



# Pathophysiology & Pharmacology in Nursing

# Chapter 1

# Introduction to pathophysiology and pharmacology

## Chapter aims

After reading this chapter you will be able to:

- explain the terms pathophysiology and pharmacology and their importance to nursing practice;
- explain three key principles of human biology: the levels of biological organisation, homeostasis and cellular communication;
- describe how absorption, distribution, metabolism and excretion affect drug activity;
- describe the general principles of how drugs work in the body;
- explain why some drug interactions occur.

## Introduction

### Scenario

You are a nursing student on a clinical placement with a practice nurse at a local medical centre. You are observing the nurse during an asthma clinic. The patient, Hannah, is an 11-year-old girl who has recently been diagnosed with asthma. She is attending the clinic for the first time with her mother, Caroline. The nurse explains about asthma to Hannah and answers questions from Caroline. After explaining to Hannah how her blue salbutamol inhaler will help her to breathe when she feels 'wheezy' by opening up her airways, the nurse shows Hannah how to use her inhaler correctly. Hannah has been given a peak flow meter which she will use to monitor her asthma. The peak flow meter measures the peak expiratory flow from the lungs. Peak flow values give an indication of the degree of airway

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obstruction which in asthma is variable. The nurse explains to Hannah and Caroline the importance of monitoring her asthma and how to identify and avoid any trigger factors.

After the consultation, the nurse asks you to reflect on your understanding of asthma, how it is triggered and how the salbutamol treatment works. You are able to describe the key characteristics of asthma (airway inflammation, bronchospasm and increased mucus secretion), the main environmental stimuli provoking asthma, and the underlying inflammatory response of early-onset atopic asthma. You are able to explain the action of salbutamol as a beta-2 adrenergic receptor agonist which results in bronchodilation reversing the bronchoconstriction found in asthma. You appreciate that you would like to know more about long-term preventative treatment for asthma which involves the use of a steroid inhaler.

This scenario is intended to illustrate how pathophysiology and pharmacology inform your nursing practice and patient education. Details of the pathophysiology of asthma and its pharmacological management can be found in Chapter 9 on Respiratory conditions.

This scenario shows the importance of pathophysiology and pharmacology for enabling effective nursing care. This knowledge will enable you to understand how your patient's treatment works or effects a change, and to be able to monitor this effectively and be aware of any side effects. Knowledge of pathophysiology and pharmacology is also needed for you to explain the condition and treatments to your patient in a way that they can understand. You will also be in a position to discuss your patient effectively with members of a multi-professional team.

In the first part of this chapter, we define the different terms used in pathophysiology to describe a disease or condition. In the second section, we ask you to consider three key principles of human biology: levels of biological organisation; homeostasis; and cellular communication. Using these three principles gives you a framework to help you understand your patient, their disease or condition. The third and final section of this chapter introduces you to the key principles of pharmacology, namely, pharmacodynamics and pharmacokinetics.

### Activity 1.1 Reflection

Before continuing with this first chapter, consider what you understand already about pathophysiology and pharmacology. What are these two subjects about? Why are they important for nursing? Write down your initial thoughts and then return to review them at the end of each chapter to see how your understanding is developing.

*There is no outline answer because from this activity you will produce a list of your own ideas or observations.*

# Pathophysiology

Pathophysiology is the study of how a disease affects the functioning of the body. In the scenario above, Hannah has asthma. The pathophysiology of asthma explains how asthma causes breathing difficulties and how this may result in insufficient oxygen reaching the cells.

Pathophysiology contributes significantly to our understanding of the disease a patient may present with. A number of other, closely related concepts are needed to give a full picture of a disease or condition. One of these additional concepts is the aetiology – or cause of a disease. For example, the **aetiology** of asthma is complex, involving a person's genes, their immune response, as well as exposure to environmental factors such as house dust or pollen. This is covered in Chapter 9. Most diseases do not have a single cause. Cardiovascular disease, for example, has many risk factors such as age, male gender, smoking, high cholesterol and lack of exercise (Chapter 8). Risk factors are factors that are associated with an increased risk for the disease. These are worked out through **epidemiology**, by studying populations of individuals with the disease and those without. Further research can then be carried out to determine a mechanism (or causal link) for how the risk factors contribute to the disease. This leads us to another term, **pathogenesis**, which describes the causal mechanisms that result in disease (McCance and Heuther, 2018).

All diseases involve damage or injury to cells which alter normal functioning or cause cell death. Asthma, for example, involves damage to the cells lining the airways from an inflammatory response which leads to airway constriction; ischaemic heart disease involve damage or even death to the heart muscle cells due to lack of oxygen (**ischaemia**) (Kumar et al., 2022).

**Clinical presentation** refers to how the disease affects the patient. It includes the signs and symptoms of a disease. Symptoms are how a person experiences their disease; signs are observations that may be made to indicate the presence of disease. As an example, a symptom of asthma is difficulty breathing and a sign would be the clinician's observation of this difficulty. With diabetes, a low blood glucose measurement is a possible sign, whereas thirst and fatigue are symptoms. Throughout this book, we highlight the clinical presentation of disease and relate these to the underlying pathophysiology.

The different terms used above to describe a disease form part of what is referred to as 'the medical model of disease'. The medical model of disease is a scientific, evidence-based framework for analysing disease. The medical model of disease should not be confused with 'a medical model of care'. A medical model of care would be one that solely focuses on treating a patient's disease or managing their symptoms. In today's healthcare system, person-centred care is advocated. A person-centred care approach places the person at the centre of their care and takes account not only of the best evidence for understanding and managing their disease, but individual patient preferences and the need for holistic care. In person-centred care, health and social care

professionals work collaboratively with people who use services. It is co-ordinated and tailored to the needs of the individual. Person-centred care supports people to develop the knowledge, skills and confidence they need to more effectively manage and make informed decisions about their own health and healthcare (The Health Foundation, 2016). As part of your role delivering holistic person-centred care, the application of pathophysiology and pharmacology will inform your clinical decision-making, including your assessment of patients and the planning, intervention and evaluation of patient care. This knowledge will enable you to communicate effectively with the multi-professional team and your patients to promote their health, facilitate early diagnosis, recovery, rehabilitation or to provide palliative and end-of-life care.

## Three key principles of human biology

### 1. Levels of biological organisation

Figure 1.1 shows the levels of organisation of the human body. You may already know that we can view the human body as a collection of cells organised into clearly defined tissues, and that tissues are the building blocks of organs. In turn, organs work together to form organ systems. The smallest levels shown in Figure 1.1 are molecules and macromolecular complexes such as the cell membrane. The smallest living unit is the cell.

#### Activity 1.2 Reflection

Reflect on your current knowledge of the organisation and function of the human body. Start by naming the eleven organ systems of the body. Can you give the function of each system?

Then identify the main component organs of each system and the function of each organ.

