1 Drug Absorption, Distribution and Elimination

Drugs can be defined as agents that modify normal biological responses and thus produce pharmacological effects. These are frequently dependent on the transfer of drugs across one or more cellular membranes, whose structure and physicochemical properties govern the rate and extent of drug transfer.

Cellular membranes are usually about 10 nm wide and consist of a bimolecular layer of phospholipid and protein (Fig. 1.1). The lipid layer is relatively fluid, and individual phospholipid molecules can move laterally within the membrane. Extrinsic (peripheral) proteins are present on the external or internal aspect of the membrane. In contrast, intrinsic (integral) proteins traverse the entire width of the cell membrane and may form an annulus surrounding small pores or ion channels approximately 0.5 nm in diameter (Fig. 1.1). Both intrinsic and extrinsic proteins can act as enzymes or receptors and may mediate the active transport of drugs.

Approximately 5–10% of the cell membrane consists of carbohydrates, mainly glycolipids or glycoproteins. They are believed to be responsible for the immunological characteristics of cells and play an important part in molecular recognition. Many cell membranes also contain inorganic ions (e.g. Ca^{2+}).

Lipid cell membranes are excellent electrical insulators. Consequently, there may be differences in electrical potential across cellular membranes, which can facilitate or impede the passive transport of charged molecules through ion channels.

Transfer of drugs across cell membranes

In general, drugs may cross cell membranes by
- Passive diffusion
- Carrier transport

Passive diffusion

In most cases, drugs cross cell membranes by passive diffusion down a concentration gradient due to random molecular movements produced by thermal energy. The rate of drug transfer is directly proportional to the difference in concentration, and to the solubility of drugs in membranes, which is extremely variable. Highly polar substances (e.g. quaternary amines) are insoluble in membrane lipids and are unable to penetrate cellular membranes. In contrast, drugs with a high lipid solubility (e.g. diazepam, fentanyl) readily dissolve in membrane phospholipids and rapidly diffuse across cellular membranes. Other less lipid-soluble drugs (e.g. morphine) diffuse more slowly and their onset of action is often delayed.

Molecular size is a less important factor in the passive diffusion of drugs. Some low molecular weight compounds may diffuse through ion channels, or penetrate small intercellular or paracellular channels (particularly in 'leaky' epithelial membranes). In contrast, molecules larger than 100–200 Da are usually unable to cross cell membranes. The permeability of vascular endothelium is greater than other tissues, and most ionized compounds can readily cross capillary membranes.

Most drugs are weak acids or weak bases and are thus present in physiological conditions in both an ionized and a non-ionized form. Their ionization or dissociation can be represented by the equations:

$$AH \rightleftarrows A^- + H^+ \quad \text{(for acids)}$$

$$BH^+ \rightleftarrows B + H^+ \quad \text{(for bases)}$$

Weak acids and bases are predominantly present as the species AH and BH^+ in acidic conditions, but as A^- and B in alkaline conditions. The non-ionized forms AH and B are lipid soluble and can readily diffuse across cell membranes, while the ionized forms A^- and BH^+ are effectively impermeable. As the proportion of the drug that is present in the non-ionized form is dependent on pH, differences

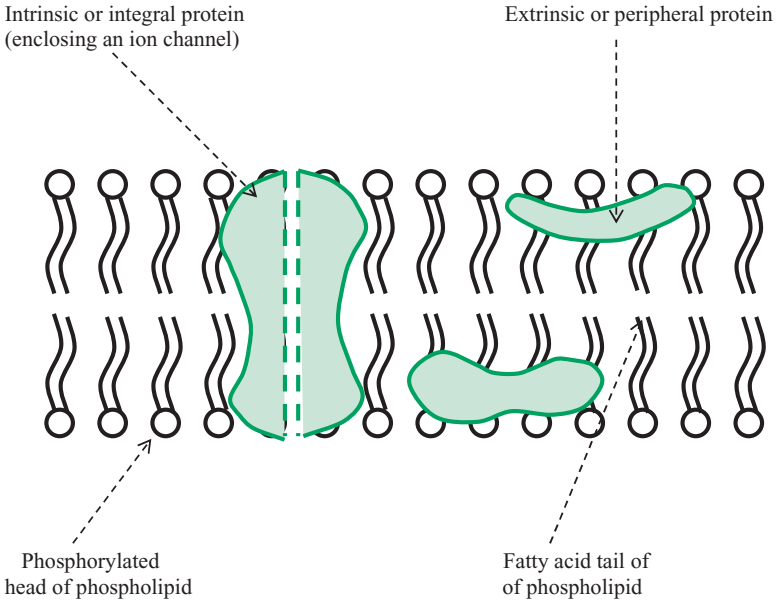

Fig. 1.1 The phospholipid and protein structure of a typical cell membrane.

in H^+ concentration across cellular membranes can provide a diffusion gradient for the passive transfer of the non-ionized form.

Consider a weak acidic drug that dissociates in the manner:

$$AH \rightleftarrows A^- + H^+$$

From the Henderson–Hasselbalch equation, it can be shown that

$$pK_a - pH \rightleftarrows \log \frac{[AH]}{[A^-]},$$

where [AH] and $[A^-]$ are the concentrations of non-ionized and ionized forms and pK_a (the negative logarithm of the dissociation constant) is the pH value at which $[AH] = [A^-]$. If the pK_a of the drug is 6, at pH 2 (e.g. in gastric fluid), almost 100% is present in the form AH (Fig. 1.2). This non-ionized form will rapidly diffuse into plasma (pH 7.4) where approximately 96% will be converted to A^-, providing a concentration gradient for the continued diffusion of AH. Subsequent transfer of the drug to other sites will also be dependent on the relative pH gradient. At pH 8, as in interstitial fluid or alkaline urine, the concentration of AH is less than at pH 7.4. A gradient is thus created for the passive diffusion of AH across renal tubular epithelium, followed by its subsequent ionization to A^- and elimination from the body (Fig. 1.2). By contrast, at a urine pH of 7 or less, the concentration of AH is greater in urine than in plasma, and the excreted drug will tend to diffuse back into plasma.

In a similar manner, pH gradients govern the non-ionic diffusion of weak bases that associate with hydrogen ions. In these conditions,

$$B + H^+ \rightleftarrows BH^+$$

From the Henderson–Hasselbalch equation, it can be shown that

$$pK_a - pH \rightleftarrows \log \frac{[BH^+]}{[B]},$$

where $[BH^+]$ and [B] are the concentrations of the ionized and the non-ionized forms and pK_a is the pH value at which $[BH^+] = [B]$. If the pK_a of the basic drug is 7, at pH 2 (e.g. in the stomach), almost 100% is present as the ionized form BH^+ (Fig. 1.3). At pH 5.5 (e.g. in the small intestine), only 3% is present as the non-ionized form B, and thus available to diffuse across the cell membrane. Although the effective pH gradient does not facilitate the non-ionic diffusion of weak bases from the small intestine (pH 5.5) to plasma (pH 7.4), the continuous perfusion of intestinal capillaries provides a small concentration gradient for their absorption.

By contrast, weak bases at pH 7.4 (e.g. in plasma) are mainly present as the non-ionized species B. In these

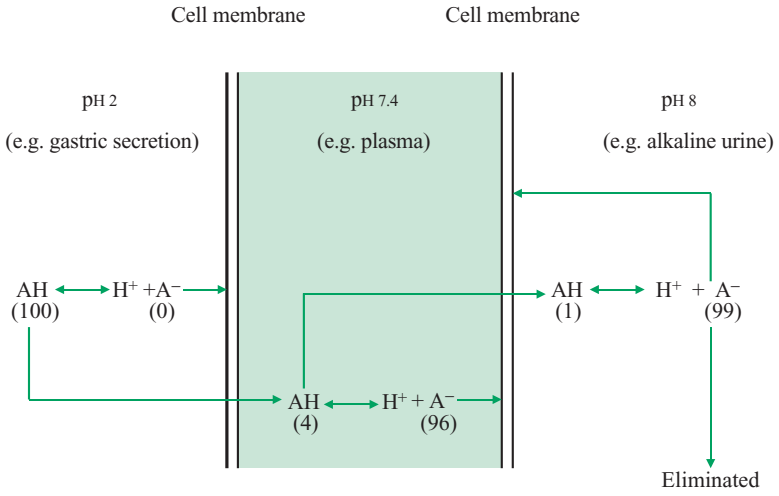

Fig. 1.2 Non-ionic diffusion of the weak acid AH ($pK_a = 6$). Only the non-ionized form AH can diffuse across cell membranes, and the diffusion gradient is dependent on pH differences between compartments or tissues. Numbers in parentheses correspond to the percentage of the drug present as AH and A^- at pH 2, 7.4 and 8.

conditions, there is a large concentration gradient that facilitates their diffusion into the stomach (pH 2) and into acid urine (pH 5). Following intravenous administration of fentanyl, the initial decline in plasma concentration may be followed by a secondary peak 30–40 minutes later. Fentanyl is a weak base which can diffuse from plasma (pH 7.4) to the stomach (pH 2), due to the large concentration gradient that is present, and its subsequent reabsorption from the small intestine is responsible for the secondary rise in the plasma concentration. Similarly, weak bases rapidly diffuse from plasma (pH 7.4) to urine (pH 5) as the non-ionized species B, where they are converted to the ionic form BH^+ and rapidly eliminated (Fig. 1.3).

