10.4.1 Poisoning by drugs and chemicals 1725

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10.4 Poisoning CONTENTS 10.4.1 Poisoning by drugs and chemicals 1725 John A. Vale, Sally M. Bradberry, and D. Nicholas Bateman 10.4.2 Injuries, envenoming, poisoning, and allergic reactions caused by animals 1778 David A. Warrell 10.4.3 Poisonous fungi 1817 Hans Persson and David A. Warrell 10.4.4 Poisonous plants 1828 Michael Eddleston and Hans Persson 10.4.1 Poisoning by drugs
and chemicals John A. Vale, Sally M. Bradberry, and D. Nicholas Bateman ESSENTIALS Poisoning is usually an acute, short-lived event which necessitates immediate care, though complications such as rhabdomyolysis may persist for a few days. Less commonly, symptoms may arise only after prolonged exposure, as occurs with many heavy metals. Rarely, sequelae may not occur until many years after exposure (e.g. with vinyl chloride). It must be stressed that exposure does not necessarily equate with poisoning as uptake of the agent involved is required but, even if this occurs, poisoning does not necessarily result as the amount absorbed may be too small. Poisoning may be accidental or deliberate; it is usually accidental in small children, but in adults it is almost invariably deliberate. Less commonly, it may be iatrogenic. Occupational poisoning is frequent in developing countries. Clinical assessment Assessment of a poisoned patient involves taking an appropriate history and performing a physical examination (including an as- sessment of the level of consciousness, ventilation, and circulation). Diagnosis is based on the history, circumstantial evidence (if avail- able), the presence of typical features, and, occasionally, on the re- sults of toxicological and other investigations. The medical approach should never be confined to the poison and its effects (e.g. deliberate self-harm may be indicative of a significant psychiatric disorder that requires diagnosis and treatment). Biochemical abnormalities due to disturbed metabolic pro- cesses are common in severely poisoned patients. These may be of diagnostic value, but mostly their recognition and treatment are important in management. Acid–base disturbances, particularly re- spiratory acidosis (due to central nervous system depression or pul- monary toxicity), and metabolic acidosis (due to lactic acidaemia or derangements of intermediary metabolism), are common. Plasma electrolyte abnormalities, particularly hypo- or hyperkalaemia, are observed and are most often due to redistribution of potassium across cell membranes. Hypoglycaemia and, less commonly, hyper- glycaemia may also occur. Management Initial

management involves the treatment of any potentially life- threatening conditions, such as airway compromise, breathing difficul- ties, haemodynamic instability, and clinically significant arrhythmias. Thereafter, convulsions and temperature disturbances should be treated and fluid, acid–base, and electrolyte abnormalities corrected. There is no evidence that the use of methods to reduce absorption from the gastrointestinal tract—such as activated charcoal, gastric lavage, syrup of ipecacuanha, cathartics, or whole-bowel irrigation— improves the clinical outcome in poisoned patients. However, ac- tivated charcoal and gastric lavage may be considered in patients who have ingested life-threatening amounts of a toxic agent up to 1 h previously. Antidotes exert their beneficial effects by a variety of mechan- isms, including forming an inert complex with the poison, acceler- ating detoxification of the poison, reducing the rate of conversion of the poison to a more toxic compound, competing with the poison for essential receptor sites, blocking essential receptors through which the toxic effects are mediated, and bypassing the effect of the poison. There are, however, only a small number of poisons for which there is a specific antidote, and few antidotes are employed regularly in clinical practice; these include acetylcysteine, naloxone, and flumazenil. To increase poison elimination, treatment with multiple-dose ac- tivated charcoal (in patients who have ingested carbamazepine, dap- sone, phenobarbitol, quinine, or theophylline), urine alkalinization

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1726 (in patients with moderately severe salicylate poisoning) or haemo- dialysis (which significantly increases the elimination of ethanol, ethylene glycol, isopropanol, lithium, methanol, and salicylate) should be considered, although there is no conclusive evidence that these treatments improve outcome. Most countries have a poisons information service, which pro- vides advice to medical staff (e.g. in the United Kingdom healthcare professionals may obtain online advice from https://www. TOXBASE.org and by telephone), and in most cases, to the general public as well. Advice should always be sought if unfamiliar poisons are encountered or if there is clinical uncertainty about optimal management. Introduction Poisoning is usually an acute event demanding immediate care and attention, but the consequences of exposure sometimes per- sist. Distinctive sequelae may not appear until many years have elapsed (e.g. with carcinoma of the oesophagus following ingestion of corrosives or hepatic haemangiosarcoma from vinyl chloride exposure). Symptoms may arise only after prolonged exposure, as with many metals. Exposure by oral, inhalational, dermal, or other routes on their own does not necessarily indicate poisoning. Uptake is required for there to be a toxic effect, but even if this occurs, poi- soning does not necessarily result as the amount absorbed may be too small. If poisoning does occur, the ensuing clinical syndrome may be distinctive; for example, fixed dilated pupils, exaggerated tendon re- flexes, extensor plantar responses, depressed respiration, and car- diac tachyarrhythmias suggest tricyclic antidepressant poisoning; anaemia, constipation, colic, and motor nerve palsies are indicative of lead poisoning. However, with many psychotropic medicines there may only be nonspecific central nervous depression, respira- tory impairment, and hypotension. Poisoning may be accidental or deliberate. It is usually accidental in small children, but in adults it is almost invariably deliberate (de- liberate self-harm) or, rarely, it may be with homicidal intent. It may also be iatrogenic in those aged under six months (e.g. involving overtreatment with paracetamol). Occupational poisoning is common in developing countries and continues to occur in the developed world. The medical approach to poisoning should never be confined to the poison and its effects. All the circumstances surrounding the episode must be considered, especially in cases where litiga- tion may follow (e.g. in the event of an occupational mishap with a chemical). It is therefore important that the doctor concerned,

having instituted any necessary life-saving measures, should take a careful history, retain all pertinent evidence such as a sui- cide note and biological specimens, make a meticulous record of symptoms, signs, progress, and outcome, and remember issues of confidentiality. Most countries have a poisons information service, which pro- vides advice to medical staff (e.g. in the United Kingdom healthcare professionals may obtain online advice from https://www. TOXBASE.org and by telephone), and in most cases, to the general public as well. Advice should always be sought if unfamiliar poisons are encountered or if there is clinical uncertainty about optimal management. Epidemiology Poisoning, either accidental or deliberate, is a common presentation in all countries throughout the world. This phenomenon is, how- ever, a relatively new one. Before the 1950s, hospital admissions from self-harm, now the most frequent cause of poisoning presen- tation to healthcare, was extremely rare worldwide. The reasons for this changing pattern of poisoning are poorly understood. Patients who have suffered toxic exposures present to healthcare facilities in a variety of ways, including to primary care physicians, hospital emergency departments, and hospital outpatients; rarely, patients are discovered dead. Collecting statistics on poisoning is, therefore, a complex issue and there is currently no universally agreed system for documenting and comparing rates of poisoning in different countries. Most statistics refer to hospital admissions (as opposed to hospital presentations in emergency departments) or poisoning-related deaths. Health statistical data from developed countries are usually more sophisticated than those from the developing world, although local surveys suggest that the incidence of self-harm is little different in these different types of society. Poisons information centres also col- lect information about the types of agent people are exposed to or ingest, many of which do not result in clinical ill health, further com- plicating health statistics. There are clear age differences in the frequencies and causes of poisoning. In children under the age of 10, accidental poisoning is extremely common, particularly in the very young who tend to place household objects into their mouths. From the age of 10 up- wards, self-harm becomes predominant, peaking in the late teens to late twenties and then gradually declining in incidence in higher age groups. The health departments of most developed countries publish data on poisoning mortality on the internet; collection of hospital admission data is less routine and is best in countries which have centralized healthcare provision. Hospital admissions due to poisoning Poisoning causes 5–10% of acute hospital medical presentations in developed countries. In the United Kingdom, there are currently 350 000 to 400 000 per annum. Since deliberate self-harm is a risk factor for further such episodes, approximately 25% of these cases occur in the same patient group. Self-harm in women and men is somewhat different, and other than young children, mortality data for out-of-hospital deaths show that men are more likely to succeed in killing themselves than women. The severity of poisoning depends on the quantities ingested, but hospital statistics do not provide adequate data to as- sess this. Mortality data provide information on the relative toxicity of different compounds if it can be expressed per head of popula- tion exposed. This is a technique that is best used for assessing the toxicity of prescription medicines; it is much less easily applied to chemicals and household products when measures of availability are not so readily obtained. Many cases of ‘poisoning’ in children are more accurately de- scribed as ‘exposures’, since symptomatic poisoning is uncommon,

10.4.1 Poisoning by drugs and chemicals 1727 particularly in developed countries. While drug errors can result in poisoning, data are very difficult to collect. Patients who harm themselves often do so because they are acutely stressed. Few have formal psychiatric diagnoses, such as depression or psychosis, or are truly suicidal, since the incident is impulsive rather than planned.

Such differences in behaviour affect mortality rates. Mortality is often higher in older age groups where overdose planning has been more careful, and has involved prescrip- tion medicines which typically are more toxic than over-the-counter preparations taken by younger patients. Impulsive behaviour is often associated with ingestion of alcohol and as many as two-thirds of men, and nearly one-half of women, take alcohol in association with an overdose. In many cases of self-harm more than one drug is in- cluded in the cocktail, making clinical management more complex, particularly if two or more agents acting on the same body system are involved. This applies particularly to drugs acting on the brain, kidney, and cardiovascular system. The increasing worldwide use of drugs of abuse has also in- fluenced patterns of poisoning, and many cases of poisoning in this population result from variations in quality of supply or experimentation. Prescription medicines are used in most self-harm episodes in the United Kingdom, the rest of Europe, North America, and countries in the developed world and their availability, therefore, influences the numbers of patients seen. The diagnoses for which the drug is used will also affect how often it is taken as a self-harm agent. Thus, self-harm with drugs for peptic ulcer disease is very uncommon, whereas overdose with antidepressants is much more frequent. The type of agent taken in overdose is culturally determined. In the United Kingdom, paracetamol contributes approximately one- third of all poisonings seen in hospitals but, although common in North America and other parts of Western Europe, the proportion of cases is lower. In developing countries, such as Sri Lanka and India, drugs are much more expensive and the agents ingested are either plants, such as yellow oleander, or the widely available pes- ticides. Agrichemicals cause less than 0.05% of hospital admissions for poisoning in England and Wales, whereas in Sri Lanka they are associated with around 70% of all cases of self-harm. Consequently, although the numbers of patients self-harming per head of popula- tion are quite similar, the mortality rates in Sri Lanka are orders of magnitude higher than in Western Europe. Deaths from poisoning In developed countries, most deaths from poisoning occur before admission, and less than 1% of patients presenting to hospital with poisoning are likely to die. The risk of mortality is very dependent on agent, and heroin, cocaine, and other high-risk recreational drugs are associated with higher death rates. In England and Wales, the mortality from drug-related poisoning was falling but has recently increased and in 2015 was higher than any time since 1993 with 3674 deaths; 2479 (67%) involved illegal drugs. In previous decades, carbon monoxide (from coal gas) and barbit- urates were common causes of death. Substitution of natural gas for coal gas and changes in prescribing patterns have altered the agents most frequently associated with death. For example, the United Kingdom and European Medicines Agencies have enacted legisla- tion on co-proxamol (paracetamol plus dextropropoxyphene) in re- sponse to concerns about its toxicity in overdose. Such changes have significantly reduced mortality rates from this cause in the United Kingdom. Childhood poisoning Accurate data on childhood poisoning are difficult to obtain. Many children with relatively mild features will be managed at home or in emergency departments, where national statistical data are not routinely collected, and so in this population national statistics are unreliable, except for agents that cause death. Deaths in children are usually attributable to inappropriate storage, including toxic pharmaceuticals, such as digoxin and quinine, household products and, increasingly, drugs of abuse. The pattern of child poisoning varies in different countries. Herbicide expos- ures are common in agricultural countries where these materials are stored in the home. In developed countries, exposures may occur when a young child finds and takes a relative’s medicines. Child-resistant containers have reduced poisoning rates in chil- dren, but tragedies still occur. Diagnosis Diagnosis of acute poisoning requires that the doctor not only es- tablish that exposure to a poison has occurred, but also its chem- ical composition and the

route and magnitude of exposure, so that the features likely to develop can be anticipated and risk assessed. As in any other branch of medicine, diagnosis of acute poisoning is based on the patient's history and on a combination of circumstan- tial evidence, the findings on physical examination and appropriate investigations. However, in acute poisoning, there are many obstacles to establishing the information required. Young children may not be able to give a history; adults are often unreliable; physical signs are rarely diagnostic; circumstantial evidence may be unavailable, tenta- tive, or misleading; and laboratory diagnosis is rarely comprehensive. History Since accidental poisoning in childhood is most common between the ages of 9 months and 5 years, an unequivocal history is unlikely to be forthcoming from the victim but may be obtainable from older witnesses. However, statements about quantities must be interpreted cautiously since an accurate assessment of the amounts in original containers is rarely available. In contrast, since 90% or more of adults presenting with acute poi- soning are conscious or drowsy, it should be possible to obtain a his- tory of self-poisoning. A few patients adamantly deny having taken poisons but most usually admit to it without hesitation, although problems arise in trying to establish precisely the nature and quan- tity of what has been taken. Comparison of patients' statements with poisons detected by laboratory analysis of blood or urine consist- ently reveals major differences in about half the cases. Consequently, patients are often thought to be deliberately untruthful. However, self-poisoning is commonly an impulsive act. The patient ingests the contents of the first bottle that comes to hand, often while under the influence of alcohol, and so inaccuracies in the history are not sur- prising. Although about 60% of episodes involve drugs prescribed for the victims or their relatives, like many other patients they are often ignorant of the names.

 Assessment of the amounts of drugs ingested are even more dif- ficult. Few patients count the number of tablets they consume and neither patient nor doctor can accurately interpret a 'handful', a 'strip', or similar arbitrary quantity. Circumstantial evidence In the diagnosis of acute poisoning, circumstantial evidence be- comes important when patients are unable to give a history (as is likely with young children), are confused, or are unconscious, or are unwilling to do so. However, although circumstantial evidence may strongly suggest poisoning, it is seldom incontrovertible. It takes several forms. Circumstances under which found In the case of infants, the mother may return to the kitchen or bath- room to find her child with some substance all over their hands, face, and clothing, or surrounded by pills, one of which the child may be eating. The assumption that some has been ingested may not be cor- rect, and the amount swallowed is a matter of speculation. Self-poisoning is a common cause of coma in previously healthy young adults. Adults may be found unconscious with tablet particles around the mouth or on clothing as the only clue to diagnosis. More often, the presence of empty drug containers with occasional tablets or capsules near the patient suggests the diagnosis. Less commonly, they are found unconscious or dead in some remote location. The lack of personal effects to indicate who they are or where they live may suggest a desire not to be identified and should arouse suspicion of poisoning. Protestations by relatives that the patient would never take an overdose are often incorrect and should not prevent full investigation in appropriate circumstances. Suicide notes Suicide notes are reliable indicators of poisoning in the absence of physical violence as a cause of coma. The note may specify what has been taken in addition to expressing despair, futility, worthlessness, and remorse. Features There are few symptoms or physical signs that cannot be attributed to one poison or another. However, a clinical feature rarely arises in isolation and clusters of features are of much greater diagnostic

value. Those most commonly encountered in present-day practice are given in Table 10.4.1.1. Conscious patients with abnormal behaviour, perhaps in com- bination with auditory and visual hallucinations, may have ingested amfetamines or other psychoactive stimulants, such as phen- cyclidine, lysergic acid diethylamide (LSD), ‘magic’ (psilocybin- containing) mushrooms (see Chapter 10.4.3), or drugs such as the older antihistamines and tricyclic antidepressants, which have marked anticholinergic actions. Drowsiness, ataxia, dysarthria, and nystagmus are common after ingestion of benzodiazepines. Coma with hypotonia and hyporeflexia may follow, particularly if alcohol has also been taken. Hypotension, hypothermia, and respiratory depression are rare. Poisoning with tricyclic antidepressants causes hypertonia, hyperreflexia, extensor plantar responses, and dilated pupils. Sinus tachycardia and pro- longation of the QRS interval on the electrocardiogram support a diagnosis of intoxication with these drugs; hypotension and hypo- thermia are uncommon. Tricyclic antidepressants and mefenamic acid are common causes of seizures. Coma with pinpoint pupils and a reduced respiratory rate is virtually diagnostic of poisoning with opioid analgesics and is an indication for a therapeutic trial of naloxone. Many patients with opioid poisoning will be habitual drug abusers and have vene- puncture marks and evidence of venous tracking, particularly in the antecubital fossae. Alcohol may be smelt on the breath, as might solvents such as toluene, acetone, or xylene as the result of ‘sniffing’ glues, cleaning agents, or other preparations. Burns around the lips or in the buccal cavity or pharynx indicate inges- tion of corrosives. Skin blisters Skin blisters may be found after poisoning with a wide variety of drugs including barbiturates, tricyclic antidepressants, benzodi- azepines, and nondrug toxins. They often occur over bony prom- inences that have been subjected to pressure and, less frequently, at sites where two skin areas have been in contact (e.g. the inner aspects of the knees) and are not specific for any poison. Neurological signs Lateralizing neurological signs Since most serious poisonings are associated with impairment of consciousness, neurological signs are particularly important. Lateralizing signs (unless they are attributable to a known neuro- logical disease) virtually exclude a diagnosis of acute poisoning. Table 10.4.1.1 Common feature clusters in the poisoned patient Feature cluster Likely poisons Coma, hypertonia, hyperreflexia, extensor plantar responses, myoclonus, strabismus, mydriasis, sinus tachycardia Tricyclic antidepressants: less commonly antihistamines, orphenadrine, thioridazine Coma, hypotonia, hyporeflexia, flexor or nonelicitable plantar responses, hypotension Barbiturates, benzodiazepines, and alcohol combinations, severe tricyclic antidepressant poisoning Coma, miosis, reduced respiratory rate Opioid analgesics Nausea, vomiting, tinnitus, deafness, sweating, hyperventilation, vasodilatation, tachycardia Salicylates Hyperthermia, tachycardia, delirium, agitation, mydriasis MDMA (Ecstasy) Amfetamines Miosis, hypersalivation, rhinorrhoea, bronchorrhoea Organophosphorus and carbamate insecticides, nerve agents

 Such findings have been recorded with barbiturate and phenytoin poisoning, but so rarely that the general rule is not compromised. Pyramidal tract signs The usual features of pyramidal tract involvement (hypertonia, hyperreflexia, and extensor plantar responses) are commonly found in tricyclic antidepressant poisoning and with other drugs with marked anticholinergic actions (e.g. the older antihistamines). However, these signs may be abolished in deep coma. Abnormal movements Unconscious patients may respond to painful stimuli with flexor and extensor limb movements of the type seen in decorticate and decere- brate states. However, in poisoning, these signs do not indicate irre- versible brain damage, and patients showing them can be expected to recover fully; hypoglycaemia must be excluded in these cases. Acute dystonic movements (including acute torticollis, orolingual

dyskinesias, and oculogyric crises) are also produced; these are usually caused by first-generation antipsychotics such as chlorpro- mazine, haloperidol, or prochlorperazine. Choreoathetosis has been reported as a rare presenting feature of poisoning with organophos- phorus insecticides. Pupillary changes in poisoning Inequality of the pupils is not uncommon in poisoned patients. Widely dilated pupils that react poorly to light may be caused by poisons with anticholinergic actions (e.g. tricyclic antidepressants) or sympathomimetic effects (e.g. amfetamines) or agents causing blindness (e.g. quinine, methanol). Miosis is usually caused by opioid analgesics or poisons with cholinergic or anticholinesterase actions (e.g. organophosphorus insecticides, nerve agents). The degree and speed of reaction of the pupils to light is of no clinical value. Ocular signs A variety of ocular signs including strabismus, internuclear oph- thalmoplegia, and total external ophthalmoplegia, may be found in acutely poisoned patients. Strabismus has been described in poi- soning with phenytoin, carbamazepine, and tricyclic antidepres- sants. Usually the optic axes diverge in the horizontal plane but, in some patients, there is additional vertical deviation. It is present transiently and only in patients who are unconscious. Dysconjugate, roving eye movements may also be seen if both eyes are observed for a period. It is important to know that such abnormalities occur so that they are not misattributed to intracranial vascular lesions or some other pathology requiring surgical intervention. Dysconjugate eye movements may become apparent only when oculovestibular reflexes are examined by caloric stimuli. Installation of ice-cold water into the external auditory meatus should make both eyes turn to the side irrigated, and failure of one eye to de- viate is evidence of internuclear ophthalmoplegia and a lesion of the medial longitudinal fasciculus. This has been reported in poisoning with a variety of drugs including tricyclic antidepressants, pheno- thiazines, benzodiazepines barbiturates, and ethanol, and can be de- tected in 10% of cases if caloric tests are carried out. Both sides are usually affected, but internuclear ophthalmoplegia on testing one side only also occurs in acute poisoning. Loss of oculocephalic and oculovestibular reflexes It is widely accepted that absence of oculocephalic and oculovesti bular responses indicates severe brainstem damage and the likeli- hood that the patient will not survive. However, this is not the case in acute poisoning where these reflexes may be abolished in patients who subsequently make a full recovery. Visual impairment Visual impairment is associated most commonly with quinine and methanol poisoning. Investigations Haematological and biochemical Information about the nature of poisons ingested can occasionally be deduced from standard haematological and biochemical investi- gations, and from arterial blood gas analysis (Table 10.4.1.2). Toxicological screening Toxicological screening for poisons in an unconscious patient is often requested when the cause of coma is unknown. Although identification of a drug or other chemical may reassure the clin- ician, this alone is not a good reason for the request. The clinician should consider how the result of a screen will alter management. The pattern of drugs involved in poisoning in most developed countries is such that specific treatment (e.g. antidotes, techniques to enhance elimination of the poison) is unlikely to be available, and management will therefore be supportive. Screening is labour- intensive, time-consuming, and expensive, and in most cases, cannot be justified on an emergency basis because it will not alter the management of the patient, though there are important excep- tions (Table 10.4.1.3).

Table 10.4.1.2 Haematological and biochemical investigations that assist in management • Serum sodium concentration (e.g. hyponatraemia in ecstasy (MDMA) poisoning) • Serum potassium concentration (e.g. hypokalaemia in theophylline poisoning, hyperkalaemia in digoxin poisoning, rhabdomyolysis, haemolysis) • Plasma creatinine concentration (e.g. renal failure in ethylene glycol and diethylene glycol poisoning) • Blood sugar concentration (e.g. hypoglycaemia in insulin and severe untreated paracetamol poisoning, hypoglycaemia, and hyperglycaemia in salicylate

poisoning) • Serum calcium concentration (e.g. hypocalcaemia in ethylene glycol poisoning) • Serum alanine aminotransferase/aspartate aminotransferase activities (e.g. increased in paracetamol poisoning) • Acid–base disturbances, including metabolic acidosis • Methaemoglobin concentration (e.g. in nitrite poisoning) • RBC cholinesterase activity (e.g. organophosphorus insecticide and nerve agent poisoning)

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1730 However, emergency measurement of the serum or plasma con- centration of the agents in Table 10.4.1.3 is important to ensure ap- propriate clinical management. ECG A routine ECG is of limited diagnostic value but is important in pa- tients who are unconscious or thought to have ingested a cardiotoxic drug. Sinus tachycardia with prolongation of the QRS interval in an unconscious patient suggests tricyclic antidepressant poisoning. With increasing cardiotoxicity, it may be impossible to detect P-waves, and the pattern then resembles ventricular tachycardia. Overdose with cardiac glycosides or potassium salts also induces characteristic ECG changes. Q–T interval prolongation is a recog- nized adverse effect of several drugs in overdose (e.g. quetiapine, terfenadine, and quinine) and predisposes to ventricular arrhyth- mias, notably torsade de pointes. X-rays Routine radiology is of little diagnostic value. It can be used to con- firm ingestion of metallic objects (e.g. coins, button batteries) or in- jection of globules of metallic mercury. Rarely, hydrocarbon solvents (e.g. carbon tetrachloride) may be seen as a slightly opaque layer floating on the top of the gastric contents with the patient upright, or outlining the small bowel. Ingested packets of illicit substances may be discernible on a plain radiograph, but CT or MRI is more reliable in detecting such objects. General management Antidotes and methods to enhance elimination are available for only very small number of poisons, and the management of the great ma- jority of poisoned patients is based on what has been called ‘an or- derly if unspectacular regimen of supportive therapy’. A small but significant number of poisoned patients arrive at hospital with respiratory obstruction, ventilatory failure, or in car- diorespiratory arrest. In these cases, conventional resuscitation takes precedence over detailed assessment of the patient and at- tempts to obtain a history. The opioid antagonist naloxone is safe and should be used whenever there is the slightest suspicion that an opioid is involved. Its use intravenously will resurrect a comatose, hypoventilating patient within seconds and, even if it is given in- appropriately, it is highly unlikely to have adverse effects. Unconscious patients need scrupulous attention to respiration, hypotension, hypothermia, and other complications, if they are to survive. Expert nursing is as important as medical measures. Airway Establishment and maintenance of an adequate airway is of para- mount importance in the management of unconscious poisoned patients. The airway may be obstructed by the tongue falling back, dental plates being dislodged, other foreign bodies, buccal secre- tions, vomitus, and flexion of the neck. In the first instance, the neck should be extended and the tongue and jaw held forwards. Secretions in the oropharynx must be removed, and an oropharyngeal airway should be inserted before turning the patient into a semi-prone pos- ition. If the cough reflex is absent, an endotracheal tube should be inserted to prevent aspiration into the lungs and allow regular suc- tion of bronchial secretions. It is then important to ensure that the inspired air is adequately warmed and humidified. Ventilation Once a clear airway has been established, the adequacy of spontan- eous ventilation should be assessed. Pulse oximetry can be used to measure oxygen saturation. The displayed reading may be inaccurate when the saturation is below 70%, when peripheral perfusion is poor, and in the presence of carboxyhaemoglobin or methaemoglobin. Only measurement of arterial blood gases, however, indicates the presence both of hypercapnia and hypoxia. The presence of venti- latory insufficiency (as determined by arterial partial pressure of

oxygen ≤9 kPa on air and/or arterial partial pressure of CO_2 ≥6 kPa) should lead to consideration of the need for intubation and assisted ventilation if the central respiratory depression cannot be reversed by administration of a specific antidote such as naloxone. Unconscious poisoned patients often have a mild, mixed respira- tory and metabolic acidosis with CO_2 tensions at the upper limit of normal, and oxygen tensions that fall with increasing depth of coma. Increasing the oxygen contents of the inspired air is often sufficient to correct hypoxia. High-inspired oxygen concentrations are impera- tive in patients with carbon monoxide and cyanide poisoning, and in pulmonary oedema resulting from inhalation of irritant gases. Cardiovascular function Cardiovascular function should be assessed by measuring pulse, blood pressure and temperature (core and peripheral). ECG should be monitored in moderately or severely poisoned patients, par- ticularly when a drug with a cardiotoxic action has been ingested. Echocardiography may occasionally be useful in such patients. Hypotension Although hypotension (systolic blood pressure <80 mm Hg) is a rec- ognized feature of acute poisoning, the classical features of shock (tachycardia and pale, cold skin) are seen only rarely because only a minority of patients are severely poisoned. Hypotension and shock may be caused by a direct cardiodepressant action of the poison (e.g. β-blockers, calcium channel blockers, tri- cyclic antidepressants); vasodilatation and venous pooling in the lower limbs (e.g. angiotensin-converting enzyme (ACE) inhibitors, phenothiazines); decrease in circulating blood volume because of Table 10.4.1.3 Poisons for which emergency measurement is important for management • Carboxyhaemoglobin • Digoxin • Ethanol (when monitoring treatment in ethylene glycol and methanol poisoning) • Ethylene and diethylene glycols • Iron • Lithium • Methanol • Paracetamol • Salicylate

 gastrointestinal losses (e.g. theophylline), increased insensible losses (e.g. salicylates), increased renal losses (e.g. diuretics), and in- creased capillary permeability. Hypotension may be exacerbated by coexisting hypoxia, acidosis, and dysrhythmias. Correct management of individual cases depends on accurate identification of the cause. Young patients are generally not at risk of cerebral or renal damage unless the systolic blood pressure falls below 80 mm Hg but, in those over the age of 40 years, it is preferable to keep the systolic blood pressure above 90 mm Hg. The treatment of hypotension depends on the cause. In all cases restoration of perfusion and oxygenation is the aim. While it is rea- sonable initially to administer a bolus of intravenous crystalloid, care must be taken to avoid volume overload in cases of primary cardiac failure. Such patients may require inotropic support with a sympathomimetic inotrope, such as dobutamine 2.5–10 micro- grams/kg/min or dopamine 2–5 micrograms/kg/min. Hypotension caused by vasodilatation that does not respond to intravascular volume expansion may warrant a vasoconstrictor sympathomimetic drug, such as noradrenaline (norepinephrine) 40 micrograms (base)/ml at an initial rate of 0.16–0.33 ml/min, or metaraminol (which has the potential advantage that it can be administered via a peripheral line) 15–100 mg by intravenous infusion. It must be recognized, however, that blood pressure may be raised at the expense of perfusion of vital organs, such as the kidneys. Response to treatment should be monitored not only by blood pressure but also other markers of improved per- fusion and oxygenation including skin colour and temperature, urine output, cerebration, and resolution of metabolic (lactic) acidosis. Hypertension A few drugs (e.g. cocaine and amfetamines), when taken in over- dose, may produce systemic hypertension. If this is mild and as- sociated with agitation, a benzodiazepine may suffice. In more severe cases, there may be a risk of arterial rupture, particularly intracranially. To prevent this, intravenous isosorbide dinitrate 2– 10 mg/h (up to 20 mg/h if necessary), or glyceryl trinitrate 10–200 micrograms/min by intravenous infusion (paediatric dose 0.2–0.5 micrograms/kg/min)