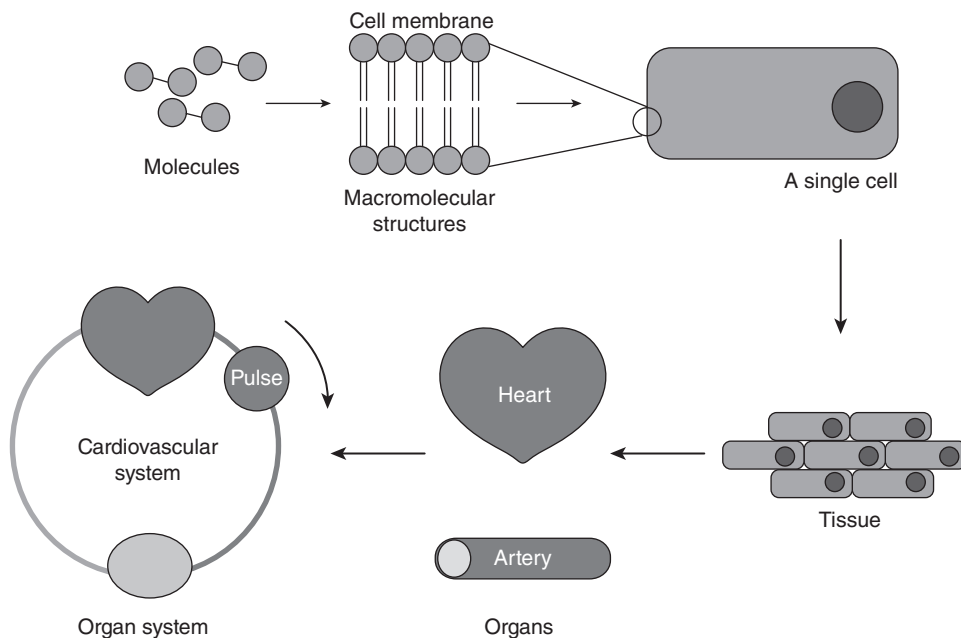
Can you name the four tissue types which make up the organs of the body?

*The best way to check your answer is using an anatomy and physiology textbook. Recommended textbooks are given in the 'Further reading' section at the end of the chapter.*

In Activity 1.2 you identified the organ systems and individual component organs of each system. Thinking about the structure and function of the human body at the tissue level is more difficult. This is because cells which make up tissues are microscopic. We cannot see directly how they are functioning. By the same reasoning, it is even more challenging to picture how molecules such as hormones, enzymes or drugs work within the body. Drawing diagrams or looking at animations from the internet can help you visualise these interactions. This will greatly enhance your understanding of the topics in this book.

## 2. Homeostasis

The maintenance of a relatively constant internal environment despite fluctuations in the external environment (homeostasis) is the second biological principle we will look at. Homeostasis ensures the best or ‘optimum’ conditions for cells to function, as well as delivering the right amount of oxygen and removing waste products, such as carbon dioxide, urea and lactic acid. Other key conditions kept in homeostasis include: body fluid and electrolytes, pH, blood glucose and temperature. To function optimally, the body needs to be in homeostasis. Conversely, a homeostatic imbalance, where one or more conditions have become too high or low, is considered as one definition of illness (Tortora and Derrickson, 2017).



Six levels of organisation of the human body are shown. The smallest is the molecular level which group to form larger macromolecular complexes such as the cell membrane. Macromolecular complexes form cells – the smallest living unit of the body. Cells of a similar type form tissues, such as cardiac muscle cells forming the myocardium, or muscle layer of the heart. Two or more tissues make up an organ, and organs work together to form an organ system, such as the cardiovascular system.

*Figure 1.1* The levels of biological organisation

To see how the concept of homeostasis can help in understanding pathophysiology, we can use the example of asthma again. Asthma affects breathing and so reduces **gas exchange** in the lungs. The level of oxygen in the body can drop to a critically low level and the level of carbon dioxide increase to produce a harmful **acidosis**. The body is ‘thrown out’ of homeostasis with respect to its **acid–base balance** and oxygen levels. This is potentially life-threatening (Chapter 9). Another example is diabetes which involves problems of glucose regulation (Chapter 11). With untreated diabetes, levels

of blood glucose can become raised and cause long-term damage. It is beyond the scope of this chapter to review in detail the physiological processes maintaining homeostasis. However, many of the diseases described in this book will affect one or more aspects of homeostasis. For example, Chapter 8 will examine the normal regulation of blood pressure as well as **hypertension**. Chapter 11 will explain the normal regulation of glucose in the context of diabetes.

One of the key reasons that homeostasis is so important to health is that cells rely on proteins to function. Proteins are large molecules that fold into particular three-dimensional shapes. The three-dimensional shape of a protein is essential for its optimum function. The shape of a protein is affected by conditions such as temperature and acid–base balance. Any change away from the optimum shape will adversely affect how the protein functions. One class of proteins you may have heard of are **enzymes**. Enzymes are biological catalysts that increase the rate of the chemical reactions within the body. The enzymes in the human body work best at 37°C (which is our normal core body temperature). Any changes from this temperature will affect the shape and function of enzymes. Very high temperatures (above 40°C) can completely destroy their shape and function. The enzyme is said to be de-natured (or ‘away’ from its natural shape) (Tortora and Derrickson, 2017).

### 3. Cellular communication

The different organs, tissues and cells must work together to form a fully functioning individual. The working-together of cells, tissues and organs is called integration. Integration requires careful control and co-ordination of the different parts of the body. This in turn requires effective communication between the different cells of the body.

Nearly all cellular communication involves a signalling cell and a target cell which receives the signal. Signalling cells release one or more chemical messengers, or signalling molecules, which act on the target cell. **Neurotransmitters**, **hormones** and **growth factors** are the main signalling molecules used by the body (Figure 1.2). These are recognised by **receptors** on target cells – the signalling molecule and receptor have complementary shapes. Most receptors are cell membrane proteins. Binding of the signalling molecule to the receptor triggers a response by the cell (see ‘Signal transduction’, below).

The difference between types of signalling lies in the distance between signalling and target cells and the means by which the signalling molecule reaches the target cell. We describe three types of signalling: nerve, endocrine and local.

1. *Nerve signalling.* Nerve signalling occurs within the nervous system and is used to regulate muscles and glands. A **neurone** is a single nerve cell that sends a message in the form of a nerve impulse (or **action potential**). Nerve impulses travel very rapidly along the neurone, often over great distances within the body. When the nerve impulse reaches the end of the neurone, signalling molecules

called neurotransmitters are released. Neurotransmitter molecules diffuse across a microscopic gap called the **synapse** to reach the target cell. The target cell has neurotransmitter receptors on its surface to receive the signal.

2. *Endocrine signalling.* Signals in the form of hormones are sent round the body in the bloodstream from endocrine glands or tissues to target cells (Figure 1.2). Endocrine signalling is slower than nerve signalling. This is because the circulation is slower to carry the signalling molecule than a nerve impulse which is very rapid. However, endocrine signals become widespread throughout the body by being distributed in the circulation. A nerve impulse can only reach a limited number of target organs. In this sense, a nerve impulse is more specific.
3. *Local signalling.* Local signalling occurs between cells that are adjacent or very close to each other. This is seen, for example, in the inflammatory response (Chapter 2) and with cancer (Chapter 5). **Inflammatory mediators** are a group of chemical messengers that we will examine in Chapter 2. Although they act locally, some enter the bloodstream and exert their effect at more distant targets. In this sense they act more like hormones.

