Section 1 The basics

Chapter 1

General organization 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). Many diseases and their systemic effects are caused by a breakdown of homeostasis.

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 which are perhaps of greater interest, it is worth revising some of the basics – the next five 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, Purkinje fibres and blood vessels, working together to propel blood through the vasculature.

How do organs differ from body systems?

The organs of the body are functionally organized 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 which 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 parts 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 semi-autonomous system of nerves which controls the digestive system.
- **Muscular system**, comprising the three different types of muscle: skeletal muscle, cardiac muscle 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**, involving 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: ovaries, testes, uterus and mammary glands.
- **Endocrine system**: endocrine cells, whose function is to produce hormones, are grouped together in glands located around the body. Hormones are chemical signalling molecules carried in the blood which regulate the function of the 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, the 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 and relatively constant environment for the 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 partial pressure of 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.
- **Electrolytes and water** – intracellular water is tightly controlled; cells do not function correctly when they are swollen or shrunken. The movement of sodium (Na^+) controls the movement of water: extracellular Na^+ concentration is therefore tightly controlled. The extracellular concentrations of other electrolytes (for example, the ions of potassium (K^+), calcium (Ca^{2+}) and magnesium (Mg^{2+})) are important in the generation and propagation of action potentials, and are therefore also tightly regulated.
- **Temperature** – all proteins work best within a narrow temperature range; thermoregulation is therefore essential.

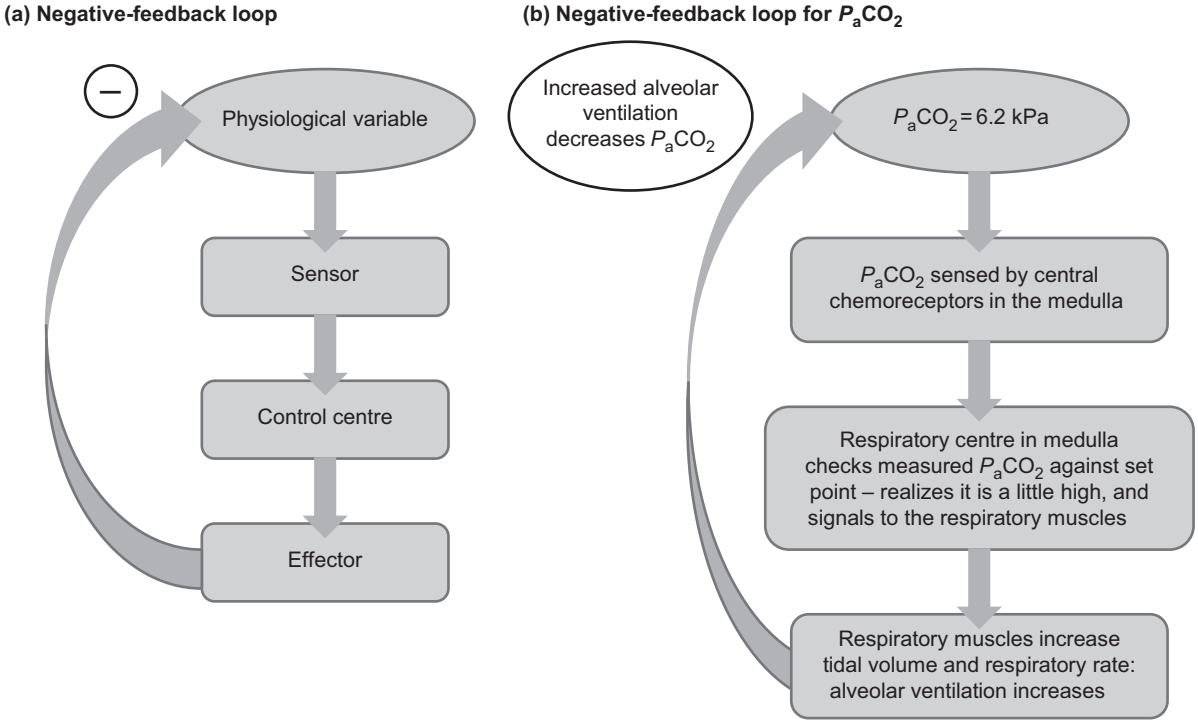

Figure 1.1 (a) Generic negative-feedback loop; (b) negative-feedback loop for P_aCO_2.

