OVERVIEW OF THE BOOK

Anatomy and physiology are two essential sciences of medicine. Anatomy is the understanding of the structure of organisms and their parts, from gross structures such as the bones of a limb to the microstructures of an individual cell. Physiology is the understanding of the normal functions of the human body, which all doctors must understand to treat the diseases that occur when these functions go wrong.

As you progress through this book and into your career in health care, you will repeatedly find that structure is intrinsically related to function and vice versa. It therefore seemed only natural to combine the learning of anatomy and physiology into one concise text.

This book will progress from introducing the building blocks of life and key concepts required to understand anatomy and physiology, to describing the normal structure and function of the human body broken down into a systems-based approach. The aim of this book is to allow the reader to gain a good understanding of the concepts of anatomy and physiology that will be sufficient to pass medical undergraduate exams.

THE CELL

Structure and function

Microstructure of the cell

Protoplasm is the collective name given to the basic components and materials that make up the cell inside the cell membrane. The protoplasm therefore includes both the nucleus and cytoplasm. The protoplasm is formed of:

- Water—the major component of the cell, forming around 80% of the cell.
- Proteins—form around 15% of the cell. The two types are:
  - structural proteins, forming the body of the cell
  - globular proteins that are mainly enzymes.
- Lipids—there are three main types of lipid in the cell:
  - phospholipids—form the outer and intracellular membranous barriers
  - cholesterol—integrated into the outer and intracellular membranous barriers
  - triglycerides—an energy source of the cell.
- Carbohydrates—stored as glycogen and provide energy for the cell
- Electrolytes—essential for cellular reactions (e.g., action potential): potassium ions (K\(^+\)), magnesium ions (Mg\(^{2+}\)), phosphate ions PO\(_4\)^{3−} and bicarbonate ions (HCO\(_3\)^{−}).

Organelles and their function

Within each cell are a number of highly organized physical structures—organelles—each with a specific function (see Fig. 1.1).

Nucleus

The nucleus is present in almost all cells and is the ‘control centre’ (see Fig. 1.2). It stores and transmits information, in the form of DNA, to the next generation. The genes within the cell's nucleus determine the types of protein made by the cell during its lifetime.
**Introduction**

**Nuclear membrane and envelope**
These two membranes surround the nucleus, containing pores that regulate the entry and exit of molecules.

**Nucleoli**
The nucleoli are highly coiled structures within the nucleus of the cell. They contain ribonucleic acid (RNA) and protein components. The nucleoli are not enveloped by a nuclear membrane.

**Ribosomes**
Ribosomes are large organelles, composed of about 70 proteins and several RNA molecules, that serve as the site of protein synthesis. They include two subunits of different sizes, 30 s and 50 s, the former being smaller.

Proteins are synthesized from amino acid building blocks, using a genetic template derived from DNA that is carried from the nucleus to the ribosomes as RNA messenger molecules. The proteins are then released into the cytosol (fluid part of the cell's cytoplasm) or transferred to other organelles via the Golgi apparatus (see later).

**Endoplasmic reticulum**
The endoplasmic reticulum (ER) forms a network of membranes within the cell. There are two types:

1. Rough (or granular) ER carries surface ribosomes. Proteins are synthesized on the attached ribosomes, enter the lumen of the ER and are subsequently distributed within the cell or secreted to other cells.
2. Smooth (or agranular) ER does not have ribosomes on its surface. This type of ER synthesizes fatty acids and regulates cellular levels of calcium (Ca\(^{2+}\)), which controls many of the cell's activities.

**Golgi apparatus**
These membranous sacs sort and modify proteins arriving from the rough ER, packaging them into vesicles before sending them to other organelles with the cell, or secreting them into the extracellular space.

**Mitochondria**
The mitochondria function to make energy available to cells in the form of adenosine triphosphate (ATP). They are double-membraned, elongated structures with a smooth outer membrane and an inner membrane that is folded into tubes (cristae) designed to increase surface area. The cristae contain DNA for mitochondrial protein synthesis.

**Lysosomes**
Lysosomes are single-membraned organelles that contain highly acidic digestive enzymes that break down bacteria, cell debris and dead organelles.

**Peroxisomes**
These single-membraned organelles destroy the highly toxic compound hydrogen peroxide (H\(_2\)O\(_2\)), a byproduct of certain cell reactions. Additionally, the peroxisomes in the liver and kidney produce H\(_2\)O\(_2\) and use it to detoxify various ingested molecules.

**Filaments**
A cell's shape is maintained by a cytoskeleton. This cytoskeleton is formed of protein filaments in the cytoplasm, which also act to aid cell movement.

**Energy production in the cell**
Cells use oxygen to break down macromolecules from food (carbohydrates to glucose, proteins to amino acids and fats to fatty acids) and form the compound ATP. ATP is the universal source of energy for all intracellular metabolic reactions.

**Structure of adenosine triphosphate**
ATP is a nucleotide containing the base adenine, the pentose sugar ribose and three phosphate molecules (Fig. 1.3). The end two phosphate molecules are connected by a high-energy bond. When broken, each liberates about 30.6 kJ/mol of energy, roughly the same as the energy in a single peanut. When the first covalent bond is hydrolysed, adenosine diphosphate (ADP) is produced; loss of another phosphate molecule forms adenosine monophosphate (AMP). Energy is released when each bond is hydrolysed.

**Formation of adenosine triphosphate**
The majority (95%) of ATP is formed in the mitochondrial matrix. One molecule of glucose produces a net of 38 molecules of ATP during aerobic respiration. Other substrates can produce more ATP than carbohydrates. For example, 1 g of fat can produce twice as much ATP as 1 g of carbohydrate. Protein is used as a substrate only when all the carbohydrate and fat reserves have been utilized, i.e., in a starvation state. There are four stages of ATP production:

- **Glycolysis**—Glycolysis is the formation of pyruvic acid (PA). Glucose, fatty acids and amino acids enter the cell cytoplasm and are converted to PA, releasing energy for the formation of two molecules of ATP (Fig. 1.4).

