Section 1 The Basics

Chapter 1

General Organisation of the Body

Physiology is the study of the functions of the body, its organs and the cells of which they are composed. It is often said that physiology concerns itself with maintaining the status quo or 'homeostasis' of bodily processes. However, even normal physiology is not constant, changing with development (childhood, pregnancy and ageing) and environmental stresses (altitude, diving and exercise). Physiology might be better described as maintaining an 'optimal' internal environment; many diseases are associated with the disturbance of this optimal environment.

Anaesthetists are required to adeptly manipulate this complex physiology to facilitate surgical and critical care management. Therefore, before getting started on the areas of physiology that are perhaps of greater interest, it is worth revising some of the basics – this chapter and the following four chapters have been whittled down to the absolute essentials.

How do the body's organs develop?

The body is composed of some 100 trillion cells. All life begins from a single totipotent embryonic cell, which is capable of differentiating into any cell type. This embryonic cell divides many times and, by the end of the second week, gives rise to the three germ cell layers:

- **Ectoderm**, from which the nervous system and epidermis develop.
- **Mesoderm**, which gives rise to connective tissue, blood cells, bone and marrow, cartilage, fat and muscle.
- **Endoderm**, which gives rise to the liver, pancreas and bladder, as well as the epithelial lining of the lungs and gastrointestinal (GI) tract.

Each organ is composed of many different tissues, all working together to perform a particular function. For example, the heart is composed of cardiac muscle, conducting tissue, including Purkinje fibres, and blood vessels, all working together to propel blood through the vasculature.

How do organs differ from body systems?

The organs of the body are functionally organised into 11 physiological 'systems':

- **Respiratory system**, comprising the lungs and airways.
- **Cardiovascular system**, comprising the heart and the blood vessels. The blood vessels are subclassified into arteries, arterioles, capillaries, venules and veins. The circulatory system is partitioned into systemic and pulmonary circuits.
- **Nervous system**, which comprises both neurons (cells that electrically signal) and glial cells (supporting cells). It can be further subclassified in several ways:
  - Anatomically, the nervous system is divided into the *central nervous system* (CNS), consisting of the brain and spinal cord, and the *peripheral nervous system* (PNS), consisting of peripheral nerves, ganglia and sensory receptors, which connect the limbs and organs to the brain.
  - The PNS is functionally classified into an *afferent limb*, conveying sensory impulses to the brain, and an *efferent limb*, conveying motor impulses from the brain.
  - *The somatic nervous system* refers to the components of the nervous system under conscious control.
  - *The autonomic nervous system* (ANS) regulates the functions of the viscera. It is divided into *sympathetic and parasympathetic nervous systems.*
  - *The enteric nervous system* is a semiautonomous system of nerves that control the digestive system.
- **Muscular system**, comprising the three different types of muscle: skeletal, cardiac and smooth muscle.

- **Skeletal system**, the framework of the body, comprising bone, ligaments and cartilage.
- **Integumentary system**, which is essentially the skin and its appendages: hairs, nails, sebaceous glands and sweat glands. Skin is an important barrier preventing invasion by microorganisms and loss of water (H_2O) from the body. It is also involved in thermoregulation and sensation.
- **Digestive system**, including the whole of the GI tract from mouth to anus and a number of accessory organs: salivary glands, liver, pancreas and gallbladder.
- **Urinary system**, which comprises the organs involved in the production and excretion of urine: kidneys, ureters, bladder and urethra.
- **Reproductive system**, by which new life is produced and nurtured. Many different organs are involved, including the ovaries, testes, uterus and mammary glands.
- **Endocrine system**, whose function is to produce hormones. Hormones are chemical signalling molecules carried in the blood that regulate the function of other, often distant cells.
- **Immune system**, which is involved in tissue repair and the protection of the body from microorganism invasion and cancer. The immune system is composed of the lymphoid organs (bone marrow, spleen, lymph nodes and thymus), as well as discrete collections of lymphoid tissue within other organs (for example, Peyer's patches are collections of lymphoid tissue within the small intestine). The immune system is commonly subclassified into:
  - *The innate immune system*, which produces a rapid but non-specific response to microorganism invasion.
  - *The adaptive immune system*, which produces a slower but highly specific response to microorganism invasion.

