PART

1

Cellular and tissue pathophysiology

1 Pathophysiological terminology, cellular adaptation and injury

KEY TERMS

Aetiology
Apoptosis
Atrophy
Caseous necrosis
Clinical manifestations
Coagulative necrosis
Dysplasia
Epidemiology
Fat necrosis
Gangrene
Homeostasis
Hyperplasia
Hypertrophy
Hypoxia
Incidence
Ischaemia
Liquefactive necrosis
Metaplasia
Necrosis
Oxygen free radicals
Pathogenesis
Pathophysiology
Prevalence
Reactive oxygen species (ROS)

LEARNING OBJECTIVES

After completing this chapter, you should be able to:

1 Define the terms 'pathophysiology', 'aetiology', 'pathogenesis', 'clinical manifestations' and 'epidemiology'.

2 Distinguish between the incidence and the prevalence of a disease.

3 Describe the types of cellular adaptations, and suggest situations in which each may occur.

4 Define 'dysplasia', differentiate it from other cell adaptations, and outline its consequences.

5 Differentiate between the characteristics of reversible and irreversible cell injury.

6 Compare and contrast necrosis and apoptosis.

7 Differentiate between the types of necrotic cell death.

8 Identify the major agents of cell injury.

9 Describe the process of cell injury resulting from an ischaemic or hypoxic agent.

WHAT YOU SHOULD KNOW BEFORE YOU START THIS CHAPTER

Can you name the main structures of the cell and their functions?

Can you describe how molecules are transported across the cell membrane?

Can you describe the cell cycle?

Can you define cellular metabolism?

Can you identify the major types of tissues and their functions?

Introduction

LEARNING OBJECTIVE 1

Define the terms 'pathophysiology', 'aetiology', 'pathogenesis', 'clinical manifestations' and 'epidemiology'.

Pathophysiology is defined as an understanding of the mechanisms by which disease and illness alter body functioning. These changes represent a breakdown of **homeostasis**, the dynamic state of equilibrium characterised by constant adjustment to changing circumstances to maintain normal function. Health professionals require a sound knowledge of pathophysiology for competent clinical practice. This knowledge is important in that it provides the rationales for care, and informs the clinical assessment and management of those in your care.

In this chapter, you are introduced to the key principles and concepts of pathophysiology that underpin your understanding of the specific diseases encountered in later chapters. These concepts include cellular responses to stimuli, cellular adaptations, types of cell injury and agents of injury. First, important terms that provide the framework for describing the pathophysiology of specific diseases in subsequent chapters are defined.

Important terminology

It is important to familiarise yourself with the four key principles of pathophysiology that form the framework in this textbook for the descriptions of specific diseases. The four important terms are aetiology, pathogenesis, clinical manifestations and epidemiology.

AETIOLOGY

Aetiology is the study of the cause, or causes, of a disease. Identifiable reasons for the development of a disease can include a person's diet, environment, inheritance and other genetic factors, occupation, health and age. Disease can arise within the body as a result of cell injury caused by immunological, metabolic, nutritional, inheritable, psychological or cancerous agents. It can also arise external to the body, due to the action of infectious organisms or traumatic physical agents, such as extreme temperature or force (see the 'Agents of cell injury' section later in this chapter for more detail).

If the cause is unknown, then an illness will be classified as an *idiopathic disease*. Alternatively, if an illness is a direct consequence of medical treatment, it is called an *iatrogenic condition*.

PATHOGENESIS

The **pathogenesis** represents the development of a disease. It usually covers the mechanisms by which a disease becomes established and progresses. Pathogenesis can be described in both chronological and spatial terms. In this aspect, the way in which homeostatic mechanisms attempt to adapt and then collapse are detailed. In detailing the pathogenesis of a disease, acute and chronic phases can be identified and differentiated.

CLINICAL MANIFESTATIONS

The **clinical manifestations** are the demonstrable changes representing the changes in function brought about by a disease process. The clinical manifestations are the changes *observed* by the affected person, their families or other people, as well as the changes *felt* by the affected person. They are also known, respectively, as the *signs* and *symptoms* of a disease. In a book such as this, common signs and symptoms are stated, but in reality a person with a particular disease may not show all of the clinical manifestations at any time during the progress of the condition.

EPIDEMIOLOGY

LEARNING OBJECTIVE 2

Distinguish between the incidence and the prevalence of a disease.

Another important term associated with pathophysiology is **epidemiology**. This is the study of the patterns of disease within populations. The factors that are frequently used to describe patterns of disease at the population level include age, sex, ethnicity, location, socioeconomic status and lifestyle. Risk factors and the aetiology can emerge from epidemiological studies.

Such studies also reveal the **incidence** and the **prevalence** of diseases within our communities. The *incidence rate* represents the number of *new* cases of a disease diagnosed within a particular period, usually over a calendar year. The *prevalence rate* is the *total* number of cases of a disease, both newly and previously diagnosed, at a particular time. Prevalence can be affected by other factors, such as disease recovery, mortality, recurrence and emigration. Health measures, such as immunisation, can lead to reductions in incidence and prevalence. Figure 1.1 illustrates the relationships between incidence, prevalence and these other factors.

Where possible in this text, we have drawn on the population statistics available for our region—Australia and New Zealand—and we have highlighted Indigenous health issues. This information is drawn from government documents, the Australian Institute of Health and Welfare, the World Health Organization and recent published epidemiological research. Where these statistics are not readily available, we will draw on those from other Western industrialised nations.

Cellular responses to stimuli

LEARNING OBJECTIVE 3

Describe the types of cellular adaptations, and suggest situations in which each may occur.

In order to maintain homeostasis, the body must make adjustments to functioning in response to changes in its internal and external environments. These environmental changes are called *stimuli*. Examples of stimuli include changes in temperature, oxygen supply or demand, pH, energy demand and body water levels. Homeostatic imbalances can arise if the adjustments to the changed conditions prove to be inadequate.

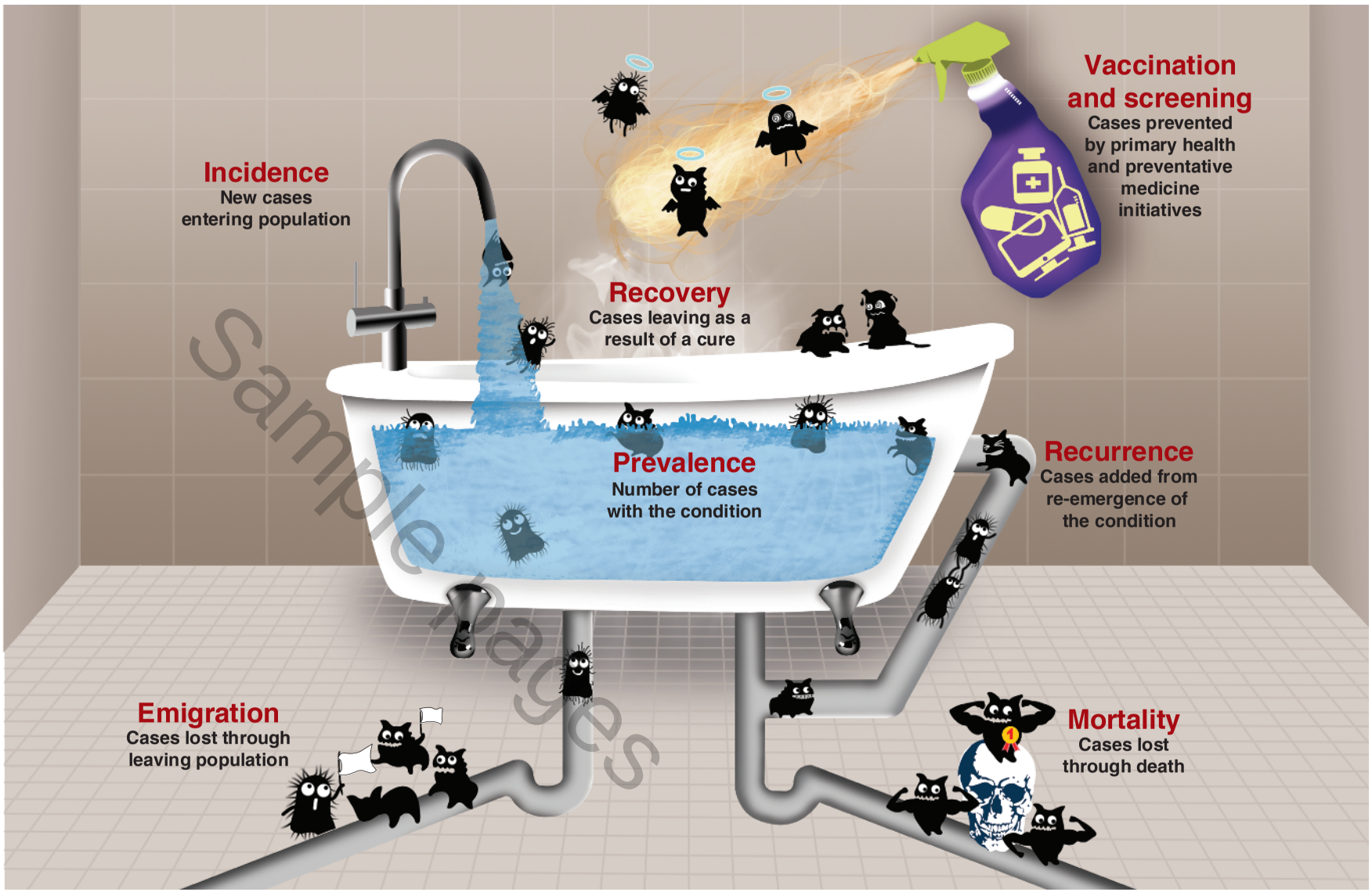

Figure 1.1

Epidemiological relationships

A conceptual representation of incidence and prevalence, and the effects of other factors and health measures on these rates.