A signalling molecule will only work if it can cause a response in the target cell. The way in which a cell responds to a signal depends upon the type of signal and the type of cell it is. Each signalling molecule has its own set of target cells in the body on which it can act.

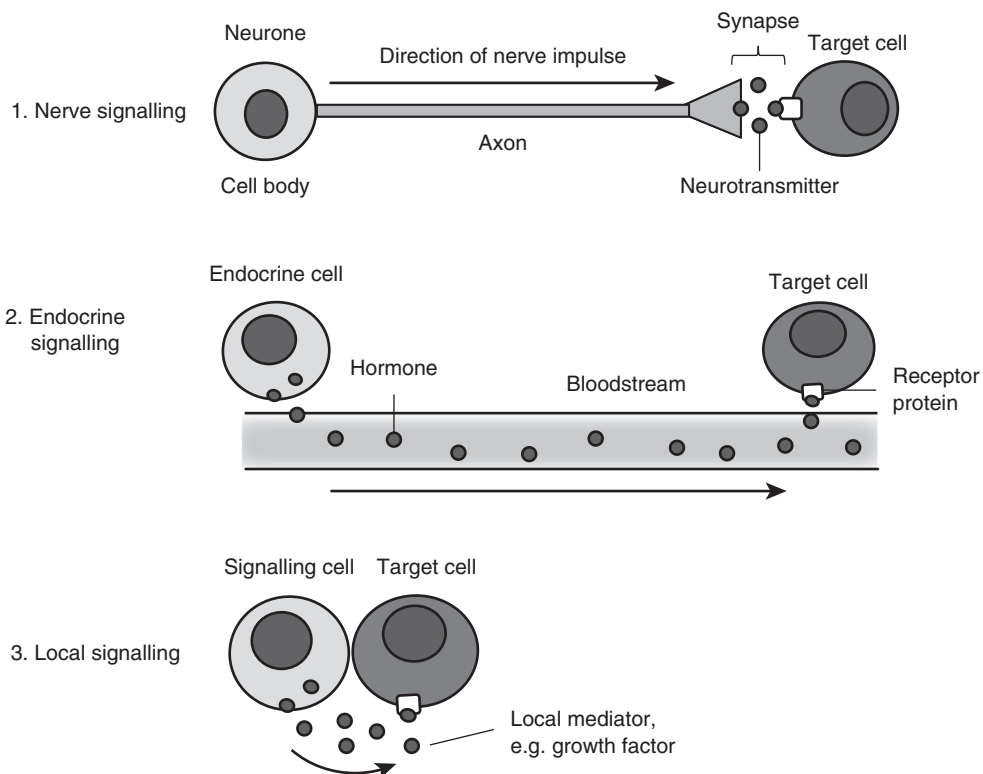
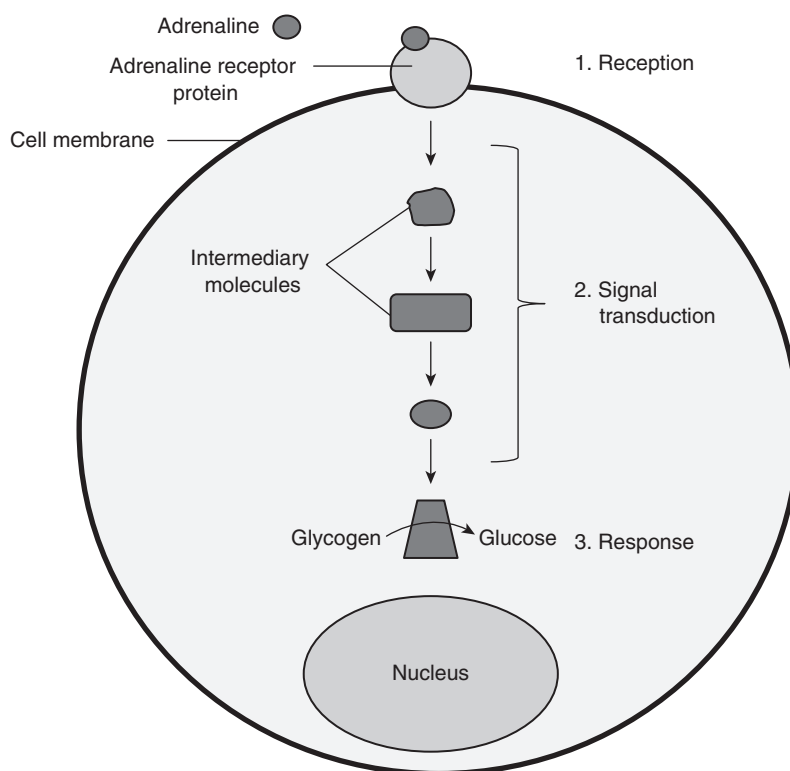


Figure 1.2 Types of cell communication



Many diseases affect cellular communication. A familiar example is type 1 diabetes which is caused by an absence of the signalling molecule insulin. In Chapter 5, you will learn that the uncontrolled growth of cancer cells is a direct consequence of alterations in cell signalling. Many of the newer cancer therapies have been engineered to block the altered signalling pathways of cancer cells. Many drugs act by blocking or enhancing the action of signalling receptors on the surface of cells (as will be described below under 'Pharmacology').

Figure 1.3 shows how the message reaches the inside of the cell for a response to be made. This process is known as **signal transduction**. The message is 'transduced' which means converted into a different form. The signal is passed on through 'intermediary' proteins within the cell. These act as messengers or 'go-betweens' until a final protein produces a response. In Figure 1.3 the original signal is the hormone adrenaline and the final response inside the cell is the activation of an enzyme that catalyses the release of glucose from glycogen.



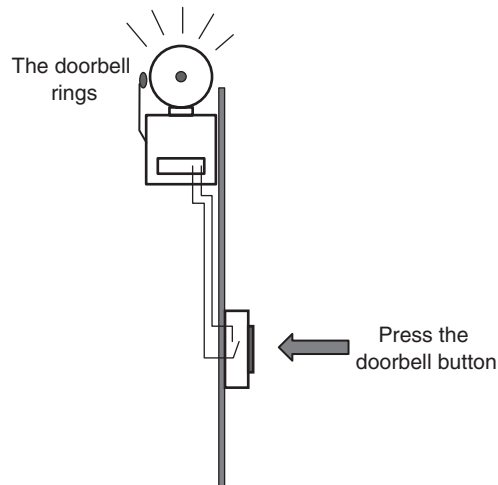
Cell signalling consists of three steps: 1. Reception: in which a signalling molecule binds to a receptor – in this case adrenaline binds to the adrenaline receptor. 2. Signal transduction: in which the signal is conveyed into the cell through intermediary molecules. 3. Response: in which the signal causes the cell's activity to change – in this case the breakdown of glycogen to glucose.