should be administered until blood pressure elevation is controlled. Arrhythmias Although many poisons are potentially cardiotoxic, the incidence of serious cardiac arrhythmias in acute poisoning is very low. Tricyclic antidepressants, β-adrenoceptor blocking drugs, calcium channel blockers, cardiac glycosides, amfetamines, cocaine, bronchodila- tors (particularly theophylline and its derivatives) and antimalarial drugs are the most likely causes. Cardiotoxicity usually occurs to- gether with other features of severe poisoning, including metabolic acidosis, hypoxia, convulsions, respiratory depression, and abnor- malities of electrolyte balance, which should be corrected before considering the use of antiarrhythmic drugs. The latter have narrow therapeutic ratios and their use may further impair myocardial function. In general, drug therapy should only be given for persistent, life-threatening arrhythmias associated with peripheral circula- tory failure. The drug used must be selected from knowledge of the pharmacology and toxicology of the poison involved and in such a way that it will not further compromise cardiac function. For ex- ample, in tricyclic antidepressant poisoning, arrhythmias are due to sodium channel blockade exacerbated by acidosis and are best treated with hypertonic sodium bicarbonate, 50–100 mmol. Convulsions Convulsions are potentially life-threatening because they cause hypoxia and metabolic acidosis and may precipitate cardiac ar- rhythmias and arrest. Short, isolated convulsions do not require treatment but those which are recurrent or protracted should be suppressed with intravenous diazepam 10–20 mg in an adult (lor- azepam 4 mg is an alternative). This drug is highly effective in ad- equate doses and alternatives are seldom needed. However, it is important to remember that giving benzodiazepines in this way may potentiate the respiratory depressant effects of the drugs inducing seizures. The combination of convulsions, coma, and vomiting, which may occur with theophylline poisoning, is particularly dangerous and, in these circumstances, it may be preferable to paralyse the patient, insert an endotracheal tube, and start assisted ventilation. However, although this ensures control of the airway and oxygenation, thus avoiding the risk of inhalation of gastric contents, it does not sup- press seizure activity; cerebral function must therefore be moni- tored, and parenteral anticonvulsants given as required. Temperature disturbances Hypothermia Any poison which depresses the central nervous system may impair temperature regulation and cause hypothermia, especially when dis- covery of the patient is delayed and environmental temperatures are low. This important complication may be missed unless tempera- ture is recorded rectally using a low-reading thermometer. In se- vere cases, peripheral and core temperatures should be monitored. Treatment includes nursing the patient in a warm room (27–29°C) and a heat-conserving ‘space blanket’. Cold intravenous fluids should be avoided and fluid bags for use should be stored in the room, or the lines should pass through a heating device. Hyperthermia Rarely, body temperature may increase to potentially fatal levels after poisoning with central nervous system stimulants such as cocaine, amfetamines (including ecstasy (MDMA)), monoamine oxidase inhibitors, or theophylline. In such cases, muscle tone is often grossly increased, and convulsions and rhabdomyolysis are common. Cooling measures should be instituted, sedation with di- azepam should be given and, in severe cases, dantrolene 2–3 mg/kg, then 1 mg/kg should be administered intravenously. Acid–base disturbances Acid–base disturbances commonly accompany coma due to drugs. Acute respiratory acidosis is less common than might be expected, but some elevation of arterial CO_2 tensions towards the upper limit of normal is usual. This, in combination with mild hypoxia in the deeper grades of coma, produces overall acidaemia. In general, acidosis should be prevented and managed by ensuring adequate ventilation, oxygenation and tissue perfusion, and control of convul- sions rather than by giving bicarbonate. However, several poisons, particularly methanol and ethylene glycol, cause life-threatening

 metabolic acidosis which should be corrected by infusion of sodium bicarbonate (see individual poisons). Acute respiratory alkalosis, often in combination with a minor metabolic acidosis, is commonly found in acute salicylate poisoning. The metabolic component may require treatment if it is the dom- inant feature and is causing overall acidaemia. Respiratory alkalosis should not be treated. Electrolyte abnormalities Electrolyte abnormalities may result from acid–base disturbances or the direct effects of poisons. Massive tissue damage, usually rhabdomyolysis, may allow potassium to leak from cells leading to potentially lethal hyperkalaemia. Cardiac glycosides cause hyperkalaemia, secondary to loss from cells due to inhibition of the membrane sodium–potassium pump, while the reverse occurs with sympathomimetic drugs. Oxalic acid and ethylene glycol (which is metabolized to oxalic acid) may cause hypocalcaemia by leading to the formation of in- soluble calcium oxalate, which is deposited in tissues. Similarly, in- gestion of fluorides is also a possible cause of hypocalcaemia; but the amounts children tend to ingest in the form of tablets to pre- vent dental caries seldom cause serious problems. Ingestion of po- tassium salts, even in sustained release formulations, may lead to hyperkalaemia and fatal arrhythmias. Bladder care Urinary retention is a common complication of acute poisoning, par- ticularly with tricyclic antidepressants and other drugs which have marked anticholinergic actions. However, bladder catheterization is all too often an unconsidered measure in unconscious poisoned pa- tients. Coma itself is not an indication for bladder catheters in poi- soned patients, the great majority of whom regain consciousness within 12 h. The bladder can usually be induced to empty reflexively (provided it is not allowed to become grossly overdistended) by ap- plying gentle suprapubic pressure. Catheterization should be reserved for those patients in whom suprapubic pressure is insufficient to empty the bladder, and in those thought to be developing renal failure. Skin, muscle, and nerve lesions Bullous lesions should be left intact until they burst, to reduce the risk of infection. De-roofing should be performed when the blister bursts; a nonadhesive dressing is then applied. Rhabdomyolysis is a further possible result of immobility and may occur in combination with skin lesions or independently. Poisoning is the most common nontraumatic cause of this condition and it may lead to acute renal failure and, rarely, to ischaemic muscle con- tractures and long-term disability. Urgent orthopaedic referral is in- dicated if a compartment syndrome is suspected. Peripheral nerves such as the radial, ulnar, and common peroneal may also be dam- aged by direct pressure while the patient is unconscious. Unconscious patients should be turned from side to side at least every 2 h. Antidotes Antidotes may exert a beneficial effect by: • forming an inert complex with the poison (e.g. deferoxamine, D-penicillamine, dicobalt edetate, dimercaprol, digoxin-specific antibody fragments, HI-6, hydroxocobalamin, obidoxime, pralidoxime, protamine, Prussian (Berlin) blue, sodium calcium edetate, succimer (DMSA), unithiol (DMPS)) • accelerating detoxification of the poison (e.g. acetylcysteine, so- dium thiosulfate) • reducing the rate of conversion of the poison to a more toxic com- pound (e.g. ethanol, fomepizole) • competing with the poison for essential receptor sites (e.g. oxygen, naloxone, phytomenadione) • blocking essential receptors through which the toxic effects are mediated (e.g. atropine) • bypassing the effect of the poison (e.g. oxygen, glucagon) The most frequently used antidote in the developed world is acetylcysteine for paracetamol poisoning. Naloxone for opioid an- algesics, oxygen for carbon monoxide and, possibly, flumazenil for benzodiazepines are the only antidotes commonly needed in the management of unconscious poisoned patients. Other antidotes of proven value are listed in Table 10.4.1.4. The reader is recom- mended to read the relevant section in the chapter to obtain further advice. Antivenoms for bites and stings by venomous animals are discussed in Chapter 10.4.2. Table 10.4.1.4 Poisons for which there are specific antidotes Poison Antidote

Aluminium Deferoxamine (Desferrioxamine) Arsenic Dimercaprol (BAL), succimer (DMSA) Benzodiazepines Flumazenil β-adrenoceptor-blocking drugs Atropine, glucagon Calcium channel blockers Atropine Carbamate insecticides Atropine Carbon monoxide Oxygen Copper d-Penicillamine, unthiol (DMPS) Cyanide Dicobalt edetate, hydroxocobalamin, oxygen, sodium nitrite, sodium thiosulfate Diethylene glycol Fomepizole, ethanol Digoxin and digitoxin Digoxin-specific antibody fragments Ethylene glycol Fomepizole, ethanol Hydrogen sulphide Oxygen Iron salts Deferoxamine (Desferrioxamine) Lead (inorganic) Succimer (DMSA), sodium calcium edetate Methaemoglobinaemia Methylthioninium chloride (methylene blue) Methanol Ethanol, fomepizole Mercury (inorganic) Unithiol (DMPS) Nerve agents Atropine, obidoxime, pralidoxime, HI-6 Oleander Digoxin-specific antibody fragments Opioids Naloxone Organophosphorus insecticides Atropine, obidoxime, pralidoxime Paracetamol Acetylcysteine Thallium Prussian (Berlin) blue Warfarin and other anticoagulants Phytomenadione (vitamin K1)

10.4.1 Poisoning by drugs and chemicals 1733 Reduction of poison absorption Prevention of absorption of volatile poisons through the lungs ob- viously requires removal from the toxic atmosphere and occasion- ally removal of soiled clothing as well. The latter is also necessary when absorption is thought to have been percutaneous. In addition, the contaminated skin should be thoroughly washed with soap and water. Although it appears logical to assume that removal of unabsorbed drug from the gastrointestinal tract (‘gut decontamination’) will be beneficial, the efficacy of current methods remains unproven, and efforts to remove small amounts of ‘safe’ drugs are clearly not worth- while or appropriate. Activated charcoal Activated charcoal adsorbs a wide variety of drugs and toxic agents; the exceptions are acids and alkalis, ethanol, ethylene glycol, iron, lithium, and methanol. In studies in volunteers given 50 g activated charcoal, the mean reduction in absorption was 40%, 16%, and 21% at 60 min, 120 min, and 180 min, respectively, after ingestion. Based on these studies, ac- tivated charcoal 50–100 g should be considered in those who have ingested a potentially toxic amount of a poison (known to be ad- sorbed by charcoal) up to 1 h previously. There are insufficient data to support or exclude its use after 1 h. There is no evidence that ad- ministration of activated charcoal improves the clinical outcome. Gastric aspiration and lavage Gastric emptying studies in volunteers provide no support for the use of gastric lavage. In the single clinical study in which benefit was claimed for lavage within 1 h of overdose, patients also received acti- vated charcoal. There was also selection bias, and hence conclusions based on these data are limited. Thus, gastric lavage should not be used routinely in the management of poisoned patients as there is no evidence that it improves outcome, and it may cause significant morbidity. The efficacy with which lavage removes gastric contents decreases with time; therefore, lavage should be considered only in patients who have ingested life-threatening amounts of a toxic agent up to 1 h previously. Emesis with syrup of ipecacuanha Syrup of ipecacuanha contains the active alkaloids emetine and cephaeline. Although syrup of ipecacuanha is an effective emetic, there is no evidence that its use prevents significant absorption of toxic material and, moreover, its adverse effects (e.g. persistent vomiting, diarrhoea, lethargy, drowsiness) may complicate diag- nosis. It is not recommended. Whole-bowel irrigation Theoretically, the more quickly a slowly absorbed poison passes through the gut, the less it is absorbed. The opposite may apply to rapidly absorbed drugs. Whole-bowel irrigation using polyethylene glycol electrolyte solutions does not result in absorption of fluid and electrolytes, even though large volumes are administered rapidly via a nasogastric tube. Some volunteer studies have shown substan- tial decreases in the bioavailability of ingested drugs, but no con- trolled clinical trials have been conducted and there is no evidence that whole-bowel irrigation improves

outcome. Based on volunteer studies, whole-bowel irrigation may be considered following potentially toxic ingestion of sustained release or enteric-coated drugs and in body packers. Cathartics Cathartics have been used alone and with activated charcoal. Cathartics alone have no role in the management of poisoned pa- tients. Based on available data, routine use of a cathartic with activated charcoal is not endorsed. Methods to increase poison elimination Once a poison has been absorbed and providing there is no antidote, it is reasonable to consider the use of treatments that might speed its elimination from the body. Multiple-dose activated charcoal Use of multiple-dose activated charcoal involves repeated admin- istration of oral activated charcoal to increase the elimination of a drug that has already been absorbed into the body. Elimination of a drug with a small volume of distribution (<1 litre/kg), low pKa (which maximizes transport across membranes), low binding af- finity, and prolonged elimination half-life following overdose is par- ticularly likely to be enhanced by multiple-dose activated charcoal. Multiple-dose activated charcoal also improves total body clearance of the drug when endogenous processes are compromised by liver and/or renal failure. Activated charcoal adsorbs material in the gut, which may be rele- vant in cases of poisoning with slow-release drug preparations. It also adsorbs drugs that are secreted in the bile, thereby preventing intestinal reabsorption, and binds any drug that diffuses from the circulation into the gut lumen. After absorption, drugs re-enter the gut by passive diffusion if the concentration in the gut is lower than that in the blood. The rate of passive diffusion depends on the con- centration gradient and the intestinal surface area, permeability, and blood flow. Occasionally, drugs such as digoxin may be secreted ac- tively by the intestinal mucosa, though the contribution of active secretion to the effect of multiple-dose activated charcoal on drug clearance is unlikely to be greater than that of passive diffusion. Although many studies have demonstrated that multiple-dose ac- tivated charcoal significantly increases drug elimination, it has not been shown to reduce morbidity and mortality in controlled studies in poisoned patients. At present, use of multiple-dose activated charcoal should be considered only in patients who have ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. Clinical experience in adults suggests that charcoal should be ad- ministered in an initial dose of 50–100 g and then at a rate of not less than 12.5 g/h, preferably via a nasogastric tube. Smaller initial doses (10–25 g) can be used in children because, generally, smaller overdoses have been ingested and the capacity of the gut lumen is smaller. If the patient has ingested a drug that induces protracted vomiting (e.g. theophylline), intravenous ondansetron is effective as an antiemetic and thus enables administration of multiple-dose ac- tivated charcoal. A total dose of 200 g (in adults) is usually sufficient.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1734 Urine alkalinization Increasing the urine pH enhances elimination of salicylate, phenobar- bital, and chlorophenoxy herbicides (e.g. 2,4-dichlorophenoxyacetic acid, mecoprop). However, except for salicylate poisoning, urine alkalinization is not recommended as first-line therapy for poisoning with these agents, as multiple-dose activated charcoal is superior for phenobarbital, and a substantial diuresis is required in addition to urine alkalinization to achieve clinically important elimination of chlorophenoxy herbicides. Urine alkalinization is a metabolically invasive procedure re- quiring frequent biochemical monitoring and medical and nursing expertise. Before commencing urine alkalinization, it is important to correct plasma volume depletion, electrolytes (administration of sodium bicarbonate exacerbates pre-existing hypokalaemia), and metabolic abnormalities. Sodium bicarbonate is most con- veniently administered intravenously as an 8.4% solution (1 mmol bicarbonate/ml). Sufficient bicarbonate should be administered (225 mmol was the mean amount

required in one study) to ensure that the pH of the urine, which is measured by narrow-range indicator paper or a pH meter, is more than 7.5 and preferably close to 8.5. As the administration of sodium bicarbonate forces potassium into cells, it is important that the patient has a normal serum po- tassium concentration before sodium bicarbonate is administered. Sodium bicarbonate 8.4% is highly irritant to veins and severe tissue damage can ensue if extravasation occurs. A secure, preferably wide- bore cannula (or central venous line), must therefore be used. Dialysis, haemodialfiltration, haemofiltration,
and haemoperfusion Haemodialysis, haemodialfiltration, and haemoperfusion are of no value in patients poisoned by drugs with large volumes of distribution (e.g. tricyclic antidepressants), because the plasma contains only a small proportion of the total amount of drug in the body. Haemodialysis, and to a lesser extent haemodialfiltration, sig- nificantly increases elimination of ethanol, ethylene glycol, isopro- panol, lithium, methanol, and salicylate, and is the treatment of choice in all cases of severe poisoning with these agents. Although haemofiltration is widely available, it is much less efficient than haemodialysis and haemodialfiltration and, therefore, should not be used unless the alternatives are unavailable. Charcoal haemoperfusion can significantly reduce the body burden of phenobarbital, carbamazepine, and theophylline, but multiple-dose activated charcoal is as effective and simpler to use. Drugs Angiotensin-converting enzyme inhibitors Clinical features Hypotension is the principal feature, occasionally accompanied by drowsiness. Angioedema, hyperkalaemia, and renal failure are rec- ognized. The fall in blood pressure is often much greater than from therapeutic doses and the suggestion that ACE inhibitors have a ‘ceiling’ effect on blood pressure is incorrect. Treatment ACE inhibitors are likely to bind to activated charcoal, which should be administered in early presentations. The principles of supportive care include volume expansion and subsequent use of inotropes. Since most patients who take these drugs in overdose are on treatment for hypertension or heart failure, careful manage- ment is necessary as they may already have impaired myocardial function.
Antibacterial agents Most patients who take an antibiotic overdose are asymptom- atic and require no treatment. There have been single case re- ports of renal failure after overdose with co-trimoxazole or aminoglycosides, pancreatitis with erythromycin, haemorrhagic cystitis with amoxicillin, and seizures with amoxicillin and other β-lactam antibiotics. Rifampicin may induce metabolism of other drugs, an effect that takes several days. Erythromycin may cause QT prolongation and torsade de pointes. Isoniazid is dealt with next. Anticoagulants Warfarin is an antagonist of the synthesis of the vitamin K de- pendent clotting factors II, VII, IX, and X. Newer oral anticoagulant agents, such as dabigatran, a thrombin inhibitor, and rivaroxaban and apixaban, both direct factor Xa inhibitors, impact specific tar- gets in the coagulation cascade. Toxicity is more likely to occur in the setting of therapeutic anticoagulation, or because of a drug interaction, than as a consequence of acute overdose. Pre-existing renal impairment is the major factor affecting the toxicity of newer agents. Clinical features Epistaxis, gingival bleeding, spontaneous bruising, haematomas, haematuria, bilateral flank pain, rectal bleeding, and haemor- rhage into any organ. Spontaneous haemoperitoneum has been re- ported. Severe blood loss may result in hypovolaemic shock, coma, and death. Treatment For warfarin if major bleeding occurs, give phytomenadione (vitamin K1) 5 mg by slow intravenous injection together with prothrombin complex dried 25–50 units/kg or if unavailable fresh frozen plasma 15 ml/kg. If the INR is 8.0 or more and there is no active bleeding discon- tinue warfarin (restart when the INR <5.0), give phytomenadione 1–3 mg by slow intravenous injection and repeat the dose if the INR is 8.0 or more 24 h later. If the INR is 6.0–8.0, and there is no active bleeding or only minor bleeding, warfarin should be discontinued and restarted when the INR is less than 5.0. If continued anticoagulation is

unnecessary and the INR is 4.0 or less and there is no active bleeding, treatment with phytomenadione is not required. If the INR is 4.0 or more, phytomenadione 5 mg by slow intravenous injection (100 µg/kg body weight for a child) should be administered. A specific monoclonal antibody, idarucizumab 5–10g should be given, to reverse the effects of dabigatran. Rivaroxaban and apixaban

10.4.1 Poisoning by drugs and chemicals 1735 have no specific antidotes, but clotting factor concentrate or fresh frozen plasma should be tried in active bleeding.
Anticonvulsants: Carbamazepine Clinical features Carbamazepine is structurally related to the tricyclic antidepressants and has similar anticholinergic actions. Overdose causes dry mouth, coma, convulsions, nystagmus, ataxia, and incoordination. The pu- pils are often dilated, divergent strabismus may be present and com- plete external ophthalmoplegia has been reported. Hallucinations may occur, particularly in the recovery phase. Treatment Multiple-dose activated charcoal has been shown to increase elimin- ation of carbamazepine significantly.
Anticonvulsants: Phenytoin Clinical features Acute overdose results in nausea, vomiting, headache, tremor, cere- bellar ataxia, nystagmus, and rarely, loss of consciousness. Treatment Multiple-dose activated charcoal may increase phenytoin elimin- ation though this has not been confirmed.
Anticonvulsants: Sodium valproate Clinical features Most frequently there is drowsiness, impairment of consciousness, and respiratory depression. In severe poisoning, myoclonic jerks and seizures may occur and cerebral oedema has been reported. Liver damage, pancreatitis, and metabolic acidosis, perhaps due to changes in fatty acid metabolism, are very unusual but potential complications. Treatment Treatment is symptomatic and supportive. Haemodialysis is ef- fective in removing sodium valproate and should be employed in severe poisoning, particularly if severe hyperammonaemia and electrolyte and acid–base disturbances are present.
Anticonvulsants: Gabapentin Clinical features and treatment Lethargy, ataxia, slurred speech, and gastrointestinal symptoms may develop. Management is supportive. Anticonvulsants: Lamotrigine Clinical features and treatment Lethargy, coma, ataxia, nystagmus, seizures, and cardiac conduction abnormalities have been reported. Management is supportive.
Anticonvulsants: Levetiracetam Clinical features and treatment Lethargy, coma, and respiratory depression have been observed. Management is supportive. Anticonvulsants: Tiagabine Clinical features and treatment Lethargy, facial grimacing, nystagmus, posturing, agitation, coma, hallucinations, and seizures have been reported. Management is supportive.
Anticonvulsants: Topiramate Clinical features and treatment Lethargy, ataxia, nystagmus, myoclonus, coma, seizures, and a normal anion gap metabolic acidosis have been observed; the latter may be due to inhibition of renal cortical carbonic anhydrase. Metabolic acidosis can appear within hours of ingestion and persist for days. Management is supportive. Antidepressants These come in a variety of pharmacological groups, but share the common effect of altering central monoamine function. Toxicity is largely dependent on other properties of these drugs.
Antidepressants: Tricyclic antidepressants Several different pharmacological actions determine the features of overdose. Reuptake of monoamines (noradrenaline and serotonin) into central and peripheral neurones is blocked. Anticholinergic ac- tions cause reduced gut motility, dry mouth, and tachycardia; sodium channel blockade (e.g. amitriptyline) with class I antiarrhythmic ac- tion prolongs the QRS complex; α-adrenergic and histamine antag- onism results in hypotension and sedation. Clinical features Clinical features evolve as the drug is absorbed, usually within 30– 60 min of ingestion. Patients who remain conscious 6 h after in- gestion are unlikely to have taken a large overdose. Early features include drowsiness, sinus tachycardia, dry mouth, and dilated pupils.

Urinary retention, increased reflexes, extensor plantar responses, and gaze palsies may then develop. Patients who become uncon- scious, Glasgow Coma Score (GCS) less than 8, or are unresponsive to pain, are at increased risk of more serious complications, particu- larly seizures. The risk of ventricular arrhythmias may be predicted from the length of the QRS complex. Changes in repolarization pat- tern may also be seen with abnormal T-waves and apparent changes in the ventricular axis. This pattern mimics the Brugada syndrome, the congenital abnormality associated with ventricular fibrillation. Features include ST elevation in leads V1–3, with right bundle block often associated with serious ventricular arrhythmias. Treatment Patients with depressed consciousness and prolonged QRS interval are at risk of seizures and arrhythmias. Maintenance of acid–base balance in these patients is crucial. Early and prompt treatment with sodium bicarbonate, even in patients who are not overtly acid- otic, ameliorates cardiac effects of tricyclics. Sodium bicarbonate 50–100 mmol (50–100 ml of 8.4%) should be administered. If given into a peripheral vein, there is a risk of necrosis if it extravasates. Indications for bicarbonate include QRS duration greater than 120 msec, existing arrhythmias or hypotension resistant to fluid

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1736 resuscitation. The aim is to maintain the arterial pH in the range 7.5–7.55 without producing greater alkalaemia. Class 1a and class 1c antiarrhythmic drugs are contraindicated because they have the same sodium channel blocking activity as tricyclic antidepres- sants. Convulsions should be treated conventionally with diazepam 10–20 mg intravenously, in an adult or lorazepam 4 mg. The α-adrenoceptor blocking properties of tricyclics can cause severe hypotension. Noradrenaline is the most appropriate inotrope to use in this situation. In the past, physostigmine was advocated to counteract the anti- cholinergic action of tricyclic antidepressants, but most European toxicologists do not recommend this. During recovery from tricyclic poisoning, there may be a pro- longed period of delirium with auditory and visual hallucinations. Sedation with diazepam is appropriate until the patient recovers. All tricyclic antidepressants may cause these features but dosulepin (dothiepin) is the most toxic in overdose, followed by amitriptyline. Antidepressants: selective serotonin reuptake
inhibitors (SSRIs) Citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are antidepressants that inhibit serotonin reuptake (SSRIs) and lack the anticholinergic actions of tricyclic antidepressants. Clinical features Clinical features of these agents are principally due to serotonin-like effects, and include nausea and vomiting, agitation, and tachycardia. Convulsions may occur after larger ingestions. Hypertonia and marked clonus are common features of significant poisoning, and increased muscle activity results in a rise in serum creatine kinase activity. Citalopram is the most toxic of the group in overdose. All SSRIs occasionally cause arrhythmias. Treatment In patients who consume more than one drug affecting serotonin receptors (e.g. tricyclic antidepressants, monoamine oxidase in- hibitors, drugs of abuse, including, in particular, ecstasy), the serotonin syndrome may occur. Features include marked agi- tation and increased muscle activity resulting in hyperpyrexia. About half the patients have central nervous system features including delirium and hallucinations. Other features include autonomic instability with tachycardia and labile blood pressure. Specific serotonin antagonists such as cyproheptadine may be useful though cannot be administered parenterally. Alternatively, benzodiazepines (e.g. diazepam orally or parenterally) may help reduce agitation. Antidepressants: Venlafaxine Venlafaxine is a drug that inhibits the reuptake of serotonin and nor- adrenaline (SNRI). In overdose, it has features of both SSRIs and tricyclic antidepressants but it lacks anticholinergic activity. Clinical features Drowsiness and convulsions are the main central nervous system effects.

Tachycardia, ventricular arrhythmias, and changes in blood pressure are the main cardiovascular effects. Treatment Management of metabolic acidosis is important to reduce the risk of arrhythmias, which are more common in patients who have had convulsions. Convulsions are managed conventionally with di- azepam 10–20 mg intravenously or lorazepam 4 mg intravenously. Activated charcoal should be considered if more than 12.5 mg/kg was ingested within the previous hour. Venlafaxine prolongs the QT interval so that torsade de pointes is a risk which, should it occur, is treated conventionally by correcting acidosis and with intravenous magnesium 1–2 g over 30–60 sec, repeated in 5–15 min. Antidepressants: Monoamine oxidase inhibitors (MAOIs) These have well-established adverse interactions with foods containing tyramine. The classical MAOIs such as phenelzine, isocarboxazid, and tranylcypromine are now rarely used, and the new more specific inhibitors of MAOI type A (moclobemide) and type B (selegiline) produce less serious adverse effects in overdose. Classical MAOIs prevent the breakdown of catecholamines within the nerve ending, and result in excess sympathomimetic effects per- ipherally, and excess adrenergic effects centrally. In patients who are naïve to the drugs, onset of inhibition of enzyme takes several hours, and clinical features may not be seen immediately. In patients on chronic therapy, the onset will be more rapid. Clinical features Principal effects are central nervous system stimulation with excite- ment, restlessness, hyperpyrexia, hyperreflexia, convulsions, and coma. These may go on to cause rhabdomyolysis. Cardiovascular ef- fects include tachycardia and changes in blood pressure, depending on whether the effects of epinephrine (vasodilation) or norepineph- rine (vasoconstriction) predominate. Treatment Treatment is supportive, with careful monitoring. Patients who develop central excitation should be treated with large doses of di- azepam. This will reduce centrally stimulated muscle contraction and hence pyrexia and muscle damage. Cardiovascular monitoring is essential. Changes in blood pressure should be managed where possible with drugs that are not sympathomimetic agonists. Use of β-blockade can result in an unopposed α-agonist effect causing large rises in blood pressure. Hypertension is best controlled with an intravenous nitrate, such as glyceryl trinitrate. Antidiabetic agents Intentional overdose with insulin and oral hypoglycaemic agents is uncommon. However, deaths from hypoglycaemia following poi- soning with insulin and sulfonyureas have been reported. Metformin rarely causes hypoglycaemia since its mode of action is to increase glucose utilization. Risk of hypoglycaemia in overdose is low from more recently introduced antidiabetics. These include subtype 2 sodium-glucose transport protein (SGLT2) inhibitors, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 analogues, and DDP-IV inhibitors. Clinical features Features of hypoglycaemia include drowsiness, coma, twitching, convulsions, depressed limb reflexes, extensor plantar responses,

10.4.1 Poisoning by drugs and chemicals 1737 tachypnoea, pulmonary oedema, tachycardia, and circulatory failure. Hypokalaemia, cerebral oedema, and metabolic acidosis might occur. Neurogenic diabetes insipidus and persistent vegeta- tive state are possible long-term complications. Lactic acidosis is a potentially serious complication of metformin overdose. SGLT2 inhibitors increase renal glucose clearance and, in overdose, cause polyuria, hypovolaemia, hypotension, and acute renal injury. Thiazolidinediones may cause hepatic dysfunction and SGLT2 in- hibitors cause diabetic ketoacidosis and renal impairment. Treatment In all cases of poisoning with insulin or a sulfonylurea, prompt diag- nosis and treatment are essential if death or cerebral damage from neuroglycopenia are to be prevented. The blood or plasma glucose concentration should be measured urgently and intravenous glucose given. Glucagon may be ineffective in hypoglycaemia due to exhaus- tion of hepatic stores of glucose. Recurring hypoglycaemia is highly

likely. A continuous infu- sion of glucose, together with carbohydrate-rich meals, is required in cases of severe insulin poisoning, though there may be difficulty in maintaining normoglycaemia. In the case of sulfonylurea poi- soning, however, further glucose (although its administration may be unavoidable) only serves to increase the already high-circulating insulin concentrations. Octreotide 50 microgram IV, followed by an infusion of 25 microgram/h is preferred in severe sulfonylurea poisoning. Antihistamines First-generation antihistamines include brompheniramine, chlorphenamine, cyclizine, diphenhydramine, promethazine, and trimeprazine. Second-generation drugs include cetirizine, loratidine, and fexofenadine. Clinical features Older antihistamines have anticholinergic actions but less potent central nervous system toxicity than other anticholinergic drugs. Delirium may be a particular problem in very young children and older people following a substantial acute overdose. Rhabdomyolysis is a well-recognized complication of severe antihistamine poisoning. The second-generation drugs generally cause less sedation and less psychomotor impairment, but some have been associated with cardiotoxicity causing QTc interval prolongation and ventricular tachycardia, including torsade de pointes. Treatment A 12-lead ECG and cardiac monitoring for at least 12 h is recom- mended after a substantial overdose. Management should otherwise follow the same principles as for tricyclic antidepressant poisoning (see earlier). Antimalarials: chloroquine Toxicity can result from doses greater than 1 g (c. 6 tablets) in adults. Clinical features Cardiac arrest is commonly the first clinical manifestation of poi- soning, but hypotension usually precedes it and may progress to cardiogenic shock with pulmonary oedema. Electrocardiographic abnormalities, bradyarrhythmias, and tachyarrhythmias are common and are similar to those seen in quinine poisoning. Visual disturbance, agitation, drowsiness, acute psychosis, dystonic reac- tions, seizures, and coma may ensue. Hypokalaemia is common and is due to potassium channel blockade. Treatment Supportive measures should be employed and hypokalaemia corrected. There is no specific antidote. Sodium bicarbonate 50–200 mmol (50–200 ml of 8.4%) is indicated if the ECG shows intraventricular block but will exacerbate hypokalaemia, which should be corrected first. Mechanical ventilation, the administra- tion of epinephrine 1–10 μg/kg per minute and high doses of di- azepam (1 mg/kg as a loading dose and 0.25–0.4 mg/kg per hour maintenance) may reduce the mortality to 10% in severe poisoning. Multiple-dose activated charcoal may enhance chloroquine elim- ination. Extracorporeal elimination techniques do not have a role. Extracorporeal life support has been utilized successfully in severely poisoned patients unresponsive to conventional measures. Antimalarials: quinine Quinine cardiotoxicity is due to sodium channel blockade. Clinical features Cinchonism (tinnitus, deafness, vertigo, nausea, headache, and diar- rhoea) is common at plasma concentrations greater than 5 mg/litre. In more serious poisoning, collapse with impairment of conscious- ness (due to ventricular arrhythmias), convulsions, hypotension, pul- monary oedema, and cardiorespiratory arrest may be observed. The latter is often preceded by ECG conduction abnormalities, particu- larly QT prolongation. Hypoglycaemia, resulting from insulin release, occurs even with therapeutic doses and must be excluded in all cases. About 40% of patients develop ocular features, which may be unilat- eral, including blindness, contracted visual fields, scotomata, dilated pupils, blurred disc margins, macular oedema, arteriolar spasm, and late optic atrophy. Oculotoxicity is likely when plasma concentrations exceed 10 mg/litre. Visual loss is permanent in about 50% of cases. Treatment Multiple-dose activated charcoal increases quinine clearance. Extracorporeal elimination techniques and stellate ganglion block are of no value. Electrolyte and acid–base disturbances and hypo- glycaemia should be corrected. Hypertonic sodium bicarbonate will correct acidosis that persists despite fluid resuscitation and adequate oxygenation and is recommended first-line therapy for conduction abnormalities due to sodium channel blockade, including QRS and QT

