chapter 12:

TOXICOLOGY

OBJECTIVES

After studying this chapter you should be able to:

- define the terms drug, xenobiotic, poison, toxin and toxicology;
- outline the absorption, distribution and excretion of drugs;
- explain the roles of the liver and kidneys in detoxification;
- outline the types and clinical effects of some common poisons;
- describe the general methods for treating and managing poisoning.

12.1 INTRODUCTION

The human body must be prepared for a daily onslaught of thousands of chemicals. Some will be food materials (*Chapter 10*) that are absorbed and metabolized because cells have membrane channels and enzymes to recognize and deal with these compounds. Other compounds may or may not enter the cells of the body. If they do, then the body can recognize such compounds and must deal with them appropriately to prevent deleterious effects. It is not always successful in this aim and many xenobiotics cause diseases and may be fatal if a threshold dose is exceeded.

Toxicology is the study of the adverse effects of chemicals on organisms, that is the study of poisons, where a poison can be defined as any substance that causes injury, illness or death. Toxicology covers the study of the adverse effects of chemicals including drugs, chemicals acquired from the environment and toxins, which are defined here as harmful substances produced by other organisms, often derived from microorganisms, for example the bacterial toxins described in *Chapter 2*.

Xenobiotics, literally meaning 'stranger to life', are substances that do not originate in the body but are pharmacologically, endocrinologically or toxicologically active. Thus, they might be drugs or synthetic chemicals or a substance produced in one organism and introduced into another where they

Margin Note 12.1 A lethal bacterial toxin

The bacterium *Clostridium botulinum* is an organism that can cause a fatal type of food poisoning. The organism produces several toxins when growing on food in anaerobic conditions. In addition, its spores are resistant to heat, hence food that has not been adequately sterilized and then stored in an anaerobic environment, such as bottled or canned foods, can give rise to food poisoning. These toxins inhibit the release of acetylcholine at neuromuscular junctions, leading to a flaccid paralysis in tissues served by susceptible neuromuscular and peripheral nerves (*Chapter 2*). The lethal dose of botulinum toxin for humans is not known with certainty but estimates from studies with other primates suggest that approximately 0.1 μg given intravenously or intramuscularly and about 1μg if inhaled would kill a 70 kg human.

Surprisingly, given their extreme toxicity, toxins from *Clostridium botulinum* are used cosmetically and therapeutically. Injections of 'Botox', the A toxin, into the skin of the face is used to relax the face muscles reducing the wrinkled appearance of aging (*Chapter 18*). The injections must be repeated every few months, as the effect is temporary. Botulinum toxin is also used in clinical practice to control conditions associated with inappropriate secretions of acetylcholine, for example the muscular spasms associated with the neurological disorder, dystonia.

would not normally occur. An example would be a compound produced by a plant and ingested as food. Equally, it might be a compound that has been completely synthesized chemically and have harmful effects, for example a poison or a carcinogen, or it could be beneficial, such as a medicinal drug.

Drugs are xenobiotics that are used to achieve certain effects. For example, paracetamol alleviates headaches and aspirin controls inflammatory responses. Alternatively, a drug may also be a compound with pharmacological activity used for 'recreational' purposes or taken by an addict. The body has to deal with these drugs and eventually get rid of them. An overdose may exceed the body's capacity to detoxify these compounds, with potentially disastrous effects. However, if the body inactivates the drug too quickly, then its effects will be short-lived. These are all considerations that pharmaceutical companies need to address when developing a new drug.

12.2 DRUG ACTION, METABOLISM, DISTRIBUTION AND EXCRETION

Drugs are xenobiotics and may be defined as any substance, other than food, that affects a living process. **Pharmacology** is the study of the effects of drugs in the prevention, diagnosis, and treatment or cure of disease. Such drugs are often referred to as medicines, which distinguishes them from other drugs that are used for pleasure, such as some narcotics. Pharmacotherapeutics is that branch of pharmacology concerned with the administration of drugs for prevention and treatment of disease.

Drugs can be classified according to their chemical structure but, more often, in terms of their pharmacological effects. For example, they can be divided into three groups: chemotherapeutic drugs, for example the antibiotics described in *Chapter 3*, which are used to treat infectious diseases; pharmacodynamic drugs, such as sedatives that are used in the treatment of noninfectious diseases; and a number of miscellaneous agents including narcotics and analgesics.

Any single drug may have a chemical, brand and a generic name. The chemical name is given according to the rules of chemical nomenclature, whereas the brand name is given by the manufacturer. The generic name is a common, established name given to a drug irrespective of that of its manufacturer.

Most drugs act on cells to alter a biological function. This pharmacological effect occurs as a consequence of the drug reacting with a receptor that controls a particular function, or because the drug alters a physiological mechanism which affects that function. For many drugs, the extent and duration of the pharmacological effect are proportional to the concentration of the drug at the receptor. The site at which the drug acts to produce a pharmacological effect is called its site of action. The mechanism of action of the drug is the biochemical or physiological process occurring at the site of action to produce the pharmacological effect. Drug receptors include enzymes and structural or transport proteins. However, some receptors are nonprotein that bind to the drug to form a complex which alters the permeability of the membranes or the transcription of DNA. Some drugs have a structure similar to endogenous molecules and compete with them for binding sites. Drugs may also act by preventing the formation, release, uptake or transport of key substances in the body or by forming complexes with molecules that can then activate receptors.

The binding of a drug to its receptor usually depends on relatively weak forces, such as van der Waals forces and hydrogen and ionic bonds and thus the formation of the drug–receptor complex that elicits the response is normally freely reversible. Hence the response to any drug is not permanent.

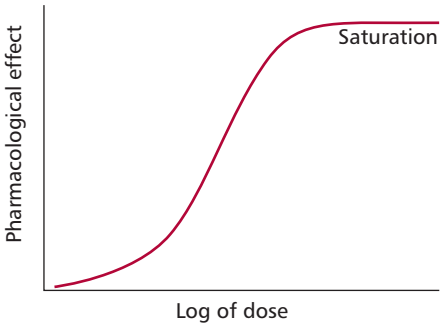


Figure 12.1 A dose–response curve for a typical drug. Saturation occurs when all the receptors are occupied by the drug.

However, the response is dose dependent and, indeed, a dose–response relationship exists between the concentration of drug in the serum and the pharmacological effect. This response eventually reaches a maximum effect because the receptor becomes saturated with the drug (*Figure 12.1*). The therapeutic range is the concentrations of drug in the serum that is appropriate for therapy. The dosage of any drug is planned to give a serum concentration within its therapeutic range. Therapeutic drug monitoring is often necessary to determine which given doses of a drug result in serum concentrations within the therapeutic range. The serum concentration of the drug must not fall below its minimum effective concentration (MEC) otherwise it will be ineffective. However, neither should it rise above its minimum toxic concentration (MTC) because of the danger of metabolic or structural damage. The time required for the concentration of a drug in the blood to decline to half its original value is referred to as its half-life ($t_{1/2}$).

It is essential that a number of properties relating to a medicinal drug, for example its pharmacodynamics and pharmacokinetics, are first ascertained. Pharmacodynamics describes how the drug interacts with its target site and the biochemical and physiological processes that result in any therapeutic or toxic effects. Pharmacokinetics relates to the uptake, distribution, metabolism and excretion from the body.

Most drugs are given orally for convenience, although they can be administered intravenously, intramuscularly or subcutaneously. When given orally, the absorption of the drug depends on its ability to disassociate from its dosing form, dissolve in gastrointestinal fluids and diffuse across the gut wall into the blood. The rate and extent of drug absorption varies with the nature of the drug, the matrix in which it is dissolved and the region of the gastrointestinal tract (GIT) where it is absorbed. The proportion of the drug absorbed into the circulation is referred to as its bioavailability. For an orally delivered drug, this should generally be greater than 70% to be of therapeutic use. However, when the site of action is the GIT lumen itself, for example treating a GIT infection, then a low bioavailability would be advantageous.

A number of drugs undergo what is referred to as first pass metabolism. They are absorbed rapidly and completely by the GIT but, nevertheless, have low bioavailability because they are transported to the liver in the hepatic portal vein and metabolized (*Section 12.3*) and have not entered the systemic circulation. Drugs with delayed absorption are sometimes required and special slow or sustained release formulations have been developed for these cases. Such drugs can be taken orally at less frequent intervals. Certain diseases that affect the GIT and the interaction of some drugs and foods in the GIT can delay their absorption.

Following absorption, drug distribution occurs when the compound enters the vascular system. The physical, chemical and molecular properties of the drug can influence its distribution. Its distribution may also be influenced by its binding to blood components and receptors and its ability to dissolve in lipids and pass through biological membranes. Many drugs bind to plasma proteins and often an equilibrium is established between protein-bound and free drug. Only the free fraction is able to interact with receptors or cross cellular membranes. Any factor that changes drug–protein interactions may alter the distribution, pharmacological effects and excretion of the drug.

Drugs are excreted from the body by the biliary, GIT, pulmonary and/or renal routes. Most drugs are excreted through the renal system, and therefore, alterations in renal function may influence the half-life and serum concentration of the drug. A decline in renal function causes an increase in the serum drug concentration with an associated increased pharmacological effect.

12.3 PHYSIOLOGICAL DETOXIFICATION MECHANISMS

Xenobiotics, whether drugs or toxins, are normally absorbed through the lungs, GIT or the skin. In addition, drugs may be injected through intramuscular, intraperitoneal, subcutaneous or intravenous routes. Following absorption, the xenobiotics are distributed around the body and a proportion will be absorbed by cells, while some may be directly excreted from the kidneys. Humans also have a number of physiological mechanisms devoted to detoxifying ingested xenobiotics, which largely involve enzyme activities in the liver and kidneys. Many of the biochemical detoxification mechanisms convert the xenobiotic to more water-soluble compounds that are more easily excreted. These mechanisms can sometimes prove inadequate. Also, in some unfortunate cases, the detoxification mechanisms form compounds that are even more toxic or carcinogenic than the original compound.

Treatment for poisoning involves administering an antidote to the toxin or drug when one is available. For many common poisons this is not the case and therapy involves general supportive measures, such as decreasing their absorption from the GIT, increasing the rate of elimination from the body or altering the distribution within the body to protect susceptible tissues. An optimal therapeutic concentration of a drug can only be maintained in the plasma if the patient fully complies with the prescribed dose. Unfortunately, the most common reason for emergency admissions to hospitals is because of an excessive intake of a drug prescribed for medication. Other causes of poisoning may be accidental, suicidal or homicidal in intent.

Many poisons are lipophilic and are only sparingly soluble in water and so cannot easily be excreted by the kidneys. Thus a major aim of detoxification in the liver is to convert them to compounds that have increased water solubility and are more readily removed by the kidneys. Detoxification reactions in the liver are favored by its microstructure, which consists of lobules with a central vein and peripheral branches of the hepatic artery and the hepatic portal vein. Blood leaves branches of the hepatic artery and hepatic portal vein and percolates from the periphery of the lobule through sinusoids, bathing the hepatocytes of the lobule as it flows (*Figure 12.2*). While it is unusual for blood to come into such close contact with tissue cells, this arrangement allows poisons to be removed as the blood flows through the lobule to be collected by branches of the hepatic vein. Also, mitotic divisions within the organ replace those liver cells that are irreparably damaged. It goes without saying that a disease of the liver can compromise its ability to deal with toxic substances, which can lead to significant clinical consequences.