The body systems do not act in isolation; for example, arterial blood pressure is the end result of interactions between the cardiovascular, urinary, nervous and endocrine systems.

What is homeostasis?

Single-celled organisms (for example, an amoeba) are entirely dependent on the external environment for their survival. An amoeba gains its nutrients directly from and eliminates its waste products directly into the external environment. The external environment also influences the cell's temperature and pH, along with its osmotic and ionic gradients. Small fluctuations in the external environment may alter intracellular processes sufficiently to cause cell death.

Humans are multicellular organisms – the vast majority of our cells do not have any contact with the external environment. Instead, the body bathes its cells in extracellular fluid (ECF). The composition of ECF bears a striking resemblance to seawater, where distant evolutionary ancestors of humans would have lived. Homeostasis is the regulation of the internal environment of the body to maintain a stable, relatively constant and optimised environment for its component cells:

- **Nutrients** – cells need a constant supply of nutrients and oxygen (O_2) to generate energy for metabolic processes. In particular, plasma glucose concentration is tightly controlled, and many physiological mechanisms are involved in maintaining an adequate and stable partial pressure of tissue O_2.
- **Carbon dioxide (CO_2) and waste products** – as cells produce energy in the form of adenosine triphosphate (ATP), they generate waste products (for example, H^+ and urea) and CO_2. Accumulation of these waste products may hinder cellular processes; they must be transported away.
- **pH** – all proteins, including enzymes and ion channels, work efficiently only within a narrow range of pH. Extremes of pH result in denaturation, disrupting the tertiary or quaternary structure of proteins or nucleic acids.
- **Electrolytes and water** – the intracellular water volume is tightly controlled; cells do not function correctly when they are swollen or shrunken. As sodium (Na^+) is a major cell membrane impermeant and therefore an osmotically active ion, the movement of Na^+ strongly influences the movement of water. The extracellular Na^+ concentration is accordingly tightly controlled. The extracellular concentrations of other electrolytes (for example, the ions of potassium (K^+), calcium (Ca^{2+}) and magnesium (Mg^{2+})) have other major physiological functions and are also tightly regulated.

- **Temperature** – the kinetics of enzymes and ion channels have narrow optimal temperature ranges, and the properties of other biological structures, such as the fluidity of the cell membrane, are also affected by temperature. Thermoregulation is therefore essential.

Homeostasis is a dynamic phenomenon: usually, physiological mechanisms continually make minor adjustments to the ECF environment. Following a major disturbance, large physiological changes are sometimes required.

How does the body exert control over its physiological systems?

Homeostatic control mechanisms may be intrinsic (local) or extrinsic (systemic) to the organ:

- **Intrinsic homeostatic mechanisms** occur within the organ itself through autocrine (in which a cell secretes a chemical messenger that acts on that same cell) or paracrine (in which the chemical messenger acts on neighbouring cells) signalling. For example, exercising muscle rapidly consumes O_2, causing the O_2 tension within the muscle to fall. The waste products of this metabolism (K^+, adenosine monophosphate (AMP) and H^+) cause vasodilatation of the blood vessels supplying the muscle, increasing blood flow and therefore O_2 delivery.
- **Extrinsic homeostatic mechanisms** occur at a distant site, involving one of the two major regulatory systems: the nervous system or the endocrine system. The advantage of extrinsic homeostasis is that it allows the coordinated regulation of many organs and feedforward control.

The vast majority of homeostatic mechanisms employed by both the nervous and endocrine systems rely on negative feedback loops (Figure 1.1). Negative feedback involves the measurement of a physiological variable that is then compared with a 'set point', and if the two are different, adjustments are made to correct the variable. Negative feedback loops require:

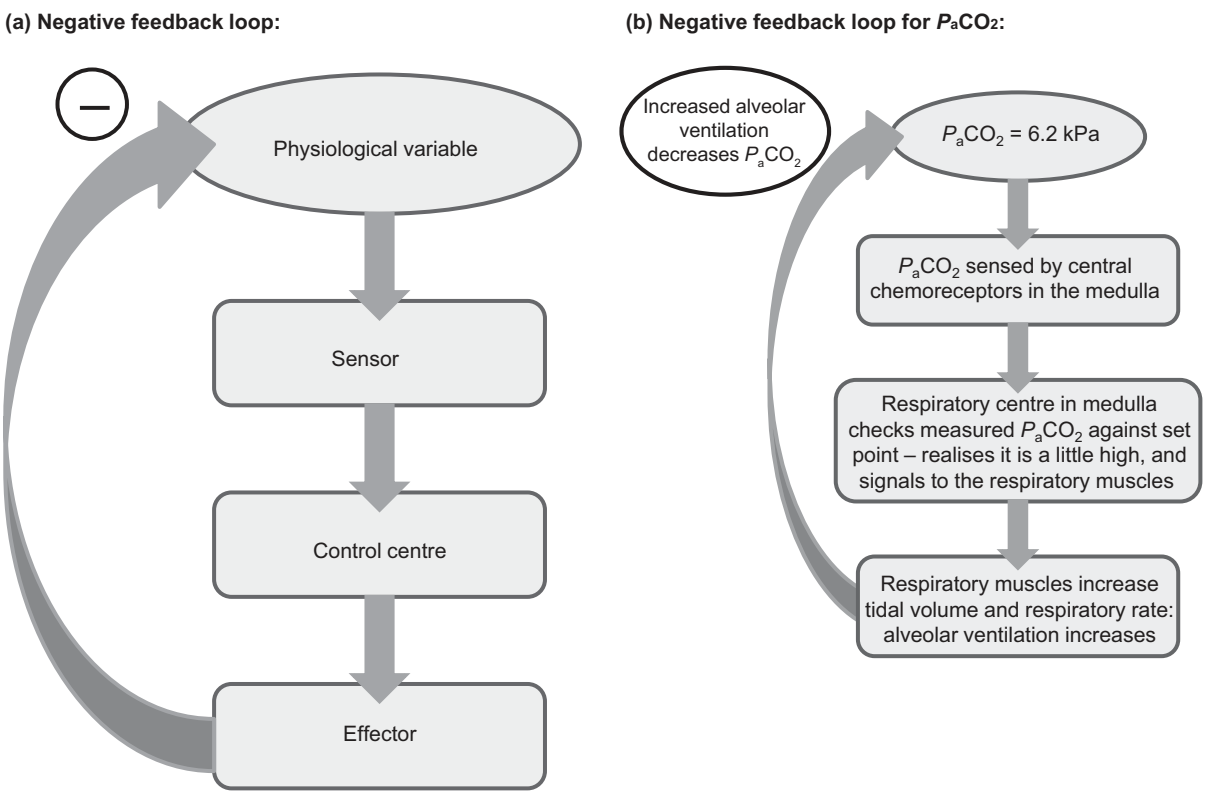

Figure 1.1 (a) Generic negative feedback loop and (b) negative feedback loop for arterial partial pressure of CO_2 (P_aCO_2).

- **Sensors**, which detect a change in the variable. For example, an increase in the arterial partial pressure of CO_2 (P_aCO_2) is sensed by the central chemoreceptors in the medulla oblongata.
- **A control centre**, which receives signals from the sensors, integrates them and issues a response to the effectors. In the case of CO_2, the control centre is the respiratory centre in the medulla oblongata.
- **Effectors**. A physiological system (or systems) is activated to bring the physiological variable back to the set point. In the case of CO_2, the effectors are the muscles of respiration: by increasing alveolar ventilation, P_aCO_2 returns to the 'set point'.

What is positive feedback?

In physiological terms, positive feedback is a means of amplifying a signal: a small increase in a physiological variable triggers a greater and greater increase in that variable (Figure 1.2). Because the body is primarily concerned with homeostasis, negative feedback loops are encountered much more frequently than positive feedback loops, but there are some important physiological examples of positive feedback:

- **Haemostasis**. Following damage to a blood vessel, exposure of a small amount of subendothelium triggers a cascade of events, resulting in the mass production of thrombin.
- **Uterine contractions in labour**. The hormone oxytocin causes uterine contractions during labour. As a result of the contractions, the baby's head descends, stretching the cervix. Cervical stretching triggers the release of more oxytocin, which further augments uterine contractions (Figure 1.2). This cycle continues until the baby is born and the cervix is no longer stretched.
- **Protein digestion in the stomach**. Small amounts of the enzyme pepsin are initially activated by decreased gastric pH. Pepsin then activates more pepsin by proteolytically cleaving its inactive precursor, pepsinogen.
- **Depolarisation phase of the action potential**. Voltage-gated Na^+ channels are opened by depolarisation, which permits Na^+ to enter the cell, which in turn causes depolarisation, opening more channels. This results in rapid membrane depolarisation.
- **Excitation–contraction coupling in the heart**. During systole, the intracellular movement of Ca^{2+} triggers the mass release of Ca^{2+} from the