prolongation. Overdrive pacing may be required if torsade de pointes occurs and does not respond to magnesium sulfate 1–2 g over 30–60 sec, repeated in 5–15 min. Antimalarials: Primaquine Clinical features The main concern about primaquine is its ability to cause methaemo- globinaemia in overdose. Other adverse effects reported are head- ache, nausea, abdominal pain, haemolytic anaemia, particularly in patients with glucose-6-dehydrogenase deficiency, and leucopenia.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1738 Treatment Treatment is supportive. Clinically significant methaemoglobin- aemia (generally >30%) is treated conventionally with intravenous methylthioninium chloride (methylene blue), 1–2 mg/kg body weight. Antipsychotics Antipsychotic drugs are thought to act predominantly by effects on dopamine D2 receptors. Older antipsychotics were phenothiazines, such as chlorpromazine, and butyrophenones, such as haloperidol. Selective (‘atypical’) antipsychotic drugs include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Conventional antipsychotics have many actions, including anti- histamine and anticholinergic activity. Chlorpromazine blocks α-, β-, and 5HT-receptors in vitro. Features such as postural hypo- tension are likely to be due to the sum of these effects. Clinical features In overdose, the predominant clinical features of all antipsychotics are sedation, loss of consciousness, and hypotension. Respiratory depression may occur in more severe cases. Hypotension and vaso- dilatation are features of chlorpromazine poisoning. Some have caused QT prolongation in overdose. A 12-lead ECG should be obtained to check QT duration. Occasionally seizures are reported. ECG abnormalities have been seen with some of the newer atyp- ical antipsychotics, but they cause less cardiovascular disturbance than the older drugs. Muscle contraction due to central extra- pyramidal effects may result in rhabdomyolysis in severe cases. Neuroleptic malignant syndrome, seen during therapeutic use of these compounds, is uncommon in acute poisoning and should be treated conventionally. Treatment Management is supportive. Dystonic reactions may occur, particu- larly in young adults. These should be treated conventionally with procyclidine 5–10 mg intravenously, or diazepam 10–20 mg intra- venously or orally. Benzodiazepines These are widely used as tranquillizers, hypnotics, sedatives, and for emergency management of convulsions and hyperthermia. They also have abuse potential. Clinical features Although many benzodiazepines have active metabolites ac- counting for their sometimes-prolonged sedative effects, all are remarkably safe when taken in excess alone. However, there is in- dividual variation in response, influenced by habituation and tol- erance, which develop during chronic therapy. Otherwise healthy elderly people may respond to an overdose with prolonged toxicity. Benzodiazepines potentiate the effects of other central nervous system depressants, particularly alcohol, tricyclic antidepressants, and barbiturates. Dizziness, drowsiness, ataxia, and slurred speech are the usual features; coma, respiratory depression, and hypoten- sion are uncommon and usually mild. Flurazepam is most likely to cause significant central nervous system depression. Amnesia of events during the period of drug effect is also seen. Treatment The use of flumazenil is potentially hazardous in patients who have co- ingested proconvulsant drugs, particularly tricyclics, or who are habituated to benzodiazepines from therapeutic use (risk of acute withdrawal and fits). Flumazenil should therefore not be used routinely in benzodiazepine poisoning, nor as a diagnostic test. It should be given to avoid assisted ventilation in a patient who is otherwise going to require intubation, particularly in those with ex- isting chronic airways obstruction. Flumazenil has a short half-life (40–80 mins) and therefore repeated doses of 0.5–2 mg IV (or an infusion) may be required. β-Adrenoceptor blocking drugs (β- blockers) β-adrenoceptor blocking drugs (β-blockers) exert their toxic effects in overdose not only by blocking the β1- and β2-adrenoceptors, but also by virtue of their membrane stabilizing activity,

which results in a quinidine-like effect on the action potential as a result of sodium channel blockade; this produces QRS widening, which predisposes to ventricular arrhythmias. Clinical features Symptoms usually occur within 6 h of ingestion of nonsustained re- lease preparations. Sinus bradycardia may be the only feature after a small overdose, but if a substantial amount has been ingested, coma, convulsions (particularly with propranolol), profound bradycardia, and hypotension may occur. Other effects include drowsiness, de- lirium, hallucinations, low-output cardiac failure and cardiorespira- tory arrest (asystole or ventricular fibrillation). Bronchospasm and hypoglycaemia occur rarely. First-degree heart block, intraventricular conduction defects, right and left bundle branch block, ST segment elevation, ventricular extrasystoles, and disappearance of the P-wave may be noted on the electrocardiogram. Sotalol has been reported to cause QT interval prolongation and ventricular arrhythmias and asystole may follow severe overdose from any β-adrenoceptor blocking drug. Treatment A delay in treatment may be fatal in patients who are severely poi- soned. The blood pressure and cardiac rhythm of the patient should be monitored immediately in an intensive care area and supportive measures implemented. Glucagon is the drug of choice for severe hypotension; it bypasses the blocked β-receptor, thus activating adenyl cyclase and pro- moting the formation of cAMP (which has a direct β-stimulant ef- fect on the heart) from adenosine triphosphate (ATP). It should be given in a bolus dose of 50–150 µg/kg (typically 10 mg in an adult) over 1 min, followed by an infusion of 1–5 mg/h according to re- sponse. Conventional inotropes are less effective than glucagon in severe cases. If bradycardia is refractory to atropine 0.6–1.2 mg intravenously, repeated as necessary, transcutaneous or transvenous pacing should be considered. Sodium bicarbonate may reverse the cardiotoxic ef- fects of β-blockers with membrane stabilizing activity and should be considered for the treatment of ventricular dysrhythmias. Occasionally, diazepam 10–20 mg intravenously may be needed for convulsions. If bronchospasm supervenes, salbutamol (albuterol) by nebulizer, should be employed. Hypoglycaemia should be corrected.

10.4.1 Poisoning by drugs and chemicals 1739 β2-Adrenoceptor agonists Poisoning with β2-adrenoceptor stimulants, including fenoterol, pirbuterol, reproterol, rimiterol, salbutamol (albuterol), and ter- butaline, has followed deliberate and accidental ingestion of these drugs and has also resulted from confusion over the difference be- tween oral and parenteral doses. β2-agonists act on β2-adrenergic receptors and increase intracel- lular cAMP. In addition to initiating relaxation of bronchial, vas- cular, and uterine smooth muscle, β2-agonists cause glycogenolysis in skeletal muscle and hepatic glycogenolysis and gluconeogenesis. Hypokalaemia is caused by β2-receptor-mediated activation of Na+- K+-ATPase, with extracellular potassium being shifted into the intracellular compartment; hypokalaemia may precipitate supraventricular and ventricular arrhythmias. Clinical features Tremor, sinus tachycardia, agitation, convulsions, supraventricular and ventricular arrhythmias, hypokalaemia, hyperglycaemia, and ketoacidosis are the typical features of severe poisoning with β2-agonists. Psychosis and hallucinations are observed occasionally. Treatment Severe hypokalaemia should be corrected as soon as possible by the administration of an infusion of potassium at a rate of 40–60 mmol/h diluted in 5% dextrose. A nonselective β-blocker, such as propranolol 1–5 mg by slow intravenous injection, will also reverse hypokalaemia and tachyarrhythmias, but its use may ex- acerbate pre-existing obstructive airways disease. Supraventricular tachycardia has been treated successfully with adenosine 6 mg IV. Convulsions are usually single and short-lived but, if necessary, diazepam, 10–20 mg intravenously, may be given. Bismuth chelate (tripotassium dicitratobismuthate) Although bismuth absorption from bismuth chelate is low after a therapeutic dose, a significant quantity may be absorbed after

overdose. Clinical features Self-poisoning with large doses of bismuth chelate has caused re- versible renal failure. Bismuth encephalopathy has occurred fol- lowing chronic excess ingestion. Treatment Chelation with unithiol or succimer enhances urine bismuth clear- ance but there is no evidence that these agents prevent nephrotox- icity. Extracorporeal renal support may be required for renal failure. Calcium channel blockers Calcium channel blockers act by blocking voltage-gated calcium channels at cardiac conducting and contractile tissue and vascular smooth muscle. Clinical features In overdose, calcium channel blockers cause nausea, vomiting, dizziness, slurred speech, confusion, sinus bradycardia and tachy- cardia, prolonged atrioventricular conduction, atrioventricular dis- sociation, hypotension, pulmonary oedema, convulsions, coma, hyperglycaemia, and metabolic acidosis. When a sustained release preparation has been ingested, the onset of severe features may be delayed for more than 12 h. Cardiac complications are usually more serious following overdose with verapamil or diltiazem than with the dihydropyridines, such as nifedipine and amlodipine. Large overdoses carry a poor prognosis, particularly in patients with is- chaemic heart disease and in those taking β-blockers. Treatment Calcium chloride (10%, 5–10 ml at 1–2 ml/min) or calcium gluconate (10% solution) 10–20 ml intravenously may reverse pro- longed intracardiac conduction times. If significant hypotension persists despite volume replacement, intravenous glucagon 10 mg (150 μg/kg) should be given to an adult and can be followed by an infusion 5–10 mg/h depending on response. If hypotension persists, administer a sympathomimetic amine intravenously. Insulin–dextrose euglycaemia has been shown to improve myo- cardial contractility and systemic perfusion and may be used as an adjuvant to a sympathomimetic amine. There is some evidence that intravenous intralipid is useful in patients who do not respond to other measures. Cardiac pacing may have a role if there is evidence of atrioventricular conduction delay, but there may be failure to capture. Successful use of intra-aortic balloon pumping, cardiac bypass, and extracorporeal membrane oxygenation (ECMO) have been reported in extremely severe cases. Dapsone Dapsone is a sulfone antibiotic used in the management of leprosy and dermatitis herpetiformis. Clinical features Dapsone poisoning is potentially very severe, resulting in meth- aemoglobinaemia, haemolysis, hepatitis, and central nervous system effects including drowsiness, coma, and seizures. Treatment Multiple-dose activated charcoal increases dapsone elimination. Methaemoglobin concentrations above 30% should be treated with methylthioninium chloride (methylene blue) 1–2 mg/kg intraven- ously. Dapsone-induced methaemoglobinaemia may persist for sev- eral days necessitating repeated doses of methylthioninium chloride or an infusion. Haemodialysis enhances dapsone elimination and has been used successfully in the management of life-threatening ingestions. Digoxin and digitoxin Digoxin and digitoxin toxicity occurs in: • patients on regular therapy who gradually accumulate drug due to excess dosing, or development of incipient renal impairment • patients who take a single, large overdose, both in those on chronic therapy and those naïve to the drug Interpretation of the clinical and biochemical features differs be- tween these situations. In acute poisoning, the most significant feature normally seen is bradycardia. Since digoxin acts on a Na+-K+-ATPase, and subse- quent changes in the myocardium develop following this, onset of the effects of digoxin in overdose may take up to 12 h. In very large overdoses, however, severe features may develop sooner than this,

 although in clinical practice very large overdoses are uncommon. Because of the action on Na+-K+-ATPase, the serum potassium concentration increases, and a very high serum potassium concen- tration is therefore a useful, rapidly measurable marker for severe di- goxin poisoning. Measurement of the

plasma digoxin concentration will confirm the diagnosis. This is particularly the case in patients on chronic therapy who may have less dramatic changes in serum po- tassium, perhaps because of coexistent diuretic therapy, and where clinical features may be more predominantly tachycardias. Patients require treatment for cardiovascular compromise, not for blood concentrations. In acute poisoning, blood concentrations may rise to quite high values (above 5 µg/litre) without necessarily causing severe clinical features. These rises may be transient as the drug redistributes into fatty stores after absorption. In chronic therapy, plasma concentrations give a better indication of the quan- tities of digoxin present in the body, and in acute overdose several plasma concentration measurements may need to be taken over a short period to assess the dose absorbed. Clinical features Nausea, vomiting, and bradycardia may occur. Sinus bradycardia is the most important and earliest feature in acute poisoning. Malignant ventricular arrhythmias are seen in patients with severe poisoning. At high doses, central nervous system features including drowsiness and hallucinations may be present. Treatment In patients who are vomiting, the airway needs to be protected, and consideration should be given to administering charcoal later than 1 h in patients who have ingested significant quantities, as this is such a toxic compound. The temptation to treat moderate hyperkalaemia should be resisted, as this will interfere with moni- toring clinical response. Patients should be treated on the basis of their cardiovascular status, not the plasma concentrations of digoxin alone. Patients with bradycardia who are symptomatic should receive atropine and have any acid–base disturbance corrected. In patients with significant bradycardia or malignant ventricular arrhythmias, the most effective therapy is neutralization of digoxin with digoxin antibody. Doses of antibody recommended by the manufacturers are designed to completely neutralize all digoxin present in the pa- tient. Such an approach is unwarranted, particularly in patients on chronic therapy with digoxin in whom complete reversal of digoxin will unmask the disorder for which they are being treated. Initially, half the calculated total neutralizing dose should be given. Further doses can be given subsequently, if necessary. In patients who receive the antibody, clinical improvement will occur rapidly, usually within 20 min. Failure to respond indicates either an incorrect diagnosis or continued absorption of digoxin. Measurement of serum digoxin concentration is not possible once the digoxin antibody has been administered, since currently avail- able assays measure both bound and free compound. Extracorporeal elimination techniques are ineffective in removing digoxin though multiple-dose activated charcoal may increase elimination. Diuretics Most diuretic overdoses are minor, although inevitably some dis- turbance of fluid and electrolyte balance will result. When combined diuretic and potassium formulations are ingested, the potassium content is likely to pose the greater risk. More serious consequences are likely if a potassium-sparing diuretic has been ingested. Clinical features Symptoms and signs of toxicity include anorexia, nausea, vomiting, diarrhoea, profound diuresis, dehydration, and hypotension. In addition, dizziness, weakness, muscle cramps, tetany and, occasion- ally, gastrointestinal bleeding may be seen. The electrolyte and meta- bolic disturbances that may be observed include hyponatraemia, hypoglycaemia or hyperglycaemia, hyperuricaemia, hypokalaemia, and metabolic alkalosis. Hyperkalaemia develops following the ingestion of combined diuretic and potassium preparations and potassium-sparing diuretics, such as amiloride, spironolactone, or triamterene. Small-bowel ulceration and stricture formation have followed poisoning due to diuretics with an enteric-coated core of potassium chloride. Treatment Symptomatic and supportive therapy should be employed with correction of fluid and electrolyte imbalance. Patients with severe hyperkalaemia may need a glucose and insulin infusion followed by oral or rectal administration of an ion-exchange resin. Iron Most medicinal preparations of iron are as the ferrous salt. Ferrous iron is oxidized to the ferric state before being absorbed. It is im-

portant to differentiate vitamin preparations that contain iron from medicinal preparations, since the former generally do not cause significant clinical problems unless very large amounts are taken. Since iron toxicity is quite closely related to dose per kilo- gram ingested, serious poisoning is more likely to occur in young children than in adults. The anticipated toxicity of iron is nor- mally estimated by calculating the dose of elemental iron present in the preparation, which varies from salt to salt. Ingestions above 150 mg/kg of elemental iron are generally extremely severe and may be fatal. Iron salts are both locally corrosive within the gastrointestinal tract and in the cell act as cellular toxins, probably by altering the function of mitochondria. In severe poisoning, patients are uncon- scious and suffer from circulatory collapse and hepatic injury. Clinical features Depending on the severity of poisoning features may vary, and in severe cases, features would be expected within the first 6 h and include nausea, vomiting, and abdominal pain. Iron will stain the vomit and faeces (diarrhoea) and may also cause intestinal ulcer- ation and result in haemorrhage. Large amounts of iron may be vis- ible on a straight abdominal radiograph, but this should not be done routinely to confirm iron ingestion in children. Following absorption of iron there is often a period of relative calm during which iron is taken into cells before its toxic effects mani- fest. In severe poisoning, profound hypotension, metabolic acidosis, coma, and features of hepatic necrosis and renal failure ensue. Such patients require intensive supportive care and mortality rates are high. In patients who recover from severe poisoning, gut strictures following scarring from ulceration may be problematic. The com- monest site is around the pylorus, particularly in young children.

10.4.1 Poisoning by drugs and chemicals 1741 Treatment Although dose is related to toxicity, patients may be sometimes in- accurate in their history, and since vomiting is a frequent early fea- ture it may be difficult to assess exactly how much iron has been absorbed. Plasma concentration measurements on more than one occasion may assist this process. High serum iron concentrations (>90 micromol/litre or 5 mg/litre) in the first 4–6 h after overdose are more likely to indicate severe poisoning. In this situation, iron will be circulating free in plasma and may result in toxicity. As iron does not bind to charcoal, patients who present early with suspected large iron ingestions should be considered for gastric aspiration or lavage, though in practice this is rarely per- formed since vomiting is a prominent early feature in these cases. Whole-bowel irrigation has been advocated following ingestion of slow-release iron preparations, though data on its efficacy is an- ecdotal. In patients with significant elevated iron concentrations (>90 micromol/litre or 5 mg/litre) and features suggestive of sig- nificant poisoning, the specific iron-chelating agent deferoxamine (desferrioxamine) should be administered intravenously. There are few human data to support the usual dose regimen of deferoxamine 15 mg/kg/h up to a maximum of 80 mg/kg, which binds relatively little elemental iron. Toxicity with reported during its use in the management of chronic disorders, such as haemachromatosis and haemoglobinopathies, is not a feature of its use in the management of iron poisoning and should not, therefore, be used as a guide to limit dosing in severe cases. Deferoxamine may cause hypotension and there are occasional reports of anaphylactoid reactions. Once deferoxamine has been administered, interpretation of iron concentrations becomes impossible because the iron bound to deferoxamine is detected in the laboratory assay. Iron-deferoxamine complex col- ours urine red. Patients who have not developed features of poisoning within 6 h have probably not ingested very large quantities of iron, unless they have taken a slow-release product. Most patients merely re- quire treatment for their gastrointestinal disturbance. Since iron preparations are more commonly given to women who are preg- nant than other groups of the population, iron overdose may be seen more frequently in pregnant women. There is currently no evidence to suggest these patients should be treated

differently because of pregnancy, and deferoxamine, should certainly not be withheld in patients who are deemed to require it. Isoniazid Poisoning with isoniazid is potentially very serious, but uncommon. Isoniazid depresses brain concentrations of γ-aminobutyric acid (GABA), thus leading to seizures. Clinical features The ingestion of isoniazid 80–150 mg/kg body weight is likely to cause severe poisoning. Nausea, vomiting, slurred speech, dizzi- ness, and visual hallucinations may develop. Stupor, coma, and con- vulsions follow rapidly and may be associated with hyperthermia, hyperreflexia, extensor plantar responses and, later, rhabdo- myolysis. In addition, dilated pupils, sinus tachycardia, and urinary retention may be observed. In severe cases, hypotension, acute renal failure, and respiratory failure may ensure. Marked metabolic (lactic) acidosis is common. Less commonly, hyperglycaemia, keto- acidosis, glycosuria, and ketonuria are found. Treatment Supportive measures, including the correction of metabolic acid- osis, should be instituted immediately if the patient is unconscious. Pyridoxine 1 g for 1 g of isoniazid ingested should be given intra- venously to control convulsions. When the ingested dose of iso- niazid is unknown, an initial intravenous dose of pyridoxine 5 g should be given. Due to the mechanism of toxicity, diazepam alone may be ineffective but the use of diazepam and pyridoxine is syner- gistic and both should be used for convulsions. Pyridoxine 5 g may be repeated if convulsions persist (in one case 52 g pyridoxine was given intravenously without ill effects). Lithium carbonate Lithium carbonate remains the drug of choice for the treatment of recurrent bipolar illness. It has a low therapeutic index and toxicity is usually the result of therapeutic overdosage (chronic toxicity) ra- ther than deliberate self-poisoning (acute toxicity). Chronic tox- icity is usually explained by a reduction in lithium renal clearance without a reduction in dose. Single large doses are occasionally in- gested by individuals on long-term treatment with the drug (acute on therapeutic toxicity). Clinical features Features of intoxication include thirst, polyuria, diarrhoea, and vomiting, and, in more serious cases, tremor, impairment of con- sciousness, hypertonia, and convulsions; irreversible neurological damage may occur. Measurement of the serum lithium concentra- tion confirms the diagnosis. Chronic toxicity is usually associated with concentrations above 1.5 mmol/litre. However, acute massive overdosage may produce much higher concentrations without causing toxic features, at least initially. This is explained by plasma lithium concentrations that are substantially higher than cen- tral nervous system lithium concentrations before distribution is complete. Treatment Activated charcoal does not adsorb lithium. Treatment is sup- portive together with measures to enhance the rate of lithium elimination. Haemodialysis should be considered if neurological features are present, if renal function is impaired and if chronic toxicity or acute on therapeutic toxicity are the modes of presen- tation. The efficacy of haemodialysis is limited by the relatively slow movement of lithium ions across cell membranes. It is easy to reduce serum lithium concentrations, but they frequently re- bound when treatment is stopped and clinical improvement is much slower. Repeated haemodialysis sessions are usually re- quired. Continuous haemodialfiltration can be used if conventional haemodialysis is not available, though clearance of lithium is less efficient. Nitrates Organic nitrates such as isosorbide mononitrate and isosorbide dinitrate are vasodilators that act by relaxing vascular smooth muscle. These drugs are essentially nitric oxide donors, which in- crease nitric oxide-induced activation of guanylate cyclase with

 subsequent elevation of cGMP concentrations. Their effects in over- dose are directly related to their therapeutic actions. These drugs undergo extensive first pass metabolism in the liver. Exposure to in- organic nitrates is principally via drinking water. Clinical features The symptoms and signs caused by pharmaceutical nitrates in overdose are due primarily to excessive arteriolar and venous

dilatation. Headache and vomiting are common, accompanied by flushing of the skin and dizziness. Sinus tachycardia, severe orthostatic hypotension, and syncope may develop. Convulsions and coma may be seen in severely poisoned patients. In contrast to poisoning by inorganic nitrates, methaemoglobinaemia is seen very rarely with organic nitrates. Methaemoglobinaemia caused by inorganic nitrates is in fact due to conversion of nitrate to nitrite by gastrointestinal bacteria, following ingestion. This is encoun- tered primarily among infants bottle-fed with formula milk that has been made up with water with high nitrate content. Treatment Treatment is supportive. Methaemoglobin concentrations exceed ing 30% should be treated with intravenous methylthioninium chloride (methylene blue) 1–2 mg/kg. Nonsteroidal anti-inflammatory drugs These include a variety of different groups of drugs, all acting by inhibition of cycloxygenase enzymes. The newer, so-called selective, agents are thought to inhibit the inducible form of cycloxygenase (COX-2) more than the other forms of the enzyme. These drugs, therefore, all tend to inhibit prostaglandin synthesis, and the main toxicity seen in overdose is on the kidney. In very large doses, central nervous system effects may be seen but these are uncommon. Nonsteroidal anti-inflammatory drugs (NSAIDs) come in different chemical groupings: oxicams (meloxicam, piroxicam, tenoxicam) and phenylpropionic (arylpropionic) acid derivatives (e.g. fenbufen, ibuprofen, naproxen, tiaprofenic acid, mefenamic acid). The COX-2 selective agents are also potentially nephrotoxic in overdose due to inhibition of renal prostaglandin synthesis. Clinical features Most NSAIDs cause only nausea except in severe cases. Mefenamic acid is an exception and produces nausea, vomiting and, occasion- ally, bloody diarrhoea; drowsiness, dizziness and headaches are common; and hyperreflexia, muscle twitching, convulsions, cardio- respiratory arrest, hypoprothrombinaemia, and acute renal failure have also been reported. Treatment Treatment of poisoning with NSAIDs is generally supportive. It is important to check renal function at an interval after ingestion in patients who have ingested large doses. Changes in serum potas- sium and elevations in serum creatinine concentrations are to be expected in patients ingesting toxic doses. Treatment of renal im- pairment is conventional. Dialysis may be required in very severe cases. Activated charcoal should only be considered in patients who have ingested very large doses of nonsteroidals (generally >20 tab- lets). Convulsions with mefenamic acid are unlikely to be persistent but, if they are, should be managed by diazepam 10–20 mg intra- venously or lorazepam 4 mg intravenously. Opiates and opioids See section later on in this chapter, ‘Opiates and opioids’. Paracetamol (acetaminophen) Mechanisms of toxicity The toxicity of paracetamol is related to its metabolism (Fig. 10.4.1.1). In therapeutic doses, 60–90% is metabolized by conjugation to form paracetamol glucuronide and sulphate. A much smaller amount (5–10%) is oxidized by mixed function oxidase enzymes to form a highly reactive compound (N- acetyl- p-benzoquinoneimine, NAPQI), which is then immediately con- jugated with glutathione and subsequently excreted as cysteine and mercapturate conjugates. Only 1–4% of a therapeutic dose of the drug is excreted unchanged in urine. In overdose, larger amounts of paracetamol are metabolized by oxidation because of saturation of the sulphate conjugation pathway. As a result, liver glutathione stores become depleted so NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 NHCOCH3 SCH2CHCO2H SCH2CHCO2H OSO3H OC6H9O6 OH N-Acetyl-p- benzoquinone- imine (NAPQI) Cysteine conjugate Glutathione conjugate Paracetamol mercapturic acid Paracetamol sulphate Paracetamol glucuronide Paracetamol O O GSH GSH OH OH δ+
Fig. 10.4.1.1 Metabolism of paracetamol.

 that the liver is unable to deactivate the toxic metabolite. NAPQI is believed to have two separate but complementary effects. Firstly, it reacts

with glutathione, thereby depleting the cell of its normal defence against oxidizing damage. Secondly, it is a potent oxidizing as well as arylating agent; it inactivates key sulphydryl groups in certain enzymes, particularly those controlling calcium homeostasis. Paracetamol-induced renal damage probably results from a mechanism similar to that causing for hepatotoxicity (i.e. by for- mation of NAPQI). As would be expected from the mechanism of toxicity, the severity of paracetamol poisoning is dose related. An absorbed dose of 15 g (200 mg/kg) or more is potentially serious in most patients. There is, however, some variation in individual susceptibility to paracetamol- induced hepatotoxicity. Those with a high alcohol intake and poor nu- trition, and those suffering from anorexia nervosa or acute starvation have glutathione depletion and are at higher risk. Individuals with HIV-related disease also appear to be more susceptible to paracetamol-induced hepatic damage. Those receiving enzyme- inducing drugs are also at greater risk. Clinical features The features of paracetamol poisoning are summarized in Table 10.4.1.5. Biochemical and haematological abnormalities may also occur (Table 10.4.1.6). Following the ingestion of an overdose of paracetamol, patients usually remain asymptomatic for the first 24 h, or at most develop anorexia, nausea, and vomiting. Paracetamol-induced kaluresis may cause hypokalaemia. Liver damage is not usually detectable by routine liver function tests until at least 12 h after ingestion of the drug, and hepatic tenderness and abdominal pain are seldom exhibited before the second day. Liver damage reaches a peak, as assessed by plasma alanine or aspartate aminotransferase (ALT, AST) activity or prothrombin time (international normalized ratio, INR), 72–96 h after ingestion. More often there is prolongation of the prothrombin time and a marked rise in aminotransferase ac- tivity (activities of several thousand are not uncommon) without the development of fulminant hepatic failure. Renal failure due to acute tubular necrosis develops in about 25% of patients with severe hepatic damage and in a few without evidence of serious disturb- ance of liver function. Other features, including hypoglycaemia and hyperglycaemia, cardiac arrhythmias, pancreatitis, gastrointes- tinal haemorrhage, and cerebral oedema may all occur with hepatic failure due to any cause and are not direct consequences of para- cetamol toxicity. Paracetamol can cause metabolic acidosis at two distinct periods after overdosage. Transient hyperlactataemia is frequently found within the first 15 h in all but minor overdoses and appears to be due to inhibition of mitochondrial respiration at the level of ubi- quinone and increased lactate production. It is rarely of clinical con- sequence, although in very severe paracetamol poisoning (plasma paracetamol concentration >500 mg/litre at 4 h after ingestion) the acidosis may be very rarely associated with coma. The second phase of hyperlactataemia and acidosis occurs in those patients who present late and go on to develop hepatic damage; in this instance, decreased hepatic lactate clearance appears to be the major cause, compounded by poor peripheral perfusion and increased lactate production. Hypophosphataemia is a recognized complication of acute liver failure, including that due to paracetamol, and may contribute to morbidity and mortality by inducing mental confusion, irrit- ability, coma, and abnormalities of platelet, white cell, and erythro- cyte functions. Phosphaturia appears to be the principal cause of hypophosphataemia in paracetamol poisoning; it may occur in the absence of fulminant hepatic failure and indicates paracetamol- induced renal tubular damage. Prediction of liver damage In the early stages following ingestion of a paracetamol overdose, most patients have few symptoms and no physical signs. There is thus a need for some form of assessment that estimates the risk of liver damage at a time when the liver function tests are still normal. Details of the dose ingested may be used but, in many cases, the his- tory is unreliable and, even when the dose is known for certain, it does not take account of early vomiting and individual variation in response to the drug. However, a single measurement of the plasma paracetamol con- centration is an accurate predictor of liver

damage provided that it is taken not earlier than 4 h after ingestion of the overdose. Information gained from several studies has enabled the production of graphs which may be used for prediction of liver damage and which serve as Table 10.4.1.5 Clinical features of untreated paracetamol poisoning (>200 mg/kg) Day 1 Day 2 Day 3 Asymptomatic May become asymptomatic or develop symptoms de novo (in severe untreated poisoning) Nausea Vomiting Jaundice → liver failure → hepatic encephalopathy Vomiting Hepatic tenderness ± generalized abdominal tenderness Back pain + renal angle tenderness → renal failure Abdominal pain Occasionally, mild jaundice Cardiac arrhythmias Anorexia Disseminated intravascular coagulation Pancreatitis Table 10.4.1.6 Biochemical and haematological abnormalities in paracetamol poisoning Biochemical abnormalities Haematological abnormalities AST/ALT ↑↑ PT ↑ Bilirubin ↑ Platelets ↓ Blood sugar ↓ Clotting factors II ↓ V ↓ VII ↓ Creatinine ↑ Lactate ↑ Phosphate ↓ Amylase ↑ Potassium ↓ early due to kaluresis
↑ later in renal failure

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1744 a guide to the need for specific treatment (Fig. 10.4.1.2). These may not be accurate with slow-release products. In patients who have taken several overdoses of paracetamol over a short period of time, the plasma paracetamol concentration will be meaningless in relation to the treatment graph. Such patients should be considered at risk and treated. Patients who regularly consume al- cohol in excess of currently recommended limits (particularly those who are malnourished), those who regularly take enzyme-inducing drugs (e.g. carbamazepine, phenytoin, phenobarbital, and rifam- picin) and those with conditions causing glutathione depletion (e.g. malnutrition and HIV infection) may be at risk of liver damage. Studies in the early 1970s showed that 60% of patients whose plasma paracetamol concentration was above the line drawn between 200 mg/litre (1.32 mmol/litre) at 4 h and 50 mg/litre (0.33 mmol/ litre) at 12 h after the ingestion of the overdose were likely to sustain liver damage (ALT or AST >1000 u/litre), unless specific protective treatment were given. There are now two approaches to risk management used world- wide. In the United Kingdom, following a decision by the MHRA in 2012 to abandon a detailed risk assessment in the decision to treat, it is deemed that patients with concentrations above a ‘treatment line’ starting at 100 mg/litre (0.66 mmol/litre 4 h after ingestion (Fig. 10.4.1.2) require therapy with antidote. In North America and Australasia, a parallel line starting at 150 mg/litre 4 h after ingestion is used. The MHRA decision aims to prevent one death in the United Kingdom approximately every 2.1 years, and has been criticized as being too cautious and resulting in many unnecessary treatments. Patients who ingest multiple overdoses, or take repeated thera- peutic excess, are at greater risk of liver damage and decisions to treat them are generally based on dose ingested. Current UK advice is very conservative with a treatment cut-off of paracetamol dose above 75 mg per kilogram in 24 h. Prognostic factors The overall mortality of paracetamol poisoning in untreated pa- tients is only of the order of 5%. A rise in transaminase (ALT/AST) activity is usually the first liver function test to become abnormal, but a rise in INR is of particular value in assessing the prognosis of an individual patient. The more rapid the increase in ALT and INR, the worse the prognosis of the patient. A prothrombin time of more than 20 s at 24 h after ingestion indicates that significant hepatic damage has been sustained, and a peak prothrombin time of more than 180 s is associated with a chance of survival of less than 8%. Acid–base disturbances are also a good guide to prognosis. Systemic acidosis developing more than 24 h after overdose in- dicates a poor prognosis; patients with a blood pH below 7.30 at this time have only a 15% chance of survival. In addition, a rise in the serum creatinine concentration is associated with poor survival;

patients with a serum creatinine concentration above 300 μmol/litre have only a 23% chance of survival. A study of prognostic indicators in patients who died of paracetamol- induced fulminant hepatic failure treated conventionally com- pared measurement of factors V and VIII with conventional tests. An admission pH below 7.30 with a serum creatinine concentra- tion above 300 μmol/litre and a prothrombin time above 100 s in patients with grade III–IV encephalopathy had a sensitivity, predictive accuracy, positive prediction value, and specificity of 91, 86, 83, and 91%, respectively. However, a factor VIII/V ratio above 30 had comparable values of 91, 95, 100, and 100%. Novel biomarkers (e.g. microRNAs) are now being studied which may give an earlier more accurate risk assessment than is possible with conventional approaches. Treatment Consider administering activated charcoal for patients presenting within 1 h of overdose. Parenteral fluid replacement should be given if nausea persists or vomiting occurs. Patients who have taken staggered overdoses should be treated with an antidote irrespective of the plasma paracetamol concentra- tions. They can be discharged after antidotal treatment, provided they are asymptomatic and the INR, plasma creatinine concentra- tion, and ALT activity are normal. Patients who present 15 h or more after overdose tend to be more severely poisoned and at greater risk of developing serious liver damage and should receive antidotal treatment as the plasma con- centration alone may not be an accurate guide of severity; it may be nondetectable at the time of late presentation. The INR, venous pH, plasma creatinine concentration, and liver function tests are helpful in determining prognosis. Acetylcysteine Acetylcysteine acts by replenishing cellular glutathione stores and may also repair oxidation damage caused by NAPQI either directly or, more probably, through the generation of cysteine and/ or gluta- thione. It may also act as a source of sulphate and so ‘unsaturate’ sulphate conjugation. Two principal regimens for acetylcysteine have been em- ployed. The most widely utilized worldwide is a 21-h protocol (Table 10.4.1.7); the oral protocol previously used in the United 240 220 200 Plasma paracetamol concentration (mg/litre) 180 160 140 120 100 80 60 40 20 0 0 2 4 6 8 10 Paracetamol nomograms 12 14 16 18 Time (hours) 20 22 24 0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 Original ‘200 mg’ Line UK ‘100 mg’ Line International ‘150 mg’ Line 1.6 Plasma paracetamol concentration (mmol/litre) Fig. 10.4.1.2 Paracetamol treatment nomograms. Those above the treatment lines are regarded at risk and treated with acetylcysteine. Thresholds differ in different countries, the ‘100 mg’ line being used in the United Kingdom. There is a scarcity of data after 15 h and the dotted lines show extrapolations used in clinical practice.