In theory, modification of urine pH can increase the proportion of weak acids ($pK_a = 3.0–7.5$) and weak bases ($pK_a = 7.5–10.5$) that are present in an ionized form in urine, and thus enhance their elimination in drug-induced poisoning. Although forced alkaline diuresis was once extensively used in drug overdosage, as with salicylates or phenobarbital, it has little or no place in current therapy. It is a potentially hazardous procedure that requires the infusion of relatively large amounts of fluid and the use of

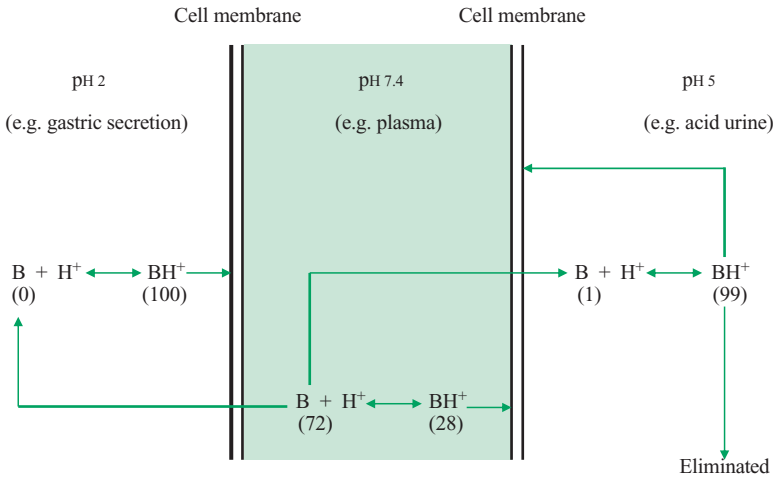

Fig. 1.3 Non-ionic diffusion of the weak base B ($pK_a = 7$). Only the non-ionized form B can diffuse across cell membranes, and the diffusion gradient is dependent on pH differences between compartments or tissues. Numbers in parentheses correspond to the percentage of the drug present as B and BH^+ at pH 2, 7.4 and 5.

loop diuretics or mannitol. In addition, pulmonary and cerebral oedema are possible complications, particularly in the elderly.

Carrier transport

Carrier transport can be divided into two main types:

- Facilitated diffusion
- Active transport

Facilitated diffusion

Facilitated diffusion is a form of carrier transport that does not require the expenditure of cellular energy. Many physiological substrates combine with specific sites on intrinsic proteins, resulting in conformational (allosteric) changes in protein structure. These changes facilitate the transcellular transport of many endogenous compounds. In these conditions, physiological substrates enter cells down a concentration gradient, but at a faster rate than anticipated from their lipid solubility or molecular size. Facilitated diffusion mediates the absorption of some simple sugars, steroids, amino acids and pyrimidines from the small intestine and their subsequent transfer across cell membranes.

Active transport

In contrast, active transport requires cellular or metabolic energy and can transfer drugs against a concentration gradient. In some instances, metabolic energy is directly produced from the hydrolysis of ATP (primary active transport). More commonly, metabolic energy is provided by the active transport of Na^+, or is dependent on the electrochemical gradient produced by the sodium pump, Na^+/K^+ ATPase (secondary active transport). It is generally considered that the drug or substrate initially combines with an intrinsic carrier protein (which may be an ion channel or Na^+/K^+ ATPase). The drug–protein complex is then transferred across the cell membrane, where the drug is released and the carrier protein returns to the opposite side of the membrane.

Active transport systems are saturable and specific and can be inhibited by other drugs (Chapter 4). They play a crucial role in the transfer of drugs across cell membranes at many sites, including the small intestine, the proximal renal tubule, the biliary canaliculus and the choroid plexus (Tables 1.1 and 1.2). A drug transport protein (P-glycoprotein) appears to play an important role as an efflux pump at many of these sites (i.e. it transports drugs from intracellular fluid across plasma membranes). Other active transport systems transfer physiological substrates across cell membranes. For example, at sympathetic nerve endings the transport of noradrenaline across the neuronal membrane ($Uptake_1$) is coupled to the active exclusion of Na^+ by the sodium pump.

Table 1.1 Some acidic and basic drugs eliminated from plasma by active transport in the proximal renal tubule.

Acidic drugs	Basic drugs
Penicillins	Dopamine
Cephalosporins	Morphine
Salicylates	Neostigmine
Sulphonamides	Lidocaine
Thiazide diuretics	Quinidine
Furosemide	
Chlorpropamide	
Methotrexate	

Plasma concentration of drugs and their pharmacological effects

Although the plasma concentrations of drugs can usually be measured, it is often impossible to determine their effective concentration in tissues. In some instances, it may be possible to derive an approximate estimate of their concentration by pharmacokinetic techniques (Chapter 2). The principal factors that determine the plasma concentration of drugs are

- Absorption
- Distribution
- Metabolism
- Excretion

Table 1.2 Some acidic and basic drugs secreted from liver cells into biliary canaliculi.

Acidic drugs	Basic drugs
Amoxicillin	Vecuronium
Ampicillin	Pancuronium
Cefaloridine	Glycopyrronium
Sulphobromophthalein	Mepenzolate
Probenecid	
Rifampicin	

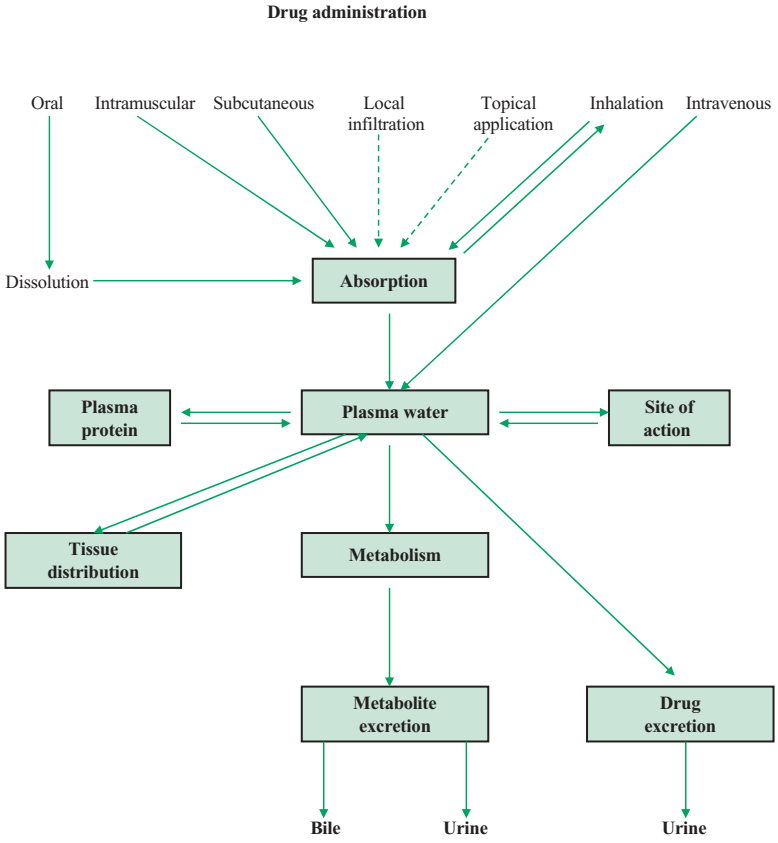

Fig. 1.4 The relation between drug absorption, distribution, metabolism and excretion, and the concentration of drugs at their site of action.

These factors also affect the concentration of drugs at their site of action (Fig. 1.4), and thus modify the magnitude and duration of their effects and the time course of drug action.

Drug administration

Drugs are most commonly administered orally, by subcutaneous, intramuscular, or intravenous injection, by local infiltration or by inhalation. Occasionally, drugs are given sublingually, rectally, or by application to other epithelial surfaces (e.g. the skin, nose or eye).

Oral administration

Oral administration is obviously most convenient and acceptable for the patient. Nevertheless, not all drugs can be taken orally. Some drugs are unstable in the acid medium of the stomach (e.g. benzylpenicillin, erythromycin), while others may irritate the gastric mucosa and cause nausea, vomiting or haemorrhage (e.g. salicylates, concentrated solutions of most salts). In recent years, these problems have been partially avoided by the use of enteric-coated tablets or slow-release preparations, which only dissolve in the upper small intestine.

When drugs are taken orally, there is usually a latent period of 30–120 minutes before they reach their maximum concentration in plasma. The presence of adequate drug concentrations in plasma is dependent on

- Drug dissolution
- Drug absorption
- The absence of significant first-pass effects in the gut wall or the liver

Drug dissolution

The dissolution of agents administered as tablets or capsules is essential before drug absorption can take place. Drug dissolution usually occurs in the stomach and may

be dependent on gastric acidity. Variations in the speed of dissolution and the rate and extent of gastric emptying can thus affect the amount of drug in solution in the upper part of the small intestine (where absorption mainly occurs).

Many pharmaceutical factors influence the dissolution of tablets and capsules, including particle size, chemical formulation, the inclusion of inert fillers and the outer coating of the tablet. In these circumstances, proprietary or generic preparations of the same drug may have different dissolution characteristics and thus produce a range of plasma concentrations after oral administration. At one time, differences in the potency of digoxin tablets suspected from clinical observations were eventually traced to variations in the dissolution of different preparations of the drug. Similarly, toxic effects were produced by diphenylhydantoin (phenytoin) tablets when an excipient (calcium sulphate) was replaced by lactose. In these conditions, dissolution was more rapid, resulting in faster and more extensive absorption, and higher blood levels of the drugs.

Sustained release preparations

Sustained release oral preparations usually consist of multi-lamellated erodable polymers and are designed to allow the slow continuous release of drugs. Other formulations may permit the release of fixed doses of a drug at regular intervals. Some preparations are osmotically active, or incorporate an ion-exchange resin that allows drugs to be released in solution at a defined ionic concentration and pH. Their use often results in greater convenience and safety, improves bioavailability and causes less variability in plasma concentrations. They may also reduce side effects, drug dosage, frequency of administration and cost.

Many drugs may be administered in this manner, including some opioid analgesics, NSAIDs, bronchodilators, antihypertensive drugs, antiarrhythmic agents and potassium salts.

