Towards Prescribing Practice

Edited by
JOHN McKINNON
MSc, PG Dip, BA (Hons), RGN, RNT, RMN, RHV
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"To my loved ones, loyal friends and colleagues. They know who they are."

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Acknowledgements

1 Understanding Basic Pharmacology

JOHN McKINNON

This chapter provides an introduction to the fundamental principles of pharmacology. Many nurses and allied health professionals approach this aspect of their prescribing studies with a sense of dread, believing it to be an area of knowledge that is unknown to them. However, the fundamental principles of pharmacology are linked to the same anatomical and physiological knowledge base that underpins many other areas of health-care practice.

As we journey through the different phases of the pharmacokinetic cycle – absorption, distribution, metabolism and elimination – examine how drugs effect their action and consider the different types of adverse drug events, a functional rather than a mathematical approach will be taken to enable the reader to grasp these principles whether or not they have a background in clinical chemistry.

Pharmacology forms a significant part of prescribing practice. It is important for prescribers to be able to construct a profile of any given drug and judge its suitability for treating any patient in their care. The starting point for this process is the *British National Formulary*, which is published every six months and is available in an electronic version online. It is structured in sections, each dealing with a different drug group and providing the specific dosage, contraindications, anticipated side effects and dose formulation for each drug. Supplements also provide instruction on prescription writing, drug licensing and monitoring.

Adherence on the part of the prescriber to drug-specific guidance in the *British National Formulary* (BNF) is essential. For the prescribing student, familiarisation with the structure and layout of the BNF is a preliminary study task that will prove beneficial. Good prescribing practice also recognises the place of collaborative working with the pharmacist where there is any doubt about prescribing issues.

To begin with some definitions, *pharmacology* is a broad term used to describe the study of drugs from their origins, chemical structure and administration to their absorption, distribution, actions, metabolism and excretion. There are other terms defining parts of this that we will mention briefly and with which you

will become better acquainted as you continue to learn and use them with confidence.

Pharmacokinetics relates to drug concentrations in body tissues and fluids, and the physiological processes that influence those concentrations over time. (In other words, what the body does to the drug.) This can be divided into absorption, distribution, metabolism and excretion.

Pharmacodynamics relates to the fundamental action of a drug on a physiological, biological or molecular level. (In other words, what the drug does to the body.)

Therapeutics is the branch of pharmacology concerned with the use of drugs to produce a desired clinical response in an individual.

ABSORPTION

Looking at the membrane of a cell (Figure 1.1) can teach us a great deal about the properties that drugs must have to be effectively absorbed by the body. The bilayer is so called because it is made up of a double layer of phospholipids arranged so that the water-loving (hydrophilic) positively charged heads face outwards towards the aqueous environment, either intracellular or extracellular, and the lipid-loving
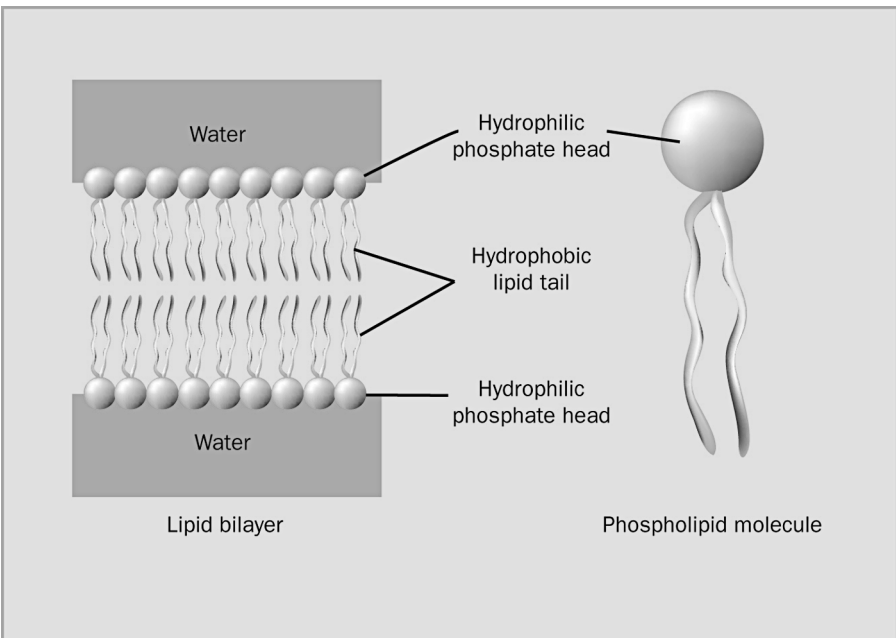
Figure 1.1 Structure of a cell membrane. Reproduced by permission of MA Healthcare. (See also colour plate 1).

(lipophilic) tails face inwards away from the aqueous environment. Over 45 % of the cell membrane is made up of lipid (Seeley et al., 2000).

Therefore the first three properties of a drug are ideally:

1. *Lipid solubility*, to diffuse easily across membranes.
2. *Water solubility*, to dissolve easily in aqueous solutions.
3. Possession of a *neutral or negative charge* so as not to be repelled by the positive charge of the external bilayer.

When a drug is dropped into oil and water, the proportion of the drug that dissolves in lipid is called the lipid *partition co-efficient*. In drug design a delicate balance must be struck between lipid and water solubility. If this is not done, the oral route will be less viable: highly lipid-soluble drugs will have delayed or failed absorption because of their reduced capacity to dissolve in the aqueous fluid of the gastrointestinal tract. Similarly, highly water-soluble drugs will not permeate the lipid bilayer of the gastrointestinal wall.