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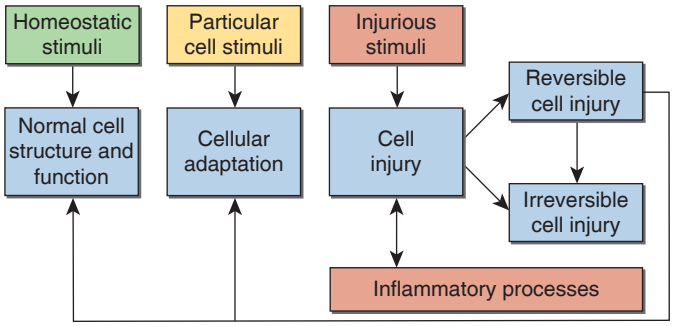


Figure 1.2

Continuum of cellular responses to stimuli

This is a representation of the interplay between normal cell structure and function, cellular adaptation and cell injury in response to stimuli. Inflammation plays an important role when cells are injured.

In response to persistent or intense stimuli, cells can adapt to the new conditions and maintain homeostasis. A number of *adaptations* are possible, and these are described.

Cellular adaptation and injury need to be considered across a continuum. If cells cannot adapt to current environmental conditions, then they may become injured. Cellular injuries can be *reversible*, where the affected cells recover after the stimulus is removed, or they can be *irreversible* and result in cell death. *Inflammation* is initiated in response to cell injury. Inflammatory processes can neutralise the agent of injury and promote healing. In some circumstances, the intensity or duration of inflammation can itself injure cells (see the chapter 'Determinants of health and illness'). The continuum of adaptation and injury is represented in Figure 1.2.

Cellular adaptations

Body cells are able to adapt to new conditions by increasing or decreasing their size, number, shape or arrangement within tissues. The terms associated with these adaptations are atrophy, hypertrophy, hyperplasia, metaplasia and dysplasia.

ATROPHY

Cell **atrophy** occurs when the demands on a population of cells decrease below normal or cannot be maintained at normal levels. The cells respond by *decreasing* in size (see Figure 1.3). An example of atrophy is during disuse when a person is bedridden for an extended period of time (i.e. disuse atrophy). The stretch and length of the skeletal muscle fibres involved decreases, which is known as *mechanical unloading*. Muscle fibres will decrease in size as an adaptation to the changed conditions. Functional changes accompany this structural adaptation so that muscle weakness can be a consequence. Muscle atrophy can also occur when a person has fractured a limb that is immobilised in plaster for months, or when astronauts are in space for a long period. Appropriate exercise/activity programs can assist in minimising the degree of atrophy experienced, or assist in the return of normal muscle function if and when the condition can be reversed.

Cell atrophy may also be induced when regulatory communication with another structure becomes compromised. Examples of this are in cases of spinal injury, when the neural stimulation of muscles is blocked, or when the hormones responsible for the maintenance of normal tissue function are not available. An example of the latter would be testicular atrophy as a result of the inhibition of luteinising hormone and follicle stimulating hormone secretion.

HYPERTROPHY

If the demands on cells are greater than normal, they may respond by *increasing* in size; this is called **hypertrophy** (see Figure 1.4). Again, skeletal muscle is a good example of a population of cells that readily undergo hypertrophy. When the mechanical loading on muscle fibres increases, they undergo hypertrophy. In skeletal muscle hypertrophy, an increase in nuclei and stem cells within the fibres is observed, and intracellular signalling and gene expression is altered, triggering the release of growth factors such as insulin-like growth factor-1 (IGF-1).

This effect can also occur in the heart. As the heart has more load placed on it, the cardiac myocytes will increase in size, which will cause cardiac hypertrophy. If the heart is diseased,

Figure 1.3

Cellular atrophy

The cells on the left are normal cells. Those on the right have undergone atrophy—a decrease in the size of the cells.

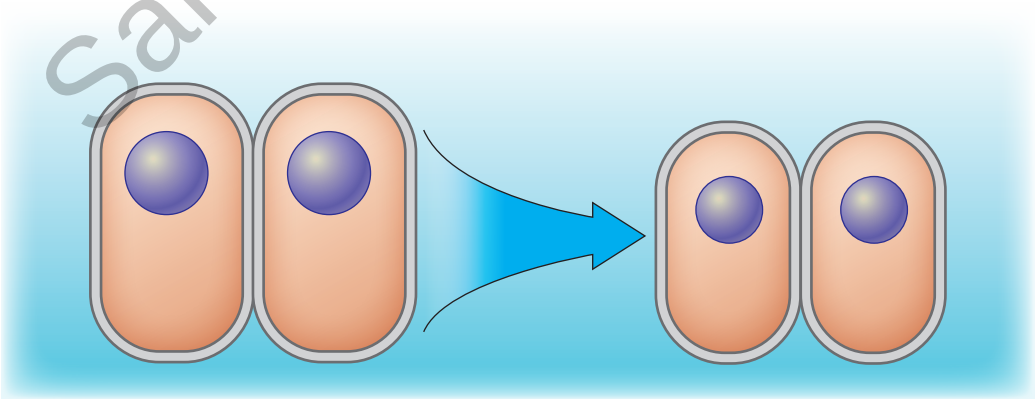
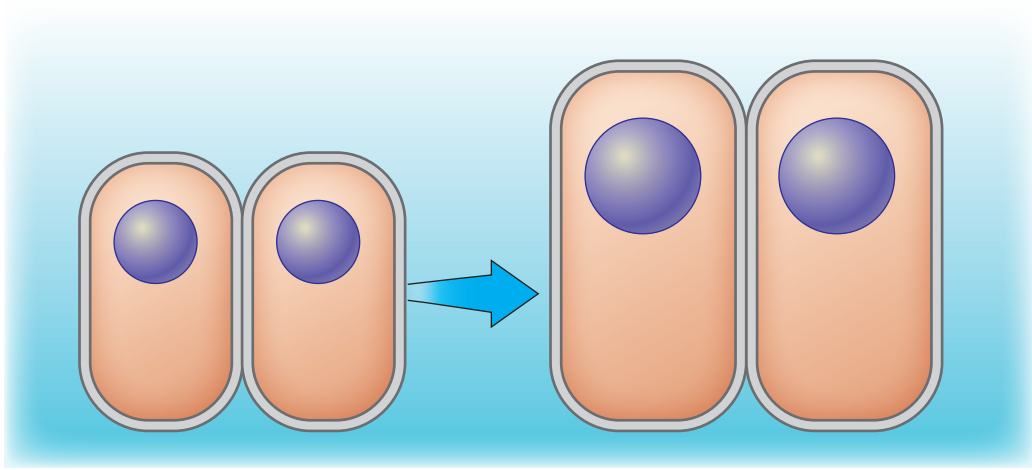


Figure 1.4

Cellular hypertrophy

The cells on the left are normal cells. Those on the right have undergone hypertrophy—an increase in the size of the cells.



such as in heart failure (see the chapter 'Cardiac muscle and valve disorders'), a normal workload is considered an increased load and results in hypertrophy. The increase in muscle mass creates an upsurge in demand on oxygen supply that cannot be met under these circumstances, worsening the cardiac impairment.

HYPERPLASIA

Hyperplasia is another form of cellular adaptation in response to increased demand. In **hyperplasia**, *cells increase in number* (see Figure 1.5); they do this by increasing their rate of mitosis. The capacity of cell populations for this is highly variable, with mature muscle cells and neurons lacking the capacity for this response. If hyperplasia occurs in these cell populations, it is usually due to a proportion of relatively undifferentiated stem cells within the tissue that proliferate in the right circumstances. Other cell populations, such as epithelial cells, can undertake hyperplasia more efficiently.

In reality, observed increases in the size of organs or other body structures are usually brought about through a combination of hyperplasia and hypertrophy. This can be demonstrated in examples where an increased exercise or mechanical loading can induce an enlargement of the heart, or the change in hormone levels during pregnancy leads to an enlargement of the uterus. In these cases, the change in organ size is largely due to hypertrophy.

METAPLASIA

In **metaplasia**, cells *change from one cell type to another* (see Figure 1.6). Importantly, these cells are fully differentiated,

Figure 1.5

Cellular hyperplasia

The cells on the left are normal cells. Those on the right have undergone hyperplasia—an increase in the number of cells.