 States being replaced by IV therapy. An alternative 12 h IV protocol (100 mg/kg over 2h, 200 mg/kg over 10 h) that is associ- ated with far fewer antidote-induced adverse events is also being employed. Provided that acetylcysteine is administered within 8–10 h of overdose, the development of hepatic damage is normally pre- vented; thereafter, the protective effects decline rapidly. Up to 10% of patients treated with intravenous acetylcysteine (20–21 h regimen) develop rash, angioedema, hypotension, and broncho- spasm. Far higher proportions (up to 70%) develop nausea and vomiting, with treatment required in up to 30%. These reactions, which are due to the initial bolus, cause very few fatalities but cause treatment interruption and patient distress. Anaphylactoid reac- tions are far more common at lower paracetamol concentrations, so more aggressive use of the antidote increases the incidence of these reactions. Antihistamines, such as chlorpheniramine and broncho- dilators (e.g. salbutamol), may be given if such anaphylactoid reac- tions do occur, but discontinuing the infusion temporarily may be all that is required. Management of severe liver damage A 10% glucose solution should be administered to prevent the onset of hypoglycaemia. If fulminant

hepatic failure supervenes, the use of a continued intravenous acetylcysteine (the 16-h infu- sion is continued until recovery or death) will reduce morbidity and mortality. In one prospective study, the survival rate in 25 patients with paracetamol-induced fulminant hepatic failure was 20%, with an in- cidence of cerebral oedema and of hypotension requiring inotropic support of 68 and 80%, respectively. With acetylcysteine, the com- parable figures in 25 matched patients were 48% (survival rate), 40% (cerebral oedema), and 48% (hypotension). A proton pump inhibitor will reduce the risk of gastrointestinal bleeding from ‘stress’ ulceration/erosion. There is no evidence that fresh frozen plasma prevents gastrointestinal haemorrhage in pa- tients with severe coagulation abnormalities (prothrombin time

> 100 s). If acute renal failure supervenes, then this should be man- aged conventionally. Liver transplantation has been performed successfully in patients with paracetamol-induced fulminant hepatic failure. Salicylates Salicylate poisoning may result from overdose of aspirin tablets, per- cutaneous absorption of salicylic acid (used in keratolytic agents), and ingestion of methyl salicylate (‘oil of wintergreen’). In therapeutic doses, aspirin is absorbed rapidly from the stomach and small intestine, but in overdose, absorption may occur more slowly, and plasma salicylate concentrations may continue to rise for up to 24 h. The pharmacokinetics of elimination of aspirin are important determinants of salicylate toxicity. Biotransformation to both salicyluric acid and salicylphenolic glucuronide (Fig. 10.4.1.3) is saturable with the following clinical consequences: (1) the time needed to eliminate a given fraction of a dose increases with increasing dose; (2) the steady state plasma concentration of sa- licylate, particularly that of the pharmacologically active non- protein-bound fraction, increases more than proportionately with increasing dose; and (3) renal excretion of salicylic acid becomes increasingly important; a pathway which is extremely sensitive to changes in urinary pH. When ingested in overdose, salicylates directly stimulate the re- spiratory centre to produce both increased depth and rate of res- piration, thereby causing a respiratory alkalosis (Fig. 10.4.1.4). At least part of this effect is due to local uncoupling of oxidative phos- phorylation within the brainstem. In an attempt to compensate, bicarbonate, accompanied by sodium, potassium, and water, is excreted in the urine resulting in dehydration and hypokalaemia. More importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows an acidosis to develop more easily. Very high salicylate concentrations in the brain depress the re- spiratory centre and may further contribute to the development of acidaemia. Simultaneously, a variable degree of metabolic acidosis develops, not only because of the presence of salicylic acid itself, but also be- cause of interference with carbohydrate, lipid, protein, and amino acid metabolism by salicylate ions (Fig. 10.4.1.4). Inhibition of citric acid cycle enzymes causes an increase in circulating lactic and pyruvic acids. Salicylates stimulate fat metabolism and cause increased production of the ketone bodies, β-hydroxybutyric acid, acetoacetic acid, and acetone. Dehydration and lack of food intake, because of vomiting, further contribute to the development of ke- tosis. Protein catabolism

> is accelerated and synthesis diminished. Aminotransferases (responsible for the interconversion of amino acids) are inhibited. Increased circulating blood concentrations of amino acids result, together with aminoaciduria; inhibition of active tubular reabsorption of amino acids also contributes. Aminoaciduria increases the solute load on the kidneys and, thereby, increases water loss from the body. A primary toxic effect of salicylates in overdose is uncoupling of oxidative phosphorylation (Fig. 10.4.1.4). ATP-dependent re- actions are inhibited, and oxygen utilization and CO2 production are increased. Energy normally used for the conversion of inorganic phosphate to ATP is dissipated as heat. Hyperpyrexia and sweating result, causing further dehydration. Fluid loss is enhanced because Table 10.4.1.7 Dosing regimen for acetylcysteine (21 h regimen) • 150 mg/kg over 60 min, then 50 mg/kg over the next 4 h and 100 mg/kg over the next 16 h • Total dose, 300 mg/kg over 21 h Conjugation with glycine Conjugation with glucuronic acid Salicyluric acid Salicylacyl glucuronide Salicylphenolic glucuronide Aspirin Salicylic acid Gentisic acid Hydrolysis Hydroxylation Fig. 10.4.1.3 Metabolism of aspirin.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1746 salicylates stimulate the chemoreceptor trigger zone and induce nausea and vomiting and, thereby, diminish oral fluid intake. If de- hydration is sufficiently marked, low cardiac output and oliguria will aggravate the metabolic acidosis already present which, if severe, can itself diminish cardiac output. Glucose metabolism also suffers as a result of uncoupled oxi- dative phosphorylation because of increased tissue glycolysis and peripheral demand for glucose (Fig. 10.4.1.4). This is seen principally in skeletal muscle and may cause hypoglycaemia. The brain appears to be particularly sensitive to this effect and neuroglycopenia can occur in the presence of a normal blood sugar level when the rate of utilization exceeds the rate at which glucose can be supplied from the blood. Increased metabolism and peripheral demand for glucose activates hypothalamic centres, resulting in increased adrenocortical stimulation and re- lease of adrenaline. Increased glucose 6-phosphatase activity and hepatic glycogenolysis contribute to the hyperglycaemia, which is sometimes seen following ingestion of large amounts of salicylate. Increased circulating adrenocorticosteroids exacerbate fluid and electrolyte imbalance. Although this is rarely a practical problem, salicylate intoxi- cation may be accompanied by hypoprothrombinaemia due to a warfarin-like action of salicylates on the physiologically important vitamin K epoxide cycle. Vitamin K is converted to vitamin K 2,3-epoxide and then reconverted to vitamin K by a liver mem- brane reductase enzyme, which is competitively inhibited by war- farin and salicylates. Clinical features and assessment of severity of salicylate intoxication The dose of salicylate ingested and the age of the patient are the principal determinants of the severity of an overdose. The plasma salicylate concentration should be determined on admission, but it is important to repeat it 2 h later to ensure that the concentration is not rising. If the concentration has risen, the level should be re- peated after a further 2 h. Generally speaking, plasma salicylate concentrations that lie between 300–500 mg/litre some 6 h after in- gestion of an overdose are associated with only mild toxicity, concen- trations between 500 and 700 mg/litre are associated with moderate toxicity, and concentrations in excess of 700 mg/litre confirm severe poisoning. Salicylate poisoning of any severity is associated with sweating, vomiting, epigastric pain, tinnitus, and deafness (Table

10.4.1.8). Young children quickly develop metabolic acidosis following the ingestion of aspirin in overdose, but by the age of 12 years the usual adult picture of a combined dominant respiratory alkalosis and mild metabolic acidosis is seen. To some extent, the presence of an alkalaemia protects against serious salicylate toxicity because salicylate remains ionized and unable to penetrate cell membranes easily. Development of acidaemia allows salicylates to penetrate tissues more readily and leads, in particular, to central nervous system toxicity characterized by excitement, tremor, delirium, convulsions, stupor, and coma. Very high plasma salicylate concentrations cause Hepatic glycogenolysis Respiratory alkalosis Stimulation of respiratory centre Stimulation of chemoreceptor trigger zone HCO_3^- (and Na^+ K^+ and H_2O) excretion Vomiting and decreased oral fluid intake Dehydration and electrolyte imbalance Glucocorticoids Catecholamines Tissue glycolysis Hyperglycaemia Respiratory rate Hyperpyrexia and sweating Uncoupling of oxidative phosphorylation Neuroglycopenia Hypoglycaemia Metabolic acidosis Ketone body formation Stimulation of lipid metabolism Respiratory acidosis Depression of respiratory centre Inhibition of Krebs cycle enzymes Inhibition of amino acid metabolism Cardiac output Renal clearance of sulphuric and phosphoric acids Circulating pyruvic and lactic acid levels Circulating amino-acid levels Buffering capacity Aminoaciduria CO_2 production O_2 consumption Fig. 10.4.1.4 Pathophysiology of salicylate poisoning. Table 10.4.1.8 Clinical features of salicylate poisoning • Nausea, vomiting, and epigastric discomfort • Irritability, tremor, tinnitus, deafness, blurring of vision • Hyperpyrexia, sweating, dehydration • Tachypnoea and hyperpnoea • Noncardiogenic pulmonary oedema • Acute renal failure • Mixed respiratory alkalosis and metabolic acidosis (except in children who usually develop metabolic acidosis alone) • Hypokalaemia, hypernatraemia, or hyponatraemia • Hyperglycaemia or hypoglycaemia • Hypoprothrombinaemia (rare) • Confusion, delirium, stupor, and coma (in severe cases)

 paralysis of the respiratory centre and cardiovascular collapse due to vasomotor depression. Pulmonary oedema is seen occasionally in salicylate poisoning and, although this is often due to fluid overload as a result of treat- ment, it may be noncardiac and occur in the presence of hypovol- aemia. In these circumstances, the pulmonary oedema fluid has the same protein and electrolyte composition as plasma, suggesting in- creased pulmonary vascular permeability. Although aspirin overdose may be complicated by inhibition of platelet aggregation and hypoprothrombinaemia, gastric erosions, and gastrointestinal bleeding are rare following acute salicylate overdose. Oliguria is sometimes seen in patients following the ingestion of salicylates in overdose. The most common cause is dehydration but, rarely, acute renal failure or inappropriate secretion of antidiuretic hormone may occur. Although the urine pH may be alkaline in the early stages of salicylate overdose, it soon becomes acidic. Measurement of ar- terial blood gases, pH, and standard bicarbonate may show a re- spiratory alkalosis in the early stages of salicylate intoxication accompanied by the development of a metabolic acidosis. The plasma potassium concentration is often low; rarely, the blood sugar may be high. Treatment The plasma salicylate concentration should be re-measured 2–3 h after the first measurement. Dehydration, electrolyte imbalance and, most importantly, metabolic acidosis should be corrected. The role of multiple-dose activated charcoal in increasing salicylate elimination is controversial and it cannot be recom- mended on current evidence. As the relationship between renal clearance of salicylates and urine pH is logarithmic, urine alkalinization should be undertaken in patients with a plasma salicylate concentration greater than 500 mg/litre, particularly if an acidosis is present. The therapeutic aim is to make the urine alkaline (ideally, pH 7.5–8.5), and in adults this may be achieved by administration of sodium bicarbonate, 225 mmol

(225 ml of 8.4%); further doses of bicarbonate are given as re- quired. Hypokalaemia should be corrected before administration of sodium bicarbonate, because this lowers the serum potassium concentration further. In patients with severe poisoning (plasma salicylate concentration >700 mg/litre or >5.1 mmol/litre), haemo- dialysis should be considered, particularly when severe acid–base abnormalities are present. Pulmonary oedema occasionally complicates salicylate toxicity. Fluid overload should be excluded as far as possible but, if increased pulmonary vascular permeability is suspected, measurement of the pulmonary artery wedge pressure may be needed both for confirm- ation of the diagnosis and to monitor subsequent fluid adminis- tration. Positive end-expiratory pressure ventilation appears to be beneficial. Theophylline Poisoning may complicate therapeutic use, as well as being the re- sult of deliberate self-poisoning. If a sustained-released formula- tion has been ingested, peak plasma concentrations of the drug are frequently not attained until 6–12 h after overdose and the onset of toxic features is correspondingly delayed. Clinical features Symptoms include nausea, vomiting, hyperventilation, haematem- esis, abdominal pain, diarrhoea, sinus tachycardia, supraventricular, and ventricular arrhythmias, hypotension, restlessness, irritability, headache, hyperreflexia, tremor, and convulsions. Hypokalaemia results from Na+-K+-ATPase activation. A mixed respiratory alkal- osis and metabolic acidosis is common. Most symptomatic patients have plasma theophylline concentrations in excess of 25 mg/litre. Convulsions are seen more commonly when concentrations are greater than 50 mg/litre. Treatment Multiple-dose activated charcoal (e.g. 50 g 4-hourly) enhances the systemic elimination of theophylline. Intractable vomiting may be alleviated by ondansetron, 8 mg intravenously in an adult. Gastrointestinal haemorrhage may require blood transfusion and the administration of a proton pump inhibitor intravenously. Tachyarrhythmias may be induced by the rapid flux of potassium across cell membranes and early correction of hypokalaemia may prevent their development. The plasma potassium concentration should therefore be measured on admission and at regular intervals thereafter while the patient is symptomatic. Potassium supplements will be needed in almost all cases and doses of up to 60 mmol/h may be required at the outset in severe cases. Nonselective β-adrenoceptor blocking drugs, such as propranolol, may also be useful in the treat- ment of tachyarrhythmias secondary to hypokalaemia. There may be a role for extracorporeal elimination techniques in very severe poisoning (plasma theophylline concentration >100 mg/litre). Thyroxine Clinical features Only a small percentage of patients who ingest large amounts of thyroid hormones develop features of toxicity. Symptoms develop within a few hours with triiodothyronine (T3) and after 3–6 days with thyroxine (T4). They tend to resolve in about the same time as they take to develop. Sinus tachycardia, tremor, anxiety, irrit- ability, insomnia, hyperactivity, sweating, diarrhoea, and fever are most common. Atrial fibrillation and convulsions have also been re- ported. Myocardial necrosis occurs rarely. Treatment Serum T4 and T3 concentrations should be measured approximately 12 h after ingestion (this need not be measured as an emergency). Those with high T4 concentrations should be reviewed for evidence of toxicity on the fourth or fifth day after ingestion. Patients who develop toxicity should be given propranolol 10–40 mg, 3–4 times a day for 5 days. Drugs of abuse Amfetamines and MDMA (ecstasy) Amfetamines, particularly methamfetamine (‘crystal meth’, ‘ice’) and MDMA, are abused widely. Features of poisoning are related predominantly to stimulation of central and peripheral adren- ergic receptors and, in addition, hyperthermia and hyponatraemia (secondary to inappropriate anti-diuretic hormone) may

 develop in severe MDMA toxicity. Poisoning is usually the result of recreational use. Clinical features These drugs

cause increased alertness and self-confidence, euphoria, extrovert behaviour, increased talkativeness with rapid speech, lack of desire to eat or sleep, tremor, dilated pupils, tachycardia, and hypertension. More severe intoxication is associated with excit- ability, agitation, paranoid delusions, hallucinations with violent behaviour, hypertonia, and hyperreflexia. Convulsions, rhabdo- myolysis, hyperthermia, and cardiac arrhythmias can develop in the most severe cases. Rarely, intracerebral and subarachnoid haemor- rhage and acute cardiomyopathy occur and may be fatal. In the case of MDMA, hyperthermia, disseminated intra- vascular coagulation, rhabdomyolysis, acute renal failure, and hyponatraemia are observed commonly in severe cases, in addition to those features described earlier. Death occurred in 2 of 17 pa- tients with serum sodium concentrations of 107–128 mmol/litre. Their clinical course was remarkably similar; initial vomiting and disturbed behaviour was followed by seizures, drowsiness, a mute state, and disorientation. Severe hepatic damage, including ful- minant hepatic failure, has also been reported. The serotonin syn- drome has been described. Treatment Intravenous fluids should be given for dehydration. Diazepam 10–20 mg intravenously or haloperidol 2.5–5.0 mg intramuscu- larly are effective in controlling agitation. The peripheral sym- pathomimetic actions of amfetamines may be antagonized by β-adrenergic blocking drugs. Although acidification of the urine increases renal elimination of amfetamines, sedation is usu- ally all that is required. Dantrolene 1 mg/kg intravenous should be administered for hyperthermia that does not respond to conventional cooling methods. In most cases, hyponatraemia responds to fluid restriction alone. Transplantation may be indicated in patients who develop MDMA-induced fulminant hepatic failure. Cannabis Cannabis is obtained from the plant Cannabis sativa which con- tains over 400 compounds including over 60 cannabinoids. The most potent cannabinoid is Δ9-tetrahydrocannabinol (THC), which is responsible for the psychoactive effects seen with use; other cannabinoids include Δ8-tetrahydrocannabinol, cannabinol, and cannabidiol. Smoking is the usual route of use, but cannabis is occasionally ingested as a ‘cake’, made into a ‘tea’ or injected intravenously. Clinical features Acute use Features include euphoria, distorted and heightened images, col- ours, and sounds; altered tactile sensations, sinus tachycardia, hypotension, and ataxia. Visual and auditory hallucinations, de- personalization, and acute psychosis are particularly likely to occur after substantial ingestion in naïve cannabis users. Cannabis im- pairs all stages of memory including encoding, consolidation, and retrieval. Memory impairment following acute use may persist for months following abstinence. Cannabis infusions injected intravenously may cause nausea, vomiting, and chills within minutes; after about 1 h, profuse watery diarrhoea, tachycardia, hypotension, and arthralgia may develop. Marked neutrophil leucocytosis is often present, and hypoglycaemia has been reported occasionally. Chronic use Heavy users suffer impairment of memory and attention and poor academic performance. There is an increased risk of anxiety and de- pression. Regular users are at risk of dependence. Cannabis use re- sults in an overall increase in the relative risk for later schizophrenia and psychotic episodes. Cannabis smoke is probably carcinogenic. Treatment Most acutely intoxicated patients require no more than reassurance and supportive care. Sedation with diazepam, 10 mg intravenously, repeated as necessary, should be administered to patients who are disruptive or distressed. Haloperidol, 2.5–5 mg intramuscularly re- peated as necessary, is occasionally required. Synthetic cannabinoid receptor agonists Synthetic cannabinoid receptor agonists (SCRAs) are full canna- binoid type 1 (CB1) receptor agonists and bind to these receptors with a higher affinity than Δ9-tetrahydrocannabinol. Furthermore, unlike the metabolites of Δ9-tetrahydrocannabinol, the metabol- ites of several synthetic cannabinoids retain high affinity for, and exhibit a range of intrinsic activities at, CB1 and CB2 receptors. Cannabinoids also bind nonspecifically to cellular membranes and act on opioid and

benzodiazepine receptors, prostaglandin syn- thetic pathways, and protein metabolism. These interactions have the potential for complex effects and are likely to contribute to toxicity. Clinical features Current third and fourth generation synthetic cannabinoid receptor agonists (SCRAs) produce more severe clinical features than earlier SCRAs. A reduced level of consciousness, tonic–clonic convulsions, transient respiratory failure, and severe agitation, particularly on re- covery, are typical. Treatment Treatment is symptomatic and supportive. As impaired ventilation is transient, supported ventilation is not usually necessary. Cathinones, benzofurans, and related compounds Cathinones are derivates of cathionine, which occurs naturally in the herb Catha edulis (Khat). Structurally these are phenylethyla mines, similar in structure to catecholamines and amfetamines. Mephedrone (4-methylmethcathinone) is one of the most widely abused cathinones, others include mexedrone, methylone, butylone, and fluoromethcathinone. Purity of these street drugs varies widely. These are usually insufflated (snorted) or swallowed. Other phenylethylamines, such as bromofurans (‘Benzofury’), have many similar effects to amfetamines, but some have more hallucinogenic effects due to the receptor specificity of the individual compounds. Methylenedioxypyrovalerone (MDPV, ‘ivory wave’) inhibits the re- uptake of dopamine and norepinephrine centrally, and is a potent cause of psychiatric features.

10.4.1 Poisoning by drugs and chemicals 1749 Clinical features These agents act as stimulants, causing agitation, hallucin- ations, increased muscle activity with bruxism (teeth grinding), hyperpyrexia, sweating, dilated pupils, tachycardia, and arrhyth- mias. Toxicity is increased if co-ingested with other stimulants, or drugs affecting central amine mechanisms (e.g. antidepressants, tramadol). Metabolic complications include hypokalaemia, hyper- glycaemia, and metabolic acidosis. Complications include seizures and rhabdomyolysis. Treatment Intravenous fluids should be given for dehydration. Diazepam, ini- tially 10–20 mg intravenously, is the drug of choice for agitation: this is also appropriate to control excess muscle activity. Large doses may be required. ECG and cardiovascular monitoring is necessary. Management of other features is symptomatic. Cocaine In recent decades, there has been a considerable increase in the rec- reational use of cocaine. It is a powerful local anaesthetic and vaso- constrictor and may be abused by smoking, ingestion, injection or by ‘snorting’ it intranasally. Users, body packers, and those who swallow the drug to avoid being found in possession of it (‘stuffers’), are at risk of overdose. ‘Street’ cocaine is cocaine hydrochloride, which is water soluble, so can be injected or snorted. It may be dis- solved in an alkaline solution from which the cocaine is extracted into ether, which is then evaporated to leave relatively pure (‘free- base’) cocaine. ‘Crack’ (cocaine also without the hydrochloride moiety) is extracted by using baking soda (sodium bicarbonate). Other drugs, such as ethanol, cannabis, and conventional hypnotics and sedatives, are frequently taken with cocaine to reduce the inten- sity of its less pleasant effects. Clinical features The features of cocaine poisoning are similar to those of amfetamine. In addition to euphoria, it also has sympathomimetic effects including agitation, tachycardia, hypertension, sweating, and hallucinations. Prolonged convulsions with metabolic acid- osis, hyperthermia, rhabdomyolysis, ventricular arrhythmias, and cardiorespiratory arrest may follow in the most severe cases. Less common features include dissection of the aorta, myocarditis, myo- cardial infarction, dilated cardiomyopathy, subarachnoid haemor- rhage, cerebral haemorrhage, and cerebral vasculitis. Several rare complications of the method of use of cocaine have been reported. These include pulmonary oedema after intra- venous injection of freebase cocaine and pneumomediastinum and pneumothorax after sniffing it. In addition, chronic ‘snorting’ has caused perforation of the nasal septum, rhinorrhoea of cerebro- spinal fluid due to thinning of the cribriform plate, and pulmonary granulomata. Treatment Users who are intoxicated

may require sedation with diazepam to control agitation or convulsions; very large doses of diazepam may be required. Measures to prevent further absorption are not usually relevant. Hypertension and severe tachycardia may be controlled with a β-blocker but, in one case at least, the use of propranolol caused paradoxical hypertension. Accelerated idioventricular rhythm should not normally require treatment but ventricular fib- rillation and asystole should be managed in the usual way. Ethanol Ethanol is commonly ingested in beverages before, or concomitantly with, the deliberate ingestion of other substances in overdose. It is also used as a solvent and is found in many cosmetic and antiseptic preparations. It is rapidly absorbed through the gastric and intestinal mucosae. Gastric alcohol dehydrogenase isoenzyme has a role in metabolizing ethanol before absorption, thereby preventing ethanol entering the systemic circulation, particularly following ingestion of moderate amounts of alcohol. Absorbed ethanol is initially and principally converted to acetaldehyde by an NAD-dependent hep- atic alcohol dehydrogenase. A small proportion is oxidized by the microsomal ethanol oxidizing system and the catalase pathway. Acetaldehyde is removed by oxidation via the NAD-dependent en- zyme aldehyde dehydrogenase, to yield acetate and, subsequently, CO_2 and water. About 95% of ingested ethanol is oxidized to acet- aldehyde and acetate; the remainder is excreted unchanged in the urine, and, to a lesser extent, in the breath and through the skin. Ethanol is a central nervous system depressant that interferes with cortical processes in small doses and may depress medullary function in large doses. The effects of ethanol on the central nervous system are generally proportional to the blood ethanol concentration. Ethanol is also a peripheral vasodilator. In the severely intoxicated, it may cause hypothermia and hypotension. Ethanol metabolism results in accumulation of free NADH, with resulting increase in the NADH:NAD ratio and inhibition of hepatic gluconeogenesis, which may cause hypoglycaemia, particularly in children or when poisoning follows fasting, exercise, or chronic malnutrition. An in- crease in the lactate:pyruvate ratio may also ensue, with develop- ment of hyperlactataemia. Clinical features Ethanol exacerbates the effects of other central nervous system de- pressants, in particular, hypnotic agents. In those not tolerant, the fatal dose of ethanol alone is between 300 and 500 ml absolute al- cohol, if this is ingested in less than 1 h. The features of ethanol poi- soning are summarized in Table 10.4.1.9. Table 10.4.1.9 Clinical features of ethanol poisoning Mild intoxication (500–1500 mg/litre) Emotional lability, and slight impairment of visual acuity, muscular coordination, and reaction time Moderate intoxication (1500–3000 mg/litre) Visual impairment, sensory loss, muscular incoordination, slowed reaction time, slurred speech Severe intoxication (3000–5000 mg/litre) Marked muscular incoordination, blurred or double vision, sometimes stupor and hypothermia, occasionally hypoglycaemia and convulsions Coma (>5000 mg/litre) Depressed reflexes, respiratory depression, hypotension, and hypothermia. Death may occur from respiratory or circulatory failure or as the result of aspiration of stomach contents in the absence of a gag reflex

 Severe hypoglycaemia typically occurs within 6–36 h of inges- tion of a moderate to large amount of alcohol by either a previously malnourished individual or one who has fasted for the previous 24 h; it is common in children 5 years of age or less. The patient is often comatose, hypothermic, and convulsing, with conjugate de- viation of the eyes, trismus, and extensor plantar reflexes; the usual features of hypoglycaemia (e.g. flushing, sweating, tachycardia) are often absent. Convulsions are the most common presenting sign in children with hypoglycaemia. Lactic acidosis (usually only mild) is an uncommon but potentially serious complication of acute ethanol intoxication and occurs particularly in patients with severe liver disease, pancreatitis, or sepsis. Hypovolaemia, which may

accompany severe intoxication, predisposes to lactic acidosis. Treatment Supportive measures are all that are required for most patients with acute ethanol poisoning, even if the blood ethanol concentration is very high. Particular care should be taken to protect the airway. In more severe cases, acid–base status should be determined. Lactic acidosis requires correction of hypoglycaemia, hypovolaemia, and circulatory insufficiency, if present. An infusion of sodium bicarbonate may be necessary in severely poisoned patients in whom a lactic acidosis persists. Blood sugar should be determined hourly in severe cases and the rate of intravenous glucose adjusted accordingly. If blood sugar concentrations decrease despite an infusion of 5–10% dextrose, a 50% glucose solution, 50 ml intravenously, should be given because hypoglycaemia is usually unresponsive to glucagon. Haemodialysis may be considered if the blood ethanol concentra- tion exceeds 7500 mg/litre and if a severe metabolic acidosis is pre- sent, which has not been corrected by the measures outlined earlier. Fructose is of negligible clinical benefit in accelerating ethanol oxi- dation and may cause acidosis; it should not be used. γ-hydroxybutyric acid and analogues γ-hydroxybutyric acid (GHB) is a liquid that is abused as a body- building agent (it stimulates growth hormone release) and as a seda- tive drug of abuse. It is a precursor of gamma-aminobutyric acid (GABA) and acts as an agonist at GABAB receptors as well as at a GHB-specific receptor in the brain. γ-butyrolactone (GBL) and 1,4- butane-diol (1,4-BD) are GHB precursors, converted into it after in- gestion. They are organic industrial solvents found in products such as acetone-free nail polish removers and paint strippers. 1,4-BD is also marketed as a dietary supplement. Clinical features Low doses cause mild agitation, excitement, nausea, and vomiting, with euphoria and hallucinations at higher doses. Coma, brady- cardia, and respiratory depression occur in the most severely poi- soned. The most unique aspect of GHB poisoning is its very brief duration. Patients may progress from deep coma, requiring intub- ation, to self-extubation and full alertness over only a few hours. A GHB withdrawal syndrome can occur in chronic abusers with clinical features occurring within 6–12 h of the last dose. Features include insomnia, tremor, and confusion, which may progress to de- lirium not dissimilar to the alcohol withdrawal syndrome. Treatment Supportive measures to maintain adequate ventilation and circula- tion should be employed, and this is often all that is required. GHB withdrawal should be managed as for acute alcohol withdrawal. Baclofen, a specific GABAB receptor agonist, has been used success- fully in conjunction with benzodiazepines, to control withdrawal from GHB and GBL. Ketamine Ketamine is a dissociative anaesthetic acting on NMDA-R recep- tors. It is used as a drug of abuse for its hallucinogenic effects. In repeated doses it is toxic to the bladder causing irreversible bladder wall thickening and infiltration, with smaller capacity, muscle in- stability, and urothelial ulceration. Urinary frequency, incontinence, and hydronephrosis are complications. Several synthetic derivates are also abused in the hope they are ‘bladder safe’. Clinical features The main features are psychological with dissociative agitation, ag- gression, and paranoia. There is a risk of physical harm both to pa- tient and carers. Hallucinations may result in injury from ‘flying’ or walking into traffic. Chronic use may result in dependency, GI symptoms and, most importantly, urological tract damage. Treatment Agitation should be managed supportively. Diazepam 10–20 mg IV initially may be used for severe agitation. Patients should be coun- selled about the risks of abuse. Lysergic acid diethylamide Lysergic acid diethylamide (LSD) acts as an antagonist at periph- eral 5-HT receptor subtypes, but as a 5-HT2A receptor agonist in the central nervous system. LSD and MDMA (ecstasy) are sometimes combined (‘XL’; ‘candyflipping’) to increase the response to MDMA. Clinical features The ability of LSD to distort reality is well known. Visual hallucin- ations, distortion of images, agitation, excitement, dilated pupils, tachycardia, hypertension, hyperreflexia, tremor, and hyperthermia are common; auditory hallucinations are rare. Time seems to pass very slowly,

and behaviour may become disturbed with paranoid delusions. Panic attacks are relatively common, but frank psychotic episodes (which may result in homicide) are not. The psychoactive effects can last for 48 h. Episodic visual disturbances (‘flashbacks’; hallucinogen per- sisting perception disorder) occur in which the effects of LSD are re-experienced without further exposure to the drug. The symp- toms include false fleeting perceptions in the peripheral fields, flashes of colour, geometric pseudohallucinations, and positive afterimages. These disturbances may persist for several years but are often treatable with benzodiazepines and exacerbated by phenothiazines. Treatment Most patients will require little more than reassurance and sedation. Supportive measures are all that can be offered to those who are seriously ill.