*Figure 1.3* Signal transduction using the example of adrenaline acting on a muscle or liver cell causing the breakdown of glycogen into glucose

A commonly used analogy to help understand this is how someone signals their presence at a house using a doorbell (Figure 1.4). The initial signal occurs when the visitor presses the button – this is like the signalling molecule binding to the receptor. The message is converted (transduced) into an electrical signal that causes the doorbell to sound inside the house. Hopefully for the visitor, a final response will be made when the owner hears the bell and goes to open the door.

Cells respond in a variety of ways to a variety of signals. The example in Figure 1.3 has a cell converting glycogen to glucose following a signal from the hormone adrenaline. Smooth muscle cells, for example, may contract; pancreatic cells may secrete insulin; cancer cells may start dividing.

These three principles will be referred to throughout this book in their applications to specific diseases.



When the doorbell button is pressed the signal is changed from one form into another, resulting in the bell ringing. The pressing of the button is converted into an electrical signal and then into the sound of the bell. This is an example of signal transduction and enables someone from outside the house to signal to those inside. The door in this example is like the cell membrane and the doorbell button is like the receptor.

Figure 1.4 The doorbell analogy of signal transduction

## Pharmacology

Pharmacology is the science that examines the composition, effects and uses of drugs. Before the science of pharmacology started, people had very little idea of how medicines really worked or even if they worked at all. Bold claims were laid down for all sorts of products. At first, pharmacologists concentrated on purified substances from plants, for example digitalis from foxgloves. However, in the twentieth century, as knowledge increased of how drugs act, chemical compounds were

synthesised in the laboratory to be used as medicines. Two very important concepts are pharmacokinetics and pharmacodynamics. Pharmacokinetics describes how the body processes the drug and pharmacodynamics describes how drugs affect the body.

## Pharmacokinetics

When you take a drug your body treats it like an ingested toxin. Pharmacokinetics is the scientific study of how the body processes the drug. Pharmacokinetics is usually broken down into four stages:

1. Absorption of the drug.
2. Distribution of the drug in the different body compartments.
3. Metabolism of the drug.
4. Excretion of the drug.

### 1. Drug absorption

#### Activity 1.3 Evidence-based practice and research

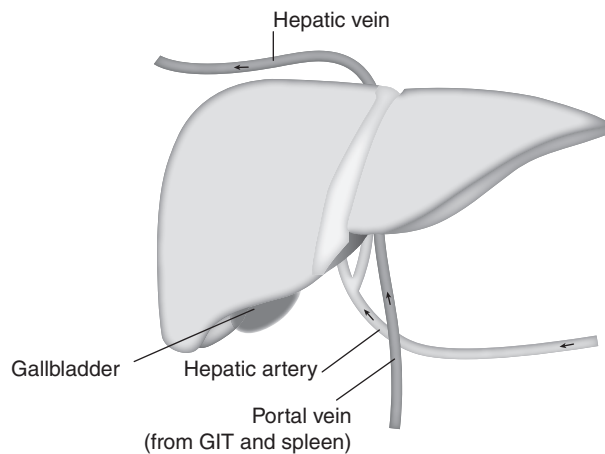
Absorption describes the movement of a drug into the blood circulation. Write down all the different routes of administration that can be used to enable a drug to be absorbed. Why do you think there are so many different routes of administration?

*An outline answer is provided at the end of the chapter.*

Activity 1.3 shows the many ways in which drugs may be administered to enable their absorption. Following ingestion (the oral route of administration), some of the drug will be absorbed through the stomach lining into the blood. However, for most drugs, absorption will occur in the small intestines. This is because the small intestines are adapted for absorption by having a very large surface area. From the small intestines, the absorbed drug passes directly to the liver. In the liver, some of the drug is chemically altered in a process called **first pass metabolism**. First pass metabolism has a significant impact on how much of a drug is available to exert its effects on the body.

Blood leaving the stomach and small intestines goes directly to the liver via the hepatic portal vein (Figure 1.5). Therefore, any drug taken orally will go first to the liver before

it reaches the general (**systemic**) circulation. Some drugs undergo extensive first pass metabolism. This means that a large proportion of the drug is chemically altered during this first passage through the liver and little of the drug may reach the systemic circulation. This is one reason why some drugs cannot be effectively given by the oral route. An example is glyceryl trinitrate which is administered under the tongue (sub-lingual). If it were swallowed it would be almost entirely broken down during its first passage through the liver. The sub-lingual route avoids the first pass metabolism because the drug is directly absorbed into the systemic circulation, diffusing into the blood through tissues under the tongue. Drugs given parenterally (by intravenous, subcutaneous and intramuscular injection) also directly enter the systemic circulation and avoid first pass metabolism in the liver. Other routes of administration avoiding first pass metabolism include the use of transdermal patches, rectal suppositories and buccal routes (given between gum and cheek).



The liver has a dual blood supply. It receives oxygenated blood from the hepatic artery, and blood containing absorbed nutrients from the hepatic portal vein. The hepatic portal vein brings blood from the gastrointestinal tract directly to the liver. Blood is drained from the liver by the hepatic vein.

*Figure 1.5* Blood supply to the liver

## Other factors affecting absorption

**Food and other medicines.** Food can affect absorption of certain drugs. Patients need to be informed if they should take their drug on an empty stomach. For example, the antibiotic flucloxacillin (Chapter 3) should be taken before food, as food will affect the amount of drug absorbed. However, the absorption of amoxicillin, another similar (penicillin type) antibiotic, is unaffected by the presence of food in the stomach and does not need to be taken on an empty stomach.

## Activity 1.4 Evidence-based practice and research

Mary, a patient in your care, asks you whether or not she should take her drugs with food. She is on Quetiapine modified release (MR) 200 mg at night and fluoxetine 20 mg in the morning. You are aware that the British National Formulary (BNF) gives the cautionary and advisory labels that need to go on drugs and this is a good source of information. Look these drugs up and advise Mary accordingly.

*An outline answer is provided at the end of the chapter.*

Sometimes, two drugs may bind to each other, making a larger compound that is not well absorbed. An example is alendronic acid and calcium which are both used in the treatment of osteoporosis. It is usually recommended that patients do not take these at the same time of day. If taken together, the calcium binds to the alendronic acid making a very large molecule that is difficult to absorb.

**Controlled release drugs.** Controlled release drugs often have 'MR', 'SR' or 'LA' attached to their names. Respectively, these stand for modified release, slow release and long-acting. For example, 'Morphgesic SR' is a long-acting form of morphine and SR stands for slow release. These medicines are carefully made (**formulated**) to be released slowly from the GI tract. As a result, the patient is able to take the tablets less frequently, which is often more convenient. Morphgesic SR can be taken twice a day whereas morphine tablets or morphine solution might need to be taken every four hours for pain relief. It is important that you are aware of the brand when you are administering a controlled release tablet. Brands are often not interchangeable as they may be formulated differently and have different effects on a patient. In addition, crushing controlled release tablets destroys the slow release mechanism. The patient would receive the whole dose in a non-controlled manner; this may be toxic and the effect of the drug would not be long-acting.