Drug absorption

The absorption of drugs in the stomach and the small intestine is primarily dependent on their physicochemical properties, particularly their lipid solubility. Non-ionized compounds (e.g. ethyl alcohol) and low molecular weight substances (e.g. urea) readily cross cell membranes by passive diffusion and are easily and rapidly absorbed from the gut. Drugs that are weak acids (e.g. aspirin) are predominantly non-ionized and lipid-soluble in acidic conditions and partially diffuse into plasma from the stomach. In contrast, basic drugs (e.g. propranolol, most benzodiazepines) are less ionized and more lipid-soluble in alkaline conditions and are preferentially absorbed from the duodenum (pH 5–6). Strong bases (e.g. quaternary amines) are always ionized in solution and are not significantly absorbed from the gut.

In practice, other factors influence the site of drug absorption. Mucosal surface area is more extensive in the upper small intestine than the stomach, and most drugs, whether acids or bases, are predominantly absorbed from the duodenum. Nevertheless, some non-ionized compounds and acidic drugs may be partially absorbed from the stomach and may produce a rapid increase in plasma concentration after oral administration.

Drugs that affect gastric motility

Compounds affecting gastric motility can modify drug dissolution, and influence the rate, but not the extent, of drug absorption. In particular, drugs that slow gastric emptying (e.g. atropine, morphine) decrease the rate of drug absorption. Other drug interactions, as between tetracyclines and iron, or colestyramine and digoxin, may affect the extent of drug absorption and thus modify systemic bioavailability. Drug absorption may be reduced in pathological conditions affecting the gastrointestinal tract, particularly in coeliac disease, Crohn's disease, obstructive jaundice, or after extensive resection of the small intestine.

Drug absorption and carrier transport

Although most drugs are absorbed from the stomach and small intestine by passive diffusion, occasionally absorption is dependent on carrier transport. Levodopa is absorbed by a carrier protein that normally transports amino acids, and fluorouracil is absorbed by the carrier that transports pyrimidine bases. In contrast, a carrier protein (P-glycoprotein) can transport many drugs from the intracellular environment to the intestinal lumen and actively opposes drug absorption. It is constitutively expressed on the luminal surface of most intestinal cells.

Subcutaneous and intramuscular administration

Some drugs do not produce adequate plasma concentrations or pharmacological effects after oral administration and are usually given subcutaneously or intramuscularly.

In particular, drugs broken down in the gut (e.g. benzylpenicillin, polypeptide hormones), are poorly or unpredictably absorbed (e.g. aminoglycosides), or drugs that have significant first-pass effects (e.g. opioid analgesics), are often given by these routes. Drugs are sometimes given by the intramuscular route when patients are intolerant of oral preparations (e.g. iron salts) or when patient compliance is known to be poor (e.g. in schizophrenia).

Absorption of drugs by subcutaneous or intramuscular administration is not usually dependent on the dissociation constant of the drug or its pH, but is often determined by regional blood flow. The onset of action of a drug given by intramuscular injection is usually more rapid and the duration of action shorter than when the subcutaneous route is used because of differences in the perfusion of muscle and subcutaneous tissues. The subcutaneous administration of relatively insoluble drugs or drug complexes is sometimes used to slow the rate of absorption and prolong the duration of action (e.g. with preparations of insulin or penicillin). In these conditions, the rate of dissolution of the drug from the complex and its subsequent absorption governs the duration of action.

Implantable subcutaneous preparations are sometimes used in hormone replacement therapy (e.g. estradiol and testosterone implants). Controlled release systems capable of an increased release rate on demand (by the external application of magnetic or ultrasonic fields, or the use of enzymes) are being developed.

Intravenous administration

Drugs are usually given intravenously when a rapid or an immediate onset of action is necessary. When given by this route, their effects are usually dependable and reproducible. This method of administration often permits the dose to be accurately related to its effects, and thus eliminates some of the problems associated with interindividual variability in drug response. Although most drugs can be safely given as a rapid intravenous bolus, in some instances (e.g. aminophylline) they must be given slowly to avoid the cardiac complications associated with high plasma concentrations. Irritant drugs must be given intravenously in order to avoid local tissue or vascular complications. Some drugs (e.g. diazepam) can cause local complications such as superficial thrombophlebitis after intravenous administration. It is uncertain if this is related to the pH of the injected solution. When drugs that release histamine from mast cells are given intravenously (e.g. vancomycin, morphine) local or generalized vasodilatation and oedema ('flare and weal') in the surrounding tissues may be observed.

Mini-infusion pumps and syringe drivers

The development of mini-infusion pumps for intermittent intravenous drug delivery is particularly valuable in pain relief. Some of these devices incorporate electronic pumps to provide 'on-demand' bolus release of the drug according to the patient's needs. Alternatively, the use of gravity methods and balloon reservoir devices provide accurate mechanical control of drug administration. Battery-operated syringe drivers for the continuous administration of opioid analgesics are particularly valuable in the domiciliary management of patients with intractable pain associated with malignant disease.

Targeted drug delivery

Some delivery systems have been designed to selectively target drugs to their desired site of action, thus avoiding excessive toxicity and rapid inactivation. For instance, microparticulate carrier systems (e.g. liposomes, red cells, microspherical beads) have been occasionally used in the treatment of infectious and neoplastic diseases. Similarly, drugs conjugated with antibodies are sometimes used in the management of malignant disease. In these conditions, the more extensive use of 'pro-drugs' often leads to greater target specificity.

Other routes of drug administration

Transmucosal administration

Drugs are frequently applied to mucous membranes at various sites, including the conjunctiva, nose, larynx and the mucosal surfaces of the genitourinary tract, to produce topical effects. Antibiotics, steroids and local anaesthetic agents are commonly used for this purpose. Systemic absorption readily occurs due to the high vascularity of mucous areas, and local anaesthetics may produce toxic effects.

Alternatively, drugs may be administered to mucosal areas in order to provide a more rapid onset of systemic action and to avoid first-pass metabolism. The buccal route (i.e. the positioning of tablets between the teeth and the gum) may be used for the administration of glyceryl trinitrate, hyoscine and prochlorperazine. Similarly, oral transmucosal administration of opioid analgesics using drug

impregnated 'lollipops' has been employed in the management of postoperative pain.

Nasal administration

Certain hypothalamic and pituitary polypeptides that are destroyed in the gut are given by nasal administration. A number of other drugs, including opioid analgesics, steroids, histamine antagonists, propranolol and vitamin B_{12}, can also be given by this route. These drugs may be partly absorbed from vascular lymphoid tissue on the nasal mucosa. Other evidence suggests that some drugs are rapidly absorbed from the nasal mucosa to the CSF and the cerebral circulation, since the submucous space of the nose is in direct contact with the subarachnoid space adjacent to the olfactory lobes. After nasal administration, the concentration of some drugs in the CSF may be significantly higher than in plasma.

Transdermal administration

Most drugs are poorly absorbed through intact skin. The stratum corneum is the main barrier to the diffusion of drugs, and its lipid lamellar bilayers prevent the penetration of polar compounds. Nevertheless, some extremely potent drugs with a high lipid solubility (e.g. glyceryl trinitrate, hyoscine) are absorbed transdermally and can produce systemic effects when applied to the skin. In these conditions, the stratum corneum may act as a reservoir for lipid-soluble drugs for several days after administration is stopped. The absorption of drugs from the skin may be influenced by the vehicle used for administration and can be increased by the use of various penetration enhancers (e.g. dimethyl sulfoxide).

Local anaesthetic preparations (EMLA, tetracaine gel) are frequently used to produce analgesia prior to venepuncture. An occlusive dressing and a relatively long contact time (30–45 min) are required to produce effective analgesia.

Infiltration techniques

Local anaesthetics are commonly infiltrated into the skin or mucous membranes when it is important to confine their action to a region or an area of the body; they are often combined with vasoconstrictors in order to restrict their absorption and prolong the duration of drug action. Alternatively, they may be injected at various sites on nerves and nerve plexuses to produce conduction anaesthesia. Local anaesthetics, analgesics and occasionally antibiotics may also be given by intrathecal injection.

Inhalation

The uptake and distribution of inhalational anaesthetic agents is dependent on their transfer from alveoli to pulmonary capillaries. Many factors, which include the inspired concentration, adequacy of pulmonary ventilation, lipid solubility and blood–gas partition coefficient of individual agents determine the rate of transfer (Chapter 8).

Corticosteroids and some bronchodilators are given to produce a local action on respiratory bronchioles and to avoid systemic effects. Particle size may influence their distribution to the site of action. In general, particles with a diameter greater than 10 μm are deposited in the upper respiratory tract. Particles with a diameter of 2–10 μm are deposited in bronchioles, while those with a diameter less that 2 μm reach the alveoli.

Drug distribution

After administration and absorption, drugs are initially present in plasma and may be partly bound to plasma proteins. They may subsequently gain access to interstitial fluid and intracellular water, depending on their physicochemical properties (in particular, their lipid solubility and ionic dissociation). Consequently, they may be rapidly distributed in other tissues and organs. When distribution is complete their concentration in plasma water and extracellular fluid is approximately equal.

The distribution of drugs in the body is extremely variable (Table 1.3). It may be assessed by preclinical studies in experimental animals or by pharmacokinetic methods. Some drugs are extensively protein-bound and are predominantly present in plasma. Similarly, ionized compounds cannot readily penetrate most cell membranes and are largely distributed in extracellular fluid. Consequently, these drugs usually have a low apparent volume of distribution. In contrast, lipid-soluble drugs with a relatively low molecular weight are widely distributed in tissues. For instance, ethyl alcohol, urea and some sulphonamides are evenly distributed throughout body water. These drugs usually have a volume of distribution similar to total body water. Other drugs penetrate cells and are extensively bound to tissue proteins, or are sequestered in fat. In these conditions, the volume of distribution is characteristically greater than total body water.

