), and prolonged apnoea in pre-term infants.

Theophylline promotes diaphragmatic contractility, mucociliary clearance, aids cardiac function, lowers pulmonary artery pressure, and exhibits anti-inflammatory property. Therapeutic levels should not exceed 5 to 10 mg/L. Minimal toxicity is seen at levels of 20 to 40 mcg/ml, moderate toxicity at 40 to 100 mcg/ml, and severe toxicity at more than 100

mcg/ml. Chronic theophylline toxicity may result from prescribing error, unintentional over-utilisation by the patient, decrease in hepatic clearance, or drug interactions (*vide infra*). Manifestations include nausea, vomiting, anorexia, palpitations and convulsions.

Common drugs which interact with theophylline are listed in **Table 32.1**.

Acute Toxicity

1. CNS: Convulsions (sometimes resulting in status epilepticus), rhabdomyolysis, hypothermia, ataxia, visual hallucinations. Coma is uncommon.
2. CVS: Cardiac arrhythmias. ECG changes include sinus tachycardia, atrial and ventricular ectopy, ventricular fibrillation, and cardiac arrest.
3. Metabolic: Hypokalaemia, hyperglycaemia, hypercalcaemia, and metabolic acidosis.

Treatment

1. *Decontamination—*
   a. Gastric lavage (unless there are contraindications such as convulsions).
   b. Activated charcoal (1 gm/kg). Multiple dose activated charcoal is even more beneficial. However, vomiting must be controlled.
2. *Stabilisation—*
   a. Monitor cardiac rhythm.
   b. Monitor serum magnesium, phosphate, calcium, and potassium levels, acid-base balance, and serum theophylline levels.
   c. Monitor urine myoglobin, and serum creatinine and creatine kinase levels (to detect evidence of rhabdomyolysis).
3. *Symptomatic measure—*
   a. Treat intractable vomiting with metoclopramide (10 mg), or slow infusion of ondansetron (8 mg in 100 ml of saline, over 20 minutes).
   b. Hypotension refractory to fluids and vasopressors such as dopamine, may respond to alpha-adrenergic drugs such as levarterenol. Propranolol has been suggested by some investigators, but caution must be exercised in asthmatics.

c. Supraventricular tachycardia and multifocal atrial tachycardia respond to propranolol and verapamil respectively.
d. Convulsions often do not respond to conventional measures, and administration of intravenous thiopentone may be necessary.
e. Correction of hypokalaemia may necessitate the use of potassium chloride (5–10 mEq/hour)
f. Hyperthermia and rhabdomyolysis can be treated with dantrolene 1 mg/kg over 20 minutes, and then 2 mg/kg/hour for 4 hours. Hydration and maintenance of high urine output are essential.

4. *Special measures—*
   a. Haemoperfusion is effective in theophylline overdose, and is the elimination procedure of choice. Indications include intractable convulsions, persistent hypotension, uncontrollable arrhythmias, and serum theophylline levels greater than 60 to 80 mcg/ml. Charcoal haemoperfusion is said to be more effective than resin haemoperfusion.
   b. Haemodialysis is less effective than haemoperfusion, while forced diuresis is not effective at all.
   c. Anecdotal reports suggest that exchange transfusion can be life-saving in those cases of severe poisoning where haemoperfusion or haemodialysis cannot be done (especially in infants).
   d. Whole-bowel irrigation may be helpful in those cases where sustained-release preparations have been ingested. Such tablets are very slowly absorbed and can lead to bezoar formation.
   e. There are no known antidotes to theophylline. But some investigators have suggested antidotal use of adenosine or pyridoxine.

Caffeine

Though caffeine is almost never used as an anti-asthmatic, it is being discussed here (along with other methylxanthines), only for the sake of convenience. Caffeine is said to be the most widely used of all mind-altering substances in the world. It is obtained mainly from the beans (**Fig 32.5**) of the coffee plant *Coffea arabica*. Today caffeine is consumed not only in the

Table 32.1: Theophylline: Drug Interactions

Drugs that decrease theophylline clearance (raise plasma concentration)		Drugs that increase theophylline clearance (decrease plasma concentration)
Verapamil	Erythromycin	Isoproterenol
Roxithromycin	Ciprofloxacin	Terbutaline
Pefloxacin	Norfloxacin	Corticosteroids
Ofloxacin	Cimetidine	Phenytoin
Famotidine	Ranitidine	Phenobarbitone
Propranolol	Diltiazem	Activated charcoal
Nifedipine	Furosemide	Benzodiazepines
Thiabendazole	Pyrantel pamoate	
Disulfiram	Interferon	
Caffeine	Rifampicin	
INH	Oral contraceptives	

Fig 32.5: Coffee beans

form of coffee, but also as chocolates, cocoa drinks, cola drinks, and tea (*vide supra*). Apart from its use as a stimulant, caffeine is also used in combination with various analgesics to increase their potency. Several common pharmaceutical preparations contain varying concentrations of caffeine.

Mode of action of caffeine is mentioned in **Table 32.2**, while **Table 32.3** lists the caffeine content of various beverages and drugs.

Acute overdoses with caffeine are rare. Most cases of toxicity arise from long-term daily consumption of excessive amounts through beverages or drugs.

Caffeine dependence syndrome—Daily intake of small quantities of caffeine (20 to 200 mg), produces mild positive effects such as a feeling of well being, alertness, and energetic disposition, but higher doses result in negative effects.

- Anxiety syndrome: Restlessness, nervousness, tremor, irritability, hyperactivity, dry mouth. Severe cases may be associated with tinnitus, ocular dyskinesias, scotomata, and dysesthesias. An offshoot of anxiety syndrome is *restless leg syndrome*, characterised by discomfort and creeping sensations of lower legs which occur only at rest, producing an irresistible urge to move the legs constantly. It is often associated with insomnia since it generally appears in the late evening or at bed time.

- Hypochondriasis syndrome: It is most commonly seen in moderate consumers of caffeine (250–750 mg/kg/day), and is characterised by non-specific aches and pains, myalgia and tremor.
- Insomnia and/or headache syndrome: It is seen in sporadic or moderate users, and is characterised by delay in onset of sleep, restless sleep, and recurring headaches.
- Depressive syndrome: Occurs in heavy users of caffeine (750 mg or more per day), and is characterised by lethargy, depression and anxiety.
- Withdrawal syndrome: Results from abrupt stoppage of daily caffeine consumption (usually moderate or heavy use), and manifests as headache which sets in 12 to 24 hours after the last dose of caffeine, drowsiness, lethargy, impaired concentration, myalgia, nausea, rhinorrhoea, sweating and blurred vision. There is usually intense craving for caffeine.
- Neonatal caffeine withdrawal: This is seen in children of women who had consumed large quantities of caffeine

Table 32.3: Caffeine Content of Foods and Drugs

Substance	Caffeine Content
Coffee	
Brewed	100 mg/cup (177 ml)
Instant	70 mg/cup (177 ml)
Decaffeinated	4 mg/cup (177 ml)
Tea	40 mg/cup (177 ml)
Cocoa	5 mg/cup (177 ml)
Drinking (milk) chocolate	4 mg/cup (177 ml)
Cola drink	45 mg/can (355 ml)
Chocolate	
Milk	6 mg/bar (29 gm)
Dark	20 mg/bar (29 gm)
Drugs	
Caffeine-containing cold remedies	25–50 mg/tablet
Caffeine-containing analgesics	25–65 mg/tablet

Table 32.2: Mechanism of Action and Physiological Effects of Caffeine

Metabolic	*Gastrointestinal*
• ↑ cAMP concentration	• ↑ gastric acid and pepsin secretion
• antagonises adenosine receptors	• ↑ small intestinal secretions
• ↑ intracellular calcium	
• hyperpolarises cell membrane	
• ↑ oxygen consumption	
• ↑ BMR	*Cardiovascular*
• ↑ plasma renin	• atrial and ventricular tachyarrhythmias, and ventricular premature beats
• ↑ lactic acid	• ↑ stroke volume
• ↑ WBC	• ↑ cardiac output
• ↑ urinary catecholamines	• ↑ blood pressure
• ↑ skeletal muscle contraction	• ↑ cerebral arteriolar vasoconstriction
• ↑ lipolysis, glycogenolysis, gluconeogenesis	
• ↑ osteoporosis	
• ↑ muscle enzymes	
• ↓ serum calcium and potassium	

during pregnancy. They demonstrate jitteriness, irritability, and vomiting which can persist for several days.

Treatment (Acute Toxicity):

1. *GI Decontamination*: Activated charcoal, cathartic.
2. *CVS*:
   - ❖ Supraventricular tachycardia: Beta-adrenergic antagonists or calcium channel blockers.
   - ❖ Ventricular tachycardia/fibrillation: Cardioversion or defibrillation, or the use of bretylium, lignocaine, or procainamide.
   - ❖ *CNS*: Benzodiazepines or barbiturates can be given for convulsions or agitation. IV glucose may help, especially in children.
   - ❖ Anti-emetics such as metoclopramide or ondansetron for persistent vomiting.
   - ❖ Antiulcer regimens may be required in some cases, utilising H_2 antagonists, hydrogen pump inhibitors, or sucralfate.
   - ❖ Potentially lethal ingestions with life-threatening complications (cardiac arrhythmias, severe CNS toxicity) can be managed by charcoal haemoperfusion.

■ Anticholinergics

Detailed description of anticholinergic poisoning is given in **Chapter 15**, (under *Datura* poisoning).

Ipratropium bromide

Today the only anticholinergic that is still recommended for the treatment of asthma is a quaternary anticholinergic agent, ipratropium bromide. It is usually administered by inhalation. Ipratropium is particularly useful as a maintenance bronchodilator for bronchospasm associated with chronic obstructive pulmonary disease. It has also been found to be beneficial in organophosphate poisoning when given intratracheally. Combined use of nebulised ipratropium and salbutamol may however precipitate acute angle-closure glaucoma, particularly in elderly patients. Combined use with terbutaline is associated with pharyngeal blistering.

Large doses of ipratropium can lead to cough, metallic taste, dry mouth, buccal or pharyngeal ulceration, blurred vision, paralytic ileus and bladder neck obstruction. Paradoxical bronchoconstriction has been reported.

Treatment consists of supportive and symptomatic measures. In most cases, symptoms resolve spontaneously over a period of 24 hours after stopping the drug.

ANTI-INFLAMMATORY DRUGS

■ Corticosteroids

Glucocorticoids have been employed in the treatment of asthma for a long time, and are especially useful in the management of severe chronic asthma or severe acute exacerbations. These drugs are usually given systemically, but the development of aerosol formulations in recent years has greatly improved the efficacy as well as safety. The toxicity of systemic glucocorticoids has been discussed in **Chapter 31**.

Inhaled Corticosteroids

Examples include beclomethasone dipropionate, triamcinolone acetonide, flunisolide, budesonide dipropionate, and fluticasone propionate. Adverse and toxic effects have been listed in **Table 32.4**. Of all the inhaled corticosteroids, fluticasone is said to be the safest, being associated with a low incidence of adverse effects. Treatment involves cessation of inhaled glucocorticoids. Oropharyngeal candidiasis can be prevented by rinsing the mouth and throat with water after each use and by employing spacer or reservoir devices attached to the dispenser.

Cromolyn and Nedocromil

Cromolyn was first synthesised in 1965 and has been in use in the management of asthma since 1973. It is the first-line drug for the treatment of mild to moderate asthma. It is also used as eye drops in the treatment of allergic conjunctivitis. A related compound, Nedocromil was released for use recently.

Mode of action is through inhibition of pulmonary mast cell degranulation in response to a variety of stimuli, and suppression of activating effects of chemoattractant peptides on human neutrophils, eosinophils, and monocytes. Cromolyn and nedocromyl are administered by inhalation using either solution (delivered by aerosol spray or nebuliser), or powdered drug (delivered by turbo-inhaler). Only about 1% of an oral dose of cromolyn is absorbed. After inhalation, peak plasma concentrations occur within 15 minutes. The biological half-life ranges from 45 to 100 minutes.

Table 32.4: Adverse and Toxic Effects of Inhaled Glucocorticoids	
Effect	*Risk*
Hypothalamic-pituitary-adrenal-axis suppression	Possible at doses of budesonide or beclomethasone beyond 1500 mg/day (adults), or 400 mg/day (children)
Bone resorption	Occurs at more than 500 mg/day
Carbohydrate & lipid metabolism	Possible at doses of beclomethasone more than 1000 mg/day
Cataract	Unproven risk
Skin thinning	Possible at doses of beclomethasone more than 400 to 2000 mg/day
Purpura	Occurs at doses of beclomethasone more than 400 to 2000 mg/day
Dysphonia	Often encountered, but of little consequence
Candidiasis	Occurs in approximately 5% cases (minimised with spacer)
Growth retardation	Unproven risk

Adverse effects are uncommon with both cromolyn and nedocromil. Occasional effects reported include cough, bronchospasm, laryngeal oedema, joint pain, headache, rash, angioedema, and nausea. Nedocromil may leave behind a bad taste.

CATECHOLAMINES

The term **catecholamine** refers to a biologically active amine derived from the amino acid tyrosine. Classic examples include adrenaline (epinephrine), and noradrenaline (norepinephrine). Other examples include dopamine and isoproterenol, both of which have been discussed elsewhere.

■ Adrenaline (Epinephrine)

Uses

1. Rapid relief of respiratory distress due to bronchospasm.
2. Rapid relief of hypersensitivity reactions.
3. Prolongation of action of local anaesthetics.
4. Restoration of cardiac rhythm in patients with cardiac arrest.
5. Topical haemostatic agent in surgical procedures of the nose, throat and larynx.

Toxicokinetics

Adrenaline is not effective orally since it is rapidly conjugated and oxidised in the GI mucosa and liver. The usual route of administration is subcutaneous injection (slow, steady absorption), but it can also be given intramuscularly, intravenously (rapid infusion can be dangerous), or by inhalation (nebulised), or topical application.

Adrenaline is quickly inactivated by the liver after absorption by COMT and MAO.

Mode of Action

Adrenaline is a potent stimlant of both alpha- and beta-adrenergic receptors, and therefore has myriad effects on the body. A comparative analysis of the effects of adrenaline and noradrenaline are mentioned in **Table 32.5**.

Adverse Effects

- Fear, anxiety, restlessness, headache, weakness, vertigo.
- Tremor, palpitations.
- Respiratory difficulty.
- Cardiac arrhythmias, subarachnoid or cerebral haemorrhage (due to rapid IV injection, or infusion of excessive dose).

Drug Interactions

- Accidental intra-arterial injection of adrenaline can lead to hypotension, loss of consciousness, ventricular tachycardia, and marked pallor of the limb. Treatment involves immediate arterial injection of phentolamine (1.5 mg).
- Rapidly acting vasodilators (sodium nitroprusside or nitrites), and α-adrenergic blockers counteract the pressor effects of adrenaline.

Table 32.5: Comparative Effects of Adrenaline and Noradrenaline

Effect	Adrenaline	Noradrenaline
Cardiac		
Heart rate	+	-
Stroke volume	++	++
Cardiac output	+++	0, -
Arrhythmias	++++	++++
Coronary blood flow	++	++
Blood pressure		
Mean arterial	+	++
Mean pulmonary	++	++
Peripheral circulation		
Total peripheral resistance		
Cerebral blood flow	-	++
Muscle blood flow	+	0, -
Cutaneous blood flow	+++	0, -
Renal blood flow	--	--
Splanchnic blood flow	-	-
	+++	0,+
Metabolic effects		
Oxygen consumption	++	0, +
Blood glucose	+++	0, +
Blood lactic acid	+++	0, +
Central nervous system		
Respiration	+	+
Subjective sensations	+	+

- Use of adrenaline during anaesthesia with halogenated hydrocarbon anaesthetics can precipitate ventricular fibrillation.
- Possibility of severe hypertension and cerebral haemorrhage is greatly increased when adrenaline is combined with beta-adrenergic blockers.

Clinical (Toxic) Features

1. *Immediate*—pallor, cyanosis, throbbing headache, sweating, tachycardia, hypertension, chest pain, palpitations, paraesthesias of hands and feet, abdominal pain, and ECG changes : premature ventricular contractions, bigeminal rhythmic changes.
2. *Delayed*—hypotension, metabolic acidosis, pulmonary oedema.
3. Accidental intra-arterial injection of adrenaline can lead to hypotension, loss of consciousness, ventricular tachycardia, and marked pallor of the limb. Treatment involves immediate arterial injection of phentolamine (1.5 mg).

■ Noradrenaline (Norepinephrine, Levarterenol)

Noradrenaline is commonly used in the treatment of shock and hypotension (especially resulting during spinal anaesthesia, or due to overdose with antihypertensives). Adverse effects are similar to those of adrenaline, but are less frequent and less pronounced. Common effects include anxiety, respiratory difficulty, headache, and a slow, forceful heartbeat. Overdose causes severe hypertension with agonising headache, photophobia, stabbing chest pain, pallor, profuse sweating, and vomiting. Treatment is on general lines as mentioned for adrenaline.

IMMUNOMODULATORS

■ Immunosuppressive Agents

Cyclosporine (Cyclosporin A)

Cyclosporine belongs to a family of cyclic polypeptides derived from the fungus *Tolypocladium inflatum Gams*. It is lipophilic and hydrophobic, and therefore must be solubilised for clinical use.

Uses

To prevent transplant rejection in the transplantation of kidney, heart, and liver. Cyclosporine is usually combined with corticosteroids. It is also being increasingly used in transplantation of other organs such as lung, pancreas, and bone marrow.

Cyclosporine is also beneficial in the treatment of psoriasis, rheumatoid arthritis, Crohn's disease, nephrotic syndrome, endogenous uveitis, atopic dermatitis, and acute ocular Behcet's syndrome.

There are also indications that cyclosporine may be useful in the treatment of primary biliary cirrhosis, pyoderma gangrenosum, polymyositis, aplastic anaemia, myasthenia gravis and severe asthma.

Toxicokinetics

Cyclosporine can be administered orally, intravenously, or by injection. When given orally, it is metabolised on first pass through the liver, its absolute bioavailability being about 35%. Peak plasma concentration occurs at about 2.5 hours. About 50% of the drug in whole blood is bound to erythrocytes. The apparent volume of distribution in adults is 4.7 L/kg. Elimination occurs predominantly by metabolism in the liver by cytochrome P450 III A oxidase, and only about 0.1% of a dose is excreted unchanged.

For therapeutic purposes, cyclosporine levels in plasma should not exceed 150 ng/ml (600 ng/ml in whole blood).

Mode of Action

- Inhibition of T-lymphocyte proliferation.
- Inhibition (reversible) of activation of primary helper T cell.
- Decreases production and secretion of interleukin-2.
- Inhibition of production of interferon gamma by lymphocytes.

Adverse Effects

- *CNS*: Tremor, palmar and plantar paraesthesia, headache, flushing, depression, visual disorders, convulsions.
- *GIT*: Anorexia, nausea, vomiting, acute pancreatitis (rare).
- *Hepatic*: Cholestasis with hyperbilirubinaemia.
- *Renal*: Nephropathy can occur in up to 75% of patients, and is the most consistent and serious of the adverse effects.
- *CVS*: Hypertension.
- *Other effects*: Hypertrichosis, gingival hyperplasia, hyperglycaemia, hyperkalaemia, gynaecomastia, myopathies, increased susceptibility to infections.

Drug Interactions

Nephrotoxicity is greatly enhanced by concomitant administration of aminoglycosides, ciprofloxacin, cotrimoxazole, NSAIDs, colchicine and amphotericin B.

Blood levels of cyclosporine are increased by diltiazem, doxycycline, erythromycin, cephalosporines, ketoconazole, H_2 antagonists, verapamil, and oral contraceptives, while they are decreased by carbamazepine, isoniazid, phenobarbitone, phenytoin and rifampicin.

Clinical (Toxic) Features

The following have been reported in cyclosporine overdose (*accidental and deliberate*):

Headache, nausea, vomiting, vertigo, hyperaesthesia of hands, burning sensation of feet, abdominal pain, diarrhoea, sinus tachycardia and hypertension.

Premature infants and neonates have developed hypotension, wheezing, tachycardia, cyanosis, metabolic acidosis, respiratory depression and renal failure.

Treatment

1. *Decontamination*: Gastric lavage or emesis, activated charcoal, etc., may be beneficial. Multiple dose activated charcoal produced good results in one reported case.
2. Admission to intensive care unit followed by monitoring of vital signs and parameters.
3. Patients with stable renal function can be treated symptomatically and supportively. Most cases recover within 24 hours.

■ Tacrolimus

Tacrolimus is a macrolide compound produced by *Streptomyces tsukubaensis*.

Uses

Immunosuppressive agent to prevent organ transplant rejection. Tacrolimus is said to be 100 times more potent than cyclosporine.

Treatment of cyclosporine-induced haemolytic uraemic syndrome, severe psoriasis, Behcet's disease, and Type I diabetes mellitus.

Toxicokinetics

Tacrolimus is poorly absorbed orally, and intravenous administration is preferred, especially at the time of starting the course. The mean bioavailability is 25%, and the mean apparent volume of distribution is about 19 L/kg. RBCs concentrate tacrolimus so that whole blood values are higher than plasma values. The drug is completely metabolised before elimination, and less than 1% of an oral or IV dose of tacrolimus is excreted in the urine. Tacrolimus is eliminated mainly by hepatic cytochrome P450 III A metabolism.

Mode of Action

Tacrolimus suppresses cell-mediated and humoral responses, and is a more potent inhibitor of lymphoproliferation than cyclosporine. It prevents the activation of T lymphocytes in response to antigenic or mitogenic stimulation.

Adverse Effects

These are more pronounced with intravenous use than with oral therapy. Common adverse effects include insomnia, tremor,

headache, paraesthesia, myalgia, visual sensitivity to light, and GI distress. Serious adverse effects include nephrotoxicity, convulsions, movement disorders, encephalopathy, psychosis, infectious complications, hyperkalaemia and hyperglycaemia.

Clinical (Toxic) Features

Overdose leads to profound immunosuppression and severe infection. Neurological complications such as those listed in **Table 32.6** are frequently seen, and generally correlate well with blood levels.

Treatment

Supportive and symptomatic measures. Hyperkalaemia responds to fludrocortisone acetate.

■ Adrenocortical Steroids

The toxicity of these compounds has been discussed on *page no*. 481.

■ Cytotoxic Drugs

Most of the cytotoxic drugs have been discussed in a subsequent section of this chapter (*vide infra*). Only **azathioprine** and **mycophenolate mofetil** will be discussed here.

Azathioprine (Azathioprimum)

Azathioprine is a purine antagonist and is mainly used as an adjunct for the prevention of kidney allografts. It is also useful in the treatment of rheumatoid arthritis. It is invariably administered orally. Azathioprine inhibits DNA synthesis, and as a purine antagonist, exerts its effect on activated lymphocytes, which require purines during their proliferative phase. The immunosuppressive effect of azathioprine is believed to be due to mercaptopurine (a metabolite).

Adverse effects include bone marrow depression, hepatic dysfunction, infection, drug fever, nausea, vomiting, and diarrhoea. Rash, urticaria, and vasculitis (allergic) have also been reported. In overdose, it causes vomiting, diarrhoea, leucopenia, hepatotoxicity.

Treatment consists of supportive and symptomatic measures. Early GI decontamination may minimise the likelihood of bone marrow depression and hepatotoxicity. Haemodialysis may be beneficial.

Mycophenolate mofetil

Mycophenolate mofetil is a recently introduced oral preparation for use as an immunosuppressant in renal transplantation.

Table 32.6: Neurological Complications of Tacrolimus	
Major	**Minor**
Akinetic mutism	Tremors
Convulsions	Headache
Psychosis	Nightmares and sleep disturbances
Encephalopathy	Vertigo
Focal deficits	Dysaesthesia
Movement disorder	Photophobia

After absorption it is hydrolysed to mycophenolic acid (MPA), which is an active metabolite, and is a potent inhibitor of inosine monophosphate dehydrogenase which is necessary for the synthesis of purines. Mycophenolate mofetil suppresses lymphocyte proliferation and antibody formation by B cells.

Toxicity results in bone marrow suppression and hepatic dysfunction.

■ Antibody Reagents

Antibody reagents represent a promising therapeutic strategy, as they cause rapid lowering of lymphocytes, as well as suppression of function of specific lymphocyte populations.

Antithymocyte globulin (Atgam)

It is a purified immunoglobulin prepared commercially from hyperimmune serum of horse, rabbit, sheep, or goat, following immunisation with human thymic lymphocytes. It is used primarily to treat allograft rejection in kidney and heart transplantation. Toxic effects include anaphylaxis, serum sickness, nephritis, leukopenia, thrombocytopenia and fever.

Muromonab-CD3 monoclonal antibody

This is a mouse monoclonal antibody which causes a more consistent immune suppressive response than Atgam. It has been used to prevent acute rejection of kidney, liver, and heart transplants. Adverse effects include anaphylactoid reactions, *cytokine release syndrome*,* and CNS toxicity.

Rh(D) immune globulin

This antibody is prepared by alcohol fraction of plasma from donors, and is used in Rh-negative mothers to prevent sensitisation to Rh(D) antigen (to prevent erythroblastosis foetalis). It is given intramuscularly. Adverse effects include local pain, fever and anaphylaxis.

IMMUNOSTIMULANTS

■ Classification

1. *Natural adjuvants* : Bacillus Calmette-Guerin (BCG), immune globulin.
2. *Synthetic agents* : Levamisole, cytokines.

Uses

Treatment of
- Immunodeficiency disorders, (e.g. AIDS).
- Chronic infectious diseases.
- Cancer.

Clinical (Toxic) Features

1. *BCG*: Hypersensitivity, shock, fever, immune complex disease.
2. *Immune globulin*: Allergic reactions.
3. *Cytokines*: Hypotension, CVS toxicity, pulmonary oedema, renal toxicity, bone marrow suppression, CNS toxicity.

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* Manifestations range from a mild flu-like illness to a life-threatening shock-like reaction. It can be prevented or minimised by pretreatment with high doses of steroids.

ANTINEOPLASTIC AGENTS

■ Classification

1. Alkylating agents:
   a. Nitrogen mustards: chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan.
   b. Ethyleneimine and methylmelamine derivatives: hexamethylmelamine, thiotepa.
   c. Alkyl sulfonates: busulfan.
   d. Nitrosoureas: carmustine, lomustine, streptozocin.
   e. Triazenes: dacarbazine.
2. Antimetabolites:
   a. Folic acid antagonists: methotrexate, trimetrexate.
   b. Pyrimidine analogues: 5-fluorouracil, floxuridine, cytarabine.
   c. Purine analogues: 6-mercaptopurine, 6-thioguanine.
   d. Adenine analogue: fludarabine-A.
   e. Adenosine deaminase inhibitors: pentostatin.
   f. Interferons: interferon alfa 2a and 2b.
3. Natural products:
   a. Vinca alkaloids: vincristine, vinblastine, vindesine.
   b. Antitumour antibiotics: aclarubicin, bleomycin, dactinomycin (actinomycin D), mitomycin C, 5-azacytidine, daunorubicin, doxorubicin, idarubicin, plicamycin.
   c. Enzymes: 6-asparaginase.
   d. Epipodophyllotoxins: etoposide, teniposide.
4. Androgen inhibitors: cyproterone acetate, flutamide, leuprolide acetate.
5. Anti-oestrogen: tamoxifen citrate.
6. Hormones: testolactone, adrenocorticosteroids, oestrogens, progestins, androgens.
7. Miscellaneous agents: platinum co-ordination complexes (cisplatin, carboplatin), hydroxyurea, procarbazine, hexamethylmelamine, amsacrine, mitoxantrone, mitotane, leucovorin, levamisole, BCG, aminoglutethimide, coumarin, estramustine, MESNA.

General treatment measures for toxicity arising out of anticancer drug overdoses are mentioned on *page no 501* The following discussion is centred on the toxicity of specific drugs and special treatment measures.

■ Alkylating Agents

The era of modern cancer chemotherapy began with the landmark clinical studies of the action of nitrogen mustards on lymphosarcoma in mice in the early 1940s.

The tumouricidal activity of alkylating agents results from the formation of reactive intermediates that bind to nucleophlilic moieties on the DNA chain. The capacity of these drugs to interfere with DNA integrity and function in rapidly proliferating tissues provides the basis for their therapeutic applications (and for many of their toxic properties). The alkylating agents are most cytotoxic to rapidly proliferating tissues in which a large proportion of the cells are in division, even though some of these agents have damaging effects on tissues with low mitotic indices, e.g. liver, kidney, and lymphocytes.

■ Nitrogen Mustards

Mechlorethamine

Mechlorethamine was the first nitrogen mustard introduced into clinical practice, and is invariably administered only intravenously. It is used primarily in the combination chemotherapy regimen MOPP (mechlorethamine, oncovin (vincristine), procarbazine, and prednisone), for the treatment of Hodgkin's disease. It is given intravenously. Adverse effects include nausea, vomiting, diarrhoea, local reaction and phlebitis, bone marrow depression, alopecia, oral ulcers, leukaemia, amenorrhoea, sterility, hyperuricaemia.

Local reaction to extravasation of mechlorethamine can be severe, and therefore must be treated promptly by infiltration of the affected area with a sterile isotonic soluton of sodium thiosulfae (1/6 M).* This is followed by intermittent application of cold compress for 6 to 12 hours.

Cyclophosphamide

Cyclophosphamide is used in the treatment of lymphomas and chronic leukaemias, and also often in combination with methotrexate or doxorubicin as adjuvant therapy after surgery for breast cancer. It has also been used effectively in the treatment of carcinomas of lung, cervix, and ovary, as well as childhood neoplasms such as neuroblastoma and retinoblastoma. Adverse effects include nausea, vomiting, hypersensitivity reactions, visual blurring, and facial burning (from IV use). Chronic use may cause bone marrow depression, alopecia, haemorrhagic cystitis (due to its irritating metabolite acrolein), sterility, pulmonary fibrosis, hyponatraemia, leukaemia, bladder cancer, and cardiotoxicity. Inappropriate secretion of antidiuretic hormone sometimes leads to water intoxication.

Overdose results in cardiac arrhythmias, myocarditis, and myocardial necrosis. Deaths have been reported.

The incidence of haemorrhagic cystitis can be greatly reduced by adequate hydration (for dilution), IV administration of MESNA (sodium 2-mercaptoethanesulfonate), and intravesical N-acetylcysteine. Treatment of haemorrhagic cystitis, once it has set in, involves any of the following suggested measures: electrocauterisation, systemic vasopressin, and intravesical administration of silver nitrate, formalin, prostaglandin F_2 alpha, and hydrostatic pressure.

Chlorambucil

Chlorambucil can be administered orally, and at the recommended dosages, it is the slowest-acting nitrogen mustard. It is mainly indicated in the treatment of chronic lymphocytic leukaemia and primary macroglobulinaemia. Adverse effects include bone marrow depression, pulmonary fibrosis, leukaemia, hepatic toxicity, and sterility. Overdose causes nausea, vomiting, ataxia, convulsions, ECG changes, coma.

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* Thiosulfate provides an ion that reacts with mechlorethamine, and thereby protects tissue constituents.

Ifosfamide

Ifosfamide is an analogue of cyclophosphamide, and is mainly employed in combination with other drugs in the treatment of germ cell testicular cancer and sarcomas. It is also useful in treating lymphomas and carcinomas, and carcinomas of cervix and lung. Ifosfamide is usually given intravenously. Adverse effects comprise bone marrow depression, haemorrhagic cystitis, alopecia, inappropriate ADH secretion, renal failure, and neurotoxicity (drowsiness, blurring of vision, hallucinations). Overdose causes nausea, vomiting, confusion, nephrotoxicity, renal Fanconi's syndrome, and cardiotoxicity.

Haemorrhagic cystitis can be prevented by adequate hydration and co-administration of MESNA which reacts at acid pH in the urine to detoxify the metabolites of ifosfamide. MESNA is given IV as boluses equal to 20% of the ifosfamide dosages at 4 hourly intervals until a total dose of 60% has been achieved. At least 2 litres of IV fluids (or oral fluids) must also be administered every day. The MESNA treatment can be repeated every 3 to 4 weeks.

Haemodialysis may be effective in treating ifosfamide overdose, since it has a low apparent volume of distribution.

Melphalan

Melphalan can be given orally and intravenously. It is mainly used in multiple myeloma. Adverse effects comprise bone marrow depression (especially platelets), hepatic toxicity, GI ulceration (oral, intestinal), and pancreatitis. Overdose results in vomiting, diarrhoea, and nephropathy. Treatment is symptomatic and supportive. Colony stimulating factors (GM-CSF, GCSF) may help in improving the prognosis.

Ethyleneimine and Methylmelamine Derivatives

Thiotepa

Thiotepa is mainly indicated in bladder cancer, and is usually given intravenously. Adverse effects include bone marrow depression, sterility, leukaemia and mucositis.

Alkyl Sulfonates

Busulfan

Busulfan is well absorbed orally and is used for treating chronic granulocytic leukaemia, polycythemia vera, and myelofibrosis. Adverse effects comprise bone marrow depression, pulmonary fibrosis, alopecia, gynaecomastia, ovarian failure, hyperpigmentation, stomatitis, azoospermia, leukaemia, cataract, and hepatitis. Overdose results in vomiting and convulsions.

Nitrosoureas

The nitrosoureas are very effective against brain tumours and gastrointestinal neoplasms. Carmustine and lomustine are lipophilic and can therefore quite easily cross the blood-brain barrier. Streptozocin has a high affinity for beta cells of the islets of Langerhans and is useful in the treatment of pancreatic (islet cell) carcinoma and malignant carcinoid tumours. While carmustine and streptozocin are administered intravenously, lomustine can be given orally.

With regard to adverse effects, carmustine and lomustine characteristically cause delayed myelosuppression (maximal at 4 to 6 weeks), nausea, vomiting, pulmonary fibrosis, renal failure, and hepatic toxicity. Streptozocin causes renal and hepatic toxicity in about two thirds of patients, but myelosuppression is relatively infrequent (20%). Overdose can cause pancytopenia.

Triazenes

Dacarbazine

Dacarbazine is used (in combination with other drugs) for the treatment of malignant melanoma, Hodgkin's disease, and adult sarcomas. It is given intravenously. Toxicity results in nausea, vomiting, flu-like syndrome, myelosuppression, alopecia, hepatotoxicity and neurotoxicity.

ANTIMETABOLITES

Folic Acid Antagonists

Methotrexate (MTX)

Folic acid antagonists or antifolates, hold a special place in anticancer chemotherapy, since they were the first to produce striking remissions in leukaemia, and the first cure for a solid tumour (choriocarcinoma). Methotrexate even today remains one of the most important of the antifolates, and is used in the treatment of lymphoma, lymphocytic leukaemia, breast cancer, small cell carcinoma, rheumatoid arthritis, and trophoblastic diseases. Methotrexate or MTX is also used as an immunosuppressive in organ transplantation.

Methotrexate (MTX) is rapidly absorbed orally if administered in small doses. Large doses are incompletely absorbed, and therefore should be given intravenously. In the latter case, the drug disappears from plasma in a triphasic fashion. The first phase is a rapid distributive phase, which is followed by a second phase of renal clearance (half-life of 2 to 3 hours), and a terminal phase of half-life of 8 to 10 hours. If the terminal phase is unduly prolonged, as in renal failure, there can be severe toxic effects. Renal excretion occurs through a combination of glomerular filtration and tubular secretion. Therefore, concomitant administration of drugs that reduce renal blood flow, or which delay drug excretion, or are nephrotoxic, can lead to severe myelosuppression.

Adverse effects include nausea, vomiting, diarrhoea, fever, anaphylaxis, and hepatic necrosis. Chronic use causes oral and gastrointestinal ulceration (sometimes perforation), bone marrow depression, hepatotoxicity (cirrhosis), renal toxicity, pulmonary fibrosis, osteoporosis, conjunctivitis, alopecia, encephalopathy, infertility, and lymphoma. Intrathecal MTX induces three types of toxic reaction—chemical arachnoiditis (self-limiting), spinal cord and/or nerve damage (may be reversible or progressively fatal), and encephalopathy, with dementia, convulsions, coma and death.

Overdose can result in pancytopenia and severe mucositis.

Mortality from high-dose MTX therapy is about 6%, and occurs primarily when the patient is not monitored regularly with MTX levels. Treatment involves gastric lavage if the victim is seen early. Activated charcoal is not effective. Good urinary output (1 to 3 ml/kg/hr) must be maintained, and the urine may be alkalinised with sodium bicarbonate. Folinic acid or leucovorin is the specific antidote for MTX. It reverses bone marrow and GI toxicity, but unfortunately does not resolve neurotoxicity. An initial dose of leucovorin estimated to produce the same plasma concentration as the MTX dose should be given as soon as possible. The toxic threshold for MTX is reported to be 2×10^{-8} mol/L (i.e. 0.02 µmol/L or 20 nmol/L). The dose of leucovorin should be repeated every 3 to 6 hours until the MTX level falls below 1×10^{-8} mol/L. Leucovorin therapy may have to be continued for 12 to 24 doses or longer. In all but the most severe cases of MTX, a leucovorin dose of 100 mg/m^2 every 6 hours should be effective. Haemoperfusion and haemodialysis have been reported to be beneficial in MTX overdose. Carboxypeptidase G2 is a new agent capable of inactivating MTX by cleaving its terminal glutamate group. However it can cause hypersensitivity reactions because of its bacterial origin. Granulocyte colony stimulating factor (G-CSF) has been used successfully in some patients with MTX overdose. The suggested dosage of G-CSF is 125 mcg/kg/day.

Intrathecal MTX overdose must be treated as follows:

- *CSF drainage*—Drainage of 30 ml CSF by lumbar puncture within the first 15 minutes after the overdose can remove upto 95% of the drug. Two hours after the overdose, drainage may remove only about 20% of MTX.
- *CSF washout*—With MTX overdoses of more than 100 mg, CSF drainage must be accompanied by ventriculolumbar perfusion.
- IV pentobarbitone and phenytoin for convulsions.
- Alkalinise urine to promote urinary excretion of MTX.
- Administration of high doses of leucovorin IV (upto 1000 mg) may be of benefit.
- Mannitol for cerebral oedema.
- Maintain fluid balance.
- Monitor arterial blood gases.
- Intubation and mechanical ventilation, if patient is comatose.

■ Pyrimidine Analogues

5-Fluorouracil (5-FU)

The 5-FU requires enzymatic conversion to the nucleotide (ribosylation and phosphorylation) in order to exert its cytotoxic activity. It is generally used to treat patients with metastatic carcinomas of the breast and GI tract. It is also beneficial in hepatoma and carcinoma of ovary, cervix, urinary bladder, prostate, pancreas, and oropharyngeal areas. 5-FU is administered parenterally and is subsequently inactivated by dihydropyrimidine dehydrogenase, deficiency of which can lead to profound toxicity even with conventional doses.

Toxic effects include anorexia, nausea, stomatitis, diarrhoea, GI ulceration, shock and death. Chronic adverse effects include myelosuppression (maximal in 2 weeks), alopecia, dermatitis, acute cerebellar syndrome and cardiotoxicity.

Cytarabine (Cytosine arabinoside)

Cytarabine is the most effective antimetabolite used in the treatment of acute myelocytic leukaemia. It has to be first "activated" by conversion to the 5$'$-monophosphate nucleotide which is catalysed by deoxycytidine kinase. This is then converted to the diphosphate and triphosphate nucleotides which cause potent inhibition of DNA synthesis in cells.

Cytarabine is usually given IV or intrathecally. Less than 10% of the injected dose is excreted unchanged in the urine, while most appears as the inactive, deaminated product arabinosyl uracil.

Adverse effects include vomiting, diarrhoea, anaphylaxis, and respiratory distress (high doses). Chronic use can cause bone marrow depression, conjunctivitis, oral ulceration, hepatic damage, fever, pulmonary oedema, neurotoxicity and rhabdomyolysis.

■ Purine Analogues

Mercaptopurine

Mercaptopurine is an important drug in the treatment of leukaemias, especially acute leukaemia in children. It also has immunosuppressive activity, but its imidazoyl derivative azathioprine is more effective in this regard. Mercaptopurine is usually given orally, though the bioavailability by this route is relatively low.

Adverse effects include bone marrow depression, anorexia, nausea, vomiting, jaundice, hepatic necrosis, pancreatitis, and dermatitis. Overdose results in dizziness, headache, abdominal pain, hepatotoxicity and death.

6-Thioguanine

Thioguanine is especially useful in the treatment of acute granulocytic leukaemia when given along with cytarabine. It is generally administered orally, though absorption is incomplete and erratic by this route. Toxic effects include bone marrow depression, GI distress and hepatic damage.

■ Natural Products

Vinca Alkaloids

The vinca alkaloids are obtained from the periwinkle plant (*Vinca rosea*) (**Fig 32.6**), which is a type of myrtle. Important alkaloids include vinblastine, vincristine, vindesine, and vinorelbine. They are mainly employed in the treatment of lymphomas, Hodgkin's disease, acute leukaemias, and certain solid tumours. Only vinorelbine can be administered orally, while the others are given IV All the vinca alkaloids are extensively metabolised by the liver, and the metabolites are excreted mainly in the bile.

Vincristine is more neurotoxic than the other alkaloids, but is much less myelotoxic, the incidence of myelosuppression being only about 5 to 10%. The following are the major adverse effects of vinca alkaloids: leukopenia, anaemia, thrombocytopenia, alopecia, constipation, nausea, vomiting,

Fig 32.6: Periwinkle (*Pic:* Dr S Sivasuthan)

abdominal pain, haemorrhagic enterocolitis, paraesthesia, peripheral neuritis, hypertension, bronchospasm, sterility, and skin vesiculation. Occasionally, a syndrome of inappropriate antidiuretic hormone secretion (SIADH) occurs. Overdose results in fever, nausea, vomiting, peripheral neuropathy, muscle weakness, convulsions, hypertension, and bone marrow suppression. Inadvertent intrathecal administration of vincristine has resulted in ascending paralysis and death. Vindesine overdosage leads to severe muscle pain, burning sensation in mouth, tinnitus, diarrhoea, hiccoughs and insomnia.

Treatment involves the administration of leucovorin which is said to be beneficial in ameliorating peripheral neuropathy and myelosuppression. However there is no uniform consensus on this. There have been reports of the utility of glutamic acid, though this matter too has not yet been clearly resolved. Plasmapheresis was successfully employed in one case of vincristine overdose. Dialysis is usually ineffective.

■ Antitumour Antibiotics

Bleomycin

It is obtained from *Strep. verticillus* and is actually a mixture of two copper-chelating peptides (bleomycin A$_2$ and B$_2$). It is mainly used against squamous carcinomas of the head and neck and lungs, lymphomas, and testicular tumours. The cytotoxic action results from its ability to cause fragmentation of DNA. It is usually given parenterally (IM or IV).

Adverse effects include pulmonary toxicity (interstitial pneumonitis, fibrosis), anaphylactoid reactions, hyperpyrexia, rash and vesiculation, hyperkeratosis, alopecia, headache and vomiting.

Dactinomycin (Actinomycin D)

It is also obtained from *Streptomyces* species, and is mainly used intravenously in the treatment of rhabdomyosarcoma and Wilms' tumour in children. It is also useful in treating Ewing's tumour and Kaposi's sarcoma.

Toxic manifestations include anorexia, nausea, vomiting, haematopoietic suppression with pancytopenia, proctitis, diarrhoea, ulcerations of oral mcosa, alopecia and dermal changes.

Mitomycin C

This is obtained from *Strep. caespitosus*, and is usually given intravenously in the treatment of carcinoma of colon or stomach.

Adverse effects include myelosuppression, vomiting, diarrhoea, dermatitis, fever, pulmonary fibrosis. The most dangerous adverse effect is a haemolytic uraemic syndrome which results in renal failure. Extravasation of the drug while infusing it can cause severe local injury.

Daunorubicin, Doxorubicin, and Idarubicin

These are called **anthracycline antibiotics** and are produced by the fungus *Strep. peucetius* var. *Caesius*. Idarubicin is actually a synthetic derivative. Daunorubicin has been useful in the treatment of acute lymphocytic and granulocytic leukaemias. It is the drug of choice in acute nonlymphoblastic leukaemia (along with cytarabine). Doxorubicin is effective not only in the treatment of acute leukaemias and malignant lymphomas, but is also useful in treating a number of solid tumours.

Toxic effects include myelosuppression, thrombocytopenia, anaemia, GI disturbances, alopecia, conjunctivitis, and severe local reactions if extravasation occurs. A serious adverse effect with all anthracyclines is cardiomyopathy. Cardiac damage may be minimised by concomitant administration of **dexrazoxane**, an iron chelator.

■ Enzymes

Bleomycin

Escherichia coli produces two L-asparaginase isozymes, only one of which (EC-2) is used as an antineoplastic agent. The purified *E.coli* enzyme is given IV or IM for the treatment of acute lymphoblastic leukaemia and other lymphoid cancers. Since this enzyme is a foreign protein and causes hypersensitivity reactions in 5 to 20% of patients, other sources have been made available including *Erwinia chrysanthemi*. Also a modified form of the enzyme (PEG-asparaginase) has been developed, which is obtained by conjugating it with polythylene glycol. These are much safer.

Toxic effects include nausea, vomiting, fever with chills, headache, hyperglycaemia, acute haemorrhagic pancreatitis, renal and hepatic toxicity, and coagulation defects. CNS toxicity has been reported, characterised by lethargy, stupor and coma, which is ascribed to a fall in CSF asparagines. "Asparagine rescue" infusions have been evolved to counter such serious adverse effects.

Epipodophyllotoxins

Podophyllotoxin is an extract of the mandrake or mayapple plant (*Podophyllum peltatum*) (**Fig 32.7**). **Etoposide** and **temiposide** are semisynthetic glycosides derived from it. Etoposide is more commonly used and is given orally or intravenously for the treatment of malignant lymphomas, acute leukaemias, small cell lung cancer, and some other solid tumours.

Toxic effects include myelosuppression, nausea, vomiting, diarrhoea, alopecia, fever, and allergic reactions. High doses are associated with hepatic damage.

Fig 32.7: Mayapple plant

■ Androgen Inhibitors

Flutamide

Flutamide is a non-steroidal anti-androgen which is administered orally for prostatic cancer. It acts directly on the target tissues either by blocking androgen uptake or by inhibiting cytoplasmic and nuclear binding of androgen.

Adverse effects include hot flashes, loss of libido (in about 50% of patients), impotence, gynaecomastia, nausea, vomiting, diarrhoea, chest pain, blurred vision, hepatitis, rash, SLE-like syndrome, confusion and depression.

■ Anti-oestrogens

Tamoxifen

Tamoxifen citrate is an anti-oestrogen that is effective as palliative treatment for patients with advanced breast cancer. It is also used as an adjuvant in postmenopausal women to prevent disease recurrence. Tamoxifen is given orally.

Adverse effects include hypercalcaemia (in patients with bone metastases), thromboembolic events, hot flushes, vaginal bleeding, pruritis vulvae, GI upset, vertigo, and an increased tendency towards endometrial cancer. The last mentioned should be watched for by conducting yearly pelvic examinations, and specific enquiries must be made regarding pelvic discomfort for vaginal bleeding.

■ Miscellaneous Agents

Platinum Co-ordination Complexes (Platinoids)

The cytotoxic effects of the platinum-containing compounds were first discovered in 1965, and since then many such compounds have been synthesised, of which the important ones include **cisplatin, carboplatin,** and **iproplatin**. The platinoids are used mainly in the treatment of ovarian and testicular tumours, and also cancers of head and neck, bladder, oesophagus and lung. They are usually given IV.

Common adverse effects include renal dysfunction,

auditory impairment, peripheral neuropathy, and myelosuppression. Overdose results in rapid renal failure and death, due to irreversible acute tubular necrosis. The presence of urinary alanine aminopeptidase and N-acetyl-beta-D-glucosamidase are early indicators of renal tubular damage. Renal dysfunction is usually preceded by encephalopathy, convulsions, visual impairment (negative-type response with electroretinogram), and high-frequency hearing loss.

Treatment involves the following measures:

Chloride diuresis promotes the inactive anionic state of cisplatin and decreases the urine platinum concentration, which is helpful in nephrotoxicity during therapy.

Hydration with 0.9% sodium chloride, and an osmotic diuretic (e.g. mannitol) should be administered to achieve a high urine output (1 to 3 ml/kg/hr), for 6 to 24 hours post-exposure.

Careful assessment of renal function by regular assays of serum BUN and creatinine, glomerular filtration, filtration fraction, and renal plasma flow.

Administration of nephroprotectants post-exposure, e.g. sodium thiosulfate* (IV bolus of 4 gm/m^2, followed by infusion of 12 gm/m^2 over 6 hours), and diethyldithiocarbamate,** i.e. DDTC (4 gm/m^2 as a 1.5 to 3.5-hour infusion). Disulfiram is metabolised to DDTC and can be used if the latter is not available.

Plasmapheresis is highly beneficial. Haemodialysis is effective if there is renal failure.

Hydroxyurea

Hydroxyurea causes cell death by specific inhibition of DNA synthesis, and is administered orally in the treatment of chronic myeloid leukaemia and some varieties of solid tumours.

Adverse effects include bone marrow suppression, nausea, vomiting, diarrhoea, stomatitis, drowsiness, convulsions, hallucinations, alopecia, fever, chills and renal dysfunction.

Mitoxantrone (Mitozantrone)

Mitoxantrone is an anthraquinone related chemically to the anthracyclines. It is indicated in the treament of advanced breast cancer, lymphoma, and acute lymphocytic leukaemia. It is given IV.

Adverse effects include myelosuppression, cardiotoxicity, vomiting, alopecia, stomatitis, fever, and neurological effects. Urine may be discoloured blue-green. Overdose results in ataxia, nystagmus, loss of vibration sense, paraesthaesia, convulsions, and hepatic dysfunction. Extravasation causes tissue necrosis.

MESNA Preparations

MESNA is usually given as a uroprotectant to prevent haemorrhagic cystitis resulting from therapy with cyclophosphamide and ifosfamide. It is usually given intravenously. Adverse effects include headache, tachycardia, and hypertension. Overdose can cause vomiting and diarrhoea.

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* Binds to free platinum to prevent cellular damage.
** Formerly recommended as an antidote for thallium. It affects platinum binding after coupling to protein adducts and greatly enhances biliary excretion.