**Enteric coated (e.c.) drugs.** Some drugs have a special coating that may delay absorption until a different part of the GI tract is reached. This coating may help to protect the stomach from the drug. A well-known example is aspirin e.c. The coating prevents aspirin being absorbed in the stomach, which helps protect the stomach from irritation by the aspirin. Crushing enteric-coated drugs is not advisable as this destroys the coating.

**Route of administration.** As highlighted above, the route of administration will have an impact on first pass metabolism. This is important for some drugs and affects how much ultimately is absorbed into the systemic circulation. In addition, some drugs, for example insulin, are broken down by enzymes in the stomach which will inactivate the drug. This is why these drugs are not administered by the oral route. Sometimes, different routes of administration are used to avoid absorption into the bloodstream altogether in an

attempt to reduce side effects. Examples include inhalers, nose drops and eye drops, which are applied directly to the site of action. However, it should be remembered that, despite this local administration, a small amount of the drug will be absorbed.

## 2. Distribution of the drug

Distribution describes the process of dispersion or dissemination of drugs throughout the fluids and tissues of the body. Drugs are not distributed equally in the different fluids and tissues. Fat-soluble drugs, for example, will concentrate in adipose tissue, and water-soluble drugs in body water. Some parts of the body are less accessible to drugs than others. The nervous tissue of the brain is separated from its blood supply by the **blood–brain barrier**. A number of drugs cannot cross the blood–brain barrier. This helps to explain the difference between sedative antihistamines, such as chlorphenamine, and non-sedative ones, such as cetirizine. Chlorphenamine causes drowsiness by binding to histamine receptors in the brain. By contrast, cetirizine cannot cross the blood–brain barrier to bind to histamine receptors in the brain.

When drugs circulate in the bloodstream, some of the drug binds to proteins in the plasma, whereas some of the drug remains ‘free’, or unbound in the plasma. The ‘bound’ drug is effectively inactive as the protein–drug complex is too large to leave the blood capillaries and enter the **tissue fluid** surrounding the body cells. The ‘free’ drug is small enough to pass through the capillary wall and enter the tissue fluid to exert its effect on the cells. Factors that affect protein binding may affect the amount of drug available to the tissues. Older adults, for example, may have lower blood albumin. Albumin is a protein in the blood that some drugs bind to extensively. As a result in older adults there may be more ‘free’ drug available and a lower dose may be needed for the same effect. Some drug interactions occur when one drug affects the protein binding of another as the case study demonstrates.

### Case study

Tom, who is stable on warfarin (an anticoagulant), is prescribed sodium valproate as a mood stabiliser. Shortly afterwards he notices that he bleeds and bruises more easily. This happens because the sodium valproate displaces the warfarin that is bound to plasma proteins. This increases the amount of free warfarin available to exert its anticoagulant effect. Close monitoring of blood clotting time is advised if the two drugs are prescribed together.

## 3. Metabolism

**Metabolism** comes from a Greek word that means ‘to change’. Metabolism of drugs occurs mainly in the liver. We often think of the liver as breaking drugs down and

making them inactive but this is too simplistic. Metabolism can reduce activity or create other active metabolites. In some cases metabolism activates drugs (see 'Evidence summary' box). The main purpose of metabolism is to make the drug more water soluble so that it can be excreted from the body by the kidneys.

### Evidence summary: Codeine

The Medicines and Healthcare Products Regulatory Agency (MHRA) issued a safety warning about codeine in 2013. They stated that codeine should only be used for acute, moderate pain in children over 12 years and only if other painkillers (analgesics) did not work. This followed cases of children receiving codeine after surgery who developed respiratory depression. Respiratory depression can be a side-effect of morphine. Codeine is a pro-drug. This means it is metabolised in the liver to morphine and this is what is responsible for the **analgesia**. A pro-drug is an inactive precursor that is converted to an active drug by metabolism. It is believed that the affected children were rapid metabolisers of codeine. As a result, these children produced unexpectedly high levels of morphine, resulting in respiratory depression. Conversely, some patients are slow metabolisers and benefit little from codeine. This is due to their slow rate of metabolism of codeine into morphine.

There are two phases of metabolism:

### Phase 1 metabolism

This is mainly carried out by a large family of enzymes in the liver called cytochrome P450 enzymes which oxidise drugs. There are different kinds of these enzymes and some are quite specific for different drugs. Drug interactions may occur when enzyme activity is altered. Some drugs can increase the activity of specific enzymes. This is known as enzyme induction. By contrast, other drugs and some foods can reduce the activity of the enzymes. This is known as enzyme inhibition. An example is the interaction between grapefruit juice and simvastatin. The grapefruit juice reduces the activity of the cytochrome P450 enzyme that metabolises simvastatin. This leads to an increase in simvastatin levels to potentially toxic levels. Another example is the drug interaction between simvastatin and erythromycin (see Chapter 8, Activity 8.2).

### Phase 2 metabolism

In phase 2 metabolism, a large ionised molecule is added to the drug. This acts to increase the water solubility of the drug.

### Activity 1.5 Evidence-based practice and research

Smoking is an enzyme inducer in that it speeds up the enzymes that usually metabolise the antipsychotic drug olanzapine. What might happen to a smoker on olanzapine who stops smoking?

*A suggested answer is provided at the end of the chapter.*

Drugs may undergo phase 1 or phase 2 metabolism or both. A drug might also be metabolised by different pathways resulting in many different **metabolites**. Factors that affect the function of the liver, such as disease and ageing, can affect how much of a drug is metabolised. As we have shown in the evidence summary, some people metabolise drugs more quickly than others. This probably reflects differences in their genetic make-up.

The liver is the main site of drug metabolism, but drugs may also be metabolised in the GI tract, the plasma and the lungs. Morphine, for example, is metabolised mainly in the liver but also in the mucosal cells of the small intestine.

## 4. Excretion (elimination)

Excretion (elimination) refers to the removal of waste products from the body. The kidney is the main organ involved in drug excretion. If you could examine the urine of a patient who is taking drugs, you would find water-soluble drugs and metabolites. Drugs may also be excreted in bile, tears, sweat and breath. In fact, any bodily fluid can contain drugs and their metabolites. Factors that affect kidney function, such as kidney disease and ageing, will affect how efficiently drugs are excreted.

### Other important pharmacokinetic concepts

- Bioavailability
- Therapeutic range or therapeutic index
- Half-life
- Peak plasma concentrations.

**Bioavailability.** Bioavailability is the proportion of the administered dose that reaches the systemic circulation. For intravenous (IV) drugs, it can be assumed to be 100% as the drug is delivered directly into the blood circulation. For oral drugs it can be considerably less. The losses occur in numerous ways. Some of the tablet may not be absorbed from the GI tract and some may be lost during first pass metabolism before reaching systemic circulation. Bioavailability is often expressed as a percentage. For example, the bioavailability of the opioid Oxycodone is 60–87%. This means 60–87% of the orally administered dose reaches the systemic circulation.



## Case study

Michael is receiving palliative care. His pain is currently controlled using morphine MST Continus tablets 60 mg twice a day. He is finding it increasingly difficult to swallow and a subcutaneous infusion has been suggested as an alternative route of administration. The equivalent subcutaneous dose of morphine is half the oral dose (British National Formulary [BNF] Palliative Care Guidance), that is 60 mg over 24 hours. This is because the bioavailability of oral morphine is less than morphine given by injection. This difference is largely due to the first pass metabolism of morphine when administered orally.