Detoxification is achieved in two phases. In Phase I, the xenobiotic is oxidized and/or hydroxylated by mixed function oxidase (MFO) activities of monooxygenase systems. There are two such systems, a flavin-containing monooxygenase (FMO) system used in oxidation reactions of drug metabolism and a cytochrome P-450 monooxygenase system that oxidizes carbon atoms. Both systems require NADPH as a coenzyme and dioxygen and are localized in the smooth endoplasmic reticulum. In Phase II, the oxidized xenobiotic product is linked to a polar compound, such as a glucuronate or sulfate group forming water-soluble conjugates in further enzyme-catalyzed reactions. The enzymes that catalyze both the Phase I and II reactions have broad specificities and are therefore able to detoxify a wide range of organic toxins and drugs. This is essential since the range of xenobiotics to which the body may be exposed is enormous, and individual enzyme systems could not be available to deal with each one separately. At least 50 different members of the cytochrome P-450 enzyme family are found in the smooth endoplasmic reticulum of hepatocytes (*Figure 12.3*). They catalyze the hydroxylation of a wide variety of substances by incorporating one of the oxygen atoms into the xenobiotic to form the hydroxyl group,

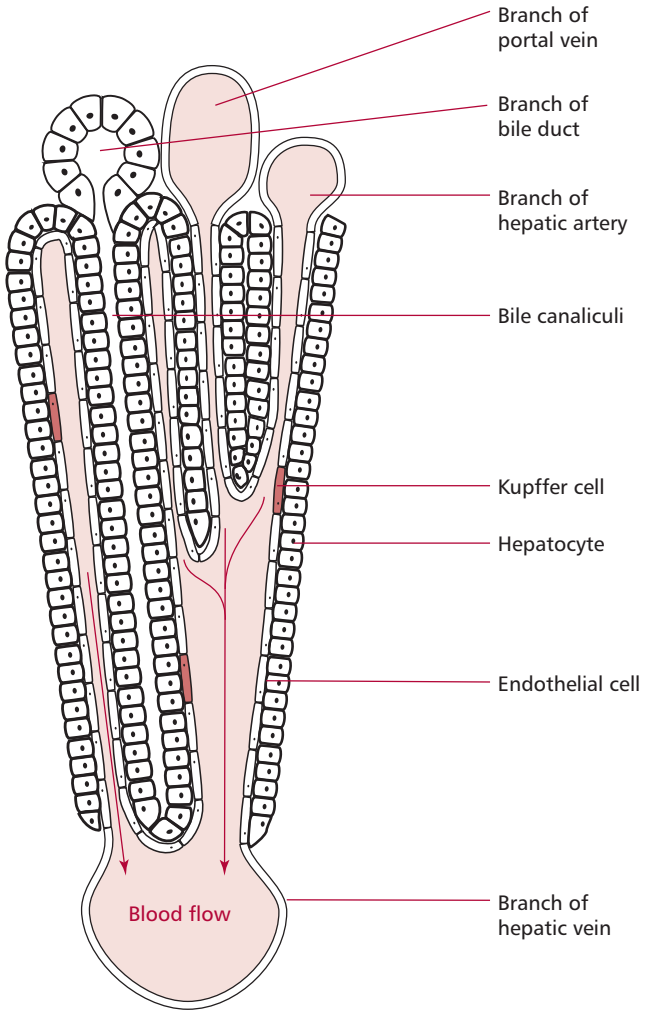
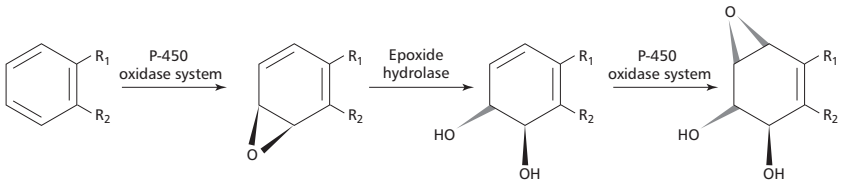


Figure 12.2 Schematic of a portion of a liver lobule. Blood enters at the periphery from a branch of the hepatic portal vein and the hepatic artery and eventually leaves at the center of the lobule via a branch of the hepatic vein. Close contact of the blood with the liver cells means that these cells are the first to contact poisons and toxins after their absorption from the GIT and transport in the portal system. The hepatocytes contain enzymes involved in detoxification.

while the other oxygen atom is reduced to water. The NADPH supplies an electron to complete the Phase I stage.

$$R\text{-}H + O_2 + NADPH + H^+ \longrightarrow R\text{-}OH + H_2O + NADP^+$$

The same enzyme system is able to convert unsaturated compounds to an epoxide, which is a substrate for epoxide hydrolase that catalyzes the conversion of the epoxide to a glycol.



The actions of these enzymes form hydroxyl groups that increase the water solubility of the original poison or drug and also form attachment points for the actions of Phase II enzymes. These include glucuronyl transferases of the smooth endoplasmic reticulum membrane and sulfotransferase in the cytosol, which use UDP-glucuronate and 3′-phosphoadenosyl 5′-phosphosulfate (PAPS) as the respective donor substrates:

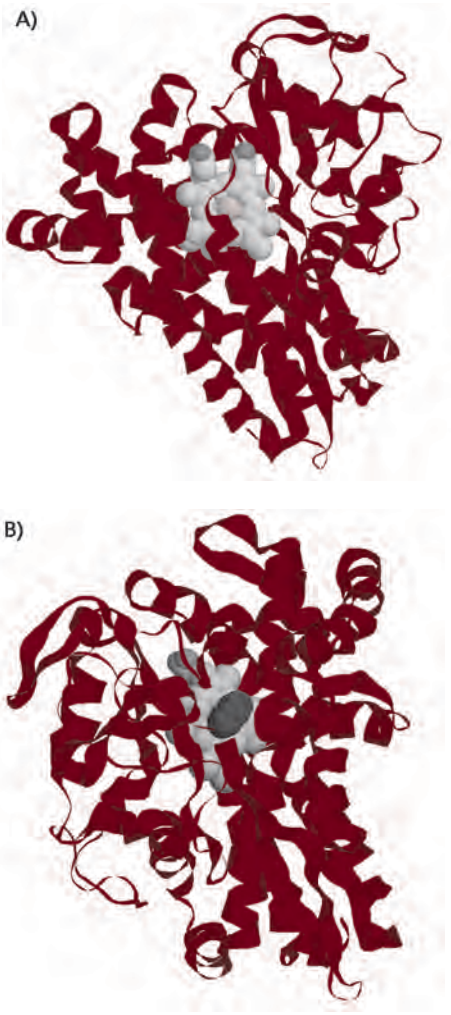


Figure 12.3 Molecular models of (A) a P-450 molecule, with a gray colored heme group containing a central iron atom and (B) with a bound aromatic substrate shown in dark gray. PDB files 1PHC and 1CP4 respectively.

glucuronyl transferase

$$\text{R-OH} + \text{UDP-glucuronate} \longrightarrow \text{R-O-glucuronate} + \text{UDP}$$

sulfotransferase

$$\text{R-OH} + \text{PAPS} \longrightarrow \text{R-O-SO}_3^- + \text{PAP}$$

The increased water solubility of the products facilitates their excretion by the kidneys, although small amounts are also lost in bile to the feces.

It is unfortunately the case that a number of poisons are rendered more toxic by oxidation by the P-450 system. Indeed, a number of fat-soluble compounds that are relatively harmless because they would normally accumulate in adipose tissue are converted into potentially lethal materials because of the increase in water solubility. Thus, a number of indirectly acting carcinogens, for example, benzo[a]pyrene, found in cigarette smoke and the toxin aflatoxin B1 from *Aspergillus flavus*, are converted to highly carcinogenic products (*Figure 12.4 (A)* and *(B)*).

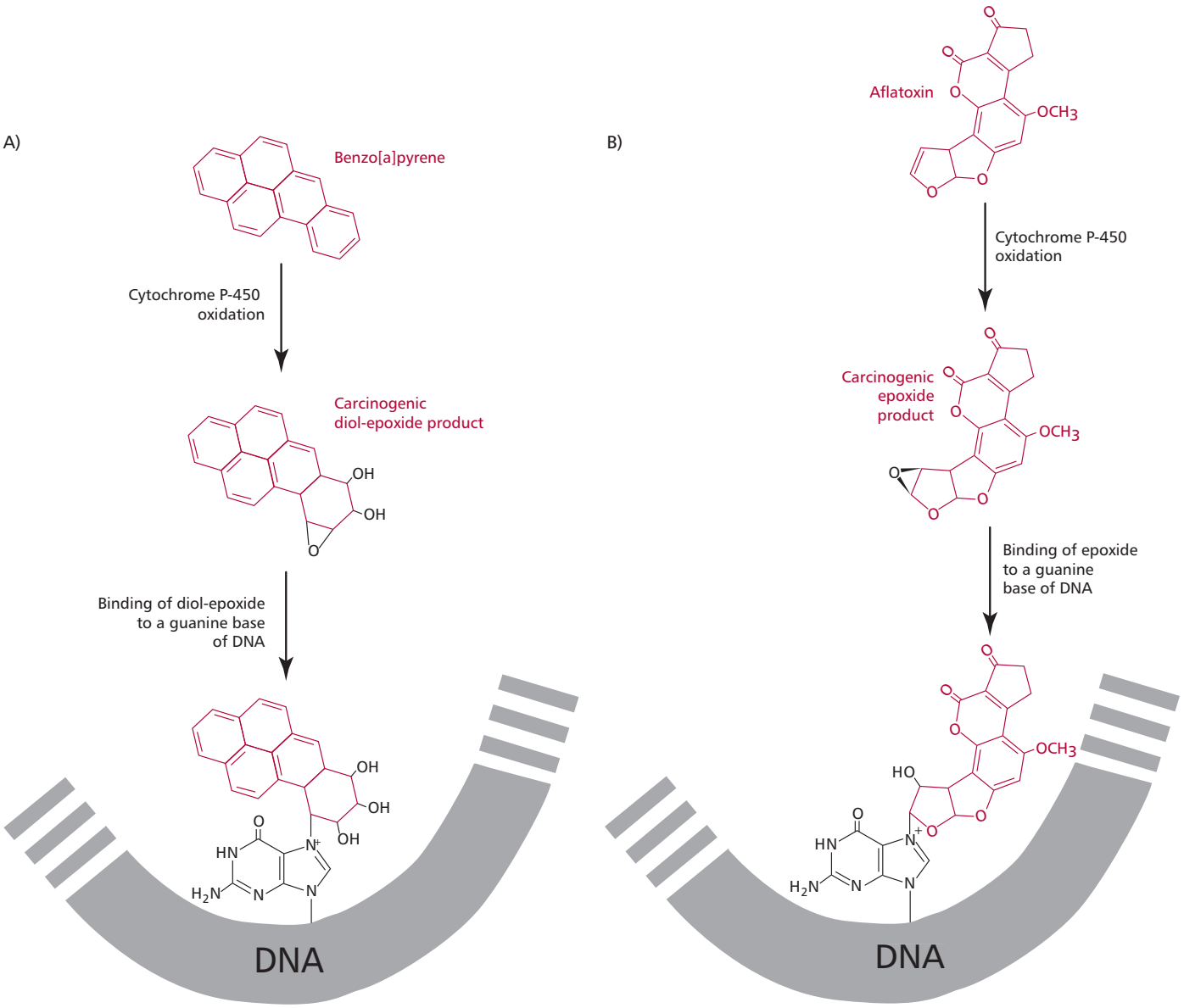


Figure 12.4 The oxidation of (A) benzo [a] pyrene and (B) aflatoxin by the cytochrome P-450 system to reactive chemicals that can bind with guanine bases of DNA and so induce carcinogenesis.

12.4 SYMPTOMATIC POISONING

In the symptomatic patient, the diagnosis of poisoning is usually made on the basis of clinical findings. However, in all cases of suspected poisoning, a number of biochemical investigations should be made as shown in *Table 12.1*. The roles of the clinical laboratory in chemical toxicology in identifying a suspected poison in blood or urine and in monitoring vital functions cannot be overestimated.

Investigation	Purpose
Monitor plasma urea, electrolytes and creatinine levels	assess renal function (*Chapter 8*)
Monitor plasma osmolality	an osmolality gap can indicate the presence of foreign substances in the serum (*Chapter 8*)
Monitor blood gases	assess acid–base status (*Chapter 9*)
Monitor liver functions	assess viability of liver functions (*Chapter 11*)
Monitor blood glucose concentrations	to detect hypo- and hyperglycemia (*Chapter 7*)

Table 12.1 Biochemical investigations of suspected poisoning

The clinical management of patients is directed towards supporting their vital functions and attempting to remove the poison from the body as rapidly as possible. Unfortunately, few of the signs or symptoms that patients present with are specific for any one type of drug or poison. Also, patients may well present in a coma and so be unable to give relevant information. A drug screen on a urine specimen may be carried out but this will only indicate that a drug has been ingested and may give no indication of the severity of the overdose.

12.5 COMMON POISONS

Humans are exposed to numerous xenobiotics, including drugs, pesticides, environmental pollutants, industrial chemicals and food additives. Any of these are potentially capable of perturbing the biochemistry and physiology of the body either directly or after being metabolically transformed. However, the most frequent poisons encountered in emergency toxicology include paracetamol (acetaminophen), aspirin, alcohols (ethanol, methanol, ethylene glycol), barbiturates (though this is now mainly historical), carbon monoxide, paraquat and several metals. The chapter will concentrate only on those most likely to be encountered in clinical practice.

PARACETAMOL

Paracetamol (*Figure 12.5*) is used as an analgesic, that is, to relieve fever and pain. It is safe when taken at recommended doses but is toxic if overdosed. It is the commonest cause of admissions to hospital due to its wide availability. In the UK, overdoses cause approximately 150 deaths annually.