■ General Treatment Measures for Anti-cancer Drug Overdoses

1. Stabilisation—
   a. Watch for and manage convulsions (if they occur), with IV diazepam.
   b. If there are vital sign abnormalities, establish IV line, cardiac monitor, oxygen, and assisted ventilation (as needed).
   c. Correct abnormalities of ventilation and blood pressure.
   d. Arrange for complete haematological analysis (RBC, haematocrit, WBC, platelets).
   e. If patient is asymptomatic even after 12 hours, discharge can be considered. However, the patient must be subsequently followed up weekly with blood counts for at least 4 weeks. Cardiovascular follow-up is necessary for several months in the case of anthracycline overdose, on account of frequently delayed onset of cardiotoxicity.
2. Decontamination—
   a. Stomach wash is indicated in oral overdoses. Syrup of ipecac is not advisable since it may provoke convulsions which are frequently encountered with antineoplastic drugs.
3. Antidotes—There are very few antidotes available for antineoplastic drug overdose. **Table 32.7** lists some of the accepted antidotal agents.
4. Elimination Enhancement—While extracorporeal treatment methods such as haemodialysis, haemoperfusion, and exchange transfusion may help in some cases of overdose, they are generally not beneficial because most anicancer drugs possess high volumes of distribution, high protein binding values, and tendency for extensive metabolite formation.
5. Supportive Care—
   a. Treat convulsions with IV diazepam.
   b. Unconscious patients, and those with respiratory difficulty must be intubated.
   c. If there is fever (with or without chills), repeated cultures should be obtained of blood, urine, and sputum. Intravenous antibiotics may be necessary if there is evidence of infection.
   d. Electrolyte depletion should be corrected by replacement therapy with IV electrolytes. This should be accompanied by careful cardiac and respiratory monitoring, and periodic arterial blood gas determinations.

e. Oral mucositis necessitates local therapy and parenteral administration of nutrition. One study indicates that topical application of 1 ml of vitamin E oil (400 mg/ml), twice a day for 5 days is effective for chemotherapy-induced mucosal lesions.
f. Conjunctivitis can be managed with saline irrigations and ocular steroids.
g. Chemotherapy-induced vomiting is the most consistent toxic effect of almost every anticancer drug, and may be extremely severe and refractory to treatment. The usual antiemetics employed include phenothiazines (e.g. prochlorperazine), butyrophenones (e.g. droperidol), and substituted benzamides (e.g. metoclopramide). Ondansetron is as effective as metoclopramide in the prevention of chemotherapy-induced vomiting.
   – **Antiemetic cocktail:** Metoclopramide + Steroids (decadron or methylprednisolone), + Lorazepam.
   – **Table 32.8** outlines common treatment regimens for chemotherapy-induced nausea and vomiting.
h. Dehydration must be managed with IV fluids and monitoring of CVP.
i. Nephrotoxicity may require prolonged dialysis.
j. Treatment of encephalopathy involves periodic EEG, lumbar punctures (for CSF analysis), CAT scan, nuclear magnetic resonance studies, and possible "CSF washout".
k. Thrombocytopenia may necessitate platelet transfusion.
l. Anaemia and low haematocrit may necessitate red blood cell transfusions.
m. Hypertension can be managed with mannitol or IV sodium nitroprusside.

DRUGS ACTING ON THE UTERUS

■ Classification

1. Drugs which cause contraction of uterine muscle:
   a. Oxytocin
   b. Prostaglandins
   c. Ergot alkaloids.
2. Drugs which relax uterine muscle:
   a. Beta-adrenergic receptor agonists: ritodrine hydrochloride, terbutaline, feneterol, albuterol.
   b. Magnesium sulfate

Table 32.7: Antidotes and Chemoprotectants for Cytotoxic Drugs

Drug	Antidote	Site Specificity, Limitations
Anthracyclines	Dexrazoxane	Cardiomyopathies
Asparaginase	L-Asparagine	Acute brain dysfunction
Cisplatin	Fosfamycin	Ototoxicity, nephrotoxicity
	MESNA	May induce neurotoxicity
	Sodium thiosulfate	Nephrotoxicity, possible myelotoxicity
	Diethyldithiocarbamate	Nephrotoxicity, may induce neurotoxicity
Cyclophosphamide	MESNA	Uroprotectant
Ifosfamide	NAC	Haematuria
Methotrexate	Leucovorin, Thymidine	Bone marrow, GI epithelium (Investigational)
5-Fluorouracil	Allopurinol, Leucovorin	Normal bone marrow (Investigational)

Table 32.8: Antiemetic Regimens for Chemotherapy-induced Vomiting

Regimen	Dose
For moderately emetogenic chemotherapy:	
Prochlorperazine	5–10 mg PO, 5–10 mg IV, or 25 mg by rectal suppository
Thiethylperazine	10 mg PO, 10 mg IM, or 10 mg by rectal suppository
Dexamethasone	10–20 mg IV
Dronabinol	10 mg PO
Ondansetron	8 mg PO or 10 mg IV
For highly emetogenic therapy :	
Dexamethasone	20 mg IV
Metoclopramide	3 mg/kg IV every 2 hours x 2
Diphenhydramine	25–50 mg IV every 2 hours x 2
Lorazepam	1–2 mg IV
Ondansetron	32 mg IV (divided doses).

c. Calcium channel blockers
d. Prostaglandin synthetase inhibitors: indomethacin
e. Oxytocin antagonists: atosiban.

Some of these drugs have been discussed elsewhere, and the reader is advised to consult the **Index** for information on their toxicity. From among the others, the important examples will be discussed in this section.

■ Oxytocin

Oxytocin is a cyclic nonapeptide produced by the supraoptic and periventricular nuclei in the hypothalamus. It is stored in the posterior pituitary. It is structurally related to vasopressin. The clinical preparation of oxytocin is a synthetic chemical compound.

Uses

1. Induction or stimulation of labour.
2. Control of postpartum uterine bleeding.
3. Treatment of incomplete or inevitable abortion.

Toxicokinetics

Oxytocin is effective after parenteral administration (IM or IV), and can also be given intranasally as a spray. Since oxytocin is absorbed to some extent from oral mucosa, it is sometimes given as buccal lozenge.

The mean apparent volume of distribution is 0.3 L/kg, while the half-life is about 10 minutes. It is removed from the plasma by the liver, kidney, and functioning mammary glands. Oxytocin can cross the human placenta, but the extent is not certain.

Adverse Effects

Routine oxytocin administration has been associated with uterine rupture, antepartum foetal death, and neonatal hyperbilirubinaemia. Large doses can cause water intoxication with convulsions (due to its antidiuretic effect). Other adverse effects include initial hypotension, followed occasionally by hypertension.

Diagnosis

■ Plasma oxytocin concentration by radioimmunoassay.
■ High serum hepatic enzyme activity and coagulopathy in foetus (after maternal oxytocin overdose).

Treatment

1. Monitor blood pressure and pulse of both mother and foetus. Monitor also foetal heart, resting uterine tone and frequency, duration and force of contractions. Discontinue immediately in the event of foetal distress. Administer oxygen to the mother. Obtain obstetric advice.
2. Manage water intoxication by restriction of fluids, diuresis, IV hypertonic saline, correction of electrolyte imbalance, and control of convulsions.

■ Prostaglandins

Prostaglandins can be considered to be local hormones since they exert most of their effects and are inactivated principally in the organs or tissues in which they are synthesised.

Those found most abundantly in the uterus, and in the menstrual and amniotic fluid are of the E and F types. Prostacyclin (PGI_2) is mainly confined to the uterine, umbilical, and foetal vasculature. Prostaglandins used in current obstetric practice include PGE_2, PG_{2alpha}, and its synthetic derivative 15-methyl PGF_{2alpha}. Misoprostol, a PGE_1 analogue has recently been introduced as an abortifacient and cervical ripening agent.

Uses

■ Abortifacient (especially PGE_2 and 15-methyl PGF_{2alpha}).
■ Treatment of postpartum haemorrhage (15-methyl PGF_{2alpha}).
■ Cervical ripening agent (local application of PGE_2).

Clinical (Toxic) Features

Routine use is associated with vomiting, diarrhoea, and fever. Large doses may cause hypertension (PGF_{2alpha} and 15-methyl PGF_{2alpha}). Misoprostol is associated with fewer side effects.

RADIOCONTRAST AGENTS

Most radiocontrast agents in use are iodinated contrast material which may be ionic or non-ionic compounds.

■ Classification

Higher-osmolality contrast agents (HOCA)—These are mostly ionic compounds and have been in use for several decades. They

are relatively cheap and safe, though occasionally severe adverse reactions can occur.

Lower-osmolality contrast agents (LOCA)—These are mostly non-ionic compounds which cause less discomfort and are associated with a lower incidence of severe adverse reactions. However they are quite expensive.

Uses

1. Urography: The agents used for urography comprise mainly small molecule, water soluble, low protein binding, high plasma concentration compounds which are given IV. Examples—
   * *Ionic monomers*: diatrizoates, iothalamates, metrizoates, iodamide, ioxithalamate.
     – *Ionic dimers* : ioxaglic acid.
     – *Non-ionic monomers* : iohexol, iopamidol, ipromide, iopentol, metrizamole.
     – *Non-ionic dimers* : iotralan, iodixanol.
2. Angiography: These agents are water soluble, with low viscocity and radiodensity.
   * Examples:
     – *Non-ionic monomers*: iohexol.
3. Contrast radiography of GI tract: These are nonabsorbable agents which form a homogenous coat on the GI mucosa and do not interact with GI secretions.
   * Examples:
     – Barium sulfate.
4. Computerised tomography of GI tract: These are non-absorbable iodinated water-soluble agents with high osmolality.
   * Examples:
     – Diatrizoate.
5. Myelography: Agents for this are non-ionic, water soluble, and miscible with CSF.
   * Examples:
     – Metrizamide, iotralan.
6. Lymphography, lymphangiography: These agents are water-insoluble with high radiodensity.
     – Examples:
     – Iodised oil, iotasol.
7. Magnetic resonance imaging:
   * Examples:
     – Gadolinium, manganese, and iron as the aminopolycarboxylate chelates and gadopentetic acid.
8. Cholecystography, cholangiography: These agents are preferentially excreted in the bile after absorption from GI tract.
   * Examples:
     – Ipodates, iocetamic acid, iopanoic acid, sodium tyropanoate.

Adverse Effects

Contrast media are known for producing severe reactions, though they are relatively infrequent (1 or 2 per 1000 examinations). Mild to moderate reactions are more common, but subside on their own.

■ Anaphylactoid reaction:

* Predisposing factors:
  – Cerebral or renal disease in patient over the age of 50 years.
  – History of allergy (including asthma).
  – History of cardiac disease.
  – History of reaction to contrast material.
  – Multiple myeloma, homocystinuria, sickle cell anaemia, phaeochromocytoma.
  – Previous study in which large dose of contrast material was used.
* Categories of reaction:
  – Mild: nausea, vomiting, cough, headache, vertigo, itching, pallor, flushing, chills, sweats, rash (hives), nasal stuffiness, and swelling of face and eyes.
  – Moderate: moderate intensity of any of the above manifestations, with/without the following—pulse changes, hypo- or hypertension, dyspnoea, bronchospasm, and laryngospasm.
  – Severe: life-threatening manifestations including severe laryngospasm, convulsions, arrhythmias, unresponsiveness and cardiopulmonary arrest.

■ Cardiovascular side effects:
  * Cardiac ischaemia with pain and arrhythmias, usually accompanied by dyspnoea. Hypotension with tachycardia is commonly observed.
  * ECG changes include sinus bradycardia, heart block, Q-T prolongation, ventricular tachycardia/fibrillation, and ST segment and T wave changes.

■ Gastrointestinal side effects: vomiting, abdominal pain.

■ Neurological side effects: Headache (may be associated with intracerebral haemorrhage), amnesia, visual blurring, cortical blindness, encephalopathy, vertigo, and convulsions.

■ Pulmonary side effects: Non-cardiogenic pulmonary oedema is relatively commonly reported.

■ Renal side effects: There have been several reports of acute renal failure following injection of water soluble contrast media. **Table 32.9** lists important predisposing factors. Clinically, there is acute tubular necrosis, presenting with oliguria within 24 hours of exposure to the agent.

A formula has been suggested for calculating the maximum dose of contrast material that can be given safely without compromising renal function:

Contrast agent (maximum limit)

$$\frac{5\,ml\,of\,contrast/kg\,of\,body\,weight\,(max\,30\,ml)}{Serum\,creatinine\,(mg/100ml)}$$

■ Thromboembolic phenomena: Serious thromboembolic events causing myocardial infarction and stroke have occurred during angiographic procedures with contrast media. Careful intravascular administration is necessary to minimise such complications. The following is a list of precautions:
  * Continuous flushing with saline solution to prevent mixing of blood and contrast media, premedication with heparin, and use of plastic syringes are important safety measures when using non-ionic contrast media.

Table 32.9: Radiocontrast-induced Acute Renal Failure: Risk Factors

Age	Hyperuricaemia
Renal insufficiency	Exposure to other nephrotoxins
Diabetes	Repeated exposure to radiocontrast
	Volume of contrast
Multiple myeloma	Intra-arterial Vs. Intravenous
Anaemia	Male sex
Proteinuria	
Abnormal liver	Cardiovascular disease
function	Hypertension
Dehydration	

- ❖ Non-ionic contrast media should not be mixed with blood before intravascular injection.
- ❖ Extra caution should be exercised when using non-ionic contrast media in high-risk patients (elderly patients, patients with coagulation defects, etc.).
- ■ Thyroid complications: Since radiocontrast agents invariably contain iodides which cannot be metabolised by deiodinating enzymes, thyrotoxicosis may be induced in susceptible patients. Prophylactic treatment with sodium perchlorate 1.2 grams administered 30 minutes before, and 6 to 8 hours after exposure, has been suggested.
- ■ Cancer induction: Thorotrast, a contrast agent which contains 25% colloidal thorium dioxide has been associated with malignancies.
- ■ Precipitation of mumps: *Iodide mumps* has occasionally been observed in patients who were administered iodinated contrast agents.

■ Clinical (Toxic) Features

1. Inadvertent administration of ionic contrast agents such as diatrizoate or iodamine, instead of iopanidol, by the intrathecal route, has resulted in fatalities.
2. In the past, methiodal sodium was commonly used for myelography. Because of high incidence of neurotoxic adverse reactions, other compounds were subsequently introduced, e.g. iothalamate meglumine and iocarmate.
3. Inadvertent myelography with diatrizoate has led to lumbar pain, tonic-clonic convulsions, hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, pulmonary oedema and death.
4. Overdose with iopanoic acid has led to vomiting, diarrhoea, hypotension, coronary insufficiency, acute hepatic necrosis, renal failure and death.
5. Overdose with iothalamate meglumine during excretory urography can lead to cardiopulmonary failure.

■ Treatment

Adverse Effects

1. Anaphylactoid reaction:
   - ❖ For urticaria:
     - – Mild:
       - - Diphenhydramine (50 mg oral/IM/IV), or hydroxyzine (25–50 mg oral/IM/IV).
       - - Cimetidine (300 mg oral/slow IV in 10 ml D5W soln), or ranitidine (50 mg oral/slow IV in 10 ml D5W solution).
     - – Severe:
       - - Adrenaline (1:1000) SC, 0.1 to 0.3 ml.
   - ❖ For facial/laryngeal oedema:
     - – Mild:
       - - Adrenaline (1:1000) SC, 0.1 to 0.3 ml; can be repeated up to 3 times (1 mg max).
       - - Oxygen, 2 to 6 L/min.
     - – Severe:
       - - Intubation.
   - ❖ For bronchospasm:
     - – Oxygen, 2 to 6 L/min.
     - – Adrenaline (1:1000) SC, 0.1 to 0.3 ml, or beta-agonist inhalers.
     - – Aminophylline 6 mg/kg, IV, in D5W, slowly, or terbutaline 0.25 to 0.5 mg, IM/SC.
   - ❖ For hypotension with tachycardia*:*
     - – Mild:
       - - Trendelenburg position, oxygen, IV fluids (Ringer lactate > normal saline > D5W).
     - – Severe:
       - - Adrenaline (1:1000) SC, 0.1 to 0.3 ml ; repeat up to 3 times (1 gm max).
   - ❖ For hypotension with bradycardia*:*
     - – Trendelenburg position, oxygen.
     - – Atropine 0.6 to 1 mg, slow IV.
     - – IV fluids (Ringer lactate > normal saline > D5W).
   - ❖ For hypertension*:*
     - – Apresoline 5 mg IV, or sodium nitroprusside.
     - – Monitor ECG, pulse oximeter, BP.
   - ❖ For convulsions:
     - – Oxygen, 2 to 6 L/min.
     - – Diazepam 5 mg, IV.
     - – Phenytoin, 15–18 mg/kg, infusion at 50 mg/min.
   - ❖ For pulmonary oedema*:*
     - – Head elevation, rotating tourniquets.
     - – Oxygen 2 to 6 L/min.
     - – Furosemide 40 mg, slow IV.
     - – Corticosteroids (optional).
2. Neurological side effects:
   - ❖ Convulsions must be treated with IV, diazepam, phenytoin, phenobarbitone, intubation, and intensive medical care.
   - ❖ If accidental intrathecal injection of ionic contrast media is suspected, the patient should not be permitted to lie down.
3. Pulmonary side effects:
   - ❖ Patients with a history of radiocontrast medium-related oedema should be given prophylactic corticosteroids.
4. Renal side effects:
   - ❖ All patients undergoing examination involving contrast media should be well hydrated, since dehydration precipitates renal dysfunction.
   - ❖ Acute renal failure has to be managed by dialysis.

Toxic Effects

1. Accidental intrathecal administration of ionic contrast agents must be treated with appropriate circulatory support, intrathecal lavage, and anticonvulsant therapy.
2. To decrease the incidence of side effects after myelography, the following have been suggested:
   - ❖ Head elevation for 6 hours after the study.
   - ❖ Avoidance of drugs that lower seizure threshold, e.g. phenothiazines, MAOIs, tricyclics, alcohol, etc.
3. Overdose with iopanoic acid can be treated with IV fluids, alkalinisation of urine, and cholestyramine (said to be a chelator of iopanoic acid). Cardiac and respiratory monitoring are mandatory.
4. General recommendations:
   - ❖ Patients with pre-existing renal impairment should be given 0.45% saline IV, for 12 hours before and 12 hours after administration of contrast agents.
   - ❖ Low-osmolality contrast agents are preferable to high-osmolality agents.
   - ❖ Pre-treatment with corticosteroids and antihistamines (with or without adrenaline), has been suggested to minimise reactions to contrast agents.

DRUGS USED IN THE TREATMENT OF IMPOTENCE

Till recently, there was no really satisfactory method or drug available to effectively treat male impotence or erectile dysfunction. The following were tried with varying degrees of success: intracavernosal injection of vasoactive agents, transurethral delivery of prostaglandin E1, implantation of penile prosthesis, and venous or arterial surgery. Oral therapy was almost non-existent (except for tentative trials with apomorphine and phentolamine), until the arrival of **sildenafil**. Today, this drug has become one of the largest selling drugs in the world, since it is claimed to be very effective.

■ Sildenafil

Sildenafil was developed by Pfizer® initially as an anti-anginal and antihypertensive agent, but as its reputation increased with respect to enhanced sexual performance among male subjects, the manufacturers decided to switch tracks and began to advertise it as an anti-impotence pill. Since then there has been no looking back, and sales of sildenafil have soared all over the world, so much so that it has become the biggest ever grosser among all pharmaceutical preparations.

Uses

1. *Male erectile dysfunction*: Sildenafil is effective only when there is at least partial erection. It is not effective in the presence of severe arteriogenic or venogenic impotence, corporal smooth muscle fibrosis, and anatomical deformities of the penis. The drug has to be taken an hour before anticipated sexual activity.
2. *Female impotence*: Trials are on to test the efficacy of sildenafil in the treatment of female impotence. Initial reports are said to be encouraging.

Toxicokinetics

Sildenafil is rapidly absorbed after oral administration, the absolute bioavailability being about 40%. Maximum plasma concentrations are achieved in about one hour, with mean terminal half-life of 3 to 5 hours. It is metabolised by hepatic microsomal enzyme systems—the CYP3A4 route mainly, and to a lesser extent by the CYP2C9 route. Major excretion occurs in the faeces (80%) and urine (13%).

Mode of Action

Sildenafil is a selective inhibitor of cyclic GMP specific phosphodiesterase (PDE) type 5, the predominant enzyme which metabolises cyclic GMP in the corpus cavernosum. When sexual excitement causes local release of nitric oxide, inhibition of PDE5 by sildenafil results in increased levels of cyclic GMP, which leads to smooth muscle relaxation and inflow of blood into the corpus cavernosum.

Sildenafil also inhibits PDE6, which is found in retina and is believed to be involved in phototransduction. This explains the colour vision abnormalities encountered at high doses of the drug.

Adverse Effects

1. *General*: headache, facial flushing, dyspepsia, and diarrhoea.
2. *CVS*: sudden drop in blood pressure (especially if the patient is on nitrate therapy).
3. *Visual*: light sensitivity, bluish tinged vision.

Clinical (Toxic) Features

Chest pain, stroke, cardiac arrhythmias, heart failure.

Forensic Issues

- Deaths have been reported in elderly males who participated in sexual activity after ingesting sildenafil. In most of these cases there was underlying cardiac diasease or hypertension.
- Since there are indications of sildenafil misuse among the youth (who do not really require the drug), in the form of a recreational drug, there are concerns about acute toxicity, especially in the presence of concomitant intake of amyl nitrite. The latter is not uncommonly abused for its "high" during the course of *rave parties*.

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Section

10

Food Poisons

Food Poisoning

Food poisoning can occur in many ways, and may be isolated instances, or may constitute an epidemic (mass food poisoning). The latter bristles with medico-social implications and necessitates prompt reporting to public health authorities who must take effective steps to contain the epidemic. Food borne illnesses are among the commonest health problems encountered world-wide, and are particularly rampant in third world countries such as India, mainly due to a relative lack of sanitation and public hygiene.

CAUSES

1. Microbes: bacteria, viruses, protozoa
2. Parasites
3. Fungi
4. Plants
5. Fish
6. Chemical additives.

DIAGNOSIS

- History.
- Clinical picture.
- Stool analysis: **Table 33.1** provides general guidelines for collection of stool samples.
- Suspect food/agent analysis.
- Measurement of serum electrolytes.

GENERAL TREATMENT MEASURES

Oral Rehydration Therapy (ORT)

This is resorted to only in the presence of mild dehydration (3 to 5% fluid deficit),* or moderate dehydration (6 to 10% fluid deficit).** Rehydration should commence with a fluid containing 50 to 90 mEq/L of sodium. The amount of fluid administered should be50 ml/kg over a period of 2 to 4 hours in mild dehydration, and 100 ml/kg in moderate dehydration. After 2 to 4 hours, hydration status should be assessed and if found to be normal, maintenance therapy can be begun, otherwise rehydration therapy is repeated.

Maintenance therapy—Oral rehydration solutions (ORS) should be administered as follows:
- 1 ml for each gram of diarrhoeal stool, or
- 10 ml/kg for every watery stool passed, or
- 2 ml/kg for each episode of vomiting.

Table 33.1: General Guidelines for Stool Sample Collection

Instructions for Collection	Suspected Causative Agent		
	Virus	*Bacterium*	*Parasite*
When to collect	Within 48 to 72 hours	During period of active diarrhoea	Any time (as soon as possible)
Quantity	10 cc stool sample	Two rectal swabs or swabs of fresh stool	10 cc stool sample
How to collect	Place fresh stool sample (unmixed with urine) in clean, dry container	Moisten rectal swabs in Cary-Blair medium, insert sequentially (1 to 1.5 inches) in rectum, and gently rotate. Place swabs into Cary-Blair medium tube and break off top portions of swab sticks	Collect bulk stool sample (unmixed with urine) in a clean container. Place a portion into 10% formalin and polyvinyl alcohol preservatives at a ratio of one part stool to three parts preservative, and mix well
Storage	Refrigerate at 4°C (do not freeze)	Refrigerate at 4°C if testing can be done quickly, otherwise freeze the sample at - 70°C	Store at room temperature or refrigerate at 4°C. (do not freeze)

* Indicated by dry mouth and increased thirst.
** Indicated by dry mouth, sunken eyes, sunken fontanelles, loss of skin turgor.

Limitations of ORT—ORT is not sufficient therapy in the presence of dysentery (bloody diarrhoea), shock, intestinal ileus, intractable vomiting, high stool output (>10 ml/kg/hr), monosaccharide malabsorption and lactose intolerance.

Intravenous Rehydration

This is necessary when dehydration is severe (> 10% fluid deficit or shock).* 20 ml/kg boluses of Ringer's lactate, normal saline, or similar solution is administered until pulse, perfusion, and mental status return to normal. Two separate IV lines may be required, or even alternative access sites such as femoral vein, venous cut-down, or intra-osseus infusion.

Oral rehydration is commenced when condition improves.

Non-specific Antidiarrhoeal Agents

Use of such agents such as kaolin-pectin, antimotility drugs (e.g. loperamide), antisecretory drugs, or toxin binders (e.g. cholestyramine), is controversial. Available data do not demonstrate significant beneficial effects. Instead, serious adverse effects can occur, including ileus and anticholinergic syndrome.

PREVENTION OF FOOD POISONING

Buying Groceries

a. Buy meat and seafood items only from hygienic outlets.
b. Do not buy items whose expiry date has elapsed.
c. Do not buy items containing undercooked or raw animal-derived ingredients.
d. Buy only pasteurised milk or cheese.
e. Do not buy eggs which are cracked or leaking.

Storage

a. Take groceries directly home and store immediately in the refrigerator.
b. Always store raw meat, poultry, or seafood in plastic bags, so that drippings do not contaminate other items in the refrigerator.
c. Hot foods should be eaten immediately, or kept hot (> 60°C), or refrigerated.
d. Do not store eggs in the egg-section of the door (provided in most refrigerators), since adequate cooling does not occur. Place them inside cartons and store them in the main section of the refrigerator.

Temperature Requirements

a. Never leave cut vegetables/meat in the open. Refrigerate them, or cook them.
b. Ensure that the temperature in the main section of the refrigerator is always below 4° C, and that of the freezer is below -18° C.
c. Cook all meat and seafood thoroughly before eating. Never consume undercooked oysters, clams, mussels, sushi, or snails.
d. Cook eggs until both the yolk and white are firm. Never eat runny yolk.

e. Reheat food or heat partially cooked foods all the way through to at least 74° C.
d. If any food item looks or smells suspicious, discard it.

Hygiene

a. Wash hands, utensils, and counters with water and soap between preparation of different foods (especially raw meat, poultry, fish, eggs).
b. Use plastic or glass cutting boards for slicing vegetables or meat. Wooden boards are extremely difficult to clean adequately.
c. Wash fresh fruits and vegetables under running water.

Dining Out

a. Avoid consuming uncooked animal-derived dishes (sushi, raw oysters, Hollandaise sauce, eggnog, mayonnaise, etc.).
b. Do not eat undercooked meat or poultry.
c. Do not consume egg preparations with runny yolk.

Foreign Travel

a. Drink only boiled or bottled water.
b Do not eat raw vegetables and salads.
c. Do not buy food items from roadside vendors.

MICROBIAL FOOD POISONING

■ Bacteria

Bacterial food poisoning is most frequently caused by *Staphylococcus*, followed by *Clostridium perfringens, Salmonella, Shigella,* and *Streptococcus* in descending order of frequency.

Bacillus cereus

Bacillus cereus is an endemic, soil-dwelling, Gram-positive, rod shaped, beta haemolytic bacterium that is well known to cause foodborne illness. It is a facultative aerobe, and like other members of the genus *Bacillus* can produce protective endospores that are resistant to extremes of temperature. Various strains have been shown to produce seven different toxins.

Source

1. Emetic form: Fried and cooked rice, pasta, pastry, and noodles.
2. Diarrhoeal form: Meat and vegetables.
3. Other potential sources of infection include spices, pasteurised fresh or powdered milk, and reconstituted milk-based infant formula.

Toxin

- Emetic form: Highly stable toxin, cereulide, which has a ring structure consisting of four amino and/or oxy acids. It is resistant to heat, pH, and proteolysis, but is not considered antigenic.
- Diarrhoeal form: Heat and acid-labile enterotoxin (a protein), that is sensitive to proteolytic enzymes.

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* Indicated by signs of moderate dehydration **plus** one of the following: rapid feeble pulse, cold extremities, rapid breathing, cyanosis, lethargy, or coma.

Incubation Period

- Emetic form: 1 to 5 hours.
- Diarrhoeal form: 8 to 16 hours.

Clinical Features

- Emetic form: Nausea, vomiting.
- Diarrhoeal form: Diarrhoea (watery), abdominal pain, and occasionally nausea.

  Fever is uncommon in both forms.

  In rare cases, fulminant liver failure developed following the consumption of food contaminated with *B. cereus* emetic toxin. *B. cereus* endophthalmitis has been reported in a toddler following eye trauma (laceration of the eye with a manure fork). In one retrospective review of surgical patients who developed *B. cereus* wound infections, most appeared to have serous and haemorrhagic drainage, often profuse, lasting 1 to 3 weeks. Endocarditis has been reported in patients following intravenous drug abuse and valvular heart disease.

Diagnosis (for food-borne illnesses)

Stool culture and growth in MYPA (mannitol, egg yolk, phenol red, polymyxin agar) medium. Diagnosis can be confirmed by detecting the organisms in the suspected food item.

Treatment

1. Supportive measures. The disease is usually mild and self-limiting.
2. Monitor fluid and electrolyte status and hepatic enzymes as indicated.
3. Patients with mild fluid deficits can often be managed with oral fluid therapy consisting of clear liquids, or specially formulated glucose and electrolyte solutions. Patients with moderate to severe dehydration must be treated with IV fluids.
4. Significant nausea and vomiting in adults may be controlled with a suitable antiemetic agent.
5. For wound infections, antibiotic susceptibility testing should be done. Chloramphenicol, tetracycline, kanamycin, gentamicin, clindamycin, vancomycin, and erythromycin are generally effective. Resistance has been reported to penicillin and cephalosporines secondary to beta-lactamase production.

Staphylococcus aureus

It is said to be the commonest cause of bacterial food poisoning.

Source

1. Previously cooked, proteinaceous food: meat, fish, milk, and milk products. Staphylococcal toxins are formed within a few hours when food is kept at room temperature.
   a. Most foods (particularly those high in protein) will support staphylococcal growth, especially custard or cream filled pastries, mayonnaise, ham, and dairy, poultry, potato and egg products.
   b. Pasteurising milk will kill the bacteria, but unfortunately will not inactivate the toxins.
   c. Other sources include canned mushrooms, rice, noodles, salads, and cooked food that has been left at room temperature.
2. Common carriers of *Staphylococcus aureus* comprise food handlers (especially those with purulent secretions or nasal discharge).
3. While most *Staphylococcus aureus* strains implicated in food poisoning have been coagulase-positive, outbreaks with coagulase-negative species have been reported.

Toxin

Relatively heat-stable enterotoxins (A, B, C_{1-3}, D, E, and H). The commonest type is A. Enterotoxin B (SEB), a pyrogenic toxin, also commonly causes food poisoning after ingestion of improperly prepared or handled food material. It causes a significantly different clinical syndrome when inhaled than when ingested. The toxin is extremely potent and stable, and may be used as a bioterrorism agent. Only a small amount of toxin (approximately 200 ng) is required to cause clinical illness. However, large numbers of organisms must be present in food in order to produce enough enterotoxin to cause illness, (10^6 organisms/gm or more). Aerosol-incapacitating dose amounts to about 30 ng/person; lethal dose is approximately 1.7 mcg/person.

Incubation Period

1. Oral: 1 to 6 hours.
2. Inhalation: 3 to 12 hours.

Clinical Features

1. Nausea and vomiting with violent retching, diarrhoea, crampy abdominal pain. Diarrhoea is usually mild, while vomiting is severe.
2. Fever is usually absent.
3. Headache, weakness, and dizziness may be present.
4. Inhalation of the toxins can cause sudden onset of fever, headache, chills, myalgia, non-productive cough, dyspnoea, and retrosternal chest pain. Nausea, vomiting, and diarrhoea may occur as a result of inadvertent swallowing of the toxin. Conjunctival congestion may be present. Postural hypotension could develop due to fluid losses.

Diagnosis

1. Staphylococcal food poisoning is usually a self limited illness; often no laboratory evaluation is required. Monitor electrolytes and fluid balance in patients with significant volume loss from vomiting and diarrhoea.
2. Serological tests are usually very sensitive, for e.g. latex agglutination and ELISA.
3. Radioimmunoassay can detect as little as 0.1 ng to 1.0 ng toxin/gm of food.

Treatment

1. Supportive measures.
2. The illness usually lasts for no more than 20 to 24 hours, and is self-limiting.

3. All persons with significant toxicity, dehydration, abnormal electrolyte levels, or a history of poor compliance should be admitted for intravenous fluid therapy. Significant nausea and vomiting can be controlled with an antiemetic agent. However, antiemetics are not usually required if alteration of the diet is successful.
4. Inhalation exposure:
   a. Move patient from the toxic environment to fresh air.
   b. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for hypoxia, respiratory tract irritation, bronchitis, or pneumonitis.
   c. Administer 100% humidified supplemental oxygen, perform endotracheal intubation, and provide assisted ventilation as required.
   d. Administer inhaled beta adrenergic agonists if bronchospasm develops.
   e. Exposed skin and eyes should be flushed with copious amounts of water.

Salmonella

Salmonella species are motile gram-negative rods, and grow both aerobically and anaerobically at an optimum temperature of 37°C (range 7 to 48°C), and at a pH between 4 and 8. They are readily killed by heat (71.7°C for 15 seconds) and acid, but are resistant to both freezing and drying, especially in the presence of proteins.

Food poisoning (Salmonella enterocolitis) can be caused by all salmonellae except *S. typhi* which causes typhoid or enteric fever. Commonest species involved include *S. typhimurium, S. enteritidis, S. hadar, S. heidelberg, S. agona, S. arizonae, S. chameleon, S. java, S. javiana, S. marinum, S. oranienburg, S. muenchen, S. paratyphi B, S. virchow, S. indiana,* and *S. anatum*.

Source

1. Eggs: Even unbroken, unsoiled eggs can be contaminated. Eating such eggs raw or undercooked can result in infection.
   a. Food products containing raw eggs are also capable of producing the illness—hollandaise sauce, eggnog, chocolate mousse, raw egg-based milk shakes, caesar salads, and home-made ice cream.
   b. It is recommended that eggs should be consumed within 3 weeks after being laid, and must be stored at temperatures below 8° C after purchase.
2. Milk and milk products*: Consuming raw, unpasteurised milk poses a real risk of being infected with salmonellosis. Even pasteurised milk may not be 100% protective. Outbreaks of salmonella infections may be associated with multiple drug-resistant strains.
3. Salmonella has also been detected in various sesame seed products, including sesame paste and *halvah* (a mixture of sesame seed paste and acidified heated glucose syrup).
4. Household pets: Chicks, turtles, iguanas, and other reptiles are known to harbour salmonellae, and can transmit the micro-organisms to household contacts. Cats may be faecal carriers of Salmonella without displaying clinical signs. The incidence ranges from 1 to 18% of cats.

Toxin

1. Enterotoxin.
2. Penetration of intestinal wall and multiplication by the bacilli.

Incubation Period

About 12 to 36 hours, but can be as short as 3 hours.

Clinical Features

- Vomiting, crampy abdominal pain, diarrhoea. Stools are loose, slimy, foul-smelling, and greenish in colour. They often turn blood-stained. These symptoms may be absent in children, who may present only with abdominal pain and nausea, which could be confused with acute appendicitis.
- Fever.
- Headache, malaise, myalgia.
- Toxic megacolon and intussusception have been reported with *Salmonella typhimurium*.
- Focal nephritis has been reported in some cases.
- The illness usually subsides in 2 to 4 days, but occasionally becomes prolonged and dysentery-like, with passage of mucus and pus in the stools.
- The carrier state is more common among females and elderly patients, and it may persist for months to years. The gall bladder is the usual focus of infection in the carrier state.
- Complications:
   a. Meningitis
   b. Septicaemia
   c. Reiter's syndrome**
   d. Death.

Diagnosis

1. Isolation of Salmonella by
   a. Analysis of suspect food item
   b. Culture of stool and blood.
2. Check WBC for leucocytosis or leukopenia.

Treatment

- Patients with significant toxicity, dehydration, electrolyte disturbances, or a history of poor compliance should be admitted for IV fluid therapy, and occasional antibiotic therapy.
- As far as possible, antibiotic treatment must be resorted to only in the following cases: bacteraemia, AIDS patients, elderly, infants, and individuals with sickle cell disease. The antibiotic of choice is chloramphenicol. Fluoroquinolones, ampicillin, ceftriaxone, and trimethoprim-sulfamethoxazole are also effective.
- Supportive measures.

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* Consuming raw milk can also cause brucellosis, campylobacteriosis, listeriosis, and tuberculosis.
** Urethritis, arthritis, and conjunctivitis.

Shigella

Shigella microbes comprise non-motile, gram-negative rods that have the same characteristics (morphological and biochemical) as *E. coli*. The common species of shigella responsible for food poisoning include *Sh. dysenteriae, Sh. flexneri, Sh. boydii,* and *Sh. sonnei*. In general, Shigella outbreaks are more likely to be caused by *S. sonnei* species in developed countries, while *S. dysenteriae* and *S. flexneri* are more frequently found in developing countries. The most severe form of infection is associated with *S. dysenteriae* serotype; case fatality rates range from 5 to 15%.

Source

1. Fruits
2. Vegetables
3. Milk.

Fruits (stewed apples), vegetables (potato salad, mashed potatoes), tossed salad and milk products are the commonest vehicles. Epidemics due to watermelon ingestion have been reported.

Children (6 months to 5 years) are at highest risk for developing shigellosis; especially children in daycare centers where the illness can spread rapidly. Also, individuals in custodial care centers, international travelers, homosexual males, and those living in houses with poor sanitation.

Toxin

Though *Sh. dysenteriae* (type I) elaborates an enterotoxin, it appears to be much less important in pathogenesis than the ability of the bacillus to penetrate and multiply in colonic mucosa.

Incubation Period

About 1 to 7 days (usually 2 days).

Clinical Features

Individual presentation varies with some patients demonstrating only minor symptoms, while others may suffer true dysentery with high fever, tenesmus, nausea, crampy abdominal pain, and profuse diarrhoea.

1. Large, watery (relatively odourless) stools, followed by bloody diarrhoea in 24 hours.
2. Abdominal cramps, tenesmus.
3. Fever.
4. Cough, rhinorrhoea.
5. Vomiting (uncommon).
6. The WBC count is usually <10,000/mm^3, with a marked shift to the left; the band count is usually very high.
7. Complications:
   a. Arthritis: Reiter's syndrome can occur as in the case of salmonellosis (*vide supra*).
   b. Toxic neuritis, convulsions.
   c. Conjunctivitis.
   d. Parotitis.
   e. Intussusception (in children).
   f. Haemolytic uraemic syndrome.

Diagnosis

- Monitor serum electrolytes.
- A CBC with differential may be useful in diagnosis.
- Stool and ingested food should be cultured.
- Faecal polymorphonuclear neutrophil leukocytes are present in many cases of shigellosis.

Treatment

1. Patients with significant toxicity, dehydration, electrolyte disturbances, or a history of poor compliance should be admitted for IV fluid therapy, and occasional antibiotic therapy.
2. Antibiotic therapy must not be resorted to as a routine measure. It is indicated only in severe cases, or in elderly patients and infants. While antibiotic resistance is a common problem, most cases still respond to nalidixic acid or norfloxacin. However, quinolone antibiotics must be used with caution in children.
   a. The following antibiotics are currently recommended by the World Health Organization for the treatment of *Shigella dysenteriae* serotype (Sd1) which is commonly seen in developing countries such as India: ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid, pivmecillinam, ciprofloxacin, norfloxacin, and enoxacin, though resistance is common with ampicillin, trimethoprim-sulfamethoxazole, and nalidixic acid.
3. Anti-motility agents (loperamide or diphenoxylate with atropine) are likely to make the illness worse and are not recommended.

Vibrio

Vibrio cholerae is responsible for causing **cholera**, while several other species (*V. parahaemolyticus, V. vulnificus, V. mimicus, V. alginolyticus*) are known to cause shellfish-associated outbreaks of gastroenteritis.

Source

1. Contaminated food and water. Oysters and crabs are notorious for harbouring the micro-organism.
2. Two types of pathogenic *Vibrio cholerae* have been identified, both belonging to Group 1:
   a. The classical biotype which is responsible for the most severe form of the disease (now restricted mainly to Bangladesh).
   b. The El Tor biotype which is responsible for some of the recent epidemics.
3. Both the classical and El Tor vibrios are further divided into 3 serological types—Inaba, Ogawa, and Hikojima. Most of the El Tor vibrios isolated in India belong to the Ogawa serotype.

Toxin

The main toxin (choleragen, cholera toxin, or CT) is a heat-labile molecule consisting of one A and 5 B sub-units. The former is the active sub-unit, and after being transported into the enterocytes, dissociates into two fragments, A$_1$ and A$_2$. The

A_1 fragment causes prolonged activation of cellular adenylate cyclate and accumulation of cAMP, leading to outpouring into the small intestinal lumen of large quantities of water and electrolytes, and the consequent watery diarrhoea.

Incubation Period

About 1 to 5 days.

Clinical Features

1. Cholera usually manifests dramatically and abruptly as profuse painless watery diarrhoea and copious effortless vomiting. Death due to massive loss of fluid and electrolytes may occur within 24 hours. Stools are colourless and watery with flecks of mucus (*rice water stools*). There is an inoffensive sweetish odour.
2. Complications:
   a. Dehydration
   b. Electrolyte abnormalities
   c. Pulmonary oedema
   d. Base-deficit acidosis and shock
   e. Haemoconcentration and hypokalaemia
   f. Renal failure
   g. Cardiac arrhythmias
   h. Paralytic ileus.

Diagnosis

1. Stool analysis:
   a. Stool specimen is best collected by introducing a lubricated rubber catheter into the rectum and letting the liquid stool flow directly into a screw-capped container. Alternatively, rectal swabs can be used.
   b. Stools must be transported at 4°C or in some appropriate holding medium such as VR (Venkatraman-Ramakrishnan) medium or alkaline peptone water. If transport media are not available, strips of blotting paper may be soaked in the watery stool and sent to the laboratory packed in plastic envelopes.
   c. Diagnosis may be accomplished by demonstration of motile vibrio under dark field or phase contrast microscopy, and by culture in appropriate media.
2. Analysis of suspect water sample: By culture.
3. Serological examination: This is generally not helpful in diagnosis, but may help in assessing the prevalence of cholera in a region.

Treatment

- Rapid fluid and electrolyte replacement.
- Antibiotic therapy: Tetracycline and doxycycline are the antibiotics of choice. Many strains are resistant to cotrimoxazole and furazolidone.
- Antiemetics, antidiarrhoeals, and antispasmodics are contraindicated.

Escherichia coli

There are five different pathogenic *E. coli* groups which cause gastroenteritis:

- **Enteropathogenic *E. coli* (EPEC):** Formerly common culprits of diarrhoeal illness, especially in infants and children.
- **Enterotoxigenic *E. coli* (ETEC):** This strain is responsible for most cases of *traveller's diarrhoea*, and is endemic in India. The condition varies in severity from mild watery diarrhoea to fatal cholera-like illness.
- **Enteroinvasive *E. coli* (EIEC):** These "atypical" strains cause shigella-like dysentery.
- **Enterohaemorrhagic *E. coli* (EHEC)*:** These strains are responsible for illnesses ranging from mild gastroenteritis to fatal haemorrhagic colitis and haemolytic uraemic syndrome.
- **Enteroaggregative *E. coli* (EAggEC):** These strains are so named because they exhibit a "stacked brick" appearance when attached to the surface of cultural epithelial cells. They can cause persistent diarrhoeal illness.
- A sixth group has recently been identified (**Enteroadherent *E. coli* or EAEC)** which may be responsible for some cases of traveller's diarrhoea.

Source

1. Enterohaemorrhagic: contaminated food, especially inadequately cooked beef, raw milk, contaminated water, person-to-person contact.
2. Enterotoxigenic: contaminated food and water; faecal transmission by contaminated hands.
3. Enteroinvasive: contaminated food.
4. Enteropathogenic: contaminated infant foods; transmission by fomites and contaminated hands.
5. Enteroaggregative: unknown.
6. Enteroadherent: unknown.

Toxin

All serotypes of *E. coli* can produce Shiga toxins and some may also cause diarrhoea, haemorrhagic colitis, and haemolytic uraemic syndrome (HUS). Serotype O157 appears to be more prevalent in developed countries, while the non-O157 serotypes are more common in other countries.

- *E. coli* serotype O111.H2
- *E. coli* serotype O157.H7
- *E. coli* serotype O111.non-motile
- *E. coli* serotype O26.H11
- *E. coli* serotype O103.H2

  E. coli serotype O157.H7 may infect all age groups, and has been reported to occur in both developed and developing countries, although it is apparently more prevalent in developed countries. Children aged less than 5 years have the highest disease rates, followed by persons aged greater than 60 years. The infection is more common in summer.

  Infection with the *E. coli* O111.H2 serotype can cause haemolytic-uraemic syndrome.

Incubation Period

1. Enteropathogenic strains: 9 to 12 hours in adult volunteers; incubation in infants not known

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* Also referred to as **Verotoxigenic E. coli (VTEC).**

2. Enteroinvasive strains: 10 to 18 hours
3. Enterotoxigenic strains: 10 to 72 hours
4. Enteroaggregative strains: 20 to 48 hours
5. Enterohaemorrhagic strains: 3 to 4 days
6. Enteroadherent strains: unknown.

Clinical Features

- *E. coli* O157.H7 infection can be asymptomatic. It can also cause non-bloody or bloody diarrhoea, abdominal cramping, nausea, vomiting, and occasionally fever. Average interval between exposure and symptoms is 3 days (range: 1 to 8 days).
- Enterohaemorrhagic: Ranges from mild diarrhoea to severe blood-stained stools.
- Enterotoxigenic: Profuse watery diarrhoea without blood or mucus. Vomiting, abdominal cramping, prostration, acidosis, and dehydration can occur. Illness usually lasts less than 5 days, and is the chief cause of "traveller's diarrhoea".
- Enteroinvasive: Severe abdominal cramps, malaise, watery stools, tenesmus, and fever. Endemic in underdeveloped countries; less common in industrialised countries.
- Enteropathogenic: Watery diarrhoea with mucus. Fever and dehydration can occur. Can be fatal if severe and prolonged. Common in infant nurseries and community outbreaks.
- Enteroaggregative: Produces infant diarrhoea which may persist for quite some time.
- Diffuse-adherence: Causes paediatric diarrhoea, principally in preschool-aged children, in developing countries.
- Headache is a commonly reported symptom following consumption of food contaminated with *E. coli*.
- **Complications:** Haemolytic-uraemic syndrome (HUS), thrombocytopenic purpura, and death.
  a. In HUS (especially in children), apart from renal complications, there could also be pancreatitis, colonic necrosis, glucose intolerance, coma, stroke, seizures, myocardial dysfunction, pericardial effusions, adult respiratory distress syndrome (ARDS), and pleural effusions. Diagnosis can be aided by faecal leukocyte counts (usually less than 10 per high-powered field), barium enema which may demonstrate "thumb-printing", suggestive of oedema and submucosal haemorrhage, particularly of the ascending and transverse colon. Colonic mucosa often appears oedematous and hyperaemic when viewed with endoscopy, and sometimes superficial ulceration or pseudomembranes are seen. Approximately 5% of patients who develop HUS have significant sequelae, including end-stage kidney disease. In one prospective study, children who went on to develop HUS had higher plasma concentrations of various markers indicating activation of the clotting cascade (prothrombin fragments 1 and 2, tissue plasminogen activator (t-PA) antigen, t-PA-plasminogen activated inhibitor type 1 complex, and D-dimer).
  b. Thrombocytopenic purpura occurs more often in adults and the elderly. It has all the features of HUS, but the renal injury is usually less severe, while the neurological manifestations are more prominent. Thrombocytopenia

is thought to result from trapping of platelets in affected organs, and removal by the liver and spleen.

Diagnosis

1. Stool culture: Differentiation between invasive and toxigenic strains may be difficult.
2. The sorbitol fermentation reaction constitutes an effective screening procedure for patients with haemolytic syndrome and haemorrhagic colitis. Most EHEC strains do not ferment sorbitol, unlike other *E. coli* organisms.

Treatment

- Traveller's diarrhoea can be prevented or treated with cotrimoxazole or doxycycline.
- Haemorrhagic colitis and haemolytic uraemic syndrome are serious conditions which require urgent hospitalisation and aggressive treatment.

Campylobacter

While *E. coli* is the commonest cause of diarrhoea in Third World countries such as India, Campylobacter accounts for a significant number of cases, and rotavirus comes in at a close third. The Campylobacter species responsible for food poisoning include *C. jejuni, C. coli,* and *C. lari*.

Source

- Undercooked meat products: chicken, beef, mutton, turkey, etc.
- Unpasteurised milk and milk products.
- Unchlorinated water.

Incubation Period

About 1 to 7 days.

Clinical Features

Like *E. coli*, Campylobacter is a common cause of "traveller's diarrhoea".

1. Watery or bloody diarrhoea.
2. Vomiting.
3. Abdominal pain.
4. Fever, malaise, headache.
5. The illness usually lasts for 5 to 6 days, but may sometimes persist for several weeks.
6. **Complications**
   a. GI haemorrhage.
   b. Haemolytic uraemic syndrome.
   c. Meningitis.
   d. Reactive arthritis.
   e. Acute anterior uveitis.
   f. Erythema nodosum.
   g. Septicaemia (extremes of life, immunocompromised patients).

Diagnosis

- Microscopy of stool sample: Leukocytes are frequently seen. Phase contrast or dark field microscopy will reveal the characteristic darting or tumbling motility of the small, curved, rod-like bacteria in stained smears.

- Stool culture.
- Graded compression ultrasonography of the right lower abdominal region may show mural thickening of terminal ileum and caecum.
- Sigmoidoscopy: Oedematous, hyperaemic mucosa with shallow grey-based aphthous ulcers.

Treatment

- Rehydration.
- Erythromycin ethyl succinate, 400 mg, four times a day, decreases faecal shedding of the organism, but may not shorten the duration or severity of symptoms. Ciprofloxacin can also be used.
- Anticholinergics and opiates are contraindicated.