Following intravenous administration, some drugs are initially sequestered by well-perfused tissues, but are subsequently redistributed to other organs as the plasma

Table 1.3 The volumes of physiological compartments and the main sites of distribution of some common drugs.

Compartment	Volume (mL kg^{-1})	Drug (V: mL kg^{-1})
Plasma	50–80	Heparin (60) Tolbutamide (100) Warfarin (140)
Extracellular fluid	150–250	Acetylsalicylic acid (150) Atracurium (160) Chlorothiazide (200) Sulphamethoxazole (210) Mivacurium (210) Vecuronium (230)
Total body water	500–700	Ethyl alcohol (500)
Total body water + cell and tissue binding	>700	Bupivacaine (1000) Lidocaine (1300) Prilocaine (2700) Thiopental (2300) Morphine (3000) Pethidine (4400) Digoxin (8500)

Values for the distribution volume (V) of the drugs are shown in parentheses.

concentration declines. Approximately 25% of thiopental is initially taken up by the brain due to its high lipid solubility and the extensive blood supply of the CNS. As the plasma concentration falls, thiopental is progressively taken up by less well-perfused tissues which have a higher affinity for the drug. In consequence, intravenous thiopental is rapidly redistributed from brain to muscle and finally to subcutaneous fat. Redistribution is mainly responsible for its short duration of action, and its final elimination from the body may be delayed for 24 hours.

Some drugs tend to be localized in certain tissues or organs, for example, iodine is concentrated in the thyroid gland and tetracyclines in developing teeth and bone. The concentration of drugs in these tissues may be much greater than in plasma. Drugs that are widely distributed in tissues and concentrated in cells may have an extremely large volume of distribution, which is usually greater than total body water (e.g. phenothiazines, tricyclic antidepressants).

Blood–brain barrier

Structure

Many drugs are widely distributed in most tissues, but do not readily enter the CNS. In cerebral capillaries, endothelial cells have overlapping 'tight' junctions restricting passive diffusion. The surrounding capillary basement membrane is closely applied to the peripheral processes of astrocytes, which play an important part in neuronal nutrition (Fig. 1.5). To pass from capillary blood to the brain, most drugs have to cross the endothelium, the basement membrane and the peripheral processes of astrocytes by simple diffusion or filtration. Some drugs cannot readily cross these restrictive barriers, which are collectively referred to as the 'blood–brain barrier'.

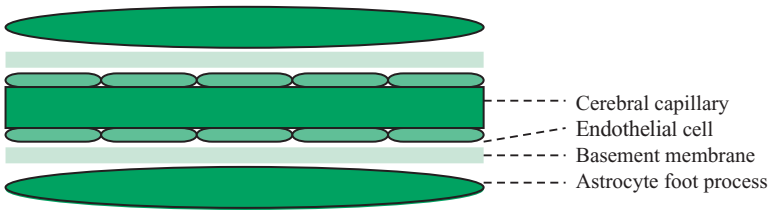

Fig. 1.5 Diagrammatic representation of the blood–brain barrier, showing the endothelial cells with tight junctions, the basement membrane and the foot processes of astrocytes.

Enzymatic blood–brain barrier

In addition to this structural barrier, there is also a metabolic or enzymatic blood–brain barrier, which is mainly associated with the peripheral processes of astrocytes. Many potentially neurotoxic agents (e.g. free fatty acids, ammonia) can readily cross the capillary endothelium, but are metabolized before they reach the CNS. Monoamine oxidase and cholinesterases are also present in capillary endothelium, and some neurotransmitters may be metabolized as they cross the blood–brain barrier. In addition, capillary endothelial cells express a transport protein (P-glycoprotein), which actively extrudes many drugs, including most opioids, from the CNS.

Consequently, the blood–brain barrier is not simply a passive and immutable structural barrier, but a dynamic membrane interface between the blood and the brain. Both its structure and function are dependent on trophic factors secreted by astrocytes. It develops during the first trimester of foetal life, but is immature at birth, when it is often less restrictive to drugs and endogenous substances than in adult life.

Drug permeability

Certain metabolic substrates and hormones, such as glucose, insulin, L-amino acids, L-thyroxine and transferrin, normally cross the blood–brain barrier by endocytosis or carrier transport. In addition, many low molecular weight, lipid-soluble drugs (e.g. general anaesthetics, local anaesthetics, opioid analgesics) can cross the barrier and enter the CNS, although their access may be restricted by P-glycoprotein. In contrast, when drugs are highly protein-bound (e.g. tolbutamide, warfarin), only the unbound fraction can readily diffuse from blood to the CNS, so that the concentration of these drugs in the brain may be 1–2% of the total plasma level. Drugs that are highly ionized (e.g. quaternary amines) cannot cross the blood–brain barrier, and muscle relaxants do not enter or affect the brain. Similarly, dyes that are protein-bound (e.g. Evans blue) and drugs with a large molecular weight (e.g. ciclosporin, erythromycin) do not readily cross the blood–brain barrier. Some drugs (e.g. benzylpenicillin) cannot penetrate the barrier or enter the brain unless its permeability is increased by inflammation (e.g. in bacterial meningitis). The normal impermeability of the blood–brain barrier can be modified by pathological changes, which include inflammation, oedema and acute and chronic hypertension.

Physiological deficiency

In some parts of the brain, principally the area postrema, the median eminence, the pineal gland and the choroid plexus, the blood–brain barrier is deficient or absent. In these areas, the diffusion of drugs and the exchange of endogenous substrates is not restricted. For example, in the choroid plexus drugs may freely diffuse from capillary blood to CSF across the relatively permeable choroidal epithelium. Similarly, the ependyma lining the cerebral ventricles does not appear to restrict the diffusion of most drugs. Neuropeptides and certain ionized compounds (e.g. benzylpenicillin, probenecid) may be actively secreted in the opposite direction, i.e. from cerebral ventricles into capillary blood.

Placental transfer

Structure and function

During late pregnancy, structural changes occur in the placenta, involving the gradual disappearance of the cytotrophoblast and the loss of chorionic connective tissue from placental villi. At term, maternal and foetal blood compartments are separated by a single layer of chorion (the syncytiotrophoblast) in continuous contact with the endothelial cells of foetal capillaries. Consequently, the placental barrier consists of a vasculosyncytial membrane, and from a functional point of view behaves like a typical lipid membrane. Most low molecular weight, lipid-soluble drugs are readily transferred across the placenta, and their rate of removal from maternal blood is dependent on placental blood flow, the area available for diffusion and the magnitude of the effective diffusion gradient. In contrast, large molecular weight or polar molecules cannot readily cross the vasculosyncytial membrane. Almost all drugs that cross the blood–brain barrier and affect the CNS can also cross the placenta, and their elimination by foetal tissues may be difficult and prolonged.

Drugs and the foetus

Some drugs that readily cross the placenta are known to produce foetal abnormalities if taken in pregnancy (Table 1.4). Many other drugs can readily diffuse from maternal plasma to the foetus and may cause complications when used in late pregnancy. These include inhalational anaesthetics, intravenous agents, local anaesthetics and many analgesics such as morphine and pethidine. Similarly, some β-adrenoceptor antagonists (e.g. propranolol) can cross the placenta and may cause foetal bradycardia and hypoglycaemia. When diazepam is used in late pregnancy as in the treatment of preeclampsia and eclampsia, it readily crosses the placenta, but is not effectively metabolized by the foetus. Several of its active metabolites (including both desmethyldiazepam and oxazepam)

Table 1.4 Drugs that may cause foetal damage or malformation (teratogenic effects) if taken during pregnancy.

Drug	Effect on foetus
Methotrexate	Hydrocephalus; neural tube defects
Tretinoin	Hydrocephalus
Phenytoin	Cleft lip and palate; cardiac defects
Sodium valproate	Neural tube defects
Oestrogens	Vaginal adenosis; testicular atrophy
Aminoglycosides	Cochlear and vestibular damage
Tetracyclines	Dental pigmentation; enamel hypoplasia
Carbimazole	Goitre; hypothyroidism
Propylthiouracil	Goitre; hypothyroidism
Warfarin	Nasal hypoplasia; epiphyseal calcification

accumulate in foetal tissues and can cause neonatal hypotonia and hypothermia. By contrast, ionized compounds (e.g. muscle relaxants) cannot readily cross the placenta.

Protein binding

Plasma protein binding plays an essential role in the transport and distribution of drugs. Most drugs are relatively lipid-soluble, but are only poorly soluble in plasma water. Consequently, binding to plasma proteins is essential for their transport in plasma.

Most drugs are reversibly bound to plasma proteins, according to the reaction:

$$\text{unbound drug} + \text{protein} \rightleftarrows \text{drug} - \text{protein complex}$$

During perfusion, the unbound drug diffuses into tissues, and as its concentration in plasma falls, protein-bound drug rapidly dissociates. Consequently, a continuous concentration gradient is present for the diffusion of drugs from plasma to tissues.

Binding by albumin and globulins

Albumin usually plays the most important role in the binding of drugs. It has a number of distinct binding sites with a variable affinity for drugs, and mainly binds neutral or acidic compounds, including salicylates, indometacin, tolbutamide, carbenoxolone and oral anticoagulants. Some basic drugs and physiological substrates such as bilirubin, fatty acids and tryptophan are also bound by albumin.

Globulins bind many basic drugs (e.g. bupivacaine, opioid analgesics). These drugs are mainly bound by β-globulins or by α_1-acid glycoprotein. Plasma globulins also play an important part in the binding of minerals, vitamins and hormones. Hydrocortisone (cortisol) is mainly transported in plasma by a specific globulin (transcortin) for which it has a high affinity.