- **Conversion of pyruvic acid to acetyl coenzyme A**—PA enters the mitochondrial matrix, where the enzyme pyruvate dehydrogenase changes transform it into acetyl coenzyme A (acetyl-CoA) (Fig. 1.4).

- **Krebs cycle**—Krebs cycle is sometimes called the citric acid or tricarboxylic acid cycle. Acetyl-CoA enters a series of chemical reactions in the mitochondrial matrix in which it is split into acetyl and CoA, as shown in Fig. 1.5. The acetyl portion enters the cycle and the CoA is used in the formation of more acetyl-CoA. During the Krebs cycle, for every glucose molecule:

![Fig. 1.3 Structure of adenosine triphosphate.](image-url)
The cell

• seven molecules of water are added
• 16 hydrogen atoms and four molecules of carbon dioxide (CO₂) are released
• two molecules of ATP are formed.

The CO₂ diffuses out of the mitochondria and is expired as a waste gas from the lungs.

**Oxidative phosphorylation (electron transport chain)—**The largest amount of ATP formation occurs during oxidative phosphorylation (remember glycolysis and the Krebs cycle only contribute 4 of the 38 ATP molecules produced) (Fig. 1.6). There are seven main steps:

1. Hydrogen is split into a hydrogen ion (H⁺) and an electron.
2. The electron enters the electron transport chain on the inner mitochondrial membrane.
3. The electron is transported from electron acceptor to electron acceptor (i.e., flavoproteins and cytochromes B, C and A) until it reaches cytochrome A₃ (cytochrome oxidase).
4. Cytochrome oxidase helps form ionic oxygen, which combines with the H⁺ to form water.
5. The large amounts of energy that are released during the electron transport chain happen because the electron transport pumps H⁺ from the inner matrix of the mitochondrion to the space between the inner and outer membrane (outer chamber).
6. The high concentration of H⁺ in the outer chamber flows over the enzyme ATPase, which is attached to the inner mitochondrial membrane. This energy from the H⁺ flow is used by ATPase to convert ADP to ATP.

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**Fig. 1.4 Glycolysis and conversion of pyruvic acid to acetyl coenzyme (acetyl-CoA).** ADP, Adenosine diphosphate; ATP, adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogen.

**Fig. 1.5 Krebs cycle.** ADP, Adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; FAD, flavin adenine dinucleotide; FADH₂, flavin adenine dinucleotide-reduced form; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide-reduced form; Pi, phosphate.
Introduction

Fig. 1.6 Oxidative phosphorylation, the electron transfer chain and the citric acid chain. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; Cyt c, cytochrome C; FAD, flavin adenine dinucleotide; FADH, flavin adenine dinucleotide–reduced form; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide–reduced form.

7. ATP is transferred by facilitated diffusion from the mitochondrion to the cell cytoplasm.

**Functions of adenosine triphosphate**
The functions of ATP are:
- the membrane transport of ions
- synthesis of chemical compounds, e.g., protein synthesis on ribosomes, formation of cholesterol, phospholipids, etc.
- mechanical work, e.g., muscle contraction, ciliary function.

**Genetic control of the cell**
Genes control cell function. They determine what proteins both enzymes and structural proteins are produced within the cell. Every gene is made of DNA, which regulates RNA to dictate the formation of the particular proteins.

**DNA**
DNA is a double helical chain composed of:
- phosphoric acid, part of the backbone of the DNA molecule
- a deoxyribose sugar, part of the backbone of the DNA molecule
- four nitrogenous bases:
  - two purines: adenine (A) and guanine (G)
  - two pyrimidines: thymine (T) and cytosine (C).

The bases connect the two DNA strands, to form the double helical chain, via hydrogen bonds. Importantly:
- Adenine can bind only to thymine
- Guanine can bind only to cytosine.

When DNA is split into its individual strands, the exposed bases provide the genetic code. Every three successive bases (triplet) codes for one amino acid. Examples of each codon composition to form an amino acid can be found in the e-book version. Chains of amino acids form proteins. The four bases can be arranged in 64 different three-letter combinations (4 × 4 × 4 = 64). As only 21 different amino acids are synthesized in the body, some amino acids are represented by more than one codon. There are also codons for start and stop signals, which indicate that the end of a genetic message has been reached.

The remainder of the DNA that does not code for proteins has been classed as redundant DNA. However, new research is challenging this idea and hinting at the possibility of this ‘junk DNA’ having important functions.

**HINTS AND TIPS**
One amino acid is coded for by a sequence of three bases (a triplet).

*Super-coiling*—DNA is a very long molecule and must be packaged very well to fit into a cell. The double helix gives it a natural twist but further twisting packs it even tighter; this called is super-coiling.

**Ribonucleic acid**
For proteins to be produced, the DNA code must be transferred to an RNA code. As DNA is in the cell nucleus and
The majority of cell function occurs in the cytoplasm, the RNA acts as an intermediary to these processes.

RNA is identical to DNA with two exceptions:
1. Deoxyribose is replaced with ribose.
2. Thymine is replaced by the pyrimidine uracil (which will only bind to adenine).

There are three types of RNA:
1. Messenger RNA (mRNA): carries the genetic code from the nucleus to the cytoplasm.
2. Transfer RNA (tRNA): transfers amino acids to the ribosomes to manufacture proteins.
3. Ribosomal RNA (rRNA): where the protein molecules are actually assembled.

**HINTS AND TIPS**

Remember that RNA is identical to DNA apart from the fact that deoxyribose is replaced with ribose and thymine is replaced by uracil.

**Protein synthesis**

There are four key steps to protein production: transcription, splicing, translation and posttranslation modifications.