Yersinia enterocolitica

Source

- Milk and milk products.
- Undercooked meat products, particularly pork.
- Household pets.
- Human to human transmission.

Incubation Period

About 1 to 7 days.

Clinical Features

Three types of illness have been reported:
1. In young children, it usually manifests as a self-limited gastroenteritis or enterocolitis.
2. In older children, the illness takes the form of mesenteric adenitis and inflammatory terminal ileitis which may mimic appendicitis.
3. The third type usually strikes adults, manifesting as bacteraemia, meningitis, arthralgia, or erythema nodosum. Complications include intestinal perforation, peritonitis, and gangrene of small bowel.

Nausea, bloody diarrhoea, and abdominal pain have been reported in patients following ingestion of pasteurised milk contaminated with *Yersinia enterocolitica*.

Iron loading can increase the virulence of *Y. enterocolitica*. Use of desferrioxamine can also predispose to systemic infection.

Diagnosis

- Stool culture by special culture technique of cold enrichment.
- Culture of food, blood, skin abscesses, pharyngeal swab, etc.
- Serologic examination of paired sera.
- Detection of the organism in foods and water can be done by polymerase chain reaction.

Treatment

- Supportive measures suffice in most cases, since the disease is usually self-limiting.
- Severe cases respond to tetracycline or cotrimoxazole.

Listeria monocytogenes

Listeria monocytogenes is a pathogenic bacterium that is food-borne, and causes an illness called listeriosis. This microorganism, which is a facultative intracellular bacterium causes illness primarily in pregnant women, neonates, the elderly, and immuno-compromised individuals. Acidity in the stomach decreases the chance of survival of Listeria. Antacids and cimetidine may increase the risk of acquiring this infection in hospitalised patients.

Listeria monocytogenes is a gram-positive, non-acid fast, non-sporulating rod facultative anaerobe, and is indistinguishable from diphtheroids. It can grow at temperatures from 1 to 45°C, and thrive on foods at refrigeration temperatures. There are more than 16 serotypes of *L. monocytogenes,* but only 3 are generally responsible for more than 90% of human infections. These include 4b, 1/2b, 1/2a.

Listeria is commonly found in the female genital tract without causing harm. It is much less common as a male genital contaminant. Thus, it is possible that females have slight immunity against more serious infection.

Source

1. Unpasteurised milk,* and milk products (ice cream, butter, soft cheese, e.g. Camembert cheese).
2. Uncooked meat, especially chicken.
3. Raw vegetables (lettuce).
4. Coleslaw, which is a salad of finely sliced or chopped raw cabbage, usually moistened with a mayonnaise dressing.

Listeria monocytogenes is also found in soil, dust, sewage, water, animal feed, and decaying organic matter. It is speculated that listeriosis is a possible occupational disease of slaughterhouse workers.

Incubation Period

Few days to three weeks.

Clinical Features

Listeria monocytogenes spreads through the body by incorporation into lymphocytes and monocytes, and can cross the blood-brain barrier to produce meningitis. Transplacental transfer is also believed to occur. Successful infection is linked to replication in the cells which phagocytise the bacteria, despite the presence of lysosomal enzymes. The phagocyte is eventually damaged.

- Perinatal infection can manifest as foetal meningitis or intrauterine death. Especially during the third trimester, listeriosis can cause mild illness in the pregnant female, with malaise, chills, fever, and back pain. However, the foetus may suffer severe uterine infection, abortion, premature delivery, or stillbirth.
- In healthy adults and children, the illness usually takes the form of a self-limiting, mild flu-like syndrome with GI disturbances and myalgia.
- Immuno-compromised individuals may suffer from meningitis and sepsis (with vomiting, headache and fever).

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* There are disturbing reports of listeriosis even after consumption of pasteurised milk.

However, the usual signs of a positive Kernig's sign and meningismus seen with meningitis are not generally present in these patients. Endocarditis and pericarditis may rarely occur.

Overall mortality in *Listeria monocytogenes* infections averages 30 to 50% with ranges from 13 to 83%, depending on susceptibility. The case fatality rate for newborn infants of infected mothers is 30 to 50%, depending on the onset of illness in the neonatal period.

Diagnosis

1. Listeria being rod-shaped bacteria, can be mistaken as a contaminant due to the resemblance to diphtheroids. A CSF gram-stain frequently fails to demonstrate the causative organism. Growth in culture is improved when incubated with reduced oxygen and 5 to 10% carbon dioxide.
2. Detection of antibodies against listeriolysin O (LLO), an extracellular haemolysin, can help in the diagnosis of listeriosis, when bacteria cannot be isolated.

Treatment

- Control vomiting and diarrhoea, provide fluids for dehydration, and undertake measures for prevention of shock.
- Intravenous administration of antibiotics such as ampicillin, penicillin G, gentamicin, erythromycin, tetracycline, doxycycline, tobramycin, cotrimoxazole, or vancomycin is usually necessary for serious listeriosis.
- Chloramphenicol has been successfully used in some meningitis patients who did not respond to other antibiotics.

■ Clostridium

The genus Clostridium consists of Gram-positive anaerobic, spore forming bacilli which are responsible for three major diseases – tetanus (*Cl. tetani*), gas gangrene (*Cl. perfringens, Cl. septicum, Cl. novyi, Cl. histolyticum, Cl. fallax,* etc.), and food poisoning (*Cl. botulinum, Cl. perfringens Types A and C*). In addition, acute colitis can result from infection with *Cl. difficile*. Rare cases of intestinal botulism have been caused by two other species of Clostridia, known as *Clostridium baratii* and *Clostridium butyricum*, which produce type F and type E botulinum-like neurotoxins, respectively. Of the cases reported, illness resulted from intestinal colonisation of the organism.

Clostridia can produce disease only when conditions are favourable. Their invasive powers are limited. Pathogenic clostridia act by elaborating powerful exotoxins.

Clostridium perfringens

Synonyms

Cl. welchii, Bacillus aerogenes capsulatus, B. phlegmonis emphysematosae.

Source

Clostridium perfringens is a ubiquitous organism which commonly contaminates meat products and poultry.

Toxins

Food poisoning is caused mainly by some strains of Type A, while necrotising enteritis is caused by Type C strains. The former produce alpha and theta toxins, and a heat-labile enterotoxin, while the latter produce mainly beta toxin.

Incubation Period

About 8 to 24 hours.

Clinical Features

- Abdominal pain, diarrhoea, vomiting. The disease is usually self-limiting, lasting for 12 to 48 hours. Necrotising enteritis is characterised by more severe manifestations and is often fatal.
- Systemic distribution of *Cl. perfringens* type A, and its toxins, has been suggested as a possible cause of sudden infant death syndrome in immunologically compromised infants.

Treatment

Supportive measures.

Clostridium botulinum

Clostridium botulinum is a strictly anaerobic, spore-forming, gram-positive rod that elaborates a potent exotoxin. The spores are capable of tolerating temperatures of 100°C for hours, whereas moist heat at 120°C usually destroys them. Eight separate toxin types (A, B, C (alpha), C (beta), D, E, F, and G) have been described. All are neurotoxins with identical mechanism of action; spores are dormant and highly resistant to damage. Toxin types A, B, E, and rarely F cause human disease; type G has been associated with sudden death in several patients in Switzerland. Illness in animals is often caused by types C and D. Toxin C2 has been described as a cytotoxin agent which can cause vascular permeability and death.

Source

- Foodborne botulism usually results from consumption of contaminated preserved food—canned meat and meat products, fruits, vegetables, pickles, and fish. A bulging can with peculiar tasting contents should raise the suspicion of botulism. On opening the can, the explosion of air that occurs is usually because of fluid under pressure (overfilled can), rather than gas. Even if gas is present, it may be due to a chemical reaction subsequent to detinning of the can lining. There may be a putrefied smell or taste if food is contaminated with type A or B toxin, but may taste and appear normal if contaminated by type E toxin.
- Wound botulism results from wound infection with *Cl. botulinum*.
- Infant botulism most probably is caused by contaminated honey. The US Centers for Disease Control stipulate that infants under the age of 6 months not be given honey, and the Honey Industry Council has extended that limit to

one year. Although honey has been defined as one source of spores, all cases cannot be attributed to this. In one case, foodborne botulism occurred in an infant following exposure to improperly prepared home-canned baby food contaminated with Botulinum toxin A.

Toxins

Clostridium botulinum elaborates a powerful exotoxin which is produced intracellularly and is released only on the death and autolysis of the organism. It is probably the most powerful toxin known to man. The lethal dose for human beings is just 1 to 2 mcg or 1 pg/kg. It is a neurotoxin, and despite its potency, acts slowly taking several hours to kill. Based on animal data, the lethal dose in a 70 kg human would be approximately 0.09 to 0.15 mcg IV or IM. The estimated lethal inhalation dose in a 70 kg human is said to be 0.70 to 0.90 mcg.

Germination of spores in food is enhanced under the following conditions: a pH of greater than 4.5, sodium chloride concentration less than 3.5%, or a low nitrite level. Food suspected to be contaminated with botulinum toxin can be rendered completely safe by pressure cooking or boiling for 20 minutes. However spores can withstand boiling at 100° C, even if it is carried out for several hours.

Mode of Action

The botulinum toxin is a protein consisting of a single polypeptide chain with a MW of 900,000 D, which includes the non-toxic protein haemagglutinin and the 150,000 MW neurotoxic component. To become fully active, the single chain molecule must be cleaved by proteolysis to geneate a heavy chain (MW 100,000) that is linked by a disulfide bond to a light chain (MW 50,000). It is the dichain form of the molecule that is responsible for the toxicity of the toxin.

The botulinum toxin enters the preganglionic nerve terminal by endocytosis and binds rapidly (and irreversibly) to the cell membrane. Once inside the cell, it inhibits calcium-dependant exocytosis, thereby preventing release of acetylcholine and resulting in presynaptic blockade. The toxin acts as a zinc-dependant endoprotease to cleave polypeptides that are essential for exocytosis. This diminution of presynaptic function interferes with cholinergic transmission at all acetylcholine-dependant synapses in the peripheral nervous system. There is no effect on the CNS, or on axonal conduction.

Three steps are necessary for toxin-induced neuromuscular blockade: transport across the intestinal wall into the serum; binding to neuronal receptors; and internalisation of bound toxin, an irreversible step leading to impairment of neurotransmitter release and resultant neuromuscular blockade. The result is hypotonia with a descending symmetric flaccid paralysis; the blockade is most prominent at the cranial nerves, autonomic nerves, and neuromuscular junction.

Incubation Period

About 12 to 36 hours (but can occur as early as 3 hours and as late as 16 days), with a median report of symptoms at 3.2 days. Type E toxin has the shortest, and type B toxin the longest incubation period. In general, the earlier the onset of symptoms, the more serious the disease and the more protracted the course.

■ Clinical Features

Food-borne botulism:

a. This is usually caused in humans by types A, B, E, and rarely F. The initial phase of the disease is often so subtle as to go unnoticed or misdiagnosed. Type A botulism generally causes a more severe illness, and is more likely to require intubation than either type B or E botulism. In general, the earlier the onset of symptoms, the more serious the disease and the more protracted the course. Even a small taste of contaminated food may result in illness.

b. Nausea, vomiting, thirst, abdominal pain. Abdominal cramps may be an early symptom of foodborne botulism. Marked abdominal distension with absent bowel sounds may be present due to paralytic ileus.

c. Constipation; refusal to feed and diarrhoea have been reported in a few cases of paediatric botulism.

d. Ptosis, difficulty with visual accommodation, photophobia, mydriasis, and diplopia (due to ocular paresis). Strabismus and nystagmus have also been reported. The triad of extraocular muscle palsy, pupillary dysfunction, and ptosis is said to be predictive of illness severity (i.e. the development of respiratory failure). Early onset of neurological symptoms, particularly ocular, generally indicates a more severe infection and worse prognosis.

e. Dizziness: Postural dizziness is a relatively frequent symptom resulting from cholinergic blockade.

f. Dry mouth,* soreness of throat due to drying of pharynx, dryness of lacrimal secretions.

g. Dysphonia, dysarthria, dysphagia.

h. Bilaterally symmetrical descending motor paralysis, beginning with abducens (VI) or oculomotor (III) nerve palsy, and progressing to respiratory insufficiency. The risk of ventilatory failure is greatest within the first two days of hospitalisation. Respiratory arrest may develop suddenly in patients with apparently adequate respiratory reserve; absent signs and symptoms of respiratory insufficiency are not necessarily indicative of normal lung function. Respiratory failure can also develop insidiously, and may be difficult to diagnose. Many patients experience dyspnoea of varying degree for a year or more after recovery from botulism, despite essentially normal pulmonary function. The cause of dyspnoea may be a residual defect of respiratory muscles.

i. Urinary retention (especially in Type E botulism): due to cholinergic blockade.

j. Mental status, sensory examination, reflexes, body temperature, and pulse are all usually normal.

k. Cardiac arrest may occur in patients with respiratory failure. It is not known whether arrest is secondary to

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* The dryness is unrelieved by drinking fluids.

hypoxia or due to a direct effect of botulinum toxin on the myocardium.

l. A syndrome of inappropriate secretion of antidiuretic hormone has been reported in some cases of botulism. Most of these patients were on a ventilator when this occurred.

m. **Toxicoinfectious Botulism:** There are a few reports of gastrointestinal colonisation by *C. botulinum* spores in adults resulting in cases of adult infectious botulism (the in vivo toxin that is produced is similar to that of infant botulism). Several factors are associated with this form of botulism: GIT abnormalities (e.g. achlorhydria), antibiotic therapy disrupting the normal GI flora, a history of abdominal surgery (e.g. gastrectomy), etc.

n. A detailed list of symptoms and signs is mentioned in **Table 33.2**. Mortality is estimated to be less than 10% with symptomatic and supportive care.

o. **Differential Diagnosis:** The common conditions confused with botulism are presented in **Table 33.3**, along with clues to help resolve a given case that may appear perplexing. The condition that is most often confounding is Guillain Barré syndrome, especially the Miller Fisher variant (**Table 33.4**).

p. **Treatment:** Supportive measures.

Table 33.2: Foodborne Botulism: Complete Clinical Picture

General Features	Gastrointestinal Features	Neurological Features	
Fatigue	Nausea, vomiting	Ocular:	Others:
Vertigo	Abdominal pain	Mydriasis	Dysphagia
Sore throat	Constipation (sometimes	Diplopia	Dysarthria
Orthostatic hypotension	diarrhoea)	Blurred vision	Dysphonia
Normal mental status	Ileus	Ptosis	Dry mouth
		Nystagmus	Facial paresis
		Ophthalmoplegia	Lingual weakness
			Decreased gag reflex
			Extremity weakness
			Descending paralysis
			Hyporeflexia
			Ataxia
			Urinary retention
			Dyspnoea
			Respiratory failure

Table 33.3: Botulism: Differential Diagnosis

Condition	Key Diagnostic Features
Anticholinergic syndrome	Mydriasis, dry mucosa, fever, vasodilation, tachycardia, hypertension, ileus, altered mental status
Carbon monoxide poisoning	Headache, nausea, tachypnoea, altered sensorium, elevated carboxyhaemoglobin
Diphtheria	Exudative pharyngitis, cranial polyneuropathy, hypotension, cardiac features
Elapid snakebite	Vertigo, weakness, nausea, salivation, vomiting, fasciculations, tremor, followed by bulbar palsy with slurred speech, diplopia, ptosis, dysphagia, dyspnoea, and respiratory failure
Encephalitis	Fever, convulsions, altered mental status, elevated CSF protein, and pleocytosis
Guillain Barré syndrome (Miller Fisher variant)	**Table 33.4**
Inflammatory myelopathies (acute myelitis, transverse myelitis, etc.)	Complete or incomplete spinal syndrome: Posterior column myelopathy with ascending paraesthesias, or ascending spinothalamic findings, or Brown-Sequard syndrome. Usually follows viral illness, with back pain, progressive paresis, asymmetric ascending paraesthesias in legs. CSF: 5 to 50 lymphocytes/mm^3
Multiple sclerosis	Weakness, visual blurring, sensory disturbances, ataxia. Mononuclear cell pleocytosis in CSF Evoked response testing: Abnormal conduction in visual, auditory, somatosensory, or motor pathways Abnormal MRI or CT
Myasthenia gravis	Aggravation of fatigue with exercise, positive Tensilon test
Organophosphate poisoning	Salivation, lacrimation, urination, defaecation, fasciculations, bronchorrhoea
Paralytic shellfish poisoning	Dysaesthesias, paraesthesias, impaired mentation, respiratory paralysis
Poliomyelitis	Fever, GI symptoms, asymmetric neurological findings, CSF pleocytosis
Tetanus	Cranial nerve defects, spasticity, rigidity
Tick paralysis	Focal findings, large muscle weakness, ascending paralysis

Table 33.4: Botulism versus Guillain Barré Syndrome

Feature	Botulism	Guillain Barré Syndrome (Miller Fisher variant)
Fever	Absent	Present (occasionally)
Pupils	Dilated or non-reactive	Normal
Ophthalmoplegia	Present early	Present late
Paralysis	Descending	Descending
Deep tendon reflexes	Present	Absent
Ataxia	Absent	Present
Sensory paraesthesias	Absent	Present
Laboratory: CSF protein	Normal	Elevated

Wound botulism

a. This is a rare, life-threatening complication of trauma which occurs after spores of *Cl. botulinum* have germinated in a wound and produced botulinum toxin resulting in flaccid paralysis. It can also result from intravenous drug abuse. Of late, cocaine and heroin (especially "black tar heroin" which is often injected subcutaneously) have been increasingly associated with cases of wound botulism. Deep wounds, crush injury, or compound fracture treated with open reduction are invariably the type of trauma predisposing to wound botulism. Incubation period varies from 4 to 18 days.

b. **Clinical Features:**
   – Fever (usually associated with sinusitis, abscess, or tissue infection which acts as the focus of infection).
   – Absence of GI manifestations.
   – Cranial nerve palsies resulting in ptosis, diplopia, poor accommodation, ophthalmoplegia, dysphagia, dysphonia, and dysarthria.
   – Other neurological features such as descending flaccid paralysis, shortness of breath, and respiratory failure.

Infant botulism

a. Infant botulism is said to be the commonest form of botulism. Since 1976, when the first case was reported till 2005, more than 2000 hospitalisations have been documented. Of these, 95% occurred in the USA, and 99% were due to botulinum neurotoxin type A or B. Most cases involved infants of 1 to 3 months age (range 1 month to 1 year).

b. It is postulated that infant botulism is the result of ingestion of *Cl. botulinum* organisms with subsequent *in vivo* production of toxin, followed by gut absorption. Some investigators suggest that bacterial growth associated with breastfeeding may favour *Bifibobacterium* development, instead of bacteria known to inhibit *Cl. botulinum* (i.e., *Coliforme, Enterococcus,* and *Bacteroides* species). Of all the food items associated with infant botulism, honey is said to be the commonest food source contaminated with *Cl. botulinum* spores.

Clinical features of infant botulism include constipation, feeding difficulty, feeble crying, and a "floppy" baby with decreased muscle tone, particularly of the neck and limbs. Loss of facial grimacing, ophthalmoplegia, diminished gag reflex, dysphagia, poor anal sphincter tone, and respiratory failure have also been reported.

■ Diagnosis

Food-borne botulism

a. Laboratory analysis: Samples of serum, stool, vomitus, gastric contents, and suspected food item should be tested for *Cl. botulinum* as well as botulinum toxin. The specimens should be handled cautiously, refrigerated, and examined as soon as possible after collection. Stool specimens must be incubated anaerobically and subcultured on egg yolk agar.

   The usual procedure is to draw 10 ml of serum before treatment has begun, for determination of toxin. The standard laboratory study is the mouse bioassay. Analysis takes 24 hours to perform, so the results cannot be used to determine treatment. Mouse bioassay for botulinum toxins is extremely sensitive and detects as little as 5 to 10 pg toxin/ml. ELISA tests have not been shown to have the same sensitivity as the mouse bioassay.

   Diagnosis is confirmed by demonstration of toxin in serum, stool, or food items, or by isolation of organism in stool or food items.

b. Tensilon test: Tensilon (edrophonium) is a rapid-acting anticholinesterase used to differentiate botulism from myasthenia gravis. 10 mg of the drug is injected IV slowly (1 to 2 mg at first, followed by the remainder over the next 5 minutes). Muscle strength in myasthenia gravis will improve dramatically within ½ to 1 minute, and last for about 5 minutes, while there will be little or no improvement in botulism.

c. Electromyography: In all forms of botulism, the EMG pattern is characterised by brief, small, abundant motor unit action potentials. Motor nerve conduction velocity is normal. Another characteristic EMG finding is an increment of small compound muscle action potential amplitude directly related to the release of acetylcholine following repetitive stimulation at 20–50 Hz.

d. Bedside spirometry to determine forced vital capacity (FVC) and inspiratory force should be done sequentially

in suspected patients. These tests may provide early clues of impending respiratory failure. Arterial blood gases may show only minor abnormalities despite substantial loss of ventilatory reserve.

e. Experimental and clinical evidence suggests that botulinum toxin may exert a direct cardiac effect. Intraventricular conduction delay, non-specific ST-T wave changes, and arrhythmias, including sudden death from ventricular fibrillation, have all been reported.

Wound botulism

a. Laboratory analysis: Wound cultures and serum assays for botulinum toxin.
b. Tensilon test.
c. Electromyography.

Infant botulism

1. History: of honey ingestion.
2. Clinical picture.
3. Tensilon test: unreliable in infants.
4. Stool analysis.

■ Treatment

1. Due to the serious nature of the illness, all cases of botulism must be admitted to hospital and continuous monitoring done with reference to respiratory status (vital capacity, peak expiratory flow rate, negative inspiratory force, pulse oximetry, and gag reflex). The moment signs of bulbar palsy begin to manifest, intubation or tracheostomy may have to be done. Because aspiration pneumonia is a frequent problem in patients with respiratory failure, intubation to protect against aspiration should be considered mandatory. Tracheostomy may be required for long-term ventilatory support. Endotracheal intubation should be performed in all patients with falling inspiratory force (less than 25 cm H_2O) or PO_2 (less than 60 mmHg), rising PCO_2 (greater than 50 mmHg), or vital capacity less than 40% predicted. (*Caution: Arterial blood gases may show only minor abnormalities despite significant ventilatory dysfunction*).

2. An attempt should be made to evacuate the GI tract of spores and toxin with the help of activated charcoal, emesis, gastric lavage, or catharsis, if the patient is seen early. Presence of gag reflex must be ascertained. If catharsis is decided upon, sorbitol is the cathartic of choice. Gut decontamination is of course not applicable in wound botulism.

3. **Botulinum antitoxin:** Trivalent botulinum antitoxin (types A, B, and E) is an equine globulin preparation that is available in the West since the 1960s, but does not appear to be produced in India. The antitoxin is produced by horses immunised against botulinum toxin, and then defibrinated, digested, dialysed, and prepared as a 20% protein antitoxin.

a. *Availability:* Each 10 ml vial of trivalent botulinum antitoxin contains 7500 IU of type A, 5500 IU of type B, and 8500 IU of type E antitoxins.

b. *Dose:* 1 vial is administered by slow IV as a 1:10 vol/vol dilution in 0.9% sodium chloride. This dose may be complemented by an IM dose of a single vial given simultaneously. Subsequently, doses are given IV every 2 to 4 hours, depending on the clinical status. In foodborne botulism, additional doses usually are not required. Botulinum antitoxin is not recommended for infant botulism because of its serious side effects and lack of effect on toxin-producing organisms in the gut.

c. *Sensitivity testing:* Skin or eye tests should be done prior to administration of the antitoxin or serum, even if the patient has previously received the antitoxin. No testing should be done unless a syringe containing 1 mL of adrenaline solution (1:1000) is immediately available. Death has resulted from some serum/antitoxin skin tests.

– Skin test (*in persons with allergic disposition*)—0.05 mL of a 1:1000 dilution (in saline), intracutaneously. Read the reaction in 5 to 30 minutes.

– Skin test (*in persons with allergic disposition*)—0.1 ml of a 1:100 dilution (in saline), intracutaneously. Read the reaction in 5 to 30 minutes.

– Eye test—Except in small children, the eye test is easier to be done, and is more specific. Instil a drop of a 1:10 dilution of antitoxin/serum in physiologic saline in 1 eye; instil a drop of physiologic saline in the other eye as a control. Positive reaction: lacrimation and conjunctivitis appears in 10 to 30 minutes in the eye treated with the antitoxin/serum.

Desensitisation is recommended if there is a history of allergy, sensitivity to horse serum, or positive reactions in skin/eye tests with antitoxin. The schedule of serial administration of diluted antitoxin/horse serum at 20-minute intervals given subcutaneously {as long as there are no adverse reactions} as recommended by the manufacturer is as follows:

– 0.05 mL of a 1:20 dilution subcutaneous (SC)
– 0.1 ml of a 1:10 dilution SC
– 0.3 ml of a 1:10 dilution SC
– 0.1 ml undiluted serum SC
– 0.2 ml undiluted serum SC
– 0.5 ml undiluted serum SC

If a reaction occurs during the desensitisation process, injections should be stopped for one hour, followed by the desensitisation schedule at the last dose which failed to cause a reaction, with 20 minute intervals between each desensitisation dose.

d. *Adverse effects:* Hypersensitivity reactions, including anaphylaxis and serum sickness. Since serum sickness reactions are more likely to occur with doses of 40 ml of antitoxin or more, the lowest effective dose is always recommended. Efforts are on in the USA to produce a pentavalent toxoid (types A, B, C, D, E).

4. **Guanidine:** The use of guanidine is controversial since it has low efficacy and high incidence of adverse effects. In case it is considered appropriate, the recommended dose is 15 to 40 mg/kg/day orally until EMG improvement occurs at least in the ocular muscles. Respiratory muscles usually do not demonstrate beneficial response. Due to the lack of respiratory improvement, significant nausea and epigastric pain associated with guanidine use, and the

lack of a parenteral form, guanidine is considered to be contraindicated by some investigators.

5. **Penicillin:** It is of no use in foodborne and infant botulism, but can be of substantial benefit in wound botulism. Penicillin G is the preferred form.

6. **Human-derived botulism immune globulin (BIG)** has recently been introduced in the West to treat infant botulism. It is a pentavalent (types A, B, C, D, and E) immunoglobulin harvested by plasmapheresis from donors who have received multiple immunisations with pentavalent botulinum toxoid. The greatest advantage of BIG is that it avoids the use of foreign equine protein, thereby eliminating the risk of hypersensitivity reactions.

7. The neuromuscular blockade antagonist, 4-aminopyridine has been used in addition to regular supportive care and antitoxin therapy. This agent, however, has shown only a transient improvement in reversing peripheral muscle paralysis, and had no effect at all on respiratory muscle. A constant infusion of 4-aminopyridine did allow prolonged reversal of peripheral paralysis in one case, but caused convulsive phenomena following the treatment.

8. Surgical debridement may be necessary for suspected wound botulism. High dose intravenous benzylpenicillin, along with appropriate antitoxin administration, has been used effectively to treat patients with wound botulism.

9. Supportive measures:
   a. Nutritional supplementation—oral feeds are contraindicated unless there is intact gag reflex.
   b. Respiratory support—forms the mainstay of treatment.
   c. Antibiotics should only be used to treat complications such as respiratory or urinary tract infections, or wound infections.

Prevention of Botulism

- Avoid consuming improperly preserved home-canned foods, especially vegetables such as green beans, asparagus, and peppers.
- Home-canning of vegetables should be done with a pressure cooker so as to attain temperatures necessary to kill botulinum spores (> 100° C for 10 minutes).
- Jams and jellies can be safely home-canned without pressure cooker, since their high sugar content will not encourage the growth of *Cl. botulinum*.
- Cooked foods should not be kept at temperatures of 4° C to 60° C for more than 4 hours.
- Boiling food for 10 minutes before eating destroys botulinum toxin.
- To prevent germination of spores in food, the pH should be maintained at less than 4.5, the sodium chloride content must be more than 3.5%, and nitrite level should be sufficiently high. Acidifying agents such as citric or phosphoric acid must be employed in canning or bottling foods with low acid content (green beans, asparagus, peppers, corn, beets, mushrooms, spinach, olives, figs).

- Food contaminated by *Cl. botulinum* types A and B often looks or smells abnormal due to action of proteolytic enzymes. If there is any doubt, the food item must be discarded.* Alarmingly, food contaminated with type E toxin usually looks and smells normal.
- Prevention of infant botulism can be done by thoroughly washing foods and objects that are placed in a child's mouth. Honey must not be given to infants.

Forensic Issues

- All the cases of botulism reported in the literature are due to accidental poisoning. Though botulinum toxin could possibly serve as a potent homicidal poison, its use for nefarious purposes has fortunately been non-existent so far. Most cases of foodborne botulism result from eating improperly preserved home-canned foods, and are virtually confined to Western countries, even though some incidents have recently been reported from Iran, Russia, Japan, and even India.
- Contrary to popular opinion, outbreaks of botulism are generally not associated with multiple cases per occurrence. However, there have been some reports of mass poisoning. An international outbreak of botulism food poisoning in 1989 was traced back to whitefish contaminated by *C. botulinum* type E sold in a New York delicatessen. Five people were hospitalised, one of whom died. Laboratory confirmation was obtained in 3 of the cases. All cases, which occurred in the US and Israel, were traced to the consumption of ribbetz, a freshwater whitefish soaked in brine, dried, and preserved by refrigeration.
- Only 2% of foodborne botulism outbreaks are due to canned foods originating from the commercial food processing industry, while 4% are associated with food purchased in restaurants, and the remaining (more than 90%) cases result from faulty home-canning. Vegetables with or without meat, are the causative agents in about 70%, meat in 17%, and fish in 13% of cases. Although home-made canned foods remain the major sources of botulism outbreaks, of late there has been an increase in commercially prepared products causing botulism outbreaks. Due to recent innovations in methods of preserving food products by using vacuum-packed and refrigerated or heat-treated foods at an inadequate temperature, the development of neurotoxinogenic Clostridium has increased in both the US and Europe.
- Types A, B, and E are the common strains involved in botulism outbreaks. The case fatality ratio for type A is about 12%, while for types B and E, it is approximately 10%. A few cases have recently been reported to have been caused by other Clostridium species—*Cl. baratii* and *Cl. butyricum*.
- Although most cases of botulism recover completely, especially when prompt treatment is administered, a few may be associated with long-term sequelae such as dysgeusia, dry mouth, constipation, dyspepsia, arthralgia, exertional dyspnoea, and easy fatiguability.

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* Do not taste it! A single taste can be fatal.

- Recently, a fourth type of botulism (apart from foodborne, wound, and infant types) was identified by the Centers for Disease Control in the USA, which affects patients older than 1 year in whom no particular food source can be implicated. This has come to be called "Infant type adult botulism". Risk factors for this type include recent antibiotic therapy, gastric achlorhydria, and previous intestinal surgery.
- Botulinum toxin is today finding an important place in therapeutics, being used for the treatment of a number of neurological and ophthalmological disorders. It is also said to be useful in controlling hyperhydrosis. Botulinum toxin Type A (BTA) has been used to treat blepharospasm, strabismus, cervical dystonia, and moderate to severe glabellar lines. Some of the side effects reported with its use have included the following: headache, ptosis, dysphagia, upper respiratory tract infection, flu-like syndrome, and nausea. Diplopia, ectropion, and lower eyelid droop have been less commonly reported.
- Of late, botulinum toxin misuse as a bioterrorism agent is gaining notoriety. The toxin can be easily delivered by aerosol, or used to contaminate food or water supplies. If inhaled, the toxin produces clinical symptoms that are similar to foodborne intoxication; however, time to onset may be delayed. The toxin is relatively easy to produce, and is highly lethal in small quantities. In recent history, countries and/or terrorist organisations (e.g. Iraq during the Persian Gulf War and the Aum Shrinrikyo in Tokyo) have been known to produce botulinum toxin as part of their offensive weapons programme.

■ Viruses

Common viruses responsible for causing gastroenteritis include astrovirus, calcivirus, enteric adenovirus, norwalk virus, parvovirus, and rotavirus (groups A, B, C).

Rotavirus is the most common cause of diarrhoeal disease in infants and children, though there is a variant, which also affects older children and adults (adult diarrhoea rotavirus or ADRV).

Adenovirus is another common agent of diarrhoeal disease in children. Incubation period of rotavirus/adenovirus diarrhoea varies from 24 to 72 hours. Vomiting begins abruptly and then resolves. Diarrhoea then settles in and lasts for 4 to 7 days. Stools are watery and foul smelling.

Parvovirus gastroenteritis is the adult variety with an incubation period of 24 to 36 hours, followed by abrupt onset of diarrhoea, vomiting, and abdominal cramps. Myalgia is often present.

Viral diarrhoeas are invariably self-limiting and require only rehydration by way of treatment. Infants must be administered oral rehydration solutions, while older children and adults can be managed on the BRATT diet (Bananas, Rice, Apples, Tea, Toast).

■ Protozoa

Table 33.5 lists common protozoa responsible for various kinds of illnesses that are transmitted through food and water. While many of these agents are more appropriately discussed in textbooks of microbiology or clinical medicine, a few merit special mention here.

Entamoeba histolytica

Source

Contaminated food and water. Raw vegetables which have not been washed well are an important source.
Human to human transmission is also quite common.

Mode of Action

Recent studies have demonstrated that *E. histolytica* can be differentiated into at least 18 zymodemes.* Pathogenic strains are all from particular zymodemes of which 7 have been identified so far.

Entamoeba histolytica exists in two forms—vegetative (trophozoite) form and cystic form. Trophozoites invade the colon where they multiply and subsequently get encysted. The cysts are excreted in stools. Ingestion of cysts results in release

Table 33.5: Pathogenic Protozoa Transmitted Through Food/Water		
Protozoan	Pathogenicity for humans	Stage transmitted
Balantidium coli	+	Cyst
Cryptosporidium parvum	+	Oocyst
Chilomastix mesnili	-/+	Cyst
Dientamoeba fragilis	-/+	Trophozoite
Endolimax nana	-/+	Cyst
Entamoeba histolytica	+	Cyst
Microsporidia	-/+	Spore
Giardia intestinalis	+	Cyst
Isospora belli	-/+	Oocyst
Sarcocystis species	+	Oocyst/tissue stages
Toxoplasma gondii	+	Oocyst/tissue stages

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* A zymodeme is a population of organisms differing from another similar group in electrophoretic characteristics of enzymes.

of trophozoites which colonise the large intestine, some of them even invading the bowel wall causing ulcerations. Occasionally the trophozoites may get transported to other organs such as liver where they produce abscesses.

Incubation Period

About 2 to 4 weeks

Clinical Features

Entamoeba histolytica produces a clinical syndrome referred to as amoebiasis, which has a worldwide distribution and is a major health problem in developing countries. It is estimated that 15% of the population in India may be affected by amoebiasis.

Intestinal amoebiasis varies in severity from mild abdominal discomfort and diarrhoea to fulminating dysentery. Extraintestinal amoebiasis may involve liver, lungs, brain, spleen, etc.

Diagnosis

1. Stool analysis: Microscopy for detection of trophozoites, cysts, and pus cells.
2. Serological tests: Indirect haemagglutination test, counter immunoelectrophoresis, ELISA, etc.

Treatment

Symptomatic cases can be treated with metronidazole (30 mg/kg/day for 8 to 10 days) or tinidazole. Abscesses must be treated surgically. Asymptomatic carriers can be treated (if they are food handlers) with diiodohydroxyquin or diloxanide furoate.

Cryptosporidium parvum

This protozoon causes severe diarrhoea in immunocompromised adult patients and immunocompetent children.

Source

Contaminated food and water, especially the latter. Decontamination of water can be done by filtration, distillation, or reverse osmosis.

Clinical Features

1. Severe persistent diarrhoea.
2. Malnutrition (in children).
3. Pulmonary manifestations.
4. Toxic megacolon.
5. Cryptosporidiosis is often fatal in AIDS patients.

Incubation Period

Biopsy of intestine (small or large) reveals Haematoxylin and eosin darkly stained structures 4 to 5 microns in diameter near the tips of microvilli of epithelial brush border.

Treatment

1. IV fluids and electrolytes.
2. Antidiarrhoeal drugs.

Microsporidia

The microsporidian genera which cause human disease include Nosema, Pleistophora, Encephalitozoon, Enterocytozoon, and Septata.

Microsporidiosis generally occurs only in immunodeficient patients and can take the form of diarrhoea, keratoconjunctivitis, hepatitis, myositis, ascites, cholangitis, and renal or urogenital infections. It has been estimated that microsporidia account for 10 to 40% of AIDS-related diarrhoea.

Treatment involves the administration of albendazole (400 mg twice daily), which helps in relieving microsporidial diarrhoea, but relapses are common.

PARASITES

While a number of intestinal parasites are responsible for producing periodic diarrhoea and malabsorption states in humans, only those responsible for a specialised condition referred to as "Japanese restaurant syndrome" will be discussed here.

■ Japanese Restaurant Syndrome

Source

Raw fish (popular culinary delicacy in Japanese cuisine).

Aetiological Agents

1. Roundworm (*Eustrongylidis anisakis*)
2. Fish tapeworm (*Diphyllobothrium* species)

Clinical Features

1. Anisakiasis or Eustrongylidiasis—After an interval of 1 to 2 hours following consumption of fish, the following symptoms occur: nausea, vomiting, and crampy abdominal pain. Perforation of intestinal wall is possible due to invasion of larvae, resulting in severe localised abdominal pain mimicking appendicitis. Diagnosis can be established by visual inspection of larvae on endoscopy, laparotomy, or pathological examination.
2. Diphyllobothriasis or Fish tapeworm disease—After an interval of 1 to 2 weeks following consumption of fish, the following symptoms occur: nausea, vomiting, abdominal cramps, flatulence, diarrhoea, and megaloblastic anaemia. Diagnosis can be made by identification of tapeworm proglottids in stool.

Treatment

Niclosamide, praziquantel, or paromomycin may be effective.

FUNGI

■ Mushrooms

The term "mushroom" actually refers to the reproductive portion of a fungus which grows up from an underground *mycelium*, i.e. mass of filaments or *hyphae* constituting the vegetative portion of the fungus. Of the numerous species of mushrooms, less than 5% are poisonous, while many are edible and are very popular in Western and Chinese cuisine. All toxic mushrooms

belong to two divisions: Basidiomycetes and Ascomycetes.

The important parts of a poisonous mushroom (careful examination of which can help in identification) include the pileus (cap), stipe (stem or stalk), lamellae (gills), volva, veil, annulus (ring), and spores (**Fig 33.1**). *Pileus* refers to the broad, cap-like structure from the undersurface of which hang the *gills* or *lamellae*. The latter radiate out like the spokes of a wheel. *Spores* are located on the lamellae, and are microscopic reproductive structures which are produced in the millions and range in colour from white to black, with shades of pink, brown, and purple in between. *Stipe* is the stalk or stem supporting the pileus. The *annulus* ("ring of death") is a ring-like structure that surrounds the stipe below its junction with the pileus. The *veil* is a membrane that completely or partially covers the lamellae. *Volva* ("death cup") represents the remnant of the veil found around the base of the stipe in some species.

The common names of important mushrooms are listed in **Table 33.6**.

Depending on the nature of toxin present, mushrooms can be classified into several groups, of which the cyclopeptide-containing mushrooms are the most important, and will be discussed here. Examples include

- Amanita species comprising *A. phalloides* (**Fig 33.2**)*, A. virosa, A. bisporigera, A. hygroscopica, A. suballiacea, A. tenuifolia, A. verna,* and *A. ocreata*
- Galerina species comprising *G. autumnalis, G. marginata, G. sulcipes,* and *G. venenata.*
- Lepiota species comprising *L. castanea, L. helveola, L. chlorophyllum, L. josserandii, L. subincarnata,* and *L. brunneoincarnata.*

Toxins

Amatoxins, phallotoxins, and virotoxins, which are all cyclopeptides.* Nine amatoxins have been identified: alpha, beta, gamma, and epsilon amanitins, amanullin, amanullinic acid, proamanullin and amanin. Amanitins are the most toxic compounds. Phallotoxins are bicyclic heptapeptides. Seven compounds have been identified: phalloidin, phalloin, prophalloin, phallisin, phallacin, phallacidin, and phallisacin. Five virotoxins (monocyclic heptapeptides) have been isolated from *Amanita virosa* (**Fig 33.3**).

Fig 33.1: Parts of a mushroom

Fig 33.2: *Amanita phalloides*

Table 33.6: Common Names of Common Mushrooms

Species	Common Name
Amanita muscaria	Fly agaric
Amanita pantherina	Panther cap/False blusher
Amanita phalloides	Death cap
Amanita virosa	Destroying angel
Clitocybe dealbata	Sweater
Coprinus atramentarius	Inky cap
Galerina autumnalis	Deadly galerina
Gyromitra esculenta	False morel/Beefsteak mushroom
Panaeolus foenisecii	Mower's mushroom
Psilocybe caerulipes	Blue foot
Psilocybe semilanceata	Liberty cap/Magic mushroom

Fig 33.3: *Amanita virosa*

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* Amatoxins are cyclic octapeptides, while phallotoxins and virotoxins are cyclic heptapeptides.

Mode of Action

Mushrooms belonging to this group have no characteristic taste or smell. The colour varies with the climate, soil, and age of the mushroom. Identification is based on the presence of white gills underneath the cap, an annulus at the top of the stalk, and a volva at its base. Specimens cut off at ground level may be misidentified. The swollen base is seen only when the entire fruiting body is dug out of the ground.

Of all the toxins, phalloidin appears to be the most rapid acting, while amanitin causes more delayed manifestations. Phalloidin interrupts actin polymerisation and impairs cell membrane function, but has a limited absorption and therefore toxicity. Phalloidin binds to the actin F (filamentous polymer) of the plasma membranes, and hence increases the permeability of the plasma membranes of hepatocytes. Amatoxins are more potent and can cause substantial hepatic, renal, and CNS damage. In vitro studies indicate that alpha-amanitin is cytotoxic on the basis of its interference with RNA polymerase II, preventing the transcription of DNA. Target organs are those with the highest rate of cell turnover—GI tract epithelium, liver hepatocytes, and kidneys. Cells with the highest rate of multiplication, such as the intestinal mucosa, are injured first, followed by the liver and kidneys.

Latent Period

There is often a latent period of 6 to 24 hours following ingestion. The toxins are <u>not</u> destroyed by cooking.

Clinical Features

1. **Phase I:**
   a. Abdominal pain, nausea, vomiting, diarrhoea fever, tachycardia, hypoglycaemia, hypotension and electrolyte imbalance, lasting for about a day. The diarrhoea is often severe, watery, and cholera-like (up to 2 to 4 litres/day).
   b. Metabolic acidosis may occur.
2. **Phase II:** Treacherous phase of remission, during which the patient may be considered to have recovered and may even be sent home, only to return moribund soon thereafter.
3. **Phase III:**
   a. Two to three days after ingestion of the toxic mushroom, the third devastating phase unfolds leading to hepatic, renal, and (occasionally) pancreatic failure. Hepatotoxicity manifests in the form of elevations of AST, ALT, and bilirubin levels, hypoglycaemia, jaundice (**Fig 33.4**), encephalopathy with convulsions, coma, and death in 7 to 10 days (after ingestion). In most cases, encephalopathy occurs 5 to 7 days after ingestion. Coagulation defects with hypofibrinogenaemia and hypoprothrombinaemia occur in hepatic failure, and may result in local or general bleeding. Fulminant hepatic failure, developing very quickly, and requiring liver transplantation has been reported following severe intoxications. Lactic acidosis and metabolic acidosis have also been reported in the 3rd phase.

Fig 33.4: Jaundice—Mushroom poisoning
(*Pic*: Dr PC Sarmah)

b. Hypoglycaemia is a grave marker signifying poor prognosis. Spontaneous hypoglycaemia results from impaired glycogenolysis and gluconeogenesis. Insulin and C-peptide concentrations are elevated in many patients. Amanita toxins appear to be able to induce a direct insulin-releasing effect, and also have a cytotoxic effect on beta cells. Some investigators suggest that aminotransferases are important biological markers, and advocate that monitoring transaminases and measuring their ratio may be of prognostic value. But the general consensus is that prothrombin time is a more useful prognostic marker for clinical outcome than serum aminotransferase levels, although close monitoring of both are recommended.

c. Cardiovascular collapse usually accompanies severe hepatic failure at the terminal stage. Sequelae which may follow include cardiomyopathy, coagulopathy, and seizures. When liver damage is reversible, patients usually make a slow and steady recovery.

d. Adult respiratory distress syndrome (ARDS) may develop in the later stages of cyclopeptide mushroom poisoning, in conjunction with severe hepatic impairment and coagulopathies. ARDS resulting in death has been reported.

e. Polyneuropathy, developing several days after mushroom ingestion, has been reported in some patients. Manifestations included the following: loss of strength in the lower extremities, absence of deep tendon reflexes, and alteration of pain, temperature and proprioceptive sensitivity.

f. Two kinds of renal failure are observed in Amanita poisoning. During the gastrointestinal phase, a functional renal failure is frequently observed, which is characterised by hypovolaemia, and is secondary to fluid losses and hypoperfusion of the kidneys. Acute renal failure with anuria occurs in the third phase of poisoning, and may be accompanied by severe hepatitis with hepatic coma and haemorrhages. This is part of the hepatorenal syndrome.

g. In pregnancy, the foetus may develop a toxic hepatitis. Since it is unclear whether amatoxins are excreted in breast milk, breastfeeding must not be allowed as far as possible.

Usual Fatal Dose

- About 2 to 3 mushrooms (*A. phalloides*).
- Concentrations of 5 to 15 mg of amatoxins per gram of dried mushroom have been found, which is equivalent to one Amanita cap. According to some investigators, 0.1 mg/kg of amatoxin may be a lethal dose for human adults.
- About 15 to 20 Galerina caps could kill a healthy adult, as will about 30 Lepiotas.

Diagnosis

1. The Meixner test (*page no 584*), a simple colourimetric spot test for detection of amatoxin, unfortunately gives false-positive reactions with samples containing psilocybin and 5-substituted tryptamines. Therefore, the test has limited clinical utility. Further, a negative reading is not necessarily indicative that a mushroom is safe; potential toxicity following ingestion may still exist.
2. Melzer's test (*page no 584*) can be done to detect an amyloid reaction in cyclopeptide containing Amanitas.
3. Hepatic and renal function tests.
4. Serum electrolytes, urea, creatinine, and glucose levels.
5. If a mushroom dish, gastric contents, or stools are all that is available, proceed as follows:
   a. A drop of material, placed on a slide and covered with a cover slip may, under high power (450X–500X) magnification, reveal spores mixed with the debris of the sample.
   b. Spores will be fairly uniform in size and shaped somewhat like an apple seed or popcorn kernel. They are about the size of a red blood cell (approximately 7 microns). Amanita spores are hyaline, thin-walled, and without a pore. Spores of less toxic species are thick-walled with a pore. Dark-coloured spores indicate a genus other than Amanita.
   c. If no spores are discernible on direct smear, proceed as follows:
      – Filter the sample through four layers of cheesecloth using water to emulsify if necessary.
      – Centrifuge the filtrate at 7000xg for ten minutes to sediment the spores.
      – Remove the supernatant carefully utilising suction or pipette.
      – Re-suspend the pellet of sediment in one to two drops of water.
      – Examine drop of solution as under step 1 above.
      – If spores are still not found, proceed as follows:
        - Place a drop of the sediment suspension on a slide.
        - Heat gently to evaporate the liquid and fix the material to the slide.
        - Add acid fuchsin (1% acid fuchsin in distilled water).

- Heat again to dryness.
- Wash off excess stain gently with water.
- Examine as described above. The spore walls will appear vivid red in contrast to the amorphous debris.

6. Detection of toxins in gastric aspirate, serum, urine, stool, and liver and kidney biopsies, using HPLC, TLC, or RIA.
7. Monitor coagulation parameters (INR or PT), especially the clotting factors synthesised by the liver, i.e. fibrinogen, prothrombin.
8. Elevated AST, ALT, LDH, and serum bilirubin are the earliest and best indicators of liver damage, while glucose, fibrinogen, and prothrombin time are the best indicators of established hepatocellular failure. Patients with prothrombin values less than 10% have high fatality rate.

Severity Classification

1. Grade 1: GI upset, no indications of liver or kidney failure. Symptomatic treatment only.
2. Grade 2: All signs of intoxication, with a mild to moderate rise in transaminases (less than 500 units/L). Symptomatic treatment only.
3. Grade 3: Severe hepatic damage with a great increase in transaminases (> 500 units/L), plus an impaired plasma clotting function (e.g. a prolonged prothrombin time). Sub-divided into two groups based on bilirubin values:
   a. Grade 3a: Bilirubin rise is mild or absent.
   b. Grade 3b: Bilirubin rise is steep and continuous (> 5 mg/dL). These patients are at risk and should be transferred to a facility where liver transplant is possible.
4. Grade 4: Steep rise in transaminases, accompanied by a steep decline in clotting function, a steep rise in bilirubin, and the onset of kidney dysfunction. These patients have a poor prognosis, and many die in spite of intensive care.

Treatment

1. Stabilisation:
   a. Restoration of fluid and electrolyte balance: vigorous and immediate correction of dehydration and hypovolaemia.
   b. IV glucose: Monitor serum glucose levels hourly at the bedside. Give intravenous solutions of 10% dextrose by continuous infusion, and additional boluses of glucose as indicated by the tests.
   c. Monitor coagulation tests (prothrombin and fibrinogen) frequently. If hypoprothrombinaemia and hypofibrinogenaemia or clinical haemorrhage is present, give vitamin K (50 to 100 mg/day IV) and fresh frozen plasma.
   d. Correction of hypokalaemia (by potassium chloride diluted in solutions of dextrose 5%, or NaCl 0.9%), and of metabolic acidosis (by sodium bicarbonate solution 1.4%) should be guided by repeated laboratory analyses.
2. Decontamination:
   a. Activated charcoal in the usual manner. Multiple dose activated charcoal is recommended by some

investigators, and its use is supported by evidence of the enterohepatic circulation of the amatoxins.

b. Emesis and catharsis are usually unnecessary.

c. Toxicokinetic studies indicate that significant amounts of amatoxins are eliminated in urine, especially during the first 48 hours following ingestion. Forced diuresis (6 to 9 L/day) may therefore help if the patient is seen within 24 to 48 hours. However it has not been proven to be really effective.

d. Haemoperfusion is said to be beneficial if performed within 24 hours of ingestion. A major risk of haemoperfusion is thrombocytopenia with increased risk of bleeding.

e. Plasma exchange has been tried without conclusive evidence of benefit.

f. Charcoal plasmaperfusion (CPP) and continuous venovenous haemofiltration (CVVH) have been tried successfully in a few cases.

g. The current view is that because amatoxins are cleared rapidly from the plasma by the kidneys, extracorporeal elimination techniques are not likely to clear significant amounts of toxin. Haemodialysis or haemoperfusion may be indicated only if a patient with previous renal failure develops Amanita intoxication.