The *size of a drug molecule or molecular weight* is also relevant. The smaller the molecular weight, the more easily the drug is absorbed across membrane barriers. The degree of acidity or *pH* also plays a part as some drugs are more 'at home' and therefore more easily absorbed in an acid environment than in an alkaline or base one or vice versa. Many drugs exist as weak acids or as weak bases and the pH of their container compartment will influence the degree of ionisation that takes place and therefore membrane solubility (Rang et al., 2000).

Theoretically then, when an acidic drug such as aspirin is given orally, we might expect most of it to be absorbed in the stomach; this is not what happens in practice. This is because it can normally be predicted that passive diffusion of a molecule down a concentration gradient will take place at a faster rate across a large surface area than a small surface area. The greater surface area of the small intestine, comparable to that of a singles tennis court (Figure 1.2), facilitates the greater amount of absorption. The quality of *local blood supply* also powers absorption. A patient with congestive heart failure, for example, will have relatively poor absorption of oral drugs. *Peristalsis* inhibits absorption; *food* delays it. For this reason oral drugs should always be taken one hour before or two hours after food unless otherwise instructed. An example of an exception to this rule is ibuprofen, which should be taken with food to protect the stomach lining from damage.

DISTRIBUTION

Once in the bloodstream, some drugs are carried in the plasma as solutes, but many drugs to a greater or lesser extent bind to plasma proteins. The three-dimensional shape of the protein molecule is what makes it ideal for this purpose. When
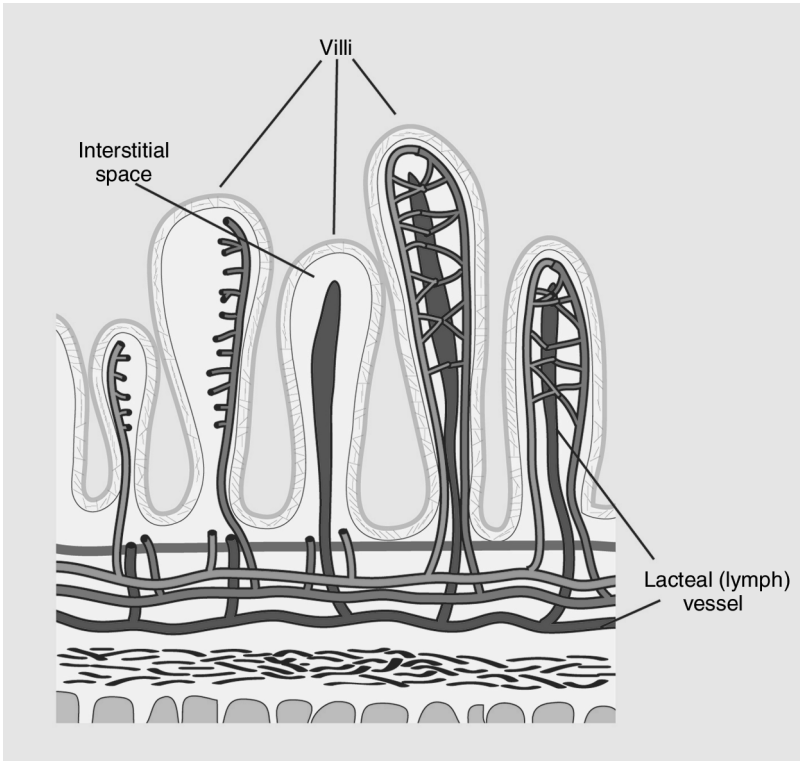
Figure 1.2 Structure of small intestinal wall, showing large surface area. Reproduced by permission of MA Healthcare. (See also colour plate 2).

drugs are bound to plasma proteins they are essentially inactive. It is the 'free' or 'unbound' drug that is active. The drug that is bound to plasma is automatically released as the free drug leaves the circulation and enters target tissues. Under normal circumstances the percentage of the drug in a bound state and that in a free state remains constant. This predictable homeostatic pattern is useful to pharmacists who are seeking to calculate viable and safe dosages (Greenblatt et al., 1982). However, problems can occur when drugs are displaced prematurely. This can happen in a disease such as liver failure, where excess bilirubin competes for binding space and the bound drug is displaced. The result is excess unbound drug in the bloodstream, which may lead to toxicity or an undesirably high clinical response (Downie et al., 1995).

Drugs that are administered orally are absorbed via the gastrointestinal tract and carried by the hepatic portal circulation to the liver. One of the functions of the liver is to change the chemical structure of drugs to allow easy disposal by the body. This role of the liver in relation to drug distribution in the body is called *hepatic first pass*. In the case of some drugs the liver is very efficient in

rendering the drug ineffective and such a drug is said to have a *high hepatic first pass*. For this reason, some drugs such as glyceryl trinitrate would be completely ineffective if given orally and must be administered by another route (e.g. sublingually, subbuccally or transdermally) so that they have the opportunity to act on the body before reaching the liver (Murphy and Carmichael, 2000; Mcleod, 2003). Other drugs such as pethidine and propranolol must be given in much higher doses when administered orally than if given intravenously in order to compensate for their high first-pass metabolism (Pond and Tozer, 1984; Young and Koda-Kimble, 1995).

SPECIALISED CAPILLARY BEDDING

THE BLOOD–BRAIN BARRIER

In most parts of the body capillary walls are one cell thick, making for easy passage of substances across the semi-permeable barrier. There are three exceptions to this. The first is the blood–brain barrier (BBB) (Figure 1.3).