**Transcription: messenger RNA synthesis**

Transcription occurs following this sequence:
1. RNA polymerase attaches to the DNA promoter and moves along the helix (Fig. 1.7).
2. The DNA double helix unwinds and the strands separate.
3. RNA nucleotides attach—via hydrogen bonds—to the exposed bases on one DNA strand.
4. Covalent bonds are formed between the RNA nucleotide phosphate and ribose, producing mRNA.
5. When RNA polymerase comes across a DNA stop signal it breaks away from the DNA strand. The stop signal indicates that the mRNA is complete.
6. The hydrogen bonds holding the mRNA to the DNA strand break and the mRNA enters the nucleoplasm.

A three-base sequence in the mRNA transcript is known as a codon and is complementary to the three-base sequence in DNA (triplet).

**Splicing**

The primary mRNA transcript contains specific segments (exons) that code for amino acids; the remainder of the transcript does not code for any protein (introns). Splicing removes the introns and combines the remaining exons. This results in the final mRNA.

**Translation**

During translation:
1. The mRNA passes from the cell nucleus to the cytoplasm.
2. rRNA binds to one end of the mRNA.
3. The three-base anticodon in an amino acid–tRNA complex pairs with its corresponding codon on the mRNA.
4. The amino acid on the tRNA forms a covalent bond with the adjacent amino acid to elongate the polypeptide chain.
5. The tRNA is liberated from the bound amino acid and released.
6. The ribosome travels one codon along the mRNA and the procedure repeats until a termination sequence is reached.

*Fig. 1.7 DNA synthesis. mRNA, messenger ribonucleic acid; RNA, ribonucleic acid.*
Introduction

Posttranslational modifications
When the polypeptide chain has been assembled, various chemical groups might be attached and/or the protein might be split into several smaller side chains (Fig. 1.8).

Cell movement
There are two types of cell movement:

1. Amoeboid movement: a protrusion from the cell—a pseudopodium—attaches to the substrate across which the cell is moving. The remainder of the cell body drags itself towards the pseudopodium (e.g., white blood cells through tissues). Amoeboid movement is initiated by chemical substances produced by the tissues (chemotaxis). The cells can move towards (positive chemotaxis) or away from (negative chemotaxis) an area of chemotactic substances.

2. Ciliary movement: whip-like movements of cilia propel the cell. Such movement occurs on the inside surfaces of the respiratory airways and fallopian tubes. In the respiratory airways, ciliary movements propel mucus towards the trachea; in the fallopian tubes, they propel the ovum towards the uterine cavity.

Membrane physiology
The cell membrane consists of three components: lipids, proteins, and carbohydrates (Fig. 1.9).

Cell membranes
Lipids
Phospholipid molecules form a lipid bilayer, which envelops the entire cell and organelle. One part of the phospholipid molecule is hydrophilic (water loving) and the other is hydrophobic (water hating). This results in the molecules lining up with the hydrophobic portions back to back, avoiding contact with water. Because there is no chemical bond linking the phospholipids to each other, they are free to move independently. This is sometimes termed ‘the fluid mosaic model’ and permits cells to change considerably without disruption to their structure.

The phospholipid bilayer regulates the movement of certain substances into and out of the cell. It prevents the entry of water-soluble substances (such as urea, glucose and ions) and allows the passage of fat-soluble substances (alcohol, oxygen and carbon dioxide).

Cholesterol, a steroid, inserts itself in the membrane with the same orientation as the phospholipid molecules. It functions to immobilize the first few hydrocarbon groups of the phospholipid molecules. If cholesterol was absent (as in a bacterium), a cell would need a cell wall. It also prevents crystallization of hydrocarbons and the membrane from shifting.

Proteins
There are two types of protein in the cell membrane:

1. Integral proteins: these extend all the way through the bilayer (i.e., are transmembranous) and form structural
channels through which ions and other water-soluble substances can permeate. They also form receptors for enzyme binding.

2. Peripheral proteins: these are located on the inside of the membrane and form enzymes.

**Carbohydrates (glycalyx)**
The carbohydrates in the cell membrane combine with proteins (to form glycoproteins) and lipids (to form glycolipids) that protrude outside the cell. They function to:
- repel other negative objects (because of their negative charge)
- attach to other cells so they can identify them or be identified
- provide binding sites for hormones.

Cells involved in immunity use the glycocalyx for recognition of host/foreign cells.

**Membranous junctions**
Adjacent cells can be joined together by different types of junction: tight junctions, gap junctions and spot desmosomes (Fig. 1.10).

**Tight junctions**
These junctions form an impermeable bond between adjacent cells. They direct the passage of substrates through the cells by preventing passage between them. They are found in the epithelial cell layer lining the small intestine and in the blood–brain barrier in the cerebral vessels.

**Gap junctions**
These are protein tunnels which form between adjacent cells. They allow for the passage of small molecules and/or ions between cells. Cells connected by gap junctions are capable of working synchronously as a unit, instead of individually. In the heart, gap junctions allow the atria and the ventricles to contract in sequence.

**Spot desmosomes**
These large filamentous adhesions between nearby cells serve as mechanical reinforcements. Tissues under stress, e.g., cardiac muscle, are connected by spot desmosomes.

**Transport**
The selective permeability properties of the cell membrane play an important role in cell function by controlling the entry into cells of small molecules and ions. Diffusion across biological membranes can be divided broadly into passive (diffusion) and active forms of transport.

**Passive (diffusion)**
The movement of small molecules and ions is dictated by their electrochemical concentration gradient. They move from high to low concentrations, or to neutralize a charge imbalance between two zones.

Size, electrical charge, shape and weight affect the rate of diffusion. If a substance is lipid soluble, diffusion across the cell membrane (which is a lipid bilayer) will occur more readily. However, with polar substances, diffusion rates through water-filled ion channels are greater.

If the solutions either side of a membrane comprise only diffusible ions, diffusion occurs until equilibrium is reached and the ion distribution on each side is the same. At this point, this is the value of diffusible anions $\times$ diffusible cations.

There are several different types of diffusion (Fig. 1.11):

Fig. 1.10 Membranous junctions, showing a tight junction and desmosomes.