3. Antidotes:

a. Benzyl penicillin at a dose of 300,000 to 1,000,000 units per day is said to be effective in displacing amatoxin from plasma protein-binding sites allowing for increased renal excretion. Some investigators dispute this.

b. Thioctic acid (alpha-lipoic acid) was initially thought to be beneficial in the treatment of hepatic damage, but subsequent studies have been discouraging.

c. Silybinin (an extract of silymarin from the milk thistle *Silybum marianum*) is being investigated for its reported beneficial effects in countering hepatotoxicity, but there is no evidence so far of clear-cut advantage.

d. Cimetidine (a potent cytochrome P450 system inhibitor) may have hepatoprotective effects against alpha-amanitin, and is suggested by some investigators as a therapeutic intervention at a dose of 4 to 6 gm/day.

e. N-acetylcysteine (NAC) has been investigated in some patients with various degrees of amanita poisoning. NAC therapy was started early, during the gastrointestinal phase of illness, and the doses used were suggested by the treatment of paracetamol poisoning. Additional treatment also included the use of haemodiaperfusion, high dose penicillin, and supportive care. Many of the patients were said to have benefited.

f. The root of the Indian plant *Picrorhiza kurroa* contains an iridoid glycoside mixture that has been shown to be hepatoprotective in certain situations. Kutkin is a mixture of the iridoid glycosides picroside 1 and kutkoside. When mice were given lethal doses of lyophilised *Amanita phalloides*, the protective effect of kutkin was comparable to that seen with silibinin.

g. Aucubin is an iridoid glycoside obtained from the leaves of *Aucuba japonica*. It has been shown to be protective against Amanita intoxication when tested in dogs.

4. Treatment of acute liver failure:

a. General principles—
   – Hospital admission.
   – Invasive monitoring to detect complications before they become clinically evident.
   – Placement of CVP monitor, arterial line, urinary catheter, and nasogastric tube.
   – Endotracheal intubation if patient is comatose.
   – Continuous pulse oximetry.
   – Mechanical ventilation, if there is evidence of hypercapnia or hypoxia.
   – Prevention of hypoglycaemia by continuous infusion of 5 or 10% dextrose.
   – If hypoglycaemia develops, infuse 50% dextrose.
   – Treatment of hypotension with crystalloid or colloid solutions, or drugs such as dopamine, noradrenaline, etc.
   – Treatment of renal failure with dialysis or arteriovenous ultrafiltration.
   – Prevention of gastroduodenal bleeding with regular doses of H_2 antagonists or omeprazole.

b. Treatment of hepatic encephalopathy—
   – Lactulose
   – Dietary protein withdrawal.
   – Metronidazole or neomycin.

c. Treatment of cerebral oedema—
   – ICP monitoring.
   – Osmotic diuretics such as mannitol (1 gm/kg, as rapid IV infusion of 20% solution). This is repeated whenever ICP rises above 30 mmHg for 5 minutes or more. Plasma osmolarity must not exceed 320 mOsm.
   – Barbiturates such as IV thiopentone (3 to 5 mg/kg) infused slowly over 15 minutes until signs of raised ICP resolve, or a maximum of 500 mg has been administered.
   – Proper positioning of the patient, i.e. head upright (with the head no higher than 30° from the horizontal).
   – Corticosteroids may not help in relieving cerebral oedema due to acute liver failure.

d. Treatment of infection—Some investigators are of the opinion that prophylactic antibiotic therapy is vital to the treatment of acute liver failure. In any case, aggressive daily microbiologic surveillance is essential.

e. Treatment of coagulopathy—Fresh frozen plasma is necessary if there is evidence of serious or persistent bleeding.

f. Liver transplantation—Orthotopic liver transplantation (OLT) is indicated in the following circumstances:
   – Grade II encephalopathy and beyond.
   – Prolonged prothrombin time (greater than two times normal), despite administration of fresh-frozen plasma.
   – Serum bilirubin greater than 25 mg%.
   – Azotaemia.
   – Evidence of acidosis, hypoglycaemia, GI haemorrhage and hypofibrinogenaemia.

g. Molecular Absorbent Regenerating System (MARS)—MARS is a method of removing protein bound substances in patients with liver failure and hepatic encephalopathy. It employs an albumin-impregnated highly permeable dialyser with albumin-containing dialysate recycled in a closed loop with a charcoal cartridge, an anion exchange resin absorber, and a conventional haemodialysis membrane. It has been used in a small number of patients with fulminant hepatic failure secondary to cyclopeptide mushroom ingestion. MARS appears to be a promising bridging technique until the patient's liver can spontaneously recover, or until liver transplantation can occur. However, there are no clinical studies comparing the survival rates of patients treated with MARS and those receiving supportive care.

Preventive Principles

1. Never eat wild mushrooms obtained by foraging in the countryside unless the identity can be confirmed by an experienced mycologist. Distinguishing edible from toxic mushrooms is extremely difficult, regardless of what some foragers may claim.
2. Even edible mushrooms can become toxic if allowed to go stale. Therefore, only fresh specimens should be eaten.
3. Most toxic mushrooms resemble edible mushrooms at some stage of their growth. Even careful examination may not help in conclusively identifying a mushroom as non-toxic. Some tests such as Meixner test or Melzer's test may be of help (*page no 584*).
4. Susceptibility to the toxicity of a poisonous mushroom varies from individual to individual, some demonstrating evidence of severe poisoning, while others do not.
5. There are a number of myths associated with mushrooms bandied about as facts by self-professed "experts", which must be disregarded.
6. Some species of mushroom may be edible in a particular geographical area, while in another location they may be toxic ("Jekyll & Hyde mushrooms").
7. Some mushrooms are toxic only if they are consumed along with alcohol.
8. Mushrooms must always be well cooked, and never eaten raw.
9. As a general rule, it must be remembered that the following kinds of mushrooms are potentially toxic: pure white mushrooms, little brown mushrooms, large brown mushrooms, and red or pink-pored boletes.

Forensic Issues

■ Mushroom poisoning has always been rare in this counry, but there are indications of rising incidence with increasing popularity of Western and Chinese cuisine. Most cases result from consuming wild mushrooms obtained by rural folk and nomads foraging in woods and the countryside. Farm grown mushrooms are usually safe. More than 90% of the reported cases of mushroom poisoning are due to *A. phalloides*, and the Amanita genus alone accounts for almost all the fatalities.

■ In the West, hallucinogenic mushrooms ("magic mushrooms") such as those of Psilocybe genus have become part of the drug culture. There are even mail-order kits of the spores of such mushrooms that can be employed to cultivate "magic mushrooms" at home.

■ In conclusion, it must be emphasised that incidents of mushroom poisoning do not constitute a recent phenomenon, but have existed since ancient times.

■ Autopsy features in a mushroom-related death may reveal jaundice, hepatomegaly or hepatic necrosis (**Fig 33.5**), and haemorrhages on the surface of the heart (**Fig 33.6**).

■ Other Fungi

There are several other fungi which elaborate various kinds of toxins (*mycotoxins*) that produce mild to moderate illness in humans (**Table 33.7**). The most important of these mycotoxins include aflatoxins, ergot alkaloids,* and trichothecenes.
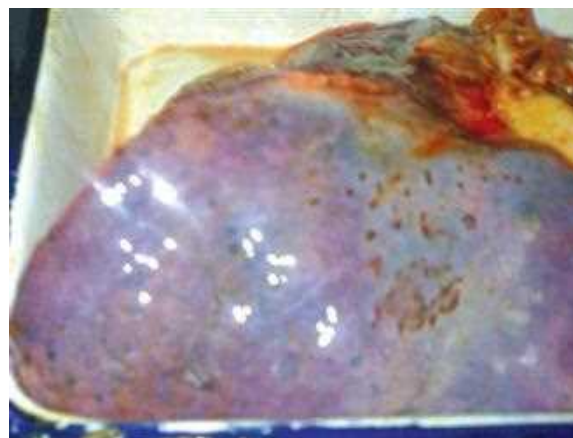
Fig 33.5: Liver in mushroom poisoning
(*Pic:* Dr PC Sarmah)
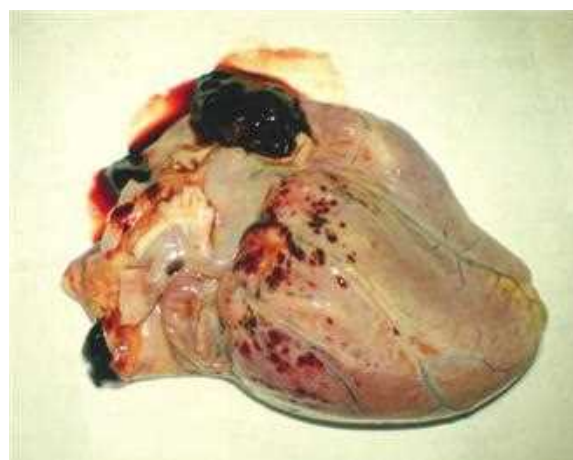
Fig 33.6: Epicardial haemorrhages—Mushroom poisoning
(*Pic:* Dr PC Sarmah)

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* See page no 278 for a detailed discussion of toxicity.

Table 33.7: Naturally Occurring Mycotoxins

Toxin	Fungus	Source
Aflatoxin	Aspergillus flavus, A. parasiticus	Peanuts, corn, rye, barley,cottonseed
Alternariol	Alternaria tenuis, A. dauci	Grain (weathered), sorghum
Citrinin	Penicillium citrinum, P. viridicatum	Wheat, barley, peanuts
Ergot alkaloids	Claviceps sps, Aspergillus sps, Penicilium sps	Ergot-infested rye, grain
Kojic acid	Aspergillus flavus, A. oryzae	Corn
Ochratoxin A	Aspergillus ochraceus, Penicillium viridicatum P. cyclopium	Wheat, rice, oats
Patulin	Aspergillus clavatus, Penicillium patulum	Apples, silage
Penicillic acid	Aspergillus clavatus, Penicillium puberutum	Corn, beans
PR toxin	Penicillium roqueforti	Silage
Sterigmatocystin	Aspergillus versicolor, A. flavus, A. ruber, Penicillium luteum	Peanuts, wheat, rice
Tenuazonic acid	Alternaria tenuis, A. tamarii, Sphaeropsidales sps Pyricularia oryzae, Phoma sorghina	Rice (diseased plants)
Trichothecenes	Fusarium roseum, F. tricinctum, F. nivale	Corn, barley
Zearalenone	Fusarium roseum, F. moniliforme, F. nivale, F. oxysporum	Wheat, corn, sorghum

Aflatoxins

Aflatoxins are naturally occurring bis-furanocoumarin compounds produced by the fungus *Aspergillus flavus* (and related species: *A. parasiticus*), and occur as contaminants of several nuts, grains, and seeds, such as peanuts, cottonseed, rye, barley, corn, etc. They are composed of highly substituted coumarin compounds that contain a fused dihydrofurofuran configuration. A dozen or more of these compounds have been identified: Aflatoxin, Aflatoxin B_1, Aflatoxin B_2, Aflatoxin B_{2a}, Aflatoxin B_3, Aflatoxin G_1, Aflatoxin G_2, Aflatoxin G_{2a}, Aflatoxin M_1, Aflatoxin M_2, Aflatoxin P, and Aflatoxin T_2. The aflatoxins are highly fluorescent. The "B" refers to blue, the "G" signifies green fluorescence, while "M" aflatoxins are fungal metabolites present in milk, and "T" compounds are found in tobacco. Most of them are associated with various types of liver damage. Aflatoxin B_1 is a potent hepatotoxin and carcinogen.

Consumption of dietary aflatoxins varies from 10 to 200 ng/kg/day, though the recommended maximum daily intake should be less than 50 ng/kg/day.

Aflatoxins are usually encountered in the context of chronic exposure, via food intake or secondary to the handling of foodstuffs. Aflatoxins have been incriminated in the pathogenesis of the following conditions:

- Hepatitis, fatty liver, cirrhosis
- Hepatocellular carcinoma
- Hepatic failure
- Reye's syndrome
- Kwashiorkor.

Aflatoxins accumulate in the presence of liver disease, and the association with hepatic cancer is confounded by the occurrence of hepatitis-B. The latter is not only a risk factor for liver cancer, but may also impair excretion of aflatoxins, causing further liver injury and DNA damage. Thus, it must be admitted that in these conditions it is not clear whether aflatoxin is a primary cause of the disease, is an incidental product which accumulates secondary to the disease process, or is a contributing cause in association with other factors.

Aflatoxins can be detected in body fluids and tissues by RIA and ELISA. HPLC with fluorescence detection has also been used to detect and quantify aflatoxins in blood or tissue. Elevation of serum alkaline phosphatase is a good indicator of aflatoxin toxicity. In one study, there was a significant correlation between urinary levels of aflatoxins and the presence of hepatitis B surface antigen in serum, with risk of an increased incidence of heptatocellular carcinoma.

Treatment is mostly supportive. In one experimental study involving ducklings which were given 5 micrograms of aflatoxin and 50 mg of turmeric for 14 days, increased weight gain was seen compared to controls. Almost complete reversal of fatty changes, granular degeneration, and necrosis was observed. Antioxidants such as vitamin A have been shown in vitro to inhibit aflatoxin-induced DNA adduct formation.

Trichothecenes

These mycotoxins are produced by *Fusarium roseum, F. moniliforme, F. nivale,* and *F. oxysporum*. Other fungal genera that produce similar toxins include Myrothecium, Trichoderma, Cephalosporium, Verticimonosporium, and Stachybotrys. Over 100 trichothecenes have been identified. The most frequent natural contaminants are deoxynivalenol, diacetoxyscirpenol, HT-toxin, nivalenol, and T-2 toxin.

Contamination of corn, sorghum, barley, or wheat with these toxins, is not uncommon leading to outbreaks of poisoning characterised by abdominal pain, throat irritation, vomiting, diarrhoea, vertigo, and headache. Trichothecene toxins are multi-toxins affecting many systems. Acute toxicity resembles the damage done by radiation, nitrogen mustard, or mitomycin C. Primary damage is to the GI tract, and lymphoid and haematopoietic systems.

Chronic toxicity has not been reported in humans. But inhalation exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*, in moisture affected office buildings, was associated with the development of cough, dyspnoea, wheezing, and chest tightness among employees. The mouldy vinyl wall covering was found to contain the trichothecene toxin, deoxynivalenol;

however it is unclear if it really was the culprit. Similarly, exposure to *Stachybotrys atra* and a Trichoderma species, has been associated with the development of pulmonary haemorrhage and haemosiderosis in infants. Contributing risk factors included tobacco smoke, and living in water-damaged homes which may enhance fungal growth. However, following investigations by the CDC, USA, it was decided that the evidence was not strong enough to prove an association between *Stachybotrys atra* found in water-damaged homes and the development of pulmonary haemosiderosis among infants.

1. Alimentary toxic aleukia, first identified in Siberia, has been associated, in humans, with the consumption of grain contaminated with T-2 toxin. The aleukia usually occurs in four stages:

    i. Hyperaemia of the mucosa, accompanied by weakness, fever, nausea, and vomiting. In more severe cases, acute oesophagitis, gastritis, and gastroenteritis may occur. Seizures and circulatory failure may occur in rare instances.

    ii. The second stage is characterised by the development of leukopenia, granulopenia, and progressive lymphocytosis.

    iii. In the third stage, severe haemorrhagic diathesis, and necrotic pharyngitis and laryngitis can occur, resulting in death in some instances, by total oclusion of the larynx. Severe bone marrow suppression may also occur.

    iv. The fourth stage is characterised by recovery, though exposed individuals are susceptible to secondary infections.

Visual disturbances and salivation have been reported in acute poisoning, as have conjunctivitis, rhinitis, pharyngitis, and epistaxis. Angina, tachycardia, and hypotension may occur. Conditions resembling septic shock, and poor perfusion of the GI system and other organs have also been reported.

Treatment involves administration of activated charcoal, which may be beneficial in decontamination of GI tract, and supportive measures for haemopoietic problems, GI damage, and skin damage.

Although prohibited by the 1972 Biological & Toxic Weapon Convention and the 1925 Geneva Protocol, these toxins were used both in Southeast Asia and Afghanistan.

PLANTS

There are a number of plants that can cause food poisoning on their own, or through inadvertent contamination/deliberate adulteration of other food products. They include cyanogenic plants, fava beans, cycads, sweet pea and prickly poppy.

■ Cyanogenic Plants

Examples

Cyanogenic plants may contain amygdalin or other glycosides, which on hydrolysis can release traces of cyanide. The following contain mostly glycosides other than amygdalin:

- Apple (*Malus species*)
- Bracken Fern (*Pteridium aquilinum*)
- Cassava (*Manihot species*)
- Clover (*Trifolium species*)
- Elderberry (*Sambucus species*)
- Hydrangea (*Hydrangea species*)
- Lima Beans (*Phaseolus species*)
- Linseed (*Linum usitatissimum, Linum neomexicanum*)
- Pear (*Pyrus species*)
- Rush (*Juncus species*)
- Sedges (*Carex species*).

Cassava

The botanical name of cassava is *Manihot esculenta*. Cassava root is said to be the second largest carbohydrate crop in the world, and constitutes a staple diet for millions of people. It is popular in several Indian states, especially in the deep South.

The edible part of manihot is the root, which is commonly referred to as *cassava*. If this is properly processed before consumption, it causes no harm. However, insufficiently processed cassava liberates cyanide in the gut from the ingested cyanogenic glycoside linamarin. This is normally converted to the less toxic thiocyanate by the enzyme rhodanese. The substrate for this reaction is sulfur originating from proteins in the diet. When dietary protein intake is low, signs of toxicity begin to manifest. The following conditions may occur:

1. *Tropical ataxic neuropathy (TAN)*: More common in males. Main feature is posterior column sensory loss with ataxic gait. Optic atrophy and perceptive deafness have also been reported. Optic neuropathy results in decreased visual acuity, abnormal pupil size or an afferent pupillary defect, pigment disturbance and clumping beneath the macula, and loss of foveal reflex, associated with pallor and/or atrophy of a sector of the disc opposite the macula. When visual field defects are present the predominant defects are central and centro-cecal scotomas. Colour testing may reveal generalised dyschromatopsia, red-green and/or blue-yellow colour blindness.

2. *Epidemic spastic paraparesis (ESP)*: More common in females and children. Main feature is spastic paralysis of lower limbs. One variety of spastic paresis is called Konzo. It is characterised by bilateral, symmetrical involvement of the pyramidal tracts affecting the lower extremities resulting in spastic gait, paraplegia, extensor plantar responses, spastic bladder, constipation and impotence. Sometimes there is visual impairment. Epidemics of spastic paraparesis have been described in many areas of the world where cassava with high cyanogenic glycosides content is consumed as a significant proportion of the diet. Pancreatitis and endemic goitre have also been reported in patients from cassava-consuming areas.

Administration of cassava or Laetrile® in animal studies have resulted in limb defects, open eye defects, microcephaly, and foetal growth retardation. Sodium thiosulfate administration protected the foetus from such teratogenic effects.

Acute toxicity is rare. However, there is one report of deaths of three patients after a single meal of cassava. Cyanide levels in the blood averaged 1.12 mg/L; urinary levels averaged 0.54 mg/L.

Treatment involves symptomatic and supportive measures.

Amygdalin-containing Plants

The common sources of naturally occurring amygdalin are mentioned below. Amygdalin is the cyanogenic diglucoside D-mandelonitrile-beta-D-gentiobioside, and is not toxic until it is metabolised by the enzyme emulsin which is present in the seeds of these plants. Synthetic amygdalin (laetrile) has been tried without significant success, in the treatment of cancer. Overdose of amygdalin can produce manifestations of cyanide poisoning.

1. Almond (*Prunus dulcis var amara*)
2. Apricot (*Prunus armeniaca*)
3. Cherry Laurel (*Prunus caroliniana & Prunus laurceroasus*)
4. Choke Cherry (*Prunus virginiana & Prunus melanocarpa*)
5. Peach (*Prunus persica*)
6. Plum (*Prunus domestica*)
7. Wild Cherry (*Prunus serotina*).

Crushed seeds of some of the mentioned varieties are marketed as health foods. They are also marketed and sold as cancer remedies or vitamin supplements. Some examples include Laetrile®, Bee Seventeen®, and Aprikern.

One of the richest sources of amygdalin is the bitter almond and it has been established that 40 to 60 seeds, yielding 70 mg of hydrocyanic acid would result in severe toxicity or death.

Acute toxicity results in dyspnoea, weakness, dizziness, sweating, vomiting, disorientation, convulsions, paralysis, cyanosis, coma, and cardiovascular collapse. Cherry red blood colouration is rarely seen, but has been reported. In most cases, symptoms are mild.

Mild to moderate toxicity requires only decontamination and supportive measures. Severe poisoning must be treated on the same lines as for cyanide poisoning (*page no 367*). The usual antidotes (nitrites and thiosulfate) should be administered in patients who are clinically symptomatic (unstable vital signs, acidosis, impaired consciousness, seizures, or coma). The goal of nitrite therapy has been to achieve a methaemoglobin level of 20–30%. Administer 100% humidified supplemental oxygen with assisted ventilation as required. Hyperbaric oxygen has been recommended as being more efficacious. Crystalloids and vasopressors can be given for hypotension. Administer sodium bicarbonate if required.

■ Sweet Pea

Other Common Names

Chickling pea, Indian pea, Grass pea, Guaya.

Botanical Name

Lathyrus sativus

Physical Appearance

This is a plant belonging to family Leguminosae, which grows well in Madhya Pradesh, Bihar, Uttar Pradesh, West Bengal, and Punjab (**Fig 33.7**). The seeds (called *kesari dal* in Hindi) (**Fig 33.8**) are used as a cheap substitute for costlier lentils by the rural folk in these states.

Toxic Principle

Beta-N-oxalyl-amino-L-alanine (BOAA) or beta-N-oxalyl-alpha-beta-diaminopropionic-acid (beta-odap).

Clinical Features

Chronic intake of kesari dal leads to the development of **lathyrism**, characterised by gradually progressing bilateral spastic paraparesis. There may be prodromal manifestations such as cramps, prickling sensation, and nocturnal calf pain. Tendon reflexes are usually exaggerated, and plantar response is extensor in type. Total spastic paraplegia may result in course of time.

Treatment

Exclusion of kesari dal from diet and symptomatic measures.

Fig 33.7: *Lathyrus sativus*

Fig 33.8: Kesari dal

■ Prickly Poppy

Other Common Names

Yellow poppy, Mexican poppy.

Botanical Name

Argemone mexicana

Physical Appearance

This is a robust, prickly, annual or perennial herb belonging to family Papaveraceae, which grows up to 4 feet in height, bearing thistle-like leaves and yellowish flowers (**Fig 33.9**) (**Fig 33.10**). The spreading branches are prickly and contain a yellow sap. The leaves are pinnately cut, while the flowers are solitary, showy, and yellowish. The fruit is a prickly capsule, and bears many small seeds which are tiny and brownish black. They resemble the dark variety of mustard (*Brassica nigra*) (**Fig 33.11**).*

Uses

There is no legitimate use for argemone seeds or the oil extracted from them. In India, mustard oil and other vegetable oils are often adulterated deliberately with argemone oil. Sometimes the dark variety of mustard seeds is adulterated with argemone seeds.

Toxic Part

Seed and expressed oil are quite toxic. Leaves are also toxic (to a lesser degree).

Toxic Principles

- Sanguinarine
- Dihydrosanguinarine.
  They are both physiologically active benzophenanthridine alkaloids. In addition, other alkaloids of lesser importance are present, such as protopine, berberine, chelerythrine, isoquinoline, and coptisine.

  Berberine and protopine are found throughout the entire plant, while sanguinarine and dihydrosanguinarine are found in the seeds.

Fig 33.9: *Argemone mexicana*

Fig 33.10: *Argemone mexicana* (close-up)
(*Pic:* Dr Shashidhar C Mestri)

Fig 33.11: Mustard and argemone seeds

Mode of Action

- Liver, heart, kidneys, and lungs are the target organs of argemone alkaloids, and it is postulated that membrane destruction is the probable mode of acion. The exact mechanism is not well understood.
- The chief effects of argemone are on the blood vessels which become abnormally permeable, resulting in the leakage of protein-rich plasma components into the extravascular compartment leading to hypovolaemia and reduced plasma osmotic pressure. Decrease in renal blood flow sets into motion a compensatory mechanism through the activation of renin-angiotensin-aldosterone system, and retention of sodium and water. Conservation of fluid and salt compensates for the expanded vascular capacity and increased permeability in mild cases.
- However in severe cases, these mechanisms become inadequate because fluid and salt conserved by kidneys are poorly held in the vascular compartment due to low

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* The light variety (*Brassica compestris*) is yellowish, and is quite distinctive.

plasma osmotic pressure. As a result, a state of relative hypovolaemia exists, which provides a constant stimulus for renal conservation of salt and water, which in turn causes marked anasarca.

■ Exudation of protein-rich fluid from pulmonary capillaries results in pulmonary oedema which gets compounded by right-sided cardiac failure. As a result, congestive hepatomegaly develops. Similar mechanisms underlie effusions in the pleural, pericardial, and peritoneal cavities.

■ Mechanisms of toxicity of argemone alkaloids are summarised in **Table 33.8**.

Clinical Features

Chronic consumption of food prepared with adulterated mustard or vegetable oils results in a condition called **epidemic dropsy**. Onset is usually insidious with slowly progressing, pitting pedal oedema, and limb pain. Diarrhoea, abdominal pain, and fever are often present in the early stages. Other features comprise the following:

■ *Skin*—Superficial patchy erythema, telangiectasias, sarcoids (purplish blotches over lower limbs), pigmentation, and hair loss.
■ *Eye*—Glaucoma, superficial retinal haemorrhages, venous dilatation, central serous retinopathy, and disc oedema.
■ *CVS*—Palpitations, tachycardia, hypotension, congestive cardiac failure.
■ *RS*—Dyspnoea, pulmonary oedema.
■ *Hepatorenal*—Hepatomegaly, renal dysfunction.
■ *Haematological*—Normocytic, hypochromic anaemia, with raised ESR.

Differential Diagnosis

■ Hypoproteinaemic states
■ Nephrotic syndrome
■ Beri Beri
■ Filariasis
■ Hypothyroidism.

Diagnosis

1. Diagnosis of epidemic dropsy:
   a. Anaemia.
   b. Raised plasma pyruvate level.

Table 33.8: Argemone Alkaloids: Mechanisms of Toxicity

• Inhibition of Na+, K+-ATPase
• Destruction of cytochrome P450
• Depletion of endogenous hepatic glutathione
• Enhanced glucogenolysis leading to depletion of glycogen levels in liver
• Inhibition of oxidation of pyruvate, lactate, and succinate
• Binding at multiple sites on DNA, decreasing capacity for DNA repair
• Blocking of hepatic enzymes
• Inhibition of RNA and DNA polymerases
• Phototoxicity

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c. *Chest X-ray:* cardiomegaly, pulmonary oedema.
d. *ECG:* ST, T wave changes, atrial/ventricular extrasystoles.
e. Hypoalbuminaemia, raised alpha-2 globulin, reversal of albumin-globulin ratio.
f. Blood urea and creatinine may be raised.

2. Identification of adulterated mustard:
   a. Adulteration of light yellow mustard seeds with argemone seeds can be easily made out by visual inspection.
   b. Adulteration of dark mustard seeds can be detected by placing the seeds in normal saline. Mustard seeds will sink, while argemone seeds will float.

3. Identification of adulterated mustard oil:
   a. *Nitric acid test:* 5 ml oil is shaken with an equal volume of HNO_3. On standing, the acid layer turns yellow, orange, or crimson, depending on the amount of argemone oil. This test has a high incidence of false positives, and therefore a positive result must always be confirmed by other tests.
   b. *Ferric chloride test:* 2 ml oil is mixed with 2 ml concentrate HCL, and heated in a water bath at 35° C for 2 minutes. 8 ml ethanol is then added, and heating continued for 1 more minute. Finally, 2 ml ferric chloride is added, and the mixture heated for a further 10 minutes. Positive result is indicated by an orange-red precipitate.
   d. *Paper chromatography:* It is the most sensitive method, and can detect down to 0.0001% adulteration with argemone oil.
   e. *Thin Layer Chromatography:* Researchers at the National Institute of Nutrition, Hyderabad, have developed a highly sensitive quantitative assay of sanguinarine by thin layer chromatography.

Treatment

1. Withdrawal of contaminated oil from the diet.
2. Bed rest, leg elevation, protein-rich diet.
3. Supplements of calcium, antioxidants (vitamins C & E), and B vitamins.
4. Corticosteroids.
5. Diuretics.
6. Management of cardiac failure: bed rest, salt restriction, digitalis, and diuretics.
7. Recalcitrant glaucoma may require surgical intervention.
8. Most patients recover with treatment in about 3 months. Mortality is around 5%. Post-recovery, pedal oedema may take up to 5–6 months to resolve completely.

Forensic Issues

■ The first case of epidemic dropsy was reported in 1877 from Calcutta (Kolkata). Since then, numerous cases usually in the form of periodic epidemics, have occurred not only in India, but also in some other countries such as South Africa, Myanmar, Mauritius, Madagascar, and the Fiji islands. It is perhaps significant that in most of these countries, a sizeable chunk of the population comprises people of Indian origin.

- Epidemic dropsy is in many ways a uniquely Indian syndrome, and more so a North Indian syndrome. The outbreaks have mostly been confined to West Bengal, Bihar, Madhya Pradesh, Orissa, Uttar Pradesh, Gujarat, Delhi, and Maharashtra. The most recent epidemic occurred in 1998 in Delhi, claiming 65 lives out of a total number of 2552 cases reported from all across the state.
- Almost all the outbreaks have been due to consumption of mustard oil or other vegetable oils contaminated with argemone oil (except the South African epidemic which occurred due to adulteration of wheat flour with argemone seeds). South Indian states have been largely spared because mustard oil is not very popular here.

FISH

Poisoning resulting from fish and other marine creatures is referred to as **ichthyism**,* which may result either from envenomation by stinging or biting, or from ingestion of toxic or decomposing fish. Only the latter will be discussed here. Poisonous fish are subdivided into:

- *Ichthyosarcotoxic fish*, which contain a toxin within their flesh,
- *Ichthyohaemotoxic fish*, which have poisonous blood, and
- *Ichthyo-otoxic fish*, which contain a toxin mainly in their gonads.

Based on the nature of toxin, there are 5 types of seafood poisoning—scombroid, ciguatera, tetrodotoxic, paralytic shellfish, neurotoxic shellfish, and amnesic shellfish poisoning.

■ Scombroid Poisoning (Histamine Fish Poisoning)

Source

Tuna, bonito, escolar, skipjack, mackerel, needlefish, saurie, kingfish, wahoo, albacore, amberjack, blue fish, dolphin, mahi mahi, marlin, anchovy, herring, swordfish, Australian ocean salmon, Bombay duck (a kind of dried fish) (**Fig 33.12**).

Fig 33.12: Bombay Duck (*Harpadon nehereus*)

Toxin

Scombroid poisoning is a form of ichthyosarcotoxicosis (the toxin is contained within the flesh of the fish). Poisoning occurs from consumption of improperly preserved fish in which the endogenous histidine has been broken down by bacteria into high levels of histamine and saurine. Unfortunately, tainted fish may look and smell normal. Rarely, there is a "sharp" or "peppery" taste. To add insult to injury, even if such contaminated fish is subsequently cooked well or smoked, the toxins are not destroyed.

The CDC (USA) has reported that scombroid fish poisoning has been most often associated with the consumption of tuna, mahi-mahi, and bluefish. Immediately after being caught the fish is generally non-toxic, but toxicity increases as the bacterial count rises. Scombrotoxin formation can also occur if the fish is improperly refrigerated.

Incubation Period

Few minutes to few hours: Symptoms may develop as early as 5 to 10 minutes after eating the fish, or be delayed up to 1 to 2 hours. Although most cases are mild and self-limiting, resolving in 3 to 36 hours, potentially life-threatening effects have occurred.

Clinical Features

1. Manifestations are mostly histamine-mediated, and comprise erythema of face, urticaria, pruritis, dermal flushing, diaphoresis, burning sensation of the mouth, dizziness, throbbing headache, vomiting, diarrhoea, and abdominal cramps.
2. Palpitations are frequently described.
3. Diarrhoea and vomiting are also common findings after scombroid poisoning.
4. Tachycardia/bradycardia and hypotension have been described.
5. Conjunctival irritation, and angioneurotic facial oedema may develop.
6. In severe cases there may be bronchospasm and respiratory distress.
   Symptoms usually subside on their own in 6 to 12 hours.

Diagnosis

1. Diagnosis of scombrotoxicosis:
   a. Clinical picture
   b. Histamine levels of serum and urine will be greatly elevated.
   c. Detection and quantitation of histamine in implicated fish flesh is more important. Normal fish has less than 1 mg of histamine per 100 gm of flesh. Illness is usually associated with more than 100 mg of histamine per 100 gm of flesh (though illness can result from much less concentrations).

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* Not the same as Ichthyosis, which is a skin condition with dryness and scaling.

2. Identification of contaminated fish:
   a. Usually such fish appear normal and may not either smell or taste bad.
   b. Occasionally, the skin may have a "honeycombed" appearance, or the taste may turn pungent or peppery.
   c. Diagnosis can be confirmed by measuring the histamine level in the fish which may exceed 100 mg%. The maximum acceptable level has been fixed at 50%. The recommended method of estimating histamine level in fish is capillary electrophoretic assay.

Treatment

1. Outlined in **Table 33.9**.
2. Activated charcoal may be useful in the early stages.
3. The role of steroids in management of scombroid poisoning is controversial.
4. Cimetidine has been successful in patients refractory to conventional antihistamines. It has also been used successfully as first-line treatment.
5. To prevent scombroid poisoning, the fish needs to be continuously frozen, or refrigerated at less than 32°F from the time the fish is caught until it is prepared for consumption.

■ Ciguatera Poisoning

Source

Ciguatera poisoning is the commonest form of seafood poisoning, accounting for more than 50% of the cases. Barracuda, sea bass, parrot fish, red snapper, grouper, amberjack, kingfish, sturgeon, and many other large-sized fish are the main culprits. The following are associated most commonly with outbreaks of poisoning: grouper (**Fig 33.13**), parrot fish, surgeon fish, emperor fish, and red snapper (**Fig 33.14**).

Large fish concentrate the main toxin (ciguatoxin) due to their food habits. The toxin is present in dinoflagellates* (**Fig 33.15**), which are marine protozoa that constitute the main nutritional source for small herbivorous fish. The latter are in turn consumed by larger carnivorous fish, and the ciguatoxin

Fig 33.13: Grouper
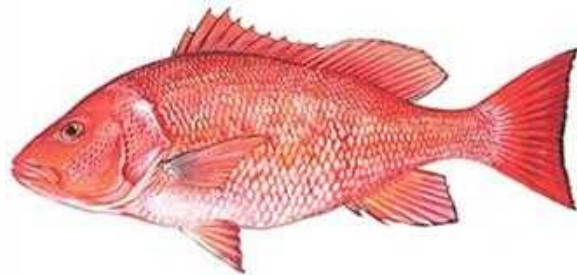
Fig 33.14: Red Snapper

Fig 33.15: Dinoflagellate (*magnified*)

Table 33.9: Treatment of Scombroid Poisoning

Degree of severity	Clinical features	Treatment
Mild	Rash, flushing, tachycardia	Antihistamines
Moderate	Rash, persistent flushing, tachycardia, headache, and GI symptoms	• Basic life support • Parenteral antihistamines (H1 and H2 antagonists) • Activated charcoal
Severe	Any of the above, and/or bronchospasm and/or hypotension and/or airway compromise and/or angioedema	• Basic life support • Oxygen • IV fluids • Adrenaline • Parenteral antihistamines (H1 and H2) • Gastric lavage • Activated charcoal • Nebulised bronchodilators

* Dinoflagellates are microscopic, single-celled, photosynthetic, often bioluminescent algae with two flagellae.

therefore becomes increasingly concentrated (in the flesh, fat, and viscera) of larger and larger fish. These fish tend to swim close to coral reefs on the ocean's bottom in subtropical and tropical latitudes. Ciguatera poisoning is said to be endemic in the Caribbean, South Pacific, and Australia. A few cases of poisoning have been reported from some areas of the Indian Ocean also, as well as from East Asia, and South Asia.

Toxin

Outlined in **Table 33.10**, along with mode of action. The toxins are mainly contained in the muscle, skin and mucosa of the fish, with the highest concentration present in the viscera (liver, intestines, gonads).

Incubation Period

About 2 to 6 hours, (range 2 to 24 hours).

Clinical Features

1. Sudden onset of sweating, abdominal cramps, nausea, vomiting, profuse watery diarrhoea, dysuria, tingling and numbness of lips, tongue, and throat, metallic taste, paraesthesias, dysaesthesias, chills, headache, myalgia, arthralgia, tremor, ataxia, vertigo, blurred vision, and convulsions. Profound weakness may occur. Patients may be unable to rise or move. Paralysis of limbs and facial muscles may develop in severe cases. Death may result.
2. Pruritus is frequently reported, and may be mild to severe. It may persist for weeks after an exposure.
3. Paraesthesias are the hallmark of ciguatera poisoning, and may also persist for weeks. A characteristic feature is reversal of temperature discrimination, i.e. cold substances feel hot. But this is not a true sensory switch; it can be described as the sensation one gets when gripping something very cold (e.g. ice), and the resultant sensation of a "burning" feeling. These sensations are usually localised to palms, soles, lips and mouth. This phenomenon is said to be due to abnormal bursts of discharges occurring specifically in the peripheral C-polymodal nociceptor fibres (cutaneous afferent unmyelinated fibres). These fibres are not spontaneously active at normal temperature in undamaged skin, but have a heat threshold above 40°C, and cold threshold below 23°C. However, contact with heat generally does not produce the reverse effect.
4. Other sensory effects include a metallic taste, and a "carbonated" sensation when food or drink is consumed. Teeth may appear loose and painful.

5. Bradycardia and orthostatic hypotension have also been reported. Transient T wave inversion has been described. Extrasystoles may occur, probably because of noradrenergic myocardial stimulation.
6. Respiratory depression, dyspnoea, and bronchospasm may also occur.
7. Neurological manifestations tend to linger for a long time even in patients who have fully recovered.
8. Ocular effects include blurred vision, photophobia, visual loss (usually temporary), mydriasis and lacrimation.
9. Painful ejaculation and dyspareunia in the unaffected partner have been reported occasionally.
10. Symptoms of ciguatera poisoning are exacerbated by ethanol and stress (physical and/or emotional).
11. Foetal distress has occurred after ingestion of ciguatera-contaminated fish by the pregnant mother. Premature labour and spontaneous abortion have been reported. Infants exposed to ciguatoxin in late pregnancy have been noted to have abnormal prenatal movement and temporary cranial nerve deficits. Several cases of ciguatera poisoning in breastfeeding infants whose mothers were poisoned have also been reported.

Diagnosis

- ELISA test for ciguatoxin.
- HPLC.
- A rapid test (dipstick immunobead assay) is being developed to test suspect fish for the presence of toxin.

Differential Diagnosis

- Other marine poisonings (scombroid poisoning, neurotoxic shellfish poisoning)
- Organophosphate poisoning
- Monosodium glutamate (in susceptible individuals)
- Botulism
- Other bacterial food poisoning.

Treatment

1. Decontamination (activated charcoal, catharsis) may be of benefit if the patient is seen within 2 hours of ingestion.
2. The primary treatment is the use of antihistamines; cold showers can also be helpful. Cyproheptadine may be of benefit.
3. Myalgias usually respond to NSAIDs or other analgesics.
4. Monitor fluid and electrolytes. Monitor vital signs and ECG.

Table 33.10: Ciguatera Toxins

Toxin	Chemical name	Molecular weight	Mode of action
Ciguatoxin	Polyether	1111.7	Enhances intracellular entry of sodium Increases intracellular calcium
Maitotoxin	Polyether	3402	Mobilises intracellular calcium
Scaritoxin	Polyether	-------	--------
Okadaic acid	Polyether	787.01	Sodium ionophore
Polytoxin	Polyether	2781	Induces tonic muscular contraction

5. Administraton of IV fluids, electrolytes.

6. IV mannitol is said to be useful in the management of neurological and muscular manifestations. The recommended dose is 0.5 to 1 gm/kg of 20% solution, administered over 30 to 45 minutes. Hypotension may occur, and must be anticipated whenever mannitol is given. Some investigators are of the opinion that mannitol is not effective in the management of neurological manifestations of ciguatera poisoning.

7. Atropine has been of some use in treating bradycardia and hypotension.

8. Dopamine, plasma expanders, and calcium gluconate may be useful for shock.

9. Chronic neurologic symptoms may resolve with tocainide, mexiletine, or amitryptiline.

10. Avoidance of alcohol and exercise (which can exacerbate symptoms), is recommended.

■ Tetrodotoxic Poisoning

Source

- Puffer fish: globe fish, balloon fish, blowfish, toad fish. In Japan, a variety of puffer fish called "fugu" (**Fig 33.16**) is considered a delicacy, but special licensing is required to prepare this extremely toxic fish.
- Newts: taricha, notophthalmus, triturus, cynops.
- Salamanders.
- Blue-ringed octopus (*Hapalochlaena maculosa*) (**Fig 33.17**): of Australia and Japan is the only known species in which tetrodotoxin has been found in extracts of venom glands, in contrast to being found in the skin, muscle, liver, ovaries, and eggs of other species.
- Snails: In a study of several outbreaks of tetrodotoxin-associated snail poisoning in Zhoushan city, China, the following snail species were identified as culprits: *Zeuxis samiplicutus, Zeuxis siguinjorensis, Zeuxis variciterus,* and *Z. succinctus*. In all the cases, the snails were steamed, boiled, or fried. The incubation period ranged from 5 minutes to 11 hours, and the time from a patient's ingestion of snails to full recovery ranged from 30 minutes to 48 hours.
- Horseshoe crab eggs.

Toxin

Tetrodotoxin (TTX) is a potent, heat-stable, water soluble, non-protein aminoperhydroquanizole neurotoxin concentrated mainly in the skin, liver, ovary, and intestine of the fish. The highest concentration is found in the ovaries, and hence the female is most poisonous, especially if eaten during the spawning season.

Mode of Action

Tetrodotoxin affects myelinated nerve fibres throughout the entire length of the axon by lowering the conduction of sodium currents at nodes of Ranvier. It is a selective and potent sodium channel blocker. TTX blocks the action potential without any effect on resting membrane potential, or the resting membrane

Fig 33.16: Fugu

Fig 33.17: Blue-ringed Octopus

resistance. It blocks nerve and muscle conduction. Its action is thought to interfere with the increase in sodium permeability associated with nerve excitation, with changing potassium permeability.

Incubation Period

Onset is usually within 4 to 6 hours, but may be delayed. Oral paraesthesia is usually the initial symptom of puffer fish poisoning. Death may occur within the first 6 to 24 hours. Prognosis is good if the patient survives the first 24 hours.

Clinical Features

- Poisoning is caused by ingestion of the flesh, viscera, ovaries, or skin containing tetrodotoxin (TTX). The highest concentration is in the viscera. Body musculature is usually free of poison.
- Main features of poisoning include headache, sweating, dysaesthesias, and paraesthesias of lips, tongue, mouth, face, fingers, and toes. Circumoral tingling may include the tongue and inner surface of the mouth, and generally

occurs within 10 to 45 minutes of ingestion.
- Later, the following are seen: salivation, dysphagia, dysarthria, nausea, vomiting, abdominal pain, ataxia, weakness, fasciculations, and ascending paralysis in 4 to 24 hours.
- Blurred vision, aphonia, and dysphagia may be seen as muscle paralysis progresses. Miosis is an early effect of TTX poisoning, but later there is mydriasis.
- Hypotension, bradycardia, and fixed and dilated pupils indicate severe poisoning. Mortality may approach 50%. Death is usually due to respiratory depression and respiratory muscle paralysis.
- Some cases of seizures have been reported in TTX poisonings. If at all they occur, seizures generally manifest only in the course of severe TTX poisonings
- A rare "locked-in" syndrome has been described with tetrodotoxic poisoning, in which the patient appears completely flaccid, but remains conscious.

Diagnosis

- Mouse bioassay: Laboratory determination of tetrodotoxin (TTX) is not commonly available. Potency of TTX must be done by bioassay; identification may be done with thin layer chromatography.
- Fluorescent spectrometry.
- Use of electrophoresis, HPLC, LC/MS, etc., have also been reported by various investigators. A relatively new immunoassay method, using a highly specific monoclonal antibody (MAb) and immunoaffinity column chromatography, has recently been developed for the isolation and identification of TTX from urine samples of poisoned patients. This method is performed in combination with fluorometric HPLC.

Treatment

Because of the differences in susceptibility, and unpredictability of an individual's course, at least 24 hours of observation is recommended in every patient.
1. Decontamination: Activated charcoal may be useful.
2. IV edrophonium (10 mg) or IM neostigmine (0.5 mg) may be effective in restoring motor strength.
3. Artificial ventilation should be implemented if necessary. Assisted ventilation may be necessary for 4 to 6 hours, and in some cases up to 12 hours.
4. Haemodialysis may be effective in the treatment of tetrodotoxin poisoning, because the toxin has low molecular weight, is water soluble, and is not significantly bound to protein.

■ Shellfish Poisoning

Source

- Shellfish (especially oysters, clams, mussels, and scallops) contaminated by dinoflagellates. Other sources include univalve mollusks, starfish, limpets, sand crabs, whelks, turban shells, top shells, xanthid crabs and various fish.

Types

Paralytic Shellfish Poisoning

There are actually several paralytic shellfish toxins (PSP toxins). PSP toxins are a group of 21 structurally related neurotoxins, and are among the most common and deadly phycotoxins. The main toxin is saxitoxin which is produced by the following dinoflagellates (unicellular algae): Pyrodinium, Gymnodinium and Alexandrium.

Because dinoflagellates can occur in tropical and moderate climate zones, shellfish can accumulate these toxins worldwide. While the primary areas of poisoning have been the east and west coasts of the United States and Canada, the area around Japan, and the area from Southern Norway to Spain, of late, reports of paralytic shellfish poisoning (PSP) have been coming in from regions of the world where it had not been previously reported. In tropical regions, *Pyrodinium bahamense var. compressa* has been a source of PSP. These toxins affect the central nervous system and can produce muscular nerve block and paralysis. Paralytic shellfish poisoning is often associated with "red tide" blooms, but may occur with or without the red tide (**Fig 33.18**). These are natural phenomena triggered by a series of events, which can include human pollution. Over 300 phytoplankton species can produce red tides*, but only 60 to 70 species are actually harmful. Swimming in the "red tide" may produce pruritus and skin irritation.

The incubation period is usually 30 minutes (occasionally can extend to 3 hours). There are 3 grades of severity:
- *Mild:* Tingling and numbness of the tongue and lips, that soon spreads to the face, neck, arms, fingers and toes; headache and nausea. Diarrhoea may also occur.
- *Moderate:* Limb weakness, ataxia, incoherent speech, difficulty breathing, hypersalivation, and sweating. Giddiness, rash, fever, tachycardia, hypertension, and dyspnoea can occur. Temporary blindness has been reported.
- *Severe:* Muscle paralysis, "choking" sensation, severe respiratory difficulty, and respiratory failure.
- *Other effects:*

Fig 33.18: Red tide

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*Red tides are not always red, but may be brown, yellow, or green, depending upon the pigmentation of the causative organisms, and their depth and concentration.

– Nystagmus, temporary blindness, iridoplegia, jaw and facial muscle incoordination, loss of gag reflex, immobilisation of the tongue, and difficulty speaking may occur after exposure.

– Tachycardia, T wave changes, and occasionally hypertension or hypotension may occur following exposure.

– Most patients remain conscious and alert, and reflexes are frequently normal throughout progression of the illness. Muscle weakness may last for weeks. Patients who survive the first 12–24 hours generally have a good prognosis and recover without sequelae. Exposure to PSP toxins offer no immunity; in fact subsequent attacks can be more severe.

Diagnosis is by mouse bioassay or enzyme immunoassay. HPLC, liquid chromatography-mass spectrometry (LC-MS), immunoaffinity chromatography (IAC), and capillary electrophoresis have also been developed to evaluate seafood and environmental samples. Saxitoxin, the main toxin found in PSP, is heat and acid-stable, and does not alter the odour or taste of food. Cooking or freezing are not effective in destroying the toxin.

Treatment

- In symptomatic patients, the following should be monitored closely: haemodynamic status, acid-base, serum electrolytes, BUN, creatinine, calcium, magnesium, phosphorous, urine output, CPK, ECG, pulse oximetry, and cardiac rhythm.
- Decontamination: Activated charcoal.
- Since saxitoxin is excreted mainly via urine, diuresis can enhance renal excretion
- Supportive measures: Most patients recover with supportive care alone. Monitor for respiratory depression. Patients with significant neurotoxicity may need endotracheal intubation and mechanical ventilation.
- Because saxitoxin acts by blocking sodium channels, sodium bicarbonate may be effective in reversing ventricular conduction delays and arrhythmias, though this has not been proved: administer 1 to 2 mEq/kg sodium bicarbonate as a bolus, and repeat as necessary.

Neurotoxic Shellfish Poisoning

Neurotoxic shellfish poisoning results from eating shellfish (cockles, oysters, whelks, and clams) that have consumed the dinoflagellates containing brevetoxins. The main dinoflagellate involved is *Ptychodiscus brevis* (formerly called *Gymnodinium breve*). "Red tides" are caused by several non-protein, lipid-soluble, neurotoxins and haemolysins such as brevetoxins found in these dinoflagellates. Besides causing major fish kills, these toxins produce various ill effects in man and other shore animals.

Brevetoxins are heat stable, and are not destroyed by boiling or cooking. Unlike saxitoxin, they produce a stimulatory rather than a depressant nervous effect, and open the sodium channels in nerves, while saxitoxin closes them.