The blood–brain barrier exists to protect brain tissue from potentially harmful substances that may be present in the blood. It is present throughout the brain and spinal cord, except the floor of the hypothalamus and the area postrema.
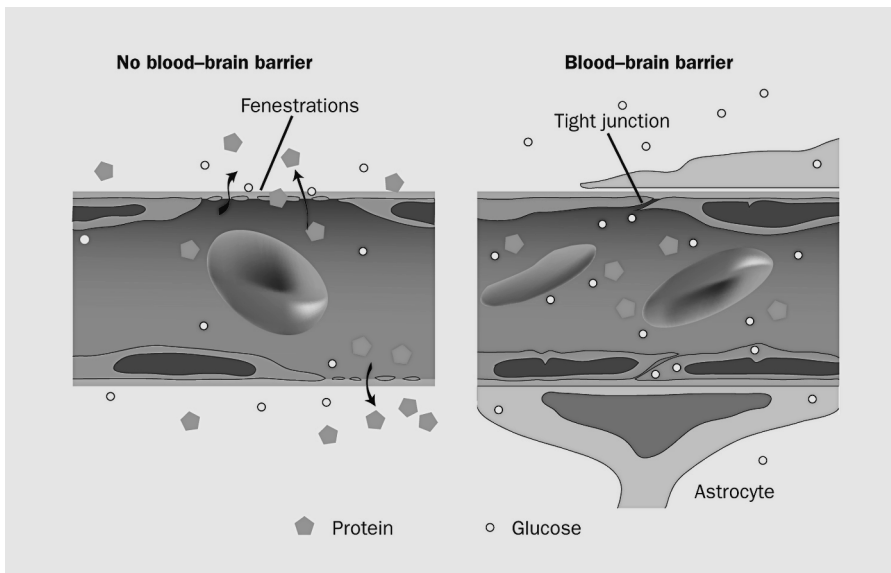
Figure 1.3 Blood–brain barrier. Reproduced by permission of MA Healthcare. (See also colour plate 3).

The fenestrations found in the endothelial tissue of the capillary bed elsewhere in the body are absent in the Circle of Willis. Instead of this, tight junctions are in place between the endothelial cells, which means that effectively materials in the bloodstream must transverse two membranes and, of course, the cytoplasm of the endothelium to reach cerebral tissue. This altogether more substantial structure is supported by foot-like processes of glial cells called astrocytes.

Although special transport systems are in place to facilitate passage of nutrients such as glucose, only drugs that are highly lipid soluble may cross this barrier. This is an advantage for clinicians seeking to use drugs that would be damaging to the central nervous system, as these drugs cannot cross the BBB. However, practitioners need to bear in mind that the BBB may not be as fully developed in infants and is less efficient in the elderly. It is a disadvantage for clinicians seeking to treat infections of the central nervous system, as antibiotics such as penicillin cannot penetrate the BBB. An exception to this would be severe meningitis, when the meningeal BBB may be damaged and some antibiotics are able to pass across the compromised buffer.

In the face of a fully functioning BBB, antibiotics must be given intrathecally (into the cerebral spinal fluid). Intrathecal injection is, however, a difficult procedure in view of the lack of room for manoeuvre and the close proximity of neural tissue that is vulnerable to damage (Tortora and Grabowski, 2003).

Since the beginning of the twenty-first century, researchers seeking to advance the treatment of conditions such as Alzheimer's disease have been experimenting with attached substances such as ascorbic acid components to act as carriers for some drugs, facilitating transfer across the BBB (Manfredini et al., 2002; Egleton and Thomas, 2005).

THE PLACENTAL BARRIER

The second exception is the *placental barrier* (Figure 1.4). This is not nearly as efficient as the BBB because the prime purpose of the structure of chorionic tissue is to allow maximum possible access to the maternal circulation for nutrition. Tree-like structured placental villi extending and carrying fetal blood from the umbilical cord originating in the amniotic sac are immersed in the maternal pool of blood present in uterine tissue. The barrier between the fetal and maternal circulation at any given time is less than wafer thin. As the surface area of this structure progressively increases in line with fetal development to permit a corresponding increase in tissue perfusion, it therefore follows that most drugs enjoy similarly easy passage across the placental barrier. This helps illustrate why pregnancy is a major consideration for prescribers and why a whole appendix in the BNF is dedicated to this subject. Groups of antibiotics that inhibit cell division (e.g. co-trimoxazole) are among the many drugs that are contraindicated in pregnancy.
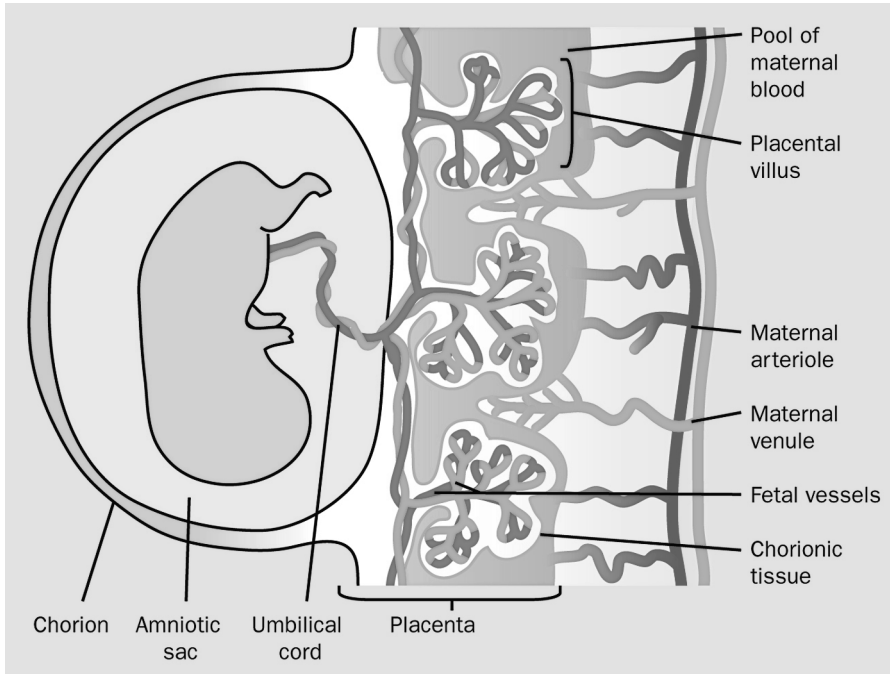
**Figure 1.4** The placental barrier. Reproduced by permission of MA Healthcare. (See also colour plate 4).