Fig. 1.11 Types of diffusion. (A) Simple diffusion. (B) Diffusion through channels: proteins and charged molecules are usually pulled through channels by water. (C) Facilitated diffusion: molecules (e.g., glucose) bind to protein, triggering a charge in protein shape. This transports the glucose molecules across the membrane.
Simple diffusion—In simple diffusion, movement of molecules occurs through a membrane opening. This opening either passes through the lipid bilayer (allowing the passage of lipid-soluble substances) or takes the form of protein channels, e.g., sodium and potassium (Na\(^+\) and K\(^+\)) channels, through which water- and lipid-insoluble molecules pass. The protein channels regulate their permeability via a gating system.

Voltage gating—The electrical potential across the cell membrane influences the entry of certain substances. For example, during an action potential, an impulse passes down a neuron; the resulting reduction in the voltage causes sodium channels in the adjacent portion of the membrane to open. This allows the influx of sodium ions (Na\(^+\)) into the neuron by diffusion through the channel and hence the continuation of the nerve impulse.

Chemical gating—Binding of another molecule permits entry. For example, acetylcholine opens the acetylcholine channel, through which sodium ions diffuse, which allows nerve signals to propagate.

Facilitated diffusion—A carrier protein is required to transport a substance across the membrane. A good example is found in the liver cells, which control the concentration of glucose in the blood. Liver cells store excess glucose as glycogen when blood sugar levels are high. The breakdown of glycogen is closely controlled by hormones. The breakdown products of glycogen are impermeable to the liver cell membrane and so a transport protein, which functions by facilitated diffusion, allows the movement of glucose.

Nonionic diffusion—Although weak acids and bases cross cell membranes with difficulty in their ionic and dissociated forms, some have increased solubility in their undissociated form. Diffusion of such undissociated substances is called nonionic diffusion; it occurs in the kidneys and gastrointestinal tract.

Active transport
By using ATP, this energy-dependent system transports ions or molecules across a membrane against an electrochemical gradient. It can thus maintain the concentration of a substance against its natural diffusion gradient, e.g., the K\(^+\) concentration is high intracellularly and low extracellularly.

Active transport depends on two types of transmembrane carrier protein, which derive their energy sources in different ways:

- Primary transmembrane carrier proteins: receive their energy from ATP. They transport many different ions (e.g., Na\(^+\), K\(^+\), Ca\(^{2+}\) into and out of muscle cells; H\(^+\) and K\(^+\) into and out of the gastric glands). The most common type is the Na\(^+/\)K\(^+\) pump system, hereafter referred to as Na\(^+/\)K\(^+\)-ATPase, which is present in all cells of the body. This pumps Na\(^+\) out of the cell, K\(^+\) into the cell and maintains the electrical potential across the cell membrane.
- Secondary transmembrane carrier proteins: energy is generated from differences in ionic concentration between two sides of a membrane.

HINTS AND TIPS
As the result of the Na\(^+/\)K\(^+\)-ATPase, K\(^+\) is predominantly intracellular and Na\(^+\) is predominantly extracellular.

Cotransport
This term refers to transport across a cell membrane when a carrier is occupied by two substances simultaneously. There are two types:

- Antiport: a membrane carrier creates a gradient for the movement of one substance in one direction and another substance in the opposite direction.
- Symport: two substances move in the same direction by means of a common carrier.

Osmosis
This is the diffusion of water, across a semipermeable membrane (i.e., a membrane that allows the passage of certain, small molecules but which prevents the passage of large molecules) (Fig. 1.12). The water molecules diffuse from a region of higher water concentration to lower water concentration. The pressure at which water is drawn from the weak solution into the more concentrated solution is known as the osmotic pressure; the higher the solute concentration, the higher the osmotic pressure. Note: a low water concentration implies a high solute concentration.

Solute particles are seen as the osmotically active particles, the total concentration of which, regardless of exact
composition, is referred to as osmolarity, which is expressed in osmoles (Osm):

\[ 1 \text{ Osm} = 1 \text{ mole} \times (6.02 \times 10^{23}) \text{ solute particles.} \]

\[ 1 \text{ mOsm} = 1/1000 \text{ mole of solute particles.} \]

The nature of the solute will dictate the osmolarity. Dissolving 1 mole of a nonionizing compound, such as glucose, in water will give a solution of 1 Osm. However, dissolving 1 mole of sodium chloride (NaCl), which dissociates into Na\(^+\) and Cl\(^-\), will give a solution of 2 Osm.

**Osmolarity**—Osmolarity (mOsm/L) is defined as the number of osmoles per unit volume.

This can be illustrated by putting \( x \) Osm of solute into a beaker, then adding water to make up 1 L of solution. Clearly, the water added would be less than 1 L.

**Osmolality**—Osmolality (mOsm/kg) is defined as the number of osmoles per unit weight.

Normally, osmolality is about the same as osmolarity. The normal value for plasma is 280–295 mOsm/kg. At these normal plasma values, there is no net water movement. Lower or higher values will cause cell swelling (with danger of lysis/bursting) or shrinking, respectively.

The solutions inside and outside cells contain water; the cell wall is a semipermeable membrane. Thus osmosis applies to the movement of water molecules into and out of the cell.

- If the solution outside the cell contains a **higher** concentration of water molecules than the interior of the cell (i.e., the external solution is hypertonic for water), then water molecules will diffuse into the cell. This will cause the cell to swell and lyse (break).
- If the solution outside the cell contains a **lower** concentration of water molecules than the inside (i.e., the external solution is hypotonic for water), then water will diffuse out of the cell. This will cause the cell to shrink (crenate).
- If the concentrations of water molecules in the intracellular and extracellular concentrations are identical (isotonic), there is no net movement of water.

**LEVELS OF ORGANIZATION IN THE BODY**

The human body, being a multicellular organism, has a wide variety of cell types. A group of similar cells that work together to perform a specific task is called a tissue, the largest of which is the skin. When two or more of these tissues are organized together to perform a particular function, they are referred to as an organ. Grouping of these organs related to function make up the different organ systems (Fig. 1.13).