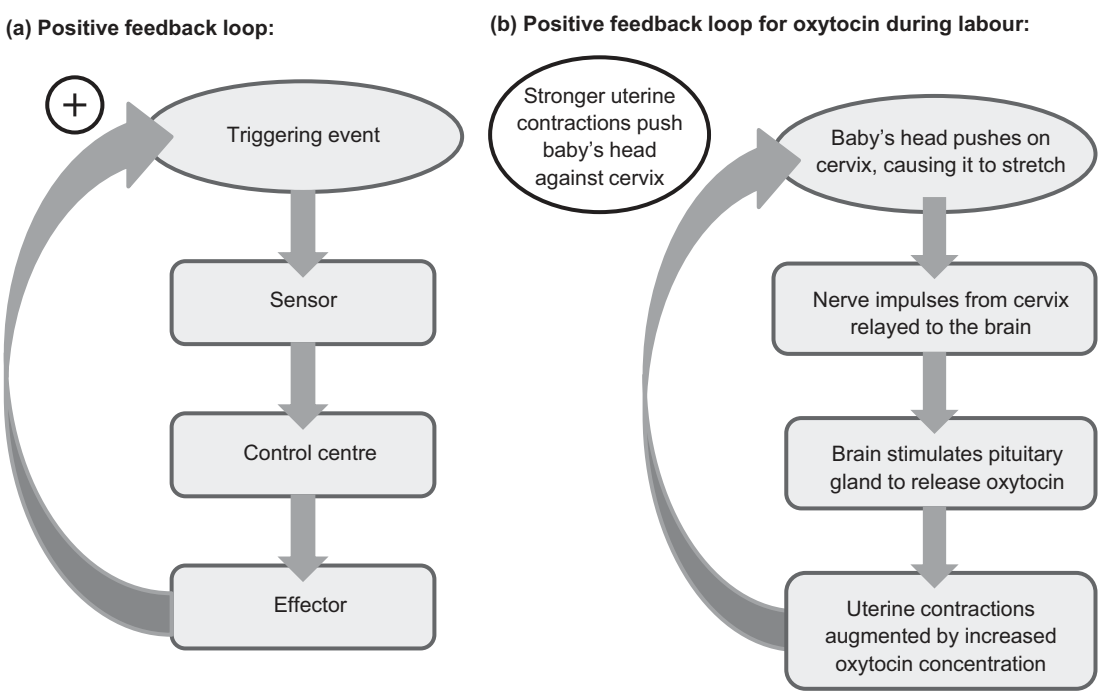

Figure 1.2 (a) Generic positive feedback loop and (b) positive feedback loop for oxytocin during labour.

sarcoplasmic reticulum (an intracellular Ca^{2+} store). This rapidly increases the intracellular Ca^{2+} concentration, facilitating the binding of myosin to actin filaments.

Where positive feedback cycles do exist in physiology, they are usually tightly regulated by a coexisting negative feedback control. For example, in the action potential, voltage-gated Na^{+} channels inactivate after a short period of time, which prevents persistent uncontrolled depolarisation. Under certain pathological situations, positive feedback may appear as an uncontrolled phenomenon. A classic example is the control of blood pressure in decompensated haemorrhage: a fall in arterial blood pressure reduces organ blood flow, resulting in tissue hypoxia. In response, vascular beds vasodilate, resulting in a further reduction in blood pressure. The resulting vicious cycle is potentially fatal.