THE BLOOD–TESTICULAR BARRIER

The third area of specialised capillary bedding is the *blood–testicular barrier*. Relatively little is known about this barrier, but it seems that the Sertoli cells (Figure 1.5) play a major part in safeguarding spermatogenesis. Sertoli cells form tight junctions with each other and the inner luminal surface of the seminiferous tubules. They encase the developing spermatocytes as they mature into sperm and prevent substances detrimental to spermatogenesis, such as antibodies, from passing from the blood to the tubular compartment. As with any other protective barrier, it is not totally impregnable. It has recently been shown that the chemical lindane can cross the testicular barrier and cause damage to spermatogenesis (Silvestroni et al., 1997).

DRUG RECEPTORS

A *drug receptor* is the site of drug action where the molecular event occurs that leads to a therapeutic response. This, like the term pharmacology, is a broad concept, because receptors can take a variety of forms. The majority are complex macromolecular proteins such as enzymes or hormones. However, certain drugs
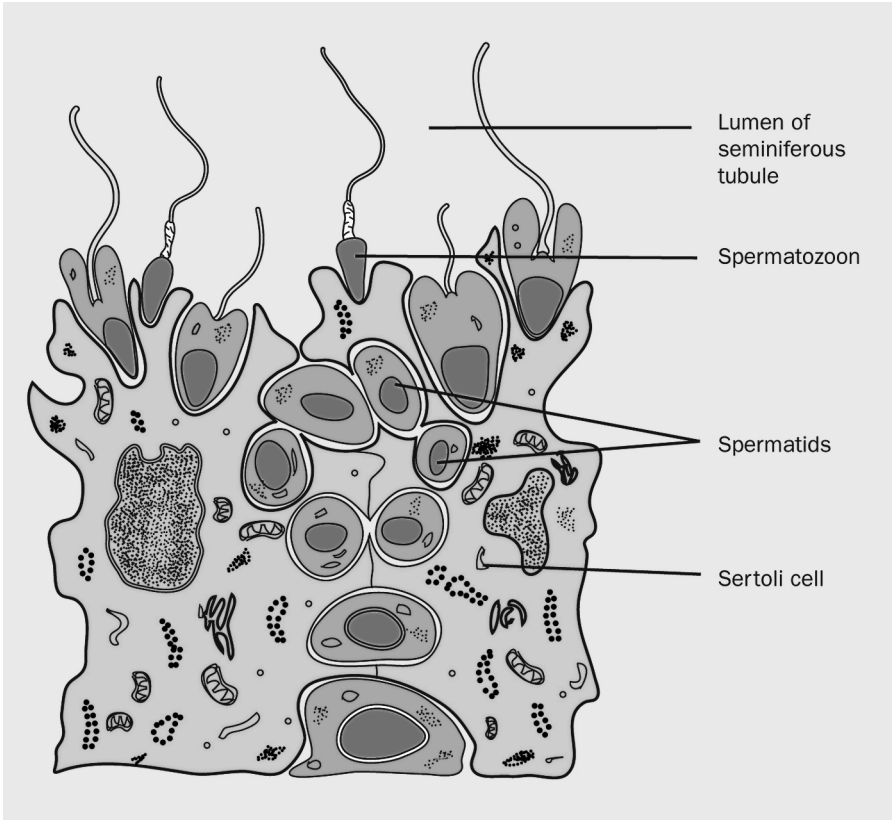
Figure 1.5 The blood–testicular barrier. Reproduced by permission of MA Healthcare. (See also colour plate 5).

can bind to non-protein substances such as nucleic acids. We can recall from our discussion of the distribution phase of pharmacokinetics that the three-dimensional shape of plasma proteins makes them natural binding sites during drug distribution. For the same reason, most drug receptors have a protein component. The meaning of the term drug receptor should help us see that drugs do not themselves bring about a therapeutic response. Rather, they work by enhancing, blocking or diminishing the body's extracellular and intracellular mechanisms. In this process the drug receptor acts as a catalyst; that is, a third-party facilitator of a reaction that changes both the participants in the molecular event, the enzyme within the receptor and the substance binding with it, without changing itself.

Receptors are located within the channel proteins embedded in the membranes of cells. Receptors are also located in the intracellular environment to act as junctions in message-conduction pathways. A substance that binds with a receptor is known as a *ligand*. There are a number of ways in which a ligand is identified by and able to bind with a receptor. For example, some receptors are gated by an electrical

charge or voltage gated. Here, the rate of ionic conductance is altered by the ligand (e.g. cardiac muscle tissue). In other cases the ligand sets a biochemical chain of events in motion that manipulates intracellular function. This is known as ligand gating. A receptor site may also bear glycoprotein pendant chains as markers to attract the appropriate ligands (Figure 1.6). This latter method is common in the immune system and is also the way an oocyte attracts sperm in the reproductive process (Seeley et al., 2000).

In order to be accepted, a drug must therefore deceive the receptor by resembling the appropriate ligand, rather like the wrong key can sometimes be placed in a lock. Drugs can broadly be categorised by their roles of action. Those that stimulate receptors are *agonists*. Those that diminish the message normally transmitted by receptors are *antagonists*. Antagonists may also be described as acting competitively when they 'compete' with the relevant ligand for the same receptor site. This is called *competitive inhibition*. Antagonists may also act non-competitively by binding to an alternative receptor site and compromising the ligand signal from there. This is called *non-competitive inhibition* (Figure 1.7).