10.4.1 Poisoning by drugs and chemicals 1751 Opiates and opioids Opioids are a large group of drugs, which act on opioid receptors and are usually used as analgesics. Abuse of opiates, particularly heroin, causes many patients to present with unintentional overdose, which is normally from intravenous injection (needle marks visible) but may occur from inhalation (‘chasing the dragon’). Oral ingestion in addicts is less common. Many addicts abuse other drugs in addition to opioids, and the combination of benzodiazepines and opioids are particularly hazardous. Some opioids have other effects not medi- ated through opioid receptors. Methadone has been shown to in- hibit potassium channels at high doses and is also associated with sudden death in susceptible patients due to QT prolongation and torsade de pointes. Buprenorphine, a partial agonist opioid, is now used as an alternative to methadone in replacement programmes. Fentanyl is a very potent opioid available in a range of formula- tions, particularly transdermal. Illicit extraction into an IV prepar- ation has been reported. Tramadol is an opioid with serotonergic metabolites. It causes both convulsions and respiratory depression in overdose. Clinical features Cardinal signs of opiate overdose are pinpoint pupils, reduced re- spiratory rate, and coma. Vomiting may also occur, particularly after intravenous injection in naïve users, and complicates the clin- ical pattern due to aspiration pneumonia. Methadone acts slowly (peak effects usually 4–6 h after ingestion), though its onset may be more rapid when given intravenously. Noncardiogenic pulmonary oedema is seen in a proportion of severe opioid overdoses and is treated by positive pressure ventilation. Hypothermia may occur in patients lying outside. Rhabdomyolysis has also been associated with opioid ingestion. Buprenorphine is potentially seriously toxic if given intraven- ously, and in some countries, has been combined with naloxone to reduce the acute hazard. Treatment Naloxone is a pure opioid antagonist. It will reverse the central ef- fects of all opioids if given in sufficient dose. In the event of veins not being accessible, intramuscular use is an alternative, but the onset will be slower. Use of naloxone by nebulizer has also been used in methadone poisoning. Failure of a suspected opioid poisoning to respond to an adequate dose of naloxone (at least 2.4 mg IV in an adult) should prompt reassessment of the diagnosis. It may indicate co-ingestion of other central nervous system depressants, or inges- tion of γ-hydroxybutyrate, which also causes small pupils and loss of consciousness. Naloxone has a half-life of approximately 45–90 min so its duration of action is, therefore, much shorter than that of the opioids for which the patient is being treated. Naloxone may there- fore be given by infusion; the normal advised dose is approximately two-thirds of that required to fully wake a patient, every hour. This dose can be reassessed at regular intervals depending on the ex- pected half-life of the ingested product. Morphine has active metabolites (morphine 6-glucoronide), which may become relevant in large overdoses. This metabolite is renally excreted and more potent than the parent compound, thus poisoning may be prolonged in older people or in patients with renal impairment or renal damage following rhabdomyolysis. Other supportive care should be administered as necessary, including re- spiratory

support. Significant hypotension due to pure opioid effects will usually re- spond to naloxone; patients who are managed just by ventilation may therefore be treated unnecessarily aggressively with fluid replace- ment. In some patients, high concentrations of opioids, such as co- deine, cause histamine release and whealing and itching of the skin, effects that should be treated conventionally with antihistamines. Tryptamines—synthetic and natural This group of drugs are hallucinogens and include the naturally occurring mushroom hallucinogenic alkaloids psilocin and psilo- cybin, and synthetic compounds such as dimethyltryptamine and α-methyltryptamine; there are also 4- and 5- substituted deriv- ates (e.g. 4-hydroxy-N,N,-diethyltryptamine (4-HO-DET) and 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT)). Toxicity is related to stimulation of serotonin 2A receptors (5HT2A). Clinical features The features of toxicity are almost universally related to the hallucino- genic potential and psychosis induced by these agents. Additional features including dizziness, weakness, and tremor are common. In severe toxicity seizures, tachycardia, arrhythmias, abdominal symp- toms, and renal injury are seen. Rarely vasospasm may occur. Treatment This is generally supportive, with reassurance the main approach. Agitation should be managed by diazepam (10–20 mg IV). Severe vasospasm should be managed aggressively by intra-arterial α-adrenoceptor antagonists or nitrates. Metals Aluminium Aluminium hydroxide is used as an antacid and occasionally as a phosphate binder in the management of chronic renal failure. Aluminium sulphate is employed in water purification and paper manufacture. Aluminium may be absorbed orally and by inhalation. More than 90% of absorbed aluminium is bound to transferrin. Though some accumulates in brain tissue, most body aluminium is stored in bone and the liver. It is excreted mainly via the kidneys so accumulation may occur in the presence of renal failure. Clinical features Acute poisoning Ingestion of a significant quantity of a soluble aluminium salt such as aluminium sulphate causes burning in the mouth and throat, nausea, vomiting, diarrhoea, abdominal pain, hypotension, seizures, haemolysis, haematuria and, rarely, hepatorenal failure. Topical alu- minium sulphate may be irritant to the skin and eyes. By contrast, insoluble aluminium salts, such as aluminium oxide, do not produce an acute toxic response. Chronic poisoning Inhalation of ‘stamped aluminium powder’ can cause a persistent cough and breathlessness due to lung fibrosis or occupational asthma.

 Increased death rates from some types of cancer have been observed in aluminium production, but these effects are believed to be the result of exposure to other substances, such as benzopyrene, rather than exposure to aluminium. Aluminium may cause contact allergy. Aluminium encephalopathy is a potential, though now very un- usual, complication in patients with chronic renal failure adminis-tered aluminium-containing phosphate binders or dialysed using aluminium-contaminated water. The latter is fortunately now very rare as a result of advancements in dialysis water filtration. The ac- cumulation of aluminium in the brain produces cognitive decline, ataxia, dysarthria, myoclonic jerks, and seizures. Aluminium intoxi- cation may also contribute to renal osteodystrophy and anaemia in patients with chronic renal impairment. Aluminium has been im- plicated in Alzheimer’s disease, but a definitive causative association has not been established. Treatment Deferoxamine forms a stable complex with aluminium which it mo- bilizes primarily from bone with subsequent urinary elimination of the chelate. Deferoxamine is absorbed poorly from the gastrointes- tinal tract and must be administered parenterally. The deferoxamine chelate is dialysable and all published clin- ical studies of aluminium chelation using deferoxamine have involved patients in renal failure undergoing either dialysis or haemofiltration. There is evidence that deferoxamine can improve aluminium-induced encephalopathy, bone disease, and anaemia in dialysis patients. Specialist

advice should be sought. Arsenic Arsenic forms organic and inorganic compounds in trivalent and pentavalent states. Inorganic arsenical compounds may generate arsine gas (see ‘Arsine’, later in this chapter) when in contact with acids, re- ducing metals, sodium hydroxide, and aluminium. Common sources of exposure include fish consumption, traditional medicines, and groundwater contamination in Asian countries. In addition, arsenic trioxide has been used in the treatment of acute promyelocytic leu- kaemia. Most inorganic arsenicals are well absorbed following inges- tion and skin absorption may occur from prolonged exposure. Soluble arsenic compounds can also be absorbed by inhalation. Arsenic crosses the placental and blood–brain barriers rapidly. Following distribution arsenic accumulates in bone, hair, and nails. The half-life is generally 2–10 days and excretion is predominantly in the urine. Clinical features Acute poisoning This can follow accidental, or deliberate ingestion, the toxicity being largely dependent on the water solubility of the ingested compound. Within 2 h of substantial ingestion of a soluble arsenical compound, severe haemorrhagic gastroenteritis may ensue with collapse and death usually within four days.
A metallic taste, salivation, mus- cular cramps, facial oedema, difficulty in swallowing, hepatorenal dysfunction, convulsions, and encephalopathy are reported. A per- ipheral neuropathy (predominantly sensory), bone marrow de- pression, striate leukonychia (Mee’s lines), and hyperkeratotic, hyperpigmented skin lesions are common in those surviving a substantial ingestion. In moderate or severe arsenic poisoning, in- vestigations may show anaemia, leucopenia, thrombocytopenia and disseminated intravascular coagulation. ECG abnormalities have been reported and include QT prolongation and ventricular arrhythmias. Chronic poisoning The ingestion of arsenic in contaminated drinking water or ‘tonics’ leads to progressive weakness, anorexia, nausea, vomiting, stoma- titis, colitis, increased salivation, epistaxis, bleeding gums, conjunc- tivitis, weight loss, and low-grade fever. Characteristically, there is hyperkeratosis of the palms and soles of the feet, ‘raindrop’ pigmen- tation of the skin, and Mee’s lines on the nails. A symmetrical periph- eral neuropathy is typical. Hearing loss, psychological impairment, and EEG changes have been reported. Other chronic effects include disturbances of liver function and ulceration and perforation of the nasal septum. In Taiwan, chronic arsenic exposure has been shown to cause blackfoot disease, a severe form of peripheral vascular dis- ease, which leads to gangrenous changes. Arsenic is classified by the International Agency for Research on Cancer (IARC) as a class 1 (confirmed) carcinogen. Chronic ex- posure to arsenic in drinking water has been causally linked to lung, skin, kidney, and bladder cancer, while occupational exposure to ar- senic is associated with lung cancer. Treatment The traditional chelator dimercaprol has been superseded by succimer (DMSA) and unithiol (DMPS). Both chelators are effective, but unithiol is thought to be superior. The intravenous dose of unithiol is 30 mg/kg/day for 5 days. Alternatively, unithiol 77 mg/kg/day orally may be administered for 5 days if the IV formulation is un- available. However, nausea and vomiting may limit oral unithiol ad- ministration. Convulsions, cardiovascular effects, and respiratory symptoms should be treated conventionally. Haemodialysis may be required to increase elimination if renal failure develops. Cadmium If hygiene is poor, workers can be exposed to cadmium from the smelting and refining of metals, from soldering or welding metal that contains cadmium, or in plants that make cadmium products such as batteries, coatings, or plastics. Itai-itai disease (literally ‘ouch-ouch’ disease, so named because of the effects of severe pain in the joints), occurred in Toyama Prefecture, Japan, in 1950 and was due to mass cadmium poisoning as a result of mining. Clinical features Cadmium compounds are poorly absorbed orally but are well ab- sorbed through the lungs. Cadmium is deposited in the liver and kidneys and very slowly excreted in the urine (half-life 10–30 years). Acute poisoning The ingestion of cadmium salts (>3 mg/kg body weight) may lead to gastrointestinal disturbance which, in severe cases, may progress to cir-

culatory collapse, acute renal failure, pulmonary oedema, and death. Inhalation of cadmium oxide fumes produced in welding or cut- ting has led to the development of severe lung damage and death. Often, there are no initial symptoms but after some 4–10 h, there is increasing respiratory distress. Dyspnoea, cough, and chest pain are accompanied by chills and tremor. Severe pulmonary oedema may develop, or chemical pneumonitis in less severe cases. Recovery may be complicated by progressive pulmonary fibrosis.

10.4.1 Poisoning by drugs and chemicals 1753 Chronic poisoning Repeated exposure to cadmium, such as occupationally, leads to renal tubular dysfunction with glycosuria, aminoaciduria, and hypercalciuria, an increased incidence of renal stones and osteomal- acia. Less common features include anosmia, anaemia, teeth dis- coloration, and neuropsychological impairment. Later, emphysema may develop. Workers repeatedly exposed to high concentrations of cadmium have developed carcinoma of the prostate or lung. Treatment There is no clinical evidence that a substantial body burden of cad- mium may be chelated by any currently available antidote. Chromium Chromium exists mainly in two oxidation states: trivalent (Cr^{3+}) and hexavalent (Cr^{6+}). Cr^{3+} exposure has limited toxicological relevance, due to its low absorption and inability to cross cell membranes. In contrast, Cr^{6+} compounds are highly reactive, powerful oxidizing agents that inflict severe local damage. They are also well absorbed through most routes of exposure and cross cell membranes readily. Somewhat paradoxically, Cr^{6+} induces its devastating systemic toxicity by intracellularly reducing to Cr^{3+}, releasing highly reactive oxygen free radicals in the process. In addition, the Cr^{3+} formed is able to bind and damage nuclear DNA, inducing genotoxicity. Chromium exposure and absorption through inhalation, ingestion, and dermal routes is primarily oc- cupational, with excretion occurring through the kidney. Clinical features Acute poisoning Soluble Cr^{6+} compounds include sodium and potassium chromate and dichromate and chromic acid (Cr^{6+} trioxide). Inhalation of these highly irritant compounds causes mucous membrane inflammation, cough, headache, chest pain, and dyspnoea; pulmonary oedema and respiratory failure may ensue. Ingestion of highly water-soluble Cr^{6+} compounds causes a burning sensation in the mouth and throat, nausea, abdominal pain, diarrhoea, and a risk of gastrointestinal haem- orrhage. Hypovolaemic shock may follow. Methaemoglobinaemia, haemolysis, coagulopathy, and renal and hepatic failure have been re- ported. Chromic acid splashes produce severe burns. Percutaneous absorption may lead to systemic toxicity; fatalities have occurred. Chronic poisoning Inhalation of Cr^{6+} compounds has led to atrophy, ulceration, and perforation of the nasal septum. Pharyngeal and laryngeal ulcers may also occur. Asthma may be precipitated by exposure to fumes. Lung fibrosis, bronchitis, emphysema, and renal proximal tubular damage result from occupational exposure. Cr^{6+} is classified by the IARC as a group I carcinogen and chronic occupational exposure is strongly associated with an increased incidence of lung cancer. ‘Chrome ulcers’ may develop after repeated topical exposure to Cr^{6+} compounds. Cr^{6+} compounds are also skin sensitizers and con- tribute to the development of cement dermatitis and contact derma- titis from paint primer, tanned leather, tattoo pigments, and matches. Treatment The principal management of chromium poisoning is avoidance of exposure. Inhalational exposure should be treated conventionally. Despite claims that topically applied ascorbic acid and sodium cal- cium edetate protect against dermal toxicity, there is insufficient evidence to advocate their use. Immediate surgical assessment is recommended in cases of severe ingestion, as resection of necrotic gastrointestinal tissue may be life-saving. There is no evidence that any chelating agent improves outcome in cases of systemic poi- soning. Haemodialysis removes chromium from the blood, but the high tissue uptake limits the value of this treatment when used alone. Cobalt Cobalt

is an essential trace element and is a constituent of vitamin B12 (cyanocobalamin). Cobalt salts have been used as blue colour- ants for thousands of years. Cobalt composited with tungsten carbide (‘hard metal’) is a very durable and temperature-resistant metal used in the manufacture of drills and other tools. Historically, cobalt salts were used in brewing to enhance the ‘head’ on beer and in the treatment of anaemia. In recent years, poorly functioning cobalt- containing hip prostheses have become an important further source of exposure. Cobalt exerts its toxicity through generating reactive oxygen species, inflicting DNA damage and disrupting ionic, enzymatic, and haemato- poietic homeostasis. Cobalt can be absorbed orally and by inhalation and most undergoes renal excretion over 7 days, but a small proportion is retained with a biological half-life of approximately 2 years. Clinical features Acute poisoning Acute poisoning is rare, though ingestion causes gastrointestinal irritation. Chronic poisoning Hard metal lung disease is a now rare form of interstitial lung dis- ease that occurs in susceptible patients exposed to hard metal and in some diamond workers who use cobalt-containing polishes. Patients usually present with exertional dyspnoea and cough. There may be associated constitutional symptoms of fever, weight loss, or malaise. Inspiratory crackles are the earliest physical sign, but finger club- bing, cyanosis, and eventually cor pulmonale can ensue. Interstitial fibrosis is seen on chest X-ray (primarily the lower zones), and a restrictive ventilatory defect is often present. Cobalt is also a recog- nized cause of occupational asthma. Historically, those consuming large amounts of cobalt- contaminated beer developed ‘beer-drinkers’ cardiomyopathy’ with heart failure often accompanied by a pericardial effusion and poly- cythaemia. Systemic cobalt toxicity also developed in patients re- ceiving cobalt chloride as treatment for anaemia (cobalt stimulates erythropoietin release), with manifestations including hypothyroid goitre (cobalt inhibits the uptake of iodine by the thyroid gland), deafness, visual disturbances, and/or peripheral neuropathy. More recently, systemic cobalt toxicity has been encountered occasionally in recipients of cobalt-containing hip prostheses. This is far more likely in those with an ill-fitting prosthesis where there is increased friction between metal surfaces, and in those who have a metal- containing hip as a revision of a damaged ceramic prosthesis (re- sidual ceramic shards abrading the metal surface). Cobalt is classified as a group 2B carcinogen by the IARC, with limited evidence to suggest a causal relationship between cobalt and cancer.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1754 Treatment Hard metal pneumoconiosis may respond to steroid therapy. Systemic features are usually at least partly reversible providing the cobalt source is removed. There is no antidote for systemic poisoning. Copper Copper is used for pipes and roofing materials, in alloys and as a pig- ment. It is a component of several endogenous enzymes, including tyrosinase and cytochrome oxidase, and is essential for the utiliza- tion of iron. Copper sulphate is used as a fungicide, an algicide, and in some fertilizers. Following ingestion, copper transport across the intestinal mucosa is facilitated by cytosolic metallothionein. In blood, copper is initially albumin-bound and transported via the hepatic portal circulation to the liver where it is incorporated into caeruloplasmin. Ninety- eight (98%) per cent of copper in the systemic circulation is bound to caeruloplasmin and free copper is excreted via a lysosome-to-bile pathway. This process is essential to normal copper homeostasis and provides a protective mechanism in acute copper poisoning. An impaired or overloaded biliary copper excretion system results in hepatic copper accumulation, as occurs in Wilson’s disease (see Chapter 12.7.2) and copper poisoning. Free reduced Cu(I) can bind to sulfhydryl groups and inactivates enzymes such as glucose-6-phosphate dehydrogenase and gluta- thione reductase. In addition, copper may interact with oxygen spe- cies (e.g. superoxide anions and hydrogen peroxide) and catalyse the production of reactive toxic hydroxyl radicals. Copper(II) ions can

oxidize haem iron to form methaemoglobin. Clinical features Acute poisoning Acute copper poisoning usually results from the ingestion of contam- inated foods or from accidental or deliberate ingestion of copper salts. Copper salt ingestion causes profuse vomiting with abdominal pain, diarrhoea, headache, dizziness, and a metallic taste. Gastrointestinal haemorrhage, haemolysis, and hepatorenal failure may ensue and fa- talities have occurred. Body secretions may be green or blue. Occupational exposure to copper fumes (during refining or welding) or to copper-containing dust causes ‘metal fume fever’ with upper respiratory tract symptoms, headache, fever, and myalgia. Chronic poisoning Chronic copper poisoning has been reported predominantly as ‘vineyard sprayer’s lung’ in those spraying fungicides containing copper sulphate. Features include progressive dyspnoea, cough, wheeze, myalgia, malaise, anorexia, micronodular, and reticular opacities on chest X-ray (which may coalesce), and a restrictive lung function defect. Lung biopsy may show pulmonary granulomata and fibrosis. Other features include hepatic copper-containing granulomas, hypergammaglobulinaemia, and hepatomegaly. There is no convincing evidence that copper is carcinogenic in humans. Treatment Blood copper concentrations correlate well with the severity of in- toxication following acute ingestion. Serum caeruloplasmin con- centrations will also be increased in acute copper salt poisoning. Supportive measures are paramount following copper salt inges- tion. Early endoscopy or CT scan with contrast is recommended if corrosive damage is suspected. An early surgical opinion should be sought if there are clinical signs of an acute abdomen or deep ulcers and/or areas of necrosis on endoscopy or CT. Methaemoglobinaemia should be treated with intravenous methylthioninium chloride 1–2 mg/kg. Oral D-penicillamine, 1.5–2 g daily, enhances urinary copper elimination in patients with Wilson’s disease but confirmed benefit in acute copper salt poisoning has not been demonstrated. Experimental studies suggest unithiol (DMPS) may be the most ef- fective antidote in copper poisoning but the presence of acute kidney injury in severely poisoned patients often limits the value of anti- dotes which enhance urine copper excretion. Extracorporeal elim- ination techniques do not enhance copper elimination significantly. Exchange transfusion has been undertaken successfully in patients with copper sulphate-induced haemolysis. Lead Occupational lead exposure occurs mainly by inhalation, for ex- ample, in the reclamation of lead from scrap metal, in the demoli- tion and flame-cutting of structures painted with lead-containing paint, in the manufacture of storage batteries, ceramics, and pig- ments and in radiation shielding. Nonoccupational lead exposure predominantly involves ingestion and important sources include ‘traditional’ remedies (particularly among ethnic minorities) and children with pica who pick at surfaces coated with lead-containing paint or eat lead-contaminated soil. Application of lead-containing cosmetics such as ‘surma’ has also resulted in lead intoxication. Both ingested and inhaled lead are absorbed readily. Most (98.5%) lead is deposited in the bones and teeth, where it remains for 10– 15 years. Of the lead in the blood, 99% is associated with erythro- cytes. Lead can cross both the blood–brain and placental barriers. Elimination is predominantly renal. As the body accumulates lead over many years, even small doses can accumulate over time and cause toxicity. There are two principal mechanisms of lead toxicity. First, lead complexes with important functional chemical groups including – COOH, –NH2, and –SH, and so disrupts the function of enzymes and other biologically important molecules. Lead inhibits several enzymes involved in haem synthesis (including δ-aminolaevulinate dehydratase and ferrochelatase) and erythrocyte maturation (erythrocyte pyrimidine 5’ nucleotidase), causing a microcytic or normocytic hypochromic anaemia. Secondly, lead substitutes for di- valent ions, particularly calcium, which explains why lead accumu- lates in bone. The critical role of calcium in neuronal differentiation, myelination, and synapse development and functionality explains why lead poisoning can induce devastating neurotoxicity. The developing nervous system is particularly

susceptible to irrevers- ible damage. Lead substitution for calcium also causes widespread chemical interactions, disrupts second messenger cellular signalling and triggers calcium-activated apoptosis. Clinical features Lead poisoning frequently presents with nonspecific features, including abdominal pain, anorexia, constipation, headache, and lethargy. Anaemia presents due to impaired haem synthesis and re- duced erythrocyte lifespan. Classically, lead poisoning presents with peripheral neuropathy in the form of foot or wrist drop, although this manifestation is now uncommon. In moderate intoxication, reversible renal tubular dysfunction occurs (causing glycosuria, aminoaciduria, and phosphaturia), which progresses to irreversible

 interstitial fibrosis and progressive renal insufficiency in severe cases. Hypertension may result from renal toxicity. Lead encephal- opathy (delirium, seizures, and coma) only occurs in very severe poi- soning (blood lead concentrations >100 µg/dl (4.8 micromol/litre)) and is much more common in children than adults. Transplacental transfer of lead from mother to fetus results in reduced fetal viability, low birth weight, and premature birth. Despite unequivocal evidence that even low blood lead concen- trations are detrimental to health, the current practice in the United Kingdom is to only enforce stopping work with lead when a worker's blood lead concentration exceeds 60 µg/dl (2.9 micromol/litre); 30 µg/dl (1.4 micromol/litre) for a woman of reproductive capacity; 50 µg/dl (2.4 micromol/litre) for an employee aged under 18 years. There is no safe blood lead concentration for children, particularly those below the age of 5 years. Treatment Primary prevention aimed at eliminating lead hazards for chil- dren and workers is crucial. The importance of primary preven- tion in children is emphasized particularly by the observation that chelation does not improve scores on tests of cognition, behav- iour, and neuropsychological function in children with moderate lead poisoning (blood lead concentrations of 22–45 µg/dl (1.0–2.2 micromol/litre)). The social dimension of the problem must also be recognized: simply giving children chelation therapy and then re- turning them to a contaminated home environment is of no value. Similarly, if an occupational source of lead exposure is implicated, a thorough evaluation of the workplace, other exposed workers and the systems for handling lead at work are appropriate. The decision to use chelation therapy is based on the symptoms present and the blood lead concentration. All symptomatic patients with blood lead concentrations of 50 µg/dl (2.4 micromol/litre) or higher should be considered for chelation therapy. Parenteral so- dium calcium edetate, 75 mg/kg per day, has been the chelating agent of choice for more than 50 years but oral succimer (DMSA) 30 mg/kg per day is of similar efficacy. Mercury Mercury is the only metal that is liquid at room temperature. It exists in three forms: metallic (Hg0), mercury(I) (mercurous), and mercury(II) (mercuric). Metallic mercury is very volatile and when spilt has a large surface area so that high atmospheric concentrations may be pro- duced in enclosed spaces, particularly when environmental temperat- ures are high. In addition to simple salts, such as chloride, nitrate, and sulphate, mercury(II) forms organometallic compounds where mer- cury is covalently bound to carbon, such as methyl-, ethyl-, phenyl-, and methoxyethyl mercury. Inorganic mercury is used extensively in industrial and pharmaceutical settings; exposure is predominantly occupational though minor nonoccupational exposure occurs via dental amalgam. By contrast, exposure to organomercury compounds most commonly occurs from dietary intake, as organomercury can accumulate up the food chain of aquatic species. The absorption of mercury depends on its chemical form. Inhaled mercury vapour is absorbed rapidly and oxidized to mercury (II) in erythrocytes and other tissues. Prior to oxidation, absorbed mercury vapour can cross the blood–brain barrier, but the divalent ion oxida- tion product serves to trap mercury in the brain. Mercury vapour is also absorbed via the skin. Less than 1% of an ingested

dose of metallic mercury reaches the systemic circulation. Organic mercuric salts are better absorbed following ingestion than are inorganic mercuric salts. Organic mercury compounds cross the blood–brain barrier readily. In contrast, the kidney is the main storage organ for inorganic mercury compounds. In vivo mercury is bound to metallothionein, which serves a protective role, since renal damage is caused only by the unbound metal. Mercury is excreted mainly in urine and faeces although a small amount of absorbed inorganic mercury is exhaled as mercury vapour. The half-life of most body mercury is 1–2 months, but a small fraction has a half-life of several years. The exact mechanism of toxicity of mercury remains unclear, but involves binding of the Hg^{2+} form to the sulfhydryl groups present on structural proteins, receptors, enzymes, intracellular organelles and DNA and to selenoproteins. The central nervous system is par- ticularly susceptible. Clinical features Acute poisoning Acute mercury vapour inhalation causes headache, nausea, cough, chest pain and bronchitis/pneumonitis. Repeated exposure to low mercury vapour concentrations presents typically with characteristic neurological features including fine tremor, lethargy, memory loss, insomnia, personality changes, and ataxia. Other features include stomatitis, gingivitis, hypersalivation, and renal tubular damage. Mixed motor and sensory peripheral neuropathy may develop. Ingestion of metallic mercury is usually without systemic effects as it is poorly absorbed from the gastrointestinal tract. However, inges- tion of inorganic mercury (II) (mercuric) or aromatic mercuric salts causes an irritant gastroenteritis with corrosive ulceration, which may lead to circulatory collapse and shock. Inorganic mercury(I) (mer- curous) compounds are less soluble, less corrosive, and less toxic than mercuric salts. Ingestion of mercurous chloride in teething powder has led to ‘pink disease’ or acrodynia in infants. This is a hypersen- sitivity reaction characterized by a desquamating erythematous rash of the extremities, irritability, profuse sweating, tachycardia, and hypertension. Systemic toxicity in the form of renal and neurological damage can present following exposure to mercury salts. There are reports of deliberate intravenous or subcutaneous me- tallic mercury injection. Accidental injection also has occurred after injury from broken thermometers. Intravascular mercury may result in pulmonary venous or peripheral arterial embolism. Subcutaneous mercury initiates a soft-tissue inflammatory reaction with granuloma formation. Signs of systemic mercury toxicity are rare following metallic mercury injection. Chronic poisoning Chronic poisoning from inorganic mercury compounds or mercury vapour causes anorexia, insomnia, abnormal sweating, headache, lassitude, increased excitability, tremor, peripheral neuropathy, gin- givitis, hypersalivation, personality changes, and memory or intel- lectual deterioration. Glomerular and tubular damage may occur, and renal tubular acidosis has been described in children. Most cases of human poisoning from alkyl mercury compounds result from ingestion of contaminated foods over a long period. There is often a latent period of several weeks between exposure and the development of symptoms which are predominantly neurological, with paraesthesiae of the lips, hands, and feet, ataxia, tremor, dysarthria, constriction of visual fields, and emotional and intellectual changes. Gastrointestinal disturbances may precede or

 accompany these features. Seizures, coma, and death have occurred. Chronic exposure to methylmercury has been associated with an in- creased incidence of liver cancer, cirrhosis, renal disease, and cere- bral haemorrhage. Treatment Although there are no controlled clinical data to show that chela- tion therapy improves outcome in patients with neurological fea- tures of mercury poisoning, unithiol 30 mg/kg/day intravenously (or 77 mg/kg/day orally) increases urinary mercury elimination and reduces blood mercury concentrations. Where extracorporeal renal support is required for the