The incubation period is usually about 3 hours (range: 15 minutes to 18 hours). Main features include nausea, vomiting, diarrhoea, abdominal pain, rectal burning, paraesthesias of the face, throat, fingers, and toes, burning sensation of the mucous membranes, reversal of hot and cold temperature sensation, myalgia, vertigo, ataxia, headache, dysphagia, bradycardia, decreased reflexes, and mydriasis. Paralysis does not occur. Seizures are seen occasionally. Coughing, sneezing, and difficulty in breathing has occurred. Severe poisoning can cause respiratory arrest.

Diagnosis is by mouse bioassay, ELISA, or RIA.

Treatment involves decontamination, administration of beta$_2$ adrenergic agonists and corticosteroids. In animal studies, 0.5 mg/kg of atropine reversed the bronchoconstrictive and bradycardic effects of brevetoxins.

Amnestic Shellfish Poisoning

The main toxin involved is domoic acid, produced by the diatom *Nitzschia pungens*. Incubation period is usually about 5 hours (range: 15 minutes to 38 hours). The main features include nausea, vomiting, diarrhoea, abdominal pain, amnesia, hemiparesis, grimacing, purposeless chewing, ophthalmoplegia, convulsions, and coma. There may be unstable blood pressure with cardiac arrhythmias. In some patients, memory loss may persist for a long time. Diagnosis is by mouse bioassay or HPLC. Treatment involves supportive and symptomatic measures.

CHEMICALS

Chemical contaminants of food include heavy metals, pesticides, and food additives. The last mentioned will be discussed in this section, while the other two entities are discussed elsewhere.

Food additives may be **antioxidants, flavouring agents, colouring agents, sweetening agents, thickening agents,** or **preservatives** (**Table 33.11**).

■ Monosodium Glutamate (MSG)

Synonyms

Accent, Ajinomoto, Chinese Seasoning, Glutacyl, Vetsin, Zest.

Uses

- Flavouring agent in foods, especially Chinese food, sausages, canned soup, etc.* MSG is generally sold as a fine, white crystalline substance, similar in appearance to salt or sugar. It has a sweetish saline taste.
- MSG has been used to treat patients with hyperammonaemia in conditions such as hepatic encephalopathy.

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* Many Western scientists believe that MSG stimulates taste receptors in the tongue, while the Chinese and Japanese believe the chemical has a unique fifth basic taste, beyond salty, sweet, sour, and bitter, that they call "umami", derived from the Japanese word meaning "deliciousness".

Table 33.11: Food Additives	
Substance	Acceptable Daily Intake (mg/kg body weight)
I. Antioxidants	
Butylated hydroxyanisole	0 – 0.5
II. Flavouring agents	
trans-Anethole	0 – 1.2
d- & l-Carvone	0 – 1.0
III. Flour-treatment agent	
Potassium bromate	0 – 60
IV. Colouring agents	
Erythrosine	0 – 0.05
V. Sweetening agents	
Maltitol	Not specified
Trichlorogalactosucrose	0 – 3.5
VI. Thickening agent	
Karaya gum	Not specified
VII. Other food additives	
Glycerol ester	
Mineral oil	Not specified for
Paraffin wax	any of these agents
Petroleum jelly	
Na, K, and Ca salts of oleic acid	

Source

- Glutamate, a major building block of proteins, is released during breakdown of a protein molecule, and occurs naturally in many foods (meat, milk, mushrooms, cheese, tomatoes, etc.). Monosodium glutamate (MSG) is the monosodium salt of L-glutamic acid. It is produced by the following processes:
  - Fermentation of carbohydrate sources such as sugar beet molasses.
  - Hydrolysis of vegetable proteins.
  - Waste from beet-sugar molasses by acid hydrolysis.
  - By action of *Micrococcus glutamicus* upon a carbohydrate, and subsequent partial neutralisation.

Clinical Features

Ingestion of large quantities of MSG is said to cause the **Chinese restaurant syndrome (CRS)**, though doubts have been expressed of late on the role of MSG in the aetiology of the syndrome.

Features include burning or tingling sensation and numbness of face, trunk, and upper limbs, weakness, dizziness, syncope, flushing, lacrimation, sweating, chest pain, headache, nausea, gastric distress, and rarely bronchospasm and angioedema. In young children, a convulsive attack may occur (*shudder attack*). Symptoms resolve on their own, and rarely last for more than half to one hour.

Treatment

Treatment is symptomatic and supportive. Gastrointestinal decontamination is generally not indicated after an acute ingestion. Toxicity is very unlikely.

Preventive Measures

The syndrome can generally be prevented by prior ingestion of "safe foods" such as a glass of milk or a slice of cottage cheese. The following preventive measures have been suggested for MSG-sensitive individuals:

- When shopping for food items, read labels and avoid foods which contain MSG—canned foods (except vegetables and fruits), soya sauce, dried foods, and processed meats.
- Avoid catered food (including airline meals).
- If it is planned to dine out at a hotel
  - Phone ahead and request food without MSG.
  - Eat a snack before you go: cottage cheese or a glass of milk.
  - Avoid alcohol.
  - Do not eat *hors d'oeuvres* or soup.
  - Avoid casserole dishes, Chinese foods, and marinated meats.
  - Avoid salad dressings.
  - Eat only freshly prepared, broiled, or *sauteed* meats or fish (without sauces or seasoning).
  - Drink a cup of coffee along with the meal, or soon thereafter.

Of late, there are doubts being raised about the actual role of MSG in human illness. The USFDA has studied adverse reaction reports and other data concerning MSG's safety for several years, and believes that while some sensitive people can have mild and transitory reactions when they consume significant amounts of MSG, it is still a safe food ingredient for the general population. In 1995, a report from the Federation of American Societies for Experimental Biology (FASEB) affirmed the FDA's belief that MSG and related substances are safe food ingredients for most people when eaten at moderate levels. This report identified short-term reactions known as 'MSG Symptom Complex' in two groups of people. Individuals in the first group suffer a reaction after eating large doses (3 gm or more per meal) of MSG, particularly on an empty stomach. In the second group, individuals with severe and poorly controlled asthma may, in addition, experience difficulty in breathing.

Although some studies have reported MSG-induced asthma attacks in asthmatic patients, several other studies could not confirm their results.

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Section

11

Substance Abuse

Substances of Dependence and Abuse

Use of psychoactive substances to experience pleasurable effects is not a recent phenomenon, but has been indulged in by human kind for hundreds, even thousands of years. Terminology in the field of substance abuse has changed frequently leading to a great deal of confusion. Therefore, it is necessary to begin this section by defining currently used terms, and to clarify the differences between them. The nomenclature and diagnostic schemes mentioned here-in are based on the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the 10th edition of International Classification of Diseases and Related Health Problems (ICD-10).

DEFINITIONS
■ Substance Dependence

Substance dependence arises out of a maladaptive pattern of substance use, leading to a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated intake. It includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.

■ Polysubstance Dependence

This term is reserved for behaviour during a 12-month period in which the person was repeatedly using at least 3 groups of substances (not including caffeine and nicotine), but no single substance predominated. Further, during this period, the dependence criteria were met for substances as a group, but not for any specific substance in isolation.

It must be mentioned here that sometimes certain non-dependence producing substances are abused by way of prolonged, unnecessary, or excessive intake, which cannot be covered by the term "substance dependence". For instance, drugs such as analgesics, laxatives, antidepressants, antacids, vitamins, steroids, or hormones, and specific herbal or folk remedies.

■ Substance Abuse

Substance abuse arises out of a maladaptive pattern of substance use, manifested by recurrent and significant adverse consequences related to the repeated intake of the substance. These problems must occur recurrently during the same 12-month period. The criteria for substance abuse do not include tolerance, withdrawal, or a pattern of compulsive use, and instead include only the harmful consequences of repeated use.

The DSM-IV criteria for substance abuse are listed in **Table 34.1**.

It is to be noted that the term "abuse" when used by itself, merely refers to the use of an illicit drug, or the use of a licit drug outside of legitimate medical practice.

■ Substance Intoxication

According to DSM-IV, this term refers to unwanted physiological or psychological effects that cause maladaptive behaviour. ICD-10 specifies that intoxication must produce disturbances in the level of consciousness, cognition, perception, affect, or behaviour that are clinically significant.

■ Substance Induced Disorders

Use of certain psychoactive substances can induce syndromes (formerly called "organic mental disorders") which include the following: substance intoxication (*vide supra*), substance withdrawal, intoxication delirium, withdrawal delirium, dementia, amnestic disorders, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunctions, and sleep disorders.

Table 34.1: DSM-IV Diagnostic Criteria for Substance Abuse

Substance abuse refers to a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems

Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

■ Substance Withdrawal

As per DSM-IV, "substance withdrawal" should be restricted to major symptoms resulting from the cessation of substance abuse, accompanied by a maladaptive behaviour change. There should be clinically significant distress or impairment in social, occupational, or other important areas of functioning. DSM-IV does not recognise withdrawal from caffeine, cannabis, or phencyclidine. ICD-10 recognises cannabinoid withdrawal state, as well as a withdrawal state from other stimulants, including caffeine.

■ Physical Dependence

The term "physical" or "physiological" dependence is defined as an alteration in neural systems which is manifested by tolerance and the appearance of withdrawal phenomena when a chronically administered drug is discontinued or displaced from its receptor.

The 1980 ADAMHA-WHO* working group recommended substituting the term "neuroadaptation" for physical dependence.

■ Addiction

The term "addiction" denotes a chronic disorder characterised by compulsive use of drugs (*craving*) resulting in physical, psychological, and social harm, and continued use despite evidence of that harm (*denial*).

CLASSIFICATION

1. **Ethanol**
2. **Tobacco**
3. **Tranquillisers and Sedatives**
   Barbiturates, benzodiazepines, chloral hydrate, chlorme-thiazole, ethchlorvynol, glutethimide, hexapropymate, meprobamate, methyprylon, methaqualone, zolpidem, zopiclone
4. **Opiates and Opioids**
5. **Cocaine**
6. **Cannabis**
7. **Amphetamines and "Designer Drugs"**
8. **Hallucinogens**
   Lysergic acid diethylamide (LSD), phencyclidine, psilo-cybine, bufotenine, mescaline, ketamine, diethyltrypt-amine (DMT)
9. **Inhalants**
   Fluorinated hydrocarbons (freons), ethers, ketones, aromatic and aliphatic hydrocarbons
10. **Miscellaneous Substances**
    Caffeine, datura seeds, analgesics, anabolic steroids, cough syrups, laxatives

Several of these compounds have been discussed in detail elsewhere, and the reader is advised to consult the *Index* for locating them. The remaining will be discussed in this section.

Globally, of the various substances abused, alcohol and tobacco head the list, followed by sedatives and tranquillisers, cannabis, opiates, and cocaine. Amphetamines and hallucinogens are less popular, though newer recreational drugs ("designer drugs") are increasingly being abused, especially by the youth. One American study found a life-time prevalence of alcoholism of 13.5%, and a life-time prevalence of other drug abuse of 6.1%. The WHO estimates that one third of the world population (15 years and above) abuses tobacco in some form or other. Currently, tobacco abuse is said to be responsible for 3.5 million deaths worldwide every year, and if the trend continues, the figure is expected to rise to 10 million deaths per year by 2020.

The most commonly abused drugs (apart from alcohol and tobacco) in India appear to be cannabis, opiates, and sedatives and tranquillisers. There are also indications of significant abuse of cocaine, hallucinogens, and "designer drugs" among the upper classes of society.

While it is a fact that many individuals experiment with drugs especially in their youth, not all become dependant on them. In fact, it is only a small proportion of susceptible individuals who go on to become addicts. **Table 34.2** lists some of the factors which predispose to dependence. Medical professionals should be familiar with these risk factors which can help them to identify potential abusers and take pre-emptive action whenever possible. It is also important to be able to recognise signs and symptoms of drug abuse as well as identify clues in the form of behavioural changes which point to surreptitious abuse (**Table 34.3**).

■ Tobacco

Sources

1. *Nicotiana attenuata* (Wild tobacco)
2. *Nicotiana glauca* (Tree tobacco)
3. *Nicotiana longiflora* (Cultivated ornamental)
4. *Nicotiana rustica*
5. *Nicotiana tabacum* (Commercial tobacco)
6. *Nicotiana trigonophylla* (Desert tobacco).

Table 34.2: Risk Factors for Substance Abuse

- Maternal or twin alcoholism
- Paternal alcohol or other drug use
- Family history of alcoholism or antisocial behaviour
- Parents with poor parenting skills or who neglect or batter their children
- Drug abuse by sibling or best friend
- Peer drug abuse
- School failure
- Rebelliousness and alienation
- Low self-esteem
- Early antisocial behaviour or delinquency
- Negative character traits
- Psychopathology (especially depression)
- Low religiosity
- Early experimentation with alcohol or other drugs
- Early sexual activity

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* Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) of the United States, and the World Health Organisation (WHO).

Table 34.3: Pointers to Surreptitious Drug Abuse
• Sudden or gradual change of personality
• Unpredictable fluctuations of mood
• Progressively diminishing interest in studies or work
• Prolonged absences from study or work
• Periodic disappearance into inaccessible places (bathroom, locked private room)
• Constant need for money
• Inexplicable lethargy/agitation
• Apathy towards family members/frequent arguments with family members
• Loss of appetite, emaciation
• Loss of interest in personal appearance, hygiene, dress
• Tattooing of areas normally chosen for IV drug abuse (bend of elbow, back of wrist)
• Pupillary constriction/dilatation
• Hallucinatory experiences
• Insomnia/hypersomnia

Tobacco is usually prepared from cured leaves of *Nicotiana tabacum* (**Fig 34.1**) belonging to family Solanaceae. Turkish tobacco is prepared from the leaves of *Nicotiana rustica*, and is more potent. Indian tobacco refers to *Lobelia inflata*.

Active Principles

Nicotiana tabacum and *N.rustica* contain the following alkaloids:
- Nicotine
- Nornicotine
- Anabasine
- Anabatine.

Fig 34.1: *Nicotiana tabacum*

Nicotiana tabacum is an annual herb, shrub, or small tree; from 0.90 to 1.50 metres tall according to the variety. The leaves are elliptical or oblanceolate; flowers are clustered at the end of the branches and have a cylindrical calyx, being greenish or reddish in the upper part (**Fig 34.2**). Fruit has different forms with globular seeds. Every part of the plant (except the seed) contains nicotine, the maximum concentration of which is in the leaves. *Lobelia inflata* contains lobeline. It is sometimes used as a nicotine substitute. Nicotine is a colourless to pale yellow, very hygroscopic, oily liquid with an unpleasant pungent odour, and sharp, burning, persistent taste. It gradually becomes brown on exposure to air or light.

Uses

Nicotine is a stimulant of the central nervous system, and is abused widely all over the world in the form of inhalation (cigarette, cigar, pipe, beedi), nasal insufflation (snuff), or chewing.

Nicotine is also used as an insecticide.

Mode of Action

By far the commonest source of nicotine poisoning (acute or chronic) results from smoking tobacco in the form of cigarettes. When a cigarette is lit and inhaled, the smoker is exposed to both gaseous and particulate matter. Nicotine and tar are part of the particulate phase of cigarette smoke (**Table 34.4**). The usual nicotine content of a "regular" cigarette varies between 13 and 20 mg, while certain European and Turkish cigarettes can contain higher amounts. "Low nicotine" cigarettes contain 7 to 10 mg of the alkaloid. Cigars contain 15 to 40 mg of nicotine. When a cigarette is smoked, more than half the nicotine escapes in the sidestream smoke, while a large fraction remains in the butt and filter, and it is only 0.5 to 2 mg (average 1 mg) of nicotine that finally is delivered to the smoker. Smoke from non-filtered cigarettes contains slightly higher amounts of nicotine. This amount depends not only on the nicotine content of the cigarette, but

Fig 34.2: *Nicotiana tabacum*—flowers

Table 34.4: Major Toxic Agents in Cigarette Smoke

Particulate Matter		Gas Phase	
Constituent	Harmful Effect	Constituent	Harmful Effect
Benzo[a]pyrene	TI	Dimethylnitrosamine	C
5- Methylchrysene	TI	Ethylmethylnitrosamine	C
Benzo[j]fluoranthene	TI	Diethylnitrosamine	C
Benz[a]anthracene	TI	Nitrosopyrrolidine	C
Other polynuclear aromatic hydrocarbons	TI	Other nitrosamines	C
Dibenz[a,j]acridine	TI	Hydrazine	C
Dibenz[a,h]acridine	TI	Vinyl chloride	C
Dibenzo[c,g]carbazole	TI	Urethane	TI
Pyrene	CoC	Formaldehyde	CT, CoC
Fluranthene	CoC	Hydrogen cyanide	CT, T
Benzo[g,h,i]perylene	CoC	Acrolein	CT
Other polynuclear aromatic hydrocarbons	CoC	Acetaldehyde	CT
Naphthalenes	CoC	Nitrogen oxides	T
1-Methylindoles	CoC	Ammonia	T
9-Methylcarbazoles	CoC	Pyridine	T
Other neutral compounds	CoC	Carbon monoxide	T
Catechol	CoC		
3- and 4-Methyl catechols	CoC		
Other catechols	CoC		
N-Nitrosonornicotine	C		
Other nonvolatile nitrosamines	C		
b-Naphthylamine	BC		
Other aromatic amines	BC		
Polonium 210	C		
Nickel compounds	C		
Cadmium compounds	C		
Arsenic	C		
Nicotine	T		
Minor tobacco alkaloids	T		
Phenol	CT		
Cresols	CT		

C = Carcinogen, BC = Bladder Carcinogen, TI = Tumour Initiator, CoC = Co-Carcinogen, CT = Cilia Toxic Agent, T = Toxic Agent

also on the individual's smoking technique (rate of puffing, puff volume, depth of inhalation, and size of residual butt).

In India, "bidis" (**Fig 34.3**) are very popular, especially among the poorer sections of society, since they are much cheaper than cigarettes. Bidis are small, brown, hand-rolled cigarettes consisting of tobacco wrapped in a *tendu* or *temburni* leaf (*Diospyros melanoxylon*) (**Fig 34.4**). They are more harmful than cigarettes and produce higher levels of carbon monoxide, nicotine, and tar. Also, because of low combustibility of tendu leaf, bidi smokers tend to inhale more often and more deeply, breathing in greater quantities of tar and other toxins than cigarette smokers.

After cigarettes, the next common source of nicotine toxicity results from smokeless tobacco which is of two kinds – snuff and chewing tobacco. There has been a resurgence of popularity in the use of snuff in recent times, paralleling the decline in cigarette smoking in most parts of the world. Because smoking is not involved, people generally believe that snuff is more socially acceptable and less harmful. This is however not true. Snuff is usually available as finely cut tobacco powder which is packaged dry or moist. It contains approximately 14 mg of nicotine per gram of tobacco.

Chewing tobacco is generally packaged as "twists" (leaf tobacco twisted into rope-like portions) (**Fig 34.5**) or "plugs" (shredded tobacco pressed into cakes) (**Fig 34.6**). These are chewed or simply placed between the cheek and gums. The nicotine dissolves in the saliva and is absorbed through the mucous membrane of the mouth, as well as through the intestinal mucosa after the saliva is swallowed. A portion of the tobacco that is placed in the mouth each time for chewing is referred to as a "quid". A typical bite-size quid contains 1.5 to 2.5 grams of tobacco. Ultimately, the tobacco chewer gets approximately the same dose of nicotine (or slightly more) than the tobacco snuffer. The smokeless tobacco user who takes 8 to 10 quids per day gets a nicotine equivalent of 30 to 40 cigarettes per day.

Fig 34.3: Bidis

Fig 34.4: Stacks of tendu leaves

Fig 34.5: Twist of chewing tobacco

Fig 34.6: Plugs of chewing tobacco

Though nicotine insecticides have been banned in most parts of the world since 1950, they are still available in some formulations. Several cases of severe nicotine poisoning due to exposure (dermal and oral) to these pesticides have been reported, some of which have ended in death.

The nicotine content of all these sources has been summarised in **Table 34.5**.

Mode of Action

1. Nicotine binds stereo-specifically to select acetylcholine receptors (nicotine receptors). These receptors are present throughout the body, particularly in the autonomic ganglia, adrenal medulla, central nervous system, spinal cord, neuromuscular junctions, and chemoreceptors of carotid and aortic bodies. In the CNS, the highest concentration of nicotine receptors is found in the limbic system, midbrain, and brainstem.

2. At moderate doses, nicotine stimulates the reticular activating system producing an alerting pattern on the EEG, with resultant favourable effects on memory and attention.

Table 34.5: Sources of Nicotine

Source	Nicotine content
Cigarette	13–19 mg
Cigarette butt	5–7 mg
Cigar	15–40 mg
Snuff Dry Wet	 12–15 mg/gm 5–30 mg/gm
Chewing tobacco	2–8 mg/gm
Tobacco leaf	1–6% nicotine per leaf
Insecticides	Up to 40%
Nicorette gum	2–4 mg/piece
Transdermal nicotine patch	Varies from 8 mg to 114 mg (delivered nicotine/day varying from 7 mg to 21 mg)

But higher doses cause tremor and convulsions due to a CNS disinhibition mechanism.

3. Nicotine stimulation of vagal centres in the medulla induces nausea and vomiting, while the gastro-oesophagal reflux is provoked due to a lowering of sphincter pressure and increased acid secretion. Larger doses cause diarrhoea due to both central and parasympathetic excitation.

4. By acting directly on nicotine receptors in endocrine glands, as well as by stimulating neurohumoral pathways in the CNS, nicotine enhances release of catecholamines, vasopressin or antidiuretic hormone, growth hormone, ACTH, cortisol, prolactin, serotonin, and beta endorphins. Nicotine also increases amylase, trypsin and chymotrypsin activity.

5. Nicotine suppresses appetite while increasing basal energy expenditure, resulting in weight loss.

6. Habitual use of nicotine by women results in decreased oestrogen levels (due to enhanced hydroxylation of oestradiol), thereby increasing the risk of osteoporosis.

The physiological effects of nicotine are summarised in **Table 34.6**.

Toxicokinetics

Mentioned in **Table 34.7**.

Drug Interactions

Smoking alters the metabolism of some commonly used drugs. Metabolism is enhanced in the case of benzodiazepines, caffeine, H_2 antagonists, imipramine, nicotine, opiates, phenacetin, propranolol, and theophylline. As a result of such interference, the therapeutic efficacy of opiates, benzodiazepines, beta-adrenergic antagonists, nifedipine, H_2 antagonists, and antacids is reduced. This alteration of drug metabolism is due to induction of microsomal enzyme systems, not by nicotine itself, but most probably by polynuclear aromatic hydrocarbons. Drugs using the P450 system are not affected by smoking.

While smoking has no effect on the clearance of alcohol, concomitant use exaggerates the cardiovascular response of nicotine, as a result of which the heart rate and blood pressure go up. This is thought to be catecholamine mediated, and it has been suggested that smokers may have increased tendency to suffer from arrhythmias and sudden death during alcohol use.

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. *Early Effects (15min to 1 hour)—*
      – GIT: Nausea, salivation, vomiting, abdominal pain.
      – CVS: Tachycardia, hypertension.
      – RS: Tachypnoea, bronchorrhoea.
      – CNS: Agitation, anxiety, sweating, headache, blurred vision, confusion, vertigo, tremor, ataxia, muscle fasciculations, convulsions. Pupils are at first constricted, but may dilate later. A primary position upbeat nystagmus is seen following cigarette smoking, chewing of nicotine gum, and ingestion of *nicotiana glauca* leaves, and is the direct result of nicotine.
   b. *Delayed Effects (after1 hour)—*
      – GIT: Diarrhoea.
      – CVS: Bradycardia, arrhythmias, hypotension, shock.
      – RS: Hypoventilation, apnoea.
      – CNS: Lethargy, weakness, hyporeflexia, hypotonia, paralysis, coma.

Death may occur, especially in the case of ingestion of cigarettes (inadvertently) by children, or exposure to insecticidal nicotine. Nicotine ingestion causes hypertension and tachycardia, followed by hypotension and bradycardia, headache, CNS stimulation followed by depression, tremors and seizures, hallucinations, confusion, hyperpnoea, mucous membrane irritation, and vomiting. Ingestion of large amount can cause weakness, paralysis, coma, and rarely respiratory failure resulting in death.

Occupational dermal exposure to wet, uncured tobacco may produce "green tobacco sickness" among workers, characterised by nausea, vomiting, headache, vertigo, pallor, and sweating. Headache occurs frequently, especially in harvesters. Contact dermatitis can occur. Harvesters who are smokers are resistant to most of these effects.

2. **Chronic Poisoning (*Addiction*):**

Nicotine dependence is the most widely prevalent and deadly of all substance dependencies. DSM-IV defines two nicotine-related disorders: nicotine dependence and nicotine withdrawal. Nicotine abuse is not included in DSM-IV, but a related term "harmful use" is mentioned in ICD-10, which means that continued use causes physical problems. The dependence-producing effects of nicotine appear to be modulated by dopamine which is increased in smokers. Nicotine also increases noradrenaline, adrenaline, and serotonin levels. Like

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Table 34.6: Physiological Effects of Nicotine

- CNS stimulation, with improvement of attention and memory
- Relief of anxiety
- Reduced hunger and body weight
- Increased metabolic rate
- Increased levels of catecholamines, vasopressin, growth hormone, ACTH, cortisol, prolactin and betaendorphin
- Lipolysis, increased free fatty acids
- Increased heart rate, cardiac output and blood pressure
- Cutaneous and coronary vasoconstriction
- Relaxation of skeletal muscles

Table 34.7: Toxicokinetics of Nicotine

Absorption	Oral mucosa, lungs, intestinal mucosa, skin
Volume of distribution	Approximately 1 L/kg
Protein binding	5 to 20%
Metabolism	80 to 90% metabolized in the liver, remaining in kidney and lung. Main metabolites are cotinine and nicotine-1´-N-oxide
Half-life	1 to 4 hours Half-life of cotinine is 19 hours
Elimination	2 to 35% excreted unchanged in urine

most substance use, nicotine use begins because of social reinforcement. With repeated exposure, many youngsters find the physiological effects of nicotine well suited to help them with the difficult periods during adolescence. In addition, physical dependence begins so that cessation of nicotine use becomes uncomfortable. Children more likely to start smoking are those who have a high need to conform, display low academic performance, rebelliousness, depressive symptoms, and have poor self-esteem. Peer and family influences also play a major role.

   a. *Health consequences of tobacco use:*
      – Lung cancer.
      – Non-pulmonary cancers: Mouth, larynx, oesophagus, stomach, liver, pancreas, bladder, uterine cervix, breast, brain.
      – Respiratory diseases: Emphysema, bronchitis, asthma, pneumonia.
      – Cardiovascular diseases: Coronary heart disease, hypertension, arterial thrombosis, stroke.
      – Obstetric and neonatal conditions: Abortion, abruptio placenta, placenta praevia, preterm labour, pre-eclampsia, growth retardation, congenital malformations, sudden infant death syndrome, foetal or neonatal death.
      – Other conditions: Peptic ulcer, osteoporosis, Alzheimer's disease.
   b. *Nicotine withdrawal:* Manifestations of nicotine withdrawal can occur within 4 to 8 hours of the last cigarette. In fact most chronic smokers experience some withdrawal symptoms on waking up each morning. Manifestations include changes in mood, insomnia, difficulty concentrating, restlessness, decreased heart rate (average decline is 8 beats per minute), and weight gain (average is 2 to 3 kg). Craving is common, and increased coughing, poor performance on vigilance tasks, etc., can occur. Clinical manifestations of nicotine withdrawal are summarised in **Table 34.8**. Nicotine withdrawal is worst in cigarette smokers, intermediate in users of smokeless tobacco, and mild in users of nicotine replacement products. The syndrome peaks in 1 to 3 days and lasts for 3 to 4 weeks. In some, it may last for several months, especially features such as craving and weight gain.

Table 34.8: Nicotine Withdrawal

Subjective manifestations	Objective features
Anxiety/hostility	Decreased heart rate
Confusion	Lowered blood pressure
Craving	Weight gain
Drowsiness	Decreased arousal (EEG)
Headache	Impaired psychomotor performance
	Impaired memory
Impaired concentration	Decreased plasma catecholamines
Restlessness	
Insomnia	
Blurred vision	
Constipation	
GI upset	
Hunger, increased appetite	

Usual Fatal Dose

Nicotine is highly toxic; 2 to 5 mg can cause nausea, and 40 to 60 mg can cause death. However, survival has occurred with ingestions of 1 to 4 grams.

Diagnosis

1. Acute poisoning can be confirmed by estimating plasma nicotine level; but the short half-life of nicotine necessitates early withdrawal of blood. High pressure liquid chromatography is generally utilised to assay nicotine levels. Plasma level greater than 40 to 50 ng/ml indicates serious toxicity.
2. Polymorphonuclear leucocytosis and glycosuria are often encountered in nicotine overdose.
3. Passive tobacco smoke exposure is usually determined by estimating cotinine levels in plasma, urine, or saliva. Urine cotinine is also used as an index to nicotine exposure in tobacco workers (especially harvesters).

Treatment

1. Acute Poisoning

Mild overdose (with spontaneous vomiting) requires only observation for 4 to 6 hours, after which the patient can be discharged. Serious overdose must be treated as follows:

   a. Decontamination by stomach wash. Emesis is contraindicated. Activated charcoal is effective and must be administered in the usual manner. In cases of dermal exposure (e.g. wet tobacco leaves, spillage of nicotine liquid), clothing should be removed, and skin thoroughly washed.
   b Since nicotine is weakly alkaline, excretion can be enhanced by acidification of urine. But it is not recommended by most investigators since it can aggravate the condition of a convulsing patient in whom there is rhabdomyolysis.
   c. Animal experiments indicate that drugs such as pempidine and mecamylamine may have antidotal effects against nicotine. Hexamethonium (a ganglionic blocking agent) has prevented nicotine-induced convulsions in animals.
   d. Symptomatic and supportive measures—
      – Benzodiazepines for convulsions.
      – Atropine for bradycardia.
      – IV fluids and vasopressors (dopamine or noradrenaline) for hypotension.
      – Respiratory compromise is managed by oxygen, intubation, and positive pressure ventilation.

2. Chronic Poisoning (Addiction)

Nicotine withdrawal must be treated by a combination of therapies including psychosocial, psychopharmacological, and nicotine replacement. A psychiatrist's help is crucial to effective management of withdrawal and prevention of relapse.

   a. Nicotine replacement therapy—
      The rationale behind nicotine replacement is to prevent or relieve nicotine withdrawal symptoms while stopping smoking behaviour by replacing it with another behaviour. Pharmacological nicotine is of various forms and dosages.

– Nicotine gum (Polacrilex): The first nicotine preparation that was made available for use is the nicotine gum (available in the West as *Nicorette* 2 mg and 4 mg strengths). It is designed to be chewed slowly and intermittently. Approximately 50 to 70% of the nicotine is absorbed through the buccal mucosa, while additional amounts are absorbed through swallowed saliva. Peak plasma concentration is reached 15 to 30 minutes after starting to chew the gum, as compared with 1 to 2 minutes after initiating smoking. Chewing the gum too rapidly and vigorously can raise nicotine concentrations to uncomfortable levels producing adverse effects (especially if the patient is also smoking at the same time). If the gum is inadvertently swallowed, there is no cause for undue concern since the nicotine is released and absorbed slowly producing only low blood concentrations. The actual efficacy of nicotine gum, and the dose and duration of therapy are highly variable.

– Nicotine transdermal patch: The disadvantages of nicotine gum (frequent administrations, unsightly chewing, bad taste, nausea, and dyspepsia) are mostly avoided by transdermal nicotine, which is available as nicotine-releasing adhesive patches of varying sizes and delivery rates. The nicotine patch is generally available in 3 sizes, 30 cm^2, 20 cm^2, and 10 cm^2, which deliver 21 mg, 14 mg, and 7 mg of nicotine respectively, over 16 or 24 hours. The nicotine is released either directly through the skin or through a membrane system in contact with the skin. Side effects are mild and include dose-related sleep disturbances, dyspepsias, myalgias, and increased cough.

– Nicotine spray: In 1996, a nicotine nasal spray was released in the United States as an alternative to gum or patch. It is available as a metered dose inhaler containing 100 mg of nicotine at 10 mg/ml, designed to deliver 200 equivalent puffs each releasing 0.5 mg of nicotine. Absorption occurs through the nasal mucosa which may be affected to some extent in the presence of rhinitis. The recommended dose is 2 sprays (one in each nostril) every ½ or 1 hour, subject to a maximum of 40 doses (80 puffs) in any 24-hour period. While initial reports have been favourable, use of the spray is relatively unpleasant and unsightly. Subsequently, a nicotine metered-dose oral inhaler was tested in the USA, designed to mimic smoking by providing airway stimulation as well as nicotine replacement. Absorption occurs through the buccal and pharyngeal mucosa, and respiratory tree (on slow deep inhalation).

b. Other therapies—

– Clonidine: Clonidine is an alpha$_2$-adrenergic agonist that has been found useful in the treatment of alcohol and opiate withdrawal. Subsequent studies on its utility in nicotine withdrawal have shown that it could be effective in promoting abstinence from cigarettes also. Although the exact mechanism is not clear, it is postulated that clonidine is effective for most withdrawal syndromes because it inhibits noradrenergic neurons in the locus ceruleus.* The usual dose recommended is 150 to 200 mcg/day for 1 month. However, clonidine use is associated with a high incidence of adverse effects including tachycardia, hypotension, headache, vertigo, sedation, and visual disturbances. These are minimised by substituting oral therapy with transdermal patches in much the same way as nicotine patches. There are recent reports of very satisfactory results by combining both transdermal nicotine and clonidine, since the former reduces behavioural withdrawal symptoms, while the latter reduces craving.

– Antidepressants: Since it is well known that smokers who stop smoking have a high incidence of depression, antidepressants such as doxepin and sertraline have been tried with varying degrees of success in combating nicotine withdrawal. The efficacy of these drugs requires validation by further studies.

– Nicotine agonists and antagonists: These drugs have the potential to block the effect of nicotine, i.e. removing its reinforcing effect on smoking behaviour. Lobeline, the first of these drugs to be studied in this regard, is a partial agonist that binds weakly and competitively to nicotine receptor sites. However, it has not been found to be very effective in practice, though it continues to be sold abroad as a smoking cessation aid under the brand name *CigArrest*. Mecamylamine is a nicotine receptor antagonist that is said to reduce the craving for cigarettes if administered for more than 6 weeks, though it can produce unpleasant side effects including abdominal cramps, constipation, and urinary retention. Adverse effects can be minimised by combining mecamylamine with nicotine skin patch.

Forensic Issues

■ Tobacco abuse has been described as being the most widespread cause of death and disability worldwide than any single disease entity. Apart from the health problems brought on by smoking and other forms of tobacco use on the user himself (detailed in earlier sections of this chapter), environmental tobacco smoke inhalation can have deleterious effects on other individuals as well. Environmental tobacco smoke (ETS) consists of mainstream smoke, sidestream smoke, and vapour-phase components that diffuse through cigarette paper into the environment. ETS exposure occurs frequently in the home, in the workplace, and in other public areas where smoking is allowed. The

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* Adrenergic hyperactivity in the locus ceruleus (a dark-coloured depression in the floor of 4th ventricle of brain) is common in many withdrawal syndromes.

Government of India is making attempts at prohibiting tobacco smoking in public, and a few states have begun to implement this with varying success rates. Passive smoking can cause the following health problems:

❖ Adults: Lung cancer, small airway damage, worsening of angina, hypertension.

❖ Children: Bronchitis, pneumonia, worsening of asthma, middle ear effusions, decreased height, sudden infant death syndrome.

❖ Neonates: Prematurity, low birth weight, neonatal death. The term "foetal tobacco syndrome" is applied in those cases where the mother had smoked 5 or more cigarettes per day throughout the pregnancy, had no evidence of hypertension during pregnancy, and the newborn baby showed symmetrical growth retardation as manifested by low birth weight (less than 2.5 kg), and a ponderal index* greater than 2.32.

■ As far as acute nicotine poisoning is concerned, the circumstances could be accidental, suicidal, or even homicidal.

❖ Accidental poisoning could occur in children who play with old tobacco pipes, or who ingest cigarettes out of curiosity. Severe poisoning can result from ingestion of just 2 or 3 cigarettes. Milder poisoning can result from "experimental smoking" by adolescents. Accidental poisoning in horticulture due to the use of nicotine as a pesticide was not uncommon in the past. Apart from occupational exposure to nicotine spray, even fruits contaminated with nicotine used to reach the general public. Careless storage of nicotine in containers which could be mistaken for some other product also sometimes caused accidental poisoning.

❖ Similarly, suicidal ingestion of nicotine pesticides used to be reported occasionally in the past, until such preparations were withdrawn from use.

❖ Homicidal cases have always been rare, though a few cases do find mention in medical literature.

■ Autopsy findings in death due to nicotine ingestion include characteristic odour (of stale tobacco) in gastric contents, brownish froth at the mouth and nose, congestion with brownish discolouration of oesophageal and gastric mucosa, and intense congestion of liver and kidneys.

■ Cocaine

Source

Cocaine (*"coke"* or *"snow"*) is a natural alkaloid present in the leaves of the coca plant, i.e., *Erythroxylon coca* (**Fig 34.7**), a shrub that grows well in South America, Mexico, Indonesia, and West Indies. Chemically, cocaine is benzoylmethylecgonine, and belongs to the tropane family of natural alkaloids, other members of which include atropine and scopolamine. It occurs as colourless to white crystals, or white crystalline powder (**Fig 34.8**).

Fig 34.7: *Erythroxylon coca*

Fig 34.8: Cocaine powder

Mode of Intake

Cocaine is usually abused by either chewing coca leaves, smoking coca paste, or "snorting" cocaine hydrochloride. The last mentioned is the most popular form of cocaine intake, i.e. the drug is inhaled in powder form through the nostrils. Occasionally, cocaine hydrochloride is injected intravenously. Today, a smokable form of cocaine (*"crack"* or *"rock"*) has virtually become a rage in the West. Pure alkaloidal cocaine (*"free-base"* or *"baseball"*) can also be smoked. Occasionally coca paste or cocaine sulfate (cocaine base, *"pasta"*, *"bazooka"*) is smoked. Cocaine freebase is prepared from cocaine hydrochloride by extracting the cocaine with an alkaline solution (buffered ammonia) and adding a solvent such as ether or acetone. The mixture separates into two layers, the top solvent

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* The ratio of an individual's height to the cube root of his weight; used to determine bodymass.

layer containing the dissolved cocaine. The solvent is then evaporated leaving almost pure cocaine crystals. "*Free-base*" is a colourless, odourless, transparent, crystalline substance that makes a popping or cracking sound when heated (hence the term "*crack*"). Both free-base and crack are more stable to pyrolysis than the hydrochloride salt, and therefore can be smoked either using a "coke pipe" or mixed into a cigarette ("*joint*"). A solution of cocaine hydrochloride can also be heated in a pan with baking soda added until a solid "rock" is formed, pieces of which can be smoked directly.

Street cocaine is often impure. The content of pure cocaine ranges from 10 to 50 per cent (most commonly 15 to 20 per cent). Cocaine which is available on the street is often adulterated with one or more of the following compounds: talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, lignocaine, strychnine, amphetamine, or heroin ("*speed ball*"). Crack cocaine adulterated with phenytoin (in order to lower cost or increase potency) has resulted in phenytoin toxicity in some patients.

Uses

- Topical anaesthetic (4 to 10% solution) for intranasal and bronchoscopic procedures.
- Ophthalmologic anaesthesia.
- Relief of severe (oncologic) pain: Cocaine is one component of Brompton's cocktail, (the others being morphine, chlorpromazine, and alcohol), which is popular in Europe for the control of intractable pain associated with some forms of cancer.
- Cocaine is one of the components of TAC (the others being tetracaine and adrenaline) which is sometimes used as a topical anaesthetic in children with scalp and facial lacerations.

Mode of Action

1. CNS:
   a. Cocaine is the most powerful naturally derived CNS stimulant known to man. Stimulation of the brain occurs in a rostral-to-caudal fashion. The cortex is stimulated first resulting in excitement, restlessness, and increased motor activity. Subsequent stimulation of lower motor centres produces tonic-clonic convulsions. The medulla is at first stimulated resulting in an initial increased respiratory rate, followed by depression with resultant respiratory failure.
   b. The CNS stimulant effects of cocaine are mediated through inhibition of dopamine reuptake in the nucleus accumbens. A recent study affirms the central importance of the dopamine-reuptake transporter in the behavioural and biochemical action of cocaine and defines it as a site on which efforts to develop an anti-cocaine medication should be focused. The dopamine-reuptake transporter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release. Cocaine, which binds strongly to the dopamine-reuptake transporter, is a classic blocker of such reuptake after normal neuronal activity. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons producing the characteristic cocaine "high".
   c. Cocaine also increases the concentrations of the excitatory amino acids, aspartate and glutamate in the nucleus accumbens. These excitatory amino acids increase the extracellular concentrations of dopamine. Excitatory amino acid antagonists attenuate the effects of cocaine induced convulsions and death. Dopamine$_2$ (D$_2$) receptor agonists accentuate cocaine craving, while dopmanie$_1$ (D$_1$) agonists diminish such craving.
   d. Cocaine also inhibits reuptake of noradrenaline and serotonin. Increase in the concentrations of the former plays an important role in the toxic effects of cocaine.
2. Peripheral nerves: Through direct blockade of fast sodium channels, cocaine stabilises the axonal membrane, producing a local anaesthetic effect. Cocaine is the only local anaesthetic that interferes with the uptake of neurotransmitter by the nerve terminals and simultaneously functions as a vasoconstrictor.
3. CVS:
   a. Initial effect of cocaine on the CVS is bradycardia, secondary to stimulation of vagal nuclei. However, the bradycardia is too transient to be clinically evident, and tachycardia becomes the prominent effect resulting from central sympathetic stimulation.
   b. Cocaine produces blockade of fast sodium channels on myocardial tissue, imparting type I antiarrhythmic properties. The cardiostimulatory effect of cocaine is due in large part to sensitisation to adrenaline and noradrenaline, preventing neuronal reuptake of these catecholamines, as well as due to increased release of noradrenaline from adrenergic nerve terminals. The increased concentrations and persistence of catecholamines near the receptors of the effector organ lead to exaggerated sympathetic effects.
   c. Studies have revealed that the peak vasopressor effects of cocaine are mediated by noradrenaline of sympathetic neural origin, while the peak tachycardic effects are mediated by direct release of adrenaline of adrenal medullary origin.
   d. The sympathomimetic effects of cocaine increase myocardial oxygen demand and the alpha-adrenergic mediated coronary vasoconstriction limits coronary artery blood flow. Cocaine inhibits endogenous fibrinolysis, increases thrombogenicity, and enhances platelet aggregation.

Toxicokinetics

- Absorption—
  ❖ Ingestion and insufflation: Cocaine is well absorbed from oral, nasal, and pulmonary routes. Onset of action on insufflation is within 1 to 3 minutes, and peak effects are seen in 20 to 30 minutes.

❖ Intravenous injection: Onset of action is within seconds, and peak action occurs in 3 to 5 minutes.

❖ Inhalation: Smoking produces effects as rapidly as IV injection.

■ Metabolism—

❖ Cocaine is metabolised by liver esterases and plasma cholinesterase to ecgonine methylester (EME), one of the major metabolites, while non-enzymatic hydrolysis results in the formation of the other major metabolite, benzoylecgonine (BE). Minor metabolites include norcocaine ecgonine, ecgonidine, norecgonidine methylester, norecgonine methylester, and m-hydroxy-benzoylecgonine.

■ Excretion—

❖ The biologic half-life of cocaine is ½ to 1½ hours. Benzoylecgonine and ecgonine methylester possess half lives of 5 to 8, and 3½ to 6 hours respectively.

❖ Excretion is mainly through urine. Due to the long elimination half-life of BE, assays for its detection in urine may be successful up to 2 to 3 days following cocaine use. In rare cases, it has been detected even after 22 days.

Clinical Features

1. Acute Poisoning

a. Hyperthermia—This results from
  – Augmentation of heat production due to increased psychomotor activity.
  – Diminution of heat dissipation due to vasoconstriction.
  – Direct pyrogenic effect due to action on thermoregulatory centres in the hypothalamus.
  – Stimulation of calorigenic activity of liver.

b. Body temperature often soars to 108° to 112°F, and does not respond to conventional antipyretics. It is often associated with rhabdomyolysis, seizures, and renal failure.
  – CNS effects—
    - Headache:
      » *Pattern 1*—Develops within minutes, and lasts for 2 to 48 hours. The headache is usually occipital or bilateral, with associated throbbing, photophobia, nausea, and vomiting.
      » *Pattern 2*—Occurs during a cocaine "binge", (4 to 14 days of abuse, 1 to 3 g/day), with onset after a few days, which increases in severity progressively. It is mostly frontal, with associated throbbing, nausea and sometimes diplopia and dizziness.
      » *Pattern 3*—Occurs 1 to 4 days after the last dose of cocaine, and worsens over the next 1 week with continued abstinence. It is also frontal, with associated throbbing, nausea, vomiting, photophobia, and occasionally neck stiffness.

– Anxiety, agitation.
– Hyperactivity, restlessness.
– Tremor, hyperreflexia.
– Convulsions: Generalised tonic-clonic, partial motor, and partial complex seizure have all been reported. Seizures may be recurrent and status epilepticus has been reported, particularly in children. Sometimes there is lethargy and decreased level of consciousness which can persist up to 24 hours ("*cocaine washed out syndrome*").
– Cerebrovascular accidents are not uncommon, and include subarachnoid haemorrhage, intracerebral haemorrhage, cerebral infarction, transient ischaemic attacks, migraine-type headache syndrome, cerebral vasculitis, and anterior spinal artery syndrome. Infarction of the brainstem/spinal cord has occurred.

c. Psychiatric effects—
  – Paranoid state with suspiciousness, hypervigilance, anxiety.
  – Stereotypy.
  – Hallucinations.
  – Toxic delirium.

d. Ophthalmologic effects—
  – Mydriasis and/or loss of eyebrow and eyelash hair from smoking crack cocaine may occur.
  – Corneal abrasions/ulcerations due to particulate matter in smoke ("*crack eye*").
  – Central retinal artery occlusion and bilateral blindness due to diffuse vasospasm. Retinal foreign body granuloma may occur with IV abuse.

e. CVS effects—
  – Tachycardia.
  – Systemic arterial hypertension.
  – Coronary artery vasoconstriction with myocardial ischaemia and infarction. Coronary artery disease, heavy smoking, and hypertension are predisposing factors. Myocardial infarction may occur even in young patients without risk factors or pre-existing cardiac pathology.
  – Tachyarrhythmias of all types can occur, including sinus tachycardia, atrial fibrillation or flutter, other supraventricular tachycardias, ventricular premature contractions, ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Sinus tachycardia is the most common finding. If hypertension is significant, a reflex bradycardia may occur. Cocaine-induced syncope and bradyarrhythmia have been reported in some cases.
  – Chronic dilated cardiomyopathy can occur.
  – Aortic dissection and rupture.

f. Pulmonary effects—
  – Thermal injuries to the upper airway leading to epiglottitis, laryngeal injury, and mucosal necrosis have been reported after smoking "crack" or free base cocaine.

– Exacerbation of asthma.
– Noncardiogenic pulmonary oedema is a common finding at autopsy.
– Pneumothorax, pneumomediastinum.
– Diffuse alveolar haemorrhage.
– Bronchiolitis obliterans with organising pneumonia.

g. Musculoskeletal effects—Rhabdomyolysis with hyperthermia, massive elevation of creatine phosphokinase, and acute renal failure. Although the mechanism of cocaine-associated rhabdomyolysis is unclear, it is postulated that it may result from ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure activity.

h. GI effects—
– Acute mucosal ischaemia.
– Colitis.
– Intestinal perforation: It is postulated that cocaine blocks the reuptake of noradrenaline leading to mesenteric vasoconstriction and focal tissue ischaemia and perforation.
– Pneumoperitoneum has been reported after smoking crack cocaine.
– Hepatic necrosis (centrilobular, midzonal, and panlobar) has been reported in overdose.

i. Renal effects—Renal failure, usually secondary to myoglobinuria and rhabdomyolysis, has been reported after intravenous or intranasal cocaine use. Renal infarction has occurred following intravenous cocaine use.

j. Uteroplacental effects—
– Increased incidence of spontaneous abortion, low birthweight, and abruptio placentae. Neonatal intoxication may also occur. Infants exposed to cocaine in utero may display tremulousness, impaired orientation, increased startle response, irritability, muscular rigidity, arousal deficits, impaired motor ability, and lower scores on the Brazelton Neonatal Behavioural Assessment Scale (measuring interactive behaviour and response to environmental stimuli).
– There are indications that cocaine may be teratogenic.
– Cocaine toxicity has been reported in breastfed infants of cocaine abusing mothers.

k. Miscellaneous effects—
– Priapism has been observed after topical application of cocaine to the glans penis.
– Severe metabolic acidosis has been reported due to seizures, agitation, and hypotension.

l. Drug combination effects—
– Cocaine is often combined with other drugs such as ethanol and heroin. Concurrent use of cocaine and ethanol produces additive effects on the brain. It results in the formation of the metabolite, cocaethylene which is more cardiotoxic, and is associated with enhanced mortality.
– Combination of cocaine with heroin is referred to as "*speed ball*" and is reputed to produce a double effect of initial high "kick" of cocaine, followed by subsequent euphoric "rush" of heroin. "*Speed ball*" is usually injected.