Paracetamol is rapidly absorbed from the stomach and upper GIT. The majority of ingested paracetamol is metabolized by conjugation with sulfate (~30%) or glucuronide (~60%) in the liver as described in *Section 12.3* to form nontoxic metabolites. However, approximately 10% is metabolized by cytochrome P-450 to produce a highly reactive intermediate called *N*-acetyl-*p*-benzoquinoneimine (NABQI). It is possible for NABQI to be

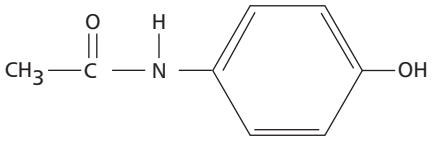


Figure 12.5 Paracetamol (called acetaminophen in the USA).

metabolized by conjugation with glutathione in hepatocytes to produce a nontoxic mercapturic acid. Glutathione is a tripeptide consisting of γ glutamate, cysteine and glycine residues, which will be further mentioned in *Chapters 13* and *18*. It functions as a coenzyme in several oxidation–reduction reactions (*Figure 12.6*). When an overdose of paracetamol is ingested, liver detoxification systems may become saturated and the large amount of NABQI produced exhausts the limited stores of glutathione. As a consequence, NABQI binds to sulfhydryl groups of hepatocyte proteins, forming irreversible complexes that result in acute hepatic necrosis, that is, cell death (*Figure 12.7*). Paracetamol is also metabolized in cells of renal tubules and, in an overdose, renal tubular necrosis may also occur. In the presence of hepatic damage there is usually only a small amount of renal damage but occasionally this may be the major presenting feature of paracetamol poisoning. Alcohol in chronic alcoholics and the drugs phenobarbitone and phenytoin, used to treat epilepsy, may induce the synthesis of cytochrome P-450 enzymes and cause increased production of NABQI. As a consequence, hepatotoxicity may occur following a relatively small overdose of paracetamol in such patients. Severe toxicity is also more likely in people whose intracellular stores of glutathione are depleted as a result of starvation or protein malnutrition (*Chapter 10*).

Substances, such as cimetidine, that inhibit the cytochrome P-450 system without interfering with glucuronidation or sulfation could potentially reduce paracetamol hepatotoxicity.

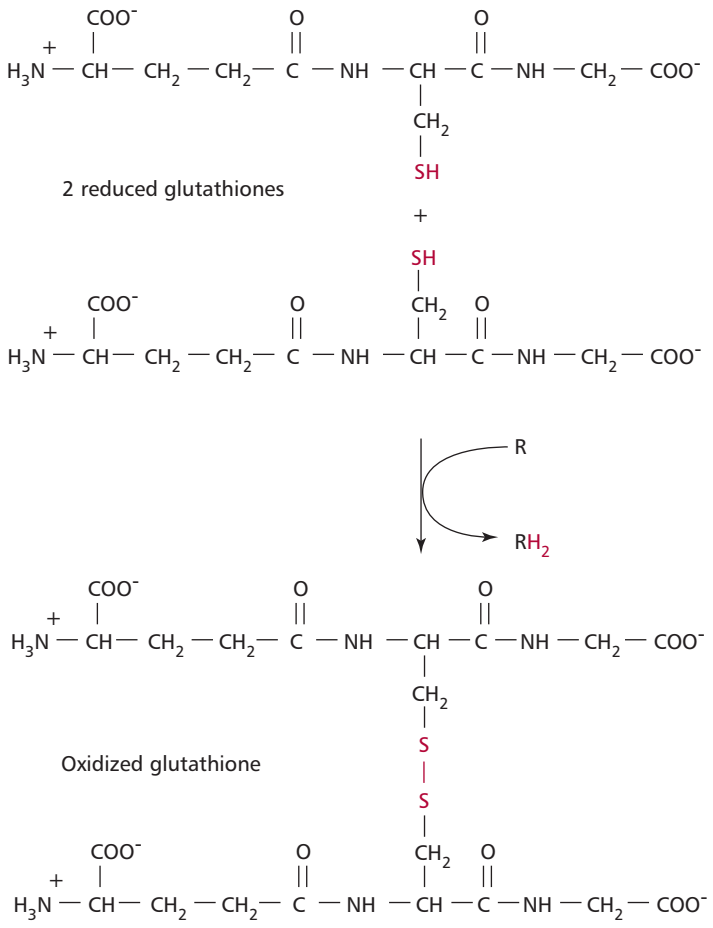


Figure 12.6 The reduction of an organic compound (R) during the oxidation of reduced glutathione. See also *Figures 13.25* and *18.4*.

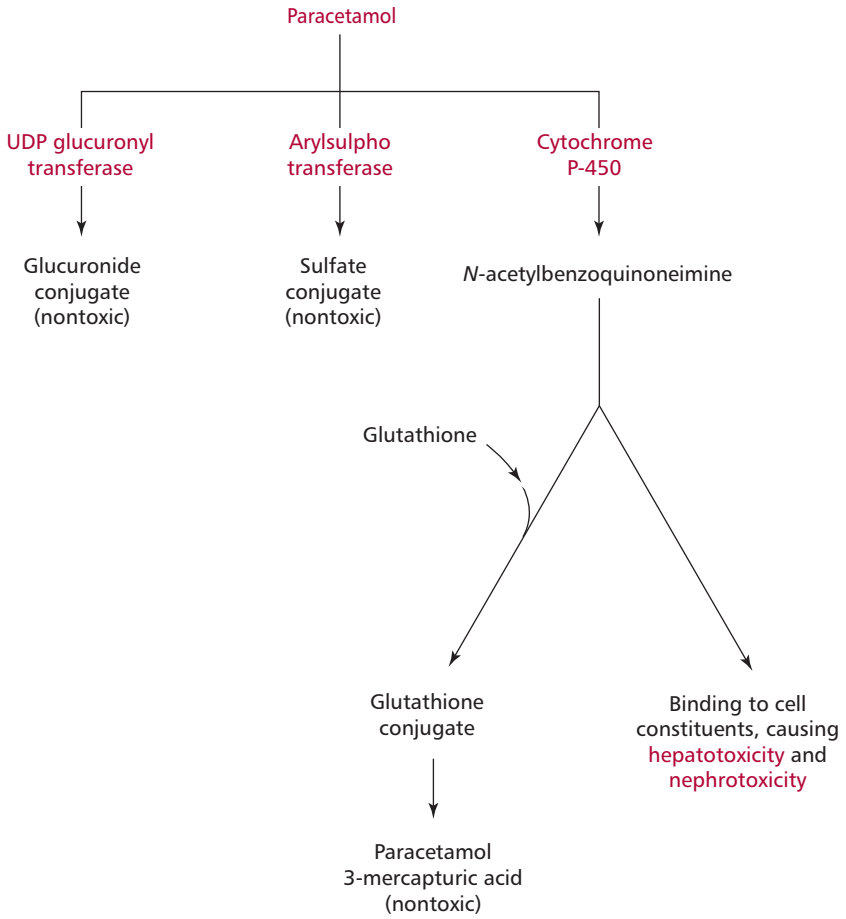


Figure 12.7 An overview of the detoxification and toxic effects of paracetamol. See text for details.

Toxic doses

A dose of 15 g for adults and 4 g for children is normally sufficient to cause hepatotoxicity. It has been suggested that this amount of paracetamol depletes liver glutathione concentrations by 70% in a 70 kg man. However, there is wide variation in the metabolic handling of paracetamol by the body and large overdoses of over 50 g have been known to have little effect in some patients. The incidence of hepatotoxicity in children is significantly lower at concentrations of paracetamol in blood that would be potentially toxic in adults. Animal studies have suggested that turnover of glutathione is age dependent, hence younger animals can tolerate higher doses of paracetamol.

Often estimates of the amount of paracetamol ingested, for example by a potential suicide, are unreliable. Thus, predictions of hepatotoxicity should be made only on the basis of serum concentrations. In general, concentrations of paracetamol greater than 300 mg dm^{-3} cause serious liver damage 4 h after ingestion whereas values below 120 mg dm^{-3} show no toxicity.

Clinical features of paracetamol poisoning

The signs and symptoms of paracetamol overdose are insidious, especially in the earlier stages. The clinical features can be divided into three phases, with a fourth occurring if the person survives toxicity and are described in *Table 12.2*.

Stage	Duration / h	Clinical features
I	0.5–24	loss of appetite and anorexia (*Chapter 10*), nausea and vomiting, general malaise, patient appears normal
II	24–48	less severe symptoms, abnormal blood chemistry with increases in liver enzymes and bilirubin, deterioration in renal functions but blood urea concentration remains low given the decrease in liver function
III	72–96	signs of hepatic necrosis, coagulation defects, jaundice and renal failure, reappearance of nausea and vomiting, death due to hepatic failure
IV	4–14 days	hepatic and renal functions return to normal if patient survives stage III

Table 12.2 Stages of paracetamol poisoning

Laboratory investigations of paracetamol poisoning

Estimating the concentration of paracetamol in plasma is useful for assessing the probability of patients developing hepatotoxicity. A nomogram (*Figure 12.8*) is available for paracetamol poisoning but should only be used when the size of the overdose and the approximate time of ingestion are known. Blood samples for paracetamol determination should be drawn at least 4 h postdose to allow for its complete absorption and the serum concentration to peak. The concentration of paracetamol in plasma can be used as a guide to patient management. Other tests that may be useful are determining the

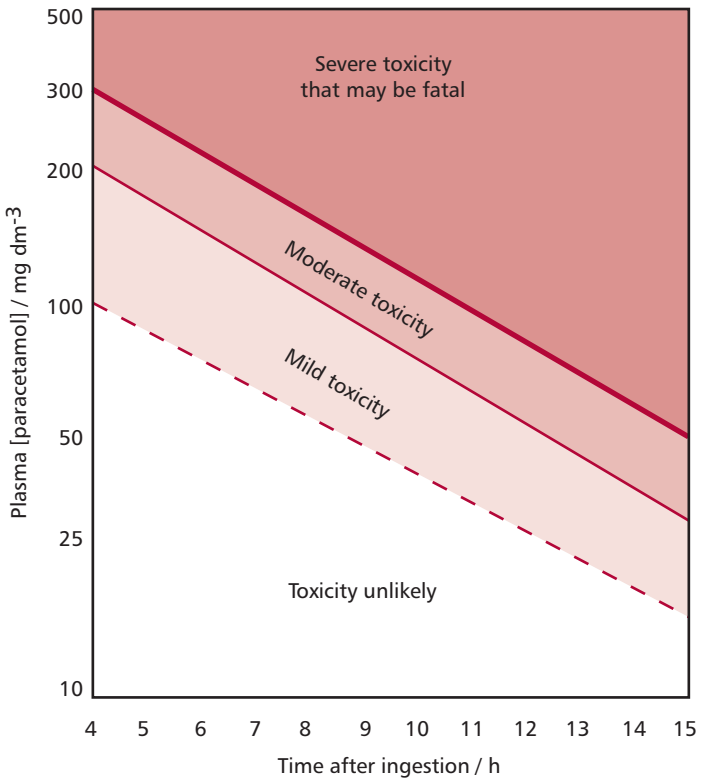


Figure 12.8 A nomogram to assess paracetamol toxicity.

activities of liver transaminases and measuring serum bilirubin to monitor liver functions (*Chapter 11*) and determining serum creatinine concentrations to assess renal function (*Chapter 8*). Paracetamol poisoning causes an increased prothrombin time (*Chapter 13*) which is the time taken for blood clotting to occur in a sample of blood to which calcium and thromboplastin have been added.

Management of paracetamol poisoning

Antidotes to paracetamol poisoning include methionine and *N*-acetylcysteine. Both promote the synthesis of glutathione in the liver, increasing its capacity to detoxify the active metabolite. Methionine may be given orally at 2.5 g every 4 h for 12 h in early or uncomplicated cases, while *N*-acetylcysteine is administered parenterally and is more appropriate for patients who present late, or are comatose or vomiting. *N*-acetylcysteine can act as a glutathione substitute and enhances conjugation with sulfate (*see earlier*). It also limits liver damage by reducing inflammation and improving the microcirculation in the liver. Treatment gives maximal benefit if started within 10 h of ingestion although it may still be beneficial for up to 24–30 h. General procedures, such as administration of activated charcoal, can reduce gastrointestinal absorption of paracetamol if given in the first hour of an overdose. Gastric lavage may be used in patients who have ingested large amounts of paracetamol and present within an hour of ingestion.