A bronchodilator such as salbutamol is an example of an agonist as it selectively stimulates the Beta 2 receptors located in the smooth muscle of the bronchioles. The vasodilator nifedipine is an example of a calcium antagonist as it blocks the
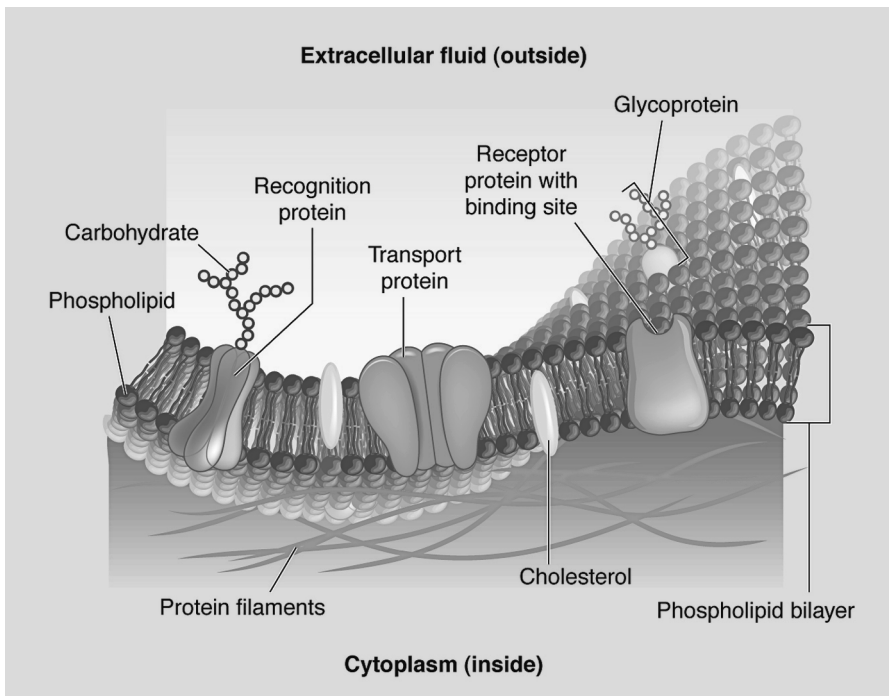
Figure 1.6 Cell membrane and receptor sites. Reproduced by permission of MA Healthcare. (See also colour plate 6).
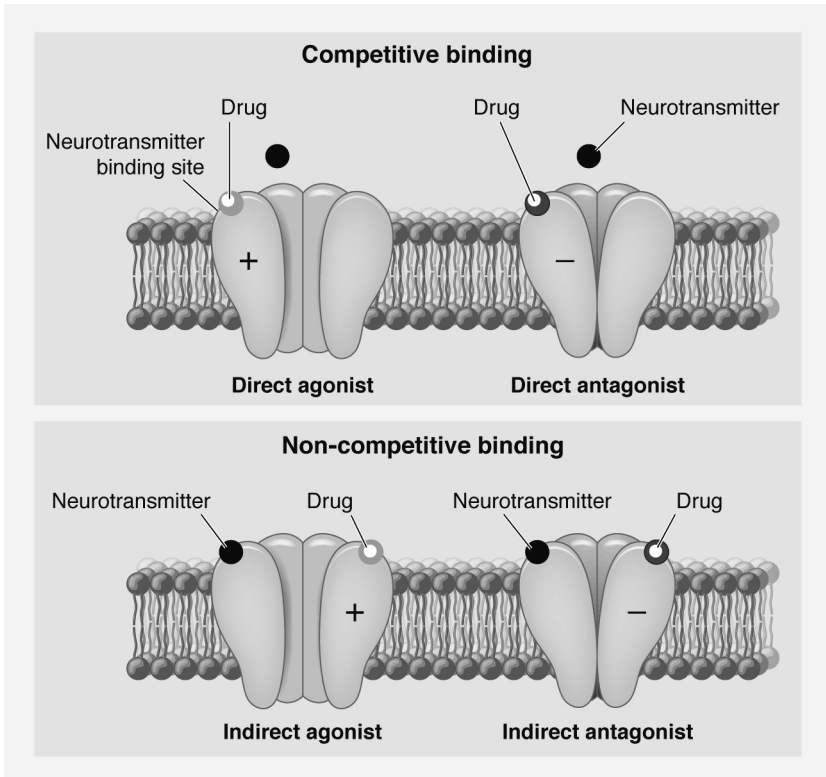
Figure 1.7 Competitive and non-competitive inhibition. Reproduced by permission of MA Healthcare. (See also colour plate 7).

calcium channels of vascular muscle. The more selective drugs are in their targeting of receptors, the less likely side effects are to occur.

METABOLISM AND ELIMINATION

Drug metabolism is the first stage of drug clearance and describes the means by which a drug is chemically altered to facilitate elimination from the body. Many drugs are essentially lipophilic to permit effective absorption. Were they to remain in this state, they would either be reabsorbed in the renals or the gut, with undesirable or even toxic consequences. Alternatively, the more hydrophilic drugs will often pass through the body unchanged. Some drugs are actually designed to take advantage of this process and in such cases it is the drug metabolite that exerts the greater therapeutic response. When this is the case the medication actually administered is termed a *prodrug*. An example of this is the antianxiolytic diazepam, which is metabolised to nordazepam and oxazepam, both of which are active substances (Lin and Lu, 1997).

Although the main organ of metabolism is the liver, metabolic properties are present in most body cells. This is particularly the case in lung tissue, which explains why some drug metabolites are exhaled. It is, of course, this route of elimination that makes measurement of blood alcohol levels by breathalyser possible. Widespread metabolic tissue distribution in the body also explains why drugs can be excreted in the host's sweat, saliva and tears in addition to the host's urine and faeces. This is the second stage of clearance.