2. **Chronic Poisoning**
a. Cocaine dependence
– Cocaine dependence is defined in DSM-IV as a cluster of physiological, behavioural, and cognitive symptoms that, taken together, indicate that the person continues to use cocaine despite significant problems related to such use.
– Some cocaine users can use cocaine intermittently without becoming dependant, though it is not clear how long such intermittent, non-dependant use can continue. Intermittent use consists of episodes or binges of use, often starting on weekends and paydays, and lasting until the drug supply is exhausted or toxicity develops. Such binges, during which the drug may be used every 15 to 30 minutes, can last 7 or more consecutive days (though usually this extends to only 3 or 4 days). When the binge comes to an end, a "*cocaine crash*" occurs.

b. Cocaine abuse
– Some cocaine abusers develop problems or adverse effects related to their drug use (i.e. their use is maladaptive). Examples of such recurrent maladaptive patterns include use that leads to multiple legal problems, failure to meet major social, school, or work-related obligations, and continued use despite social or vocational difficulties caused by, or aggravated by cocaine use. When one or more such substance-related problems occur in a 12-month period, the diagnosis of cocaine abuse is made.
– Chronic use of cocaine leads to CNS dopamine depletion and increases in the number and sensitivity of dopamine receptors. The dysphoric state associated with cocaine withdrawal (*vide infra*) and craving for cocaine appears to be a result of the dopamine-depleted condition.
– Features of chronic cocaine use:
- Anorexia, emaciation.
- Mydriasis.
- Agitation, restlessness: A cocaine-associated *agitated delirium syndrome* has been identified, comprising the following in sequence: hyperthermia, delirium with agitation, respiratory arrest and death.
- Hallucinations, especially tactile, characterised by a crawling sensation under the skin ("*cocaine bugs*") with resultant excoriation, leading to irregular scratches and ulcers (Magnan's sign). Perceptual disturbances or pseudo-hallucinations involving vision ("snow lights", geometric patterns), smell, hearing and taste have also been reported.
- Tremor.
- Recurrent chest pain.
- Cardiomyopathy.
- Psychiatric changes: depression, psychosis,

panic disorders, attention deficit disorders, and eating disorders.

- Decreased libido, impotence, gynaecomastia, galactorrhoea, amenorrhoea, and sexual dysfunction are common with chronic cocaine abuse.
- Cocaine abuse may be associated with cerebral atrophy.
- *"Crack hands"*: A syndrome of multiple, blackened, hyperkeratotic lesions (linear or circular), of the fingers and palms has been described in crack cocaine smokers. These lesions probably result from the heat of the glass cocaine pipe.
- Maternal chronic cocaine use during pregnancy has been suggested as a possible factor in Sudden Infant Death Syndrome. Cocaine readily passes into breast milk and can cause adverse effects in the nursing infant.
- Evidence of medical complications (**Table 34.9**).

c. Cocaine withdrawal
  – Conventionally, cocaine withdrawal is said to occur in 3 phases:

  Phase I ("Crash"): The total duration of this phase lasts for anywhere between 9 hours and 4 days, and is subdivided further into the following stages—
  » Early: Agitation depression, anorexia, intense craving for cocaine.
  » Intermediate: Fatigue, tendency to sleep, decreased craving.
  » Late: Exhaustion, hypersomnia, hyperphagia, absence of craving.

Phase II: Normalised sleep, improved mood, followed subsequently by return of anergia, anhedonia, anxiety, and increased craving.

Phase III: ("Extinction"): Increased tendency to relapse. The extinction phase may be prolonged and consists of brief, episodically evoked cravings that occur months to years after withdrawal.

– Additional points of importance:
  - Impaired colour vision (blue-yellow), which may persist for up to 2 months or more, has been reported in some patients with cocaine withdrawal. A dysregulation of blue cone function has been suggested, since significantly reduced blue cone electroretinogram responses have been observed in recently withdrawn cocaine-dependant patients.
  - Silent ischaemia has occurred upon cocaine withdrawal, and acute myocardial infarction may occur up to 2 weeks after the last cocaine use.
  - ECG changes: Increased PR intervals have been found to correlate with length of abstinence, which is thought to reflect the remediation of a depolarisation variant. Chronic cocaine users may be subject to rapid cardiac depolarisation (decreased PR intervals) that gradually returns to normal over 20–30 days.
  - EEG changes: Evaluation of quantitative EEGs in cocaine-dependant persons after a 10-day drug free interval revealed increased power in the beta-2 band that correlated with the frequency of cocaine use during the last

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Table 34.9: Medical Complications of Cocaine

CNS—
Tremors, convulsions, "sympathomimetic storm", migraine headaches, cerebral vasculitis, cerebral infarction, intracranial haemorrhages

CVS—
Hypertension, cardiac arrhythmias, myocardial ischaemia, myocardial infarction, cardiomyopathies, myocarditis, endocarditis, aortic rupture

RS—
Alveolar haemorrhage, ARDS, pneumomediastinum, pneumothorax, pulmonary thrombosis

GI—
Mesenteric ischaemia, malnutrition

ENT—
Rhinitis, nasal septal necrosis, sinusitis, laryngitis

Metabolic—
Hyperthermia, hypoglycaemia, lactic acidosis, hypo/hyperkalaemia

Renal—
Rhabdomyolysis-induced renal failure

Psychiatric—
Depression, paranoia, violent behaviour

Obstetric & Paediatric—
Abruptio placentae, abortion, prematurity, growth retardation

Infections (IV use)—
Hepatitis B, AIDS, endocarditis

30 days before hospital admission. Elevated power of EEG beta (fast EEG activity) could be a neurophysiological cocaine withdrawal sign.

- Persistently elevated serum creatine kinase (CPK) levels (>374 Units/L) have been demonstrated in abstinent cocaine abusers, with evidence of impaired spatial motor performance, and tendency to coarse motor control and impulsive movements.

- Withdrawal from cocaine sometimes results in hyperprolactinaemia during the first month, which may be due to its effect on serotonergic function. Bromocriptine (0.625 mg orally, twice daily) may be of value for treating cocaine withdrawal-induced hyperprolactinaemia.

- Cocaine readily crosses the placental barrier, causing an alteration of the central neurotransmitter state, and increasing peripheral catecholamines in the foetal circulation. In utero cocaine exposure in a foetus nearing term could result in altered behaviour after delivery, consistent with drug abstinence, and in decreased flow velocity in the anterior cerebral artery consistent with the vasoconstrictive effects of cocaine. Abstinence symptoms are seen in the first and second postnatal days, and may last for several weeks. Cocaine-exposed infants may be at an increased risk for sudden infant death syndrome (SIDS). Symptoms of neonatal cocaine abstinence syndrome include irritability, hypertonia/poor muscle tone, tremor, hyperactive Moro reflex, loose stools, sleep disturbances, poor feeding/excessive sucking, nasal stuffiness, tachypnoea, visual function disturbance.

Usual Fatal Dose

- About 500 mg (*oral*).
- About 100 mg (*mucosal contact*).
- Lethal blood level: 0.2 mg/100 ml.
  Chronic users of cocaine can tolerate much higher doses.

Diagnosis

1 Blood or plasma cocaine levels are not clinically useful, although they may be advisable to be done in medico-legal cases. Qualitative urine tests using kits may be helpful in clinical diagnosis (by utilising chromatography, radioimmunoassay, enzyme immunoassay, fluorescence polarisation immunoassay, and enzyme-multiplied immunoassay technique). Cocaine metabolites can be identified in the urine and provide a method for qualitatively identifying suspected cocaine poisoning or abuse. Benzoylecgonine, the major metabolite of cocaine, can usually be detected in urine for 48 to 72 hours after cocaine use.

2. Other diagnostic clues—
    a. *Hair analysis*: Cocaine benzoylecgonine and ecgonine methylester can be analysed in hair samples by GC-MS and RIA. This can be done in adults, as well as in any infant whose mother was a cocaine user. It must be noted that external contamination of hair can occur from crack smoke, but that can be washed off, whereas systemic exposure is not affected by washing the hair.
    b. *ECG*: Non-Q-wave myocardial infarction, with the presence of a T-wave infarct ECG pattern is often seen in cocaine users. During acute cocaine use abnormalities are more prevalent, and the QT interval is prolonged. Two-dimensional echocardiography may be useful in detecting the presence of new regional wall-motion abnormalities in patients experiencing cocaine-induced chest pain.
    c. Troponin levels may be more useful in evaluating potential myocardial injury than creatinine kinase.
    d. *Acid-base abnormalities*: Arterial blood gases in cocaine abusers show a pH varying from 7.35 to 7.5. Alkalosis (pH > 7.45) is caused by hyperventilation, and is manifested by tachypnoea and low $PaCO_2$. About one third of patients show evidence of acidosis which may be the result of hypoventilation secondary to depressed mental status or chest trauma. Metabolic acidosis is not uncommon, and usually results from convulsions, agitation, or trauma.
    e. Estimate serum creatine kinase for evidence of rhabdomyolysis. Monitor renal function and urine output in patients with elevated CPK.
    f. *X-ray*: Body packer syndrome (*page no 179.*) can be diagnosed by plain films of the abdomen in the supine and upright positions. However, false negatives have been reported. Radiography may not detect cellophane-wrapped packets or crack vials. Even false-negative abdominal CT scans have been reported. It is therefore advisable to perform a contrast study of the bowel with follow-up X-rays 5 hours after the oral ingestion of a water-soluble contrast compound such as meglumine amidotrizoate (50 ml). Daily views are performed thereafter until negative views coincide with the passage of two drug packet-free stools.

Treatment

1. **Acute Poisoning**
    Activated charcoal adsorbs cocaine in vitro under both acidic and alkaline conditions, and can be administered in cases of ingestion.
    a. Hyperthermia:
        – Minimise physical activity and sedate with benzodiazepines.
        – Ice baths, packs, cool water with fans, etc.
        – Oxygen $D_{50}W$ (as necessary).
        – Diazepam 5 mg IV or lorazepam 2–4 mg IV titrated to effect.
        – Paracetamol 2000 mg (in the form of 500 mg rectal suppositories).
        – Severe, intractable cases may respond to dantrolene (1 mg/kg) every 6 hours. Alternatively, bromocriptine can be administered orally in a nasogastric tube.

b. Anxiety and agitation:
   – Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect.
   – Physical restraints.
   – Antipsychotics such as haloperidol or droperidol, and phenothiazines are not recommended since they can induce malignant hyperthermia and convulsions.

c. Convulsions:
   – Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect.
   – Phenobarbitone 25–50 mg/min up to 10–20 mg/kg.
   – If seizures are not controlled by the above measures, consider continuous infusion of midazolam (0.2 mg/kg slow bolus, or 0.75 to 10 mcg/kg/min as infusion), or propofol (1 to 2 mg/kg, followed by 2 to 10 mg/kg/hr) or pentobarbitone (10 to 15 mg/kg at a rate of 50 mg/min, followed by 0.5 to 1 mg/kg/hr).
   – Intractable convulsions may require neuromuscular paralysis with intubation and mechanical ventilation.

d. Cerebrovascular accidents: Neurosurgical consultation is mandatory.

e. Hypertension: It is usually short-lived and often followed by significant hypotension. Mild hypertension generally responds to sedation with benzodiazepines. For severe hypertension—
   – Without tachycardia:
     - Phentolamine 0.02 to 0.1 mg/kg IV
     - Nifedipine 0.1 to 0.2 mg/kg IV
     - Nitroprusside 2 to 10 mcg/kg/min IV
   – With tachycardia: If the above measures are not effective, the following may be used—
     - Labetolol 10 to 20 mg IV, repeated every 10 minutes (max: 300 mg).
     - Nitroglycerine IV titrated to effect.
   – With chest pain—
     - Nitroglycerine drip.
     - Oxygen by nasal cannula (5 L/min).
     - Monitor cardiac status.
     - If systolic BP is higher than 120 mmHg, administer nitroglycerine sublingually (up to 3 tablets or 3 sprays of 0.4 mg each).
     - If pain does not respond to nitroglycerine, use morphine (2 mg IV titrated to pain relief).
     - Obtain ECG.
     - If chest pain is strongly suggestive of a myocardial infarction, consider thrombolytic therapy.
     - Diazepam 5 mg IV, or lorazepam 2–4 mg IV titrated to effect can prevent excess production of catecholamines by the CNS.
     - Mechanical reperfusion (angioplasty).

f. Arrhythmias:
   – Sinus tachycardia:
     - Observation
     - Oxygen
     - D$_{50}$W (as necessary)

   - Diazepam 5–10 mg IV, or lorazepam 2–4 mg IV titrated to effect (if indicated).
   – Supraventricular tachycardia:
     - Observation
     - Oxygen
     - D$_{50}$W (as neccesary)
     - Diltiazem 20 mg IV, or verapamil 5 mg IV
     - Adenosine 6–12 mg IV for AV node re-entry
     - Cardioversion (if necessary).
   – Ventricular arrhythmias: Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalaemia, hypocalcaemia, and hypomagnesaemia).
     - Oxygen
     - D$_{50}$W (as necessary)
     - Hypertonic sodium bicarbonate: Sodium bicarbonate may be useful in the treatment of QRS widening and ventricular arrhythmias associated with acute cocaine use. A reasonable starting dose is 1 to 2 mEq/kg repeated as needed. Monitor arterial blood gases, maintain pH 7.45 to 7.55.
     - Diazepam 5 mg IV, or lorazepam 2–4 mg IV.
     - Lignocaine 1.5 mg/kg IV bolus, followed by 2 mg/min infusion. Watch out for adverse effects (**Table 34.10**). Procainamide may also be used with caution.
     - Defibrillation (if haemodynamically unstable).

g. Myocardial infarction: Acute myocardial infarction due to cocaine toxicity must be treated on the same lines as myocardial infarction in non-cocaine users, except for the use of beta blockers. The following measures are recommended:
   – IV line
   – Oxygen
   – Aspirin to inhibit platelet aggregation. Watch out for increased thyroxine levels.
   – For systolic BP higher than 100 mmHg, administer sublingual nitroglycerine or nifedipine 10 mg orally, or phentolamine 1 to 5 mg IV (followed by a drip of 10 mg in 1 litre of D$_5$W at 10 ml/min).

Table 34.10: Drugs to be Avioded in the Treatment of Cocaine Poisoning

Drugs	Adverse Effect
Beta blockers (especially propranolol)	Coronary artery spasm (paradoxical hypertension)
Lignocaine, procainamide, quinidine	Convulsions Arrhythmias
Haloperidol, droperidol, phenothiazines	Hyperpyrexia Convulsions
Dantrolene	Cardiac insufficiency
Bromocriptine	Coronary artery constriction
Aspirin	Thyrotoxicosis (thyroid storm)

- For life-threatening arrhythmias, use of type IA antiarrhythmic agents may be considered (with caution).
- Thrombolytic therapy may be necessary if myocardial infarction is not amenable to relief by nitrates, calcium channel blockers, or phentolamine. Caution about the use of thrombolytics in cocaine-associated acute myocardial infarction (AMI) is generally advocated. Thrombolytics should be avoided in patients with cocaine-induced myocardial infarction and uncontrolled hypertension, because of the increased risk of intracranial haemorrhage. However, some investigators feel that the risk is often exaggerated.

h. Aortic dissection: The hypertension that precipitated aortic dissection must be controlled immediately with nitroprusside and calcium channel blockers.

i. Pulmonary oedema:
   – Frusemide 20–40 mg IV.
   – Morphine sulfate 2 mg IV titrated to pain relief.
   – Nitroglycerine drip titrated to blood pressure or respiratory status.
   – Phentolamine or nitroprusside (if necessary).
   – Incubate and ventilate.
   – Monitor fluids with pulmonary artery catheter.

j. Rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is not routinely recommended.
   – Cardiac monitoring.
   – Serial potassium determinations.
   – Serial serum creatine kinase and urine myoglobin studies.
   – IV hydration (urine output must be maintained at 3 ml/kg/hr).
   – Dopamine (3 mcg/kg/day) and frusemide (60 mg three times a day) may reduce renal vascular resistance and help in reducing the number of haemodialysis required to reverse oliguria.

k. Acidosis: Correction of acidaemia through supportive care measures such as hyperventilation, sedation, active cooling, and sodium bicarbonate infusion can have beneficial effects on conduction defects.

l. Elimination enhancement measures: Cocaine is rapidly metabolised. Forced diuresis, urine acidification, dialysis, and haemoperfusion are ineffective in significantly altering elimination. Increasing the level of butyrylcholinesterase in the blood (which metabolises cocaine to inactive compounds) could help in rapidly inactivating cocaine in acute intoxications.

2. Chronic Poisoning

A number of psychological and pharmacological approaches to the treatment of cocaine dependence have been tried with varying degrees of success. A combined approach judiciously tailored to the needs of individual patients offers the best hope of preventing relapses.

a. Psychotherapy: This involves cognitive-behavioural, psychodynamic, and general supportive techniques. One example of a cognitive-behavioural method uses contingency contracting, in which it is agreed in advance that for a specified period of time (e.g. 3 months), if the patient uses cocaine (as detected by supervised urine testing), the therapist will initiate action that will result in serious adverse consequences for the patient, such as informing the employer.

b. Group psychotherapy:
   – Interpersonal group therapy focuses on relationships, and uses the group interactions to illustrate the interpersonal causes of individual distress, and to offer alternative behaviours.
   – Modified dynamic group therapy is concerned with emphasising character as it manifests itself individually and intrapsychically, and in the context of interpersonal relationships with a focus on affect, self-esteem and self-care.

c. Group counselling: The most widely used form of psychosocial treatment for cocaine dependence is group counselling, in which the group is open-ended with rolling admissions; the group leaders are drug counsellors, many of whom are recovering from addiction, and the emphasis is on providing a supportive atmosphere, discussing problems in recovery, and encouraging participation in multistep programmes.

d. Pharmacotherapy:
   – Several drugs have been tried to help ameliorate the manifestations of cocaine withdrawal. Many of these (fenfluramine, trazodone, neuroleptic agents, etc.) have either not demonstrated clinical efficacy, or have produced serious side effects.
   – Bromocriptine has successfully reduced cocaine craving and decreased withdrawal symptoms in several studies. Oral doses of 0.625 mg given 4 times daily may produce a rapid decrease in psychiatric symptoms. When given in a single dose of 1.25 mg, bromocriptine has been found to decrease cocaine craving. In one study, the dosage suggested was 1.25 mg orally twice daily, with titration up to 10 mg per day within the first 7 days. Dose can be decreased in patients experiencing adverse effects.
   – Amantadine, a dopamimetic agent, increases dopaminergic transmission and has been found to be useful in the treatment of early withdrawal symptoms and short-term abstinence. The usual dose recommended is 200 mg to 400 mg orally, daily, for up to 12 days. It is probably as effective as bromocriptine, and less toxic.
   – Tricyclic antidepressants may be useful for selected cocaine users with comorbid depression or intranasal use.

– Initial studies with fluoxetine promised good results, but craving actually worsened in some patients. Several studies indicated better efficacy with carbamazepine for controlling craving. Carbamazepine at doses of 200 to 800 mg orally, 2 to 4 times daily has benefited some patients. Phenytoin also shows promise in helping to sustain abstinence from cocaine in some patients.

– Recent approaches include the employment of agents that selectively block or stimulate dopamine receptor subtypes (e.g. selective D_1 agonists), and drugs that can selectively block the access of cocaine to the dopamine transporters, and yet still permit the transporters to remove cocaine from the synapse.

– Another approach is aimed at preventing cocaine from reaching the brain by using antibodies to bind cocaine in the blood stream ("cocaine vaccine").

e. Acupuncture: Use of auricular acupuncture to treat cocaine abuse has become popular of late, though controlled studies of its efficacy have not shown convincing results. Herbal teas are often consumed as part of the treatment. Unfortunately, drop-out rates are generally high.

3. Bodypacker Syndrome

The practice of swallowing balloons, condoms, or plastic packets filled with illegal drugs for the purpose of smuggling is called "body packing", (**Fig 34.9**) and the individual who does this is referred to as a "mule". This must be differentiated from "body stuffing" in which an individual who is on the verge of being arrested for possession of illegal drugs, swallows his illicit contraband to conceal the evidence. Leaking from these poorly wrapped packets can produce cocaine toxicity. Sudden death due to massive overdose can occur in either a bodypacker or a bodystuffer, if one or more of the ingested packages burst within the gastrointestinal tract. Fatal cocaine poisoning has occurred with the rupture of just a single package.

a. Diagnosis: Mentioned on *page no 558*

b. Treatment:

– Emesis, lavage, charcoal, as applicable.

Fig 34.9: Cocaine packets recovered from a bodypacker

– Cathartic/whole bowel irrigation to flush the packages out of the intestines.

– Symptomatic patients should be considered a medical emergency, and be evaluated for surgical removal of the packets.

– Asymptomatic patients should be monitored in an intensive care unit until the cocaine packs have been eliminated. This must be confirmed by follow-up plain radiography and barium swallows.

– Bowel obstruction in asymptomatic patients may necessitate surgery. Endoscopic removal has been successful in some cases.

Autopsy Features

1. There are no specific findings at autopsy, except for nasal septal ulceration and perforation if the deceased had been a long-term abuser of cocaine. Histological study of nasal septal mucosa in such cases may reveal characteristic changes including arteriolar thickening, increased perivascular deposition of collagen and glycoprotein, and chronic inflammatory cellular infiltration.

2. Histopathology of heart may demonstrate microfocal lymphocytic infiltrates, acute coronary thrombosis, early coagulation necrosis of myocardial fibres, and non-atherosclerotic coronary obstruction due to intimal proliferation.

3. Cocaine can be recovered by sampling from recent injection sites, or by swabs from the nasal mucosa. It can also be recovered from the liver and especially brain, where cocaine may be found not only in dopamine-rich areas such as caudate, putamen, and nucleus accumbens, but also in other extra-striatal regions. Specimens obtained postmortem should be preserved with sodium fluoride, refrigerated, and analysed quickly. Tissue specimens should be frozen.

Forensic Issues

■ Cocaine has been abused for centuries, but its toxic properties have been studied extensively only in the last couple of decades. In the current drug subculture, cocaine has become the "*champagne drug*" because of its cost and relative scarcity. Cocaine is a "rich man's drug" since the poorer classes cannot afford to sustain a drug habit that costs thousands of rupees every week. Therefore in India, cocaine abuse is restricted mainly to the affluent classes of society. The prevalence and extent of the problem among newer generation Indian film actors in recent times has become apparent with the arrest of several filmstars for possession of cocaine. Several high profile artists, socialites, and even politicians have been caught with cocaine possession.

■ Cocaine has always been popular with musicians (especially jazz and rock), other artistes, and film personalities. There are innumerable rock songs eulogising the drug directly or indirectly.

■ Today cocaine has made inroads into the general population, especially adolescents. After the cocaine epidemic of the 1970s ("snorting seventies") in the West, there had been

a relative lull in the 1980s and early 1990s. A recent survey shows the cocaine resurgence of the 21st century has not only affected Western countries, but even poorer countries such as India. In fact a sizeable chunk of youth (including girls) from well-to-do families in metropolitan cities such as Mumbai, Delhi, and Bangalore have no qualms about drug abuse, and even openly admit to using "party drugs" such as cocaine as a "cool" mode of recreation. Since cocaine has a reputation of enhancing sexual pleasure, such wide-spread abuse has also led to increased spread of sexually transmitted diseases such as AIDS because of high-risk sexual practices among the users.

- Cocaine abuse by pregnant mothers can lead to devastating effects on the foetus and the new-born (**Table 34.11**). There is convincing evidence that cocaine is teratogenic and can play an important role in the causation of several serious congenital anomalies (**Table 34.12**).
- Cocaine abuse is well known for its propensity to cause sudden death not only due to its deleterious effects on health (cerebrovascular accidents, myocardial infarction, malignant hyperthermia, renal failure), but also due to its capacity to provoke the user to commit acts of aggression and violence. Deaths due to massive overdose are especially common among those who smuggle the drug within their bodies ("cocaine packers").
- Cocaine toxicity has been reported in children receiving topical adrenaline and cocaine for local anaesthesia.

Table 34.11: Complications of Cocaine Abuse during Pregnancy

Spontaneous abortion
Placenta praevia
Abruptio placentae
Prematurity
Placental infarction
Intrauterine growth retardation
Low-birth-weight
Congenital anomalies
Foetal death

Table 34.12: Some Teratogenic Effects of Cocaine

Body Area	Anomaly
Cranio-spinal	Exencephaly, hydrocephaly, cephaloma-lacia, encephalocoele, myelomeningocoele
Facial	Cleft lip, cleft palate, facial diplegia, ptosis, cutis aplasia
CVS	Atrial septal defect, ventricular septal defect, transposition of great vessels, pulmonary artery stenosis, cardiomegaly
GI and GU tracts	Ileal atresia, inguinal hernia, renal agenesis, multicystic kidneys, hydronephrosis, hypo-spadias, hydrocoele, undescended testis
Extremities	Phocomelia, polydactyly, syndactyly

■ Cannabis

Source

Cannabis preparations (*vide infra*) are derived from Indian hemp plant (*Cannabis sativa*),* which is a hardy, aromatic annual herb that grows wild under most climatic conditions (**Fig 34.10**). The plant grows to a height of 5 to 15 feet, and is characterised by an odd number of leaflets on each leaf (varying from 5 to 9), all having serrated or saw-tooth edges, and small, green flowers. The male and female flowers are borne on separate plants. After pollination, the male plants die back.

Active Principles

The main active principle is δ^9 (delta-9) tetrahydrocannabinol (THC) which is a cannabinoid found in both the male and female plants. The concentration of THC is highest in the bracts, flowers, and leaves, while it is practically non-existent in the stem, root, and seeds. The THC content of the plant varies greatly, and is probably controlled more by the type of seed than by the soil or climatic conditions. Depending on the THC content, *Cannabis sativa* plants are sub-divided into fibre-type (less than 0.5% THC), or drug-type (more than 1% THC). Seedless (unpollinated female) plant, referred to as "sinsemilla" can contain up to 5% THC.

THC is a lipid-soluble, water-insoluble compound which can be synthesised in the laboratory. The synthetic form, however, is very expensive to produce, and so frequently, other illicit drugs such as phencyclidine, mescaline, or LSD are sold in the guise of THC. A product called "super weed" or "super grass" is dusted with phencyclidine.

Apart from THC, *Cannabis sativa* contains a number of other cannabinoids, including cannabidiol, cannabinol, cannabidolic acid, cannabicyclol and cannabigerol.

Fig 34.10: *Cannabis sativa*

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* Named and described by Linnaeus in 1753. *Cannabis indica* and *C. ruderalis* are usually considered synonymous with *C. sativa*. *Cannabis sativa indica* and *americana* are varieties of *Cannabis sativa*.

Mode of Intake

1. Marijuana: The term "marijuana" refers to any part of the plant or its extract that is used to induce psychotomimetic or therapeutic effects. Synonyms include Mary Jane, MJ, maconha, pot, weed, grass, puff, and dagga.
2. Ganja: Although some texts refer to ganja as being synonymous with marijuana, while others consider it to be a resinous mass composed of leaves and bracts, in India (where the term actually originated), it is used to refer to crushed leaves and inflorescences of female plants (**Fig 34.11**). It is usually smoked in a pipe ("chillum") or in the form of cigarettes ("reefer" or "joint" or "number"). Ganja is said to contain 1 to 2% THC.
3. Bhang: Bhang consists of dried mature leaves and flower stems that are ground with water and mixed with milk or fruit juice (**Fig 34.12**). It is consumed by Hindus in India during festivals such as Holi and Shiv Ratri.
4. Hashish (Charas) (**Fig 34.13**): This preparation is made out of dried resin collected from flower tops, and contains varying concentrations of THC up to 10%. It is popular in the Middle East and North Africa. Hashish oil or "liquid hashish" is an alcohol or petrol extract which occurs as a dark green viscous liquid with the consistency of tar. It is the most potent of all cannabis preparations and contains 20 to 30% (or more) THC.
5. Sinsemilla: It is the most popular form of cannabis in the USA, and refers to seedless (unpollinated female) plant which averages 5% of THC.
6. Marijuana "Blunts": This is nothing but cheap cigars sliced open, packed with cannabis, and resealed. The harsh stench of the cigar masks the characteristic sweet smell of cannabis. Blunts are very popular among the youth in some parts of the USA.

Uses

1. The durable fibres of the woody trunk of cannabis, referred to collectively as Indian hemp, has been used for centuries to produce rope and twine, as well as fine or rough cloth. The cannabis plant is possibly the most efficient source of paper pulp, producing up to 5 times as much cellulose per acre per year, as trees.
2. Cannabis seeds are used as food by man, poultry, and other birds, as well as furnishing hemp-seed oil for paint and soap.
3. Therapeutic uses:
   a. THC in the form of a synthetic oral cannabinoid ("dronabinol") has been shown to be effective in controlling the nausea and diarrhoea associated with AIDS, as well as the nausea and vomiting caused by chemotherapy for cancer or AIDS. It also increases appetite and produces weight gain in both AIDS and cancer patients. It is available from Roxane under the trade name Marinol®, as round, amber, soft gelatin capsules filled with sesame oil in which either 2.5, 5, or 10 mg of THC is dissolved. Another synthetic cannabinoid, nabilone, is available from Lilly under the trade name Cesamet® in the form of 1 mg capsules.

Fig 34.11: Huge cache of illegal ganja

Fig 34.12: Bhang

Fig 34.13: Charas

   b. Since smoked cannabis lowers intraocular pressure, it has been suggested that this effect though short-lived (3 to 4 hours), can be utilised for treating glaucoma.
   c. Some studies suggest a possible role for cannabis in the treatment of multiple sclerosis, epilepsy, and dystonic states, though convincing scientific evidence is lacking.
   d. THC possesses analgesic properties and has been tried in the treatment of pain due to cancer.

Mode of Action

Recently a receptor site has been identified in rat brain that binds reversibly and selectively with cannabinoids. Receptor binding was also found in the peripheral B lymphocyte-rich

areas such as the marginal zone of the spleen, nodular corona of Peyer's patches, and cortex of lymph nodes. A cannabinoid antagonist was also discovered that antagonises cannabinoid-induced inhibition of adenylcyclase and smooth muscle contraction. All this suggests the presence of a cannabinoid neurochemical pathway. It appears that cannabinoids exert many of their actions by influencing several neurotransmitter systems and their modulators. These include GABA, dopamine, acetylcholine, histamine, serotonin, noradrenaline, and prostaglandins.

Cannabinoid receptor location and density in animal models has correlated well with clinical effects in humans. The highest density of receptors occurs in the basal ganglia and molecular layer of cerebellum, which correlates with its interference in motor co-ordination. Intermediate levels of binding were found in the hippocampus, dentate gyrus, and layers I and IV of cortex, consistent with effects on short-term memory and cognition. Low receptor density is noted in the brainstem areas controlling cardiovascular and respiratory functions, which correlates with the cannabinoids' known lack of lethality.

After binding to receptors, cannabinoids also produce effects through second-messenger systems including inhibition of adenylcyclase and calcium channels, and also probably by enhancing potassium channels activity.

Toxicokinetics

Smoking cannabis generally produces immediate effects, while ingestion results in slow and unpredictable effects due to the instability induced by the acidic environment of the stomach. The most important factor in determining the bioavailability of THC happens to be the smoking dynamics (manner in which the cannabis is smoked). It takes about 15 seconds for the lungs to absorb the THC and transport it to the brain. Peak effects are seen in 10 to 30 minutes and may last for 1 to 4 hours. The mean terminal half-life of THC in plasma of frequent cannabis smokers is 4.3 days (range: 2.6–12.6 days).

Tetrahydrocannabinol (THC) is highly protein-bound (97 to 99%), has a Vd of 10 L/kg, and is enterohepatically recirculated. THC is metabolised primarily to 11-hydroxy-delta-9-THC, which is pharmacologically active, but it is further metabolised to 11-nor-delta-9-THC carboxylic acid, which is not active.

Clinical Features

1. **Acute Poisoning**
   a. Euphoria with increased garrulity and hilarity, especially when smoked in a social group setting.
   b. Temporal and spatial disorientation with intensification of sensation (colours become brighter, sounds become more distinct, music is heard with heightened fidelity) and increased clarity of perception.
   c. At high doses, the user experiences ataxia, dizziness, hallucinations, sedation, and sometimes dysphoria characterised by unpleasant sensations, fear, and panic.
   d. Sometimes an acute toxic psychosis is precipitated with suicidal ideation, anxiety, and paranoia. Occasionally, schizophrenic symptoms occur. Flashback phenomena have been reported.
   e. Tachycardia, palpitations, hypertension (high doses). Large doses can also cause postural hypotension.
   f. Stimulation of appetite (especially for sweets).
   g. Reduced bowel motility and urinary retention have occasionally been observed.
   h. Bloodshot eyes due to conjunctival congestion.
   i. Pupils are usually not affected. Occasionally, mydriasis and nystagmus may occur.
   j. Coma has been reported in children.

2. **Chronic Poisoning**
   a. *Amotivational Syndrome:* Chronic indulgence is said to induce an amotivational syndrome characterised by apathy, poor concentration, social withdrawal, and lack of motivation to study or work. However, the actual existence of such a syndrome is being questioned by some investigators today who state that previous studies had not attempted to adequately distinguish between the effects of cannabis and pre-existing psychological status. In other words, it is difficult to determine which came first, the drug or the amotivation.
   b. Heavy cannabis users demonstrate an increased tendency to develop manic, schizophreniform, and confusional psychoses over a period of time. The development of acute psychosis after chronic use is controversial because of questions about the contribution of premorbid personalities and multiple-drug use.
   c. Medical complications: Chronic heavy cannabis use is associated with an increased incidence of the following conditions:
      – Chronic lung disease and carcinogenesis: Long-term smoking of cannabis has been associated with chronic sore throat, rhinitis, bronchitis, and deterioration of pulmonary function suggesting airway narrowing. Experiments have revealed that cannabis smoking can cause a five-fold increase in blood CoHb level and three-fold increase in the amount of tar inhaled when compared with tobacco.
      – Cancers of mouth and larynx.
      – Aspergillosis: Studies have shown that cannabis is often contaminated with Aspergillus spores which can cause aspergillosis in immunocompromised individuals.
      – Non-specific ST wave changes have been reported. Prolonged intake of high doses of THC may result in bradycardia and congestive heart failure.
      – Several investigators have reported residual poor cognitive performance in heavy cannabis users, which may be due to alterations in brain function, residue of the drug present in the brain, or withdrawal effect.
      – Digital clubbing has been reported in chronic hashish users.
      – Gynaecomastia has been observed in males. Chronic use may also decrease sperm count and fertility.
      – Abrupt discontinuation of chronic cannabis use can cause a mild abstinence syndrome consisting of

agitation, aggressiveness, tremulousness, insomnia, sweating, and recurrent migraine headaches.

Usual Fatal Dose

- There are no authentically documented cases of lethality from cannabis intoxication alone. The few cases of fatality that have been reported have not adequately ruled out the possibility of multiple-drug intoxication.
- In spite of such lack of documented fatalities, some authors have suggested that the fatal dose for IV cannabis is about 1 to 2 grams, while it is 700 grams for ingestion (of bhang).
- According to some investigators, the estimated lethal dose of cannabis in humans is 30 mg/kg of absorbed cannabis.

Diagnosis

1. Clinical:
   a. Symptomatology
   b. Characteristic 'burnt rope' odour in the breath of a recent smoker.
2. Identification of suspected specimen: Suspend leaf or stem fragments in several drops of chloral hydrate (10%) on a microscope slide and examine under low power for characteristic "cystolith hairs". These hairs look like bear claws or elephant tusks. At the base of these claws is a wart-like cluster composed of calcium carbonate deposit. Add a drop of 20% HCl and note the gentle effervescent release of carbon dioxide gas in tiny bubbles.
3. Urine levels of cannabinoids: THC is hydrophobic and accumulates in adipose tissue. Screening tests may be positive for up to 70 or more days, depending on the cut-off levels used and the individual's lipid stores of THC. False positive results may occur with therapeutic use of ibuprofen, fenoprofen, and naproxen. False negatives may result from dilution, diuretic use, common salt, or other contaminants (Visine®*, soap, bleach, vinegar, etc.). Concomitant testing of urine specific gravity, pH, temperature, and creatinine could help in eliminating these confounders. Screening tests usually employ EMIT or RIA, while confirmation is done by using GC-MS. A semiquantitative EMIT homogenous enzyme immuno-assay is available for measurement of cannabinoids in urine. Hair analysis can detect drug usage up to 90 days after cessation, and cut-off values are lower for hair than urine. But it is more expensive, and invariably no more useful than urine for cannabis detection.

Treatment

1. **Acute Poisoning:**
   a. Decontamination measures in cases of ingestion. Activated charcoal is beneficial.
   b. Acute psychotic reactions respond to benzodiazepines. 5 to 10 milligrams of diazepam orally is usually sufficient.
   c. Patients suffering from postural hypotension should be placed in the Trendelenberg position until the blood pressure stabilises.
   d. Supportive measures.
2. **Chronic Poisoning:**
   a. Psychosocial therapy consisting of attempts to promote realistic and rewarding alternatives to the drug and associated life styles, along with a commitment to abstinence from self-administered or unprescribed psychotropic drugs.
   b. A combination of interventions is recommended, including urine testing, participation in multi-step programmes, education about drug effects, drug coun-selling, psychotherapy and family therapy.
   c. Drug-focussed group therapy comprising strategies such as social pressure to reinforce abstinence, teaching socialisation and problem solving skills, reducing stress and the sense of isolation common with drug abuse, relapse prevention exercises and varying degrees of confrontation.
   d. Short-term use of anxiolytic agents such as benzodiaz-epines may be necessary in some cases when anxiety symptoms are severe.
   e. Short-term use of antipsychotic medication may be required if there are persistent delusional ideas or frightening flash backs.

Forensic Issues

- Cannabis has been around for thousands of years, initially touted for its "medical" uses, and later condemned for its abuse potential.
- The mind-altering properties of cannabis probably did not receive wide attention until about 1000 BC when it became an integral part of Hindu culture in India. After AD 500, cannabis began creeping westward, and references to it began appearing in Persian and Arabic literature.
- Cannabis was brought to Europe by Napoleon's soldiers returning from Egypt in the early part of 19th century. It made its entry into the USA at about 1920 when Mexican labourers smuggled the weed across the border into Texas. Its popularity spread quickly, and by 1937 most of the American states had enacted laws prohibiting the use or possession of marijuana. Today, inspite of all efforts at minimising the abuse of cannabis, the drug is the most commonly used illicit substance in the USA.
- The use of cannabis among youth reached its peak in the 1960s when the drug became associated with social protest. The hippie generation ("flower people") was particularly found of cannabis, to whom it was a "gateway drug" opening the doors to more potent "hard drugs" such as opiates and hallucinogens.
- Recent reports of medical uses of cannabis have led to the resurgence of "pot culture" beginning with the 1990s. Consumption of cannabis in various forms has always been

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* Of the various components of Visine®, benzalkonium chloride is primarily responsible for the interference, although the borate buffer also has some effect.

popular in India. Sanyasis and temple poojaris use it to induce a trance-like state for the purpose of religious meditation. There are several festivals such as Holi and Shiva Ratri when widespread consumption occurs even among the general populace. In some areas there are "Bhang shops" openly selling various recipes of bhang (**Fig 34.14**).

- While long-term cannabis use can cause serious health problems (*vide supra*), acute intoxication sometimes leads to medicolegal complications. The danger lies in the capacity of cannabis to interfere with motor skills and judgement. Operating a motor vehicle or other machinery under the influence of the drug could lead to potential loss of life or limb.

- Occasional acute psychotic reactions precipitated by long-term heavy cannabis use can cause the user to "run amok" in homicidal frenzy. This became well known during the Vietnam war when several American soldiers began suffering from acute toxic psychosis arising out of heavy abuse. Cannabis is also known to induce suicidal ideation brought on by anxiety and paranoia.

- While cannabis does not appear to have teratogenic effects on the foetus, some studies have indicated that infants whose mothers had used the drug during pregnancy exhibited impaired foetal growth.

■ Amphetamines

Amphetamine belongs to the phenylethylamine family with a methyl group substitution in the alpha carbon position. Numerous substitutions of the phenylethylamine structure are possible, resulting in several amphetamine-like compounds. These compounds have now collectively come to be known as "amphetamines", and include amphetamine phosphate, amphetamine sulfate, benzphetamine, chlorphentermine, clobenzorex hydrochloride, dextroamphetamine, diethylpropion, mazindol, methamphetamine, 4-methylthioamphetamine, methylphenidate, pemoline, phendimetrazine, phenmetrazine, and phentermine.

In the late 1980s, a pure preparation of methamphetamine hydrochloride made its appearance for the first time in Hawaii where it was referred to as "batu". It quickly made its way across to the United Kingdom, Australia, Western Europe, and USA, where it became popular by the slang name "ice" (or "glass") (**Fig 34.15**). While ice is produced by the ephedrine reduction method and is very pure, occurring as large translucent crystals, a variant produced by an oil-based method is called "crystal" (or "crank"), and is a white to yellow crystal product.

Methamphetamine abuse began in the 1950s and reached a peak in the 1970s. It used to be referred to as "speed" or "go". The newer avatars "ice" and "crystal" are virtually the same in their pharmacological and toxic effects. Other slang names include "chalk" and "meth". Methamphetamine powder can be inhaled, smoked, ingested, or injected. Ice and crystal are almost always smoked.

Uses

Some amphetamines have therapeutic uses and are still available as prescription drugs in Western countries (**Table 34.13**). They are not available in India.

Fig 34.14: Govt authorised bhang shop

Fig 34.15: Ice amphetamine

Mode of Action

The major mechanism of action of amphetamines involves the release of monoamines from storage sites in axon terminals, which leads to increased monoamine concentration in the synaptic cleft. The release of dopamine in the nucleus accumbens and related structures is responsible for the reinforcing and mood elevating effects of amphetamines. Cardiovascular effects result from the stimulation of release of noradrenaline.

The dopamine released into the cytoplasm of neurons undergoes oxidation, resulting in the production of several toxic chemicals (oxygen radicals, peroxides and hydroxyquinones).

Methylphenidate has a different mechanism of action. Like cocaine, it produces CNS action by blocking the dopamine transporters responsible for the reuptake of dopamine from synapses following its release. The relatively low abuse potential of orally administered methylphenidate is due to slow occupation of dopamine transporters in the brain. Also, unlike cocaine, methylphenidate occupies the transporter sites for a much longer time.

Amphetamines also have weak monoamine oxidase inhibiting property, but the significance of this is not clear.

The most prominent effects of amphetamines are the catecholamine effects as a result of stimulation of peripheral alpha- and beta-adrenergic receptors. Enhanced concentration of noradrenaline at the locus coeruleus is responsible for the anorexic and stimulating effects, as well as to some extent, for the motor-stimulating effects. The increase in central

Table 34.13: Therapeutic Uses of Amphetamines

Drug	Use
Amphetamine (Benzedrine)	Attention-deficit/hyperactivity disorder, weight reduction
Dextroamphetamine (Dexedrine)	Attention-deficit/hyperactivity disorder, narcolepsy
Methamphetamine (Desoxyn)	Attention-deficit/hyperactivity disorder, weight reduction.
Methylphenidate (Ritalin)	Attention-deficit/hyperactivity disorder, narcolepsy
Benzphetamine (Didrex)	Weight reduction
Fenfluramine (Pondimin)* Dexfenfluramine (Redux)*	Weight reduction
Diethylpropion (Tenuate, Tepanil, Ten-tab, Dospan)	Weight reduction
Pemoline (Cylert)**	Attention-deficit/hyperactivity disorder
Phendimetrazine (Bontril, Phenzine, Plegine, Prelu-2, Statobex)	Weight reduction
Phentermine (Adipex-P, Fastin, Ionamin, Termene, Phentrol, Obermine) Chlorphentermine (Pre-Sate)*	Weight reduction
Mephentermine (Wyamine)	Hypotension
Clobenzorex hydrochloride	Weight reduction

*Banned Since 1997 in most countries.
**No longer considered as first-line therapy for ADHD based on reports of severe hepatotoxicity in some patients.

dopamine (especially in the neostriatum) provokes stereotypical behaviour and some motor effects. The activity of dopamine in the neostriatum appears to be linked to glutamate release and inhibition of GABA-ergic efferent neurons, contributing significantly to the stereotypical behaviour, locomotor effects, and neurotoxicity of amphetamines. The effects of serotonin and dopamine at the mesolimbic system alter perception and induce psychotic manifestations.

Toxicokinetics

In general, peak plasma levels are seen in about 30 minutes after intravenous or intramuscular injection, and about 2 to 3 hours after oral amphetamine ingestion. Amphetamines are extensively metabolised in the liver, but much of what is ingested is excreted unchanged in the urine. They differ from catecholamines in that they lack the catechol structure and therefore cannot be metabolised by catechol-o-methyl transferase (COMT), which permits oral efficacy. In general, amphetamines are lipophilic, and hence can cross the blood-brain barrier easily.

Protein binding is 16% for amphetamine, 15% for methylphenidate, and less than 40% for pemoline. Amphetamines have large volumes of distribution, varying from 3 to 5 L/kg for amphetamine, to 11 to 33 L/kg for methylphenidate. The half-life ranges from 7 to 30 hours. The half-life is considerably shortened when the urine is acidic. The excretion of unchanged amphetamine is dependant on pH, and at urine pH less than 6.6, a range of 67 to 73% of unchanged drug is excreted in the urine. At urine pH greater than 6.7, the percent excreted unchanged in the urine is reported to be 17 to 43%.

Clinical Features

1. **Acute Poisoning:**
   a. *CNS*
      – Euphoria
      – Agitation
      – Headache

   – Paranoia
   – Anorexia
   – Hyperthermia: can be severe, and may result from hypothalamic dysfunction, metabolic and muscle hyperactivity, or prolonged seizures.
   – Hyperreflexia
   – Choreoathetoid movements
   – Convulsions: Seizures are associated with a high mortality rate
   – Intracerebral haemorrhage: Abuse of amphetamine and related drugs can increase the risk for cerebro-vascular incidents in young adults
   – Coma: If it occurs, is associated with a high mortality rate.
   b. *CVS*
      – Tachycardia: Tachycardia is common, however, reflex bradycardia secondary to hypertension can occur.
      – Hypertension: Hypertension is common following amphetamine use and may result in end organ damage. Pulmonary hypertension has been associated with methamphetamine use. Hypotension and cardiovascular collapse may result from severe toxicity, and is associated with a high fatality rate.
      – Arrhythmias.
      – Vasospasm.
      – Myocardial ischaemia: Infarction can occur (*vide infra*).
      – Cardiomyopathy: Acute and chronic cardiomyopathy can result from hypertension, necrosis, or ischaemia.
   c. *Sympathetic Effects:*
      – Mydriasis
      – Sweating
      – Tremor
      – Tachypnoea
      – Nausea.

d. *Other Effects:*
   – Muscle rigidity
   – Pulmonary oedema
   – Ischaemic colitis: More common in chronic poisoning (*vide infra*).
   – Rhabdomyolysis: Develops in patients with severe agitation, muscular hyperactivity, hyperthermia, or seizures.
      - Metabolic acidosis: This occurs with severe poisoning, and has even been reported after smoking crystal methamphetamine.
e. *Complications:*
   – Psychosis with visual and tactile hallucinations.
   – Cerebral infarction
   – Myocardial infarction
   – Aortic dissection: Several cases of fatal aortic dissection associated with chronic amphetamine use have been reported.
   – Ventricular fibrillation
   – Acute renal failure: Renal failure may develop secondary to dehydration or rhabdomyolysis in patients with severe amphetamine poisoning.

Death due to amphetamine toxicity most commonly results from arrhythmias, hyperthermia, or intracerebral haemorrhage. In cases of survival, symptoms gradually resolve as the drug is excreted over a period of 24 to 48 hours.

2. **Chronic Poisoning:** Amphetamines can be taken orally, by injection, by absorption through nasal and buccal membranes; or by heating, inhalation of the vapours, and absorption through the pulmonary alveoli. Inhaled amphetamine is almost immediately absorbed with a rapid onset of effects. Unlike cocaine, amphetamines can be vapourised without much destruction of the molecule, thus obviating the need for preparing a free-base form for smoking. As with opiates, the rapid onset of effects from amphetamine injection or inhalation produces an intensely pleasurable sensation referred to as "rush". Chronic users of amphetamines tend to fall into one or the other of the following categories:

   a. **Intermittent low-dose misuse:** Some individuals (students studying for exams, military personnel on extended exercises, athletes, truck drivers on night trips, etc.), consume amphetamines periodically to overcome fatigue, prolong wakefulness, or elevate mood. They usually do not develop dependence.

   b. **Sustained oral misuse:** Some individuals who have been prescribed amphetamines for legitimate purposes, as well as some others who have been using these drugs illicitly may continue to ingest them in relatively large daily doses of 40 to 100 mg or more (as tolerance develops). Attempts to reduce the dose result in depression and lethargy.

   c. **High-dose IV abuse:** Individuals who relish the euphoria induced by amphetamines quickly progress to IV injections in order to enhance the "rush" or "flash". These individuals ("speed freaks") classically manifest the symptomatology of chronic amphetamine toxicity. They are also prone to "speed binges" wherein there are repeated cycles of action and reaction phases. The former is due to intake of the drug resulting in a "high", while the latter is due to stoppage, and is associated with acute hunger followed by intense depression or "crash". This provokes him to go on the action phase again, and the cycle continues until collapse or financial ruin.

   d. **Inhalant abuse:** When *Benzedrine* inhalers were available, a significant proportion of users became addicted. The 1959 FDA ban on these inhalers led to the introduction of *Benedrex* inhalers (containing propylhexedrine, methanol, and aromatic compounds). By the 1970s, addiction to these inhalers became a major problem. Today, all amphetamine analogues have been banned from inhalers. However, there are indications that the apparently innocuous *Vicks Nasal Inhaler* (containing *l*-desoxyephedrine, which is actually *l*-methamphetamine)* may have high abuse potential.

   e. **Manifestations of heavy chronic amphetamine use:**
      – Hyperactivity, hyperexcitability.
      – Anorexia, loss of weight, emaciation: Weight loss is one of the most characteristic findings with chronic use of amphetamine or its derivatives, and is said to be the most striking effect in chronic "ice" smoking.
      – Vomiting and diarhoea are common. Ischaemic colitis may occur.
      – Stereotyped behaviour (skin picking, pacing, interminable chattering).
      – Dyskinesias: bruxism, tics.
      – Paranoid psychosis, unpredictable violence: In one study, the most common symptoms in patients with methamphetamine-induced psychosis were auditory and visual hallucinations, persecutory delusions, and delusions of reference. They also demonstrated a high tendency for major depressive disorder, alcohol dependence, and antisocial personality disorder.
      – Heightened sexual activity initially, followed by impotence and sexual dysfunction.
      – Occasionally, very rapid IV injection of a large dose produces a condition called "overamped", characterised by inability to speak or move even though consciousness is fully retained. Blood pressure and temperature are usually elevated. There may be respiratory distress.
      – Deterioration of *social* (family problems), *physical* (slovenly, unkempt appearance), and *economic* (loss of job, bankruptcy) status.
      – Adverse psychological reactions—anxiety reactions, amphetamine psychosis, exhaustion syndrome, depression and hallucinosis.
      – One study revealed that postmortem levels of striatal dopamine in some methamphetamine users were reduced to levels similar to those seen in patients with Parkinson's disease in the caudate,

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* The other ingredients include menthol, camphor, methyl salicylate, and bornyl acetate.

but not in the putamen subdivision of the striatum. This reduction of the neurotransmitter in the striatal subdivision could explain the presence of cognitive problems in methamphetamine users.