Some drugs (e.g. pancuronium) are bound by both globulins and albumin. Indeed, the resistance to muscle relaxants that often occurs in liver disease may be due to their increased binding by plasma globulins.

Extent of plasma protein binding

The extent of plasma protein binding of drugs ranges from 0% to almost 100%, even among closely related drugs (Table 1.5). Thus, the binding of local anaesthetics to α_1-acid glycoprotein ranges from 6% (procaine) to 95% (bupivacaine). In some instances (diazepam, phenytoin, warfarin) unbound, pharmacologically active concentrations are only 1–5% of total plasma levels. The concentration of drugs in salivary secretions and CSF often reflects the level of the unbound drug in plasma. Alternatively, the concentration of the unbound drug can be determined by various *in vitro* techniques, such as equilibrium dialysis or ultrafiltration.

Table 1.5 Plasma protein binding of some common anaesthetic drugs.

Drug	Plasma protein binding (%)
Prilocaine	55
Lidocaine	65
Tetracaine	75
Ropivacaine	94
Bupivacaine	95
Morphine	30
Pethidine	64
Fentanyl	80
Alfentanil	90
Atracurium	<20
Vecuronium	<20
Pancuronium	30
Thiopental	80
Etomidate	75
Propofol	97
Diazepam	97

Drug competition and displacement

Drugs and endogenous substrates that are extensively bound to proteins may compete for (and be displaced from) their binding sites. In most instances, binding of drugs at clinical concentrations only occupies a small proportion of the available binding sites and does not approach saturation. Consequently, competition between drugs resulting in clinically significant displacement from plasma protein binding is extremely rare (Chapter 4).

Protein binding and drug elimination

The hepatic clearance of many drugs is limited by liver blood flow and is not restricted by plasma protein binding (which is a rapidly reversible process). Drug dissociation from binding to plasma proteins probably occurs within microseconds or milliseconds. By contrast, the hepatic perfusion time may be several seconds or more. Thus, extensive protein binding only decreases hepatic clearance when the ability of the liver to extract, metabolize or excrete the drug is low. Similarly, protein binding is unlikely to restrict the renal elimination of drugs, either by the glomerulus or the renal tubule. Only the unbound drug is secreted by the proximal tubule, but the resultant decrease in its plasma concentration leads to the immediate dissociation of protein-bound drug in order to maintain equilibrium. Indeed, a number of protein-bound drugs are completely cleared in a single passage through the kidney (e.g. benzylpenicillin).

Protein binding in pathological conditions

Binding to plasma proteins is modified in pathological conditions associated with hypoalbuminaemia, as in hepatic cirrhosis, nephrosis, trauma or burns. In these conditions, the concentration of the unbound drug tends to increase and may result in toxic effects (e.g. with phenytoin or prednisolone). Significant changes are particularly likely when high doses of drugs are used, or when drugs are given intravenously. In these conditions, binding to albumin and other plasma proteins may be saturated, causing a disproportionate increase in the concentration of the unbound drug. Tissues and organs that are well perfused (e.g. brain, heart, abdominal viscera) may receive a higher proportion of the dose, predisposing them to potential toxic effects. Similar effects may occur in elderly patients and in subjects with renal impairment, possibly due to alterations in the affinity of drugs for albumin. The plasma concentration of α_1-acid glycoprotein can also be modified by a number of pathological conditions including myocardial infarction, rheumatoid arthritis, Crohn's disease, renal failure and malignant disease, as well as operative surgery. In these conditions, the binding of basic drugs (e.g. propranolol, chlorpromazine) is increased, and the concentration of the free, unbound drug is reduced.

Drug metabolism

Most drugs are eliminated by drug metabolism, which mainly occurs in the liver. Nevertheless, certain drugs are partly or completely broken down by other tissues. Some esters that are used in anaesthesia are hydrolysed by plasma cholinesterase (e.g. suxamethonium, mivacurium) or red cell acetylcholinesterase (e.g. esmolol, remifentanil). In addition, drugs may be partly or completely metabolized by the gut (e.g. morphine, chlorpromazine), the kidney (e.g. midazolam, dopamine) or the lung (e.g. angiotensin I, prilocaine).

Nevertheless, the liver is mainly responsible for the breakdown of drugs. Hepatic metabolism decreases the concentration of the active drug in plasma, and thus promotes its removal from the site of action. This mainly involves the enzymatic conversion of lipid-soluble nonpolar drugs into water-soluble polar compounds, which can be filtered by the renal glomerulus or secreted into urine or bile.

Metabolism usually reduces the biological activity of drugs, and most metabolites have less inherent activity than their parent compounds. In addition, their ability to penetrate to receptor sites is limited because of their poor lipid solubility. Nevertheless, some drugs are relatively inactive when administered, and require metabolism to produce or enhance their pharmacological effects (Table 1.6). Other drugs may be metabolized to compounds

Table 1.6 Drugs that require metabolism to produce their pharmacological effects.

Drug	Active metabolite
Prontosil red	Sulphanilamide
Chloral hydrate	Trichlorethanol
Cyclophosphamide	Phosphoramide mustard
Cortisone	Hydrocortisone
Prednisone	Prednisolone
Methyldopa	Methylnoradrenaline
Proguanil	Cycloguanil
Enalapril	Enalaprilat

Table 1.7 Phase 1 reactions resulting in drug oxidation, reduction and hydrolysis.

Reaction	Site	Enzyme	Example
Oxidation	Hepatic endoplasmic reticulum	Cytochrome P450	Thiopental → pentobarbital
	Mitochondria	Monoamine oxidase	Dopamine → dihydroxyphenylacetaldehyde
	Hepatic cell cytoplasm	Alcohol dehydrogenase	Alcohol → acetaldehyde
Reduction	Hepatic endoplasmic reticulum	Cytochrome P450	Halothane → chlorotrifluoroethane
	Hepatic cell cytoplasm	Alcohol dehydrogenase	Chloral hydrate → trichlorethanol
Hydrolysis	Hepatic endoplasmic reticulum	Carboxyesterase	Pethidine → pethidinic acid
	Plasma	Cholinesterase	Suxamethonium → succinate + choline
	Erythrocyte	Acetylcholinesterase	Remifentanil → carboxylated derivatives
	Neuromuscular junction	Acetylcholinesterase	Acetylcholine → acetate + choline
	Hepatic cell cytoplasm	Amidase	Lidocaine → 2,6-xylidine + diethylglycine

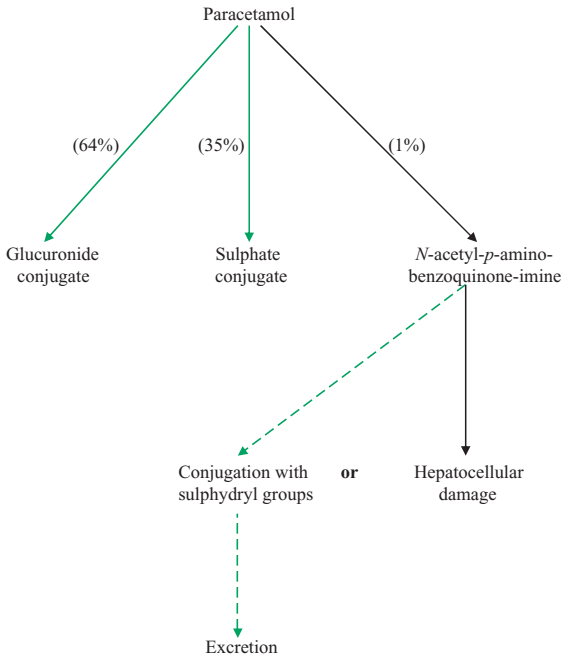

Fig. 1.6 The metabolism of paracetamol to the toxic metabolite *N*-acetyl-*p*-amino-benzoquinone-imine.

with a different spectrum of pharmacological activity (e.g. pethidine, atracurium). Certain antibiotics (e.g. ampicillin, chloramphenicol) may be administered orally as esters. In this form, they are better absorbed than their parent drugs and are subsequently hydrolysed to active derivatives.

Occasionally, drug metabolism results in the formation of compounds with toxic effects. Paracetamol, for example, is partially converted to *N*-acetyl-*p*-amino-benzoquinone-imine, and if this metabolite is not rapidly conjugated, it alkylates macromolecules in liver cells, resulting in necrosis (Fig. 1.6). Similarly, one of the metabolites of halothane (trifluoroacetyl chloride) is covalently bound by lysine residues in liver proteins, resulting in hepatocellular damage. The breakdown of halothane to reactive intermediate metabolites plays an important role in halothane hepatitis.

The enzymic changes carried out by the liver during drug metabolism are divided into two types. Phase 1 reactions (non-synthetic or functionalization reactions) usually result in drug oxidation, reduction or hydrolysis (Table 1.7). Phase 2 reactions (synthetic or conjugation reactions) involve combination of phase 1 reaction products (or unchanged drugs) with other groups, including glucuronide, sulphate, acetate or glycine radicals. Both phase 1 and phase 2 reactions increase the water solubility of drugs and promote their elimination from the body.