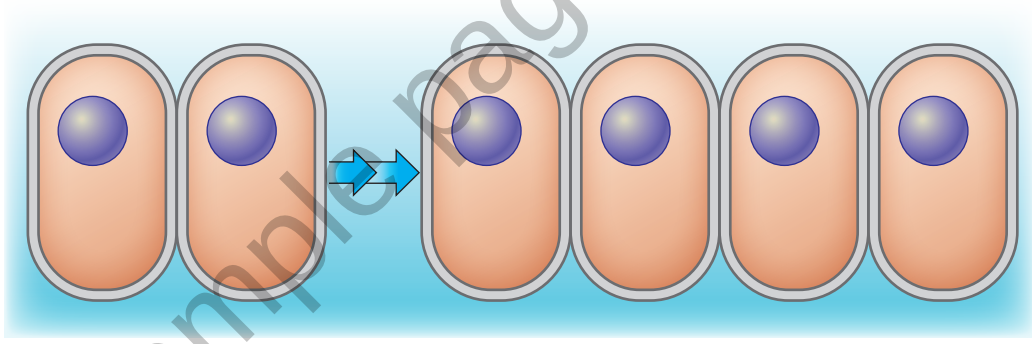
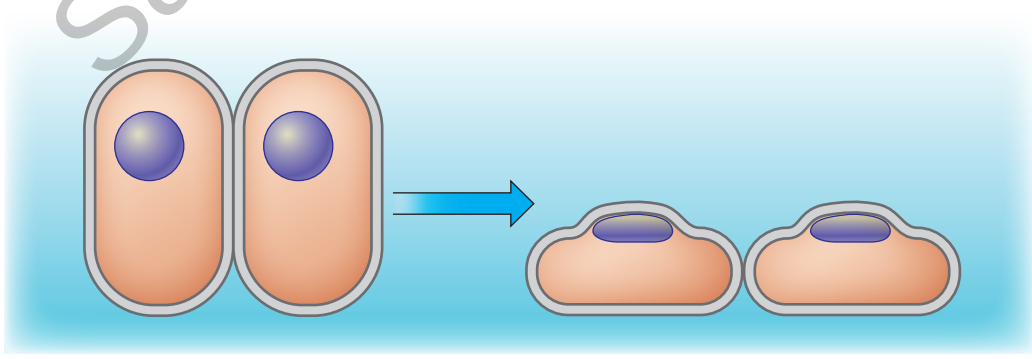


Figure 1.6

Cellular metaplasia

The cells on the left are normal cells. Those on the right have undergone metaplasia—a transition from one cell type to another.



and if the stimulus is removed the cells may revert back to their original type. However, metaplasia may also be a transitional form leading to pre-cancerous dysplasia (see 'Dysplasia'). Metaplastic transition is regulated by the altered expression of local transcription factors.

The most common example of this involves epithelial tissue. If the lining of the bronchial tree is exposed to persistent irritation (e.g. from cigarette smoke or exposure to air pollutants), the ciliated columnar epithelial cells can transform into stratified squamous epithelium. These cells endure the irritation better than the original cell type, but the downside may be some resultant localised deficit in the function of this region. This is brought about by the loss of the ciliated mucus-secreting cells, meaning debris is not cleared out of the airways as effectively. Metaplasia has also been observed in intestinal, glandular, cervical and skin tissue in response to noxious environmental stimuli.

DYSPLASIA

LEARNING OBJECTIVE 4

Define 'dysplasia', differentiate it from other cell adaptations, and outline its consequences.

In some instances, the adaptive response to a stimulus can be flawed, and the consequences can lead to a profound homeostatic imbalance and the onset of disease. An example of this maladaptive response is dysplasia. **Dysplasia** is characterised by a *variation in the size and shape of cells* within a tissue. This leads to a breakdown in the organisation and arrangement of the tissue (see Figure 1.7). Dysplasia is frequently identified by histological examination of tissue. In contrast to metaplasia, it can occur in undifferentiated and immature cell types.

In some circumstances, cell dysplasia may be considered a pre-cancerous stage. Dysplastic cells can show delays in maturation and differentiation that reflect the characteristics of cancer. Epithelial cell dysplasia in the cervix of the uterus is considered a potential sign of carcinoma in situ (where cancer cells proliferate in their native tissue without spreading to other sites) or invasive cancer, and when detected by a Pap smear is subjected to close monitoring. Dysplasias affecting liver cells, bronchiolar columnar cells and erythrocytes may also be linked to cancer development.

Cellular injury

LEARNING OBJECTIVE 5

Differentiate between the characteristics of reversible and irreversible cell injury.

A failure to adapt to a stimulus leads to cell injury. The injury can be reversible, eventually leading to a return to the pre-injured state, or irreversible, resulting in cell death.

REVERSIBLE CELL INJURY

Reversible injury is characterised by the cell swelling with water (*hydropic swelling*) or by the excessive inclusion of substances within the cell cytoplasm (*intracellular accumulations*). A common cause of these changes is the failure of the enzymes involved in normal cellular metabolism. The injury may be reversible if the stimuli can be extinguished or the cell develops compensatory processes to neutralise further damage. However, the tissue may not be able to return to full function if significant injury has occurred.

Hydropic swelling occurs when the membrane sodium pump (Na^+/K^+-ATPase) fails; more specifically, allowing sodium influx into the cell. As an energy-dependent pump, a poor supply of ATP (adenosine triphosphate), due to a deficient oxygen supply or the unavailability of glucose, often leads to this situation. As a consequence, sodium ions accumulate within the cell, creating an osmotic gradient that draws water into the cell. Cells undergoing hydropic swelling can enlarge as the cytoplasm and cellular organelles expand. If these conditions persist, the organelles may actually rupture and vacuoles appear in the cytoplasm (see Figure 1.8).

Substances that can accumulate within cells include the normal nutrients (lipids, carbohydrates and proteins), pigments and inorganic particles. These substances tend to accumulate due to excessive supply and/or metabolic dysfunction. Some of the compounds are naturally present inside cells (although not normally at these levels), whereas others are abnormal (see Figure 1.9).

When excessive levels of fats, carbohydrates or proteins occur in the body, some tissues will attempt to take them up and store them. An example of a condition where this occurs is diabetes mellitus (see the chapter 'Diabetes mellitus'). High blood lipid levels can lead to the uptake of fats into the walls of blood vessels, which may lead to the development of atherosclerosis (see the chapter 'Diabetes mellitus'), as well as into the liver (i.e. hepatosteatosis). Diabetes mellitus is also characterised by

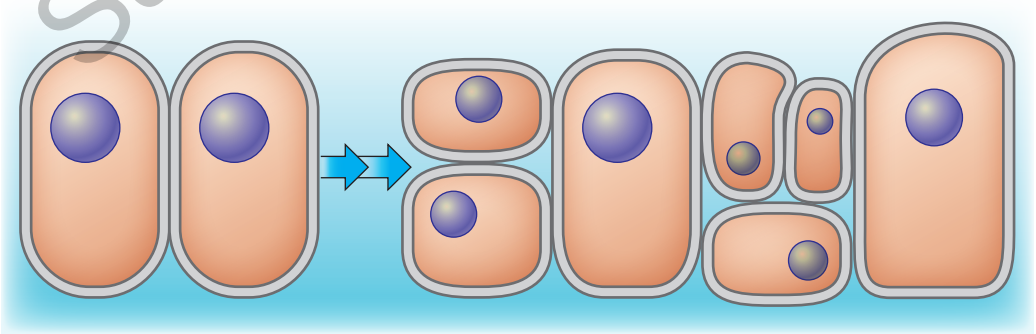


Figure 1.7

Cellular dysplasia

The cells on the left are normal cells. Those on the right have undergone dysplasia—variability in size and shape of cells—which leads to an alteration in tissue arrangement.

Figure 1.8

Hydropic swelling

Poor ATP production leads to dysfunction of the membrane pumps, resulting in reduced sodium ion influx. This exerts a strong osmotic pressure that draws water into the cell. The cell and its organelles swell. This swelling can lead to membrane rupture and irreversible cell injury.

ATP = adenosine triphosphate.

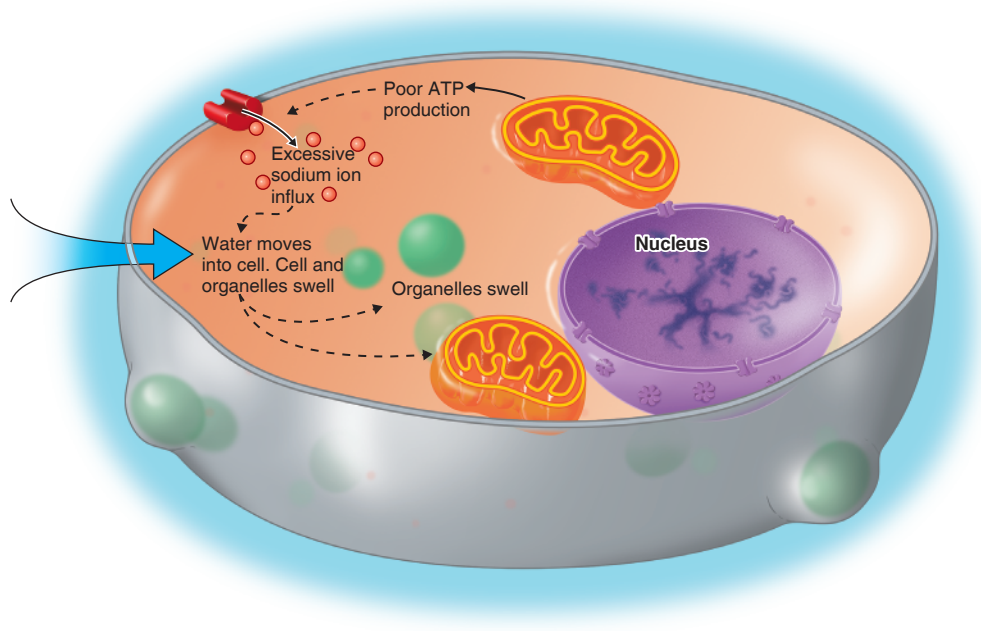
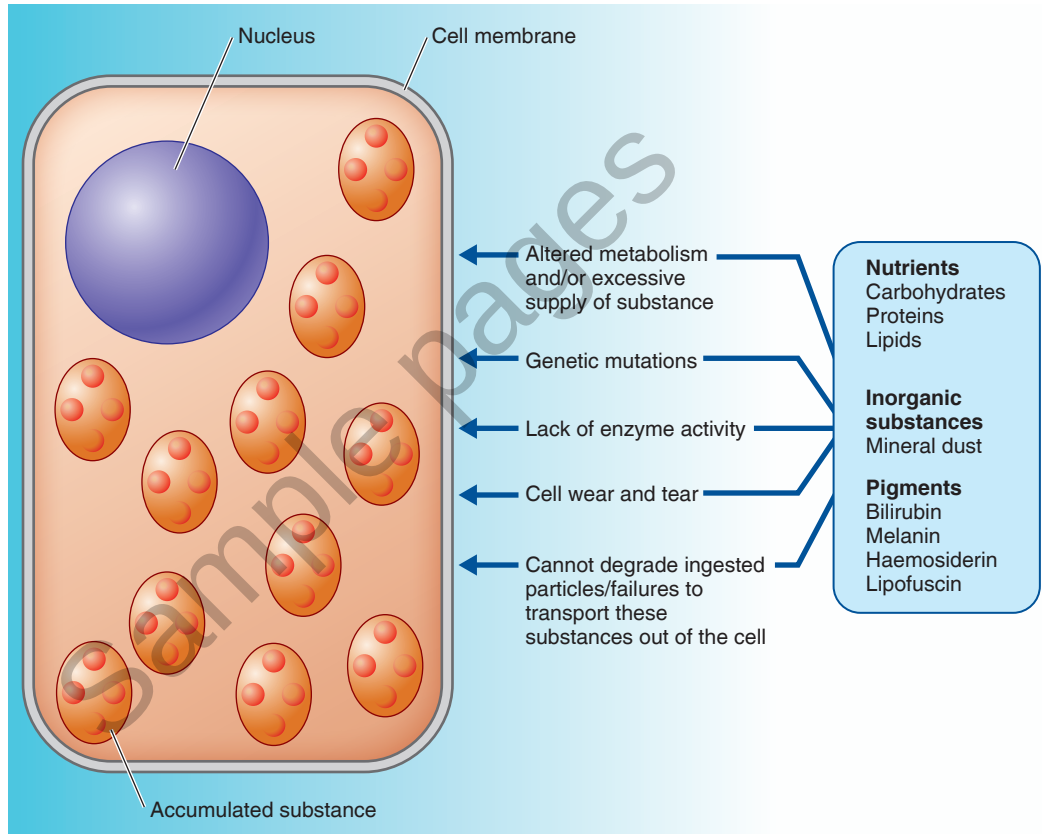


