ROSS & WILSON

Anatomy and Physiology in Health and Illness

14th Edition

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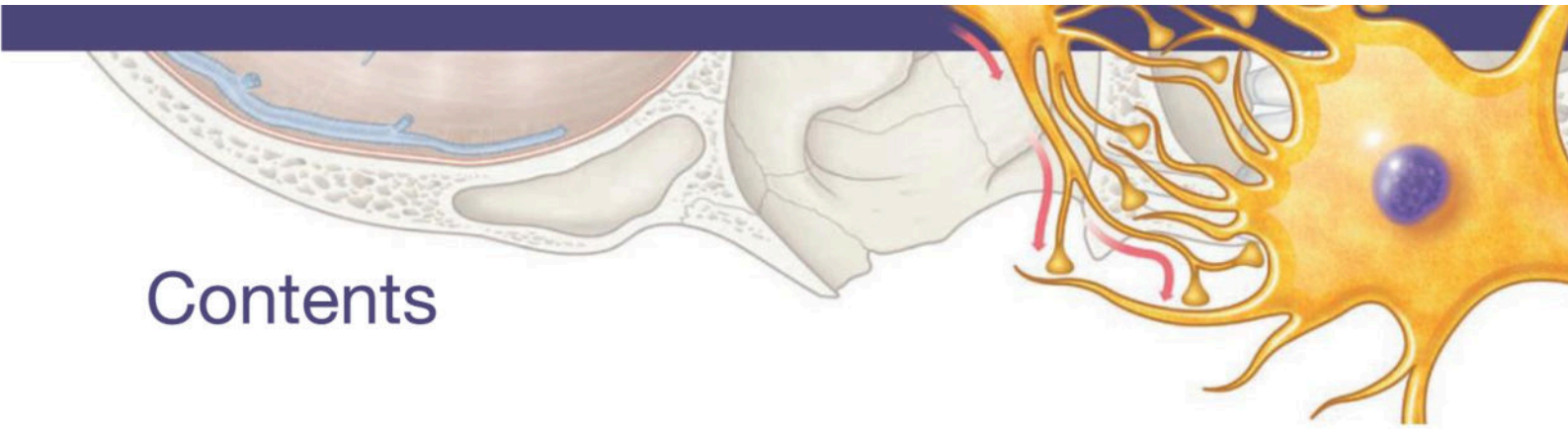

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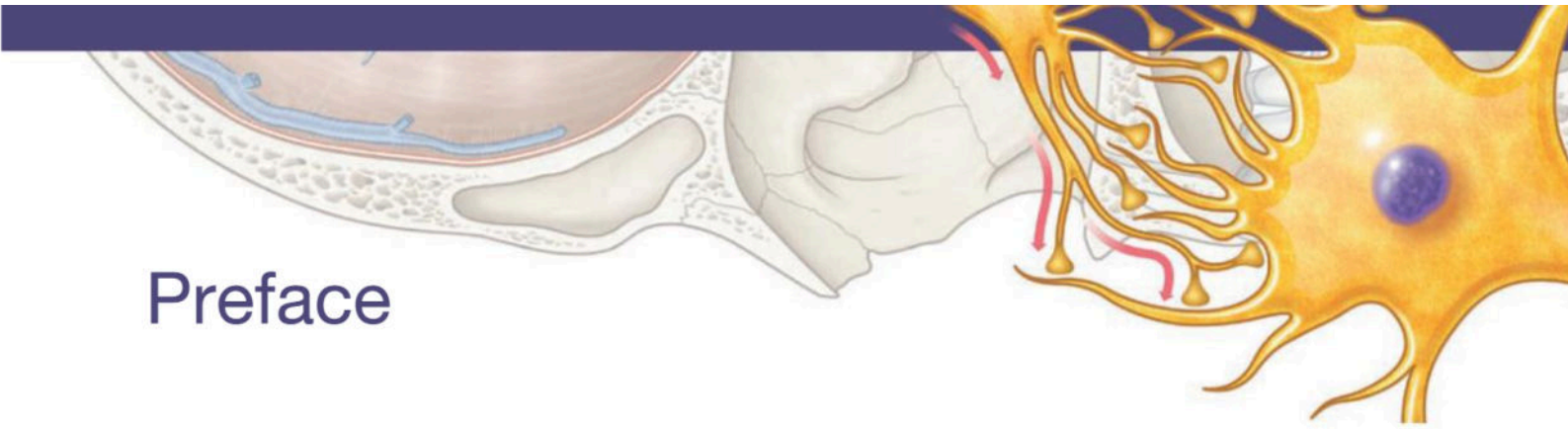

Preface

Ross & Wilson is entering its 60th year in print. The first edition quickly established itself as a leading core text for students of anatomy and physiology and has remained so ever since. Like each new edition, the 14th edition has been extensively revised and updated, taking into account the needs of healthcare professionals, including nurses and students of nursing, the allied health professions and complementary therapies, many of whom have found previous editions invaluable. It retains the successful and straightforward approach to the description of body systems and how they work, supported by a range of clear, informative illustrations. In each chapter, discussion and explanation of the anatomy and physiology of the healthy body is followed by sections describing common age-related changes to structure and function. Lastly, the pathology and pathophysiology of some important disorders and diseases are considered.

The human body is presented system by system. The reader must, however, remember that physiology is an integrated subject and that, although the systems are considered in separate chapters, all function cooperatively to maintain health. The first three chapters provide an overview of the body and describe its main structures and fundamental processes.

The later chapters are organised into three further sections, reflecting those areas essential for normal body function: communication; intake of raw materials and elimination of waste; and protection of the body and survival of the species.

Additional features and resources to support your learning include a comprehensive glossary, a list of common prefixes, suffixes and roots, a list of key sources for further reading and extensive in-text chapter cross-references. Every main section is signposted with learning outcomes and concludes with short 'spot check' questions. Chapters end with 'review and revise' questions that allow you to test your understanding of the content. Answers to all self-test questions are provided at the end of the book.

New features for this edition include an introduction to surface anatomy to support later explanations of the anatomy of deeper structures, extensive new artwork, and case studies at the end of each chapter to explore key themes.

This edition is accompanied by a companion website (https://evolve.elsevier.com/Waugh/anatomy/) with over 100 animations and an extensive range of online self-test activities reflecting the content of each chapter. The material in this textbook is also supported by the new 6th edition of its accompanying study guide (ISBN: 9780323872409), which gives students who prefer paper-based activities the opportunity to test their learning and deepen their knowledge.

We are always pleased to receive feedback from readers, which informs future editions of Ross & Wilson, ensuring it continues to meet the learning needs of students in an evolving educational environment.

Anne Waugh
Allison Grant
April 2022

This edition of *Ross & Wilson* comes with **bespoke 3D videos**, prepared by Dr Sarah Haywood-Small, that incorporate ***Complete Anatomy*** content to present summaries of key topics in a uniquely learner-friendly and accessible way. ***Complete Anatomy*** gives students and faculty the tools they need to deepen and improve their understanding of anatomy. With high-definition 3D visuals, the ***Complete Anatomy*** learning platform helps users explore the human body in a way that is practical, educational and intuitive. You can **access the videos by following the instructions on the inside cover.**

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Acknowledgements

Preparation of a new textbook relies on the contribution of a range of professionals and the 14th edition of this textbook would not have been possible without the efforts of many people.

The publishing team at Elsevier provided excellent support at all stages of the project and we are particularly indebted to Poppy Garraway and Betsy McCormac. Special thanks to the talented illustration team for their beautiful and detailed artwork.

We are always grateful for information, suggestions and constructive comments concerning the content and organisation of the material in this textbook, because this feedback informs future editions. To everyone who took the time and trouble to offer feedback we give our sincerest thanks.

This textbook has a long and distinguished history in providing quality anatomy and physiology education for health professionals. The first edition was published in 1963 by Kathleen Ross and Janet Wilson, and we gratefully acknowledge their role in founding this title.

We owe special thanks to our families for their love and support:

Andy: thank you for your continued patience (AW)

Seona and Struan: this is all for you (AG).

Anne Waugh
Allison Grant
April 2022

The Publisher would like to thank Dr Sarah Haywood-Small for her help in preparing the 3D videos.

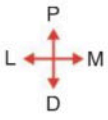
Anatomical directions and orientation

Orientation compasses are used beside some of the figures, with paired directional terms above and below and on each side of the compass.

A/P: anterior/posterior. This indicates that the figure has been drawn from above or below using a transverse section and shows the relationship of the structures to the front/back of the body.

L/R: left/right.

e.g. Figure 16.24



P/D: proximal/distal. This indicates the relationship of the structures to their point of attachment to the body.

L/M: lateral/medial. This indicates the relationship of the structures to the midline of the body.

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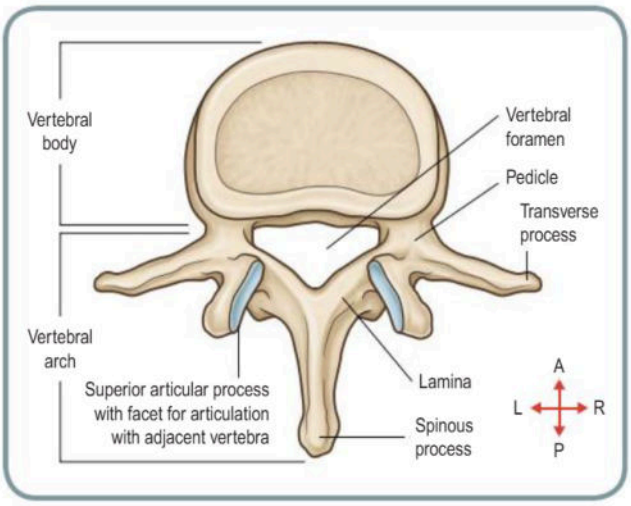
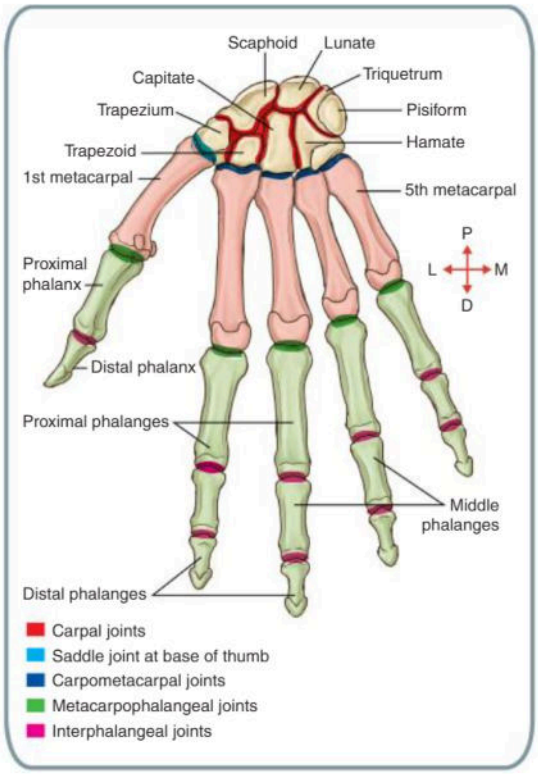
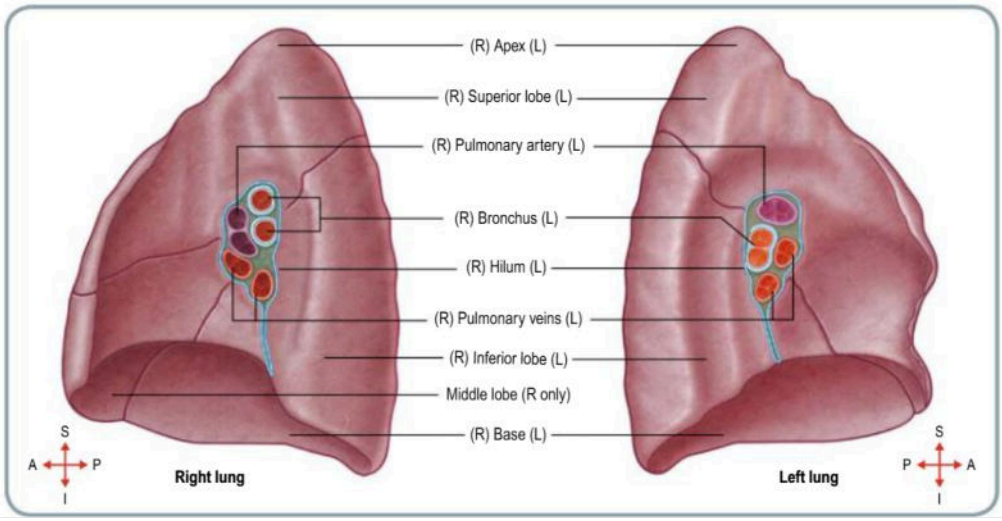




S/I: superior/inferior. This indicates the relationship of the structures to the upper/lower parts of the body.

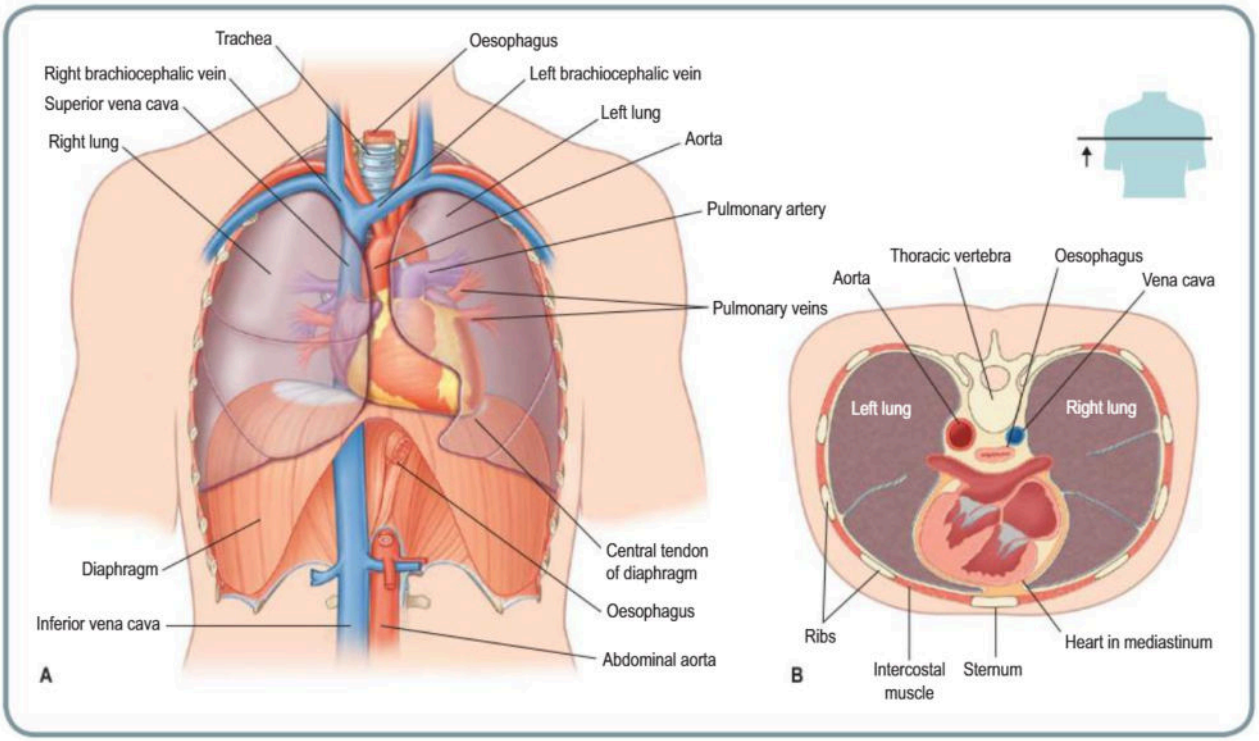
A/P: anterior/posterior. This indicates the relationship of the structures to the front/back of the body.

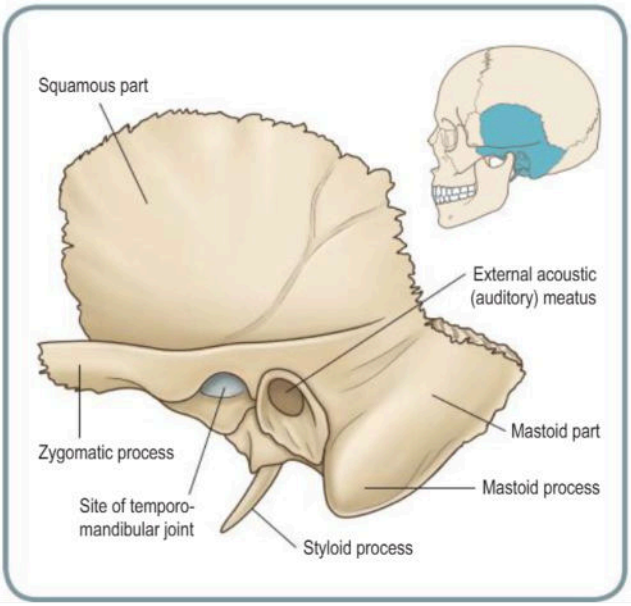
e.g. Figure 10.17

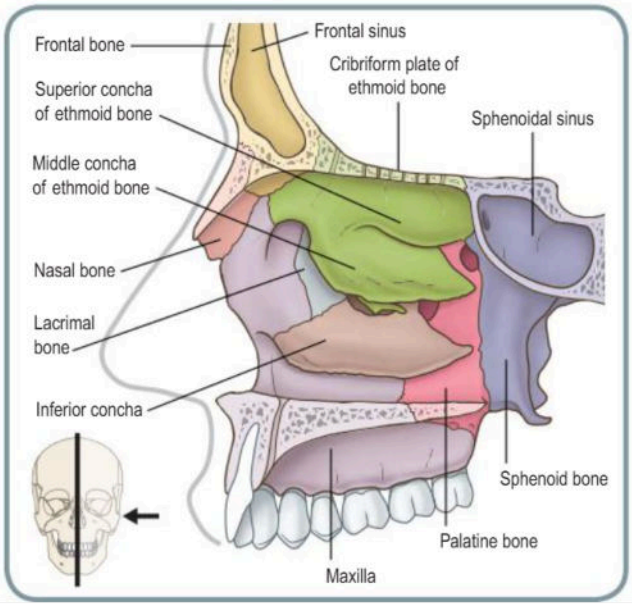


Anatomical directions and orientation

Many of the artworks have icons to help you locate/orientate bones and other structures.
e.g. Figures 5.8, 16.16 and 16.19







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SECTION ONE

CHAPTER 1

Anatomy and organisation of the body

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The human body can be likened to a highly technical and sophisticated machine. It operates as a single entity, but is made up of several systems that work co-operatively. Each system is associated with a specific function that is normally essential for the well-being of the individual. If one system fails, the consequences can extend to others, and may greatly reduce the ability of the body to function normally. Integrated working and control of the body systems ensures survival. The human body is therefore complex in both structure and function, and this book uses a systems approach to explain the fundamental structures and processes involved.

Anatomy is the study of the structure of the body and the physical relationships between its constituent parts. Physiology is the study of how the body systems work, and the ways in which their integrated activities maintain the life and health of the individual. Pathology is the study of abnormalities and pathophysiology considers how they affect body functions, often causing illness.

This chapter introduces the body systems and outlines how they are organised. The following section provides an overview of the levels of structural complexity found within body systems; the smallest units of living matter are cells that form the building blocks for the diverse body organs. The human body contains around 30 trillion cells.

A wide range of physiological processes co-operate in ensuring survival of the individual. Some involve communication and transport, others relate to taking in raw materials and getting rid of wastes and yet others ensure the body is able to protect itself and to reproduce. These processes are used as headings in the next section to introduce the body systems, which are then explored in depth in later chapters.

Standardised anatomical terminology allows the physical relationships between structures within the body to be described accurately and communicated consistently. This chapter also explains some of this fundamental terminology, which is then applied to provide an overview of the organisation of the body, focusing on the skeleton and body cavities.

Most body systems become less efficient with age. Physiological decline is a normal part of ageing and should not be confused with illness or disease, although some conditions do become more common in older life. Maintaining a healthy lifestyle can not only slow the effects of ageing but also protect against illness. The general impact

of ageing is outlined in this chapter and its effects on body function are explored in more detail in later chapters.

The final section of this chapter provides a framework for studying diseases, an outline of mechanisms that cause disease and some common disease processes. Building on the normal anatomy and physiology, a systems approach is adopted to consider common illnesses at the end of the later chapters.

Levels of structural complexity

Learning outcome

After studying this section, you should be able to:

- describe the levels of structural complexity within the body.

The human body can be considered at different levels of structural organisation and complexity. The most fundamental of these is chemical. Atoms combine to form molecules, and the structures, properties and functions of important biological molecules are considered in Chapter 2.

Molecules combine in an enormous range of ways to construct the cells of the body. Cells are the smallest independent units of living matter. They are too small to be seen with the naked eye, but different types can be distinguished by their size, shape and the dyes they absorb when stained in the laboratory and examined under the microscope. Most cells have become specialised (differentiated), to carry out a particular role; there are about 200 different types of cells in the human body, each contributing in their own way to maintenance of health and function. For example, Figure 1.1 shows some highly magnified nerve cells, whose specialised function is to generate and transmit electrical signals (nerve impulses). Nerve impulses are integrated and coordinated, allowing the millions of nerve cells in the body to provide a rapid and sophisticated communication system. In complex organisms such as the human body, cells with similar structures and functions are found together, forming tissues. The structure and functions of cells and tissues are explored in Chapter 3.

Organs are made from different types of tissue and have evolved to carry out a specific function. There are around 80 organs, each of which is associated with one or more body systems. Figure 1.2 shows that the stomach is lined by a layer of epithelial tissue and that its wall contains layers of smooth muscle tissue. Both tissues contribute to the functions of the stomach, but in different ways.

Systems generally consist of several organs and tissues that together contribute to one or more survival needs of the body. For example, the pancreas, stomach and liver are all organs of the digestive system. They all contribute to the digestion and absorption of nutrients, but individually have very different functions. The body's systems work co-operatively and must coordinate their functions for the body to remain healthy. The structure and functions of the body systems are considered in later chapters.

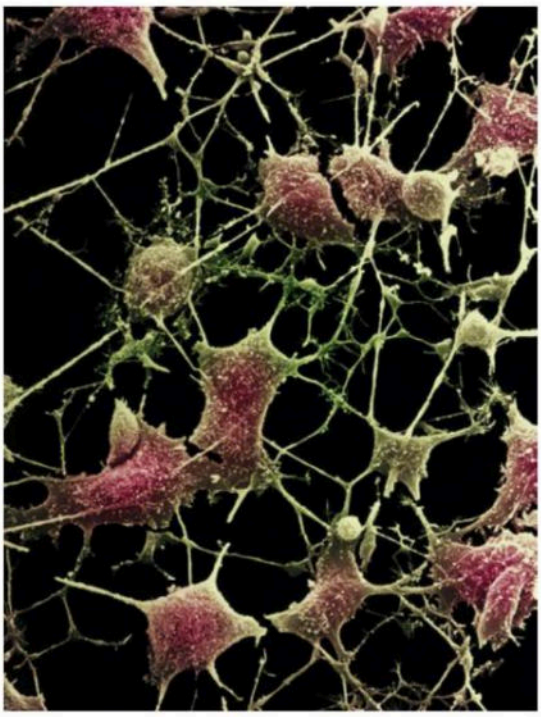

Figure 1.1 Nerve cells (neurones). Coloured scanning electron micrograph. (Steve G Schmeissner/Science Photo Library, reproduced with permission.)

SPOT CHECK

1. Define the term 'cell differentiation'.

Survival needs of the body

Learning outcomes

After studying this section, you should be able to:

- describe the roles of the body transport systems
- outline the roles of the nervous and endocrine systems in internal communication
- explain how raw materials are absorbed by the body
- state the waste materials eliminated from the body
- describe ways by which the body is protected from the external environment and defends itself against infection.

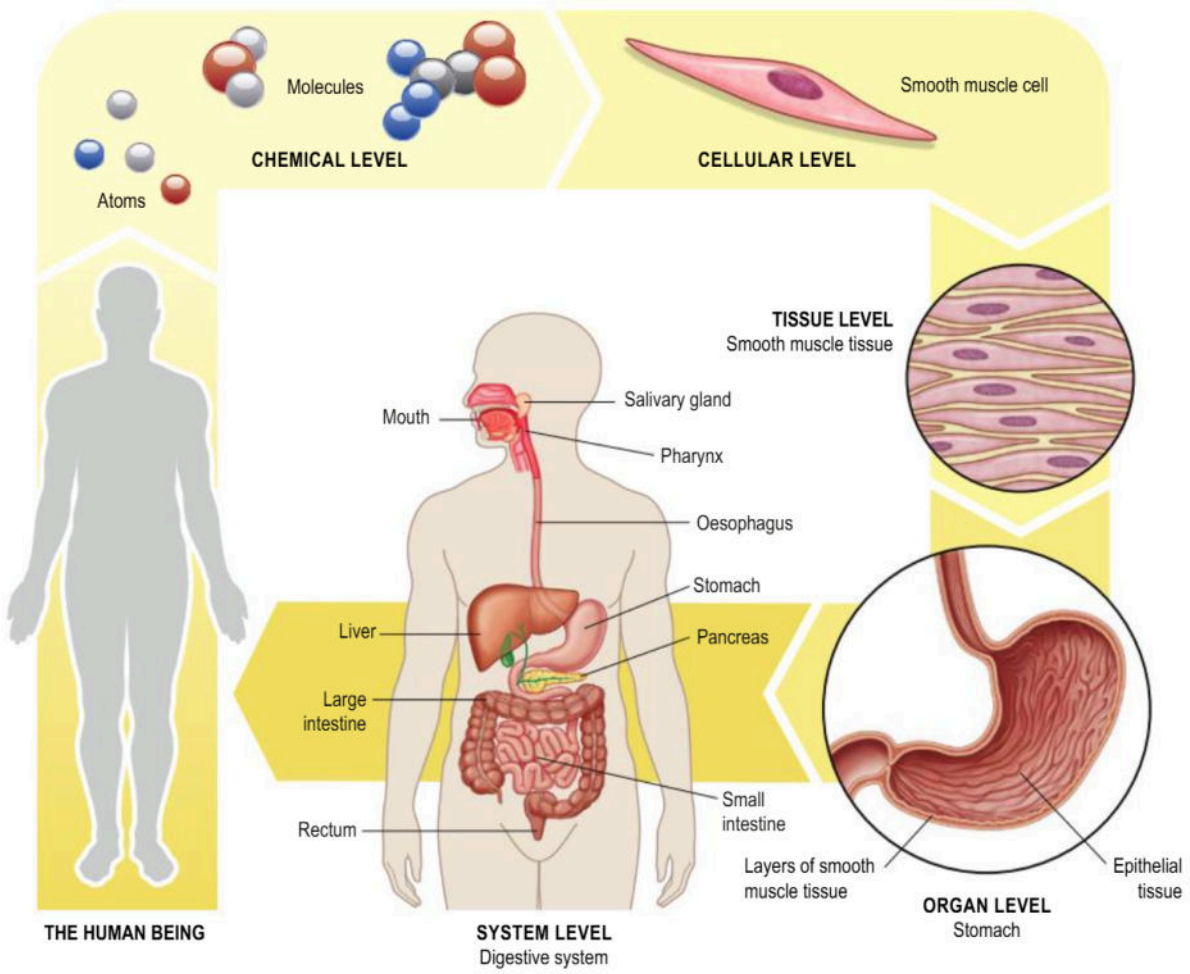

Figure 1.2 The levels of structural complexity.

By convention, body systems are described separately in the study of anatomy and physiology, but in reality they work co-operatively. This section introduces essential body activities and links them to survival needs: communication, intake of raw materials and elimination of waste, and survival of the body and continuation of the species (Table 1.1).

Communication

Communication requires transport systems to ensure that all body cells are supplied with all the many substances they need to carry out their specific function, as well as taking away waste for excretion; this involves the blood and the cardiovascular and lymphatic systems.

Communication systems receive, collate and respond to information that may originate either within the body (internally) or from its environment (externally). Internal communication involves mainly the nervous and endocrine systems; these are important in the maintenance of homeostasis (Ch. 2) and regulation of vital body functions. Communication with the external environment involves the

Table 1.1 Survival needs and related body activities

Survival need	Body activities
Communication	Transport systems: blood, cardiovascular system, lymphatic system
	Internal communication: nervous system, endocrine system
	External communication: special senses, verbal and non-verbal communication
Intake of raw materials and elimination of waste	Intake of oxygen
	Ingestion of nutrients (eating)
	Elimination of wastes: carbon dioxide, urine, faeces
Protection of the body and continuation of the species	Protection against the external environment: skin
	Defence against microbial infection: resistance and immunity
	Body movement
	Survival of the species: reproduction and transmission of inherited characteristics

special senses, and verbal and non-verbal activities; all of these also depend on the nervous system.

Transport systems

Blood

The blood (Ch. 4) transports substances around the body through a large network of blood vessels. In adults the body contains 5–6 litres of blood. It consists of two parts: a fluid called plasma, and blood cells suspended in the plasma.

Plasma

This is 90% water with a wide range of dissolved or suspended substances and in which the blood cells are carried. Dissolved substances include nutrients absorbed from the alimentary canal, oxygen absorbed from the lungs and waste materials produced by all cells to be eliminated from the body by excretion.

Blood cells

There are three distinct groups, classified according to their functions (Fig. 1.3).

Erythrocytes (red blood cells) transport oxygen and carbon dioxide between the lungs and all body cells.

Leukocytes (white blood cells) are mainly concerned with defence against infection and foreign substances. There are several types of leukocytes, which carry out their protective functions in different ways (Ch. 15).

Platelets (thrombocytes) are tiny cell fragments that play an essential part in blood clotting.

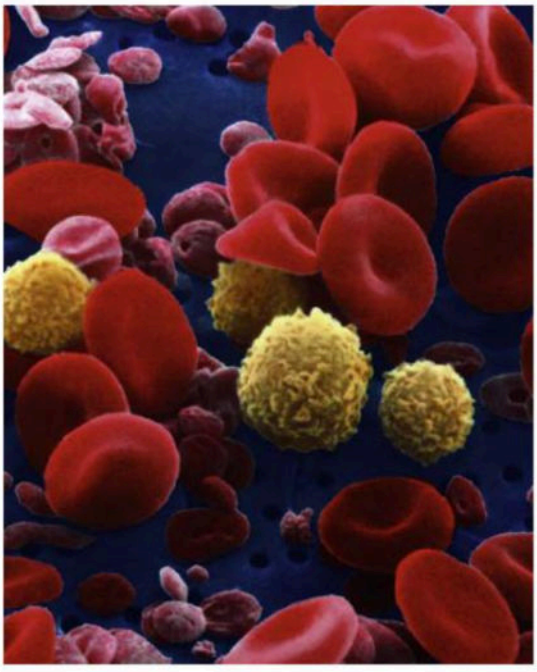

Figure 1.3 Blood showing red blood cells, white blood cells *(yellow)* and platelets *(pink)*. Coloured scanning electron micrograph. (National Cancer Institute/Science Photo Library, reproduced with permission.)

Cardiovascular system

The cardiovascular system (Ch. 5) consists of a network of blood vessels and the heart (Fig. 1.4).

Blood vessels

There are three types:

- arteries, which carry blood away from the heart
- veins, which return blood to the heart
- capillaries, which link the arteries and veins. The wall of these tiny vessels are only one cell thick to allow exchange of nutrients, gases and wastes between the blood and the body tissues.

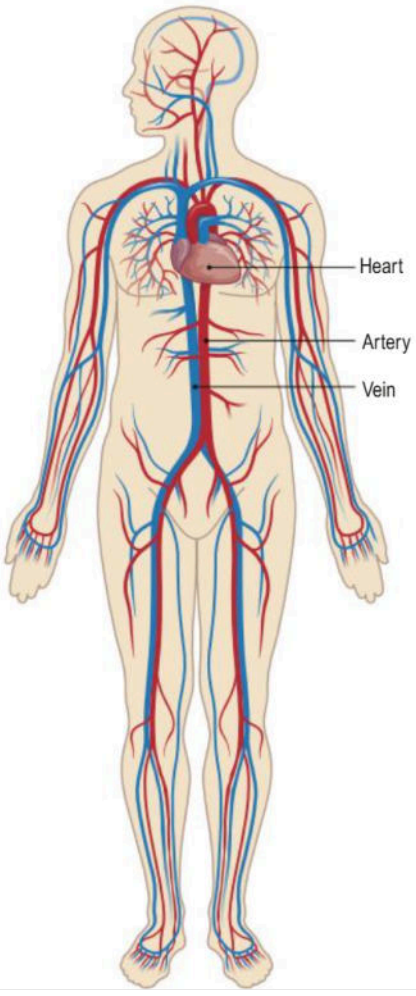

Figure 1.4 The circulatory system.

Blood vessels form an extensive network that transports blood to and from:

- the lungs (pulmonary circulation); oxygen is absorbed from the air in the lungs and, at the same time, carbon dioxide is excreted from the blood into the air
- cells in all other parts of the body (general or systemic circulation) (Fig. 1.5).

Heart

The heart is a muscular sac with four chambers, which pumps blood round the body and maintains the blood pressure.

The heart muscle (myocardium) is not under conscious (voluntary) control. At rest the heart contracts, or beats, between 65 and 75 times per minute. Heart rate is greatly increased when body oxygen requirements are increased, e.g. during exercise.

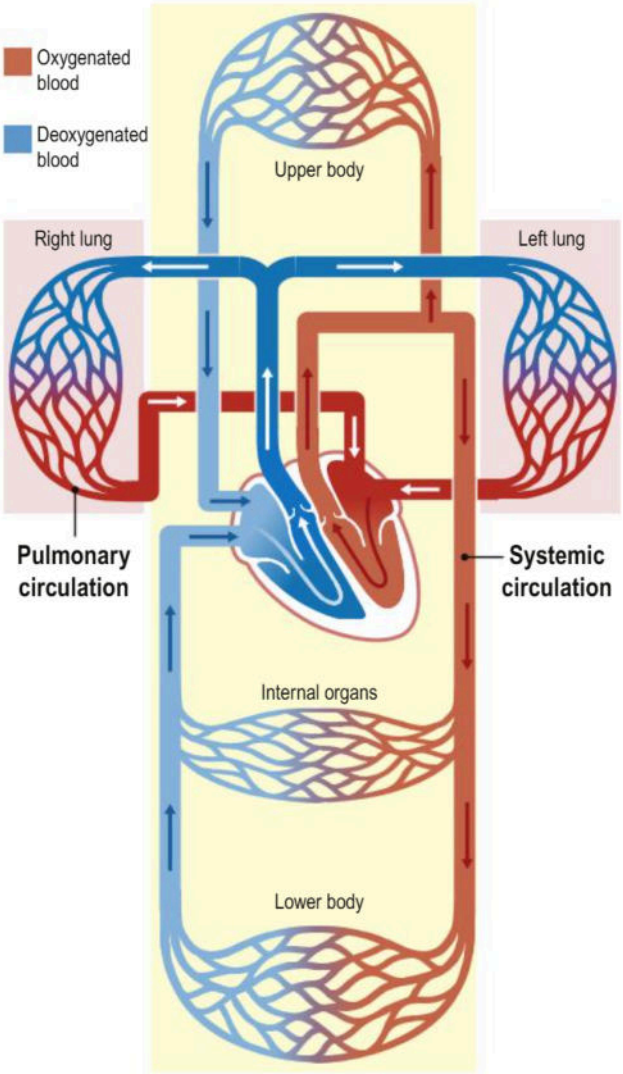

Figure 1.5 Circulation of the blood through the heart and the pulmonary and systemic circulations.

Lymphatic system

The lymphatic system (Ch. 6; Fig. 1.6) consists of a series of lymph vessels, which begin as blind-ended tubes in the tissue spaces between the blood capillaries and tissue cells. Structurally, they are similar to veins and blood capillaries but the pores in the walls of the lymph capillaries are much larger than those of the blood capillaries. Lymph is tissue fluid that also contains material drained from tissue spaces, including plasma proteins and, sometimes, bacteria or cell debris. It is transported along lymph vessels and returned to the bloodstream near the heart.

Collections of lymph nodes are situated at various points along the length of the lymph vessels. Lymph is filtered as it passes through these nodes, removing microbes and other materials. Other lymphatic organs include the spleen and the thymus.

The lymphatic system also provides the sites for formation and maturation of lymphocytes, the white blood cells involved in immunity (Ch. 15).

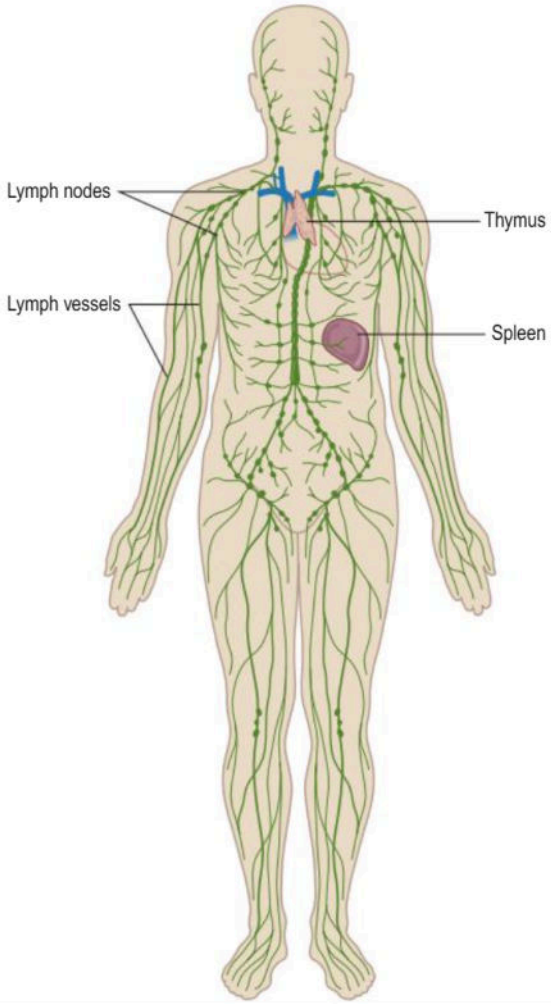

Figure 1.6 The lymphatic system. Lymph nodes and vessels.

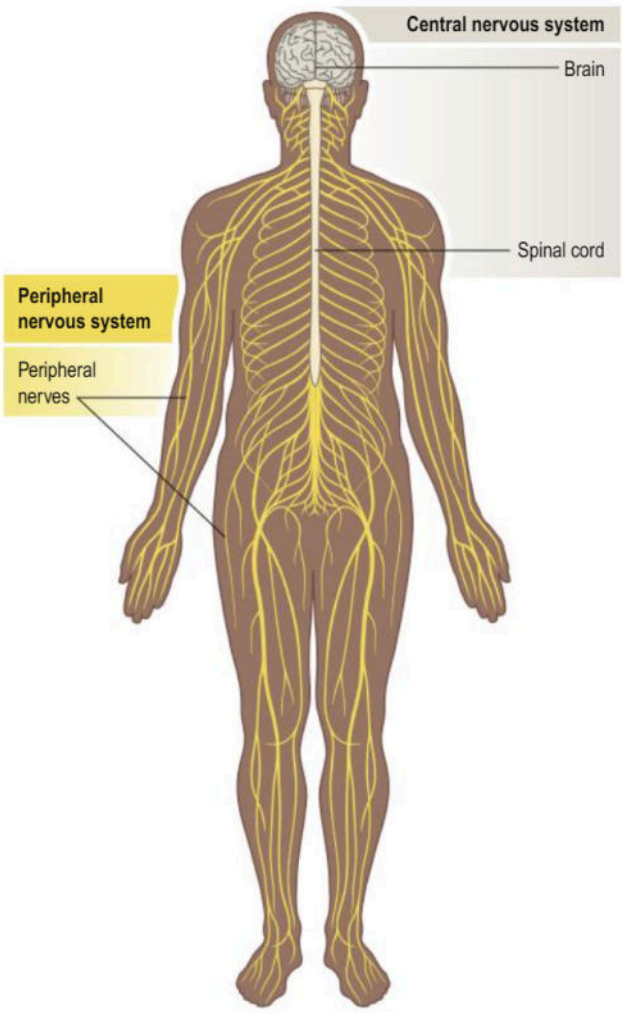

Figure 1.7 The nervous system.

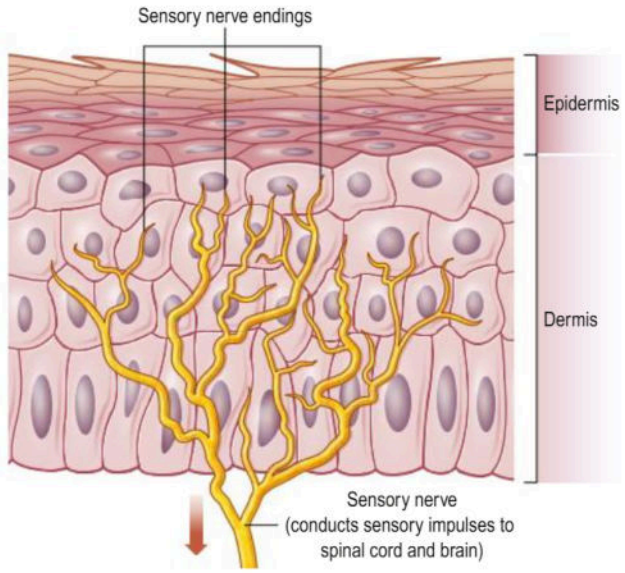

Figure 1.8 Sensory nerves in the skin.

Internal communication

The nervous and endocrine systems work together to enable effective communication within the body.

Nervous system

The nervous system (Ch. 7) is a rapid communication system. It is described in two parts: the central nervous system and the peripheral nervous system (Fig. 1.7).

The central nervous system consists of:

- the brain, that lies well protected within the skull
- the spinal cord, which extends from the base of the skull to the lumbar region (lower back). Like the brain, it is also protected from injury as it lies within the bones of the spinal column.

The peripheral nervous system is a network of nerve fibres, which are either:

- sensory or afferent nerves – these transmit signals from the body to the brain, or
- motor or efferent nerves – these transmit signals from the brain to the effector organs, such as muscles and glands.

The somatic (common) senses are pain, touch, heat and cold. These sensations arise following stimulation of specialised sensory receptors at nerve endings found widely distributed throughout the skin (Fig. 1.8).

Sensory nerve endings within muscles and joints respond to changes in the position and orientation of the body, maintaining posture and balance. Yet other sensory receptors are activated by stimuli in internal organs and control vital body functions, e.g. heart rate, respiratory rate and blood pressure. Stimulation of any of these receptors sets up impulses that are conducted to the brain in sensory (afferent) nerves.

Communication along nerves is by electrical impulses generated when nerve endings are stimulated. Nerve impulses (action potentials) can travel at speeds of over 100 metres per second, so responses are almost immediate, making rapid and fine adjustments to body functions possible.

Communication between nerve cells is also required, because more than one nerve is involved in the chain of events occurring between the initial stimulus and the reaction to it. Nerves communicate with each other by releasing a chemical (the neurotransmitter) into tiny gaps between them. In only a few thousandths of a second, the neurotransmitter travels across the gap and either stimulates or inhibits the next nerve cell, transmitting the message.

Many areas within the brain integrate and analyse the incoming information. When appropriate, the brain responds by sending impulses along motor (efferent) nerves to effector organ(s). In this way, many aspects of body function are continuously monitored and adjusted, usually by negative

feedback control (Ch. 2), and usually subconsciously, e.g. regulation of blood pressure.

Reflex actions are fast, involuntary, and usually protective motor nerve responses to specific stimuli. They include withdrawal of a finger from a very hot surface and control of blood pressure.

Endocrine system

The endocrine system (Ch. 9) consists of a number of discrete glands situated in different parts of the body. They synthesise and secrete chemical messengers called hormones that circulate round the body in the bloodstream. Hormones stimulate target glands or tissues, where they influence metabolic and other cellular activities and regulate body growth and maturation. Endocrine glands detect and respond to levels of particular substances in the blood, including specific hormones. Changes in blood hormone levels are usually controlled by negative feedback mechanisms (see Figs 2.12 and 2.13). The endocrine system provides slower and more precise control of body functions than the nervous system.

In addition to the glands that have a primary endocrine function, it is now known that many other tissues also secrete hormones as a secondary function; some of these are explored further in Chapter 9.

Communication with the external environment

Special senses

Stimulation of specialised receptors in sensory organs or tissues gives rise to the sensations of sight, hearing, balance, smell and taste (Ch. 8). Although these senses are usually considered to be separate and different from each other, one sense is rarely used alone (Fig. 1.9). For example, when the smell of smoke is perceived, other senses such as sight and sound are used to try to locate the source of a fire. Similarly, taste and smell are closely associated in the enjoyment, or otherwise, of food. The brain collates incoming information with information from the memory and initiates a response by setting up electrical impulses in motor (efferent) nerves to effector organs, muscles and glands. Such responses enable the individual to escape from a fire, or to subconsciously prepare the digestive system for eating.

Verbal communication

Sound is produced in the larynx when expired air coming from the lungs passes through and vibrates the vocal cords (see Fig. 10.8) during expiration. Speech is produced during expiration by coordinated contraction of the muscles of the throat and cheeks and movements of the tongue and lower jaw.

Non-verbal communication

Posture and movements are often associated with non-verbal communication, e.g. nodding the head, facial expression and shrugging the shoulders.

Figure 1.9 Combined use of the special senses: vision, hearing, smell, taste and balance.

Intake of raw materials and elimination of waste

This section considers substances taken into and excreted from the body, which involves the respiratory, digestive and urinary systems. Oxygen, water and food are taken in, and wastes such as carbon dioxide, urine and faeces are excreted.

Intake of oxygen

Oxygen gas makes up about 21% of atmospheric air. A continuous supply is essential for life because it is essential for the series of chemical reactions that result in the release of energy from nutrients. This chemical energy is essential fuel for all cellular activity.

The upper respiratory system carries air between the nose and the lungs during breathing (Ch. 10). Air passes through a system of passages, including the nasal cavity, the pharynx (throat, also part of the digestive tract), the larynx (voice box), the trachea, two bronchi (one bronchus to each lung) and a large number of smaller bronchial passages (Fig. 1.10). These end in alveoli, millions of tiny air sacs in each lung. They are surrounded by a network of tiny capillaries and are the sites where vital gas exchange between the lungs and the blood takes place.

Ingestion of nutrients (eating)

Nutrition is considered in Chapter 11. A balanced diet is important for health and provides nutrients, substances absorbed from the gastrointestinal tract usually following digestion, and which promote body function, including fuel for energy and the building blocks for cell division and tissue growth and repair. Nutrients include water, carbohydrates, proteins, fats, vitamins and mineral salts.

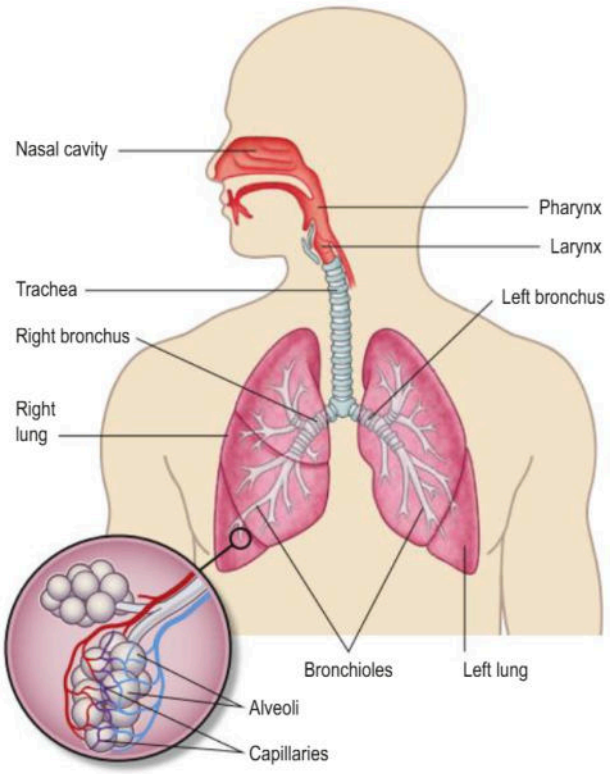

Figure 1.10 The respiratory system.

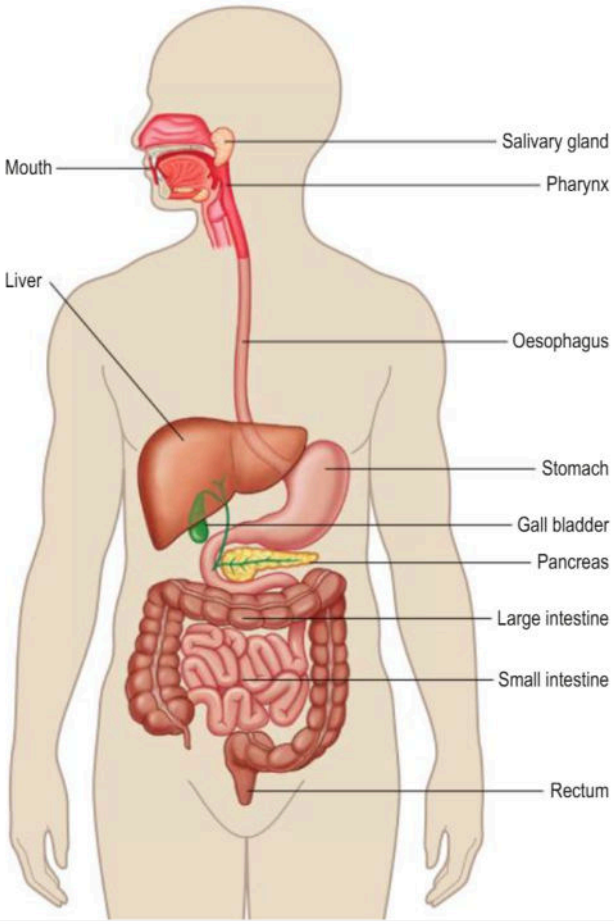

Figure 1.11 The digestive system.

Digestion

The digestive system evolved because food is chemically complex and usually not eaten in a form that body cells can use. Its function is to break down, or digest, food so that it can be absorbed into the circulation and then used by body cells. The digestive system consists of the alimentary canal and accessory organs (Fig. 1.11).

Alimentary canal

This is essentially a tube, about 9m long in the average adult, that begins at the mouth and continues through the pharynx, oesophagus, stomach, small and large intestines, rectum and anus.

Accessory organs

These are the salivary glands, pancreas and liver (see Fig. 1.11), which lie outside the alimentary canal. The salivary glands and pancreas synthesise and release digestive enzymes, which are involved in the chemical breakdown of food, while the liver secretes bile; these substances enter the alimentary canal through connecting ducts.

Metabolism

Chemical reactions occur continuously in all body cells and the overall activity is called metabolism. Metabolic reactions are classified into two main groups:

- anabolism, building or synthesising large and complex substances
- catabolism, breaking down substances to provide energy and raw materials for anabolism, and substances for excretion as waste.

The sources of energy are mainly dietary carbohydrates and fats. However, if these are in short supply, proteins are used.

Elimination of wastes

Carbon dioxide

This gas is a waste product of cellular metabolism. Because it dissolves in body fluids to make an acid solution, excess must be excreted to maintain pH (acidity or alkalinity, see Fig. 2.6) within the normal range. Most carbon dioxide is excreted through the lungs during expiration.

Urine

Urine is formed by the kidneys, which are part of the urinary system (Ch. 13). The organs of the urinary system are shown in Figure 1.12. Urine consists of water and waste products, mainly those of protein breakdown, e.g. urea. Under the influence of hormones, the kidneys regulate body salt and water balance. They also play a role in maintaining blood pH within the normal range. The bladder stores urine until it is excreted during micturition.

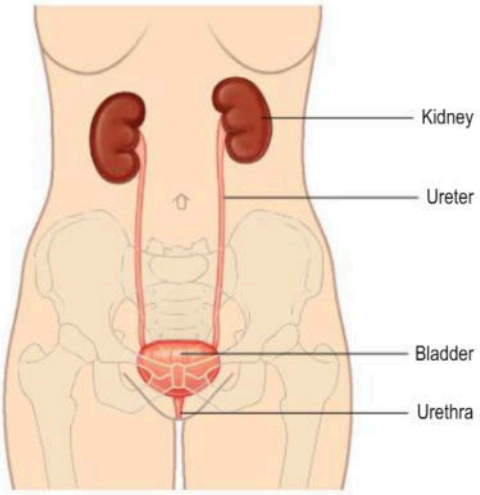

Figure 1.12 The urinary system.

Faeces

Waste materials from the digestive system are excreted as faeces during defaecation. They contain indigestible food residue that remains in the alimentary canal because it cannot be absorbed, as well as large numbers of microbes.

Protection of the body and continuation of the species

The body needs and related activities explored in this section are protection against the external environment, defence against infection, movement and survival of the species.

Protection against the external environment

The skin (Fig. 1.13) forms a physical barrier against invasion by microbes, chemicals and dehydration (Ch. 14). It consists of two layers: the epidermis and the dermis.

The epidermis lies superficially and is composed of several layers of cells that grow towards the surface from its deepest layer. The skin surface consists of dead flattened cells that are constantly being rubbed off and replaced from below. The epidermis provides the barrier between the moist internal environment and the dry atmosphere of the external environment.

The skin also plays an important role in the regulation of body temperature. The dermis contains tiny sweat glands that have little canals or ducts, leading to the surface; sweating is important in heat loss.

The dermis is rich in sensory nerve endings sensitive to pain, temperature and touch (see Fig. 1.8). It is a vast organ that constantly provides the central nervous system with sensory input from the body surfaces.

Defence against infection

The body has many defence mechanisms against invaders, some of which confer resistance and/or immunity (Ch. 15).

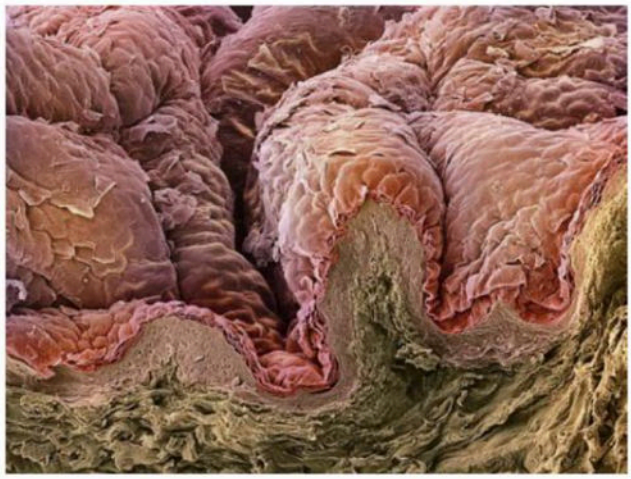

Figure 1.13 The skin. Coloured scanning electron micrograph. (Steve G Schmeissner/Science Photo Library, reproduced with permission.)

There are two categories: specific and non-specific defence mechanisms.

Non-specific defence mechanisms

These are effective against a range of threats. The skin protects most of the body surface, although there are also other protective features at body surfaces; for example, sticky mucus secreted by mucous membranes traps microbes and other foreign materials. Some body fluids contain antimicrobial substances; for example, gastric juice contains hydrochloric acid, which kills most ingested microbes. If microbes succeed in entering the body to infect the tissues, other non-specific (general) defence mechanisms are activated, including complement and the inflammatory response (Ch. 15).

Specific defence mechanisms

The body generates a specific (immune) response against any substance it identifies as foreign. Such substances are called antigens and include pollen from flowers and plants, microbes including bacteria and abnormal cells such as those from a tumour or transplanted tissue.

Following exposure to an antigen, lifelong immunity against further invasion by the same antigen often develops. Over a lifetime, an individual gradually builds up immunity to millions of antigens. Allergic reactions are abnormal immune responses to an antigen that usually poses no threat to the body, e.g. the effects of pollen in people with hay fever.

Movement

Movement of the whole body, or parts of it, is essential for many body activities, e.g. obtaining food, running from danger, avoiding injury and reproduction.

Most body movement is under conscious (voluntary) control. Exceptions include protective movements (reflexes) that are carried out before the individual is aware of them, e.g. the rapid withdrawal of the hand from a hot cooker.

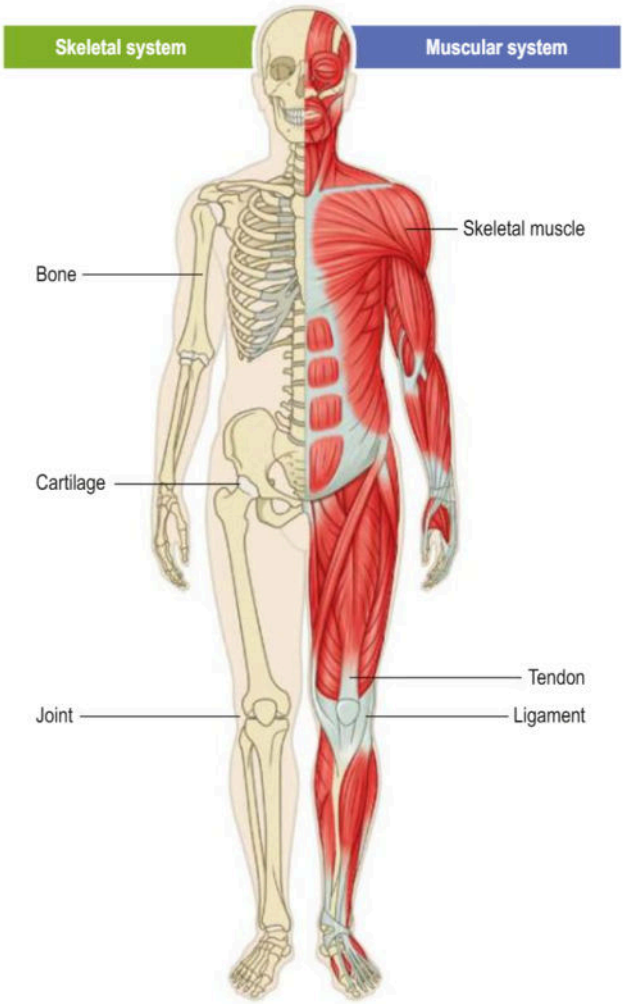

Figure 1.14 The musculoskeletal system.

The musculoskeletal system includes the bones of the skeleton, skeletal muscles and joints (Fig. 1.14). The skeleton provides the rigid body framework and movement takes place at joints between two or more bones. Skeletal muscles, under the control of the voluntary nervous system, maintain posture and balance, and are attached to the bones they move by tendons. Moveable joints are supported by outer sleeves of fibrous tissue called ligaments, which link one bone directly to an adjacent bone. Learned movement and balance often becomes subconsciously controlled, e.g. riding a bicycle, dancing, writing and other precise skills. An overview of the skeleton is given later in this chapter, and a more detailed account of bones, muscles and joints is presented in Chapter 16.

Survival of the species

Survival of a species depends on successful reproduction, with parents transmitting their genetic material to their children. As in many other species, this involves fusion of a male and a female sex cell, a process called sexual reproduction.

Transmission of inherited characteristics

Individuals with the most advantageous genetic make-up are most likely to survive, reproduce and pass their genes on to the next generation. This is the basis of natural selection, i.e. 'survival of the fittest'. Chapter 17 explores the transmission of inherited characteristics.

Reproduction

Successful reproduction (Ch. 18) is essential to ensure the continuation of a species and its genetic characteristics from one generation to the next. Ova (eggs) are produced by two ovaries situated in the female pelvis (Fig. 1.15). In the female, the reproductive years begin at puberty and end at the menopause. The female reproductive cycle takes about a month and is controlled by several key hormones. At ovulation (see Fig. 18.9), which occurs mid-cycle, an ovum is released from one of the ovaries and travels towards the uterine tube.

In the male, under the control of sex hormones, spermatozoa are continuously produced after puberty in large numbers by the two testes, situated in the scrotum. Spermatozoa are stored in the epididymis and deferent duct (see Fig. 18.16).

During sexual intercourse spermatozoa from both testes pass from the epididymis through the deferent duct (vas deferens) and urethra before being deposited in the vagina. They travel upwards through the uterus and fertilise the ovum in the uterine tube. Fertilisation (Fig. 1.16) occurs when a female egg cell or ovum fuses with a male sperm cell or spermatozoon. The fertilised ovum (zygote) then passes into the uterus, embeds itself in the uterine wall and grows to maturity during pregnancy or gestation, a period lasting about 40 weeks.

If the ovum is not fertilised, it is expelled from the uterus along with part of the uterine lining in a short period of bleeding called menstruation.

SPOT CHECK

2. Outline the role of arteries in the transport of blood.
3. What is a neurotransmitter?

Introduction to anatomy and organisation of the body

Learning outcome

After studying this section, you should be able to:

- define common anatomical terms
- identify the principal bones of the axial skeleton and the appendicular skeleton
- state the boundaries of the four body cavities
- list the contents of the body cavities
- identify some important surface anatomy landmarks.

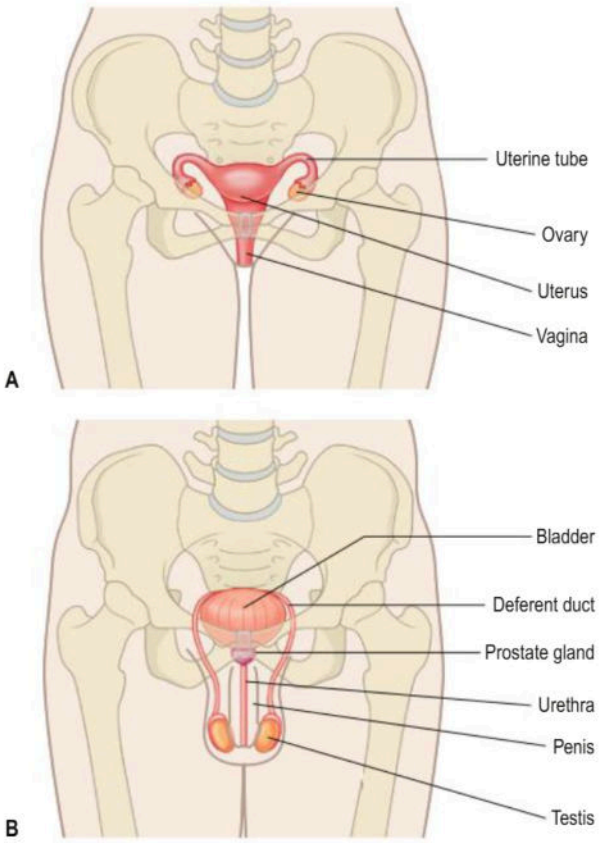

Figure 1.15 The reproductive systems. (A) Female. (B) Male.

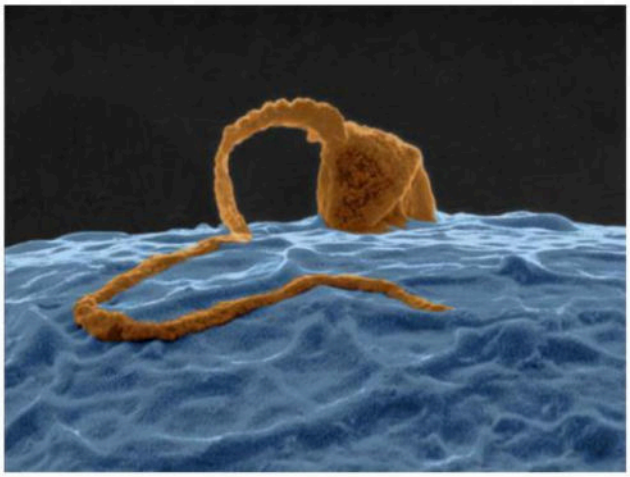

Figure 1.16 Fertilisation showing a spermatozoon (orange) penetrating an ovum (blue). Coloured scanning electron micrograph. (Thierry Berrod, Mona Lisa Production/Science Photo, reproduced with permission.)

This part of the chapter explains the anatomical terminology used to ensure that relationships between body structures are described accurately and consistently. An overview of the bones forming the skeleton is provided and the contents of the body cavities are explored. Finally, the principles of surface anatomy and some important surface landmarks are described.

Anatomy, the study of the structure of the human body, is the oldest medical science and is the basis from which contemporary understanding of physiology developed. Until the early microscopes were developed in the sixteenth century, anatomical study relied on dissection of cadavers to enable visual inspection of internal body organs and structures. Discovery of ionising radiation at the end of the nineteenth century led to development of X-rays and since then, more sophisticated scanning techniques emerged that allow very detailed examination of internal structures; these include ultrasound scans, magnetic resonance imaging (MRI scans) and computed, or computerised, tomography (CT scans).

Anatomical terms

The anatomical position

The position is used in all anatomical descriptions to ensure accuracy and consistency. The body is described as viewed standing upright with the head facing forward, the arms at the sides with the palms of the hands facing forward, and the feet together.

Directional terms

These paired terms are used to describe the location of body parts in relation to others and are defined in Table 1.2.

Regional terms

These are used to describe parts of the body and are illustrated in Figure 1.17.

Table 1.2 Paired directional terms used in anatomy

Directional term	Meaning	Example
Medial	Nearer to the midline	The heart is medial to the humerus
Lateral	Further from the midline or at the side of the body	The humerus is lateral to the heart
Proximal	Nearer to a point of attachment of a limb, or origin of a body part	The femur is proximal to the fibula
Distal	Further from a point of attachment of a limb, or origin of a body part	The fibula is distal to the femur
Anterior or ventral	Nearer the front of the body	The sternum is anterior to the vertebrae
Posterior or dorsal	Nearer the back of the body	The vertebrae are posterior to the sternum
Superior	Nearer the head	The skull is superior to the scapulae
Inferior	Further from the head	The scapulae are inferior to the skull

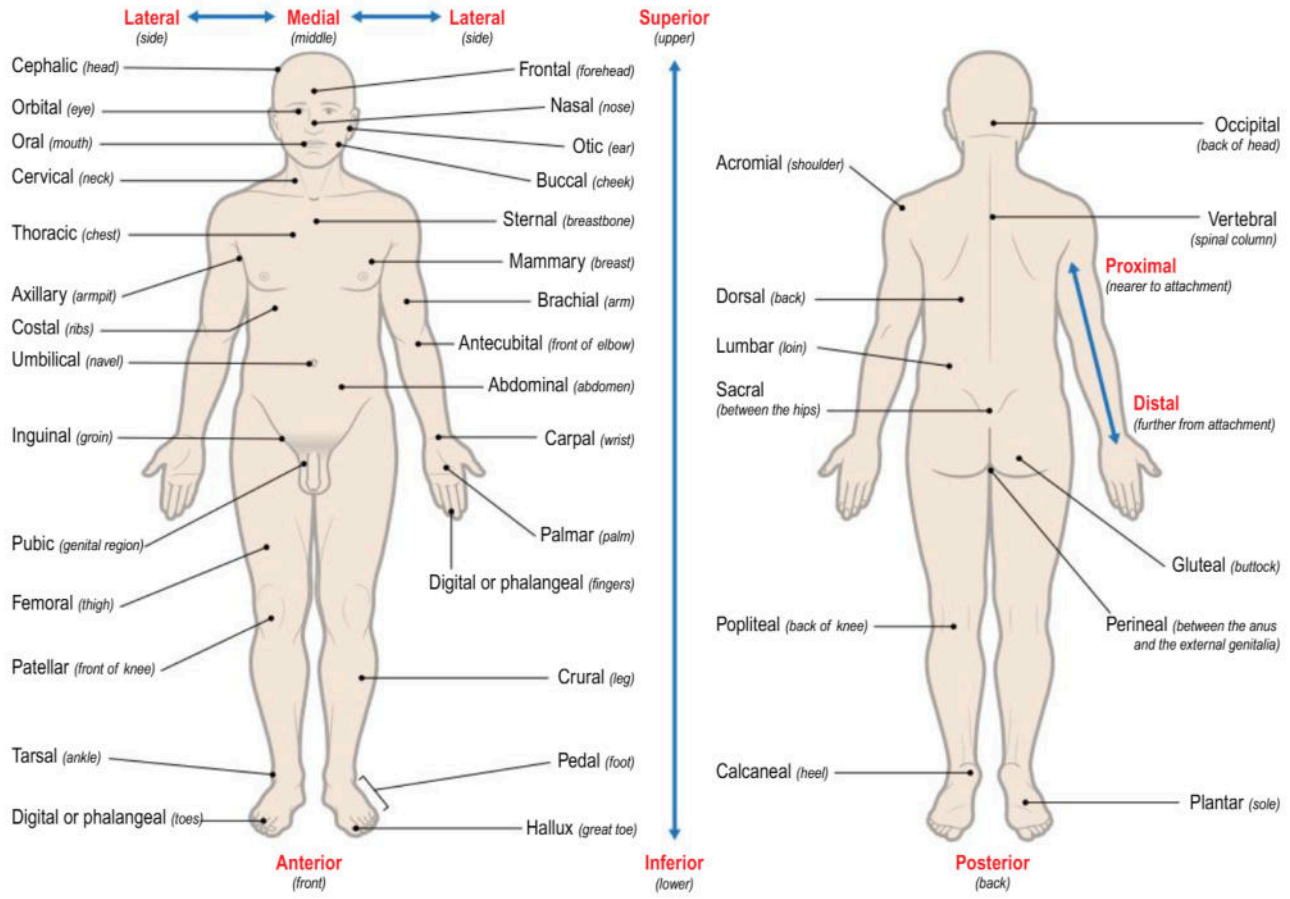

Figure 1.17 Regional and directional terms. Regional terms are shown in red.

Body planes

There are three body planes (Fig. 1.18), which lie at right angles to each other. These divide the body into sections and are used to visualise or describe its internal arrangement from different perspectives. The anatomical position (described above) is used as the reference position in descriptions using body planes.

Median plane

When the body is divided longitudinally through the midline into right and left halves, it has been divided in the median plane, e.g. Figure 10.4. A sagittal section is any section made parallel to the median plane.

Frontal (coronal) plane

A coronal or frontal section divides the body longitudinally into its anterior (front) and posterior (back) sections, e.g. Figure 7.19.

Transverse plane

A transverse or horizontal section provides a cross-section dividing the body or body part into upper and lower parts. This may be at any level, e.g. through the head, thorax, abdomen, a limb or an organ, e.g. Figure 7.27.

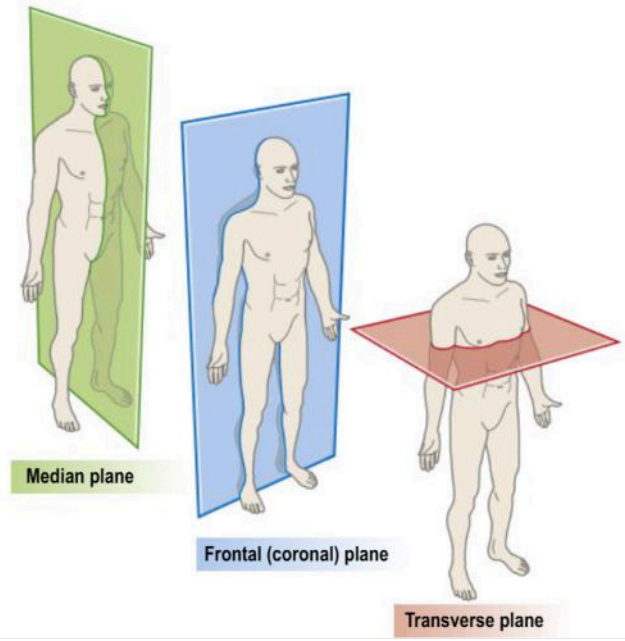

Figure 1.18 Body planes.

Anatomical reference icons used in this book

These icons have been used in some of the figures to clarify relationships between body parts. Many figures have a compass-like icon labelled with anatomical directions corresponding to the paired directional terms shown in Table 1.2. A full description of all the icons used in the book is provided on page xi.

Organisation of the body

This section outlines how the skeleton is organised and provides an overview of the body cavities and their contents.

The skeleton

The skeleton (Fig. 1.19) is the bony framework of the body. It forms the cavities and fossae (depressions or hollows) that protect some structures, forms the joints and gives attachment to muscles. A detailed description of skeletal anatomy and bone physiology is given in Chapter 16. Table 16.1 (p. 439) defines common terminology related to features of bones.

The skeleton is described in two parts, axial and appendicular; the appendages are attached to the axial skeleton.

Axial skeleton

This forms the axis of the body and consists of the skull, vertebral column, sternum (breast bone) and ribs.

Skull

The skull is described in two parts: the cranium, which contains the brain, and the face. The only movable bone is the mandible or lower jaw. The names and positions of the individual bones of the skull are shown in Figure 1.20.

Functions

The primary function of the skull is to protect the brain, eyes and inner ears.

Vertebral column

This consists of 24 movable bones (vertebrae) plus the sacrum and coccyx. The bodies of the bones are separated from each other by intervertebral discs consisting of fibrocartilage. The vertebral column is described in five parts and the bones of each part are numbered from above downwards (Fig. 1.21):

- 7 cervical
- 12 thoracic
- 5 lumbar
- 1 sacrum (5 fused bones)
- 1 coccyx (4 fused bones).

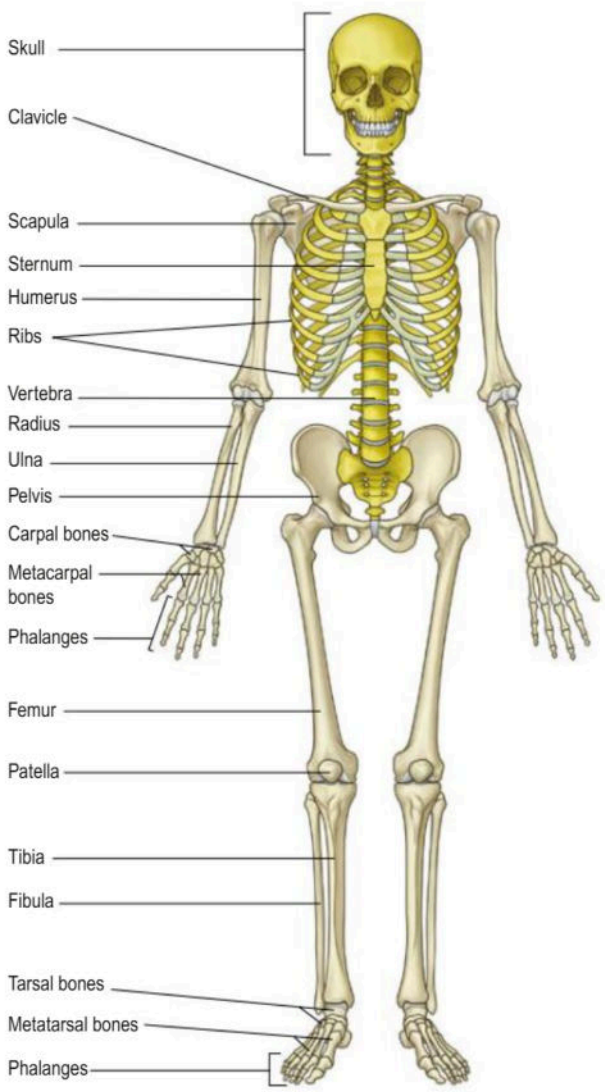

Figure 1.19 The skeleton. Anterior view showing the axial skeleton in gold and appendicular skeleton in brown.

The first cervical vertebra is called the atlas and it forms a joint (articulates) with the skull. Thereafter, each vertebra forms a joint with the vertebrae immediately above and below. More movement is possible in the cervical and lumbar regions than in the thoracic region.

The sacrum consists of five vertebrae fused into one bone that articulates with the fifth lumbar vertebra above, the coccyx below and an innominate (pelvic or hip) bone at each side.

The coccyx consists of the four terminal vertebrae fused into a small triangular bone that articulates with the sacrum above.

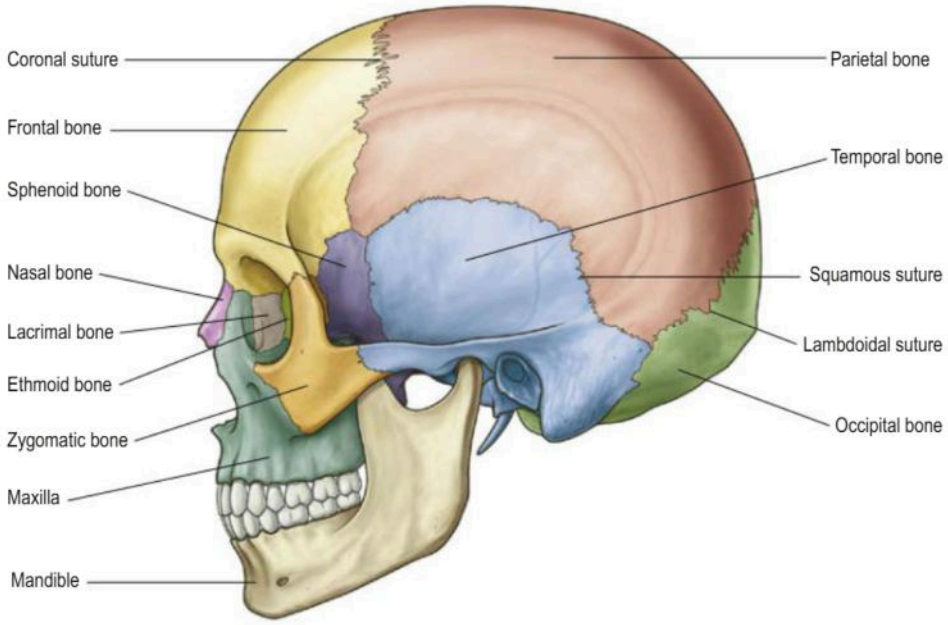

Figure 1.20 The skull. Bones of the cranium and face viewed from the left side.

Functions

The stacked arrangement of the vertebrae encloses a central channel that runs the length of the vertebral column; the spinal cord lies well protected within this channel.

Thoracic cage

The thoracic cage (see Fig. 1.24A) is formed by:

- 12 thoracic vertebrae
- 12 pairs of ribs
- 1 sternum or breast bone.

Functions

The thoracic cage:

- Protects the vital organs within it, including the heart, lungs and large blood vessels.
- Enables breathing by giving attachment to the muscles of respiration – the diaphragm, and the intercostal muscles between the ribs (see Fig. 1.24).

Appendicular skeleton

This consists of the shoulder girdles and upper limbs, and the pelvic girdle and lower limbs (see Fig. 1.19). The appendicular skeleton enables movement of the body and its parts, is the site of blood cell production and protects soft tissues especially blood vessels and nerves which run along the length of long bones.

The shoulder girdles and upper limbs. Each shoulder girdle consists of a clavicle and a scapula. It supports the upper limb, each of which comprises:

- 1 humerus
- 1 radius
- 1 ulna
- 8 carpal bones
- 5 metacarpal bones
- 14 phalanges.

The pelvic girdle and lower limbs. The bones of the pelvic girdle are the two innominate bones and the sacrum. The pelvic girdle supports the lower limb, each of which consists of:

- 1 femur
- 1 tibia
- 1 fibula
- 1 patella
- 7 tarsal bones
- 5 metatarsal bones
- 14 phalanges.

Cavities of the body

The body organs are contained and protected within four cavities: cranial, thoracic, abdominal and pelvic (Fig. 1.22).

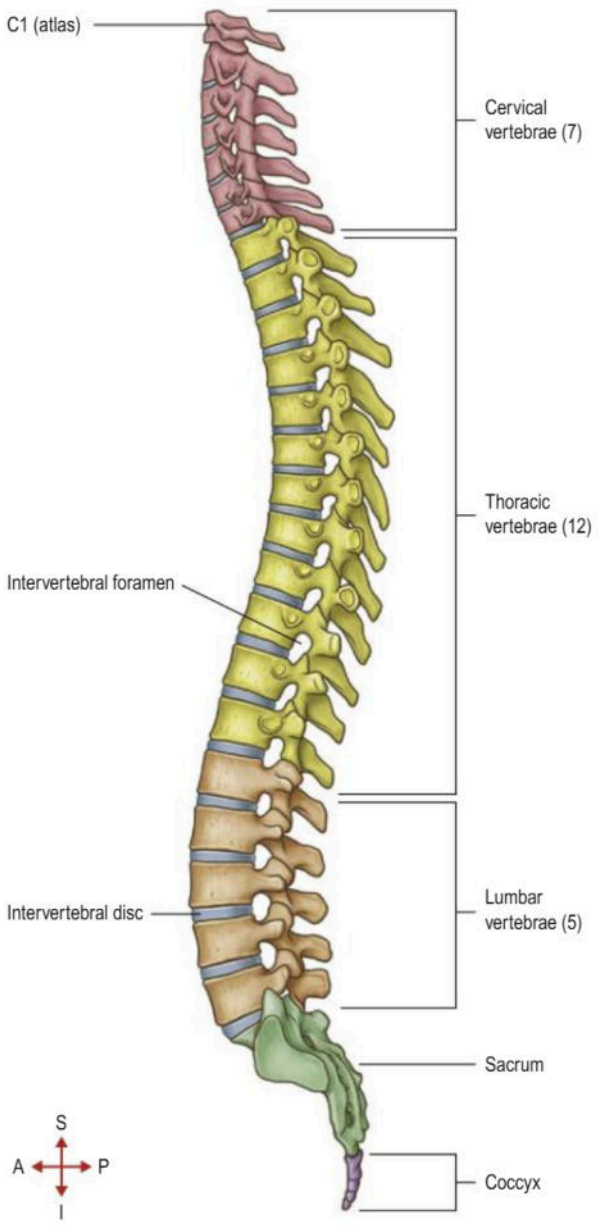

Figure 1.21 The vertebral column. Lateral view.

Cranial cavity

The cranial cavity contains the brain. Its boundaries are formed by the bones of the skull (Fig. 1.23):
Anteriorly – 1 frontal bone
Laterally – 2 temporal bones
Posteriorly – 1 occipital bone
Superiorly – 2 parietal bones
Inferiorly – 1 sphenoid and 1 ethmoid bone and parts of the frontal, temporal and occipital bones.

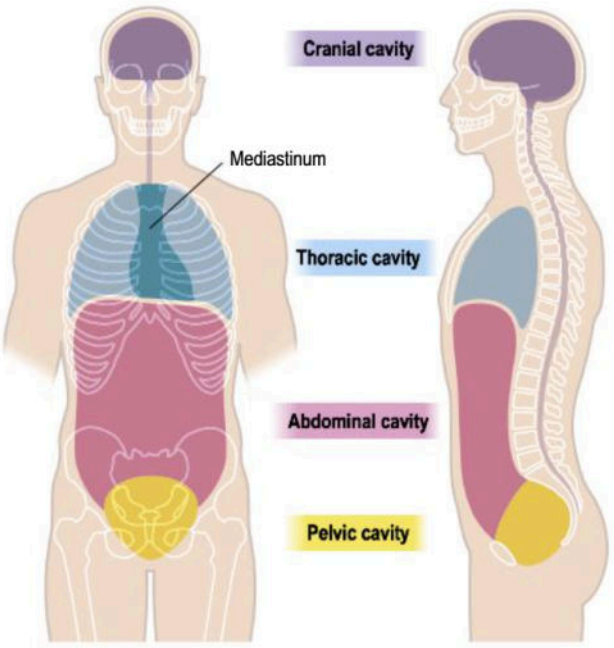

Figure 1.22 The body cavities.

Thoracic cavity

This cavity is situated in the upper part of the trunk. Its boundaries are formed by the thoracic cage and supporting muscles (Fig. 1.24A):
Anteriorly – the sternum and costal cartilages of the ribs
Laterally – 12 pairs of ribs and the intercostal muscles
Posteriorly – the thoracic vertebrae
Superiorly – the structures forming the root of the neck
Inferiorly – the diaphragm, a dome-shaped muscle.

Contents

The main organs and structures contained in the thoracic cavity are shown in Figure 1.24B. These include:
- the trachea, 2 bronchi, 2 lungs
- the heart and numerous large blood vessels including the aorta, superior and inferior venae cavae
- the oesophagus
- lymph vessels and lymph nodes
- some important nerves.

The mediastinum is the space between the lungs, including the structures found there, such as the heart, oesophagus and blood vessels (see Fig. 1.22).

Abdominal cavity

This is the largest body cavity and is oval in shape (Figs 1.25 and 1.26). It occupies most of the trunk and its boundaries are:
Superiorly – the diaphragm, which separates it from the thoracic cavity

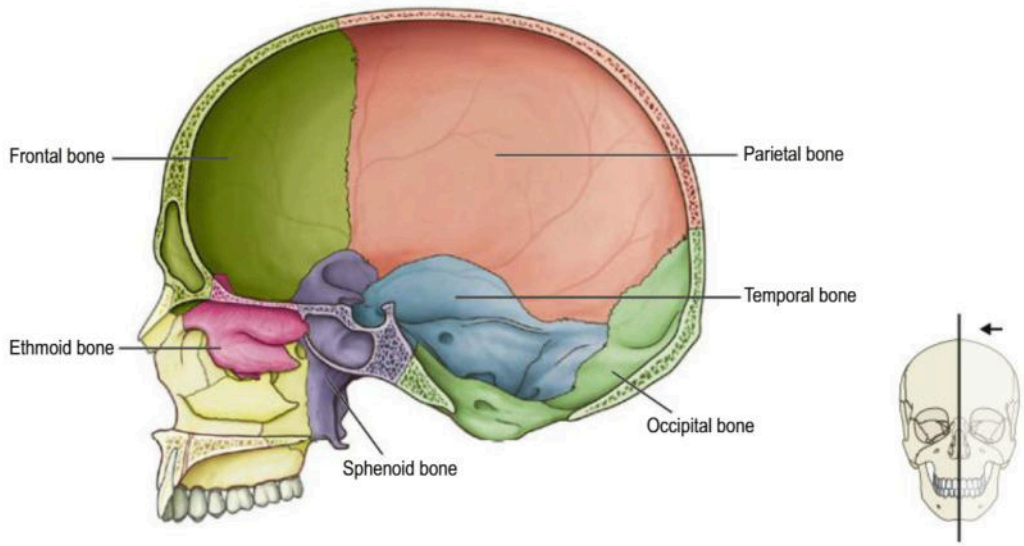

Figure 1.23 The bones forming the cranial cavity. Lateral view.