ASPIRIN

Aspirin (acetylsalicylic acid) is hydrolyzed in the body to salicylate, the active form of the drug (*Figure 12.9*), which has analgesic, antipyretic and anti-inflammatory properties. Salicylate is eliminated from the body by conjugation with glycine to form salicyluric acid and, to a lesser extent, with glucuronide to form phenol and acylglucuronides. A small amount is hydroxylated to gentisic acid. In an overdose, these pathways may become saturated and a large proportion of salicylate may be excreted unchanged in urine.

Like paracetamol, aspirin is widely and easily available and poisoning by aspirin overdose is therefore relatively common. Salicylate toxicity is due to a number of effects (*Figure 12.10*). An increase in the concentration of salicylate in the brain stimulates the respiratory center leading to hyperventilation, which can result in dehydration. In addition, hyperventilation causes a decline in the PCO_2 and a rise in pH, that is, respiratory alkalosis (*Chapter 9*). As PCO_2 declines, the pH rises and less H_2CO_3 is formed. The kidneys compensate by excreting more hydrogen carbonate (HCO_3^-) and K^+ whilst retaining H^+. These activities, rather than helping correct the respiratory alkalosis, contribute towards a latent metabolic acidosis. Salicylate also uncouples oxidative phosphorylation, decreasing ATP formation and increasing heat production, with sweating and hyperpyrexia, which further contributes to the dehydration and fluid loss. The decline in the amount of ATP stimulates glycolysis, and therefore pyruvate and lactate accumulate. An increase in glycogenolysis (*Margin Note 12.2*) provides the required glucose for this increase. Eventually there may be depletion of glycogen giving rise to

Margin Note 12.2 Glycogenolysis

Glycogenolysis is the breakdown of glycogen reserves to yield glucose 1-phosphate in a reaction catalyzed by glycogen phosphorylase:

$$\text{Glycogen}_{(\text{n glucose residues})} + P_i \xrightarrow{\text{glycogen phosphorylase}} \text{Glycogen}_{(\text{n-1 glucose residues})} + \text{Glucose 1-phosphate}$$

The glucose 1-phosphate can be oxidized to give ATP for use by the cell or, in liver cell particularly, hydrolyzed to form glucose that can be released into the bloodstream to maintain blood glucose concentrations.

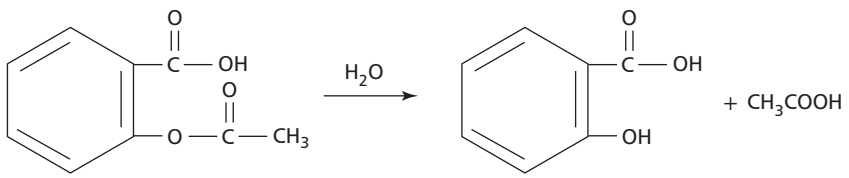


Figure 12.9 The conversion of aspirin to salicylic acid.

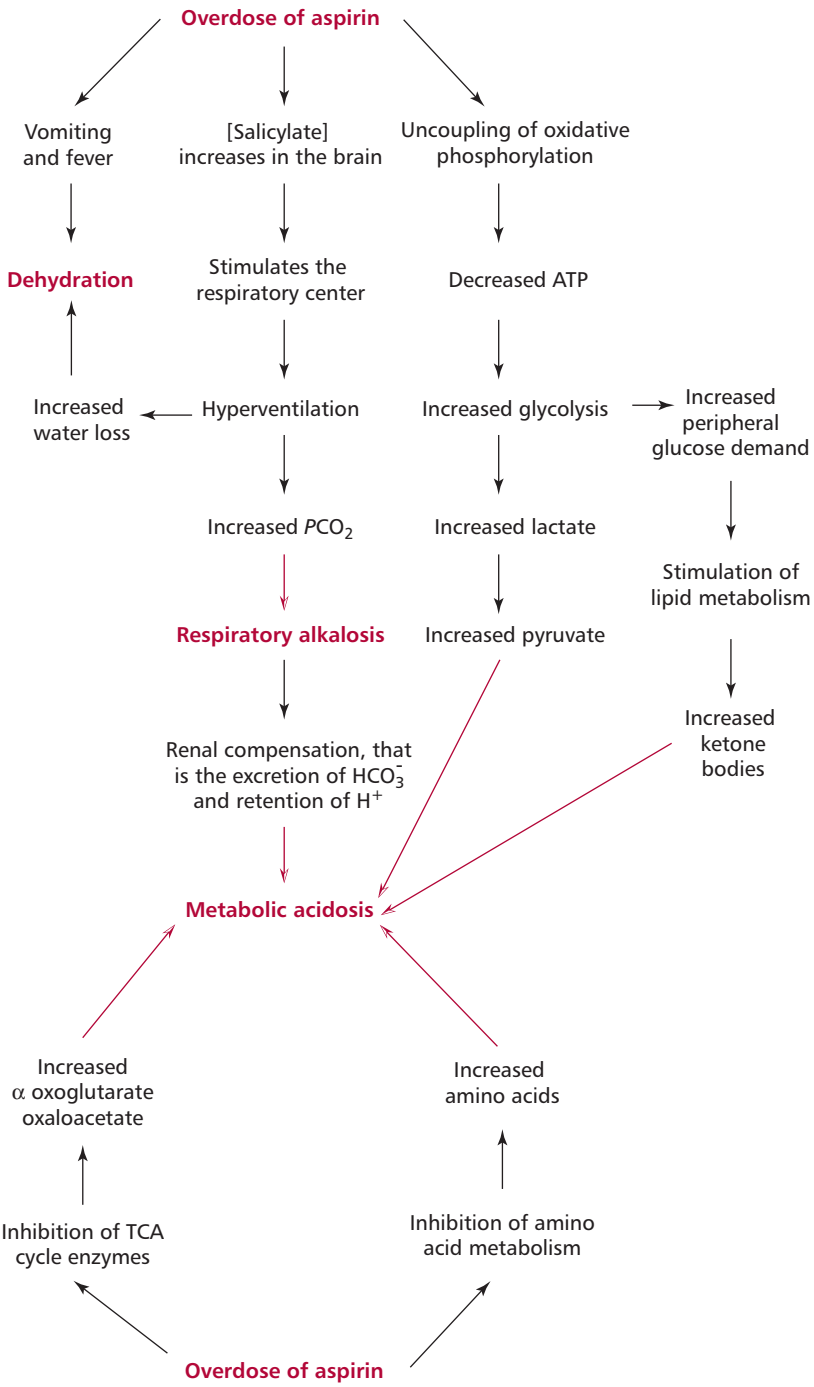


Figure 12.10 An overview of the toxic effects of aspirin. See text for details.

hypoglycemia and the catabolism of lipids producing ketone bodies (*Chapter 7*). Salicylate also inhibits enzymes of the TCA cycle, leading to an accumulation of oxoglutarate and oxaloacetate, and of amino acid metabolism, causing an increase in amino acids that accentuates the metabolic acidosis. Fluid and electrolyte losses are increased by the nausea and vomiting.

Toxic dose

Common therapeutic levels of salicylate are 50 mg dm^{-3} although they can be as high as 250 mg dm^{-3} in the serum of patients with rheumatoid arthritis (*Chapter 5*). The potentially lethal dose of aspirin in adults is 24 to 30 g but

death can occur in children under 18 months from as little as 300 mg. Signs of salicylate toxicity occur when concentrations are greater than 300 mg dm^{-3}. In severe cases of aspirin poisoning, the concentrations in serum can be as high as 1000 mg dm^{-3}.

Clinical features of aspirin poisoning

Numerous symptoms are associated with aspirin poisoning, including nausea, vomiting, sweating, hyperventilation, tinnitus (buzzing noise in ear), confusion and/or unconsciousness and a severe loss of fluid.

Laboratory investigations of aspirin poisoning

The concentration of salicylate in plasma should be measured on presentation and every 4 to 6 h until it has fallen below the toxic range. This is necessary as salicylates precipitate in acid conditions and may therefore deposit in large amounts in the stomach. The consequence is delayed absorption and this means that the concentration in plasma may continue to rise for many hours following a severe overdose.

Management of aspirin poisoning

A variety of measures can be taken to alleviate salicylate poisoning, which are aimed at decreasing the absorption of salicylate, increasing its rate of elimination and correcting the acid–base and electrolyte disturbances. These measures include gastric lavage for up to 24 h after ingestion as salicylate may remain unabsorbed in the GIT for long periods. Patients may also be given 50 g of activated charcoal followed by 25 g every 4 h. The charcoal binds salicylate and prevents its absorption. The ionization state of salicylate affects its reabsorption by the kidneys. If the provisional urine is acidic, salicylate is not ionized and is filtered at the glomerulus but reabsorbed from tubules (*Chapter 8*); if the urine is alkaline the salicylate is ionized and its tubular reabsorption is reduced and more salicylate is lost from body. Hence patients are infused with sodium hydrogen carbonate to increase the pH of urine and promote loss of salicylate. Fluid replacement and corrections of acid–base, electrolyte imbalance, especially the hypokalemia, and hypoglycemia are all required.

Hemodialysis may be necessary in severe cases of poisoning, such as when plasma concentrations of salicylate exceed 800 mg dm^{-3}. As well as removing the salicylate, hemodialysis also corrects the acid–base and electrolyte imbalances. The technique requires a dialyzer (*Figure 12.11*). Blood from a patient's artery is circulated through the dialyzer on one side of a semipermeable membrane while a solution of normal electrolytic composition circulates on the other side. Waste products, poisons, including salicylate, and small molecules cross the membrane and the dialyzed blood is returned to the body via a vein.

ETHANOL

Ethanol is an addictive drug and its abuse can lead to dependency and alcoholism. Its abuse is increasingly common in the developed world. The toxic effects of chronic alcohol abuse on the liver, brain and GIT are widely known. Ethanol can also modify the effects of other drugs, for example it inhibits the hydroxylation of barbiturates by the P-450 system preventing their ready excretion by the kidneys.

The metabolism of ethanol occurs mainly in the liver by one of two mechanisms. Normally only small amounts are degraded by the P-450 system (*Figure 12.12*), although this oxidation can become of major importance because the P-450 system is induced by chronic alcohol consumption. The

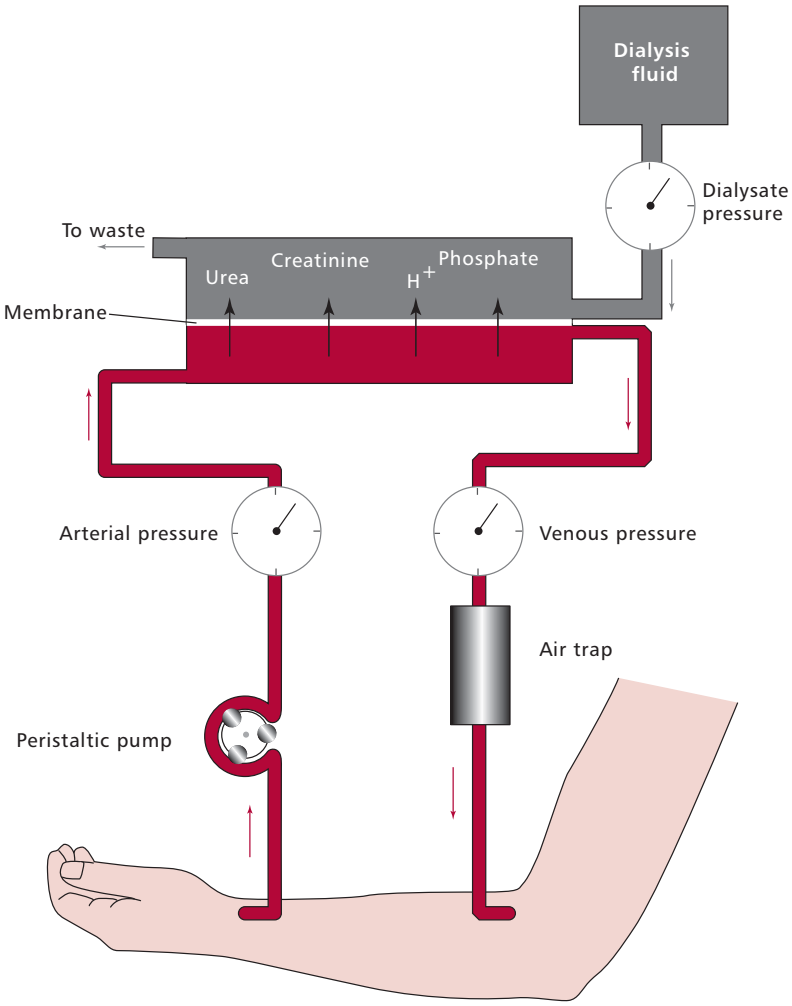


Figure 12.11 A schematic illustrating the procedure of hemodialysis.