Figure 1.9

Examples of the types of substances that accumulate intracellularly, and some general causes



chronically elevated levels of glucose or proteins in urine. Renal tubule cells have the capacity to take up these nutrients, and can store them in excess; glucose is stored as glycogen.

Under some circumstances, the nutrient does not need to be present in surplus for excessive accumulation to occur. In the early stages of alcohol-related liver disease (see the chapter 'Disorders of liver, gallbladder and pancreas'), the liver appears to preferentially metabolise alcohol over lipids. This leads to the intracellular accumulation of fat particles within the liver, giving rise to a condition known as alcoholic fatty liver or alcoholic

hepatosteatosis. It is a mild condition and may be asymptomatic. Unlike later stages in alcoholic liver disease, it is reversible if alcohol intake is reduced or stopped.

Proteins can accumulate inside cells in the presence of a persistent injurious agent. Under these circumstances, the proteins have become denatured, so they take up abnormal shapes, greatly altering their function. If they are not cleared from the cell, they will cause irreversible injury. This pathophysiological process is considered to be the basis of the development of some of the neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease (see the chapter 'Neurodegenerative disorders'). Intracellular entities, such as a group of chaperone proteins known as heat shock proteins, are present in the endoplasmic reticulum to assist in the reshaping of denatured proteins, but these can be overwhelmed by the rate of formation of the latter in the presence of the injurious agent.

Certain genetic disorders are characterised by cell accumulations, although these are not usually considered reversible. In these conditions, a key enzyme involved in intracellular nutrient metabolism is missing, giving rise to the term 'inborn errors of metabolism'. The substrate or some intermediate product (e.g. glycogen or lipid) accumulates in cells. Glycogen can accumulate in cells, particularly liver and/or muscle tissue, greatly diminishing the availability of glucose to these and other body cells. This group of conditions is called the *glycogen storage diseases (GSD)*. The form of GSD depends on which enzyme in the process is dysfunctional; currently, approximately 10 types of GSD have been identified.

Lipid storage diseases can also arise as inborn errors of metabolism. In these conditions, lipids accumulate in many body tissues, including the liver, kidneys, lung, spleen, brain and bone marrow, causing widespread deficits in function. Examples of inheritable lipid storage diseases include Gaucher disease, Niemann–Pick disease and Tay–Sachs disease (see the chapter 'Genetic disorders').

Natural body pigments can accumulate in cells when they are present in excess quantities. Melanin, a skin pigment responsible for tanned or darkened skin, can be present in the skin in excessive quantities during excessive pituitary activation associated with an endocrine disorder called Addison's disease (see the chapter 'Adrenal gland disorders').

Bilirubin and haemosiderin are pigments formed from the breakdown of haemoglobin in erythrocytes. Bilirubin can be present in excess within the body, and can be taken up by cells when there is a disproportionately large breakdown of erythrocytes, in obstructive biliary disorders or during liver disease. Body tissues take on a characteristic yellow hue, referred to as 'jaundice'.

Lipofuscin is an insoluble yellowish-brown pigment which accumulates in cells, especially muscle, skin and nerve cells. It is formed from the breakdown of the cellular organelles, called lysosomes, and is considered a normal marker of the ageing process and the 'wear and tear' of living, as more of it is observed in tissues as we get older. Pigmented blemishes, called liver spots, can be seen in the skin of the aged. Excessive lipofuscin accumulation has been implicated in diseases of the aged such as macular degeneration, where the lipofuscin accumulates in the retina, and in Alzheimer's disease, where it accumulates in the brain.

Mineral dust contains insoluble inorganic particles that can be very problematic once they enter the body. Once inhaled, these particles are taken up by lung cells and accumulate there, because they cannot be degraded by phagocytosis or cleared from the tissues. Their presence induces chronic inflammatory responses (see the chapter 'Inflammation and healing') that severely damage the lung tissue and lead to disease. Exposure to these agents is most commonly associated with the mining of coal, asbestos, iron and lead.

IRREVERSIBLE CELL INJURY

LEARNING OBJECTIVE **6**

Compare and contrast necrosis and apoptosis.

Irreversible injury results in cell death. Two physiological processes are associated with cell death: necrosis and apoptosis.

Necrosis

LEARNING OBJECTIVE **7**

Differentiate between the types of necrotic cell death.

Necrosis is the process whereby the injury directly leads to premature pathologic *cell death* and *autolysis* (self-digestion). Characteristic changes in structure accompany this process, affecting all parts of the cell: the plasma membrane, nucleus, cytoplasm and cellular organelles. Most of these changes can be observed histologically. Within the nucleus, the chromatin threads degrade and the organelle shrinks. This is called *pyknosis*. Mitochondrial membranes break down, causing the mitochondria to swell and rupture. Vacuoles form within the cytoplasm. The impairment of ATP production leads to the seizing up of the membrane pumps, allowing sodium ions to accumulate intracellularly. Water is drawn into the cell, expanding the cytoplasm. Ultimately, the cell ruptures (see Figure 1.10).

The contents of the cell, including intracellular enzymes, spill out into the extracellular fluid and eventually diffuse into the bloodstream. The level of these substances in the blood correlates to the degree of necrotic cell death. These intracellular substances, particularly enzymes, may be characteristic to particular cell types—representing a kind of cellular signature. As a result, their presence in the blood is indicative of necrotic cell death in specific organs, such as the heart or the liver (Table 1.1), and can be used in clinical diagnosis. The release of chemical mediators from dying cells during necrosis triggers an inflammatory reaction. The purpose of this reaction is to clear away the cellular debris and facilitate the healing process (see the chapter 'Inflammation and healing').

There are four identifiable types of necrosis: coagulative, liquefactive, caseous and fat. The type of necrosis induced can depend on the type of tissue affected and the nature of the injurious agent (Table 1.2). **Coagulative necrosis** is characterised by protein denaturation. A good everyday example of coagulative protein denaturation is when an egg is poached. The protein turns white and forms a firm, gelatinous mass that holds its shape well. Cells that undergo coagulative necrosis behave in a similar fashion, and because of this the affected tissue initially holds its shape before breaking down. Ischaemic injury affecting the heart or kidneys is a good example of coagulative necrosis.

Liquefactive necrosis occurs when lysosomal digestive enzymes are released rapidly in large amounts during cell death, which leads to immediate autolysis. Infections are often associated with

Figure 1.10

Necrotic processes

Poor ATP production leads to dysfunction of the membrane pumps, resulting in excessive sodium ion influx. This exerts a strong osmotic pressure that draws water into the cell. The cell and its organelles swell. Calcium ions are released from cytoplasmic stores, activating intracellular enzymes, which further impair mitochondrial function and damage membranes. The plasma membrane forms blebs (blisters), which weaken its integrity. Toxic chemicals accumulate inside the cell, which can also damage its structures. The nucleus shrinks and forms a dense structure (pyknosis), which breaks up. Numerous vacuoles form within the cell. Cell membranes rupture, and inflammation follows.

ATP = adenosine triphosphate.