- Medical complications—cardiomyopathy, vasculitis, pulmonary hypertension, permanent neurological deficits, HIV infection, hepatitis, endocarditis, osteomyelitis, and pulmonary abscesses. Case reports of hepatotoxicity resulting in hepatocellular injury have been reported in children receiving pemoline. As of September 1999, pemoline has been withdrawn from some Western countries. In one case, a young boy unresponsive to other drugs in the treatment of his attention deficit/hyperactivity disorder (ADHD), received 75 mg/day of pemoline. This resulted in liver failure which required transplantation.
- Obstetric complications (in pregnant users)—eclampsia, intrauterine growth retardation, prematurity, etc. Amphetamine use during pregnancy has also been associated with birth defects, increased risk of cardiac malformations and cleft palate.
- Intravenous injection abusers may display skin lesions, such as "tracks", abscesses, ulcers, cellulitis, or necrotising angitis.

f. Withdrawal syndrome: Withdrawal after prolonged amphetamine abuse may precipitate severe depression and suicide attempts. Anxiety, abdominal cramps, gastroenteritis, headache, diaphoresis, lethargy, and dyspnoea may result. Increased appetite is common.

Diagnosis

1. Urine is the specimen of choice. Levels above 2 mg/100 ml indicate acute toxicity. Methods of analysis include TLC, RIA, HPLC, and GC-MS. The first three methods often give false positive results, and hence confirmation of a positive test must always be done by GC-MS.
2. A new method (electron-impact mass fragmentography) enables detection and even quantitation of methamphetamine in hair, nails, sweat and saliva.
3. Hair analysis may provide documentation of methamphetamine or other drug exposure for several months or longer. The condition of the hair (wet, dry, dirty, permed or dyed) does not affect results. To obtain hair samples, a new disposable scissors should be used to cut a very small amount of hair (100 mg total, about the width of a pencil) from about 10 different places. The hair must be cut as close to the scalp as possible.

Usual Fatal Dose

The fatal dose of amphetamines is highly variable, and while death can occur with as little as 1.5 mg/kg of methamphetamine, survival has been recorded with 28 mg/kg. This in fact represents the usual range of amphetamine's lethal dose—150 mg to 2 grams. However, because of tolerance, addicts can tolerate up to 5 grams (single IV dose), or 15 gm/day (smokable methamphetamine).

Lethal blood level is said to be around 0.2 mg per 100 ml, though addicts can tolerate much higher levels with hardly any toxic effects.

Treatment

1. **Acute Poisoning:**
   a. *Stabilisation*:
      - IV line, cardiac monitoring.
      - Oxygen.
      - Evaluate blood glucose, BUN, and electrolyte levels.
      - Consider the necessity of a CBC, urinalysis, coagulation profile, chest X-ray, CT scan of head, and lumbar puncture, depending on the presentation.
      - Measure core temperature.
      - Shock is a poor prognostic sign and needs to be managed effectively. Consider the need for right-sided heart catheterisation to measure right-sided filling pressure and cardiac output.
   b. *Supportive Measures*:
      - Airway management, ventilatory support.
      - Rapid rehydration.
      - Mannitol diuresis promotes myoglobin clearance to prevent renal failure.
      - Assess psychological and neurological status.
      - Gastric decontamination (in cases of ingestion) with appropriate tracheal protection. Activated charcoal is beneficial.
   c. *Specific Measures*:
      - Anxiety, agitation, and hyperactivity can usually be controlled with benzodiazepines. Diazepam is the drug of choice, and is administered in a dose of 10 mg IV at intervals (up to a maximum of 100 mg). Much larger doses (hundreds of milligrams) may be required to obtain adequate sedation. Titrate dose to clinical response. Control of agitation is an important aspect to the treatment of amphetamine overdose, since it often leads to hyperthermia, a common cause of mortality in amphetamine overdose. Neuroleptics are generally not preferred since they may aggravate hyperthermia, convulsions, and cardiac arrhythmias. Physical restraint is inadvisable, since resistance against such measures will aggravate rhabdomyolysis and hyperthermia.
      - Extreme agitation and hallucinations may require the administration of IV droperidol (up to 0.1 mg/kg). Since haloperidol lowers the seizures threshold, and is associated with neuroleptic malignant syndrome, it is not advisable.
      - Convulsions can be managed with benzodiazepines (IV diazepam), phenytoin, or barbiturates. Refractory cases may require curarisation.
      - Hyperthermia should be tackled aggressively with hypothermic blankets, ice baths, and dantrolene infusions. Large IV doses of benzodiazepines can help. Refractory cases must be subjected to neuromuscular paralysis and mechanical ventilation.

– Tachycardia can be managed with beta blockers (atenolol). Labetolol which has combined alpha and beta blocking effects, may be preferable if tachycardia is associated with hypertension. Sedation with intravenous benzodiazepines (diazepam 5 to 10 mg IV repeated every 5 to 10 minutes as needed) is usually sufficient for treating hypertension. A short acting, titratable agent such as sodium nitroprusside should be considered if unresponsive to benzodiazepines.

– For ventricular arrhythmias: Lignocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia. Sotalol is a good alternative. Amiodarone and sotalol should be used with caution if the QT interval is prolonged, or if torsades de pointes is involved in the overdose. Unstable rhythms require cardioversion. Atropine may be used when severe bradycardia is present, and PVCs are thought to represent an escape complex.

– For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy, and may help prevent renal insufficiency. Diuretics such as mannitol or furosemide may be needed to maintain urine output. Urinary alkalinisation is not routinely recommended.

– Diazepam and chlorpromazine have been effective in treating amphetamine-induced chorea.

– Other complications should be anticipated and treated as and when they arise.

– Although peritoneal dialysis and haemodialysis have been demonstrated to enhance elimination of amphetamine, the clinical efficacy of these procedures in human overdose has not been proven and they are rarely if ever clinically indicated. Acidification of urine enhances amphetamine excretion, but may precipitate acute renal failure in patients with myoglobinuria and is therefore contraindicated.

2. **Chronic Poisoning:**

   a   Most casual users of amphetamines do not need treatment. Those with moderately severe dependence can be treated on an outpatient basis without using drugs. Strategies range from residential and ambulatory detoxification to day treatment, multistep activities, and case management. It is preferable to provide a structured and manualised cognitive behavioural treatment, making use of a combination of group and individual counselling.

   b.   A wide variety of pharmacological agents have been tried as adjuncts to (or major elements in) the treatment of amphetamine dependence. These include drugs such as imipramine and fluoxetine, but results have been disappointing.

   c.   In some European countries, low-dose amphetamines are administered to addicts as part of the detoxification programme in the initial stages, to assist the subject overcome the phase of "craving". There are however doubts expressed by other investigators over such an approach.

■ Designer Drugs

Designer drugs are congeners of active compounds that have been modified from legitimate pharmaceutical agents, and are used for recreational purposes. Apart from amphetamines, there are several other groups of designer drugs (**Table 34.14**) which have been discussed in detail elsewhere.

Designer drugs are usually stronger and cheaper than the parent compound, and can be easily synthesised in clandestine laboratories. The term "designer drug" does not include new forms or new dosing routes of old drugs (e.g. cocaine used in freebase form, i.e. "crack"). It also does not include legal drugs which are abused (e.g. ephedrine, caffeine, phenylpropanolamine, etc.).

Since 1983 it has become increasingly popular among adolescents and college students as a recreational drug to be used during "rave parties" which are extended dance parties often lasting all night long (**Fig 34.16**). The other designer amphetamines quickly followed and are mostly available as gelatin capsules or loose powder for ingestion. They have made their way into India in the late 1990s, and are quite openly abused by college students from affluent families.

Uses

Methylenedioxymethamphetamine (MDMA) was used in the early years following its synthesis, by psychologists to enhance psychotherapy. Today, there are no legal uses for any of the designer amphetamines.

A herbal stimulant ('S-5 tablets') marketed in the Netherlands was found to contain para-methylthioamphetamine

Table 34.14: Designer Drugs				
Amphetamines	*Opiate Derivatives*	*Methaqualone Derivatives*	*Arylhexylamines*	*Phenylethylamines*
Methamphetamine ("Speed" "Crystal" "Ice")	Fentanyl derivatives: α-Methylfentanyl ("China white") 3-Methylfentanyl	Mecloqualone Nitromethaqualone	Phencyclidine	Mescaline
Methylenedioxymethamphetamine or MDMA ("Adam," "Ecstasy," "XTC" "MDM," "M&M") Methylenedioxyethamphetamine (MDEA) ("Eve")	Pethidine derivatives: Methylphenylpropionoxypiperidine (MPPP) Methylphenyltetrahydropyridine (MPTP)			
Bromomethyl loxy phenylethylamine ("Afterburner")				
Trifluoromethylphenylpiperazine ("Molly")				

Fig 34.16: A "Rave party" in an undisclosed location in India

(p-MTA or 4-methylthioamphetamine {4-MTA}). It appears to be a potent selective serotonin releaser without serotonin neurotoxic effects. Efforts are on to make 4-MTA a controlled substance in the United Kingdom under the Misuse of Drugs Act. The street name for these tablets containing 100 mg of 4-MTA is "flatliners".

Mode of Action

While designer amphetamines share a number of properties with the original amphetamines, unlike the latter, they are potent releasers of serotonin. Chronic administration can result in permanent damage to serotonergic neurons. There is strong evidence to suggest that MDMA use can result in alterations and potential damage to serotonin neurons. Studies have also indicated that the effects of MDMA on 5-HT neurons in the human cortex may be reversible in individuals who stop using MDMA, but the effects of MDMA on memory function may be long-lasting.

Clinical Features

1. Designer amphetamines are abused by teenagers and young adults for inducing euphoria, facilitating intimacy and verbosity, and heightening sexuality. Users of MDMA report that it "expands consciousness" without making them lose control. Sometimes these drugs are labelled "entactogens" for their alleged ability to increase sensitivity to touch, or "empathicogens", for their alleged ability to create empathy, especially before sexual encounters. MDMA is considered an "entheogen" which means "to become divine from within". Entheogen refers to a state of shamanic or ecstatic possession induced by ingestion of mind-altering drugs.

2. "*Candyflipping*" refers to the intentional combination of ecstasy with LSD. Another method of use is called "*stacking*" in which 3 or more tablets of MDMA are taken at once; or MDMA is mixed with alcohol, cannabis or some other drug (ketamine, GHB, cocaine, etc.) in order to modify the "high". Stacking can increase the risk of overdose, since MDMA, acting as a stimulant, can mask the sedative effects of alcohol or any other drug. There is current vogue for combining ecstasy with sildenafil to enhance sexual pleasure (*"sexstasy"*).

3. **Acute toxicity** results in nausea, anorexia, anxiety, mydriasis, hyperthermia, muscle rigidity, trismus, sinus tachycardia, sweating, tachypnoea, cardiac arrhythmias, cardiac arrest, metabolic acidosis, rhabdomyolysis, myoglobinuria, acute renal failure, and disseminated intravascular coagulation. The following have been reported: convulsions, cerebral infarcts, hallucinations, paranoia, chest pain, hyperkalaemia, and fulminant hepatic failure.

4. Effects are seen 30 to 45 seconds after ingestion (on an empty stomach) in the form of a 'rush', which lasts 15 to 30 minutes. This is followed by a sense of clarity and joy. A booster dose may be taken at this point, to prolong these feelings. About ½ hour to 3 hours after the initial ingestion, a "plateau" phase occurs in which repetitive or trance-like movements become extremely pleasurable. The "coming down" phase occurs 3 to 6 hours after the initial ingestion, and can lead to negative feelings or emotions (depression, anxiety). Symptoms may persist for several days.

5. Hallucinations are common, and may be auditory or visual in nature. Users often describe seeing trails of lights. Flashbacks have been reported in several MDMA users. Acute panic attacks and panic disorder following use of MDMA have also been reported.

6. Hyperthermia is common in severe cases, and can contribute to death. It is similar in mechanism to malignant hyperthermia, which is biochemically caused by a rise of calcium ions in the myoplasm.

7. Hypertension and tachycardia are also common, while hypotension and cardiovascular collapse can occur in severe poisoning.

8. Cardiac arrhythmias are common in patients with severe toxicity following MDMA overdose.

9. Chest pain can occur with ecstasy use combined with physical exertion. Myocardial infarction has been reported. Spontaneous pneumomediastinum occurred in another case following the ingestion of three ecstasy tablets. He also recovered, and was discharged without sequelae.

10. Pulmonary oedema and ARDS may occur in severe intoxications.

11. Convulsions are common in severe toxicity.

12. Coma may develop in severe cases.

13. Intracranial haemorrhages have been reported with the use of these drugs, as in the case of regular amphetamines and cocaine.

14. Acute renal failure has been reported in patients who develop rhabdomyolysis and/or disseminated intravascular coagulation associated with MDA, MDEA or MDMA.

15. Metabolic (lactic) acidosis may occur in severe cases. Hyperkalaemia and dehydration have been reported. Hyponatraemia associated with SIADH has also been reported.

16. Prolonged INR/PT and PTT, thrombocytopenia, anaemia and elevated fibrin degradation products have been observed in severe poisonings. A few cases of aplastic anaemia associated with MDMA use have been reported.

17. Muscle spasms, jaw clenching, tremors, and hyperreflexia are common. Idiopathic temporomandibular joint syndrome (TMJ) has been reported in some patients,

partly due to the secondary effects of bruxism and trismus observed following acute exposure.

18. Rhabdomyolysis is a common complication in patients who develop hyperthermia, seizures, coma, or muscular hyperactivity.

19. Eye pain, blurred vision and diffuse, punctate epithelial erosions of the cornea have been reported in patients who ingested MDMA and remained awake for long periods of time.

20. **Chronic use** results in anorexia, weight loss, exhaustion, jaundice, irritability, flashbacks, paranoia, depression, or psychosis. However, since frequent use diminishes the pleasurable effects of these drugs, users often take them only at intervals of 2 to 3 weeks, and then gradually lose interest and stop intake altogether over a period of time.* There appear to be no reports of individuals who take excessive doses of these drugs frequently over an extended period of time.

21. There are indications that chronic use of MDMA may cause mild-to-moderate subclinical impairment in cognitive function, which may be related to deficits in serotonin (5-HT) function. Chronic paranoid psychosis has been reported in several cases of individuals chronically abusing MDMA.

22. Parkinsonian symptoms occurred in some patients following regular ingestion of MDMA over a prolonged period.

23. Hepatitis has been reported with chronic abuse.

24. Ecstasy has been associated with cardiovascular and musculoskeletal malformations in babies exposed in utero.

Treatment

Treatment measures are essentially the same as for all amphetamine poisonings.

Forensic Issues

Amphetamines are the most widely used illicit drugs (second only to cannabis) in the United Kingdom, Australia, and many parts of Europe. Significant abuse also occurs in the USA. After the introduction of amphetamines into clinical use in the early 1930s, they were available as prescription drugs for various indications (obesity, narcolepsy, attention deficit disorder, psychotherapy), and even sold over the counter in the form of nasal inhalers till the early 1970s. Since then their pharmaceutical use has been greatly curtailed, though many of these drugs are still available (under restriction) in Western countries. They are virtually banned in India.

Today, designer amphetamines are a rage among adolescent party-goers, and are used extensively in the course of "rave parties". This fad has now gripped several metropolitan Indian cities where tablets of Ecstasy** (**Fig 34.17**) are available freely among elite circles (each tablet costing Rs.300 to 500). Much of this popularity has to do with the copious amount of information existing on these drugs on the Internet, and the fact that unlike certain other drugs like heroin and cannabis, designer drugs are considered "hep" and "cool". Also, unlike many other

Fig 34.17: Tablets of "Ecstasy"

hard drugs, designer drugs can be easily consumed (ingested) without the messiness of nasal insufflations, smoking, or injection. Although MDMA is classified as a Schedule I drug, it is estimated by the US media that every year, hundreds of thousands of doses are used illegally. It is most commonly used by youngsters as they "roll" at underground rave parties that can last for many hours.

■ Hallucinogens (Psychedelics, Psychotomimetics)

Hallucinogens are substances that induce changes in thought, perception, and mood, without causing major disturbances in the autonomic nervous system. Perceptual alterations can take the form of illusions, synaesthesias, or hallucinations. An *illusion* is the result of misinterpretation of an actual experience, while *synaesthesias* are sensory misperceptions (e.g. hearing colour or seeing sounds). Both require external stimuli for their institution. *Hallucinations* differ from them in this important respect, since they are perceptual alterations without any external stimulation whatsoever. Hallucinations may be visual, auditory, olfactory, gustatory, or tactile in nature. Most hallucinogens induce visual or auditory hallucinations; a few cause tactile or olfactory manifestations. While a number of therapeutic drugs can cause hallucinations in overdose, they are not classified as hallucinogens. A true hallucinogen is a drug that induces hallucinations in small doses (sometimes, as in the case of LSD, in microgram doses). Most genuine hallucinogens cause vivid visual hallucinations, while the other types of hallucinations are relatively uncommon. **Table 34.15** lists common hallucinogens, some of which will be discussed in detail in this section, while the others have been discussed in appropriate sections elsewhere.

1. Lysergic Acid Diethylamide

Lysergic acid diethylamide (LSD) is the synthetic diethylamide derivative of ergot alkaloids, and was originally synthesised

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* Freshmen love it, sophomores like it, juniors are ambivalent, and seniors dislike it!

** The term "Ecstasy" which is most often associated with MDMA has also been used to refer to gammahydroxybutyrate (GHB, 'liquid ecstasy' 'herbal ecstasy'), an ephedrine-containing preparation.

Table 34.15: True Hallucinogens

Indole Alkaloid Derivatives	Piperidine Derivatives	Phenylethylamine Derivatives	Cannabinoids
LSD	Datura	Mescaline	δ^9 tetrahydrocannabinol
Psilocin, psilocybin	Cocaine	Designer amphetamines	
Ibogaine	Phencyclidine		
Harmine	Ketamine		
DMT, DET, DPT, etc.			
Bufotenine			

exclusively from these alkaloids produced by the fungus *Claviceps purpurea*, which is a contaminant of rye and certain other grains (*page no 284*) (**Fig 34.18**). Today, most LSD is synthesised entirely in the laboratory, and typically sold to addicts as liquid-impregnated blotting paper (**Fig 34.19**) or sugar cubes, tiny tablets ("microdots"), gelatin squares ("window panes"), liquid, or powder. LSD is said to be the most powerful of all hallucinogens, and is active in doses of 50 to 100 µg. It occurs as a water-soluble, colourless, tasteless and odourless powder.

Fig 34.18: Ergot infested rye

Fig 34.19: LSD-impregnated blotters

Drugs related to LSD (lysergamides) also occur naturally in plants such as "Morning glory" (*Rivea corymbosa*) (**Fig 34.20**) and "Hawaiian baby woodrose" (*Ipomoea violacea*). Seeds of morning glory contain lysergic acid hydroxyethylamide, which is 1/10th as powerful as LSD. At least 200 to 300 seeds have to be pulverised—intact seed coat resists digestion—and ingested, for inducing hallucinogenic effects.

Mode of Intake

The LSD is almost always ingested. Other less common routes of intake include intranasal, sublingual, smoking, conjuctival instillation, and very rarely injection.

Mode of Action

The LSD is structurally related to serotonin (5-hydroxy-tryptamine) and is an agonist at the 5-HT$_1$ receptor. Serotonin modulates many psychological and physiological processes including mood, personality, affect, appetite, sexual desire, motor function, temperature regulation, pain perception, and sleep induction. LSD inhibits central raphe neurons of brainstem through stimulation of 5-HT$_{1A}$ receptors, which are coupled to adenylcyclase. LSD is also an agonist at 5-HT$_{2A, 2C}$ receptors, which are not located presynaptically on serotonergic cell bodies but on certain subpopulations of neurons in postsynaptic regions. The majority of 5-HT$_2$ receptors in the brain are located in the cerebral cortex. Animal experiments have shown that LSD is anatomically distributed maximally in the visual and auditory cortex, and the limbic cortex (besides the pituitary, pineal, and hypothalamic areas), which parallels the finding of high concentration of 5-HT$_2$ receptors in human cerebral cortex. Recent studies also suggest that

Fig 34.20: Morning glory

activation of D_1 (dopamine) receptors may contribute to the neurochemical effects of LSD.

Toxicokinetics

The LSD has a half-life of 2.5 hours, while the duration of effects lasts for up to 8 hours. But psychotropic effects can occur for several days, and urine-screen is usually positive for 100 to 120 hours. The route of metabolism is hepatic hydroxylation. The usual dose of abuse is 100 to 300 mcg. Doses over 0.2 mg/kg are potentially lethal.

Clinical (Toxic) Features

1. **Acute Poisoning:**
   a. Physical
      – Mydriasis, hippus.
      – Vertigo.
      – Tachycardia, hypertension.
      – Sweating, piloerection.
      – Hyperthermia.
      – Tachypnoea.
      – Muscle weakness, ataxia.
      – Hyperactivity.
      – Coma.
   b. Psychological
      – Euphoria or dysphoria.
      – Vivid hallucinations, synaesthesias.
      – *Bizarre perceptual changes:* People's faces and body parts appear distorted, objects undulate, sounds may be magnified and distorted, colours seem brighter with halos around objects. Occasionally there is depersonalisation, and the hallucinating person may feel as if he is observing an event instead of being involved in it.

2. **Chronic Poisoning:**
   a. Prolonged psychotic reactions which are mainly schizophrenic in nature.
   b. Severe depression.
   c. *Flashback phenomena:* The person relives the LSD experience periodically in the absence of drug intake for months or years.
   d. *Post-hallucinogen perception disorder:* A persistent perceptual disorder often described by the person as if he is residing in a bubble under water in a "purple haze", with trailing of lights and images. Associated anxiety, panic, and depression are common. The following unusual phenomena have also been reported:
      – **Pareidolias**: images of faces on floor and walls, floating faces hovering in space.
      – **Aeropsia:** visualisation of air in the form of numerous vibrating pinpoint-sized dots ("molecules").

Diagnosis

- Radioimmunoassay of serum or urine (limit of detection 0.1ng/ml).
- HPTLC (high performance thin layer chromatography) can detect LSD in urine in concentrations less than 1 mcg/litre.
- HPLC (high pressure/performance liquid chromatography) of serum and urine.
- GC-MS (gas chromatography–mass spectrometry) can confirm positive LSD urine levels to a lower limit of 5 pg/ml.

Treatment

- Avoid gut decontamination as LSD is ingested in microquantities and rapidly absorbed, rendering decontamination procedures totally redundant.
- Do not use restraints in agitated patients; it will only exacerbate the condition.
- Because of the short half-life and few serious medical reactions, elimination enhancement procedures such as haemodialysis, haemoperfusion, etc. are not warranted.
- Treat acute panic attacks with quiet environment, reassurance, supportive care, and administration of diazepam (5–10 mg IV) or haloperidol (in severe cases).
- Treat acute psychotic reactions with cautious administration of neuroleptics such as haloperidol. Avoid phenothiazines which can cause hypotension, sedation, extrapyramidal reactions, lowered seizure threshold, and potentiation of anticholinergic effects.
- Treat flashbacks with psychotherapy, anti-anxiety agents, and neuroleptics.
- Treat post-hallucinogen perception disorder with long-lasting benzodiazepines such as clonazepam, and to a lesser extent anticonvulsants such as valproic acid and carbamazepine. This approach must be combined with behavioural therapy. The patient must be instructed not to consume alcohol, cannabis, caffeine, and other drugs which can intensify the disorder.

2. **Phencyclidine**

Source

Phencyclidine (PCP), a phenylcyclohexylamine compound, is easily synthesised from piperazine, cyclohexanone, and potassium cyanide. It is commonly referred to by addicts as "angel dust" or "PCP".

Phencyclidine was developed in the 1950s as a potential general anaesthetic by Parke-Davis under the brand name Sernyl. It was termed a "dissociative anaesthetic" because unlike conventional anaesthetics which induced a state of relaxed sleep, PCP induced a state of catatonia with flat facies, open mouth, fixed staring, rigid posturing, and waxy flexibility. Patients seemed dissociated from the environment without classical coma. However, a significant proportion of patients showed severe adverse reactions during emergence, including agitation and hallucinations. Some suffered from psychosis for up to 10 days. PCP was therefore quickly withdrawn. Today, ketamine a less potent PCP derivative is quite popular as an anaesthetic.

Mode of Intake

Phencyclidine (PCP) is abused by smoking, insufflation, ingestion, or rarely IV injection. It is commonly sold on the street as tablets (about 5 mg), capsules, powder, aqueous or alcoholic solution, or as "rock salt" crystal. It is often mixed with parsley, mint, oregano,

or marijuana. Sometimes "crack" is dipped in PCP and smoked ("tragic magic"), or cannabis is dipped in PCP ("love boat").

Mode of Action

Phencyclidine antagonises the action of glutamate at the NMDA (N-methyl-d-aspartate) receptor. It binds within the ion channel (PCP binding site) to block Ca^{++} influx which results from glutamate binding. Unlike the other types of glutamate receptor channels, NMDA channels are permeable to both Ca^{++} and Na^+. Following NMDA receptor activation, NMDA-mediated Ca^{++} flux may lead to stimulation of calmodulin-dependant kinases with activation of postsynaptic second-messenger pathways. Opening the NMDA channel facilitates access of PCP to its receptor, accelerating the rate at which PCP-induced blockade of NMDA receptor-mediated neurotransmission takes place.

At doses much higher than at which it exerts its unique behavioural effects by blocking NMDA receptor-mediated neurotransmission, PCP also blocks presynaptic monoamine reuptake, thus directly increasing synaptic levels of dopamine and noradrenaline. At even higher doses, PCP blocks neuronal Na^+ and K^+ channels, as well as muscarinic cholinergic receptors. This may explain the occurrence of convulsions in PCP overdose.

Toxicokinetics

The volume of distribution of phencyclidine is 6.2 L/kg. Plasma protein binding is about 65%. Since it is highly lipid soluble, it accumulates in brain and adipose tissue. Metabolism of the latter causes release of PCP which contributes to the recurrence of symptoms. PCP can be detected in urine up to 20 to 30 days (usually 2 weeks).

Clinical (Toxic) Features

1. *CNS*:
   a. Level of consciouness ranges from fully alert to comatose. The coma is usually preceded as well as followed (upon recovery) by agitation and psychosis.
   b. Confusion, disorientation, amnesia.
   c. Catatonia with unusual posturing, mutism, and staring.
   d. Myoclonic and dystonic movements, choreoathetoid, opisthotonus, torticollis.
   e. Acute toxic psychosis with bizarre behaviour, agitation, and violence.
   f. Cholinergic (sweating, miosis, salivation, bronchospasm), or anticholinergic (mydriasis, tachycardia, urinary retention) signs may be present.
   g. Hallucinations (auditory and visual).
   h. Convulsions.
   i. Hyperthermia.
2. *Eye*:
   a. Blank stare
   b. Dysconjugate gaze
   c. Nystagmus (horizontal, vertical, or rotatory)
   d. Blurred vision
   e. Miosis (occasionally mydriasis).
3. *CVS*:
   a. Sinus tachycardia
   b. Hypertension.

4. *GIT*:
   a. Vomiting.
5. *RS*:
   a. Tachypnoea.
6. *Renal*:
   a. Myoglobinuria
   b. Acute renal failure.

Usual Fatal Dose

- Approximately 100 mg or more.
- Lethal blood level: 0.1 mg/100 ml.

Diagnosis

1. Serum PCP levels usually do not correlate well with clinical picture. Therefore, a qualitative test is adequate in most cases.
2. Laboratory findings:
   a. Leukocytosis
   b. Hypoglycaemia
   c. Hyperkalaemia
   d. Elevated muscle enzymes
   e. EEG: Diffuse slowing with theta and delta waves.

Treatment

1. The need for syrup of ipecac or gastric lavage should be assessed carefully. Often such measures may exacerbate agitation and violence.
2. Activated charcoal is highly beneficial and can be administered at a dose of 1 gm/kg every 4 hours for several doses.
3. A single dose of a suitable cathartic such as sorbitol can be given (unless there are specific contraindications).
4. Some authors recommend urinary acidification to enhance excretion of PCP (which is a weak base). But only 10% of the drug is excreted in the urine, while the remaining 90% is metabolised in the liver. Hence the practical utility of urinary acidification is negligible.
5. Haemodialysis and haemoperfusion are not beneficial.
6. As of now there is no antidote for PCP, though efforts are on to develop PCP-specific antigen binding fragmens (Fab) which can prove to be very useful.
7. Agitated patients should be restrained, at first physically and later pharmaceutically. Hypoglycaemia, if present, must be treated with 50% dextrose in water. Subsequently if agitation persists, administer titrated doses of diazepam 5 to 10 mg IV, every 10 minutes, until the patient is calmed. Phenothiazines should be avoided since they can worsen dystonic reactions, hypotension, hyperthermia, and lower the seizure threshold.
8. Specific antihypertensive therapy should be instituted in patients with very high blood pressure.
9. Myoglobinuria should be treated with IV infusion of 1 litre of 5% dextrose in water (containing 25 gm of mannitol and 100 mEq of sodium bicarbonate), at a rate of 250 ml/hour. Monitor the patient for hypokalaemia. If renal failure has occurred, haemodialysis should be undertaken.

Forensic Issues (Hallucinogens)

Hallucinogen abuse has been traditionally a Western phenomenon, and drugs of abuse such as LSD and phencyclidine have always been popular only in countries such as the USA, UK, Australia, and parts of Europe. The popularity of such drugs has been fuelled by their, glamourous representation in films and rock music. The 1960s saw an explosion of hallucinogen use almost in the form of an epidemic, and though it declined steeply in the 1970s and 1980s, there has been an alarming resurgence over the last decade.

The dangers of hallucinogen use do not have as much to do with acute toxicity, as with long-term psychological damage. The inevitable fallout is violent crime manifesting as assaultative behaviour, homicides, and suicides. Several horrific crimes have been committed by drug-crazed individuals acting out their bizarre fantasies.

■ Inhalants ("Glue Sniffing", Volatile Substance Abuse, Inhalant-related Disorders)

Inhalant drugs (volatile substances) are widely available and frequently abused, especially by adolescents from poor socioeconomic background. These substances are mostly volatile hydrocarbons which are used as solvents, propellants, thinners, and fuels (**Table 34.16**). The hydrocarbon is typically inhaled by pouring into a container for "sniffing", a rag or sock for "huffing", or a plastic/paper bag for "bagging". Abusers often begin with "sniffing" (lower concentrations), and progress subsequently to "huffing" and "bagging" (higher levels of exposure).

The most commonly abused inhalants include toluene from paints and glues; petrol; butane from cigarette lighter fluids; butyl and isobutyl nitrite; and halogenated hydrocarbons from typewriter correction fluids, propellants, and dry cleaning fluids.

Inhalation of volatile substances produces intoxicating effects rapidly. They are well absorbed through the lungs and distributed quickly to the CNS. One or two huffs will begin to intoxicate the user within seconds, and the effects usually last for several hours. Chronic users can maintain a prolonged high with periodic inhalations every few hours.

Clinical (Toxic) Features

1. **Acute**
   a. *CNS*—Excitation, agitation, hallucinations, headache, vertigo, nystagmus, ataxia, convulsions, lethargy, stupor, respiratory depression.
   b. *CVS*—Arrhythmias and sudden death ("*sudden sniffing death*").
   c. *Other Effects*—
      – Methaemoglobinaemia (butyl and isobutyl nitrites).
      – Carbon monoxide poisoning (methylene chloride).
      – Hepatitis (chlorinated hydrocarbons).
      – Metabolic acidosis, rhabdomyolysis, renal failure, hypokalaemia (toluene).

2. **Chronic**
   a. *Chronic painter syndrome*—A neurobehavioural syndrome due to solvent-induced encephalopathy, characterised by memory loss, anxiety, depression, sleep disorders, neurasthenia, and personality changes. CT

Table 34.16: Common Inhalants of Abuse

Inhalant	Constituent
Acrylic paint	Toluene
Aerosol propellant	Fluorocarbons, nitrous oxide
Anaesthetics	Enflurane, halothane, isoflurane, nitrous oxide
Dyes	Acetone, methylene chloride
Fire extinguisher	Bromochlorodifluoromethane (BCF)
Bottled gas, torches	Propane, butane
Glues/adhesives	Toluene, benzene, xylene, acetone, naphtha, n-hexane, trichloroethylene, ethylacetate, tetrachloroethylene, trichloroethane, carbon tetrachloride, methylethyl ketone
Lighter fluid	Butane
Nail polish remover	Acetone, amyl acetate, isopropanol
Paint stripper	Methylene chloride
Paint varnish/lacquer	Trichloroethylene, toluene, mineral spirits
Petrol (gasoline)	Hydrocarbons
Polystyrene cements	Acetone, toluene, trichloroethylene, n-hexane
Refrigerants	Fluorochloromethanes
Rubber cement	Benzene, n-hexane, trichloroethylene
Shoe polish	Chlorinated hydrocarbons, toluene
Solvent (laboratory)	Carbon tetrachloride, chloroform, diethylether, n-hexane, methyl isobutylketone
Spot remover	Trichloroethane, trichloroethylene, carbon tetrachloride
Typewriter correction fluid	Trichloroethane, trichloroethylene, perchloroethylene.

scan often reveals areas of atrophy, and EEG readings are usually abnormal.

b. Cerebellar dysfunction with chorea (petrol).
c. Peripheral neuropathy (n-hexane).
d. Increased incidence of leukaemia, aplastic anaemia, and multiple myeloma (benzene).
e. Abdominal pain, nausea, vomiting, haematemesis.
f. Cardiomyopathy.
g. Hepatotoxicity.
h. Pulmonary disorders—pulmonary hypertension, acute respiratory distress.
i. Dementia (leaded petrol, toluene).

Treatment

Inhalant intoxication, like alcohol intoxication, usually requires no special treatment and resolves spontaneously. However, complications such as cardiac arrhythmias, bronchospasm, coma, etc. will require prompt treatment. Essentially, medical care primarily involves reassurance, quiet environment, and attention to vital signs and level of consciousness. Sedative drugs such as benzodiazepines are contraindicated, since they may aggravate intoxication. Severe agitation may require cautious control with haloperidol (5 mg for adults) intramuscularly, repeated once after 20 minutes if necessary.

Inhalant dependence requires specialised treatment by a qualified psychiatrist, and may take 3 to 12 months for achieving total abstinence. Relapses are not uncommon.

Forensic Issues

Volatile substances abuse (VSA) is a uniquely adolescent phenomenon, and is particularly common among lower socioeconomic classes, mainly because these substances are cheap, easily available, and legal to possess. Also, the mode of intake is relatively simple. VSA is quite common among street urchins of major Indian cities, probably because these inexpensive substances offer a rare exciting experience to escape from the daily misery of poverty (**Fig 34.21**). Persons with adolescent conduct disorder and adult antisocial personality disorder are especially prone to VSA.

Fig 34.21: "Glue Sniffing"
(*Pic*: Dr Rais Vohra)

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Section

12

Analytical Toxicology

Biochemical and Haematological Tests

■ INTRODUCTION

Scientific methods of analysis for poisons have only recently been developed. Until the 19th century, doctors and scientists harboured faulty notions about the effect of poisons on the human body. It was believed that if a dead body was black, blue, or spotted in places, or "smelled bad", the cause of death was a poison. Other fallacious ideas were that the heart of a poisoned person could not be destroyed by fire, and that the body of a person dying from arsenic poisoning would not decay. The first person to suggest a method for detecting poisons in tissues was the Dutch physician Hermann Boerhoave who theorised that various poisons in hot vaporous condition yielded typical odours. He placed substances suspected of containing poisons on hot coals and tested their smells.

Owing to the widespread use of arsenic as a homicidal poison in the middle ages, it is small wonder that the first milestones in the chemical isolation and identification of a poison in body tissues and fluids centred around arsenic. In 1775, Karl Wilhelm Scheele, the famous Swedish chemist, discovered that white arsenic (arsenic trioxide) was converted to arsenious acid by chlorine water, and the addition of metallic zinc reduced the arsenious acid to arsine gas. Gently heating the ensuing gas led to deposition of metallic arsenic on the surface of a cold vessel. In 1821, Sevillas utilised the decomposition of arsine for the detection of small quantities of arsenic in stomach contents and urine in poisoning cases. In 1836, James M Marsh, a London chemist developed the first reliable method to determine an absorbed poison (arsenic) in body tissues and fluids such as liver, kidney and blood.

We have come a long way since then to the present era of sophisticated analytical techniques which can detect even micrograms of virtually any poison in almost any kind of biological specimen. Today, an analytical (toxicology) laboratory has become a vital adjunct to the proper management of poisoned patients. However it is to be noted that the cornerstone of the management of such patients—*intensive supportive therapy*—is mostly independent of the kind of poison implicated, and hence routine employment of expensive analytical techniques should be avoided. The attending physician must be judicious in calling for necessary investigations, and exercise discretion in the choice of tests to be done.

The potential indications for seeking the assistance of a toxicology laboratory are as follows :

1. **P**rognosis—to assess the outcome of a case of poisoning.
2. **R**esearch—into toxicokinetics and mechanisms of toxicity.
3. **O**rder—from court, or law enforcement officer.
4. **M**onitoring—of treatment measures and their efficacy.
5. **I**dentification—of the nature of poison.
6. **S**everity—to assess the seriousness of a given case.
7. **E**xclusion—or confirmation of toxic exposure.

All the 7 indications mentioned can be remembered by the mnemonic PROMISE.

Mahoney and associates have categorised treatment of a poisoning case into 4 groups with respect to toxicological evaluations:

1. Toxicity correlates very well with serum levels, and specific drug therapy can be instituted, e.g. digoxin, ethylene glycol, lithium, methanol, paracetamol, salicylates, theophylline.
2. Toxicity correlates closely with serum level, but only non-specific care is required, e.g. barbiturates, ethanol, phenytoin.
3. Toxicologic testing only serves to confirm fairly clear-cut clinical parameters suggestive of poisoning, e.g. cyanide, narcotics, organophosphates, tricyclics.
4. Toxicity correlates poorly with serum level, and only non-specific care is required, e.g. amphetamines, benzodiazepines, cocaine, hallucinogens, neuroleptics.

In fact, most poisoned patients can be treated successfully without any contribution from the laboratory other than routine clinical biochemistry and haematology. This is particularly true for those cases where there is no doubt about the poison involved and when the results of a quantitative analysis would not significantly affect therapy. In those cases where an analytical toxicological investigation is deemed beneficial, an orderly progression is desirable in the performance of necessary tests and their interpretation (**Table 35.1**).

BIOCHEMICAL TESTS

1. **Blood Glucose:** Apart from insulin and other anti-diabetic drugs, hypoglycaemia is a feature of poisoning with ethanol, iron salts, paracetamol, and salicylates. Hyperglycaemia may be seen less commonly in

Table 35.1: Phases of Analytical Toxicological Investigation	
Pre-analytical Phase	*Analytical Phase*
1. Obtain details of current admission, including circumstantial evidence of poisoning, and results of biochemical and haematological investigations 2. Obtain patient's medical history, and decide the priorities for analysis	1. Interpret the results and discuss them with the clinician looking after the patient 2. Perform additional analyses, if indicated

salicylates, while it is more common in salbutamol and theophylline overdose.

2. **Electrolytes, Blood Gases and pH:** The value of these parameters in various kinds of poisoning have been discussed in **Chapter 3**.

3. **Plasma Enzymes:** Shock, coma, and convulsions are often associated with non-specific increase in plasma or serum activities of enzymes such as *lactate dehydrogenase, aspartate aminotransferase,* and *alanine aminotransferase*. In severe cases, there may be evidence of rhabdomyolysis and disseminated intravascular coagulation manifested by high serum aldolase or creatine kinase, together with myoglobinuria. High serum or plasma potassium, uric acid, and phosphate concentrations usually indicate the onset of acute renal failure. The plasma activities of hepatic enzymes are enhanced in poisoning due to carbon tetrachloride, copper salts, and paracetamol. Chronic alcoholism is often associated with increased *gamma glutamyl transferase activity*. Depressed plasma *cholinesterase* activity is a useful indicator of exposure to organophosphate or carbamate pesticide, (*page no 389*).

HAEMATOLOGICAL TESTS

1. **Blood Clotting:** Prothrombin time and other blood clotting parameters are likely to be abnormal in acute poisoning with hepatotoxic agents, rodenticides containing anticoagulants, as well as in certain types of snake bite, (especially viper).

2. **Haematocrit:** Acute overdose involving iron salts, NSAIDs, and salicylates can cause gastrointestinal bleeding leading to anaemia. Anaemia may also result from chronic exposure to heavy metals such as arsenic and lead. A less common (indirect) cause is *glucose-6-phosphate dehydrogenase* deficiency when any of the following drugs have been administered : chloramphenicol, chloroquine, nitrofurantoin, primaquine, etc.

3. **Leucocyte Count:** Leucocytosis is a recognised feature of acute metabolic acidosis resulting from ingestion of poisons such as ethylene glycol and methanol. It is also seen as a secondary feature of hypostatic pneumonia following prolonged coma.

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ANALYTICAL METHODS USED IN TOXICOLOGY

Toxicology laboratories use several methods to screen for poisons/drugs, since there is no single, accurate, inexpensive method for this purpose. Each method differs in cost, accuracy, complexity, speed, and specificity. The actual equipment required depends on the size of the laboratory and the kind of testing done. A basic, ideal laboratory should have the following facilities/resources:

1. Calibrated laboratory balances
2. Bench top centrifuge
3. Vortex mixer
4. Water bath and heating block
5. Butane gas burner
6. Fume cupboard
7. Refrigerator and Freezer
8. pH metre
9. Automatic/semi-automatic pipettes
10. Low power polarising microscope
11. Thin layer chromatography (TLC) plates
12. UV spectrophotometer
13. UV lamp
14. Conway microdiffusion apparatus
15. Porcelain spotting tile
16. Modified Gutzeit apparatus.

In addition, it is desirable to have the following specialised equipment, though they are quite expensive:

1. High Performance Liquid Chromatography (**HPLC**)*
2. Gas Chromatography (**GC**)
3. Mass Spectrometry (**MS**)
4. Facility for Radio Immuno Assay (**RIA**)
5. Enzyme Mediated Immuno Assay Technique (**EMIT**)**.

There should also be access to sophisticated systems of analysis which are normally beyond the scope of a toxicology laboratory, such as Atomic Absorption Spectrophotometry (**AAS**), and Neutron Activation Analysis (**NAA**).

In a given case of poisoning it may be sufficient to know just the nature of poison (**qualitative analysis**), or there may be a need for identification as well as estimation of its concentration in the body (**quantitative analysis**).

A. QUALITATIVE TESTS

1. **Bedside Tests**
   a. **Colour Tests**
      – **Trinder's test:** Add 100 ml of *Trinder's reagent* (40 gm mercuric chloride in 850 ml water and 120 ml aqueous hydrochloric acid mixed with 40 gm hydrated ferric nitrate diluted to 1 litre with warm water), to 2 ml urine, and mix for 5 seconds.

      A violet or purple colour indicates the presence of salicylates (salicylic acid, salicylamide, and methyl salicylic acid). If the specimen merely darkens, the result is considered negative.

      If only stomach contents or scene residues are available, hydrolyse by heating with 0.5 mol/L hydrochloric acid in a boiling water bath for 2 minutes, and neutralise with 0.5 mol/L sodium hydroxide before performing the test.

      – **Ferric chloride test:** Add 1 ml of 5% ferric chloride solution to 2 ml urine. A persistent purple colour indicates the presence of phenol, phenothiazines, phenylbutazone, oxyphenbutazone, or salicylates.

      – **FPN test:** Add 1 ml of *FPN reagent* (a mixture of 5 ml aqueous ferric chloride, 45 ml aqueous perchloric acid, and 50 ml aqueous nitric acid), to 1 ml of urine or stomach contents and mix for 5 seconds.

      Colours ranging from pink, red, violet, to blue may indicate the presence of phenothiazines. Tricyclics may give green or blue colour.

      – **O-Cresol test:** Add 0.5 ml concentrated hydrochloric acid to 0.5 ml urine or stomach contents,

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* Also referred to as High Pressure Liquid Chromatography

** Also referred to as Enzyme Multiplied Immuno Assay Technique

heat in a boiling water bath for 10 minutes, and cool. Add 1 ml of aqueous O-cresol solution (10 gm/L) to 0.2 ml of the hydrolysate, followed by 2 ml ammonium hydroxide, and mix for 5 seconds.

A blue or blue-black colour indicates the presence of paracetamol or phenacetin.

– **Dichromate test:** Add equal volumes of 10% sodium dichromate in 50% sulfuric acid to the urine sample. Development of green colour indicates the presence of ethanol.

– **Marquis test:** Add a mixture of 3 ml concentrated sulfuric acid and 3 drops of formalin to the gastric fluid. A purple colour which gradually turns blue, indicates the presence of opium or its derivatives.

– **Lee-Jones test:** Add a few crystals of ferrous sulfate and 4 to 5 drops of 2% sodium hydroxide to 5 ml gastric fluid. Boil and cool. Add 8 to 10 drops of 10% hydrochloric acid.

A greenish-blue colour indicates cyanide, while purple colour indicates salicylates in the sample.

– **Reinsch test:** 20 ml of stomach contents or urine is placed in a conical flask along with 10 ml hydrochloric acid and a small strip of copper. This is gently heated for an hour in a boiling water bath inside a fume cupboard. The copper is then removed and examined. A silvery deposit indicates mercury poisoning, while a black deposit indicates arsenic or bismuth, and a purplish-black deposit indicates antimony.

– **Qualitative desferrioxamine colour test (QDCT):** 2 ml of gastric fluid and 2 drops of 30% hydrogen peroxide are placed in two plastic tubes. 5 ml of desferrioxamine solution (500 mg in 4 ml of distilled water) is placed in one tube, and the resulting colour change is compared with the other tube (control).

If an orange or red colour develops, it indicates the presence of toxic levels of iron. The test must be done within 2 hours of poisoning or else it is unreliable.

A variation of this test is the **Desferrioxamine challenge test (DCT)**, in which 25 to 50 mg/kg of desferrioxamine is administered to the patient by intramuscular injection. Iron poisoning is indicated if the urine which is voided subsequently is pinkish in colour (*vin rose′urine).*

– **Meixner test:** This test can be done on either stool or gastric sample. Dilute the sample with methanol, centrifuge, and filter it. Add a drop or two to a piece of newspaper. Encircle the spot with a pencil and dry it. Add a few drops of concentrated hydrochloric acid to the spot.

If a blue colour forms within a few minutes, it is indicative of the presence of amatoxin (present in most toxic mushrooms).

– **Forrest test:** Add 1 ml *Forrest reagent* (a mixture of 25 ml aqueous potassium dichromate, 25 ml aqueous sulphuric acid, 25 ml aqueous perchloric acid, and 25 ml aqueous nitric acid) to 0.5 ml of the sample, and mix for 5 seconds. A yellow-green colour deepening to blue indicates the presence of imipramine or related compounds.

– **Fujiwara test:** To three 10 ml tubes, add respectively 1 ml portions of (a) the sample, (b) purified water, and (c) aqueous trichloroacetic acid (10 mg/L). Add 1 ml sodium hydroxide solution (5 mol/L), and 1 ml pyridine to each tube, mix carefully, and heat in a boiling water bath for 2 minutes. An intense red/purple colour in the top layer of tube (a) as in tube (c) indicates the presence of trichloro compounds such as chloral hydrate, chloroform, and trichloro ethylene. Tube (b) should show no colouration.

b. Other Tests

– **Isonitrile test:** Mix a small amount of gastric contents with 10 ml water and add 1 ml purified aniline, followed by 2 ml 20% sodium hydroxide. Heat gently for a few minutes.

A foul odour (*skunk odour)* will be perceived if one of the following poisons is present: carbon tetrachloride, chloral hydrate, chloroform, methyl bromide, or any other chlorinated hydrocarbon.

– **Tensilon (edrophonium challenge) test:** When 10 mg edrophonium is given intravenously in a case of sudden paralysis, there will be dramatic recovery if it is due to myasthenia gravis, while a case of poisoning (e.g. botulism) will not show any improvement.

– **Melzer's test:** This is a test done to confirm whether a given mushroom is toxic (especially *Amanita phalloides*). The spores obtained from the mushroom are stained with 1 drop of Melzer's reagent (mixture of 20 ml water, 1.5 gm potassium iodide, 0.5 gm iodine, and 20 gm chloral hydrate), and viewed under a microscope. Spores of *A. phalloides* and a few other deadly mushrooms will show a bluish black colour ("amyloid reaction"). However, a negative reaction does not mean that the mushroom is non-toxic.

2. Thin Layer Chromatography

This is a qualitative technique which involves the movement by capillary action of a liquid phase (usually an organic solvent) through a thin, uniform layer of stationary phase (usually silica gel) held on a rigid support (usually a glass, aluminium, or plastic sheet). Compounds are separated by partition between the mobile and stationary phases.

A very thin layer of silica gel or aluminium oxide is applied to a glass plate 20 × 20 × 0.5 cm, and vertical lines are drawn 1.5 cm apart to allow individual runways for each sample. Purified tissue extracts dissolved in 0.5 ml of methanol are serially spotted with a micropipette and dried in a small circle in the lower centre of a runway 1.5 cm from the bottom. Other samples are similarly spotted in other runways. A horizontal line (stop point) is drawn 10 or 15 cm above these starting

points. A TLC tank is filled with suitable developing solvents to a depth of about 1 cm from the bottom. The plate properly spotted is then dipped into the solvent, the lid is firmly closed and the atmosphere is allowed to saturate with vapour. When the solvent front just touches the 10 cm horizontal mark, quickly remove the plate and examine under UV light (at 254 nm and 366 nm) for characteristic fluorescence or absorbance (**Fig 36.1**). Calculate the Rf value. This can also be done after spraying the plate with appropriate reagents to bring out characteristic colour spots.* This widens the scope of the analysis and increases the confidence of identification.

$$\text{Rf is the ratio of } \frac{\text{Solute front}}{\text{Solvent front}} \times 100$$

Approximate quantitation can be done by comparison with standards similarly prepared on the same plate, for intensity of colour and area size. The Rfs suggested in the literature can be used as a guide for identifying various poisons, though it is preferable that each analyst should prepare and establish his own Rf according to his own conditions and technique.