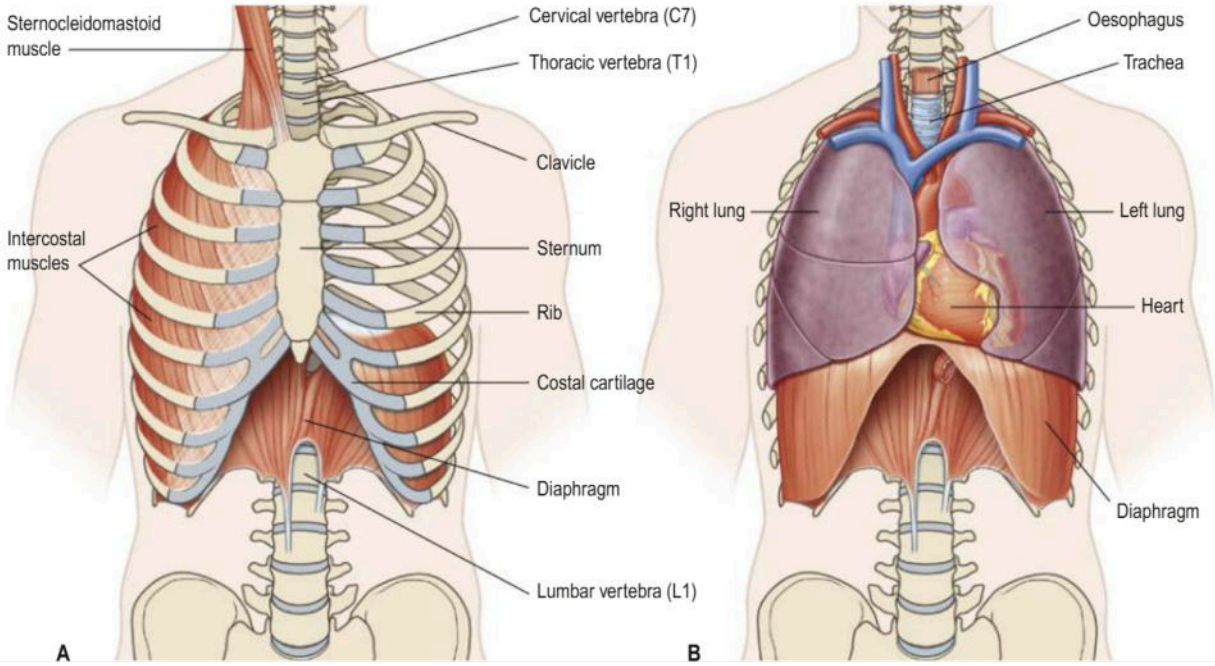

Figure 1.24 The thoracic cavity. (A) Structures forming the walls. (B) Internal organs.

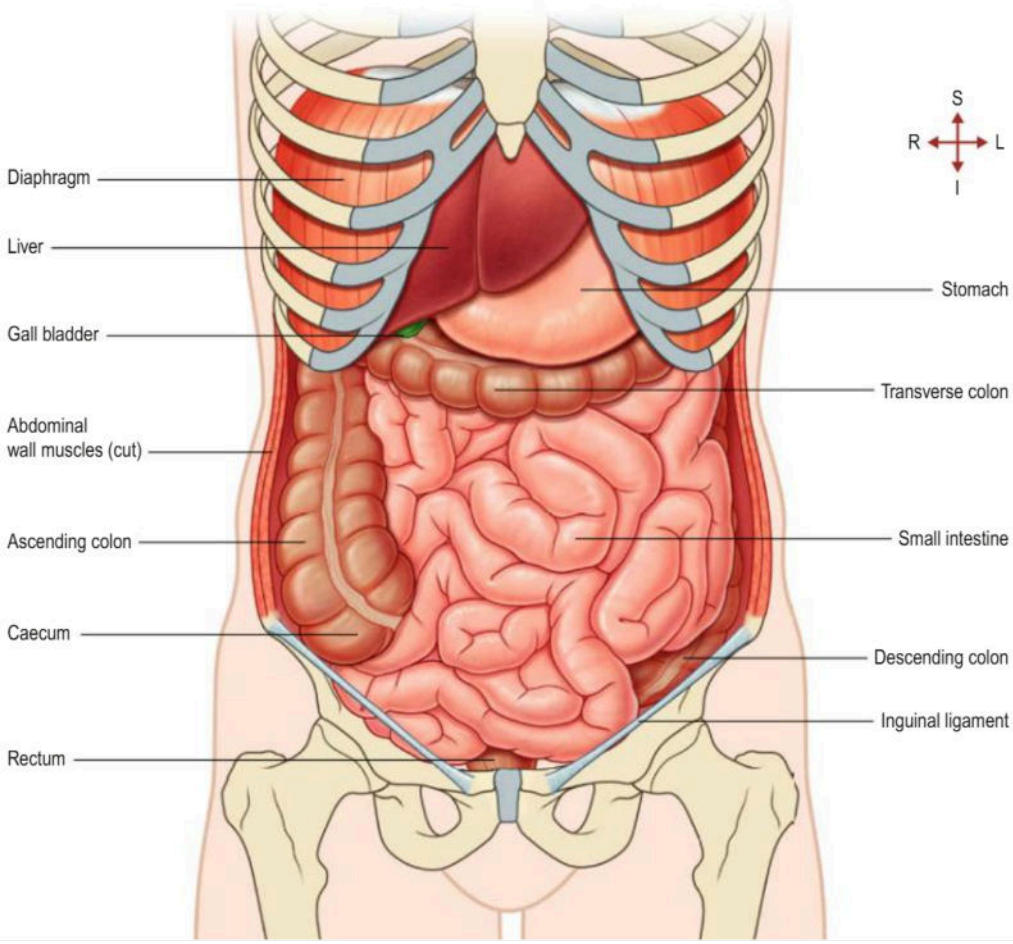

Figure 1.25 Organs occupying the anterior part of the abdominal cavity and the diaphragm (cut).

Anteriorly – the muscles forming the anterior abdominal wall
Posteriorly – the lumbar vertebrae and muscles forming the posterior abdominal wall
Laterally – the lower ribs and parts of the muscles of the abdominal wall
Inferiorly – it is continuous with the pelvic cavity.

The abdominal cavity is lined with a membrane called peritoneum (see Figs 1.28 and 1.29).

By convention, the abdominal cavity is divided into nine regions shown in Figure 1.27, which facilitates consistent description of the positions of the organs and structures it contains.

Contents

Most of the abdominal cavity is occupied by the organs of the digestive system (see Fig. 1.25). These are:
- the stomach, small intestine and most of the large intestine
- the liver, gall bladder, bile ducts and pancreas.

Other abdominal structures include:
- the spleen
- 2 kidneys and the upper part of the ureters
- 2 adrenal (suprarenal) glands
- numerous blood vessels, nerves, lymph vessels and lymph nodes.

Pelvic cavity

The pelvic cavity is roughly funnel-shaped and extends from the lower end of the abdominal cavity (Figs 1.28 and 1.29). Its boundaries are:
Superiorly – it is continuous with the abdominal cavity
Anteriorly – the pubic bones
Posteriorly – the sacrum and coccyx
Laterally – the innominate (hip) bones
Inferiorly – the muscles of the pelvic floor.

Contents

The pelvic cavity contains the following structures:
- sigmoid colon, rectum and anus
- some loops of the small intestine
- the urinary bladder, lower parts of the ureters and the urethra
- in the female, the reproductive organs: the uterus, uterine tubes, ovaries and vagina (see Fig. 1.28)
- in the male, some of the reproductive organs: the prostate gland, seminal vesicles, spermatic cords, deferent ducts, ejaculatory ducts and the urethra (common to the reproductive and urinary systems) (see Fig. 1.29).

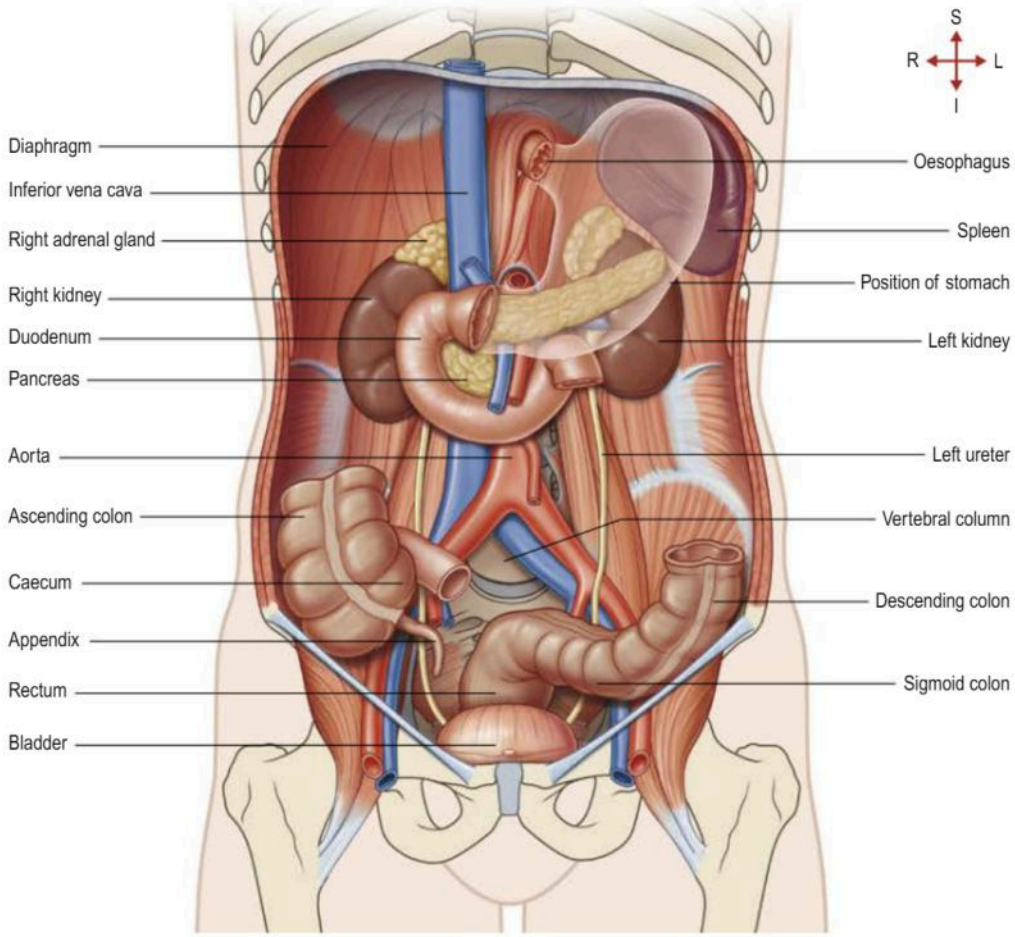

Figure 1.26 Organs occupying the posterior part of the abdominal and pelvic cavities. The stomach is shown as a transparent structure.

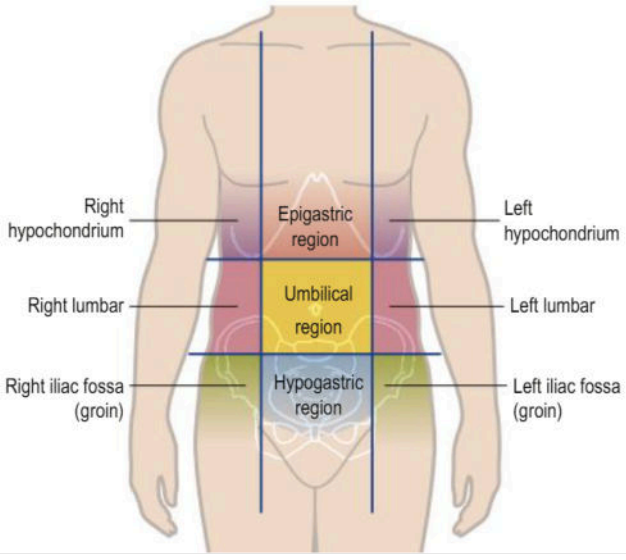

Figure 1.27 Regions of the abdomen.

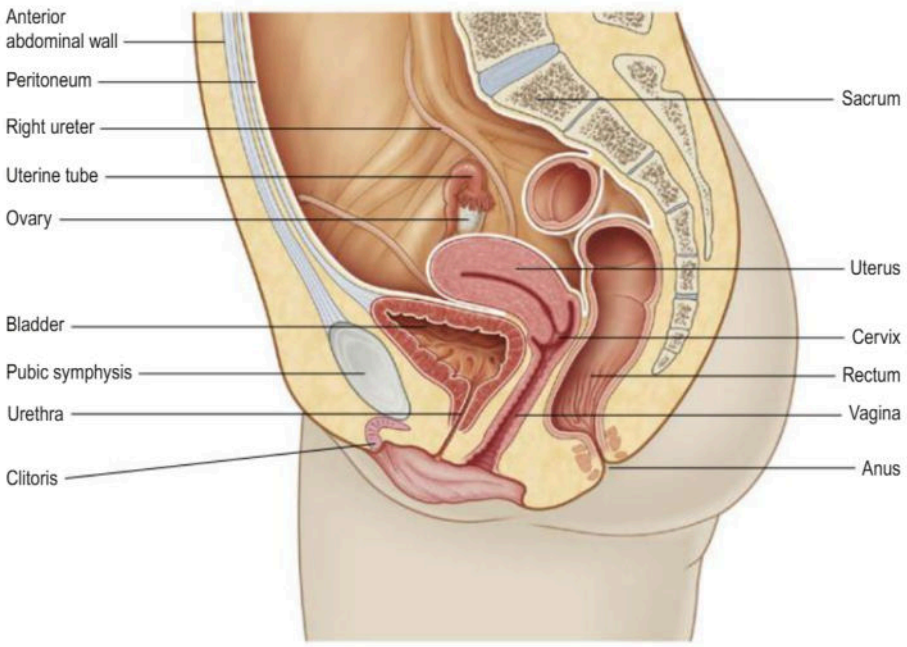

Figure 1.28 Female reproductive organs and other structures in the pelvic cavity. Lateral view.

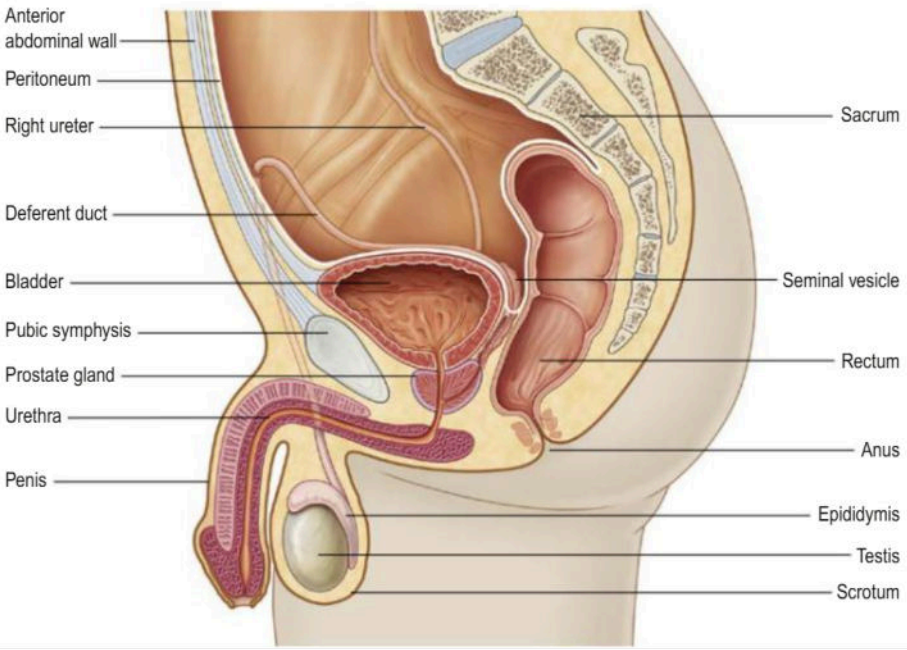

Figure 1.29 The male reproductive system and structures in the pelvic cavity. Lateral view.

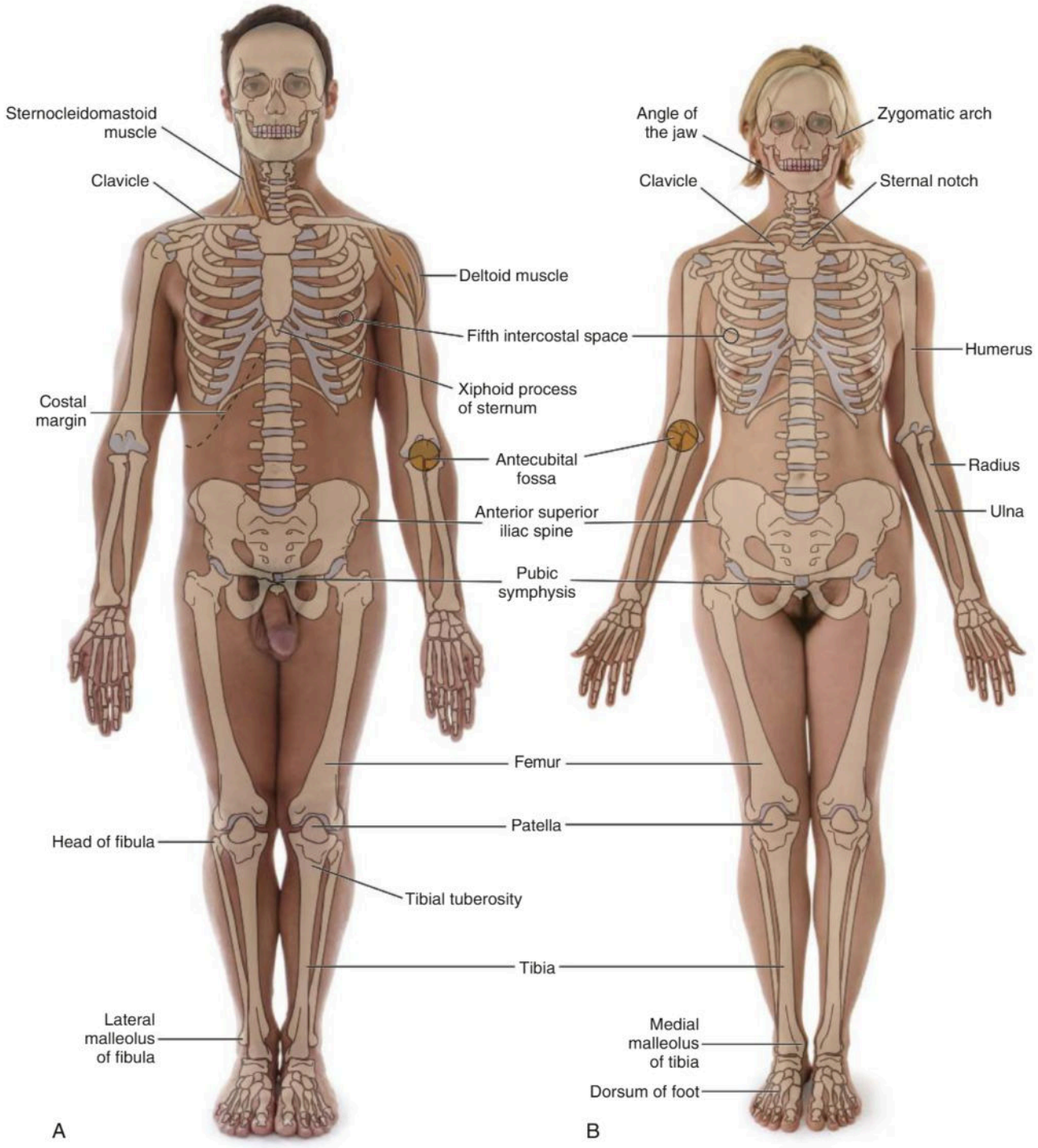

Figure 1.30 Surface anatomy: body landmarks. Anterior view in the male (A) and female (B). (Modified from Patton K, et al. 2019. Brief atlas of the human body. Adapted International Edition, Elsevier.)

Surface anatomy

Accurate identification of surface body features is a key area in the study of human biology. Surface anatomy is the study of the external body features that can be examined without dissection or by visual inspection or palpation. It includes recognition of bony features and other prominent external landmarks that indicate position of deeper, related structures. Body landmarks are often used in healthcare practice to guide clinical assessment, investigations and treatment.

Some of these are shown in Figures 1.30 and 1.31. For example, safe and suitable sites must be identified for giving intramuscular injections, e.g. the deltoid muscle

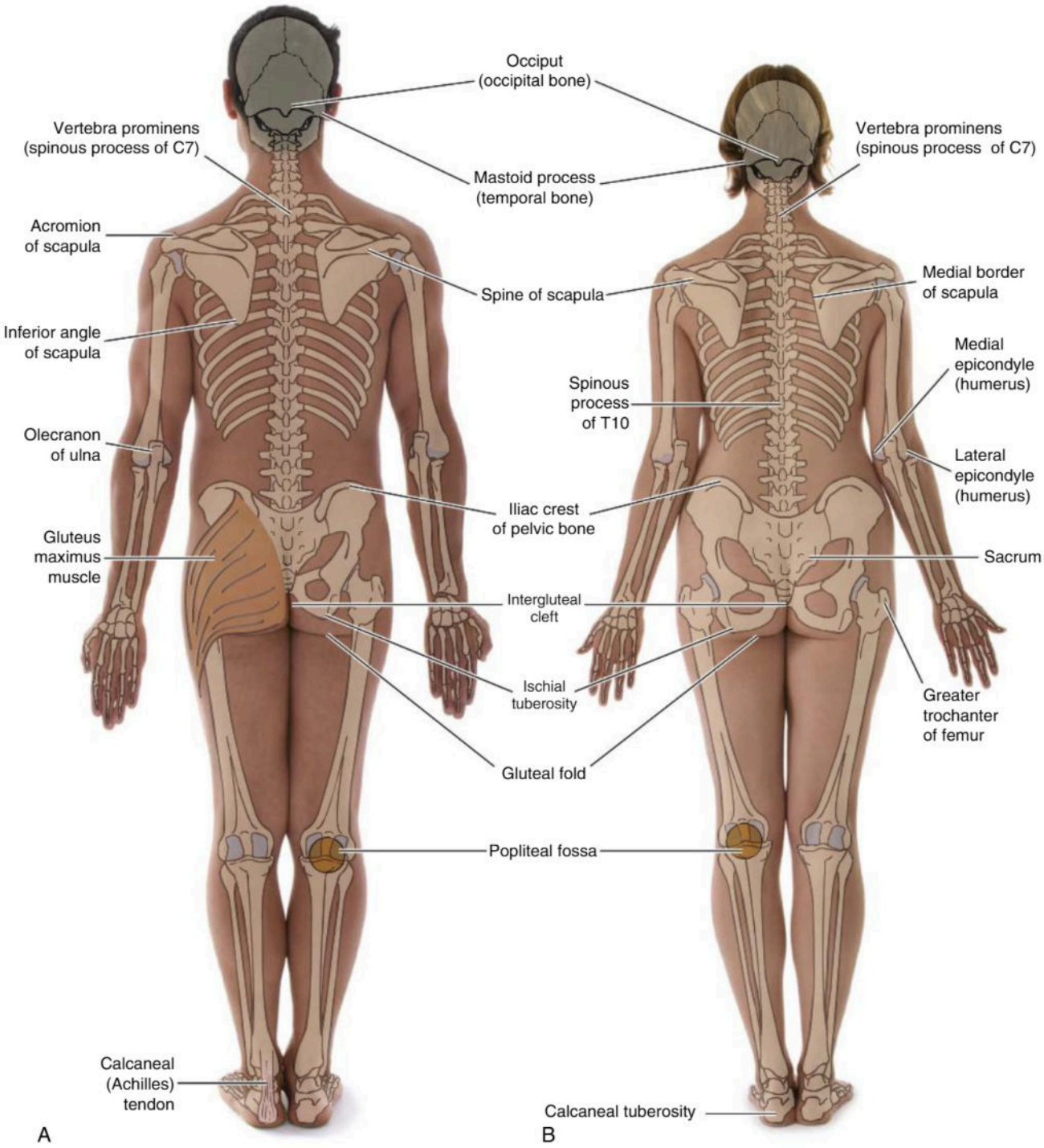

Figure 1.31 Surface anatomy: body landmarks. Posterior view in the male (A) and female (B). (Modified from Patton K, et al. 2019. Brief atlas of the human body. Adapted International Edition, Elsevier.)

(Fig. 1.30) and for venepuncture, e.g. the antecubital fossa (Fig. 1.30). Pulse points are identified using surface landmarks e.g. the popliteal pulse (Fig. 1.31 and see also Fig. 5.27). Identifying the fifth intercostal space is important for stethoscope placement when assessing heart sounds (Fig. 1.30 and see Fig. 5.20). The tissues overlying bony prominences such as the sacrum and greater trochanter are susceptible to damage from sustained pressure and are common sites for the development of pressure (decubitus) ulcers in prolonged immobility. The vertebra prominens (prominent spinous process of C7) can be readily identified and the other spinous processes identified and counted; as a guide, T10 is normally around the level of a woman's bra strap (Fig. 1.31).

The surface of the abdomen can be divided into the nine regions (see Fig. 1.27), which facilitates diagnosis of abdominal disorders and identification of the origin of abdominal pain.

SPOT CHECK

4. Describe the anatomical position and its significance.
5. List the components of the axial skeleton.
6. In which region of the abdominal cavity is the liver situated?

Introduction to ageing

Learning outcomes

After studying this section, you should be able to:

- list the main features of ageing
- outline the implications of ageing human populations.

Many changes occur as the body grows and develops to maturity over the first decades of life. The peak of mature physiological function is often relatively short-lived, as age-related changes begin to impair performance; for example, kidney function begins to decline from about 30 years of age. At both extremes of the lifespan, many aspects of body function are less efficient; for example, temperature regulation is less effective in infants and older adults.

Maturity of most body organs occurs during puberty and maximal efficiency during early adulthood. Most organs are able to repair and replace their tissues, with the notable exceptions of the brain and myocardium (heart muscle). At maturity, many organs have considerable functional reserve, or 'spare capacity', which usually declines gradually thereafter. The functional reserve means that considerable loss of function can occur before physiological changes become evident. Alterations in body function during older life need careful assessment, because ageing is generally associated with decreasing efficiency of body organs and/or increasing frailty. Although a predisposing factor for some conditions, ageing itself is not accompanied by any specific illnesses or diseases.

The process of ageing is poorly understood, although it affects people in different ways. There is no single known cause, although many theories have been proposed, and there is enormous individual variation in the rate of ageing. The lifespan of an individual is influenced by many factors, some of which are hereditary (Ch. 17) and beyond individual control. Others not readily susceptible to individual influence include poverty, which is associated with poor health. However, people's lifestyle choices may also strongly influence longevity; for example, lack of exercise, obesity, cigarette smoking and alcohol misuse contribute to a shorter lifespan.

Several common age-associated changes that occur in particular organs and systems are well recognised, including greying hair and wrinkling of the skin. Further examples are shown in Figure 1.32, and these and other changes are highlighted, together with their physiological and sometimes clinical consequences, at the end of the physiology section in relevant chapters. Increasing age is a risk factor for some diseases, e.g. most cancers, coronary heart disease and dementia.

The World Health Organization (WHO, 2019) predicts that the proportion of the global population aged over 65 years will increase substantially in the coming decades (Fig. 1.33). The 20th century saw the proportion of older people increasing mainly in high-income countries; over the first half of the 21st century, this trend is predicted to spread to most areas of the world, including low- and middle-income countries. Increasing life expectancy will impact on healthcare, and the role of prevention of and early interventions in ill-health will become increasingly important.

SPOT CHECK

7. Explain the term 'functional reserve'.

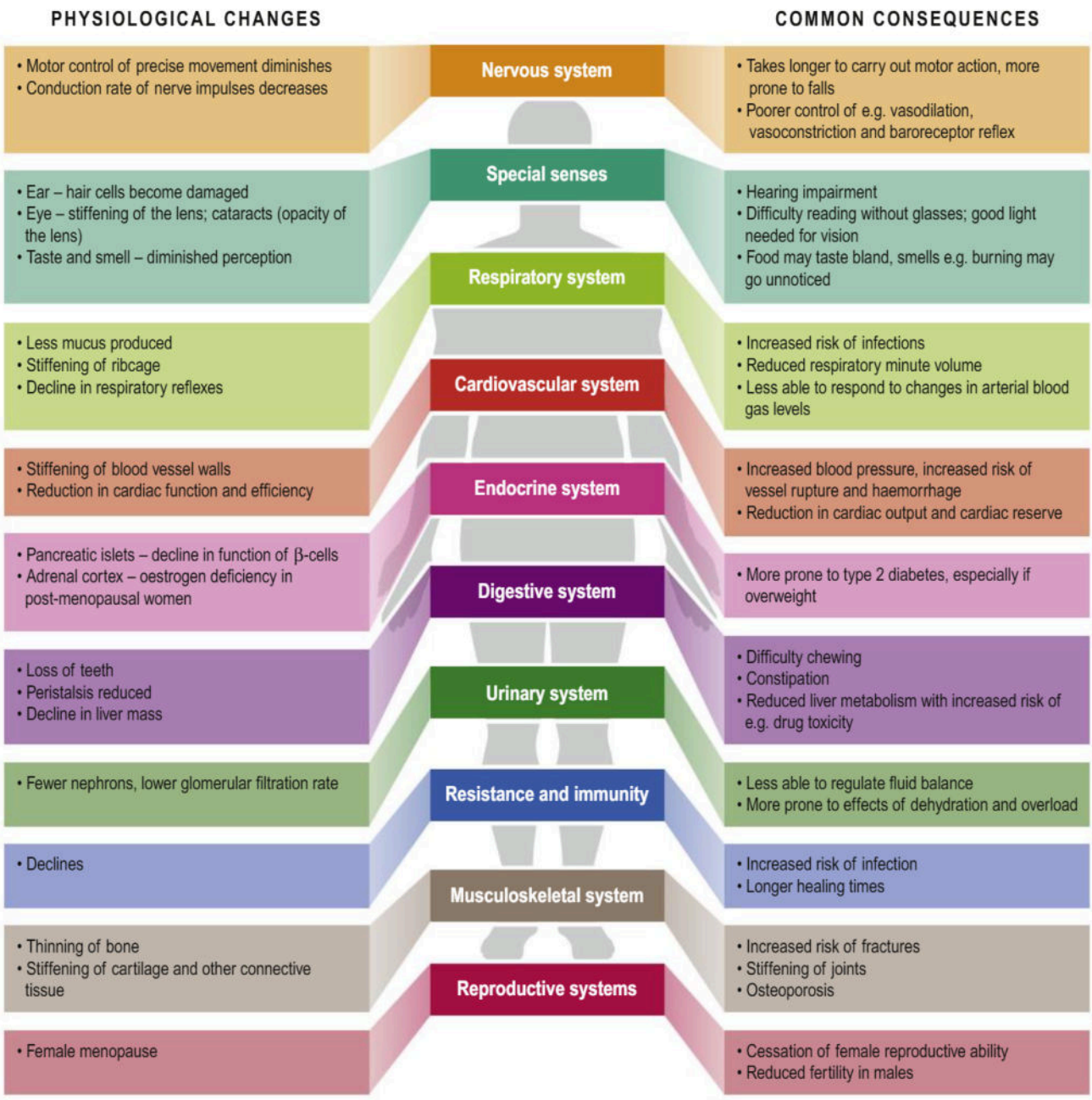

Figure 1.32 Effects of ageing on body systems.

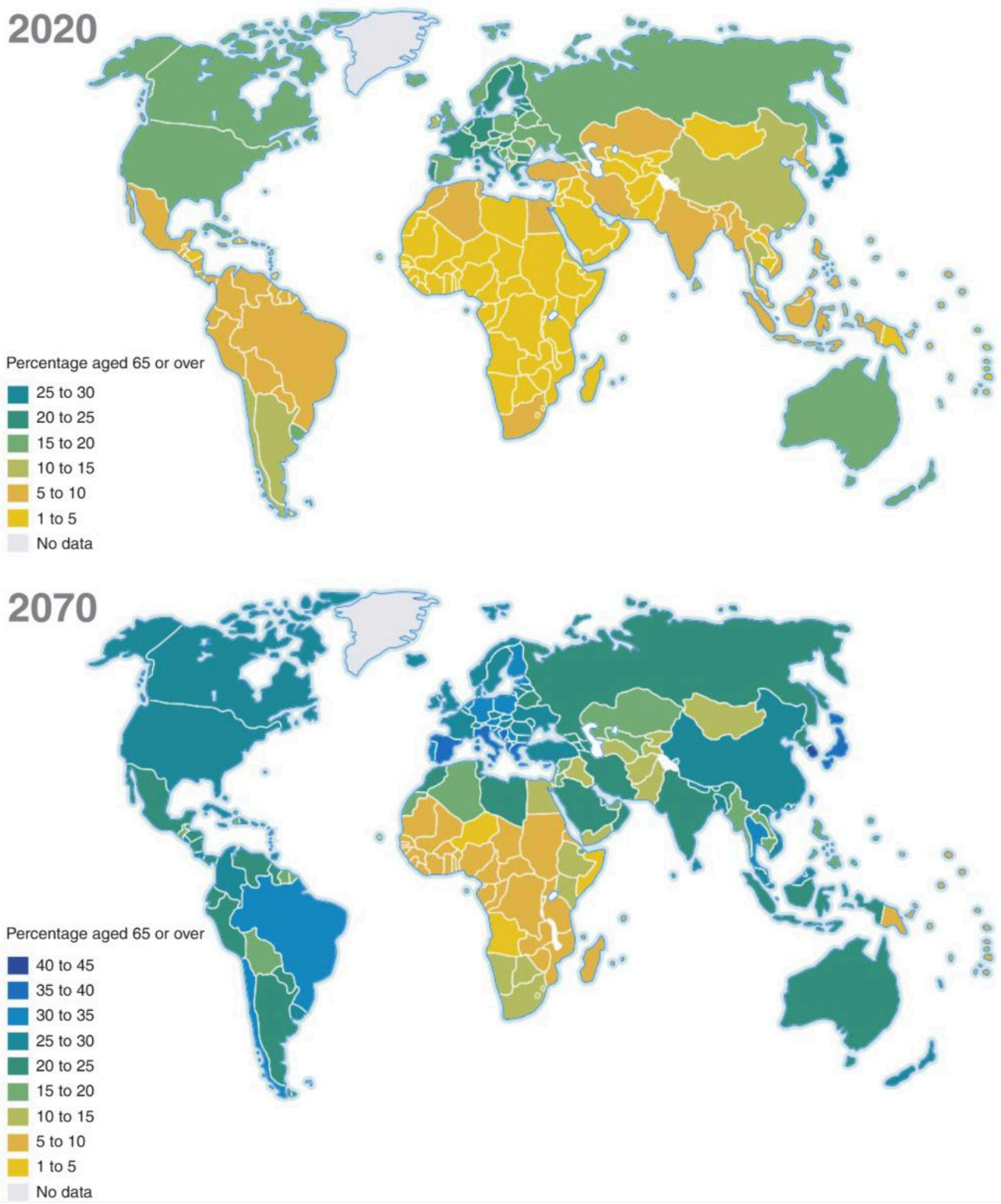

Figure 1.33 Global ageing trends. (United Nations 2019, reproduced with permission from WHO.)

Introduction to the study of illness

Learning outcomes

After studying this section, you should be able to:

- list mechanisms that commonly cause disease
- define the terms aetiology, pathogenesis and prognosis
- name some common disease processes.

To understand the specific diseases described in later chapters, knowledge of the relevant anatomy and physiology is necessary, as well as familiarity with the pathological processes outlined here.

Human beings can suffer from a wide range of illnesses, disorders and diseases, which vary from minor but often very troublesome conditions to the very serious. The study of abnormalities can be made much easier when a systematic approach is adopted. In order to achieve this in later chapters where specific diseases are explained, the headings shown in Box 1.1 will be used as a guide. Causes (aetiology) are outlined first when there are clear links between them and the development, consequences and effects of the disorder.

Aetiology

Diseases are usually caused by one or more broad mechanisms, including:

- genetic abnormalities, either inherited or acquired
- infection by microorganisms, such as bacteria, viruses, microbes or parasites, e.g. worms
- chemicals
- ionising radiation
- physical trauma
- degeneration, e.g. due to excessive use or ageing.

In other conditions, no specific aetiological factors or cause may be identified and they may be described as essential, idiopathic or spontaneous. Although the precise cause of a disease may not be known, predisposing (risk) factors are often well established.

Box 1.1 Suggested framework for understanding diseases

Aetiology: the cause of the disease

Pathogenesis: the nature of the disease process and its effect on normal body functioning

Prognosis: the likely outcome

Complications: potential consequences that might arise if the disease progresses

Pathogenesis

Pathogenesis means the origin and development of a disease. The main processes causing illness or disease are outlined below; these are often used to classify the nature of the disease. Box 1.2 contains a glossary of disease-associated terminology.

Inflammation

Inflammation (p. 417) is a tissue response to any kind of tissue damage, such as trauma or infection. Inflammatory conditions are indicated by the suffix '-itis', e.g. appendicitis.

Tumours

Tumours (p. 59) arise when abnormal cells escape normal growth control mechanisms and proliferate in an unregulated manner. Their proliferation rate exceeds that of normal cell death, causing a mass to develop. Tumours are indicated by the suffix '-oma', e.g. carcinoma.

Abnormal immune mechanisms

Abnormal immune mechanisms (p. 426) are undesirable responses of the normally protective immune system. Allergic conditions (p. 426) are the result of an abnormal immune response to a foreign trigger known as an antigen, e.g. hay fever (p. 292). In autoimmune diseases, such as rheumatoid arthritis (p. 480), the body's immune mechanisms mistakenly attack and damage its own tissues.

Thrombosis, embolism and infarction

These are effects and consequences of abnormal changes in the blood and/or blood vessel walls:

- thrombosis – this is blood clotting inside a blood vessel
- embolism – this is blocking of a blood vessel by a travelling mass, often a blood clot

Box 1.2 Glossary of terminology associated with disease

Acquired: a disorder that develops any time after birth (compare with congenital)

Acute: a disease with sudden onset often requiring urgent treatment (compare with chronic)

Chronic: a long-standing disorder that cannot usually be cured (compare with acute)

Communicable: a disease that can be transmitted (spread) from one individual to another

Congenital: a disorder that one is born with (compare with acquired)

Iatrogenic: a condition that results from healthcare intervention

Sign: an abnormality seen or measured by people other than the patient

Symptom: an abnormality described by the patient

Syndrome: a collection of signs and symptoms that tend to occur together

- infarction – this is death of tissue after its blood supply has been blocked (p. 129)

If such events affect the heart they may cause a heart attack (myocardial infarction). If the brain is affected, they may cause a stroke.

Degeneration

Degeneration is the steady deterioration of a body tissue or structure with time, with associated loss of function. It is often associated with normal ageing but may also arise prematurely as a result of disease, e.g. muscular dystrophy (p. 483).

Metabolic abnormalities

Metabolism is the term meaning the biochemical processes continuously ongoing in living cells on which life depends. Failure or abnormalities in metabolic pathways may impact significantly on health, e.g. diabetes mellitus (p. 261).

Genetic abnormalities

These may be either inherited (e.g. phenylketonuria, p. 497) or caused by environmental factors such as exposure to ionising radiation (p. 61).

SPOT CHECK

8. Compare and contrast the terms 'congenital' and 'acquired'.

References and further reading

World Health Organization, 2019. Department of economics and social affairs, population dynamics. World population prospects 2019. WHO: Geneva. Available online at: https://population.un.org/wpp/Maps/.

Case study

Jason arrived at the scene of an accident where a cyclist had been hit by a passing car. There was already a first aider at the scene but he offered to help. When the paramedics arrived Jason heard the first aider describe the injuries as a suspected broken left femur, an absent pedal pulse on the same side and severe epigastric pain.

Which descriptions accurately describe the injuries?

1. The femur is a bone in:

   a. The upper arm
   b. The forearm
   c. The thigh
   d. The lower leg

2. The femur is:

   a. Superficial to the tibia
   b. Proximal to the tibia
   c. Anterior to the tibia
   d. Inferior to the tibia

3. A pedal pulse is felt:

   a. On the foot
   b. At the calf
   c. Behind the knee
   d. In the groin

4. Epigastric pain arises from:

   a. The head
   b. The upper limb
   c. The lower limb
   d. The abdomen

Review and revise

Complete each of the following statements:

1. The three types of blood vessels are _____, _____ and _____.

2. The menstrual cycle occurs monthly in women between the stages of life called _____ and the _____.

Choose one answer to complete each of the following statements:

3. The blood cells that transport oxygen in the blood are the: ____
   a. Lymphocytes
   b. Erythrocytes
   c. Thrombocytes
   d. Leukocytes

4. The female egg cell is also known as the: _____
   a. Spermatozoon
   b. Zygote
   c. Thrombocyte
   d. Ovum

Indicate whether each of the following statements is true or false:

5. Most body movement is involuntary. _____

6. Lymph nodes act as filters. ____

7. Match each letter in List A to the appropriate number in List B:

List A

_____ (a) Kidney
_____ (b) Catabolism
_____ (c) Erythrocyte
_____ (d) Enzyme
_____ (e) Vein
_____ (f) Hormone
_____ (g) Platelet
_____ (h) Antigen
_____ (i) Pulse
_____ (j) Carbon dioxide

List B

1. Waste product of cellular metabolism
2. Carries blood towards the heart
3. Needed for digestion of nutrients
4. Needed for formation of urine
5. Rate at which the heart beats
6. Chemical messenger that travels in the blood to a target gland
7. Red blood cell
8. Breakdown of larger substances into smaller ones
9. Essential for blood clotting
10. Stimulates a specific immune response

8. Match each letter in List A to the appropriate number in List B:

List A

_____ (a) Pedal
_____ (b) Axillary
_____ (c) Femoral
_____ (d) Cephalic
_____ (e) Thoracic
_____ (f) Frontal
_____ (g) Carpal
_____ (h) Brachial

List B

1. Head
2. Thigh
3. Wrist
4. Arm
5. Armpit
6. Chest
7. Foot
8. Forehead

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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CHAPTER 2

Physiological chemistry and processes

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- Amino acids and proteins 34
- Lipids 35
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- Enzymes 36

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- Fluid compartments 39

Review and revise 42

Because living tissues are composed of chemical building blocks, the study of anatomy and physiology depends on some understanding of biochemistry, the chemistry of life. This chapter introduces core concepts in chemistry that underpin the remaining chapters in this book. Some of the key physiological processes on which body function depends, including homeostasis and the movement of fluids between body compartments, will also be explored.

Atoms, molecules and compounds

Learning outcomes

After studying this section, you should be able to:

- define the following terms: atomic number, atomic weight, isotope, molecular weight, ion, electrolyte, pH, acid and alkali
- describe the structure of an atom
- discuss the types of bond that hold molecules together
- outline the concept of molar concentration
- explain the importance of buffers in the regulation of pH.

All matter in the universe is built of particles called atoms. An element is a substance containing only one type of atom, e.g. carbon, sulphur or hydrogen. Substances containing two or more types of atom combined are called compounds. For example, water is a compound containing both hydrogen and oxygen atoms.

There are 92 naturally occurring elements, but the wide variety of compounds making up living tissues are composed almost entirely of only four of them: carbon, hydrogen, oxygen and nitrogen. Small amounts (about 4% of body weight) of others are present, including sodium, potassium, calcium and phosphorus (in the form of phosphate).

Atomic structure

Atoms are mainly empty space, with a central nucleus containing protons and neutrons surrounded by clouds of tiny orbiting electrons: the subatomic particles (Fig. 2.1). Neutrons carry no electrical charge, but protons are positively charged, and electrons are negatively charged. Because atoms contain equal numbers of protons and electrons, they carry no net charge. Subatomic particles differ also in terms of their mass. Electrons are so small that their mass is negligible, but the bigger neutrons and protons carry one atomic mass unit each. The physical characteristics of electrons, protons and neutrons are summarised in Table 2.1.

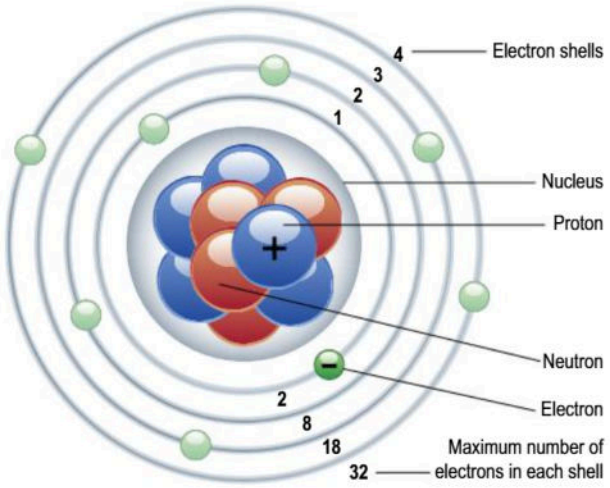

Figure 2.1 The atom, showing the nucleus and four electron shells.

Table 2.1 Characteristics of subatomic particles

Particle	Mass	Electric charge
Proton	1 unit	1 positive
Neutron	1 unit	Neutral
Electron	Negligible	1 negative

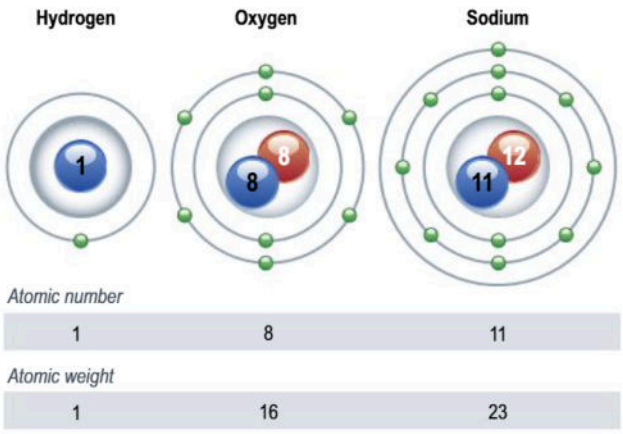

Figure 2.2 The atomic structures of the elements hydrogen, oxygen and sodium.

Atomic number and atomic weight

What makes one element different from another is the number of protons in the nucleus of its atoms (Fig. 2.2). This is called the atomic number and each element has its own unique atomic number. For instance, hydrogen has only 1 proton per nucleus, oxygen has 8 and sodium has 11, so their atomic numbers are 1, 8 and 11, respectively. The atomic weight of an element is the sum of the protons and neutrons in the atomic nucleus.

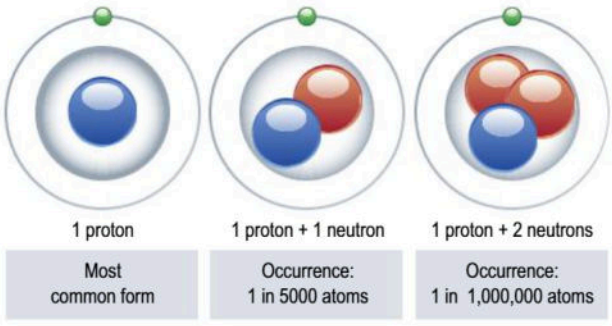

Figure 2.3 The isotopes of hydrogen.

The electrons are shown in Fig. 2.1 as though they orbit in concentric rings round the nucleus. These shells represent the different energy levels of the atom's electrons, not their physical positions. The first energy level can hold only two electrons and is filled first. The second energy level can hold only eight electrons and is filled next. The third and sub-sequent energy levels hold increasing numbers of electrons, each containing more than the preceding level.

When the atom's outer electron shell does not contain a stable number of electrons, the atom is reactive and can donate, receive or share electrons with one or more other atoms to achieve stability. The great number of possible combinations of different types of atom yields the wide range of molecules and compounds from which the world is built and on which biology is based. This is described more fully in the section below discussing molecules and compounds.

Isotopes

Isotopes are atoms of an element that have a different number of neutrons in the nucleus. This does not affect the electrical activity of these atoms because neutrons carry no electrical charge, but it does affect their atomic weight. For example, there are three isotopes of the hydrogen atom. The most common isotope has one proton in the nucleus and one orbiting electron. Another isotope, deuterium, has one proton and one neutron in the nucleus and a single orbiting electron. A third isotope, tritium, has one proton and two neutrons in the nucleus and one orbiting electron (Fig. 2.3).

Because the atomic weight of an element is actually an average atomic weight calculated using all its atoms including all the isotopes, the true atomic weight of hydrogen is 1.008, although for most practical purposes it is taken as 1.

Chlorine has an atomic weight of 35.5 because it contains two isotopes, one with an atomic weight of 35 (with 18 neutrons in the nucleus) and the other 37 (with 20 neutrons in the nucleus). Because the proportion of these two forms is not equal, the average atomic weight is 35.5.

Some isotopes are unstable because of these extra neutrons in the nucleus, and achieve a more stable state by emitting radiation, which can be detected with a Geiger counter. These radioactive isotopes are called radioisotopes, and are useful in many branches of science, including medicine. For

example, the radiation they emit can be used to kill cancer cells, and other radioisotopes are used as tracer materials and injected into the bloodstream to identify obstructions or abnormalities in blood vessels and other hollow passageways and organs.

Molecules and compounds

As mentioned earlier, the atoms of each element have a specific number of electrons around the nucleus. When the number of electrons in the outer shell of an element is either the maximum number (see Fig. 2.1) or a stable proportion of this fraction, the element is described as inert or chemically unreactive, and does not easily combine with other atoms. These elements are the inert gases – helium, neon, argon, krypton, xenon and radon.

Molecules consist of two or more atoms that are chemically combined. The atoms may be of the same element; for example, a molecule of atmospheric oxygen (O_2) contains two oxygen atoms. Most molecules, however, are compounds and contain two or more different elements; for example, a water molecule (H_2O) contains two hydrogen atoms and an oxygen atom.

Compounds containing carbon and hydrogen are classified as organic, and all others as inorganic. Living tissues are based on organic compounds, but the body requires inorganic compounds too.

Covalent and ionic bonds

The vast array of chemical processes on which life is based is completely dependent on the way atoms are combined into molecules and how molecules are broken down again into their constituent atoms. For example, the water molecule is a crucial foundation of all life on Earth. If water was a less stable compound and its hydrogen and oxygen atoms separated readily, human biology could never have evolved. On the other hand, the body is dependent on the breaking down of various molecules (e.g. sugars, fats) to release energy for cellular activities. When atoms are joined together, they form a chemical bond that is generally one of two types: covalent or ionic.

Covalent bonds form when atoms share their electrons with each other. Most molecules are held together with this type of bond; it forms a strong and stable link between its constituent atoms. A water molecule is built using covalent bonds. Hydrogen has one electron in its outer shell, but the optimum number for this shell is two. Oxygen has six electrons in its outer shell, but the optimum number for this shell is eight. Therefore, if one oxygen atom and two hydrogen atoms combine, each hydrogen atom will share its electron with the oxygen atom, giving the oxygen atom a total of eight outer electrons, making it stable. The oxygen atom shares one of its electrons with each of the two hydrogen atoms, so that each hydrogen atom has two electrons in its outer shell, and they too are stable (Fig. 2.4).

Ionic bonds are weaker than covalent bonds and form when electrons are transferred from one atom to another. For

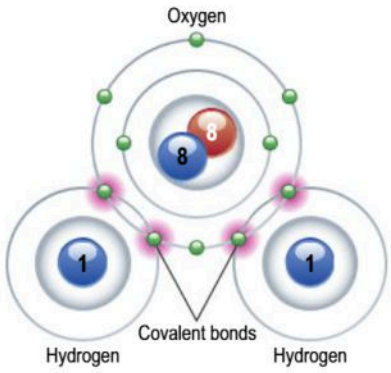

Figure 2.4 A water molecule, showing the covalent bonds between hydrogen and oxygen atoms.

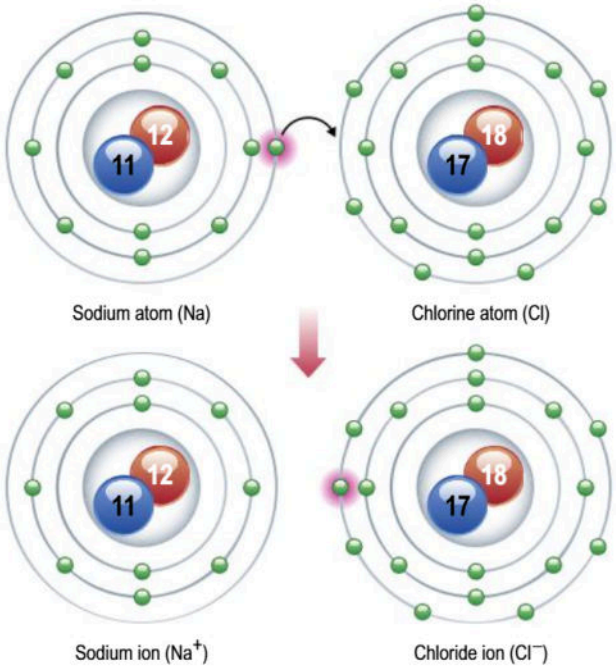

Figure 2.5 Formation of the ionic compound, sodium chloride.

example, when sodium (Na) combines with chlorine (Cl) to form sodium chloride (NaCl), the only electron in the outer shell of the sodium atom is transferred to the outer shell of the chlorine atom (Fig. 2.5). This leaves the sodium atom with eight electrons in its outer (second) shell, which is stable. The chlorine atom also has eight electrons in its outer shell, which, although not filling the shell, is a stable number. The sodium atom is now positively charged because it has given away a negatively charged electron, and the chloride ion is now negatively charged because it has accepted sodium's extra electron. The two atoms therefore stick together because they are carrying opposite, mutually attractive, charges.

When a sodium chloride molecule dissolves in water, the ionic bond breaks and the two atoms separate. The resulting particles are charged because they have traded electrons, so

are no longer called atoms, but ions. Sodium, with the positive charge, is a cation, written Na^+, and negatively charged chloride is an anion, written Cl^-. By convention the number of electrical charges carried by an ion is indicated by the superscript plus or minus signs: so a sodium ion (Na^+) carries one additional positive charge, but a calcium ion (Ca^{2+}) has two. Most ionic compounds dissolve well in water, releasing their charged ions into the solution: these ions in solution are called electrolytes.

Electrolytes

Electrolytes in a solution allow it to conduct electricity. Important electrolytes include sodium (Na^+), chloride (Cl^-), potassium (K^+), calcium (Ca^{2+}), bicarbonate (HCO_3^-) and phosphate (PO_4^{3-}). In the body electrolytes:

- permit the generation and conduction of action potentials, electrical signals essential for muscle and nerve function
- exert osmotic pressure, keeping body fluids in their own compartments
- act as buffers (p. 33) to resist pH changes in body fluids.

Many biological compounds, e.g. carbohydrates, are not ionic, and therefore have no electrical properties when dissolved in water.

Measurement of substances in body fluids

There is no single way of measuring and expressing the concentration of different substances in body fluids. Sometimes the unit used is based on weight in grams or fractions of a gram, e.g. milligrams (mg), micrograms (μg or mcg) or nanograms (ng). If the molecular weight of the substance is known, the concentration can be expressed as moles, millimoles or nanomoles per litre. A related measure is the milliequivalent (mEq) per litre.

Sometimes a substance is measured in terms of its activity; insulin, for instance, is measured in international units (IU).

Table 2.2 gives examples of the normal plasma levels of some important substances, given in molar concentrations and alternative units.

Acids, bases and pH

The measuring system used to express the concentration of hydrogen ions, denoted as $[H^+]$, in a fluid is pH, which is an indicator of its acidity or alkalinity. Living cells are very sensitive to changes in $[H^+]$, and since the biochemical processes of life continually produce or consume hydrogen ions, sophisticated homeostatic mechanisms in the body constantly monitor and regulate pH.

An acid substance releases hydrogen ions when in solution, e.g. hydrochloric acid, HCl, releases H^+ and Cl^- ions when dissolved. On the other hand, a basic (alkaline) substance accepts hydrogen ions, often with the release of hydroxyl (OH^-) ions, e.g. sodium hydroxide, NaOH, which dissociates into Na^+ and OH^- when dissolved. A neutral substance, e.g. water, releases equal concentrations of H^+ and OH^- ions. A salt releases anions and cations other than H^+ or OH^- when dissolved; sodium chloride is therefore a salt because in solution it releases sodium and chloride ions.

The pH scale

The standard scale for measurement of hydrogen ion concentration in solution is the pH scale (Fig. 2.6). The scale measures from 0 to 14, with 7, the midpoint, as neutral; this is the pH of pure water. Water is a neutral molecule, neither acid nor basic (alkaline), because when its molecule breaks up into its constituent ions, it releases equal numbers of H^+ and OH^- ions.

A pH below 7 indicates an acid solution, while readings of above 7 indicate basic (alkaline) solutions. Figure 2.6 shows the pH of some common fluids. A change of one whole number on the pH scale indicates a 10-fold change in $[H^+]$. Therefore, a solution of pH 5 contains 10 times as many hydrogen ions as a solution of pH 6.

Not all acids ionise completely when dissolved in water. The hydrogen ion concentration is, therefore, a measure of the amount of dissociated acid (ionised acid) rather than of

Table 2.2 Some normal plasma levels

Substance	Molar concentrations	Equivalent concentration in other units
Chloride	97–106 mmol/L	97–106 mEq/L
Sodium	135–143 mmol/L	135–143 mEq/L
Glucose	3.5–5.5 mmol/L	60–100 mg/100 mL
Iron	14–35 mmol/L	90–196 mg/100 mL

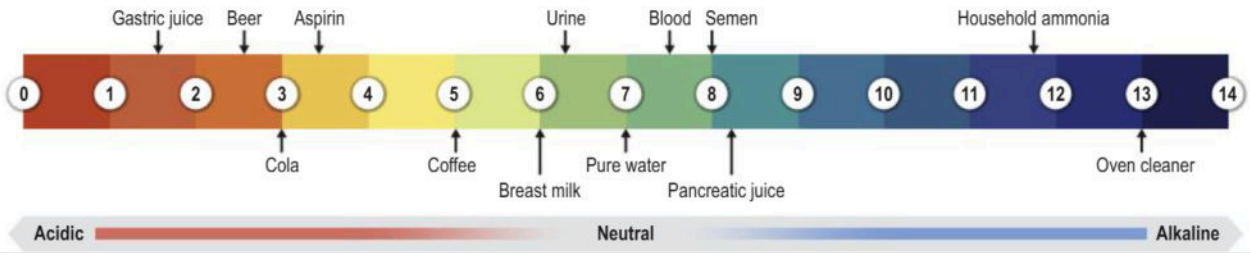

Figure 2.6 The pH scale.

the total amount of acid present. Strong acids dissociate more extensively than weak acids; for example, hydrochloric acid dissociates extensively into H^+ and Cl^-, while carbonic acid dissociates much less freely into H^+ and HCO_3^-.

Likewise, not all bases dissociate completely. Strong bases dissociate more fully, i.e. they release more OH^- than weaker ones.

pH values of body fluids

The pH of body fluids is generally maintained within relatively narrow limits.

With the notable exception of gastric juice, most body fluids are close to neutral pH (Fig. 2.6). The highly acid pH of the gastric juice is maintained by hydrochloric acid secreted by the parietal cells in the walls of the gastric glands. The low pH of the stomach fluids destroys microbes and toxins swallowed in food or drink. Blood pH is kept between 7.35 and 7.45, and outside this narrow range there is severe disruption of normal physiological and biochemical processes. Normal metabolic activity of body cells constantly produces acids and bases, which would tend to alter the pH of the tissue fluid and blood. Chemical buffers, which can reversibly bind hydrogen ions, are responsible for keeping body pH stable.

Buffers

Despite the constant cellular production of acids and bases, body pH is kept stable by systems of buffering chemicals in body fluids and tissues. These buffering mechanisms are important homeostatic mechanisms and temporarily neutralise fluctuations in pH until excess acid or bases can be excreted from the body. The most important organs of excretion are the lungs and the kidneys. The lungs are important regulators of blood pH because they excrete carbon dioxide (CO_2). CO_2 increases $[H^+]$ in body fluids because it combines with water to form carbonic acid, which then dissociates into a bicarbonate ion and a hydrogen ion. Bicarbonate ion is an important body buffer, because it readily combines with and neutralises excess H^+ ions.

$$\underset{\text{carbon dioxide}}{CO_2} + \underset{\text{water}}{H_2O} \leftrightarrow \underset{\text{carbonic acid}}{H_2CO_3} \leftrightarrow \underset{\text{hydrogen ion}}{H^+} + \underset{\text{bicarbonate ion}}{HCO_3^-}$$

The lungs, therefore, help to control blood pH by excreting excess CO_2. The brain detects rising $[H^+]$ in the blood and stimulates breathing, increasing CO_2 loss in exhaled air and reducing $[H^+]$. Conversely, if blood pH becomes too basic, the brain can reduce the respiration rate to increase CO_2 levels and increase $[H^+]$, decreasing pH towards normal (see Ch. 10).

The kidneys regulate blood pH by adjusting the excretion of hydrogen and bicarbonate ions as required, but more slowly than excretion of excess H^+ by the lungs. If pH falls (becomes more acid), H^+ excretion is increased and bicarbonate conserved; the reverse happens if pH rises. In addition, the kidneys generate bicarbonate ions as a by-product of amino acid breakdown in the renal tubules; this process also generates ammonium ions, which are rapidly excreted.

Other buffer systems include body proteins, including haemoglobin in red blood cells, which absorb excess H^+, and phosphate, which is particularly important in controlling intracellular pH. The buffer and excretory systems of the body together maintain the acid–base balance so that the pH range of body fluids remains within normal limits.

Acidosis and alkalosis

The buffer systems just described compensate for most pH fluctuations, but these reserves are limited and, in extreme cases, can become exhausted. When the pH falls below 7.35 and all the reserves of alkaline buffers are used up, the condition of acidosis develops. In the reverse situation, when the pH rises above 7.45, the increased alkali uses up all the acid buffer reserve and the state of alkalosis develops.

Acidosis and alkalosis are both dangerous, particularly to the central nervous system and the cardiovascular system. In practice, acidotic conditions are more common than alkalotic ones because the metabolic processes of the body tend to produce more acid than alkali. Acidosis may follow respiratory problems if the lungs are not excreting CO_2 as efficiently as normal, or if the body is producing excess acids (e.g. diabetic ketoacidosis, p. 263), or in kidney disease if renal H^+ excretion is reduced. Alkalosis may be caused by loss of acidic substances through vomiting, diarrhoea, endocrine disorders or diuretic therapy, which stimulates increased renal excretion. Rarely, it may follow increased respiratory effort, as in an acute anxiety attack where excessive amounts of CO_2 are lost through hyperventilation.

SPOT CHECK

1. How many isotopes of hydrogen exist? Explain the differences in atomic structure between them.
2. Release of cellular acidic waste products does not usually lead to a significant drop in pH. Explain why.

Important biological molecules

Learning outcomes

After studying this section, you should be able to:

- describe in simple terms the chemical nature of sugars, proteins, lipids, nucleotides and enzymes
- discuss the biological importance of each of these important groups of molecules.

Carbohydrates

Carbohydrates (sugars and starches) contain carbon, oxygen and hydrogen, usually in the ratio 1 : 1 : 2. The carbon

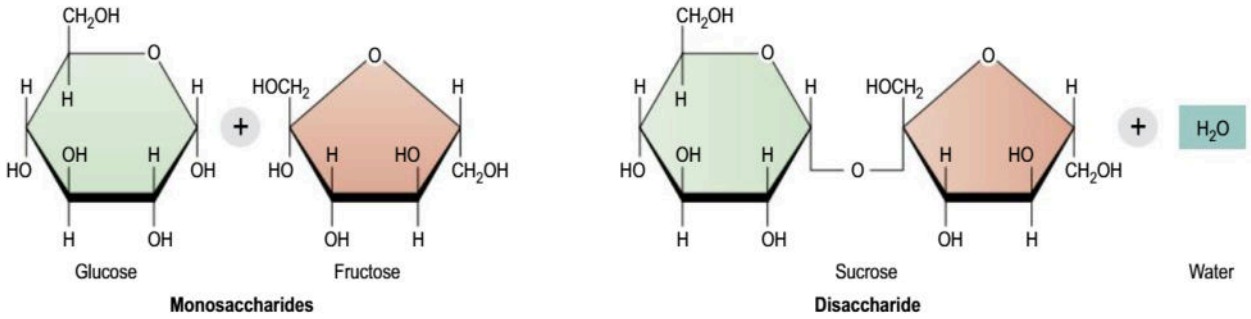

Figure 2.7 The combination of glucose and fructose to make sucrose.

atoms are normally arranged in a ring, with oxygen and hydrogen atoms linked to them. The structures of glucose, fructose and sucrose are shown in Figure 2.7. When two sugar molecules combine to form a bigger sugar molecule, a water molecule is expelled and the bond formed is called a glycosidic linkage.

Glucose, the cells' preferred fuel molecule, is a monosaccharide (mono = one; saccharide = sugar). Monosaccharides can be linked together to form bigger sugar molecules, ranging in size from two sugar units (disaccharides), e.g. sucrose (table sugar) (see Fig. 2.7), to long chains containing many thousands of monosaccharides, such as starch. Such complex carbohydrates are called polysaccharides.

Glucose can be broken down in either the presence (aerobically) or the absence (anaerobically) of oxygen, but the process is much more efficient when O_2 is used. During this process, energy, water and carbon dioxide are released (p. 349). To ensure a constant supply of glucose for cellular metabolism, blood glucose levels are tightly controlled. Functions of sugars include:

- a ready source of energy to fuel cell metabolism (p. 348)
- energy storage, e.g. glycogen (p. 349)
- forming an integral part of the structure of DNA and RNA (p. 487 and p. 490)
- acting as receptors on the cell surface, allowing the cell to bind and respond to biologically important substances such as neurotransmitters, hormones and drugs, and to attach to adjacent cells and structural molecules.

Amino acids and proteins

Amino acids always contain carbon, hydrogen, oxygen and nitrogen, and many also have sulphur, magnesium, phosphate, iron or other trace metals. In human biochemistry, 20 amino acids are used as the principal building blocks of protein, although there are others; for instance, some amino acids are used only in certain proteins, and some are found only in microbial products. The amino acids found in human proteins have a common structure, including an amino group (NH_2), a carboxyl group (COOH) and a hydrogen atom. What makes one amino acid different from the next is their variable side chain. The basic structure and three common amino acids are shown in Figure 2.8. As in the formation

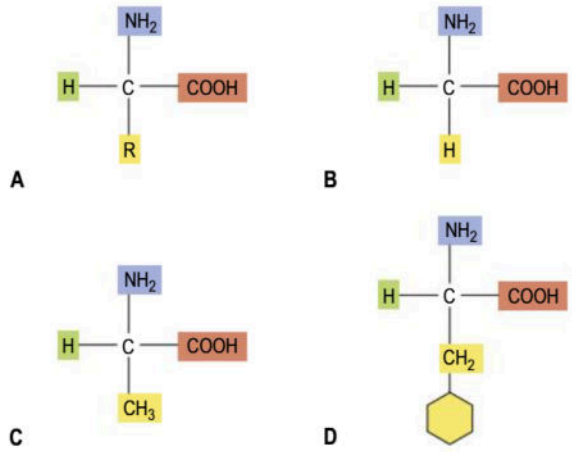

Figure 2.8 Amino acid structures. (A) Common structure. *R*, Variable side chain. (B) Glycine, the simplest amino acid. (C) Alanine. (D) Phenylalanine.

of glycosidic linkages, when two amino acids combine the reaction expels a water molecule and the resulting bond is called a peptide bond.

Proteins are made from amino acids linked together and are the main family of molecules from which the human body is built. Protein chains can vary in size from a few amino acids long to many thousands. They may exist as simple, single strands of protein – for example, some hormones – but more commonly are twisted and folded into complex and intricate three-dimensional structures that may contain more than one kind of protein, or incorporate other types of molecule, e.g. glycoproteins, which contain protein and carbohydrate chains and have a wide range of functions in cell biology including as cell surface markers and receptors. Such complex structures are stabilised by internal bonds between constituent amino acids, and the function of the protein depends on the three-dimensional shape into which it has been twisted. One reason why changes in pH are so damaging to living tissues is that hydrogen ions disrupt these internal stabilising forces and change the shape of the protein (denaturing it), leaving it unable to function. Many important groups of biologically active substances are proteins, e.g.:

- carrier molecules, e.g. haemoglobin (p. 69)
- enzymes (p. 36)

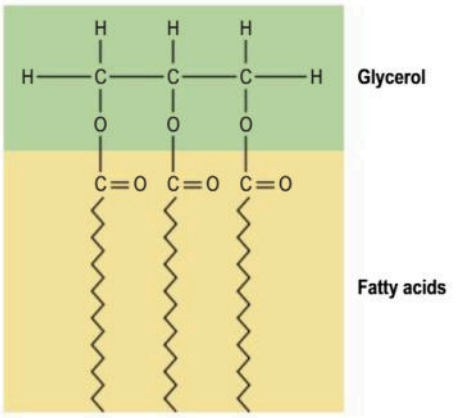

Figure 2.9 Structure of a fat (triglyceride) molecule.

- many hormones, e.g. insulin (p. 251)
- antibodies (p. 422).

Proteins can also be used as an alternative energy source, usually in starvation. The main source of body protein is muscle tissue, so muscle wasting is a feature of starvation (see Fig. 11.2).

Lipids

The lipids are a diverse group of substances all unable to mix with water (i.e. they are hydrophobic). They contain mainly carbon, hydrogen and oxygen atoms, and some contain additional elements, like nitrogen or phosphorus. The most important groups of lipids include:

- Fats (triglycerides), stored in adipose tissue (p. 53) as an energy source. Fat also insulates the body and protects internal organs. A molecule of fat contains three fatty acids attached to a molecule of glycerol (Fig. 2.9). When fat is broken down under optimal conditions, more energy is released than when glucose is fully broken down. Fats are the most common type of lipid and are classified as saturated or unsaturated, depending on the chemical nature of the fatty acids present. Saturated fat tends to be solid, whereas unsaturated fats are fluid (oils).
- Phospholipids, integral to cell membrane structure. They form a double layer, providing a water-repellent barrier separating the cell contents from its environment (p. 43).
- Certain vitamins (p. 310). The fat-soluble vitamins are A, D, E and K.
- Prostaglandins, important chemicals derived from fatty acids. They are involved in inflammation and other processes.
- Steroid hormones, including the sex steroids produced by the gonads (the ovaries and testes, p. 506 and p. 511) and glucocorticoids and mineralocorticoids from the adrenal glands (p. 248). The steroid cholesterol stabilises cell membranes and is the precursor of steroid hormones, as well as being used to make bile salts for digestion.

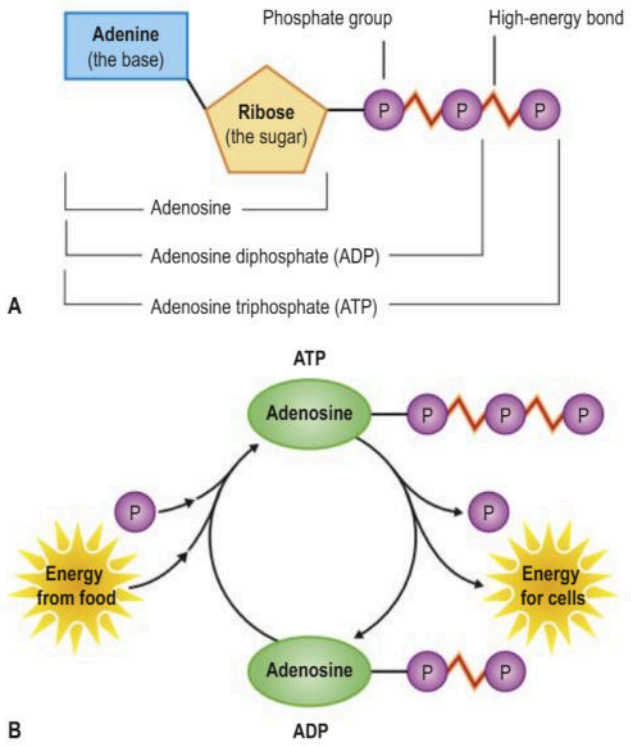

Figure 2.10 Adenosine triphosphate and adenosine diphosphate. (A) Structures. (B) Conversion cycle.

Nucleotides

A nucleotide contains a sugar, a base and a phosphate group.

Nucleic acids

These are the largest molecules in the body and are built from nucleotides. They include deoxyribonucleic acid (DNA, p. 487) and ribonucleic acid (RNA, p. 490).

Adenosine triphosphate

Adenosine triphosphate (ATP) is a nucleotide containing ribose (the sugar), adenine (the base) and three phosphate groups attached to the ribose (Fig. 2.10A). It is sometimes called the energy currency of the body, which implies that the body has to 'earn' (synthesise) it before it can 'spend' it. Cells synthesise ATP in the specialised organelles called mitochondria (p. 46). Many of the body's huge number of reactions release energy, e.g. the breakdown of sugars in the presence of O_2, and mitochondrial enzymes capture the energy released by these reactions, using it to make ATP from adenosine diphosphate (ADP). When the cells need chemical energy to fuel metabolic activities, ATP is broken down again into ADP, releasing water, a phosphate

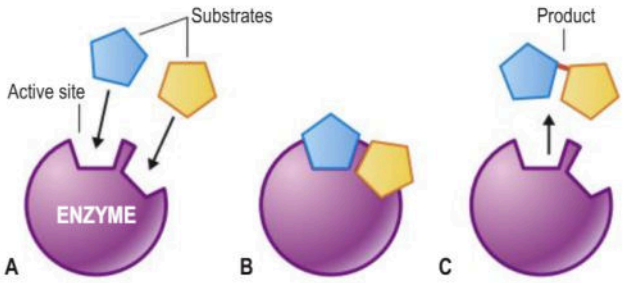

Figure 2.11 Action of an enzyme. (A) Enzyme and substrates. (B) Enzyme–substrate complex. (C) Enzyme and product.

group, and energy from the splitting of the high-energy phosphate bond (Fig. 2.10B). Energy generated from ATP breakdown fuels muscle contraction, motility of spermatozoa, anabolic reactions and the transport of materials across membranes.

Enzymes

Many of the body's chemical reactions can be reproduced in a test-tube. However, the rate at which the reactions then occur usually plummets to the extent that, for all practical purposes, chemical activity ceases. Body cells have developed a solution to this problem – they are equipped with a huge array of enzymes. Enzymes are proteins that act as catalysts for biochemical reactions: that is, they speed the reaction up but are not themselves changed by it, and so can be used over and over again. Enzymes are very selective and usually catalyse only one specific reaction or closely related groups of reactions. The molecule (or molecules) entering the reaction is called the substrate and binds to a very specific area on the enzyme, called the active site. While the substrate(s) is bound to the active site the reaction proceeds, and once it is complete the product (or products) of the reaction breaks away from the enzyme and the active site is ready for use again (Fig. 2.11).

Enzyme action is reduced or stopped altogether if conditions are unsuitable. Increased or decreased temperature is likely to reduce activity, as is any change in pH. Some enzymes require the presence of a cofactor, an ion or small molecule that allows the enzyme to bind its substrate(s). Some vitamins act as cofactors.

Enzymes can catalyse both synthetic (anabolic) and breakdown (catabolic) reactions, and enzyme names usually end in -ase. When an enzyme catalyses the combination of two or more substrates into a larger product, this is called an anabolic reaction, for example the synthesis of glycogen from individual molecules of glucose for storage is catalysed by glycogen synthase. Catabolic reactions involve the breakdown of the substrate into smaller products, as occurs during the digestion of foods in the gastrointestinal tract so that absorption can take place, for example the breakdown of fats in the small intestine by lipase.

Box 2.1 Examples of physiological variables

Core temperature
Water and electrolyte concentrations
pH (acidity or alkalinity) of body fluids
Blood glucose levels
Blood and tissue oxygen and carbon dioxide levels
Blood pressure

SPOT CHECK

3. How do the structures of amino acids and monosaccharides differ from each other?
4. Explain the mechanism of action of enzymes.

The internal environment and homeostasis

Learning outcomes

After studying this section, you should be able to:

- define the terms 'internal environment' and 'homeostasis'
- compare and contrast negative and positive feedback control mechanisms
- outline the potential consequences of homeostatic imbalance.

The external environment is the collection of physical, chemical and biological conditions external to a living organism. It is the source of oxygen and nutrients required by all cells, but it is constantly changing and is often hostile to the body.

The internal environment is the water-based medium in which body cells exist. Cells are bathed in fluid called interstitial or tissue fluid, from which they absorb oxygen and nutrients and into which they excrete their wastes. The composition of the interstitial fluid is largely determined by the circulating blood, which supplies oxygen and nutrients and absorbs and carries away wastes.

Homeostasis

The composition of the internal environment is tightly controlled, and this fairly constant state is called homeostasis. Literally, this term means 'unchanging', but in practice it describes a dynamic, ever-changing situation where a multitude of physiological mechanisms and measurements are constantly adjusted to keep them

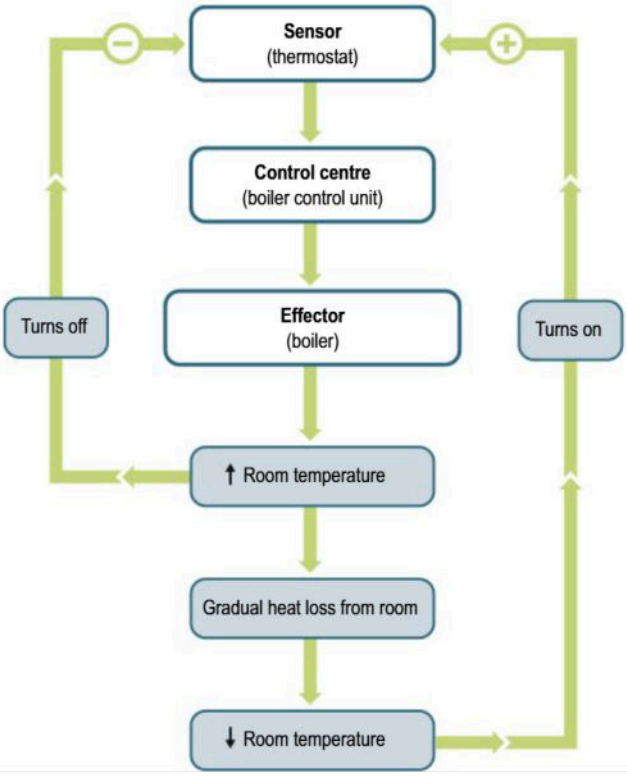

Figure 2.12 Example of a negative feedback mechanism. Control of room temperature by a domestic boiler.

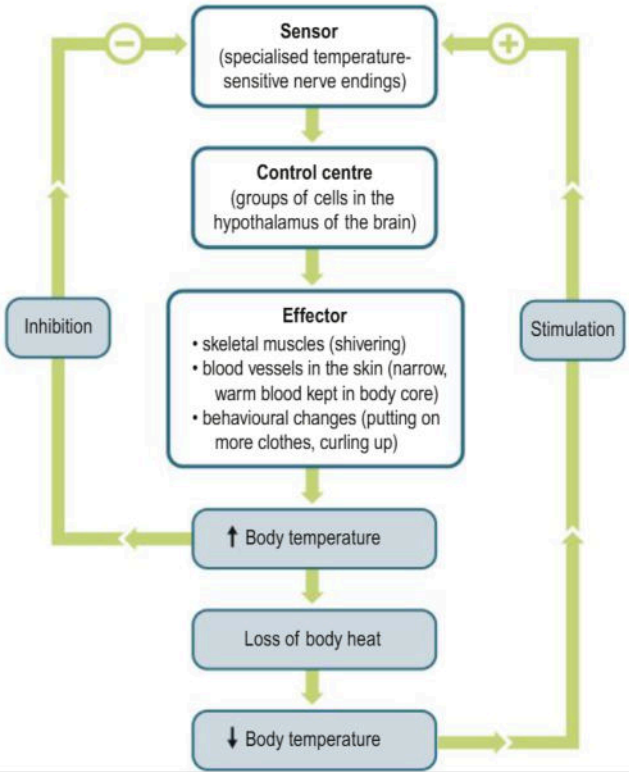

Figure 2.13 Example of a physiological negative feedback mechanism. Control of body temperature.

within narrow limits. When this balance is threatened or lost, there is a serious risk to the well-being of the individual. Box 2.1 lists some important physiological variables maintained within narrow limits by homeostatic control mechanisms.

Control systems

Homeostasis is maintained by control systems that detect and respond to changes in the internal environment. A control system has three basic components: sensor (detector), control centre and effector. The control centre determines the limits within which the variable factor should be maintained. It receives and integrates information from the sensor. When the incoming information indicates that an adjustment is needed, the control centre responds and changes its output to the effector, which actually makes the change. This dynamic process allows constant, flexible readjustment of many physiological variables. Nearly all are controlled by negative feedback mechanisms. Positive feedback is much less common but important examples include control of uterine contractions during childbirth and blood clotting.

Negative feedback mechanisms

Negative feedback (Fig. 2.12) means that any movement of a control system away from its normal set point is negated (reversed). If a variable rises, negative feedback brings it down again, and if it falls, negative feedback brings it back up to its normal level. The response to a change therefore reverses the change, keeping the system in a steady state and maintaining homeostasis.

Control of body temperature is similar to the non-physiological example of a domestic central heating system. The thermostat (temperature sensor) measures changes in room temperature. The thermostat is connected to the boiler control unit (control centre), which controls the boiler (effector). The boiler control unit constantly compares the information from the thermostat with the preset temperature range and, when necessary, adjusts boiler activity to alter the room temperature. When the thermostat senses that the room temperature is low, the boiler control unit switches the boiler on. The result is heat production by the boiler, warming the room. When the preset maximum temperature is reached, the system is reversed. The thermostat detects the higher room temperature and the boiler control unit turns the boiler off. Heat production from the boiler stops and the room slowly cools as heat is lost. This series of events is a negative feedback mechanism allowing continuous self-regulation, or control, of a variable factor within a narrow range.

Body temperature is one example of a physiological variable controlled by negative feedback (Fig. 2.13). A fall in body temperature below the preset level (close to 37°C)

is detected by specialised temperature-sensitive nerve endings, mainly in the skin. They relay this information to the body's temperature control centre, found in the hypothalamus of the brain. The hypothalamus then activates mechanisms that raise body temperature (effectors). These include:

- stimulation of skeletal muscles, causing shivering
- constriction of the blood vessels in the skin, reducing blood flow and heat loss through the skin
- behavioural changes, e.g. we put on more clothes, get up and move around or have a hot drink.

When body temperature rises within the normal range again, the temperature-sensitive nerve endings are no longer stimulated and their signals to the hypothalamus stop. Therefore, shivering stops and blood flow through the skin returns to normal.

Most of the homeostatic controls in the body use negative feedback mechanisms to prevent sudden and serious changes in the internal environment. Many more of these are explained in the following chapters.

Positive feedback mechanisms

There are only a few of these cascade or amplifier systems in the body. In positive feedback mechanisms, the stimulus progressively increases the response, so that as long as the stimulus is continued, the response is progressively amplified. Examples include blood clotting and uterine contractions during labour.

During labour, contractions of the uterus are stimulated by the hormone oxytocin. These force the baby's head into the uterine cervix, stimulating stretch receptors there. In response to this, more oxytocin is released, further strengthening the contractions and progressing labour. After the baby is born the stimulus (stretching of the cervix) is no longer present and so the release of oxytocin stops (see Fig. 9.5).

Homeostatic imbalance

The body's homeostatic mechanisms are sophisticated and highly efficient, but their capacity to adapt to stress is limited. If the change in a system is excessive, especially if it happens rapidly, they may not be able to adapt and the system may shift outside the normal physiological range. This can lead to disruption or disease if it is not corrected.

SPOT CHECK

5. Core body temperature is usually kept very close to 37°C. Using the terms 'negative feedback', 'hypothalamus' and 'effectors', explain what happens when the external temperature begins to fall.

Body fluids

Learning outcomes

After studying this section, you should be able to:

- explain why homeostatic control of the composition of these fluids is vital to body function, using examples
- compare and contrast the processes of diffusion and osmosis
- define the terms 'intracellular fluid' and 'extracellular fluid'
- describe how molecules move within and between fluid compartments.