Homeostasis is a dynamic phenomenon: usually, physiological mechanisms continually make minor adjustments to the ECF, keeping its composition and temperature constant. Sometimes following a major disturbance, large physiological changes are 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 and the endocrine system. The advantage of extrinsic homeostasis is that it allows the coordinated regulation of many organs.

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:

- **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

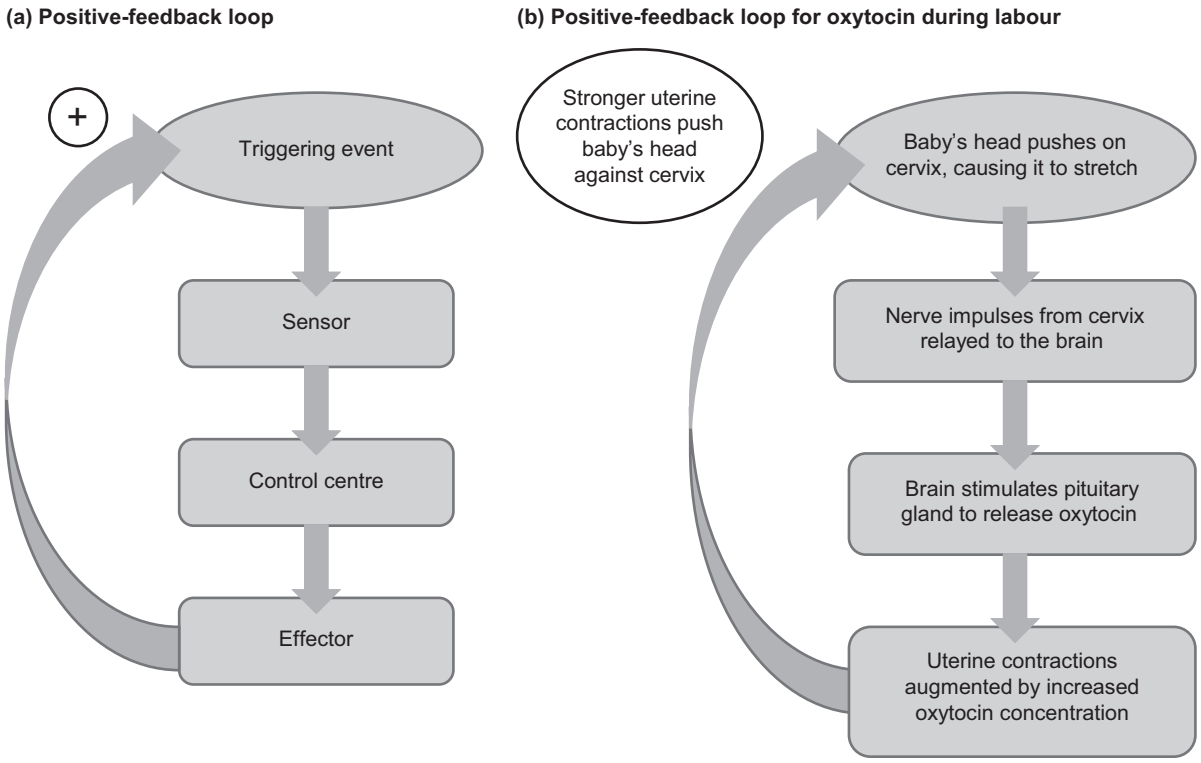

Figure 1.2 (a) Generic positive-feedback loop; (b) positive-feedback loop for oxytocin during labour.

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. This cycle continues until the baby is born and the cervix is no longer stretched.
- **Depolarization phase of the action potential**. Voltage-gated Na^+ channels are opened by depolarization, which permits Na^+ to enter the cell, which in turn causes depolarization, opening more channels. This results in rapid membrane depolarization.
- **Excitation–contraction coupling in the heart**. During systole, the intracellular movement of Ca^{2+} triggers the mass release of Ca^{2+} from the sarcoplasmic reticulum (SR – an intracellular Ca^{2+} store). This rapidly increases the intracellular Ca^{2+} concentration, facilitating the binding of myosin to actin filaments.