The recommended TLC visualisation reagents are as follows:

    i. Mercurous nitrate reagent (acidic extract) which gives white spots with a grey centre on a darker background with barbiturates and related compounds.

    ii. Acidified iodoplatinate reagent (basic extract) which gives mainly purple, blue, or brown spots with a range of basic and neutral drugs and metabolites.

    iii. Mandelin's reagent (basic extract) which gives colours ranging from blue and green to orange and red with a variety of basic compounds.

    iv. Sulfuric acid (500 ml/L)(basic extract) gives red, purple, or blue spots with many phenothiazines and their metabolites.

It is to be noted that many additional mobile phase and spray reagent combinations could be used in place of those suggested here.

Thin layer chromatography (TLC) is a simple, inexpensive technique which is widely used. It takes only about 2 hours from beginning to completion. It is also a very versatile method since the order of separation of compounds can be altered simply by changing the nature of the developing agent. However, interpretation of the plates can prove difficult and calls for a trained eye with considerable experience in recognising colours, spot shapes, and metabolite patterns.

■ Troubleshooting

- The compound runs as a streak rather than a spot: The sample was overloaded. Run the TLC again after diluting the sample. Or, the sample might just contain many components, creating many spots which run together and appear as a streak, i.e. the procedure did not go as well as expected. Repeat!

- The sample runs as a smear or an upward crescent: Compounds which possess strongly acidic or basic groups (amines or carboxylic acids) sometimes show up on a TLC plate with this behaviour. Add a few drops of ammonium hydroxide (amines) or acetic acid (carboxylic acids) to the eluting solvent to obtain clearer plates.

- The sample runs as a downward crescent: Likely, the adsorbent was disturbed during the spotting, causing the crescent shape.

- The plate solvent front runs crookedly: Either the adsorbent has flaked off the sides of the plate, or the sides of the plate are touching the sides of the container (or the paper used to saturate the container) as the plate develops. Crookedly run plates make it harder to measure Rf values accurately.

- No spots are seen on the plate: The operator may not have spotted enough compound, perhaps because the solution of the compound is too dilute. This can be resolved by concentrating the solution, or, spotting it several times in one place, allowing the solvent to dry between applications. Some compounds do not show up under UV light; try another method of visualising the plate.

  If the solvent level in the developing jar is deeper than the origin (spotting line) of the TLC plate, the solvent will dissolve the compounds into the solvent reservoir instead of allowing them to move up the plate by capillary action. In such a case also, spots will not be seen after the plate is developed.
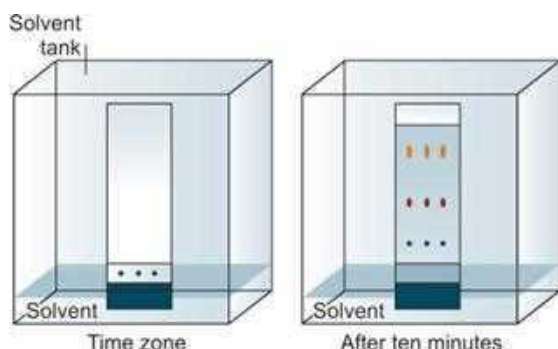
B. QUANTITATIVE ASSAYS

1. Ultraviolet-Visible (UV-Vis) Spectrophotometry

This technique is based on the principle that many drugs when in solution will absorb UV radiation. The degree of absorption depends on the chemical structure of the drug, its concentration in the solution, and the wavelength of the UVR. The functioning of this instrument is relatively straightforward. A beam of light from a visible and/or UV light source is separated into its component wavelengths by a prism or diffraction grating. The monochromator can select from the light source an ultraviolet ray of any given wavelength ranging from 200 to 340 nm. The

Fig 36.1: Thin layer chromatography

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* **Caution:** All spray reagents used are very toxic. Spraying must be performed in a fume cupboard, or under an efficient fume hood.

sample extract in aqueous medium is placed in a transparent quartz cuvette in the path of the radiation. Each monochromatic (single wavelength) beam in turn is split into two equal intensity beams by a half-mirrored device. One beam, the sample beam passes through a small transparent container (cuvette) containing a solution of the compound being studied in a transparent solvent. The other beam, the reference, passes through an identical cuvette containing only the solvent. The intensities of these light beams are then measured by electronic detectors and compared (**Fig 36.2**). The intensity of the reference beam, which should have suffered little or no light absorption, is defined as I_0. The intensity of the sample beam is defined as I. Over a short period of time, the spectrometer automatically scans all the component wavelengths in the manner described. The ultraviolet (UV) region scanned is normally from 200 to 400 nm, and the visible portion is from 400 to 800 nm.

If the sample compound does not absorb light of a given wavelength, $I = I_0$. However, if the sample compound absorbs light then I is less than I_0, and this difference may be plotted on a graph versus wavelength. Absorption may be presented as **transmittance** ($T = I/I_0$) or **absorbance** ($A = \log I_0/I$). If no absorption has occurred, $T = 1.0$ and $A = 0$. Most spectrometers display absorbance on the vertical axis, and the commonly observed range is from 0 (100% transmittance) to 2 (1% transmittance). The wavelength of maximum absorbance is a characteristic value, designated as λ_{max}. Different compounds may have very different absorption maxima and absorbances. Intensely absorbing compounds must be examined in dilute solution, so that significant light energy is received by the detector, and this requires the use of completely transparent (non-absorbing) solvents. The most commonly used solvents are water, ethanol, hexane and cyclohexane. Solvents having double or triple bonds, or heavy atoms (e.g. S, Br & I) are generally avoided. Because the absorbance of a sample will be proportional to its molar concentration in the sample cuvette, a corrected absorption value known as the **molar absorptivity** is used when comparing the spectra of different compounds. Molar absoptivities may be very large for strongly absorbing compounds ($\varepsilon > 10,000$), and very small if absorption is weak ($\varepsilon = 10$ to 100).
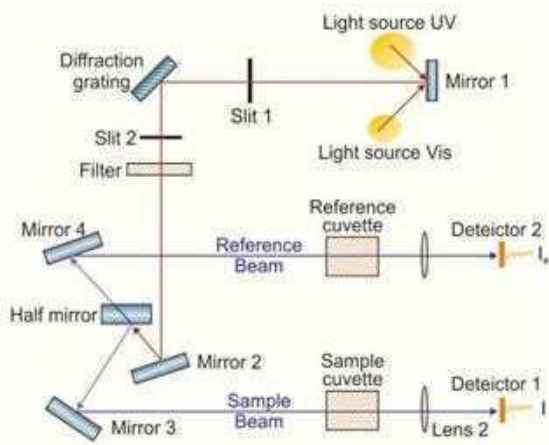
Fig 36.2: UV-Vis spectrophotometry

The amount of UV radiation which passes through the solution is measured by the photocell. By steady rotation of the monochromator, it is possible to pass sequentially UV rays of all wavelength from 200 to 340 nm through the extract. The photocell monitors the amount of radiation absorbed at each wavelength and this is transcribed on to a recorder chart. The shape of the spectrum, the wavelength at which absorption is at a maximum, and any changes brought about by changing the pH of the extract are all used as an aid to characterise the agent present. This technique is ideal to quantitate blood levels of paracetamol and salicylates, as well as urine levels of phenothiazines.

A major disadvantage of UVS is the possibility of interference in multiple drug overdose. In such a case, UV scanning can produce a composite spectrum of bewildering complexity from which neither qualitative nor quantitative information can be derived. Conventional spectrophotometric methods are known for producing false positive results which can be disastrous in medico-legal cases.

2. Gas Chromatography (GC)

This is a more sophisticated system of quantitative analysis and has found great favour with analytical toxicologists since it offers a way of simultaneously separating, identifying, and measuring drugs and other organic poisons. Gas chromatography, specifically gas-liquid chromatography, involves a sample being vapourised and injected onto the head of the chromatographic column. The sample is transported through the column by the flow of inert, gaseous mobile phase. The column itself contains a liquid stationary phase which is adsorbed onto the surface of an inert solid. The liquid or solid specimen dissolved in a solvent is injected into the chromatograph. The specimen is vapourised by heat and is carried through a column by an inert carrier gas (usually nitrogen). The choice of carrier gas is often dependent upon the type of detector which is used. The carrier gas system also contains a molecular sieve to remove water and other impurities. The column is packed with a substance like carbowax or adiponitrile which is capable of changing the migration time of the specimen as it traverses the column.

For optimum column efficiency, the sample should not be too large, and should be introduced onto the column as a "plug" of vapour - slow injection of large samples causes band broadening and loss of resolution. The most common injection method is where a microsyringe is used to inject sample through a rubber septum into a flash vapouriser port at the head of the column. The temperature of the sample port is usually about 50^0C higher than the boiling point of the least volatile component of the sample. For packed columns, sample size ranges from tenths of a microlitre up to 20 microlitres. Capillary columns, on the other hand, need much less sample, typically around 10^{-3} microlitre. For capillary GC, split/splitless injection is used.

The injector can be used in one of two modes; split or splitless. The injector contains a heated chamber containing a glass liner into which the sample is injected through the septum. The carrier gas enters the chamber and can leave by three routes (when the injector is in split mode). The sample vapourises to form a mixture of carrier gas, vapourised solvent

and vapourised solutes. A proportion of this mixture passes onto the column, but most exits through the split outlet. The septum purge outlet prevents septum bleed components from entering the column.

A detector recognises the presence of the chemical and graphically plots its emergence as a function of time (**Fig 36.3**). The retention time and peak area for a chemical compared to known standard are used to identify and to quantitate its presence. There are many detectors which can be used in gas chromatography. Different detectors will give different types of selectivity. A *non-selective* detector responds to all compounds except the carrier gas, a *selective detector* responds to a range of compounds with a common physical or chemical property and a *specific detector* responds to a single chemical compound. Detectors can also be grouped into *concentration dependent detectors* and *mass flow dependent detectors*. The signal from a concentration dependant detector is related to the concentration of solute in the detector, and does not usually destroy the sample. Dilution with make-up gas will lower the detectors response. Mass flow dependant detectors usually destroy the sample, and the signal is related to the rate at which solute molecules enter the detector. The response of a mass flow dependant detector is unaffected by make-up gas.

The most common means of detecting the compounds is by flame ionisation. On leaving the column the inert gas is mixed with hydrogen and either air or oxygen, and the mixture is ignited to give a continuous jet of flame. It is decomposed into electrically charged fragments which are collected at an electrode. This results in an electrical signal which is amplified and transmitted to a pen recorder operating at a constant chart speed. This peak is transcribed each time a compound emerges from the column. Flame ionisation detectors (FIDs) are mass sensitive rather than concentration sensitive; this gives the advantage that changes in mobile phase flow rate do not affect the detector's response. The FID is a useful general detector for the analysis of organic compounds; it has high sensitivity, a large linear response range, and low noise. It is also robust and easy to use, but unfortunately, it destroys the sample.

Gas chromatography (GC) is most commonly employed to quantitate blood levels of volatile liquids such as ethanol, ethylene glycol, and methanol.

Other detectors have recently been developed which widen the scope of plasma screening, such as the **electron capture detector**, and the **alkali flame detector** (**nitrogen detector**).
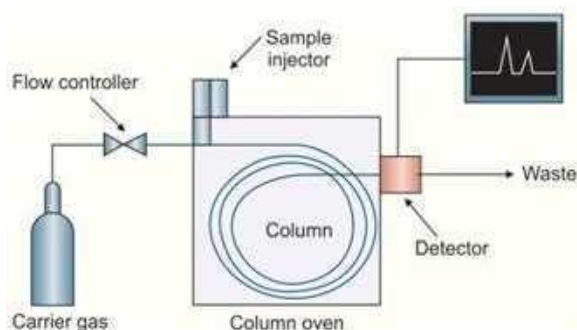
3. High Performance Liquid Chromatography (HPLC)

This is similar to GC, except that it is not restricted to volatile compounds. A high pressure (1000 to 6000 pound per square inch) pump facilitates movement of the specimen through the columns packed with chromatographic adsorbents e.g. silica gel and alumina. The effluent stream passes through a detector, usually an ultraviolet spectrophotometer, and the appearance of a drug in the solvent is signalled by a recorder peak in the same way as in GC (**Fig 36.4**). Again, the size of the peak is proportional to the concentration of drug in the sample. HPLC can be used to separate and analyse complex mixtures.

■ Applications of HPLC:

- **Preparative HPLC** refers to the process of isolation and purification of compounds. Important is the degree of solute purity and the throughput, which is the amount of compound produced per unit time. This differs from **analytical HPLC**, where the focus is to obtain information about the sample compound. The information that can be obtained includes identification, quantification, and resolution of a compound.
- **Chemical Separations** can be accomplished using HPLC by utilising the fact that certain compounds have different migration rates given a particular column and mobile phase. Thus, the chromatographer can separate compounds from each other using HPLC; the extent or degree of separation is mostly determined by the choice of stationary phase and mobile phase.
- **Purification** refers to the process of separating or extracting the target compound from other (possibly structurally related) compounds or contaminants. Each compound should have a characteristic peak under certain chromatographic conditions. Depending on what needs to be separated and how closely related the samples are, the chromatographer may choose the conditions, such as the proper mobile phase, to allow adequate separation in order to collect or extract the desired compound as it elutes from the stationary phase. The migration of the compounds and contaminants through the column need to differ enough so that the pure desired compound can be collected or extracted without incurring any other undesired compound.
- **Identification** of compounds by HPLC is a crucial part of any HPLC assay. In order to identify any compound by HPLC a detector must first be selected. Once the detector

Fig 36.3: Gas chromatography
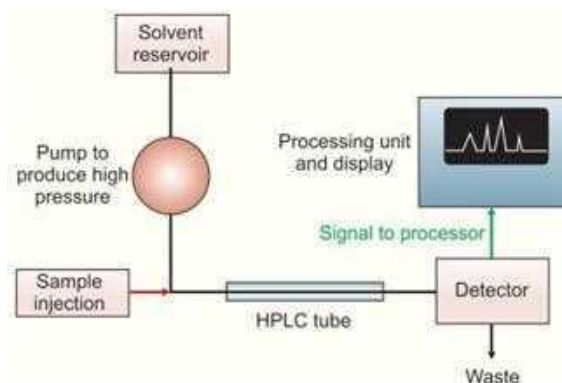
Fig 36.4: High performance liquid chromatography

is selected and is set to optimal detection settings, a separation assay must be developed. The parameters of this assay should be such that a clean peak of the known sample is observed from the chromatograph. The identifying peak should have a reasonable retention time and should be well separated from extraneous peaks at the detection levels which the assay will be performed. To alter the retention time of a compound, several parameters can be manipulated. The first is the choice of column, another is the choice of mobile phase, and last is the choice in flow rate. Identifying a compound by HPLC is accomplished by researching the literature and by trial and error. A sample of a known compound must be utilised in order to assure identification of the unknown compound. Identification of compounds can be assured by combining two or more detection methods.

- **Quantification** of compounds by HPLC is the process of determining the unknown concentration of a compound in a known solution. It involves injecting a series of known concentrations of the standard compound solution onto the HPLC for detection. The chromatograph of these known concentrations will give a series of peaks that correlate to the concentration of the compound injected.

4. Mass Spectrometry (MS)

This is usually combined with gas chromatography (**GC-MS**), and is considered to be the best technique for quantitative analysis of a wide variety of chemicals, but its expense (capital as well as operational costs) greatly restricts its use.

In the simplest terms the GC-MS instrument represents a device that separates chemical mixtures (the GC component) and a very sensitive detector (the MS component) with a data collector (the computer component). Once the sample solution is introduced into the GC inlet it is vapourised immediately because of the high temperature (250°C) and swept onto the column by the carrier gas (usually helium). The sample flows through the column experiencing the normal separation processes. As the various sample components emerge from the column opening, they flow into the capillary column interface (**Fig 36.5**). This device is the connection between the GC column and the MS. Some interfaces are separators and concentrate the sample via removal of the helium carrier. The sample then enters the ionisation chamber.

Two potential methods exist for ion production. The most frequently used method for toxicological purposes is electron impact (EI). The occasionally used alternative is chemical ionisation (CI). For electron impact ionisation a collimated beam of electrons impact the sample molecules causing the loss of an electron from the molecule. A molecule with one electron missing is represented by M+ and is called the molecular ion (or parent ion). When the resulting peak from this ion is seen in a mass spectrum, it gives the molecular weight of the compound. Chemical ionisation begins with ionisation of methane (or other gas), creating a radical which in turn will impact the sample molecule to produce MH+ molecular ions. Some of the molecular ions fragment into smaller daughter ions and neutral fragments. Both positive and negative ions are formed but only positively charged species will be detected.
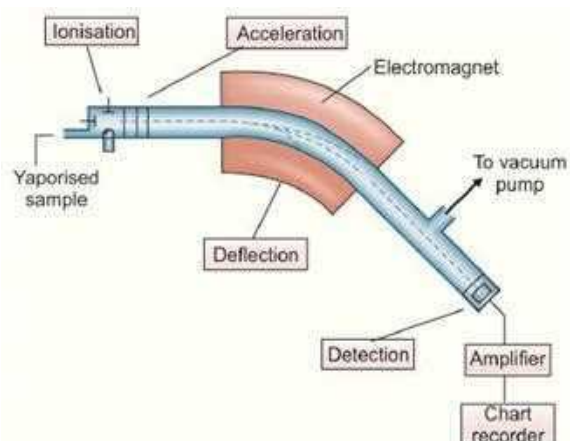
Fig 36.5: Mass spectrometry

Less fragmentation occurs with CI than with EI, hence CI yields less information about the detailed structure of a molecule, but does yield the molecular ion; sometimes the molecular ion cannot be detected by the EI method, hence the two methods complement one another. Once ionised, a small positive potential is used to repel the positive ions out of the ionisation chamber.

The next component is a mass analyser (filter), which separates the positively charged particles according to their mass. Several types of separating techniques exist; quadrupole filters, ion traps, magnetic deflection, time-of-flight, radio frequency, cyclotron resonance and focusing to name a few. The most common are quadrupoles and ion traps. After the ions are separated according to their masses, they enter a detector and then on to an amplifier to boost the signal. The detector sends information to the computer which acts as a "clearing house". It records all the data produced, converts the electrical impulses into visual displays and hard copy displays. The computer also drives the mass spectrometer.

Identification of a compound based on it's mass spectrum relies on the fact that every compound has a unique fragmentation pattern. Even isomers can be differentiated by the experienced operator. Generally, more information is generated than could possibly be used. A library of known mass spectra which may be several thousand compounds in size is stored on the computer and may be searched using computer algorithms to assist the analyst in identifying the unknown. It is important to incorporate all other available structural information (chemical, spectral, sample history) into the interpretation wherever appropriate.

5. Radio Immunoassay (RIA)

It is a slow and expensive method of detecting drugs in the blood, but is highly accurate. It involves mixing known quantities of drug specific antibody with known amount of radioactively labelled drug which allows analysis of the precipitate with a gamma counter. The amount of emittance inversely correlates with the presence of assayed drug. This test is excellent for detection of drugs in extremely low blood concentrations (cannabis, digoxin, LSD, paraquat, etc.).

Principle: In radioimmunoassay (RIA), a fixed concentration of labelled tracer antigen is incubated with a constant amount of antiserum such that the concentration of antigen binding sites on the antibody is limiting, for example, only 50% of the total tracer concentration may be bound by antibody. If unlabelled antigen is added to this system, there is competition between labelled tracer and unlabelled antigen for the limited and constant number of binding sites on the antibody, and thus the amount of tracer bound to antibody will decrease as the concentration of unlabelled antigen increases. This can be measured after separating antibody-bound from free tracer and counting either the bound fraction, the free fraction or both. A calibration or standard curve is set up with increasing amounts of known antigen, and from this curve the amount of antigen in the unknown samples can be calculated. Thus the four basic necessities for a radioimmunoassay system are an antiserum to the compound to be measured, the availability of a radioactively labelled form of the compound, a method whereby antibody-bound tracer can be separated from unbound tracer, and a standard unlabelled material.

Radioimmunoassay is widely-used because of its great sensitivity. Using antibodies of high affinity ($K_0 = 10^8–10^{11}$ M^{-1}), it is possible to detect a few picograms (10^{-12} gm) of antigen in the tube.

6. Enzyme Mediated Immunoassay Technique (EMIT)

This is a fast, expensive method with good accuracy, which works on the principle that the amount of drug present is proportional to the inhibition of an enzyme-substrate reaction. A known quantity of a drug is labelled by chemical attachment to an enzyme. Drug specific antibodies added to the specimen bind the drug-enzyme complex thereby reducing enzyme activity. Free drug in the specimen competes with enzyme labelled drug and limits the antibody-induced enzyme inactivation. Enzyme activity correlates with drug concentration in the specimen as measured by absorbance change resulting from the enzyme catalytic action on a substrate.

Enzyme mediated immunoassay technique (EMIT) is preferred over other radioimmunoassay methods in the emergency situation because of its simplicity and speed in providing information on toxic drug concentrations (approximately one sample per minute). It eliminates the complex separation phase necessary in **RIA**. There are two types : **EMIT-st** (*single test*) which consists of a compact spectrophotometer for small laboratories, and **EMIT-dau** *(drugs of abuse)* for larger hospitals.

The two main disadvantages are:
1. Negative result does not exclude the ingestion of a drug that may be present in undetectable quantities.
2. Antibody cross-reactions can produce false positive results.

7. Atomic Absorption Spectrophotometry (AAS)

This is the best method for detecting inorganic elements (arsenic, lead, mercury, thallium, etc.). However it requires a large sample of blood for accurate analysis. The blood sample is introduced into a high temperature oxyacetylene flame situated in the path of a beam of radiation. The organic matrix is combusted and the metal forms a cloud of atoms which absorbs a fraction of the radiation in proportion to the concentration of metal in the sample. Light of a suitable wavelength for a particular element is shone through the flame, and some of this light is absorbed by the atoms of the sample. The amount of light absorbed is proportional to the concentration of the element in the solution, and hence in the original object (**Fig 36.6**). Measurements are made separately for each element of interest in turn to achieve a complete analysis of an object, and thus the technique is relatively slow to use. However, it is very sensitive and it can measure trace elements down to the part per million level, as well as being able to measure elements present in minor and major amounts.

The equipment is highly complex and can be operated only by trained personnel. The capital cost is prohibitive. Flame AAS techniques are the oldest methods, and they can measure parts-per-million element concentrations with accuracies in the 1–3% range. Graphite furnace AAS, a more recent development, uses much smaller samples, and can make parts-per-billion measurements with about 20% accuracy. The newest technique, diode laser AAS, can look at several elements in a sample simultaneously using an array of lasers that emit various wavelengths of light. A mathematical process is then used to separate the mixture of light wavelengths that reaches the detector.

Inductively Coupled Plasma Atomic Emission Spectroscopy (**ICP-AES**) is a new development that allows simultaneous multi-element analysis. Seventeen elements can be measured from a single sample : aluminium, barium, cadmium, chromium, copper, iron, lanthanum, lead, manganese, molybdenum, nickel, platinum, silver, strontium, tin, titanium, and zinc.

Table 36.1 gives the comparative status of efficiency of the commonly used laboratory techniques in toxicology.

8. Neutron Activation Analysis (NAA)

This is a highly sophisticated and expensive method of detection of a variety of inorganic elements at levels well below the limits of conventional analytical techniques. The sensitivity attained is remarkable—sometimes 100 or even 1000 times better than by any other method. It is based on the principle that many substances become radioactive when exposed to bombardment by neutrons. The induced radioactivity is highly specific of the elements contributing to it. Consequently, a study of this radioactivity permits identification and quantitative
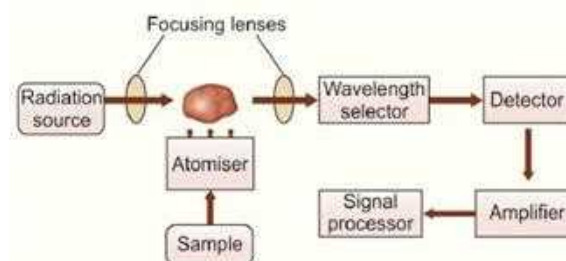
Fig 36.6: Atomic absorption spectrophotometry

Table 36.1: Comparison of Analytical Methods Used in Toxicology

Method	Specificity	Sensitivity	Speed
Thin-Layer Chromatography	+ +	+ +	+ +
Gas-Liquid Chromatography	+ + +	+ + +	+
High Performance Liquid Chromatography	+ + +	+ + +	+
Spectrophotometry	+	+ +	+ + +
Gas Chromatography-Mass Spectrometry	+ + + +	+ + + +	+
Immunology	+ + +	+ + +	+ + + +

estimation of many elements. Radioactivity is a spontaneous disintegration of the atomic nucleus. It occurs in a number of naturally occurring elements including radium, uranium, and thorium. Radioactive varieties (isotopes) of all other elements may be made artificially as explained above, by exposing them to bombardment by neutrons. However this requires the use of a nuclear reactor, though attack by charged particles such as protons and deuterons obtained from high energy accelerators may also be serviceable. Assay of the induced radioactivity can be done by means of either a Geiger counter or a scintillation counter.

Neutron activation analysis is a sensitive analytical technique useful for performing both qualitative and quantitative multi-element analysis of major, minor, and trace elements in samples from almost every conceivable field of scientific or technical interest. For many elements and applications, NAA offers sensitivities that are superior to those attainable by other methods, on the order of parts per billion or better. In addition, because of its accuracy and reliability, NAA is generally recognised as the "referee method" of choice when new procedures are being developed or when other methods yield results that do not agree. Worldwide application of NAA is so widespread it is estimated that approximately 100,000 samples undergo analysis each year. Neutron activation analysis can be used for the estimation of any of the 90 naturally occurring elements including antimony, arsenic, cadmium, copper, iron, lead, mercury, selenium, thallium, and zinc.

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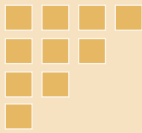
Appendices

GLASGOW COMA SCALE

The **Glasgow Coma Scale** or **GCS**, is a neurological scale which aims to give a reliable, objective way of recording the conscious state of a person, for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 15 (relatively normal). GCS was initially used to assess level of consciousness after head injury, and the scale is now used by first aid, EMS and doctors as being applicable to all acute medical and trauma patients.

The scale comprises three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person).

■ Best eye response (E)

There are 4 grades starting with the most severe:
1. No eye opening.
2. Eye opening in response to pain. (*Patient responds to pressure on the patient's fingernail bed; if this does not elicit a response, supraorbital and sternal pressure or rub may be used*).
3. Eye opening to speech.
4. Eyes opening spontaneously.

■ Best verbal response (V):

There are 5 grades starting with the most severe:
1. No verbal response.
2. Incomprehensible sounds (*moaning, but no words*).
3. Inappropriate words (*random speech, but no conversational exchange*).
4. Confused (*patient responds to questions coherently but there is some disorientation and confusion*).
5. Oriented (*patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.*).

Glasgow Coma Scale	
Feature observed	*Score*
1. *Eye Opening*	
a. Spontaneous	E4
b. To speech	3
c. To pain	2
d. Nil	1
2. *Best Motor Response*	
a. Obeys	M6
b. Localises	5
c. Flexes (withdrawal)	4
d. Flexes abnormally (decorticate rigidity)	3
e. Extends (decerebrate rigidity)	2
f. Nil	1
3. *Best Verbal Response*	
a. Oriented	V5
b. Confused conversation	4
c. Inappropriate words	3
d. Incomprehensible sounds	2
e. Nil	1

■ Best motor response (M):

There are 6 grades starting with the most severe:
1. No motor response.
2. Extension to pain (*abduction of arm, internal rotation of shoulder, pronation of forearm, extension of wrist—decerebrate response*).
3. Abnormal flexion to pain (*adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist—decorticate response*).
4. Flexion/withdrawal to pain (*flexion of elbow, supination of forearm, flexion of wrist when supra-orbital pressure applied; pulls part of body away when nailbed pinched*).
5. Localises to pain (*purposeful movements towards painful*

stimuli; e.g. hand crosses mid-line and gets above clavicle when supra-orbital pressure applied).

6. Obeys commands (*patient does simple things as asked*).

■ Interpretation

Individual elements as well as the sum of the score are important. Hence, the score is expressed in the form "GCS 9 = E2 V4 M3 at 07:35".

Generally, brain injury is classified as:
Severe—GCS ≤ 8
Moderate—GCS 9 – 12
Minor—GCS ≥ 13

The GCS has limited applicability to children, especially below the age of 36 months (where the verbal performance of even a healthy child would be expected to be poor). Consequently the **Paediatric Glasgow Coma Scale**, a separate yet closely related scale, was developed for assessing younger children.

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APPENDIX 2

List of Drugs Prohibited for Manufacture and Sale Through Gazette Notifications Under Section 26A of Drugs and Cosmetics Act 1940 by The Ministry of Health and Family Welfare

DRUGS PROHIBITED FROM THE DATE OF NOTIFICATION

1. Amidopyrine.
2. Fixed dose combinations of vitamins with anti-inflammatory agents and tranquilisers.
3. Fixed dose combinations of atropine in analgesics and antipyretics.
4. Fixed dose combinations of strychnine and caffeine in tonics.
5. Fixed dose combinations of yohimbine and strychnine with testosterone and vitamins.
6. Fixed dose combinations of iron with strychnine, arsenic and yohimbine.
7. Fixed dose combinations of sodium bromide/chloral hydrate with other drugs.
8. Phenacetin.
9. Fixed dose combinations of antihistaminics with anti-diarrhoeals.
10. Fixed dose combinations of penicillin with sulphonamides.
11. Fixed dose combinations of vitamins with analgesics.
12. Fixed dose combinations of tetracycline with vitamin C.
13. Fixed dose combinations of hydroxyquinoline group of drugs with any other drug except for preparations meant for external use.
14. Fixed dose combinations of corticosteroids with any other drug for internal use.
15. Fixed dose combinations of chloramphenicol with any other drug for internal use.
16. Fixed dose combinations of crude ergot preparations except those containing ergotamine, caffeine, analgesics, antihistamines for the treatment of migraine, headaches.
17. Fixed dose combinations of vitamins with anti-TB drugs, except combination of isoniazid with pyridoxine hydrochloride (vitamin B_6).
18. Penicillin skin/eye ointment.
19. Tetracycline liquid oral preparations.
20. Nialamide.
21. Practolol.
22. Methapyrilene, its salts.
23. Methaqualone.
24. Oxytetracycline liquid oral preparations.
25. Demeclocycline liquid oral preparations.
26. Combination of anabolic steroids with other drugs.
27. Fixed dose combination of oestrogen and progestin (other than oral contraceptive) containing per tablet oestrogen content of more than 50 mcg (equivalent to ethinyl oestradiol), and progestin content of more than 3 mg (equivalent to norethisterone acetate), and all fixed dose combination injectable preparations containing synthetic oestrogen and progesterone.
28. Fixed dose combination of sedatives/ hypnotics/anxiolytics with analgesics-antipyretics.
29. Fixed dose combination of rifampicin, isoniazid and pyrazinamide, except those which provide daily adult dose.
30. Fixed dose combination of histamine H-2 receptor antagonists with antacids except for those combinations approved by Drugs Controller, India.
31. The patent and proprietary medicines of fixed dose combinations of essential oils with alcohol having percentage higher than 20% proof, except preparations given in the Indian Pharmacopoeia.
32. All pharmaceutical preparations containing chloroform exceeding 0.5% weight to weight or volume to volume whichever is appropriate.
33. Fixed dose combination of ethambutol with INH other

than the following: INH-ethambutol 200 mg, 300 mg, 600 mg, 800 mg.

34. Fixed dose combination containing more than one anti-histamine.
35. Fixed dose combination of any anthelmintic with cathartic/purgative except for piperazine/santonin.
36. Fixed dose combination of salbutamol or any other drug having primarily bronchodilatory activity with centrally acting anti-tussive and/or antihistamine.
37. Fixed dose combination of laxatives and/or anti-spasmodic drugs in enzyme preparations.
38. Fixed dose combination of metoclopramide with systemically absorbed drugs, except fixed dose combination of metoclopramide with aspirin/paracetamol.
39. Fixed dose combination of centrally acting antitussive with antihistamine, having high atropine-like activity in expectorants.
40. Preparations claiming to combat cough associated with asthma containing centrally acting anti-tussive and/or an antihistamine.
41. Liquid oral tonic preparations containing glycerophosphates and/or other phosphates, and/or central nervous system stimulant, and such preparations containing alcohol more than 20% proof.
42. Fixed dose combination containing pectin and/or kaolin with any drug which is systemically absorbed from GI tract, except for combinations of pectin and/or kaolin with drugs not systemically absorbed.
43. Chloral hydrate as a drug.
44. Dovers Powder IP
45. Dover's Powder Tablets IP
46. Anti-diarrhoeal formulations containing kaolin or pectin or attapulgite or activated charcoal.
47. Antidiarrhoeal formulations containing phthalyl sulpha-thiazole or sulphaguanidine or succinyl sulphathiazole.
48. Antidiarrhoeal formulations containing neomycin or streptomycin or dihydrostreptomycin, including their respective salts or esters.
49. Liquid oral antidiarrhoeals or any other dosage form for paediatric use containing diphenoxylate or loperamide or atropine or belladonna, including their salts or esters or metabolites, hyoscyamine or their extracts or their alkaloids.
50. Liquid oral antidiarrhoeals or any other dosage form for paediatric use containing halogenated hydroxyquinolines.
51. Fixed dose combination of antidiarrhoeals with electro-lytes.
52. Patent and proprietary oral rehydration salts other than those conforming to specified guidelines.
53. Fixed dose combination of oxyphenbutazone or phenyl-butazone with any other drug.
54. Fixed dose combination of analgin with any other drug.
55. Fixed dose combination of dextropropoxyphene with any other drug other than anti-spasmodics and/or non-steriodal anti-inflammatory drugs (NSAIDs).
56. Fixed dose combination of a drug, standards of which are prescribed in the Second Schedule to the said Act with an Ayurvedic, Siddha or Unani drug.
57. Mepacrine hydrochloride (quinacrine and its salts) in any dosage form for use for female sterilization or contraception.
58. Fenfluramine and dexfenfluramine.
59. Fixed dose combination of diazepam and diphenhydramine hydrochloride.

Drugs Prohibited for Manufacture, Sale and Distribution from Subsequent Date

	Drugs Formulation	Effective date	Notification
1.	Cosmetics licensed as toothpaste/tooth powder containing tobacco	With immediate effect	GSR 444(E) dated 30.4.92
2.	Parenteral preparations fixed dose combination of streptomycin with penicillin	Jan 1,1998	GSR 93(E) dated 25.2.97
3.	Fixed dose combination of vitamin B_1, vitamin B_6 and vitamin B_{12} for human use	Jan 1,2001	GSR 702(E) dated 14.10.99
4.	Fixed dose combination of haemoglobin in any form (natural or synthetic)	Sep 1,2000	GSR 814(E) dated 16.12.99
5.	Fixed dose combination of pancreatin or pancrelipase containing amylase, protease and lipase with any other enzyme	Sep 1,2000	GSR 814(E) dated 16.12.99
6.	Fixed dose combination of nitrofurantoin and trimethoprim	Jan 1,2002	GSR 170(E) dated 12.3.01
7.	Fixed dose combination of phenobarbitone with any anti-asthmatic drugs	Jan 1,2002	GRS 170(E) dated 12.3.01
8.	Fixed dose combination of phenobarbitone with hyoscine and/or hyoscyamine	Jan 1,2002	GSR 170(E) dated 12.3.01
9.	Fixed dose combination of phenobarbitone with ergotamine and/or belladonna	Jan 1,2002	GSR 170(E) dated 12.3.01
10.	Fixed dose combination of haloperidol with any anticholinergic agent including propantheline bromide	Jan 1,2002	GSR 170(E) dated 12.3.01

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11.	Fixed dose combination of nalidixic acid with any anti-amoebic including metronidazole	Jan 1,2002	GSR 170(E) dt.12.3.01
12.	Fixed dose combination of loperamide hydrochloride with furazolidone	Jan 1,2002	GSR 170(E) dt.12.3.01
13.	Fixed dose combination of cyproheptadine with lysine or peptone	Jan 1,2003	SSR 170(E) dt.12.3.01
14.	Astemizole	Apr.1,2003	GSR 191(E) dt.5.3.03
15.	Terfenadine	Apr.1,2003	GSR 191(E) dt.5.3.03
16.	Phenformin	Oct.1,2003	GSR 780(E) dt.1.10.03
17.	Rafecoxib	Dec 13, 2004	GSR 810(E) dt. 13.12.04
18.	Valdecoxib and its formulations	July 25,2005	GSR 510(E) dt. 25.07.05
19.	Diclofenac and its formulations for animal use	July 4, 2008	GSR 499(E) dt.4.07.08

APPENDIX 3

OCCUPATIONAL TOXICOLOGY

Occupational toxicology is defined as the application of the principles of toxicology to the chemical and biological hazards encountered at work. The main objective is to prevent adverse health effects in workers arising from their work environment. Occupational toxicology is a discipline that draws on occupational hygiene, epidemiology, occupational medicine and regulatory toxicology.

Diseases and illnesses related to specific occupations are commonly encountered in general medical practice, though many of them may be misdiagnosed as to the cause. In fact, it is estimated that the proportion of occupation-related medical ailments in primary care may be 15–20% of outpatient cases, although this includes patients with complaints such as body aches (musculo-skeletal pain). However, approximately 5–10% of all symptomatic Poison Control Centre consultations are occupational in nature, suggesting a large number of chemical exposures.

■ General Considerations

The problem with occupational illness is that it is rarely pathognomonic. Often, the link between an ailment and the workplace is obscure, and a special effort is required to connect the exposure to the disease. A few cases may involve massive exposure leading to acute onset of symptoms, such as an irritant gas release. But these are relatively uncommon. In most cases, the onset of symptoms is insidious, following a subacute or chronic pattern, e.g. heavy metal poisoning. To make matters more difficult, there could be long latency, extending to years, between exposure and disease, making the establishment of cause and effect even more of a conundrum, e.g. occupational chronic lung disease, or various types of occupational cancer.

■ Occupational Exposure Limits

One of the goals of occupational toxicology is to contribute data to the process of establishing standards, as well as determining the appropriateness of those standards. Workplace exposure limits exist for chemical, biological and physical agents, and are recommended as guidelines or promulgated as standards in order to promote worker's health and safety. For chemical and biological agents, exposure limits are expressed as acceptable ambient concentration levels (occupational exposure limits) or as concentrations of a toxicant, its metabolites, or a specific marker of its effects (biological exposure indices).

Occupational exposure limits (OELs) are established as standards by regulatory agencies, or as guidelines by research groups or trade organizations. In the United States, the Occupational Safety and Health Administration (OSHA) under the Department of Labour promulgates legally enforceable standards known as permissible exposure limits (PELs). These are generally applicable worldwide, including India, and are designed to apply the best scientific evidence to ensure that no employee will suffer material impairment of health or

functional capacity with regular exposure, for the period of his working life. The National Institute for Occupational Safety and Health (NIOSH), under the Centers for Disease Control and Prevention, USA, publishes recommended exposure limits (RELs) that are more frequently updated and are generally more stringent than PELs. NIOSH also performs research and disseminates information on workplace hazards and their prevention. Most countries (including India) have governmental inspectorate agencies analogous to OSHA that are responsible for establishing and enforcing these exposure limits.

The American Conference of Governmental Industrial Hygienists (ACGIH) is a trade organisation that annually publishes occupational exposure limits for chemicals and for physical agents.

■ Threshold Limit Values (TLVs) And Biological Exposure Indices (BEIs):

These have been developed as guidelines which have been adopted by many industries as internal occupational exposure limits. As stated by the ACGIH, TLVs "refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects". Three types of TLVs exist, depending on the time scale of adverse effects inducible by the toxicants. The time weighted average TLV (TLV-TWA) is an occupational exposure limit for exposure averaged over an 8-hour day, 5-day week, work regimen. These are generally applied to toxicants that exert their effect over long periods. The short-term exposure limit (TLV-STEL) is an occupational exposure limit for a 15-minute measurement sampling window, and there should be 60 minutes or more between exposures in this range. The ceiling limit (TLV-C) represents a concentration that should never be exceeded. These usually are applied to toxicants that cause acute effects (such as potent sensory irritation), and for which real-time monitoring devices are available. Biological exposure indices are guidelines of biological monitoring and represent levels most likely to be observed in specimens collected from healthy workers who have been exposed to chemicals to the same extent as workers with inhalation exposure at the Threshold Limit Value. BEIs are recommended for analysis of urine, blood and exhaled air. While hair and fingernails are used in forensic toxicology, there are no BEIs for these specimens.

■ Common Types of Occupational Illnesses

1. **Occupational Lung Diseases**
   a. **Acute Pulmonary Injury From Irritant Gas Exposure:** The onset of symptoms is usually within minutes to 24–48 hours after exposure. Main effects include mucous membrane irritation, lacrimation, rhinorrhoea, and tracheobronchial oedema progressing to adult respiratory distress syndrome (ARDS). Typical causative agents include chlorine, ammonia, etc.
   b. **Heavy Metal Pneumonitis**: This is clinically similar to irritant inhalation injury. However, upper-airway mucous membrane irritation is minimal; thus, the exposure may have poor warning properties. Offending agents include cadmium, mercury, etc.
   c. **Febrile Inhalational Syndromes**: These are acute, self-limited flue-like syndromes and include the following:
      – Metal Fume Fever: Caused by galvanized-metal fumes.
      – Polymer Fume Fever: Due to inhalation of fumes arising from thermal breakdown of certain fluoropolymers.
      – Organic Dust Toxic Syndrome (ODTS): Caused by heavy exposure to high levels of organic dust, e.g. shovelling wood chip mulch.
      In none of these syndromes is lung injury marked. If there is presence of hypoxaemia or significant lung infiltrates, an alternative diagnosis must be considered.
   d. **Work-Related Asthma:** This is a frequent occupational problem. Classical occupational asthma occurs after sensitisation to either high-molecular-weight chemicals (e.g. inhaled foreign proteins) or small chemicals that appear to act as haptens (e.g. urethane isocyanates such as toluene diisocyanate). After acute, high-level irritant inhalations, for example chlorine, a chronic irritant-induced asthma may persist. This is called Reactive Airways Dysfunction Syndrome or RADS.
   e. **Chronic Fibrotic Occupational Lung Diseases:** These include asbestosis, silicosis, coal workers' pneumoconiosis, and a few other less common fibrotic lung diseases (associated with occupational exposures to substances such as beryllium). These conditions occur after years of exposure and with long latency, although patients may present for evaluation after an acute exposure.
   f. **Hypersensitivity Pneumonitis:** This is also called allergic alveolitis and includes a group of diseases caused by chronic exposure to organic materials, especially thermophilic bacteria. The most common of these is "Farmer's Lung". Although the process is chronic, acute illness can occur in a sensitised host after heavy exposure to the offending agent. In such cases the illness may need to be differentiated from exposure to an irritant inhalant leading to acute lung injury.
2. **Musculoskeletal Conditions**
   a. **Mechanical Trauma:** Acute mechanical trauma is one of the most common occupational problems, but it rarely has any direct toxicological implications.
   b. **Raynaud's Syndrome:** Raynaud's phenomenon may rarely be associated with chemical exposure (e.g. vinyl chloride monomer).
   c. **High-Pressure Injection Injuries:** This type of injury can result from paint spray guns, and are important not because of systemic toxicity due to absorption of an injected substance (e.g. paint

thinner), but because of extensive irritant-related tissue necrosis. Emergency surgical evaluation of such cases is mandatory.

3. **Occupational Cancer**

Occupational cancer is a major cause for concern, and often requires toxicological evaluation. A variety of different cancers have been associated with workplace exposure, some more strongly than others. However, identifying the chemical causes of cancer has proved a great challenge for occupational toxicologists and epidemiologists. Often, the practitioner is faced with an individual patient who seeks an assessment of the relative attribution of disease due to chemical exposures in that particular case, for purposes of gaining compensation or establishing liability.

4. **Cardiovascular Disease**

a. Atherosclerotic cardiovascular disease is associated with carbon disulfide. This chemical solvent is used in rayon manufacturing and specially in the applications and research of laboratories. It is also a principal metabolite of disulfiram.

b. Carbon monoxide at high levels can cause myocardial infarction in otherwise healthy individuals and, at lower levels, can aggravate ischaemia in the face of established atherosclerotic heart disease. Nitrate withdrawal-induced coronary artery spasm has been reported among workers heavily exposed to nitrates during munitions manufacturing.

c. Hydrocarbon solvents, especially chlorinated hydrocarbons and chlorofluorocarbon propellants can enhance the sensitivity of the myocardium to catecholamine-induced arrhythmias.

5. **Reproductive Problems**

Adverse reproductive outcomes have been associated with or implicated in occupational exposures to heavy metals (e.g. lead, organic mercury, etc.) and hospital chemical exposures (anaesthetic and sterilising gases).

6. **Central Nervous System Disorders**

a. Acute central nervous system (CNS) toxicity can occur with many pesticides (including both cholinesterase-inhibiting and chlorinated hydrocarbons). The CNS is also the target of methyl bromide, and cytotoxic and anoxic asphyxiant gases (e.g. carbon monoxide, cyanide, hydrogen sulfide, etc.).

b. Chronic CNS toxicity is the hallmark of heavy metals. This includes inorganic forms (tetraethyl lead and methyl mercury). Chronic manganese exposure can cause psychosis and Parkinsonism. Post-anoxic injury, especially from carbon monoxide can also lead to Parkinsonism.

c. Peripheral neuropathy can be caused by lead, arsenic, mercury, carbon disulfide, n-hexane and certain organophosphates.

7. **Hearing Disorders**

Occupational ototoxicity is common, but is usually noise induced rather than chemical related. Pre-existing noise-induced hearing loss may magnify the impact of common ototoxic drugs.

8. **Dermal Disorders**

Dermal exposure depends upon toxicant concentration: work conditions, including the degree and duration of wetness; and the ambient conditions at the work site. Some determinants of dermal dosing relate to the physicochemical properties of the chemicals as they affect the percutaneous absorption rate. These include solubility, temperature, pH, molecular size, and chemical characteristics of the vehicle. Host factors also influence dermal absorption and distribution. Important factors include the surface area of the skin that is exposed, the integrity of the skin, blood flow and biotransformation.

a. Allergic and irritant contact dermatitis and acute caustic chemical or acid injuries are the most common toxin-related skin problems. Systemic toxicity may occur, but is not a common complicating factor.

b. Hydrofluoric acid burns present a specific set of management problems on account of its propensity to induce systemic problems, apart from intense local effects. Relevant occupations include not only the micro-electronics industry but also maintenance or repair jobs in which hydrofluoric acid-containing rust removers are used.

9. **Psychiatric Disorders**

Work-related psychological disorders include a heterogeneous mix of syndromes. Of these, "post-traumatic stress disorder" and "mass psychogenesis illness" are of great relevance to medical toxicology because the patients in these cases may believe that their symptoms have a chemical aetiology. After eliminating common toxicological causes, psychological diagnoses should be considered when non-specific symptoms or multiple somatic complaints cannot be linked to abnormal signs or physiological effects.

10. **Hepatic Disease**

a. Acute chemical hepatitis can be caused by exposure to industrial solvents such as halogenated hydrocarbons (methylene chloride, trichloroethylene, trichloroethane, carbon tetrachloride, etc.), dimethyl formamide, dinitropropane, dimethylacetamide, etc. The jet and rocket fuel components hydrazine and monomethyl hydrazine are also potent hepatic poisons.

b. Other occupationally related hepatic disorders include steatosis, cholestatic injury, hepatoportal sclerosis and hepatic porphyria.

11. **Renal Disease**

a. Acute tubular necrosis can follow high-level exposure to a number of toxins, although the more frequent exposure scenario is a suicide attempt rather than workplace inhalation.

b. Interstitial nephritis is associated with chronic exposure to heavy metals, while hydrocarbon exposure has

been associated epidemiologically with glomerular nephritis, particularly Goodpasture's disease.

12. Haematological Disorders

a. Industrial oxidants are an important cause of chemically induced methaemoglobinaemia, especially in the dyeing and munitions industries.

b. Bone marrow is an important target organ for certain chemicals such as benzene, which can cause pancytopenia. Benzene exposure is known to cause leukaemia in humans. Lead causes anaemia through interference with haemoglobin synthesis.

c. Arsine gas is a potent cause of massive haemolysis.

13. Miscellaneous Disorders

Heat and other forms of radiation in the workplace are important because they can cause systemic effects that mimic chemical toxidromes. The most important example is heat stress, which is a major hazard in several occupations. Ionising radiations and non-ionising radiations (such as ultraviolet, infrared and microwave exposure) produce their own specific effects. Except for extremes of exposure, the adverse effects of these physical factors are generally chronic in nature.

Systemic poisons fit poorly into organ system categories, but are clearly of major importance in occupational toxicology. Main examples include the cytotoxic asphyxiants hydrogen cyanide (especially in metal plating and metal refining), hydrogen sulfide (important as a natural by-product of organic material breakdown), and carbon monoxide (principally encountered as a combustion by-product, but is also a metabolite of the solvent methylene chloride). Arsenic, like most other heavy metals is a multi-organ toxin with myriad effects. It has been widely used in agriculture, and is an important metal smelting by product. Toxicity from dinitrophenol, an industrial chemical that uncouples oxidative phosphorylation, is also best categorised as a systemic effect.

■ Laboratory Investigations

Testing for specific occupational toxins has a limited, but important role. For significant irritant inhalation exposures, in addition to assessing oxygenation and chest radiographic status, early spirometric assessment is often important. General laboratory testing for chronic exposure assessment should be driven by the potential organ toxicity described already. Standard recommendations often include a complete blood count, electrolytes, tests of renal and liver function, and periodic chest radiographic and pulmonary function studies.

■ Treatment

Removal of the affected worker from further exposure is the cornerstone of medical intervention in occupational toxicology. Workplace modification and control, especially with regard to substitution by less hazardous materials, should always be the first line of defence. Worker-required personal protective equipment must be made mandatory in all hazardous occupations.

The medical treatment of occupation-related illnesses must follow the general principles of management, with particular emphasis on the use of specific antidotes. In most cases, symptomatic and supportive measures are all that can be instituted. For more specific aspects of management, guidance may be sought from a regional poison control centre or toxicology specialist. This is especially important before embarking on potentially risky antidotal measures such as chelation therapy for heavy metal poisoning.

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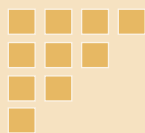
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