Movement of substances within body fluids

Movement of substances within and between body fluids, sometimes across a barrier such as the cell membrane, is essential in normal physiology.

In liquids or gases, molecules distribute from an area of high concentration to one of low concentration, assuming that there is no barrier in the way. A concentration gradient is said to exist between an area of high concentration and an area of low concentration, and movement of substances occurs *down* the concentration gradient, or downhill, until the molecules are evenly distributed, i.e. equilibrium is reached. No energy is required for such movement, so this process is described as passive.

There are many examples in the body of substances moving uphill, i.e. against the concentration gradient; in this case, energy is required, usually from the breakdown of ATP. These processes are called active. Movement of substances across cell membranes by active transport is described on page 44.

Passive movement of substances in the body usually proceeds in one of two main ways: diffusion or osmosis.

Diffusion

Diffusion is the movement of molecules from an area of high concentration to an area of low concentration, and occurs mainly in gases, liquids and solutions. Sugar molecules heaped at the bottom of a cup of coffee that has not been stirred will, in time, become evenly distributed throughout the liquid by diffusion (Fig. 2.14). The process of diffusion is speeded up if the temperature rises and/or the concentration of the diffusing substance is increased.

Diffusion can also occur across a semipermeable membrane, such as the cell membrane or the capillary wall. Only molecules small or soluble enough to cross

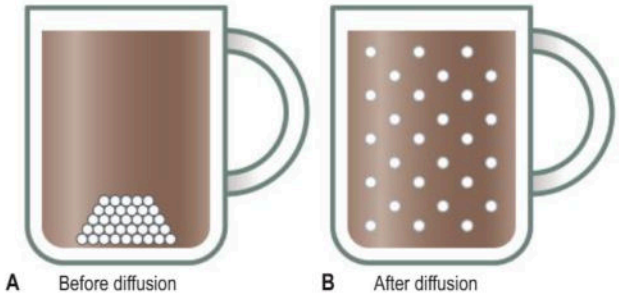

Figure 2.14 Diffusion. A spoonful of sugar in a cup of coffee. (A) Before diffusion. (B) After diffusion.

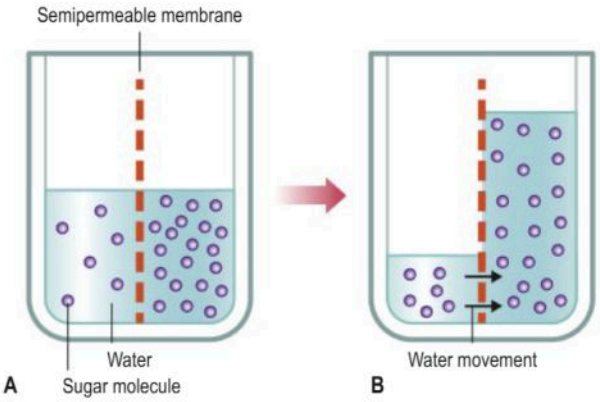

Figure 2.15 Osmosis across a semipermeable membrane. The pores in the membrane are too small to allow the sugar molecules through, so only water can pass. (A) The sugar concentration in the right hand compartment is higher than in the left. (B) To keep the sugar concentration the same on both sides of the membrane, water molecules move into the right hand compartment.

the membrane can diffuse through. For example, oxygen diffuses freely through the walls of the alveoli (air sacs in the lungs) where oxygen concentrations are high, and the thin walls of blood capillaries into the bloodstream, where oxygen concentrations are low. However, blood cells and large protein molecules in the plasma are too large to cross and so remain in the blood.

Osmosis

While diffusion of molecules across a semipermeable membrane results in equal concentrations on both sides of the membrane, osmosis (Fig. 2.15) refers specifically to diffusion of water down its concentration gradient through a semipermeable membrane. This is usually because any other molecules present are too large to pass through the pores in the membrane. The force with which this occurs is called the osmotic pressure. Imagine two sugar solutions separated by a semipermeable membrane whose pores are too small to let the sugar molecules through. On one side, the sugar solution is twice as concentrated as on the other. After a period of time, the concentration of sugar molecules will have equalised on both sides of the membrane, not because sugar

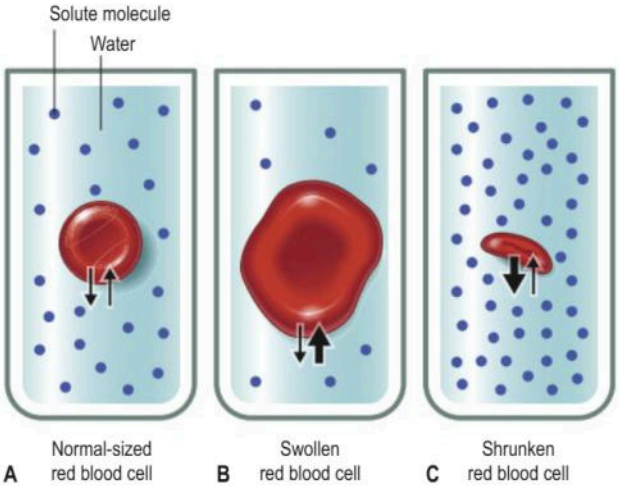

Figure 2.16 Osmosis. Net water movement when a red blood cell is suspended in solutions of varying concentrations (tonicity). (A) Isotonic solution. (B) Hypotonic solution. (C) Hypertonic solution.

molecules have diffused across the membrane, but because osmotic pressure across the membrane 'pulls' water from the dilute solution into the concentrated solution, i.e. water has moved down its concentration gradient. Osmosis proceeds until equilibrium is reached, at which point the solutions on each side of the membrane are of the same concentration, although not the same volume (see Fig. 2.15) and are said to be isotonic. The importance of careful control of solute concentrations in the body fluids can be illustrated by looking at what happens to a cell (e.g. a red blood cell) when it is exposed to solutions that differ from normal physiological conditions.

Plasma osmolarity is maintained within a very narrow range because if the plasma water concentration rises, i.e. the plasma becomes more dilute than the intracellular fluid within the red blood cells, then water moves down its concentration gradient across their membranes and into the red blood cells. This may cause the red blood cells to swell and burst. In this situation, the plasma is said to be hypotonic – it is more dilute than the fluids within the red blood cells. Conversely, if the plasma water concentration falls so that the plasma becomes more concentrated or hypertonic than the intracellular fluid within the red blood cells, water passively moves by osmosis from the blood cells into the plasma and the blood cells shrink (Fig. 2.16).

Fluid compartments

The total body water in adults of average build is about 40 litres, around 60% of body weight. This proportion is higher in babies, young people and adults of below average weight. It is lower in the elderly and in obesity in all age groups. It is also lower in females than males because females have proportionately more adipose tissue than muscle tissue than males, and adipose tissue is only 10% water compared to 75% in muscle tissue.

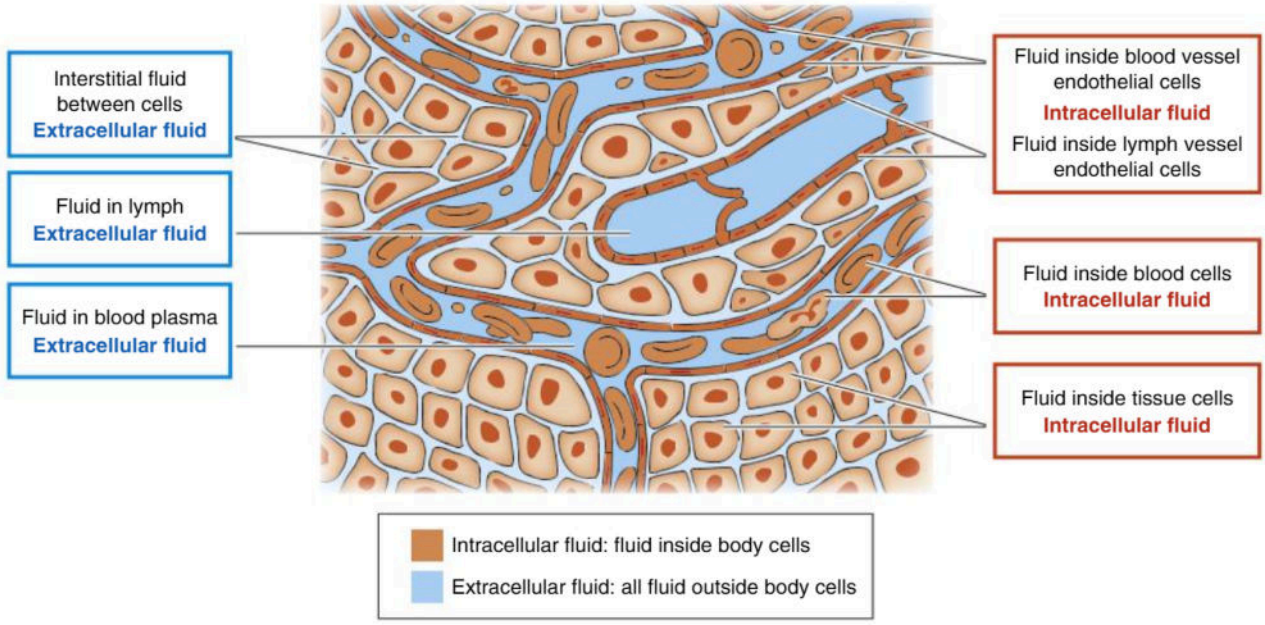

Figure 2.17 The two main fluid compartments of the body: intracellular fluid (orange) and extracellular fluid (blue).

The two main fluid compartments of the body are the intracellular fluid, which is all fluid inside the body cells, and the extracellular fluid, which is all fluid found outside cells, including interstitial fluid and blood plasma (Fig. 2.17). Water and very small solutes exchange freely between these two compartments across the cell membranes, but larger molecules depend on specific transport mechanisms and so their movement is controlled.

Most body water is intracellular (about 70%, or 28 litres of the average 40 litres). The remaining 30% (12 litres) is extracellular, mostly in the interstitial fluid bathing the tissues, with nearly all the remainder found in plasma (Fig. 2.18).

About 22% of body weight is extracellular water and about 38% is intracellular water.

Extracellular fluid

The extracellular fluid (ECF) consists mainly of blood plasma, lymph, cerebrospinal fluid and interstitial (tissue) fluid. Other extracellular fluids are present in very small amounts; their role is mainly in lubrication, and they include joint (synovial) fluid, pericardial fluid (around the heart) and pleural fluid (around the lungs).

Interstitial fluid bathes all body cells except the outer layers of skin. It is the medium through which substances diffuse from the blood to body cells, and from cells to the blood. Every body cell in contact with ECF is directly dependent on the composition of that fluid for its well-being. Even slight changes can cause permanent damage; therefore, ECF composition is closely regulated. For example, a fall in plasma potassium levels may cause muscle weakness and cardiac arrhythmia because of increased excitability of muscle and nervous tissue. Rising blood potassium also interferes with cardiac function and can even cause the heart to stop beating.

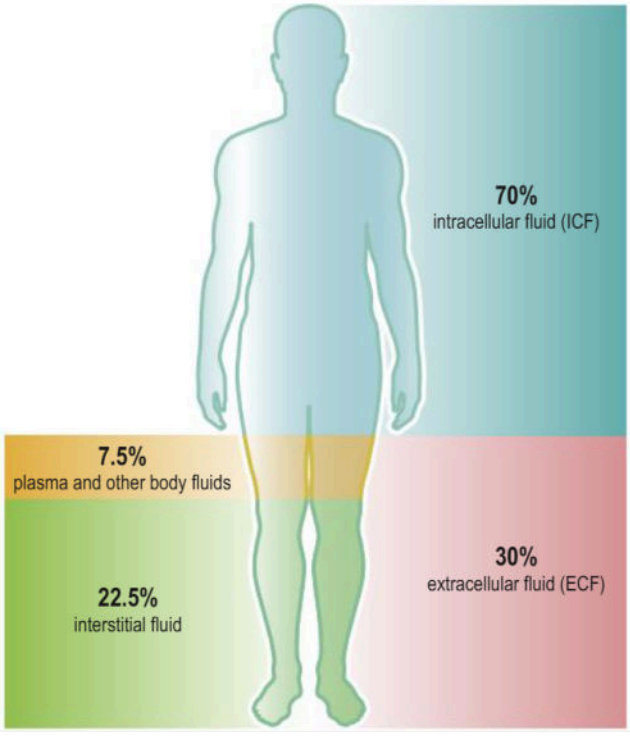

Figure 2.18 Distribution of body water in a 70-kg person.

Intracellular fluid

The composition of intracellular fluid (ICF) is largely controlled by the cell itself because there are selective uptake and discharge mechanisms present in the cell membrane. Water concentrations are equal in the ICF and the ECF, because water passes freely across the cell membrane – water

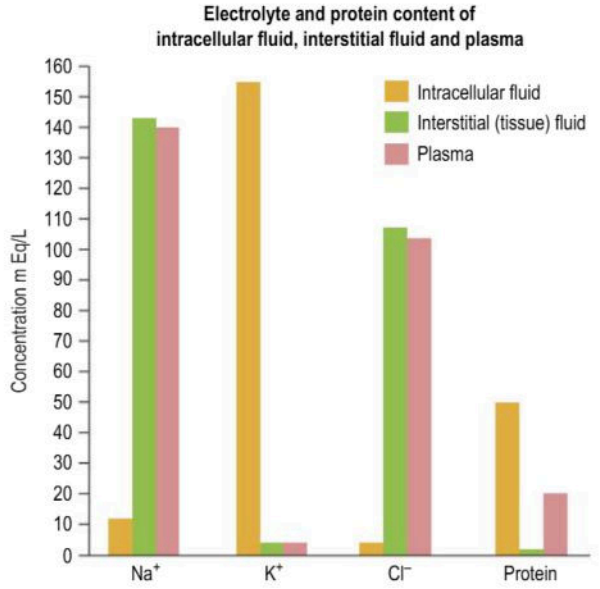

Figure 2.19 Electrolyte and protein content of intracellular fluid, extracellular fluid and plasma.

distributes evenly both inside and outside cells. This means that any change in the ECF water content is directly reflected in the ICF. However, in other respects, the composition of ICF is very different from that of ECF. For example, sodium levels are nearly 10 times higher in the ECF than in the ICF (Fig. 2.19). This concentration difference occurs because, although sodium diffuses into the cell down its concentration gradient, there is a pump in the membrane (the Na^+/K^+ pump, p. 45) that selectively pumps it back out again. This concentration gradient is essential for the function of excitable cells, mainly nerve and muscle. Conversely, many substances are found inside the cell in significantly higher amounts than outside, e.g. ATP, protein and potassium. Figure 2.19 compares the composition of intracellular fluid with blood plasma and interstitial fluid, showing these differences clearly.

SPOT CHECK

6. A red blood cell placed in a hypotonic solution swells and bursts. Explain the process that causes this.

Case study

Sushanta is enjoying a quiet hour reading his book, drinking a cup of tea and eating a bar of chocolate.

1. The excess calories in the chocolate are stored in adipose tissue as which of the following forms of lipid?

   a. Phospholipid
   b. Triglyceride
   c. Cholesterol
   d. Fatty acids

2. Which form of reaction breaks down the complex molecules in Sushanta's chocolate into smaller molecules for absorption?

   a. Catabolic
   b. Anabolic
   c. Synthetic
   d. Active

3. As Sushanta's blood glucose levels begin to rise, insulin is released from the pancreas to bring the levels back down to normal. In this negative feedback reaction, the pancreas is acting as the:

   a. Variable factor
   b. Positive control
   c. Modulator
   d. Effector

4. The glucose molecules in Sushanta's chocolate contain carbon, oxygen and hydrogen, in which chemical ratio?

   a. 1:1:1
   b. 1:1:2
   c. 2:1:2
   d. 2:1:1

5. Sushanta has put sugar in his tea but forgotten to stir it. Which of the following describes the movement of the sugar molecules in his teacup?

   a. They move more quickly as the tea cools down
   b. They distribute from areas of low sugar concentration into areas of higher sugar concentration
   c. They travel by diffusion through the tea
   d. Stirring the tea delays reaching equilibrium

Review and revise

Complete each of the following statements:

1. Atoms are mainly empty space, with a central _____ containing subatomic particles called _____ and _____. Orbiting this central entity are subatomic particles called _____, which carry a _____ electrical charge.

2. The main energy currency of the cell is a molecule called _____. The sugar portion of this molecule is _____, which is attached to three _____ groups and to a base, called _____.

3. Indicate which one of the following statements is true: _____
   a. Covalent bonds are stronger than ionic bonds.
   b. Ionic bonds are formed between the atoms in a water molecule.
   c. Covalent bonds produce ions when they dissociate.
   d. Ionic bonds form when atoms share electrons.

4. Indicate which one of the following statements is true: _____
   a. Diffusion is the movement of particles up their concentration gradient
   b. Diffusion requires energy
   c. Diffusion specifically refers to the movement of water molecules
   d. Diffusion is slowed down at lower temperatures.

5. Complete the statements in List A with the appropriate answer from List B. You may use the items in List B more than once:

List A

(a) Enzymes are made of this _____
(b) Glucose is an example of this type of molecule _____
(c) Prostaglandins are derived from these _____
(d) Glycogen is an example of this type of molecule _____
(e) The common structure of this type of molecule includes a variable side group and a carboxyl group _____
(f) Combined with glycerol, this type of molecule is used to store energy in the body _____
(g) Insulin is an example of this type of molecule _____, produced by combining _____

List B

1. Protein
2. Monosaccharide
3. Amino acid
4. Polysaccharide
5. Fatty acid(s)

6. Match each letter in List A to the appropriate number in List B. You may use the items in List B more than once:

List A

_____ (a) Percentage of body water found inside body cells.
_____ (b) pH values above this figure indicate alkalosis
_____ (c) Number of electrons in the innermost electron shell
_____ (d) Number of oxygen atoms in atmospheric oxygen
_____ (e) Atomic weight of sodium
_____ (f) Number of fatty acids in a triglyceride molecule
_____ (g) Number of principal amino acids used in human biochemistry

List B

1. 2
2. 3
3. 7.45
4. 20
5. 23
6. 70

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 3

Cells and tissues

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Cells are the body's smallest functional units. Similar cells are grouped together to form tissues, each of which has a specialised function, e.g. blood, muscle, bone. Different types of tissue form organs, e.g. the heart, stomach and brain. Systems are usually formed by several organs, each of which performs a set of related functions that maintain homeostasis and contribute to the health of the individual (see Fig. 1.2). For example, the digestive system is responsible for taking in, digesting and absorbing food, which involves a number of organs, including the stomach and intestines. The structure and functions of cells and different types of tissue are explored in this chapter.

The final section considers features of benign and malignant tumours, and how they grow and may spread.

The cell: structure and functions

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the plasma membrane
- compare and contrast active, passive and bulk transport of substances across cell membranes
- explain the functions of the principal organelles
- outline the process of mitosis.

The human body develops from a single cell called the zygote (fertilized egg), which results from the fusion of the ovum (female egg cell) and the spermatozoon (male sex cell). Cell division follows and, as the fetus grows, cells with different structural and functional specialisations develop, all with the same genetic make-up as the zygote. Individual cells are too small to be seen with the naked eye. However, they can be seen when thin slices of tissue are stained in the laboratory and magnified using a microscope.

A cell consists of a plasma membrane enclosing a number of organelles suspended in a watery fluid called cytosol (Fig. 3.1). The cell contents, excluding the nucleus, are made up of the cytoplasm, namely the cytosol and other organelles.

Plasma membrane

The structure and functions of membranes are fundamental to cell survival, as they control passage of substances into and out of it, regulating the intracellular environment.

Structure

The plasma membrane (Fig. 3.2) consists of two layers of phospholipids (p. 35) with proteins and sugars embedded

in them. In addition to phospholipids, the lipid cholesterol is also present. The phospholipid molecules have a head, which is electrically charged and hydrophilic (meaning 'water-loving'), and a tail, which has no charge and is hydrophobic (meaning 'water-hating', Fig. 3.2A). The phospholipid bilayer is arranged like a sandwich with the hydrophilic heads aligned on the outer surfaces of the membrane and the hydrophobic tails forming a central water-repelling layer. These differences influence the transfer of substances across the membrane.

Membrane proteins

The membrane contains different types of proteins (Fig. 3.2A) that perform several functions:

- Some have branched carbohydrate molecules attached to the outer surface, giving the cell its immunological identity – 'self' markers (p. 420).
- Others act as receptors (specific recognition sites) for hormones and other chemical messengers.
- Some are enzymes (p. 36).
- Transmembrane proteins form channels that are filled with water and allow very small, water-soluble ions to cross the membrane.
- Some are involved in pumps that transport substances across the membrane.

Figure 3.2B shows a false-coloured atomic micrograph of the outer surface of the plasma membrane.

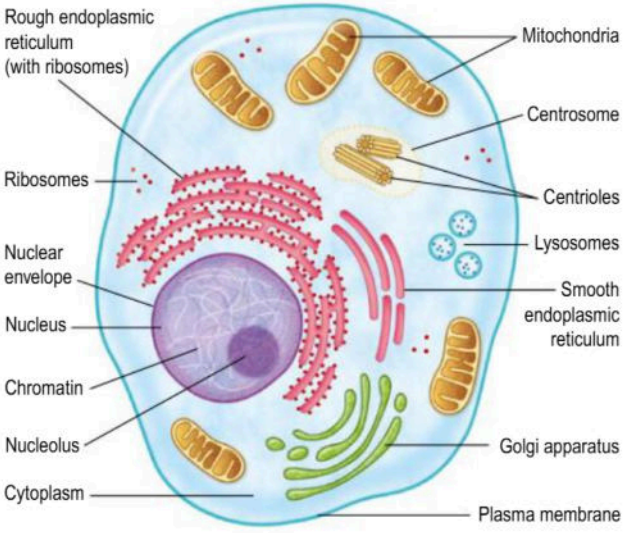

Figure 3.1 The simple cell.

Transport of substances across cell membranes

Each cell is enclosed by its plasma membrane, which provides a selective barrier to substances entering or leaving. This property, called selective permeability, allows the cell (plasma) membrane to control the entry or exit of many substances, thereby regulating the composition of its internal environment. Particle size is important, as many small molecules, e.g. water, can pass freely across the membrane by simple diffusion, while large molecules cannot and may therefore be confined to either the interstitial fluid or the intracellular fluid: in Figure 3.3A, the pink and orange particles are too big to diffuse through the membrane pores, so the pink particles are trapped inside the cell and the orange particles are excluded.

Pores or specific channels in the plasma membrane admit certain substances but not others. In Figure 3.3B, although the green and yellow particles are the same size, the membrane has channels only for the green ones, so the yellow particles are excluded.

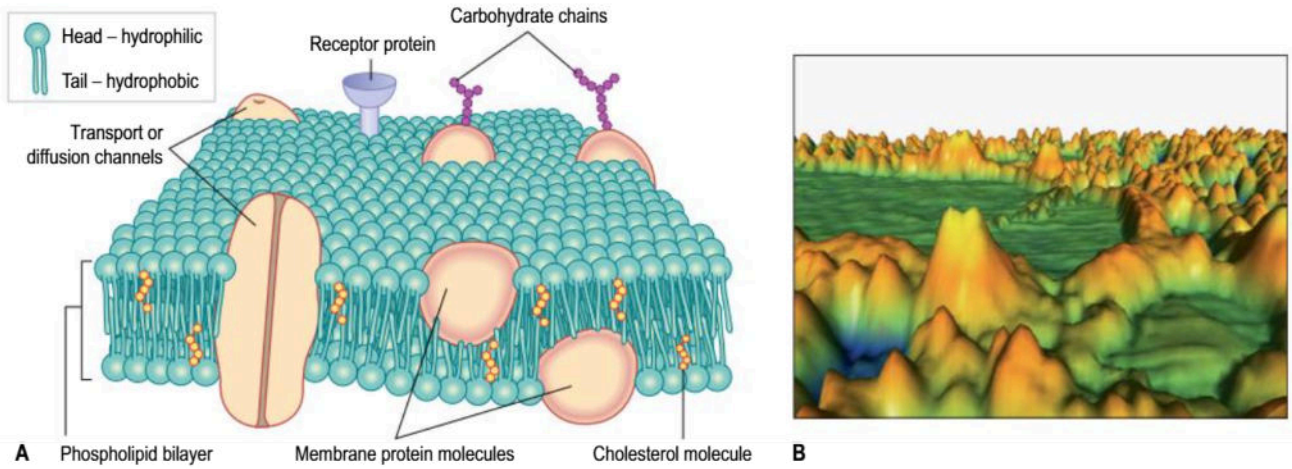

Figure 3.2 The plasma membrane. (A) Diagram showing structure. (B) Coloured atomic force micrograph of the external surface showing plasma proteins. (B, Hermann Schillers, Prof. Dr H Oberleithner, University Hospital of Münster/Science Photo Library, reproduced with permission.)

The membrane is also studded with specialised pumps or carriers that import or export specific substances. In Figure 3.3C the membrane has pumps that actively import the pink particles and other pumps that actively export the blue particles; pink particles therefore concentrate within the cell and blue particles concentrate outside the cell.

Selective permeability together with passive and active transport mechanisms (see below) ensures that the chemical composition of the fluid inside cells is different from the interstitial fluid that bathes them.

Passive transport

This occurs when substances can cross the semipermeable plasma and organelle membranes, and move down the concentration gradient (downhill) without using energy.

Diffusion

Small molecules that diffuse down their concentration gradient (p. 38) include:

- Lipid-soluble materials, e.g. oxygen, carbon dioxide, fatty acids and steroids, that cross by dissolving in the lipid part of the membrane
- Water-soluble materials, e.g. sodium, potassium and calcium, that cross the membrane by passing through water-filled channels.

Facilitated diffusion

This passive process is used by some substances that cannot diffuse through the semipermeable membrane unaided, e.g. glucose, amino acids. Specialised protein carrier molecules in the membrane have specific sites that attract and bind substances to be transferred, like a lock and key mechanism. The carrier then changes its shape and deposits the substance on the other side of the membrane (Fig. 3.4). The carrier sites are specific and can be used by only one substance. As there are a finite number of carriers, there is a limit to the amount of a substance that can be transported at any time. This is known as the transport maximum.

Osmosis

Osmosis is passive movement of water down its concentration gradient across a semipermeable membrane towards equilibrium (see p. 39).

Active transport

This is the transport of substances up their concentration gradient, i.e. from a lower to a higher concentration. Chemical energy in the form of adenosine triphosphate (ATP, p. 35) drives specialised protein carrier molecules that transport substances across the membrane in either direction (Fig. 3.4). The carrier sites are specific and can be used by only one substance; therefore the rate at which a substance is transferred depends on the number of sites available. Active transport mechanisms include the sodium/potassium pump and bulk transport.

The sodium–potassium pump

All cell membranes possess this pump, which indirectly supports other transport mechanisms such as glucose uptake, and is essential in maintaining the electrical gradient needed to generate action potentials in nerve and muscle cells.

This active transport mechanism maintains the unequal concentrations of sodium (Na^+) and potassium (K^+) ions on either side of the plasma membrane. It may use up to 30% of cellular ATP requirements.

Potassium levels are much higher inside the cell than outside – it is the principal intracellular cation. Sodium levels are much higher outside the cell than inside – it is the principal extracellular

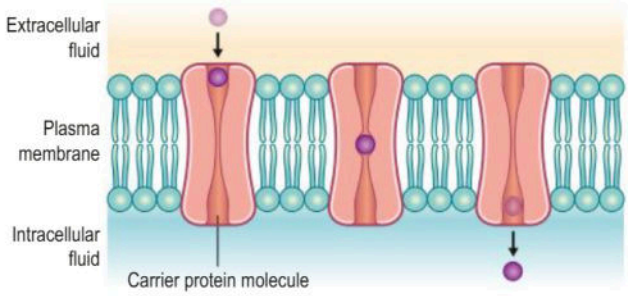

Figure 3.4 Specialised membrane protein carrier molecules involved in facilitated diffusion and active transport.

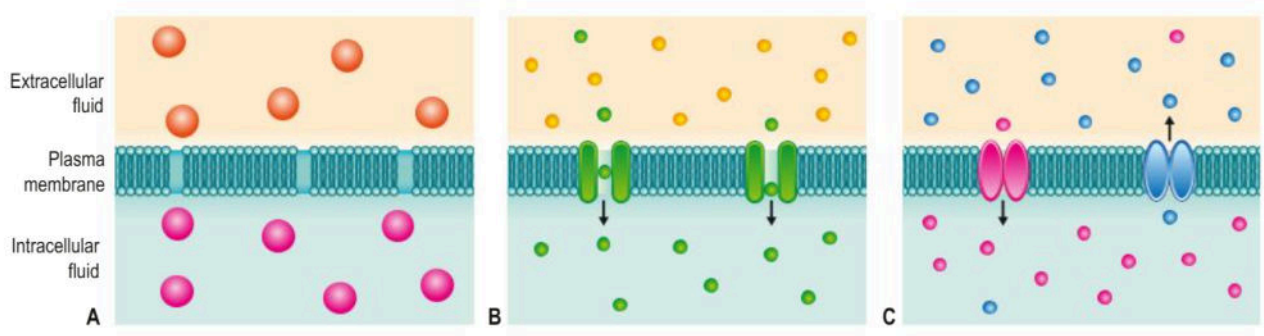

Figure 3.3 Role of the cell membrane in regulating the composition of intracellular fluid. (A) Particle size. (B) Specific pores and channels. (C) Pumps and carriers.

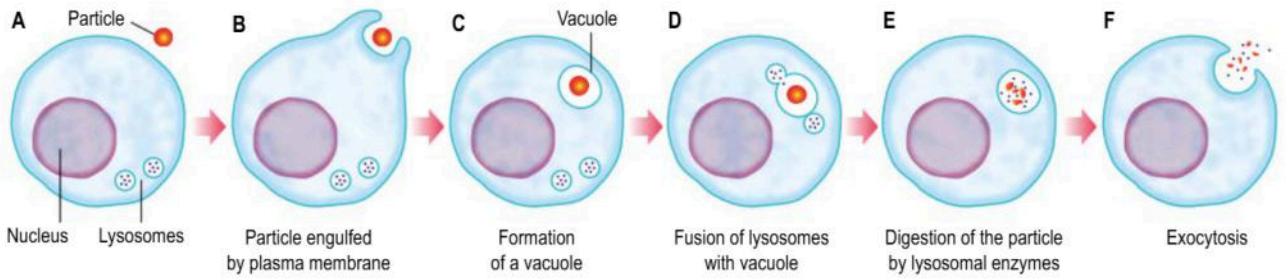

Figure 3.5 Bulk transport across plasma membranes. (A–E) Phagocytosis. (F) Exocytosis.

cation. These ions tend to diffuse down their concentration gradients, K^+ outwards and Na^+ into the cell. In order to maintain their concentration gradients, excess Na^+ is constantly pumped out across the cell membrane in exchange for K^+.

Bulk transport

Transfer of particles too large to cross cell membranes occurs by pinocytosis ('cell-drinking') or phagocytosis ('cell-eating'). These particles are engulfed by extensions of the cytoplasm (Fig. 3.5; see also Fig. 15.1), which enclose them, forming a membrane-bound vacuole. Pinocytosis allows the cell to bring in fluid. In phagocytosis, larger particles (e.g. cell fragments, foreign materials, microbes) are taken into the cell. Lysosomes (see later) then adhere to the vacuole membrane, releasing enzymes that digest the contents.

Extrusion of waste material by the reverse process through the plasma membrane is called exocytosis (Fig. 3.5F). Vesicles formed by the Golgi apparatus (see below) leave the cell in this way, as do any indigestible residues of phagocytosis.

Organelles

Organelles (see Fig. 3.1), literally meaning 'small organs', have individual and highly specialised functions, and are often enclosed by their own membrane within the cytoplasm. They include the nucleus, mitochondria, ribosomes, endoplasmic reticulum, Golgi apparatus, lysosomes and cytoskeleton.

Nucleus

All human cells, except mature erythrocytes (red blood cells) have a nucleus. Some cell types including skeletal muscle cells contain several nuclei. The nucleus is the largest organelle and is contained within the nuclear envelope, a membrane similar to the plasma membrane but with tiny pores through which some fairly large substances can pass between it and the cytoplasm.

The nucleus directs all the cell's metabolic activities and contains the body's genetic material, in the form of deoxyribonucleic acid (DNA, p. 487). In a non-dividing cell, DNA is present as a fine network of threads called chromatin, but when the cell prepares to divide, the chromatin forms distinct structures called chromosomes (see Fig. 17.1). A small amount of ribonucleic acid (RNA), a related substance, is also found in the nucleus.

Within the nucleus there is a roughly spherical structure called the nucleolus, which is involved in manufacture and assembly of the components of ribosomes, the organelles that synthesise new proteins (see below).

Mitochondria

Mitochondria are membranous, sausage-shaped organelles, sometimes described as the 'power house' of the cell (Fig. 3.6). The enzymes that synthesise ATP are found on the folded inner membranes packed into the mitochondria. ATP is the energy currency of the cell and releases energy when the cell breaks it down (see Fig. 2.10). Synthesis of ATP is most efficient in the final stages of aerobic respiration (p. 350), a process that requires oxygen. The most metabolically active cells have the greatest number of mitochondria, e.g. liver, muscle and spermatozoa.

Ribosomes

These are tiny granules composed of ribosomal RNA and protein. They synthesise proteins from amino acids, using messenger RNA as the template (see Fig. 17.5). When present in free units or in small clusters in the cytoplasm, the ribosomes make proteins for use within the cell, including the enzymes required for cellular metabolism. Ribosomes are also found on the outer surface of the nuclear envelope and rough endoplasmic reticulum (Fig. 3.6), where they manufacture proteins for export from the cell, e.g. some hormones.

Endoplasmic reticulum

Endoplasmic reticulum (ER) is an extensive series of interconnecting membranous canals in the cytoplasm (Fig. 3.6). There are two types: smooth and rough. Smooth ER synthesises lipids and steroid hormones. Some of these lipids are used to replace and repair the plasma membrane and membranes of organelles. Smooth ER detoxifies some drugs and converts glycogen to glucose when cells need energy. Rough ER is so-called as it is studded with ribosomes. These are the site of synthesis of proteins, some of which are 'exported' from cells, i.e. enzymes and hormones that leave the parent cell by exocytosis (Fig. 3.5F) for use elsewhere.

Golgi apparatus

The Golgi apparatus consists of stacks of closely folded flattened membranous sacs (Fig. 3.7). It is present in all cells

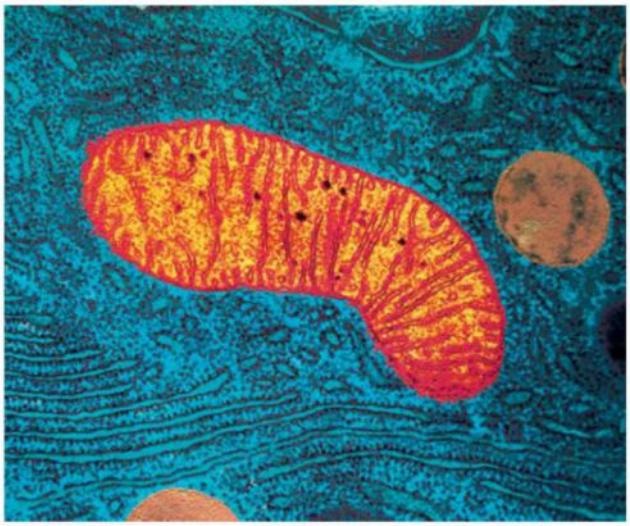

Figure 3.6 Mitochondrion and rough endoplasmic reticulum. False colour transmission electron micrograph showing mitochondrion *(orange)* and rough endoplasmic reticulum *(turquoise)* studded with ribosomes *(dots)*. (Bill Longcore/Science Photo Library, reproduced with permission.)

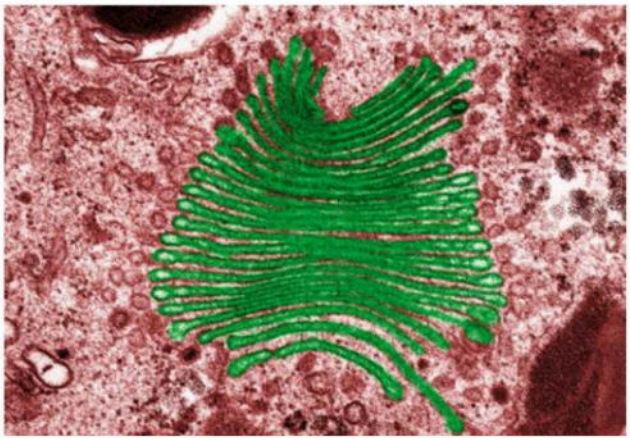

Figure 3.7 Coloured transmission electron micrograph showing the Golgi apparatus *(green)*. (Science Photo Library, reproduced with permission.)

but is larger in those that synthesise and export proteins. The proteins move from the ER to the Golgi apparatus, where they are packaged into membrane-bound vesicles. The vesicles are stored and, when needed, they move to the plasma membrane and fuse with it, expelling the contents from the cell. This process is called exocytosis (Fig. 3.5F).

Lysosomes

Lysosomes are small membranous vesicles pinched off from the Golgi apparatus. They contain a variety of enzymes involved in breaking down fragments of organelles and large molecules (e.g. RNA, DNA, carbohydrates, proteins) inside the cell into smaller particles that are either recycled, or exported from the cell as waste material (Fig. 3.5). Some

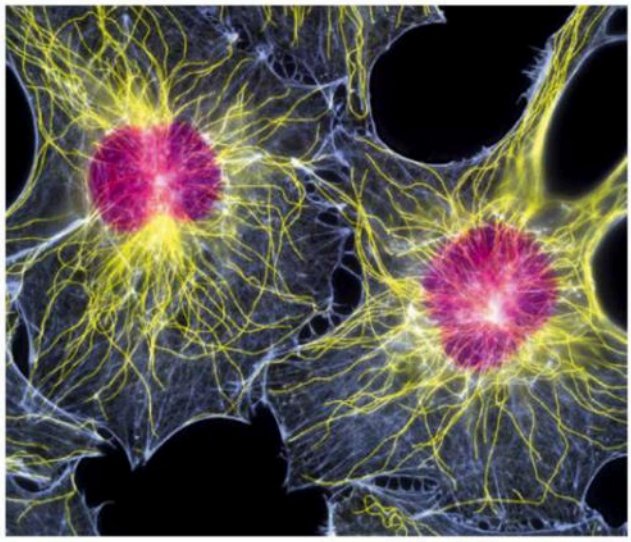

Figure 3.8 Fibroblasts. Fluorescent light micrograph showing nuclei *(purple)* and cytoskeletons *(yellow and blue)*. (R. Torsten Wittman/Science Photo Library, reproduced with permission.)

lysosomes, including those in white blood cells, contain enzymes that digest foreign material such as microbes.

Cytoskeleton

This consists of an extensive network of tiny protein fibres (Fig. 3.8). The cytoskeleton provides an internal support system for organelles within the cell, as well as guiding movement of materials around its interior.

Microfilaments

These tiny fibres, made of actin, are anchored to the inside of the cell membrane and give the cell support and shape. Actin is also involved in the contractile process in muscle cells (p. 467).

Microtubules

These fibres are large, rigid proteins that give the cell mechanical support and also provide pathways for internal movement of, for example:

- organelles
- chromosomes during cell division.

Centrosome

This directs organisation of microtubules within the cell. It consists of a pair of centrioles (small clusters of microtubules) and plays an important role in cell division.

Cell extensions

These project from the plasma membrane in some cell types and their main components are microtubules, which allow movement. They include:

- Microvilli – tiny projections that cover the exposed surface of certain types of cell, e.g. absorptive cells that line the small intestine (Fig. 3.9). By greatly increasing the

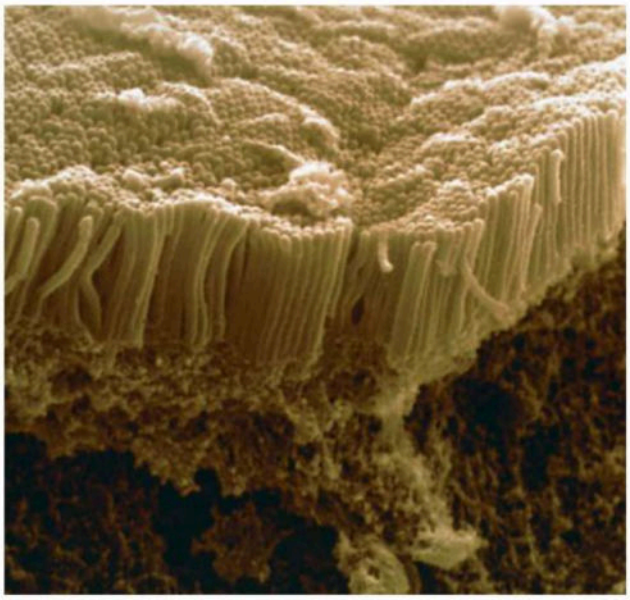

Figure 3.9 Microvilli in small intestine. Coloured scanning electron micrograph. (Eye of Science/Science Photo Library, reproduced with permission.)

surface area, microvilli maximise absorption of nutrients from the small intestine.

- Cilia – microscopic hair-like projections containing microtubules that lie along the free borders of some cells (see Fig. 10.12). They beat in unison, moving substances along the surface, e.g. in the respiratory tract, mucus and trapped particles are transported by ciliary action away from the lungs towards the mouth to be swallowed.
- Flagella – single, long, whip-like projections containing microtubules, which form the 'tails' of spermatozoa (see Fig. 1.15) that propel them through the female reproductive tract.

The cell cycle

Damaged, dead and worn-out cells, depending on their type, can often by replaced by cell division, maintaining tissue integrity and function. The frequency with which cell division occurs varies with different types of tissue (p. 56). Normally, this is carefully regulated to allow effective maintenance and repair of body tissues. At the end of their natural lifespan, ageing cells are programmed to 'self-destruct' and their breakdown products are removed by phagocytosis in a process known as apoptosis (p. 58).

Cells with nuclei have 46 chromosomes and divide by mitosis, a process that results in two new, genetically identical daughter cells. The only exception to this is the formation of gametes (sex cells), i.e. ova and spermatozoa, which takes place by meiosis (p. 492).

The period between two cell divisions is known as the cell cycle. This has two phases that can be seen on light microscopy: mitosis (M phase) and interphase (Fig. 3.10).

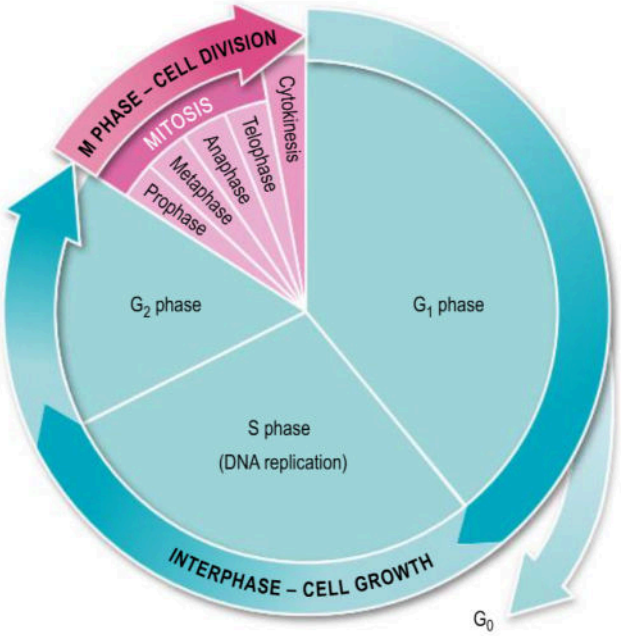

Figure 3.10 The cell cycle.

Interphase

Three separate stages are recognised:

- First gap phase (G_1) – the cell grows in size and volume. This is usually the longest phase and most variable in length. Sometimes cells do not continue round the cell cycle but enter a resting phase (G_0); despite being called the resting phase, cells at this stage are highly active, carrying out their specific functions. The cell may stay in G_0 permanently, but several cell types can be stimulated to re-enter the cell cycle and start dividing again if need be.
- Synthesis of DNA (S phase) – the chromosomes replicate, forming two identical copies of DNA (p. 489). Therefore, following the S phase, the cell now has 92 chromosomes, i.e. enough DNA for two cells, and is nearly ready to divide by mitosis.
- Second gap phase (G_2) – there is further growth and preparation for cell division.

Progress through the cell cycle is normally tightly controlled with checkpoints between the stages to detect any errors appearing in the cell's DNA. Disruption to this orderly process may lead to tumour development (p. 59).

Mitosis

Mitosis (Figs 3.11 and 3.12) is a continuous process involving four distinct stages visible by light microscopy.

Prophase

During this stage the replicated chromatin becomes tightly coiled and easier to see under the microscope. Each of the original 46 chromosomes (called a chromatid at this stage)

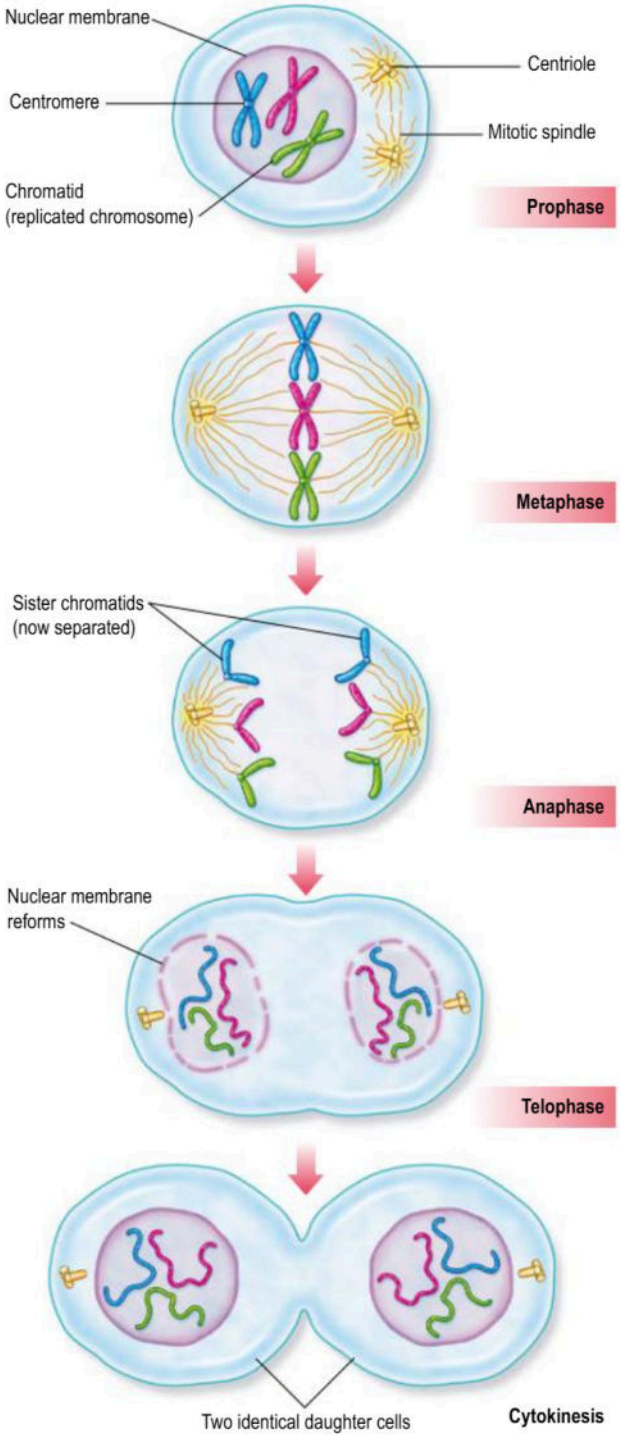

Figure 3.11 The stages of mitosis.

is paired with its copy in a double chromosome unit. The two chromatids are joined to each other at the centromere (see Fig. 3.11). The mitotic apparatus appears; this consists of two centrioles separated by the mitotic spindle, which is formed from microtubules. The centrioles migrate, one to each end of the cell, and the nuclear envelope disappears.

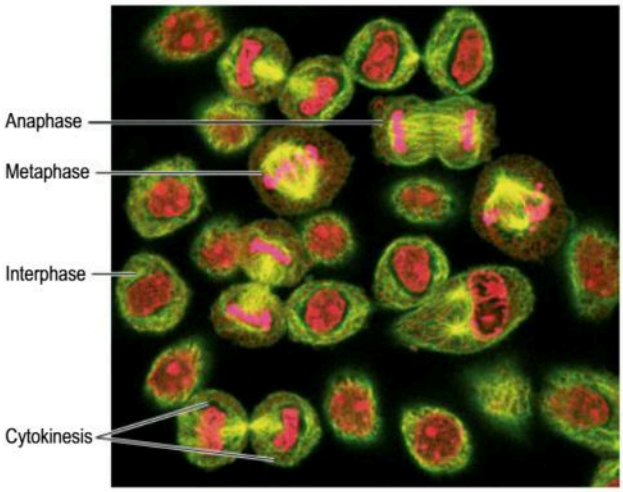

Figure 3.12 Mitosis. Light micrograph showing cells at different stages of reproduction with chromatin/chromatids shown in pink. (Dr Gopal Murti/Science Photo Library, reproduced with permission.)

Metaphase

The chromatids align on the centre of the spindle, attached by their centromeres.

Anaphase

The centromeres separate, and one of each pair of sister chromatids (now called chromosomes again) migrates to each end of the spindle as the microtubules that form the mitotic spindle shorten.

Telophase

The mitotic spindle disappears, the chromosomes uncoil and the nuclear envelope reforms.

Following telophase, cytokinesis occurs: the cytosol, intracellular organelles and plasma membrane split, forming two identical daughter cells.

SPOT CHECK

1. Outline the main events in phagocytosis.
2. List, in order, the stages of the cell cycle.

Tissues

Learning outcomes

After studying this section, you should be able to:

- describe the structure and functions of epithelial, connective and muscle tissue
- outline the structure and functions of epithelial and synovial membranes
- compare and contrast the structure and functions of exocrine and endocrine glands.

Tissues consist of large numbers of the same type of cells and are classified according to the size, shape and functions of their constituent cells. There are four types of tissue:

- epithelial tissue or epithelium
- connective tissue
- muscle tissue
- nervous tissue.

Epithelial tissue

This tissue type covers the body and lines its cavities, hollow organs and tubes. It is also found in glands. The structure of epithelium (Fig. 3.13) is closely related to its functions, which include:

- protection of underlying structures from, for example, dehydration or chemical and mechanical damage
- secretion
- absorption.

The cells are very tightly packed and the intercellular substance, the matrix, is minimal. The cells usually lie on a basement membrane, an inert connective tissue made by the epithelial cells themselves. Epithelial tissue may be:

- simple: a single layer of cells
- stratified: several layers of cells.

Simple epithelium

Simple epithelium consists of a single layer of identical cells and there are three types. It is usually found on absorptive or secretory surfaces, where the single layer enhances these processes, and seldom on surfaces subject to stress. The types are named according to the shape of the cells, which differs according to their functions. The more active the tissue, the taller the cells.

Squamous (pavement) epithelium

This is composed of a single layer of flattened cells (Fig. 3.13A). The cells fit closely together like paving stones, forming a thin and very smooth membrane across which diffusion occurs easily. It forms the lining of the following structures:

- heart – where it is known as endocardium
- blood vessels | where it is also known
- lymph vessels | as endothelium
- alveoli of the lungs
- collecting ducts of nephrons in the kidneys (see Fig. 13.8).

Cuboidal epithelium

This consists of cube-shaped cells fitting closely together and lying on a basement membrane (Fig. 3.13B). It forms the walls of kidney tubules and is found in some glands such as the thyroid (see Fig. 9.8). Cuboidal epithelium is actively involved in secretion, absorption and/or excretion.

Columnar epithelium

This is formed by a single layer of tall, thin cells on a basement membrane (Fig. 3.13C). It lines many organs and often has adaptations that make it well suited to a specific function. The lining of the stomach is formed from simple columnar epithelium without surface structures. The free surface of the columnar epithelium lining the small intestine is covered with microvilli (see Fig. 3.9). Microvilli provide a very large surface area for absorption of nutrients from the small intestine. In the trachea, columnar epithelium is ciliated (see Fig. 10.12) and contains goblet cells that secrete mucus. This means that inhaled particles that stick to the mucus layer are moved towards the throat by cilia in the respiratory tract. In the uterine tubes, ova are propelled along towards the uterus by ciliated columnar epithelium.

Stratified epithelium

Stratified epithelium consists of several layers of cells of various shapes. Continual cell division in the lower (basal) layers pushes cells above nearer and nearer to the surface, where they are shed. Basement membranes are usually absent. The main function of stratified epithelium is to protect underlying structures from mechanical wear and tear. There are two main types: stratified squamous and transitional.

Stratified squamous epithelium

Stratified squamous epithelium (Fig. 3.14) is composed of several layers of cells. In the deepest layers the cells are mainly columnar and, as they grow towards the surface, they become flattened and are then shed.

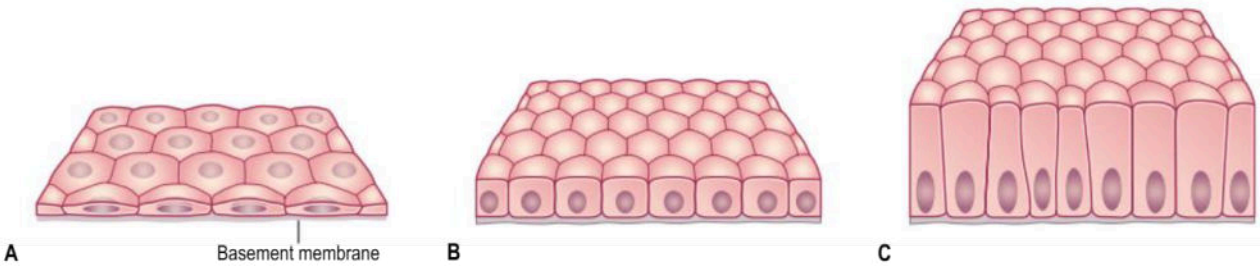

Figure 3.13 Simple epithelium. (A) Squamous. (B) Cuboidal. (C) Columnar.

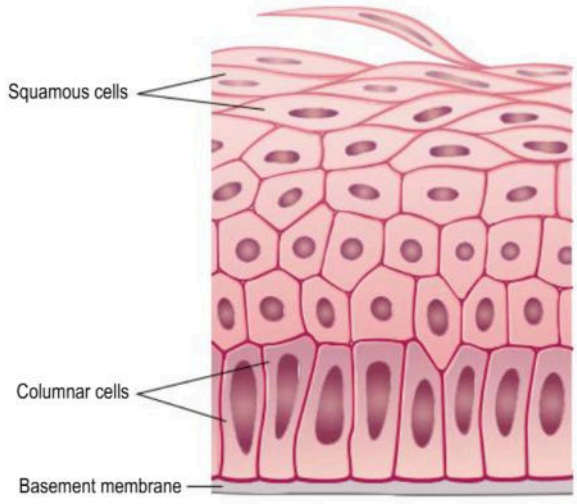

Figure 3.14 Stratified epithelium.

Keratinised stratified epithelium

This is found on dry surfaces subjected to wear and tear, i.e. skin, hair and nails. The surface layer consists of dead epithelial cells that have lost their nuclei and are packed with the protein keratin. This forms a tough, relatively waterproof protective layer that prevents drying of the live cells underneath. The surface layer of skin is continually rubbed off and replaced from below (see Figs 1.13 and 14.5).

Non-keratinised stratified epithelium

This protects moist surfaces subjected to wear and tear, and prevents them from drying out, e.g. the conjunctiva of the eyes, the lining of the mouth, the pharynx, the oesophagus and the vagina (Fig. 3.15).

Transitional epithelium

Transitional epithelium (Fig. 3.16) is composed of several layers of pear-shaped cells. It lines parts of the urinary tract including the bladder and ureters, allowing for stretching, e.g. as the bladder fills.

Connective tissue

Connective tissue is the most abundant and most diverse tissue in the body and includes, for example, bone, blood and fat tissue. The cells are more widely separated from each other than in epithelial tissues, and intercellular substance (matrix) is present in considerably larger amounts. There are usually fibres present in the matrix, which vary in consistency depending on the position and function of the tissue, and form a supporting network to which the cells attach. Most types of connective tissue have a good blood supply and their main functions are:

- binding and structural support
- protection
- transport
- insulation.

Figure 3.15 Section of non-keratinised stratified squamous epithelial lining of the vagina. (Magnified ×100.) (Telser AG, Young JK, Baldwin KM 2007 *Elsevier's integrated histology*. Mosby: Edinburgh.)

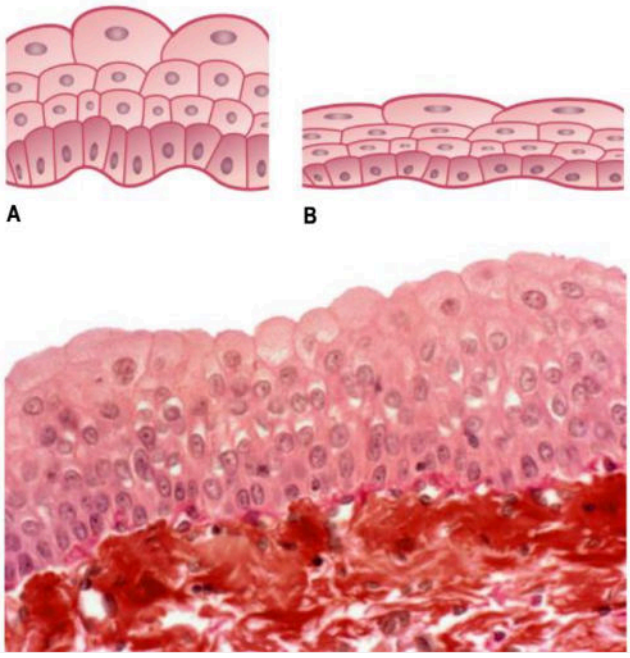

Figure 3.16 Transitional epithelium. (A) Relaxed. (B) Stretched. (C) Light micrograph of the bladder wall showing transitional epithelium *(pink)* above the smooth muscle and connective tissue layer *(red)*. (C, Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

Cells in connective tissue

Connective tissue, excluding blood (Ch. 4), is found in all organs, where it supports the specialised tissue. The cell types present include fibroblasts, fat cells, macrophages, leukocytes and mast cells.

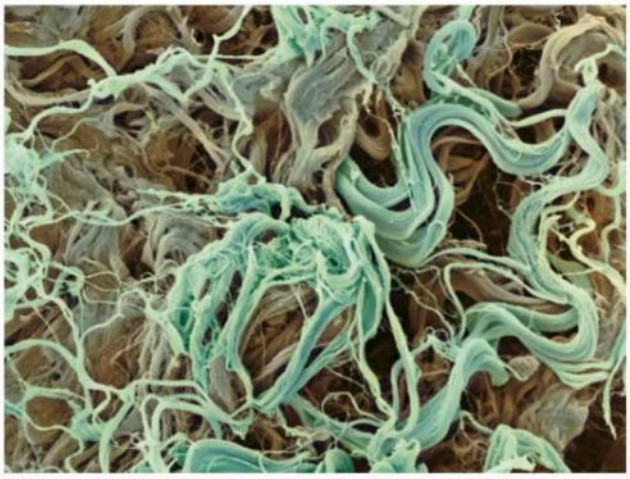

Figure 3.17 Collagen fibres. Coloured scanning electron micrograph. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

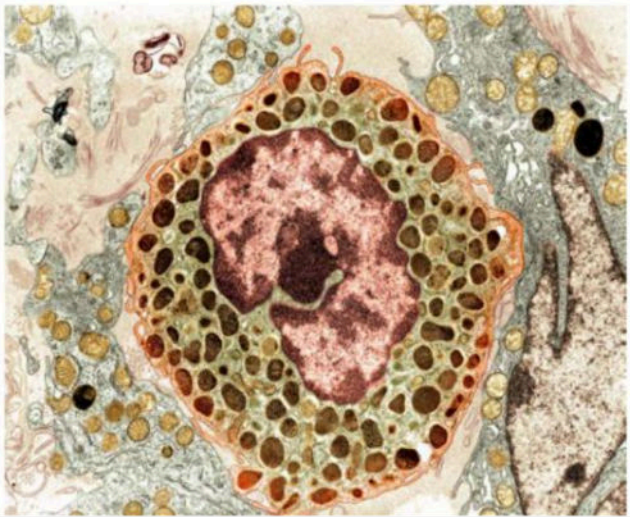

Figure 3.18 Mast cell. Coloured transmission electron micrograph showing nucleus *(pink and brown)* and cytoplasm *(green)* packed with granules *(brown)*. (Medimage/Science Photo Library. Reproduced with permission.)

Fibroblasts

Fibroblasts are the most abundant connective tissue cells; they are large and possess irregular processes (see Fig. 3.8). They manufacture collagen and elastic fibres, and a matrix of extracellular material. Tough, inelastic collagen fibres are the main structural proteins of the body (Fig. 3.17). Very fine collagen fibres, sometimes called reticular fibres, provide a supporting fibrous network in highly active tissue, such as the liver and lymphoid tissue. Fibroblasts are particularly active in tissue repair (wound healing) when they may bind together the cut surfaces of wounds or form granulation tissue following tissue destruction (see Fig 14.8).

Fat cells

Also known as adipocytes, these cells occur singly or in groups in many types of connective tissue and are especially abundant in adipose tissue (see Fig. 3.20B). They vary in size and shape according to the amount of fat they contain.

Macrophages

These are large irregular-shaped cells with granules in the cytoplasm. Some are fixed, i.e. attached to connective tissue fibres, and others are motile. They are an important part of the body's defence mechanisms because they are actively phagocytic, engulfing and digesting cell debris, bacteria and other foreign bodies. Some tissues including the liver, lymph nodes, spleen and the brain have specific collections of fixed macrophages (see Fig. 4.13).

Leukocytes

White blood cells (p. 72) are normally found in small numbers in healthy connective tissue but neutrophils migrate in significant numbers during infection, and play an important part in tissue defence. Plasma cells develop from B-lymphocytes, a type of white blood cell (see Fig. 4.3). They synthesise and secrete specific defensive antibodies into the blood and tissues (Ch. 15).

Mast cells (Fig. 3.18)

These are similar to basophil leukocytes (p. 73). They are found in loose connective tissue, especially in areas exposed to external invaders, e.g. the GI and respiratory tracts and the skin as well as under the fibrous capsule of some organs, e.g., liver and spleen. Their cytoplasm is packed with granules containing heparin, histamine and other substances, which are released following tissue damage. Release of the granular contents is called degranulation. Histamine is involved in local and general inflammatory reactions; it stimulates secretion of gastric juice and is associated with the development of allergies and hypersensitivity states (p. 426). Heparin prevents coagulation of blood, which helps to maintain blood flow through inflamed tissues, supplying cells with oxygen and glucose and bringing additional defensive leukocytes to the area.

Loose (areolar) connective tissue

This is the most generalised type of connective tissue. The matrix is semisolid with many fibroblasts and some fat cells (adipocytes), mast cells and macrophages, widely separated by elastic and collagen fibres (Fig. 3.19). It is found in almost every part of the body, binding tissues loosely together while also providing elasticity and tensile strength. For example, it connects and supports other tissues:

- under the skin
- between muscles
- around blood vessels and nerves
- in glands supporting secretory cells.

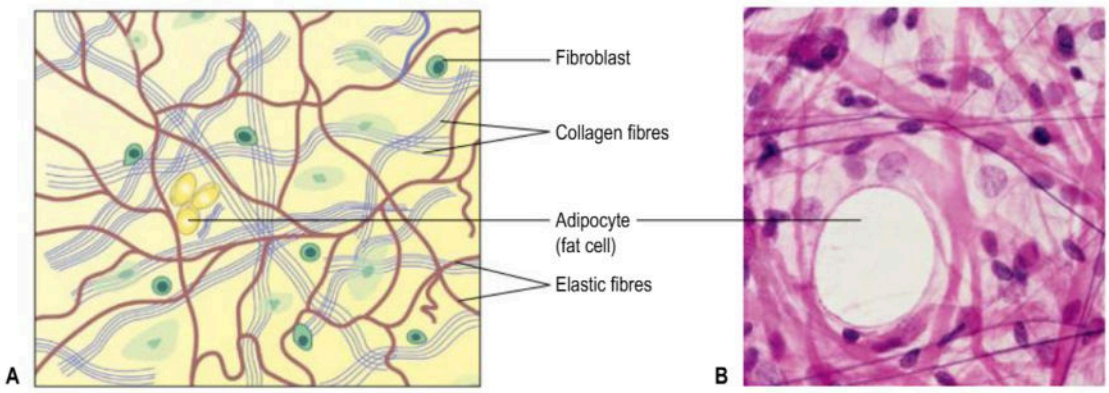

Figure 3.19 Loose (areolar) connective tissue. (A) Diagram of basic structure. (B) Light micrograph. (B, Biophoto Associates/Science Photo Library. Reproduced with permission.)

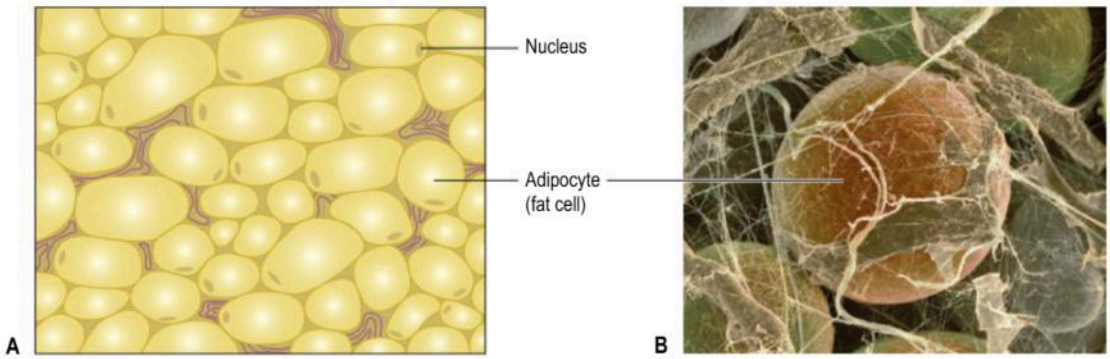

Figure 3.20 Adipose tissue. (A) Diagram of basic structure. (B) Coloured scanning electron micrograph of fat cells surrounded by strands of connective tissue. (B, Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

Adipose tissue

Adipose tissue consists of fat cells (adipocytes), containing large fat globules, in a matrix of areolar tissue (Fig. 3.20). There are two types: white and brown.

White adipose tissue

This makes up 20%–25% of body weight in adults with a normal body mass index (Ch. 11), more in obese people and less in those who are underweight. Its main function is storage (rather than generation) of chemical energy. Adipose tissue also secretes the hormone leptin (see Table 9.4). It supports the kidneys and the eyeballs in their sockets, and provides thermal insulation under the skin.

Brown adipose tissue

This has more mitochondria and a more extensive capillary network than white adipose tissue. It is important in keeping infants warm; it is more metabolically active and its breakdown generates more heat than white adipose tissue. In adults, brown fat is found in only small amounts.

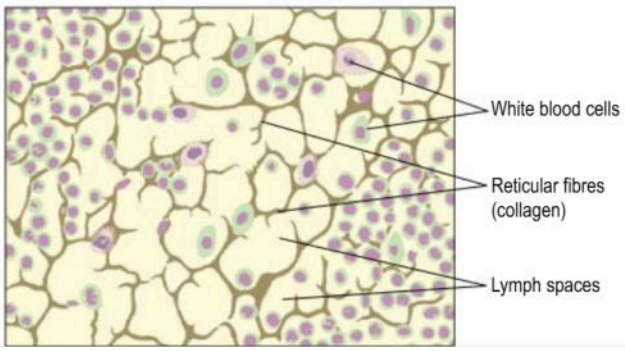

Figure 3.21 Lymphoid tissue.

Lymphoid tissue

Lymphoid tissue (Fig. 3.21) is strategically situated where defence from body invaders is required, e.g., the tonsils. It also forms the framework of lymph nodes and the spleen (see Fig. 6.1) and consists of a semisolid matrix with fine, branching reticular fibres containing white blood cells (monocytes and lymphocytes).

Dense connective tissue

This contains more fibres and fewer cells than loose connective tissue.

Fibrous tissue

Fibrous tissue (Fig. 3.22A) is made up mainly of closely packed bundles of collagen fibres (see Fig. 3.17) with very little matrix. Fibrocytes (old and inactive fibroblasts) are few in number and lie in rows between the bundles of fibres. Fibrous tissue is found:

- forming ligaments, which bind bones together
- as the outer protective covering of bones, called periosteum
- as the outer protective covering of some organs, e.g. the kidneys, lymph nodes and brain
- forming muscle sheaths, called muscle fascia (see Fig. 16.59), which extend beyond the muscle to become the tendon that attaches the muscle to bone.

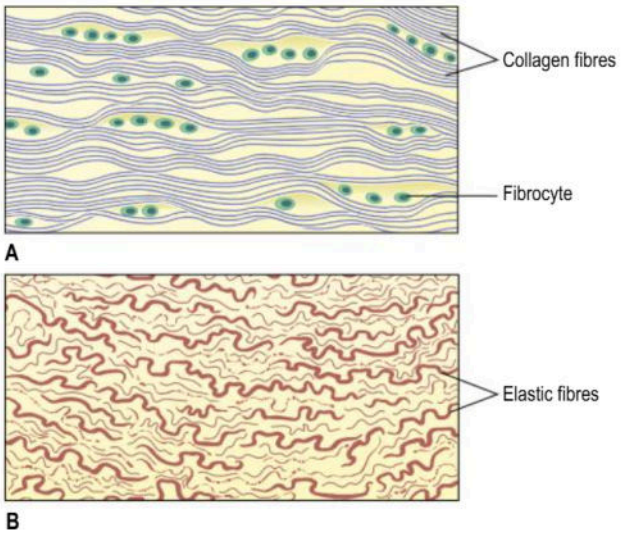

Figure 3.22 Dense connective tissue. (A) Fibrous tissue. (B) Elastic tissue.

Elastic tissue

Elastic tissue (Fig. 3.22B) is capable of considerable extension and recoil. There are few cells, and the matrix consists mainly of masses of elastic fibres secreted by fibroblasts. It is found in organs where stretching or alteration of shape is required, e.g., in large blood vessel walls, the trachea and bronchi, and the lungs.

Blood

This fluid connective tissue is described in detail in Chapter 4.

Cartilage

Cartilage is firmer than other connective tissues. The cells (chondrocytes) are sparse and lie embedded in matrix, reinforced by collagen and elastic fibres. There are three types: hyaline cartilage, fibrocartilage and elastic fibrocartilage.

Hyaline cartilage

The chondrocytes in this tissue are arranged in small groups within cell nests and the bluish-white matrix is solid and smooth (Fig. 3.23A). Hyaline cartilage provides flexibility, support and smooth surfaces for movement at joints. It is found:

- as articular cartilage on the ends of long bones that form synovial joints
- forming the costal cartilages, which attach the ribs to the sternum
- forming rings around the larynx, trachea and bronchi.

Fibrocartilage

This consists of dense masses of white collagen fibres in a matrix similar to that of hyaline cartilage with the cells widely dispersed (Fig. 3.23B). It is a tough, slightly flexible, supporting tissue found:

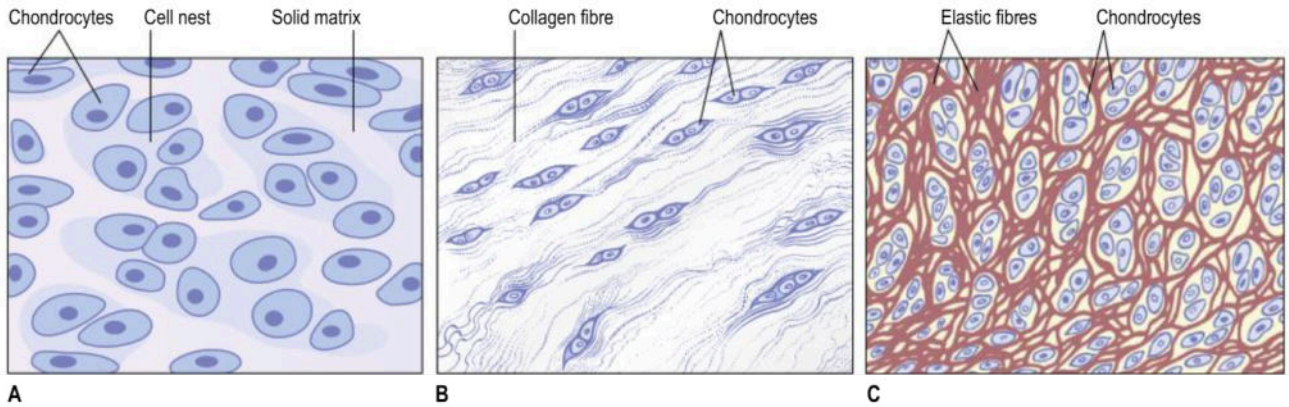

Figure 3.23 Cartilage. (A) Hyaline cartilage. (B) Fibrocartilage. (C) Elastic fibrocartilage.

- as pads called the intervertebral discs between the bodies of the vertebrae
- between the articulating surfaces of the bones of the knee joint, called semilunar cartilages
- on the rim of the bony sockets of the hip and shoulder joints, deepening the cavities without restricting movement.

Elastic fibrocartilage

This flexible tissue consists of yellow elastic fibres lying in a solid matrix with chondrocytes lying between the fibres (Fig. 3.23C). It provides support and maintains the shape of, for example, the pinna or lobe of the ear, the epiglottis and part of the tunica media of blood vessel walls.

Bone

Bone cells (osteocytes) are surrounded by a matrix of collagen fibres strengthened by calcium and phosphate salts. This provides bones with their characteristic strength and rigidity. Bone also has considerable capacity for growth in the first two decades of life, and for regeneration throughout life. Two types of bone can be identified by the naked eye:

- compact bone, having a solid or dense appearance
- spongy or cancellous bone, having a 'spongy' or fine honeycomb appearance.

These are described in detail in Chapter 16.

Muscle tissue

This tissue is able to contract and relax, providing movement within the body and of the body itself. Muscle contraction requires a rich blood supply providing sufficient oxygen, calcium and nutrients and removing waste products. There are three types of specialised muscle cells, also known as fibres: skeletal muscle, smooth muscle and cardiac muscle.

Skeletal muscle

This type is described as skeletal because it forms those muscles that move the bones of the skeleton, striated because striations (stripes) can be seen on microscopic examination (Fig. 3.24) and voluntary as it is under conscious control. Although most skeletal muscle moves bones, it also forms the diaphragm allowing a degree of voluntary control in breathing. In reality, many movements can be finely and consciously coordinated, e.g., writing, but may also be controlled subconsciously. For example, maintaining an upright posture does not normally require thought unless a new locomotor skill is being learned, e.g., skating or cycling, and the diaphragm maintains breathing during sleep despite lack of conscious input.

These fibres (cells) are cylindrical, contain multiple nuclei and can be up to 35 cm long. Skeletal muscle contraction is stimulated by motor nerve impulses originating in the brain or spinal cord and ending at the neuromuscular junction (p. 467). The properties and functions of skeletal muscle are explained in detail in Chapter 16.

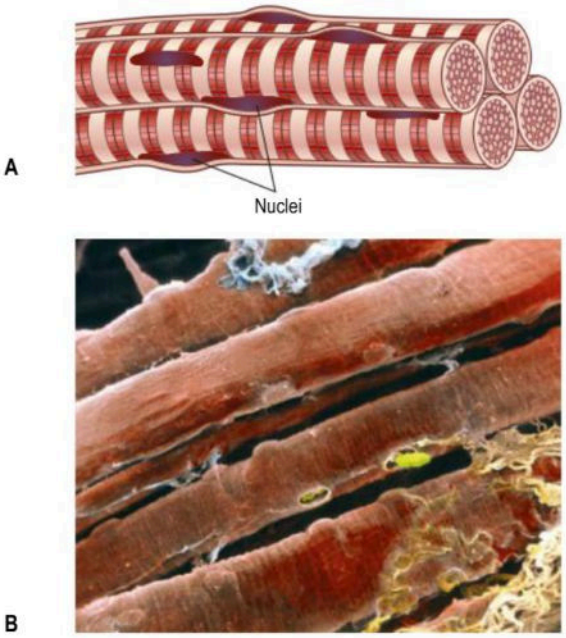

Figure 3.24 Skeletal muscle fibres. (A) Diagram. (B) Coloured scanning electron micrograph of skeletal muscle fibres and connective tissue fibres *(bottom right)*. (B, Professors PM Motta, PM Andrews, KR Porter and J Vial/Science Photo Library. Reproduced with permission.)

Smooth muscle

Smooth muscle (Fig. 3.25) is described as non-striated, visceral or involuntary, as it does not have striations and is not under conscious control. Some smooth muscle has the intrinsic ability to initiate its own contractions (automaticity), e.g., peristalsis of the gastrointestinal tract (p. 323). It is innervated by the autonomic nervous system (p. 190) but some hormones and local metabolites also regulate its contraction. Smooth muscle is rich in mitochondria that fuel its slow and sustained activity. It fatigues much more slowly than skeletal muscle. Smooth muscle cells are usually organised in sheets in the walls of hollow organs, so that contraction and relaxation determine pressure within the organ, for example:

- regulating the diameter of blood vessels and airways within
- propelling contents along tubular structures, e.g., the ureters, ducts of glands and the gastrointestinal tract
- expelling contents of the urinary bladder and uterus.

When examined under a microscope, the cells are seen to be spindle-shaped with only one central nucleus.

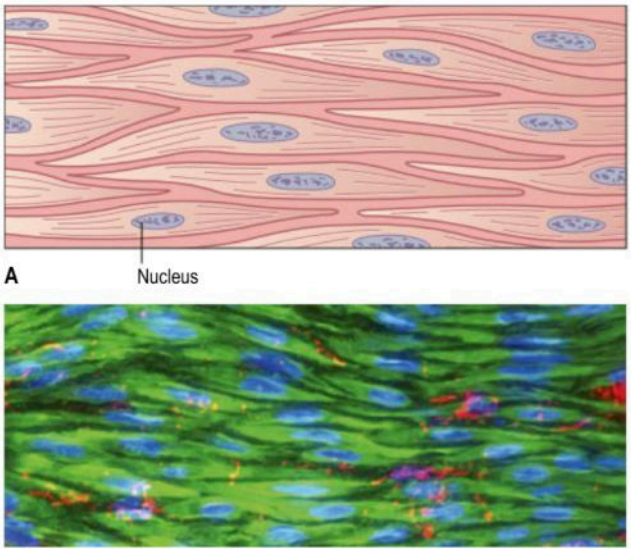

Figure 3.25 Smooth muscle. (A) Diagram. (B) Fluorescent light micrograph showing actin, a contractile muscle protein *(green)*, nuclei *(blue)* and capillaries *(red)*. (B, R Bick, B Poindexter, UT Medical School/Science Photo Library. Reproduced with permission.)

Cardiac muscle

This is found only in the heart wall. It is not under conscious control but, when viewed under a microscope, cross-stripes (striations) characteristic of skeletal muscle can be seen. Each fibre (cell) has one nucleus and one or more branches (Fig. 3.26). The ends of the cells and their branches are in very close contact with the ends and branches of adjacent cells. Microscopically, these 'joints', or intercalated discs, appear as lines that are thicker and darker than the ordinary cross-stripes. This arrangement gives cardiac muscle the functionality of a sheet of muscle rather than a very large number of individual fibres. This is significant when the heart contracts, as a wave of contraction spreads from cell to cell across the intercalated discs, which means that cardiac muscle fibres do not need to be stimulated individually.

The heart has an intrinsic pacemaker system, which means that it beats in a coordinated manner without external nerve stimulation, although the rate at which it beats is influenced by autonomic nerve impulses, some hormones, local metabolites and other substances (Ch. 5).

Nervous tissue

Two types of tissue are found in the nervous system:

- Excitable cells – these are called neurones and they initiate, receive, conduct and transmit information.
- Non-excitable cells – these are known as glial cells and they support the neurones.

Both types are described in detail in Chapter 7.

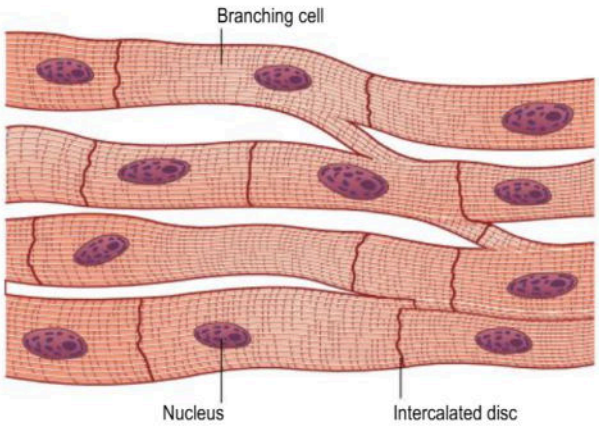

Figure 3.26 Cardiac muscle fibres.

Tissue regeneration

The extent to which regeneration is possible, following tissue damage, depends on the normal rate of turnover of particular cell types. Those with a rapid turnover regenerate most effectively. There are three general categories:

- Labile cells in which replication is a continuous process regenerate quickly; these include epithelial cells of, for example, the alimentary, urinary and uterine tracts, the skin, mucous membranes and secretory glands.
- Stable cells retain the ability to replicate but do so infrequently under normal conditions. These include liver, kidney, bone, and endocrine cells but, when stimulated to do so, remain capable of rapid division.
- Permanent cells are normally unable to replicate; these include nerve cells (neurones) and skeletal and cardiac muscle cells, meaning that damaged tissue cannot be replaced.

Extensively damaged tissue is usually replaced by fibrous tissue, meaning that the functions of the original tissue are lost and the function of the organ as a whole is often impaired.

Membranes

Epithelial membranes

These membranes are sheets of epithelial tissue and supporting connective tissue that cover or line many internal structures or cavities. The main types are mucous membrane, serous membrane and the skin (cutaneous membrane; Ch. 14).

Mucous membrane

This is the moist lining of the gastrointestinal, respiratory and genitourinary tracts and is sometimes referred to as the mucosa. The membrane surface consists of epithelial cells, some of which produce a secretion called mucus, a slimy, tenacious fluid that is discharged on to the epithelial surface. As the cells fill with mucus they develop the appearance

of a goblet or flask and are known as goblet cells (see Fig. 12.5). Mucus protects membranous linings from drying, mechanical and chemical injury, and invading microbes. In the respiratory tract mucus traps inhaled particles, preventing them from entering the alveoli of the lungs.

Serous membrane

Serous membranes, or serosa, secrete serous watery fluid. They consist of a double layer of loose areolar connective tissue lined by simple squamous epithelium. The parietal layer lines a cavity and the visceral layer surrounds organs (the viscera) within the cavity. The two layers are separated by serous fluid secreted by the epithelium itself. Serous membranes are found at three sites:

- the pleura lining the thoracic cavity and surrounding the lungs (p. 276)
- the pericardium lining the pericardial cavity and surrounding the heart (p. 90)
- the peritoneum lining the abdominal cavity and surrounding abdominal organs (p. 322).

The serous fluid between the visceral and parietal layers enables organs to glide freely within the cavity without being damaged by friction on movement. For example, the heart changes its shape and size during each beat, and friction damage is prevented by the arrangement of the pericardium and its serous fluid.

Synovial membrane

This membrane lines the cavities of synovial joints, e.g. the hip joint, and surrounds tendons that could be injured by rubbing against bones on movement, e.g. over the wrist joint. It is not an epithelial membrane but instead consists of areolar connective tissue and elastic fibres.

Synovial membrane secretes synovial fluid, which lubricates and nourishes the joints (Ch. 16).

Glands

Glands are groups of epithelial cells that produce specialised secretions. Those that discharge their secretion on to the epithelial surface of hollow organs, either directly or through a duct, are called exocrine glands and they vary considerably in size, shape and complexity, as shown in Figure 3.27. Their secretions include mucus, saliva, digestive juices and earwax. Figure 3.28 shows simple tubular glands of the large intestine.

Other glands discharge their secretions into blood and lymph. These are called endocrine glands (ductless glands) and they secrete hormones (Ch. 9).

SPOT CHECK

3. Outline the structure and functions of mucous membrane.
4. Endocrine and exocrine glands are both secretory, but what is the important functional difference between them?

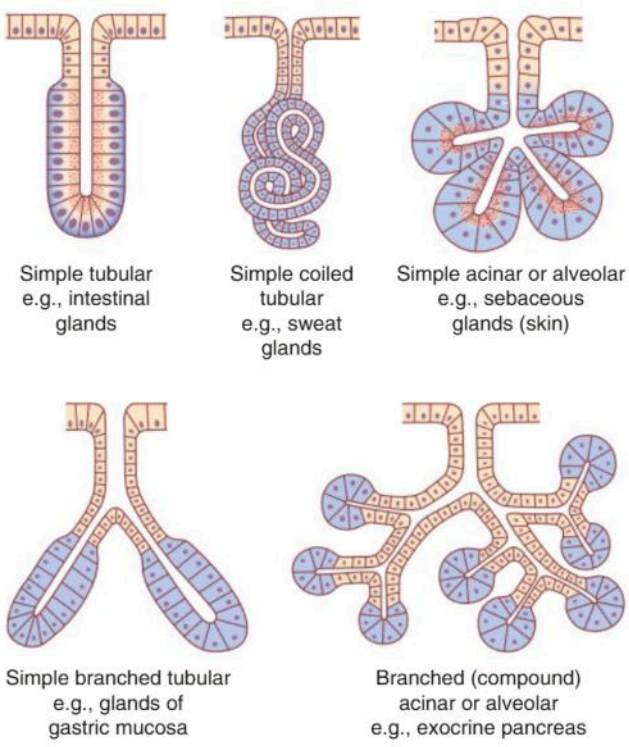

Figure 3.27 Exocrine glands: structural classification.