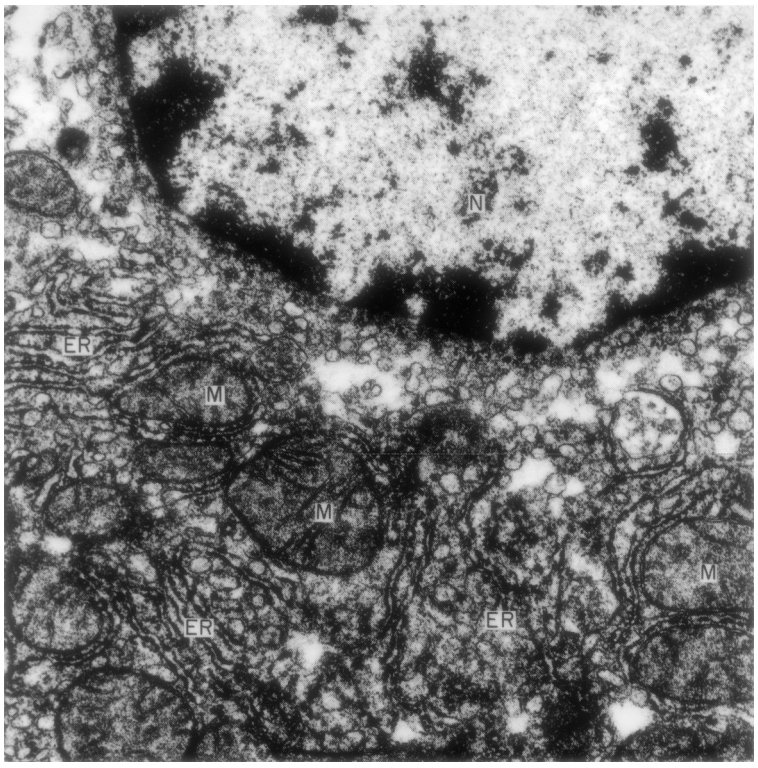

Fig. 1.7 Electron micrography of part of a mouse liver cell, showing mitochondria (M), endoplasmic reticulum (ER) and the nuclear membrane enclosing the nucleus (N) (×30,000).

Some drugs (e.g. sodium salicylate) are almost entirely metabolized by phase 2 reactions.

Phase 1 reactions

Most phase 1 reactions and glucuronide conjugation are carried out by the smooth endoplasmic reticulum or the microsomes (Fig. 1.7). Most drug oxidation and reduction, and some hydrolysis, is carried out by a non-specific microsomal enzyme system (cytochrome P450 or the 'mixed function oxidase system'). Cytochrome P450 consists of many distinct but genetically related forms of a superfamily of haem proteins. Their name is derived from their ability, in the reduced state, to combine with carbon monoxide and form a complex that maximally absorbs light at a wavelength of 450 nm.

Cytochrome P450

Drug oxidation by cytochrome P450 depends on the flavoprotein NADPH-CYP reductase, the electron donor NADPH and molecular oxygen (as well as cytochrome b_5 and NADPH-cytochrome b_5 reductase). The reaction involves a complex enzymatic cycle (Fig. 1.8), which results in the breakdown of molecular oxygen. A single oxygen atom (from O_2) is released as H_2O and the other is transferred to the substrate (D), according to the equation:

$$DH + O_2 + NADPH + H^+ \rightarrow DOH + H_2O + NADP^+$$

Cytochrome P450 enzymes may also mediate the reductive metabolism of certain drugs, such as halothane (Table 1.7). This is dependent on the ability of drugs to directly accept electrons from the reduced cytochrome P450 drug complex (Fig. 1.8) and is enhanced by hypoxia.

Isoforms of cytochrome P450

Different forms of human cytochrome P450 are classified by the similarity in their amino acid sequences into gene families and gene subfamilies. The members of each gene family (CYP 1, CYP 2 etc.) have a common amino acid sequence of 40% or more, while members of each subfamily (CYP 1A, CYP 1B etc.) have a sequence similarity of more than 55%. At the present time, 17 different gene families have been identified, and at least six of these

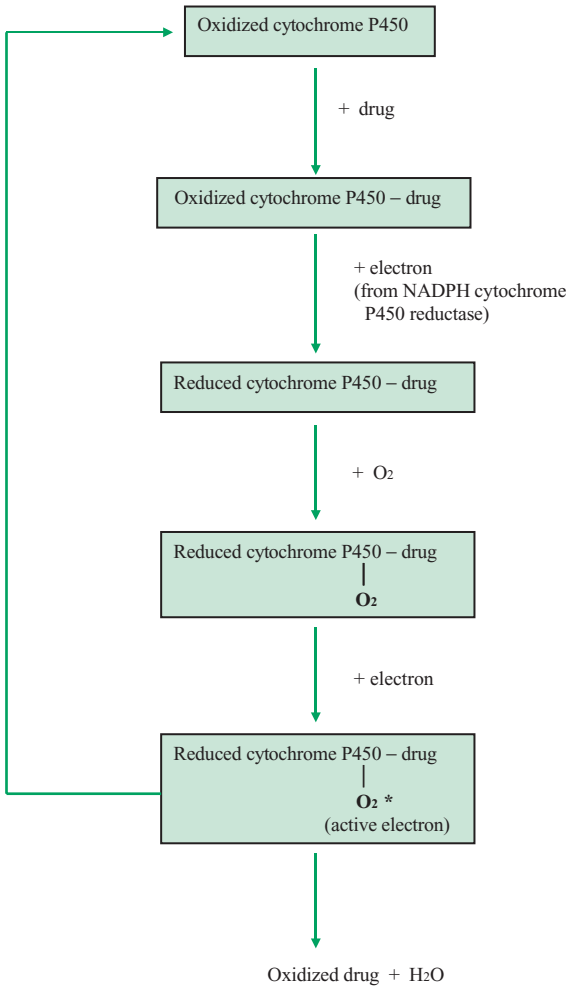

Fig. 1.8 The mixed-function oxidase system (cytochrome P450).

families (CYP 7, CYP 11, CYP 17, CYP 19, CYP 21 and CYP 27) appear to be solely concerned with the synthesis of steroids, bile acids and cholesterol, and play no part in drug metabolism. The CYP 1, CYP 2 and CYP 3 families account for more than 75% of hepatic cytochrome P450, and seven distinct isoforms (CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, CYP 3A4) are responsible for most phase 1 reactions in man (Table 1.8). The individual isoforms have different but overlapping substrate specificities, metabolize drugs at different rates, and also differ in their susceptibility to enzyme induction and inhibition. Their expression in different organs is extremely variable, and some of them (e.g. CYP 2D6) are subject to genetic polymorphism.

The isoform CYP 2E1 is specifically responsible for defluorination and degradation of many common fluorinated inhalational agents. The rate of anaesthetic defluorination, as assessed by fluoride production, occurs in the order sevoflurane > enflurane > isoflurane > desflurane. Enzyme induction with ethanol or phenobarbital increases the rate of defluorination. CYP 2E1 may also be induced by fasting, obesity, diabetes, isoniazid, ketones and isopropyl alcohol (Table 1.8). In some cases, it may produce activation of some carcinogens.

Cytochrome P450 isoenzymes have also been identified at many extrahepatic sites. Cerebral isoenzymes are considered to play an important role in the regulation of certain steroids that control mood and sleep patterns.

Other phase 1 reactions

Although most drug oxidation and reduction is dependent on isoforms of cytochrome P450, some endogenous compounds (e.g. dopamine, tyramine) are metabolized by monoamine oxidase, which is predominantly present in mitochondria. Similarly, ethyl alcohol is oxidized and chloral hydrate is reduced by alcohol dehydrogenase, which is present in the cytoplasm of liver cells (Table 1.7).

Most esters and amides are primarily metabolized by hydrolysis. Drug breakdown may be dependent on certain microsomal enzyme systems (e.g. the carboxylesterases, which hydrolyse diamorphine to 6-monoacetylmorphine, and pethidine to pethidinic acid). Alternatively, it may occur in plasma (e.g. the hydrolysis of suxamethonium by butyrylcholinesterase), in erythrocytes (the hydrolysis of esmolol and remifentanil by acetylcholinesterase), or at the neuromuscular junction (e.g. the hydrolysis of acetylcholine). Many amides (e.g. lidocaine, prilocaine) are broken down in the liver by amidases.

Phase 2 reactions

Phase 2 reactions (synthetic reactions) involve the conjugation of other chemical groups with the oxidized, reduced or hydrolysed products of phase 1 reactions. Some relatively polar drugs may only be metabolized by phase 2 reactions. The metabolic changes that occur during phase 2 reactions usually involve the addition of glucuronide, sulphate, acetate, glycine or methyl groups to the products of phase 1 reactions. The most important of these reactions is glucuronide conjugation.

Table 1.8 The main forms of cytochrome P450 involved in hepatic drug metabolism in humans.

Enzyme isoform	Typical substrates	Inhibitors	Biological properties
CYP 1A2	Caffeine Clomipramine Imipramine Lisophylline Oestrogens Ondansetron Phenacetin Ropivacaine Theophylline R-warfarin	Benzoflavone Cimetidine Fluvoxamine Furafylline	13% of total hepatic cytochrome P450 Only present in liver Induced by phenobarbital, phenytoin, omeprazole, cigarette smoke Polycyclic aromatic hydrocarbons Cruciferous vegetables Marked interindividual variation in expression (40-fold)
CYP 2C8	Carbamazepine Diazepam Pioglitazone Paclitaxel Rosiglitazone Taxol Zopiclone	Cimetidine	4% of total hepatic cytochrome P450 Narrow substrate specificity Inducible by phenobarbital and rifampicin
CYP 2C9	Diclofenac Fluoxetine Ibuprofen Losartan Omeprazole Phenytoin S-warfarin	Fluconazole Fluvastatin Sulfaphenazole Sulfinpyrazone Trimethoprim	17% of total hepatic cytochrome P450 Individual variation in expression in human liver, due to genetic variants with low activity Unaffected by enzyme inducing agents
CYP 2C19	Citalopram Diazepam Imipramine S-mephenytoin Omeprazole Proguanil	Sulfaphenazole	3% of total hepatic cytochrome P450 Subject to genetic polymorphism A mutation is inherited as an autosomal recessive trait
CYP 2D6	β-blockers Codeine Dextromethorphan Flecainide Morphine Fluphenazine	Cimetidine Haloperidol Methadone Quinidine SSRIs	2–5% of total hepatic cytochrome P450 Metabolizes 25% of all drugs Subject to genetic polymorphism (debrisoquine/sparteine polymorphism); presents as autosomal recessive trait Catalyses many O-demethylation reactions
CYP 2E1	Desflurane Ethanol Enflurane Isoflurane Isoniazid Sevoflurane	Diallylsulphide Diethylcarbamate Disulfiram 4-methylpyrazole	6% of total cytochrome P450 Induced by fasting, obesity, ethanol, isoniazid and benzene Metabolizes small molecular weight halogenated compounds
CYP 3A4	Alfentanil Cortisol Ciclosporin Erythromycin Lidocaine Midazolam Nifedipine Testosterone	Cimetidine Ketoconazole Gestodene Grapefruit juice Propofol Troleandomycin	30–60% of total hepatic cytochrome P450 Metabolizes 50% of all drugs Catalyses many *N*-demethylated reactions Induced by barbiturates, rifampicin, phenytoin, glucocorticoids, St John's Wort

Table 1.9 Drugs that induce and inhibit cytochrome P450.