Sometimes the bioavailability of different brands and **formulations** can be different. For example, the bioavailability of Lanoxin (digoxin) elixir is 75% compared to 63% for Lanoxin tablets. For many drugs this does not matter clinically but, in cases where the drug has a narrow therapeutic index or range, it can be important.

*Narrow therapeutic index or range.* This describes the difference between the blood levels that need to be reached for a drug to be effective and the level above which the drug is toxic. For many drugs, this range is very wide. For example, with paracetamol, most adult patients need a dose of 1 g to relieve their pain. For drugs with a narrow therapeutic range, including digoxin, gentamycin, vancomycin and lithium, small differences in dose or blood concentration may lead to therapeutic failures or adverse drug reactions. It is often necessary to adjust the dose according to measurement of the actual blood level achieved in the person taking it. Changes in the brand or formulation can result in toxic or sub-therapeutic levels in the blood because of differences in bioavailability.

*Plasma half-life.* The plasma half-life of a drug is the time it takes for the concentration or amount of the drug in the plasma to reduce by one half. It is a constant for any given drug, although a range is often given as some people metabolise and excrete drugs faster than others. Plasma half-life is a useful measure as it can help you to work out how long drugs remain in the body.

## Scenario

You are a nurse and one of your patients, Linda, is on Risperidone 4 mg at night for schizophrenia. Her psychiatrist stopped the drug as she was experiencing tremors. She asks you how long it will take for the drug to 'get out of her system'. You ask for advice and learn that Risperidone has an active metabolite with a half-life of 24 hours. It can take 4 to 5 half-lives for a drug to be excreted. You can tell Linda that it might take 4 or 5 days ( $4-5 \times 24$  hours) for the Risperidone to be out of her system, but the side effects should improve every day as, each day, the remaining drug is broken down and excreted.

**Peak plasma concentrations.** The timing of the peak plasma concentration gives useful information about when drug levels are at their highest in a patient's blood. Some side effects tend to be most problematic at this time.

Peak concentration and therapeutic range are illustrated in Figure 1.6.

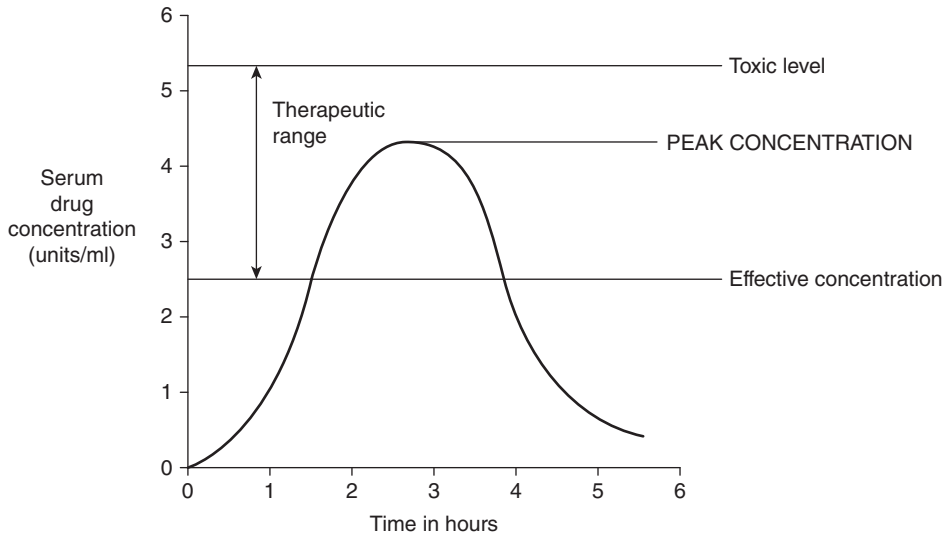


Figure 1.6 Graph showing drug concentration after oral administration of single dose

## Pharmacodynamics

Pharmacodynamics, sometimes described as ‘what drugs do to the body’, is defined as the study of the biochemical and physiological effects of drugs on the body. This includes the mechanism of drug action and the side effects drugs cause.

In order for a drug to exert an effect, it must first come into contact with, and bind to, the cells of the body it is acting upon. Different drug molecules have different shapes and will only bind to certain proteins in the body. Have you ever experienced a patient who asked you how a drug knows where to go? For example, ‘How does paracetamol know to go to the head and stop a headache?’ The drug does not ‘know’, but will bind to certain binding sites in the body. Most of these binding sites are proteins. As identified earlier in the chapter, there are many different proteins in the body, all with different shapes. The following are common binding sites for drugs: receptors, enzymes and carrier molecules.

### Drugs acting at receptors

Many drug receptors are protein molecules on the surface of a cell. As referred to above under ‘Cellular communication’, signalling molecules bind to these receptors to cause a response in the cell.

The general name for a chemical that binds to a receptor and activates it to produce a response is an **agonist** (Figure 1.7). Many drugs acting at receptors are agonists. For example, adrenaline is an agonist. It binds to beta receptors on heart muscle cells to set off a chain of events which lead to the heart beating faster and more forcefully (Chapters 8 and 9).

Whilst an agonist causes a response, an **antagonist** binds to the receptor but does not cause a response (Figure 1.7). Antagonists block the receptor so that an agonist cannot exert its effect.