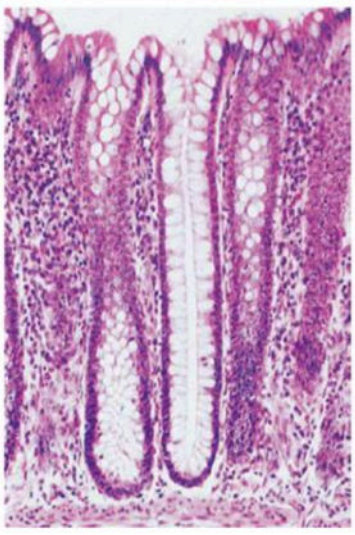

Figure 3.28 Simple tubular glands in the large intestine. A stained photograph (magnified ×50). (Young B, Lowe JS, Stevens A et al. 2006 *Wheater's functional histology: a text and colour atlas*. Edinburgh: Churchill Livingstone. Reproduced with permission.)

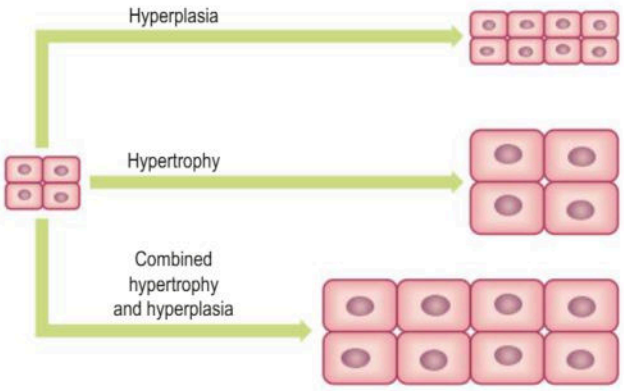

Figure 3.29 Hyperplasia and hypertrophy.

Changes in cell size and number

The earlier part of this chapter explored characteristics typical of normal cells and tissues, but these may be affected by physiological and/or pathological changes.

Cells within a tissue may enlarge, a process known as hypertrophy (Fig. 3.29), in response to additional demands; for example, skeletal muscle cells hypertrophy in response to fitness training, increasing the bulk and tone of exercised muscle. A decrease in the size or the number of cells is referred to as atrophy. Without use, muscle fibres atrophy (and muscle mass also decreases), e.g., those of a limb in a plaster cast applied to immobilise a fracture. Impaired nutrient or oxygen supply can also lead to atrophy.

Hyperplasia (Fig. 3.29) occurs when cells divide more quickly than previously, increasing cell numbers (and size of the tissue/organ), e.g., the glandular milk-producing tissue of the breasts during pregnancy and breast feeding. Abnormal hyperplasia can lead to the development of tumours when mitosis is no longer controlled and the daughter cells may show abnormal internal characteristics (see cell differentiation, p. 61).

Cell death

Two different mechanisms are recognised: apoptosis and necrosis.

Apoptosis

This is normal, genetically programmed cell death, in which an ageing cell at the end of its life cycle disintegrates and its remaining fragments are rapidly phagocytosed by local macrophages without any inflammatory reaction. In later life, fewer cells lost by apoptosis are replaced, contributing to the general reduction in tissue mass and organ size in older adults.

Necrosis

This is cell death resulting from lack of oxygen (ischaemia), tissue injury or a pathological process. The plasma membrane ruptures, releasing the intracellular contents and triggering the inflammatory response. Inflammation is the first stage of tissue repair and is needed to clear the area of cell debris before healing and tissue repair can progress (Ch. 14).

SPOT CHECK

5. Outline the difference between the terms hypertrophy and hyperplasia.
6. Name the process that refers to the death of cells at the end of their natural lifespan.

Neoplasms or tumours

Learning outcomes

After studying this section, you should be able to:

- outline the common causes of tumours
- explain the terms 'well differentiated' and 'poorly differentiated'
- compare and contrast the effects of benign and malignant tumours
- outline causes of death in malignant disease

Table 3.1 Typical differences between benign and malignant tumours

Benign	Malignant
Slow growth	Rapid growth
Cells well differentiated (closely resemble tissue of origin)	Cells poorly differentiated (may not resemble tissue of origin)
Usually encapsulated	Not encapsulated
No distant spread (metastasis)	Spreads (metastasises): • By local infiltration • Via lymph • Via blood • Via body cavities
Recurrence is rare	Recurrence is common

A tumour or neoplasm (literally meaning 'new growth') is a mass of tissue that grows faster than normal in an uncoordinated manner and continues to grow after the initial stimulus has ceased.

Tumours are classified as benign or malignant. Characteristic differences are shown in Table 3.1 although a clear distinction is not always possible. Benign tumours only rarely change their character and become malignant. Whether malignant or benign, tumours may be classified according to their tissue of origin, e.g. adeno- (glandular) or sarco- (connective tissue); the latter may be further distinguished, e.g. myo- (muscle) or osteo- (bone). Malignant tumours are further classified according to their origins; for example, a carcinoma, the most common form of malignancy, originates from epithelial tissue and a sarcoma arises from connective tissue. Hence, an adenoma is a benign tumour of glandular tissue but an adenocarcinoma is a malignant tumour of the epithelial component of glands; a benign bone tumour is an osteoma, whereas a malignant bone tumour is an osteosarcoma.

Common cancers

Some 17 million cases of cancer were diagnosed worldwide in 2018. Globally the commonest cancers are of the lung, female breast, bowel and prostate, which together account for more than 40% of cancers. In the UK, deaths (mortality) from cancer in 2018 reflect the situation above (see Fig. 3.30). However, worldwide in 2018 most deaths from cancer were

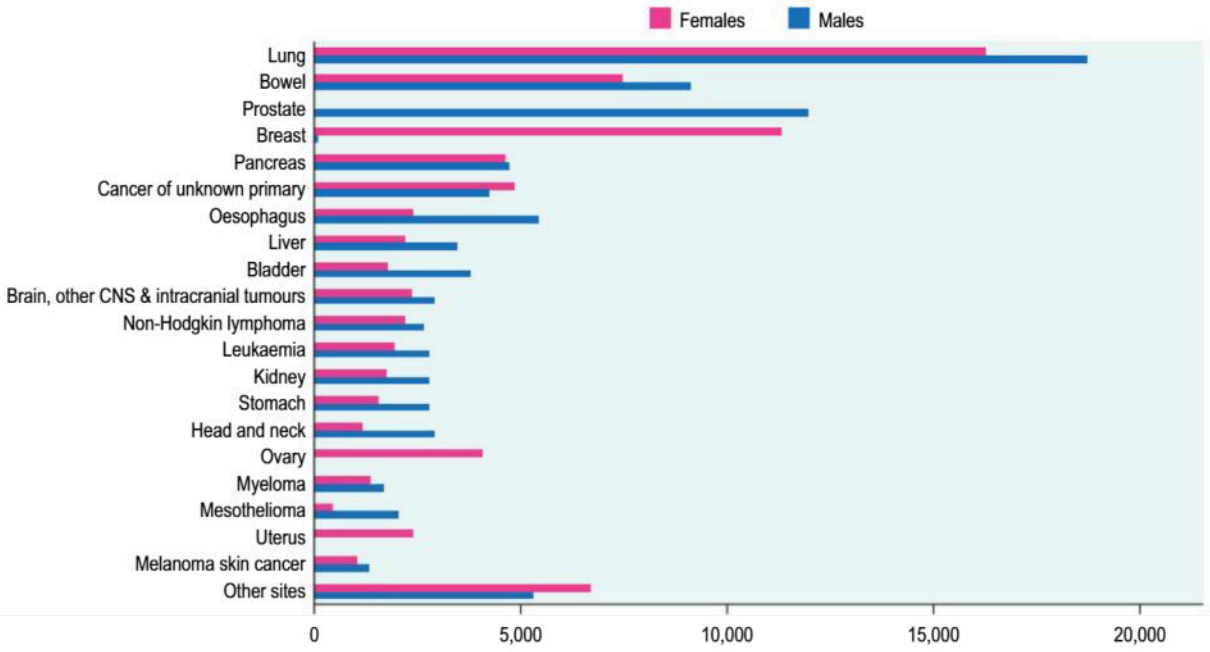

Figure 3.30 The most common causes of cancer deaths in the UK between 2015 and 2017. (From Cancer Research UK, 2020. https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero)

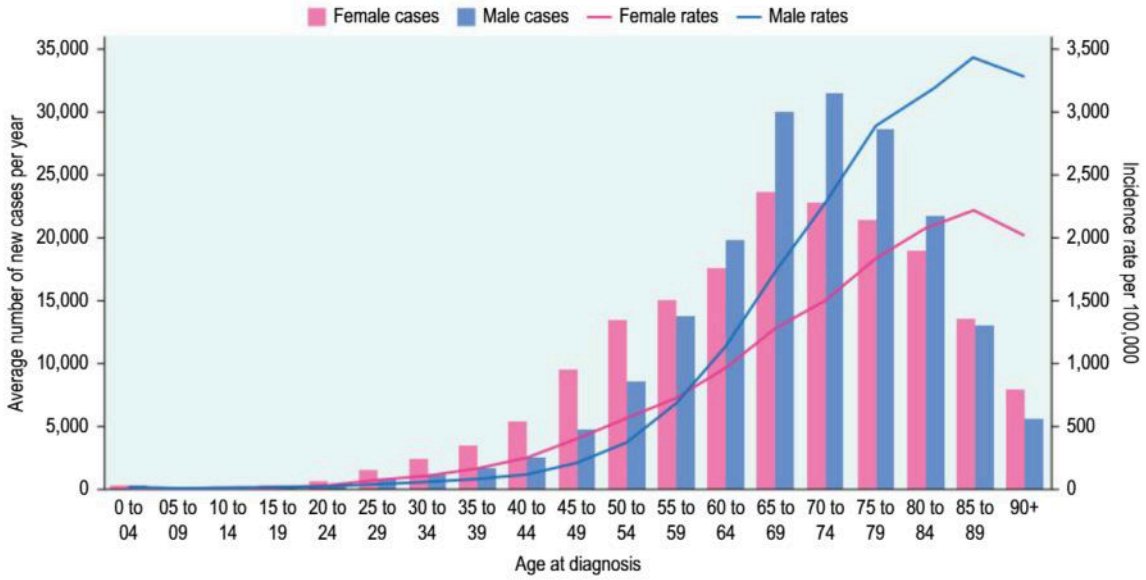

Figure 3.31 Incidence of cancer in the UK: number of cases and incidence rates in 2017 by age and sex. (From Cancer Research UK, 2020. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero)

from tumours of the lung, liver, stomach and bowel (Cancer Research UK, 2020).

Incidence

It is estimated that cancer will affect around half of people born in the UK after 1960 sometime during their lives. Although cancer affects people of all ages, UK data from 2015 to 2017 clearly shows the incidence rate rises with age (Fig. 3.31). The graphs in this figure show the incidence rate per 100,000 people rises steeply especially after 55 to 59 years, and particularly in men.

The histograms in Figure 3.31 show the number of new cases by age group and gender. Children and young people under 24 years comprise under 1% of the total number of cases while adults aged between 25 and 49 account for one tenth (9%); over half (54%) arose in adults between the ages of 50 and 75 years while the remainder (36%) of cases occurred in elderly people over 75 years. This data also demonstrates that women between the ages of 25 and 54 are significantly more likely to be diagnosed with cancer than men but that this difference is reversed in later life when the incidence rate in men over 60 years exceeds that in women.

Causes of neoplasms

There are more than 200 different types of cancer; all are caused by mutations (changes) within the cell's genetic material. Some mutations are spontaneous, i.e., happen by chance during cell division; others are related to exposure to a mutagenic agent (a carcinogen) and a few are inherited. Advancing knowledge has led to identification of many specific gene/chromosome mutations associated directly with particular cancers. Cell division is regulated by genes, some that inhibit the cell cycle (tumour suppressor genes) and others that stimulate it (proto-oncogenes). One important tumour suppressor gene, *p53*, is thought to be defective in 50%–60% of cancers. A proto-oncogene that becomes abnormally activated and allows uncontrolled cell division can also cause cancers and is then referred to as an oncogene.

Carcinogens

These cause malignant changes in cells by irreversibly damaging (mutating) their DNA. It is impossible to specify a maximum 'safe dose' of a carcinogen. A small dose may initiate change but may not cause malignancy unless there are repeated doses over time that have a cumulative effect. There are also widely varying latent periods between exposure and signs of malignancy.

Host factors. Individual characteristics can influence susceptibility to tumours. Some are outwith individual control, e.g. race, increasing age and inherited (genetic) factors. Others can be modified and are referred to as lifestyle factors; these include diet and obesity, smoking habits and exercise levels. Making healthy lifestyle choices where possible is important, as these factors are implicated in the development of nearly half of all malignant tumours.

Chemical carcinogens. Examples include:

- many substances in cigarette smoke, which is the main risk factor for lung (bronchial) cancer (p. 299)
- aniline dyes, which predispose to bladder cancer (p. 397)
- asbestos, which is associated with pleural mesothelioma (p. 299).

Ionising radiation. Exposure to ionising radiation, including X-rays, radioactive isotopes, environmental radiation and ultraviolet rays in sunlight, may cause mutations in some cells and kill others. Cells are affected during mitosis and so those that normally divide frequently are most susceptible, namely labile tissues including the skin, mucous membranes of the gastrointestinal tract, bone marrow, and gametes in the ovaries and testes. For example, repeated episodes of sunburn (caused by exposure to ultraviolet rays in sunlight) predispose to development of skin cancer (p. 413).

Oncogenic viruses. Some viruses cause neoplastic change. Such viruses enter cells and incorporate their DNA or RNA into the host cell's genetic material, introducing a mutation, and the mutant cells may be neoplastic. Examples include hepatitis B virus, which can cause liver cancer (p. 370), and human papilloma virus, which is associated with cervical cancer (p. 520).

Characteristics of tumours

Normally, cells divide in an orderly manner. Neoplastic cells have escaped from the normal controls and multiply in a disorderly and uncontrolled manner, forming a tumour. Malignant cells become immortal when they develop the ability to replicate indefinitely.

Cell differentiation

Differentiation into specialised cell types with particular structural and functional characteristics occurs at an early stage in fetal development; for example, epithelial cells develop a different set of structural and functional characteristics compared to lymphocytes. When cell division occurs, e.g. in wound healing, daughter cells have the same appearance, functions and genetic make-up as the parent cell. In benign tumours, the cells are very similar to the parent cell, i.e. tumour cells are well differentiated. Tumours with well-differentiated cells are usually benign although some may be malignant. Malignant tumours show varying levels of differentiation ranging from:

- Mild dysplasia – the tumour cells retain most of their normal features and their parent cells can usually be identified. Affected tissue retains much of its original appearance
- Anaplasia – the tumour cells have lost most of their normal features, their parent cells cannot be identified, and the original structure of affected tissue is largely lost.

Encapsulation and spread of tumours

Benign tumours

Most benign tumours are contained within a fibrous capsule derived partly from the surrounding tissues and partly from the tumour. They neither invade local tissues nor spread to other parts of the body, even when they are not encapsulated.

Table 3.2 Common sites of primary tumours and their metastases

Primary tumour	Metastatic tumours
Bronchi	Adrenal glands, brain
Alimentary tract	Abdominal and pelvic structures, especially liver
Prostate gland	Pelvic bones, vertebrae
Thyroid gland	Pelvic bones, vertebrae
Breast	Vertebrae, brain, bone

Malignant tumours

Malignant tumours do not have a capsule. Initially they grow from a single mutated cell and enlarge within the tissue of origin, this is known as cancer in situ (Fig. 3.32). Malignant cells secrete factors that stimulate development of new blood vessels within the tumour (angiogenesis), providing it with a good supply of oxygen and nutrients that further promotes its growth. It may spread locally by growing into and infiltrating nearby tissue: this is called invasion (Fig. 3.32). Tumour fragments may break off and travel to other parts of the body in the blood or lymph. Some of the spreading tumour cells may be recognised as 'non-self' and phagocytosed by macrophages or destroyed by defence cells of the immune system, e.g., cytotoxic T-cells and natural killer cells (Ch. 15). Others may escape detection and lodge in tissues away from the primary site, growing into secondary tumours (metastases). Metastases are often multiple. Table 3.2 shows common sites of primary tumours and their metastases.

The likely prognosis may by determined using staging, a process that assesses the size and spread of the tumour. A commonly used example is the TNM system, where T is tumour size, N indicates affected regional lymph nodes and M identifies metastatic sites. For most tumours, the larger the size and the more extensive the spread, the poorer the prognosis.

Local spread

As benign tumours enlarge they may damage local structures impairing their function but they do not spread to other parts of the body Both benign and malignant tumours may compress local structures (see below).

Body cavity spread

This occurs when a malignant tumour penetrates the wall of a cavity. The peritoneal cavity is most frequently involved. If, for example, a malignant tumour in an abdominal organ invades the visceral peritoneum, tumour cells may metastasise to folds of peritoneum or any abdominal or pelvic organ. Where there is less scope for the movement of fragments within a cavity, the tumour tends to bind layers of tissue together; for example, a pleural tumour binds the

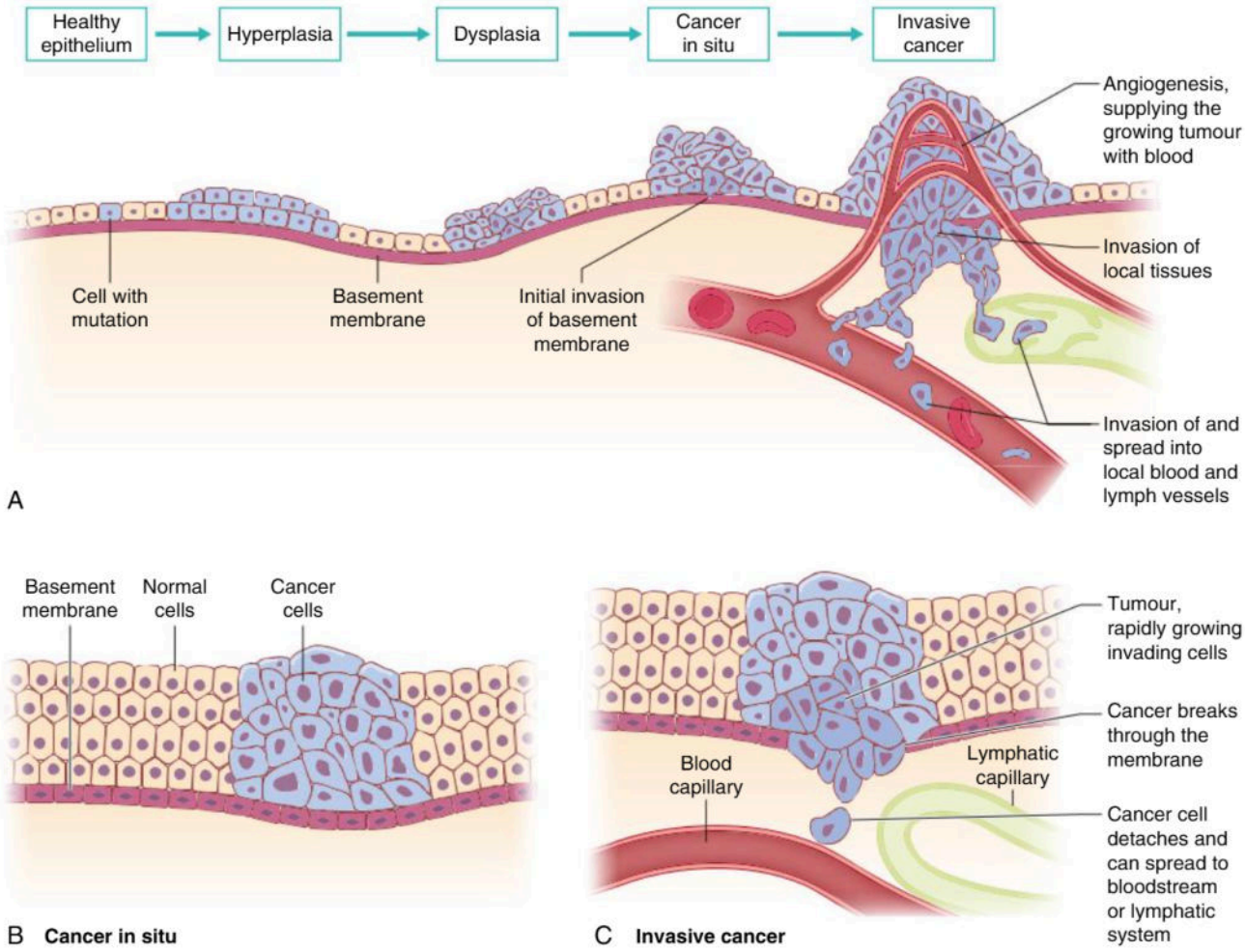

Figure 3.32 Growth of malignant tumours. (A) Growth of malignant tumours. (B) Cancer in situ. (C) Invasive cancer.

visceral and parietal pleura together, limiting expansion of the lung.

Lymphatic spread

As a malignant tumour invades nearby lymph vessels, tumour cells may break off and be carried to lymph nodes, where they become lodged and grow into secondary tumours. There may be further spread through the lymphatic system and via the blood because lymph drains into the subclavian veins (Fig. 3.32C).

Blood spread

This occurs when a malignant tumour erodes a blood vessel wall. A thrombus (blood clot) may form at the site and emboli, consisting of tumour fragments and blood clot, enter the bloodstream. These emboli block small blood vessels, causing infarcts (areas of dead tissue) and development of metastatic tumours. Phagocytosis of tumour cells in these emboli is unlikely to occur because they are protected from immune surveillance within the blood clot. Single tumour cells can also lodge in the capillaries of other body organs. Division and subsequent growth of secondary tumours, or metastases, may then occur. The sites of blood-spread metastases depend on the location of the original tumour and the anatomy of the circulatory system in the area. The most common sites of these metastases are bone, the lungs, the brain and the liver.

Effects of tumours

Compression of local structures

Both benign and malignant tumours may compress and damage adjacent structures, especially within a confined space. The effects depend on the site but are most marked in areas where there is little space for expansion, e.g., inside the skull, under the periosteum of bones, in bony sinuses and respiratory passages. Compression of adjacent structures may impair their function, for example, blocking ducts and damaging and/or displacing organs. Pressure on blood vessels can lead to ischaemia (lack of oxygen) and necrosis

(death) of the tissue they supply, similarly compression of nerves can lead to pain and loss of nerve control of the tissues and organs they supply.

Hormone secretion

Benign and malignant tumours of endocrine glands may secrete hormones, producing the effects of hypersecretion. The extent of cell dysplasia is an important factor; well-differentiated benign tumours are more likely to secrete hormones than markedly dysplastic malignant tumours. High levels of hormones are found in the bloodstream, as secretion occurs independently of the normal stimulus and homeostatic control mechanism. Some malignant tumours produce uncharacteristic hormones; for example, some lung tumours produce insulin. Endocrine glands may be destroyed by invading tumours, causing hormone deficiency.

Cachexia

This is severe weight loss accompanied by progressive weakness, loss of appetite, wasting and anaemia often associated with advanced metastatic cancer. The severity usually relates directly to the stage of the disease, and the cause of cachexia is unknown.

Causes of death in malignant disease

Acute infection is a common cause of death when superimposed on advanced malignancy. Predisposition to infection is increased by prolonged immobility or bedrest, and by depression of the immune system by cytotoxic drugs and radiotherapy or radioactive isotopes used in treatment. The most common infections are pneumonia, septicaemia, peritonitis and pyelonephritis.

Organ failure occurs when a tumour destroys so much healthy tissue that it becomes unable to function, often with fatal consequences. The lungs, brain, liver and kidneys are most often affected.

Fatal haemorrhage may occur when a tumour grows into and ruptures the wall of a large vein or artery. The most common sites are the gastrointestinal tract, brain, lungs and peritoneal cavity.

Carcinomatosis is the presence of widespread metastatic disease and is often associated with cachexia. Increasingly severe physiological and biochemical disruption follows, causing death.

SPOT CHECK

7. List four lifestyle factors that reduce an individual's risk of cancer.
8. Describe how malignant tumours may spread.

References and further reading

Cancer Research UK, 2020a. Cancer incidence with age. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero.

Cancer Research UK, 2020b. Cancer mortality for common cancers. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero.

Case study

Donna found a lump in her breast and was referred by her GP for further investigations. Fortunately, tests showed the lump to be a benign tumour (the commonest type of breast tumour), which was easily removed.

1. Skin covering the breast is made from:
   a. Connective tissue
   b. Epithelial tissue
   c. Nervous tissue
   d. Muscle tissue
2. Breast tissue contains abundant fat cells, also known as:
   a. Leukocytes
   b. Chondrocytes
   c. Adipocytes
   d. Macrophages
3. Normally body cells divide by:
   a. Hypertrophy
   b. Apoptosis
   c. Meiosis
   d. Mitosis
4. The organelles that generate cellular energy needed for division are:
   a. Mitochondria
   b. Ribosomes
   c. Lysosomes
   d. Golgi apparatus
5. Features of a benign tumour typically include:
   a. A fibrous capsule
   b. Local spread
   c. Lymphatic spread
   d. Blood-borne spread

Review and revise

Complete each of the following statements:

1. Some membrane proteins act as specific recognition sites called _____, others have branched carbohydrate molecules attached conferring the cell with its_____ while others are involved in _____ that actively transport substances across it.

2. The mitotic apparatus consists of two _____ separated by the _____ _____.

3. The four main types of tissue are _____tissue, _____ tissue, _____ tissue and _____ tissue.

Choose one answer to complete each of the following statements:

4. Phagocytosis is a form of: ____
   a. Passive transport
   b. Osmosis
   c. Bulk transport
   d. Diffusion.

5. In order, the stages of mitosis are: _____
   a. Telophase, anaphase, metaphase, prophase
   b. Prophase, metaphase, anaphase, telophase
   c. Metaphase, prophase, telophase, anaphase
   d. Anaphase, prophase, metaphase, telophase.

Indicate whether each of the following statements is true or false:

6. Hydrophobic means 'water-loving'. _____

7. Osmosis is passive movement of water down its concentration gradient. ____

8. Smooth muscle is under conscious control. ____

9. Match each letter in List A to the appropriate number in List B:

List A

_____ (a) Endoplasmic reticulum
_____ (b) Nucleolus
_____ (c) Centrosome
_____ (d) Lysosome
_____ (e) Mitochondrion
_____ (f) Nucleus
_____ (g) Flagellum
_____ (h) Ribosome

List B

1. Found inside the nucleus and involved in the assembly of ribosomes
2. Consists of a pair of centrioles
3. A tiny granule found free in the cytoplasm and attached to rough endoplasmic reticulum
4. A small membranous vesicle that contains digestive enzymes
5. Formed by an extensive network of membranous canals
6. A cell extension that resembles a whip
7. The largest organelle, which directs cellular activity
8. The site of aerobic respiration – the 'power house' of the cell

10. Match each letter in List A to the appropriate number in List B:

List A

_____ (a) Adipocyte
_____ (b) Hyperplasia
_____ (c) Apoptosis
_____ (d) Neurone
_____ (e) Necrosis
_____ (f) Osteocyte
_____ (g) Hypertrophy
_____ (h) Chondrocyte

List B

1. Cell death due of lack of oxygen
2. Nerve cell
3. Increase in cell size
4. Cartilage cell
5. Death of cells at the end of their normal life cycle
6. Increase in cell numbers
7. Fat cell
8. Bone cell

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

SECTION TWO

CHAPTER 4

The blood

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Blood is a fluid connective tissue. It circulates constantly around the body, propelled by the pumping action of the heart. It transports:

- dissolved gases including oxygen
- nutrients
- hormones
- heat
- antibodies and cells of the immune system
- plasma proteins, including clotting factors
- drugs
- wastes.

Blood is composed of a clear, straw-coloured, watery fluid called plasma, in which several different types of blood cell are suspended. Plasma normally constitutes 55% of the volume of blood and the cell fraction 45%. A whole blood sample, mixed with an anticoagulant to prevent clotting and gently centrifuged, separates into its plasma fraction and its cellular fraction (Fig. 4.1A). The cells are heavier than plasma and sink to the bottom of the sample. Gentle shaking or stirring of the sample will resuspend the cells in the plasma, reconstituting whole blood.

Blood makes up about 7% of body weight (about 5.6 litres in a 70-kg man). This proportion is less in women and considerably greater in children, gradually decreasing until the adult level is reached. The total blood volume in adults is about 80 mL/kg body weight in males and 70 mL/kg in females.

Blood never stops moving in the blood vessels, and the continual blood flow maintains a fairly constant environment for body cells, controlling key factors such as water distribution and the pH of body fluids. The blood also helps to maintain core body temperature by distributing heat produced by metabolically active organs, such as working skeletal muscles and the liver, around the body. Total blood volume and the concentration of blood constituents, e.g. glucose and electrolytes, are kept within narrow limits by homeostatic mechanisms.

The first part of the chapter discusses normal blood physiology and the later sections describe some blood disorders. Effects of ageing on white blood cell function are described in Chapter 15.

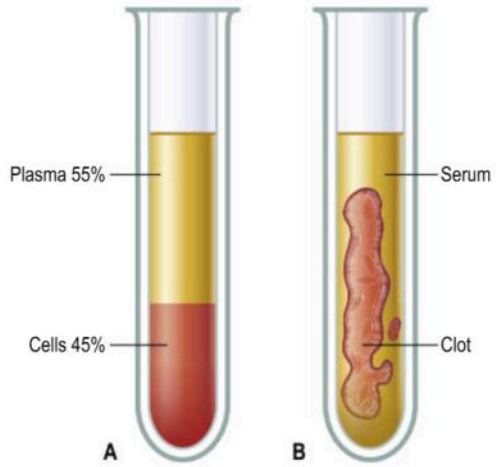

Figure 4.1 Whole blood. (A) The proportions of blood cells and plasma in anticoagulated whole blood separated by gravity. (B) A blood clot in serum.

Plasma

Learning outcomes

After studying this section, you should be able to:

- list the constituents of plasma
- describe their functions.

The main constituent of plasma is water (90%–92%), carrying a range of dissolved and suspended substances, including:

- plasma proteins (7% of plasma)
- electrolytes
- nutrients, principally from digested foods
- waste products
- hormones
- gases.

Plasma proteins

Most plasma proteins are synthesised in the liver, with the notable exception of immunoglobulins (antibodies), which are produced by B-cells of the immune system (p. 420). Because they are too big to escape through the capillary walls into the tissues, plasma proteins are retained in the bloodstream and are the main factor maintaining the osmotic pressure of blood (p. 89), which controls water distribution between the plasma and the tissues. If plasma protein levels fall, because of either reduced production or loss from the blood vessels, osmotic pressure is also reduced, and fluid shifts into the tissues (oedema) and body cavities. The main groups of plasma proteins are the albumins, globulins and the clotting protein fibrinogen.

Albumins

These are the most abundant plasma proteins (about 60% of total) and their main function is to maintain normal plasma osmotic pressure. Albumins also act as carrier molecules for free fatty acids, some drugs and steroid hormones.

Globulins

The two most important groups of globulins are:

- Antibodies (immunoglobulins), complex proteins produced by lymphocytes that play an important part in immunity. They bind to and neutralise foreign materials (antigens) such as micro-organisms (p. 422).
- Transport globulins, which bind to and transport some hormones and mineral salts in the bloodstream. For example, thyroglobulin transports the hormone thyroxine and transferrin transports iron.

Fibrinogen and other clotting proteins

There are several clotting proteins (clotting factors) present in the bloodstream, of which fibrinogen is the most abundant. A blood sample not treated with an anticoagulant rapidly begins to clot when exposed to the air and to the surfaces of its container. It separates into a soft clot that sinks to the bottom of the container, and a clear straw-coloured fluid called serum (Fig. 4.1B). Serum and plasma are very similar in composition other than serum has little or no clotting proteins left because they have been used up in producing the clot.

Electrolytes

The main cation (positively charged ion) in blood is sodium (Na^+) and the main anion (negatively charged ion) is chloride (Cl^-). Electrolytes have a range of functions, including muscle contraction (e.g. Ca^{2+}), transmission of nerve impulses (e.g. Ca^{2+}, K^+ and Na^+), and maintenance of acid–base balance (e.g. phosphate, PO_4^{3-}). Blood pH is maintained between 7.35 and 7.45 (slightly alkaline) by an ongoing buffering system (p. 33).

Nutrients

Nutrients, substances essential for cellular growth and metabolism, include glucose, amino acids and vitamins. They are transported in the bloodstream from sites of production (e.g. the liver) or absorption (the gastrointestinal tract) to the tissues for immediate use or storage.

Waste products

Urea, creatinine and uric acid are the waste products of protein metabolism. They are formed in the liver and carried in blood to the kidneys for excretion. Carbon dioxide from tissue metabolism is transported to the lungs for excretion.

Hormones

Hormones (Ch. 9) are chemical messengers synthesised by endocrine glands; they are secreted directly into the blood which transports them to their target tissues and organs.

Gases

Oxygen is not very soluble in water, and less than 2% is transported dissolved in plasma. This is nowhere near enough to supply the body's needs, so an additional oxygen transport mechanism is needed: oxygen is bound to haemoglobin in red blood cells. Over 98% of oxygen in the blood is carried this way, as oxyhaemoglobin (p. 69). Haemoglobin also binds some carbon dioxide, although most carbon dioxide is converted to bicarbonate ions in red blood cells, and then transported dissolved in the plasma (p. 287).

SPOT CHECK

1. List the three main functions of the globulins.
2. What is the main constituent of plasma?

Cellular content of blood

Learning outcomes

After studying this section, you should be able to:

- discuss the structure, function and formation of red blood cells, including the systems used to classify the different types
- discuss the functions and formation of the different types of white blood cell
- outline the role of platelets in blood clotting.

There are three types of blood cell (Fig. 4.2; see also Fig. 1.3).

- erythrocytes (red cells)
- leukocytes (white cells), including neutrophils, lymphocytes, monocytes, eosinophils and basophils
- platelets (thrombocytes).

Most blood cells are produced in red bone marrow. Additionally, some lymphocytes are produced in lymphoid tissue. The red bone marrow is populated with a large number of continually dividing pluripotent stem cells, i.e. cells capable of developing into any one of a number of cell types, and all blood cells develop from these. Each type of blood cell follows a separate line of development, and the process of blood cell formation is called haemopoiesis (Fig. 4.3).

In children, red marrow completely fills the space within bone, to produce enough blood cells to meet the needs of the rapidly growing child. Over the next 20 years, however, it is largely replaced by fatty yellow marrow with no haemopoietic function.

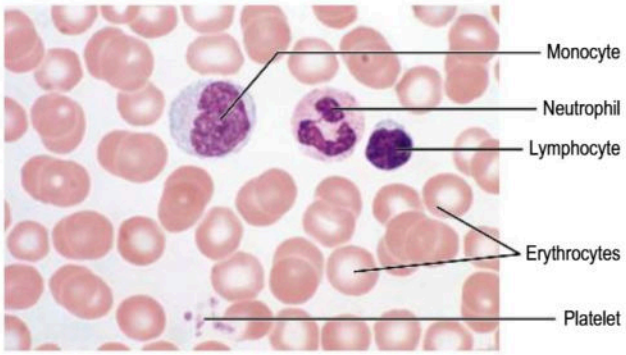

Figure 4.2 A blood smear, showing erythrocytes, a monocyte, a neutrophil, a lymphocyte and a platelet. (Biophoto Associates/ Science Photo Library. Reproduced with permission.)

In adults, haemopoiesis in the skeleton is confined to red bone marrow found in flat bones, irregular bones and the ends of long bones, the main sites being the sternum, ribs, pelvis and skull.

Erythrocytes (red blood cells)

Erythrocytes are by far the most abundant type of blood cell; 99% of all blood cells are red blood cells (see Fig. 4.2). They are thin, flattened biconcave discs with no nucleus, and their diameter is about 7 μm (Fig. 4.4). Their main role is to transport respiratory gases, mainly oxygen, but they also carry some carbon dioxide. Their characteristic shape is suited to their function: the biconcavity increases their surface area for gas exchange, and the thin central portion allows fast entry and exit of gases. The cells are flexible, to fold and squeeze through narrow capillaries, and contain no intracellular organelles, leaving more room for haemoglobin, the pigmented protein responsible for gas transport. Their flattened shape allows them to stack like dinner plates in the bloodstream, streamlining blood flow and reducing turbulence.

Measurements of red cell numbers, volume and haemoglobin content are routine and useful assessments made in clinical practice (Table 4.1). The letters in brackets in the first column of the table are the abbreviations commonly used in laboratory reports.

Lifespan and function of erythrocytes

There are approximately 30 trillion (10^{14}) red blood cells in the average human body, about 25% of the body's total cell count, and around 1%, mainly older cells, are cleared and destroyed daily. Because they have no nucleus, erythrocytes cannot divide in the bloodstream and their numbers are maintained by balancing production in the red bone marrow and breakdown, mainly in the liver and spleen. Over two million new erythrocytes are released from the red bone marrow every second and their lifespan in the circulation is about 120 days.

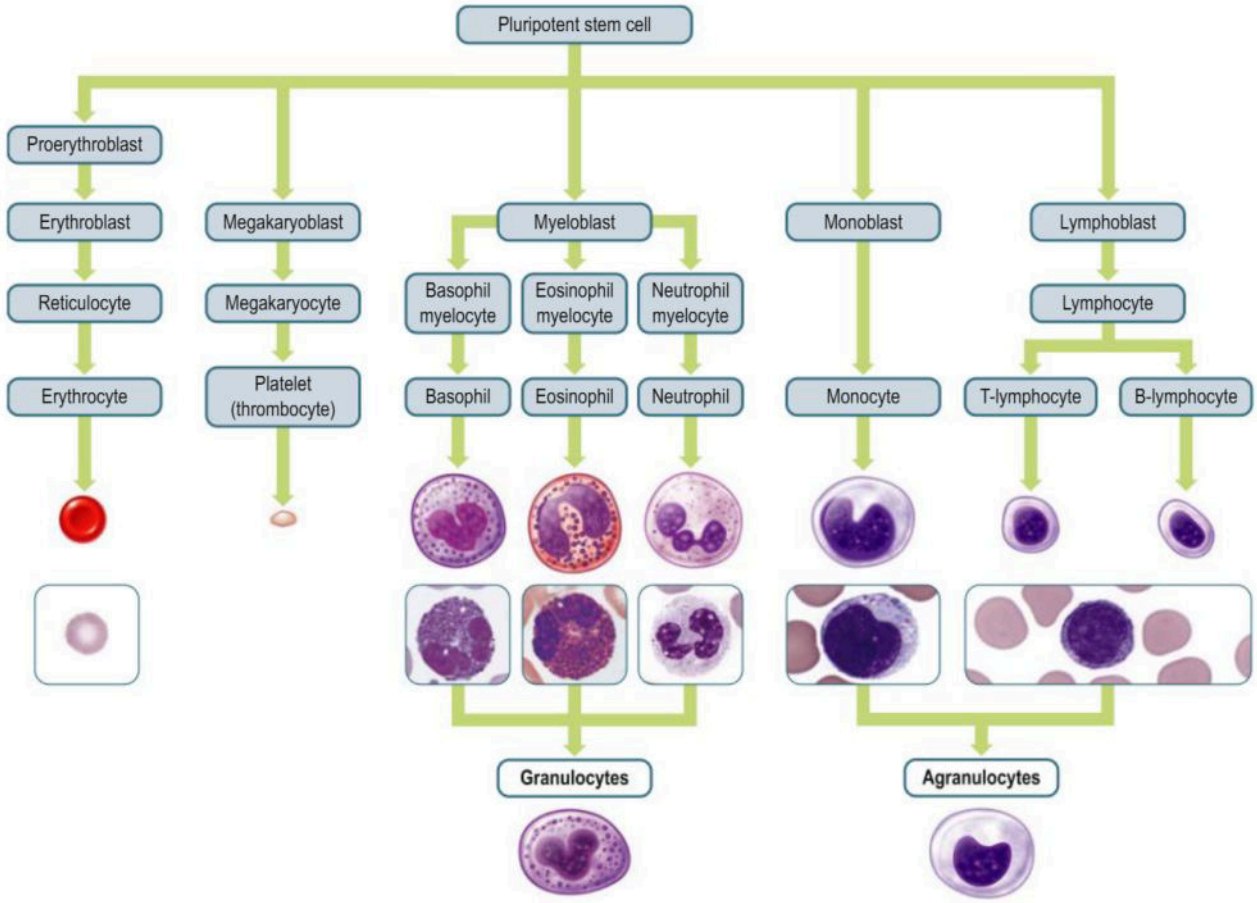

Figure 4.3 Haemopoiesis. Stages in the development of blood cells. (Photographic inserts from Telser AG, Young JK, Baldwin KM 2007 *Elsevier's integrated histology*. Mosby: Edinburgh; and Young B, Lowe JS, Stevens A et al. 2006 *Wheater's functional histology: a text and colour atlas*. Edinburgh: Churchill Livingstone. Reproduced with permission.)

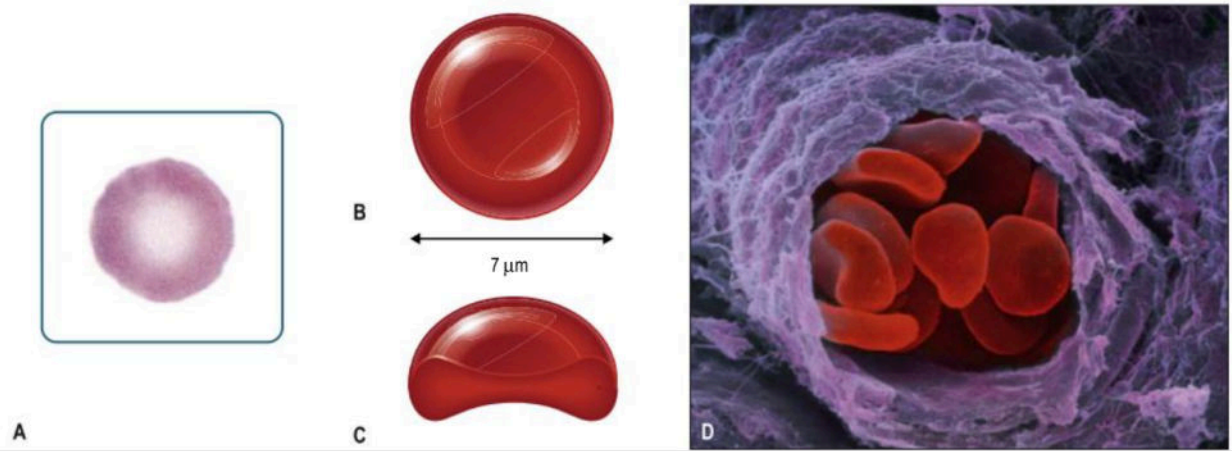

Figure 4.4 The red blood cell. (A) Under the light microscope. (B) Drawn from the front. (C) Drawn in section. (D) Coloured scanning electron micrograph of a group of red blood cells travelling along an arteriole. (A, Telser AG, Young JK, Baldwin KM 2007 *Elsevier's integrated histology*. Edinburgh: Mosby. Reproduced with permission. D, Professors PM Motta and S Correr/Science Photo Library. Reproduced with permission.)

Table 4.1 Erythrocytes – normal values

Measure	Normal values
Erythrocyte count – number of erythrocytes per litre, or cubic millilitre (mm^3), of blood	Male: 4.5×10^{12}/L to 6.5×10^{12}/L (4.5–6.5 million/mm^3)
	Female: 3.8×10^{12}/L to 5.8×10^{12}/L (3.8–5.8 million/mm^3)
Packed cell volume (PCV, haematocrit) – the volume of red cells in 1 litre or mm^3 of blood	0.40–0.55 L/L
Mean cell volume (MCV) – the volume of an average cell, measured in femtolitres (1 fL = 10^{-15} litre)	80–96 fL
Haemoglobin (Hb) – the weight of haemoglobin in whole blood, measured in grams/100 mL of blood	Male: 13–18 g/100 mL
	Female: 11.5–16.5 g/100 mL
Mean cell haemoglobin (MCH) – the average amount of haemoglobin per cell, measured in picograms (1 pg = 10^{-12} gram)	27–32 pg/cell
Mean cell haemoglobin concentration (MCHC) – the weight of haemoglobin in 100 mL of red cells	30–35 g/100 mL of red cells

The process of erythrocyte development from stem cells takes about 7 days and is called erythropoiesis (Fig. 4.3). The immature cells are released into the bloodstream as reticulocytes and mature into erythrocytes over a few days within the circulation. Vitamin B_{12} (cobalamin) and folic acid are required for red blood cell synthesis. They are absorbed in the small intestine, although vitamin B_{12} must be bound to intrinsic factor (p. 335) for absorption. Both vitamins are present in dairy products, meat and green vegetables. The liver usually contains substantial stores of vitamin B_{12} – several years' worth – but signs of folic acid deficiency appear within a few months. The life cycle of the erythrocyte is shown in Figure 4.5.

Haemoglobin

Haemoglobin is a large, complex molecule containing a globular protein (globin) and a pigmented iron-containing complex called haem. Each haemoglobin molecule contains four globin chains and four haem units, each with one atom of iron (Fig. 4.6). Because each atom of iron can combine with an oxygen molecule, a single haemoglobin molecule can carry up to four molecules of oxygen. An average red blood cell carries about 280 million haemoglobin molecules, giving each cell a theoretical oxygen-carrying capacity of over a billion oxygen molecules!

Iron is carried in the bloodstream bound to its transport protein, transferrin, and stored in the liver. Haemoglobin production requires a steady supply of iron. Iron absorption from the gastrointestinal tract is very slow, even when the diet is rich in iron, meaning that iron deficiency can readily occur if iron loss exceeds intake.

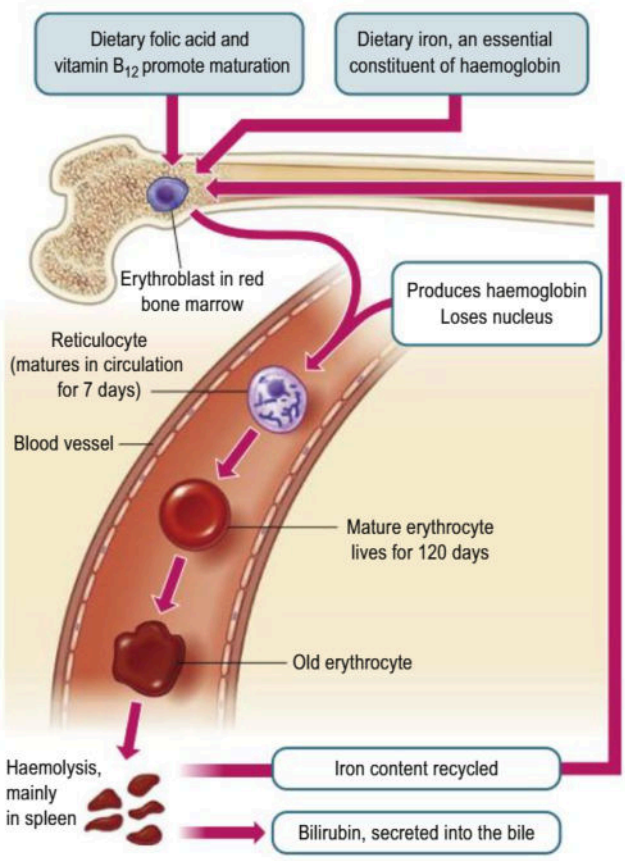

Figure 4.5 Life cycle of the erythrocyte.

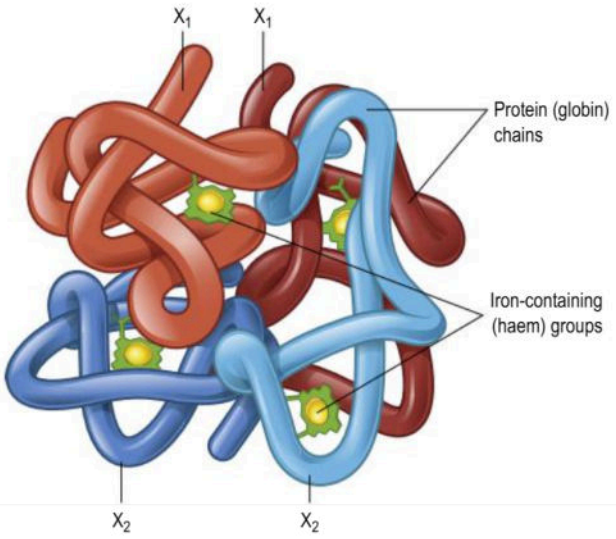

Figure 4.6 The haemoglobin molecule.

Oxygen transport

When all four oxygen-binding sites on a haemoglobin molecule are occupied by an oxygen molecule, it is described

as saturated. Haemoglobin binds reversibly to oxygen to form oxyhaemoglobin, according to the equation:

Haemoglobin	+	oxygen	↔	oxyhaemoglobin
(Hb)		(O_2)		(HbO_2)

As the oxygen content of blood increases, its colour changes too. Blood rich in oxygen (usually arterial blood) is bright red because of the high levels of oxyhaemoglobin it contains, compared with blood with lower oxygen levels (usually venous blood), which is dark bluish in colour. However, even venous blood contains significant quantities of oxygen, providing an important reserve capacity.

The binding of oxygen to haemoglobin is loose, so that oxyhaemoglobin releases its oxygen readily, especially under certain conditions: low pH, low oxygen levels and raised tissue temperature. This is essential to ensure that tissues with higher than normal oxygen requirements receive an adequate oxygen supply.

Low pH

Metabolically active tissues, e.g. exercising muscle, release acid waste products, and so the local pH falls. Under these conditions, oxyhaemoglobin readily breaks down, giving up additional oxygen for tissue use.

Low oxygen levels

Where oxygen levels are low, oxyhaemoglobin breaks down, releasing oxygen. In the tissues, which constantly consume oxygen, oxygen levels are always lower than in the blood. This increases oxygen release to the cells. In addition, the lower the tissue oxygen level, the more oxygen is released, meaning that as tissue oxygen demand rises, so does the supply to match it. The term hypoxia is used to mean oxygen levels in the blood or tissues are not enough to meet the tissues needs, and under hypoxic conditions oxyhaemoglobin dissociates rapidly to increase oxygen supply to the cells. On the other hand, when oxygen levels are high, as they are in the lungs, oxyhaemoglobin formation is favoured. In health, this means that blood leaving the lungs is around 98% saturated with oxygen.

Higher temperature

Actively metabolising tissues, which have higher than normal oxygen needs, are warmer than less active ones, driving the equation above to the left and increasing oxygen release. This ensures that very active tissues receive a higher oxygen supply than less active ones. In the lungs, where the alveoli are exposed to inspired air, the temperature is lower, favouring oxyhaemoglobin formation.

Control of erythropoiesis

Red cell numbers remain fairly constant because the bone marrow produces erythrocytes at the rate at which they are destroyed. The hormone that regulates red blood cell production is erythropoietin, produced mainly by the kidney.

The main stimulus for increased erythropoiesis is hypoxia, i.e. deficient oxygen supply to body cells, and the homeostatic mechanism that controls erythropoietin release is shown in Figure 4.7. Hypoxia can develop in a range of situations, including anaemia, reduced blood volume, poor blood flow, reduced oxygen content of inspired air (as at altitude) or lung disease. Each of these stimulates erythropoietin production in an attempt to increase erythrocyte production and restore oxygen supplies to the tissues.

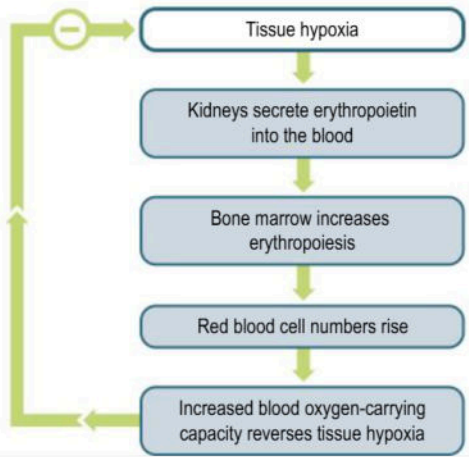

Figure 4.7 Control of erythropoiesis: the role of erythropoietin.

Erythropoietin increases the production of proerythroblasts and the release of more reticulocytes into the blood. It also speeds up reticulocyte maturation. These changes increase the oxygen-carrying capacity of the blood and reverse tissue hypoxia, the original stimulus. When oxygen levels rise and the hypoxia is corrected, erythropoietin production declines. Without erythropoeitin, erythrocyte production declines even in the presence of hypoxia, and anaemia (the inability of the blood to carry adequate oxygen for body needs) develops.

Destruction of erythrocytes

As erythrocytes age, their cell membranes become more fragile and so more susceptible to rupture. It is important that this does not happen in the circulation, because the products of erythrocyte breakdown would trigger blood clotting and a damaging inflammatory response. Ageing erythrocytes are therefore extracted from the circulation by macrophages in the spleen, bone marrow and liver, and broken down (haemolysed) under controlled conditions. Iron released by haemoglobin breakdown is returned to the bone marrow for ongoing haemoglobin synthesis. The haem part of the haemoglobin is broken down to the green pigment biliverdin, which in turn is almost completely reduced to the yellow pigment bilirubin, before being bound to plasma globulin and transported to the liver (see Fig. 4.5 and Fig. 12.39). In the liver bilirubin is converted from a fat-soluble to a water-soluble form to be excreted in bile.

Blood groups

Early attempts to transfuse blood from one person to another or from animals to humans were only rarely successful, the

recipient of the blood usually becoming very ill or dying. It is now known that the erythrocyte membrane carries a range of different proteins (called antigens) that can stimulate an immune response if transferred from one individual (the donor) into the bloodstream of an incompatible recipient. These antigens, which are inherited from the parents, determine the individual's blood group. This can be used to help identify parentage in paternity testing: a child cannot have a blood group antigen that is not present in either or both parents. In addition, individuals can make antibodies to these antigens, but not to their own type of antigen, since if they did the antigens and antibodies would react, causing a potentially fatal transfusion reaction.

If a recipient is transfused with blood of the same group, i.e., possessing the same cell surface antigens, their immune system will not recognise them as foreign and will not reject them. However, if they are given blood from an individual of a different blood type, i.e., with a different type of antigen on the red cells, their immune system will generate antibodies to the foreign antigens and destroy the transfused cells. This is the basis of the transfusion reaction: the two blood types, the donor and the recipient, are incompatible.

There are many different collections of red cell surface antigens, but the most important are the ABO and the Rhesus systems.

The ABO system

About 55% of the UK population has either antigen A (blood group A), antigen B (blood group B) or both (blood group AB) on their red cell surface. The remaining 45% have neither A nor B antigens (blood group O). Antibodies to these antigens are called anti-A antibodies and anti-B antibodies, respectively. Blood group A individuals cannot make anti-A antibodies (and therefore do not have anti-A antibodies in their plasma), since otherwise a reaction to their own cells would occur; they can, however, make anti-B antibodies, because the B antigen is non-self and foreign. Blood group B individuals, for the same reason, can make only anti-A antibodies. Blood group AB makes neither antibody, and blood group O makes both anti-A and anti-B antibodies (Fig. 4.8).

Because blood group AB people make neither anti-A nor anti-B antibodies, they are sometimes known as universal recipients: transfusion of either type A or type B blood into these individuals is likely to be safe, since there are no antibodies to react with them. Conversely, group O people have neither A nor B antigens on their red cell membranes, and their blood may usually be safely transfused into A, B, AB or O types; group O is sometimes called the universal donor. The terms universal donor and universal recipient are misleading, however, since they imply that the ABO system is the only one that needs to be considered. In practice,

Blood group	Antigen + antibody(ies) present	As donor, is	As recipient, is
A	Antigen A; Makes anti-B	Compatible with: A and AB Incompatible with: B and O, because both make anti-A antibodies that will react with A antigens	Compatible with: A and O Incompatible with: B and AB, because type A makes anti-B antibodies that will react with B antigens
B	Antigen B; Makes anti-A	Compatible with: B and AB Incompatible with: A and O, because both make anti-B antibodies that will react with B antigens	Compatible with: B and O Incompatible with: A and AB, because type B makes anti-A antibodies that will react with A antigens
AB	Antigens A and B; Makes neither anti-A nor anti-B	Compatible with: AB only Incompatible with: A, B and O, because all three make antibodies that will react with AB antigens	Compatible with all groups **UNIVERSAL RECIPIENT** AB makes no antibodies and therefore will not react with any type of donated blood
O	Neither A nor B antigen; Makes both anti-A and anti-B	Compatible with all groups **UNIVERSAL DONOR** O red cells have no antigens, and will therefore not stimulate anti-A or anti-B antibodies	Compatible with: O only Incompatible with: A, AB and B, because type O makes anti-A and anti-B antibodies

Figure 4.8 The ABO system of blood grouping. Antigens, antibodies and compatibility.

although the ABO systems may be compatible, other antigen collections on donor erythrocytes may be foreign to the recipient's body and cause a transfusion reaction (p. 80). For this reason, cross-matching before transfusion is always required to ensure that there is no reaction between donor and recipient bloods. Inheritance of ABO blood groups is described in Chapter 17.

The Rhesus system

The erythrocyte membrane antigen important here is the Rhesus (Rh) antigen, or Rhesus factor, sometimes also called the D antigen. About 85% of people have this antigen; they are Rhesus-positive (Rh^+) and do not therefore make anti-Rhesus antibodies. The remaining 15% have no Rhesus antigen (they are Rhesus-negative, or Rh^-). Rh^- individuals will produce anti-Rhesus antibodies if they are exposed to the Rhesus antigen, but this generally happens only in certain circumstances, e.g. in pregnancy (p. 79), or as the result of an incompatible blood transfusion.

Leukocytes (white blood cells)

Leukocytes have an important function in defence and immunity. They detect foreign or abnormal (antigenic) material and destroy it, through a range of defence mechanisms described below and in Chapter 15. Leukocytes are the largest blood cells but they account for only about 1% of the blood volume because they are much less numerous than erythrocytes (Table 4.2). They contain nuclei and some have granules in their cytoplasm (Fig. 4.2). There are two main types:

- granulocytes (polymorphonuclear leukocytes) – neutrophils, eosinophils and basophils
- agranulocytes – monocytes and lymphocytes.

Increased leukocyte numbers in the bloodstream (leukocytosis) usually indicate a physiological problem, e.g. infection, trauma or malignancy.

Granulocytes (polymorphonuclear leukocytes)

During their formation, called granulopoiesis, granulocytes follow a common line of development through myeloblast to myelocyte before differentiating into the three types (Fig. 4.9; see also Fig. 4.3). All granulocytes have complex, multilobed nuclei in their cytoplasm. Their names reflect the dyes they take up when stained in the laboratory. Eosinophils take up the red acid dye eosin, basophils take up alkaline methylene blue and neutrophils are purple because they take up both dyes.

Table 4.2 Normal leukocyte counts in adult blood

	Number × 10^9/L	Percentage of total
Granulocytes		
Neutrophils	2.5–7.5	40–75
Eosinophils	0.04–0.44	1–6
Basophils	0.015–0.1	< 1
Agranulocytes		
Monocytes	0.2–0.8	2–10
Lymphocytes	1.5–3.5	20–50
Total	5–9	100

Neutrophils

These small, fast and active scavengers protect the body against bacterial invasion and remove dead cells and debris from damaged tissues. They are attracted in large numbers to any area of infection by chemicals called chemotaxins, which are released by damaged cells. Neutrophils are highly mobile, and can squeeze through capillary walls in the affected area by diapedesis (Fig. 4.10). Their numbers rise

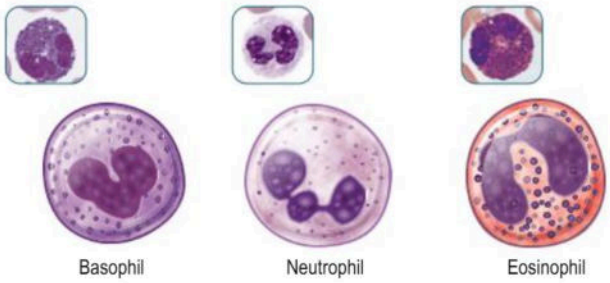

Figure 4.9 The granulocytes (granular leukocytes). (Adapted from Telser AG, Young JK, Baldwin KM 2007 *Elsevier's integrated histology*. Edinburgh: Mosby; and Young B, Lowe JS, Stevens A et al. 2006 *Wheater's functional histology: a text and colour atlas*. Edinburgh: Churchill Livingstone. Reproduced with permission.)

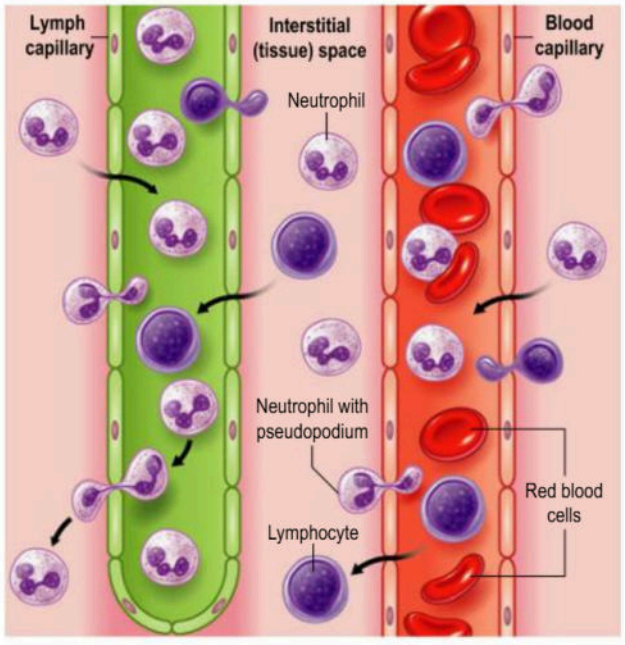

Figure 4.10 Diapedesis of leukocytes across the capillary wall.

very quickly in an area of damaged or infected tissue. Once there, they engulf and kill bacteria by phagocytosis (Fig. 4.11; see also Fig. 15.1). Their nuclei are characteristically complex, with up to six lobes (see Fig. 4.2), and their granules are lysosomes containing enzymes to digest engulfed material. Neutrophils live for up to five days in the bloodstream, but once actively phagocytosing target material, their survival time is probably less than an hour. Pus forming in an infected area consists of dead tissue cells, dead and live microbes, and phagocytes killed by microbes.

Eosinophils

Eosinophils, although capable of phagocytosis, are less active in this process than neutrophils; their specialised role appears to be in the elimination of parasites, such as worms, which are too big to be phagocytosed. They are equipped with toxic chemicals, stored in their granules, which they release (degranulation) when the eosinophil binds to an invading organism.

Local accumulation of eosinophils may occur in allergic inflammation, such as the asthmatic airway and skin allergies.

Basophils

Basophils are closely associated with allergic reactions and contain cytoplasmic granules packed with heparin (an anticoagulant), histamine (an inflammatory agent) and other substances that promote inflammation. Usually, the stimulus for basophil degranulation is an allergen (an antigen that causes allergy) of some type. This binds to antibody-type receptors on the basophil membrane, triggering release of the basophil's inflammatory mediators. Mast cells (see Fig. 3.18) are very similar to basophils, except that they are fixed in the tissues. Mast cells degranulate within seconds of binding an allergen, accounting for the rapid onset of allergic symptoms following exposure to, for example, pollen in hay fever (p. 426).

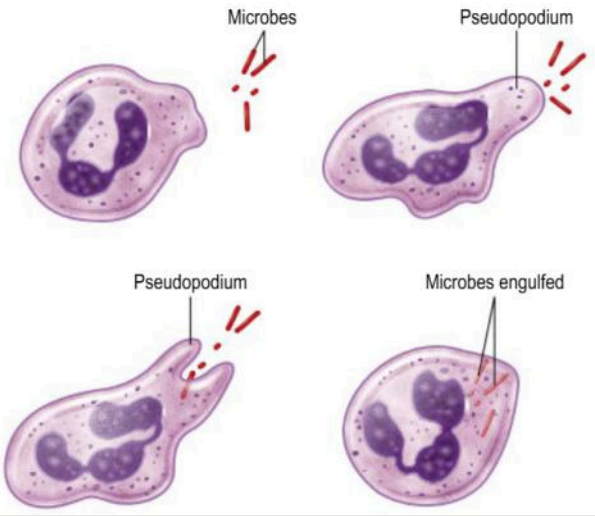

Figure 4.11 Phagocytic action of neutrophils.

Agranulocytes

Monocytes and lymphocytes together make up 25%–50% of the total leukocyte count (Fig. 4.12; see also Fig. 4.3). They have a large nucleus and no cytoplasmic granules.

Monocytes

These are the largest of the white blood cells (see Fig. 4.2). Shortly after release from the red bone marrow, they migrate into the tissues and develop into macrophages. Macrophages have important functions in inflammation (p. 417) and immunity (Ch. 15). Both monocytes and macrophages produce interleukin 1, which:

- acts on the hypothalamus, causing the fever (pyrexia) associated with microbial infections. Interleukin 1 is therefore called a pyrogen
- stimulates the production of some globulins by the liver, including fibrinogen, complement proteins and inflammatory markers
- enhances the production of activated T-cells, important in immunity (p. 421).

The mononuclear phagocyte system

This is sometimes called the reticuloendothelial system and it consists mainly of the body's population of monocytes and macrophages. Some macrophages are mobile, whereas others are fixed, e.g. in the liver and lung, providing effective defence at key body locations. The main collections of fixed macrophages are shown in Figure 4.13.

Macrophages have a diverse range of protective functions. They are actively phagocytic (their name means 'big eaters') and are much more powerful and longer-lived than the smaller neutrophils. They synthesise and release an array of biologically active chemicals, called cytokines, including interleukin 1 as mentioned above. They also have a central role linking the non-specific and specific (immune) systems of body defence (Ch. 15) and produce factors that are important in inflammation and tissue repair. They can 'wall off' indigestible pockets of material, called granulomas, isolating them from surrounding normal tissue. In the lungs, for example, resistant bacteria such as tuberculosis bacilli and inhaled inorganic dusts can be sealed off in granulomas.

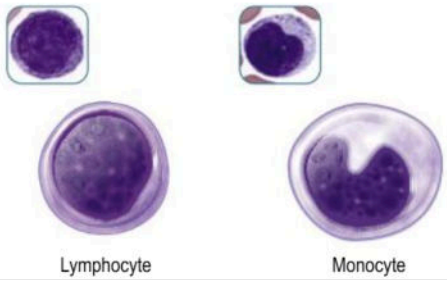

Figure 4.12 The agranulocytes.

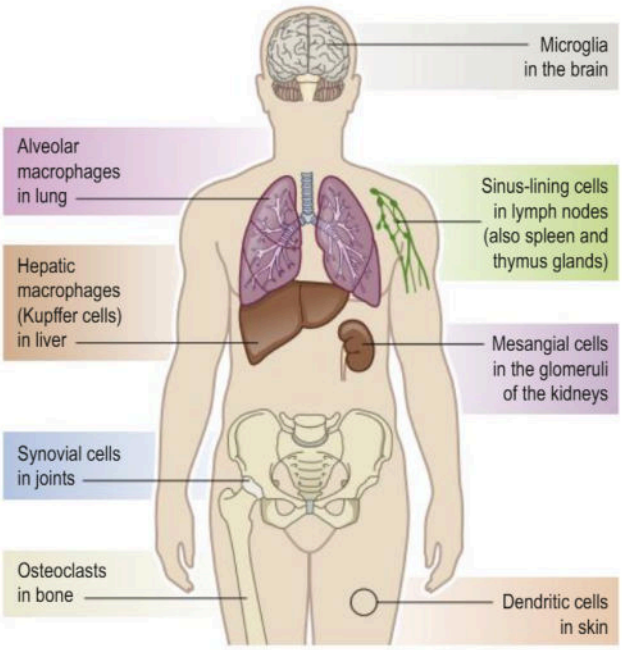

Figure 4.13 The body's main fixed macrophage collections.

Lymphocytes

Lymphocytes are smaller than monocytes and have large nuclei. Some circulate in the blood but most are found in tissues, including lymphatic tissue such as lymph nodes and the spleen. Lymphocytes develop from pluripotent stem cells in red bone marrow and from precursors in lymphatic tissue.

Although all lymphocytes originate from only one type of stem cell, the final steps in their development lead to the production of two distinct types of lymphocyte – T-lymphocytes and B-lymphocytes. The specific functions of these two cell types are discussed in Chapter 15.

Platelets (thrombocytes)

These are very small, disc-shaped cell fragments, 2–4μm in diameter, budded off from the cytoplasm of megakaryocytes in red bone marrow (Figs 4.2 and 4.3). Although they have no nucleus, their cytoplasm is packed with granules containing a variety of substances essential for blood clotting, which causes haemostasis (cessation of bleeding). They also contain contractile actin fibres, allowing the platelets within a developing clot to retract.

The normal blood platelet count is between 200 × 10^9/L and 350 × 10^9/L (200,000–350,000/mm^3). The mechanisms that regulate platelet numbers are not fully understood, but the hormone thrombopoietin from the liver stimulates platelet production.

The lifespan of platelets is between 8 and 11 days and those not used in haemostasis are destroyed by macrophages, mainly in the spleen. About a third of platelets are stored in the spleen rather than in the circulation; this is an emergency store, released when needed to control excessive bleeding.

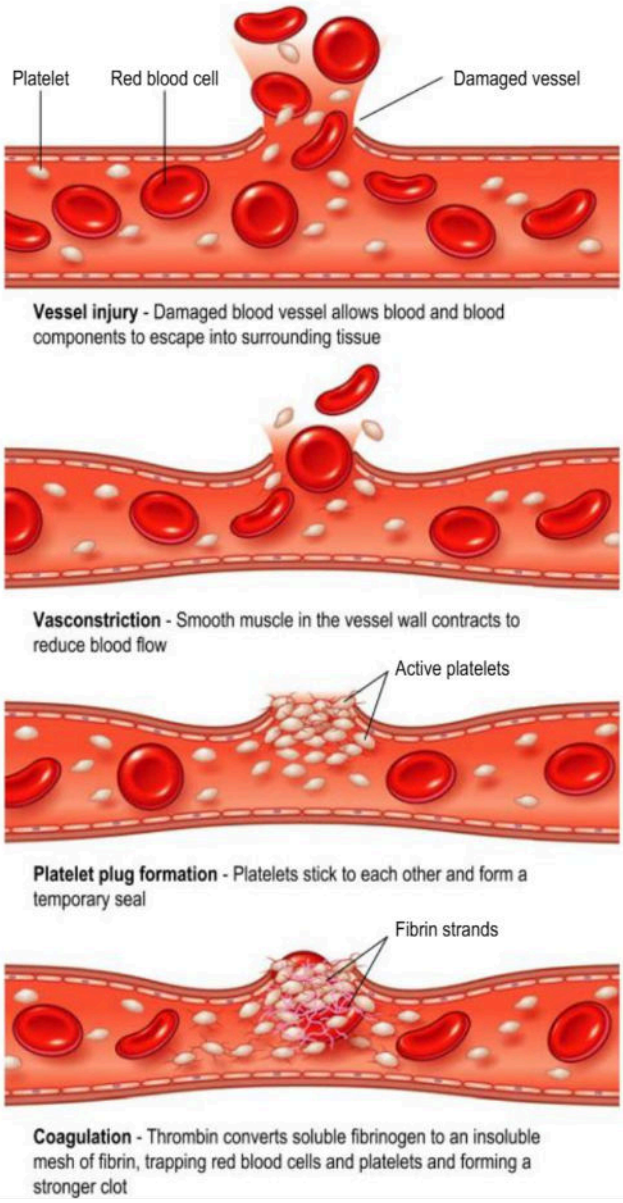

Figure 4.14 The stages of blood clotting.

Haemostasis

When a blood vessel is damaged, blood loss is stopped (haemostasis; Fig. 4.14) and healing occurs in a series of overlapping processes, in which platelets play a vital part. The more badly damaged the vessel wall is, the faster coagulation begins, sometimes as quickly as 15 seconds after injury.

1. Vasoconstriction

When platelets come into contact with a damaged blood vessel wall, their surface becomes sticky and they adhere to the site. They then release serotonin (5-hydroxytryptamine, 5-HT) and thromboxanes, which constrict the vessel, reducing

Box 4.1 Blood clotting factors

I Fibrinogen
II Prothrombin
III Tissue factor (thromboplastin)
IV Calcium (Ca^{2+})
V Labile factor, proaccelerin, Ac-globulin
(There is no factor VI)
VII Stable factor, proconvertin
VIII Antihaemophilic globulin (AHG), antihaemophilic factor A
IX Christmas factor, plasma thromboplastin component (PTC), antihaemophilic factor B
X Stuart–Prower factor
XI Plasma thromboplastin antecedent (PTA), antihaemophilic factor C
XII Hageman factor
XIII Fibrin stabilising factor
Vitamin K is essential for synthesis of factors II, VII, IX and X

or stopping blood flow through it. Other vasoconstrictors, e.g., endothelins, are released by the damaged vessel itself.

2. Platelet plug formation

The sticky platelets clump together and release other substances, including adenosine diphosphate (ADP), which attract more platelets to the site. Passing platelets stick to those already at the damaged vessel and they too release their chemicals. This is a positive feedback system accelerating platelet accumulation at the site of vascular damage and quickly forming a temporary seal – the platelet plug. Platelet plug formation is usually complete within 6 minutes of injury and acts as a temporary repair. The plug is, however, soft and easily disrupted, and is the precursor to the much more durable blood clot.

3. Coagulation (blood clotting)

This complex process also involves a positive feedback system, and only key stages are described here. The clotting factors involved are listed in Box 4.1. Their numbers represent the order in which they were discovered and not the order of participation in coagulation. These clotting factors are mainly enzymes, that are produced in the liver and circulate as inactive forms in the bloodstream. During the clotting cascade, they activate each other in a specific order, eventually resulting in the formation of prothrombin activator, which is the first step in the final common pathway. Prothrombin activates the enzyme thrombin, which converts inactive fibrinogen to insoluble threads of fibrin (Fig. 4.15). As clotting proceeds, the platelet plug is progressively stabilised by increasing amounts of fibrin laid down in a three-dimensional meshwork within it. The maturing blood clot traps blood cells and other plasma proteins, including plasminogen (which will eventually destroy the clot), and is much stronger than the rapidly formed platelet plug.

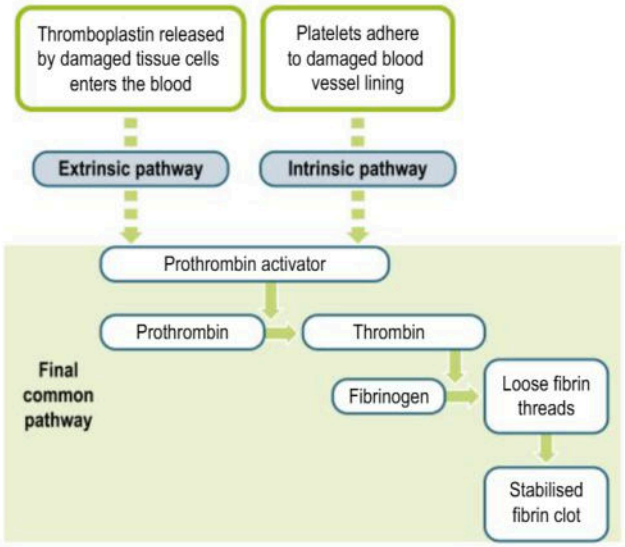

Figure 4.15 The final common pathway in blood clotting.

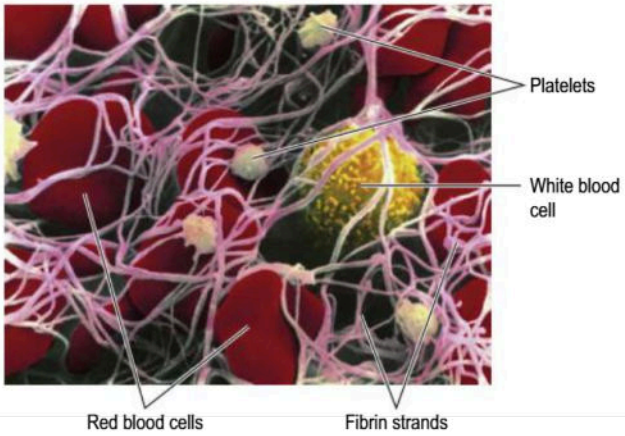

Figure 4.16 A blood clot. Scanning electron micrograph showing the fibrin meshwork *(pink strands)*, red blood cells, platelets and a white blood cell. (CNRI/Science Photo Library. Reproduced with permission.)

The final common pathway can be initiated by two processes, which often occur together: the extrinsic and intrinsic pathways (Fig. 4.15). The extrinsic pathway is activated rapidly (within seconds) following tissue damage and is probably the more important of the two. Damaged tissue releases a complex of chemicals called thromboplastin or tissue factor, which initiates coagulation. The intrinsic pathway is slower (3–6 minutes) and is triggered when blood comes into contact with damaged blood vessel lining (endothelium).

After a time the clot shrinks (retracts) because the actin fibres in the platelets contract, squeezing out serum. Clot retraction pulls the edges of the damaged vessel together, reducing blood loss and closing off the hole in the vessel wall.

Figure 4.16 shows a scanning electron micrograph of a blood clot. The fibrin strands (pink) have trapped red blood cells, platelets and a white blood cell.

4. Thrombolysis

After the clot has formed, the process of removing it and healing the damaged blood vessel begins. The breakdown of fibrin, or fibrinolysis, is the first stage. The plasma protein plasminogen, the inactive precursor of the active enzyme plasmin, is trapped within the clot as it forms. It is converted to plasmin by activators released from the damaged endothelial cells. Plasmin breaks down fibrin, progressively removing the clot to allow tissue repair to proceed.

Control of coagulation

The process of blood clotting relies heavily on several self-perpetuating processes – that is, once they have started, a positive feedback mechanism promotes their continuation. For example, thrombin is a powerful stimulator of its own production. Control and braking mechanisms are therefore essential to limit clotting to the affected area and terminate the process at the appropriate time. Factors that oppose and shut down the clotting process include:

- The endothelial lining in healthy, undamaged blood vessels is perfectly smooth, preventing platelet adhesion.
- Activated clotting factors are rapidly deactivated by anticoagulants, such as heparin and antithrombin III.
- Activated clotting factors are quickly cleared from the blood by the liver.

SPOT CHECK

3. Relate the main structural features of the red blood cell to its function.
4. Define diapedesis.
5. What is the difference between a platelet plug and a blood clot?

Erythrocyte disorders

Learning outcomes

After studying this section, you should be able to:

- define the term anaemia
- compare and contrast the causes and effects of iron deficiency, megaloblastic, aplastic, hypoplastic and haemolytic anaemias
- explain why polycythaemia occurs.

Anaemias

Anaemia is the inability of the blood to carry enough oxygen to meet body needs, and is a global issue, with prevalence estimated at between one quarter and one third of the world's population. It is usually due to low haemoglobin levels but is sometimes caused by production of faulty haemoglobin. Haemoglobin content in erythrocytes below 130 g/L in men and 115 g/L is the generally accepted indication of anaemia.

Anaemia is classified depending on the cause:

- Production of insufficient or defective erythrocytes – if the number of red blood cells being released is too low or the red blood cells are defective in some way, the haemoglobin content and oxygen-carrying capacity of the blood are reduced. Important causes include iron deficiency, vitamin B_{12}/folic acid deficiency and bone marrow failure.
- Blood loss or excessive erythrocyte breakdown (haemolysis) – anaemia can develop if erythrocytes are lost from the circulation, either through blood loss in haemorrhage or by accelerated haemolysis.

Anaemia can be associated with abnormal changes in red cell size or colour, detectable microscopically. Characteristic changes are listed in Table 4.3. However, sometimes anaemia may exist even with a normal red cell count and no abnormalities of erythrocyte structure (normochromic normocytic anaemia). For example, following sudden haemorrhage, the red cells in the bloodstream are normal in size, shape and colour, but their numbers are fewer.

Table 4.3 Terms used to describe red blood cell characteristics

Term	Definition
Normochromic	Cell colour normal
Normocytic	Cells normal-sized
Microcytic	Cells smaller than normal
Macrocytic	Cells bigger than normal
Hypochromic	Cells paler than normal
Haemolytic	Rate of cell destruction raised
Megaloblastic	Cells large and immature

Mild anaemia may be asymptomatic, or the symptoms so minor or generalised that they are ignored. Perceptible signs and symptoms relate to the inability of the blood to supply body cells with enough oxygen, and include pallor, fatigue and breathlessness on exertion. Additionally, when more severe, the body's attempt to compensate can lead to:

- tachycardia – the heart rate increases to improve blood supply and increase blood flow
- palpitations or angina pectoris (p. 138) – caused by the increased effort of the overworked heart muscle.

Iron deficiency anaemia

Globally, this is the most common form of anaemia. Dietary iron comes mainly from red meat, fortified cereals and highly coloured vegetables. Normally, only about 10% of dietary iron is absorbed, although this increases in iron deficiency, such as following haemorrhage or in pregnancy. Daily iron requirement in men is about 1–2 mg, and women need 3 mg daily to replace blood loss during menstruation and to meet the needs of the growing fetus during pregnancy. Children require more than adults to meet their growth requirements, and this is the population group most commonly affected by iron deficiency anaemia.

In iron deficiency anaemia, the red blood cell count is often normal, but the cells are small, pale and of variable size and they contain less haemoglobin than normal.

The amount of haemoglobin in each cell is considered below normal when the mean cell haemoglobin (MCH) is less than 27 pg/cell (see Table 4.1). Anaemia is considered severe when the haemoglobin level is below 9 g/100 mL blood.

Iron deficiency anaemia can result from deficient intake, unusually high iron requirements, or poor absorption from the alimentary tract.

Deficient intake

Because of the relative inefficiency of iron absorption, deficiency is common, even in individuals whose iron requirements are normal. It generally develops slowly over a prolonged period of time, and symptoms appear only once the anaemia is well established. The risk of deficiency increases if the daily diet is restricted in some way, as in poorly planned vegetarian or vegan diets, or in weight-reducing diets where the range of foods eaten is small. Babies dependent on milk may also suffer mild iron deficiency anaemia if weaning on to a mixed diet is delayed much past the first year, because the child's liver carries only a few months' store and milk is a poor source of iron. Other at-risk groups include older adults and the alcohol-dependent, whose diet can be poor.

High requirements

In pregnancy, iron requirements are increased to support both fetal growth and the additional load on the mother's cardiovascular system. Iron requirements also rise when there is chronic blood loss, the causes of which include peptic ulcers (p. 359), heavy menstrual bleeding (menorrhagia),

haemorrhoids, regular aspirin intake or gastrointestinal cancer. Children have higher requirements than adults, and their iron intake may be restricted if they are fussy eaters or raised on a poor quality diet.

Malabsorption

Because iron absorption is dependent on an acid environment in the stomach, an increase in gastric pH may reduce it; this may follow excessive use of antacids or removal of part of the stomach, or may occur in pernicious anaemia (see later), when the parietal (acid-releasing) cells of the stomach lining are destroyed. Loss of surface area for absorption in the intestine, e.g., after surgical removal, can also cause deficiency.

Vitamin B_{12}/folic acid deficiency anaemias

Deficiency of vitamin B_{12} and/or folic acid impairs erythrocyte maturation (see Fig. 4.5) and abnormally large erythrocytes (megaloblasts) appear in the blood. During normal erythropoiesis (see Fig. 4.3), several cell divisions occur and the daughter cells at each stage are smaller than the parent cell because there is not much time for cell enlargement between divisions. In vitamin B_{12} and/or folic acid deficiency, the rate of DNA and RNA synthesis is reduced, delaying cell division. The cells therefore grow larger than normal between divisions. Circulating cells are immature and larger than normal, and some are nucleated (mean cell volume (MCV) >94 fL). The haemoglobin content of each cell is normal or raised. The cells are fragile and their lifespan is reduced to between 40 and 50 days. Reduced production and early lysis cause anaemia.

Vitamin B_{12} deficiency anaemia

Pernicious anaemia

This is the most common form of vitamin B_{12} deficiency anaemia. It is an autoimmune disease in which autoantibodies destroy intrinsic factor (IF) and gastric parietal cells (p. 333). Females are affected more often than males, and there is frequently an association with other autoimmune disorders, particularly thyroid disease. It is common in the elderly.

Dietary deficiency of vitamin B_{12}

Vitamin B_{12} is widely available in animal-derived foods, including dairy products, meat and eggs, so deficiency is rare except in strict vegans, who never eat animal products. The liver has extensive stores of the vitamin, so deficiency can take several years to appear.