In certain disease states, positive feedback may be uncontrolled. A classic example is 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. Death rapidly ensues.

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 membrane**, a thin barrier which separates the interior of the cell from the ECF. Structurally, the cell membrane is a phospholipid bilayer, a hydrophobic barrier that prevents the passage of hydrophilic substances. The most important function of the cell membrane is regulation of the passage of substances between the ECF and the intracellular fluid (ICF). Small, gaseous and lipophilic molecules may pass through unregulated (see Chapter 4).
- **The nucleus**, which is the site of the cell's genetic material. The nucleus is the site of messenger ribonucleic acid (mRNA) expression 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, deoxyribonucleic acid (DNA). The nucleus is the control centre of the cell, regulating the functions of the organelles through gene 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.
- **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 synthesized. Nucleoli are more plentiful in cells which synthesize large amounts of protein.

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

What are the organelles? Describe the major ones

Organelles (literally 'little organ') are permanent, specialized components of the cell, usually enclosed within their own phospholipid bilayer membrane. 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; for example, red muscle. Unusually, mitochondria contain both an outer and an inner membrane, which creates two compartments, each with a specific function:

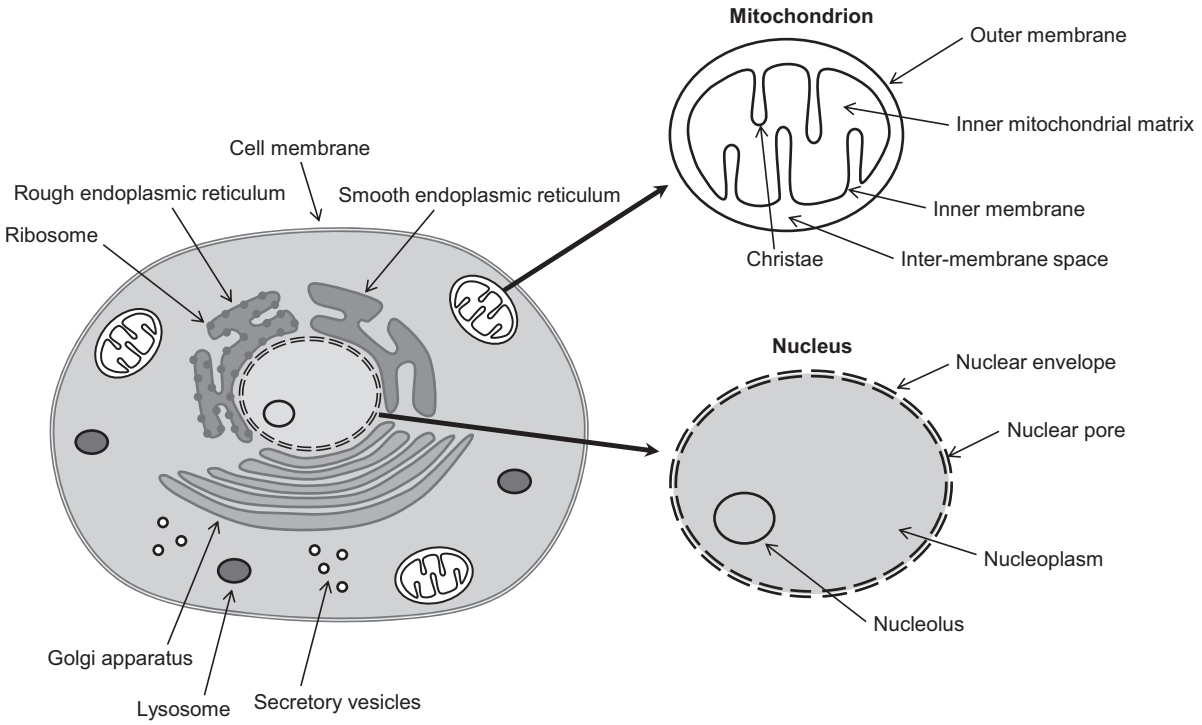

Figure 2.1 Layout of a typical cell.