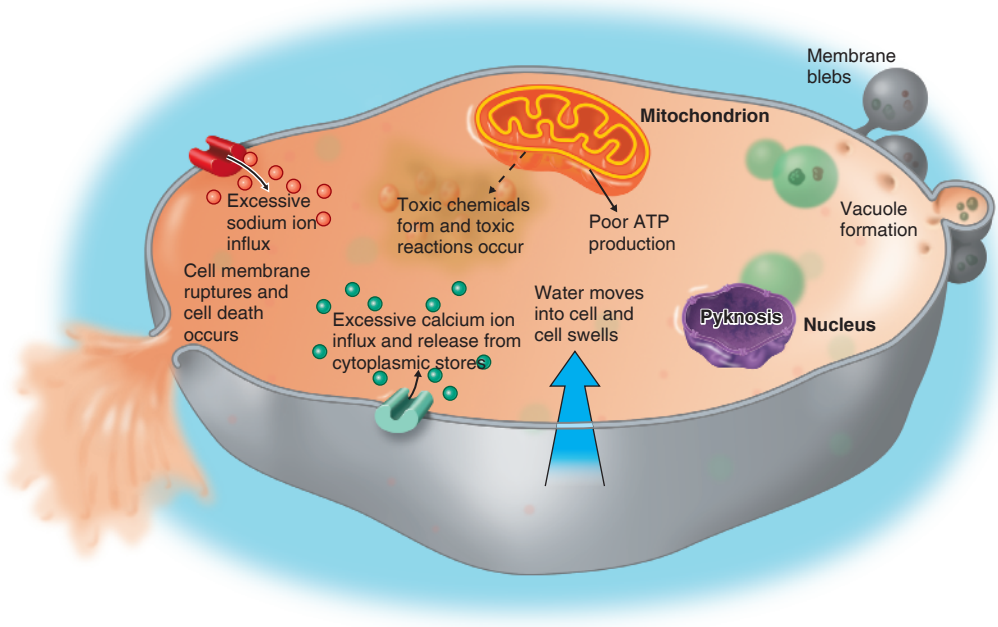


Table 1.1 Common intracellular enzymes released in cell injury

Enzymes	Tissue damage marker
Alanine aminotransferase (ALT)	Heart, liver and kidney
Alkaline phosphatase (ALP)	Liver and bone
Amylase	Pancreas
Aspartate aminotransferase (AST)	Liver, skeletal muscle, heart, pancreas and kidney
Creatine kinase (CK)	Brain, heart and skeletal muscle
Lactate dehydrogenase (LDH)	Liver, kidneys, skeletal muscle and erythrocytes
Cardiac troponin I (cTnI)	Heart
Troponin T (cTnT)	Heart and skeletal muscle

Table 1.2 Types of necrosis

Type	Features
Coagulative	Primarily characterised by protein denaturation. The cell holds its shape well during necrosis.
Liquefactive	Characterised by the rapid release of large amounts of lysosomal enzymes. The cell liquefies.
Caseous	Tissue framework not completely liquefied. The cell looks cheese-like.
Fat	Fat cell membranes are damaged, causing the release of triglycerides. The triglycerides are converted into free fatty acids that bind to calcium ions. The tissue becomes chalky and white.

this form of necrosis as the microorganism may release enzymes that contribute to the liquefaction. The affected tissue degrades rapidly, losing its framework and becoming a semi-solid mass. Irreversible ischaemic brain injury results in liquefactive necrosis.

Caseous necrosis is a combination of liquefactive and coagulative processes, where the tissue framework is not completely broken down by lysosomal enzyme action. The necrotic area is contained in an immune response, rather than being removed from the body. The affected tissue has the consistency of cottage cheese, giving rise to the term *caseous*, which means 'cheese-like'. An example is a chronic tuberculotic lesion in the lung, where the microbe escapes immune attack within infected macrophages (see the chapter 'Respiratory infections, cancers and vascular conditions').

Fat necrosis occurs in adipose tissue. Fat cell membranes are damaged, leading to a release of triglycerides into the tissue. Lipases act on the triglycerides to degrade them, leading to the formation of free fatty acids. Calcium ions bind to these tissue fatty acids, forming calcium soaps, a process called *saponification*. The affected tissue becomes chalky and white. Fat necrosis occurs in pancreatitis, when pancreatic lipasess attack surrounding adipose tissue as a result of injury caused by infection, trauma, toxin release or ischaemia. Another structure prone to fat necrosis is breast tissue as a result of traumatic injury.

Gangrene is a term associated with the necrosis of a relatively large amount of tissue as a result of ischaemia. The affected tissue usually turns black, and may feel cold and smell fetid; there is usually a clearly identifiable boundary between the affected and normal tissue. This distinctive boundary is due to necrotic cells releasing their concentrated contents, leading to injury to neighbouring cells. Gangrene can involve liquefactive or coagulative necrosis. Gangrene that develops in the skin, affecting a foot or toe, for example, usually undergoes coagulative necrosis. The affected area becomes wrinkled and black, and in this form is called *dry gangrene*. Internal organs when infected usually undergo liquefactive necrosis, and this is termed *wet gangrene*. In some cases of infection, the metabolic processes of the infective organism result in gas bubbles in the affected tissue area. This is called *gas gangrene*, and can occur in tissue infections caused by anaerobic *Clostridium* bacteria.

Apoptosis

Programmed cell death, **apoptosis**, is an integral part of the normal process of tissue maintenance and development during our lives. Within the nervous system, neurons that do not make the appropriate connections die. This also happens during developmental processes while we are in utero. We see it in the repair of a bone after a fracture as it is remodelled to its normal appearance. This physiological cell death is also a key part of immune system regulation, when a body cell is infected by a virus or an immune cell reacts against our own tissue. Apoptosis occurs rapidly in response to a specific stimulus that indicates that the cell is no longer required or has become redundant as a result of tissue maturation.

Upon receiving this stimulus, the cell initiates a cascade of enzymic reactions that leads to its death. Initially, the cell will decrease in size and the nucleus condenses. At this time, other cellular organelles remain normal in their appearance. As the reaction progresses, the cell membrane blebs, as the nucleus and its contents fragment. Eventually the whole cell fragments, forming apoptotic bodies that are engulfed by neighbouring phagocytes. In contrast to necrosis, the death of the cell does not induce an inflammatory response (see Figure 1.11).

Figure 1.11

Apoptosis

Apoptosis can be triggered by the activation of so-called 'death signal' receptors (tumour necrosis factor [TNF] and Fas receptors) or a variety of other stimuli. These receptors activate a cascade of intracellular reactions, involving caspase enzymes. Other stimuli induce cytochrome c synthesis within the mitochondria. Cytochrome c can also activate the caspases. Within the nucleus, the cascade triggers the condensation of chromatin and nuclear fragmentation. The fragmented cell components are captured within membrane-bound structures called apoptotic bodies, which are phagocytosed. There is no subsequent inflammatory response. Bcl-2 proteins appear to have a key role in regulating apoptosis.

DNA = deoxyribonucleic acid.

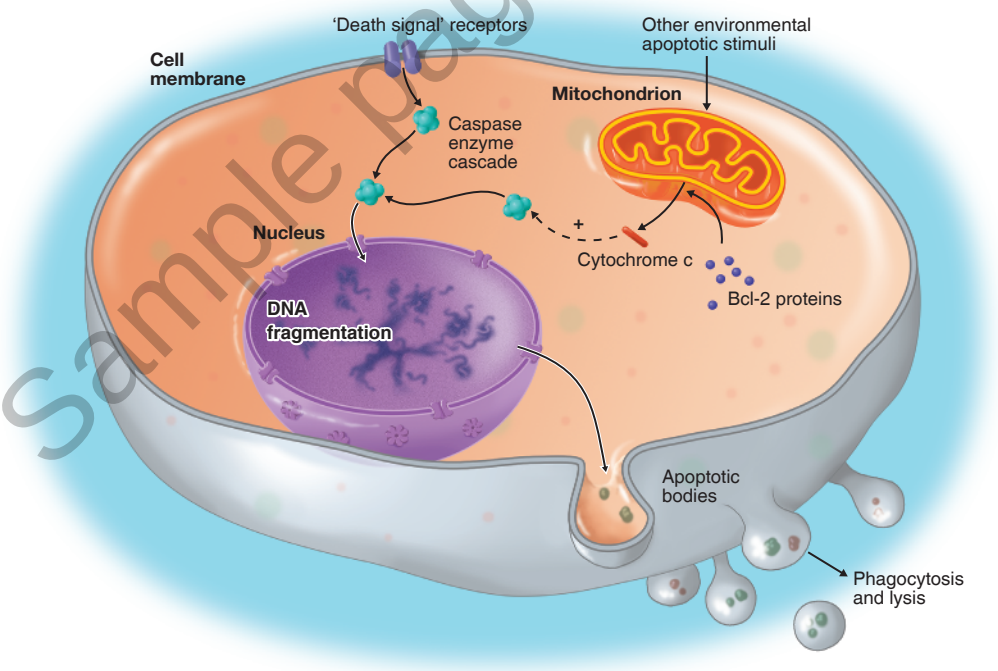


Table 1.3 A typical comparison between necrosis and apoptosis

Necrosis	Apoptosis
Pathological cell death	Cell suicide or programmed cell death
Numerous cells in the tissue affected	One or a few cells in the tissue affected
Cells swell, organelles disrupted (including the nucleus), and loss of membrane integrity	Cells shrink, organelles remain normal, nucleus and organelles broken down into membrane-bound fragments
Induces inflammation	No inflammation

The differences between necrosis and apoptosis are summarised in Table 1.3.

Key mediators of the apoptotic process include the proteolytic enzymes called *caspases*, the tumour-suppressing gene *p53*, calcium ions and the so-called *'death signal' receptors* on cell surfaces—the *Fas receptor* and the *tumour necrosis factor (TNF) receptor*. On the other hand, a family of intracellular proteins grouped as *Bcl-2* have been shown to suppress apoptosis under a variety of conditions. It appears that the intracellular balance of Bcl-2 proteins may be important in the regulation of apoptosis.

Apoptosis has been linked to the development of certain diseases. If apoptosis does not occur when it should, is induced prematurely, or in the presence of the correct stimulus does not take place at all, disease may develop. Examples where evidence of this is apparent include certain cancers (see the chapter 'Neoplasia'), neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (see the chapter 'Neurodegenerative disorders') and some congenital abnormalities.

Agents of cell injury

LEARNING OBJECTIVE 8

Identify the major agents of cell injury.