The chapters of this book have been largely arranged into the organ systems.

**Skin**

The skin completely covers the body surface. The functions of the skin include:

- protection from ultraviolet light, mechanical, chemical and thermal insults
- sensation of pain, temperature, touch and pressure
- thermoregulation
- metabolic functions, e.g., vitamin D synthesis.

The skin is composed of the following layers (Fig. 1.14):

- The epidermis is the outermost layer of the skin. It is stratified squamous keratinized epithelium, which forms a protective waterproof barrier. The epidermis is avascular, and is continually shed and replaced.
- The dermis lies deep to and supports the epidermis. It is composed largely of interlacing collagen fibres, with some elastic fibres, giving the skin strength and elasticity. It also contains nerve endings (detecting pain, touch, pressure and temperature), blood vessels and glands. It contains mast cells, lymphocytes and macrophages, which play a role in immunity. It is the site of inflammation, growth and repair.
- The hypodermis, or superficial fascia, lies deep to the dermis. It is composed of loose areolar tissue.

![Fig. 1.13 An example of levels of organization in the body.](image)
**Introduction**

(subcutaneous fatty tissue), which provides thermal insulation and protection for underlying structures.

The skin appendages include:

- **Hair follicles** (containing hair shafts)—tubular invaginations of the epidermis, into the dermis, lined by stratified squamous epithelium. At the base of each follicle, cell division, growth and maturation results in formation of a column of dead, keratinized cells (hair shaft) that extrude from the follicle.

- **Sebaceous glands**—associated with the hair follicles. They produce sebum, which lubricates the skin and hair and creates a protective bactericidal layer.

- **Sweat glands**—produce sweat, which plays a role in thermoregulation.

- **Nails**—located at the distal end of the dorsal surface of each digit. They are composed of a nail plate and a nail bed. The nail plate is composed of tightly packed keratinized cells.

**CLINICAL NOTES**

**MALIGNANT MELANOMA**

Melanocytes are melanin-producing cells (melanin determines skin colour), located in the epidermis. A malignant melanoma is a tumour of the melanocytes. Women most commonly develop melanoma of the lower limb, men on the trunk. Early signs of melanoma can be summarized as follows:

- **Asymmetry**
- **Border** (irregular)
- **Colour** (variegated)

**PHYSIOLOGY OF THE BLOOD AND BODY FLUIDS**

**Overview of body fluids and fluid compartments**

The major component of the human body is water, which accounts for 63% of an adult male. In descending order of relative percentage composition, the remaining is comprised of proteins and related substances, fat and minerals. An increased body fat content is associated with ageing, obesity and being female. Consequently, the percentage of water in females falls to 52%. Dissolved within this water are carbon dioxide (CO₂), nutrients, proteins and charged particles (ions).

Fluid in the body is distributed into different compartments (Fig. 1.15):

- **Intracellular fluid (ICF):** the fluid inside the cells (60%).
- **Extracellular fluid (ECF):** all fluids outside cells (40%), comprising:
  - 75% interstitial fluid (ISF): the ECF that bathes the cells and lies outside the vascular system
  - 25% plasma: the noncellular part of the blood (within the vascular system).

Interstitial fluid and plasma are in a state of continual exchange via pores in the highly permeable capillary membrane. The two fluids therefore have a similar composition, with the exception of large proteins, which are trapped within the capillaries in the vascular system.
Transcellular fluid is another small compartment of body fluid. Although it can be viewed as a specialized type of ECF, their compositions vary greatly.

**Fluid movement between body compartments**

The body's fluid compartments are normally in osmotic equilibrium, although they contain different amounts of various ions:

- ICF: $K^+$ contributes ~50% of osmolality
- ISF and plasma: $Na^+$ and $Cl^-$ are responsible for ~80% of osmolality.

**Plasma and interstitial fluid exchange**

In the capillaries, the osmolality of plasma is approximately 1 mOsm/L greater than the osmolality of ICF and of ISF. Much of this is due to plasma proteins. This osmotic pressure draws fluid into the capillaries and is counterbalanced by the capillary hydrostatic pressure, which is 20 mmHg greater than that of the ISF.

The exchange of water and ions occurs across the thin capillary wall, which is composed of endothelial cells. Substances can pass via:

- vesicular transport (not discussed further but requires energy expenditure)
- junctions between endothelial cells
- fenestrations (when present).

As well as this vesicular transport, simple diffusion and filtration are responsible for transport (see previously). Simple diffusion is responsible for 90% of exchange, relating mainly to net efflux of $O_2$ and glucose from plasma and influx of $CO_2$ into the plasma. Filtration is responsible for 10% of exchange. The rate of filtration relies on Starling forces (Fig. 1.16), which are derived from two aspects of the ISF and capillary fluid:

- Oncotic pressure, which resists filtration.
- Hydrostatic pressure, which favours filtration.

**Hydrostatic pressure**

The following determine vessel hydrostatic pressure:

- arteriolar blood pressure
- venous blood pressure
- arteriolar resistance, on which depends the extent to which blood pressure is transferred along the capillary.

Hydrostatic pressure is maximal at the arteriolar end of the capillary (32 mmHg), where it exceeds oncotic pressure (which is 25 mmHg) and thus favours filtration. At the venous end, fluid reentry into the capillary is favoured; hydrostatic pressure (12 mmHg) is lower than oncotic pressure (25 mmHg).

**Exchange between interstitial fluid and the lymphatic vessels**

The overall efflux of fluid from the capillaries would be expected to cause an increase in ISF hydrostatic pressure. However, this fluid, along with plasma proteins lost from the vascular space, enters a network of lymphatic channels, which is present in all organs and tissues. The fluid is returned to the circulatory system when the lymphatic system empties into the venous system via the thoracic duct in the neck. Normal lymph flow is 2–4 L per day.