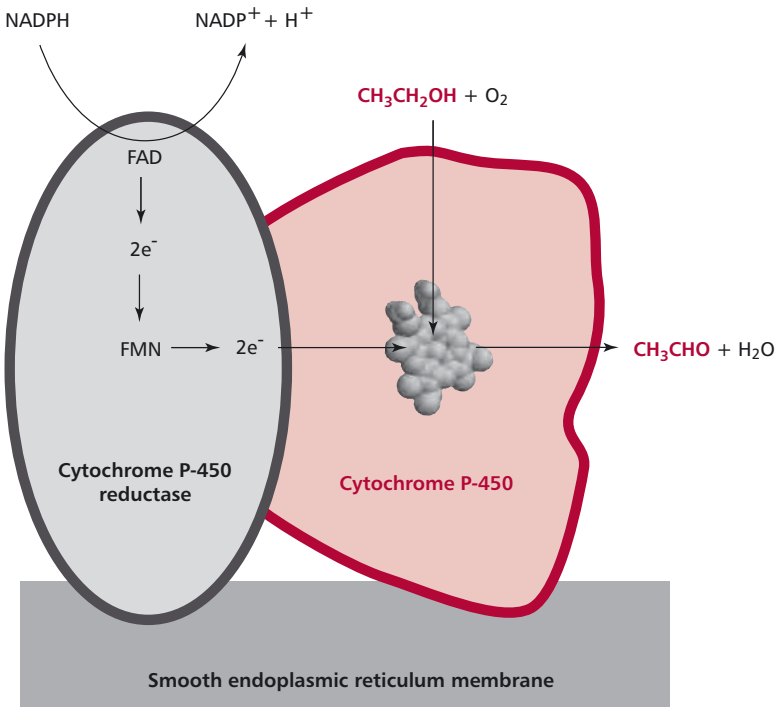


Figure 12.12 The role of P-450 in the detoxification of ethanol.

Figure 12.13 Molecular model of alcohol dehydrogenase. The black spheres represent Zn atoms and the bound NADH is shown in gray. PDB file 1HSO.

major catabolic pathway is to oxidize ethanol to the corresponding aldehyde, ethanal, in a reaction catalyzed by alcohol dehydrogenase, ADH (*Figure 12.13*).

Alcohol dehydrogenase

$$CH_3CH_2OH + NAD^+ \longrightarrow CH_3CHO + NADH + H^+$$

The effectiveness of ADH varies between different populations and hence the undesirable effects of drinking can appear after widely varied intakes. The ethanal may subsequently be oxidized to ethanoic acid (acetic acid) by aldehyde dehydrogenase, ALDH (*Figure 12.14*).

Aldehyde dehydrogenase

$$CH_3CHO + NAD^+ \longrightarrow CH_3COOH + NADH + H^+$$

Much of the acetate made from ethanol escapes into the blood and can result in acidosis (*Chapter 9*). The effect of both enzymes is to increase the $NADH/NAD^+$ ratio, that is, alcohol consumption leads to the accumulation of NADH with consequent severe effects. The increased NADH inhibits fatty acid oxidation and stimulates the synthesis of triacylglycerols in the liver producing a fatty liver. The oxidation of lactate to pyruvate is also inhibited, slowing gluconeogenesis (*Margin Note 12.3*). The increased lactate exacerbates the acidosis and the decreased gluconeogenesis may cause hypoglycemia.

The capacity of liver mitochondria to oxidize acetate to CO_2 is limited because the activation of acetate to acetyl CoA requires ATP:

$$\text{Acetate} + \text{Coenzyme A} + ATP \longrightarrow \text{acetyl CoA} + AMP + PP_i$$

Adenosine triphosphate is now in short supply because glycolysis, which requires free NAD, is slowed and because the processing of acetyl CoA by the TCA cycle is blocked since NADH inhibits the regulatory enzymes isocitrate dehydrogenase and 2-oxoglutarate dehydrogenase. Acetyl CoA is converted to ketone bodies (*Chapter 7*) that are released into the blood, intensifying the acidosis caused by acetate and lactate. Acetaldehyde also accumulates and this extremely reactive compound can bind to liver proteins, impairing their functions and causing severe damage to liver cells, leading to their death. Acetaldehyde can also escape from the liver and react with blood proteins to form stable adducts. These can provide useful markers of the past drinking activity of an individual.

Liver damage from excessive alcohol consumption occurs in three stages. The first stage is the formation of the fatty liver described above. This condition, in the absence of other complications, is readily reversible within four to six weeks if alcohol is avoided. The second stage is the occurrence of alcoholic hepatitis when groups of liver cells die. This leads to inflammation and can be fatal. In the third stage, the patient may develop cirrhosis, a condition seen in 10% to 15% of alcoholics (*Figure 12.15 (A)* and *(B)*). Approximately half of all cases of cirrhosis are due to alcoholic liver disease. Cirrhosis occurs when fibrous structures and scar tissue are produced around the dead cells. This impairs many of the biochemical functions of the liver, for example, cirrhotic liver cannot convert ammonia to urea and the concentration of ammonia in the blood rises. Ammonia is toxic to the nervous system and can cause coma

Figure 12.14 Molecular model of aldehyde dehydrogenase. The black spheres represent Mg atoms and the bound NADH is shown in gray. PDB file 1O02.

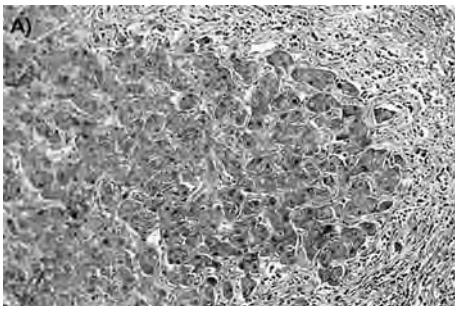
Margin Note 12.3 Gluconeogenesis

Gluconeogenesis is the synthesis of glucose using materials that are not carbohydrates as precursor molecules. These include pyruvate, the end product of glycolysis, oxaloacetate, an intermediate of the TCA cycle, and dihydroxyacetone phosphate, which can be made from glycerol obtained from the hydrolysis of triacylglycerols.

and death. Ethanol also directly affects the central nervous system (CNS). For example, it enhances the inhibitory affects of γ aminobutyric acid (GABA) at the $GABA_A$ receptor and the functions of some 5-hydroxytryptamine receptors, in addition to numerous other membrane proteins. The resulting depressive effects of these activities are well known.

Chronic liver damage invariably results in malnutrition, partly due to malabsorption and partly because the metabolism of nutrients by the liver is defective. However, many alcoholics are malnourished because of dietary inadequacies. While ethanol supplies most of their energy needs they may be ingesting insufficient amounts of other nutrients, particularly proteins and vitamins (*Chapter 10*). In addition, chronic alcohol ingestion can damage the mucosal lining of the GIT and pancreas as well as the liver (*Chapter 11*). Alcoholics require increased amounts of vitamins and some trace elements because of the metabolic load experienced and their increased excretion. For example, niacin, although not strictly a vitamin since it can be formed, albeit very inefficiently, from tryptophan (*Chapter 10*), is necessary to form the coenzymes, NAD^+ and $NADP^+$. A borderline deficiency of niacin leads to **glossitis** (redness) of the tongue while a pronounced deficiency leads to pellagra, with dermatitis, diarrhea and dementia. In developed countries, pellagra is rarely encountered other than in alcoholics, given their severe malabsorption problems, hence dietary supplies of niacin and tryptophan are required. A severe zinc deficiency (*Chapter 10*) also occurs primarily in alcoholics, especially those suffering from cirrhosis. Heavy drinkers frequently suffer from GIT varicose veins (*Chapter 14*) and diarrhea caused by a variety of factors, including ethanol-exacerbated lactase deficiency and interference with normal peristalsis. Steatorrhea is also common, due to deficiencies in folic acid and bile salts in the GIT (*Chapter 11*).

The obvious treatment for alcoholic liver disease and cirrhosis is abstinence. Given the addictive nature of ethanol, this may be difficult to maintain. Unfortunately, patients presenting with severe alcoholic hepatitis have a high mortality even when abstinence is successful. Although a number of pharmacological treatments have been attempted as therapies, none has been successful. However, supportive nutritional management in cases of acute and chronic liver disease is essential to achieve electrolyte, vitamin and protein replenishments. The only treatment for advanced cirrhosis is a liver transplant (*Chapter 6*).



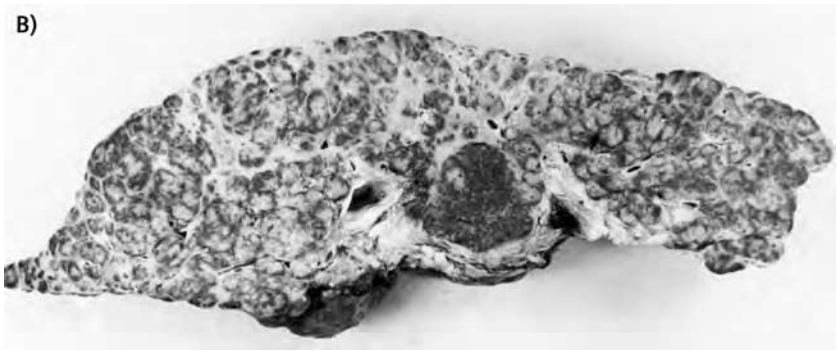


Figure 12.15 Cirrhosis in alcohol related liver disease. (A) A slide showing how alcohol abuse has led to diffuse scarring of the liver which has regenerated at numerous points to form nodules. The sinusoidal fibrosis is well established in this small regenerative nodule where the regenerating cells are darkly stained compared with the lighter fibrous tissue. As the nodules get larger, the fibrous tissue round the outside becomes compressed giving the characteristic hob-nail appearance to the liver as shown in (B), which is a transected cirrhotic liver from an alcoholic. The extensive damage in the form of nodules of varying sizes separated by bands of fibers is apparent. Courtesy of Professor F.A. Mitros, The University of Iowa, USA and Dr N.P. Kennedy, Trinity College Dublin, Republic of Ireland respectively.

The major enzyme involved in ethanol metabolism, alcohol dehydrogenase, has a broad specificity and can catalyze the oxidation of a range of alcohols. This allows ethanol to be used as a competitive inhibitor of the enzyme in the treatment of poisoning by other alcohols, such as methanol and ethylene glycol.

METHANOL

Methanol is widely used as a solvent and as antifreeze. It is a potent poison with as little as 10 cm^3 causing blindness and 30 cm^3 can cause death. Toxicity can come from ingestion, inhalation and skin exposure. Mass poisonings have occurred from drinking alcoholic beverages made with contaminated ethanol and from accidental exposure. The major cause of methanol toxicity is its initial oxidation to formaldehyde, which is then converted to formate. The first step in the pathway is catalyzed by alcohol dehydrogenase and the production of formate is the result of several enzyme activities.

While both formaldehyde and formate are toxic, formaldehyde has a short metabolic half-life, whereas formate accumulates since its metabolism to CO_2 is slow in humans. This leads to metabolic acidosis. The symptoms of methanol poisoning are an initial mild inebriation and drowsiness. Visual disturbances, such as blurred vision, diminished visual acuity, dilated pupils occur after about 6 h. Within 8–36 h nausea, vomiting, abdominal pain, headaches and possibly coma occur. Treatment for methanol poisoning is, first, to administer ethanol. This blocks metabolism since alcohol dehydrogenase has a greater affinity for ethanol than methanol. Second, sodium hydrogen carbonate is given intravenously to correct the metabolic acidosis.