The *cytochrome P450 enzymes* exist within endoplasmic reticulum of liver and other body cells in a sufficiently wide range of varieties to enable them to metabolise a correspondingly wide range of drugs. They achieve this by:

- *Oxidation*, in which the positive charge of the drug molecule is increased.
- *Reduction*, the addition of an oxygen atom to the drug molecule.
- *Hydrolysis*, the breakdown of the drug molecule through the addition of water.
- *Conjugation*, the coupling of the drug molecule with an acid making for greater water solubility.

Oxidation, reduction and hydrolysis are known as phase one metabolism. Conjugation constitutes phase two metabolism. Essentially the outcome of both phase one and phase two reactions is an increase in the hydrophilicity of a drug, which facilitates excretion by the kidneys.

Most drugs follow *first-order kinetics*, where the rate of metabolism and elimination is related to the level of plasma concentration. Here an increase in the plasma concentration of the drug leads to stimulation of synthesis of cytochrome P450 enzymes, often called *enzyme induction*. A minority of drugs follow *zero-order kinetics*, in which metabolism is not related to the rate of plasma concentration but takes place at a constant rate. This is often the case when drugs such as alcohol are taken in excess and *enzyme saturation* takes place. Put simply, first-order kinetics is rather like a supermarket queue that as it increases in length leads to other checkouts being opened and customers being processed at a faster rate. Zero-order kinetics is like a supermarket checkout queue that regardless of length is served by the same number of checkouts.

In the kidneys, drugs of a low molecular weight are eliminated by glomerular filtration (Figure 1.8). Further secretion takes place in the proximal tubule. Here carriers exist to remove both bound and unbound drug through the creation of a concentration gradient that favours dissociation and passage from the capillary bed into the tubular lumen. Reabsorption also takes place in the tubules by active and passive diffusion. Drugs that are lipophilic are normally reabsorbed. Drugs that are unionised in a low pH medium such as urine but ionised in a higher pH medium such as plasma will be partially reabsorbed by means of a phenomenon known as ion trapping. Here the pH of the new compartment of the translocated molecule – that is, the blood – ensures that the drug compound is ionised and cannot permeate back from whence it came (Brody et al., 1998; Rang et al., 2000).
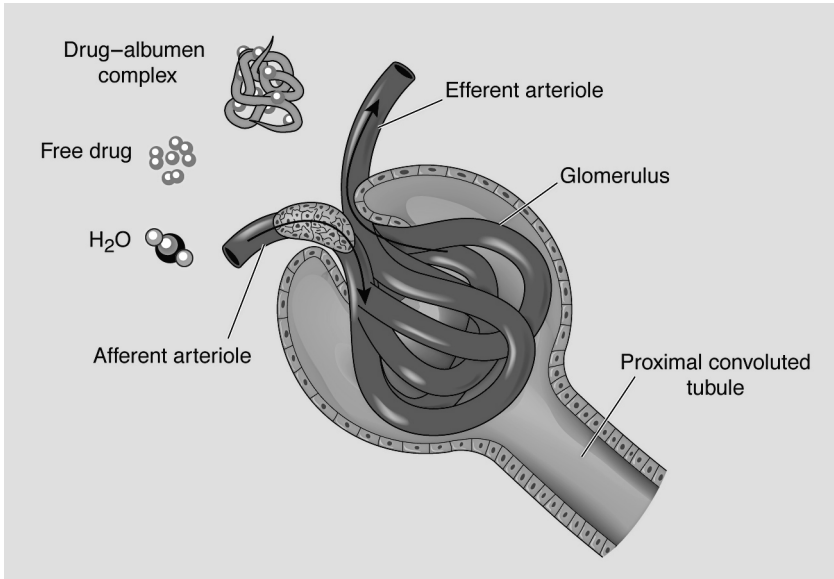
Figure 1.8 Glomerular filtration of drugs of low molecular weight. Reproduced by permission of MA Healthcare. (See also colour plate 8).

These reabsorption mechanisms underline the value of phase one and phase two metabolism to irreversible elimination of a drug from the body (Brody et al., 1998; Seeley et al., 2000).

PLASMA CONCENTRATION

Sustaining drug serum plasma levels within the range in which a therapeutic agent is simultaneously safe and effective is a major part of good medicines management. Clearance is the singularly most important parameter, but there are a number of others that deserve consideration.

THERAPEUTIC INDEX

The margin of safety within which drug treatment is delivered and sustained is called the *therapeutic index (TI)*. The TI is calculated by dividing the plasma level above which the drug becomes toxic, the maximum safe concentration (MSC) or *toxic threshold*, by the level below which the drug is ineffective, the *subtherapeutic threshold* or minimum effective concentration (MEC) (Figure 1.9). When this ratio is 2.0 or less the drug in question is said to have a narrow therapeutic index and must be used in conjunction with strict regular monitoring of plasma levels. The cardiac drug digoxin (Gibbs et al., 2000), the antibiotic gentamicin (Sorger et al.,
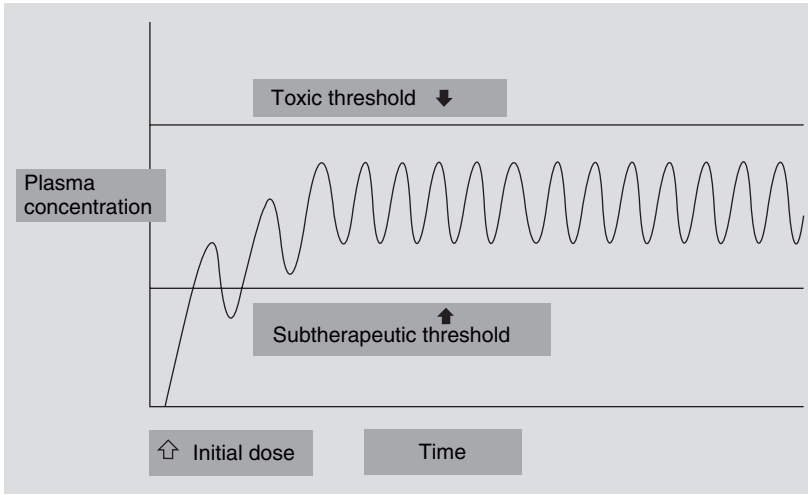
Figure 1.9 The therapeutic index. (See also colour plate 9).