Inducers of cytochrome P450	Inhibitors of cytochrome P450
Barbiturates	Imidazoles (cimetidine, etomidate, ketoconazole, omeprazole)
Phenytoin	Macrolide antibiotics (erythromycin, clarithromycin)
Carbamazepine	Antidepressants
Rifampicin	HIV protease inhibitors
Griseofulvin	Ciclosporin
Alcohol (chronic consumption)	Amiodarone
Polycyclic hydrocarbons (tobacco smoke, grilled meat)	Gestodene
	Grapefruit juice

Glucuronide conjugation

The conjugation of drugs to glucuronides is mainly dependent on enzyme systems in the hepatic endoplasmic reticulum. The microsomal enzyme glucuronyl transferase catalyses the transfer of glucuronide residues from UDP-glucuronide to unconjugated compounds. This process is responsible for the conjugation of endogenous compounds (e.g. bilirubin, thyroxine) as well as many drugs (e.g. morphine, steroid hormones). Glucuronide conjugation usually results in the formation of acidic drug metabolites with a low pK_a (i.e. relatively strong acids) and consequently increases their water solubility.

Other conjugation reactions

Sulphate conjugation may occur in the gut wall or in the cytoplasm of the liver cell. The enzymes involved are normally concerned with the synthesis of sulphated polysaccharides (e.g. heparin). Sulphate conjugation may be the final step in the metabolism of chloramphenicol, isoprenaline, noradrenaline, paracetamol and certain steroids.

Drug acetylation may take place in several tissues (e.g. spleen, lung, liver). In the liver, Kupffer cells rather than hepatocytes may be responsible for conjugation, which involves the transfer of acetyl groups from coenzyme A to the unconjugated drug. The rate and extent of acetylation in man are under genetic control. Isoniazid, many sulphonamides, hydralazine and phenelzine are partly metabolized by acetylation.

Glycine conjugation occurs in the cytoplasm of liver cells. Bromosulphonphthalein and several other drugs are partly eliminated in bile as glycine conjugates.

Methylation is mediated by enzymes that are present in the cytoplasm of many tissues, and plays an important part in the metabolism of catecholamines by the enzyme catechol-0-methyltransferase.

Induction and inhibition of cytochrome P450

Induction

Several drugs selectively increase the activity of cytochrome P450, including phenytoin, carbamazepine and rifampicin (Table 1.9). Enzyme induction usually occurs within several days and increases liver weight, microsomal protein content and biliary secretion. Chronic alcohol consumption, brussels sprouts, and polycyclic hydrocarbons in tobacco and grilled meats, also increase the activity of certain isoforms. Polycyclic hydrocarbons mainly induce CYP 1A2, while barbiturates and phenytoin affect CYP 1A2 and CYP 3A4. Rifampicin is a potent inducer of CYP 2D6 and CYP 3A4, while ethyl alcohol induces CYP 2E1. Enzyme induction usually increases the activity of glucuronyl transferase, and thus enhances drug conjugation. In some instances, drugs may induce their own metabolism (autoinduction).

Induction of cytochrome P450 may have secondary effects on other enzyme systems. Hepatic enzyme induction decreases intracellular haem, reducing its inhibitory effects on porphyrin synthesis, and this may be significant in acute porphyria.

Inhibition

Many imidazole derivatives (e.g. omeprazole, etomidate) combine with the ferric (Fe^{3+}) form of haem, resulting in

reversible non-competitive inhibition of CYP 3A4 and various other isoforms. Quinidine is a competitive inhibitor of CYP 2D6 (although it is not metabolized by this isoform). In addition, some synthetic corticosteroids (e.g. gestodene) are oxidized by CYP 3A4 and combine with it covalently ('suicide inhibition'). Furafylline affects CYP 1A2 in a similar manner. Many other drugs also inhibit some cytochrome P450 isoforms, particularly CYP 3A4 (Table 1.9). Enzyme inhibition may increase plasma concentrations of other concurrently used drugs, resulting in drug interactions (Chapters 4 and 5).

First-pass metabolism

After oral administration, some drugs are extensively metabolized by the gut wall (e.g. chlorpromazine, dopamine) or by the liver (e.g. lidocaine, pethidine) before they enter the systemic circulation ('presystemic' or 'first-pass metabolism'). In these conditions, oral administration may not produce adequate plasma concentrations in the systemic circulation and may result in an impaired response to drugs. First-pass metabolism by the liver is relatively common with drugs that have a high hepatic extraction ratio (i.e. when the concentration in the hepatic vein is less than 50% of that in the portal vein). In these conditions, clearance is primarily dependent on liver blood flow rather than the activity of drug-metabolizing enzymes, and drugs that reduce hepatic blood flow (e.g. propranolol) may influence the magnitude of the first-pass effect. Drugs are sometimes given by sublingual or rectal administration in order to avoid first-pass metabolism in the liver.

Individual differences in drug metabolism

When some drugs are administered in the same dose to different patients, plasma concentrations may vary over a 10-fold range. The phenomenon is sometimes due to interindividual differences in drug metabolism, which is an important cause of the variability in response to drugs (Chapter 5). Most of the available evidence suggests that the rate and the pattern of drug metabolism are mainly controlled by genetic factors, including sex, race and ethnicity. Some metabolic pathways are subject to genetic polymorphism (e.g. drug acetylation, ester hydrolysis). For example, individuals who are deficient in CYP 2D6 (Table 1.8) may have an impaired analgesic response to codeine, since they convert little or none of the drug to morphine.

Environmental factors, including diet, cigarette smoking, alcohol consumption and exposure to insecticides, are probably of lesser importance. However, interindividual differences in plasma concentrations and variable responses are sometimes related to drug interactions (Chapter 4), particularly with agents that induce or inhibit hepatic enzyme systems. Interactions with enzyme inducers or inhibitors are commoner with low extraction, extensively protein-bound drugs whose clearance is dependent on metabolism rather than hepatic blood flow. High extraction drugs whose clearance is dependent on hepatic blood flow are unlikely to be involved in significant metabolic reactions.

Drug metabolism may be related to age, and the hepatic metabolism of many drugs is modified in childhood and in the elderly. Neonates have impaired drug metabolizing systems, and some isoforms of cytochrome P450 and glucuronyl transferase may be relatively immature. In the elderly, drug metabolism is also modified, although altered environmental influences may be of more importance.

Pathological changes

Pathological changes may affect the metabolism and clearance of drugs in an unpredictable manner. In severe hepatic disease (e.g. cirrhosis or hepatitis), the elimination of drugs that are primarily metabolized may be impaired. The reduction in clearance may result in drug cumulation, and the urinary elimination of metabolites may be decreased. Liver disease may also enhance and prolong the effects of drugs that are metabolized by plasma cholinesterase. Any decrease in cardiac output (e.g. due to heart block, myocardial infarction or hypertension) may reduce the elimination of drugs whose clearance is dependent on hepatic blood flow. Renal disease usually has little or no effect on drug metabolism, although polar metabolites may accumulate in plasma and produce toxic effects. Thus, norpethidine (a demethylated metabolite of pethidine) is normally eliminated in urine, but in renal failure its excretion is impaired, and may sometimes cause cerebral excitation and convulsions.

Hepatic, renal and cardiac diseases are important factors affecting the variable response to drugs (Chapter 5).

Drug excretion

Almost all drugs and their metabolites are eventually eliminated from the body in urine or in bile. Small amounts of some drugs are excreted in saliva and in milk.

The molecular weight of drugs and their metabolites plays an important part in determining their route of

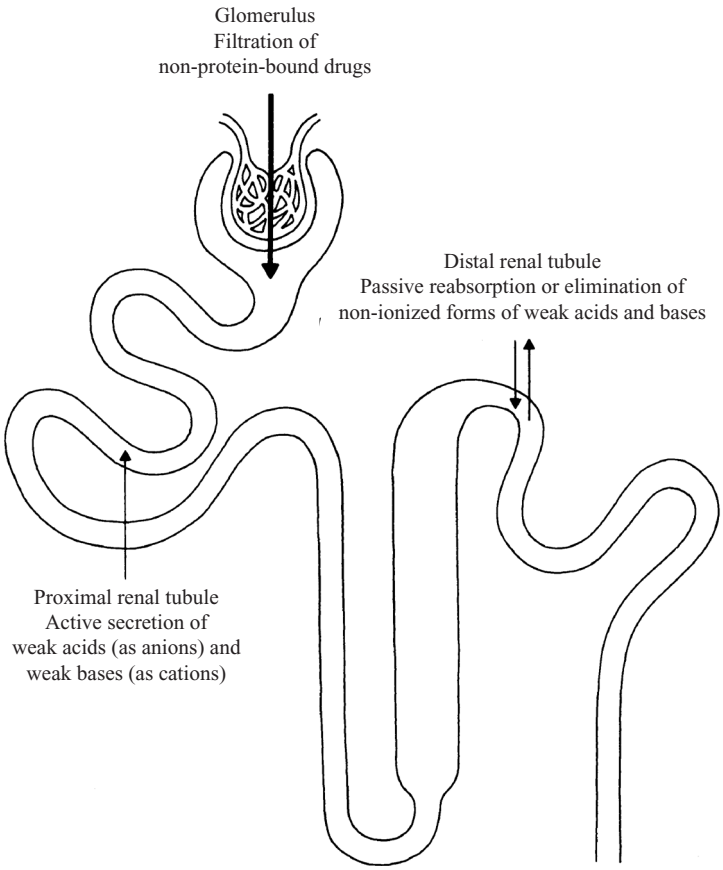

Fig. 1.9 The renal elimination of drugs by glomerular filtration, proximal tubular secretion and distal tubular reabsorption or excretion. In the distal renal tubule, weak acids and weak bases may be reabsorbed or excreted into urine, depending on their pK_a values and the pH gradient between plasma and urine.

elimination. Most low molecular weight compounds and their metabolites are excreted in urine. By contrast, drugs with a higher molecular weight (above 400–500 Da in man) are preferentially eliminated in bile. Thus, biliary secretion plays an important part in the elimination of some muscle relaxants, many steroid conjugates and certain antibacterial drugs (Table 1.2).