treatment of renal failure, there is evidence that continuous veno–venous haemodialfiltration is more effective than haemodialysis at removing unithiol–mercury com- plexes. Substantial exposure to corrosive mercury salts may warrant immediate surgical assessment, as resection of necrotic gastrointes- tinal tissue may be life-saving. Nickel Nickel is a ubiquitous trace metal mined in the form of sulphide ore. It is used primarily for producing stainless steel and other alloys. Nickel forms inorganic soluble (sulphate, chloride) and insoluble (oxide, sulphide) salts, used in electroplating and battery manufac- ture. Nickel carbonyl ($Ni(CO)_4$) is a colourless, volatile liquid used as a catalyst in the petroleum, plastic, and rubber industries. It is an intermediate compound in nickel purification and is released as fumes when nickel is thermally decomposed. Nickel metal and inorganic salts can be absorbed orally and by inhalation, though absorption is generally poor. By contrast, nickel carbonyl is highly lipophilic and rapidly absorbed. Nickel is principally bound to al- bumin in the blood and is concentrated in the kidneys, liver, and lungs prior to renal excretion. The mechanism of nickel toxicity is thought to involve the induction of oxidative stress through reactive oxygen species production. Clinical features Acute poisoning Nickel carbonyl inhalation leads within a few minutes to dizziness, headache, vertigo, nausea, vomiting, cough, and dyspnoea. In many cases these symptoms disappear and there follows a symptom-free period lasting 12–36 h before tachypnoea, dyspnoea, haemoptysis, cyanosis, chest pain, vomiting, tachycardia, weakness, and muscle fatigue supervene. Paraesthesiae, diarrhoea, abdominal distension, delirium, and convulsions have also been reported. Death from car- diorespiratory failure may occur 4 to 11 days after exposure. At high concentrations, soluble nickel salts are primary skin, gut, and eye irritants. Workers at an electroplating plant who drank water accidentally contaminated with nickel sulphate experienced nausea, vomiting, diarrhoea, abdominal pain, headache, cough, and breathlessness, which persisted for up to 2 days. A 2-year-old child died 4 h after ingesting 15 g nickel sulphate crystals. Chronic poisoning Chronic exposure to aerosols of nickel salts may lead to chronic rhin- itis and sinusitis and, in rare cases, anosmia and perforation of the nasal septum. Inhaled nickel can produce a type I hypersensitivity re- action, manifest as bronchial asthma with circulating IgE antibodies to nickel. Pulmonary eosinophilia (Loeffler’s syndrome) due to a type III hypersensitivity reaction to nickel has also been described. A significant increase in deaths from nonmalignant respiratory disease or pneumoconiosis has been observed in nickel refinery workers. Nickel compounds are classified by the IARC as class I car- cinogens, with evidence that occupational exposure increases the risk of cancer of the lung and nasal sinuses. Metallic nickel and nickel salts cause allergic contact dermatitis in up to 10% of females and 1% of males and is due to a type IV delayed hypersensitivity. Treatment Blood nickel concentrations immediately following exposure to nickel carbonyl provide a guide to severity of exposure and the need for chelation therapy. Unithiol (DMPS) enhances the urinary excre- tion of nickel in nickel-intoxicated animals. Diethyldithiocarbamate and disulfiram (which is metabolized to diethyldithiocarbamate) are effective agents in the treatment of nickel dermatitis, but their role in the treatment of acute severe nickel carbonyl poisoning has not been confirmed in a controlled clinical study. Phosphorus Elemental phosphorus exists in several crystalline forms (allo- tropes), of which yellow phosphorus (sometimes referred to as white) is the most important toxicologically. Phosphorus oxidizes spontaneously in contact with air to form phosphorus pentoxide which, by an exothermic reaction, forms phosphoric acid on contact with water. Hence, dermal and gastrointestinal exposures to phos- phorus rapidly become exposures to phosphoric acid. Clinical features Typically, patients who have ingested phosphorus present with ei- ther gastrointestinal features (most commonly) or central nervous system features; 20% have a combination of both. Features gener- ally begin within minutes of ingestion and include nausea, vomiting, abdominal pain, burns of the pharynx,

oesophagus, and stomach, which may lead to gastrointestinal haemorrhage. Shock in part due to fluid loss and GI haemorrhage follows. In other cases, central nervous system features (restlessness, irritability, delirium, coma, convulsions, and cerebral oedema) predominate. Metabolic compli- cations (metabolic acidosis, hypoglycaemia, hyperphosphataemia and hypocalcaemia) and hepatorenal failure ensue. Cardiovascular collapse and arrhythmias are the most common cause of death following ingestion, but in other cases cerebral oe- dema and haemorrhage complicating fulminant hepatic failure are responsible. Treatment Treatment is supportive. Hypotension/shock should be corrected vigorously with intravenous fluid and inotropes. If metabolic acid- osis is not responsive to fluid resuscitation, give intravenous sodium bicarbonate. Early fibreoptic endoscopy and CT is indicated to grade the severity of the injury in any patient who is symptomatic or has evidence of oropharyngeal burns. Thallium Thallium sulphate was previously used as a rodenticide but is now banned for this use in many countries. Thallium salts have also been employed in the manufacture of optical and electrical equipment, as catalysts in organic synthesis, and in isotopic form for medical imaging of the myocardium.

10.4.1 Poisoning by drugs and chemicals 1757 Clinical features Initial symptoms (if ingested) include nausea, vomiting, abdominal pain, and, less commonly, gastrointestinal bleeding. Constipation follows in most patients. After a few days (usually between two and five), paraesthesiae develop, which start in the feet and progress to the hands and fingers; painful and tender extremities (‘burning feet syndrome’) and ascending sensory neuropathy then supervene. In severe cases confusion, delirium, convulsions, renal failure, respira- tory failure, heart failure, and coma occur; the mortality is high. If death does not occur within the first week, tremor, ataxia, and (usually lower limb) muscle weakness develops, due to the onset of motor neuropathy, which is usually distal. Ocular features include nystagmus, ptosis, and abnormalities of gaze due to involvement of the third, fourth, and sixth cranial nerves. Retrobulbar neuritis, fa- cial paralysis, decreased visual acuity, optic atrophy, and defective colour vision may develop. Characteristically, alopecia develops within 1–3 weeks and it is often this sign which leads to the diagnosis being made. If the patient survives, the hair usually regrows, but is often abnormally fine and unpigmented. Nail growth is impaired with the develop- ment of ridges, Mees’ lines, and erosion of the proximal parts of the nails. Treatment As thallium ions are excreted into the gastrointestinal tract via the saliva, the bile, and through the intestinal mucosa, it is possible to sequester thallium ions in the gut and prevent reabsorption by the oral administration of colloidally soluble Prussian blue (potassium ferric hexacyanoferrate (II)) 250–300 mg/kg/day (approximately 10 g twice daily for an adult). Thallium ions are exchanged for po- tassium ions in the lattice of the Prussian blue molecule and are sub- sequently excreted in faeces. During treatment with Prussian blue, plasma concentrations of thallium fall and urine excretion declines exponentially. In contrast, faecal excretion of thallium is detectable even when urine excretion of the metal has ceased and, therefore, administration of Prussian blue should be continued until thallium can no longer be detected in the faeces. Zinc Zinc oxide fumes are emitted in any process involving molten zinc and are the most common cause of metal fume fever. Exposure to zinc chloride occurs in soldering; in the manufacture of dyes, paper, and deodorants; and on military exercises when it is used as a smoke screen. Poisoning has followed the accidental or deliberate inges- tion of elemental zinc and zinc chloride and fatal intoxication has followed inadvertent intravenous administration. Inhalation of zinc chloride and oxide may lead to nasopharyngeal and respiratory tox- icity. Zinc may be absorbed through broken skin when zinc oxide paste is used to treat wounds and burns. Clinical features Zinc sulphate ingestion causes gastrointestinal irritation, sometimes in association with

headache and dizziness. Zinc chloride is highly corrosive, and ingestion has led to erosive pharyngitis, oesophagitis, and haematemesis. Acute renal failure and pancreatitis have also been recorded after ingestion of zinc salts. Topical exposure to zinc chloride causes ulceration and dermatitis of the exposed skin. Zinc chloride is highly irritant to the eye. In contrast to the relatively mild clinical course after zinc oxide in- halation, exposure to zinc chloride ammunition bombs (hexite) pro- duces a chemical pneumonitis with marked dyspnoea, a productive cough, fever, chest pain, and cyanosis. The acute respiratory distress syndrome may ensue. Metal fume fever occurs most commonly in individuals who per- form welding involving zinc. It presents generally with influenza-like symptoms, fever, shaking chills, arthralgias, myalgias, headache, and malaise, some 4–10 h following exposure. In patients with ongoing metal fume exposure over the course of a workweek, tachyphylaxis occurs resulting in improvement in symptoms over the course of the workweek and maximal symptoms occurring after an exposure-free period such as a weekend. Treatment Management is supportive. Endoscopy and CT should be performed following zinc chloride ingestion to assess the severity of oesopha- geal or gastric burns. Pesticides Aluminium and zinc phosphides Aluminium and zinc phosphides are highly effective insecticides and rodenticides, which are used to protect grain during transport and storage. The phosphide interacts with moisture in the surrounding air to liberate phosphine, which is the active pesticide. Acute poi- soning, therefore, results either from the ingestion of the salts them- selves or inhalation of the phosphine generated during their use; the latter is discussed later on in this chapter. In cases of poisoning by phosphide ingestion, toxic effects are due to phosphine release when the phosphide comes into contact with gut fluids. Phosphine is absorbed through the alimentary mucosa and widely distributed to tissues. Clinical features Early features include nausea, vomiting, retrosternal, and epigas- tric pain, gastric, or duodenal erosions causing haematemesis and dyspnoea. Diarrhoea is less common. Shock and circulatory failure occurring early in the course of poisoning are of ominous prognostic importance, as circulatory failure is a common and frequent cause of death. Impaired myocardial contractility and global dyskinesia are frequent in those severely poisoned. This group of patients is characterized by severe hypotension, reduced cardiac output, raised systemic venous pressure, normal pulmonary artery wedge pressure and inadequate systemic vasoconstriction. Severe metabolic acid- osis, renal failure, and disseminated intravascular coagulation are common accompaniments. Treatment Treatment is symptomatic and supportive. Gastric lavage should be avoided as it might increase the rate of disintegration of the product ingested and increase toxicity. Activated charcoal does not bind metal phosphides. Anticoagulant rodenticides Warfarin was widely used as a rodenticide until target species de- veloped resistance to it. The newer anticoagulant rodenticides

 (sometimes termed ‘super warfarins’), such as brodifacoum, bromodialone, chlorophacinone, coumatetralyl, difenacoum, diphacinone and flocoumafen, are more potent and longer-acting antagonists of vitamin K1 than warfarin. While accidental ingestion of small amounts rarely results in altered coagulation, deliberate in- gestion may result in prolongation of the INR for several weeks or months and fatal haemorrhage has occurred. These anticoagulants inhibit vitamin K1-2,3-epoxide reductase and thus the synthesis of vitamin K and subsequently clotting fac- tors II, VII, IX, and X. There is no anticoagulant effect until existing stores of vitamin K and clotting factors are depleted. The greater po- tency and duration of action of long-acting anticoagulant rodenti- cides compared to warfarin is attributed to their greater affinity for vitamin K1-2,3-epoxide reductase, their ability to disrupt the vitamin K1-epoxide cycle at more than one point, hepatic accumulation,

and unusually long biological half-lives due to high lipid solubility and enterohepatic circulation. Clinical features Gastrointestinal bleeding, haematuria, and bruising are the most common features, though the most common site of fatal haemor- rhage is intracranial. The onset of bleeding may be delayed for sev- eral days since the peak anticoagulant effect does not occur until some 72–96 h after ingestion. Treatment Routine measurement of the INR is generally not indicated in chil- dren as the amounts they ingest are almost invariably small. In all other cases, the INR should be measured on presentation and 36 to 48 h after exposure. If the INR is normal at this time, no further action is required. If a patient presents within 1 h of a large ingestion, the adminis- tration of activated charcoal (50 g for adults; 10–15 g for children) should be considered, as it is known that warfarin is adsorbed to charcoal. In patients with severe poisoning who have ingested a long-acting formulation, oral cholestyramine 4 g three times daily for an adult should be considered in order to shorten the plasma half-life of the rodenticide. If active bleeding occurs, dried prothrombin complex (which contains factors II, VII, IX, and X) 25–50 units/kg, or fresh frozen plasma 15 ml/kg (if no concentrate is available) should be given, to- gether with phytomenadione 5 mg by slow intravenous injection (100 µg/kg body weight for a child). If active bleeding occurs in a pa- tient who is being prescribed an anticoagulant, warfarin (or another anticoagulant) should be discontinued. If there is no active bleeding and the INR is less than 4.0, treat- ment with phytomenadione is not required. If the INR is more than 4, phytomenadione 5 mg by slow intravenous injection (100 µg/kg body weight for a child) should be administered, unless the patient is anticoagulated for therapeutic reasons. If the patient is prescribed anticoagulants, the INR is more than 8, and there is no active bleeding or only minor bleeding, stop warfarin (restart when the INR <5), give phytomenadione 0.5 mg by slow intravenous injection and repeat the dose if the INR is more than 8 12–24 h later. If the INR is between 6.0 and 8.0, and there is no active bleeding or only minor bleeding, warfarin should be discontinued and restarted when the INR is less than 5. Patients who require reversal of coagulopathy after exposure to long-acting formulations should have their INR measured for two weeks after cessation of treatment. Failure to do so may result in recurrence of anticoagulation and risk haemorrhage being missed. Bipyridyl herbicides The bipyridyl herbicides include diquat, morfamquat, and para- quat. Paraquat has been removed from the market in the EU; diquat remains widely available and morfamquat is not readily available. Clinical features The features of toxicity are largely dependent on the amount of para-quat swallowed. Ingestion of more than 6 g paraquat ion is likely to be fatal within 24–48 h, while 3–6 g is likely to lead to a more pro- tracted, but still fatal, outcome. After the ingestion of more than 6 g paraquat ion, nausea, vomiting, abdominal pain, and diarrhoea, are rapidly followed by peripheral circulatory failure, metabolic acidosis, impaired consciousness, convulsions, and increasing breathlessness secondary to acute pneumonitis. Breathlessness, tachypnoea, wide-spread crepitations, and central cyanosis progress relentlessly until the patient dies from hypoxia a few days later. Mild jaundice may be seen and renal failure is usually severe. After 3–6 g paraquat ion, the cardiovascular and central nervous system complications are not seen, and the course of poisoning is dominated by alimentary features, particularly painful ulceration of the mouth, tongue, and throat, which makes it difficult to swallow, speak, and cough. Perforation of the oesophagus with subsequent mediastinitis has been reported. Ingestion of 1.5–2.0 g of paraquat causes nausea, vomiting, and diarrhoea, mild renal tubular necrosis, and pain in the throat. Respiratory involvement may not be apparent until 10–21 days after ingestion, but may progress till the patient dies of respiratory failure as late as 5 or 6 weeks after taking the paraquat. The features of diquat poisoning are similar. In severe and usu- ally fatal cases, gastrointestinal mucosal ulceration, paralytic ileus, hypovolaemic shock, acute renal failure, and coma predominate. Treatment The

diagnosis of paraquat poisoning can be confirmed by a simple qualitative test on urine passed within 4 h of ingestion using alka- line sodium dithionite (a blue colour indicates paraquat is present); a negative test indicates that not enough paraquat has been taken to cause problems. In the case of diquat poisoning, the urine goes a green colour in the alkaline sodium dithionite test. The outcome of paraquat poisoning can be predicted with reasonable confidence within a few hours of ingestion by relating the plasma paraquat concentration to the time after ingestion, but this assay is not readily available in Europe following the withdrawal of paraquat from the market. There is no evidence that the outcome of paraquat or diquat poi- soning can be altered by any form of intervention. Symptomatic measures including antiemetics, mouth washes and analgesics are indicated, and intravenous fluids may be necessary to replace gastro- intestinal losses. Carbamate insecticides Carbamate insecticides inhibit acetylcholinesterase, causing ac- cumulation of acetylcholine at central and peripheral cholinergic nerve endings, including neuromuscular junctions. The duration of this effect is comparatively short-lived (compared to organophos- phorus insecticides) as the carbamate–enzyme complex tends to dissociate spontaneously.

10.4.1 Poisoning by drugs and chemicals 1759 Clinical features After substantial carbamate ingestion, patients usually develop cho- linergic symptoms within a few minutes, and in most severe cases, constriction of the pupils, muscle twitching, profound weakness, profuse sweating, excessive salivation, bronchorrhoea, chest tight- ness, coughing, incontinence, confusion, and progressive cardiac and respiratory failure ensue. Seizures are relatively uncommon as a primary complication, because carbamate penetration into the cen- tral nervous system is limited, though they may occur secondary to hypoxia. Death is usually due to respiratory failure. In less substan- tial ingestions, cholinergic symptoms are evident within 2 h in most cases and typically resolve within 24 h. Treatment Bronchorrhoea requires removal of secretions by suction and prompt relief with intravenous atropine 2 mg (0.02–0.1 mg/kg in a child) intravenously together with supplemental oxygen to maintain arterial PaO_2 greater than 10 kPa (>75 mm Hg). The atropine dose should be titrated to control rhinorrhoea and bronchorrhoea. If the initial dose produces only a partial response, it should be doubled and doubled again if there is only a limited clinical response. If these measures fail, the patient should be intubated and mechanical ven- tilation instituted. At present there is insufficient evidence to either recommend or ad- vise against the use of pralidoxime in severe poisoning with carbamate insecticides. Pralidoxime seldom should need to be administered in less severe cases since carbamates have a relative short duration of action. However, if intoxication is life-threatening and unresponsive to atro- pine and supportive measures, pralidoxime chloride 30 mg/kg body weight by intravenous injection over 20 minutes should be given. Chloralose Chloralose is marketed for amateur use as cereal or paste baits con- taining 2 to 4% rodenticide. Technical α-chloralose (c. 90% pure) is used by professionals against bird pests and rodents. Clinical features Toxic amounts of chloralose cause severe central nervous system ex- citation with hypersalivation, increased muscle tone, hyperreflexia, opisthotonus, myoclonic jerks, and convulsions. Rhabdomyolysis is a potential complication. Coma, generalized flaccidity, and respira- tory depression may follow. Treatment Children who ingest small amounts of baits (amateur formulations) containing chloralose are unlikely to develop symptoms. In contrast, patients who have deliberately ingested large amounts of bait or the technical compound are likely to require admission to intensive care for management of convulsions, myoclonus, and coma. Chlorates Sodium and potassium chlorates are nonselective herbicides. Potassium chlorate is also used in matchstick heads, explosives, and fireworks. Sodium chlorate and potassium chlorate are powerful oxi- dizing agents that induce methaemoglobinaemia and haemolysis. Clinical features

Features of chlorate toxicity may develop within as little as two hours of ingestion and are usually due to gastrointestinal irritation. Early features include nausea, vomiting, diarrhoea, abdominal pain, and cyanosis secondary to methaemoglobinaemia. The combination of methaemoglobinaemia and haemolysis results in varying degrees of hypoxaemia and symptoms such as general weakness, fatigue, diz- ziness, agitation, anxiety, confusion, and headache. Chest pain and dyspnoea may also be experienced. Intravascular haemolysis causes hyperkalaemia and jaundice. Poisoning with chlorate is also com- monly complicated by acute renal failure, though the underlying mechanisms are not fully understood. Treatment Methaemoglobinaemia can be corrected by slow intravenous injec- tion of methylthioninium chloride (methylene blue) 1–2 mg/kg body weight as a 1% solution, although this treatment is less effective in the presence of major intravascular haemolysis. Blood transfusion may be required. Plasma potassium concentrations should be moni- tored and reduced if necessary. Haemodialysis/haemodialfiltration may remove chlorate and will also be required for the management of renal failure and hyperkalaemia. Plasmapheresis and plasma ex- change or exchange transfusion have also been employed to remove chlorate, circulating free haemoglobin, and red cell stroma, but data are too limited to make a firm recommendation. Chlorophenoxy herbicides Chlorophenoxy (phenoxyacetate) herbicides are weed killers that act as synthetic auxins (plant ‘hormones’) and cause plant death by disrupting nutrient transport and growth. They comprise an aliphatic carboxylic acid moiety attached to a chlorine- or methyl-substituted aromatic ring. Important examples are listed in Table 10.4.1.10. These herbicides are usually formulated as salts or esters of the active compound and sometimes coformulated with the chemically related herbicides ioxynil, bromoxynil and/or dicamba. Most in- stances of serious poisoning have been due to deliberate ingestion, mainly in the developing world. Mechanisms of toxicity include dose-dependent cell membrane damage, chemical mimicry of acetyl coenzyme A and uncoupling of oxidative phosphorylation. Clinical features Ingestion causes nausea and vomiting which may be accompanied by burning in the mouth and throat and abdominal pain. Severe corro- sive injury to the gastrointestinal tract is rare. Hypotension, which is common, is due predominantly to intravascular volume loss, although vasodilation and direct myocardial toxicity may also contribute. Coma, hypertonia, hyperreflexia, ataxia, nystagmus, miosis, hallu- cinations, convulsions, fasciculation, and paralysis may then ensue. Hypoventilation is commonly secondary to central nervous system Table 10.4.1.10 Chlorophenoxy herbicides Chemical name Other names 2,4-Dichlorophenoxy acetic acid 2,4-D 4-(2,4-Dichlorophenoxy) butyric acid 2,4-DB 2-(2,4-Dichlorophenoxy) propionic acid 2,4-DP, dichlorprop 4-Chloro-2-methylphenoxyacetic acid MCPA 4-(4-Chloro-2-methylphenoxy) butyric acid MCPB 2-(4-Chloro-2-methylphenoxy) propionic acid Mecoprop 2-(2, 4-Dichloro-m-tolyoxy) propionanilide Clomeprop

 depression, but respiratory muscle weakness is a factor in the devel- opment of respiratory failure in some patients. Myopathic symptoms, including limb muscle weakness, loss of tendon reflexes, myotonia, and increased creatine kinase activity, have been observed. Metabolic acidosis, rhabdomyolysis, renal failure, increased aminotransferase activities, pyrexia, and hyperventilation have been reported. Treatment In addition to supportive care, urine alkalinization with high-flow urine output will enhance herbicide elimination and should be con- sidered in all seriously poisoned patients. Haemodialysis produces similar herbicide clearances to urine alkalinization and should be considered if high-flow urine alkalinization cannot be performed for clinical reasons. Glyphosate Glyphosate-containing herbicides are very popular because their mode of action is plant-specific

(by inhibition of an enzyme pathway not present in mammals), they act only on contact with plant foliage and are inactivated on contact with soil. Formulations usually contain the isopropylamine salt of glyphosate, together with a surfactant. The latter is often an animal fat derivative (a tallow amine) polyoxyethylene amine (POEA), which contributes substantially to the toxicity of the formulation. Dilute, ready-to-use glyphosate/POEA preparations are rarely associated with systemic toxicity, which usually requires the deliberate ingestion of a concentrate (typically 41% glyphosate/15% POEA). Clinical features Ingestion of more than 85 ml of the concentrated glyphosate/POEA formulation is likely to cause significant toxicity in adults. Fatal in- gestions have usually involved more than 200 ml. The most prom- inent effects are on the alimentary tract with burning in the mouth, throat, nausea, vomiting, dysphagia, and diarrhoea. Upper gastro- intestinal haemorrhage is a much less common complication. Renal and hepatic impairment are also frequent and usually reflect reduced organ perfusion. Respiratory distress, impaired consciousness, pul- monary oedema, infiltration on chest radiograph, shock, arrhyth- mias, renal failure requiring haemodialysis, metabolic acidosis, and hyperkalaemia may supervene in severe cases and, together with advancing age and late presentation, are poor prognostic indicators. Treatment Management is symptomatic and supportive. Intravenous fluids or blood transfusion may be required. Respiratory and renal failure should be managed conventionally. The fatality rate in case series of glypho- sate concentrate ingestion is approximately 6%. Death most frequently ensues within 72 h and is related to refractory cardiovascular collapse. Metaldehyde Metaldehyde in the form of pellets is used widely for killing slugs and in some countries as a solid fuel. Clinical features Nausea, vomiting, diarrhoea, abdominal pain, agitation, dizzi- ness, and tachycardia are common, but it is central nervous system and skeletal muscle complications that characterize the most severe toxicity. Convulsions may develop within 3 h of ingestion and recur frequently, and over days. Consciousness is impaired. Tremor, hypertonia, exaggerated limb reflexes, muscle twitching or spasms, including jaw clenching in the absence of overt seizures, superior lateral gaze fixation, and opisthotonus have all been described. This increase in motor activity, in turn, results in raised creatine kinase ac- tivity, rhabdomyolysis, hyperpyrexia, and metabolic acidosis in some cases. Less frequent complications include hyperventilation, respira- tory alkalosis, minor elevation of transaminase activities, upper gastrointestinal bleeding, and mildly deranged coagulation. Treatment Treatment is supportive. Intravenous diazepam 10 mg IV or lor- azepam 4 mg IV in an adult should be given to suppress convulsions and a clear airway and adequate ventilation ensured, using endo- tracheal intubation if necessary. Rhabdomyolysis and its complica- tions should be managed conventionally. Methyl bromide The uses of methyl bromide (bromomethane) have gradually be- come restricted as it is an ozone-depleting chemical. It is currently used to fumigate mills, warehouses, shipping containers, stored products, and soil in greenhouses to eradicate pests such as wood- worm and rodents that damage crops and buildings. In most countries application is now restricted to trained and licensed personnel. Methyl bromide is absorbed readily through the lungs and is ex- creted largely unchanged by the same route. Clinical features Inhalation causes respiratory tract irritation with shortness of breath, cough, and varying degrees of pulmonary oedema. Hypoxaemia and respiratory failure are inevitable consequences. Neurotoxicity manifests hours or days later with agitation, delirium, ataxia, in- tention tremor, nystagmus, dysdiadochokinesis, and hyperreflexia. Abnormal movements of the limbs are common and convulsions occur frequently. Consciousness may be impaired to the point of coma in severe cases. Proteinuria, oliguria (due to renal tubular and cortical necrosis), and jaundice have been described. Treatment The casualty should be removed promptly from the contamin- ated atmosphere and undressed, as methyl bromide can penetrate clothing and rubber gloves.

Contaminated skin should be washed with water. Treatment is supportive. Systemic uptake can be quanti- fied by measuring serum and urine bromide concentrations. Neonicotinoids Neonicotinoids are now employed widely as systemic insecticides and some (imidacloprid, dinotefuran, thiamethoxam, nitenpyram) are used as flea control agents for dogs and cats. They block postsynaptic nicotinic receptors (nAChRs), particularly the α4ß2 subtype. The high specificity of neonicotinoids for insect nicotinic receptors, their low affinity for human nAChRs and relatively poor penetration of the human blood–brain barrier should result in much lower toxicity to humans than nicotine-containing pesticides. Human poisoning with neonicotinoids is well recognized and may be severe and fatal, though the solvents and surfactants present in many formulations may also contribute to toxicity. Clinical features Poisoning with neonicotinoids is characterized by the rapid onset of symptoms including nausea and vomiting, fever, sweating, increased

10.4.1 Poisoning by drugs and chemicals 1761 salivation, bronchorrhoea, agitation, lack of coordination, disorienta- tion, muscle weakness, seizures, and coma. Breathlessness, depressed respiration, cyanosis, and respiratory arrest have been reported. Bradycardia is sometimes present, but tachycardia is observed more frequently; ventricular tachycardia/fibrillation has occurred occasion- ally, as has cardiac arrest. Severe hypotension and shock supervene in those severely poisoned. Miosis is present in some cases but not the majority. Metabolic acidosis and renal failure have been observed. Treatment In patients who are unconscious a clear airway should be established and, if ventilation is impaired, assisted ventilation should be com- menced. Hypotension and cardiac dysrhythmias should be managed conventionally and acid–base and electrolyte balance corrected. Since the clinically important features, notably bronchorrhoea, are caused by cholinergic overactivity, atropine sulphate 2 mg intraven- ously (in an adult) should be given and the dose repeated until the signs of atropinization are present (dry skin and sinus tachycardia). There is some evidence that activated charcoal can bind neonicotinoids and if administered within 1 h of ingestion may reduce absorption; gastric lavage is contraindicated because of the presence of solvents unless it can be performed with a cuffed endotracheal tube in situ. Organophosphorus insecticides Organophosphorus insecticides are among the most widely used pesticides throughout the world. They inhibit acetylcholinesterase causing accumulation of acetylcholine at central and peripheral cholinergic nerve endings, including neuromuscular junctions. The clinical presentation and severity of OP poisoning depends not only on the pesticide and the magnitude of exposure but also on several other factors, including the route of exposure, the age of the patient, whether exposure was a suicidal attempt (when a substantial inges- tion is more likely), and the presence of a solvent in the formula- tion. Not only may skin absorption of the OP itself be enhanced by the presence of the solvent, but also ingestion of a solvent may in- duce vomiting with risk of aspiration; depressed consciousness may follow. In addition, there is increasing evidence that the solvents in formulations are responsible for the high morbidity and mortality. Clinical features The first symptom of mild poisoning, particularly in individuals oc- cupationally exposed, is often a feeling of exhaustion and weakness. Vomiting, cramping abdominal pain, sweating, and hypersalivation may follow. Constriction of one or both pupils and a sensation of tightness in the chest during inspiration also may occur at an early stage, but these signs are not reliable indices of the severity of systemic poisoning because they may be caused by local anticholinesterase ef- fects of spray mist on the eye or bronchi. In cases of more severe poisoning, the nicotinic features tend to appear first, but a combination of muscarinic, nicotinic, and cen- tral nervous system symptoms is apparent in many severe cases. Muscle twitching may affect the eyelids, tongue, face muscles, and calf muscles; respiratory muscles then become

involved, and gen- eral muscle weakness ensues. Convulsions may occur, though OPs vary in their potency to induce seizures. Bronchial hypersecretion/ bronchorrhoea, with bronchoconstriction, is followed in severe cases by cyanosis, respiratory depression, and coma. Death may follow from respiratory failure. Coma is usually due to direct central nervous system depression by the pesticide and solvents in the com- mercial formulation. Aspiration pneumonia is common. Though bradycardia would be expected from the mode of action of organophosphorus insecticides, it is present in only about 20% of cases; sinus tachycardia is more common. Rarely, complete heart block and arrhythmias occur. Relapse after apparent resolution of cholinergic symptoms has been reported, particularly in patients who have ingested highly lipophilic insecticides, and is termed the intermediate syndrome. This involves the onset syndrome of muscle paralysis affecting particularly upper limb muscles, neck flexors, and cranial nerves some 24–96 h after exposure, though there are reports of paralysis occurring before 24 h and even after 96 h. It is often associated with the development of respiratory failure. Delayed neuropathy is a rare complication of acute exposure to some insecticides. It results from phosphorylation and subse- quent ageing of at least 70% of neuropathy target esterase (NTE). Only a small number of marketed insecticides, for example methamidophos, are capable of causing this syndrome. The fea- tures resulting from distal degeneration of some axons in both the peripheral and central nervous systems occur 1–4 weeks after ex- posure. Cramping muscle pain in the lower limbs, distal numbness, and paraesthesiae are followed by progressive weakness, depres- sion of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. Signs include a high-stepping gait from bilat- eral foot drop and, in severe cases, quadriplegia with foot and wrist drop, as well as pyramidal signs. In time, there might be significant recovery of peripheral nerve function but, depending on the de- gree of pyramidal involvement, spastic ataxia may be permanent The diagnosis is confirmed by measuring erythrocyte acetyl- cholinesterase activity; plasma butyrylcholinesterase activity is a less preferable alternative. Treatment Management involves supportive measures and judicious admin- istration of antidotes. Bronchorrhoea requires prompt relief with intravenous atropine 2 mg (0.02–0.1 mg/kg in a child). The atropine dose should be titrated to control rhinorrhoea and bronchorrhoea, to raise the pulse rate above 80 bpm, and restore systolic blood pressure to more than 80 mm Hg. If the initial dose produces only a partial response, it should be doubled and doubled again if there is only a limited clinical response. In addition, supplemental oxygen should be given to maintain PaO_2 greater than 10 kPa (75 mm Hg). If neces- sary, the patient should be intubated and mechanical ventilation (with positive end-expiratory pressure) should be instituted. There are consistent animal data supporting the effectiveness of oximes, when given early. While there are also some clinical studies which support the benefit of oxime therapy, others do not. Recent studies indicate that solvents in the formulations play a crucial role in toxicity, which could explain why oximes seem to be less effective clinically than in experimental studies where pure insecticide is often employed. Pralidoxime chloride 30 mg/kg by intravenous injection over 20 min, repeated at 4–6 h intervals, should be administered as soon as possible in any patient requiring atropine; alternatively, an intravenous infusion of 8–10 mg/kg/h in an adult may be employed after the bolus injection. Administration of pralidoxime should con- tinue for as long as atropine is required, that is, until clear, irrevers- ible clinical improvement is achieved, which may take many days while residual insecticide is cleared from the body stores.