There are many agents of cell injury; the most common are chemical, physical, nutritional, ischaemic and hypoxic, and infectious and immunological. These agents act as stimuli that can induce either reversible or irreversible cell injury.

CHEMICAL AGENTS

In our modern world, we are constantly being exposed to chemicals that can damage our cells. The chemicals are present as air pollutants produced by industry and motor vehicles (e.g. carbon monoxide, sulfur dioxide, heavy metals and cyanide), or available as agricultural and domestic pesticides, cleaning agents such as carbon tetrachloride, and even drugs used for clinical or recreational purposes. Some of these agents are acutely toxic to cells, while others accumulate in our bodies and become toxic after reaching a particular threshold level.

Some of these chemicals, such as the heavy metals, produce widespread toxicity affecting a number of body systems. Other chemicals target specific organs; for example, an overdose of paracetamol can irreversibly damage the liver. A chemical may even attack a specific population of cells within an organ, as the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) does when it selectively destroys the dopaminergic neurons of the nigrostriatal motor pathway in the brain. MPTP has been implicated in some forms of Parkinson's disease pathophysiology (see the chapter 'Neurodegenerative disorders').

Some toxic environmental agents can react with oxygen molecules within the cell and lead to the formation of free radicals. *Free radicals* are highly **reactive oxygen species (ROS)** that can then disrupt cell membranes, intracellular lipid and deoxyribonucleic acid (DNA) structure. Fortunately, these free radicals can be neutralised by chemicals with antioxidant properties, such as some vitamins. Under certain conditions, cells can become saturated with free radicals, and, if the availability of antioxidants is exhausted, irreversible cell injury can result (see Figure 1.12).

PHYSICAL AGENTS

Abrupt or *extreme changes in temperature or pressure* are good examples of physical agents of injury. These changes can involve increases or decreases. Physical agents can also include exposure to electricity, significant mechanical force (trauma) and electromagnetic radiation.

At the cellular level, these agents can disrupt cell structures such as the plasma membrane, nucleus and organelles. *High temperatures and electricity* can lead to the denaturation of proteins, resulting in coagulation within the cell. *Low temperatures* can lead to the formation of ice crystals within cell membranes, which disrupt their integrity, leading to changes in permeability and possible cell death. *Mechanical force* can damage bones and organs. At the cellular level, trauma can rupture cell membranes, leading to cell death.

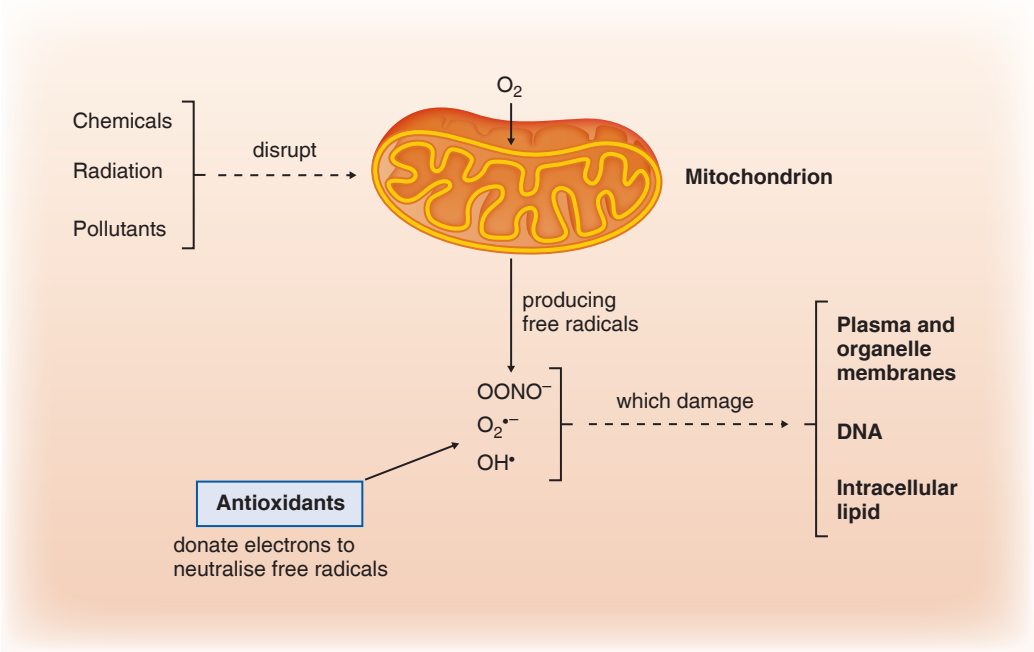
Exposure to *electromagnetic radiation* can change the structure of DNA such that it may induce gene mutations that alter the structure and/or function of the cell. Such an alteration can trigger the onset of cancer. Changes to DNA could also lead to impairments in cell growth or a breakdown in DNA

Figure 1.12

Free radical formation and antioxidant action

Oxygen free radicals are formed as part of aerobic metabolism. They are also formed when stimuli, such as those shown, disrupt mitochondrial function. These highly reactive chemicals interact with and damage cell structures to acquire electrons in order to form stable bonds. Antioxidant substances, such as vitamins and flavonoids, can neutralise free radicals by donating electrons without disrupting their chemical structures.

DNA = deoxyribonucleic acid;
$OH^{\bullet}$ = hydroxyl radical;
O_2 = oxygen;
$O_2^{\bullet -}$ = superoxide radical;
$OONO^-$ = peroxynitrite ion.



integrity that result in cell death. Like some of the chemical agents, radiation can also ionise oxygen molecules, leading to the formation of damaging free radicals.

NUTRITIONAL AGENTS

Nutrient balance is a key aspect of homeostasis. When nutritional *imbalances* develop, they can have a significant effect on the capacity of the body to maintain equilibrium, resulting in cell injury. Proteins, carbohydrates, lipids, vitamins and minerals are vital for normal cell function. Although the body can manufacture a number of these nutrients, most of these substances, or their precursors, must be obtained from our diet.

Nutrition-related cell injuries can arise as a result of nutrient deficiencies. Vitamin deficiencies can lead to a diverse range of conditions, including anaemia, bleeding disorders, dermatitis, skeletal and nervous system dysfunction, as well as altered immunity. Conditions associated with mineral deficiencies include anaemia (iron deficiency), hypothyroidism (iodine deficiency), tooth decay (fluoride deficiency) and impaired healing and immunity (zinc deficiency). Malnutrition develops when the macronutrients (proteins, lipids and carbohydrates) become unavailable to body cells. This can be the result of inadequate intake, absorption, distribution or cellular uptake (see the Part 'Gastrointestinal pathophysiology').

Cells can also be damaged in states of nutritional excess, resulting from higher intake or poor cellular uptake. Obesity as a result of the excessive intake of calories is a major concern today in most Western countries, and is considered a major risk factor for cardiovascular, joint and biliary diseases.

ISCHAEMIC AND HYPOXIC AGENTS

LEARNING OBJECTIVE 9

Describe the process of cell injury resulting from an ischaemic or hypoxic agent.

Body cells require a ready supply of oxygen for normal metabolism to occur, although oxygen requirements may vary greatly between cell types. Oxygen is required for normal energy production and storage in the form of *adenosine triphosphate (ATP)* molecules, and is delivered to cells via the bloodstream. The bloodstream is also the means by which cellular wastes are removed before they can accumulate.

When oxygen supply via the blood is compromised, a state of **hypoxia** will develop. The interruption of blood supply to a tissue is called **ischaemia**. Hypoxia will eventually develop as a result of ischaemia. This state can happen very quickly if the degree of interruption of blood flow is severe and the tissue's metabolic needs are high. Examples of ischaemic conditions are angina pectoris (see the chapter 'Coronary artery disease'), peripheral vascular disease (see the chapter 'Vascular disorders and circulatory shock') and the most common form of stroke (see the chapter 'Brain and spinal cord dysfunction').

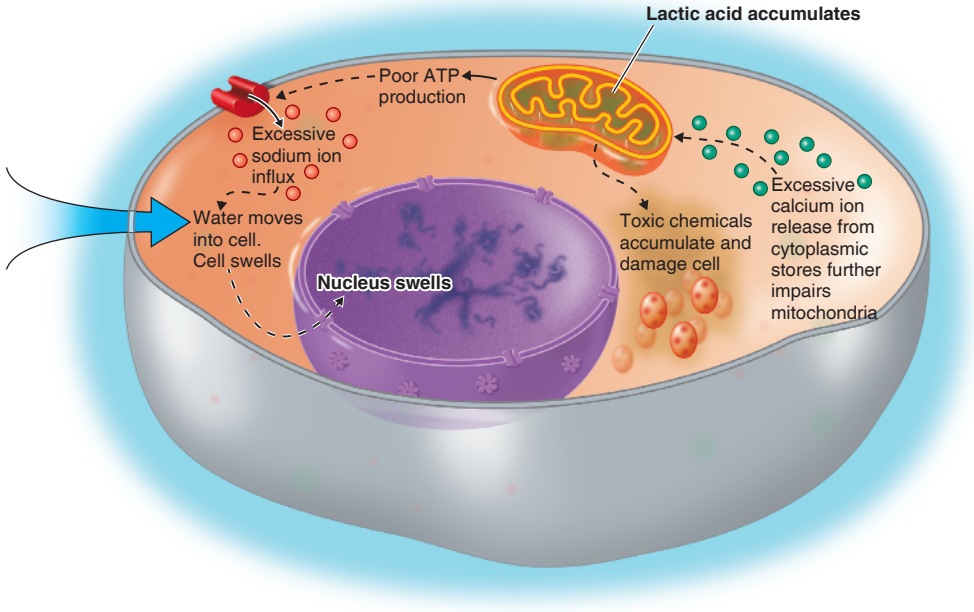
Hypoxia can also develop in the absence of ischaemia. Examples where this can happen include *poor oxygen levels in the blood* (*anaemia*), *impaired oxygenation* (lung disease) or *heart disease*. A number of toxic agents can induce hypoxia through a *disruption of cellular respiration*. These agents include carbon monoxide, hydrogen sulfide and cyanide.