**Fluid and ion movement between the body and the external environment**

A careful balancing of fluid intake against output maintains the composition of body fluids (Fig. 1.17). Daily water intake can be from two sources:
Introduction

- Ingestion of fluids as liquids and as water in food: 2000 mL.
- Oxidative metabolism of food: 400 mL.

Daily water loss occurs by several different mechanisms:
- Lung—water evaporates continuously from the respiratory tract. The amount varies with climate and humidity.
- Skin—diffusion through the skin occurs independent of sweating and is minimized by the cornified cholesterol-filled skin layer. Sweating can account for variable water loss. Values are normally 100 mL/day, although it can increase to 1–2 L/h, depending on weather or exercise.
- Faeces—water loss can be excessive with diarrhoea, compared with the small amount normally lost.
- Urine/kidney—the excretion of electrolytes and water by the kidney is the most important mechanism the body has to regulate fluid balance. The rate of water excretion is adjusted according to the body’s needs and water intake. This occurs by filtration and reabsorption and can maintain body fluid volumes despite change in fluid intake or loss elsewhere, e.g., haemorrhage.

Blood physiology

Functions and components of the blood

Blood is the only liquid tissue. Blood volume can be estimated as approximately 70 mL/kg for adults and 80 mL/kg in children (roughly 5 L in a normal adult), which comprises approximately 8% of total body weight. The functions of blood relate to its composition:

- Transport—of gases, nutrients, waste products and hormones.
- Immunological—defence against bacteria, viruses and foreign bodies by leukocytes.
- Homeostatic—temperature, pH, haemostasis and fluid exchange.

There are two main components of blood (Fig. 1.18):

1. Plasma (55%)—a watery substance containing dissolved solutes and proteins in suspension.
2. Cells and cellular fragments (45%):
   - Erythrocytes (99%), also known as red blood cells (RBCs)
   - Platelets (<1%)
   - Leukocytes (<1%) or white blood cells (WBCs).
Plasma

Plasma comprises:

- **Water**—forms a medium for the suspension and transport of proteins, solutes and gases and so influences partial pressures and gas exchange. Water is important in temperature regulation because it releases heat. It also removes waste and breakdown products.

- **Solute**—electrolytes in particular create osmotic pressure. Ions, e.g., $\text{HCO}_3^-$, are important in buffering pH change.

- **Protein**—these are important transporters and buffers and also exert oncotic pressure. They include:
  - **Albumin**—particularly important for vascular oncotic pressure and fluid exchange. It also transports fatty acids, lipid-soluble hormones and some drugs.
  - **Globulins**—$\alpha$ and $\beta$ globulins transport hormones and iron, respectively. $\gamma$ Globulins (antibodies) defend against viruses and bacteria.
  - Other components: e.g., fibrinogen, which is important in the process of blood clotting.

Cells

The types of cells found in blood are:

- **RBCs**—small, flexible, anucleate cells containing haemoglobin (~8 μm diameter). The biconcave shape suits their function in gas exchange and transport.

- **Platelets**—small cell fragments derived from megakaryocytes in the bone marrow. They initiate haemostasis and thrombus formation at injury sites (see later).

- **WBCs**—their numbers increase during infection, surgery or strenuous exercise and they include:
  - Neutrophils (60%)—engulf and phagocytose bacteria, and are also involved in inflammation. Numbers increase with bacterial infection, inflammation, burns and stress.
  - Lymphocytes (20%)—there are type B and type T cells, the immunological roles of which include generation of the specific immune response, including antigen–antibody reactions. Numbers increase in viral infections and some leukaemias.
  - Monocytes (5%)—phagocytose after transforming into macrophages. Numbers increase in viral or fungal infections, tuberculosis and some chronic diseases.
  - Eosinophils (3%)—destroy worm parasites. In allergic reactions, they combat histamine. Numbers increase in parasitic infections, allergic reactions and autoimmune diseases.
  - Basophils (<1%)—amplify the inflammatory response via the release of heparin and vasoactive substances. Numbers increase in allergic reactions, cancers and leukaemias.

**Fig. 1.18** Blood composition. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; vWF, von Willebrand Factor.
Haemostasis

Haemostasis refers to the control of bleeding. Following injury to a blood vessel, responses occur in two phases:

1. **Rapid**—reactions of blood vessel and platelets:
   - slowing of blood flow
   - aggregation of platelets to form a plug at the site of injury
   - diffusion of tissue factors from the extravascular compartment, initiating the extrinsic coagulation pathway.

2. **Slow**—intrinsic coagulation pathway: formation of insoluble fibrin mesh that stabilizes the platelet plug. Three mechanisms are involved with haemostasis:
   1. Vasoconstriction.
   2. Formation of a platelet plug.
   3. Coagulation (formation of a blood clot) with eventual clot retraction.

Vasoconstriction

Immediately after an injury to a blood vessel, the smooth muscle in the vascular wall contracts, decreasing diameter and blood loss. This occurs in response to:

- Nervous reflexes—as a result of pain and traumatized vessels causing release of catecholamines and vasopressin.
- Local myogenic spasm.

Formation of a platelet plug

The formation of a platelet plug is through adhesion, activation and aggregation (Fig. 1.19).

**Adhesion**—Damage to the vascular endothelium exposes collagen and other connective tissue to which platelets adhere. This increases the concentration of platelets at the site of vascular injury.

**Activation**—During activation, platelets undergo:

- Shape change—they swell then extend many projections that facilitate greater contact with other platelets.
- Granule release—contractile proteins contract, causing release of the following from granules:
  - ADP and thromboxane A₂—which activate and make platelets sticky.
  - Serotonin and thromboxane A₂—which cause vasoconstriction, so reducing blood loss.
- Expression of new receptors: lycoprotein (GP) IIb/IIIa. Activated platelets recruit nearby platelets so that the effects are amplified.

**Aggregation**—The sticky, activated platelets attract one another and adhere, forming a loose clump. This platelet plug is effective at blocking small holes and coagulation will not be necessary. However, injury to a blood vessel often requires coagulation.