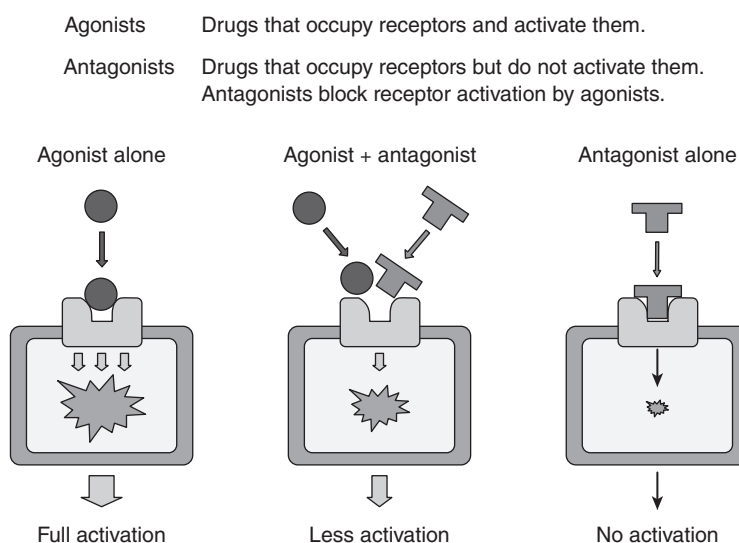


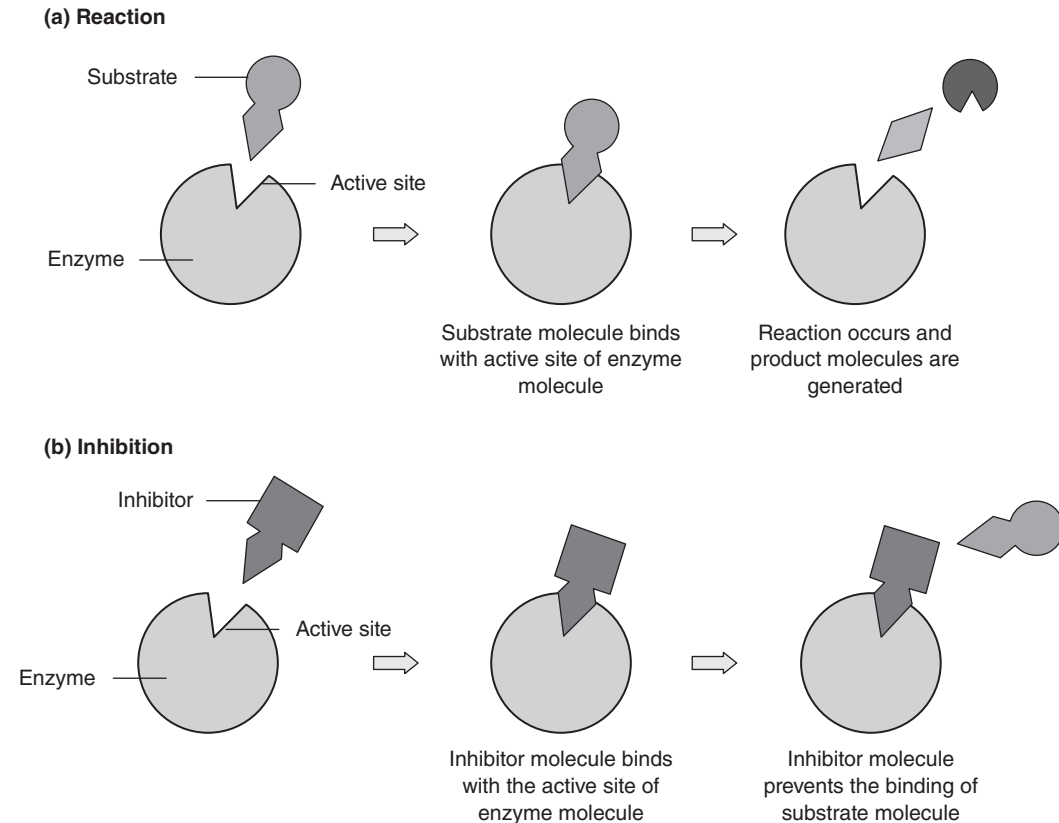
Figure 1.7 Agonists and antagonists

An example of an antagonist is propranolol, a beta-blocker. Propranolol attaches to the beta receptors on the heart muscle cells preventing adrenaline binding. This consequently prevents the action of adrenaline.

**Partial agonists** bind to receptors to cause a response, but the response is less than the maximum possible. The opioid buprenorphine is an example of a partial agonist. This makes it a useful drug in the treatment of opioid dependence, where the opioid agonist heroin (also known as diamorphine) is replaced by another agonist, in this case buprenorphine, to prevent withdrawal symptoms. We shall come across many drugs acting as agonists and antagonists in the following chapters.

## Drugs acting on enzymes

As mentioned under 'Homeostasis' earlier in the chapter, enzymes are chemicals (usually proteins) that speed up the chemical reactions and keep cells functioning. Drugs that act as enzyme inhibitors bind to the enzyme and decrease its activity (Figure 1.8).



- a. Reaction – an enzyme is shown breaking down a molecule (the substrate)  
 b. Inhibition – a drug can act as an inhibitor by preventing the substrate from binding to the ‘active site’ of the enzyme

*Figure 1.8* Enzyme inhibition

An example of an enzyme inhibitor is the non-steroidal anti-inflammatory drug (NSAID) ibuprofen. Ibuprofen binds to, and inhibits, enzymes called cyclo-oxygenases (COXs). COXs are enzymes that are needed to make a group of inflammatory molecules called prostaglandins. In turn, prostaglandins cause pain and fever (Chapters 2 and 6). Ibuprofen inhibits the COXs and reduces the amount of prostaglandins synthesised. The action of NSAIDs is described more fully in Chapter 6.

## Drugs acting on transporters

Transporter proteins are located in the cell membrane. Their function is to transport substances across the cell membrane (Tortora and Derrickson, 2017). An example of a drug acting on transporter proteins is the type of antidepressant drug called a selective serotonin reuptake inhibitor (SSRI). Examples of SSRIs include fluoxetine and citalopram. Between nerve cells there is a gap called a synapse. In order for a message to be carried from one cell to another, a chemical called a neurotransmitter is needed. Serotonin is a type of neurotransmitter. Antidepressant drugs act to increase the level

of neurotransmitters in the synapse. SSRIs do this by preventing the reuptake of serotonin from the synapse. This means more serotonin is available for longer to stimulate serotonin receptors on the nerve cell on the other side of the synapse (Figure 1.9). For a fuller explanation of the synapse see Chapter 6.

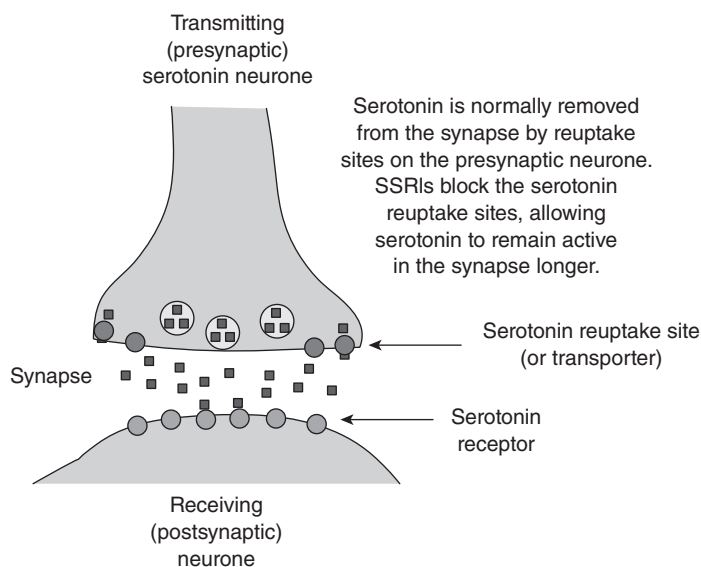


Figure 1.9 Action of selective serotonin reuptake inhibitors at the synapse

## Pharmacogenomics

Pharmacogenomics investigates the effects of genetic variation on how people respond to drugs. Our genetic make-up can determine how effective a drug is and whether or not we are likely to get side effects. There are both pharmacokinetic and pharmacodynamics effects. One important example of this is seen in the action of the cytochrome P450 enzymes. As we discussed earlier, these enzymes are involved in the metabolism of drugs by the liver. Our genes determine the types of cytochrome P450 enzymes we make and, in some cases, can determine whether we are 'slow' or 'fast' metabolisers. Genetic variation can also affect transporter proteins and receptors that will influence pharmacodynamics.