Further reading

L. S. Costanzo. *Physiology, 6th edition*. Philadelphia, Elsevier, 2018.

W. F. Boron, E. L. Boulpaep. *Medical Physiology, 3rd edition*. Philadelphia, Elsevier, 2017.

B. M. Koeppen, B. A. Stanton. *Berne and Levy Physiology, 7th edition*. Philadelphia, Elsevier, 2017.

Section 1 The Basics

Chapter 2

Cell Components and Function

Describe the basic layout of a cell

Whilst each cell has specialist functions, there are many structural features common to all (Figure 2.1). Each cell has three main parts:

- **The cell surface membrane**, a thin barrier that separates the interior of the cell from the extracellular fluid (ECF). Structurally, the cell membrane is a phospholipid bilayer into which are inserted glycoproteins akin to icebergs floating in the sea. The lipid tails form a hydrophobic barrier that prevents the passage of hydrophilic substances. The charged phosphate-containing heads of the lipids are hydrophilic and thereby form a stable lipid–water interface. The most important function of the cell membrane is to mediate and regulate the passage of substances between the ECF and the intracellular fluid (ICF). Small, gaseous and lipophilic substances may pass through the lipid component of the cell membrane unregulated (see Chapter 4). The transfer of large molecules or charged entities often involves the action of the glycoproteins, either as channels or carriers.
- **The nucleus**, which is the site of the cell's genetic material, made up of deoxyribonucleic acid

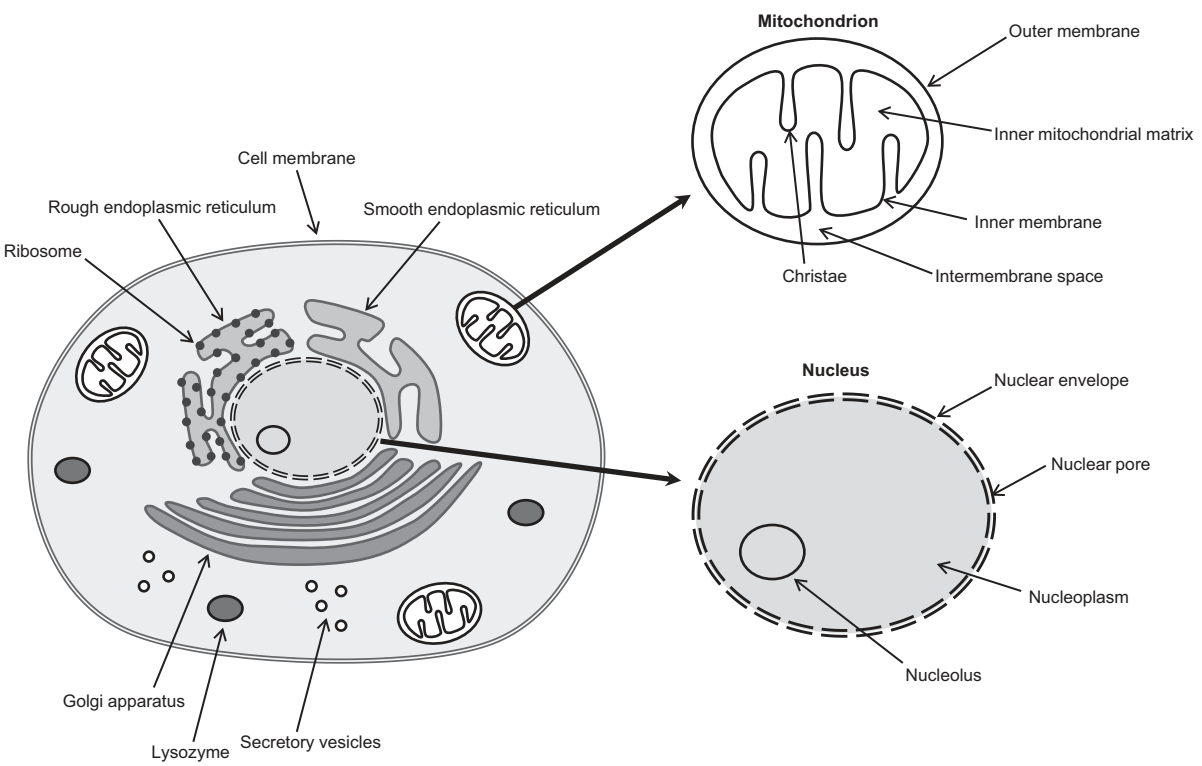

Figure 2.1 Layout of a typical cell.

(DNA). The nucleus is the site of messenger ribonucleic acid (mRNA) synthesis by transcription of DNA and thus coordinates the activities of the cell (see Chapter 3).

- **The cytoplasm**, the portion of the cell interior that is not occupied by the nucleus. The cytoplasm contains the cytosol (a gel-like substance), the cytoskeleton (a protein scaffold that gives the cell shape and support) and a number of organelles (small, discrete structures that each carry out a specific function).