The renal elimination of drugs is dependent on three separate processes that take place at different sites in the nephron (Fig. 1.9). These are

- Glomerular filtration
- Proximal tubular secretion
- Distal tubular diffusion

Glomerular filtration

Glomerular filtration is partly responsible for the elimination of poorly lipid-soluble drugs and drug metabolites in urine. Only the free or unbound fraction in plasma water is available for filtration by the renal glomerulus. Nevertheless, since glomerular perfusion time is probably much longer than the dissociation time from the rapidly reversible binding to plasma proteins, significant amounts of protein-bound drugs may be filtered by the glomerulus.

Proximal tubular secretion

The active secretion of drugs by the proximal renal tubule may lead to their rapid elimination from the body. Proximal tubular secretion is an example of carrier transport, requires the expenditure of cellular energy, and may take place against a concentration gradient. A wide number of drugs and drug metabolites are partly eliminated by this process (Table 1.1). Acidic and basic drugs are secreted by two separate and distinct transport systems. These are located in related sites in renal tubule cells, and both have a requirement for cellular energy. Acidic drugs may compete with each other for tubular secretion, and

basic drugs may interfere with the elimination of other bases or cations. Acids do not usually compete with or affect the secretion of bases. Occasionally, the competitive inhibition of the tubular transport of acids or bases is of practical significance (e.g. the inhibition of penicillin secretion by probenecid, or the reduction of urate transport by thiazide diuretics).

During tubular secretion, only the unbound drug is transferred from plasma to tubular cells. Nevertheless, protein or red cell binding does not apparently restrict tubular secretion, and some drugs that are significantly bound to plasma proteins (e.g. phenol red, some penicillins) are completely cleared by the kidney in a single circulation. As discussed above, this probably reflects the rapid dissociation from plasma protein in relation to the time required for renal tubular perfusion.

Distal tubular diffusion

In the distal renal tubule, non-ionic diffusion is partly responsible for the reabsorption and elimination of acids and bases. In this region of the nephron, there is a considerable H^+ gradient between plasma and acid urine. Most acidic drugs are preferentially excreted in alkaline urine, where they are present as non-diffusible anions. In acid urine, they are usually present as non-ionized molecules that can readily diffuse back into plasma. In these conditions, they are slowly eliminated from the body and their half-lives may be prolonged. For instance, the weak acid probenecid is actively secreted in the proximal renal tubule as an anion, i.e. $R\text{-}COO^-$. In acidic conditions (e.g. in the distal renal tubule), it is partially present in the non-ionized form R-COOH and is extensively reabsorbed. In consequence, its elimination from the body is relatively slow and its half-life is approximately 6–12 hours.

By contrast, basic drugs (e.g. secondary and tertiary amines) are preferentially excreted in acid urine (Fig. 1.3). In these conditions they can readily diffuse from plasma to urine where they are trapped as cations. This provides a gradient for the diffusion of the non-ionized drug from plasma to urine. Many basic drugs are highly lipid-soluble and extensively bound to plasma proteins and may not be significantly eliminated by glomerular filtration or by tubular secretion. Diffusion of the non-ionized fraction from the relatively alkaline plasma to acid urine (Fig. 1.3) may be the only method responsible for the elimination of these drugs. At one time, the effects of changes in urine pH on the elimination of weak acids and bases were sometimes utilized in the treatment of drug overdosage.

Biliary excretion

The biliary excretion of drugs and drug metabolites is usually less important than their renal elimination. Nevertheless, almost all drugs or their metabolites can be identified in bile after oral or parenteral administration (although only trace amounts of many compounds may be detected). Biliary excretion is usually the major route of elimination of compounds with a molecular weight of more than 400–500 Da.

Ionized or partly ionized drugs and their metabolites are usually eliminated from liver cells by active transport. High molecular weight anions (including glucuronide and sulphate conjugates) and cations (including quaternary amines) are actively transferred from hepatocytes to the biliary canaliculus by separate transport systems, which are dependent on Na^+/K^+ ATPase. Biliary secretion is relatively non-specific, saturable and can be competitively or non-competitively inhibited by other drugs. Thus, anions compete with each other for canalicular transport, while basic drugs interfere with the elimination of other bases or cations. In many respects, the biliary secretion of anions and cations is similar to their active transport in the proximal renal tubule, and accounts for the high concentrations of certain drugs in bile (in some instances, more than 100 times their plasma level).

The phenomenon is sometimes of practical significance. The visualization of contrast media during radiological examination of the biliary tract is dependent on their active secretion and concentration in bile. Similarly, the high concentrations of ampicillin and rifampicin that are eliminated in bile may account for their effectiveness in enteric infections. Many muscle relaxants are also present in high concentrations in bile. Monoquaternary compounds (e.g. vecuronium) are more extensively eliminated than their bisquaternary analogues (pancuronium), and this may partly account for the differences in their duration of action.

Enterohepatic circulation

Many compounds that are eliminated in bile as glucuronide conjugates are hydrolysed in the small intestine by bacterial flora that secrete the enzyme glucuronidase. After hydrolysis the unchanged drug is reabsorbed, metabolized and re-excreted as a glucuronide conjugate (Fig. 1.10). This 'enterohepatic circulation' of drugs may occur many times before compounds are finally eliminated from the body and is often associated with a substantial first-pass effect and a prolonged plasma half-life.

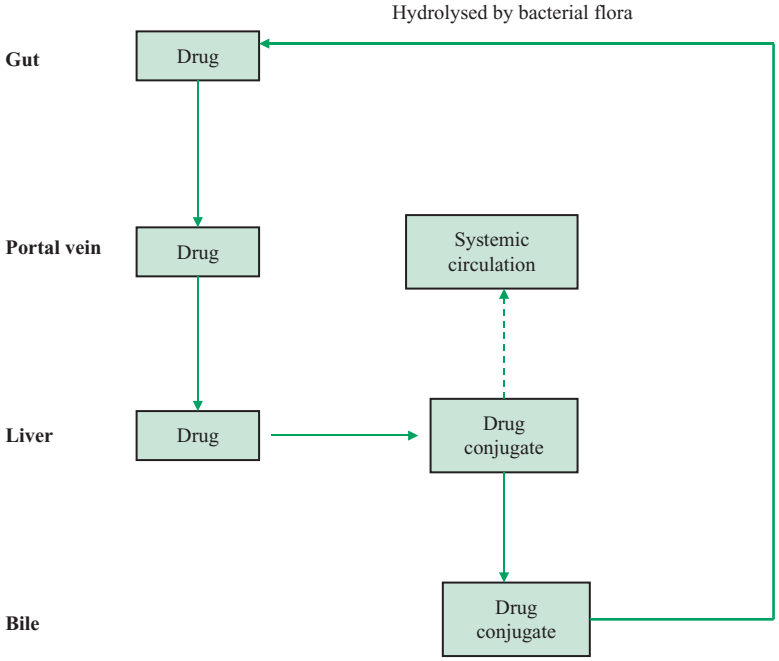

Fig. 1.10 The enterohepatic circulation of drugs. Only small amounts of the absorbed drug and its conjugates escape recirculation and enter the systemic circulation.

Many oestrogens have an extensive enterohepatic circulation. During broad-spectrum antibiotic therapy, oestrogen conjugates may not be hydrolysed in the small intestine, and their elimination in the gut is enhanced. This phenomenon may sometimes be responsible for the failure of oral contraception in these patients.

The trace amounts of many drugs that are eliminated unchanged in bile are probably directly transferred from hepatic arterial blood to intrahepatic bile ducts via the peribiliary plexus. The transference of drugs may be modified by the hormone secretin, which also increases bile flow by its action at this site.

Excretion in saliva and milk

Small amounts of most drugs are excreted unchanged in saliva and in milk. The elimination of drugs by these routes is usually dependent on simple physical principles. Non-protein bound, lipid-soluble, small molecular weight drugs can readily diffuse into saliva and milk, where their levels may be similar to the plasma concentration. As the pH of saliva and milk is slightly acid compared with plasma, the concentration of weak acids will be reduced (although weak bases may be slightly concentrated). Some ions (e.g. chloride, iodide) may be actively secreted into saliva and milk. Nevertheless, drug excretion by these routes is usually of little quantitative significance. Occasionally, the elimination of trace amounts of certain drugs in milk (e.g. many opioid analgesics and most hypnotic and tranquillising drugs) may make breast-feeding inadvisable when patients are on continual therapy. Muscle relaxants and their antagonists are not significantly eliminated in saliva or in milk.

Suggested reading

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