1999) and the mood stabiliser lithium carbonate (Jefferson, 2002) are all examples of drugs with a narrow TI.

HALF LIFE

The *half life* $(t_{\frac{1}{2}})$ is the time taken for the drug's plasma concentration to decrease by half. This means that 500 mg of a drug with a half life of four hours entering the bloodstream at 9 a.m. has a plasma concentration of 250 mg by 1 p.m. and 125 mg by 5 p.m. A *steady state concentration (SSC)* is a plateauing drug plasma level achieved when the amount of drug eliminated per dose interval is equal to the dose of that interval. A good rule of thumb is that drug plasma levels reach a therapeutic level after four or five half lives from the time of the initial dose and that doses should be given with every passing half life in order to sustain an SSC. In Figure 1.9 the SSC is represented by the wave form, with maintenance doses being given at the low points of the configuration. In the example given above repeat doses would be given every four hours.

Knowledge of the half life and TI of a drug is important when calculating the recommended dosage and frequency of administration, because a drug with a long half life and a narrow therapeutic index may only be given once a day. In contrast, a drug with a short half life and a broad therapeutic index may be given several times per day. In some cases, the drug half life is so short that an initial 'loading dose' of twice the maintenance dose is given to ensure a higher initial plasma concentration level and that maximal therapeutic effect is attained quickly. For example, in cases where a patient has a severe infection and the drug of choice has a sufficiently broad TI, a loading dose may be given to accelerate clinical response time. The

individual half life of a drug also helps calculate total clearance time if there is a need to subsequently administer a drug that might adversely interact with any plasma remnants of the previous agent. This explains why adherence to an agreed medication schedule is vital for effective treatment (Downie et al., 1995).

VOLUME OF DISTRIBUTION

The volume of distribution (Vd) is a measurement of the extent to which a drug is dissolved throughout the body's compartments. In a man weighing 70 kg, the total blood volume is 5 litres and the total fluid volume of body compartments is 40 litres. A blood sample is taken at 'time zero' (the point at which the drug enters the bloodstream) and if plasma concentration is found to be significantly lower than the administered dose, it is assumed that substantial tissue perfusion has taken place. Because of the hypothetical nature of the estimation, the term 'apparent' volume of distribution is often used. Some drugs that are very lipophilic will have a greater binding affinity to adipose tissue and therefore their overall Vd may appear to be in excess of total body fluid volume (Brody et al., 1998).

Table 1.1   Learning exercise

1. Choose any one drug commonly used in your practice.
2. List your working knowledge of this drug in practice, including dosage range, formulation and route of administration.
3. Construct a pharmacological profile of the drug including absorption, half life, volume of distribution and elimination route. Describe the drug's therapeutic action at receptor level and explain any contraindications and side effects.
4. Justify your practical working knowledge of the drug using the profile you have constructed.

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THE RELATIONSHIP BETWEEN PARAMETERS

All pharmacokinetic parameters should be seen as relating to one another. Although clearance and volume of distribution are independent in their function, they have a direct impact in health and disease states on the half life and margin of therapeutic safety. Hepatic and renal disease both compromise clearance and can increase the half life of drugs. Increased absorption also increases the volume of distribution. Drug interactions are also relevant. Digoxin is one of many drugs that when interacting with others at different points in the pharmacokinetic cycle may have its volume of distribution and peak plasma concentration adversely altered, with toxic results (Haji and Movahed, 2000).

AGE

EARLY LIFE

Children cannot be treated as linear adults in terms of prescribed dosage. The *British National Formulary for Children* should be adhered to when prescribing medicines for children and adolescents. The age ranges identified against which to prescribe for the young (neonate, infant, child and adolescent) reflect the variance in the pace of growth during a specific time period (National Prescribing Centre, 2000).

Absorption

The pH gradient of a young child's alimentary tract is not as steep as in adulthood and the rate of gastric emptying varies a great deal in infants of under 6 months. Peristalsis is also slower. This can lead to higher levels of drug absorption. Peripheral perfusion and muscle mass are lower in the young, which can compromise absorption from an injection site. A child's topical surface area is proportionately larger and skin thinner, which results in greater absorption of topical agents.

Distribution

The higher body water content associated with the early years of life means that there will overall be a lower concentration of a drug at intracellular and receptor levels. Adipose tissue acts as a bank for residual drug and, as children have less body fat content, the pharmacodynamic response is likely to be swifter and more potent.

Metabolism and Elimination

Drug potency in neonates is also increased by the reduced plasma protein concentration and consequently higher levels of unbound active drug. The development of the cytochrome P450 enzymes continues until 3 years old. This, together with the fact that glomerular fitration and renal perfusion rates are reduced in infants, means that hepatic and renal clearance of drugs is less efficient in the very young, leading to longer half lives of administered medication, greater pharmacological effect and potential toxicity (National Prescribing Centre, 2000; Walker and Edwards, 2003).

ADVANCED AGE

Absorption

Gastric emptying, reduced mesenteric blood flow, reduced peripheral perfusion and skeletal muscle mass are all characteristic of advanced age. While overall the resultant pattern is one of slowed absorption from the gut and injection sites and therefore a delayed therapeutic response, there are some exceptions to this rule.