Figure 1.13

Ischaemic injury

When blood flow to cells becomes compromised, they can switch to anaerobic metabolism for a short period in order to maintain ATP production. As a by-product of anaerobic metabolism, lactic acid can accumulate in the cell and disrupt mitochondrial function. Poor ATP production leads to dysfunction of the membrane pumps, leading to excessive sodium ion influx. This, in turn, exerts a strong osmotic pressure that draws water into the cell. The cell and its organelles swell. Calcium ions are released from cytoplasmic stores, activating intracellular enzymes that further impair mitochondrial function and damage membranes. Toxic chemicals accumulate inside the cell, which can also damage its structures.

ATP = adenosine triphosphate.



Once the oxygen supply to cells is compromised, the production of ATP decreases markedly. Cells will attempt to compensate for this change by switching to anaerobic metabolism, which results in relatively lower levels of ATP production and the accumulation of lactic acid. This cannot be sustained, because high levels of lactic acid can be toxic to cells. Impaired ATP production leads to a failure of the membrane pumps controlling the movement of sodium, potassium and calcium into and out of the cell. Sodium ions accumulate intracellularly, drawing water into the cell, which causes the cell to swell, damaging membranes and disrupting organelle functions. Calcium ions are also released into the cytoplasm from intracellular stores, which further impairs mitochondrial function. In ischaemia, cellular waste products cannot be cleared away, and so accumulate in the cell's environment. These wastes can contribute to cell injury (see Figure 1.13).

Intuitively, one would think that simply restoring blood flow would allow the affected cells to recover and return to normal. Unfortunately, this is not the case. Re-perfusion of the tissue with blood can lead to further damage and cell death. This secondary injury is termed *re-perfusion injury*. As the cellular membrane pumps are still impaired, restoration of blood flow can lead to an uncontrolled influx of calcium ions. The calcium ions can trigger processes that result in the breakdown of membrane lipids and cell death. Large numbers of **oxygen free radicals** are produced, which can cause extensive and potentially irreversible cell injury by attacking cell membranes, denaturing proteins and damaging cell DNA (see Figure 1.14).

Re-perfusion injury plays a major role in the potentially catastrophic cell death associated with *stroke* and *acute myocardial infarction (AMI)*. Interestingly, research has shown that the degree of re-perfusion injury that occurs in AMI can be reduced by pre-exposure to a sublethal ischaemic state that primes the heart for a subsequent ischaemic episode. This process is called *ischaemic pre-conditioning*, and may have a role to play in the clinical management of someone at high risk of AMI.

INFECTIOUS AND IMMUNOLOGICAL AGENTS

Microbes are common and effective agents of cell injury. This group includes organisms such as bacteria, viruses and parasites. The earliest human records show that microbes have plagued us for aeons, most likely from the time that the first humans appeared on Earth.

Once microbes gain access to cells, they can cause extensive damage. They can do this by entering the cell and *disrupting normal function*, or they can remain in the extracellular space and *secrete powerful chemicals*, usually enzymes, that disable or kill cells. Viruses, comprised of the nucleic acids RNA or DNA, can enter a body cell and *change its programming* so that it becomes a factory for making new virus particles, or *alter its structure* in such a way that it is irreversibly damaged.

The immune system is responsible for neutralising and removing these microbial invaders. Infected body cells are recognised, and immune reactions then triggered. Immune cells

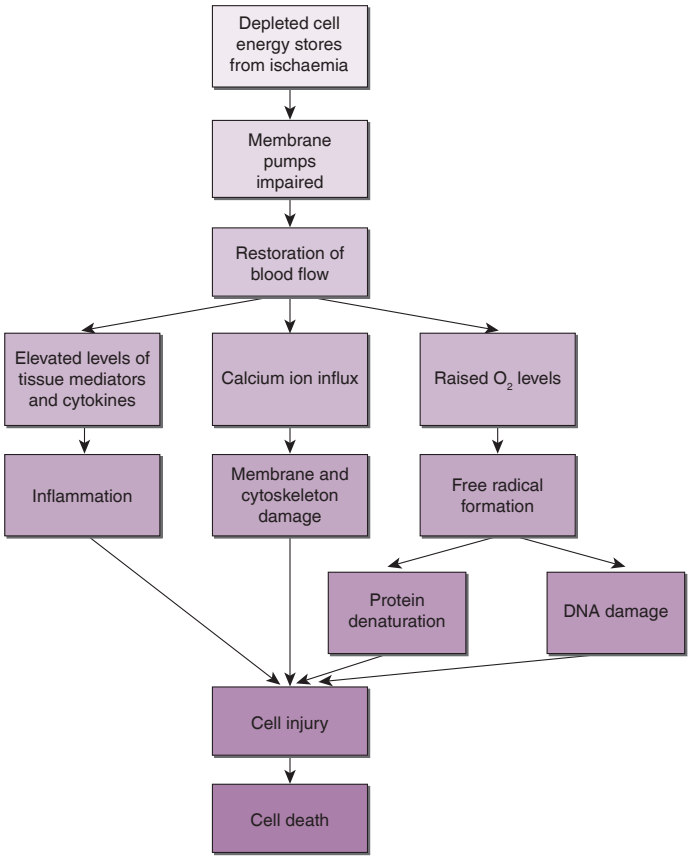


Figure 1.14

Reperfusion injury

DNA = deoxyribonucleic acid; O_2 = oxygen.

are recruited to the site, and release a range of chemicals (see the chapters 'Inflammation and healing' and 'Infectious diseases') that lead to the death of the infected cell. Unfortunately, the lack of specificity of this immune response and/or its magnitude may lead to injury to a significant number of normal cells that are in close proximity.

INDIGENOUS HEALTH FAST FACTS AND CULTURAL CONSIDERATIONS

ALTERED NUTRITIONAL STATE AS AN AGENT OF INJURY

- *Poor nutrition contributes to approximately 9.7% of the burden of disease for Aboriginal and Torres Strait Islander peoples.*
- *Estimations of food costs in rural and remote communities are considered to be approximately 30% higher than in major cities, which probably contributes to the very low fruit and vegetable intake described among Aboriginal and Torres Strait Islander groups.*
- *Poor nutrition results in the birth of low-birth-weight babies almost twice as frequently in Aboriginal and Torres Strait Islander women as in non-Indigenous women.*
- *Food security is a greater issue for Aboriginal and Torres Strait Islander peoples, with 22% of people reporting that at least one person went without food when the household ran out of food, compared to 3.7% in non-Indigenous Australian households.*
- *Māori or Pacific Islands babies are less likely than European New Zealand children to be breastfed.*
- *Based on a set of predetermined risk factors, Maori children make up 66% of children at risk of developing poor outcomes later in life, compared to 21% of European New Zealand children, 12% of Pacific Islands children and only 2.1% of Asian New Zealand children.*
- *European New Zealand babies are, on average, given their first solids at approximately 5½ months of age. Maori babies are more likely to be given solids before 4 months of age.*

Sources: Australian Bureau of Statistics (2019); Australian Health Ministers' Advisory Council (2017); Australian Indigenous HealthInfoNet (2022); Australian Institute of Health and Welfare (2020); National Health and Medical Research Council (2019); New Zealand Ministry of Health (2022).

LIFESPAN ISSUES: CELLULAR ADAPTATIONS

CHILDREN AND ADOLESCENTS

- Assessment of a child's quadriceps femoris for atrophy or hypertrophy is a good clinical indicator of the need to continue investigations for the presence of neuromuscular disease.
- Hormonal changes from transition through growth stages can influence a child's tissue. Tonsils can hypertrophy during childhood and atrophy after puberty; many other tissues hypertrophy as a result of puberty (e.g. secondary sex characteristics).

OLDER ADULTS

- As an individual ages, significant atrophy occurs in most major organs. These changes result in the increased need to observe for drug toxicities, hydration status, malnutrition and changes to strength and balance.
- Exercise can moderate age-related muscular atrophy to some degree.
- Hyperplasia of the prostate gland occurs as a direct result of ageing, and can negatively affect an older man's urological and sexual function.

KEY CLINICAL ISSUES

- Observations for muscle or limb atrophy and hypertrophy should be undertaken during the course of a physical examination.
- When collecting a health history, including questions about exposure to potential agents of cell injury (such as chemicals) can assist in determining contributing factors to the development of signs and symptoms.
- Gaining an understanding of an individual's nutrition behaviours and food choices can provide an insight into possible deficiencies or excesses.
- Infection control practices are important when caring for individuals with active infections. Understanding the concepts of the chain of infection can help to protect the healthcare professional and other individuals, to prevent the spread of infectious disease.