Each of us has a unique DNA sequence that makes up our genome. In the future, it is envisaged that each of us could have our complete genome sequenced which may enable 'personalised' medicine. Personalised medicine is a type of medical care that is customised for an individual patient on the basis of genetic make-up. It is already used in the treatment of some kinds of cancer. In this case, the genetic make-up of the cancer is used to target or 'individualise' treatment. This is discussed further in Chapter 5 with respect to cancer treatment.

It is now time to review what you have learned in this chapter by undertaking some multiple-choice questions.

### Activity 1.6 Multiple-choice questions

1. The scientific study of the causes of disease is known as:
  - a) Pathophysiology
  - b) Pathogenesis
  - c) Aetiology
  - d) Pharmacology
2. The smallest living unit of the body is the:
  - a) Organ system
  - b) Organ
  - c) Tissue
  - d) Cell
3. The working together of cells, tissues and organs is called:
  - a) Homeostasis
  - b) Integration
  - c) Communication
  - d) Signal transduction
4. Endocrine signalling involves the release of:
  - a) Hormones
  - b) Local growth factors
  - c) Neurotransmitters
  - d) Nerve signals
5. The transmission of a molecular signal from a cell's exterior to its interior is known as:
  - a) Nerve signalling
  - b) Signal transduction
  - c) Endocrine signalling
  - d) Signalling pathway
6. Pharmacokinetics is the study of:
  - a) The action of drugs on the body
  - b) The action of the body on drugs

*(Continued)*

(Continued)

- c) The production and manufacture of medicines
  - d) The study of genetic differences in drug metabolism
7. Which of the following will NOT affect drug absorption?
- a) Plasma albumin concentration
  - b) Food
  - c) Route of administration
  - d) Formulation of medicine
8. The antidepressant fluoxetine can increase the concentration of the antipsychotic clozapine by affecting metabolism by liver enzymes. This is an example of:
- a) Enzyme induction
  - b) Enzyme inhibition
  - c) Enzyme blocking
  - d) Enzyme agonism
9. What is the definition of plasma half-life?
- a) Half the time it takes to reach therapeutic plasma concentration
  - b) The time it takes for half of the drug to be excreted
  - c) The time it takes for the plasma concentration of a drug to reduce by half
  - d) The time it takes for half of a dose to be absorbed into the plasma
10. A drug which undergoes extensive first pass metabolism will have:
- a) A low bioavailability
  - b) A high bioavailability
  - c) A low therapeutic range
  - d) A high therapeutic range

## Chapter summary

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In this chapter we have introduced you to the subject of pathophysiology and identified its importance for nursing practice. We discussed the concept of the aetiology of a disease, which is another name for the cause of the disease. Often diseases do not have a single cause but many risk factors. An understanding of the risk factors for a disease is important as some of these can be modified to reduce a person's chance of developing the disease. The idea of risk factors will be important in the subsequent chapters of this book and will help you to give appropriate information of health promotion. The mechanism of pathogenesis of a disease will be an important focus of this book. The pathogenesis, or disease

mechanism, can help you to understand the clinical manifestations of a disease, and help you to understand the treatment and management. We revised three principles of human biology: organisation, homeostasis and cellular communication. It is important that you understand these concepts before moving on to the following chapters, where these concepts will be developed to explain specific diseases.

We introduced the two concepts of pharmacology: pharmacodynamics and pharmacokinetics. The science of pharmacology helps us to understand how and why drugs work to alleviate or cure disease (pharmacodynamics). Our bodies also affect the drugs that are taken or administered (pharmacokinetics). This has implications for how medicines are formulated and how kidney and liver impairment may affect metabolism and excretion. Understanding pharmacology can also help explain why patients get certain side effects, why some drugs interact with each other, and why some patients must avoid certain drugs.

## Activities: Brief outline answers

### Activity 1.3 Evidence-based practice and research (p 22)

There are many routes of administration but some examples are: oral, intravenous, subcutaneous, intramuscular, sub-lingual (under the tongue), buccal (between cheek and gum), topical, rectal, inhaled.

The many different routes can be useful to suit the needs of patients. Unconscious patients or those with swallowing difficulties have alternatives. Routes, other than oral, also avoid first pass metabolism which, in some cases, would break down most of the drug. This would mean that little of the drug would reach the systemic circulation. Sometimes the routes enable the drug to be delivered directly to where it is needed. Inhaled drugs for asthma reach the lungs and less is absorbed into the whole body than if the same drug was given orally.

### Activity 1.4 Evidence-based practice and research (p 24)

In the BNF there are numbers that relate to the warning labels given at the start of the Appendix. If a product has the number 23 next to it, this means the pharmacist must put the following on the label: 'Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food'. Quetiapine m/r would need this label. For fluoxetine it is not important. Therefore Mary should take her Quetiapine on an empty stomach, but fluoxetine could be taken with breakfast if that suited the patient.

### Activity 1.5 Evidence-based practice and research (p 27)

A smoker might need to be on a higher dose of olanzapine as the enzymes that metabolise olanzapine will be speeded up. If the patient stops smoking the enzymes slow back down again. This would mean olanzapine levels rise. This could lead to toxicity or increased side effects. You would want to advise the patient of this and that their dose of olanzapine may need to be reduced when they have stopped smoking.

### Activity 1.6 Multiple-choice questions (p 33)

1. The scientific study of the causes of disease is known as:
  - c) Aetiology



*Core concepts and key pathophysiological processes*

2. The smallest living unit of the body is the:
  - d) Cell
3. The working together of cells, tissues and organs is called:
  - b) Integration
4. Endocrine signalling involves the release of:
  - a) Hormones
5. The transmission of a molecular signal from a cell's exterior to its interior is known as:
  - b) Signal transduction
6. Pharmacokinetics is the study of:
  - b) The action of the body on drugs
7. Which of the following will NOT affect drug absorption?
  - a) Plasma albumin concentration
8. The antidepressant fluoxetine can increase the concentration of the antipsychotic clozapine by affecting metabolism by liver enzymes. This is an example of:
  - b) Enzyme inhibition
9. What is the definition of plasma half-life?
  - c) The time it takes for the plasma concentration of a drug to reduce by half
10. A drug which undergoes extensive first pass metabolism will have:
  - a) A low bioavailability

## Further reading

**British National Formulary (BNF) 85** (2023) London: Pharm Press.

The essential practical, evidence-based information for healthcare professionals who prescribe, dispense and administer medicines.

**Simonsen, T, Aarbakke, J, Kay, I, Coleman, I, Sinnott, P and Lysaa, R** (2006) *Illustrated pharmacology for nurses*. London: Hodder Arnold.

A clearly written and well-illustrated pharmacology book aimed at nurses.

**Tortora, G and Derrickson, B** (2017) *Principles of anatomy and physiology* (17th edition). Oxford: Wiley.

A comprehensive and clearly written anatomy and physiology textbook.

## Useful websites

<http://bnf.org/>

Online version of the British National Formulary.

[www.medicines.org.uk/](http://www.medicines.org.uk/)

The electronic Medicines Compendium (eMC) contains information about medicines licensed for use in the UK. Summaries of product characteristics (SPC) and patient information leaflets (PILs) are available.