Other causes of vitamin B_{12} deficiency

These include:

- *Gastrectomy* (removal of all or part or the stomach) – this leaves fewer cells available to produce IF.
- *Chronic gastritis, malignant disease and ionising radiation* – these damage the gastric mucosa, including the parietal cells that produce IF.
- *Malabsorption* – if the terminal ileum is removed or inflamed, e.g. in Crohn's disease, the vitamin cannot be absorbed despite normal IF levels.

Consequences of vitamin B_{12} deficiency anaemia

These may appear before the signs of anaemia. Because vitamin B_{12} is also used in myelin production, deficiency leads to irreversible neurological damage, commonly in the spinal cord. Mucosal abnormalities, such as glossitis (inflammation of the tongue), are also common, although they are reversible.

Folic acid deficiency anaemia

Folic acid deficiency causes a form of megaloblastic anaemia identical to that seen in vitamin B_{12} deficiency, but not associated with neurological damage. It may be due to:

- dietary deficiency, e.g., in infants if there is a delay in establishing a mixed diet, in alcoholism, in anorexia, in diets poor in fresh food and in pregnancy
- malabsorption from the jejunum caused by coeliac disease, tropical sprue or some anticonvulsant drugs
- interference with folate metabolism by cytotoxic and some anticonvulsant drugs.

Aplastic anaemia

Aplastic (hypoplastic) anaemia results from bone marrow failure. Because the bone marrow produces erythrocytes, leukocytes and platelets, reduced erythrocyte count, leukopenia (low white cell count) and thrombocytopenia (low platelet count) are present. When all three cell types are low, the condition is called pancytopenia, and is accompanied by anaemia, diminished immunity and a tendency to bleed. The condition is occasionally inherited. Usually no cause is identified (idiopathic disease) but in these cases there is usually evidence of abnormal immune function and the disorder is considered to be autoimmune in origin. Known causes include:

- some drugs, e.g. cytotoxic therapy; rarely, aplastic anaemia may occur as an adverse reaction to anti-inflammatory and anticonvulsant drugs and some antibiotics.
- ionising radiation.
- some chemicals, e.g. benzene and its derivatives.
- viral disease, including hepatitis.

The presenting symptoms are usually infection, anaemia, bleeding and bruising.

Haemolytic anaemias

These occur when erythrocyte breakdown is increased beyond normal. Most haemolysis takes place in the liver or spleen and the normal erythrocyte lifespan of about 120 days can be as little as 24 hours. If the condition is relatively mild, red cell numbers may remain stable because the red bone marrow production of erythrocytes increases to compensate, so there may be ongoing haemolysis without anaemia.

However, if the bone marrow cannot compensate, red blood cell numbers will fall and anaemia results.

Even in the absence of symptoms of anaemia (pallor, tiredness, dyspnoea, etc.), haemolytic anaemias can cause additional symptoms such as jaundice or splenomegaly (enlargement of the spleen).

Congenital haemolytic anaemias

In these diseases, genetic abnormality leads to the synthesis of abnormal haemoglobin and increased red cell membrane fragility, reducing their oxygen-carrying capacity and lifespan. The most common forms are sickle cell anaemia and thalassaemia.

Sickle cell anaemia

The abnormal haemoglobin molecules become misshapen when deoxygenated, making the erythrocytes sickle-shaped (Fig. 4.17). If the cells contain a high proportion of abnormal haemoglobin, sickling is permanent. Sickled cells are rapidly removed from the bloodstream and haemolysed, leading to anaemia. Because of their distorted shape, sickle cells do not move smoothly through the circulation. They obstruct blood flow, leading to intravascular clotting, tissue ischaemia and infarction. Acute episodes (sickle crises), caused by blockage of small vessels, cause acute pain in the affected area, often the hands and feet. Longer-term problems arising from poor perfusion and anaemia include cardiac disease, kidney failure, retinopathy, poor tissue healing and slow growth in children. Obstruction of blood flow to the brain greatly increases the risk of stroke and seizures, and both mother and child are at significant risk of complications in pregnancy. Respiratory complications, including pulmonary hypertension, are common and can be fatal. Children's growth and development can be impaired, and there may be a delay in sexual maturity.

The disease is more prevalent in people of African origin, as well as those of middle Eastern, Asian, Indian and Mediterranean descent. It is caused by a fault in one of the genes responsible for synthesis of one of the globin chains in haemoglobin, and an individual must have two copies of the faulty gene (i.e. one inherited from each parent) for the disease to be present. If an individual inherits only one copy of the faulty gene they are a carrier, or are said to have sickle cell trait, and are generally clinically well or only mildly symptomatic. Up to 40% of individuals in equatorial Africa are sickle cell carriers, which gives them a degree of immunity to malaria because the lifespan of the sickled cells is shorter than the time needed for the malaria parasite to mature inside the erythrocytes. This explains why the sickle cell gene has become so common in populations where malaria is endemic.

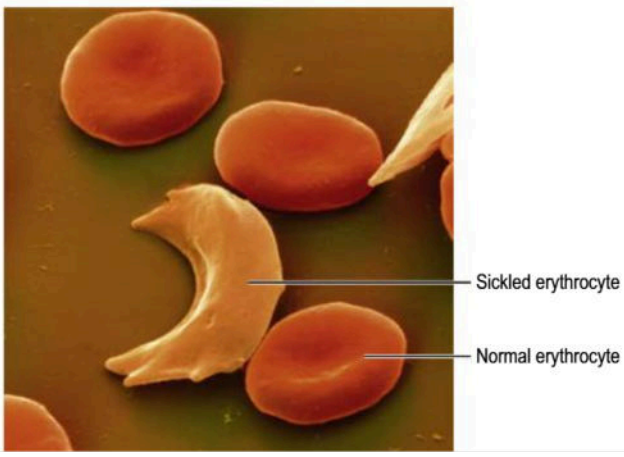

Figure 4.17 Scanning electron micrograph showing three normal erythrocytes and one sickled erythrocyte. (Eye of Science/Science Photo Library. Reproduced with permission.)

Thalassaemias

These inherited conditions are caused by excessive synthesis and accumulation of one of the globin chains used in haemoglobin production, which damages developing erythrocytes and stimulates haemolysis. The resultant anaemia may present in a range of forms, from mild and asymptomatic to profound and life-threatening. Symptoms in moderate to severe thalassaemia include bone marrow expansion and splenomegaly, as production of red blood cells increases in an attempt to correct the anaemia. In the most severe form of the disease, regular blood transfusions are required, which can lead to iron overload.

Haemolytic disease of the newborn

In this disorder, the mother's immune system makes antibodies to the baby's red blood cells and destroys them. The antigen system involved is usually (but not always) the Rhesus (Rh) antigen.

An Rh^- mother carries no Rh antigen on her red blood cells, but she can produce anti-Rh antibodies. If she conceives a child fathered by an Rh^+ man, and the baby inherits the Rh antigen from him, the baby may also be Rh^+, i.e., different from the mother. During pregnancy, the placenta protects the baby from the mother's immune system, but at delivery a few fetal red blood cells may enter the maternal circulation as the placenta separates from the uterus. Because they carry the Rh antigen, foreign to the mother, her immune system reacts and produces neutralising antibodies to her baby's erythrocytes. These antibodies cross the placenta, enter the child and destroy its red cells. The first pregnancy involving a Rh^+ baby is usually not affected, because escape of the baby's erythrocytes into the mother's circulation does not usually happen until delivery, and by the time the mother has produced significant antibody levels, the baby has been delivered. However, the red cells of second and subsequent Rh^+ babies are attacked by these maternal antibodies (Fig. 4.18). In the most severe cases the baby dies in the womb from profound anaemia. In less serious circumstances the baby suffers some degree of anaemia, which is corrected with blood transfusions.

The disease is much less common than it used to be following the discovery that if an Rh^- mother is given an injection of anti-Rh (anti-D) antibodies within 72 hours of the delivery of a Rh^+ baby, the anti-D binds to and destroys any fetal blood cells in the mother's bloodstream before her own immune system detects and responds to them. She therefore

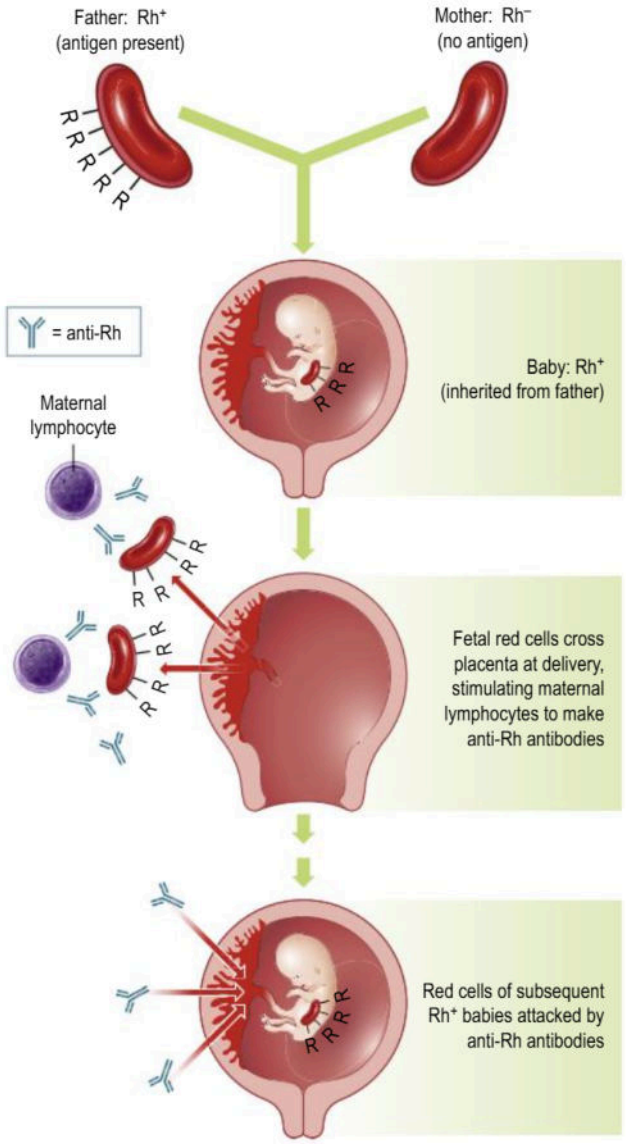

Figure 4.18 The immunity of haemolytic disease of the newborn.

does not produce anti-Rh antibodies and subsequent Rh+ pregnancies are therefore not affected.

Acquired haemolytic anaemias

In this context, 'acquired' means haemolytic anaemia in which no familial or racial factors have been identified and the haemolysis is caused by exposing the red cells to one or more predisposing factors.

Chemical agents

These substances cause early or excessive haemolysis, for example:

- some drugs, especially when taken long term in large doses, e.g. sulphonamides
- chemicals encountered in the general or work environment, e.g. lead, arsenic compounds
- microbial toxins, e.g. *Streptococcus pyogenes*, *Clostridium perfringens*.

Autoimmunity

In autoimmunity, individuals make antibodies to their own red cell antigens, causing haemolysis. It may be acute or chronic, and primary or secondary to other diseases, e.g. cancer, viral infection or other autoimmune diseases.

Blood transfusion reactions

Individuals do not normally produce antibodies to their own red blood cell antigens; if they did, the antigens and antibodies would react, causing clumping and lysis of the erythrocytes (see Fig. 4.8). However, if individuals receive a transfusion of incompatible blood carrying antigens different from their own, their immune system will recognise them as foreign, make antibodies to them and destroy them in the circulation (transfusion reaction). The breakdown products of haemolysis lodge in and block the filtering mechanism of the nephron, causing kidney failure, and triggering formation of multiple clots throughout the circulatory system (disseminated intravascular coagulation, DIC, p. 83). Other important signs of a transfusion reaction include fever, chills, tachycardia, respiratory distress and shock.

Polycythaemia

This is an abnormally high red blood cell count, which increases blood viscosity, slows blood flow and raises the risk of intravascular clotting, ischaemia and infarction. Cardiac workload is increased because the blood is thicker than usual and heart failure may ensue. Erythrocyte count may be abnormally high simply because the plasma volume is reduced, as in burns, and this is called relative polycythaemia. True polycythaemia occurs when plasma volume is normal, but erythrocyte numbers are genuinely high.

Primary polycythaemia

Most cases of primary polycythaemia are associated with a specific genetic mutation that interferes with erythropoietin control of erythrocyte numbers, leading to a condition called polycythaemia vera. Patients present with itching, tiredness, headache, and sometimes complications from thrombosis. There is often liver and splenic enlargement. It is most common in the over-60s.

Secondary polycythaemia

This is polycythaemia due to an identified cause and may be an expected compensatory response in hypoxic situations, such as living at altitude, heart failure or heavy smoking. It may also result from abnormally high erythropoietin levels, seen in some kidney tumours, for example.

SPOT CHECK

6. What is pernicious anaemia?
7. Describe the pathology of sickle cell anaemia.

Leukocyte disorders

Learning outcomes

After studying this section, you should be able to:

- define the terms leukopenia and leukocytosis
- review the physiological importance of abnormally increased and decreased leukocyte numbers in the blood
- discuss the main forms of leukaemia, including the causes, signs and symptoms of the disease.

Leukopenia

In this condition, the total blood leukocyte count is less than 4×10^9/L (4000/mm^3).

Granulocytopenia (neutropenia)

This general term means abnormally low numbers of circulating granulocytes (polymorphonuclear leukocytes), commonly called neutropenia because 40%–75% of granulocytes are neutrophils. Neutropenia predisposes to severe infections that can lead to sepsis and death. Sepsis (sometimes called septicaemia, although this is an older term) is the presence of significant numbers of active pathogens in the blood (see also septic shock, p. 127).

Reduced numbers of circulating granulocytes occur when production rates fall below normal, e.g. in bone marrow failure, or when the lifespan of the cells is shortened. Extreme shortage or the absence of granulocytes is called agranulocytosis. A temporary reduction occurs in response to inflammation because activated granulocytes engaged in phagocytosis have a significantly shortened lifespan but the numbers are usually quickly restored by an increased production. Inadequate granulopoiesis may be caused by:

- some drugs, e.g. cytotoxic agents, phenothiazines, and some antibiotics including sulphonamides
- irradiation of the bone marrow, e.g. radiotherapy, which reduces cell proliferation
- red bone marrow disorders, e.g. leukaemias and some anaemias
- severe infections.

Leukocytosis

An increase in the number of circulating leukocytes occurs as a normal protective reaction in a variety of pathological conditions, especially infections. When the infection subsides, the leukocyte count returns to normal.

Pathological leukocytosis exists when a blood leukocyte count of more than 11×10^9/L (11,000/mm^3) is unnecessarily sustained and can involve more than one type of leukocyte.

Leukaemia

Leukaemia is a malignant proliferation of white blood cell precursors in the bone marrow. It results in the uncontrolled increase in the production of leukocytes and/or their precursors. As the tumour cells enter the blood the total leukocyte count is usually raised, although in some cases it may be normal or even low. The proliferating immature leukaemic blast cells crowd out other blood cells formed in bone marrow, causing anaemia, thrombocytopenia and leukopenia (pancytopenia). Because the leukocytes are immature when released, immunity is reduced and the risk of infection increased.

Causes of leukaemia

Some causes of leukaemia are well understood but many cases cannot be accounted for. Some people may have a genetic predisposition triggered by environmental factors, including viral infection. Other known causes include ionising radiation and some chemicals.

Ionising radiation

Radiation from, for example, X-rays and radioactive isotopes causes malignant changes in the leukocyte precursors. The DNA of the cells may be damaged and some may die while others reproduce at an abnormally rapid rate. Leukaemia may develop at any time after irradiation, even 20 or more years later.

Chemicals

Some chemicals, e.g. benzene, cytotoxic drugs and asbestos, generate mutations in the DNA of the white blood cell precursors in the bone marrow.

Genetic factors

Identical twins of leukaemia sufferers have a much higher risk than normal of developing the disease, suggesting involvement of genetic factors.

Types of leukaemia

Leukaemias are usually classified according to the type of cell involved, the maturity of the cells and the rate at which the disease develops.

Acute leukaemias

These types usually have a sudden onset and affect the poorly differentiated and immature 'blast' cells (see Fig. 4.3). They can be aggressive diseases, especially in older people, and without treatment cause death in a very short time.

Acute leukaemia is usually characterised by leukocytosis, and most of the white cells are immature and abnormal blasts. The bone marrow becomes packed with large numbers of blasts, and the rapid progress of bone marrow invasion quickly causes bone marrow failure, with anaemia, haemorrhage and susceptibility to infection. There are two main types: acute myeloblastic leukaemia (AML), of which the incidence increases with age, and acute lymphoblastic leukaemia (ALL), seen mainly in people under 20 years of age.

Acute myeloblastic leukaemia

AML involves proliferation of myeloblasts (see Fig. 4.3), and is classified into a number of different types, depending on the genetic abnormalities found and the clinical presentation. Depending on the subtype present, the disease can often be cured or long-term remission achieved.

Acute lymphoblastic leukaemia

ALL is most common in children between the ages of 2 and 4 years. In general, this disorder carries a better prognosis in children than adults, with up to 70% achieving cure. The cell responsible is a primitive B-lymphocyte.

Chronic leukaemias

These conditions are less aggressive than the acute forms and the leukocytes are more differentiated, i.e., at the '-cyte' stage (see Fig. 4.3).

Leukocytosis (raised leukocyte count) is a feature of chronic leukaemia; there is crowding of the bone marrow with immature and abnormal leukocytes, although this varies depending on the form of the disease.

Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) occurs at all ages. Although its onset is gradual, in most patients it eventually reaches a rapidly progressive stage similar to AML and proves fatal; sometimes it progresses to ALL, which has a better prognosis. It is caused by an abnormality of chromosomes 22 and 9 (Philadelphia chromosome). Death usually occurs within 5 years.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) involves proliferation of B-lymphocytes; it is usually less aggressive than CML. It is most often seen in the elderly; disease progression is usually slow, and survival times can be as long as 25 years.

SPOT CHECK

8. Why is leukaemia often associated with anaemia?
9. Which disorder is associated with the Philadelphia chromosome?

Haemorrhagic diseases

Learning outcomes

After studying this section, you should be able to:

- indicate the main causes and effects of thrombocytopenia
- outline how vitamin K deficiency relates to clotting disorders
- explain the term 'disseminated intravascular coagulation', including its principal causes
- describe the physiological deficiencies present in the haemophilias.

Thrombocytopenia

This is defined as a blood platelet count below 150×10^9/L (150,000/mm^3) but spontaneous bleeding does not usually occur unless the count falls below 30×10^9/L (30,000/mm^3). It may be due either to a reduced rate of platelet production or increased rate of destruction.

Reduced platelet production

This is usually secondary to bone marrow deficiencies, and therefore production of erythrocytes and leukocytes is also reduced, giving rise to pancytopenia. It is often caused by:

- crowding out of platelets from the bone marrow in bone marrow diseases, e.g. leukaemias, pernicious anaemia, malignant tumours
- ionising radiation, e.g. X-rays or radioactive isotopes, which damages the rapidly dividing precursor cells in the bone marrow
- drugs that damage bone marrow, e.g. cytotoxic drugs, chloramphenicol, chlorpromazine, sulphonamides.

Increased platelet destruction

A reduced platelet count occurs if production does not keep pace with destruction of damaged and worn-out platelets. This occurs in disseminated intravascular coagulation (see later) and autoimmune thrombocytopenic purpura.

Autoimmune thrombocytopenic purpura

This condition, which usually affects children and young adults, may be triggered by a viral infection such as measles. A significant feature of this disease is the presence of purpura, which are haemorrhages into the skin ranging in size from pinpoints to large blotches. Bleeding may be mild or severe. When the platelet count is very low there may be severe bruising, haematuria and gastrointestinal or intracranial haemorrhages. Antiplatelet antibodies are formed that coat platelets, leading to platelet destruction and their removal from the circulation.

Vitamin K deficiency

Vitamin K is needed by the liver for the synthesis of many clotting factors and deficiency predisposes to prolonged clotting times.

Haemorrhagic disease of the newborn

Newborn babies, especially if premature, have limited stores of vitamin K and this can cause bleeding in the first few months of life. Bleeding may be minor, but significant prolonged bleeding, e.g. into the brain, can occur.

Deficiency in adults

Vitamin K is fat soluble and bile salts are required in the colon for its absorption. Deficiency may occur in liver disease, prolonged obstruction of the biliary tract or any other disease where fat absorption is impaired, e.g. coeliac disease (p. 367). Dietary deficiency is rare because a sufficient supply of vitamin K is usually synthesised by bacteria in the colon. However, it may occur during treatment with drugs, e.g. antibiotics, that kill these bacteria.

Disseminated intravascular coagulation

In disseminated intravascular coagulation (DIC), the coagulation system is inappropriately activated within blood vessels, leading to formation of intravascular clots and fibrin deposition in the tissues. Because this depletes clotting factors and platelets in the bloodstream, there is a tendency to serious haemorrhage. DIC is a common complication of a number of other disorders, including:

- severe infection, such as septicaemia, when endotoxins are released by Gram-negative bacteria
- severe trauma
- premature separation of the placenta, when amniotic fluid enters the maternal blood
- acute pancreatitis, when digestive enzymes are released into the blood
- advanced cancer
- transfusion of very large volumes of blood.

Congenital disorders

The haemophilias

Haemophilia A and haemophilia B are inherited clotting disorders, clinically identical but caused by deficiencies in two different clotting factors. Haemophilia A is due to deficient factor VIII and Christmas disease (haemophilia B) is due to deficient clotting factor IX (Christmas factor). The genes for both are present on the X chromosome (i.e., inheritance is sex-linked, p. 495), and faults in the genes reduce clotting factor production. Because the disorder is sex-linked, almost all cases arise in males.

Haemophiliacs experience repeated episodes of severe and prolonged bleeding at any site, even in the absence of trauma. Recurrent bleeding into joints is common, causing severe pain and, in the long term, permanent joint damage. The disease ranges in severity from mild forms, where there is enough of the deficient factor to control bleeding in most situations, to extreme forms, where bleeding is spontaneous and can take days or weeks to control.

von Willebrand disease

This is the commonest inherited bleeding disorder. von Willebrand factor (vWF) is needed for clotting because although it is not itself a clotting factor, it transports factor VIII in the plasma. When it is deficient, factor VIII levels are also reduced and clotting is impaired. As its inheritance is not sex-linked, haemorrhages due to reduced clotting occur equally in males and females.

SPOT CHECK

10. Why does coeliac disease sometimes lead to prolonged clotting times?

Case study

Harold has had surgery for a bleeding ulcer. During surgery and in the post-operative period, he is transfused with several units of whole blood. The day after surgery, his surgeon reviews his blood results, given below.

1. Which of the results is not within the normal range?

   a. Erythrocyte count 4.6×10^{12}/L
   b. Leukocyte count 12×10^{9}/L
   c. Platelet count 300×10^{9}/L
   d. Haematocrit 0.5 L/L

2. The results above suggest that Harold:

   a. is anaemic
   b. is haemorrhaging
   c. is at increased risk of a blood clot
   d. has an infection

3. Harold is blood group A and needed six units of blood during and after surgery. The blood bank only had five units of group A blood and suggested blood group O for the sixth unit. Why is this likely to be safe?

   a. The erythrocytes in blood group O do not possess A or B antigens.
   b. Harold does not produce anti-O antibodies.
   c. Group O blood does not contain anti-A or anti-B antibodies.
   d. Harold produces anti-A antibodies.

4. As Harold recovers from surgery and the ulcer site begins to heal, which enzyme breaks down clotted blood at the site to allow tissue repair to progress?

   a. Thrombin
   b. Thromboplastin
   c. Prothrombin activator
   d. Plasmin

References and further reading

Keohane EM, Otto CN, Walenga JM, 2019. Rodak's Hematology: Clinical principles and applications, 6th ed Elsevier.

Review and revise

Complete each of the following statements:

1. Haemoglobin (Hb) is a complex molecule containing a pigment group, the _____ portion, which gives the blood its red colour. Each Hb molecule contains _____ atoms of the metal _____, which is responsible for transporting molecular _____ to supply body cells. An average red blood cell contains _____ million molecules of Hb. When Hb is broken down, the pigment group is degraded in the _____ to produce the coloured waste product _____.

Choose one answer to complete each of the following statements:

2. Erythrocytes survive in the bloodstream for an average of: _____
   a. 6 days
   b. 6 months
   c. 3 weeks
   d. 3 months.

3. Mast cells are structurally and functionally similar to: _____
   a. Eosinophils
   b. Basophils
   c. Macrophages
   d. Platelets.

4. Thalassaemia is associated with abnormal: _____
   a. Fibrinogen
   b. Plasmin
   c. Haemoglobin
   d. Lysosomal enzymes.

5. The following terms are used to describe red blood cells. Match each letter in List A to the appropriate number in List B:

List A
- ____ (a) Normochromic
- ____ (b) Normocytic
- ____ (c) Macrocytic
- ____ (d) Microcytic
- ____ (e) Hypochromic
- ____ (f) Megaloblastic

List B
1. Cell is large and immature
2. Cell is smaller than normal
3. Cell colour is as expected
4. Cell is larger than normal
5. Cell size is as expected
6. Cell is paler than normal

6. The following substances are associated with blood physiology. Match each letter in List A to the appropriate number in List B:

List A
- ____ (a) Fibrinogen
- ____ (b) Creatinine
- ____ (c) Plasmin
- ____ (d) Serotonin
- ____ (e) Erythropoietin
- ____ (f) Thrombin
- ____ (g) Heparin
- ____ (h) Vitamin K
- ____ (i) Folic acid

List B
1. Released by platelets during clotting
2. Anticoagulant released from mast cells
3. The most abundant plasma protein
4. Required for blood cell synthesis
5. Stimulates red cell production
6. Breaks down blood clots
7. Required for clotting factor production
8. Waste product of protein breakdown
9. Enzyme that releases fibrin

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 5

The cardiovascular system

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The first part of this chapter describes the structure and function of the cardiovascular system, which comprises the heart, a fist-sized muscular organ lying between the lungs, and an extensive system of blood vessels, carrying blood pumped by the heart to all body tissues. Impressively, the average adult contains nearly 100,000 km of blood vessels, more than enough to stretch around the equator twice, and the heart beats over two and a half billion times in an average 70-year lifespan. Cardiovascular function normally declines with age, as discussed on page 126. Nearly one-third of deaths globally are due to cardiovascular disease, and some common cardiovascular conditions are discussed in the illnesses section.

The lymphatic system is closely connected, both structurally and functionally, with the cardiovascular system and is discussed in Chapter 6.

The heart pumps blood into two anatomically separate systems of blood vessels (Fig. 5.1):

- the pulmonary circulation
- the systemic circulation.

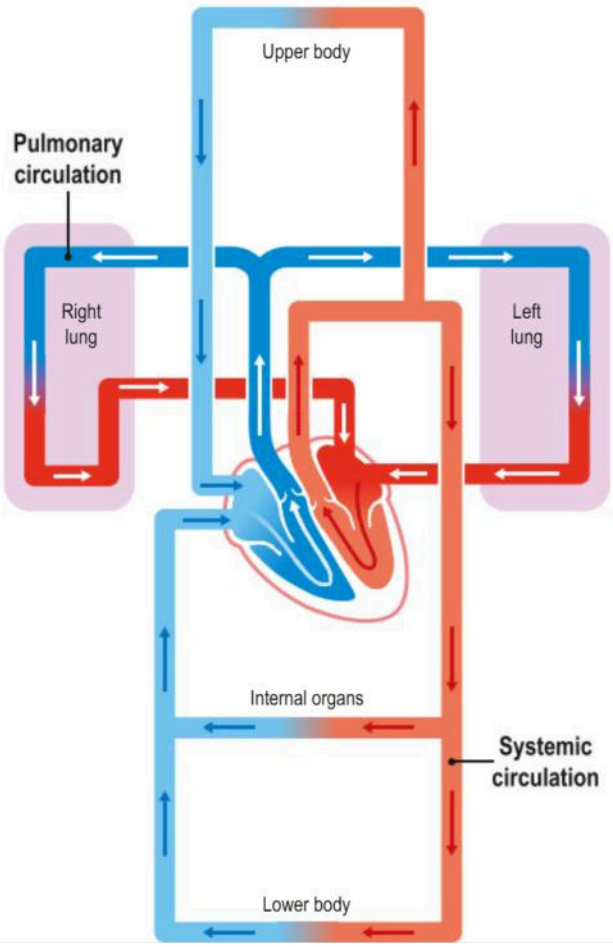

Figure 5.1 The relationship between the pulmonary and the systemic circulations.

The right side of the heart pumps blood into the pulmonary circulation to the lungs, where gas exchange occurs: here, the blood collects oxygen from the air sacs and excess carbon dioxide diffuses into the air sacs for exhalation. The left side of the heart pumps blood into the systemic circulation, which supplies the rest of the body. Here, tissue wastes diffuse into the blood for excretion, and body cells absorb nutrients and oxygen.

The cardiovascular system ensures a continuous flow of blood to all cells and is subject to continual physiological adjustments to meet tissue needs. If the supply of oxygen and nutrients to body cells become inadequate, tissue damage occurs and cell death may follow.

Blood vessels

Learning outcomes

After studying this section, you should be able to:

- describe the structures and functions of arteries, veins and capillaries
- explain the relationship between the different types of blood vessel
- explain the mechanisms by which exchange of nutrients, gases and wastes occurs between the blood and the tissues.

Blood vessels vary in structure, size and function. Arteries and their smaller branches, arterioles, carry blood away from the heart. Arterioles branch into enormous networks of thin-walled capillaries, tiny exchange vessels which allow nutrients, water and oxygen to diffuse into the tissues, and cellular wastes such as carbon dioxide to diffuse into the bloodstream and be transported away. Capillaries merge to form small venules, which in turn merge to form large veins, carrying blood back to the heart (Fig. 5.2).

Although the structure of the walls of arteries and veins displays important differences which reflect their different functions, both contain three layers of tissue:

- Tunica adventitia, an outer layer of fibrous tissue containing large quantities of collagen and other connective tissue components. It protects and supports the vessel.
- Tunica media, a middle layer containing variable amounts of smooth muscle and elastic tissue.
- Tunica intima, or endothelium, a smooth lining only one cell thick.

Blood supply

The outer layers of tissue of thick-walled blood vessels receive their blood supply via a network of blood vessels called the vasa vasorum. Thin-walled vessels and the endothelium of the others receive oxygen and nutrients by diffusion from the blood passing through them.

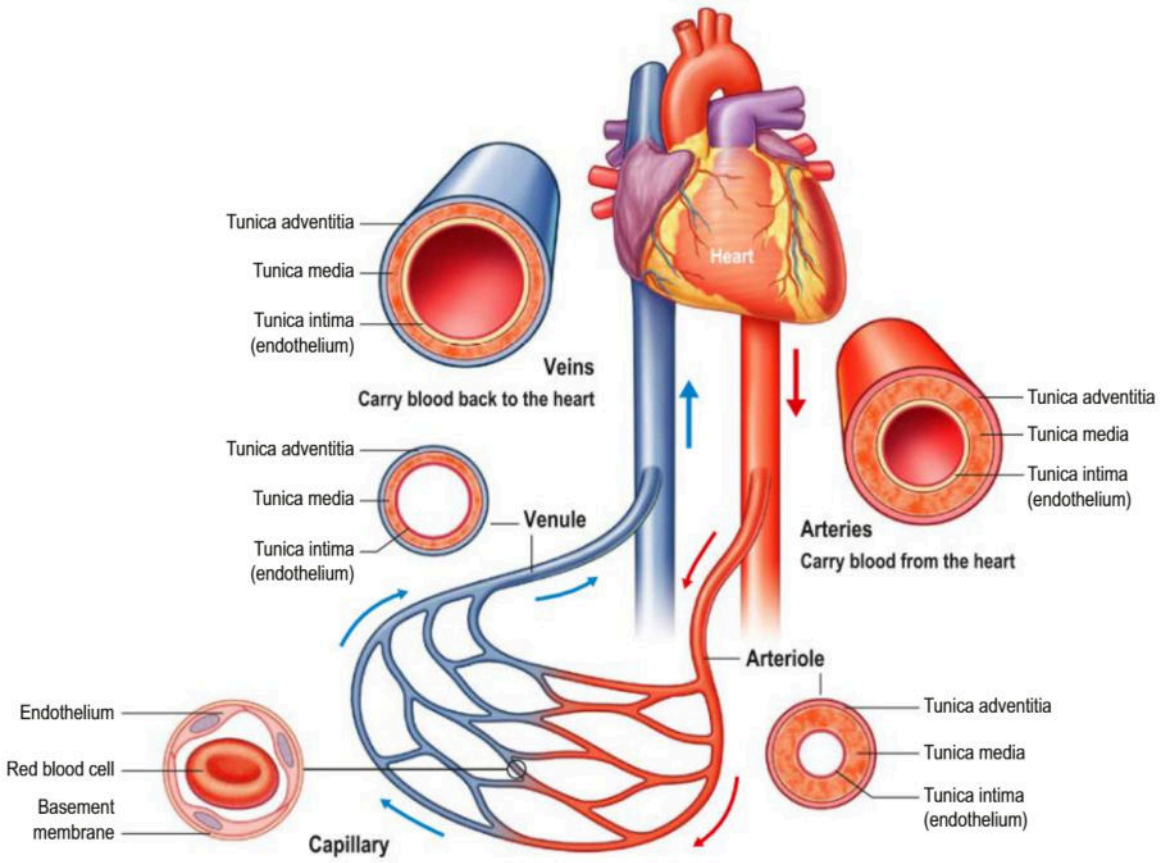

Figure 5.2 The relationship between the heart and the different types of blood vessel.

Arteries and arterioles

Arterial walls are thicker than venous walls to withstand the higher pressure of blood in the arterial system, and bleeding from a cut artery is often pulsatile (matching the heartbeat) and hard to staunch because the blood is flowing quickly under pressure. The structure of arterial walls varies, depending on how close the artery lies to the heart. In the largest arteries, which range in diameter from 1 cm to 2.5 cm, the tunica media contains considerable quantities of elastic tissue and little smooth muscle. This allows the artery wall to stretch, absorbing the pressure wave generated by the heart as it beats, and as it recoils, it squeezes the blood and pushes it forward through the arterial system. Arteries near the heart have a large amount of elastic tissue in their walls and are sometimes called elastic arteries. The elastic tissue content decreases and smooth muscle increases as the arteries branch many times and become smaller, until in the arterioles (the smallest arteries) the tunica media consists almost entirely of smooth muscle. These vessels are called muscular arterioles. Contraction and relaxation of the smooth muscle allows precise control of their diameter, regulating blood pressure and flow within them. Systemic blood pressure is mainly determined by the resistance these tiny muscular arteries offer to blood flow, and for this reason they are sometimes called resistance vessels.

Anastomoses and end-arteries

Anastomotic arteries are connecting arteries forming direct links between arteries supplying an area, e.g. the arterial supply to the palms of the hand and soles of the feet, the circle of Willis supplying the brain, and to a limited extent, the heart muscle. They provide a backup route for blood flow, should one artery supplying the area become blocked. This is called a collateral circulation and is most likely to maintain an adequate blood supply if the blockage occurs gradually, giving the anastomotic arteries time to dilate.

An end-artery is one that is the sole source of blood to a tissue, e.g. the branches that radiate from the circle of Willis in the brain, or the central artery to the retina of the eye. When an end-artery is blocked, the tissues it supplies die because there is no alternative blood supply; this is called infarction (p. 130).

Capillaries and sinusoids

The smallest arterioles branch into extensive networks (beds) of microscopic capillaries, whose walls consist of a single layer of endothelial cells sitting on a very thin basement membrane. Capillary walls are permeable to water and other small molecules but blood cells and large molecules such as plasma proteins are normally too large to pass through. The capillary bed is the site of exchange of substances between the blood and the tissue fluid, which bathes and nourishes body cells. Nutrients and oxygen transfer across the capillary wall into the interstitial (tissue) fluid and from there into the cells. Metabolic wastes from the cells diffuse into the bloodstream and are carried away in the blood. With the exception of those on the skin surface and the cornea of the eye, all body cells lie close to a capillary. On average, capillaries are between 3 and 4 μm in diameter, about half the diameter of erythrocytes, which must therefore bend and fold to squeeze through.

In certain places, including the liver and bone marrow, the capillaries are significantly wider and leakier than normal. These capillaries are called sinusoids and because their walls are incomplete and their lumen is much larger than average, blood flows through them more slowly under low pressure and can come directly into contact with the cells outside the sinusoid wall. This allows much faster exchange of substances between the blood and the tissues. For example, in the liver, where capillary diameter is around 170 μm, the slow blood flow through these wide and leaky sinusoids allows the liver to adjust the composition of blood arriving from the gastrointestinal tract (see Fig. 12.37).

Some capillaries are less porous than average. Capillary beds in large parts of the brain and in the spinal cord are significantly less permeable than most, to restrict movement of solutes and water in and out of delicate neural tissue. This is the so-called blood–brain barrier (see Fig. 7.11).

Capillary refill time

When an area of skin is pressed firmly with a finger, it turns white (blanches) because blood flow through the capillaries under the finger has been obstructed. Normally it should take less than 2 seconds for the capillaries to refill once the finger is removed and for the skin to turn pink again. A prolonged capillary refill time suggests poor perfusion or dehydration.

Veins and venules

Capillaries converge to form tiny venules. Blood pressure drops significantly in the capillary beds, so blood travels through the venous system at low pressure. Because they do not have to withstand high blood pressure, venous walls are thinner than arterial walls, although they have the same three layers of tissue.

Some large veins possess valves, which prevent backflow of blood (Fig. 5.3). They are formed by a fold of tunica intima and strengthened by connective tissue. The cusps are semilunar (half-moon) in shape with the concave cup-shape facing towards the heart, so that any backflow fills the valve cups, pushing their edges together and blocking the vessel. Valves are abundant in the veins of the limbs, especially the lower limbs where blood must travel a considerable distance against gravity when the individual is standing. There are none in veins in the thorax, abdomen, head and neck. Valves and the skeletal muscle pump (see Fig. 5.22) ensure one-way flow back to the heart.

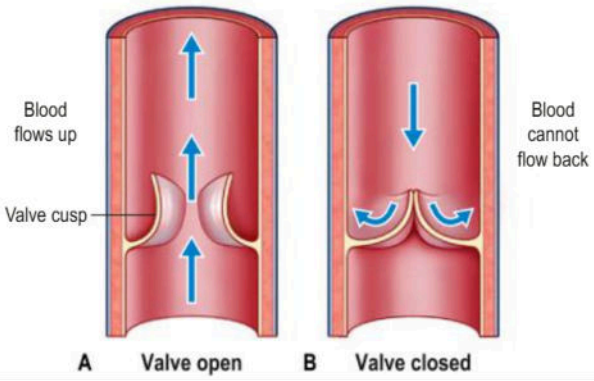

Figure 5.3 Interior of a vein. (A) The valves and cusps. (B) The direction of blood flow through a valve.

Veins are called capacitance vessels because they stretch, and therefore have the capacity to hold a large proportion of the body's blood. At any one time, about two-thirds of the body's blood is in the venous system. This helps the cardiovascular system to adjust to sudden changes in blood volume, such as in haemorrhage; the veins constrict, helping to prevent a sudden fall in blood pressure. Because blood pressure in veins is low, bleeding from a cut vein is slow and steady. The venous walls tend to collapse, and bleeding is stopped more easily than from a cut artery.

Capillary exchange

The capillary beds are the only sites of exchange between the blood and the tissues. Capillary density varies between tissues: organs with high oxygen requirements, for example the heart, the brain and the liver, have extensive capillary beds. The alveoli of the lungs are individually wrapped in dense capillary networks to maximise oxygen uptake (see Fig. 10.21). Capillary density is much lower in other tissues, e.g. adipose tissue, and a few have none at all, e.g. cartilage and the cornea of the eye.

Exchange of gases

Internal respiration (Fig. 5.4; see also p. 287) is the process by which gases are exchanged between capillary blood and local body cells. Exchange of gases in the lungs takes place across the capillary and alveolar walls, is called external respiration.

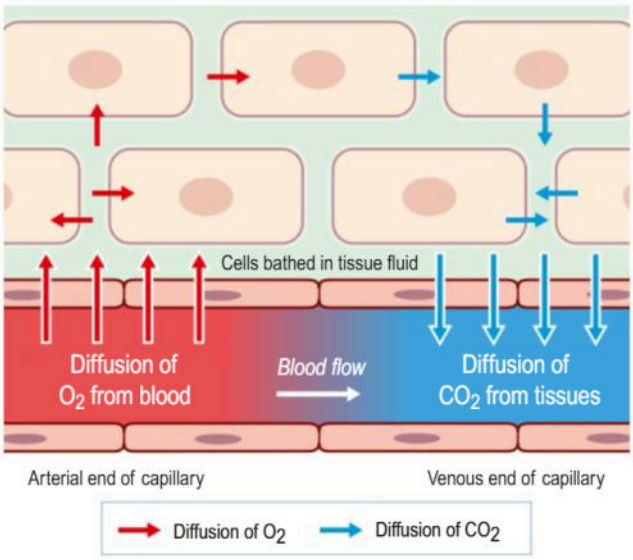

Figure 5.4 The exchange of gases in internal respiration.

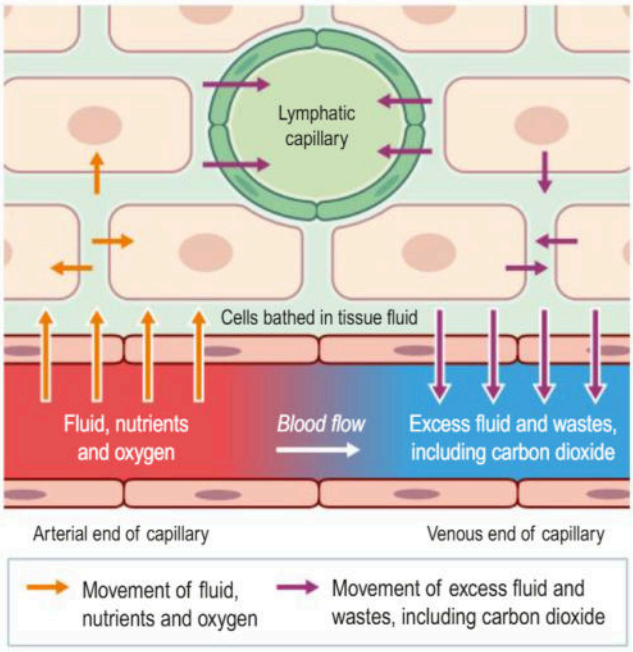

Figure 5.5 Diffusion of fluid, nutrients and waste products between capillaries and cells.

Oxygen is carried from the lungs to the tissues in combination with haemoglobin (p. 69) as oxyhaemoglobin. As arterial blood flows through a capillary bed, oxygen diffuses down its concentration gradient from the oxygen-rich blood into the tissues, where levels are lower because of constant tissue oxygen consumption.

Carbon dioxide is one of the waste products of cell metabolism and diffuses down its concentration gradient into the blood across the thin capillary wall.

Exchange of other substances

Only here can nutrients, including glucose, amino acids, fatty acids, vitamins and mineral salts, diffuse from the blood through the semipermeable capillary walls into the tissues (Fig. 5.5). Water exchanges freely between the plasma and interstitial fluid by osmosis.

Capillary fluid dynamics

Two main forces determine overall fluid movement across the capillary wall:

- hydrostatic pressure of the blood (blood pressure), which tends to push fluid out of the bloodstream
- osmotic pressure of the blood, which tends to pull fluid from the tissues into the blood and is due mainly to the presence of plasma proteins, especially albumin. The protein content of interstitial fluid is normally very low, creating an osmotic difference between the bloodstream and interstitial fluid (see Fig. 2.19).

At the arterial end of a capillary bed the hydrostatic pressure is about 5 kPa (35 mmHg), and the opposing osmotic pressure of the blood is only 3 kPa (25 mmHg). The net force at the arterial end of the capillary is therefore an outward pressure of 2 kPa (15 mmHg) and this drives fluid out of the capillary and into the tissue spaces (Fig. 5.6).

This net loss of fluid from the bloodstream must be reclaimed to prevent the tissues becoming water-logged because over 24 litres of fluid are filtered out of the body's capillaries every day.

At the venous end of the capillary the situation is reversed. Blood flow is slower than at the arterial end because the hydrostatic pressure drops along the capillary to only 2 kPa (15 mmHg). The osmotic pressure remains unchanged at 3 kPa (25 mmHg) and, because this now exceeds hydrostatic pressure, fluid is pulled back into the capillary. However, not all the water and cell waste products that leave the blood through capillary walls return to the bloodstream. Of the 24 litres or so of fluid that move out of the blood into body tissues every day, only about 21 litres return to the bloodstream at the venous end of the capillary bed. The remaining 3 litres drain away from the tissue spaces in the minute lymph capillaries, which originate as blind-ended tubes with walls similar to, but more permeable than, those of the blood capillaries (Fig. 5.5). This extra tissue fluid and some cell waste materials enter the lymph capillaries, forming lymph that is eventually returned to the bloodstream (Ch. 6).

SPOT CHECK

1. List the three layers of tissue found in the walls of arteries and veins and identify their functions.
2. Compare and contrast the structure and function of capillaries and sinusoids.

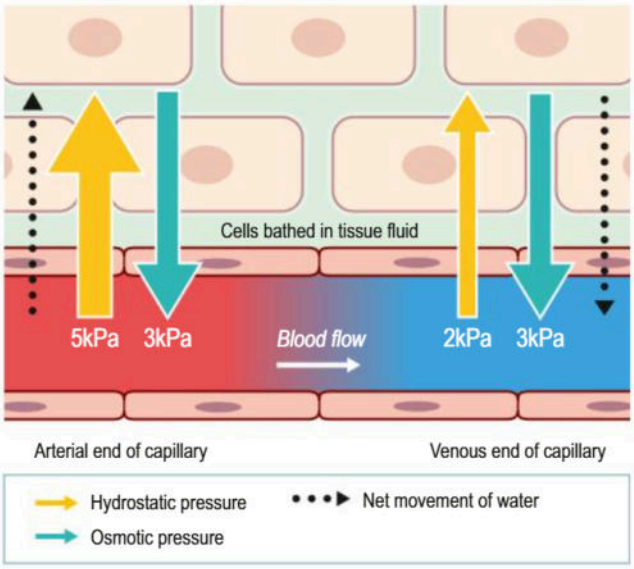

Figure 5.6 Effect of capillary pressures on water movement between capillaries and cells.

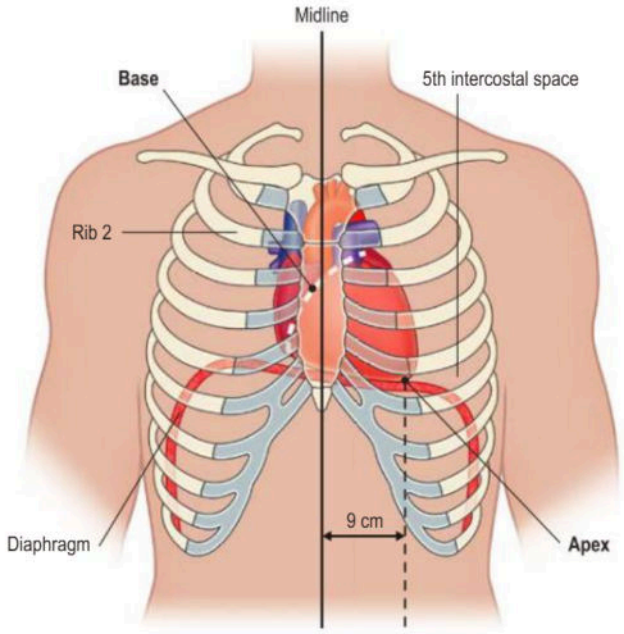

Figure 5.7 Position of the heart in the thorax. Anterior view.

Heart

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the heart and its position within the thorax
- trace the circulation of the blood through the heart and the blood vessels of the body
- outline the conducting system of the heart
- relate the electrical activity of the cardiac conduction system to the cardiac cycle
- describe the main factors determining heart rate and cardiac output.

The heart is a roughly cone-shaped hollow muscular organ about 10 cm long and weighing about 225 g in women and 310 g in men.

Position

The heart lies obliquely in the thoracic cavity (Fig. 5.7) in the mediastinum (the space between the lungs), slanted slightly to the left. The inferior tip of the heart, the apex, lies about 9 cm to the left of the midline at the level of the 5th intercostal space and points downwards and left. The flattened superior surface is called the base.

Organs associated with the heart

Inferiorly – the apex, which rests on the central tendon of the diaphragm (Fig. 5.8).
Superiorly – the great blood vessels, i.e. the aorta, superior vena cava, pulmonary artery and pulmonary veins, which enter the heart at its base.
Posteriorly – the oesophagus, trachea, left and right bronchus, descending aorta, inferior vena cava and thoracic vertebrae.
Laterally – the lungs; the left lung overlaps the left side of the heart.
Anteriorly – the sternum, ribs and intercostal muscles.

Structure

The heart wall

The heart wall is composed of three layers (Fig. 5.9A): pericardium, myocardium and endocardium.

Pericardium

The pericardium is the outermost layer and is made up of two sacs. The outer sac, called the fibrous pericardium, consists of fibrous tissue. It is continuous with the tunica adventitia of the great blood vessels above and is attached to the diaphragm below. It is fibrous, inelastic, and protects and prevents over-distension of the heart.

The inner, called the serous pericardium, is a continuous double layer of serous membrane. It is formed by a single layer of endothelial cells and is folded over itself, forming a

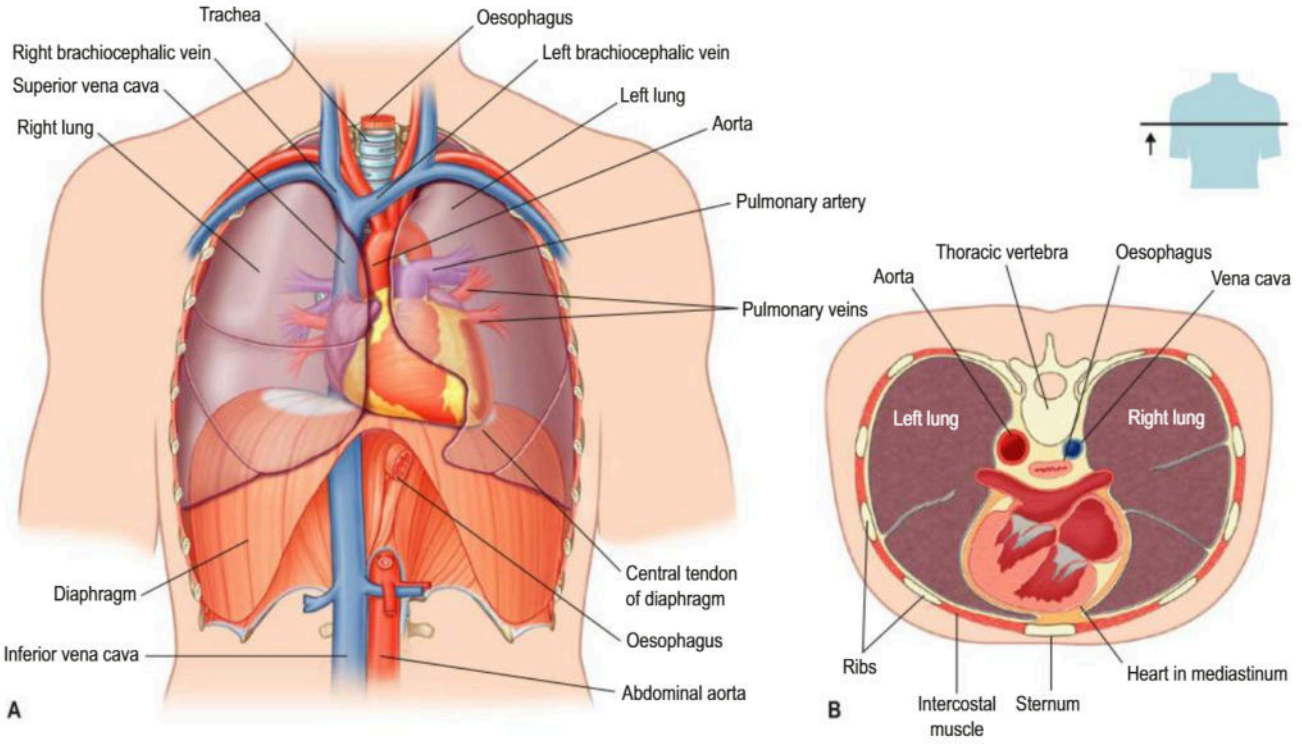

Figure 5.8 Organs associated with the heart. (A) Viewed from the front. (B) Transverse section, viewed from below.

double membrane around the heart with an enclosed space in between the layers (Fig. 5.10). A similar arrangement is seen round the lungs with the pleura (see Fig. 10.18).

The inner layer, called the visceral pericardium, is firmly attached to the myocardium below. The outer layer, called the parietal pericardium, lines the fibrous pericardium. About 20 mL of lubricating fluid, the pericardial fluid, lie between the two layers, so that the heart can beat without rubbing against the fibrous pericardium.

Myocardium

The myocardium is specialised cardiac muscle found only in the heart. It is striated, like skeletal muscle, but is not under voluntary control. Each fibre (cell) has a nucleus and one or more branches and is rich in mitochondria to supply its high energy needs. The ends of the cells and their branches are in very close contact with the ends and branches of adjacent cells. Microscopically, these 'joints', or intercalated discs, are thicker, darker lines than the striations (Fig. 5.9B). This arrangement gives cardiac muscle the functionality of a sheet of muscle rather than a number of individual cells. Because of the end-to-end continuity of the fibres, each one does not need a separate nerve supply. When an impulse is initiated, it spreads from cell to cell via the branches and intercalated discs over the whole 'sheet' of muscle. The 'sheet' arrangement of the myocardium enables the whole heart to contract in a coordinated and efficient manner.

The myocardium is thickest at the apex and thins out towards the base where the atria lie (Fig. 5.11). Running through the myocardium is the network of specialised conducting fibres responsible for transmitting the heart's electrical signals.

Specialised muscle cells in the walls of the atria secrete the hormone atrial natriuretic peptide (ANP, see Table 9.4).

Fibrous tissue in the heart

The atria and ventricles are separated by a ring of fibrous tissue called the fibrous skeleton of the heart, which cannot conduct electrical impulses. This acts as an insulating layer between the upper and lower chambers, so that electrical activity can pass from atria to ventricles only via fibres of the specialised conducting pathway (the AV node, see Fig. 5.18).

Endocardium

This thin membrane lines the chambers and valves of the heart. It consists of a single layer of flattened epithelial cells and is continuous with the endothelium lining the blood vessels; like the endothelium, it is very smooth to minimise friction as the blood flows over it.

Interior of the heart

The heart is divided into a right and left side by the septum (Fig. 5.11), a partition consisting of myocardium covered

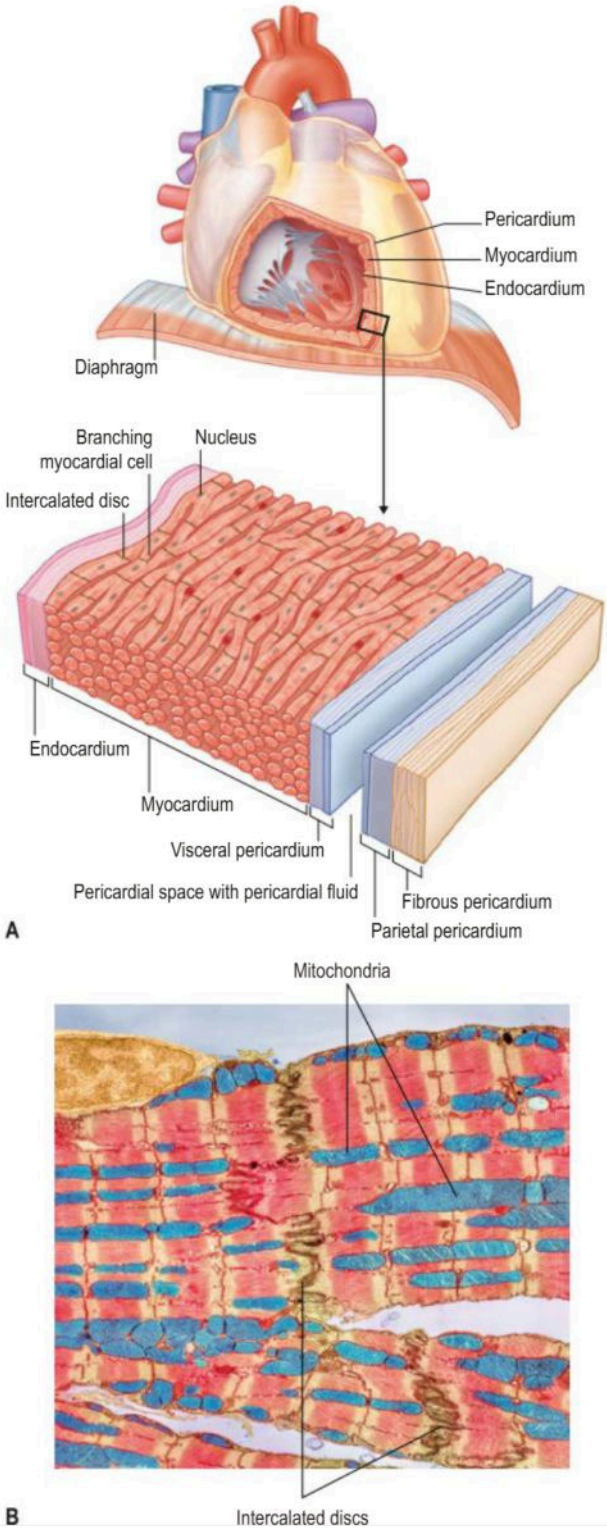

Figure 5.9 Tissues of the heart wall. (A) Layers of the heart wall: endocardium, myocardium and pericardium. (B) Coloured electron micrograph of cardiac muscle tissue. (Thomas Deerinck, NCMIR/ Science Photo Library. Reproduced with permission.)

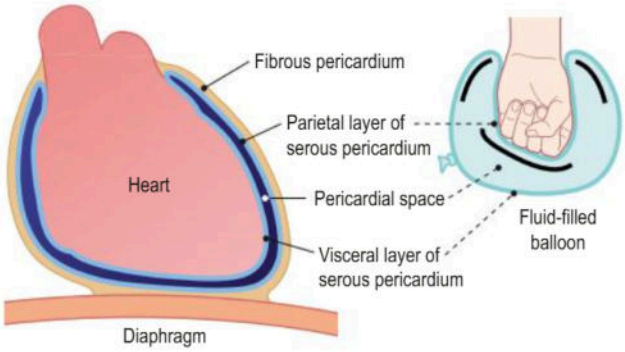

Figure 5.10 Structure of the pericardium.

by endocardium, and after birth there is no communication between the right and left sides of the heart. Each atrium opens into the ventricle below through an atrioventricular (AV) valve (Fig. 5.12A), formed from double folds of endocardium strengthened by a little fibrous tissue. The right AV (tricuspid) valve has three flaps or cusps, and the left AV (mitral) valve has two cusps. The valves ensure that blood flow in the heart is one-way. Figure 5.13 is an echocardiogram (ultrasound) image showing the four chambers and the AV valves of a healthy heart. Echocardiograms use sound waves to generate images of internal body structures and allow the operator to visualise in real time the pumping action of the heart, the function of the heart valves and blood flow through the chambers. They are useful tools in the diagnosis of heart conditions (see Fig. 5.59)

The AV valves open and close passively, according to changes in pressure in the chambers (Fig. 5.12B and C). They open when the pressure in the atria is greater than that in the ventricles, pushing the valve cusps apart and allowing blood to flow into the ventricles. During ventricular systole (contraction) blood pressure in the ventricles rises above atrial pressure and the valves snap shut, preventing backward flow of blood. The valves are prevented from opening upwards into the atria by inelastic tendinous cords called chordae tendineae (Fig. 5.14), which fasten the inferior surface of the cusps to the papillary muscles. The papillary muscles, tiny extensions of the myocardium, anchor the chordae tendineae firmly to the ventricular wall.

Blood flow through the heart

The two largest veins of the body, the superior vena cava and inferior vena cava (Fig. 5.15), empty their contents into the right atrium. Blood then passes through the right AV valve into the right ventricle, and from there is pumped into the pulmonary arteries. The opening of the pulmonary artery is guarded by the pulmonary valve, formed by three semilunar cusps (Fig. 5.16). This valve prevents backflow of blood into the right ventricle when the ventricular muscle

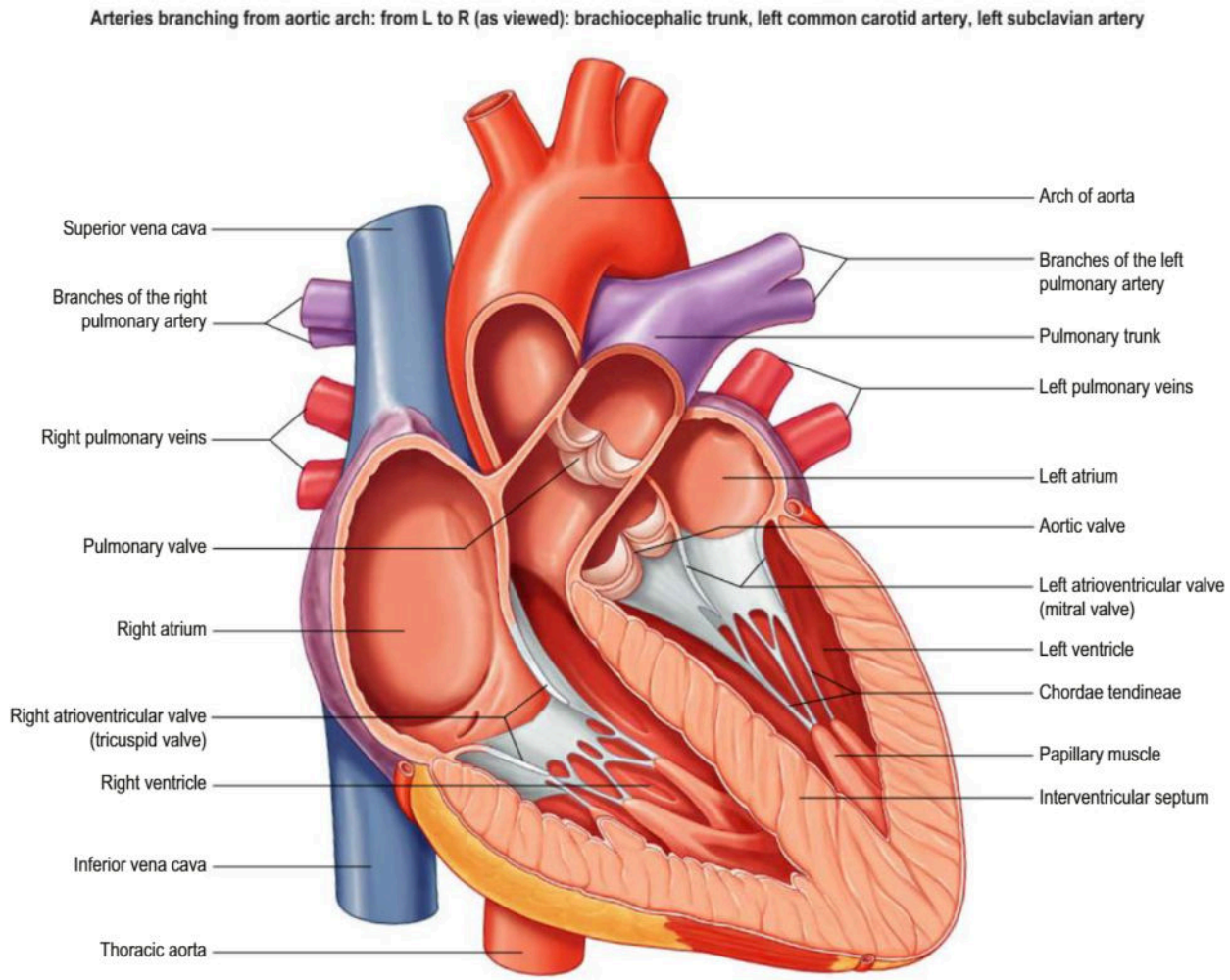

Figure 5.11 Interior of the heart.

relaxes and pressure in the ventricle starts to drop. The right and left pulmonary arteries carry the venous blood to the lungs, where exchange of gases takes place: carbon dioxide is excreted and oxygen is absorbed.

Two pulmonary veins from each lung carry oxygenated blood back to the left atrium. Blood then passes through the left AV valve into the left ventricle, and from there it is pumped into the aorta, the first artery of the general circulation. The opening of the aorta is guarded by the aortic valve, formed by three semilunar cusps (Fig. 5.16), which prevents blood flowing back into the left ventricle at the end of each contraction.

The blood thus passes from the right to the left side of the heart through the lungs via the pulmonary circulation (see Fig. 5.1). Both atria contract at the same time and this is followed by the simultaneous contraction of both ventricles.

The atrial myocardium is thinner than in the ventricles (see Fig. 5.11) because their workload is less. The atria, significantly helped by gravity, pump the blood only through the AV valves into the ventricles, whereas the more powerful ventricles pump the blood to the lungs and round the whole body. The left ventricular wall is thicker than that of the right because it has to pump blood into the systemic circulation with enough force to circulate it to the most distal tissues, whereas the right ventricle has only to pump blood the short distance to the lungs.

Blood supply to the heart (the coronary circulation)

Arterial supply

The heart is supplied with arterial blood by the right and left coronary arteries, which branch from the aorta immediately distal to the aortic valve (Figs 5.16 and 5.17). The coronary

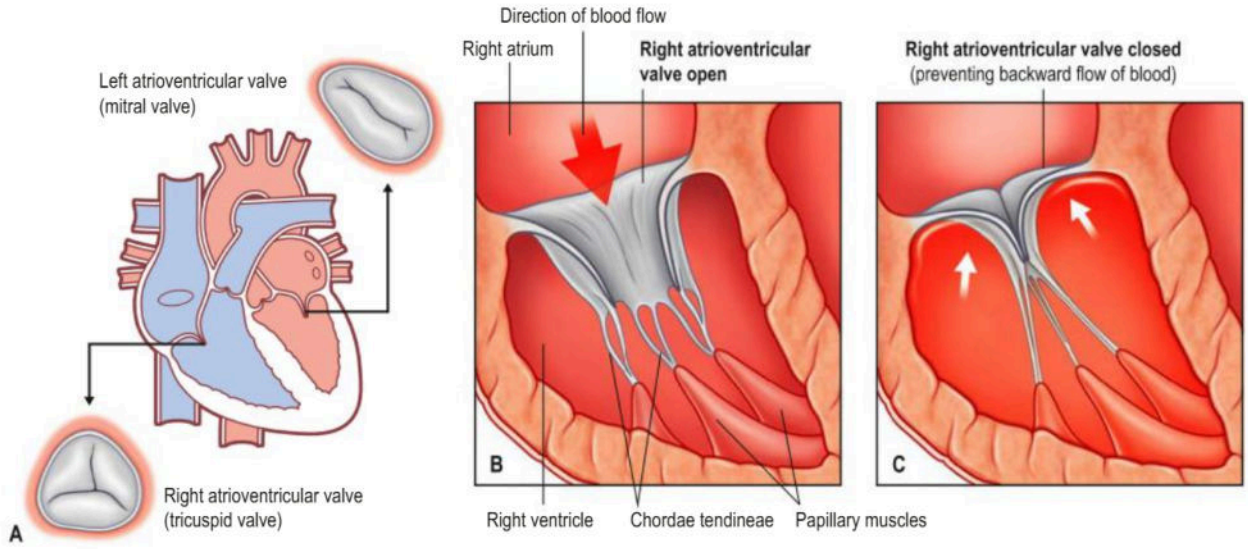

Figure 5.12 The left atrioventricular (mitral) valve. (A) Its position in the heart. (B) Valve open. (C) Valve closed.

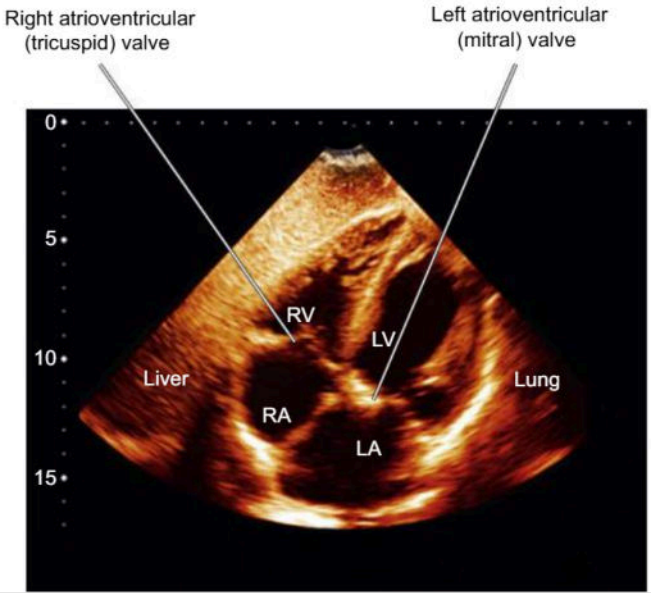

Figure 5.13 False coloured echocardiogram of the normal heart during systole, showing the chambers and the atrioventricular valves. (From Science Photo Library. Reproduced with permission.)

arteries branch extensively throughout the heart, forming a vast network of capillaries to ensure the myocardium has a constant and generous supply of oxygen and glucose. The left coronary artery and its branches, including the left anterior descending artery and the circumflex artery, supply the left ventricle and left atrium in most people. The right coronary artery supplies the right ventricle and right atrium, including the sinoatrial and atrioventricular nodes in most people, but there is considerable individual variation in the arrangement of the coronary circulation. The coronary arteries receive about 5% of the blood pumped from the heart, although the heart is only about 0.5% of body weight. Most of this disproportionately large blood supply goes to the left ventricle, the chamber with the highest workload.

Venous drainage

Most of the venous blood is collected into a number of cardiac veins that join to form the coronary sinus, which empties into the right atrium. The rest passes directly into the heart chambers through little venous channels.

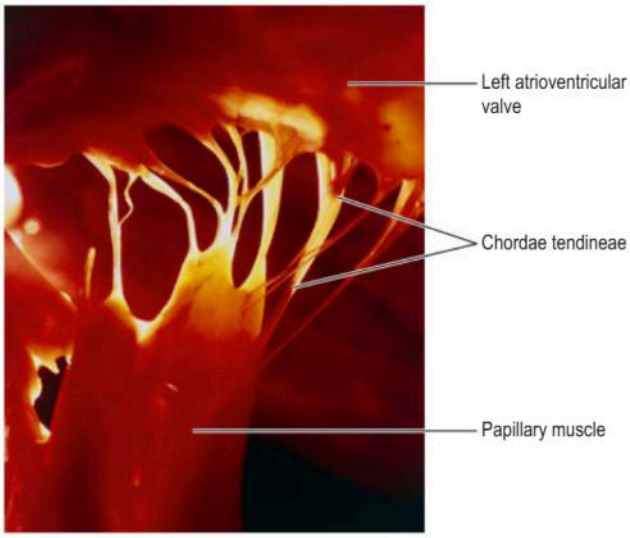

Figure 5.14 Photograph of the chordae tendineae (Philippe Plailly/ Science Photo Library. Reproduced with permission.)

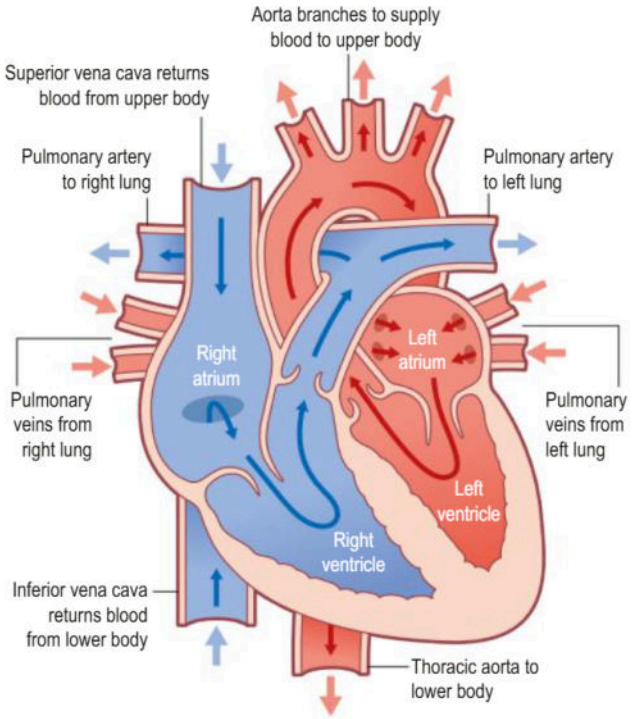

Figure 5.15 Direction of blood flow through the heart.

Conducting system of the heart

The heart possesses the property of autorhythmicity, which means it generates its own electrical impulses and beats independently of nervous or hormonal control and is not reliant on external mechanisms to initiate each heartbeat.

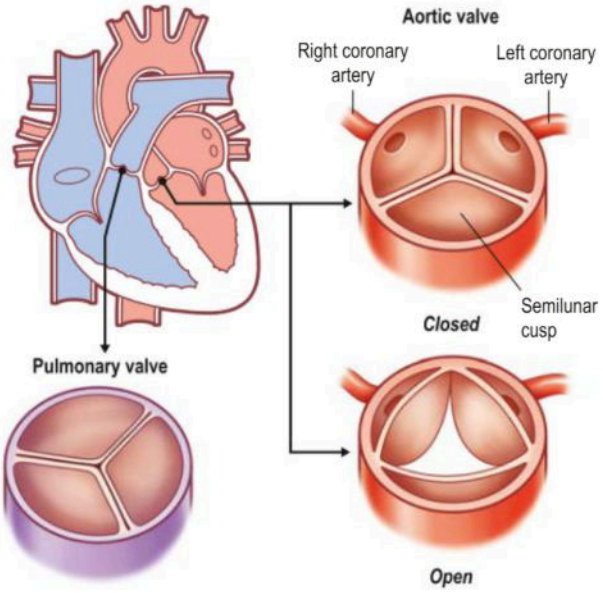

Figure 5.16 Structure of the aortic and pulmonary valves.

However, it is supplied with both sympathetic and parasympathetic nerve fibres, which increase and decrease the intrinsic heart rate, respectively. In addition, the heart responds to a number of circulating hormones, including adrenaline (epinephrine) and thyroxine.

Small groups of specialised neuromuscular cells in the myocardium form the cardiac conduction system: they initiate and conduct impulses, causing coordinated and synchronised contraction of the heart muscle (Fig. 5.18).

Sinoatrial node

The sinoatrial node (SA node) is a small mass of specialised cells lying in the wall of the right atrium near the opening of the superior vena cava (Fig. 5.18).

The sinoatrial cells generate regular impulses because they are electrically unstable, causing them to discharge (depolarise) regularly, usually between 60 and 90 times a minute. Each time the SA node depolarises, it initiates a new heartbeat. Depolarisation is followed by recovery (repolarisation), but almost immediately it depolarises again, stimulating the next contraction. Because the SA node discharges faster than any other part of the conduction system, it normally sets the heart rate and is therefore called the pacemaker of the heart.

The impulse from the SA node takes about 0.1 second to spread through the atrial muscle, triggering atrial contraction, and to reach the atrioventricular node. This is the only conducting pathway linking the atria and the ventricles because of the ring of fibrous non-conducting tissue separating the upper and lower heart chambers.

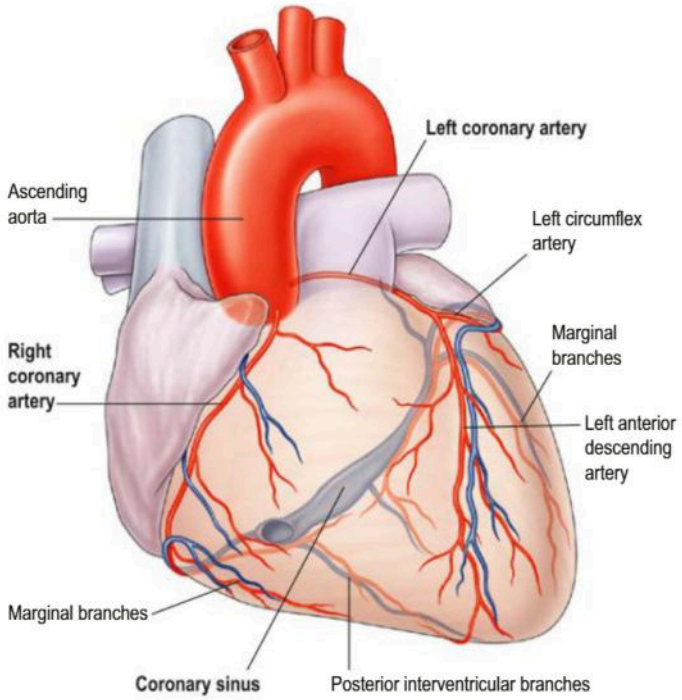

Figure 5.17 The coronary arteries.

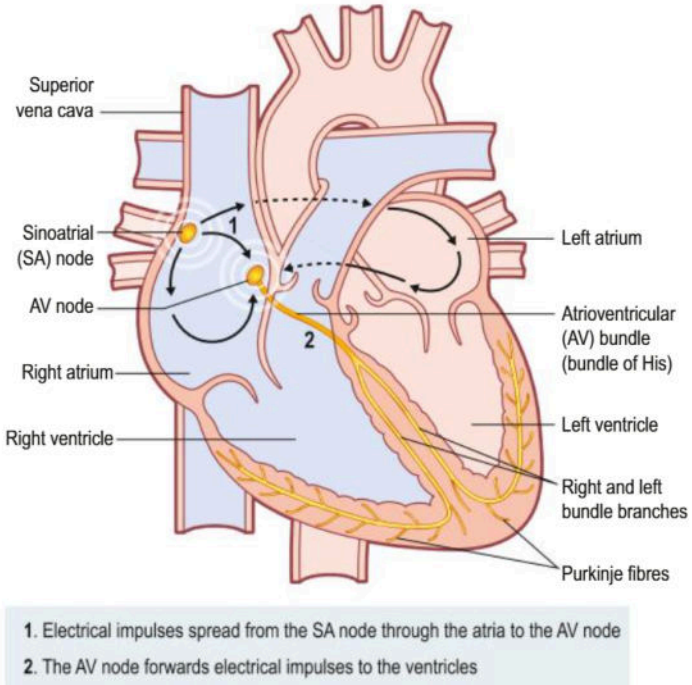

Figure 5.18 The conducting system of the heart.

Atrioventricular node

The atrioventricular (AV) node is a small mass of neuromuscular tissue situated in the wall of the atrial septum near the atrioventricular valves (Fig. 5.18). Normally, the AV node merely transmits the electrical signals from the atria into the ventricles. There is a delay here; the electrical signal takes 0.1 second to pass through into the ventricles. This allows the atria to finish contracting before the ventricles start.

The AV node also has a secondary pacemaker function and takes over this role if there is a problem with the SA node itself, or with the transmission of impulses from the atria. Its intrinsic firing rate, however, is slower than that set by the SA node (40–60 per minute).

Atrioventricular bundle

The atrioventricular bundle (AV bundle or bundle of His) is a mass of specialised fibres that originates from the AV node. At the upper end of the ventricular septum it divides into right and left bundle branches. Within the ventricular myocardium the branches break up into the fine Purkinje fibres, which synapse directly with the myocardial cells. The AV bundle, bundle branches and Purkinje fibres transmit electrical impulses from the AV node throughout the ventricular myocardium, triggering ventricular contraction.

Nerve supply to the heart

As mentioned earlier, the heart is influenced by autonomic (sympathetic and parasympathetic) nerves originating in the cardiovascular centre in the medulla oblongata.

The vagus nerve (parasympathetic) supplies mainly the SA and AV nodes and atrial muscle. Vagal stimulation reduces the rate of SA node firing, decreasing the rate and force of the heartbeat.

Sympathetic nerves supply the SA and AV nodes and the myocardium itself, and stimulation increases the rate and force of the heartbeat.

Factors affecting heart rate

The most important ones are listed in Box 5.1 and explained in more detail on page 100.

Box 5.1 The main factors affecting heart rate

Autonomic activity
Circulating hormones
Activity and exercise
Gender
Age
Temperature
Baroreceptor reflex
Emotional states

Cardiac cycle

At rest, the healthy adult heart is likely to beat at a rate of 60–90 beats per minute (bpm). During each heartbeat, or cardiac cycle (Fig. 5.19), the heart contracts (systole) and then relaxes (diastole).

Stages of the cardiac cycle

Taking a typical heart rate of 74 bpm as an example, each cycle lasts about 0.8 second and consists of three stages:

- complete cardiac diastole – this is the rest period between beats, and the myocardium in the atria and ventricles is completely relaxed
- atrial systole – atrial contraction
- ventricular systole – ventricular contraction.

It does not matter at which stage of the cardiac cycle a description starts. Complete cardiac diastole, when the heart chambers are relaxed and passively filling has been chosen here.

While the heart is at complete rest, the atria are continuously filling with blood from the superior and inferior venae cavae (into the right atrium) and the pulmonary veins (into the left atrium). As pressure rises in the atria, the atrioventricular valves are pushed open and blood flows passively into the ventricles, helped by gravity if the thorax is upright. Up to 70% of ventricular filling can be accomplished without any atrial contraction at all.

Atrial systole commences when the SA node triggers a wave of contraction that spreads over the myocardium of both atria, emptying the atria and completing ventricular filling (atrial systole 0.1 second; Fig. 5.19A). When the electrical impulse reaches the AV node it slows down, delaying atrioventricular transmission. This allows the atria to finish emptying into the ventricles before the ventricles begin to contract. After this brief delay, the AV node triggers its own electrical impulse, which quickly spreads to the ventricular muscle via the AV bundle, the bundle branches and Purkinje fibres. This results in a wave of contraction that sweeps upwards from the apex of the heart and across the walls of both ventricles, pumping the blood into the pulmonary artery and the aorta (ventricular systole 0.3 second; Fig. 5.19B). The high pressure generated during ventricular contraction forces the atrioventricular valves to close, preventing backflow of blood into the atria.

Contraction of the ventricles is followed by complete cardiac diastole, a period of 0.4 second, when atria and ventricles are relaxed. During this time the myocardium recovers, ready for the next heartbeat, and the atria refill, ready for the next cycle (Fig. 5.19C).

The valves of the heart and those of the great vessels open and close according to the pressure within the chambers of the heart. The atrioventricular valves open during atrial filling and systole because pressure in the atria is

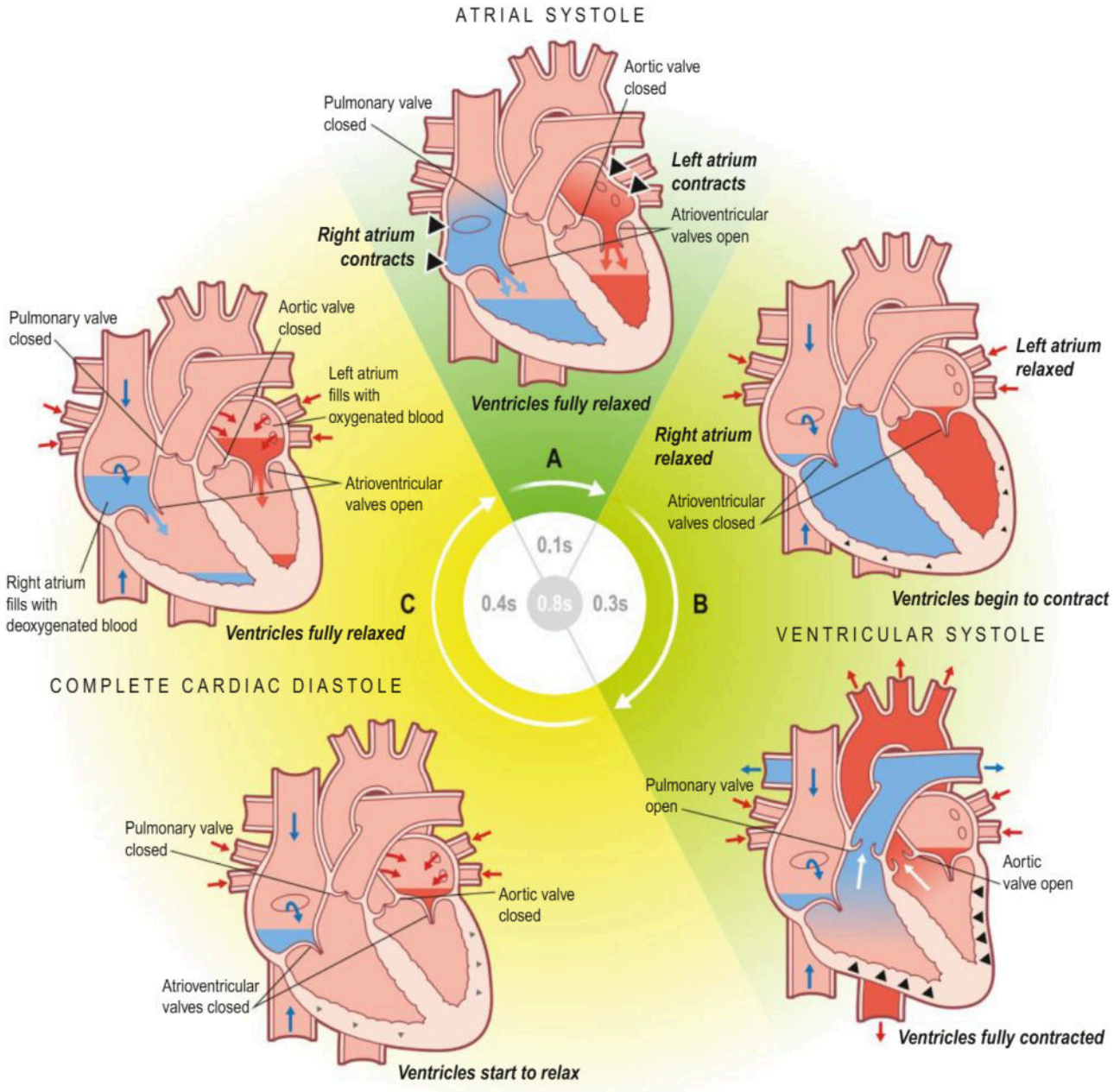

Figure 5.19 The cardiac cycle.

higher than in the ventricles. When the ventricles contract, ventricular pressure rises rapidly, and when it exceeds atrial pressure the atrioventricular valves are pushed shut. When the ventricular pressure rises above that in the pulmonary artery and in the aorta, the pulmonary and aortic valves are pushed open and blood flows into these vessels. When the ventricles relax and the pressure within them falls, the reverse process occurs. First the pulmonary and aortic valves close, then the atrioventricular valves open and the cycle begins again. This sequence of opening and closing valves ensures that the blood flows in only one direction.