ETHYLENE GLYCOL

The alcohol ethylene glycol is a commonly used component of antifreeze, paints, polishes and cosmetics. It is a poison with a minimum lethal dose of approximately 100 cm^3. The toxicity of ethylene glycol is due to its oxidation to oxalate, which humans cannot rapidly excrete. The oxidative steps produce excessive NADH resulting in lactate production (*Figure 12.16*). The oxalate and lactate can result in metabolic acidosis, while the organic acids produced by the breakdown of ethylene glycol inhibit a number of metabolic processes

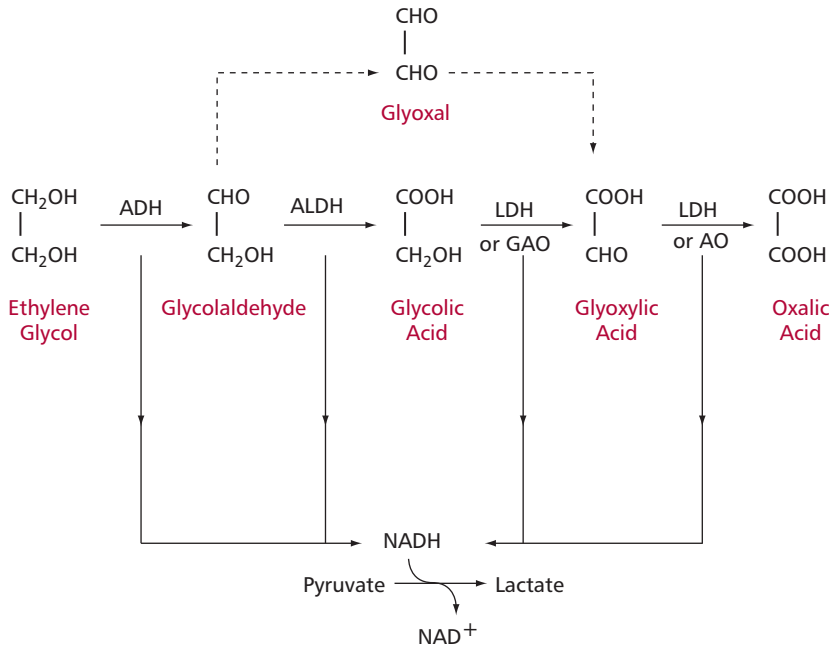
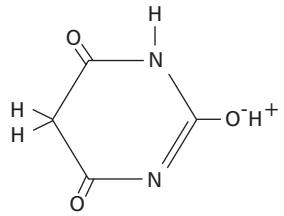


Figure 12.16 The formation of lactate during the catabolism of ethylene glycol.

A)



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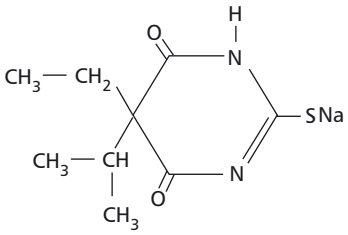

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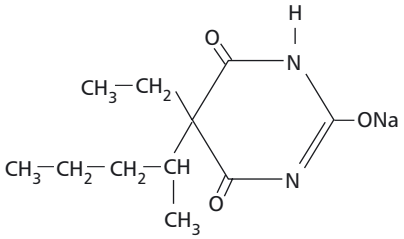

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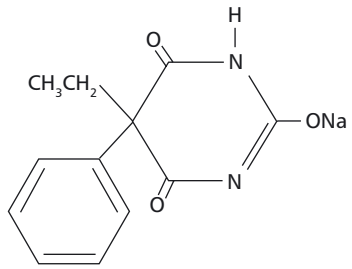


Figure 12.17 The barbiturates (A) barbituric acid, (B) thiobarbitone, (C) pentobarbitone and (D) phenobarbitone.

including oxidative phosphorylation. The production of oxalate also results in its deposition as insoluble calcium oxalate in renal tubules and the brain. These biochemical events reduce the concentrations of hydrogen carbonate and Ca^{2+}, but increase that of K^+ in plasma. Crystals, blood and protein may all leak into the urine, giving rise to three distinct clinical phases. Within 30 min to 12 h, intoxication, nausea, vomiting, coma, convulsions, nystagmus, papilloedema, depressed reflexes, myclonic jerks, tetanic contractions and permanent optic atrophy may occur. In 12 to 23 h tachypnea, tachycardia, hypertension, pulmonary edema and congestive cardiac failure may all present. In the following 24 to 72 h kidney damage with pain and acute renal tubular necrosis may feature. Death may occur within 24 h due to damage to the CNS, or between eight to 12 days due to renal failure.

Treatment of ethylene glycol poisoning is to apply gastric lavage to reduce its absorption, combined with supportive therapies for the shock and respiratory distress. Administration of ethanol is standard since it competes effectively for the active site on alcohol dehydrogenase, inhibiting the metabolism of the absorbed ethylene glycol. Sodium hydrogen carbonate, administered intravenously, and calcium gluconate are used to correct the acidosis and hypocalcemia respectively. Dialysis is also used to remove ethylene glycol.

BARBITURATES

Barbiturates are a group of drugs based on the parent compound, barbituric acid (*Figure 12.17 (A)*). All are sedatives, that is, they depress certain activities of the CNS. Although they have well-established therapeutic uses, barbiturates can be toxic if taken as an overdose, indeed, they are one of the commonest methods for attempting suicide. They were once used as recreational drugs, for example in purple hearts, and this too led to accidental overdoses. Barbiturates have now largely been replaced by benzodiazepines and barbiturate overdose is less likely to be encountered today.

Barbiturates induce drug dependence and this involves three distinct and independent components: tolerance, physical dependence and compulsive abuse or psychic craving. Barbiturate dependence stimulates all three components to such an extent that they produce major problems for the individual user as well as for society at large. Once barbiturate dependence has developed, abrupt withdrawal from the drug induces a particularly unpleasant withdrawal syndrome. This is characterized by weakness, tremors, anxiety, increased respiratory and pulse rates with a corresponding increased blood pressure, vomiting, insomnia, loss of weight, convulsions of the grand mal type and a psychosis resembling alcoholic delirium tremens. Thus during withdrawal, it is appropriate to reduce the dosage gradually over an extended period.

The length of time barbiturates act *in vivo* varies. Some, for example thiobarbitone (*Figure 12.17 (B)*), are short acting, others, such as pentobarbitone (*Figure 12.17 (C)*), act in the medium term, while the group including the best known barbiturate, phenobarbitone (*Figure 12.17 (D)*), induce long-lasting effects. Barbiturates act by enhancing the effects of GABA by binding to a different site on the receptors on target neurons of the CNS to those for GABA itself. The blood–brain barrier (*Figure 3.4*) prevents the easy entry of many substances into the brain compared with their uptake into other tissues. However, lipid-soluble substances, such as the barbiturate thiopentone, enter the brain quickly by passive diffusion. This rapid uptake allows thiopentone to exert its anesthetic effects extremely quickly. In contrast, other barbiturates, such as phenobarbitone, are weak acids and so may be ionized. This slows their entry into the CNS but produces a longer lasting effect. The life-threatening effects of barbiturate poisoning include depression of the centers in the CNS that control respiration and blood

circulation. Some barbiturates, for example phenobarbitone, can also induce the synthesis of monooxygenase enzymes and so, by altering the rate or route of metabolism of other drugs, can alter their toxicities.

There is no antidote for barbiturate poisoning. Primary care is to maintain a free airway, administer artificial respiration if required and forced alkaline diuresis. The pH dependence of ionization of many common barbiturates is exploited by infusions of large volumes of sodium hydrogen carbonate containing the osmotic diuretics urea or mannitol. This increases the pH of plasma relative to the cytoplasm of cells and increases the proportion of ionized barbiturate in the plasma causing more of the un-ionized drug to diffuse out of the tissues, including the brain, into the plasma. This can promote a diuresis as large as 12 dm^3 in 24 h. The ionized form is also excreted more rapidly since the alkalinity of the provisional urine ensures it remains ionized and cannot cross the tubule wall back into the plasma.

CARBON MONOXIDE

Carbon monoxide (CO) is a poisonous gas. However it is not an irritant and is odorless. Hence it is insidious and concentrations can build up with the victim being unaware of any danger. Carbon monoxide is no longer present in domestic gas in the UK but is still a major cause of poisoning, both accidental and intentional and results in the deaths of several hundred people in the UK each year. Sources of CO include domestic fires, ovens and boilers, coal gas, furnace gas, cigarette smoke, burning plastic and car exhausts, although catalytic converters have reduced the CO output from car petrol engines. Thus traffic policemen, firemen, those trapped in fires and some factory workers are all potentially at a greater risk. In the UK, the major cause of poisoning results from exposure to inefficient oxidation in engines and poorly maintained gas fires, ovens and boilers, especially where ventilation is inadequate.

The mechanism of CO poisoning is well understood at the biochemical level. The gas is absorbed rapidly through the lungs and binds to the iron atom of hemoglobin at same site as dioxygen, but about 240 times more strongly. This prevents the efficient distribution of oxygen to the tissues. The product of CO binding is carboxyhemoglobin. Carbon monoxide is potentially extremely poisonous at low concentrations. Given that air contains 21% O_2, approximately 0.1% CO will saturate 50% of the hemoglobin. Concentrations of 60% carboxyhemoglobin in the blood are usually fatal, even if maintained for only a few minutes. A concentration of 20% carboxyhemoglobin may not present obvious symptoms but the ability to perform tasks can be impaired. At 20–30%, the victim may have a headache, with raised pulse, dulling of the senses and feelings of weariness. Concentrations of 30–40% accentuate these symptoms and decrease the blood pressure so that exertions may lead to faintness. At 40–60% and above, the victim becomes unconscious and will suffer convulsions. Other clinical features include pink skin, nausea, vomiting, loss of hearing, hyperpyrexia, hyperventilation, a decrease in light sensitivity, renal failure and acidosis.

The main target organs of CO poisoning are the heart and brain. These organs extensively utilize aerobic metabolic pathways and so their abilities to sustain an oxygen debt are relatively poor. Death is due to brain tissue hypoxia although cardiac arrythmias and heart and respiratory failures may also occur. The duration of exposure is also a factor since hypoxic cell death is not instantaneous. Also, some individuals, for example those with anemia (*Chapter 13*), are more sensitive to CO poisoning than healthy people.

The treatment of CO poisoning involves removing its source and supplying the victim with fresh air or oxygen. The use of 100% oxygen at 2.5×10^5 Pa pressure, that is hyperbaric oxygen, increases the rate of dissociation of

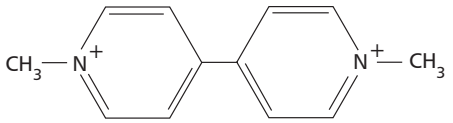


Figure 12.18 Paraquat.

carboxyhemoglobin and reduces its plasma half-life from 250 min in a patient breathing air to 23 min. Adding carbon dioxide can be useful as this reduces the half-life to 12 min at normal pressure.

PARAQUAT

Paraquat (*Figure 12.18*) is used widely as a weed killer, hence is often found in the home. Unfortunately paraquat has caused many hundreds of deaths both by accidental and deliberate poisoning, the latter including both suicide and homicide.

Paraquat is a local skin irritant, causing inflammation, although poisoning usually follows oral ingestion. The toxic effects are dose related and with small amounts there may be minimal damage that is reversible. Fatal doses cause a painful death within several days or weeks, with extreme abdominal pain, vomiting and diarrhea. The major target organs are the lungs with larger doses causing alveolar edema, resulting in destruction of lung tissues and fibrosis, if the patient survives beyond a few days. Pulmonary fibrosis and respiratory failure can, however, develop up to six weeks after ingestion. The kidneys, heart and liver may also be damaged but the lungs are particularly susceptible in paraquat poisoning because alveolar epithelial cells actively accumulate paraquat to toxic concentrations. Furthermore, the presence of large concentrations of oxygen in the organs exacerbates the morbid effects. Paraquat in alveolar epithelial cells is reduced by electron donors, such as NADH, to a stable reduced form (*Figure 12.19*). Given the

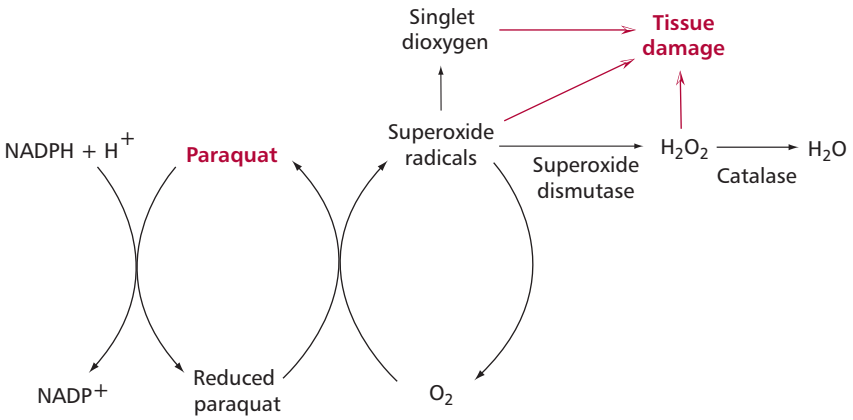


Figure 12.19 An overview of the detoxification and toxic effects of paraquat. See text for details.

prevailing aerobic conditions, this transfers an electron to dioxygen to form a superoxide radical:

$$O_2 + e^- \longrightarrow O_2^{\bullet-}$$

(superoxide radical)

Superoxide dismutases (SOD) can remove superoxide radicals by converting them to hydrogen peroxide:

$$2H^+ + O_2^{\bullet-} + O_2^{\bullet-} \xrightarrow{\text{SOD}} H_2O_2 + O_2$$

(hydrogen peroxide)

which can be degraded to water and dioxygen by the action of catalase:

$$2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O + O_2$$

However, the actions of SOD and catalase are likely to be overwhelmed in aerobic conditions and the superoxide radicals accumulate and react with hydrogen peroxide to give highly toxic hydroxyl radicals, particularly in the presence of ions of transition metals, such as iron and copper:

$$O_2^{\bullet-} + H_2O_2 \xrightarrow{Fe^{2+}/Cu^{2+}} OH^{\bullet} + OH^- + O_2$$

(hydroxyl radical)

These lead to a variety of toxic effects, such as lipid peroxidation (*Figure 12.20*). The resulting lipid peroxides may give rise to lipid radicals and membrane damage leading to tissue damage and fibrosis. Lipid peroxides will also oxidize glutathione (*Figure 12.6*) and its reoxidation further reduces the depleted amount of NADPH. This reduces the ability of the alveolar cells to carry out essential functions, such as biosynthetic repairs.