Delayed gastric emptying may mean that enteric coated medication intended for absorption in the gut may be absorbed earlier in the stomach. Also changes in bowel habit, not uncommon in old people, may interfere with the enterohepatic cycle (Heath and Scofield, 1999; National Medicines Information Centre, 2000).

Distribution

Old people have reduced intracellular fluid levels, an indication of increased concentration of drug at the receptor sites with enhanced effects. Increased levels of adipose tissue in the older patient predispose lipid-soluble drugs to a longer half life. Reduced plasma protein concentration means that more unbound active drug is present at any one time. On the other hand, a more sluggish systemic circulation results in slower 'bulk flow' transport of therapeutic agents (Heath and Scofield, 1999).

Metabolism and Elimination

Reduced hepatic perfusion would appear to be more responsible for reduced hepatic clearance in old age than enzymatic changes. While there is considerable variation among individuals, the overall tendency in the older population is one of decline in glomerular filtrate rate and tubular function. This, together with reduced renal blood flow, means that the risk of drug toxicity and overdose is increased (Heath and Scofield, 1999; Walker and Edwards, 2003).

Prescribing Implications for Older People

Receptor Sensitivity

The ageing process is known to produce drug receptor changes that appear to cause increased sensitivity to some drugs. These changes include a decrease in the number of receptors, reduced receptor affinity for specific ligands and the reduced response of target tissues (Department of Health, 2001).

Cognition

There is evidence (discussed in more detail in Chapter 2) to suggest that older people are not as forgetful and easily confused as previously thought and that many retain judgement, skill and independence throughout life. Nevertheless, cognitive centre changes mean that such problems are incidental to old age and that individual assessment, dosage and dose titration are required. Regular evaluation and review are also important to measure progress and address any practical difficulties arising from the prescribed regimen. Anticholinergics, H_2 antagonists and beta-blockers are examples of drugs that can cause confusion in the elderly and should be used with caution.

Cardiovascular Stability

Altered orthostatic circulatory response means that drugs that reduce sympathetic nervous activity such as barbiturates, benzodiazepines, antihistamines and morphine are more likely to cause hypotension in older people. The same applies to agents that block adrenoreceptors, such as trycyclic antidepressants and phenothiazines. Some anti-Parkinsonian drugs also fall within this category.

Postural Control

Increased corrective movement aimed at sustaining balance is required of many old folk. Consequent prospects of prolonged complicated recovery from injury caused by falls means that hypnotics and tranquillisers are contraindicated in this age group, as they can exacerbate problems with postural control. The fragmented sleep patterns that often characterise this time of life also make the use of hypnotics unsound in older people, as they merely induce sleep rather than sustain it.

Body Temperature Regulation

The problems sometimes experienced by the old relating to thermoregulation make inadvisable the prescribing of drugs that have a sedative effect leading to vasodilation. Benzodiazepines, tricyclic antidepressants and opiods all meet this description. Even the moderate consumption of alcoholic beverages with or without drugs should be viewed with caution for the same reasons.

Visceral Muscle Function

Altered visceral muscle function occurs in old age. Medicines that directly or indirectly affect muscle tone may cause unnecessary discomfort and distress to older patients. Loop diuretics may exacerbate episodes of incontinence in patients with genito-urinary problems. Anticholinergic drugs have been known to cause urinary retention in older men. Reduced motility of the gut means that constipation as a documented side effect of opiates, trycyclic antidepressants and anticholinergic drugs is more likely to occur if prescribed for older people (Heath and Scofield, 1999; Walker and Edwards, 2003; Curtis et al., 2004).

Safe and effective prescribing behaviour is all the more challenging when treating groups who are vulnerable or who have special needs. Health advice that provides alternative and less risk-laden strategies to medicine is always an important part of the consultation. This is discussed in Chapter 4.

ADVERSE REACTIONS: PATHOGENESIS AND TREATMENT

Concern over public safety in the face of increasing adverse drug events means that pharmacovigilance has become a key part of the prescribing practitioner's

armoury in the drive for optimum medicines management (NPC and National Primary Care Research and Development Centre, 2002; Walker and Edwards, 2003). The Audit Commission (2002) reported an increase in the number of patients suffering adverse drug events, adding that this resulted in extended hospital stays, increased professional deployment and an additional cost to the NHS of over £1 billion.

An adverse drug event or reaction has been defined by the World Health Organization as 'any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function' (Consultant Council for International Organizations of Medical Sciences, 1993: 45). However, this definition has been criticised as failing to include the reactions occurring as a result of human error. For many, a more comprehensive definition might simply be 'an undesirable response to a therapeutic agent'.

CLASSIFICATION

According to Rawlins and Thompson (1977), adverse reactions can be broadly divided into two types: A and B. Type A reactions are related to the pharmacokinetics of a drug and are therefore predictable when these are known. Many such adverse drug events result from interaction with other agents at different points in the pharmacokinetic process. They are dose related and, while morbidity and incidence are high, mortality is usually low and the effects of the reaction subside when the drug is withdrawn. Type B reactions are largely unpredictable and individual to the patient. Such reactions also take place at different points in the pharmacokinetic process, but instead of being dose related have their roots in the patient's genetic make-up. Mortality is high.

Aronson and Ferner (2003) proposed a new classification system for adverse drug reactions based on dose responsiveness, time course and susceptibility. While this can be recommended to the prescribing student as a valuable multidimensional tool for practice, Rawlins and Thompson's system is used here as it facilitates a better understanding of the processes at work.

Predisposing Factors

Polypharmacy by virtue of increased risk of synergistic interaction predisposes the patient to an adverse drug event (National Prescribing Centre, 1999). However, it should be remembered that multiple drug therapy is usually in place to treat multiple disease states, which may also affect pharmacokinetics. The very old and the very young are also susceptible and women are at greater risk, although it is uncertain why this is so. Genetic and familial factors also play a part (Walker and Edwards, 2003).