Heart sounds

If the ear or the diaphragm of a stethoscope is placed in appropriate locations on the chest wall, the sounds produced by the closure of the heart valves during the cardiac cycle can be heard. This is called auscultation.

There are two main heart sounds. The first, called S1, is due to the closure of the mitral and tricuspid valves as the ventricles begin to contract, and can be heard if the stethoscope is placed over the tricuspid and mitral areas as shown in Figure 5.20. It is sometimes called 'lub' because of its characteristic sound. The second sound, S2, sometimes

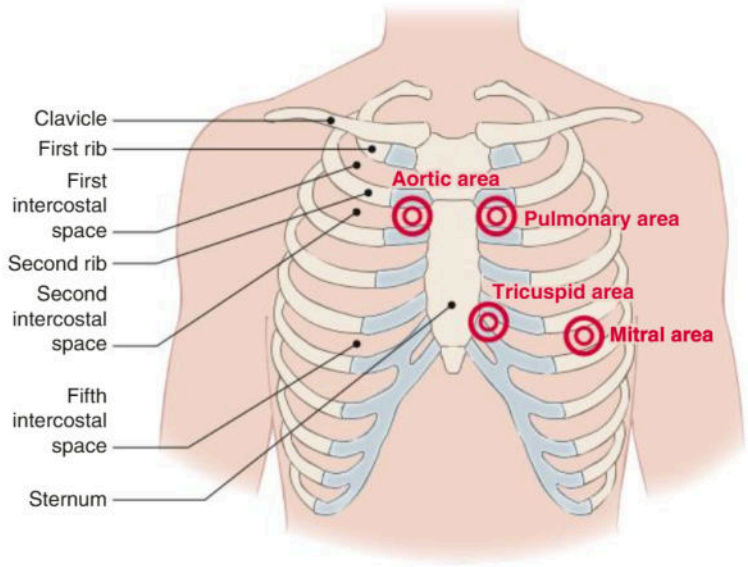

Figure 5.20 Stethoscope placement on the chest for the heart sounds.

called 'dub', is the sound of the pulmonary and aortic valves snapping shut as the ventricles relax after systole. It is softer than S1 and can be heard over the pulmonary and aortic areas of the chest (Fig. 5.18).

Electrical activity in the heart

The body tissues and fluids conduct electricity well, so the electrical activity in the heart can be recorded on the skin surface using electrodes positioned on the limbs and/or the chest. This recording, called an electrocardiogram (ECG), shows the spread of the electrical signal generated by the SA node as it travels through the atria, the AV node and the ventricles. The ECG is a fundamental clinical tool that can precisely identify conduction abnormalities and the location of areas of ischaemic myocardium.

The normal ECG tracing shows five waves, which, by convention, have been named P, Q, R, S and T (Fig. 5.21).

The P wave represents the impulse from the SA node sweeping over the atria (atrial depolarisation).

The QRS complex represents the spread of the impulse from the AV node through the AV bundle and the Purkinje fibres, and the electrical activity of the ventricular muscle (ventricular depolarisation). Note the delay between the completion of the P wave and the onset of the QRS complex. This represents the conduction of the impulse through the AV node, which is much slower than conduction elsewhere in the heart and allows atrial contraction to finish completely before ventricular contraction starts.

The T wave represents the relaxation of the ventricular muscle (ventricular repolarisation). Atrial repolarisation occurs during ventricular contraction, and so is not seen because of the larger QRS complex.

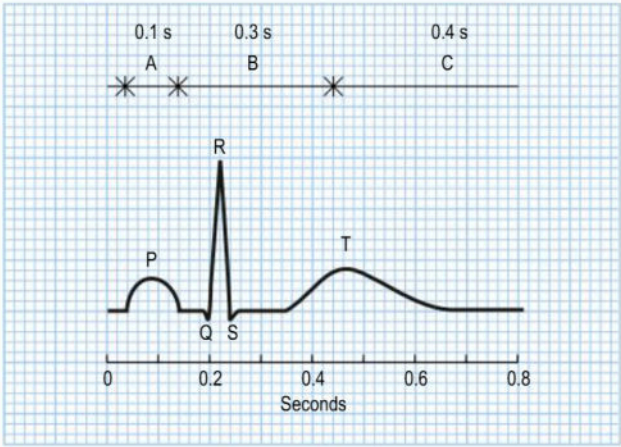

Figure 5.21 Normal electrocardiogram (ECG) of one cardiac cycle. (A), (B) and (C) correspond to the phases of the cardiac cycle shown in Fig. 5.19.

The ECG described above and shown in Fig. 5.21 represents normal heart rhythm originating from the SA node, and so is called sinus rhythm. Normally, the heart rate is between 60 and 90 bpm. A heart rate over 100 bpm is called tachycardia, and below 60 bpm is bradycardia.

Cardiac output

The cardiac output is the amount of blood ejected from each ventricle every minute. The amount expelled by each

Box 5.2 Summary of factors affecting cardiac output

Cardiac output = Stroke volume × Heart rate

Factors affecting stroke volume

Ventricular end-diastolic volume (VEDV – preload)

Venous return:

- Position of the body
- Skeletal muscle pump
- Respiratory pump

Strength of myocardial contraction

Blood volume

contraction of each ventricle is the stroke volume. Cardiac output is expressed in litres per minute (L/min) and is calculated by multiplying the stroke volume by the heart rate (measured in beats per minute):

Cardiac output = Stroke volume × Heart rate

In a healthy adult at rest the stroke volume is approximately 70 mL and if the heart rate is 72/min, the cardiac output is 5 L/min (72 bpm × 70 mL). This can increase to around 25 L/min in exercise, and up to 35 L/min in athletes. This increase available during exercise is called the cardiac reserve.

Factors affecting cardiac output are listed in Box 5.2.

Stroke volume

The stroke volume is determined by the volume of blood in the ventricles immediately before they contract, called the ventricular end-diastolic volume (VEDV), and sometimes called preload. Preload depends on the amount of blood returning to the heart through the superior and inferior venae cavae (the venous return). It increases when the heart rate increases, e.g. in exercise, because larger volumes of blood are returning to the heart each minute. Increased preload stretches the walls of the heart chambers, stimulates stronger myocardial contraction and expels more blood, increasing stroke volume and cardiac output. In this way, the heart, within physiological limits, always pumps out all the blood that it receives, allowing it to adjust cardiac output to match body needs. However, this capacity to increase the stroke volume with increasing preload is finite, and when the limit is reached, i.e. venous return to the heart exceeds cardiac output (i.e. more blood is then arriving in the atria than the ventricles can pump out), cardiac output decreases and the heart begins to fail. Other factors that increase the force and rate of myocardial contraction include increased sympathetic nerve activity and circulating hormones, including adrenaline (epinephrine), noradrenaline (norepinephrine) and thyroxine.

Arterial blood pressure

This affects the stroke volume, because it creates resistance to blood being pumped from the ventricles into the great arteries. This resistance, sometimes called afterload, is determined by the distensibility, or elasticity, of the large arteries and the peripheral resistance of arterioles. If elastic arteries become stiffer, as they tend to do naturally with age, or if a large proportion of arterioles are constricted, afterload increases. This increases the workload of the ventricles because it elevates the pressure against which they have to pump.

Blood volume

This is normally kept constant by the kidneys. If blood volume falls, e.g. in sudden haemorrhage, this can immediately reduce stroke volume, cardiac output and venous return. The body's compensatory mechanisms will try to return the situation to normal, e.g. by increasing heart rate, but if the blood loss is sudden or severe, cardiovascular failure may follow (see shock, p. 127).

Venous return

Venous return is the major factor controlling cardiac output and the heart normally pumps out all blood arriving in the atria. Systemic venous pressure is much lower than arterial pressure, because the pressure wave from the heart steadily diminishes as blood flows through capillaries at low pressure. Despite this low pressure and opposition from gravity, venous blood returns to the heart, helped by venous valves, the action of skeletal muscles and the respiratory pump.

Effect of gravity

When the body is upright, gravity opposes venous return from all structures below the level of the heart and can lead to pooling of blood in the lower limbs. Lying down and/or elevating the feet improves blood flow back to the heart.

The skeletal muscle pump

The contraction of skeletal muscles surrounding the deep veins compresses them, pushing blood towards the heart. In the lower limbs, this is called the skeletal muscle pump (Fig. 5.22). Wearing compression stockings and doing exercises on long flights or during periods of inactivity or immobility promotes the action of the skeletal muscle pump, helping venous return and reducing the risk that blood pooling in the legs might clot.

The respiratory pump

During inspiration, chest expansion creates a negative pressure within the thorax and the blood vessels in the chest, including the superior and inferior venae cavae. This reduced pressure expands the venae cavae slightly, sucking blood into the right atrium.

Heart rate

The heart rate is a major determinant of cardiac output. If heart rate rises, cardiac output increases, and if it falls, cardiac output falls too. The main factors determining heart rate are outlined here.

Autonomic nervous system

The intrinsic rate at which the heart beats is a balance between sympathetic and parasympathetic activity and this is the

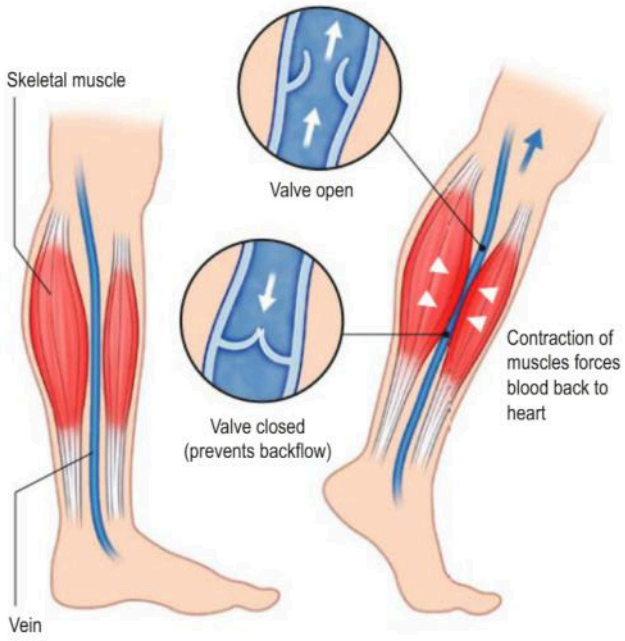

Figure 5.22 The skeletal muscle pump.

most important factor in determining heart rate. Sympathetic nervous system activity increases heart rate, whereas parasympathetic activity decreases it. The main influence on the resting heart rate is exerted by parasympathetic innervation. The SA node has a natural discharge rate of between 100 and 120 impulses per minute, but the resting heart rate is usually only 70–80 bpm. This is because the SA node is under constant parasympathetic restraint, which slows its intrinsic discharge rate down considerably. This is called vagal tone, because parasympathetic input to the heart is from the vagus nerve (cranial nerve X, see Fig. 7.14).

Circulating chemicals

Adrenaline (norepinephrine) secreted by the adrenal medulla has the same effect as sympathetic stimulation, i.e. it increases the heart rate and strength of contraction. Hypoxia, elevated carbon dioxide levels, e.g. in exercise, and other hormones, e.g. thyroxine, also stimulate the heart. Electrolyte imbalances may also affect it; for example, hyperkalaemia depresses cardiac function and leads to bradycardia. Some drugs, such as the β-receptor antagonists (e.g. atenolol) used in hypertension, can also cause bradycardia.

Exercise and level of physical fitness

Exercise increases heart rate to meet the increased metabolic needs of working skeletal muscle and the heart itself. Individuals with a high degree of cardiovascular fitness generally have a lower heart rate than less fit people, because regular exercise strengthens the myocardium, allowing it to pump the same amount of blood with fewer beats.

Position

When a person is upright, the heart rate is usually faster than when lying down.

Gender

The heart rate is faster in women than men.

Age

In babies and small children the heart rate is more rapid than in older children and adults. For example, the resting heart rate in a newborn baby may be as high as 200 bpm, and in a three-year-old 110 bpm.

Temperature

The heart rate rises and falls with body temperature.

Baroreceptor reflex

See page 103.

SPOT CHECK

3. Describe the location of the heart and its relationship to surrounding structures.
4. What is the function of the sinoatrial node and what is the consequence if it fails?

Blood pressure

Learning outcomes

After studying this section, you should be able to:

- define the term blood pressure
- describe the main factors controlling blood vessel diameter
- list the factors that influence blood pressure
- explain the two main mechanisms that control blood pressure.

Blood pressure (BP) is the force or pressure that the blood exerts on the walls of blood vessels. Blood pressure maintains the essential flow of blood through the body organs and ensures adequate venous return. Keeping blood pressure within normal limits is very important. High blood pressure can damage and weaken blood vessel walls, causing rupture with potentially serious consequences, e.g. into the brain (stroke). However, if blood pressure is too low, blood flow through tissue beds may be inadequate and tissues become starved of essential oxygen and nutrients. This is particularly dangerous for essential organs such as the heart, brain or kidneys, which have autoregulation mechanisms (p. 102) to protect them from fluctuations in systemic blood pressure.

Blood pressure falls at rest and during sleep. It increases with age and is usually higher in women than in men. Arterial blood pressure is measured with a sphygmomanometer and is usually expressed as two readings, the systolic and diastolic, with the systolic pressure being written above the diastolic pressure:

$$BP = \frac{120}{80}\ mmHg$$

Systolic and diastolic pressures

When the left ventricle contracts and pushes blood into the aorta, arterial blood pressure rises sharply and produces the systolic blood pressure. An average adult systolic reading is about 120 mmHg. In complete cardiac diastole, when the heart is resting between beats, the pressure within the arteries is much lower and is called diastolic blood pressure. An average adult diastolic reading is about 80 mmHg. Whereas systolic pressure reflects the peak pressure generated by left ventricular contraction, diastolic blood pressure reflects the degree of constriction within the vascular system and tends to fluctuate less than the systolic pressure. The difference between systolic and diastolic blood pressures is called the pulse pressure. Factors that increase systolic pressure, e.g. increased cardiac output, or that reduce the compliance of blood vessels increase pulse pressure. Increased pulse pressure is seen in older people with atherosclerosis (p. 130) whose blood vessels are stiffer and less compliant, so that each time the heart beats, the pressure in the vascular system rises very sharply.

Relationship between pressure, flow and blood vessel diameter

Blood pressure, blood flow and blood vessel diameter are all very closely interrelated.

Tunica media and vessel diameter

The tunica media of large arteries contains much elastic tissue, to allow them to expand easily with each heartbeat and to minimise the workload of the heart. When the left ventricle ejects blood into the elastic aorta, the vessel expands to accommodate it and then recoils elastically. This pushes the blood forwards into the arterial system, and a wave of distension and recoil occurs throughout the large arteries, keeping pressure high and the blood moving forwards. In contrast, the tunica media of the smallest arteries and their branches, the arterioles, are rich in smooth muscle and contain much less elastic tissue. Autonomic nerve fibres supply this smooth muscle and control the vessel diameter, regulating flow and pressure. These are the most important vessels in the control of systemic blood pressure and are called resistance vessels because by constricting and dilating they control the resistance against which the heart has to pump.

Veins contain only a little muscle in their walls, which contracts in response to a fall in blood pressure. Because the venous system contains the majority of the body's blood, even a small degree of venoconstriction can make a significant difference to blood pressure, e.g. following haemorrhage.

Blood vessel diameter and blood flow

Resistance to flow of fluids along a tube is determined by three factors: the diameter of the tube, the length of the tube and the viscosity of the fluid. The most important factor determining how easily blood flows through blood vessels is the first of these factors, i.e. the diameter of the resistance vessels (the peripheral resistance), because unlike the other two variables, it can be rapidly adjusted. Peripheral resistance is a major factor in blood pressure regulation, which is discussed further on page 103.

Blood vessel diameter is regulated by the smooth muscle of the tunica media, which is supplied by sympathetic nerves of the autonomic nervous system (p. 190). There is no parasympathetic nerve supply to most blood vessels and therefore vascular smooth muscle tone (degree of contraction) is determined by the degree of sympathetic activity. Sympathetic activity generally constricts vascular smooth muscle and causes vasoconstriction, increasing the pressure inside the vessel. A degree of resting sympathetic activity maintains a constant baseline tone in the vessel wall and prevents pressure falling too low (Fig. 5.23). Decreased sympathetic nerve stimulation relaxes the smooth muscle, causing vasodilation. This results in increased blood flow under less pressure.

Constant adjustment of blood vessel diameter helps to regulate peripheral resistance and systemic blood pressure.

Although sympathetic stimulation of most arterioles results in vasoconstriction, this is much less marked in some arteriolar beds, e.g. in skeletal muscle and the brain. This is important so that in a stress response, such as the flight or fight response (p. 192), when sympathetic activity is very high, blood flow is not restricted to these essential tissues. Another important vasoconstrictor is angiotensin II (p. 385), released as part of the systemic response to a fall in blood pressure.

Autoregulation

The oxygen and nutrient requirements of tissues vary, depending on activity, so it is important that blood flow is regulated locally to ensure that blood flow matches tissue needs. The ability of an organ to control its own blood flow through local vasodilation or vasoconstriction according to need is called autoregulation. Some organs, including the brain, liver and kidneys, receive proportionately higher blood flow as a matter of course. Other tissues, such as resting skeletal muscle, receive much less, but through autoregulation mechanisms their blood supply can increase as much as 20-fold during heavy exercise. Other examples of autoregulation include increased blood flow through the gastrointestinal tract after a meal to allow for greater activity there, vasodilation to maintain blood flow to

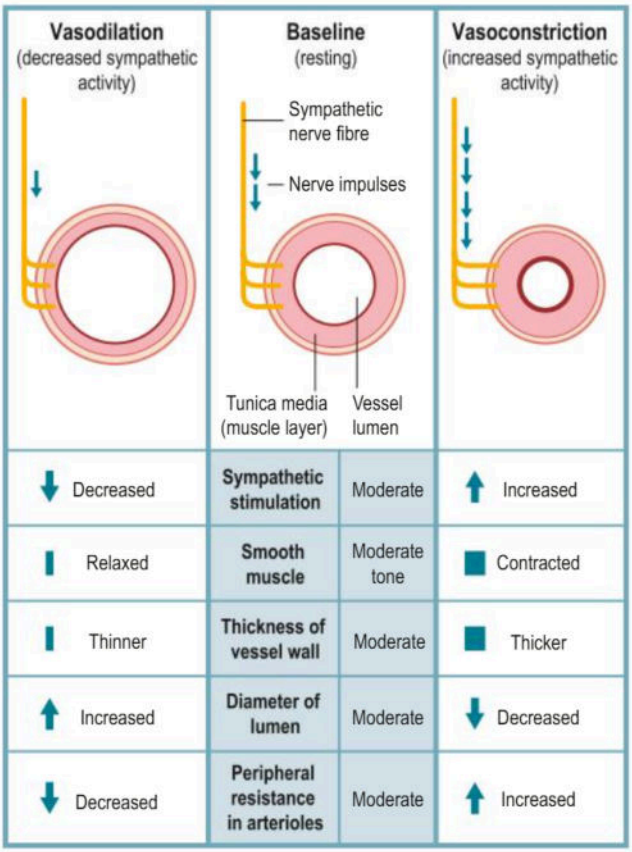

Figure 5.23 The relationship between sympathetic stimulation and blood vessel diameter.

the brain when blood pressure falls, and adjustments to blood flow through the skin to control body temperature (p. 405). Autoregulation in the kidney causes vasoconstriction and reduced blood flow to protect the delicate glomerular capillaries from damage if systemic blood pressure is high.

The main mechanisms that cause local vasodilation and increased blood flow include:

- Increased production of metabolic waste products, e.g. CO_2 and lactic acid
- Increased tissue temperature from a rise in metabolic activity
- Hypoxia
- Local release of vasodilator chemicals – inflamed and metabolically active tissues produce a number of vasodilators, which increase blood supply to the area. One important vasodilator is nitric oxide, which is very short-lived but important in dilating the larger arteries supplying an organ. Other agents include substances released in the inflammatory response, such as histamine and bradykinin (see Table 15.1).

Factors determining blood pressure

Blood pressure is determined by cardiac output and peripheral resistance. Change in either of these tends to alter systemic blood pressure, although the body's compensatory mechanisms usually adjust for any significant change.

Blood pressure = Cardiac output × Peripheral resistance

Cardiac output

Cardiac output is determined by stroke volume and heart rate. Factors that affect the heart rate and stroke volume were described earlier they may increase or decrease cardiac output and, in turn, blood pressure. An increase in cardiac output raises both systolic and diastolic pressures. An increase in stroke volume increases systolic pressure more than diastolic pressure.

Peripheral resistance

The heart pumps blood into the closed circulatory system against the pressure of blood already there. This is called peripheral resistance and is determined mainly by the diameter of the small muscular arteries (the resistance vessels). If there is a high degree of systemic vasoconstriction, the resistance to blood flow and the blood pressure increase. Vasodilation, on the other hand, reduces peripheral resistance and blood pressure. Age-related stiffening of the arterial walls increases peripheral resistance and blood pressure (p. 131).

Control of blood pressure

Blood pressure is regulated in two ways:

- short-term control, on a moment-to-moment basis, which involves mainly the baroreceptor reflex, discussed below, and also chemoreceptors and circulating hormones
- longer-term control, which involves regulation of blood volume by the kidneys and the renin–angiotensin–aldosterone system (RAAS, see Fig. 13.15).

Short-term blood pressure regulation

The cardiovascular centre (CVC) is a collection of interconnected neurones responsible for control of cardiac output and blood pressure and located in the medulla and pons within the brain stem. The CVC receives, integrates and coordinates inputs from:

- baroreceptors (pressure receptors)
- chemoreceptors
- higher centres in the brain.

The CVC sends sympathetic and parasympathetic nerves to the heart and blood vessels (Table 5.1). Activity in these nerves slows down or speeds up the heart rate and dilates or constricts blood vessels, essential for control of blood pressure (Fig. 5.24).

Baroreceptors

Within the wall of the aortic and carotid sinuses are baroreceptors, nerve endings sensitive to stretch (pressure) (Figs. 5.24 and 5.25). They are responsible for the

Table 5.1 The effects of the autonomic nervous system on the heart and blood vessels

	Sympathetic stimulation	Parasympathetic stimulation
Heart	↑Rate	↓Rate
	↑Strength of contraction	↓Strength of contraction
Blood vessels	Most constrict, but arteries supplying skeletal muscle and brain dilate	Most blood vessels do not have a parasympathetic blood supply

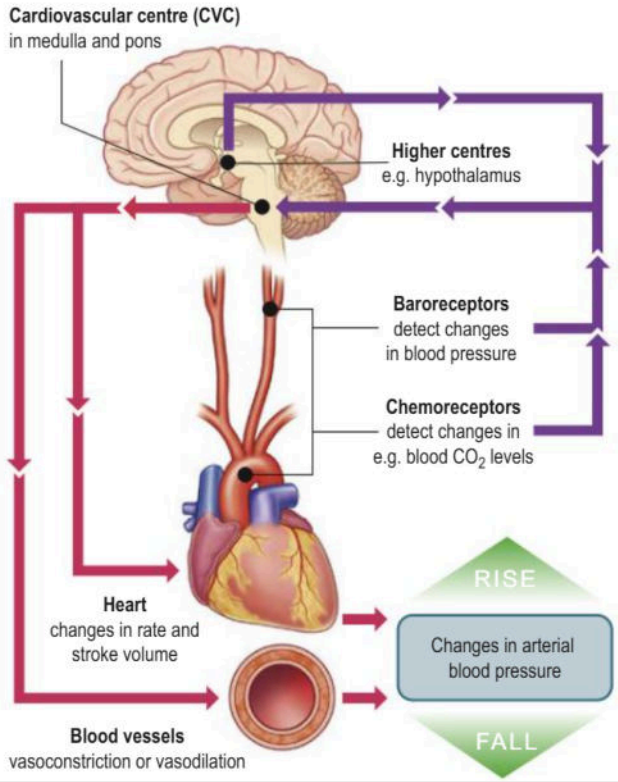

Figure 5.24 Summary of the main mechanisms in blood pressure control.

baroreceptor reflex, the body's main moment-to-moment mechanism for controlling blood pressure. They continuously feed information into the CVC regarding the degree of stretch in the arterial walls, which directly reflects the pressure in the vessel. A rise in blood pressure in these arteries stretches the vessel wall and stimulates the baroreceptors, increasing their input to the CVC. The CVC responds by increasing parasympathetic nerve activity to the heart, slowing the heart down. At the same time, the CVC inhibits sympathetic stimulation to the blood vessels, causing vasodilation. The net result is a fall in systemic blood pressure to reverse the initial rise.

Conversely, if pressure within the aorta and carotid arteries falls, the rate of baroreceptor firing also falls. The CVC responds by increasing sympathetic drive to the heart to speed it up. It also increases sympathetic activity to the smooth muscle in blood vessel walls, causing vasoconstriction. Both these measures counteract the falling blood pressure.

Chemoreceptors

These are nerve endings situated in the carotid and aortic bodies and are mainly involved in control of respiration (see Fig. 10.29). They are sensitive to changes in the levels of carbon dioxide, oxygen and the pH of the blood (Fig. 5.26). Rising blood CO_2, falling blood O_2 levels and/or falling arterial blood pH all indicate failing tissue perfusion. When these changes are detected by the chemoreceptors, they send signals to the CVC, which then increases sympathetic drive to the heart and blood vessels, pushing blood pressure up to improve tissue blood supply. Because respiratory effort is also stimulated, blood oxygen levels rise as well.

Chemoreceptor input to the CVC affects its output only when severe disruption of respiratory function occurs or when arterial blood pressure falls to less than 80 mmHg. Similar chemoreceptors are found on the brain surface in the medulla oblongata, which respond to changes in carbon dioxide/oxygen levels and pH of the surrounding cerebrospinal fluid. Changes from normal activate responses similar to those described earlier for the aortic/carotid receptors.

Higher centres in the brain

The hypothalamus in the brain controls body temperature and influences the CVC, which responds by adjusting the diameter of blood vessels in the skin. This important mechanism regulates heat loss and conservation to maintain core body temperature (p. 405). The hypothalamus also mediates the cardiovascular reaction to emotional stress, and activates the flight-or-fight response, with adrenaline release, increased heart rate, increased blood pressure and generalised vasoconstriction associated with for example pain, anger or fear.

Long-term blood pressure regulation

Slower, longer-lasting changes in blood pressure follow alterations in circulating blood volume. These are regulated by the RAAS (see Fig. 13.15) and the action of antidiuretic hormone (ADH, p. 245). Both of these mechanisms increase water reabsorption in the kidney, increasing the body's fluid load and circulating blood volume, which increases blood pressure. In opposition to this, atrial natriuretic peptide (ANP, see Table 9.4), a hormone released by the heart itself, causes sodium and water loss from the kidney and reduces blood pressure.

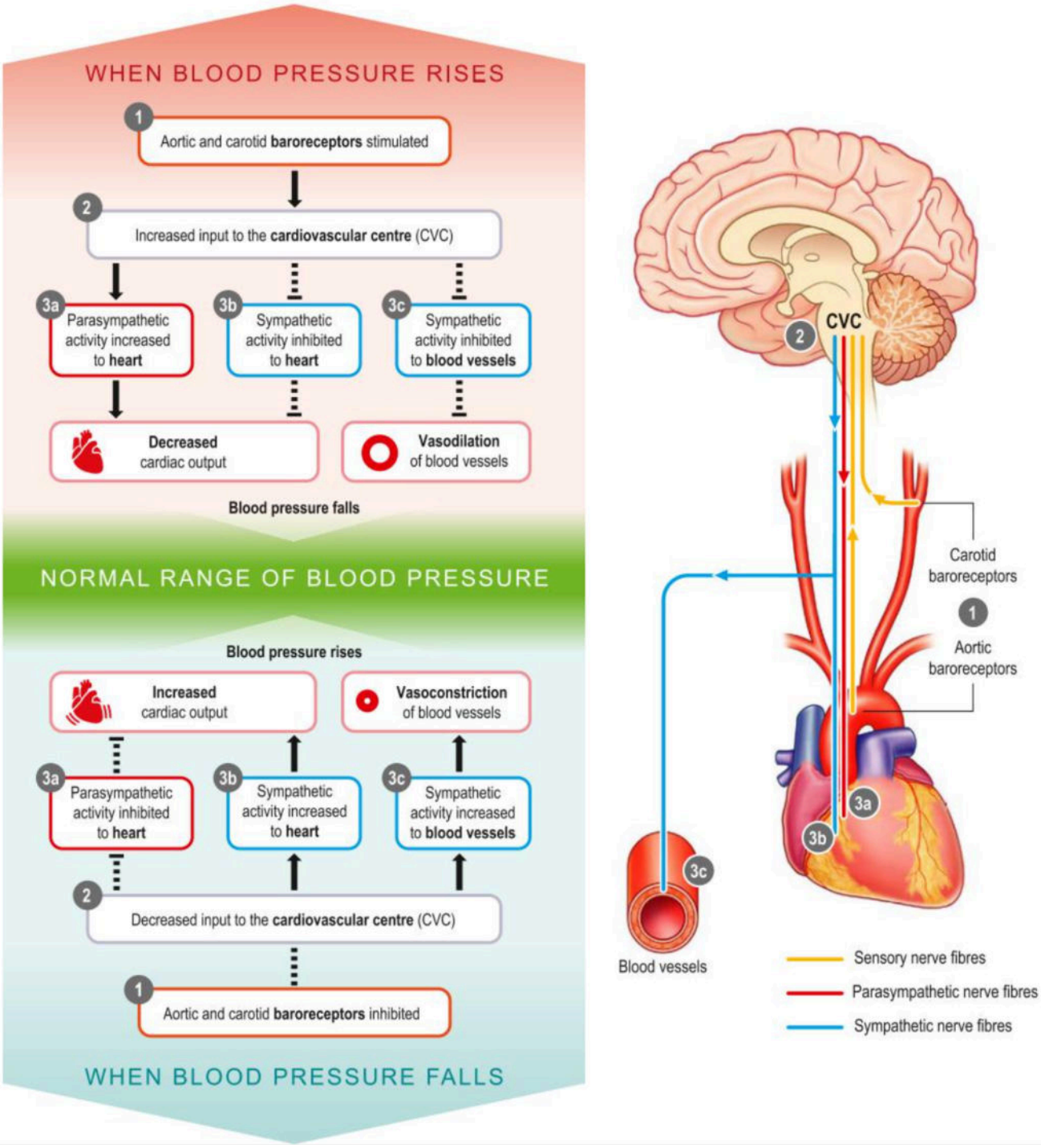

Figure 5.25 The baroreceptor reflex.

Pressure in the pulmonary circulation

Pulmonary blood pressure is much lower than pressure in the systemic circulation. This is because the pulmonary circulation contains only about 10% of the total circulating blood volume, and there are so many capillaries in the lungs that pressure is kept low. If pulmonary capillary pressure exceeds 25 mmHg, fluid is forced out of the bloodstream and into the air sacs (pulmonary oedema, p. 143), with very serious consequences. Autoregulation in the pulmonary circulation ensures that blood flow through the vast network of capillaries is directed through well-oxygenated air sacs and diverted away from less well-ventilated alveoli (p. 288).

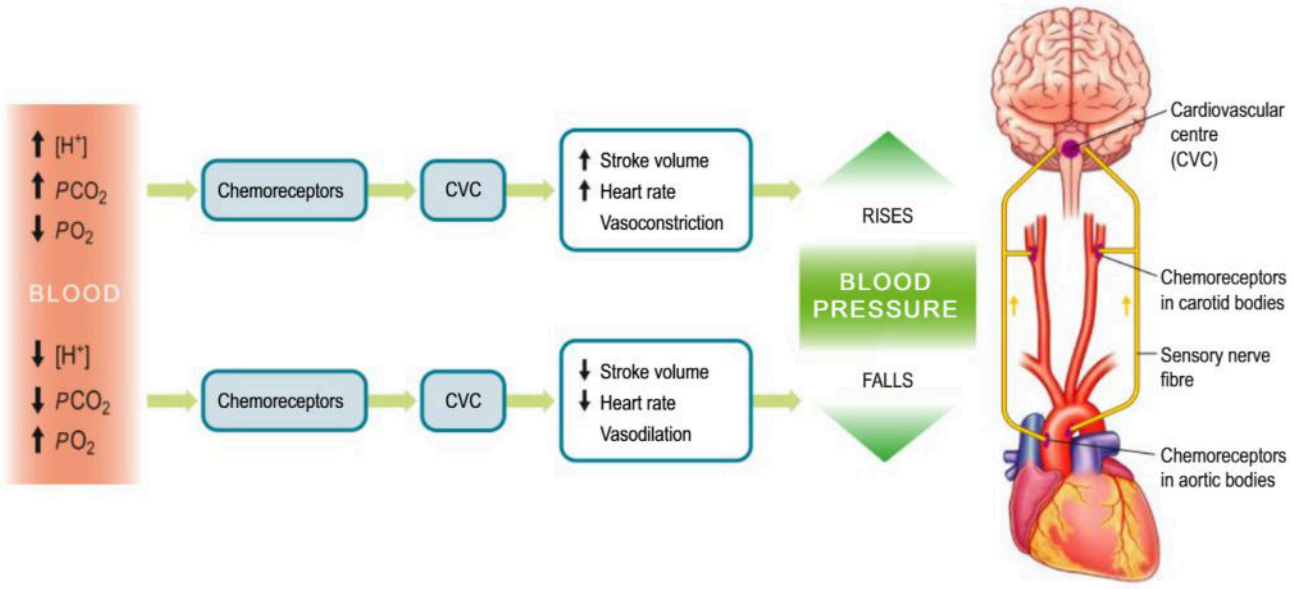

Figure 5.26 The role of chemoreceptors in the control of arterial blood pressure.

SPOT CHECK

5. What do systolic and diastolic blood pressures represent?
6. How does the baroreceptor reflex respond to a rise in blood pressure?

Pulse

Learning outcomes

After studying this section, you should be able to:

- define the term 'pulse'
- list the main sites on the body surface where the pulse is detected
- describe the main factors affecting the pulse.

The pulse can be felt with gentle finger pressure at any point where a superficial artery can be pressed firmly but gently against a bone (Fig. 5.27). Each contraction of the left ventricle forces about 60–80 mL of blood into the aorta, generating a pressure wave that is transmitted throughout the arterial system, causing a brief distension of the arteries that passes quickly as the arterial wall recoils. The number of pulse beats per minute normally represents the heart rate and varies considerably in different people and in the same person at

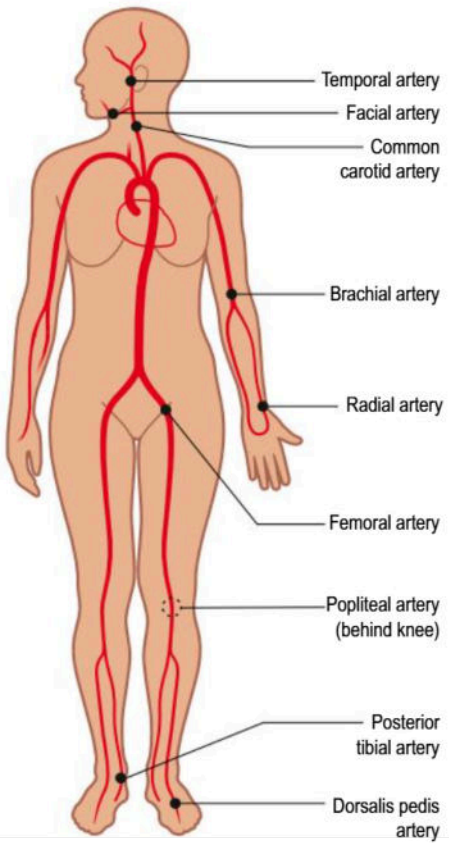

Figure 5.27 The main pulse points.

different times. An average of 60–80 bpm is common at rest. Information that may be obtained from the pulse includes:

- The heart rate.
- The regularity of the heartbeat – the intervals between beats should be equal.
- The volume or strength of the beat – it should be possible to compress the artery with moderate pressure, stopping the flow of blood; the compressibility of the blood vessel gives some indication of the blood pressure and the state of the blood vessel wall.
- The tension of the artery wall, which should feel soft and pliant under the fingers.

Factors affecting the pulse

In health, the pulse rate and the heart rate are identical. Factors influencing heart rate are summarised on page 100. In certain circumstances, the counted pulse may be less than the heart rate. This may occur, for example, in the following circumstances:

- If the arteries supplying the peripheral tissues are narrowed or blocked and blood flow is reduced or obstructed. This can happen in peripheral vascular disease of the leg, reducing blood flow to the foot and making the dorsalis pedis pulse undetectable. Provided enough blood is reaching an extremity to nourish it, it will remain pink in colour and warm to touch, even if the pulse cannot be felt.
- In some disorders of cardiac contraction, e.g. atrial fibrillation (p. 140), and the heart is unable to generate enough force with each contraction to pump blood to the peripheral arteries.

SPOT CHECK

7. Explain why the carotid pulse rate may be different from the dorsalis pedis pulse rate when counted simultaneously in the same person.

Circulation of the blood

Learning outcomes

After studying this section, you should be able to:

- describe the circulation of the blood through the lungs, naming the main vessels involved
- list the arteries supplying blood to all major body structures
- outline the venous drainage involved in returning blood to the heart from the body
- explain the arrangement of blood vessels relating to the portal circulation.

It is convenient to describe circulation of blood round the body in two parts (Fig. 5.1):

- pulmonary circulation
- systemic or general circulation (Figs 5.28 and 5.29).

Pulmonary circulation

This is the route taken by blood from the right ventricle to the lungs, where exchange of gases occurs, and its return to the heart at the left atrium.

The main pulmonary artery or trunk, carrying deoxygenated blood, leaves the upper part of the right ventricle. It passes upwards and divides into left and right pulmonary arteries at the level of the 5th thoracic vertebra. The pulmonary arteries enter their respective lungs at the hilum, and divide into smaller branches that in turn eventually give rise to the dense network of capillaries surrounding the alveoli, the tiny air sacs of the lungs.

Venous capillaries containing oxygenated blood merge into progressively larger venules, and eventually form two pulmonary veins. These two pulmonary veins leave each lung, returning oxygenated blood to the left atrium of the heart. During atrial systole, this blood is pumped into the left ventricle, and during ventricular systole, it is forced into the aorta, the first artery of the general circulation.

Systemic or general circulation

The blood pumped out from the left ventricle is carried by the branches of the aorta around the body and returns to the right atrium of the heart by the superior and inferior venae cavae. Figure 5.28 shows the general positions of the aorta and the main arteries of the limbs. Figure 5.29 provides an overview of the venae cavae and the veins of the limbs.

The circulation of blood to the different parts of the body is described below in the order in which their arteries branch off the aorta.

Major blood vessels

The aorta is the largest artery of the body. The two largest veins, the superior and inferior venae cavae, return blood from all body parts to the heart.

Aorta

The aorta opens from the upper part of the left ventricle and, after passing upwards for a short way, it arches backwards and to the left. It then descends behind the heart through the thoracic cavity, passes behind the diaphragm, and travels downwards in the abdominal cavity to eventually divide into the right and left common iliac arteries (Fig. 5.30).

Throughout its length the aorta gives off numerous branches. Some of the branches are paired, i.e. there is a right and left branch with the same name (e.g. the right and left renal arteries supplying the kidneys), and some are single or unpaired (e.g. the coeliac artery).

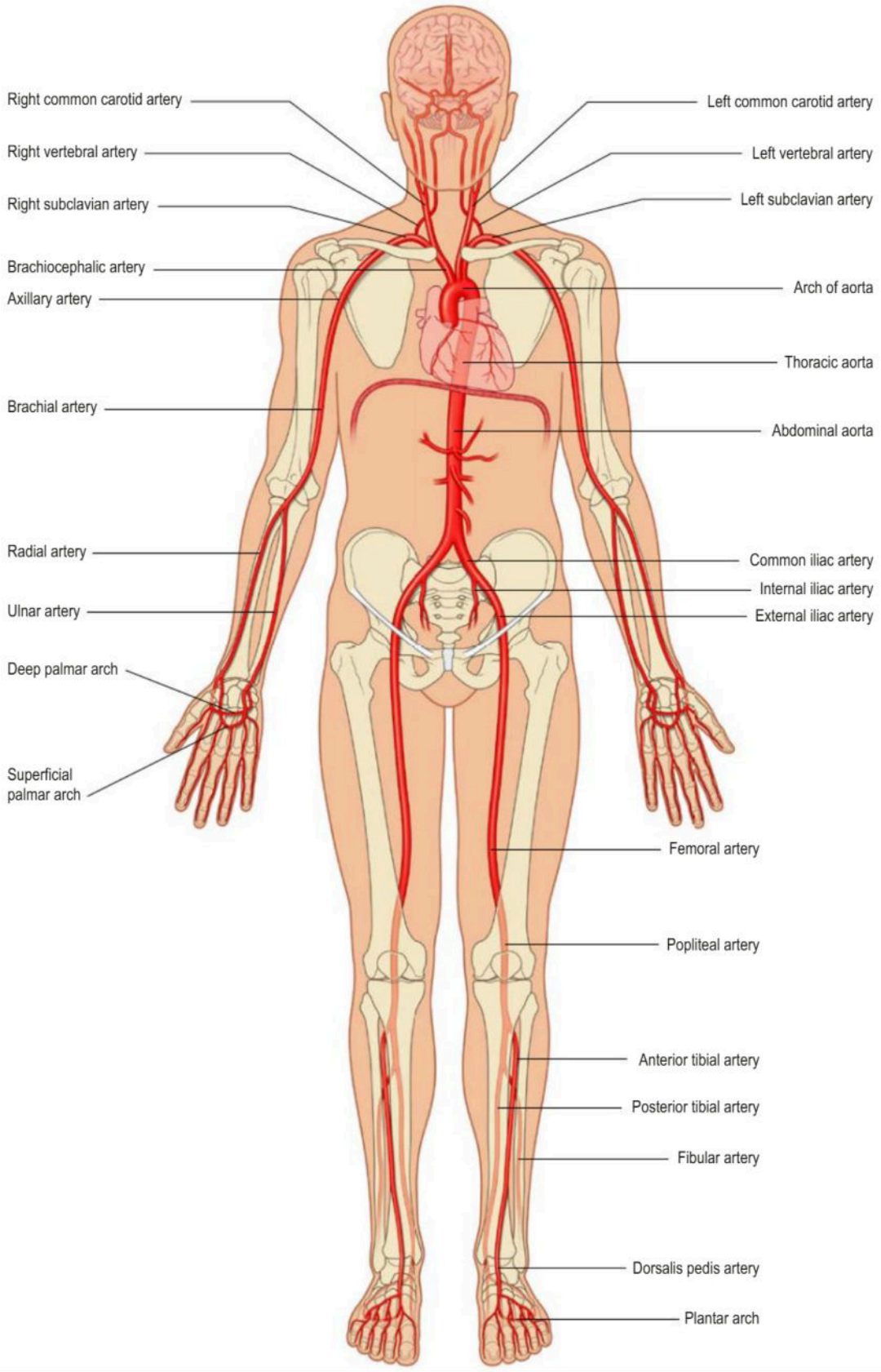

Figure 5.28 The aorta and the main arteries of the limbs.

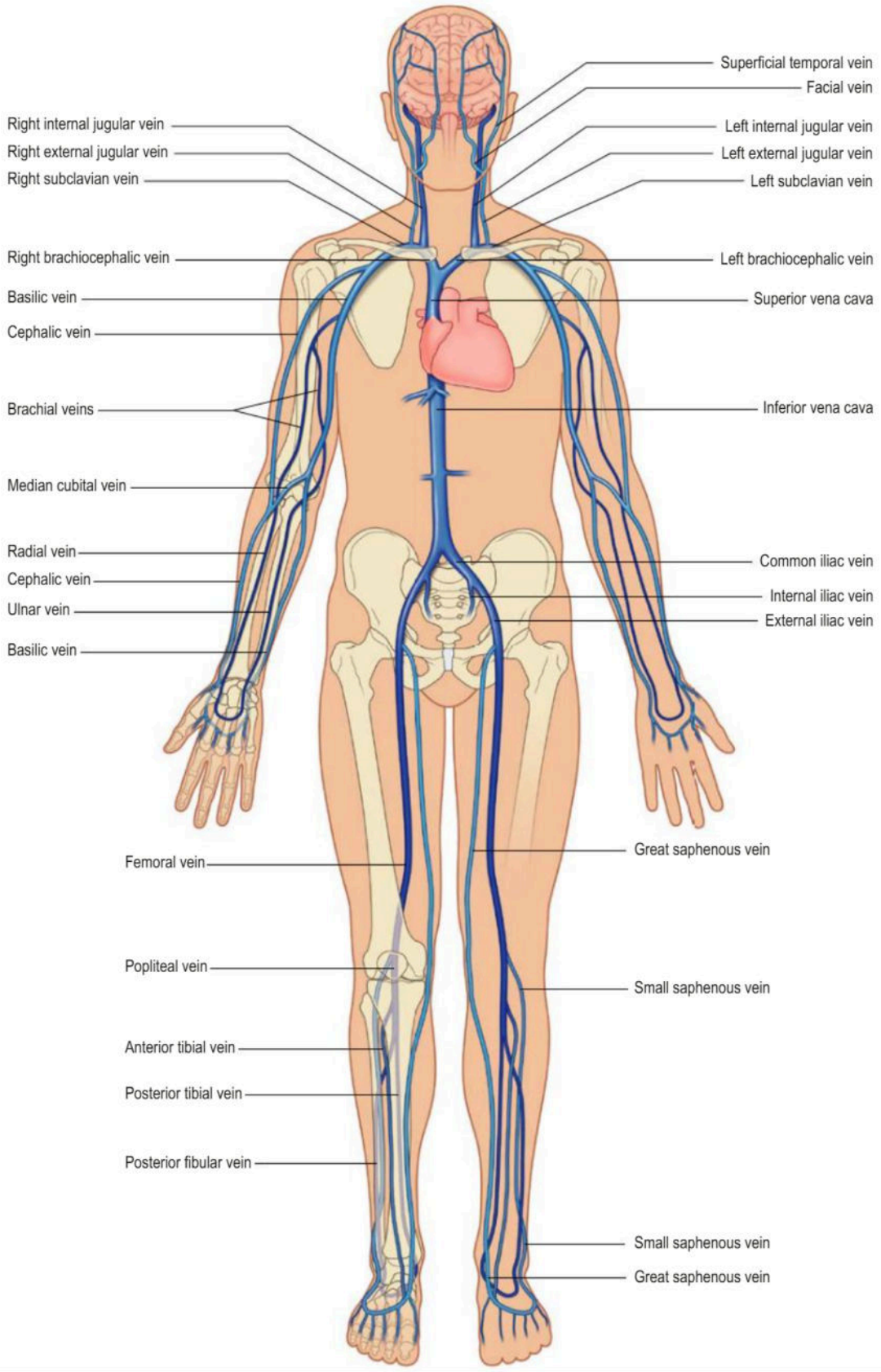

Figure 5.29 The venae cavae and the main veins of the limbs.

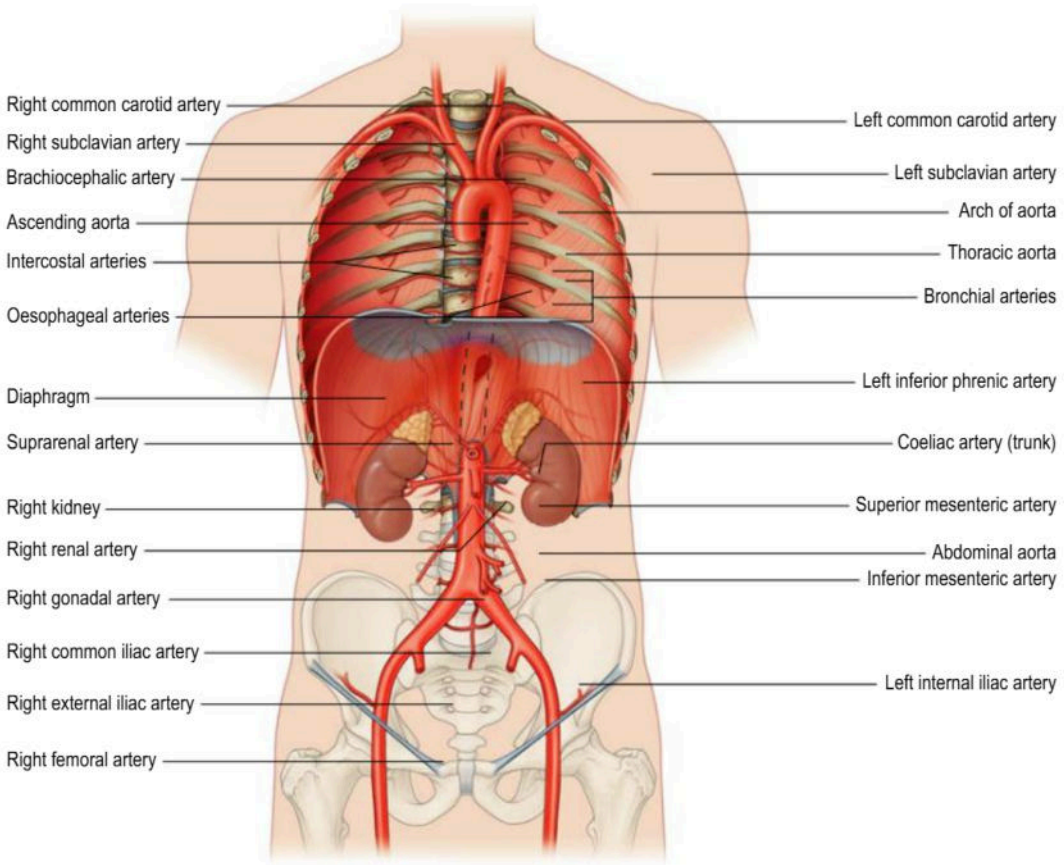

Figure 5.30 The aorta and its main branches.

The aorta is described here according to its location:

- thoracic aorta
- abdominal aorta.

Thoracic aorta

The thoracic part of the aorta (Fig. 5.30) lies above the diaphragm and is described in three parts:

- ascending aorta
- arch of the aorta
- descending aorta in the thorax.

Ascending aorta. This is the short section of the aorta that rises from the heart. It is about 5 cm long and lies well protected behind the sternum. The right and left coronary arteries are its only branches. They open just above the level of the aortic valve (see Fig. 5.16) and supply the myocardium.

Arch of the aorta. The aorta curves sharply downwards behind the left side of the heart, in front of the trachea, forming the aortic arch. The arch is clearly visible on plain chest X-rays, and three arteries arise from its upper curve: the brachiocephalic artery, the left common carotid artery and the left subclavian artery (see Fig. 5.33).

The brachiocephalic artery is 4–5 cm long and passes obliquely upwards, backwards and to the right. At the level of the sternoclavicular joint it divides into the right common carotid artery and the right subclavian artery.

Descending aorta in the thorax. This is the long segment of the aorta that begins at the level of the 4th thoracic vertebra and descends to the diaphragm. It extends downwards immediately in front of the bodies of the spinal column to the level of the 12th thoracic vertebra, where it passes behind the diaphragm to become the abdominal aorta.

The descending aorta in the thorax gives off many paired branches that supply the walls and organs of the thoracic cavity (p. 116).

Abdominal aorta

The abdominal aorta (Fig. 5.30) is a continuation of the thoracic aorta. The name changes when the aorta passes behind the diaphragm and enters the abdominal cavity. It descends in front of the vertebral column to the level of the 4th lumbar vertebra, where it divides into the right and left common iliac arteries.

Many branches arise from the abdominal aorta, some paired and some unpaired, supplying the abdominal structures and organs (p. 116).

Venae cavae

The superior and inferior venae cavae (Fig. 5.31) are the largest veins in the body and empty blood directly into the right atrium

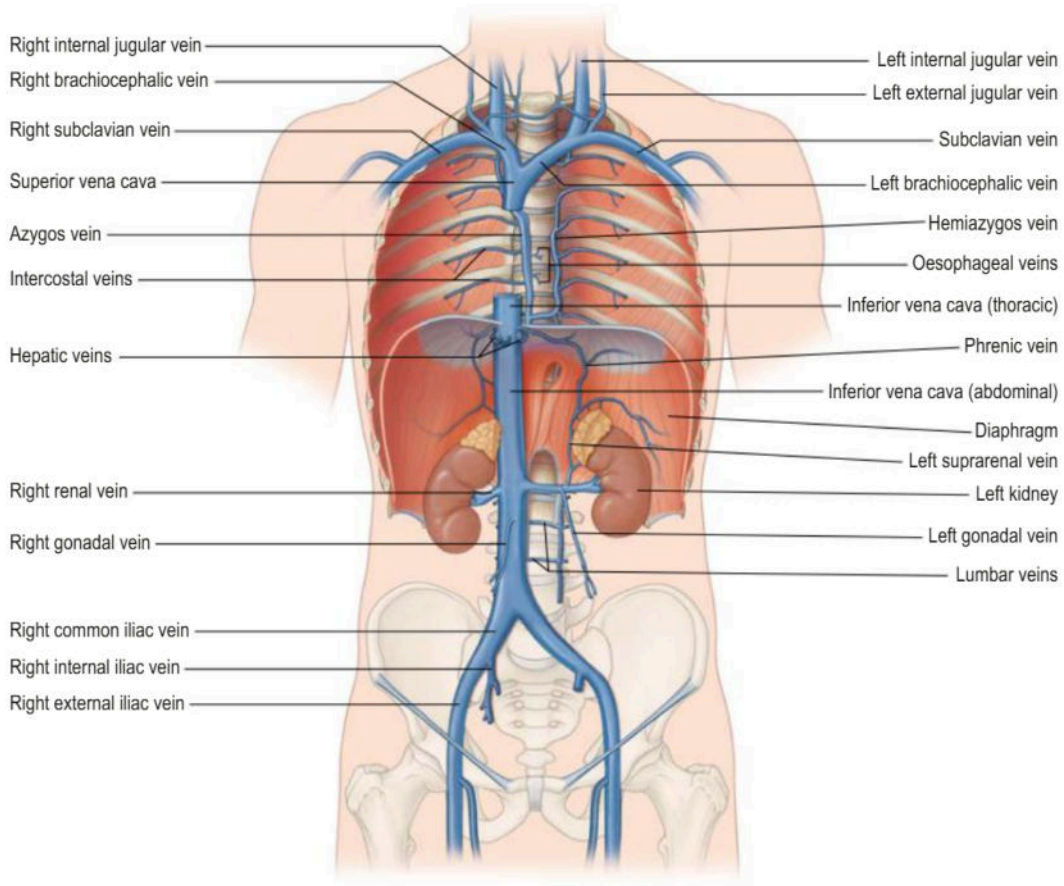

Figure 5.31 The venae cavae and the main veins that form them.

of the heart (Fig. 5.15). The superior vena cava drains all body structures lying above the diaphragm and the inferior vena cava drains blood from all structures below the diaphragm.

Superior vena cava

This is about 7 cm long and is formed by the union of the left and right brachiocephalic veins.

Inferior vena cava

This is formed at the level of the 5th lumbar vertebra by the union of the right and left common iliac veins, and ascends through the abdomen, lying close against the vertebral column and parallel to and just to the right of the descending abdominal aorta. It passes through the central tendon of the diaphragm into the thorax at the level of the 8th thoracic vertebra. As the inferior vena cava ascends through the abdomen, veins draining pelvic and abdominal organs empty into it.

Circulation in the head and neck

Arterial supply

The paired arteries supplying the head and neck are the common carotid arteries and the vertebral arteries (Figs 5.32 and 5.33).

Carotid arteries

The right common carotid artery is a branch of the brachiocephalic artery. The left common carotid artery arises directly from the arch of the aorta. They pass upwards on either side of the neck and have the same distribution on each side. The common carotid arteries are embedded in a fascia, called the carotid sheath. At the level of the upper border of the thyroid cartilage each divides into an internal carotid artery and an external carotid artery.

The carotid sinuses are slight dilations at the point where the common carotid arteries divide into their internal and external branches. The walls of the sinuses are thin and contain numerous nerve endings of the glossopharyngeal nerves. These nerve endings, or baroreceptors, are stimulated by changes in blood pressure in the carotid sinuses. The resultant nerve impulses initiate reflex adjustments of blood pressure through the cardiovascular centre in the medulla oblongata (see Fig. 5.24).

The carotid bodies are two small groups of chemoreceptors, one lying in close association with each common carotid artery where it divides into its internal and external branches. They are supplied by the glossopharyngeal nerves and are stimulated by changes in the carbon dioxide and oxygen content of blood. When activated, they initiate reflex adjustments of respiration through the respiratory centre in the medulla oblongata (see Fig. 10.29).

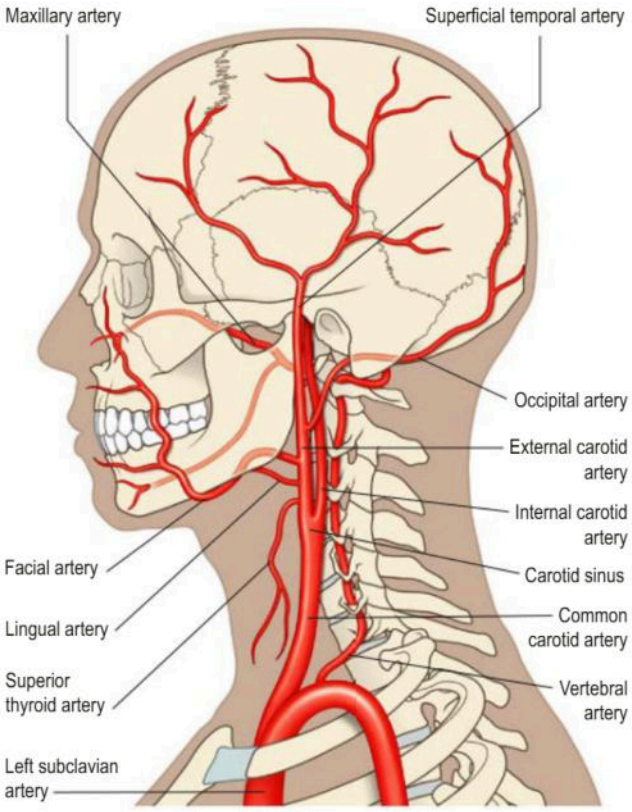

Figure 5.32 Main arteries of the left side of the head and neck.

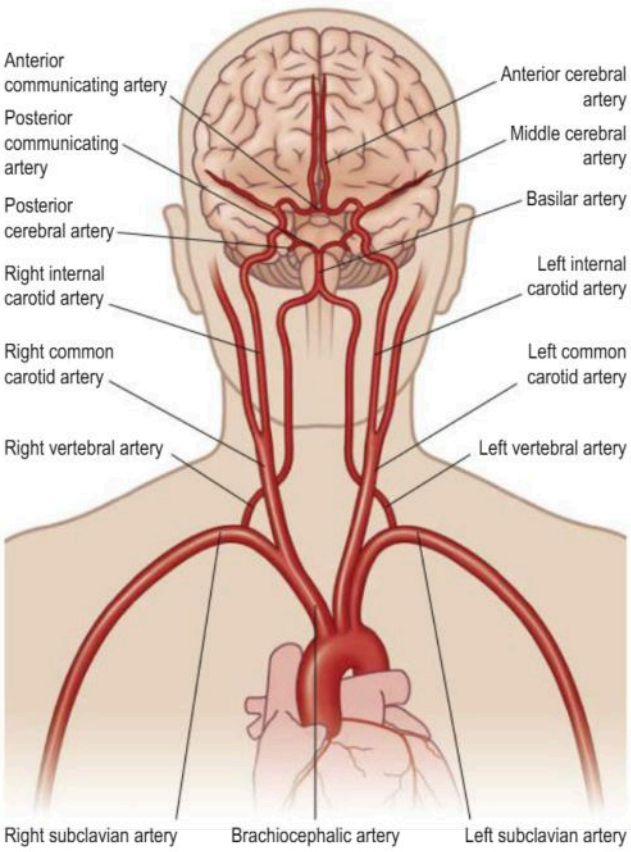

Figure 5.33 Arteries forming the circulus arteriosus (circle of Willis).

External carotid artery (Fig. 5.32). This artery supplies the superficial tissues of the head and neck, via a number of branches:

- The superior thyroid artery supplies the thyroid gland and adjacent muscles.
- The lingual artery supplies the tongue, the membrane that lines the mouth, the structures in the floor of the mouth, the tonsil and the epiglottis.
- The facial artery passes outwards over the mandible just in front of the angle of the jaw and supplies the muscles of facial expression (see Fig. 16.64) and structures in the mouth. A pulse can be felt where the artery crosses the jawbone.
- The occipital artery supplies the posterior part of the scalp.
- The temporal artery passes upwards over the zygomatic process in front of the ear and supplies the frontal, temporal and parietal parts of the scalp. The temporal pulse can be felt in front of the upper part of the ear.
- The maxillary artery supplies the muscles of mastication; a branch of this artery, the middle meningeal artery, runs deeply to supply structures in the interior of the skull.

Internal carotid artery. The internal carotid artery is a major contributor to the circulus arteriosus (circle of Willis, Figs 5.33 and 5.34), which supplies most of the brain. It also has branches that supply the eyes, forehead and nose. It ascends to the base of the skull and passes through the carotid foramen in the temporal bone.

Circulus arteriosus (circle of Willis). Most of the brain is supplied with arterial blood by an arrangement of arteries called the circulus arteriosus or the circle of Willis. Four large arteries, the right and left internal carotid arteries and the two vertebral arteries (Fig. 5.33), unite to form this complete circular channel lying in the subarachnoid space on the underside of the brain (Fig. 5.34). The vertebral arteries arise from the subclavian arteries, pass upwards through the foramina in the transverse processes of the cervical vertebrae, enter the skull through the foramen magnum, and then join to form the basilar artery. The arrangement in the circulus arteriosus is such that the brain receives an adequate blood supply even if a contributing artery is damaged and during extreme movements of the head and neck.

Anteriorly, the two anterior cerebral arteries arise from the internal carotid arteries and are joined by the anterior communicating artery.

Posteriorly, the two vertebral arteries join to form the basilar artery. After travelling for a short distance the basilar artery divides to form two posterior cerebral arteries, each of which is joined to the corresponding internal carotid artery

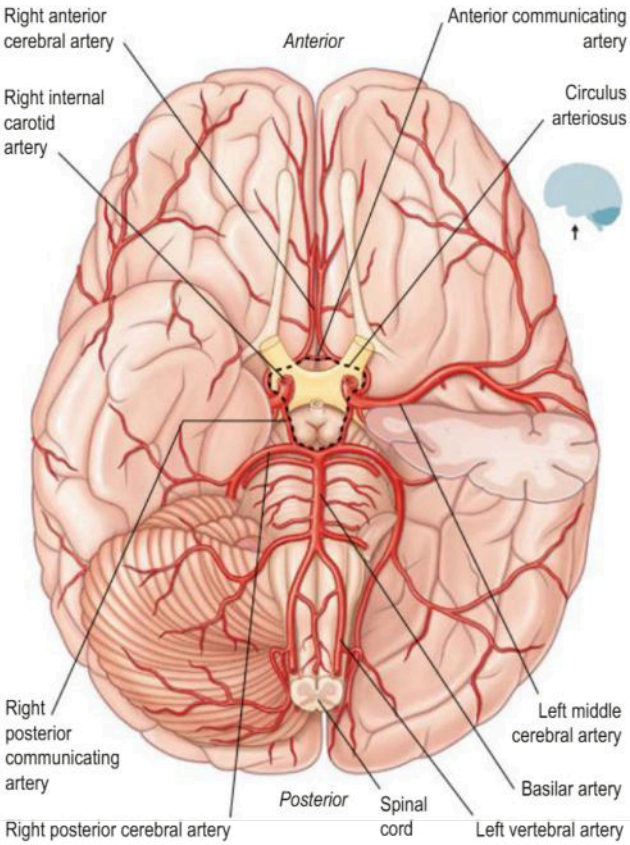

Figure 5.34 The circulus arteriosus (circle of Willis) viewed from below.

by a posterior communicating artery, completing the circle. The circulus arteriosus is therefore formed by:

- two anterior cerebral arteries
- two internal carotid arteries
- one anterior communicating artery
- two posterior communicating arteries
- two posterior cerebral arteries
- one basilar artery.

From this circle, the anterior cerebral arteries pass forwards to supply the anterior part of the brain, the middle cerebral arteries pass laterally to supply the sides of the brain, and the posterior cerebral arteries supply the posterior part of the brain.

Branches of the basilar artery supply parts of the brain stem.

Venous return

Venous blood from the head and neck is returned by deep and superficial veins.

Superficial veins with the same names as the branches of the external carotid artery return venous blood from the superficial structures of the face and scalp and unite to form the external jugular vein (Fig. 5.35).

The external jugular vein begins in the neck at the level of the angle of the jaw. It passes downwards in front of the sternocleidomastoid muscle, travels behind the clavicle and enters the subclavian vein.

Venous blood from the deep areas of the brain is collected into channels called the dural venous sinuses (Fig. 5.36), which are formed by layers of dura mater lined with endothelium. The dura mater is the outer protective covering of the brain (see Fig. 7.13). The main venous sinuses are described below.

- The superior sagittal sinus (see Fig. 7.13) drains venous blood from the superior part of the brain. It begins in the frontal region and passes directly backwards in the midline of the skull to the occipital region, where it turns to the right side and continues as the right transverse sinus.
- The inferior sagittal sinus lies deep within the brain and passes backwards to form the straight sinus.
- The straight sinus runs backwards and downwards to become the left transverse sinus.
- The transverse sinuses begin in the occipital region. They run forwards and medially in a curved groove of the skull, to become continuous with the sigmoid sinuses.
- The sigmoid sinuses are a continuation of the transverse sinuses. Each curves downwards and medially, and lies in a groove in the mastoid process of the temporal bone. Anteriorly, only a thin plate of bone separates the sinus from the air cells in the mastoid process of the temporal bone. Inferiorly, it continues as the internal jugular vein.

The internal jugular veins begin at the jugular foramina in the middle cranial fossa (see Fig. 16.15) and each is the continuation of a sigmoid sinus. They run downwards in the neck behind the sternocleidomastoid muscles. Behind the clavicle they unite with the subclavian veins, carrying blood from the upper limbs, to form the brachiocephalic veins.

The brachiocephalic veins are situated one on each side in the root of the neck. Each is formed by the union of the internal jugular and the subclavian veins. The left brachiocephalic vein is longer than the right and passes obliquely behind the manubrium of the sternum, where it joins the right brachiocephalic vein to form the superior vena cava (Fig. 5.31).

The superior vena cava, which drains all the venous blood from the head, neck and upper limbs, is about 7 cm long. It passes downwards along the right border of the sternum and opens into the right atrium of the heart.

Circulation in the upper limb

Arterial supply

The subclavian arteries

The right subclavian artery arises from the brachiocephalic artery, and the left branches directly from the arch of the aorta. They arch behind the clavicles and over the first ribs before entering the axillae, where they continue as the axillary arteries (Fig. 5.37). Before entering the axilla, each subclavian artery gives off two branches: the vertebral artery,

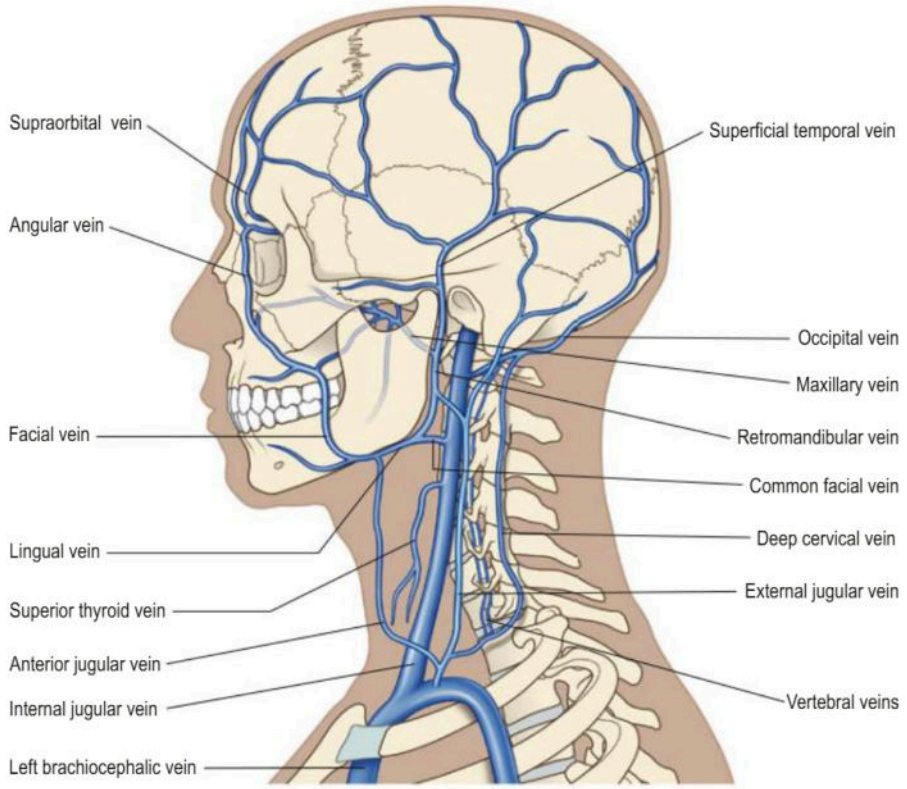

Figure 5.35 Veins of the left side of the head and neck.

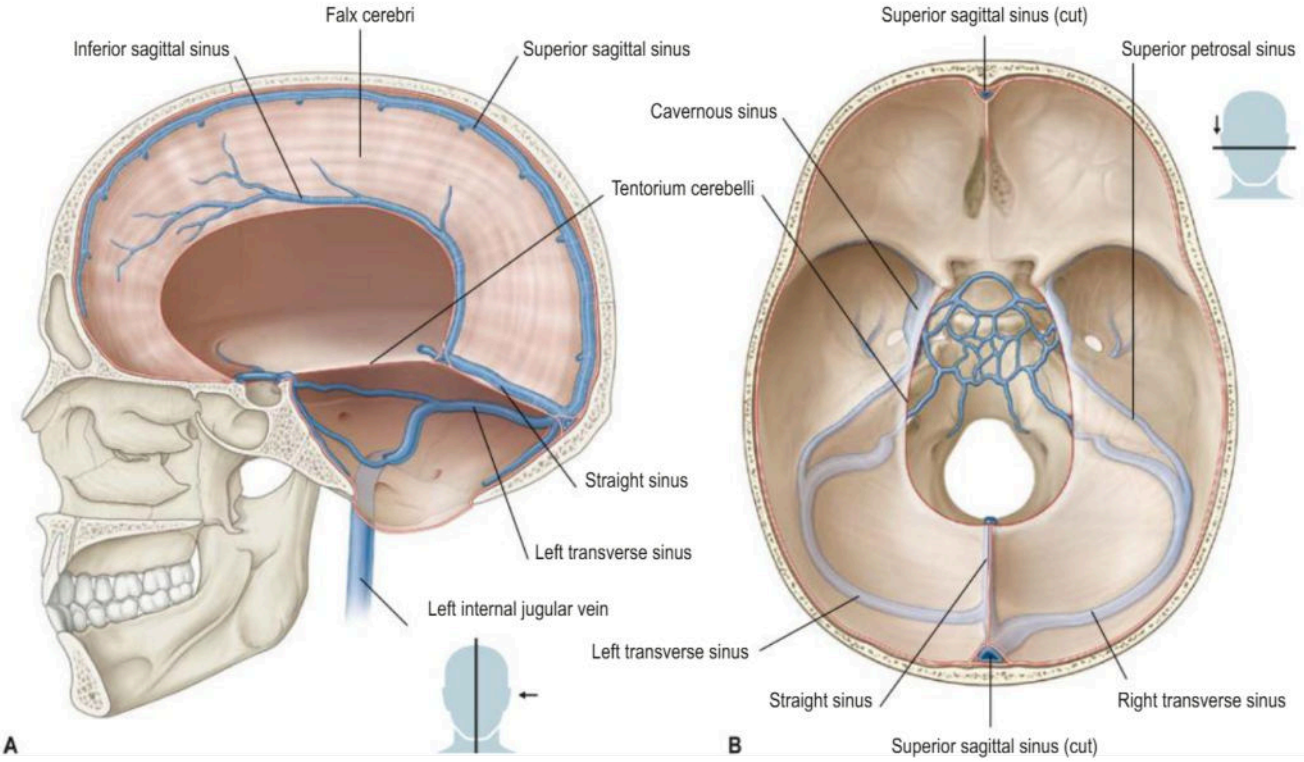

Figure 5.36 Venous sinuses of the brain. (A) Viewed from the left. (B) Viewed from above.

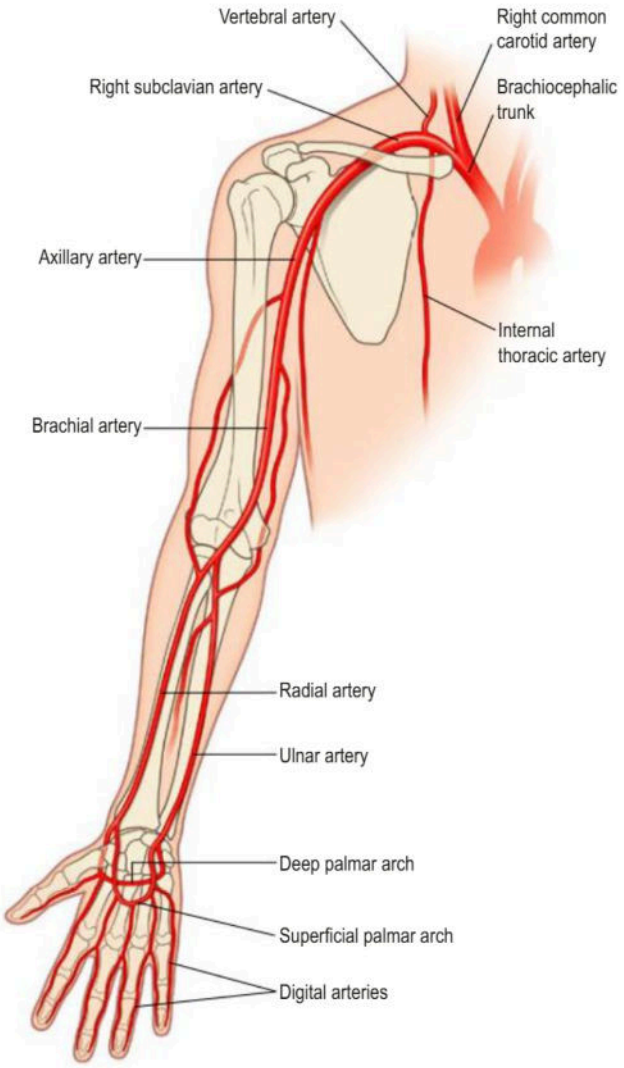

Figure 5.37 The main arteries of the right arm.

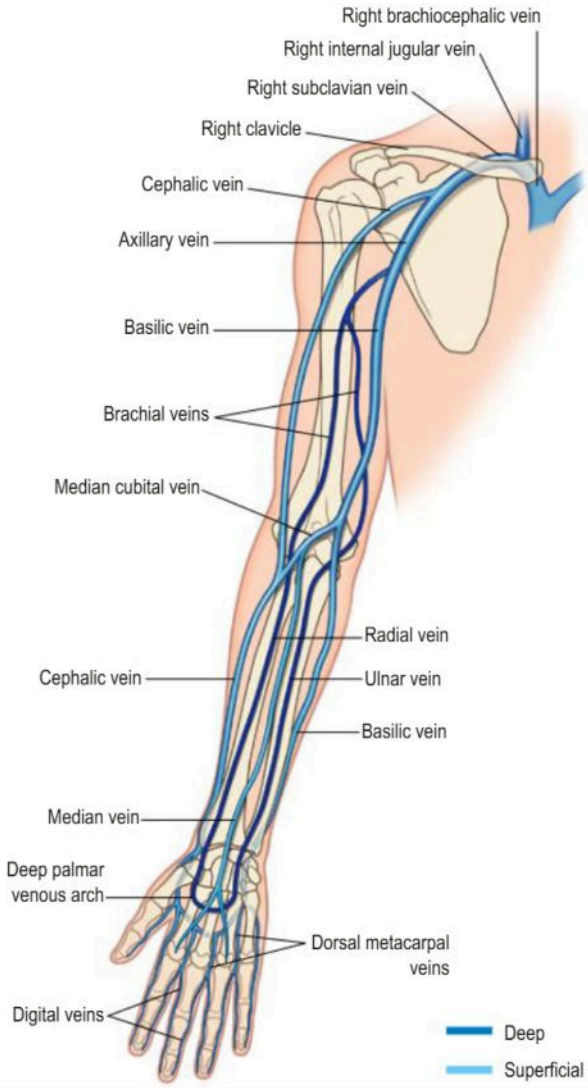

Figure 5.38 The main veins of the right arm.

which passes upwards to supply the brain (Fig. 5.33), and the internal thoracic artery, which supplies the breast and some structures in the thoracic cavity.

The first part of the axillary artery lies deeply, then it runs more superficially and becomes the brachial artery. The brachial artery runs down the medial aspect of the upper arm, passes to the front of the elbow and extends to about 1 cm below the joint, where it divides into the radial and ulnar arteries.

The radial artery passes down the lateral (radial) side of the forearm to the wrist. Just above the wrist it lies superficially and can be felt over the radius, as the radial pulse. It then passes between the first and second metacarpal bones and enters the palm of the hand. The ulnar artery runs downwards on the medial (ulnar) aspect of the forearm to cross the wrist and pass into the hand.

There are anastomoses between the radial and ulnar arteries, called the deep and superficial palmar arches, from which palmar metacarpal and palmar digital arteries arise to supply the structures in the hand and fingers.

Venous return

The upper limb is drained by both deep and superficial veins (Fig. 5.38). The deep veins follow the course of the arteries and have the same names:

- palmar metacarpal veins
- deep palmar venous arch
- ulnar and radial veins
- brachial vein
- axillary vein
- subclavian vein.

The superficial veins begin in the hand and consist of the following:

- cephalic vein
- basilic vein

- median vein
- median cubital vein.

The cephalic vein begins at the back of the hand, where it collects blood from a complex of superficial veins, many of which are visible through the skin. It then winds round the radial side to the anterior aspect of the forearm. In front of the elbow it gives off a large branch, the median cubital vein, which slants upwards and medially to join the basilic vein. After crossing the elbow joint the cephalic vein passes up the lateral aspect of the arm and in front of the shoulder joint to end in the axillary vein. Throughout its length it drains blood from the superficial tissues on the lateral aspects of the hand, forearm and arm.

The basilic vein begins at the back of the hand on the ulnar aspect. It ascends on the medial side of the forearm and upper arm, then joins the axillary vein. It collects blood from the medial aspect of the hand, forearm and arm. Many small anastomotic veins link the cephalic and basilic veins.

The median vein is small and not always present. It begins at the palmar surface of the hand, ascends on the front of the forearm and ends in the basilic vein or the median cubital vein.

The brachiocephalic vein is formed from the union of the subclavian and internal jugular veins. There is one on each side.

The superior vena cava is formed when the two brachiocephalic veins unite. It drains all the venous blood from the head, neck and upper limbs and opens into the right atrium. It is about 7 cm long and passes downwards along the right border of the sternum.

Circulation in the thorax

Arterial supply

Branches of the thoracic aorta (Fig. 5.30) supply structures in the chest, including:

- bronchial arteries, which supply lung tissues not directly involved in gas exchange
- oesophageal arteries, which supply the oesophagus
- intercostal arteries, which run along the inferior border of each rib and supply the intercostal muscles, some muscles of the thorax, the ribs, skin and its underlying connective tissues.

Venous return

Most of the venous blood from the organs in the thoracic cavity is drained into the azygos vein and the hemiazygos vein (Fig. 5.31). Some of the main veins that join them are the bronchial, oesophageal and intercostal veins. The azygos vein joins the superior vena cava and the hemiazygos vein joins the left brachiocephalic vein. At the distal end of the oesophagus, some oesophageal veins join the azygos vein, and others the left gastric vein. A venous plexus is formed by anastomoses between the veins joining the azygos vein and those joining the left gastric veins, linking the general and portal circulations (see Fig. 12.49). There are many anastomotic connections between veins draining the thoracic and abdominal cavities, so that if one channel becomes blocked, the blood has an alternative route back to the heart.

Circulation in the abdomen

Arterial supply

Branches of the abdominal aorta (Fig. 5.30) supply structures in the abdomen.

Paired branches

These include the:

- Phrenic arteries, supplying the diaphragm.
- Renal arteries, supplying the kidneys.
- Suprarenal arteries, supplying the adrenal glands.
- Gonadal arteries, supplying the ovaries (female) and testes (male). These arteries are much longer than the other paired branches because the gonads begin their development high in the abdominal cavity. As fetal development proceeds, they descend into the pelvis and their supplying arteries become correspondingly longer to maintain their blood supply.

Unpaired branches

These include the:

- Coeliac artery (sometimes called the coeliac trunk, Fig. 5.39), a short, thick artery about 1.25 cm long. It arises immediately below the diaphragm and divides into three branches:
  - the left gastric artery supplying the stomach
  - the splenic artery supplying the spleen and pancreas
  - the hepatic artery supplying the liver, gall bladder and parts of the stomach, duodenum and pancreas.
- Superior mesenteric artery (Fig. 5.40), which branches from the aorta between the coeliac artery and the renal arteries. It supplies the entire small intestine and about half the proximal large intestine.
- Inferior mesenteric artery (Fig. 5.40), which arises from the aorta about 4 cm above its division into the common iliac arteries. It supplies the distal half of the large intestine and part of the rectum.

Venous return

Blood drains from some abdominal organs directly into the inferior vena cava via veins named as their corresponding arteries (see Fig. 5.31). Hepatic veins drain the liver, renal veins drain the kidneys, suprarenal veins drain the adrenal glands, lumbar veins drain lower abdominal structures and gonadal veins drain the ovaries and testes. However, most blood from the digestive organs in the abdomen is drained into the hepatic portal vein and passes through the liver before being emptied into the inferior vena cava (the portal circulation).