Describe the composition of the cell nucleus

The cell nucleus contains the majority of the cell's genetic material in the form of DNA. The nucleus is the control centre of the cell, regulating the functions of the organelles through gene – and therefore protein – expression. Almost all of the body's cells contain a single nucleus. The exceptions are mature red blood cells (RBCs; which are anuclear), skeletal muscle cells (which are multinuclear) and fused macrophages (which form multinucleated giant cells).

The cell nucleus is usually a spherical structure situated in the middle of the cytoplasm. It comprises:

- **The nuclear envelope**, a double-layered membrane that separates the nucleus from the cytoplasm. The membrane contains holes called 'nuclear pores' that allow the regulated passage of selected molecules from the cytoplasm to the nucleoplasm, as occurs at the cell surface membrane.
- **The nucleoplasm**, a gel-like substance (the nuclear equivalent of the cytoplasm) that surrounds the DNA.
- **The nucleolus**, a densely staining area of the nucleus in which RNA is synthesised. Nucleoli are more plentiful in cells that synthesise large amounts of protein.

The DNA contained within each nucleus contains the individual's 'genetic code', the blueprint from which all body proteins are synthesised (see Chapter 3).

What are the organelles? Describe the major ones

Organelles (literally 'little organs') are permanent, specialised components of the cell, usually enclosed within their own phospholipid bilayer membranes. An organelle is to a cell what an organ is to the body – that is, a functional unit within a cell. Organelles found in the majority of cells are:

- **Mitochondria**, sometimes referred to as the 'cellular power plants', as they generate energy in the form of ATP through aerobic metabolism. Mitochondria are ellipsoid in shape and are larger and more numerous in highly metabolically active cells, such as red skeletal muscle. Unusually, mitochondria contain both an outer and an inner membrane, which creates two compartments, each with a specific function:
  - *Outer mitochondrial membrane*. This is a phospholipid bilayer that encloses the mitochondria, separating it from the cytoplasm. It contains porins, which are transmembrane proteins containing a pore through which solute molecules less than 5 kDa (such as pyruvate, amino acids, short-chain fatty acids) can freely diffuse. Longer-chain fatty acids require the carnitine shuttle (see Chapter 77) to cross the membrane.
  - *Intermembrane space*, between the outer membrane and the inner membrane. As part of aerobic metabolism (see Chapter 77), H^+ ions are pumped into the intermembrane space by the protein complexes of the electron transport chain. The resulting electrochemical gradient is used to synthesise ATP.
  - *Inner mitochondrial membrane*, the site of the electron transport chain. Membrane-bound proteins participate in redox reactions, resulting in the synthesis of ATP.
  - *Inner mitochondrial matrix*, the area bounded by the inner mitochondrial membrane. The matrix contains a large range of enzymes. Many important metabolic processes take place within the matrix, such as the citric acid cycle, fatty acid metabolism and the urea cycle.

  As all cells need to generate ATP to survive, mitochondria are found in all cells of the body (with the exception of RBCs, which gain their ATP from glycolysis alone). Mitochondria also contain a small amount of DNA, suggesting that the mitochondrion may have been a microorganism in its own right prior to its evolutionary incorporation into larger cells. The cytoplasm and hence mitochondria are exclusively

acquired from the mother, which underlies the maternal inheritance of mitochondrial diseases.