There is no antidote for paraquat poisoning and once it has accumulated in the lungs little can be done to prevent its toxic effects. Treatment largely consists of trying to prevent absorption by the gut by gastric lavage and by using Fullers Earth as an adsorbent. Hemoperfusion may also be used to reduce the concentration of any paraquat already absorbed.

METALS

The presence of certain metals in high concentrations may be toxic to humans. To diagnose metal toxicity, three features have to be identified, namely, a source of the toxic metal, the presence of signs and symptoms typical of toxicity by that metal and increased concentrations of the metal in the body tissues. Metals that are commonly screened for toxicity include lithium, aluminum and the heavy metals lead, arsenic, cadmium and mercury. Lithium is widely used therapeutically to treat patients with certain psychiatric disorders. However, plasma concentrations of lithium in excess of 1.5 mmol dm^{-3} should be avoided and regular measurements of serum lithium concentrations are important in monitoring therapy. Lithium toxicity is associated with tremors, drowsiness, tinnitus, blurred vision, polyuria, hypothyroidism and, in severe cases, renal failure and coma.

Acute poisoning with aluminum is extremely rare. Indeed, aluminum compounds are used for their antacid properties. The dietary intake of aluminum is 5 to 10 mg day^{-1} and this amount is removed completely by the kidneys. Unfortunately, patients with renal failure are susceptible to aluminum toxicity. They cannot remove the aluminum and, as the water used in dialysis may contain aluminum that can enter the body through the dialysis membrane, the metal can build up to toxic concentrations and cause osteodystrophy and encephalopathy. Aluminum toxicity is diagnosed by determining its concentration in plasma. Chronic toxicity occurs at concentrations above only 3 µmol dm^{-3} whereas 10 µmol dm^{-3} can cause acute poisoning. The treatment is aimed mainly at prevention. When aluminum poisoning does occur, then its excretion may be enhanced using chelating agents such as desferrioxamine.

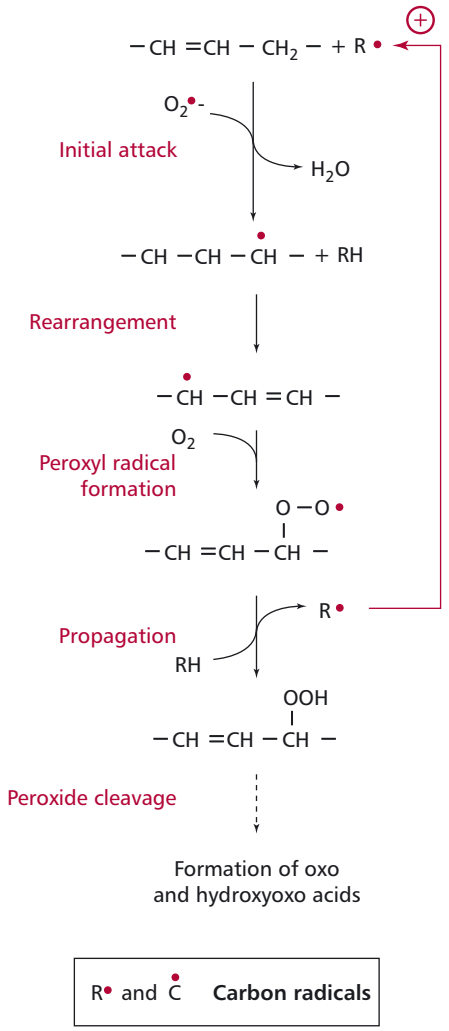


Figure 12.20 An overview of lipid peroxidation reactions. The peroxidation is initially started by a reactive radical. However, as carbon radicals are formed, the peroxidation becomes self sustaining.

BOX 12.1 Aluminum poisoning and Camelford, Cornwall

If aluminum sulfate, $Al_2(SO_4)_3.18H_2O$ (*Figure 12.21 (A)*) is dissolved in water it hydrolyzes to form sulfuric acid and a gelatinous precipitate of aluminum hydroxide:

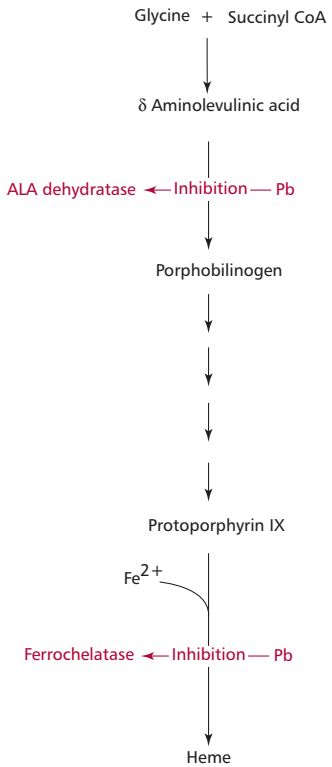
$$Al_2(SO_4)_3 + 6H_2O \rightarrow 3H_2SO_4 + 2Al(OH)_3$$

An 8% solution of aluminum sulfate is commonly used in sewage treatment and water purification (*Figure 12.21 (B)*) because it is a highly effective coagulant that reacts with suspended organic matter to form flocs of large size. These rapidly settle, reducing the load of suspended solids and the turbidity of the water or sewage so improving their quality and lengthening the effective life of water and sewage filters.

The discharge of aluminum sulfate into aquatic environments should be minimized as it can clog the gills of marine organisms. With regard to handling, it is regarded as a weak acid and should be treated accordingly: contact with eyes, skin and clothing and repeated and prolonged exposure should be avoided. However, tests have shown it to be a minimal irritant and a nonirritant to rabbit eyes and skin respectively. Its LD_{50} dose in rabbits is greater than 5 g kg^{-1} so, in general, its ingestion is thought to be relatively harmless.

Unfortunately, in 1988 a contractor accidentally dumped 20 tons of aluminum sulfate into the wrong tank at a water

Figure 12.21 (A) Hydrated aluminum sulfate as seen using polarized light. (B) A modern water purification plant. Courtesy of United Utilities, Warrington, UK.



Lead is a heavy metal found in the environment. Common sources include paints, old water pipes, petrol fumes, industrial pollution and medication and cosmetics from the Indian subcontinent. Poisoning by lead can be acute, which is rare, or, more commonly, chronic. It results from inhalation, dermal absorption or ingestion, where it is actively absorbed by the GIT through the calcium transport system. All tissues are affected by lead poisoning although organ pathology is associated primarily with the nervous system and the blood. In the blood, lead is concentrated in the erythrocytes where it inhibits the activities of aminolevulinic acid (ALA) dehydratase and ferrochelatase, enzymes involved in the synthesis of heme (*Figure 12.22*). Inhibition of ALA dehydratase is the most sensitive measure of lead poisoning. Concentrations of lead in the blood in excess of 0.49 μmol dm^{-3} are associated with illness in children. If the concentration of lead increases above 3.4 μmol dm^{-3}, individuals

Figure 12.22 A schematic showing the enzymes of heme biosynthesis affected by lead poisoning. ALA is aminolevulinic acid. See text for details.

treatment plant that supplied the 2500 residents of the small town of Camelford in Cornwall, UK, with domestic water. The mistake was later attributed to the contractor being a relief driver who was not familiar with the layout of the plant, itself an unmanned installation and so on site advice was not available. The contaminated water entered the town's supplies. Its pH was as low as 3.9 and contained concentrations of aluminum and sulfate of 620 and 4500 mg dm^{-3} respectively. Within two days, many residents of Camelford complained about the poor taste of the water, skin irritation and corrosive effects of the water on plumbing and fixtures. Although the cause of the problem with the water was not solved for two days, the responsible water authority assured the towns people that the water, while tasting slightly acidic, was safe to drink. Once the cause of the problem was determined, a program of flushing the water supplies rapidly reduced the concentration of aluminum to 1 mg dm^{-3}. After several months, over 400 complaints had been made relating to skin rashes, sore throats, painful joints, memory losses and exhaustion. Following the incident, the water authority responsible was prosecuted for causing a public nuisance and fined £10 000 with additional legal costs of £25 000.

Reports were published in 1989 and 1991 following investigations by a UK government appointed Lowermoor Incident Health Advisory Group into complaints of long-standing ill health in residents of Camelford. Both studies concluded that there was no evidence of any increase in ill health in the community related to any toxic effects of the aluminum contamination of the water. Rather, the symptoms suffered by affected individuals were largely attributed to anxiety. However, these findings are inconsistent with those of a scientific study conducted in 1991, but not published until 1999 for legal reasons, which showed that there was an association between the contamination and reduced cerebral functions in affected residents. Criticisms have been aimed at this study. The incident is still surrounded with considerable controversy, with multiple claims for damages, and a more in-depth third inquiry into possible delayed or persistent health effects was established by the UK government in 2001. This inquiry reported in 2005 and concluded that although it was unlikely that any of the chemicals involved in the water contamination were responsible for any long-term effects, it did recommend further studies on the effects of the contaminants on neurological health, on diseased joints in the area and on the development of children below the age of 12 months at the time of the aluminum sulfate discharge.

whose occupation exposes them to lead must be removed from its source. Clinical features of lead poisoning include lethargy, abdominal discomfort, anemia, constipation, encephalopathy and motor peripheral neuropathy.

The management of patients with lead poisoning involves identifying the lead source and removing the patients from it. Patients are placed on chelating agents, such as EDTA (*Figure 12.23*) that is effective in both acute and chronic lead poisoning, but has to be given intravenously. Another chelating agent, dimercaptosuccinic acid is less efficient as a chelator but can be given orally.

Chronic arsenic poisoning is associated with well water contaminated with arsenical pesticides or, classically, with murder! Arsenic occurs in a number of different forms, most of which are toxic although arsenite (AsO_2^-) is much more

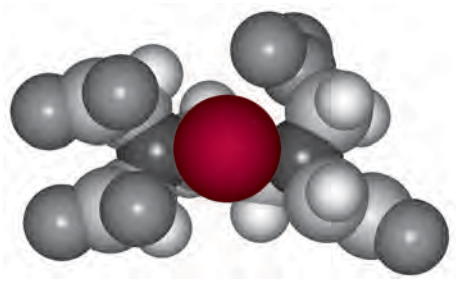


Figure 12.23 Computer generated structure of lead EDTA. The large central red sphere represents the bound lead atom.

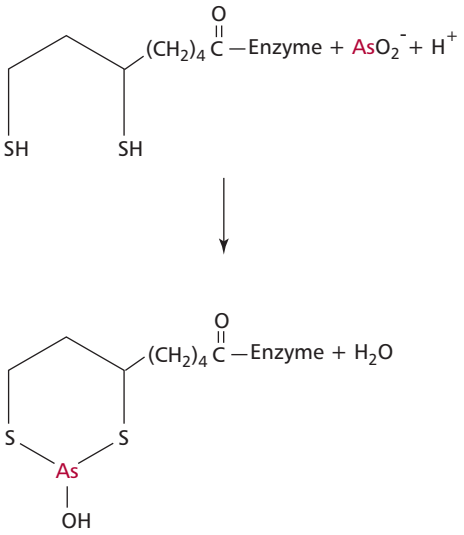


Figure 12.24 The reaction of arsenite with enzyme-bound lipoic acid.

so than arsenate ($HAsO_4^-$). Arsenate substitutes for P_i in biological systems, hence less ATP is produced. Arsenite toxicity is associated with the formation of a stable complex with enzyme-bound lipoic acids (*Figure 12.24*). Indeed, arsenic poisoning can be explained by its ability to inhibit enzymes, such as pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase and branched chain α-oxoacid dehydrogenase, that require lipoic acid as a coenzyme. Chronic poisoning with arsenic is usually associated with diarrhea, polyneuropathy and dermatitis whereas acute poisoning with arsenic gives rise to severe gastrointestinal pain, vomiting and shock. Poisoning can be diagnosed by determining the concentration of arsenic in the hair or fingernails of the victim. Values larger than 0.5 μg g^{-1} of hair indicate a significant exposure to arsenic. The hair of a person chronically exposed to arsenic could have 1000 times as much as this. Treatment of arsenic poisoning is aimed at enhancing its excretion using chelating agents.