**Fig. 1.19** Platelet structure.
Coagulation comprises a sequence of enzyme-catalysed conversions of inactive factors to more active forms, culminating in the conversion of fluid blood into a solid clot.

Blood clot formation begins within seconds after severe trauma to the vascular wall, and in minutes after injury to other areas of the body.

Two pathways are involved (Fig. 1.20):

1. The intrinsic pathway:
   - is triggered by trauma to blood and exposure to collagen
   - involves many enzyme-catalysed steps
   - is slow (minutes).

2. The extrinsic pathway:
   - requires factors external to blood vessels, e.g., tissue factor (tissue thromboplastin)
   - involves few enzymes and steps

**Fig. 1.20** Coagulation pathways.
Introduction

- is limited by the amount of tissue factor
- is fast (seconds).

Both pathways produce prothrombinase (prothrombin activator), the formation of which appears to be the rate-limiting step in haemostasis. After this stage, pathways follow a common set of reactions, which is known as the final common pathway:

1. Prothrombinase and ionized Ca$^{2+}$ cause prothrombin → thrombin (factor II).
2. 2a. Thrombin and ionized Ca$^{2+}$ cause fibrinogen (soluble) → fibrin fibres (insoluble).
3. 2b. Thrombin activates fibrin-stabilizing factor (XIII), which cross-links the fibrin fibres.

The cross-linked fibrin strands mesh plasma, the platelet plug, plasmin and RBCs to form a blood clot. In clinical practice:

- The intrinsic pathway is monitored by partial or accelerated thromboplastin time (APTT).
- The extrinsic pathway is monitored using the prothrombin time (PT). The PT forms the basis of the international normalised ratio (INR).

Role of thrombin—Thrombin formed in the first stage of the final common pathway exerts positive feedback effects on the coagulation cascade (Fig. 1.21):

- acceleration of the formation of prothrombinase
- platelet activation.

Role of platelets—Platelet phospholipids are required for the assembly of prothrombinase; these interact with activated factors X and V, and with Ca$^{2+}$, to produce prothrombinase. Furthermore, GP IIb/IIIa receptors bind to fibrin causing platelet aggregation with the fibrin glue.

Thrombus formation—A thrombus is a clot that forms within an intact blood vessel. This results from inappropriate activation of haemostasis with one of the following consequences:

- The thrombus dissolves spontaneously.
- The thrombus remains intact, with the risk of embolization.

Venous and arterial thrombi differ. Arterial thrombi (typically from rupture of atherosclerotic plaques):

- contain large platelet and small fibrin components
- are associated with atheroma formation and turbulent blood flow
- have a rough endothelial surface that attracts the platelets.

Venous thrombi (typically from a combination of factors from Virchow triad—see later):

- contain large fibrin and large fibrin components
- are associated with slow blood flow, which causes a large increase in procoagulant factor concentration.

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**CLINICAL NOTES**

TRANEXAMIC ACID

Tranexamic acid is an antifibrinolytic agent used to treat excessive blood loss after haemorrhage, especially in trauma patients. It reversibly binds to plasminogen or plasmin, preventing fibrin becoming degraded and therefore stabilizing the fibrin mesh.

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**CLINICAL NOTES**

VIRCHOW TRIAD

Virchow triad describes the three conditions that predispose to thrombosis formation: endothelial damage, stasis/turbulent flow of blood and hypercoagulability. To a certain degree, the thrombotic risk caused by each condition of the triad can be manipulated, i.e., stopping smoking or reducing blood pressure to limit damage of the blood vessel endothelium.

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**CLINICAL NOTES**

PRIMARY AND SECONDARY PREVENTION OF THROMBOSIS

Because arterial thromboses are mainly composed of platelets, they are treated with antiplatelet medications, e.g., aspirin or clopidogrel. Alternatively, as venous thrombosis is typically rich in fibrin, anticoagulants such as heparin and warfarin are used for treatment.
**Clot retraction**—Within a few minutes of its formation, the clot begins to contract owing to platelets applying tension to the fibrin fibres that are attached to damaged blood vessels, the ends of which are therefore brought closer together. In addition, fluid is squeezed out of the clot. Platelets are suited to clot retraction because they:
- release factor XIII (fibrin-stabilizing factor), causing more cross linking of fibrin and permitting further compression of the clot.
- activate the self-contractile proteins thrombosthenin, actin and myosin; these allow the platelet to pull harder on the fibrin fibres.

**Normal prevention of coagulation**
The normal vascular system employs a number of mechanisms to keep haemostasis in check:

**Prevention of activation of a haemostatic plug**
- Smooth endothelial cells discourage any activation of the intrinsic pathway.
- The glycosaminoglycan layer on the endothelium repels both platelets and clotting factors.

**Inhibition of the coagulation cascade**
- Endothelial-bound thrombomodulin—binds thrombin and activates protein C, which is a plasma protein.
- Protein C—inactivates factors V and VIII.
- Antithrombin III (α-globulin and most important circulating anticoagulant)—combines with thrombin, inactivating it for up to 20 minutes and blocking its effects on fibrinogen.
- Heparin molecule—is not active by itself but potentiates antithrombin III 100–1000-fold, with the added effect of removing activated factors XII, XI, X and IX.

**Fibrinolysis**—Plasmin is particularly important for removing inappropriately formed small blood clots; it acts to digest fibrin fibres and inactivate clotting substances: fibrinogen, prothrombin, and factors V, VIII and XII (Fig. 1.22). Plasmin is formed from the inactive plasma enzyme plasminogen by:
- Tissue plasminogen activator (t-PA)—released by damaged endothelial cells at the periphery. It activates plasminogen in the presence of fibrin.
- Clotting factors—thrombin and activated factor XIII can activate plasminogen.

**Clinical Notes**
**Thrombolysis**
Certain acute thrombotic conditions such as cerebrovascular attack (i.e., stroke) or pulmonary embolism causing severe haemodynamic compromise, may be treated with thrombolytic drugs. Commonly, these drugs, such as alteplase, are recombinant tissue plasminogen activators (t-PAs), which aid in the formation of plasmin.