- **Endoplasmic reticulum** (ER), the protein- and lipid-synthesising apparatus of the cell. The ER is an extensive network (hence the name) of vesicles and tubules that occupies much of the cytosol. There are two types of ER, which are connected to each other:
  - *Rough ER*, the site of protein synthesis. The 'rough' or granular appearance is due to the presence of ribosomes, the sites where amino acids are assembled together in sequence to form new protein. Protein synthesis is completed by folding the new protein into its three-dimensional conformation. Rough ER is especially prominent in cells that produce a large amount of protein; for example, endocrine and antibody-producing plasma cells.
  - *Smooth ER*, the site of steroid and lipid synthesis. Smooth ER appears 'smooth' because it lacks ribosomes. Smooth ER is especially prevalent in cells with a role in steroid hormone synthesis, such as the cells of the adrenal cortex. In muscle cells, the smooth ER is known as the sarcoplasmic reticulum, an intracellular store of Ca^{2+} that releases Ca^{2+} following muscle cell-membrane depolarisation.
- **Golgi apparatus**, responsible for the modification and packaging of proteins in preparation for their secretion. The Golgi apparatus is a series of tubules stacked alongside the ER. The Golgi apparatus can be thought of as the cell's 'post office': it receives proteins, packs them into envelopes, sorts them by destination and dispatches them. When the Golgi apparatus receives a protein from the ER, it is modified through the addition of carbohydrate or phosphate groups, processes known as glycosylation and phosphorylation respectively. These modified proteins are then sorted and packaged into labelled vesicles into which they can be transported. Thus, the vesicles are transported to other parts of the cell or to the cell membrane for secretion (a process called 'exocytosis').
- **Lysosomes** are found in all cells, but are particularly common in phagocytic cells (macrophages and neutrophils). These organelles contain digestive enzymes, acid and free radical species and they play a role in cell housekeeping (degrading old, malfunctioning or obsolete proteins), programmed cell death (apoptosis) and the destruction of phagocytosed microorganisms.

Further reading

B. Alberts, D. Bray, K. Hopkin, et al. *Essential Cell Biology, 4th edition*. Oxford, Garland Science, 2013.

Section 1 The Basics

Chapter 3

Genetics

In 2003, the completion of the Human Genome Project resulted in the sequencing of every human gene and subsequently heralded the 'age of the genome'. Whilst the knowledge of genetics has revolutionised medicine, the phenotypic significance of most genes remains poorly understood. This will be a major focus of physiological research in the future.

What is a chromosome?

An individual's genetic code is packed into the nucleus of each cell, contained in a condensed structure called chromatin. When the cell is preparing to divide, chromatin organises itself into thread-like structures called chromosomes; each chromosome is essentially a single piece of coiled deoxyribonucleic acid (DNA). In total, each cell contains 46 chromosomes (23 pairs), with the exception of the gamete cells (sperm and egg), which contain only 23 chromosomes.

There are two main types of chromosome:

- **Autosomes**, of which there are 22 pairs.
- **Allosomes** (sex chromosomes), of which there is only one pair, XX or XY.

Both types of chromosome carry DNA, but only the allosomes are responsible for determining an individual's sex.

What is DNA?

DNA is a polymer of four nucleotides in sequence, which is usually bound to a complementary DNA strand and folded into a double helix (Figure 3.1). The DNA strand can be thought of as having two parts:

- **A sugar–phosphate backbone**, made of alternating sugar (deoxyribose) and phosphate groups. The sugars involved in the DNA backbone are pentose carbohydrates, which are produced by the pentose phosphate pathway (PPP; see Chapter 77).
- **Nucleobases**, four different 'bases' whose sequence determines the genetic code:
  - Guanine (G);
  - Adenine (A);
  - Thymine (T);
  - Cytosine (C).

  The nucleobases are often subclassified based on their chemical structure: A and G are purines, whilst T and C are pyrimidines.

The double-helical arrangement of DNA has a number of features:

- **Antiparallel DNA chains**. The two strands of DNA run in antiparallel directions.
- **Matching bases**. The two strands of DNA interlock rather like a jigsaw: a piece with a tab cannot fit alongside another piece with a tab – nucleotide A does will not fit alongside another nucleotide A. The matching pairs (called complementary base pairs) are:
  - C matches G;
  - A matches T.

  Therefore, for the two DNA strands to fit together, the entire sequence of nucleotides of one DNA strand must match the entire sequence of nucleotides of the other strand.
- **Hydrogen bonding**. The two strands of DNA are held together by hydrogen bonds (a particularly strong type of van der Waals interaction) between the matching bases.

What is RNA? How does it differ from DNA?