 The use of diazepam 5–10 mg intravenously in an adult will reduce anxiety and restlessness, but larger doses may be required to control convulsions; diazepam also reduces morbidity and mortality. Phosphine

Phosphine is used extensively as a fumigant to control rodents and a wide variety of insects in sealed containers or structures. It is also used in the semiconductor industry. Clinical features The initial symptoms are often alimentary rather than respiratory. Indeed, the nausea, vomiting, diarrhoea, and epigastric pain may be so striking that physicians are misled into making a diagnosis of acute gastroenteritis. However, respiratory complaints do occur. Chest tightness, breathlessness, chest pain or soreness, and palpitations are commonly reported. Inhaled phosphine is as cardiotoxic as in- gested metal phosphides (see earlier). Acute heart failure, pulmonary oedema (which may be both cardiogenic and noncardiogenic) and cardiac arrhythmias have been observed, particularly in children. Convulsions, ataxia, and intention tremor have also been reported. Treatment The casualty should be removed from exposure as soon as possible. Thereafter, treatment is supportive and symptomatic. Pyrethroids Pyrethroids are used widely as insecticides both in the home and com- mercially, and in medicine for the topical treatment of scabies and head lice. In tropical countries, mosquito nets are commonly soaked in pyrethroid solutions as part of antimalarial strategies. Pyrethroid sprays are used to ‘disinsect’ the interiors of aircraft. Despite their ex- tensive worldwide use, severe poisoning with pyrethroids is extremely rare. The most important mechanism of toxicity is modification of the gating characteristics of voltage-sensitive sodium channels, causing delayed closure. A protracted sodium influx ensues, which, if it is suf- ficiently large and/or long, lowers the action potential threshold and causes repetitive firing which manifests as paraesthesiae. Clinical features Pyrethroids are best known for their ability to cause facial paraes- thesiae following occupational cutaneous exposure; these symptoms last only a few hours at most. Inhalation of pyrethroid-containing dust or aerosol droplets may cause respiratory tract irritation, but systemic toxicity is unusual. Ingestion causes irritation of the gastro- intestinal tract with nausea and vomiting, increased salivation, and mouth ulceration. Coma, convulsions, and pulmonary oedema may ensue in the most severe cases and fatalities have occurred rarely. Treatment Symptomatic and supportive measures should be employed, and reassurance given that facial paraesthesiae will not be a long-term problem. Other chemicals Acetone Acetone is a clear liquid with a characteristic pungent odour and sweet taste, used widely in industrial and household products including paints, nail polish, and nail polish removers. It is absorbed rapidly through the lungs and gut and metabolized in the liver to pyruvate. Metabolism is saturable with elimination of the parent compound in expired air (it can be smelt on the breath) and urine at high doses. Clinical features There is irritation of mucous membranes of eyes, nose, and throat. Systemic toxicity causes headache, excitement, restlessness, chest tightness, incoherent speech, nausea and vomiting and, occasion- ally, gastrointestinal bleeding, coma, convulsions, and hypergly- caemia (resulting from the metabolism of pyruvate to glucose). Treatment If toxicity has followed inhalation, remove from exposure, give sup- portive treatment, and correct hyperglycaemia. Since acetone is a small molecule, there may be a role for dialysis in the management of seriously poisoned patients, particularly if plasma acetone con- centrations are high. Acids Acids commonly involved in cases of poisoning include the inor- ganic acids hydrochloric, hydrofluoric (see ‘Hydrogen fluoride/ hydrofluoric acid’, further on in this chapter), nitric, phosphoric, and sulphuric acids; and organic acids such as acetic, formic, lactic, and trichloroacetic acids. Car battery acid typically contains 28% sulphuric acid. Proprietary cleaning agents and antirust compounds often comprise a mixture of hydrochloric and phosphoric acids. Inorganic acids generally are of concentrations more likely to be cor- rosive at the normally available solution. Clinical features Acid burns of the skin cause erythema, blistering and, in severe cases, ulceration and necrosis. In the eyes, intense pain and bleph- arospasm are common, and corneal burns may occur. When ingested, acids tend to damage the stomach more than the oe-

sophagus, but oropharyngeal and oesophageal injuries may also occur. Immediate pain is followed by vomiting and/or haematemesis. Severe injury results in inability to swallow saliva with drooling. Gastric and oesophageal perforation may occur, resulting in chemical peritonitis and shock. Other effects include hoarseness, stridor, and respiratory distress secondary to laryngeal and epiglottic oedema, metabolic acid- osis leucocytosis, acute tubular necrosis, renal failure, hypoxaemia, re- spiratory failure, intravascular coagulation, and haemolysis. Treatment Acid burns to the skin should be irrigated liberally with water or sa- line and managed as a thermal burn. Skin grafting may be necessary and specialist advice should be sought. After ocular exposure with acid, the eye should be irrigated, pref- erably with saline for 15–30 min. Topical local anaesthetic is usually required to relieve pain and to overcome blepharospasm. Specialist advice should be sought. After ingestion, a clear airway should be established. Opioids are often necessary for analgesia. Dilution and/or neutralization is contraindicated. Features of severe tissue injury (severe abdom- inal pain, abdominal distension, circulatory collapse, or lactic acid- osis) may indicate the presence of bowel necrosis or perforation. Immediate surgical assessment is recommended because early re- section of necrotic tissue and intraluminal stenting has been shown

 to improve survival and reduce the risk of oesophageal stricture for- mation. Both CT scan and fibreoptic endoscopy have been shown to be useful in assessing the severity of injury, risk of mortality, and risk of subsequent stricture formation. These two imaging modalities are complimentary and when combined provide the best understanding of the injury and risk. If there are severe clinical features, then en- doscopy is best performed by a surgeon capable of undertaking de- finitive treatment. Corticosteroids confer no benefit and may mask abdominal signs of perforation; antibiotics should be given for es- tablished infection only. Acid ingestion may result in antral, pyloric, or jejunal strictures, achlorhydria, protein-losing enteropathy, and gastric carcinoma. Alkalis Alkalis are commonly found in the home and those encountered in cases of poisoning include sodium hydroxide (drain, lavatory, pipe cleaners), sodium carbonate, sodium silicate, sodium perborate, sodium phosphate, sodium carbonate (denture cleaning tablets), sodium dichloroisocyanurate (water sterilizing tablets), sodium hypochlorite (a bleaching agent), and alkaline batteries. Clinical features The features of eye, skin and laryngeal contamination with alkalis are similar to those produced by acids (see ‘Acids’) though when ingested, alkalis are more likely to damage the oesophagus. Oropharyngeal pain, together with epigastric pain are followed by vomiting and diar- rhoea. Oesophageal ulceration with or without perforation may be complicated by mediastinitis or pneumonitis. Oesophageal perfor- ation may result in catastrophic aorto-enteric fistula formation. Treatment The treatment of corrosive injuries caused by alkalis is largely the same as for those produced by acids (see ‘Acids’). In severe cases, following resuscitation and stabilization, early assessment by endos- copy and/or CT imaging is the priority. Alkali ingestion may result in stricture formation and there is a risk of malignancy. The mean latent period for development of carcinoma of the oesophagus fol- lowing alkali ingestion is more than 40 years. Arsine Arsine is a colourless, nonirritating gas. Arsine binds with oxidized haemoglobin causing massive intravascular haemolysis. Clinical features There is usually a delay of some 2–24 h after exposure before the onset of headache, malaise, weakness, dizziness, breathlessness, migratory abdominal pain, fever, tachycardia, tachypnoea, nausea, and vomiting. A bronze skin colour is noted in some patients, but most have the typ- ical appearance of a jaundiced patient. Acute renal failure is observed by the third day after substantial exposure, and the urine is dark red, then brown (from haemoglobinuria), before anuria (due to acute renal tubular necrosis) ensues. Investigations will show leucocytosis, reticulocytosis, elevated plasma

haemoglobin, and haemoglobinuria. Treatment If haemolysis is severe, the use of red cell exchange and plasma exchange may be more beneficial than red cell exchange alone, though plasma exchange alone is also effective in the treatment of intravascular haemolysis. Blood transfusion will be required in cases of severe haemolysis. If renal failure ensues, haemodialysis/ haemodialfiltration should be undertaken. Antidotes to remove ar- senic are of no value. Benzene Benzene is a colourless, volatile liquid with a pleasant odour. It is an ingredient in many paints and varnish removers, and in some petrols. About 10% of inhaled benzene is excreted unchanged in the breath. The remainder is metabolized by mixed function oxidase en- zymes predominantly in the liver, but also in the bone marrow, the target organ of benzene toxicity. Benzene is a human carcinogen. Clinical features Acute exposure Following inhalation or ingestion, euphoria, dizziness, weakness, headache, blurred vision, mucous membrane irritation, tremor, ataxia, chest tightness, respiratory depression, cardiac arrhyth- mias, coma, and convulsions occur. Direct skin contact with liquid benzene may produce marked irritation. Chronic exposure The toxic effects of chronic poisoning may not become apparent for months or years after initial contact and may develop after all ex- posure has ceased. Anorexia, headache, drowsiness, nervousness, and irritability are well described. Anaemia (including aplastic anaemia), leucopenia, thrombocytopenia, pancytopenia, leukaemia, lymphomas, chromo- somal abnormalities, and cerebral atrophy have been reported. There is also an association between occupational benzene exposure and non-Hodgkin's lymphoma. Patients have recovered after as long as a year of almost complete absence of formation of new blood cells. A dry, scaly dermatitis may develop on prolonged or repeated skin exposure to liquid benzene. Treatment Following removal from the contaminated atmosphere, treatment should be directed towards symptomatic and supportive measures. Gastric lavage is hazardous as aspiration is likely to occur. Benzyl alcohol Benzyl alcohol has been used as a preservative in intravascular flush solutions and in drug formulations, which has led to severe toxicity in neonates. Benzyl alcohol is metabolized to benzoic acid, which is then con- jugated with glycine in the liver and excreted as hippuric acid. The immature liver's capacity to metabolize benzoic acid is limited and, when exceeded, leads to accumulation of this metabolite and meta- bolic acidosis. Clinical features In 1982, a syndrome consisting of metabolic acidosis, convulsions, neurological deterioration (due to intraventricular haemorrhage), gasping respirations, hepatic and renal abnormalities, cardiovas- cular collapse, and death was described in small premature infants between 2 to 14 days of age. This was due to IV solutions containing benzyl alcohol. In contrast, healthy adult humans are able to tolerate as much as 30 ml of 0.9% benzyl alcohol by rapid intravenous in- fusion without signs of toxicity. However, a 5-year-old girl devel- oped hypernatraemia and metabolic acidosis due to the infusion of

 diazepam for 36 hours to control status epilepticus. The presence of benzyl alcohol has been used as marker of toluene exposure. Treatment Metabolic acidosis, hepatic and renal failure should be treated con- ventionally and administration of fluids or drugs containing benzyl alcohol should be discontinued. Carbon dioxide Carbon dioxide is a colourless gas that is also available commer- cially as a solid for refrigeration purposes ('dry ice'). High concen- trations may accumulate in wells, silos, manholes, mines, and in several volcanic lakes in Africa. In 1986, Lake Nyos in Cameroon emitted a cloud of carbon dioxide that killed 1700 villagers and 3500 of their livestock. Clinical features Dyspnoea, cough, headache, dizziness, sweating, restlessness, par- aesthesiae, and sinus tachycardia are features after modest exposure. Higher concentrations (>10%) produce psychomotor agitation, myoclonic twitches, eye flickering, coma, and convulsions. Death occurs from acute

cardiorespiratory depression, typically at concen- trations exceeding 17%. Skin contact with solid carbon dioxide (dry ice) may result in frostbite and local blistering. Treatment The casualty should be removed from the contaminated envir- onment and oxygen administered. Thereafter, care is supportive. Dry ice burns are treated similarly to other cryogenic burns, with thawing of the affected tissue and suitable analgesia. Carbon disulphide Carbon disulphide is used as a fumigant for grain and as a solvent, particularly in the rayon industry. It is a clear, colourless, volatile li- quid with an odour like that of decaying cabbage. Clinical features Acute exposure Acute poisoning is rare. Absorption occurs through the skin as well as by inhalation. Because of its potent defatting activity, carbon di- sulphide causes reddening, cracking, and peeling of the skin, and a burn may occur if contact continues for several minutes. Splashes in the eye cause immediate and severe irritation. Acute inhalation may result in irritation of the mucous membranes, blurred vision, nausea and vomiting, headache, delirium, hallucinations, coma, tremor, convulsions, and cardiac and respiratory arrest. Chronic exposure There is an increased incidence of cardiovascular disease (hyperten- sion, arteriosclerosis, ischaemic heart disease, elevated cholesterol) among workers exposed to carbon disulphide. In addition, sleep disturbances, fatigue, anorexia, and weight loss are common com- plaints. Intellectual impairment, cerebellar signs, diffuse vascular encephalopathy, parkinsonism, peripheral polyneuropathy, hepatic damage, and permanent impairment of reproductive performance have been described. Treatment Treatment involves removal from exposure, washing contaminated skin, irrigation of the eyes with water and supportive measures. In most cases, however, preventive measures to keep carbon disul- phide concentrations in the workplace as low as possible are more important. Carbon monoxide Carbon monoxide is a tasteless, odourless, colourless, nonirritating gas produced by incomplete combustion of organic materials. Normal endogenous carbon monoxide production is sufficient to maintain a resting carboxyhaemoglobin concentration of 1 to 3% in urban nonsmokers and 5–6% in smokers. Common sources of carbon monoxide are car exhaust fumes (in the absence of a catalytic converter), improperly maintained and ventilated heating systems, and smoke from all types of fire, typically charcoal barbecues used indoors. Carbon monoxide derived from domestic heating systems is a major cause of accidental death in the developing world. Inhalation of methylene chloride (from paint strippers) may lead to carbon monoxide poisoning due to break- down of the parent compound. Symptoms and signs that follow inhalation of carbon monoxide are the result of tissue hypoxia. The affinity of haemoglobin for carbon monoxide is approximately 240 times greater than that for oxygen. Carbon monoxide combines with haemoglobin to form carboxyhaemoglobin, reducing the total oxygen-carrying capacity of the blood. In addition, the oxygen dissociation curve shifts to the left due to modification of oxygen-binding sites. As a result, the affinity of the remaining haem groups for oxygen is increased, the oxygen dissociation curve is distorted as well as being shifted and the resulting tissue hypoxia is thus far greater than that which would result from simple loss of oxygen-carrying capacity. Carbon monoxide may also inhibit cellular respiration as a result of reversible binding to cytochrome oxidase a3. At higher concentra- tions, carbon monoxide causes brain lipid peroxidation and it has been suggested this may be relevant to the development of delayed neuropsychiatric sequelae. Clinical features The clinical features of carbon monoxide poisoning may be divided into those caused acutely, predominantly due to hypoxia, and those that result from tissue damage by the mechanisms detailed earlier. These later toxicities are therefore related to the initial amounts of carbon monoxide inhaled and length of time before rescue and treatment. In acute poisoning, organs with high oxygen demand are at special risk of damage and this includes, in particular, the heart and brain. The symptoms of mild to moderate exposure are nonspecific and include headache, nausea, and confusion. These

nonspecific symp- toms require a high degree of suspicion in patients at potential risk of poisoning with the gas. As concentrations increase, metabolic acidosis ensues from interference with metabolic processes, and central nervous system features progress to cause loss of conscious- ness with hypertonia and hypereflexia, extensor plantar responses, papilloedema, and convulsions. Cardiovascular changes include ar- rhythmias and ischaemic myocardial damage. Other complications tend to be detected later and include per- sistent neurological damage in any part of the brain, which may

 result in either paralysis or midbrain damage causing parkinsonism or akinetic mutism, deafness due to central ischaemia of the brain stem nuclei and cochlea, muscle necrosis causing rhabdomyolysis and renal failure and skin changes (bullae) due to prolonged unconsciousness. The degree of intoxication is correlated to some extent with carb- oxyhaemoglobin concentrations but, by the time patients arrive in hospital, they will often have received oxygen in an ambulance, which may lower carbon monoxide concentrations from those pre- sent at the scene of the injury. Very severe features are to be expected with carboxyhaemoglobin above 60%, but significant features would not generally be expected at concentrations below 30%. Neuropsychiatric problems may occur after recovery from carbon monoxide intoxication and are said to develop insidiously over several weeks. Defining limits of these changes may be difficult in patients with relatively mild exposure, and ascribing causation is particularly difficult in low-level exposures where formal studies suggest no effect. Treatment Removal from exposure and administration of 100% oxygen using a tightly fitting facemask are essential. If patients are unconscious, endotracheal intubation and mechanical ventilation is required. Prolonged administration of oxygen is necessary to ensure carbon monoxide bound in tissues is released. Traditionally, hyperbaric oxygen has been used in carbon mon- oxide poisoning, although there remains significant controversy about its efficacy. A trial in the United States of America has shown some suggestion of benefit, but commentators are divided about the relevance of the relatively small changes noted, and the wider appli- cation of these results. In part, this is because patients were brought for treatment for quite some distance, and the debate remains as to whether any potential small therapeutic benefit warrants transfer to a distant treatment facility. Cyanide Hydrogen cyanide and its derivatives are used widely in industry and are released during the thermal decomposition of polyurethane foams. Cyanide poisoning may also result from the ingestion of the cyanogenic glycoside amygdalin, which is found in the kernels of almonds, apples, apricots, cherries, peaches, plums, and other fruits. Cyanide reversibly inhibits cellular enzymes which contain ferric iron notably cytochrome oxidase a3 so that electron transfer is blocked, the tricarboxylic acid cycle is paralysed, and cellular respiration ceases. Clinical features Acute poisoning The ingestion by an adult of 50 ml of (liquid) hydrogen cyanide or 200–300 mg of one of its salts is likely to prove fatal. Inhalation of hydrogen cyanide gas may produce symptoms within seconds and death within minutes. Acute poisoning is characterized by dizziness, headache, palpitation, anxiety, a feeling of constriction in the chest, dyspnoea, pulmonary oe- dema, confusion, vertigo, ataxia, coma, and paralysis. Cardiovascular collapse, respiratory arrest, convulsions, and metabolic acidosis are seen in severe cases. Cyanosis may occur, and the classical ‘brick red’ colour of the skin is noted occasionally. There is sometimes an odour of bitter almonds on the breath, but the ability to detect this is genetically determined and some 40% of the population are unable to do so. Chronic exposure Chronic exposure results predominantly in neurological damage which can include ataxia, peripheral neuropathies, amblyopia, optic atrophy, and nerve deafness. Treatment The immediate administration of oxygen is of paramount import-

ance, as there is evidence that it prevents inhibition of cytochrome oxidase a3 and accelerates its reactivation. Treatment thereafter de- pends on the severity and type of exposure. If hydrogen cyanide has been inhaled and the patient remains conscious 10 min after ex- posure has ceased, no antidotal treatment is required. In more severe cases an antidote is invariably necessary. Methaemoglobin binds cyanide, forming cyanmethaemoglobin. Methaemoglobinaemia may be induced efficiently by the adminis- tration of intravenous sodium nitrite 300 mg over 5 min. Because the effect of sodium nitrite is relatively rapid and methaemoglobin formation slower, the benefit of sodium nitrite may also be from its vasodilator action and the consequent improved tissue perfusion. Intravenous sodium nitrite is usually given with intravenous sodium thiosulfate; they have been shown to act synergistically in experi- mental cyanide poisoning by providing sulphane sulphur to en- hance endogenous metabolism. Sodium thiosulfate is administered intravenously in a dose of 12.5 g over 10 min. Dicobalt edetate solutions contain free cobalt, which complexes six times more cyanide than dicobalt edetate. Cobalt is toxic, how- ever, and use of this formulation in the absence of cyanide poisoning may cause cobalt toxicity. Dicobalt edetate should, therefore, be given only when the diagnosis is certain. Dicobalt edetate is admin- istered intravenously in a dose of 300 mg over 1 min, with a further 300 mg being given if recovery does not occur. One mole of hydroxocobalamin inactivates one mole of cyanide, but, on a weight-for-weight basis, 50 times more hydroxocobalamin is needed than cyanide because hydroxocobalamin is a far larger molecule. If available, hydroxocobalamin 5 g is given intravenously over 30 min; a second dose (5 g) may be required in severe cases. Diethylene glycol Diethylene glycol is used as a coolant, as a building block in organic synthesis and as a solvent. It can be also found in some hydraulic fluids and brake fluids. Occupational exposure is by the dermal route, but the most common route of exposure is ingestion, often unintention- ally as a result of contamination of medicines. Diethylene glycol has been responsible for several mass poisonings in Australia, Bangladesh, Haiti, India, Nigeria, South Africa, and the United States of America. Diethylene glycol is metabolized by alcohol dehydrogenase to 2-hydroxyethoxyacetaldehyde and by aldehyde dehydrogenase to 2-hydroxyethoxyacetate and a small amount of diglycolic acid. The metabolic acidosis observed in diethylene glycol poisoning is pri- marily due to 2-hydroxyethoxyacetate, but lactate also plays a part in severe poisoning. Diglycolic acid is the metabolite responsible for the development of proximal tubular necrosis. Clinical features Nausea and vomiting, headache, abdominal pain, coma, seizures, metabolic acidosis, and acute renal failure have most commonly been reported. Renal dysfunction in those who do not develop dialysis de- pendence often improves over several months. Pancreatitis and hepa- titis have been observed, together with cranial neuropathies, such as

 facial nerve motor deficits, and demyelinating peripheral neuropathy, demonstrated clinically as bilateral lower extremity numbness. Treatment Supportive measures to correct metabolic acidosis should be in- stituted promptly. If the patient presents early after ingestion, the priority is to inhibit metabolism using either intravenous fomepizole or ethanol. Fomepizole requires less monitoring, but is more expensive than ethanol. After a loading dose of fomepizole 15 mg/kg over 30 min, four 12-hourly doses of 10 mg/kg should be given, followed by 15 mg/ kg 12-hourly until the glycol concentration is not detectable. If haemodialysis is used, the frequency of dosing should be increased to 4-hourly as fomepizole is dialysable. Alternatively, a loading dose of intravenous ethanol 50 g for an adult (50 ml of absolute ethanol in 1 L 5% dextrose, i.e. a 5% ethanol solution) should be given, followed by an intravenous infusion of ethanol, 10–12 g/h (most easily given as 1 L 5% ethanol solution over

4–5 h), to achieve a blood ethanol concentration of approxi- mately 1000 mg/litre. Administration of ethanol should be con- tinued until the glycol is undetectable in the blood. If haemodialysis/ haemodialfiltration is used, greater amounts of ethanol (17–22 g/h) must be given, because ethanol is readily dialysable. Haemodialysis/haemodialfiltration will remove diethylene glycol, but it is not known whether the metabolites are also removed. Ethylene glycol Ethylene glycol has a variety of commercial applications and is com- monly used as an antifreeze fluid in car radiators. Its sweet taste and ready availability have contributed to its popularity as a suicide agent and as a poor man's substitute for alcohol. It is thought that the minimum lethal dose of ethylene glycol is about 100 ml for an adult, although recovery after treatment has been reported following the ingestion of up to 1 L. The toxicity of ethylene glycol depends predominantly on its metabolites (Fig. 10.4.1.5) though the initial inebriation is due to ethylene glycol itself. Central nervous system symptoms coincide with the peak production of glycolaldehyde; aldehydes inhibit many aspects of cellular metabolism. Glycolate is largely responsible for the marked acidosis seen in severe cases; lactate concentrations are generally not very high. Lactate is produced as a result of the large amount of NADH formed by the oxidation of ethylene glycol and by inhibition of the tricarboxylic acid cycle by the condensation products of glyoxylate. There is increasing evidence that calcium ox- alate monohydrate crystals are the cause of renal failure and cerebral oedema. Clinical features The clinical features of ethylene glycol poisoning may be divided into three stages depending on the time after ingestion (Table 10.4.1.11). Although the three stages are useful theoretical descriptions of ethylene glycol poisoning, the onset and progression of the clinical course is frequently not as consistent or predictable. After a brief period of inebriation due to the intoxicating effect of ethylene glycol itself, metabolic acidosis develops, followed by tachyp- noea, coma, seizures, hypertension, and hypocalcaemia, together with calcium oxalate crystalluria, the appearance of pulmonary infiltrates, and oliguric renal failure. If untreated, death from multiorgan failure usually occurs 24–36 h after ingestion. Severe acidosis, hyperkalaemia, seizures, and coma carry a poor prognosis. A serum ethylene glycol concentration more than 500 mg/litre indicates severe poisoning. Treatment Supportive measures to combat cardiorespiratory depression should be employed and metabolic acidosis, hypocalcaemia, and renal failure should be treated conventionally. (For further information on treatment with fomepizole or ethanol, please see the section 'Diethylene glycol'.) If admission plasma concentrations show that the ethylene glycol in- gested has already been metabolized, fomepizole or ethanol adminis- tration will not be of benefit and ethanol might exacerbate the acidosis. Haemodialysis/haemodialfiltration removes ethylene glycol, glycolaldehyde, and glycolate (but not oxalate), and will also correct acid–base disturbances. Dialysis should be employed particularly if presentation is late and marked metabolic acidosis is present. It should be continued until the glycol and glycolate are no longer detectable in the blood. Ethylene glycol GO Ethanol Fomepizole ALDH AO ADH Glycolate Glycoaldehyde Oxalate Glyoxylate LDH or GO Fig. 10.4.1.5 Metabolism of ethylene glycol. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AO, aldehyde oxidase; GO, glycolate oxidase; LDH, lactate dehydrogenase. Table 10.4.1.11 Clinical features of ethylene glycol poisoning Stage 1 (30 min–12 h): gastrointestinal and nervous system involvement • Apparent intoxication with alcohol (but no ethanol on breath) • Nausea, vomiting, haematemesis • Coma and convulsions (often focal) • Nystagmus, ataxia, ophthalmoplegias, papilloedema, depressed reflexes, myoclonic jerks, tetanic contractions • Cranial nerve II, V, VII, VIII, IX, X, XII palsies Stage 2 (12–24 h): cardiorespiratory involvement • Tachypnoea, tachycardia • Mild hypertension • Metabolic acidosis • Myocarditis • Pulmonary oedema • Congestive cardiac failure Stage 3 (24–72 h): renal involvement • Flank pain, renal angle tenderness • Hypocalcaemia • Acute tubular necrosis • Calcium oxalate crystalluria

10.4.1 Poisoning by drugs and chemicals 1767 Formaldehyde Formaldehyde is a flammable, colourless gas with a pungent odour. It is most commonly available commercially as a 30–50% w/w aqueous solution and is an important raw material in the synthesis of organic compounds such as plastics and resins. It is added to cos- metics and foodstuffs as a preservative and antimicrobial agent and is used in embalming. Formaldehyde also occurs naturally in the environment. It is released during the combustion of organic ma- terials (e.g. in forest fires, wood-burning stoves, and waste inciner- ators), and is a product of incomplete petrol combustion in internal combustion engines. Absorption may follow ingestion, inhalation, or dermal contact. Once absorbed, formaldehyde is oxidized rapidly to formate then converted more slowly to carbon dioxide and water. Clinical features Severe irritation of the mucous membranes of the eyes, nose, and upper airways occurs after minimal exposure to low (<5 ppm) for- maldehyde concentrations, which tends to prevent higher exposure in even the most tolerant subjects. Substantial exposure may result in severe bronchospasm, pulmonary oedema, and death. Formaldehyde is a recognized cause of occupational asthma. Formaldehyde solutions splashed into the eye have caused corneal damage and skin contamination has resulted in dermatitis. Spillage of phenol-formaldehyde resin on to the skin has produced extensive necrotic skin lesions, fever, hypertension, adult respiratory distress syndrome, proteinuria, and renal impairment. Ingestion of for- maldehyde solution has resulted in severe corrosive damage to the buccal cavity and tonsils, oesophagus, and stomach with ulceration, necrosis, and subsequent fibrosis and contracture. Shock, metabolic acidosis (due in part to high formate concentrations), respiratory in- sufficiency, and renal impairment usually ensue. Death may follow ingestion of less than 100 ml in an adult. Treatment Supportive measures, including the correction of acid–base disturb- ance, should be employed. Folinic acid 50 mg (1mg/kg in children) IV 6 hourly accelerates formate metabolism. Haemodialysis is only moderately effective in increasing formate elimination. n-Hexane n-Hexane is an extremely volatile liquid that is used as a solvent. It is metabolized oxidatively to several compounds, including 2,5-hexanedione, which is eliminated through the urine and is impli- cated in the neurotoxic effect of this solvent. Clinical features When ingested n-hexane causes nausea, dizziness, central nervous system excitation, and then depression, and presents an acute as- piration hazard. Following inhalation, either inadvertently or delib- erately, similar symptoms occur. The development of a progressive sensorimotor neuropathy is the principal hazard of chronic exposure. Treatment Treatment is supportive and symptomatic. Hydrogen fluoride/hydrofluoric acid Hydrogen fluoride is a corrosive, fuming, nearly colourless liquid (hydrofluoric acid) at atmospheric pressures and temperatures below 19°C; above 19°C it is gaseous. Hydrogen fluoride is very soluble in cold water and for this reason it fumes strongly in moist air. Aqueous solutions dissolve glass. Hydrogen fluoride is particularly dangerous because of its unique ability among acids to penetrate tissue. The reason for this is the high electronegativity of fluorine, which forms a strong covalent bond with the hydrogen. The result is a weak acid that exists predomin- antly in the undissociated state. In this state, hydrogen fluoride can penetrate skin and soft tissue by nonionic diffusion. Once in the tis- sues, hydrogen fluoride dissociates and causes liquefactive necrosis of soft tissue, bony erosion, and extensive electrolyte abnormalities by binding the cations calcium and magnesium. Clinical features Hydrogen fluoride can cause severe systemic toxicity from even rela- tively small dermal exposures. Inhalation or ingestion of hydrogen fluoride causes severe corrosive damage similar to other acids (see ‘Acids’ section). Following absorption by whatever route, fluoride chelates calcium and lowers the serum ionized calcium concentra- tion and causes weakness, paraesthesiae, tetany, and convulsions. Hypotension and cardiac arrhythmias, including ventricular fibrilla- tion, may be observed. Central effects of fluoride include confusion, clouding of consciousness, and coma.