**Descriptive Anatomical Terms**

The anatomical position
This is a standard position used in both anatomy and clinical practice, to allow an accurate and reproducible description of one body part in relation to another (Fig. 1.23).
- The head is directed forwards with the eyes looking into the distance.
- The body is upright, the legs together and the feet facing forwards.
- The arms are by the side of the body, with the palms facing forwards and the thumbs laterally.
- The penis is erect.

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**Fig. 1.22** Fibrinolysis pathway.
Introduction

Anatomical planes

The anatomical planes are hypothetical planes used to trans-ssect the body (Fig. 1.23). They are useful when describing the location of structures in gross anatomy and the direction of movements. Cross-sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) commonly produces images of the body in one or more of these planes.

- The sagittal plane—A vertical plane passing through the midline of the body from the head to the feet. Any plane parallel to this (i.e., to the left or right of the parasagittal median sagittal plane) is termed paramedian or sagittal.
- The coronal plane—These are vertical planes passing through the body from the head to the feet. They lie perpendicular to the sagittal planes.
- Transverse or axial horizontal plane—These pass horizontally through the body from the front to the back. They lie at right angles to the sagittal and coronal planes.
- Oblique plane—A plane that divides the body at an angle and is therefore not parallel to either of the former three.

Terms of position

The terms of position commonly used in anatomy and clinical practice are described in Table 1.1.

Terms of movement

The movements of the body are described as follows (Fig. 1.24):

- Flexion—a movement in the sagittal plane where there is a reduction in the angle between two parts of the body. There are exceptions to this, e.g., flexion at the glenohumeral joint increases the angle between the upper limb and the trunk.

<table>
<thead>
<tr>
<th>Table 1.1 Terms of position</th>
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<tbody>
<tr>
<td>Position</td>
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<tr>
<td>Anterior</td>
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<td>Contralateral</td>
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• Extension—a backward movement in the sagittal plane where there is an increase in the angle between two body parts. Again, there are exceptions to this, e.g., at the knee joint, as a result of limb rotation during embryonic development.
• Abduction—movement away from the median sagittal plane.
• Adduction—movement towards the median sagittal plane.
• Supination—lateral rotation of the forearm causing the palm to face anteriorly, i.e., into the anatomical position.
• Pronation—median rotation of the forearm causing the palm to face posteriorly.
• Eversion—movement of the sole away from the median plane (turning the sole of the foot outwards).
• Inversion—movement of the sole towards the median plane (turning the sole of the foot inwards).
• Rotation—movement of part of the body around its long axis.
• Circumduction—a combination of flexion, extension, abduction and adduction

The terms used to describe movements of the thumb refer to its being at a right angle to the movements of the fingers (see Video 1).
Introduction

Chapter Summary

• Within a cell are a number of highly organized structures termed organelles. From energy production to toxic compound destruction, each organelle has a specific and vital function.
• Approximately 80% of a human cell is water.
• Adenosine triphosphate (ATP) is the universal source of energy for all intracellular metabolic reactions. During aerobic respiration (glycolysis, Krebs cycle and oxidative phosphorylation), mitochondria produce a large number of ATP molecules from glucose, fatty acids or amino acids (38 molecules of ATP can be produced from one molecule of glucose). Anaerobic respiration yields less ATP per unit of macromolecule and produces lactic acid.
• Every gene is made of deoxyribonucleic acid (DNA), which regulates ribonucleic acid (RNA) to dictate the formation of the particular proteins.
• DNA is a double helical chain composed of a deoxyribose sugar, phosphoric acid and four nitrogenous bases (adenine can bind to thymine, guanine can bind to cytosine). RNA is identical to DNA apart from ribose replacing deoxyribose and uracil replacing thymine, which only binds to adenine.
• Protein production occurs in four stages: transcription (mRNA synthesis), splicing, translation and posttranslation modifications.
• A phospholipid bilayer forms the majority of a cell membrane, enveloping the entire cell and organelles. Throughout the cell membrane exist both integral and peripheral proteins and glycoproteins (carbohydrates attached to proteins). Cells can be attached to other cells via tight junctions, gap junctions or spot desmosomes. Cell membranes are selectively permeable. Diffusion across the membrane may occur through passive diffusion or may require ATP if molecules are moving against an electrochemical gradient. Substances may pass through the lipid bilayer (if lipid soluble) or more commonly pass through protein channels.
• Skin is formed of epidermis (stratified squamous keratinized epithelium), dermis (site of inflammation, growth and repair) and hypodermis. Skin has an abundance of appendages: hair follicles, sebaceous glands, sweat glands and nails.
• Water forms approximately 63% of the body (age, sex and body habitus dependant). Fluid is distributed into different compartments: 60% is within cells (intracellular) and 40% is outside of cells (extracellular) of which 75% is interstitial fluid bathing the cells and 25% is plasma within blood. \( K^+ \) is predominantly intracellular and \( Na^+ \) predominantly extracellular.
• Blood is the only liquid tissue, of which 55% is plasma (a suspension of dissolved solutes and proteins) and the remaining 45% cells and their fragments; 99% of cells within the blood are erythrocytes. A normal adult has roughly 5000 mL of blood.
• Haemostasis refers to the control of bleeding and involves three mechanisms: vasoconstriction, formation of a platelet plug (rapid onset with subsequent initiation of the extrinsic coagulation pathway) and coagulation (slow onset involving the intrinsic coagulation pathway forming an insoluble fibrin mesh that stabilizes the platelet plug). Under normal conditions, inappropriate coagulation is prevented through a number of pathways.
• The anatomical position describes a human stood upright, facing forwards with the legs together, arms by the side of the body with the feet and palms facing forwards (with the penis erect in males). Terms of position are described in relation to this position.
• The anatomical planes are hypothetical planes used to transect the body. Anatomical images, specimens and radiographic imaging (e.g., computed tomography images) will be presented in either the sagittal, coronal, oblique or transverse/horizontal plane.