- *Outer mitochondrial membrane*. This is a phospholipid bilayer that encloses the mitochondria, separating it from the cytoplasm. It contains large holes called porins. Molecules less than 5 kDa (such as pyruvate, amino acids, short-chain fatty acids) can freely diffuse across the membrane through these pores. Longer chain fatty acids require the carnitine shuttle (see Chapter 72) to cross the membrane.
- *Intermembrane space*, the space between the outer membrane and the inner membrane. As part of aerobic metabolism (see Chapter 72), H^+ ions are pumped into the intermembrane space by the protein complexes of the electron transport chain. The resulting electrochemical gradient is used to synthesize 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 the cells of the body (with the exception of RBCs, which gain their ATP from glycolysis alone).

- **Endoplasmic reticulum** (ER), the protein and lipid-synthesizing 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 'conformation', or three-dimensional arrangement. Rough ER is especially prominent

in cells that produce a large amount of protein; for example, 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; for example, the cells of the adrenal cortex. In muscle cells, the smooth ER is known as the SR, an intracellular store of Ca^{2+} that releases Ca^{2+} following muscle cell-membrane depolarization.
- **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 (a sphere for transport). 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 powerful digestive enzymes, acid and free radical species, that 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*, 3rd edition. Garland Publishing, 2009.

Section 1 The basics

Chapter 3

Genetics

Genetics has revolutionized medicine. The human genome project has resulted in a clarification of the code of every human gene. However, their functional significance, the physiology, remains poorly understood.

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 organizes itself into thread-like structures called 'chromosomes'; each chromosome is essentially a single piece of coiled 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 chromosomes 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, 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 72).
- **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 synthesize a protein, the code is