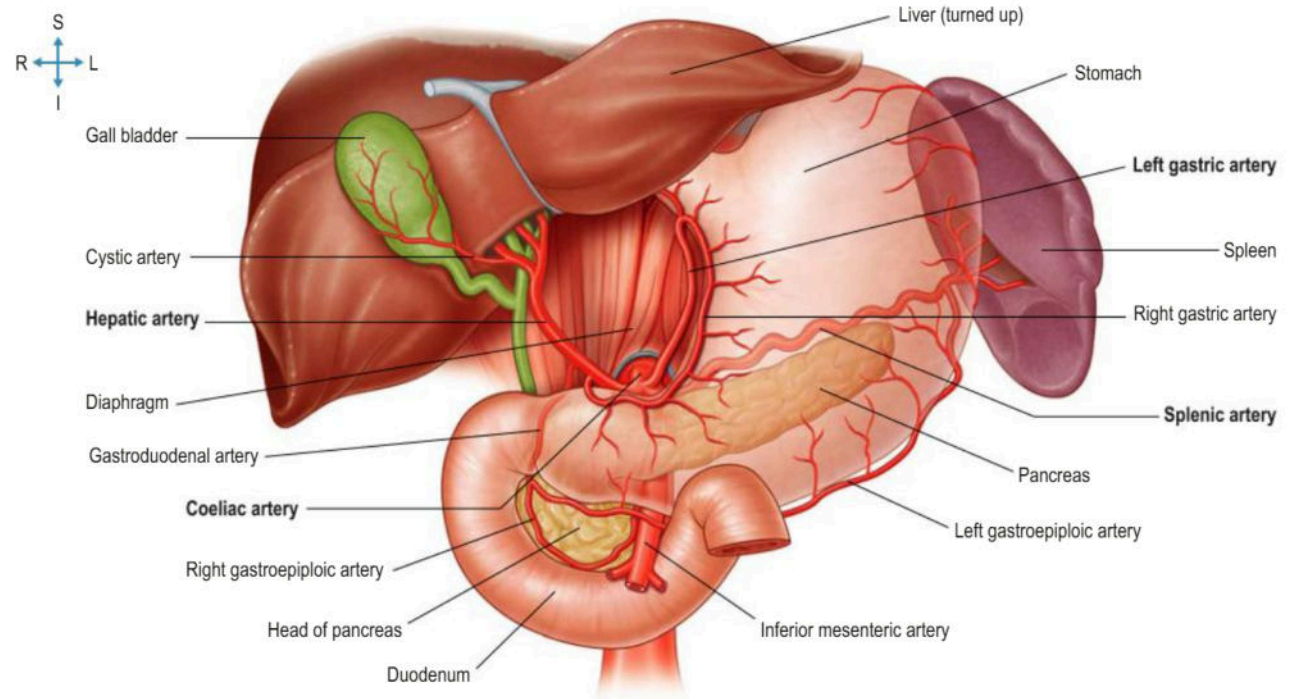

Figure 5.39 The coeliac artery and its branches.

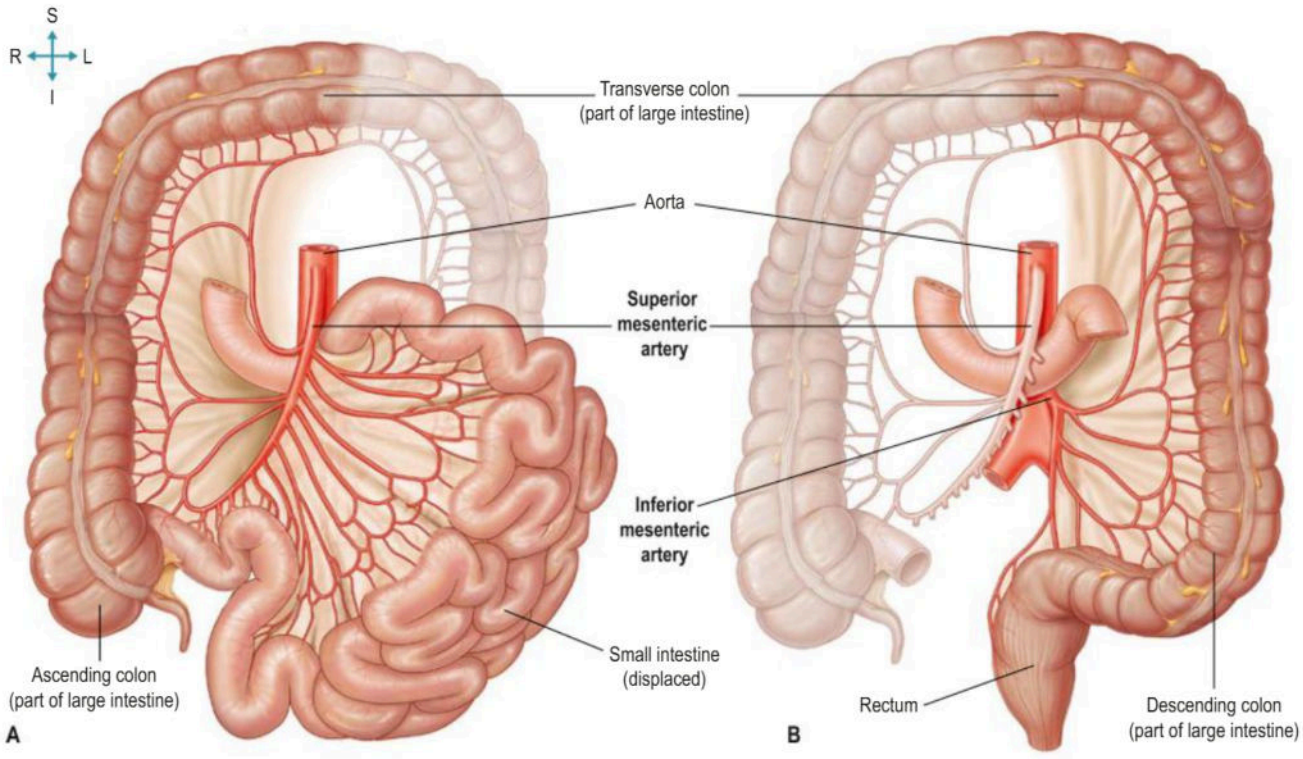

Figure 5.40 The superior and inferior mesenteric arteries and their branches. (A) The arteries of the small intestine. (B) With the small intestine removed.

Portal circulation

As a general rule, venous blood passes from the tissues to the heart by the most direct route through only one capillary bed. In the portal circulation, venous blood from the capillary beds of the stomach, small intestine, most of the large intestine, the spleen and the pancreas travels first to the liver in the hepatic portal vein (Fig. 5.41). In the liver, it passes through a second capillary bed, the hepatic sinusoids, and leaves via the hepatic vein which then merges with the inferior vena cava. In this way, blood with a high concentration of nutrients absorbed from the gastrointestinal tract reaches the liver first. This supplies the liver with a rich source of nutrients for its extensive metabolic activities and regulates the composition of blood leaving the gastrointestinal tract. It also ensures that unwanted and/or potentially toxic materials such as drugs are eliminated before the blood is returned into general circulation. This is called first-pass metabolism.

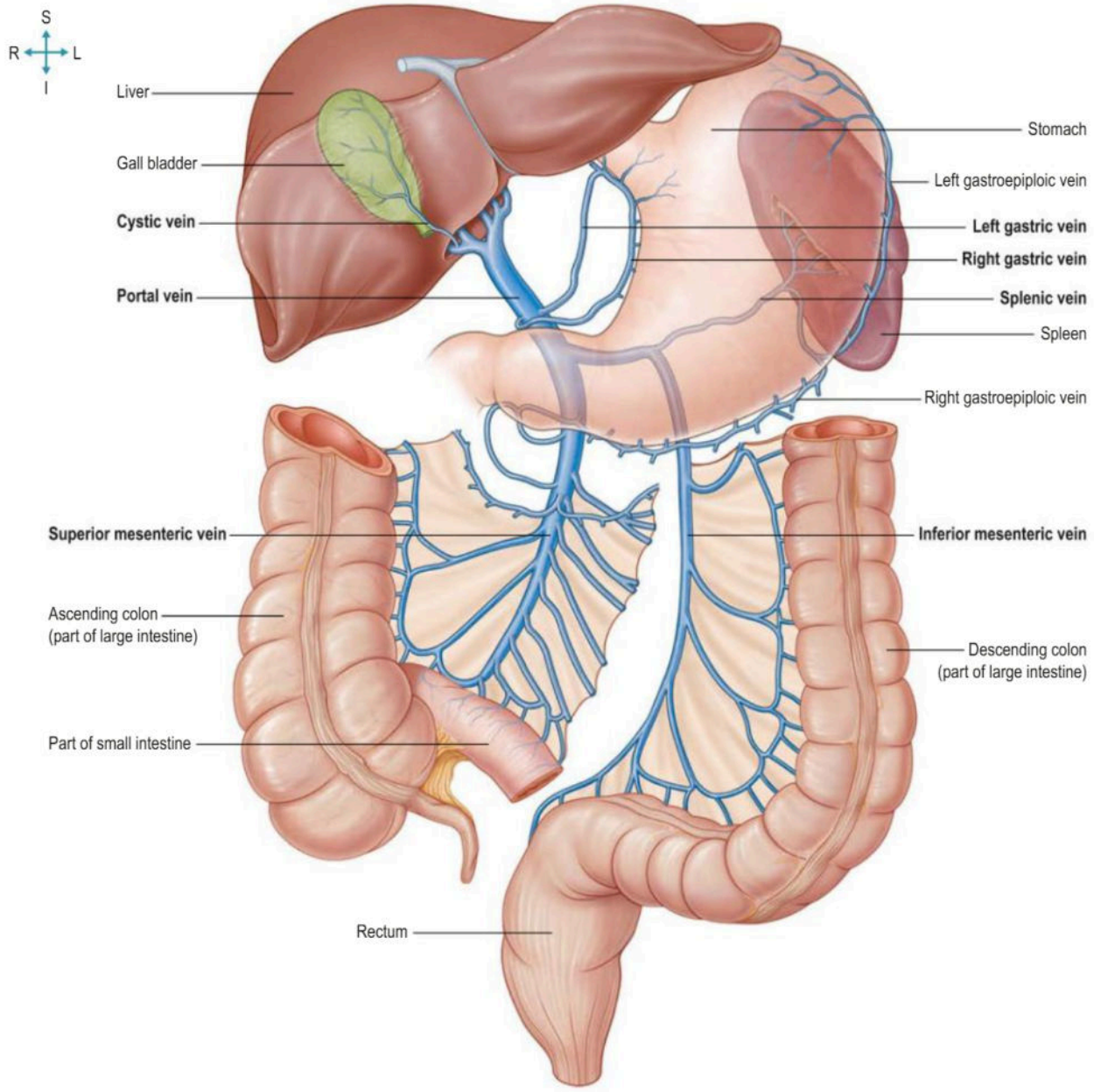

Figure 5.41 Venous drainage from the abdominal organs and the formation of the portal vein.

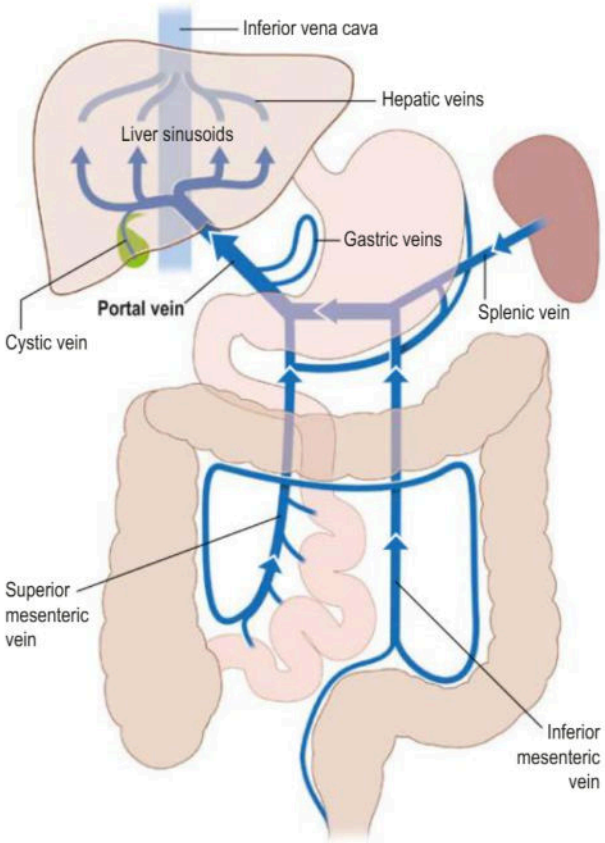

Figure 5.42 The portal vein: origin and termination.

Note that rectal veins draining blood from the lower two-thirds of the rectum empty directly into systemic veins, not the portal vein, and so this blood travels to the heart without first passing through the liver. Drugs absorbed from rectal formulations are therefore absorbed directly into the general circulation. This delays their elimination by the liver, which can be very useful clinically.

Portal vein

This is formed by the union of several veins (Figs. 5.41 and 5.42) each of which drains blood from the area supplied by the corresponding artery.

- The splenic vein drains blood from the spleen, the pancreas and part of the stomach.
- The inferior mesenteric vein returns the venous blood from the rectum, pelvic structures and descending colon of the large intestine. It joins the splenic vein.
- The superior mesenteric vein returns venous blood from the small intestine and the proximal parts of the large intestine, i.e. the caecum and ascending and transverse colon. It unites with the splenic vein to form the portal vein.
- The gastric veins drain blood from the stomach and the distal end of the oesophagus, then join the portal vein.
- The cystic vein drains venous blood from the gall bladder and joins the portal vein.

Blood from the hepatic portal circulation is then returned directly to the inferior vena cava through the hepatic veins.

Circulation in the pelvis and lower limb

Arterial supply

Common iliac arteries

The abdominal aorta divides at the level of the 4th lumbar vertebra into the right and left common iliac arteries (see Fig. 5.30). In front of the sacroiliac joint each divides into the internal and the external iliac arteries.

The internal iliac artery runs medially to supply the organs within the pelvic cavity. In the female, one of the largest branches is the uterine artery, which provides the main arterial blood supply to the reproductive organs.

The external iliac artery runs obliquely downwards and passes behind the inguinal ligament into the thigh, where it becomes the femoral artery.

The femoral artery (Fig. 5.43) begins at the midpoint of the inguinal ligament and extends downwards in front of the thigh. The femoral pulse can be felt at the origin of the femoral artery. It then turns medially and eventually passes round the medial aspect of the femur to enter the popliteal space, where it becomes the popliteal artery. It supplies blood to the structures of the thigh and some superficial pelvic and inguinal structures.

The popliteal artery (Fig. 5.44) passes through the popliteal fossa behind the knee, where the popliteal pulse can be felt. It supplies the structures in this area, including the knee joint. At the lower border of the popliteal fossa it divides into the anterior and posterior tibial arteries.

The anterior tibial artery (Fig. 5.44) passes forwards between the tibia and fibula and supplies the structures in the front of the leg. It lies on the tibia, runs in front of the ankle joint and continues over the dorsum (top) of the foot as the dorsalis pedis artery, supplying local tissues. The dorsalis pedis pulse can be felt here. The dorsalis pedis artery passes between the first and second metatarsal bones into the sole of the foot, where it contributes to the formation of the plantar arch.

The posterior tibial artery (Fig. 5.44) runs downwards and medially on the back of the leg. Near its origin it gives off a large branch called the peroneal artery, which supplies the lateral aspect of the leg. In the lower part it becomes superficial and passes medial to the ankle joint to reach the sole of the foot, where it continues as the plantar artery.

The plantar artery supplies the structures in the sole of the foot. This artery, its branches and the dorsalis pedis artery form the plantar arch, from which the digital branches arise to supply the toes.

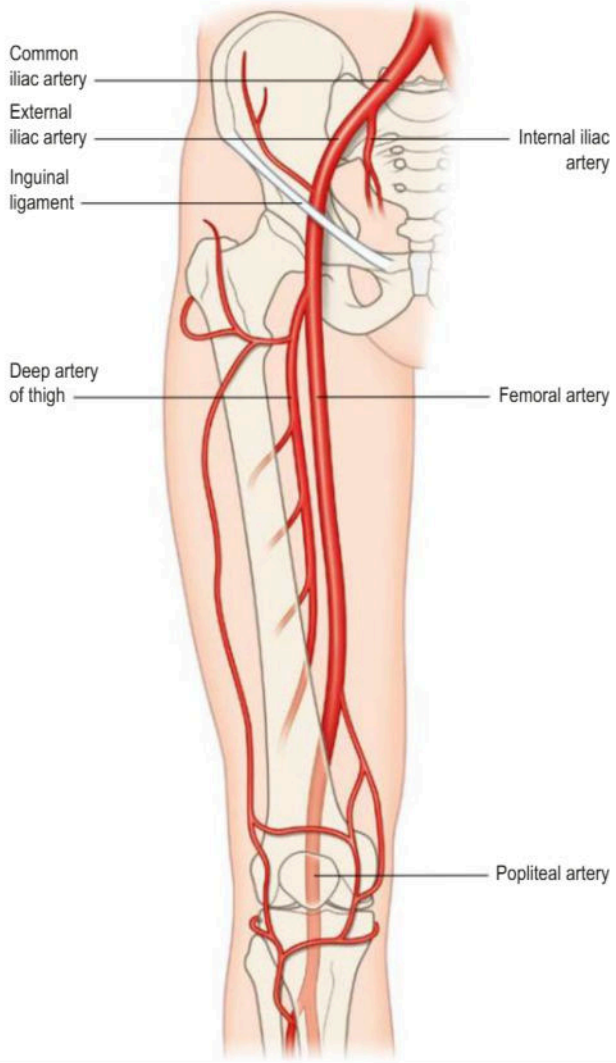

Figure 5.43 The femoral artery and its main branches.

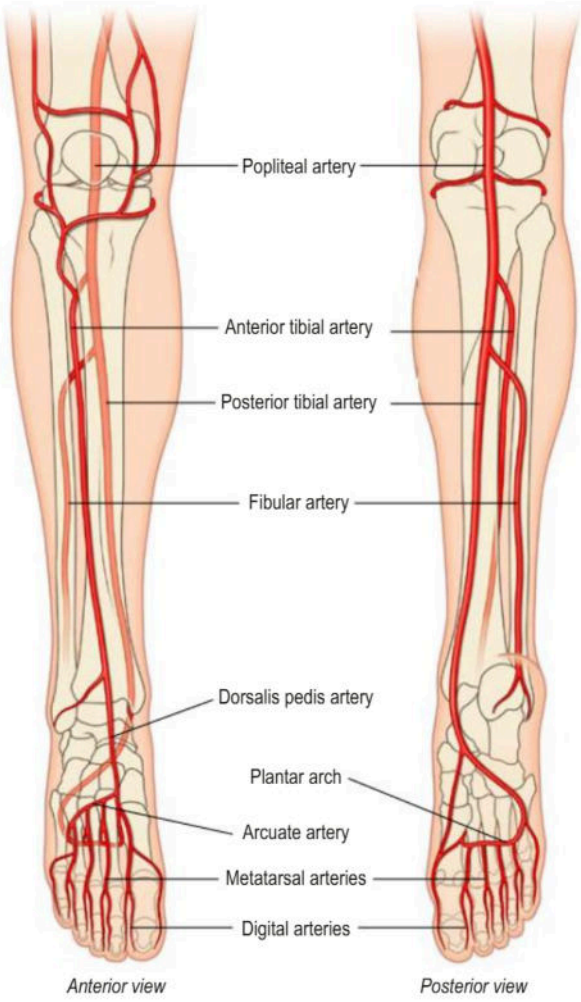

Figure 5.44 The right popliteal artery and its main branches.

Venous return

There are both deep and superficial veins in the lower limb (Fig. 5.45). Blood entering the superficial veins passes to the deep veins through communicating veins. Movement of blood towards the heart is partly dependent on contraction of skeletal muscles and backward flow is prevented by a large number of valves. Superficial veins receive less support from surrounding tissues than deep veins.

Deep veins

The deep veins (Fig. 5.45) accompany the arteries and their branches and have the same names. They are:

- The femoral vein, which ascends in the thigh to the level of the inguinal ligament, where it becomes the external iliac vein.
- The external iliac vein, the continuation of the femoral vein where it enters the pelvis lying close to the femoral artery. It passes along the brim of the pelvis, and at the level of the sacroiliac joint it is joined by the internal iliac vein to form the common iliac vein.
- The internal iliac vein, which receives tributaries from several veins draining the organs of the pelvic cavity.
- Two common iliac veins, which begin at the level of the sacroiliac joints. They ascend obliquely and unite to form the inferior vena cava a little to the right of the body of the 5th lumbar vertebra.

Superficial veins

The two main superficial veins (Fig. 5.45) draining blood from the lower limbs are the small and the great saphenous veins.

The small saphenous vein begins behind the ankle joint, where many small veins that drain the dorsum of the foot join together. It ascends superficially along the back of the leg and in the popliteal space it joins the popliteal vein, a deep vein.

The great saphenous vein is the longest vein in the body. It begins at the medial half of the dorsum of the foot and runs upwards, crossing the medial aspect of the tibia and continuing up the inner side of the thigh. Just below the inguinal ligament it joins the femoral vein.

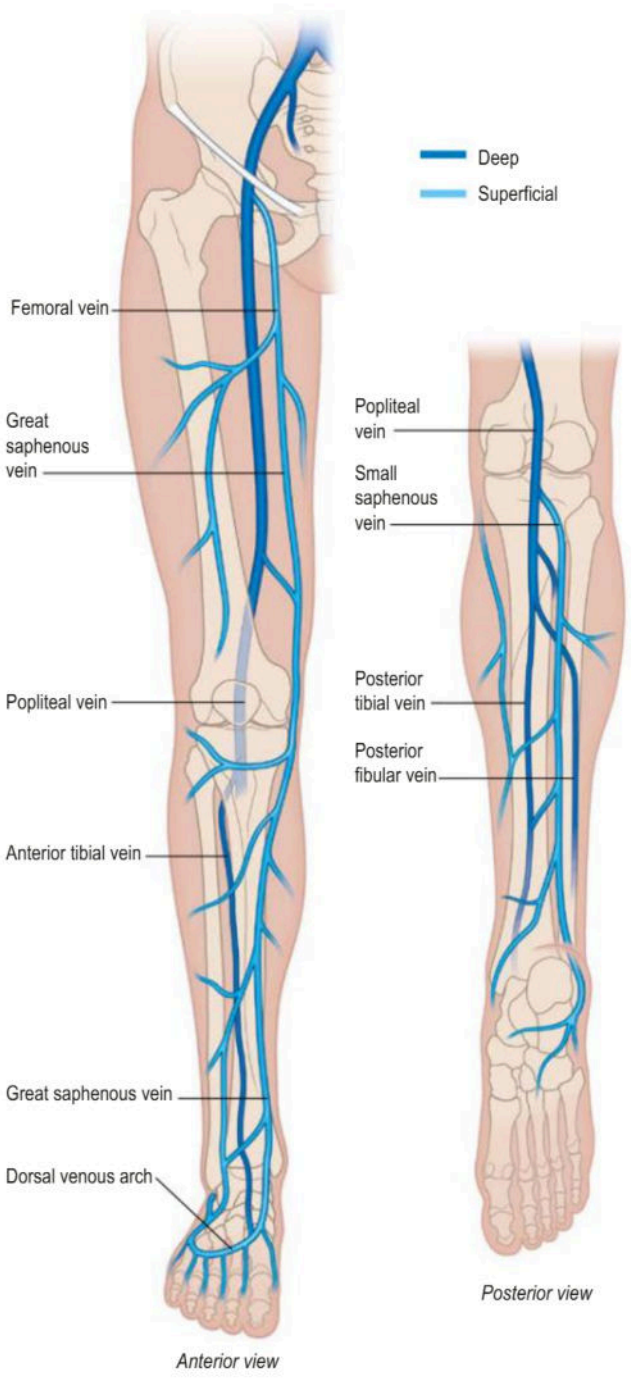

Figure 5.45 Veins of the leg.

Many communicating veins link the superficial veins, and also link the superficial and deep veins of the lower limb.

SPOT CHECK

8. Name the three sections of the aorta.
9. What is the key feature of the hepatic portal circulation?

Summary of the main blood vessels

The main blood vessels are summarised in Figure 5.46.

Fetal circulation

Learning outcomes

After studying this section, you should be able to:

- outline the functions of the placenta
- describe the fetal circulation
- compare blood flow through the heart, lungs and liver before and shortly after birth.

Features of the fetal circulation

The developing fetus obtains its oxygen and nutrients, and excretes its waste, via the mother's circulation. To this end, both maternal and fetal circulations develop specific adaptations unique to pregnancy. Because the lungs, gastrointestinal system and kidneys do not begin to function till after birth, certain modifications in the fetal circulation divert blood flow to meet prenatal requirements.

Placenta

This is a temporary structure that provides an interface between the mother and fetus and allows exchange of substances between their circulatory systems. It develops when the blastocyst, the ball of cells formed by repeated cell division after fertilisation of the ovum, embeds itself in the wall of the uterus at the beginning of pregnancy (Fig. 5.47). It is expelled from the uterus during the final stage of labour.

Structure

The mature placenta (Fig. 5.47A) is pancake-shaped, weighs around 500 g, has a diameter of 20 cm and is about 2.5 cm thick, although wide individual variations occur. The placenta is firmly attached to the uterine wall and consists of an extensive network of fetal capillaries bathed in maternal blood. Although the fetal capillaries lie very close to the maternal blood supply, the two circulations are kept completely separate by the placental membranes. Branches of the uterine artery bring maternal blood (about 500 mL/min) into chambers in the placenta called intervillous spaces (Fig. 5.47B). Projecting into the intervillous spaces are bundles of capillaries bringing blood from the fetus. Oxygen and nutrients diffuse or are actively transported into the fetal blood from the maternal blood, and fetal wastes diffuse into the mother's blood. The placenta is attached to the fetus by the umbilical cord, which is usually about 50 cm long and contains two umbilical arteries and one umbilical vein

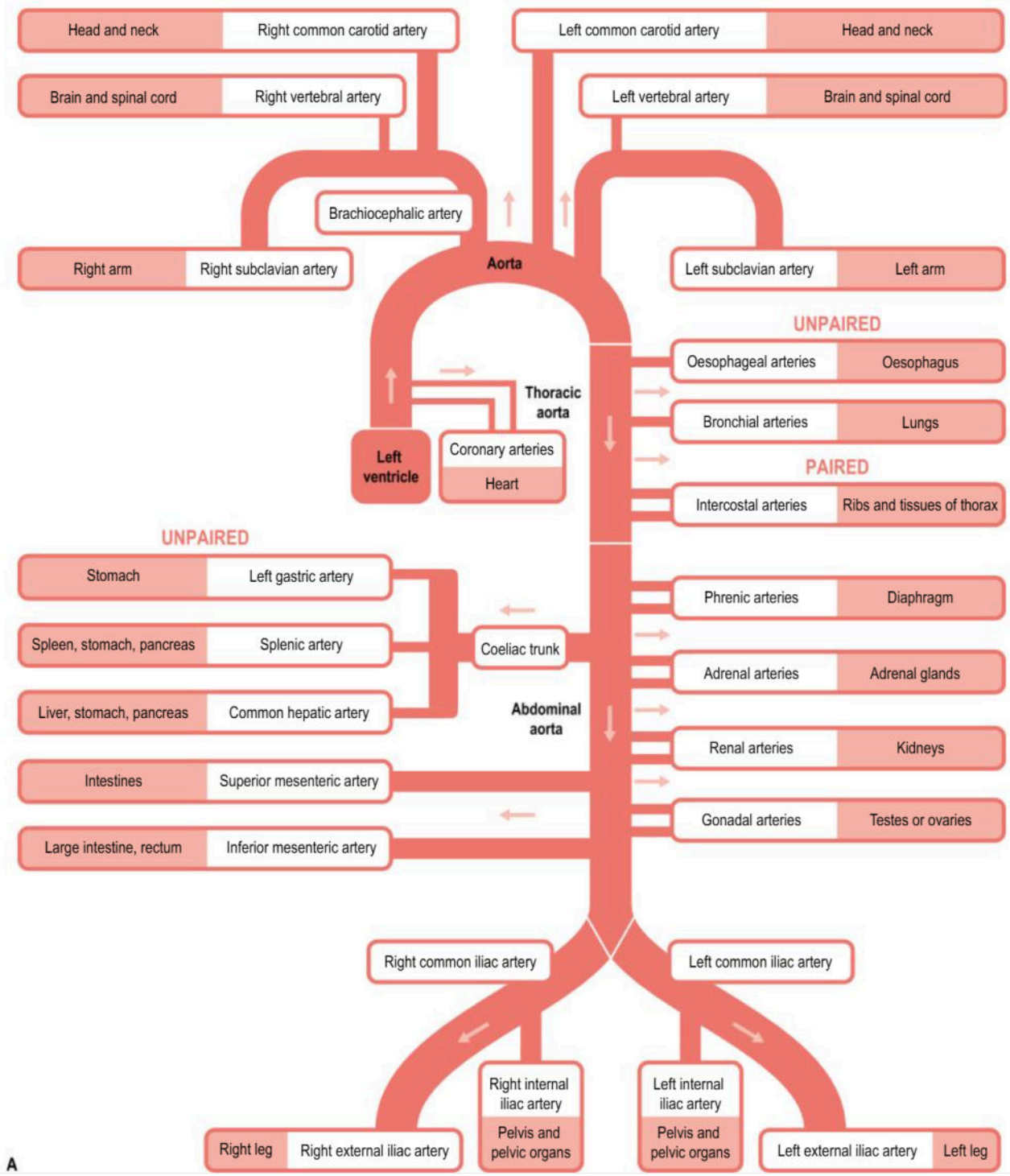

Figure 5.46 Summary of the main blood vessels. (A) The aorta and main arteries of the body.

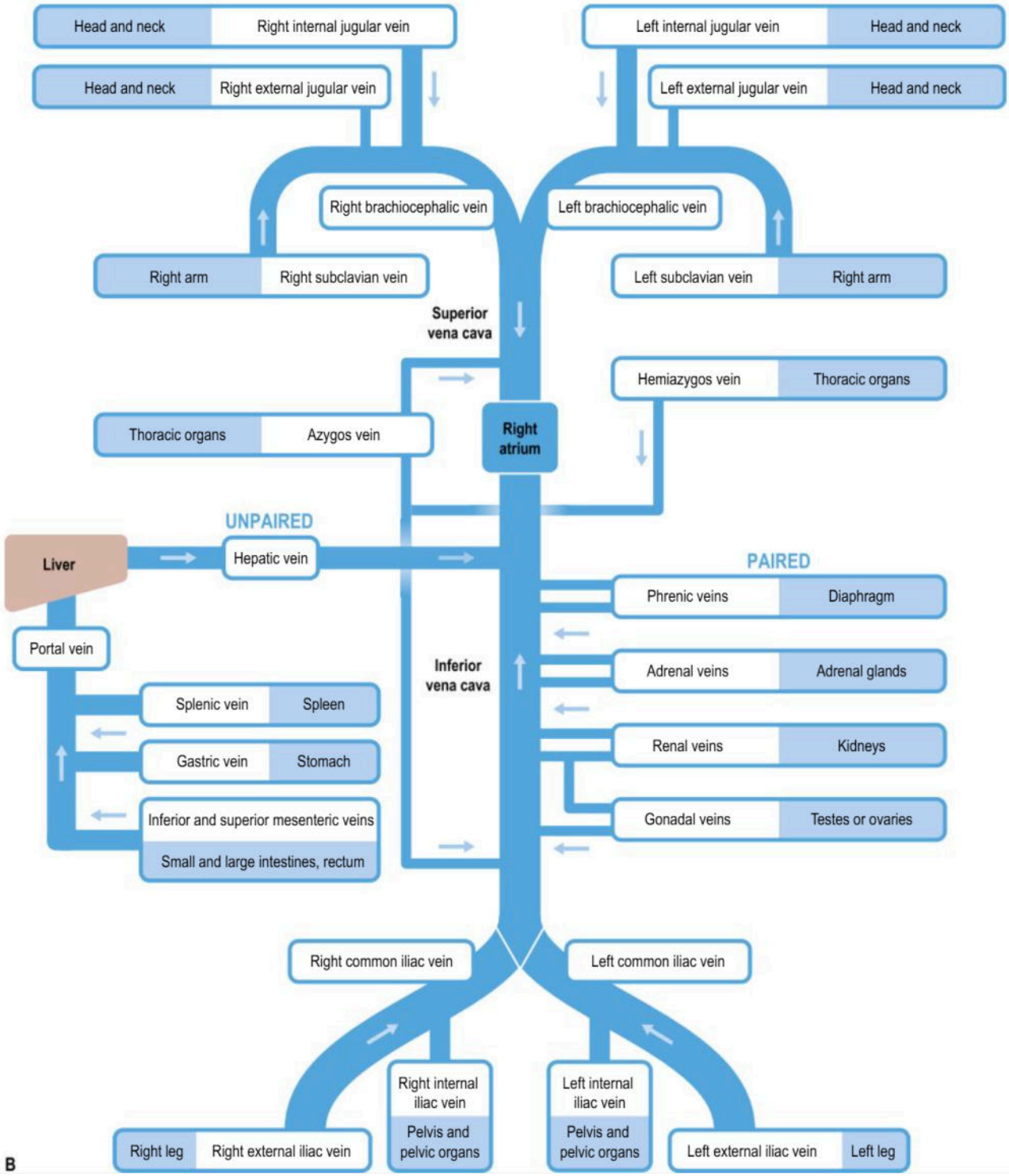

Figure 5.46, cont'd (B) The venae cavae and main veins of the body.

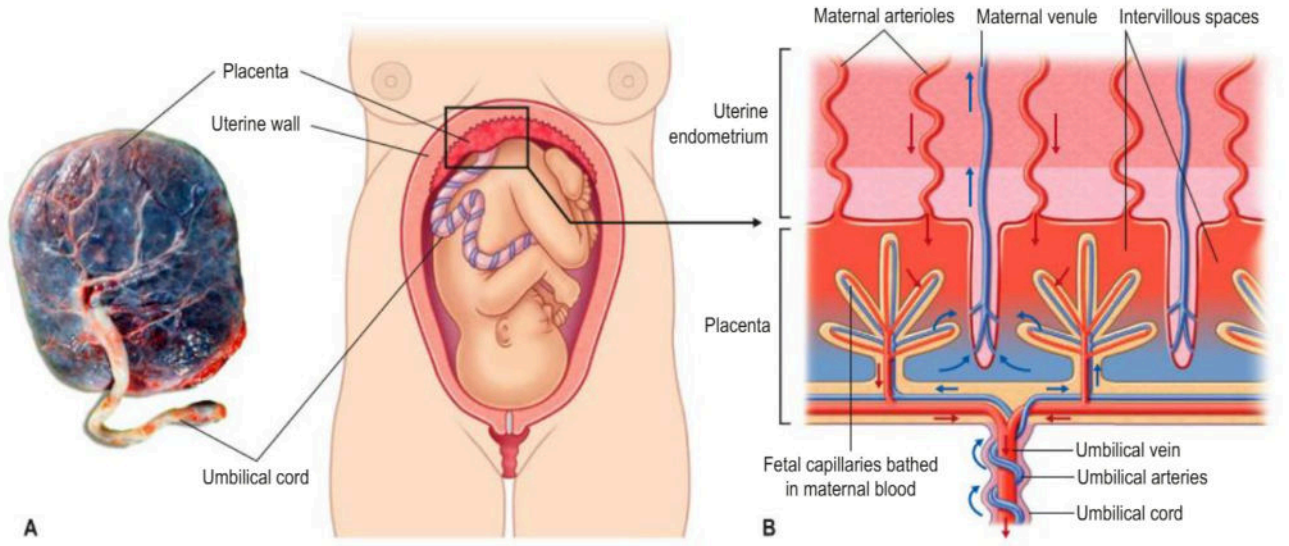

Figure 5.47 The placenta. (A) The mature placenta. (B) The relationship between the uterine wall and the placenta. (Photograph from Biophoto Associates/Science Photo Library. Reproduced with permission.)

wrapped in a soft connective tissue coat. The cord enters the fetal abdomen at the umbilicus.

Functions

Placental functions include exchange of substances, protection of the fetus and maintenance of pregnancy.

Exchange of nutrients and wastes

Deoxygenated fetal blood flowing through the network of placental capillaries absorbs oxygen and nutrients from maternal blood and excretes its wastes.

Protection of the fetus

In the last three months of pregnancy, maternal IgG antibodies cross the placenta into the fetal circulation and provide passive immunity (p. 424). After birth, these antibodies persist in the baby for the first few months of its life, providing vital protection while the child's immune system is at its most immature.

Although the placenta may protect the baby from some potentially harmful substances, including infections and some drugs, it cannot prevent small molecular weight or very fat-soluble molecules from transferring from mother to baby. Many drugs, toxins, pesticides, alcohol and other chemicals cross the placenta and may affect fetal development. Any substance causing abnormal fetal development is called a teratogen. Some infections in the mother, including rubella (German measles), syphilis and cytomegalovirus are particularly associated with fetal abnormalities.

Maintenance of pregnancy

The placenta has an essential endocrine function and secretes the hormones that maintain pregnancy.

Human chorionic gonadotrophin (hCG). Human chorionic gonadotrophin (hCG) is secreted in early pregnancy, peaking at around 8 or 9 weeks and thereafter in smaller amounts. It stimulates the corpus luteum to continue secreting progesterone and oestrogen, which prevent menstruation and maintain the uterine endometrium, sustaining pregnancy in the early weeks (see Fig. 18.11).

Progesterone and oestrogen. As pregnancy progresses, the placenta takes over secretion of these hormones from the corpus luteum, which degenerates after about 12 weeks. From 12 weeks until delivery, the placenta secretes increasing levels of oestrogen and progesterone, essential for maintenance of pregnancy.

Fetal adaptations

These are shown in Fig. 5.48A.

Ductus venosus

This is a continuation of the umbilical vein which returns blood directly into the fetal inferior vena cava, and most blood returning from the placenta therefore bypasses the non-functional fetal liver.

Ductus arteriosus

This small vessel connects the pulmonary artery to the descending thoracic aorta and diverts blood into the systemic circulation, meaning that very little blood passes through the fetal lungs (see Fig. 5.63).

Foramen ovale

This is an opening in the septum separating the two atria. It is covered with a flap of tissue that acts as a one-way valve (the

atrioseptal valve, Figs 5.48 and see Fig. 5.64), allowing blood to flow between the right and left atria, so that most blood bypasses the non-functional fetal lungs.

Changes at birth

These are summarised in Fig. 5.48B.

When the baby takes its first breath the lungs inflate for the first time, increasing pulmonary blood flow. Blood returning from the lungs increases the pressure in the left atrium, closing the flap over the foramen ovale and preventing blood flow between the atria. Blood entering the right atrium is therefore diverted into the right ventricle and into the pulmonary circulation through the pulmonary arteries. As the pulmonary circulation is established (see Fig. 5.1), blood oxygen levels increase, causing constriction and closure of the ductus arteriosus. If these adaptations to extrauterine life do not take place after birth, they may become evident as congenital abnormalities (see Figs 5.63 and 5.64). When the placental circulation ceases, soon after birth, the umbilical vein, ductus venosus and umbilical arteries collapse, as they are no longer required.

SPOT CHECK

10. Describe the structure and function of the placenta.
11. What is the function of the ductus venosus?

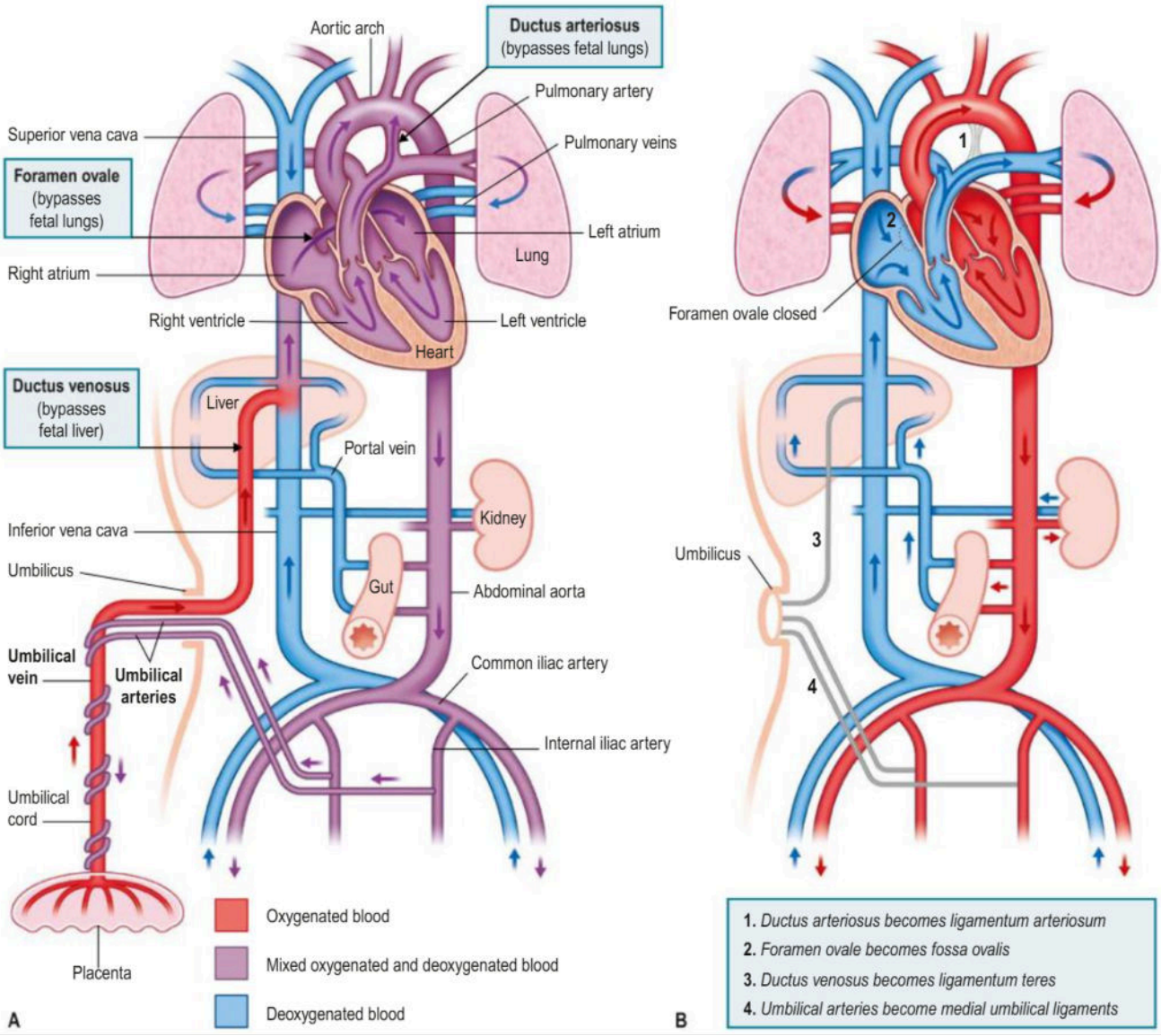

Figure 5.48 The fetal circulation. (A) Before birth. (B) Changes at birth.

Effects of ageing on the cardiovascular system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the cardiovascular system.

Ageing and the heart

As the heart gets older, its function generally declines; cardiac output falls and the conduction pathways become less efficient. Cardiac muscle cell numbers steadily reduce with age, but hypertrophy (cell enlargement) generally balances this and the ventricles of the heart in older adults are actually slightly larger than in younger people. The compliance (stretchability) of the heart falls with age, mainly because the fibrous skeleton of the heart stiffens, increasing the heart's workload. The ability of the heart muscle to respond to sympathetic stimulation lessens, and the contractile strength of the heart and cardiac reserve are reduced. The older heart is therefore more prone to heart failure (p. 136).

These changes occur in the healthy ageing heart and are not consequences of disease. It is notable that age-related decline in cardiovascular function is greatly slowed in individuals who take regular exercise, even in old age.

Ageing and blood vessels

Vasoconstriction and vasodilation responses are less efficient in ageing blood vessels, so regulation of blood flow to the tissues is less well controlled. Arterial and arteriolar walls become stiffer and less compliant, which raises blood pressure and increases the work of the left ventricle. Blood pressure tends to rise with age, even in the absence of any overt cardiovascular disease. The amount of smooth muscle in the walls of most arteries, including those of the heart, kidneys and brain, rises with age, which contributes to their stiffening. This means that the blood supply to most body organs tends to fall, but in healthy old age it does not cause problems because it is matched by a general reduction in metabolic rate.

The baroreceptor reflex (p. 103) becomes less brisk with age, not only because the heart and blood vessels are slower to respond but also because of neuronal ageing. This may lead to postural hypotension (p. 143).

SPOT CHECK

12. Outline how age-related decline in heart function can be minimised.

Shock

Learning outcomes

After studying this section, you should be able to:

- define the term 'shock'
- describe the main physiological changes that occur during shock
- explain the underlying pathophysiology of the main causes of shock.

Shock (circulatory failure) occurs when the metabolic needs of cells are not met because of inadequate blood flow. In effect, there is a reduction in circulating blood volume, in blood pressure and in cardiac output. This causes tissue hypoxia, an inadequate supply of nutrients and the accumulation of waste products. There are different ways of classifying shock, including by cause, which is described here.

Hypovolaemic shock

This occurs when the blood volume is reduced by 15%–25%. Cardiac output may fall because of low blood volume and hence low venous return, as a result of different situations:

- Severe haemorrhage – whole blood is lost.
- Extensive burns – serum is lost.
- Severe vomiting and diarrhoea – water and electrolytes are lost.

Cardiogenic shock

This occurs in acute heart disease when damaged heart muscle cannot maintain an adequate cardiac output. The commonest cause is myocardial infarction.

Septic shock

Sepsis is the over-reaction of the immune system to serious insult, usually infection, and can develop into septic shock, multi-organ failure and death. White blood cells are activated and a wide range of powerful inflammatory mediators are released into the blood, with widespread effects on organ function. Septic shock has a high mortality rate, even when treated. Symptoms include hypotension due to extensive vasodilation, depression of cardiac contractility, poor tissue perfusion and deteriorating mental state.

Neurogenic shock

The commonest cause of neurogenic shock is spinal cord damage, which impairs spinal autonomic nerve outflow. Loss of sympathetic nervous system output causes widespread vasodilation and bradycardia; the resultant hypotension is so severe that shock follows.

Anaphylactic shock

Anaphylaxis (p. 426) is a rare but severe allergic response that may be triggered in sensitive individuals by substances like penicillin, peanuts or latex rubber. Vasodilation, provoked by systemic release of inflammatory mediators, e.g. histamine and bradykinin, causes venous pooling and hypotension. Severe bronchoconstriction leads to acute respiratory difficulty and hypoxia. Onset is usually sudden, and in severe cases can cause death in a matter of minutes if untreated.

Physiological changes during shock

In the short term, changes are associated with physiological attempts to restore an adequate blood circulation – this is called compensated shock (Fig. 5.49). If not corrected, the longer-term changes may be irreversible.

Compensated shock

As blood pressure falls, a number of compensatory mechanisms are activated in an attempt to restore it. They raise blood pressure by increasing peripheral resistance, blood volume and cardiac output (Fig. 5.49).

Increased sympathetic stimulation increases heart rate and cardiac output, and also causes vasoconstriction, all of which increase blood pressure. Low blood volume and increased osmolarity of the blood stimulate secretion of ADH (p. 245) and activate the RAAS (see Fig. 13.15). Consequent release of aldosterone reduces water and sodium excretion and promotes vasoconstriction. Veins also constrict, helping to reduce venous pooling and increase venous return.

If these compensatory mechanisms, plus any medical interventions available, are sufficient, then perfusion of the heart and brain can be maintained and the patient's condition may be stabilised.

Uncompensated shock

If the insult is more severe, shock becomes a self-perpetuating sequence of deteriorating cardiovascular function – uncompensated shock (Fig. 5.50). Tissue hypoxia causes cellular metabolism to switch to anaerobic pathways (p. 351), resulting in accumulation of lactic acid and progressive acidosis, which damages capillaries. The capillaries then become more permeable, leaking fluid from the vascular system into the tissues, further lowering blood pressure and tissue perfusion. Also, the accumulation of waste products causes vasodilation, making it harder for control mechanisms

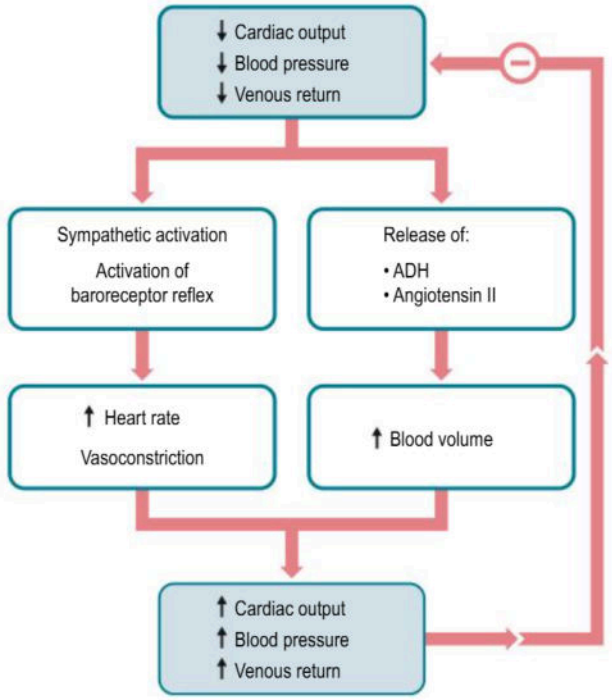

Figure 5.49 Compensatory mechanisms in shock. *ADH*, antidiuretic hormone.

to support blood pressure. Organs, including the heart, are deprived of oxygen and may start to fail.

Eventually, the cardiovascular system reaches the stage when, although its compensatory mechanisms are running at maximum, it is unable to supply the brain's requirements. As the brain, including the cardiovascular and respiratory centres in the brain stem, becomes starved of oxygen and nutrients, it begins to fail and there is loss of central control of the body's compensatory mechanisms. Circulatory collapse follows. Finally, degenerating cardiovascular function leads to irreversible and progressive brain stem damage and death.

SPOT CHECK

13. What is compensated shock?
14. How does severe allergy cause shock?

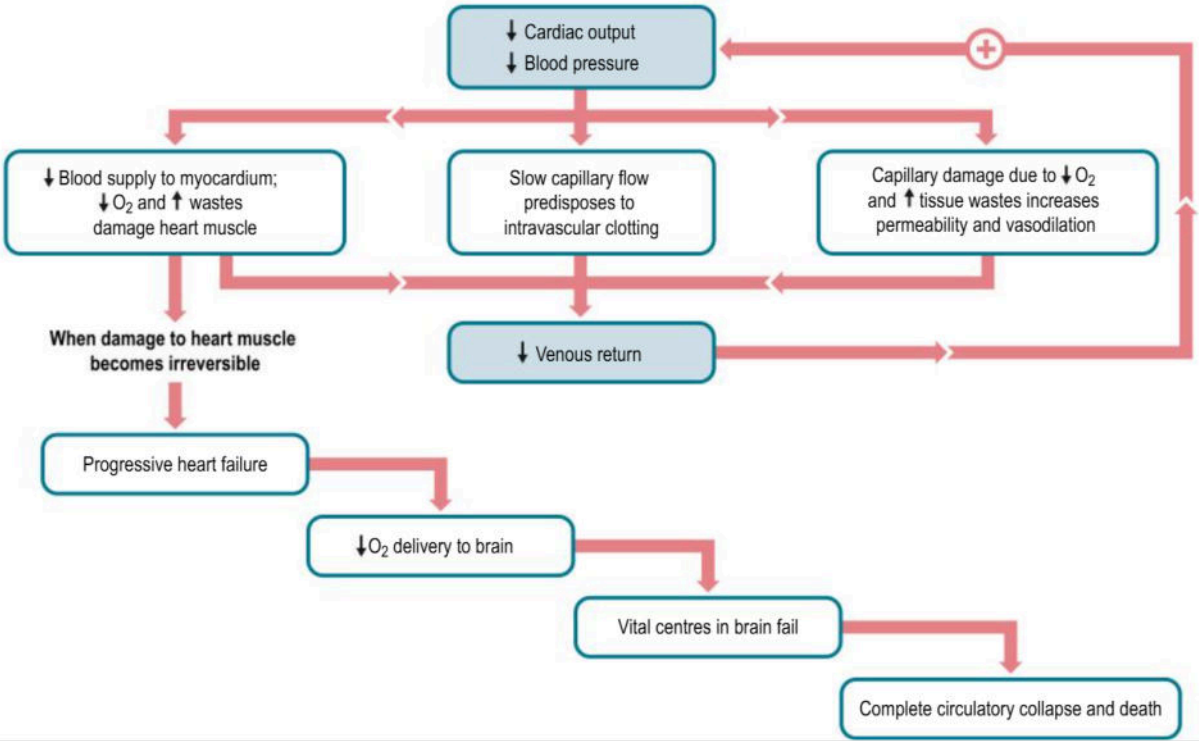

Figure 5.50 Uncompensated shock.

Thrombosis and embolism

Learning outcomes

After studying this section, you should be able to:

- define the terms thrombosis, embolism, ischaemia and infarction
- explain, in general terms, the effects of the above on the body
- describe three risk factors for thrombosis formation.

Thrombosis

Thrombosis is the formation of a blood clot (thrombus) inside a blood vessel, interrupting blood supply to the tissues. The risk of a thrombus developing within a blood vessel is increased by several factors.

Slow blood flow

This may happen in immobility, most frequently in the deep veins of the leg, e.g. with prolonged sitting, bedrest or on long-haul flights. Other causes of slow blood flow include compression of a blood vessel by an adjacent structure such as a tumour or tight clothing, or a sustained fall in blood pressure, as in shock.

Damage to the blood vessel endothelium

This is usually associated with atherosclerosis (p. 130).

Increased blood coagulability

Dehydration, pregnancy and childbirth, blood clotting disorders, some malignant disease, the presence of an intravenous cannula and oestrogen (including when used as a contraceptive) all increase the risk of intravascular blood clots.

Embolism

Embolism is the blocking of a blood vessel by any mass of material (an embolus) travelling in the blood. This is usually a thrombus or a fragment of a thrombus, but other embolic materials are shown in Box 5.3.

Emboli originating in an artery travel away from the heart until they reach an artery too narrow to let them pass where they lodge, partly or completely blocking blood supply to tissues beyond. This is a common cause of stroke (p. 201), myocardial infarction (p. 138) and gangrenous limbs (Fig. 5.51). Emboli originating in veins (deep vein thrombosis, or DVT, p. 132) travel towards the heart, and from there to the lungs in the pulmonary artery, where they may cause a pulmonary embolism.

Pulmonary embolism

Blockage of a pulmonary artery or one of its larger branches immediately obstructs blood flow through the lung, one of

Box 5.3 Potential embolic materials

Fragments of atheromatous plaques (p. 130)
Fragments of vegetations from heart valves, e.g. in infective endocarditis (p. 139)
Tumour fragments, which may cause metastases
Amniotic fluid, during childbirth
Fat, from bone fractures
Air, from a punctured blood vessel, e.g. by a broken rib or during a clinical procedure
Nitrogen bubbles in decompression sickness (the 'bends')
Pus from an abscess

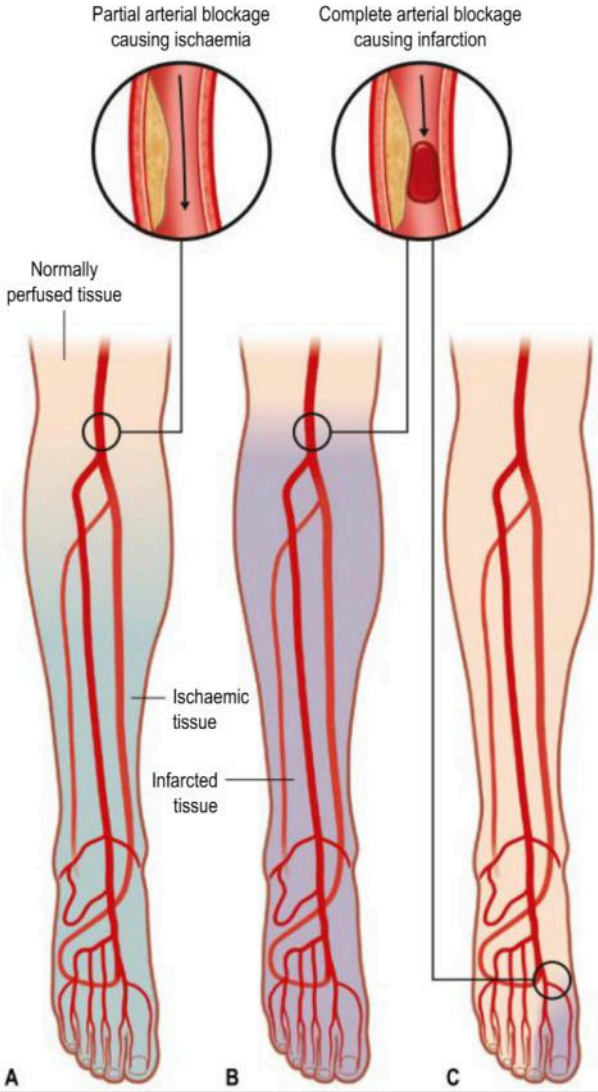

Figure 5.51 Ischaemia and infarction. (A) Partial blockage with reduced perfusion. (B) and (C) Complete blockage causes distal tissue ischaemia and infarction, dependent on the location of the blockage.

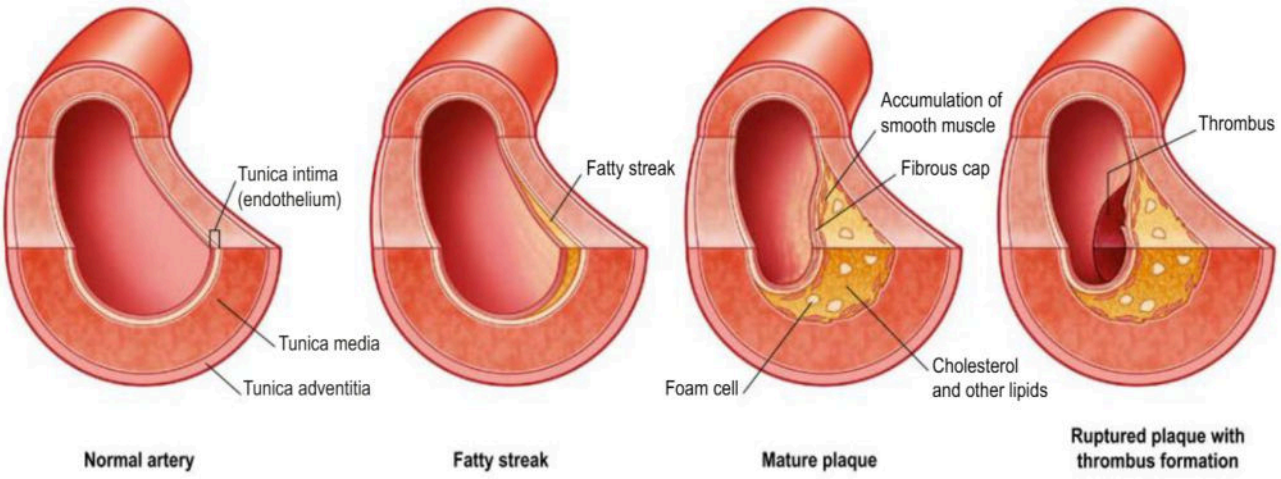

Figure 5.52 Stages in the formation of an atheromatous plaque.

the most serious consequences of venous embolism. Massive pulmonary embolism blocks a main pulmonary artery and usually causes sudden collapse and death.

Infarction and ischaemia

Infarction means tissue death because of interrupted blood supply. The consequences of interrupting tissue blood supply depend on the size of the blocked artery and the functions of the affected tissue. Ischaemia is impaired tissue function due to hypoxia and accumulation of cellular wastes (Fig. 5.51).

SPOT CHECK

15. What is the difference between a thrombus and an embolism?
16. What is the difference between ischaemia and infarction?

Blood vessel pathology

Learning outcomes

After studying this section, you should be able to:

- discuss the main causes, effects and complications of arterial disease, including atheroma, arteriosclerosis, venous thrombosis and aneurysm
- discuss the underlying abnormality in varicose veins
- list the predisposing factors and the common sites of occurrence of varicose veins
- describe the main tumours that affect blood vessels.

Atheroma

Pathological changes

Atheromatous plaques are patchy changes that develop in the endothelium of large and medium-sized arteries. Initial changes show a fatty streak in the artery wall. Mature plaques consist of accumulated cholesterol and other lipids, excess smooth muscle and fat-filled monocytes (foam cells). The plaque is covered with a rough fibrous cap. As plaques grow and thicken, they spread along the artery wall and bulge into the lumen. Eventually, the whole thickness of the wall and long sections of the vessel may be affected (Fig. 5.52). Plaques may rupture, exposing subintimal materials to the blood. This may cause thrombosis and vasospasm, and compromises blood flow.

Arteries most commonly involved are those in the heart, brain, kidneys, small intestine and lower limbs.

Causes of atheroma

Atherosclerosis (the presence of plaques) is most common in developed countries and is considered to be a disease of older people because it is usually in this age group that clinical signs appear. Plaques start to form in childhood, however, and may be the origin of atheromatous disease in later life. Some of the main risk factors relate to lifestyle and are therefore modifiable. The main risk factors are listed in Box 5.4.

Effects of atheroma

Atheromatous plaques may partially or completely obstruct an artery (Fig. 5.52). The blockage may be complicated by clot formation. The consequences of this depend on the site and size of the artery involved and the extent of collateral circulation.

Box 5.4 Risk factors in atherosclerosis

Modifiable factors are shown in *italics*

Heredity – family history

Obesity

Gender – males are more susceptible than females, until after the female menopause

Diets rich in saturated fats and cholesterol

Increasing age

Cigarette smoking

Diabetes mellitus

Excessive emotional stress

Hypertension

Sedentary lifestyle

Hyperlipidaemia, especially high levels of low-density lipoprotein (p. 309). Hyperlipidaemia may be inherited, associated with disease e.g. diabetes, or due to a high-fat diet

Excessive alcohol consumption

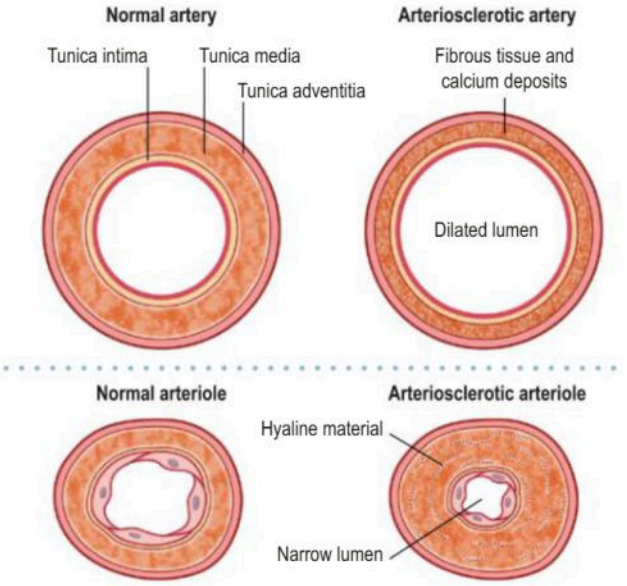

Figure 5.53 Arteriosclerotic changes in arteries and arterioles.

Narrowing of an artery

The tissues distal to the narrow point become ischaemic because they are deprived of oxygen and essential nutrients. The cells may receive enough blood to meet their minimum needs but not enough to cope with an increase in demand, e.g. in an exercising muscle. This causes acute cramp-like ischaemic pain, which disappears when exertion stops. Cardiac muscle and skeletal muscles of the lower limb are most commonly affected. Ischaemic pain in the heart is called angina pectoris (p. 138), and in the lower limbs is called intermittent claudication (Fig. 5.51A).

Occlusion of an artery

When an artery is completely blocked, the tissues it supplies become ischaemic, which leads to infarction (p. 130). If a major artery supplying a large amount of tissue is blocked, the consequences are usually more severe than with obstruction of a smaller artery (Fig. 5.51B and C). If the tissue is well provided with a collateral circulation (such as the circulus arteriosus provides in the brain), tissue damage is less than if there are few collateral vessels (which may be the case in the heart).

Blockage of a coronary artery causes myocardial infarction (p. 138). Occlusion of arteries in the brain causes cerebral ischaemia and infarction (stroke, p. 201).

Complications of atheroma

Thrombosis and infarction

If the fibrous cap overlying a plaque breaks down, exposure of the blood to subendothelial materials activates platelets, and an intravascular blood clot forms (thrombosis), blocking the artery and causing ischaemia and infarction. Emboli may break away from the main clot, travel in the bloodstream and lodge in small arteries distal to the clot, causing further infarcts.

Haemorrhage

With age, plaques may become calcified, making the arterial wall brittle, rigid and more prone to aneurysm formation, increasing the risk of rupture and haemorrhage.

Aneurysm

When the arterial wall is weakened by spread of the plaque between the layers of tissue, a local dilation (aneurysm) may develop (see Fig. 5. 53). This may cause thrombosis and embolism, or the aneurysm may rupture, causing severe haemorrhage. The most common sites for aneurysm development are the aorta and the abdominal and pelvic arteries, where blood pressure is high.

Arteriosclerosis

This is a progressive degeneration of arterial walls, associated with ageing and accompanied by hypertension.

In large and medium-sized arteries, the tunica media gradually becomes infiltrated with fibrous tissue and calcium. This causes the vessels to become dilated, inelastic and tortuous (Fig. 5.53). Loss of elasticity increases systolic blood pressure and widens the pulse pressure (p. 102).

When arterioles are affected, their lumen becomes narrower because of deposition of a substance called hyaline material, which reduces the elasticity of the vessel wall. Because arterioles control peripheral resistance

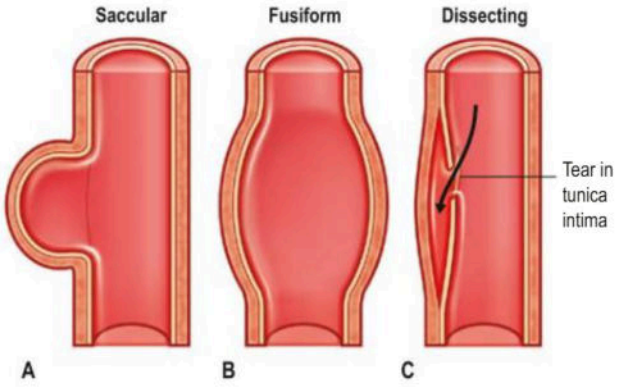

Figure 5.54 Types of aneurysm. (A) Saccular. (B) Fusiform. (C) Dissecting.

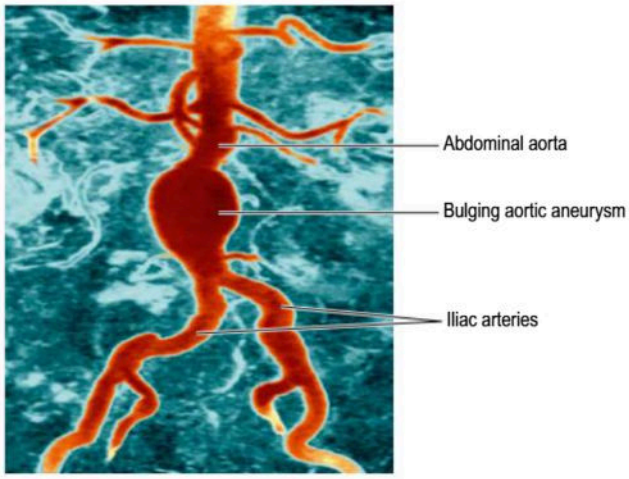

Figure 5.55 Abdominal aortic aneurysm. (Zephyr/Science Photo Library. Reproduced with permission.)

(p. 102), this narrowing increases peripheral resistance and blood pressure. It reduces blood flow, leading to ischaemia of tissues supplied by affected arteries. In the limbs, the resultant ischaemia predisposes to gangrene, a significant consequence of diabetes mellitus. If arteries supplying the brain are affected, cerebral ischaemia can result in cognitive impairment and dementia (p. 202).

Aneurysms

Aneurysms are abnormal local dilations of arteries, which vary considerably in size (Fig. 5.54). Predisposing factors include atheroma, hypertension and defective collagen, all of which can cause weak spots in the arterial wall.

If an aneurysm ruptures, haemorrhage follows, the consequences depending on the site and extent of the bleed. Rupture of the aorta is likely to be fatal, while bleeding into the subarachnoid space can also cause death or permanent disability. Bleeding in the brain can lead to stroke (p. 201). An aneurysm damages and roughens the blood vessel endothelium, increasing the risk of clot formation. Clots may block circulation locally, or elsewhere if they travel in the bloodstream as emboli. In addition, the swelling associated with the distended artery can cause pressure on local structures such as other blood vessels, nerves or organs.

Types of aneurysm

Saccular aneurysms (Fig. 5.54A) bulge out on one side of the artery. When they occur in the relatively thin-walled arteries of the circulus arteriosus (see Fig. 5.34) in the brain, they are sometimes called 'berry' aneurysms. They may be congenital, develop at the site of an atheromatous plaque or be associated with defective collagen production.

Fusiform or spindle-shaped distensions (Fig. 5.54B) occur mainly in the abdominal aorta and are usually associated with atheroma.

Dissecting aneurysms (Fig. 5.54C) occur mainly in the arch of the aorta. They are caused when blood is forced between the endothelium and tunica media, beginning at a site of endothelial damage. These aneurysms are particularly associated with hypertension, which can weaken and tear the arterial wall.

Figure 5.55 shows the bulging abdominal aortic wall caused by an aneurysm.

Venous thrombosis

The risk factors predisposing to development of a clot within a vein are discussed on page 129.

Venous thrombosis may be superficial thrombophlebitis, which usually resolves spontaneously, or may be deep vein thrombosis.

Superficial thrombophlebitis

When a thrombus forms in a superficial vein, the tissue around the affected vein becomes inflamed, red and painful. The most common causes are intravenous infusion and varicosities in the saphenous vein.

Deep vein thrombosis

Deep vein thrombosis (DVT) usually affects the lower limb, pelvic or iliac veins but occasionally the upper limb veins. It may be accompanied by local pain and swelling but is often asymptomatic. Risk factors for DVT include varicose veins, surgery, pregnancy and prolonged immobility, e.g. long journeys with restricted leg room ('economy class syndrome'). It carries a significant risk of death, often from pulmonary embolism if a large clot fragment travels to the lungs.

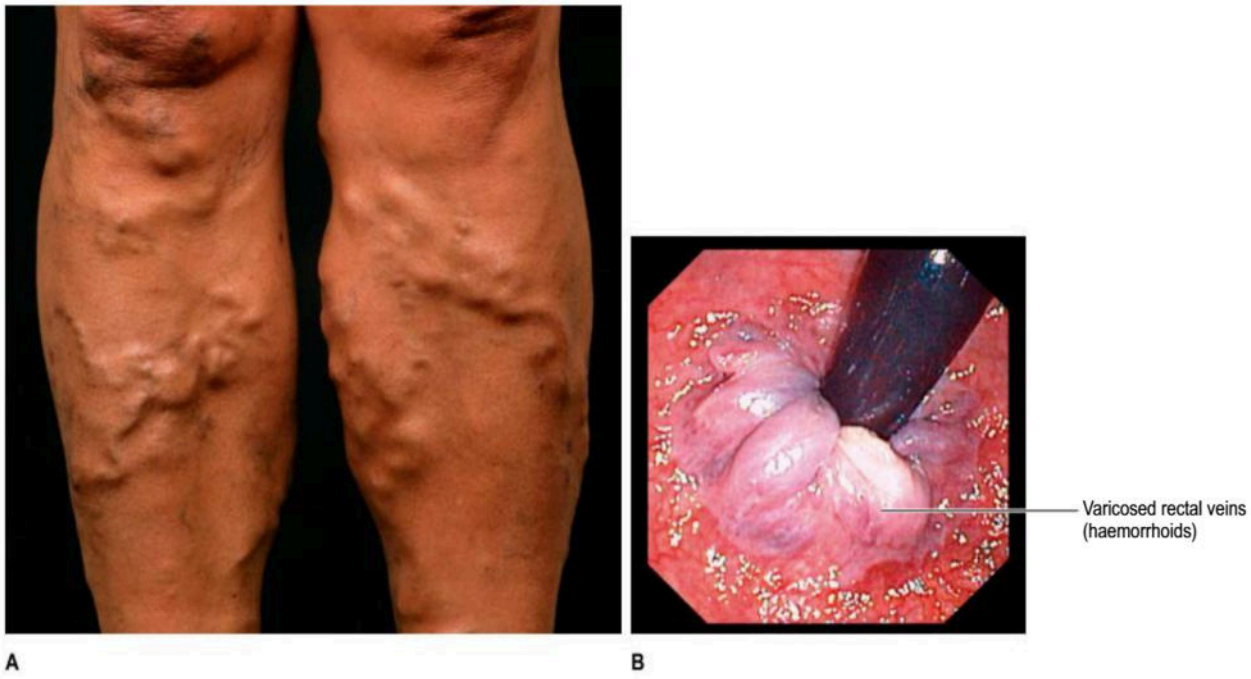

Figure 5.56 Varicose veins. (A) Of the leg. (B) In the rectum (haemorrhoids). (A, B, Alex Barte/Science Photo Library. Reproduced with permission.)

Varicosed veins

When blood flow through veins becomes sluggish, blood pools within them, stretching and damaging their soft walls. Over time, the veins lose elasticity, dilate and become coiled and tortuous. The valves then cannot close properly because the vein is distended, and pooling and engorgement get worse.

Sites and effects of varicose veins

Varicose veins of the legs

Blood in the leg veins is constantly subject to gravity, which can lead to sluggish venous return and pooling of blood in these veins. If the valves become incompetent, pooling gets worse and the leg veins become chronically dilated, twisted and lengthened. The superficial veins are more prone to this than deeper ones because there is less support from surrounding tissues such as muscle, and the varicose veins become clearly visible (Fig. 5.56A). The great and small saphenous veins and the anterior tibial veins are most commonly affected, causing aching and fatigue of the legs, especially during long periods of standing. These dilated, inelastic veins rupture easily if injured, causing bleeding. Venous return is maintained because superficial veins are usually connected into the network of deeper veins, which are better supported by surrounding tissues and less likely to become varicosed (Fig. 5.57).

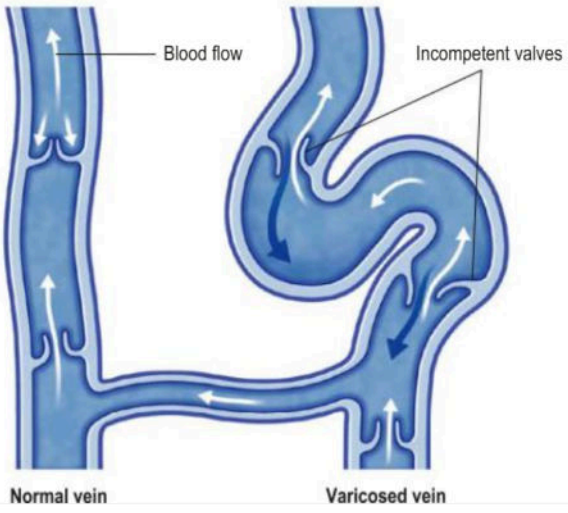

Figure 5.57 Anastomotic connection between superficial and varicosed vein (right) and deeper unaffected vein (left).

The skin over a varicose vein may become poorly nourished due to stasis of blood, leading to varicose ulcer, usually on the medial aspects of the leg just above the ankle.

Risk factors include increasing age, obesity, pregnancy, standing for long periods, wearing constricting clothing, family history and female sex.

Haemorrhoids

Sustained pressure on the network of veins in the rectum and anus increases venous pressure and causes them to dilate and their walls become fragile and easily damaged. As a result, they bleed readily, and passing bright red blood from the rectum is the most common presenting symptom. This is sometimes called piles (Fig. 5.56B). Increased anorectal pressure may be due to advanced pregnancy, obesity, prolonged sitting, straining to pass stool and a slouched posture. Severe haemorrhage is rare, but regular minor bleeding over extended periods of time can cause anaemia.

Scrotal varicocele

Each spermatic cord is surrounded by a plexus of veins that may become varicosed, especially in men whose work involves standing for long periods. If the varicocele is bilateral, the increased temperature due to venous congestion may depress spermatogenesis and reduce fertility.

Oesophageal varices

Raised pressure in the lower oesophageal veins can rupture them, leading to a potentially fatal haemorrhage (p. 357).

Tumours of blood and lymph vessels

Angiomas

Angiomas are benign tumours of either blood vessels (haemangiomas) or lymph vessels (lymphangiomas). The latter rarely occur, so angioma is usually taken to mean haemangioma.

Haemangiomas

These are an excessive, disorganised growth of blood vessel tissues interspersed with collagen fibres.

Capillary haemangiomas. Excess capillary growth interspersed with collagen in a localised area makes a dense, plexus-like network of tissue. Each haemangioma is supplied by only one blood vessel, and if it thromboses, the haemangioma atrophies and disappears.

Haemangiomas are usually present at birth and are seen as a purple or red mole or birthmark. They may be quite small at birth but grow at an alarming rate in the first few months, keeping pace with the growth of the child. After 1–3 years atrophy may begin, and after 5 years about 80% have disappeared.

SPOT CHECK

17. What is the difference between a fatty streak in a blood vessel and a mature atheromatous plaque?
18. What is a varicose vein?

Oedema

Learning outcomes

After studying this section, you should be able to:

- define the term 'oedema'
- describe the main causes of oedema
- relate the causes of oedema to relevant clinical problems
- explain the causes and consequences of excess fluid collecting in body cavities.

In oedema, excess tissue fluid accumulates, causing swelling. It may occur in either superficial tissues or deeper organs.

Sites of oedema

Oedema of the superficial tissues causes pitting, i.e. an indentation remains after firm finger pressure. Dependent oedema is the term given to gravity-related oedema. When standing or sitting dependent oedema develops in the lower limbs, beginning in the feet and ankles, whereas patients on bedrest tend to develop oedema in the sacral area.

In pulmonary oedema, venous congestion in the lungs or increased pulmonary capillary permeability results in accumulation of fluid in the alveoli. This reduces the area available for gaseous exchange and leads to dyspnoea (breathlessness), cyanosis and coughing up of frothy sputum. The most common causes of pulmonary oedema are cardiac failure, inflammation or infection of the lungs, and excessive infusion of intravenous fluids.

Causes of oedema

Fluid accumulates in the tissues when some aspect of capillary fluid dynamics is abnormal. Figure 5.58A shows normal capillary fluid dynamics. All fluid leaving the arterial end of the capillary is either reabsorbed into the bloodstream at the venous end of the capillary or is drained away by lymphatic vessels. Capillary wall permeability is normal, so that plasma proteins cannot escape from the bloodstream into the tissues (see also p. 89).

Increased venous blood (hydrostatic) pressure

If there is congestion in the venous circulation, venous blood pressure rises, reducing the net effect of osmotic pressure that draws fluid back into the capillary at the venous end. Excess fluid then remains in the tissues. This may be caused by heart failure, kidney disease or compression of a limb due to prolonged sitting or tight clothes.

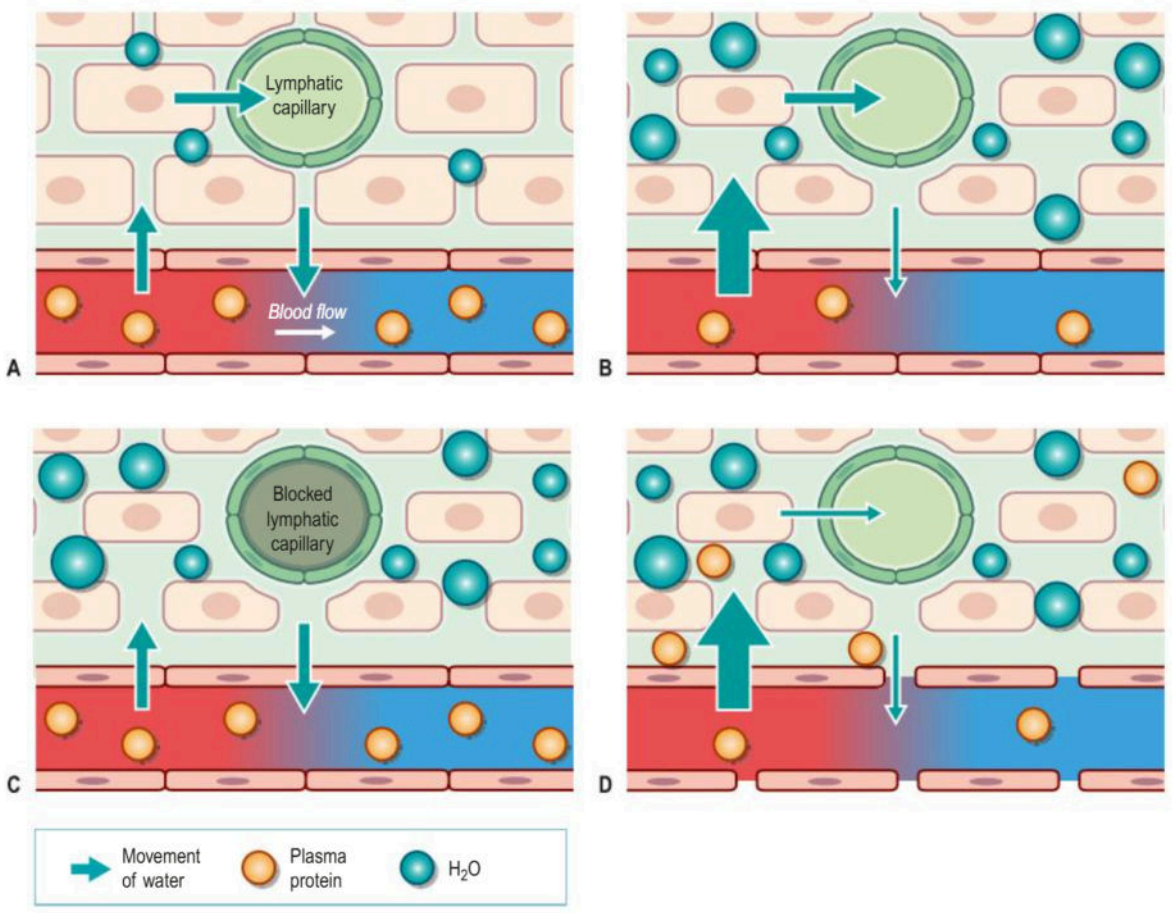

Figure 5.58 Capillary fluid dynamics. (A) Normal. (B) Effect of reduced plasma proteins. (C) Effect of impaired lymphatic drainage. (D) Effect of increased capillary permeability.

Decreased plasma osmotic pressure

When plasma protein levels fall, less fluid returns to the circulation at the venous end of the capillary (Fig. 5.58B), and remains in the tissues, causing oedema. Causes include excessive protein loss in kidney disease, and reduced plasma protein levels caused by liver failure or a protein-deficient diet.

Impaired lymphatic drainage

Some fluid returns to the circulation via the lymphatic system, and if lymph flow is obstructed, fluid remains in the tissues and oedema develops (Fig. 5.58C). Causes include a tumour compressing lymphatic vessels, surgical removal of lymph nodes or lymph node destruction by chronic inflammation.

Increased capillary permeability

In inflammation, chemical mediators increase local capillary permeability. Plasma proteins then leave the circulation (Fig. 5.58D), increasing tissue osmotic pressure and pulling more fluid into the area, causing swelling. This type of oedema also occurs in allergic reactions, e.g. anaphylaxis, asthma or hay fever.

Effusions and ascites

Abnormal accumulation of excess fluid in body spaces, e.g. the pericardial sac or a joint space, is often associated with inflammatory, infective or obstructive conditions and is called an effusion.

Pleural effusion

This is excess pleural fluid in the pleural cavity. It is usually due to pleural infection or inflammation, or to left ventricular failure, which increases pressure in the pulmonary circulation because the left ventricle is not able to pump out all the blood returning there from the lungs.

Ascites

This is accumulation of excess fluid in the peritoneal cavity. The most common causes include cirrhosis or other liver disease that reduces its capacity to produce plasma proteins.

Other causes include obstruction of abdominal lymph nodes draining the peritoneal cavity and heart failure, which can cause venous congestion in the peritoneal and hepatic veins. Cancer can cause ascites because many tumours release pro-inflammatory mediators that increase permeability of vessels, allowing fluid to leak out and accumulate in body cavities.

SPOT CHECK

19. Why can left ventricular failure cause pulmonary oedema?
20. How can liver failure cause ascites?

Diseases of the heart

Learning outcomes

After studying this section, you should be able to:

- describe the consequences of failure of either side or both sides of the heart
- explain the compensatory mechanisms that occur in heart failure
- explain the causes and consequences of faulty heart valve function
- define the term 'ischaemic heart disease'
- discuss the main conditions associated with ischaemic heart disease
- describe rheumatic heart disease and its effects on cardiac function
- explain the underlying pathophysiology of endocarditis
- describe, with reference to the standard ECG trace, the main cardiac arrhythmias
- describe the principal congenital cardiac abnormalities.

Heart (cardiac) failure

The heart is described as failing when it is unable to circulate sufficient blood to meet the needs of the body. In mild cases, cardiac output is adequate at rest and becomes inadequate only when tissue needs are increased, e.g. in exercise. Either side of the heart may fail, but because both sides of the heart are part of one circuit, when one side begins to fail, it frequently leads to increased strain on, and eventual failure of, the other side too. The main clinical manifestations depend on which side of the heart is most affected. Left ventricular failure is more common than right because of the greater workload of the left ventricle.

Compensatory mechanisms in heart failure

In acute heart failure the body has little time to make compensatory changes, but if the heart fails over a period of time the following changes are likely to occur in an attempt to maintain cardiac output and tissue perfusion, especially of vital organs:

- The cardiac muscle mass increases (hypertrophy, see Fig. 3.29), thickening the walls of the chambers.
- The heart chambers enlarge.
- Decreased renal blood flow activates the RAAS (see Fig. 13.15), which leads to salt and water retention. This increases blood volume and cardiac workload. The direct vasoconstrictor action of angiotensin II increases peripheral resistance and puts further strain on the failing heart.