Chronic cadmium toxicity may occur in workers exposed to fumes in cadmium-related industries, although concentrations of cadmium are twice as high in tobacco smokers compared with nonsmokers. Concentrations in the serum greater than 90 nmol dm^{-3} are associated with toxicity. Cadmium poisoning causes influenza-like symptoms, such as chills, fever, muscular aches, nausea, vomiting, abdominal pain, and diarrhea. However, these symptoms may resolve after a week provided there is no respiratory damage. More severe exposures can cause bronchitis and pulmonary edema and occasionally cardiovascular collapse. Long-term exposure may lead to nephrotoxicity with proteinuria, bone disease and hepatotoxicity. The treatment of cadmium

BOX 12.2 The death of Napoleon: arsenic and wallpaper

Following his defeat at the Battle of Waterloo in 1815, Napoleon Bonaparte was exiled on St Helena. This is a volcanic island only about 6 by 8 miles in size in a remote region of the south Atlantic. During most of his exile, Napoleon lived in Longwood House with a retinue of about 20. Napoleon never left St Helena and he died in 1821 (*Figure 12.25*). A postmortem of the body showed an enlarged liver and stomach lesions. It was concluded he had died of a perforated stomach ulcer that had turned cancerous. Napoleon was initially buried on St Helena but his body was removed 20 years later and reburied at Les Invalides on the banks of the Seine in Paris, as had been his wish.

In 1952, Forshufvud read an account of Napoleon's death and, given his symptoms, concluded that Napoleon may have been murdered by arsenic poisoning. White arsenic or arsenic oxide is extremely poisonous and its symptoms, stomach pains, diarrhea, shivering and swollen limbs, can be confused with other illnesses. Indeed, a few days prior to his death, Napoleon had requested that his doctor make a full examination, particularly of his stomach and some of his symptoms did correspond to those of arsenic poisoning.

It is possible to poison a person by slow exposure to small quantities of arsenic over an extended period. A number of

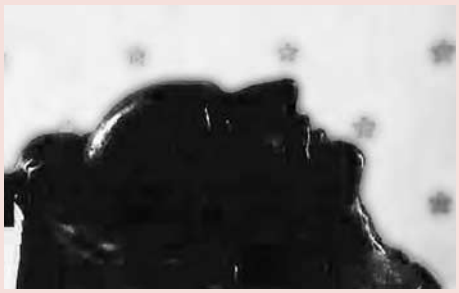


Figure 12.25 Napoleon's deathmask. Courtesy of H. Ball, www.grand-illusions.com.

Napoleon's staff had kept locks of his hair, which were subsequently passed down the generations. Hair is largely composed of keratin, a protein that contains sulfur. If arsenic is ingested, some of it will bind to the sulfur atoms and since hair is constantly growing it can even show how the concentrations of arsenic in the body change with time. Hair is resistant to degradation and some of the samples of Napoleon's hair could still be analyzed in the 1960s using neutron activation

poisoning usually involves removal from exposure. Treatment with chelating agents is not effective because the soluble form of cadmium damages the kidney.

Mercury poisoning can be acute or chronic. It occurs following exposure to mercury vapor, inorganic salts or organic compounds of mercury. Mercury poisoning is primarily occupational but can be caused by contaminated food. The clinical features of acute mercury poisoning include coughing, bronchiolitis, pulmonary edema, pneumonitis, peripheral neuropathy and neuropsychiatric problems. Chronic mercury poisoning causes anorexia, sweating, insomnia, impaired memory, paresthesiae of the lips and extremities and renal tubular damage. Mercury poisoning is usually diagnosed by determining the concentration of mercury in serum and urine. Urine mercury/creatinine ratios are often used to assess exposure. Ratios of 40 to 100 nmol $mmol^{-1}$ require monitoring and further investigation, while values of greater than 100 nmol $mmol^{-1}$ require the patient to be removed from the source of mercury.

Acute mercury poisoning is treated with chelating agents such as dimercaprol, to increase its excretion into bile and urine. Methylmercury is an organic form of mercury that has been used to preserve seed grain. Methylmercury poisoning can be caused by eating meat from animals which have been fed treated seedgrain. An outbreak of mercury poisoning began in the 1950s in Minamata bay in Japan and affected over 3000 villagers who ate fish contaminated with methylmercury.

techniques. A number of hairs were found to contain abnormal amounts of arsenic. Naturally this led to speculation that Napoleon had been murdered. However, other possible sources of arsenic poisoning are paints and wallpapers. The pigment, Scheele's Green contains copper arsenite and has been used in fabrics and wallpapers since about 1770. Unfortunately throughout the nineteenth century many people were made ill or killed by this wallpaper. In 1893, Gosio determined the pathological mechanism: if wallpapers containing Scheele's Green become damp and contaminated with molds, such as *Scopulariopsis brevicaulis*, the molds can metabolize the arsenic salts to volatile poisonous compounds, for example trimethyl arsine, which are released in a vaporous form into the atmosphere. Following a public appeal in 1980 for help in making a radio program, a small piece of wallpaper from the wall of the drawing room of Longwood House was located (*Figure 12.26*). The sample of paper showed a single star and its main colors are green and brown. Gold and green were the Imperial colors but it is possible that the brown was originally gold in color. More significantly, X-ray fluorescence spectroscopy analysis showed the wallpaper to contain appreciable quantities of arsenic. Longwood House was notoriously damp, and the paper would have degraded to release volatile arsenic compounds. Further, many of its inhabitants other than Napoleon had apparently also become ill and complained of the 'bad air', so it is possible that he might have been a victim of British wallpaper makers rather than a deliberate murder plot. However, the amount of arsenic released could not have been large, and apparently was insufficient to have killed Napoleon although once he did become ill with a stomach ulcer, the arsenic could have exacerbated his condition.

Figure 12.26 A sample of Napoleon's wallpaper. Courtesy of H. Ball, www.grand-illusions.com.

CASE STUDY 12.1

Helen, an 18-year-old, was admitted to the Accident and Emergency Department of her local hospital. She was found in her bedroom with an empty bottle of aspirin tablets. On admission, Helen was in a confused state, sweating and breathing heavily. There was clinical evidence for mild dehydration. She had a pulse rate of 112 per min and blood pressure of 110/70 mmHg. Her body temperature was 39°C. Laboratory investigations give the following profile (reference ranges are shown in parentheses).

Na^+	132 mmol dm^{-3} (135–145 mmol dm^{-3})
K^+	3.4 mmol dm^{-3} (3.6–5.0 mmol dm^{-3})
HCO_3^-	11 mmol dm^{-3} (22–30 mmol dm^{-3})
Urea	11 mmol dm^{-3} (3.3–6.7 mmol dm^{-3})
Glucose	3.5 mmol dm^{-3} (2.8–6.0 mmol dm^{-3})
Salicylate	4.6 mmol dm^{-3} (up to 2.5 mmol dm^{-3} is therapeutic)
pH	7.20 (7.36–7.44)
*P*CO2	3.6 kPa (4.5–6.0 kPa)
Prothrombin time	18 s (14 s)

Questions

(a) What can be concluded from the clinical data?

(b) What treatment would be suitable?

CASE STUDY 12.2

Olga, a 25-year-old, was admitted to hospital after being found unconscious by her flatmate. It was reported that empty vodka and paracetamol bottles had also been discovered in her flat. On admission to an Accident and Emergency Department, Olga's breath smelt of alcohol and her serum paracetamol concentration was 105 mg cm^{-3}. Her liver function tests were normal as was the prothrombin time. Her serum alanine aminotransferase levels showed a transient increase over the next few days but gradually fell back within the reference range.

Questions

(a) Comment on these clinical findings.

(b) What treatment should Olga be given?

CASE STUDY 12.3

Ed is a building site worker aged 58 who has been a heavy drinker for over 30 years. He was admitted to hospital after collapsing outside a public house. He smelt strongly of alcohol, was confused and unsteady on standing. He complained of fatigue, nausea, particularly early in the morning, and a loss of appetite. A physical examination detected abdominal tenderness and enlargement of the liver and gastrointestinal varicose veins. His blood alcohol concentration was 79 mmol dm^{-3}.

Maureen aged 52 was admitted into hospital at a similar time. She presented with general GIT problems and frequent diarrhea. She was subjected to considerable stress at work and admitted she had been drinking 'rather heavily'.

Ed's Ca^{2+} and Mg^{2+} blood concentrations were low and his clotting time extended. His urinary urea excretion was also subnormal. Liver function tests were performed on sera from both patients. The results are shown below (reference ranges are shown in parentheses).

	Ed	Maureen	
Total protein / g dm^{-3}	67	78	(60–84)
Albumin / g dm^{-3}	31	39	(35–50)
Total bilirubin	57	14	(3–15)
Alkaline phosphatase / U dm^{-3}	720	335	(100–300)
Alanine transaminase / U dm^{-3}	34	91	(5–35)
Aspartate transaminase / U dm^{-3}	41	162	(10–40)
γ-glutamyltransferase / U dm^{-3}	780	455	(7–45)

Questions

(a) Suggest why the tests above are particularly indicative of the state of the health of the liver.

(b) Does Ed or Maureen show the greater liver degeneration?

CASE STUDY 12.4

John's girlfriend found him in his closed garage unconscious in his car with the engine running. He was taken to the hospital immediately. The following blood results were obtained (reference ranges are shown in parentheses).

H^+	50 nmol dm^{-3}	(36–46 nmol dm^{-3})
HCO_3^-	15 mmol dm^{-3}	(22–30 mmol dm^{-3})
PCO_2	3.5 kPa	(4.5–6.0 kPa)
Hemoglobin	150 g dm^{-3}	(130–180 g dm^{-3})
Lactate	10 mmol dm^{-3}	(0.65–2.0 mmol dm^{-3})

Questions

(a) Suggest a plausible explanation for these data?

(b) How should John be treated?

12.6 SUMMARY

The body is exposed daily to many chemicals, some of which have the potential for harm. These chemicals may be ingested with food and drink, they may be therapeutic or recreational drugs or they may be toxins from microorganisms or the abiotic environment. Xenobiotics may be detoxified in the liver, by conversion to more water-soluble compounds, which are then excreted through the kidneys. Sometimes this process results in more harmful compounds being produced, as is the case with paracetamol poisoning. Clinical investigations of suspected poisoning include liver function tests, analysis of blood gases and determination of acid–base status.

The commonest cases of poisoning involve accidental or deliberate overdose with common analgesics such as paracetamol or aspirin but abuse of alcohol is an increasing problem in developed countries, leading to liver damage in the patient. In addition, carbon monoxide poisoning may be insidious and fatal, in badly ventilated houses warmed by faulty gas heaters. Treatment of poisoning first involves identification and removal of the poison; thereafter treatment depends on the nature of the poison involved. Unfortunately, some poisons, such as paraquat, are invariably fatal.

QUESTIONS

1. Which of the following produces a combination of respiratory alkalosis and metabolic acidosis?
   (a) paracetamol poisoning;
   (b) ethylene glycol poisoning;
   (c) aspirin poisoning;
   (d) lead poisoning;
   (e) carbon monoxide.

2. Which of the following is the toxin produced during paracetamol poisoning?
   (a) paracetamol-3-mercapturic acid;
   (b) glutathione;
   (c) *N*-acetylbenzoquinoneimine;
   (d) UDP-glucuronyl transferase;
   (e) trimethylarsine.

3. What are the possible prognoses for a patient who has taken an overdose of paracetamol if treated within hours or if treatment is delayed for several days?

4. Disulfiram is an inhibitor of aldehyde dehydrogenase. It was used as the drug antabuse to deter alcohol consumption in chronic alcoholics. Suggest a plausible reason why treatment with it should deter alcoholics from consuming alcoholic drinks.

5. Suggest why alcohol should be consumed with caution or avoided when taking other drugs.

6. A 10-year-old Asian girl was admitted to hospital where she presented with vomiting, nausea, and neurological symptoms. She had been using a traditional cosmetic called surma that was applied around the eyes. What laboratory investigations should be applied to this patient?

7. A 50-year-old scientific instrument technician repaired old scientific gauges that often contain mercury. One winter, he complained of weight loss, weakness, symptoms that resembled influenza and depression. On examination he had muscle weakness and wasting. A urine sample was examined and was found to contain 180 nmol Hg per mmol creatinine. How should this patient be treated?

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