Hepatic and renal failure may develop. Skin contact with anhydrous hydrogen fluoride produces liquefactive necrosis and severe burns that are felt immediately. Concentrated aqueous solutions also cause an early sensation of pain but more dilute solutions may give no warning of injury. If the solution is not removed promptly, penetration of the skin by fluoride ion may occur, leading to painful ulcers that heal only slowly. Treatment Inhalation Following inhalation of hydrogen fluoride, the casualty should be removed immediately from the contaminated atmosphere. Further treatment is symptomatic and supportive. Mechanical ventilation with positive end-expiratory pressure may be needed to treat pul- monary oedema. Ingestion If hydrofluoric acid has been ingested, management is as for other acids (see ‘Acids’). An intravenous injection of 10 ml of 10% calcium gluconate solution should be given. Eye and skin exposure Skin contact requires immediate thorough washing of the af- fected area, for 1 min, even if there is no apparent burn or pain. Contaminated clothing should be removed, with rescuers protecting their hands with suitable gloves. Skin burns should be coated repeat- edly with 2.5% calcium gluconate gel; the gel should be massaged continuously into the skin until at least 15 min after pain is relieved. The area should then be covered with a dressing soaked in the gel and lightly bandaged. Eye contact requires immediate thorough washing with water. An urgent opthalmological opinion should be sought. Hydrogen sulphide Hydrogen sulphide is a colourless gas that smells of rotten eggs, al- though high concentrations cause olfactory nerve paralysis. The gas

 is also found in mines and sewers and is liberated from decomposing fish (a hazard in fishing boats if the hold is filled with ‘trash’ fish used for making fish meal) and liquid manure systems. The serious sequelae following exposure to high concentrations of hydrogen sulphide are due principally to inhibition of cytochrome oxidase a3, in which respect it is more potent than cyanide. Clinical features Exposure to low concentrations leads to blepharospasm, pain and redness of the eyes, blurred vision, and coloured haloes round lights. Headache, nausea, dizziness, drowsiness, sore throat, and cough may also occur. With exposure to higher concentrations, cyanosis, con- fusion, pulmonary oedema, coma, and convulsions are common. Death ensues in some 6% of cases. Treatment The casualty should be moved to fresh air from the contaminated atmosphere by a rescuer who has donned breathing apparatus be- forehand. Thereafter the treatment is symptomatic and supportive. Irritant gases (ammonia, chlorine, sulphur dioxide) Ammonia, chlorine, and sulphur dioxide are water soluble (forming ammonia water, hypochlorite and hydrochloric acid, and sulphurous acid, respectively) and, therefore, dissolve easily in the mucus of the upper airways. These compounds react with elements of the cell walls, resulting in release of mediators causing an inflammatory cascade that alters vascular permeability and acts as chemotactic factors. The altered vascular permeability may lead to influx of plasma that can decrease airway calibre, and consequently increase airway resistance. Clinical features Inhalation Following exposure to these gases, the clinical symptoms appear immediately and consist of lacrimation, nasal discharge, broncho- spasm, increased mucus production, and cyanosis. In more severe cases bronchospasm, bronchial oedema, glottal oedema, and in- creased mucus production may be present. Although pulmonary oedema is observed, it is never the sole presenting feature. Patients with chronic bronchitis or asthma are usually more susceptible. Eye and skin exposure Exposure of the skin and eyes to concentrated ammonia water (li- quid ammonia) may cause corrosive damage; evaporation of ammonia may cause extreme cooling when spilled on the skin or eyes; cold burns may result. Ingestion Ingestion of ammonia water induces severe caustic lesions of the mucous membranes of the oropharynx, oesophagus, and stomach. Oesophageal or gastric perforation may occur, causing

mediastinitis or peritonitis, respectively. Treatment Inhalation The priority is to remove the casualty from exposure. Early inspec- tion of the upper airways is important because the mucosal mem- branes may be very oedematous in severe cases, precluding oral endotracheal intubation; tracheostomy or coniotomy (emergency airway puncture) may be necessary. Pulmonary complications should be treated with humidified supplemental oxygen, broncho- dilators and, if necessary, assisted ventilation with positive end- expiratory pressure. Early administration of corticosteroids for a few hours may be beneficial, though later administration offers no benefit. Prophylactic antibiotics have not been shown to be of value. Eye and skin exposure If there is no mucosal irritation of the eyes or nose, it can be con- cluded that the exposure was not severe and that the individual is not at risk of delayed pulmonary oedema, and there is no need to admit such patients to hospital for observation. If the eyes are affected, they should be irrigated with water or saline 0.9% for 15–30 min and an ophthalmic opinion sought. Eye irrigation is facilitated by the use of a topical anaesthetic. If exposed, the skin should be irrigated with water. Ingestion Neutralizing agents should not be administered after ingestion of ammonia water because the resultant exothermic reaction may worsen the injury. Induction of vomiting and gastric lavage are contraindicated. Urgent endoscopy and CT should be performed to identify the damage and to insert a nasogatric tube under direct observation. If endoscopy is delayed in severe cases, the mucous membranes become very swollen, increasing the risk of perforation. Healing of oesophageal lesions is often accompanied by strictures. Systemic corticosteroids do not improve the outcome in patients with severe oesophageal lesions. Isopropanol Isopropanol is used as a sterilizing agent and as ‘rubbing alcohol’. It is also found in aftershave lotions, disinfectants, and window-cleaning solutions. Intoxication can result from both ingestion and skin ab- sorption. The accidental use of an isopropanol-containing enema has resulted in death. Isopropanol is oxidized in the liver to acetone. Clinical features The major features of severe poisoning are due to central nervous system and respiratory depression, shock, and circulatory collapse. The most common metabolic effects are an increased osmolal gap, ketonaemia, and ketonuria. There may also be the odour of acetone on the breath, gastritis, haematemesis, hypothermia, renal tubular necrosis, acute myopathy, and haemolytic anaemia. Treatment In addition to supportive measures, haemodialysis/haemodialfiltra tion should be employed in severely poisoned patients as it removes isopropanol and acetone. No advantage is gained by administering ethanol or fomepizole to block alcohol dehydrogenase, because the toxicity of isopropanol is caused principally by the parent com- pound and not by acetone. Moreover, such treatment will enhance the toxicity of isopropanol. Methanol Methanol is used widely as a solvent. It is also found in antifreeze solutions, paints, duplicating fluids, paint removers and varnishes, and shoe polishes. The ingestion of as little as 10 ml of pure methanol has caused permanent blindness and 30 ml is potentially fatal, al- though individual susceptibility varies widely. Toxicity may also occur as a result of inhalation or percutaneous absorption.

10.4.1 Poisoning by drugs and chemicals 1769 Methanol is metabolized by alcohol dehydrogenase and catalase enzyme systems to formaldehyde and formate (Fig. 10.4.1.6). The concentration of formate increases greatly and is accompanied by ac- cumulation of hydrogen ions, causing metabolic acidosis. Clinical features Ingested alone, methanol causes mild and transient inebriation and drowsiness. After a latent period of 8–36 h, nausea, vomiting, ab- dominal pain, headaches, dizziness, and coma supervene. Blurred vision and diminished visual acuity may occur and the presence of dilated pupils, unreactive to light, suggests that permanent blindness is likely to ensue. A severe metabolic acidosis may develop, and this may be accompanied by hyperglycaemia and

raised serum amylase activity. A blood methanol concentration of more than 500 mg/litre confirms serious poisoning. Mortality increases with the severity and duration of the metabolic acidosis. Survivors may show permanent neurological sequelae including blindness, rigidity, hypokinesis, and other parkinsonian-like signs; these features follow the development of optic neuropathy and necrosis of the putamen. Treatment The treatment of methanol poisoning is directed towards the inhib- ition of methanol metabolism by the administration of fomepizole or ethanol (see the section ‘Diethylene glycol’), the correction of metabolic acidosis and the removal of circulating methanol and its toxic metabol- ites by haemodialysis or haemodialfiltration. Substantial quantities of bicarbonate may be required and since this must be accompanied by sodium, hypernatraemia, and hypervolaemia may result. If admission plasma concentrations show that the methanol in- gested has already been metabolized, fomepizole, or ethanol ad- ministration will not be of benefit and ethanol might exacerbate the acidosis. Dialysis is indicated when a patient has ingested more than 30 g of methanol, or develops metabolic acidosis, mental, visual, or fundoscopic abnormalities attributable to methanol, or a blood methanol concentration in excess of 500 mg/litre. Folinic acid 50 mg (1 mg/kg in children) intravenously 6-hourly may protect against ocular toxicity by accelerating formate metabolism. Methylene chloride (dichloromethane) Methylene chloride is a common ingredient in paint removers and is used as a solvent for plastic films and cements and also as a degreaser and aerosol propellant. Exposures usually follow inhalation, though deliberate ingestion is recognized. Methylene chloride is metabol- ized to CO_2 and carbon monoxide. Carboxyhaemoglobin concen- trations of 3–10% (exceptionally 40%) are attained. Clinical features Skin contact with liquid methylene chloride can cause a chemical burn. Following inhalation, dizziness, tingling and numbness of the extremities, throbbing headache, nausea, irritability, fatigue, and stupor have been reported. Severe and prolonged exposure may lead to irritant conjunctivitis, lacrimation, and respiratory depression. Hepatorenal dysfunction and pulmonary oedema have also been described. Fatalities have occurred. If high concentrations of carboxyhaemoglobin are present, the features of acute carbon monoxide poisoning may also ensue, al- though these tend to be mild even in the presence of such high concentrations. Methylene chloride ingestion causes corrosive injury to the gastrointestinal tract, agitation, diaphoresis, and drowsiness with rapid progression to coma in severe cases. Consciousness is typically regained after several hours unless hypoxic encephalopathy ensues. Pancreatitis, hepatic dysfunction, and renal and respiratory failure are potential complications. Carboxyhaemoglobin concentrations may remain raised for days. Treatment Prompt removal from exposure prior to death usually results in complete recovery. Thereafter, treatment is supportive and should include the use of supplemental oxygen. Nitrites Volatile alkyl nitrites, for example, amyl and butyl (predominantly isobutyl) nitrite, are recreational drugs marketed as aphrodisiacs or ‘room odourizers’. They are alleged to improve sexual performance by enhancing and prolonging orgasm and/or as a smooth muscle re- laxant to relax the anal sphincter. They also are claimed to promote a sense of increased well-being with temporary detachment from reality. The intended route of exposure is inhalation, but they are oc- casionally also ingested, either accidentally or deliberately. Alkyl nitrites cause vasodilatation via nitric oxide mediated vas- cular smooth muscle relaxation. Vasodilatation accounts for many of the effects observed or described by users following abuse. More important toxicologically is the ability of these agents to oxidize fer- rous haem from the Fe^{2+} to the ferric (Fe^{3+}) state, resulting in meth- aemoglobinaemia after substantial inhalation or ingestion. Clinical features These reflect vasodilation with headache, flushing, blurred vision, postural hypotension, and syncope, followed by reflex vasoconstric- tion with sinus tachycardia. With continued exposure, methaemo- globinaemia results. Irritant effects including burning in the

nose and eyes; cough and facial dermatitis are recognized; and transient ECG changes (T wave inversion and ST segment depression) have been reported. Methaemoglobin concentrations less than 20% are usually asymptomatic though they cause slate-grey ‘cyanosis’ due predomin- antly to the presence of pigmented methaemoglobin. When 20–40% total haemoglobin is replaced by methaemoglobin, there may be diz- ziness and headache, features not dissimilar to those caused by vaso- dilatation. Higher methaemoglobin concentrations reflect increasing tissue hypoxia and are unusual following volatile nitrite abuse, unless inhalation is substantial or ingestion has occurred. However, in these circumstances, life-threatening methaemoglobinaemia may result. Treatment The vasodilatory effects of volatile nitrite abuse are not usually se- vere and can be managed supportively. In healthy adults, meth- aemoglobin concentrations less than 30% total haemoglobin are unlikely to warrant specific treatment. At higher methaemoglobin Methanol Formaldehyde Ethanol Fomepizole Formate CO_2 + H_2O 10-FTS FDH ADH Fig. 10.4.1.6 Metabolism of methanol. ADH, alcohol dehydrogenase; FDH, formaldehyde dehydrogenase; 10-FTS, 10-formyltetrahydrofolate synthetase.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1770 concentrations, or where clinical features suggest tissue hypoxia, antidotal therapy with intravenous methylthioninium chloride (methylene blue) 1–2 mg/kg body weight as a 1% solution should be given over 5–10 min. Treatment is effective within 30 min and a second dose is required rarely. Nitrogen dioxide Nitrogen dioxide is the most toxic nitrogen oxide and causes hyp- oxic asphyxia by displacing oxygen. It dissolves poorly in water and therefore penetrates deeper into the lung (i.e. to the alveoli and ter- minal bronchioles). The ciliated cells of the bronchioles and the al- veolar type I cells are especially susceptible to injury. Following the alveolar damage, an influx of plasma and inflammatory cells occurs, causing acute lung injury. Clinical features The clinical features following acute exposure depend on the con- centration and duration of exposure to the gas. Modest acute ex- posure (<50 ppm) for a short time often produces no immediate symptoms, although throat irritation, cough, transient choking, tightness in the chest, and sweating have been observed. By contrast, exposure to a massive concentration of nitrogen dioxide, such as that found in a silo, can produce severe and immediate hypoxaemia, which may be fatal. As symptoms can be absent during the first hours after exposure, physical examination of the patient immediately after exposure may not provide information regarding the full extent of the clinical se- verity of the intoxication. However, if 6 h after exposure, the patient has normal arterial blood gases and chest X-ray, there is little like- lihood that life-threatening lung damage will develop. Patients can then be discharged with instructions that they must undergo med- ical observation again if increased dyspnoea occurs after discharge. Bronchiolitis obliterans may develop within 2–6 weeks. Treatment Adequate supportive therapy such as supplemental oxygen and bronchodilators should be given. Early administration of cortico- steroids for a few hours may be beneficial, though later adminis- tration offers no benefit. Use of prophylactic systemic antibiotics is not recommended because of the increased risk of infection with resistant organisms. When intubation is required, the largest prac- ticable tube should be introduced to allow adequate bronchial toilet. Assisted ventilation with positive end-expiratory pressure offers the best hope of reducing the mortality. Paraffin oil (kerosene) Paraffin oil has three physical properties accounting for its tox- icity. Its low viscosity and surface tension allow it to spread rapidly throughout the lungs when aspirated after ingestion, and its low va- pour pressure makes it unlikely to cause poisoning by inhalation. Clinical features Repeated local application to the skin results in dryness, dermatitis, and, rarely, epidermal necrolysis. Paraffin ingestion causes a burning sensation in the mouth and throat, vomiting,

diarrhoea, and ab- dominal pain. Pulmonary features may occur within 1 h of ingestion with cough, tachypnoea, tachycardia, basal crackles, and cyan- osis. Nonsegmental consolidation or collapse is seen radiologic- ally. Pneumatocoele formation, pneumothorax, pleural effusion, or pulmonary oedema may occur. Other complications include hepatic dysfunction and, in severe cases, atrial fibrillation and ventricular fibrillation. Treatment Gastric lavage and emesis should be avoided because of the increased risk of chemical pneumonitis. There is no evidence that corticoster- oids and antibiotics reduce morbidity or mortality; mechanical ven- tilation with positive end-expiratory pressure may be necessary in severe cases of aspiration. Petrol (gasoline) Petrol is a complex mixture of volatile hydrocarbons containing a small proportion of nonhydrocarbon additives. Clinical features Following the inhalation of petrol, dizziness, and irritation of the eyes, nose and throat may occur within 5 min followed by euphoria, headache, and blurred vision. If inhalation continues, or if significant quantities of petrol are ingested, then excitement and depression of the nervous system occurs; incoordination, restlessness, excitement, confusion, disorientation, hallucinations, ataxia, nystagmus, tremor, delirium, coma, and convulsions may be seen. Inhalation of high concentrations of petrol may cause immediate death, probably from ventricular fibrillation or respiratory failure. Chemical pneumonitis may occur as in paraffin oil ingestion (see ‘Paraffin oil (kerosene)’) and the clinical features and management are then identical. Treatment Following removal from exposure, supportive measures provide the basis of treatment. Phenol Phenol (‘carbolic acid’) is nearly always recognizable by its odour and, distinctively, the pain to which it gives rise is much less than might be expected. This is due to its ability to damage afferent nerve endings. Clinical features If phenol is spilt on the skin, pain is followed promptly by numb- ness. The skin becomes blanched, and a dry opaque eschar forms over the burn. When the eschar sloughs off, a brown stain remains. Phenol penetrates intact skin rapidly and is well absorbed through the lungs. After ingestion, nausea, vomiting, and abdominal pain result. Depending on the concentration of the solution corrosive injury may result in bleeding, perforation, and subsequent stricture formation. Systemic toxicity may follow exposure by any route. Signs of sys- temic toxicity include sweating, headache, tinnitus, and dizziness. An initial rise in blood pressure is followed by hypotension precipi- tated by phenol-induced loss of vasoconstrictor tone. Loss of con- sciousness, respiratory depression, coma, seizures, and shock follow, which may result in renal failure. An initial phase of central nervous system stimulation, and rarely convulsions, has sometimes been ob- served in children. Phenol poisoning is associated with grey or black urine and though this is due in part to metabolites of phenol, Heinz body haemolytic anaemia, as well as methaemoglobinaemia and hyperbilirubinaemia, contribute.

 Treatment Fluid resuscitation and prompt assessment of the extent of corro- sive damage is crucial following ingestion. Management is otherwise supportive. Skin and eye contamination, renal failure and meth- aemoglobinaemia are managed conventionally. Phosgene Phosgene is used in the synthesis of isocyanates, polyurethane and polycarbonate resins, and dyes. It is also produced in fires and has been used as a chemical weapon. When combined with water, phosgene produces hydrogen chloride and carbon dioxide, although as the gas is poorly soluble in water, only small amounts of hydrochloric acid are produced under normal physiological conditions. It is thought that this is only relevant in causing mucus membrane and eye symptoms when phosgene is present at relatively high concentrations. Biologically, acylation and free radical-mediated reactions occur between phos- gene and important cellular constituents. Acylation reactions involving phosgene occur with biological molecules containing sulfhydryl, amino and hydroxyl moieties. Clinical features Exposure to

phosgene causes irritation of the eyes, dryness or burning sensation in the throat, cough, chest pain, and nausea and vomiting. There is usually a latent period lasting between 30 min and 24 h (rarely, 72 h) during which the casualty suffers little discomfort and has no abnormal chest signs. Subsequently, pulmonary oedema develops due to increased capillary permeability; circulatory collapse may follow. Treatment Treatment is supportive. There are experimental data to sug- gest that an intravenous bolus of high-dose corticosteroid (e.g. methylprednisolone 1 g) < 6h after exposure may be of benefit. There is no benefit from nebulized steroid even when administered 1 h after exposure. Consideration should also be given to administra- tion of nebulized acetylcysteine 1–2 g, though there is no substantive evidence of benefit outside a small animal, isolated lung model. If the oxygen saturation falls below 94%, patients should receive the lowest concentration of supplemental oxygen to maintain their SaO2 in the normal range. Once patients require oxygen, nebulized β-agonists (e.g. salbutamol (albuterol) 5 mg by nebulizer every 4 h) may reduce lung inflammation if administered within 1 h of exposure. Elective intubation should be considered early using an ARDSNet protective ventilation strategy. Propylene glycol Propylene glycol is used widely as a preservative and solvent for oral, intravenous, and topical medications. It is oxidized to lactic acid and pyruvate via hepatic alcohol and aldehyde dehydrogenases in a similar way to the metabolism of other glycols such as ethylene glycol. Clinical features The ingestion of substantial quantities of propylene glycol or its ad- ministration to neonates, those in renal failure, or in exceptionally large doses (such as patients requiring massive parenteral doses of propylene glycol-containing benzodiazepines in the management of acute alcohol withdrawal) may cause convulsions, coma, cardiac arrhythmias, hepatorenal damage, intravascular haemolysis, metabolic acidosis, and increased serum osmolality. Treatment Metabolic acidosis, renal failure, and respiratory depression should be treated conventionally. Haemodialysis removes propylene glycol efficiently. Ethanol or fomepizole may be used to inhibit propylene glycol metabolism in a similar way to their use in ethylene glycol poisoning, but in practice the diagnosis is often not made until a sig- nificant acidosis is present and thus it is too late for antidotal treat- ment to be useful. Tetrachloroethylene Tetrachloroethylene is used widely as an industrial solvent, par- ticularly for dry-cleaning and degreasing. Poisoning may occur by inhalation or ingestion. A considerable proportion of an inspired dose is exhaled unchanged, and that retained is excreted only slowly (half-life c.144 h), mainly by metabolism to trichloroacetic acid, the major urine metabolite. Clinical features Following inhalation or ingestion, there is depression of the central nervous system; nausea and vomiting may occur and persist for sev- eral hours. Irritation of the eyes, nose, and throat may occur from direct exposure. Hepatic and renal dysfunction may also develop and ventricular arrhythmias and noncardiogenic pulmonary oe- dema have been reported. Treatment After removal from exposure, treatment is supportive and symptomatic. Toluene Toluene has much lower volatility and toxicity than benzene. It is used extensively as a solvent in the chemical, rubber, paint, glue, and pharmaceutical industries and as a thinner for inks, perfumes, and dyes. Following inhalation or ingestion, toluene is oxidized to ben- zoic acid, then to hippuric acid benzoylglucuronates, which are ex- creted in the urine. Clinical features Acute poisoning results in euphoria, excitement, dizziness, confu- sion, increased lacrimation, headache, nervousness, nausea, tin- nitus, ataxia, tremor, and coma. A review of adults who had abused toluene indicated three major patterns of presentation: (1) muscle weakness, (2) gastrointestinal complaints (abdominal pain, haematemesis), and (3) neuropsychi- atric disorders (altered mental status, cerebellar abnormalities, per- ipheral neuropathy). In addition, hypokalaemia, hypophosphataemia and hyperchloraemia were common. Rhabdomyolysis occurred in 40% of cases. Distal renal tubular acidosis and urinary calculi were also reported. Cardiac and haematological toxicity due to toluene

appears to be uncommon. Treatment If poisoning results from inhalation, whether accidental or intentional, the patient should be removed from the contaminated

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1772 environment. Thereafter, treatment consists of symptomatic and supportive measures. 1,1,1-Trichloroethane 1,1,1-Trichloroethane is a liquid of high volatility used as a solvent in industry. Most of an inhaled dose is expired unchanged, though small amounts of trichloroacetic acid and trichloroethanol are formed. Concomitant ingestion of ethanol is known to enhance toxicity. Clinical features Following inhalation of a sufficiently large dose, central nervous system depression occurs; hepatic and renal dysfunction may also result. Deaths have followed exposure to very high concentrations in unventilated tanks. In such cases, death may either be due to cen- tral nervous system depression, culminating in respiratory arrest, or to fatal arrhythmias as a result of myocardial sensitization to circu- lating catecholamines in the presence of hypoxia. Treatment The casualty should be removed from the contaminated environ- ment. Thereafter treatment is symptomatic and supportive. Trichloroethylene Trichloroethylene is a volatile liquid used as an industrial solvent, particularly in metal degreasing and extraction processes. Following exposure, it is excreted unchanged in the breath and metabolized via chloral hydrate to trichloroethanol and trichloroacetic acid, which are excreted in the urine. Clinical features Following exposure by any route, central nervous system depres- sion occurs with nausea and vomiting, hepatic and renal dysfunc- tion, cranial nerve damage, cerebellar dysfunction, and convulsions have been described. ‘Degreaser’s flush’ (in which the skin of the face and arms becomes markedly reddened) may occur if ethanol is consumed shortly before or after exposure to trichloroethylene. Treatment The casualty should be removed from the contaminated environ- ment. Thereafter treatment is symptomatic and supportive. Household products Automatic dishwashing tablets The traditional tablets for automatic dishwashing machines are contained within an external wrapper that requires removal prior to loading the enclosed tablet into the machine. Soluble film auto- matic dishwashing tablets are enclosed by a water-soluble poly- vinyl alcohol film and are loaded straight into the dishwashing machine, unlike their traditional counterparts. However, the in- tegrity of the soluble film can be compromised and the contents of the tablet can be released prematurely when in contact with moist hands or saliva. The tablets most commonly contain a source of hydrogen per- oxide (often as sodium percarbonate) and nonionic surfactants. Other constituents in some formulations include sodium carbonate, sodium tripolyphosphate, and sodium silicate, which reduce water hardness. The pH once dissolved in water is alkaline. Clinical features Toxicity from hydrogen peroxide occurs as a result of its corro- sive effects and release of oxygen causing embolism. Ingestion may cause irritation of the gastrointestinal tract with nausea, vomiting, foaming at the mouth, paraesthesia around the mouth, blistering in the mouth, stomatitis, mouth bleeding, laryngitis, pharyngitis, and haematemesis. The foam may then obstruct the respiratory tract re- sulting in stridor or pulmonary aspiration. Sodium carbonate in- gestion has led to stridor, drooling, coughing, and oedematous lips. Treatment If several tablets have been ingested, upper gastrointestinal endoscopy and CT oesophagus should be considered. Batteries Batteries are usually swallowed accidentally. They contain metal salts, usually of nickel, lithium, cadmium, manganese, zinc, or silver. Code numbers on button batteries will help identify the content. While most batteries are passed without complications, problems may arise if the battery becomes lodged, particularly in the oe- sophagus, where local necrosis, bleeding, and perforation are po- tential complications. Fatalities have occurred in young children following button battery ingestion, although toxicity from metal content is a potential risk, in reality this is vanishingly rare. Clinical features These relate to

whether or not the battery lodges or leaks. Symptoms are uncommon. Lodged batteries may perforate within 2–4 h, and delayed bleeding is a further hazard after battery removal. Treatment A chest X-ray is necessary in those who have swallowed a battery, and those lodged in the oesophagus must be removed as soon as possible. Further X-rays 48 h later may be needed if batteries have not passed per anus. If symptoms develop, particularly of GI bleeding or obstruction, urgent surgical intervention is required, if possible by endoscopy. Bleaches Most household bleaches contain sodium hypochlorite, but some chlorine–free bleaches contain 6% hydrogen peroxide. Chlorine is not released from bleach solutions in appreciable amounts under normal use conditions. However, the mixing of hypochlorite with acids (e.g. when cleaning the toilet bowl) can result in the substantial release of chlorine and lung injury. Mixing bleach with ammonia produces chloramine compounds (mainly monochloramine) which can produce severe chemical pneumonitis. Clinical features Following the ingestion of weak concentrations of sodium hypo- chlorite (<5%), symptoms are usually mild. With stronger bleaches, particularly of over 10% sodium hypochlorite, features are more se- vere. Small amounts cause a sensation of burning. Larger doses cause nausea, retching, vomiting, diarrhoea and, rarely, haematemesis. In

10.4.1 Poisoning by drugs and chemicals 1773 severe cases a hypernatraemic hyperchloraemic acidosis, hypoten- sion, coma, convulsions, and cardiorespiratory arrest can occur. The gastrointestinal mucosa may become haemorrhagic, ulcerated, and perforated. For the features of hydrogen peroxide, please see the earlier section ‘Automatic dishwashing tablets’. Treatment If concentrated bleach (>10% sodium hypochlorite) or hydrogen peroxide-containing bleaches are ingested, upper gastrointes- tinal endoscopy and CT should be considered. Detergents Liquid laundry detergent capsules (also called single-use detergent sacs; laundry pods) are a pouch of concentrated liquid laundry de- tergent in a water-soluble polyvinyl alcohol membrane that can be placed directly in washing machines. In Europe, these liquid detergents most commonly contain anionic surfactants (20–35% per capsule), nonionic surfactants (10–20%), propylene glycol (8–20%) and ethanol (2–5%), and have a pH of 7–9. The capsules are designed to release their contents when they come into contact with water and this can happen prematurely if they come into con- tact with moisture (e.g. in the hands or mouth). Clinical features As a result, there have been a substantial number of exposures to laundry liquid detergent capsules, predominantly involving children less than 5 years of age. Although most patients remain asymptom- atic or suffer only minor features, a small proportion develop fea- tures such as central nervous system depression, stridor, pulmonary aspiration and/or airway burns following ingestion and conjunctiv- itis leading to corneal ulceration from eye exposure. Treatment Treatment is symptomatic and supportive. Disinfectants Disinfectants are antimicrobial agents that contain chlorophenol or chloroxylenols (dichlorometaxylenol and parachlorometaxylenol), quarternary ammonium compounds (such as benzalkonium chloride, cetyl trimethylammonium bromide, cetylpyridinium chloride, and benzethonium chloride). Sodium hypochlorite and hydrogen peroxide (see bleaches) are also effective disinfectants because they release chlorine and oxygen, respectively, which oxi- dizes the cell membrane of microorganisms. Clinical features Chloroxylenols and chlorophenol cause a burning sensation in the mouth and throat, vomiting, coma, hypothermia, hypotension, and respiratory depression. Metabolic acidosis and bradycardia can occur and aspiration pneumonia and pulmonary oedema have been reported; ingestion of a large quantity can cause renal impairment. Concentrated solutions of quarternary ammonium compounds can cause immediate burning pain in the mouth, throat, and ab- domen, hypersalivation, and ulceration of mucous membranes, followed by vomiting, haematemesis, diarrhoea, and confusion. In severe cases there

can be hypotension, shock, convulsions, respira- tory paralysis, and coma. Metabolic acidosis and increased liver enzyme activities can occur. Dermal burns have been reported and eye exposures can cause corneal damage. Treatment Treatment is symptomatic and supportive. FURTHER READING Epidemiology Bateman DN, et al. (2006). Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol, 62, 573–81. Dart RC, et al. (2015). Poisoning in the United States: 2012 emergency medicine report of the national poisons data system. Ann Emerg Med, 65, 416e22. Martins SS, et al. (2015). Worldwide prevalence and trends in unin- tentional drug overdose: a systematic review of the literature. Am J Public Health, 105, e29e49. McCarthy M (2015). Drug overdose has become leading cause of death from injury in US. Br Med J, 350, h3328. Morrison EE, Dear JW, Sandilands EA (2015). Self-poisoning in the elderly: a 10-year observational study. Clin Toxicol, 53, 284e5. Immediate treatment Barceloux D, et al. (2004). Position paper: cathartics. Clin Toxicol, 42, 243–53. Benson B E, et al. (2013). Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol, 51, 140–6. Chyka PA, et al. (2005). Position paper: single-dose activated charcoal. Clin Toxicol, 43, 61–87. Höjer J, et al. (2013). Position paper update: ipecac syrup for gastro- intestinal decontamination. Clin Toxicol, 51, 134–39. Thanacoody R, et al. (2015). Position paper update: whole bowel ir- rigation for gastrointestinal decontamination of overdose patients. Clin Toxicol, 53, 5–12. Methods to increase poison elimination Eddleston M, et al. (2008). Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. Lancet, 371, 579–87. Kay TD, Playford HR, Johnson DW (2003). Hemodialysis versus con- tinuous veno–venous hemodiafiltration in the management of se- vere valproate overdose. Clin Nephrol, 59, 56–8. Proudfoot AT, Krenzelok EP, Vale JA (2004). Position paper on urine alkalinization. Clin Toxicol, 42, 1–26. Vale JA, et al. (1999). Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poi- soning. Clin Toxicol, 37, 731–51. Drugs Angiotensin-converting enzyme (ACE) inhibitors Prasa D, et al. (2013). Angiotensin II antagonists—an assessment of their acute toxicity. Clin Toxicol, 51, 429–34. Antibacterial agents Dharnidharka VR, et al. (1998). Ciprofloxacin overdose: acute renal failure with prominent apoptotic changes. Am J Kidney Dis, 31, 710–12. Holdiness MR (1989). A review of the red man syndrome and rifam- picin overdose. Med Toxicol Adverse Drug Exp, 4, 444–51. Jones DP, et al. (1993). Acute renal failure following amoxycillin over- dose. Clin Pediatr, 32, 735–9.

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