CHAPTER REVIEW

- *Pathophysiology* is defined as the study of the mechanisms by which disease and illness alter the functioning of the body. *Aetiology* is the study of the cause or causes of a disease. The *pathogenesis* represents the development of a disease. The *clinical manifestations* are the demonstrable changes representing the changes in function brought about by a disease process.
- *Epidemiology* is the study of the patterns of disease within populations. The *incidence* rate of a disease represents the number of new cases diagnosed within a particular period, usually over a calendar year. The *prevalence* rate of a disease is the total number of cases, both newly and previously diagnosed, at a particular time.
- *Cellular adaptations* to stimuli allow the cell to maintain homeostasis under new conditions. If the cell cannot adapt, then it may become injured—either reversibly or irreversibly.
- The types of cellular adaptation are atrophy, hyperplasia, hypertrophy, metaplasia and dysplasia.
- *Atrophy* is a decrease in cell size; *hypertrophy* is an increase in cell size; *hyperplasia* is an increase in cell number; and *metaplasia* is a transformation from one cell type to another. *Dysplasia* is a maladaptive response to a stimulus that results in a variation in cell size and shape. Dysplasia leads to a breakdown in the organisation and arrangement of the tissue.
- Two forms of *irreversible cell injury* result in cell death: necrosis and apoptosis.
- *Necrosis* is a form of premature pathologic cell death. In necrosis, the cell swells and characteristic changes occur in the nucleus, including degradation and shrinkage. The contents of the cell spill out into the extracellular space, which induces an inflammatory response.
- *Apoptosis* is a form of programmed cell death. A series of enzymic reactions leads to fragmentation of the nucleus and the cytoplasm into apoptotic bodies. These bodies are phagocytosed and do not induce an inflammatory response.
- The *major agents* of cell injury are chemical, physical, nutritional, ischaemic, hypoxic, infectious and immunological.
- *Reversible cell injury* is characterised by cell swelling and intracellular accumulations. If the stimulus ceases or compensatory mechanisms can be established, the cell may be able to recover.

REVIEW QUESTIONS

1 Define the following terms:
   a epidemiology
   b pathogenesis
   c aetiology
2 Differentiate between the incidence and the prevalence of disease.
3 Define the following cellular adaptations, and provide an example of each:
   a metaplasia
   b hyperplasia
4 Explain why histological evidence of dysplasia within a tissue is considered a reason for concern.
5 Indicate which type of necrosis matches each of the following descriptions, and suggest an example.
   a The affected tissue has a cheese-like appearance.
   b The injury triggers immediate and widespread autolysis of cells.
   c A large area of tissue is damaged in an ischaemic injury. The tissue turns black and smells foul.
6 Briefly explain why an inflammatory response is not triggered by apoptotic cell death.
7 Indicate whether each of the following mediators triggers or suppresses apoptosis:
   a TNF receptors
   b Bcl-2 proteins
   c caspases
8 Provide an example of each of the following types of injurious agents:
   a nutritional
   b chemical
   c infectious
   d ischaemic
9 Briefly describe the process of hypoxic cell injury.
10 Outline the potential consequences of re-perfusing the heart with blood after an acute myocardial infarction.

HEALTH PROFESSIONAL CONNECTIONS: CELLULAR ADAPTATIONS

Midwives A neonate's heart is 'rate-dependent'. This means that blood pressure is directly related to heart rate. The younger an individual, the less hypertrophy has occurred, as the heart has not been beating for as long as an adult's. As a heart 'ages', the ability to contract with more force develops. An increase in contractility allows a decrease in heart rate. However, a neonate has not developed sufficient cardiac hypertrophy to permit the manipulation of contractility; therefore, cardiac output is maintained by rate alone. (Remember the equation: cardiac output = rate × stroke volume.) Increasing contractility increases stroke volume. If stroke volume cannot be increased, then rate is the only other factor.

Physiotherapists/Exercise scientists Atrophy occurs with disuse. When working with individuals experiencing long-term disuse (from paralysis) or short-term disuse (from temporary immobilisation, e.g. splinting), atrophy can be expected. Research on paralysis-induced atrophy has indicated that clinical outcomes can be improved through the use of resistance-training equipment; for example, using a specially modified exercise bike, where the limbs of paralysed individuals are electronically stimulated to allow them to move the pedals. This type of functional electronic stimulation can slow the cellular adaption of atrophy, decrease osteoporosis and increase circulation in affected limbs.

Conversely, muscular hypertrophy as a result of the overload principle is the mechanism by which muscle bulk and strength are achieved. Intermittent resistance training using concentric and eccentric contractions with a progressive increase in either load or repetition is known to be one of the most successful methods of muscle development. This process is manipulating cellular adaptation. It is important that, when prescribing exercise for bulking or rehabilitation, the exercise health professional should have an understanding of protein synthesis and degradation.

Nutritionists/Dieticians Maintaining adequate nutrition is imperative to reduce cellular adaptation. Protein anabolism and catabolism are significantly influenced by diet. Insufficient nutrients within a diet will affect all organ systems. Gastrointestinal adaptation can also occur related to diet. Education and meal planning to ensure appropriate nutrition will enable the gastrointestinal system to adjust as necessary. Supplementation may be required to correct inadequacies in absorption. Knowledge of cellular adaption (especially gastrointestinal adaptation) is important for those responsible for assisting people with nutritional health.

CASE STUDY

Ms Sofia Cassidy is a 29-year-old woman (UR number 156784) who sustained a fracture-dislocation to her right ankle after falling down a two-metre ravine while on a bush walk in a national park with her partner. Sofia is healthy, athletic and, apart from her current situation, considers herself in good physical condition. Once the medical team arrived, she was stabilised, airlifted out of the national park and taken to the nearest metropolitan hospital. Following primary and secondary assessments, pain relief and X-rays, it was determined that, apart from some minor grazes that needed cleaning and dressing, her ankle fracture was the only injury that required further intervention. She was kept 'nil by mouth' in anticipation of the need for an open reduction internal fixation (ORIF).

Ms Cassidy had blood drawn for a full blood count, electrolytes and coagulation profile. Her pathology results have returned as follows:

HAEMATOLOGY

Patient location:	Ward 3	**UR:**	156784		
Consultant:	Smith	**NAME:**	Cassidy		
		Given name:	Sofia	**Sex:**	F
		DOB:	03/11/XX	**Age:**	29
Time collected	11:13				
Date collected	XX/XX				
Year	XXXX				
Lab #	456563645				

FULL BLOOD COUNT		UNITS	REFERENCE RANGE
Haemoglobin	122	g/L	115–160
White cell count	6.3	$\times 10^9$/L	4.0–11.0
Platelets	244	$\times 10^9$/L	140–400
Haematocrit	0.43		0.33–0.47
Red cell count	4.67	$\times 10^{12}$/L	3.80–5.20
Reticulocyte count	1.2	%	0.2–2.0
MCV	94	fL	80–100

Neutrophils	4.43	$\times 10^9$/L	2.00–8.00
Lymphocytes	1.1	$\times 10^9$/L	1.00–4.00
Monocytes	0.48	$\times 10^9$/L	0.10–1.00
Eosinophils	0.31	$\times 10^9$/L	< 0.60
Basophils	0.11	$\times 10^9$/L	< 0.20
ESR	2	mm/h	< 12
COAGULATION PROFILE			
aPTT	29	secs	24–40
PT	14	secs	11–17

BIOCHEMISTRY

Patient location:	Ward 3	**UR:**	156784		
Consultant:	Smith	**NAME:**	Cassidy		
		Given name:	Sofia	**Sex:**	F
		DOB:	03/11/XX	**Age:**	29

Time collected	11:13
Date collected	XX/XX
Year	XXXX
Lab #	456563646

ELECTROLYTES		UNITS	REFERENCE RANGE
Sodium	138	mmol/L	135–145
Potassium	4.1	mmol/L	3.5–5.2
Chloride	102	mmol/L	95–110
Bicarbonate	25	mmol/L	22–32
Glucose	5.9	mmol/L	3.5–5.4
Iron	15.6	µmol/L	11–30

Her neurovascular observations were acceptable, and once the orthopaedic team reviewed her X-rays she was given a 'procedural sedation' in the emergency department and underwent a closed reduction of her ankle fracture-dislocation. Her observations were as follows:

Temperature	Heart rate	Respiration rate	Blood pressure	SpO_2
36.9°C	92	18	142/84	96% (RA*)

*RA = room air.

A backslab splint was applied, and 12 hours post-procedure she was discharged into the care of her partner. A physiotherapist provided her with appropriate-sized crutches, and assessed Ms Cassidy's safety with mobilising and negotiating stairs. She was given analgesia, fracture care instructions and a fracture clinic appointment, and told to return to the emergency department or her local doctor if she had any concerns. Ms Cassidy is vegan, and she asked whether there were any dietary considerations that would influence the healing of her injury. The nurse discussed the importance of good nutrition and of selected macro- and micronutrients necessary for fracture repair.

Once the swelling in her ankle subsided, the plaster clinic applied a fibreglass cast, and her ankle remained immobilised for a further six weeks.

Finally, after X-rays, a consultation with the orthopaedic team, and waiting what seemed like an eternity, it was time for Ms Cassidy's cast to be removed. Once the technician removed her cast, she was able to see her lower leg again. She was surprised and a little embarrassed when she saw her very dry, scaly-skinned, hairy leg… but then she noticed the size of her gastrocnemius. She became a little teary, as she had prided herself on the size of her calf muscles. She always felt she had lovely, defined calves that any dedicated cyclist would envy. Now, her right calf seemed almost half the size of her left.

CRITICAL THINKING

1. Consider Ms Cassidy's physical condition prior to her accident and her dietary preferences. Discuss what and how these factors may influence her fracture healing.
2. Ms Cassidy was proud of the size of her gastrocnemius muscles prior to her accident. What do you think accounted for that physiological state?
3. Once Ms Cassidy's fracture has healed, the new bone tissue in the area surrounding the fracture will be larger than the normal continuity of the bone. By the end of the healing process the fracture zone will be continuous with the rest of the bone. What process has occurred to shape the bone?
4. When the cast was removed from Ms Cassidy's right leg, she noticed that her gastrocnemius was almost half the size of that of her left leg. Explain what has happened to her muscle at a cellular level. Why did this occur?
5. What interventions could have been implemented during Ms Cassidy's recovery to reduce the effects of immobilisation? What interventions are required now that this has occurred? Which healthcare professionals are best placed to assist Ms Cassidy with her current situation?

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