The amino acid sequence of a protein is encoded by the DNA sequence in the cell nucleus. But when the cell needs to synthesise a protein, the code is anchored in the nucleus, and the protein-manufacturing apparatus (the endoplasmic reticulum (ER) and Golgi

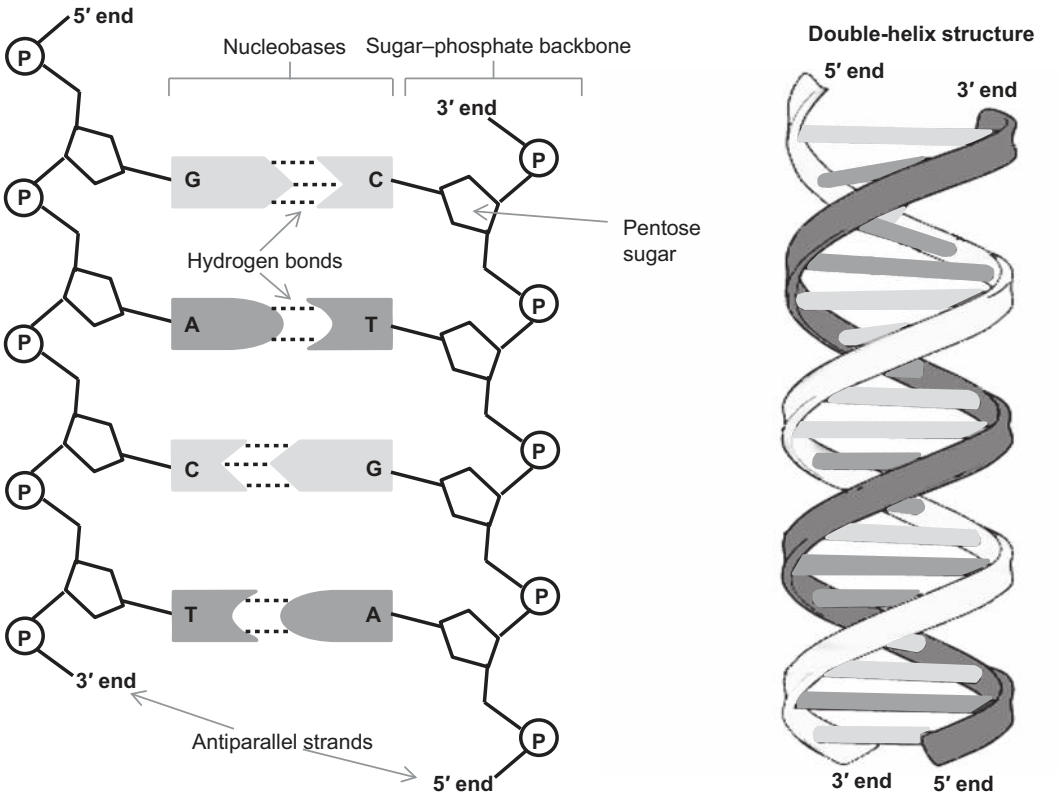

Figure 3.1 Basic structure of DNA.

apparatus; see Chapter 2) is located within the cytoplasm. RNA overcomes this problem: RNA is produced as a copy of the DNA genetic code in the nucleus and is exported to the cytoplasm, where it is used to synthesise protein.

In some ways, RNA is very similar to DNA. RNA has a backbone of alternating sugar and phosphate groups attached to a sequence of nucleobases. However, RNA differs from DNA in a number of ways:

- RNA sugar groups have a hydroxyl group that DNA sugars lack (hence 'deoxy'-ribonucleic acid).
- RNA contains the nucleobase uracil (U) in place of thymine (T).
- RNA usually exists as a single strand; there is no antiparallel strand with which to form a double helix.

There are three major types of RNA:

- **Messenger RNA** (mRNA). In the nucleus, mRNA is synthesised as a copy of a specific section of DNA – this process is called transcription. mRNA then leaves the nucleus and travels to the ribosomes of the rough endoplasmic reticulum (ER), the protein-producing factory of the cell.
- **Transfer RNA** (tRNA). In the cytoplasm, the 20 different types of tRNA gather the 20 different amino acids and transfer them to the ribosome, ready for protein synthesis.
- **Ribosomal RNA** (rRNA). Within the ribosome, rRNA aligns tRNA units (with the respective amino acids attached) in their correct positions along the mRNA sequence. The amino acids are joined together and a complete protein is released.

What is a codon?

A codon is a small piece of mRNA (a triplet of nucleosides) that encodes an individual amino acid. For example, GCA represents the amino acid alanine. tRNA also uses codons; as tRNA must bind to mRNA, the codons are the 'jigsaw match' of the mRNA codons (called anticodons). For example, CGU is the complementary anticodon tRNA sequence to GCA. CGU tRNA therefore binds alanine.