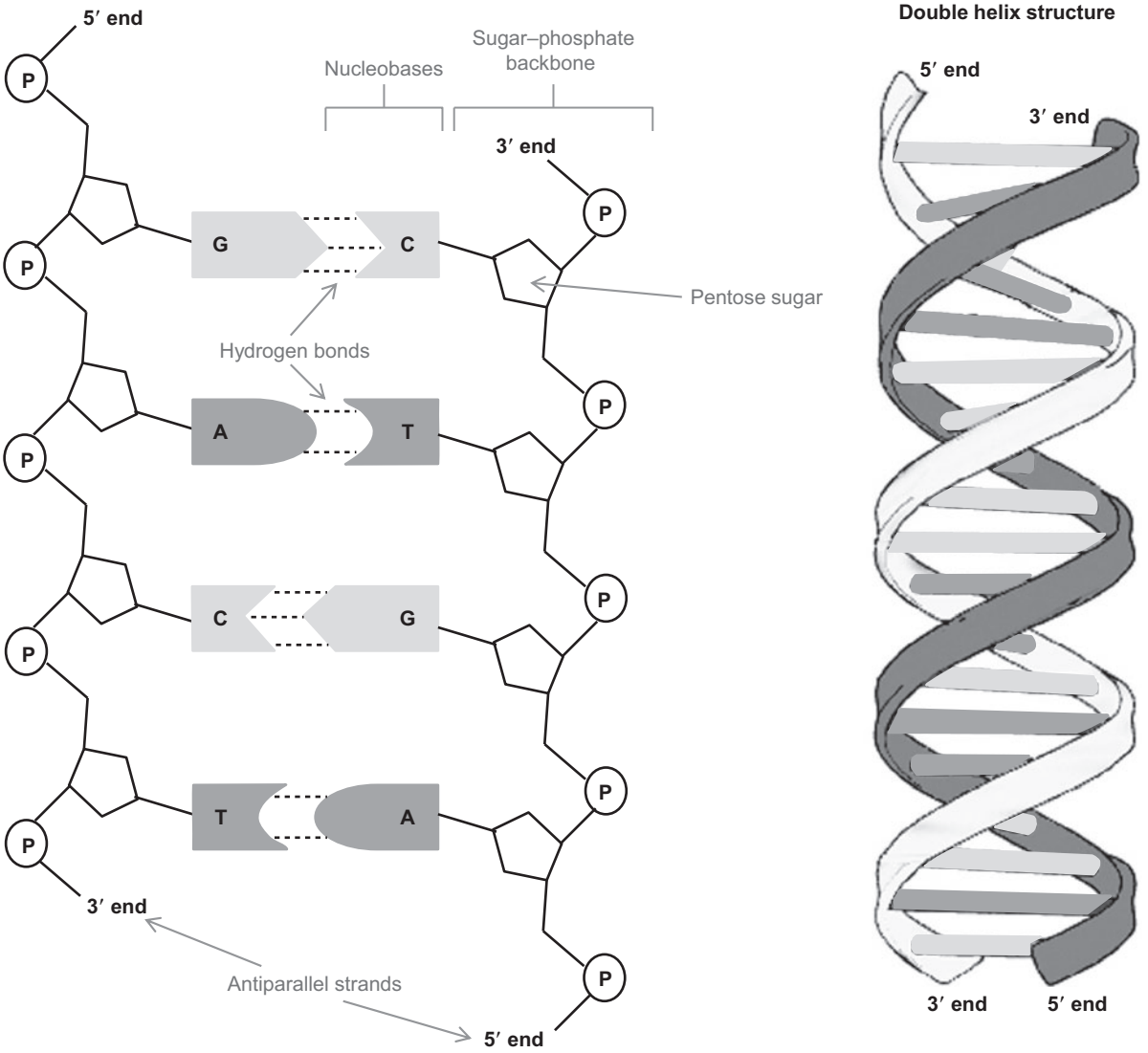

Figure 3.1 Basic structure of DNA.

anchored in the nucleus, and the protein-manufacturing apparatus (the ER and Golgi 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 exported to the cytoplasm, where it is used to synthesize 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 types of RNA:

- **Messenger RNA (mRNA)**. In the nucleus, mRNA is synthesized 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 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.

Clinical relevance: gene mutations

Errors may occur during DNA replication or repair. This abnormal DNA is then used for protein synthesis: transcribed mRNA incorporating the error is exported to the ribosome and translated into an abnormal protein. Common types of error are:

- **Point mutations**, where a single nucleoside is incorrectly copied in the DNA sequence.
- **Deletions**, where one or more nucleosides are accidentally removed from the DNA sequence.
- **Insertions**, where another short sequence of DNA is accidentally inserted within the DNA sequence.

Deletions and insertions are far worse than point mutations as 'frame shift' may occur, with the ensuing DNA encoding a significantly altered protein. The resulting abnormal proteins have clinical consequences, for example:

- **Sickle cell disease** results from a point mutation in the DNA code for the β-chain of haemoglobin (Hb) on chromosome 11. Instead of the codon for the sixth amino acid of the DNA sequence reading GAG (which encodes glutamic acid), it reads GTG (which encodes valine). The substitution of a polar amino acid (glutamic acid) for a non-polar amino acid (valine) causes aggregation of Hb, and thus a shape change of the erythrocyte, under conditions of low O_2 tension.
- **Cystic fibrosis** results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a transmembrane chloride (Cl^-) channel. The abnormal CFTR gene is characterized by reduced membrane Cl^- permeability. The clinical result is thickened secretions that prevent effective clearance by ciliated epithelium, resulting in blockages of small airways (causing pneumonia), pancreatic ducts (which obstructs flow of digestive enzymes) and vas deferens (leading to incomplete development and infertility). There are over 1000 different point mutations described in the CFTR gene. The most common is the ΔF508 mutation, where there is a deletion of three nucleotides (i.e. an entire codon, which encodes phenylalanine, F) at the 508th position.
- **Huntingdon's disease** is a neurodegenerative disorder caused by the insertion of repeated segments of DNA. The codon for the amino acid glutamine (CAG) is repeated multiple times within the Huntingdon gene on chromosome 4. This is known as a trinucleoside repeat disorder.

What are the modes of Mendelian inheritance? Give some examples

Almost all human cells are diploid, as they contain 46 chromosomes (23 pairs). Gamete cells (sperm or egg) are haploid, as they contain 23 single chromosomes. When the gametes fuse, their chromosomes pair to form a new human with 23 pairs of chromosomes. During the formation of the gametes (a process known as meiosis), separation of pairs of chromosomes into single chromosomes is a random process. Each person can therefore theoretically produce 2^{23} genetically different gametes, and each couple can theoretically produce 2^{46} genetically different children!

A 'trait' is a feature (phenotype) of a person encoded by a gene. A trait may be a physical appearance (for example, eye colour), or may be non-visible (for example, a gene encoding a plasma protein). Each unique type of gene is called an allele (for example,