Acute heart failure

If heart failure occurs abruptly, the supply of oxygenated blood to body tissues is suddenly and catastrophically reduced and there is no time for significant compensation to take place. Death may follow if the brain's vital centres are starved of oxygen. Even if the person survives the acute phase, the damage to the heart may lead to chronic heart failure. Common causes include:

- Myocardial infarction (p. 138). This is the commonest cause of acute heart failure.
- Pulmonary embolism blocking blood flow through the pulmonary circulation. The heart fails if it cannot pump hard enough to overcome the obstruction.
- Life-threatening cardiac arrhythmia, which can badly impair or arrest the pumping action of the heart.
- Rupture of a heart chamber or valve cusp, which greatly increases the cardiac effort required to maintain adequate output.
- Severe malignant hypertension (p. 142), which greatly increases peripheral resistance and increases cardiac workload.

Chronic heart failure

This develops gradually and the early stages may be asymptomatic because compensatory changes occur, as described above. When compensatory mechanisms are exhausted, myocardial function gradually declines. Underlying causes include degenerative heart changes with advancing age, and many chronic conditions, including anaemia, lung disease, hypertension or pre-existing cardiac disease.

Right-sided (congestive cardiac) failure

The right ventricle fails when it cannot generate enough force to push blood through the lungs.

When compensation has reached its limit and the ventricle can no longer empty adequately, the right atrium and venae cavae

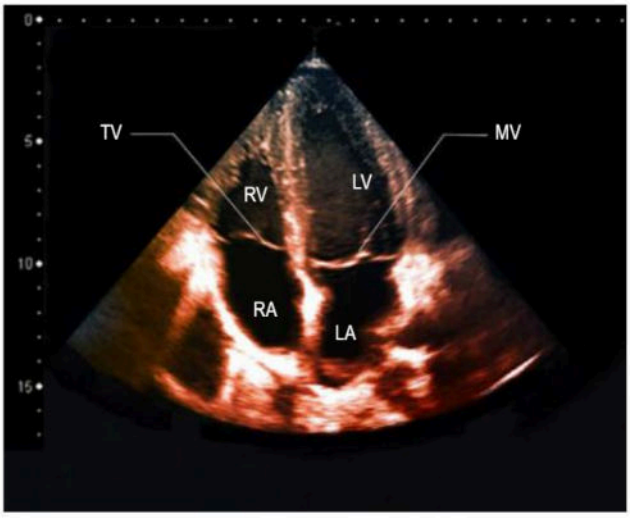

Figure 5.59 Left ventricular enlargement. Coloured ultrasound scan taken during systole. RV: right ventricle; LV: left ventricle; RA: right atrium; LA: left atrium; TV: tricuspid valve; MV: mitral valve. (From Science Photo Library. Reproduced with permission.)

become congested with blood and eventually congestion backs up throughout the venous system. The organs affected first are the liver, spleen and kidneys. Oedema of the limbs and ascites usually follow.

Right ventricular failure may be caused by increased vascular resistance in the lungs or weakness of the myocardium.

Resistance to blood flow through the lungs

When pulmonary artery resistance is high, the right ventricle has more work to do. The two most common causes are pulmonary embolism and left ventricular failure, when the pulmonary circulation is congested because the left ventricle is not clearing all the blood flowing into it.

Weakness of the myocardium

This is caused by myocardial damage following ischaemia or infarction.

Left-sided (left ventricular) failure

This occurs when the left ventricle cannot contract strongly enough to force blood into the aorta, and the ventricle cannot then pump out the blood it receives from the left atrium. Causes include ischaemic heart disease, which reduces the contractility of the myocardium, and hypertension, when cardiac workload is increased because of raised peripheral resistance. Disease of the mitral and/or aortic valves may prevent efficient emptying of the heart chambers, increasing myocardial workload.

In the initial stages of left ventricular failure, the chamber may enlarge in compensation (Fig. 5.59). Left ventricular failure leads to congestion and dilation of the left atrium and an increase in pulmonary blood pressure. This can back up through the right side of the heart and eventually cause systemic venous congestion.

Exercise tolerance becomes progressively reduced as the condition worsens and is accompanied by cough, caused by pulmonary oedema. The person is easily tired, with poorly perfused peripheral tissues and low blood pressure.

Congestion in the lungs causes pulmonary oedema and dyspnoea, often worse at night. This may be due to raised blood volume as fluid from peripheral oedema is reabsorbed when the person slips down in bed during sleep.

Disorders of heart valves

The heart valves prevent backflow of blood in the heart during the cardiac cycle. The mitral and aortic valves are subject to greater pressures than those on the right side and are therefore more susceptible to damage. Distinctive heart sounds arise when the valves close during the cardiac cycle (see Fig. 5.19), and damaged valves generate abnormal heart sounds called murmurs. A severe valve disorder causes heart failure because the heart must work harder to pump blood through narrowed or distorted valves. The most common causes of valve defects are rheumatic fever (p. 139), fibrosis following inflammation, and congenital abnormalities.

Stenosis

This is the narrowing of a valve opening, partially obstructing blood flow through the valve. It occurs when inflammation and encrustations roughen the edges of the cusps so that they stick together, reducing blood flow. Healing forms fibrous tissue that shrinks as it ages, increasing the stenosis and leading to incompetence.

Incompetence

Sometimes called regurgitation, this is caused by failure of a valve to close completely, allowing blood to flow backwards.

Ischaemic heart disease

Ischaemia of the myocardium is usually caused by atheromatous plaques narrowing or blocking one or more branches of the coronary arteries (Fig. 5.60). The blockage may be due simply to the bulging plaque itself, or plaques complicated by thrombosis. The overall effect depends on the size of the coronary artery involved and whether it is partially or completely blocked. Narrowing of an artery causes angina pectoris, and complete blockage causes myocardial infarction.

When atheroma develops slowly, a collateral arterial blood supply may have time to develop and maintain blood supply. The collateral supply is due to dilation of the anastomotic arteries (p. 87) forming a network of linking vessels in the coronary artery system. However, if narrowing or blockage of an artery occurs suddenly, for example by a travelling blood clot, the anastomotic arteries may not be able to dilate quickly enough to supply enough blood to meet myocardial needs.

Angina pectoris

This is sometimes called angina of effort because the increased cardiac output required during extra physical effort causes myocardial ischaemia with severe chest pain which may also radiate to the arms, neck and jaw. Other precipitating factors for angina include cold weather and emotional states, both of which increase heart rate and cardiac workload.

A narrowed coronary artery may supply sufficient blood to the myocardium to meet its needs during rest or moderate exercise but not when greatly increased cardiac output is needed; for example, walking may be tolerated but not running. The thick, inflexible atheromatous artery wall is unable to dilate to allow for the increased blood flow needed by the more active myocardium, which then becomes ischaemic. In the early stages of the disease, the chest pain stops when the exercise stops.

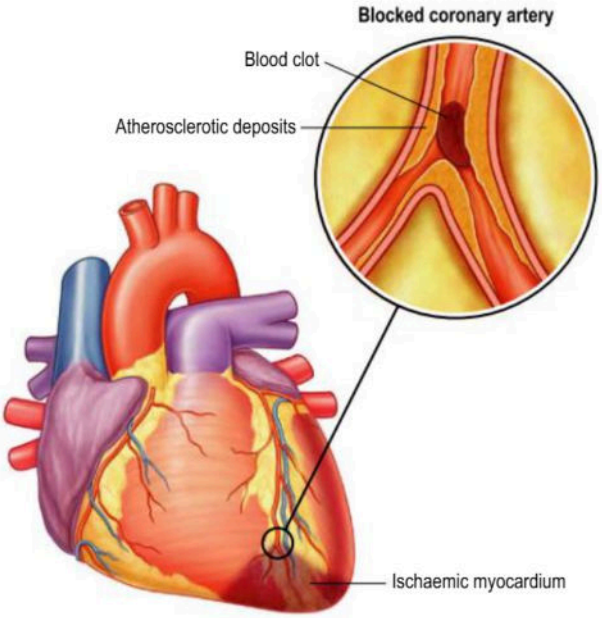

Figure 5.60 Coronary artery blockage and myocardial infarction.

Myocardial infarction

This is a significant cause of death in the developed world. The myocardium may infarct when a branch of a coronary artery is blocked, usually by an atheromatous plaque complicated by thrombosis (Fig. 5.60). Prolonged loss of blood supply causes permanent damage because cardiac muscle cannot regenerate, and the dead muscle is replaced with non-functional fibrous tissue. Speedy restoration of blood flow through the blocked artery using thrombolytic (clot-dissolving) drugs can greatly limit damage and improve prognosis, but treatment must be started within a few hours of the infarction occurring. Figure 5.61 is an angiogram showing obstruction of the left circumflex artery, which supplies a large portion of the lateral and posterolateral walls of the left ventricle. Obstruction here, or in the left anterior descending artery, is likely to lead to life-threatening infarction because the left ventricle supplies the body with oxygenated blood.

Myocardial infarction is usually accompanied by severe crushing chest pain behind the sternum, which, unlike angina pectoris, continues even when the individual is at rest.

Complications

These may be fatal and include:

- severe and sometimes life-threatening arrhythmias, especially ventricular fibrillation (p. 139), due to disruption of the cardiac conducting system

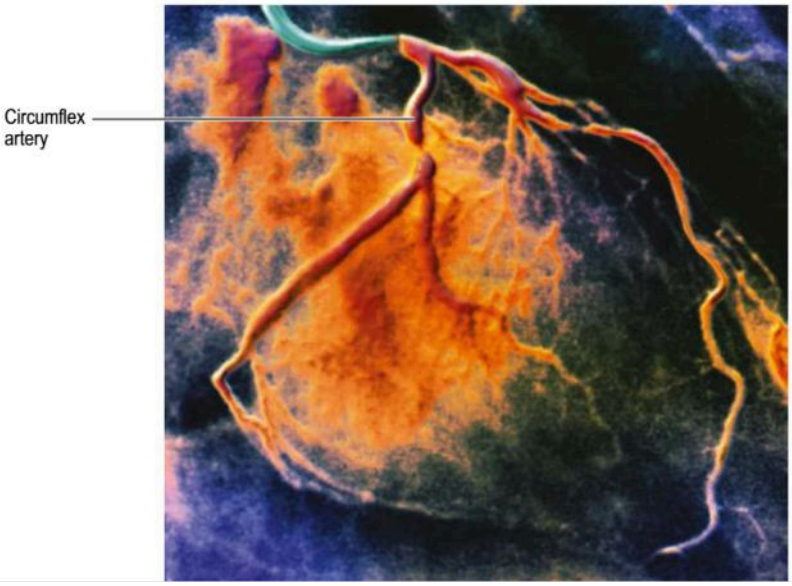

Figure 5.61 Coloured coronary angiogram showing obstruction of the circumflex branch of the left coronary artery. (From Science Photo Library. Reproduced with permission.)

- acute heart failure (p. 136), if the damage is so extensive that cardiac output cannot be maintained, and, in severe cases causes cardiogenic shock
- rupture of a ventricle wall, usually within 2 weeks of the original episode, which occurs because the damaged tissue liquefies, weakening the muscle at the site
- pulmonary or cerebral embolism originating from any clot that forms inside the heart over the infarct
- pericarditis
- angina pectoris (see above)
- recurrence.

Rheumatic heart disease

Rheumatic fever is an inflammatory illness that sometimes follows streptococcal throat infections, usually in children and young adults. It is an autoimmune disorder; the antibodies produced to combat the original infection attack and damage connective tissues, including the heart, joints (rheumatoid arthritis, p. 481) and skin.

Death rarely occurs in the acute phase but the heart valves may be permanently damaged, eventually leading to disability and possibly cardiac failure.

Acute rheumatic heart disease

In the acute stages, all layers of the heart wall are inflamed (pancarditis, 'pan-' meaning 'all of'). The heart valves, especially the mitral valve, are frequently affected, and chronic valvular incompetence follows recovery in at least half of acute cases. The inflamed myocardium can fail, leading to signs of heart failure, including tachycardia, breathlessness and cardiac enlargement. Inflammation of the pericardium can lead to friction within the pericardial cavity as the heart beats, pain behind the sternum and interference with the pumping action of the heart. Permanent fibrotic damage may fuse the visceral and parietal layers of the serous pericardium together, restricting the heart's action.

Chronic rheumatic heart disease

Inflamed myocardium is replaced by fibrous tissue as it heals; this fibrous tissue interferes with the action of the myocardium and the heart valves. Fibrotic nodules develop on their cusps, which shrink as they age, distorting the cusp and causing stenosis and incompetence of the valve. Most of these patients have mitral valve damage but the aortic valve is frequently affected too. Chronic fibrotic changes in the pericardium and myocardium cause heart failure.

Sometimes rheumatic valvular disease presents with no history of acute rheumatic fever or streptococcal infection.

Infective endocarditis

Microbes travelling in the bloodstream cannot adhere to healthy endothelium, but they can attach and establish growths at areas of endothelial damage. In the heart, common sites of endocardial roughening or damage include those around the heart valves (including prosthetic valves), especially if they have been damaged by rheumatic disease. The margins of congenital heart defects, e.g. ventricular septal defect (p. 141), are also vulnerable. The endothelium in these areas are exposed to rapid, possibly turbulent blood flow, which can cause minor endothelial damage, to which microbes can attach. The incidence of this serious disease is therefore increased in people with pre-existing cardiac abnormalities. It may be acute or subacute and is sometimes fatal without treatment.

It is usually bacterial, either staphylococcal or streptococcal, although other bacteria or fungi can be involved. The causative bacteria usually enter the bloodstream from a skin wound or from the mouth, perhaps as the result of dental surgery or untreated dental caries. They adhere to platelets and form tiny infected emboli, which settle on damaged valves and develop into masses of platelets, fibrin and bacteria called vegetations. Microbes within vegetations are protected from normal body defences and antibiotics and so can be resistant to treatment. Immunosuppression, e.g. in cancer therapy or in immune disease, increases the risk of infective endocarditis.

Cardiac arrhythmias

The heart rate is normally determined by regular firing of the SA node. The rhythm is determined by the route of impulse transmission through the conducting system and recorded on a standard ECG tracing (Fig. 5.62A). A cardiac arrhythmia is any disorder of heart rate or rhythm and is the result of abnormal generation or conduction of impulses. The normal cardiac cycle (see Fig. 5.19) gives rise to normal sinus rhythm, which has a rate between 60 and 100 bpm.

Sinus bradycardia

This is normal sinus rhythm below 60 bpm. This may occur during sleep and is common in athletes. It is abnormal when it follows myocardial infarction or accompanies raised intracranial pressure (p. 198).

Sinus tachycardia

This is normal sinus rhythm above 100 bpm when the individual is at rest. It accompanies exercise and anxiety, but is also seen in some disorders, e.g. fever, hyperthyroidism and some cardiac conditions.

Asystole

This occurs when there is no electrical activity in the ventricles and therefore no cardiac output. The ECG shows a flat line (Fig. 5.62B). Ventricular fibrillation and asystole cause sudden and complete loss of cardiac output, i.e. cardiac arrest and death.

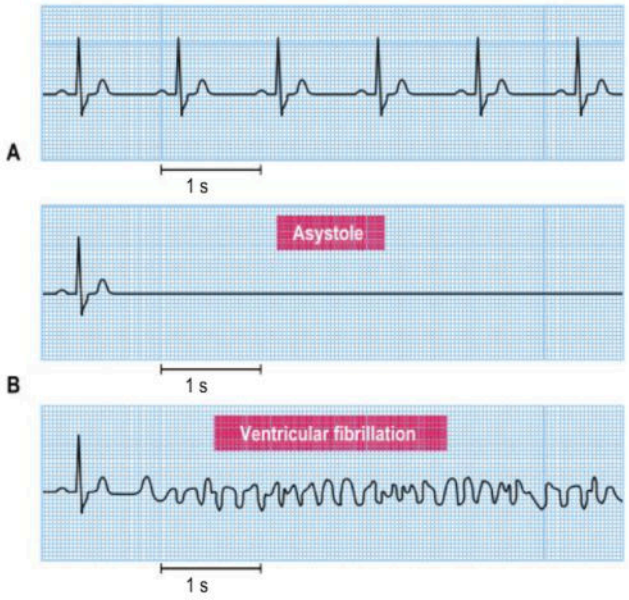

Figure 5.62 ECG traces. (A) Normal sinus rhythm. (B) Life-threatening arrhythmias.

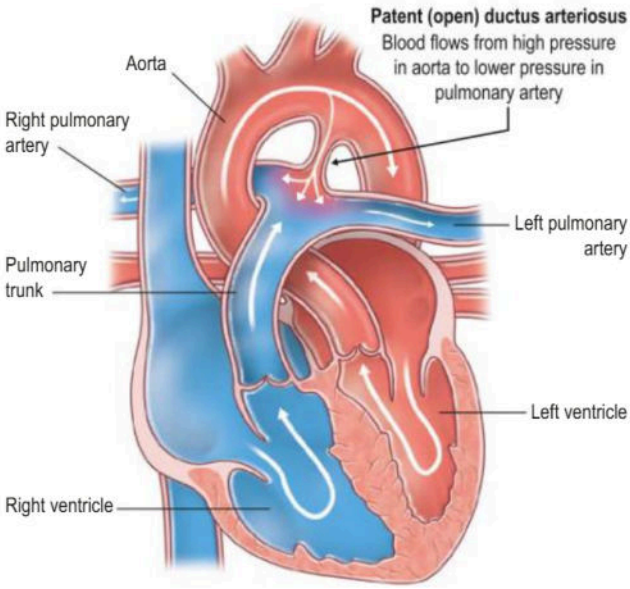

Figure 5.63 The ductus arteriosus in the fetus.

Fibrillation

This is disorderly and uncoordinated contraction of the cardiac muscle fibres. The chambers do not contract as a coordinated unit and the pumping action is disrupted.

In atrial fibrillation (AF), atrial pumping is ineffective and stimulation of the AV node is irregular. AF is very common, especially in older adults. It may be asymptomatic because, although atrial function is disordered, most ventricular filling happens passively and atrial contraction only tops it up, so cardiac output is maintained. However, common symptoms include unpleasant palpitations, breathlessness and fatigue. The pulse is irregular and there are no discernible P waves on the ECG. Often the cause is unknown but AF can develop as a result of many forms of heart disease, thyrotoxicosis (p. 256), alcoholism and lung disease.

Ventricular fibrillation is a medical emergency that is swiftly fatal if untreated because the chaotic electrical activity within the ventricular walls cannot coordinate an effective pumping action, leading to cardiac arrest. The heart stops pumping into both the pulmonary and the systemic circulations. No pulses can be felt, consciousness is lost and breathing stops. The ECG shows an irregular chaotic trace with no recognisable wave pattern (Fig. 5.62B).

Heart block

Heart block occurs when normal impulse transmission is blocked or impaired. A common form involves obstruction of impulse transmission through the AV node, but less commonly conducting tissue in the atria or ventricles can also be affected. When the AV node is involved, the delay between atrial and ventricular contraction is increased. The severity depends on the extent of loss of stimulation of the AV node.

In complete heart block, none of the SA node impulses are transmitted through the AV node and ventricular contraction becomes entirely independent of atrial activity. Freed from the normal pacing action of the SA node, the ventricles are driven by impulses generated by the pacemaker activity of the AV node, resulting in slow, regular ventricular contractions and a heart rate of about 30–40 bpm. In this state the heart is unable to respond quickly to a sudden increase in demand by, for example, exercise. The most common causes are:

- acute ischaemic heart disease
- myocardial fibrosis following repeated infarctions or myocarditis involving part of the induction pathway
- drugs used to treat cardiovascular disease, e.g. digitalis, propranolol.

When heart block develops gradually, there is some degree of adjustment in the body to reduced cardiac output but, if progressive, it eventually leads to death from cardiac failure and cerebral anoxia.

Congenital abnormalities

Abnormalities of the heart and great vessels at birth may be due to intrauterine developmental errors or to the failure of the heart and blood vessels to adapt to extrauterine life after birth. Sometimes there are no symptoms and the abnormality is recognised only when complications appear.

Patent ductus arteriosus

In the fetus, the ductus arteriosus bypasses the non-functional lungs (Fig. 5.63). At birth, when the pulmonary circulation is established, the ductus arteriosus should close completely. If it remains patent (open), blood regurgitates from the aorta to the pulmonary artery where the pressure is lower, reducing the volume entering the systemic

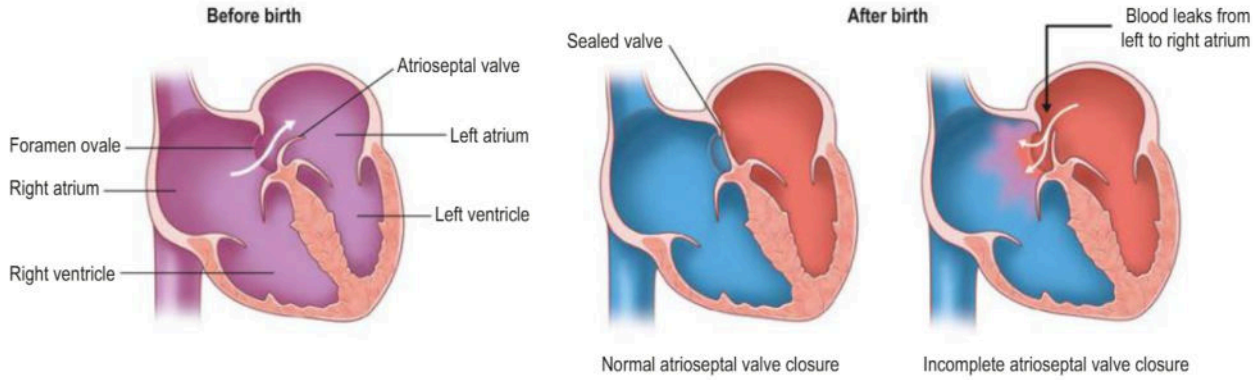

Figure 5.64 Atrioseptal valve. Normal and incomplete closure after birth.

circulation and increasing the volume of blood in the pulmonary circulation. This leads to pulmonary congestion and eventually cardiac failure.

Atrial septal defect

This is commonly called a 'hole in the heart' and occurs if closure of the foramen ovale (Fig. 5.64) does not occur properly after birth. After birth, when the pulmonary circulation is established and the pressure in the left atrium exceeds that in the right atrium, the atrioseptal valve closes. Later the closure becomes permanent due to fibrosis.

If the atrioseptal valve does not completely seal the hole, an opening between the atria remains patent. In many cases, it is too small to cause symptoms in childhood but they may appear in adulthood. However, in severe cases, blood flows back to the right atrium from the left. This increases the right ventricular and pulmonary pressure, causing hypertrophy of the myocardium and eventually cardiac failure. As pressure in the right atrium rises, blood flow through the defect may be reversed, but this is not an improvement because deoxygenated blood is then entering the general circulation.

Coarctation of the aorta

The most common site of coarctation (narrowing) of the aorta is between the left subclavian artery and ductus arteriosus. This forces more blood than normal into the brachiocephalic, left common carotid and left subclavian arteries, leading to hypertension in the upper body. There may be systemic hypotension if there is inadequate flow past the coarctation into the descending aorta and its branches.

Fallot's tetralogy

This is a characteristic combination of four congenital cardiac abnormalities, which causes cyanosis, growth retardation and exercise intolerance in babies and young children. The four abnormalities are:

- stenosis of the pulmonary artery at its point of origin, which increases right ventricular workload
- ventricular septal defect, i.e. an abnormal communicating hole between the two ventricles, just below the atrioventricular valves
- aortic misplacement, i.e. the origin of the aorta is displaced to the right so that it is immediately above the septal defect
- right ventricular hypertrophy to counteract the pulmonary stenosis.

Cardiac function is inadequate to meet the needs of the growing child; surgical correction carries a good prognosis.

SPOT CHECK

21. What is a heart murmur?
22. How can a streptococcal throat infection lead to heart disease?

Disorders of blood pressure

Learning outcomes

After studying this section, you should be able to:

- define the term 'hypertension'
- define essential and secondary hypertension and list the main causes of the latter
- discuss the effects of prolonged hypertension on the body, including elevated blood pressure in the lungs
- explain the term 'hypotension'.

Hypertension

Hypertension means a level of blood pressure that, taking all other cardiovascular risk factors into account, would benefit the patient if reduced. Blood pressure readings where systolic and diastolic values are below 130/85 mmHg, respectively, are generally considered normal. Readings that indicate the severity of hypertension are listed in Table 5.2.

Table 5.2 Hypertension: indicative blood pressure readings (NICE, 2019)

	Systolic reading (mmHg)	Diastolic reading (mmHg)
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	160–179	100–119
Severe hypertension	≥180	≥120

Hypertension is classified as essential (primary, idiopathic) or secondary to other diseases. Irrespective of the cause, hypertension commonly affects the kidneys (p. 392).

Essential hypertension

Essential hypertension is hypertension of unknown cause and is very common in the developed world. It accounts for 95% of all cases. Its cause is likely to be multifactorial, and the main risk factors are listed below. Treatment aims to prevent complications, which can be serious, primarily cardiovascular and renal disease. Sometimes complications, such as heart failure, cerebrovascular accident or myocardial infarction, are the first indication of hypertension, but often the condition is asymptomatic and only discovered during a routine examination.

Risk factors

Risk factors for hypertension include obesity, diabetes mellitus, family history, cigarette smoking, a sedentary lifestyle and high intakes of salt or alcohol. Stress may increase blood pressure, and there is a well-documented link between low birth weight and incidence of hypertension in later life.

Malignant (accelerated) hypertension

This is a rapid and aggressive acceleration of hypertensive disease. Diastolic pressure in excess of 120 mmHg is common. The effects are serious and quickly become apparent, e.g. retinal haemorrhage, papilloedema (oedema around the optic disc), cerebral oedema and progressive renal disease, leading to cardiac failure.

Secondary hypertension

Hypertension resulting from other diseases accounts for 5% of all cases (Box 5.5).

Box 5.5 Some causes of secondary hypertension

- Kidney disease (p. 392)
- Adrenal gland disorders
- Excessive steroid secretion (Conn's syndrome, Cushing's syndrome, p. 259)
- Excessive adrenaline (epinephrine) secretion, e.g. phaeochromocytoma (p. 261)
- Thyrotoxicosis (p. 256)
- Alcohol
- Obesity
- Pregnancy
- Drug treatment, e.g. oral contraceptives containing oestrogen, corticosteroids

Effects and complications of hypertension

The effects of long-standing and progressively rising blood pressure are serious (Fig. 5.65). Hypertension predisposes to atherosclerosis and has specific effects on particular organs.

Heart

The rate and force of cardiac contraction are increased to maintain cardiac output against a sustained rise in arterial pressure. The left ventricle hypertrophies to increase its contractile strength, but begins to fail when compensation has reached its limit. This is followed by back-pressure and accumulation of blood in the lungs (pulmonary congestion) and hypertrophy of the right ventricle, and eventually by right ventricular failure. Hypertension also predisposes to ischaemic heart disease (p. 137) and aneurysm formation (p. 132).

Brain

Stroke, caused by cerebral haemorrhage (p. 201), is common, the effects depending on the position and size of the ruptured vessel. Although the cerebral circulation is protected from fluctuations in systemic blood pressure by autoregulatory mechanisms (p. 102), sustained high blood pressure causes cerebral vascular damage. When a series of small blood vessels rupture, e.g. microaneurysms, at different times, there is progressive disability. Rupture of a large vessel causes extensive loss of function or death.

Kidneys

Autoregulation (p. 102) to an extent protects the kidneys from fluctuations in systemic blood pressure, but sustained hypertension causes kidney damage. If damage is sustained for only a short time, recovery may be complete. Otherwise the kidney damage causes further hypertension owing to activation of the RAAS (see Fig. 13.15), progressive loss of kidney function and kidney failure.

Blood vessels

High blood pressure damages blood vessels. The walls of small arteries become hardened, and in larger arteries the development of atheroma is accelerated. If other risk factors for vascular disease are present, such as diabetes or smoking, damage is more extensive. The vessel wall may become so badly weakened by these changes that an aneurysm develops, and as the blood vessels become progressively damaged and less elastic, hypertension worsens.

The capillaries of the retina and the kidneys are particularly susceptible to the effects of chronic hypertension, leading to retinal bleeding and reduced renal function. Damaged retinal blood vessels are clearly visible through an ophthalmoscope

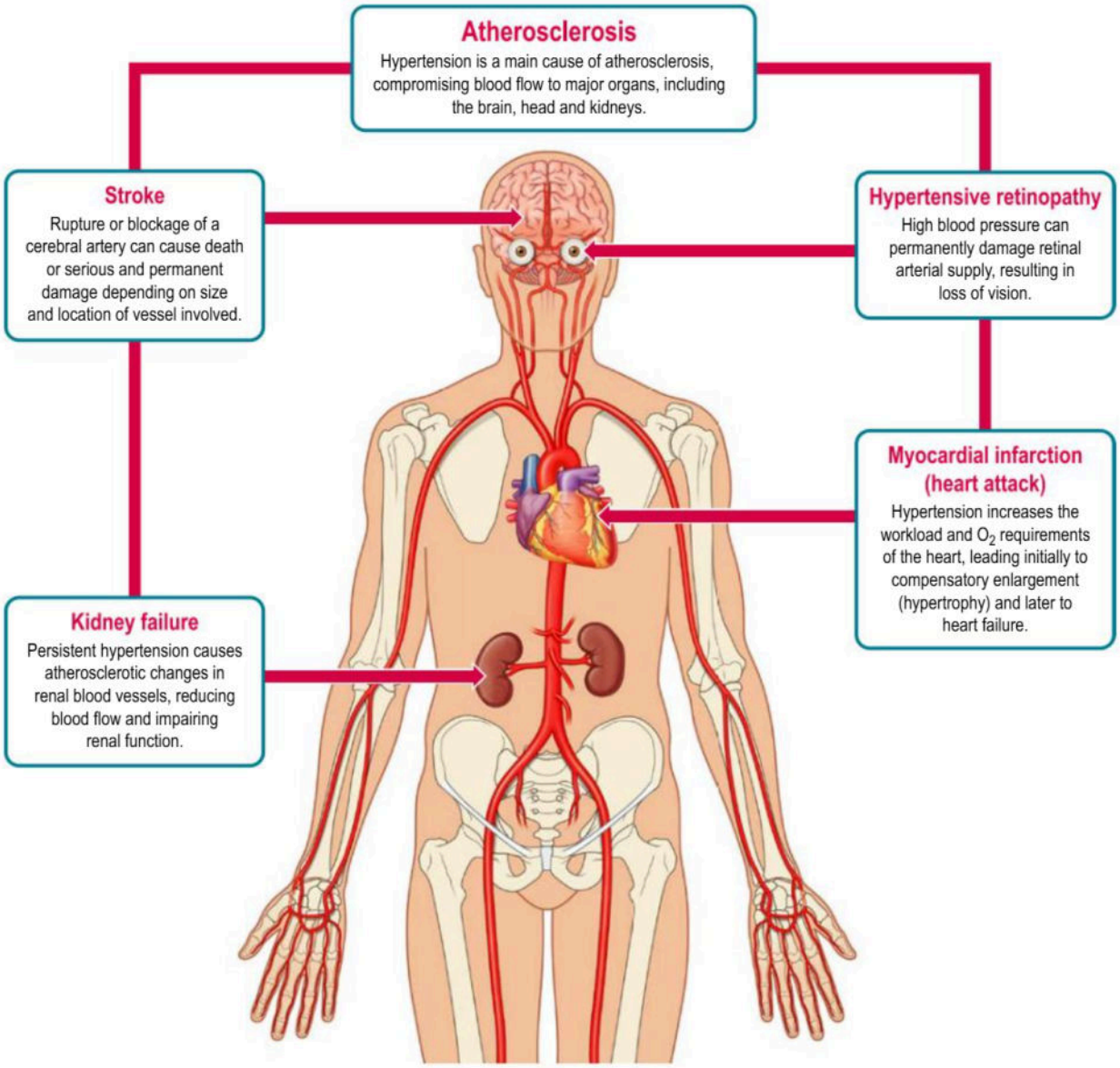

Figure 5.65 The main complications of hypertension.

on examination, and the first indication of hypertension may be picked up during a routine eye test.

Pulmonary hypertension

Normally, the pulmonary circulation is a low-pressure system, to prevent fluid being forced out of the pulmonary capillaries into the alveoli. When blood pressure rises, alveoli begin to fill with fluid (pulmonary oedema), which blocks gas exchange. Rising pulmonary blood pressure may result from left-sided heart failure (p. 137) or other problems with left ventricular function, when blood accumulates in the pulmonary circulation because the left ventricle is not pumping efficiently. Lung disease can also increase pulmonary blood pressure if there is destruction of lung capillaries, e.g. in emphysema. Primary pulmonary hypertension, where there is no identifiable cause, is rare.

Hypotension

This usually occurs as a complication of other conditions, such as shock (p. 127) or Addison's disease (p. 260). Low blood pressure leads to inadequate blood supply to the brain. Depending on the cause, unconsciousness may be brief (fainting) or more prolonged, possibly causing death.

Postural hypotension is an abrupt fall in blood pressure on standing up suddenly from a sitting or lying position. It causes dizziness and occasionally syncope (fainting). It is most common in older people, whose baroreceptor reflex

does not respond quickly enough to maintain blood pressure during sudden changes of body position.

SPOT CHECK

23. Explain the difference between primary and secondary hypertension.
24. Which capillary bed can be examined by non-invasive means and may be an early indication of hypertension?

Case study 1

Ayesha is listening to a patient's heart through a stethoscope. The bell of the stethoscope is laid on the chest wall over the mediastinum.

1. Which of the following structures is not found in the mediastinum?

   a. The thymus gland
   b. The pulmonary artery
   c. The trachea
   d. The first rib

2. The first heart sound corresponds to which event in the cardiac cycle?

   a. Closure of the mitral valve
   b. Closure of the aortic valve
   c. Opening of the pulmonary valve
   d. Opening of the tricuspid valve

3. Ayesha's patient has a heart rate of 55 bpm, with a regular rhythm. This is best described as:

   a. Sinus rhythm
   b. Sinus tachycardia
   c. Sinus bradycardia
   d. Sinus arrhythmia

4. Ayesha records her patient's ECG. On examination, the ECG shows a normal P wave followed by a normal QRS complex, but each QRS complex is slightly delayed (a prolonged P-R interval). This tells Ayesha that the electrical signal travelling through the heart is being slowed down as it travels through the:

   a. Atrioventricular bundle (of His)
   b. Atrioventricular node
   c. Sinoatrial node
   d. Atrioventricular valves

Case study 2

Chandler flew back from holiday four days ago. His flight home was a long one – twelve hours – and he is still recovering from jet lag. However, he has noticed a nagging, throbbing pain in his right calf, and the area is swollen, red and tender to touch. His colleague at work suggests this could be a blood clot, specifically a deep venous thrombosis, probably secondary to having sat still in a cramped aeroplane seat over an extended period of time.

1. In which of the following blood vessels is it most likely that Chandler's clot has formed?

   a. Femoral vein
   b. Radial vein
   c. Tibial vein
   d. Iliac vein

2. Why has obstruction of blood flow in Chandler's leg caused swelling?

   a. Increased blood hydrostatic pressure
   b. Increased blood osmotic pressure
   c. Increased lymphatic osmotic pressure
   d. Increased interstitial fluid hydrostatic pressure

3. Chandler puts off going to the doctor because he is catching up with work following his holiday. Two days after the conversation with his colleague, he is woken in the morning with pain in his chest and difficulty breathing. What is the likeliest cause?

   a. Myocardial infarction
   b. Bacterial pneumonia
   c. Acute bronchitis
   d. Pulmonary embolism

4. The pain in Chandler's chest is caused by accumulation of tissue wastes and inadequate blood supply. The correct term for inadequate blood supply to a tissue is:

   a. Necrosis
   b. Ischaemia
   c. Infarction
   d. Embolism

References and further reading

National Institute for Health and Care Excellence (NICE), 2019. Hypertension in adults: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng136.

Review and revise

Complete each of the following statements:

1. The heart is a muscular bag containing _____ chambers. The upper chambers are called _____ and the lower ones are the _____. The muscular wall between the right and left sides of the heart is the _____. The valves separating the upper and lower chambers are the _____ valves. The membrane lining the heart chambers is called the _____ and the muscle of the heart wall is the _____.

2. Arterial circulation to the right arm is through the _____ artery, which branches directly off the brachiocephalic artery. This artery continues through the armpit area as the _____ artery, and becomes the _____ artery as it crosses the elbow. On the distal side of the elbow, it divides into the _____ and the _____ arteries, which run down the lateral and medial aspects of the forearm, respectively. The branches supplying the hand are the _____ arteries, and those supplying the fingers are the _____ arteries.

Choose one answer to complete each of the following statements:

3. The ECG records: _____
   a. The muscular contraction of the heart
   b. The passage of an electrical signal through the heart muscle
   c. Blood flow through the heart chambers
   d. The opening and closing of the heart valves.

4. The cardiovascular centre is found in the: _____
   a. Carotid sinuses
   b. Atrial wall
   c. Cerebrum
   d. Brain stem.

5. In the placenta: _____
   a. Fetal and maternal blood is separated by the umbilical cord
   b. Blood coming from the maternal circulation travels through the umbilical artery
   c. Maternal blood fills the intervillous spaces
   d. Fetal blood oxygen levels fall as the blood flows through the placental circulation.

6. This change is associated with cardiovascular function in older age: _____
   a. A rise in average blood pressure
   b. Increased compliance of blood vessel walls
   c. A reduction in the likelihood of postural hypotension
   d. A tendency of the metabolic rate to rise.

7. An aneurysm involving bleeding directly into the arterial wall is called a: _____
   a. Berry aneurysm
   b. Fusiform aneurysm
   c. Dissecting aneurysm
   d. Saccular aneurysm.

8. This blood vessel links the gastrointestinal tract and the liver: _____
   a. Mesenteric vein
   b. Hepatic artery
   c. Gastroepiploic artery
   d. Hepatic portal vein.

9. Oedema is: _____
   a. Low blood volume
   b. Excess interstitial fluid
   c. Slow blood flow
   d. An electrolyte imbalance.

10. Starting at the right atrium in List A, place the items in List B in the correct order to describe the circulation of the blood:

List A

Right atrium

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Right atrium

List B

Pulmonary vein
Left ventricle
Pulmonary capillaries
Left atrioventricular valve
Systemic capillaries
Right ventricle
Aorta
Pulmonary artery
Systemic veins
Right atrioventricular valve
Aortic valve
Left atrium
Systemic arteries

11. Match each letter in List A to the appropriate number(s) in List B:

List A

_____ (a) Tunica intima
_____ (b) Tunica media
_____ (c) Tunica externa

List B

1. Rich in smooth muscle
2. Fibrous for protection
3. Regulates tone
4. The only layer present in capillaries
5. Only one cell thick
6. Responds to autonomic stimulation
7. Covers valves in veins
8. Continuous with the endocardium

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 6

The lymphatic system

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Body cells are bathed in interstitial (tissue) fluid, which leaks constantly out of the bloodstream through the permeable walls of blood capillaries. It is therefore very similar in composition to blood plasma. Most fluid that escapes from the bloodstream is reabsorbed into the venous ends of the blood capillaries, but the excess, along with any particulate matter including cell debris and bacteria, is drained from the tissue spaces by a network of thin-walled lymphatic capillaries. This prevents the tissues from becoming swollen. Fluid in the lymphatic vessels, called lymph, is filtered through lymph nodes, which are packed with immune cells, before being returned to the bloodstream. This fulfils an important defence function, monitoring the health of the tissues and alerting the immune system to invaders. Like blood capillaries, the lymphatic capillaries merge to form progressively larger and larger lymphatic vessels, which eventually empty into a major vein.

The lymphatic system (Fig. 6.1) consists of:

- lymph
- lymph vessels
- lymph nodes
- lymph organs, e.g. spleen and thymus
- diffuse lymphoid tissue, e.g. tonsils
- bone marrow.

The first sections of this chapter explore the structures and functions of these organs. In the final section, the consequences of disorders of the immune system are considered. The main effects of ageing on the lymphatic system relate to declining immunity, described in Chapter 15.

Functions of the lymphatic system

Tissue drainage

Every day, around 21 litres of fluid from plasma, carrying dissolved substances and some plasma protein, escape from the arterial end of the capillaries and into the tissues. Most of this fluid returns directly to the bloodstream via the capillary at its venous end but the excess, about 3–4 litres, is drained away as lymph by the lymphatic vessels. If this did not happen, the tissues would rapidly become waterlogged, and the cardiovascular system would begin to fail as the blood volume fell. The relationship between the lymphatic and circulatory systems is shown in Figure 6.2.

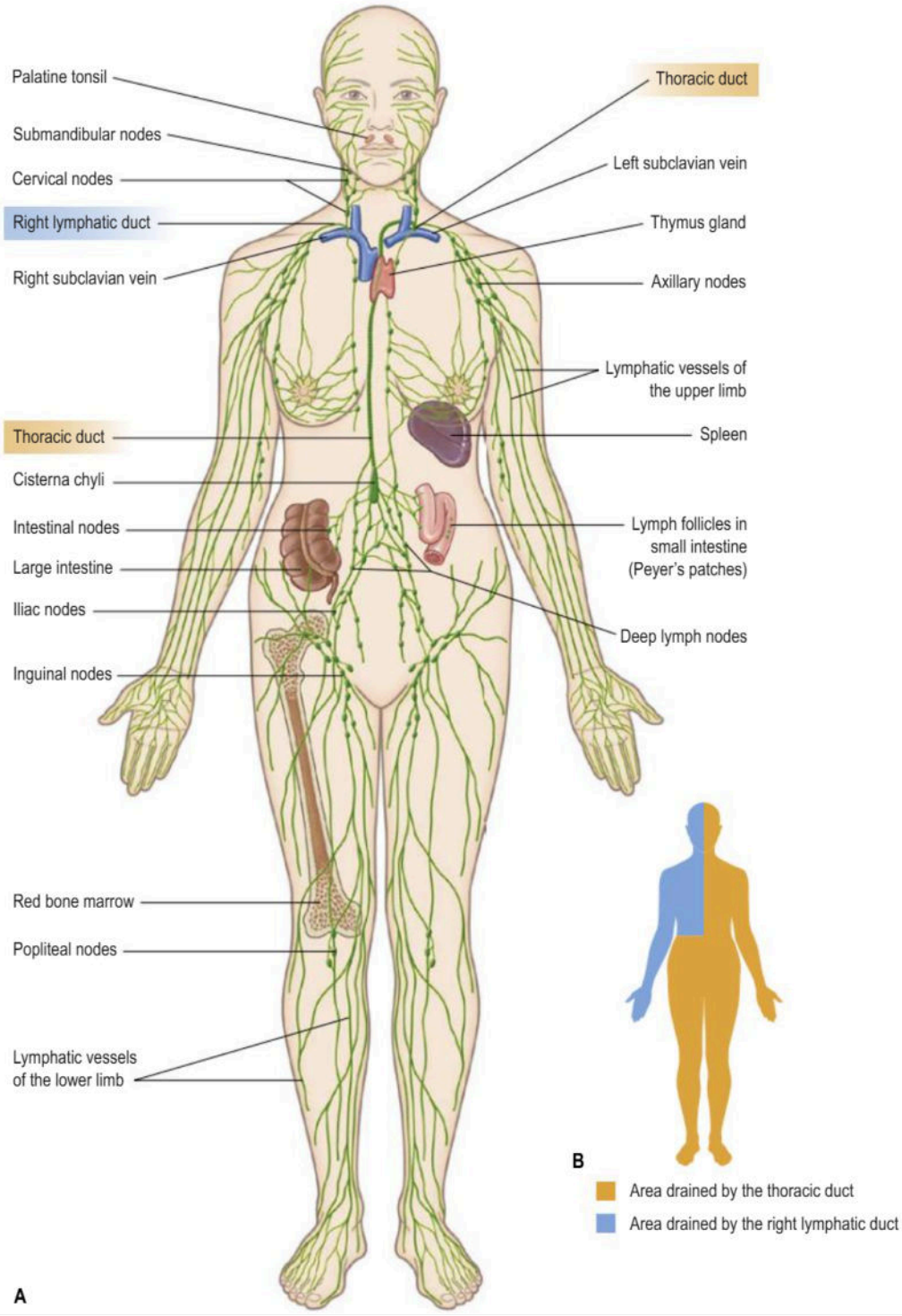

Fig. 6.1 The lymphatic system. (A) Major parts of the lymphatic system. (B) Regional drainage of lymph.

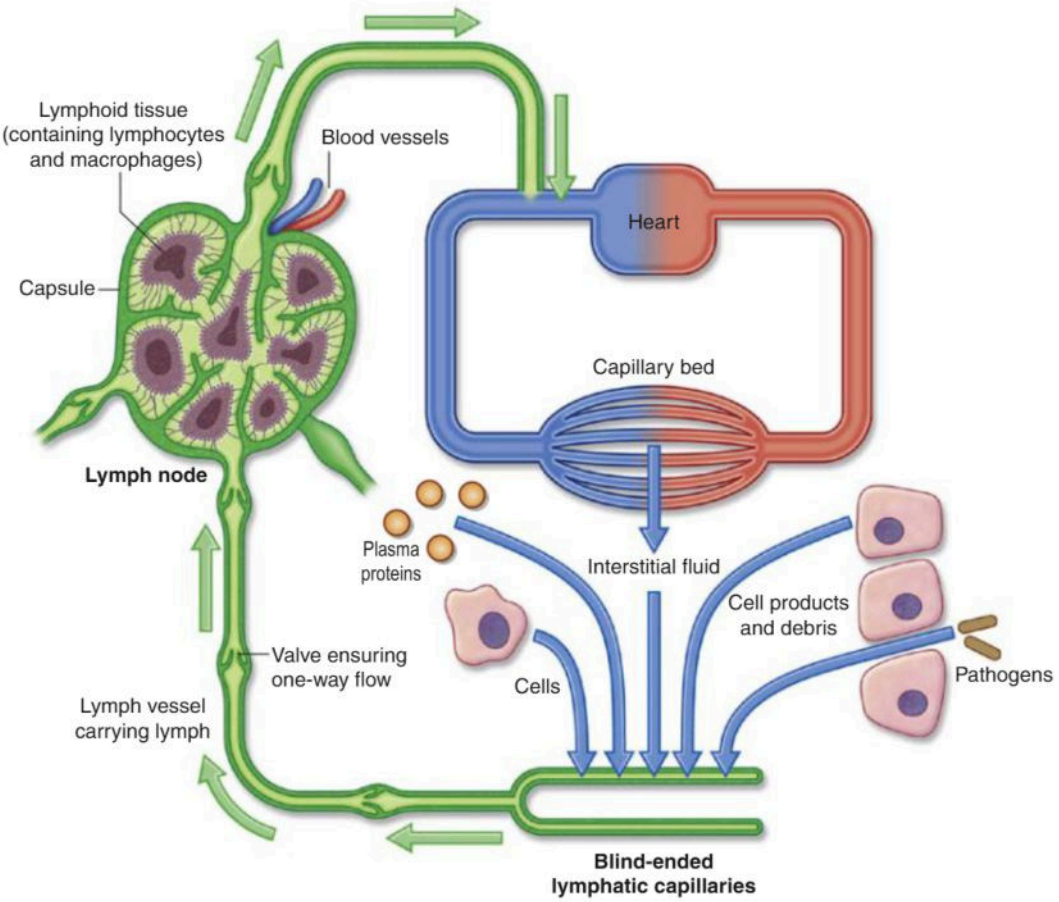

Fig. 6.2 The relationship between the lymphatic and circulatory systems, showing the formation of lymph. (Modified from Drake R, et al. 2020. Gray's Anatomy for Students, 4th ed. Elsevier.)

Absorption in the gastrointestinal tract

Breakdown products of fat and fat-soluble materials, e.g. the fat-soluble vitamins, are absorbed into the central lacteals (lymphatic vessels) of the villi in the small intestine (Ch. 12; Fig. 12.26).

Immunity

The lymphatic organs are concerned with the production and maturation of lymphocytes, the white blood cells responsible for immunity (Ch. 15). For this reason, bone marrow is considered to be lymphatic tissue.

Lymph vessels and lymph

Learning outcomes

After studying this section, you should be able to:

- identify the locations and functions of the main lymphatic vessels of the body
- describe the composition, circulation and the main functions of lymph.

Lymphatic vessels

The network of lymphatic vessels forms a one-way drainage system linking the interstitial spaces and the bloodstream.

Lymph capillaries

These originate as tiny blind-ended drainage tubes in the interstitial spaces (Fig. 6.2 and see Fig. 2.17). Like blood capillaries, their walls are formed from a single layer of endothelial cells, but they are even more permeable and permit some fairly large molecules and particulate matter to enter, including cell debris and some plasma proteins. The tiny capillaries merge to form larger lymph vessels, which ultimately return their contents to the bloodstream.

Nearly all tissues have a network of lymphatic vessels, important exceptions being the central nervous system, the cornea of the eye, the bones and the most superficial layers of the skin.

Larger lymph vessels

Lymph vessels are often found running alongside the arteries and veins serving the area. Their walls are about as thick as

those of small veins and have the same layers of tissue, i.e. a fibrous covering, a middle layer of smooth muscle and elastic tissue, and an inner lining of endothelium. Like veins, lymph vessels have numerous cup-shaped valves to ensure that lymph flows in a one-way system towards the thorax (Fig. 6.2).

Lymph vessels become larger as they merge, eventually forming two large ducts, the thoracic duct and right lymphatic duct, which empty lymph into the subclavian veins.

Thoracic duct

This duct begins at the cisterna chyli, a dilated lymph channel situated in front of the bodies of the first two lumbar vertebrae. It is about 40 cm long and empties lymph into the left subclavian vein in the root of the neck. It drains both legs, the pelvic and abdominal cavities, the left half of the thorax, head and neck, and the left arm (Fig. 6.1).

Right lymphatic duct

This is a dilated lymph vessel about 1 cm long. It lies in the root of the neck and empties lymph into the right subclavian vein from the right half of the thorax, head and neck and the right arm (Fig. 6.1).

Lymph

Lymph is a clear, watery fluid very similar in composition to interstitial fluid, although it contains less protein. It transports any plasma proteins that seep out of the capillaries back to the bloodstream, and carries away larger particles, e.g. pathogens, cells, cell products and cell debris from damaged tissues, which can then be filtered out and destroyed in the lymph nodes. Lymph contains lymphocytes (p. 420), which use the lymphatic system as a transport network, allowing them to patrol tissues throughout the body. In the lacteals of the small intestine, fats absorbed into the lymphatics give the lymph there (now called chyle) a milky appearance.

Transport of lymph

Lymph flows through the network of lymph vessels and is returned to the bloodstream (Fig. 6.2). There is no pump, like the heart, actively propelling lymph flow, but the muscle layer in the walls of the large lymph vessels has an intrinsic ability to contract rhythmically (the lymphatic pump). In addition, lymph vessels are compressed by activity in adjacent structures, such as contraction of muscles and the regular pulsation of large arteries. This 'milking' action on the lymph vessel wall helps to push lymph along. Like veins, lymphatic vessels have valves to prevent backflow.

Changes in thoracic pressure associated with the respiratory cycle also help lymph flow. At the peak of inspiration, when the pressure in the chest is at its lowest, lymph is 'sucked' along the right lymphatic duct and so increases lymph flow into the subclavian vein.

SPOT CHECK

1. Which lymphatic vessel drains lymph from the right arm?
2. Name three factors that keep lymph moving at low pressure, even against gravity.

Lymphatic organs and tissues

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the structure and functions of a typical lymph node with those of the spleen
- describe the location, structure and function of the thymus gland
- describe the locations and function of the tonsils
- describe the location, structure and function of mucosa-associated lymphatic tissue (MALT).

Lymph nodes

Lymph nodes are oval or bean-shaped organs that lie along the length of lymph vessels, often in groups. They are most numerous along lymph vessels carrying lymph from tissues potentially vulnerable to infection, e.g. the respiratory and gastrointestinal systems. Lymph usually flows through 8–10 nodes before returning to the venous circulation. Nodes vary considerably in size, ranging from 1 mm to 25 mm in diameter.

Structure

Lymph nodes (Fig. 6.3) have an outer capsule of fibrous tissue that dips down into the node substance, forming partitions or trabeculae. The main substance of the node consists of reticular and lymphoid tissue. Reticular cells produce the network of reticulin fibres which provide internal structure within the lymph node. The lymphatic tissue is packed with immune and defence cells, including lymphocytes and macrophages (Fig. 6.4).

As many as four or five afferent lymph vessels may enter a lymph node, but only one efferent vessel carries lymph away from the node. Each node has a concave surface called the hilum, where its artery enters and its vein and the efferent lymph vessel leave.

Lymph nodes are arranged in deep and superficial groups. Lymph from the head and neck passes through deep and superficial cervical nodes (Fig. 6.5). Lymph from

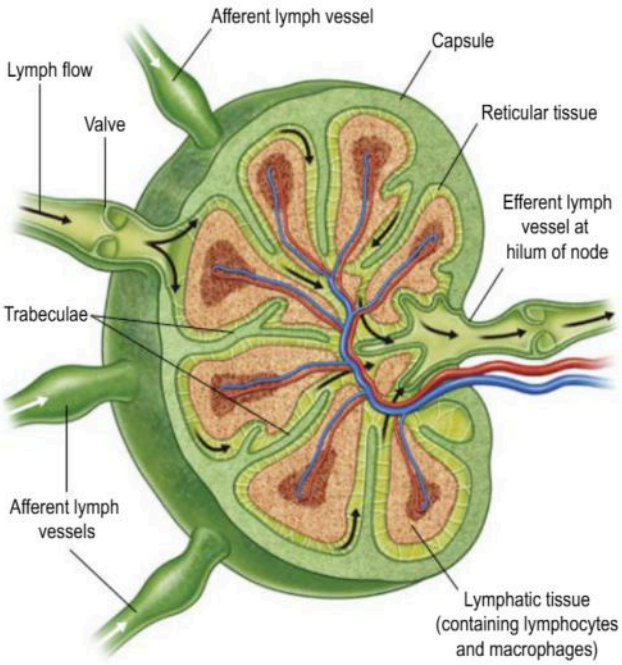

Fig. 6.3 Section through a lymph node. Arrows indicate the direction of lymph flow.

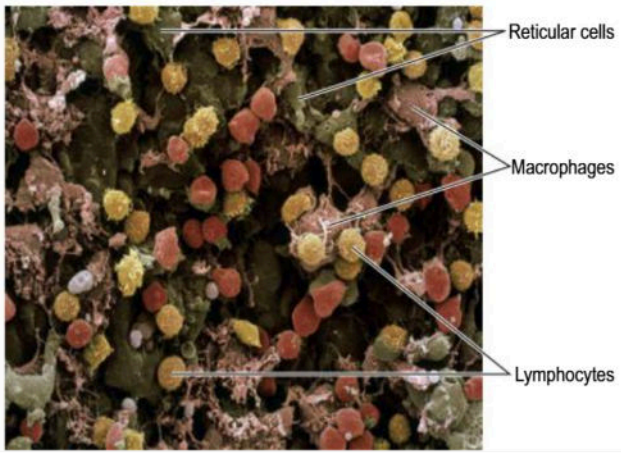

Fig. 6.4 Colour scanning electron micrograph of tissue in a lymph node. The cell population includes reticular cells *(brown)*, macrophages *(pink)* and lymphocytes *(yellow)*. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

the upper limbs passes through nodes situated in the elbow region, then through the deep and superficial axillary nodes.

Lymph from organs and tissues in the thoracic cavity drains through groups of nodes situated close to the mediastinum, large airways, oesophagus and chest wall. Most of the lymph from the breast passes through the axillary nodes.

Lymph from the pelvic and abdominal cavities passes through many lymph nodes before entering the cisterna chyli. The abdominal and pelvic nodes are mainly situated close

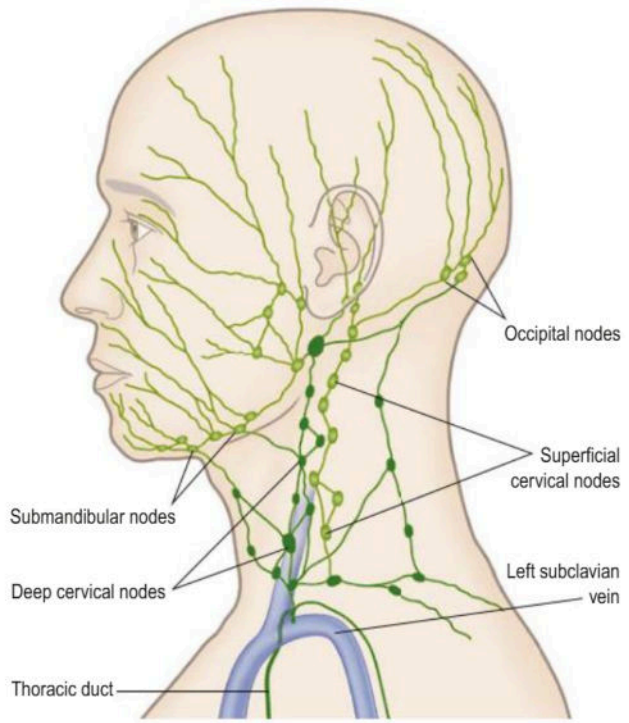

Fig. 6.5 Some lymph nodes of the face and neck.

to the blood vessels supplying the organs and also to the main arteries, i.e. the aorta and the external and internal iliac arteries. Lymph from the lower limbs drains through deep and superficial nodes, including groups of nodes behind the knee (popliteal nodes) and in the groin (inguinal nodes).

Functions

Defence

Lymph flows slowly through lymph nodes and is cleaned by the reticular and lymphatic tissue as it passes. Organic matter is removed and destroyed by macrophages. This may include bacteria, dead and live phagocytes containing ingested microbes, cells from malignant tumours and worn-out and damaged tissue cells. Some inorganic inhaled particles, e.g. from air pollution, cannot be destroyed by phagocytosis. These remain inside the macrophage, either causing no damage or killing it. Material not filtered out and dealt with in one lymph node passes on to successive nodes, and by the time lymph enters the blood it has usually been cleared of foreign matter and cell debris. If phagocytosis of bacteria is incomplete and viable bacteria survive, they may stimulate inflammation and enlargement of the node (lymphadenopathy).

Maturation and proliferation of lymphocytes

Some lymphocytes complete their maturation in lymph nodes and activated T- and B-lymphocytes (p. 420) multiply here. Antibodies produced by sensitised B-lymphocytes enter lymph and blood draining the node.

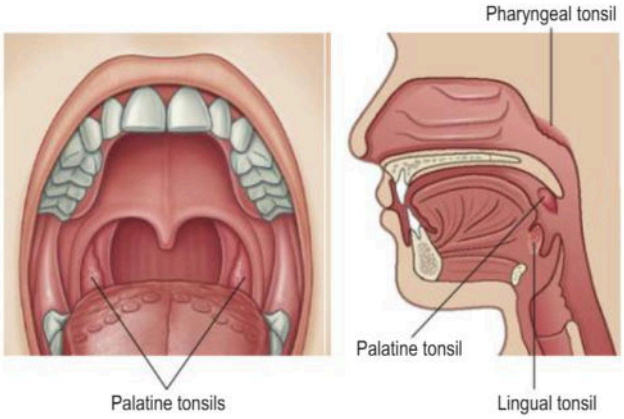

Fig. 6.6 The main tonsils of the mouth and pharynx.

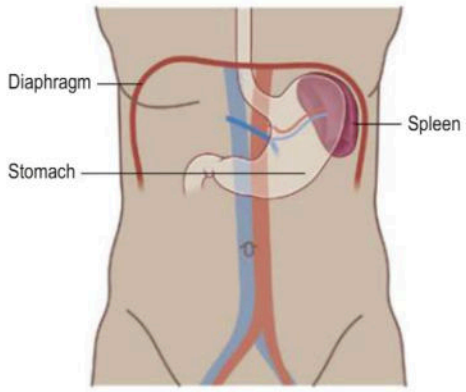

Fig. 6.7 The position of the spleen in the abdomen.

Tonsils

Tonsils (Fig. 6.6) are uncapsulated collections of lymphoid tissue located strategically in the back of the mouth and the throat, ideally placed to intercept swallowed or inhaled antigens. They are generally largest in childhood and regress with age. They possess deep pits or clefts that trap bacteria, which are then destroyed by the T-lymphocytes and macrophages packed into the tonsil. Infection and inflammation of tonsils (tonsillitis) may cause pain and obstruct breathing, especially in children, requiring their removal (tonsillectomy). There are three main groups of tonsils.

Pharyngeal tonsil

This is a single tonsil lying at the back of the nasal cavity, on the upper posterior wall of the pharynx.

Palatine tonsils

These paired tonsils are found on the pharyngeal wall at the back of the mouth.

Lingual tonsils

These are collections of lymphoid tissue at the back and sides of the tongue.

Spleen

The spleen contains reticular and lymphoid tissue and is the largest lymph organ. It lies in the left hypochondriac region of the abdominal cavity between the fundus of the stomach and the diaphragm (Fig. 6.7). It is purplish in colour and is usually about 12 cm long, 7 cm wide and 2.5 cm thick. It weighs about 200 g. The spleen is a soft organ and its anterior, medial and inferior surfaces are moulded by adjacent structures, producing the gastric, renal and colic impressions where it sits against the stomach, left kidney and large intestine, respectively (Fig. 6.8).

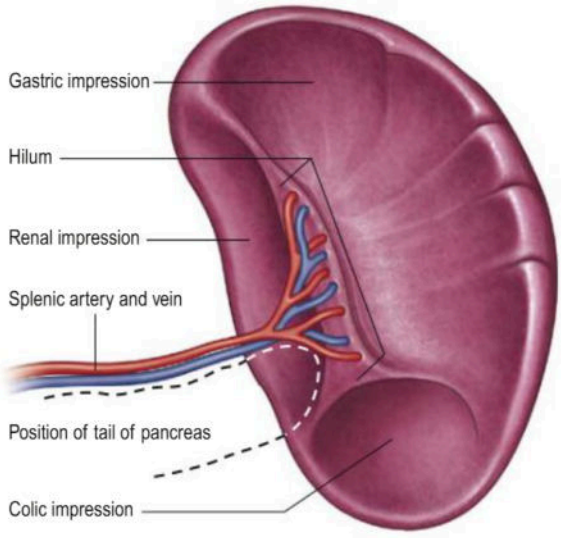

Fig. 6.8 The surface anatomy of the anterior, medial and inferior faces of the spleen.

Organs associated with the spleen

Superiorly and posteriorly – diaphragm.
Inferiorly – left colic flexure of the large intestine.
Anteriorly – fundus of the stomach.
Medially – pancreas and left kidney.
Laterally – diaphragm, which separates the spleen from the 9th, 10th and 11th ribs and the intercostal muscles.

Structure

The spleen is slightly oval in shape with the hilum on the lower medial border (Fig. 6.8). The anterior surface is covered with peritoneum. It is enclosed in a fibroelastic capsule that dips into the organ, forming trabeculae (Fig. 6.9). The cellular material, consisting of lymphocytes and

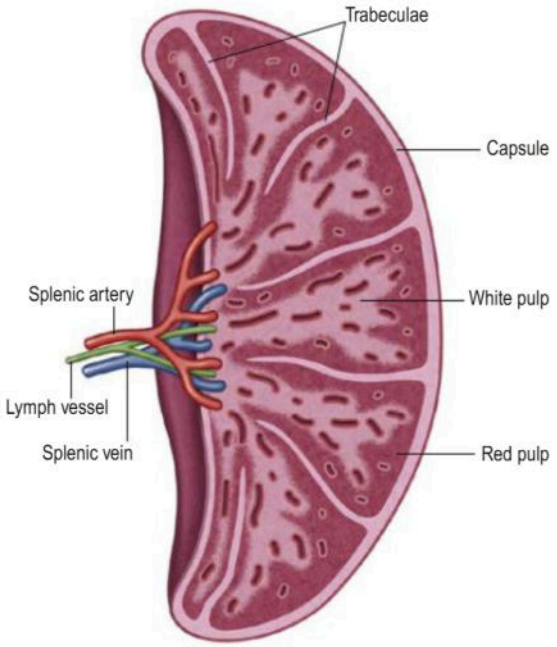

Fig. 6.9 A transverse section through the spleen.

macrophages, is called splenic pulp, and lies between the trabeculae. There are two types of pulp: red pulp, which stores large numbers of red blood cells, and white pulp, areas consisting of lymphatic tissue where sleeves of lymphocytes and macrophages surround the blood vessels.

The structures entering and leaving the spleen at the hilum are:

- the splenic artery, a branch of the coeliac artery
- the splenic vein, a branch of the portal vein
- lymph vessels (efferent only)
- nerves.

Blood passing through the spleen flows in sinusoids (p. 88), which have distinct pores between the endothelial cells, bringing it into close association with splenic pulp. This allows it to remove ageing or damaged cells from the bloodstream.

Functions

Phagocytosis

Old and abnormal erythrocytes are destroyed mainly in the red pulp of the spleen, and the breakdown products, bilirubin (see Fig. 12.39) and iron, are transported to the liver via the splenic and portal veins. Other cellular material, e.g. leukocytes, platelets and bacteria, is also phagocytosed in the red pulp.

Unlike lymph nodes, the spleen has no afferent lymphatics entering it, so it is not exposed to diseases spread by lymph.

Storage of blood

The spleen contains up to 350 mL of blood within the red pulp, and in response to sympathetic stimulation can rapidly return most of this volume to the circulation, e.g. in haemorrhage.

Immune response

The white pulp of the spleen contains T- and B-lymphocytes, which are activated by the presence of antigens, e.g. in infection. This plays an important role in immunity, and removal of the spleen leaves an individual at increased risk of infection. Lymphocyte proliferation during serious infection can cause enlargement of the spleen (splenomegaly).

Erythropoiesis

The spleen and liver are important sites of fetal blood cell production, and the spleen can also fulfil this function in adults in times of great need.

Thymus gland

The thymus gland lies in the upper part of the mediastinum behind the sternum and extends upwards into the root of the neck (Fig. 6.10). It weighs about 10–15 g at birth and grows until puberty, when it begins to atrophy. Its maximum weight is between 30 and 40 g and by middle age it has returned to approximately its weight at birth.

Organs associated with the thymus

Anteriorly – sternum and upper four costal cartilages.
Posteriorly – aortic arch and its branches, brachiocephalic veins, trachea.
Laterally – lungs.
Superiorly – structures in the root of the neck.
Inferiorly – heart.

Structure

The thymus consists of two lobes joined by areolar tissue. The lobes are enclosed by a fibrous capsule that dips into their substance, dividing them into lobules that consist of an irregular branching framework of epithelial cells and lymphocytes.

Functions

Lymphocytes originate from stem cells in red bone marrow (see Fig. 4.3). Those that enter the thymus develop into T-lymphocytes (T-cells, p. 420).

Thymic processing produces mature T-cells that can distinguish 'self ' tissue from foreign tissue, and also provides each T-cell with the ability to react to only one specific antigen from the millions it will encounter. Mature T-cells leave the thymus and enter the blood. Some enter

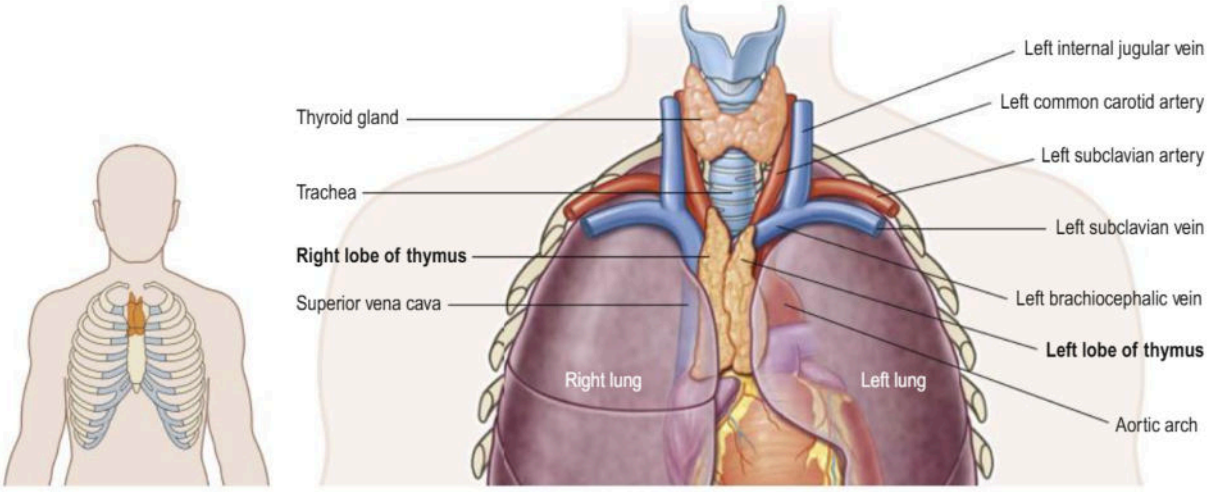

Fig. 6.10 The thymus gland and related structures in the adult.

lymphoid tissues and others circulate in the bloodstream. T-cell production, although most prolific in youth, probably continues throughout life from a resident population of thymic stem cells.

The maturation of the thymus and other lymphoid tissue is stimulated by thymosin, a hormone secreted by the epithelial cells forming the framework of the thymus gland. Shrinking of the gland begins after puberty and, with increasing age, the effectiveness of the T-cell response to antigens declines.

Mucosa-associated lymphoid tissue

Throughout the body, at strategically placed locations, are collections of lymphoid tissue that, unlike the spleen and thymus, are not enclosed within a capsule. They contain B- and T-cells, which have migrated from bone marrow and the thymus, and are important in the early detection of invaders. However, as they have no afferent lymphatic vessels, they do not filter lymph, and so are not exposed to diseases spread by lymph. Mucosa-associated lymphoid tissue (MALT) is found throughout the gastrointestinal tract, in the respiratory tract and in the genitourinary tract, all systems of the body exposed to the external environment.

Table 6.1 Common terms used in lymphatic system pathology

Term	Definition
Lymphangitis	Inflammation of lymph vessels
Lymphadenitis	Infection of lymph nodes
Lymphadenopathy	Enlargement of lymph nodes
Splenomegaly	Enlargement of the spleen
Lymphoedema	Swelling in tissues whose lymphatic drainage has been obstructed

The main groups of MALT are the tonsils (described earlier) and aggregated lymphoid follicles (Peyer's patches, see Fig. 12.25), which are large collections of lymphoid tissue in the small intestine.

SPOT CHECK

3. Describe briefly the structure of a lymph node.
4. What is the function of sinusoids in the spleen?

Lymph vessel pathology

Learning outcomes

After studying this section, you should be able to:

- explain the role of lymphatic vessels in the spread of infectious and malignant disease
- discuss the main causes and consequences of lymphatic obstruction.

The main involvements of lymph vessels in disease relate to the spread of disease in the body and the effects of lymphatic obstruction. Table 6.1 defines some common terms used when describing lymphatic system pathology.

Spread of disease

The materials most commonly spread via the lymphatic network from their original site to the bloodstream are tumour cells and infection.

Malignant disease

Malignant tumours shed cells into the surrounding interstitial fluid, which drains into local lymphatic vessels and carries the tumour cells to the nearest group of lymph nodes. Here, if tumour cells arrive in sufficient numbers, they can establish secondary growths (metastases). From local lymph nodes, the tumour usually spreads from node to node through the lymphatic system and/or via the bloodstream to distant organs.

Infection

Pathogens may enter lymph vessels from infected tissues. If the defensive cells in the lymph nodes are unable to destroy all the microbes, the infection may travel from node to node, eventually reach the bloodstream, and spread to other body organs.

Lymphangitis

This occurs in some acute bacterial infections in which the microbes in the lymph draining from the area infect and spread along the lymph vessel itself, causing swelling and inflammation that may be clearly visible as a red line through the skin (Fig. 6.11). The infection may be stopped at the first lymph node or may spread through the lymph drainage network to the blood.

Lymphatic obstruction

If a lymph vessel is obstructed, lymph accumulates behind the obstruction (lymphoedema). The amount of resultant swelling and the size of the area affected depend on the size of the vessel involved. Figure 6.12 shows gross lymphoedema in the arm following radiotherapy for breast cancer. Lymphoedema usually leads to low-grade inflammation and fibrosis of the lymph vessel, which further obstructs lymph flow and worsens the condition. The most common causes are tumours and surgical removal of lymph nodes.

Fig. 6.11 Lymphangitis. (From Science Photo Library. Reproduced with permission.)

Fig. 6.12 Lymphoedema. (From Science Photo Library. Reproduced with permission.)

Tumours

Tumours can compress lymph vessels, blocking lymph flow and tissue drainage. A tumour may also grow into, and block, a lymph vessel or node, obstructing lymph flow.

Surgery

In some surgical procedures, lymph nodes are removed because cancer cells may have already spread to them. This aims to prevent growth of secondary tumours in local lymph nodes and further spread of the disease via the lymphatic system, e.g. axillary nodes may be removed during mastectomy (breast removal), which can obstruct lymph drainage and cause lymphoedema of the affected arm.

SPOT CHECK

5. Explain why removal of a breast can lead to swelling of the arm on the same side.

Diseases of lymph nodes

Learning outcomes

After studying this section, you should be able to:

- explain the term 'lymphadenitis', listing the main causes
- describe the effects of the two main forms of lymphoma
- explain why secondary disease of the lymph nodes is commonly found in individuals with cancer.

Lymphadenitis

Acute lymphadenitis (acute infection of lymph nodes) is usually caused by microbes transported in lymph from infected tissues. Infected nodes become inflamed, enlarged and congested with blood, and chemotaxis (directed movement of defensive cells into infected or damaged tissues) attracts large numbers of phagocytes. If lymph node defences (phagocytes and antibody production) are overwhelmed, an abscess (see Fig. 14.10) can form inside the node. Adjacent tissues may become involved, and infected materials may be transported through other nodes and into the blood.

Acute lymphadenitis is secondary to a number of conditions. Minor lymphadenitis accompanies many infections and indicates the normal proliferation of defence cells. More serious infection occurs in, for example, measles, typhoid and cat-scratch fever, and wound or skin infections. Chronic lymphadenitis occurs following unresolved acute infections, and in tuberculosis, syphilis and some low-grade infections.

Infectious mononucleosis (glandular fever)

This is a highly contagious viral infection, usually of young adults, spread by direct contact and caused by the Epstein–Barr virus (EBV). During the incubation period of 7–10 days, viruses multiply in the epithelial cells of the pharynx. They subsequently spread to cervical lymph nodes, then to lymphoid tissue throughout the body. Clinical features include fatigue, malaise, tonsillitis, lymphadenopathy and splenomegaly. A common complication is myalgic encephalitis (chronic fatigue syndrome, p. 205).

Lymphomas

These are malignant tumours of lymphoid tissue and are classified as either Hodgkin's or non-Hodgkin's lymphomas.

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is a group of diseases that almost always presents with painless enlargement of lymph nodes throughout the body, as lymphoid tissue within them proliferates. The superficial lymph nodes in the neck are often the first to be noticed. The disease is malignant and the cause is unknown. Males are more commonly affected than females and the two age groups displaying the highest incidence are 20–35 years and 50–70 years. The prognosis varies considerably but the pattern of spread is predictable because the disease spreads from one node to the next and to adjacent tissues, following local lymphatic channels. The effectiveness of treatment depends largely on the stage of the disease at which it begins, but is often curable, especially if caught early. The disease reduces immunity because lymphocyte function is depressed, and recurrent infection is therefore common. As lymph nodes enlarge, they may compress adjacent tissues and organs. Anaemia and changes in leukocyte numbers occur if the bone marrow is involved. It is rare for the disease to spread to non-lymphoid tissues or organs.

Non-Hodgkin's lymphomas

Non-Hodgkin's lymphomas (NHLs) are a group of lymphomas more common than HL; they may be associated with immunodeficiency states and certain viral infections, including HIV (p. 427). NHLs include multiple myeloma and Burkitt's lymphoma and may occur in any lymphoid tissue or in bone marrow. They are classified according to the type of cell involved and the degree of malignancy, i.e. low, intermediate or high grade. Low-grade tumours consist of well-differentiated cells and disease progress is slow, with over half of patients surviving for at least 10 years. High-grade lymphomas consist of poorly differentiated cells and disease progress is rapid, death occurring in weeks or months. Some low- or intermediate-grade tumours change their status to high grade with increased rate of progress.

The expanding lymph nodes may compress adjacent tissues and organs. Immunological deficiency leads to increased incidence of infections, and if the bone marrow or spleen (or both) is involved there may be varying degrees of anaemia and leukopenia.

SPOT CHECK

6. Why does lymphadenitis often accompany infection?
7. In relation to lymphomas, describe the degree of differentiation and rate of progress of high-grade tumours.

Disorders of the spleen

Learning outcome

After studying this section, you should be able to:

- identify the main causes of splenomegaly.

Splenomegaly

This is enlargement of the spleen, and is usually secondary to other conditions, including infections, circulatory disorders, blood diseases and malignant tumours.

Infections

The spleen may be infected by blood-borne microbes or by local spread of infection. The red pulp becomes congested with blood, and phagocytes and plasma cells accumulate within. Acute infections are rare.

Some chronic infections cause splenomegaly but this is usually less severe than with acute infections. The most common primary infections include tuberculosis (p. 298), typhoid fever (p. 361), malaria and infectious mononucleosis (see earlier).

Circulatory disorders

If blood flow through the liver is blocked – by fibrosis in liver cirrhosis, for example, or portal venous congestion in right-sided heart failure – blood backing up through the portal circulation can cause congestion and enlargement of the spleen.

Blood diseases

Splenomegaly may be caused by blood disorders when the spleen enlarges to deal with the extra workload associated with removing damaged, worn-out and abnormal blood cells. Examples include haemolytic and macrocytic anaemia, polycythaemia and chronic myeloid leukaemia (Ch. 4).

Splenomegaly may itself cause blood disorders. When the spleen is enlarged for any reason, especially in portal hypertension, excessive and premature haemolysis of red cells or phagocytosis of normal white cells and platelets leads to marked anaemia, leukopenia and thrombocytopenia.

Tumours

Benign and primary malignant tumours of the spleen are rare but blood-spread tumour fragments from elsewhere in the body may cause metastases. Splenomegaly caused by infiltration of malignant cells is characteristic of some conditions, especially chronic leukaemia, HL and NHL.

Diseases of the thymus gland

Learning outcome

After studying this section, you should be able to:

- describe the principal disorders of the thymus gland.

Enlargement of the thymus gland is associated with some autoimmune diseases, such as thyrotoxicosis, Addison's disease and myasthenia gravis. In myasthenia gravis (p. 483), most patients have either thymic hyperplasia (the majority) or thymoma (a minority), although the role of thymic function in this disorder is not understood.

Tumours are rare, although pressure caused by enlargement of the gland may damage or interfere with the functions of adjacent structures, e.g. the trachea, oesophagus or large veins in the neck.

Case study

As the result of a motorcycle accident, Rahul has had to have his spleen removed surgically. The surgical team tried to save it, but it was ruptured and causing serious haemorrhage.

1. Why does splenic injury lead to severe internal bleeding?
   a. The spleen is the main site of blood cell synthesis in adults.
   b. The spleen has a very rich blood supply.
   c. The spleen stores up to 1 L of blood, released when the spleen is injured.
   d. A healthy spleen produces 90% of the body's clotting factors.
2. Without his spleen, Rahul will live a healthy life, but his surgeon will warn him that he is at increased risk of:
   a. Cancer
   b. Autoimmune disease
   c. Nutritional deficiency
   d. Infection
3. The spleen lies:
   a. Above the diaphragm
   b. Behind the right kidney
   c. Behind the fundus of the stomach
   d. Below the tail of the pancreas
4. The spleen:
   a. Destroys old erythrocytes
   b. Filters bacteria from lymph
   c. Controls blood glucose levels
   d. Has no nerve supply.

Review and revise

Complete each of the following statements:

1. The spleen is roughly _____ in shape and weighs about _____ grams in the average adult. It is enclosed in a _____ that is penetrated at the _____ by the _____ artery, which supplies the organ. The anterior face is indented by adjacent organs, including the _____, _____, _____ and _____.

2. Lymph nodes of the neck are called the _____ nodes. Lymph nodes of the armpit are called the _____ nodes. Lymph nodes of the groin are called the _____ nodes.

Choose one answer to complete each of the following statements:

3. The bone marrow is classified as a lymphoid tissue because:
   a. It filters blood.
   b. It produces mature T-cells.
   c. It produces plasma proteins.
   d. Lymphocytes are produced there.

4. Lymphatic capillaries are:
   a. Thick-walled
   b. Equipped with valves
   c. Blind-ended
   d. In direct communication with blood capillaries

5. Glandular fever:
   a. Is viral in origin
   b. Is not infectious
   c. Involves bone marrow failure
   d. Often recurs

6. Match each letter in List A to the appropriate number in List B. You may use any item in List B more than once:

List A

____ (a) Spleen
____ (b) Thymus
____ (c) Lymph nodes

List B

1. Filters lymph
2. Produces lymphocytes
3. Is/are found in the abdominal cavity
4. Filters blood
5. Is usually enlarged in myasthenia gravis
6. Is located behind the sternum
7. Stores blood
8. Is the largest lymphoid organ

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 7

The nervous system

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The nervous system detects and responds to changes inside and outside the body. Together with the endocrine system, it coordinates and controls vital aspects of body function and maintains homeostasis. To this end the nervous system provides an immediate response while endocrine activity (Ch. 9) is usually slower and more prolonged.

The nervous system consists of the brain, the spinal cord and peripheral nerves. The structure and organisation of the tissues that form these components enable rapid communication between all parts of the body.

For descriptive purposes, the nervous system has two parts (Fig. 7.1):

- the central nervous system (CNS), consisting of the brain and the spinal cord
- the peripheral nervous system (PNS), consisting of all the nerves outside the brain and spinal cord.

The PNS comprises paired cranial and spinal nerves. Some of these are sensory (afferent), transmitting impulses to the CNS; some are motor (efferent), transmitting impulses from the CNS; and others are mixed, with both sensory and

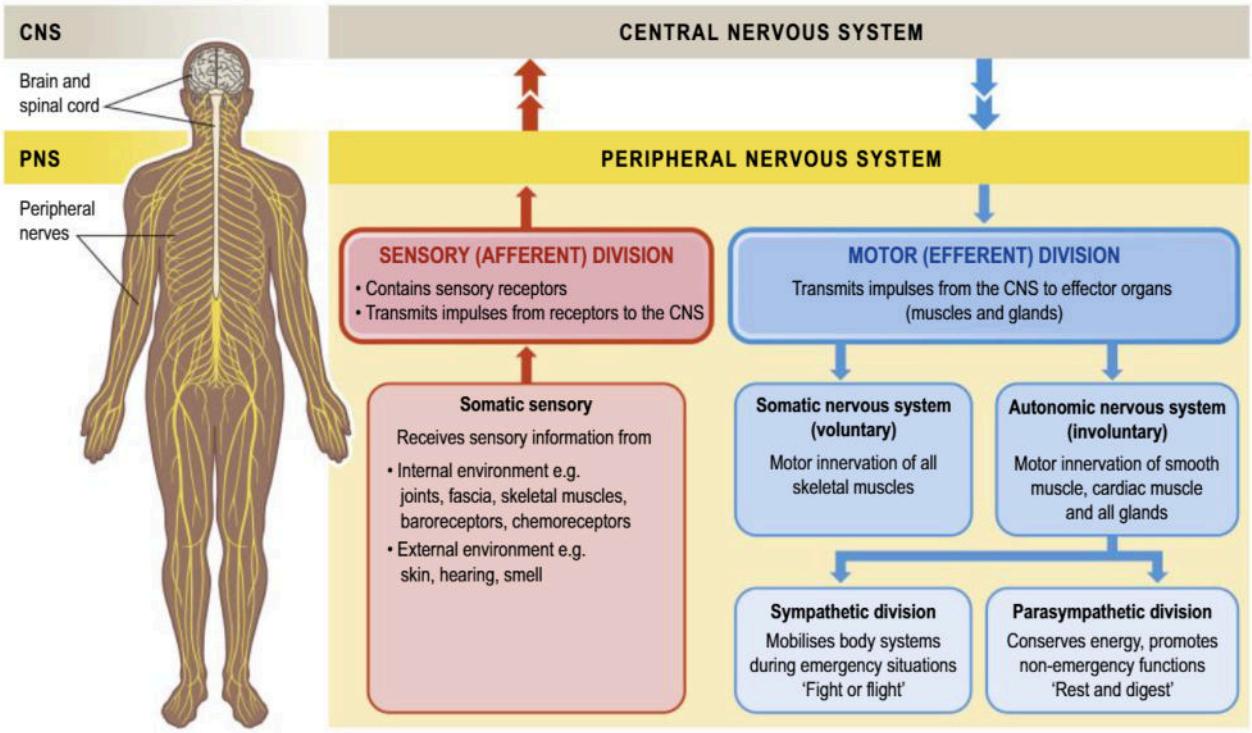

Figure 7.1 Functional components of the nervous system.

motor fibres. It is useful to consider two functional divisions within the PNS:

- the sensory division
- the motor division (Fig. 7.1).

The motor division has two parts:

- the somatic nervous system, which controls voluntary movement of skeletal muscles
- the autonomic nervous system which controls involuntary processes such as the heartbeat, peristalsis and glandular activity. The autonomic nervous system has two divisions: sympathetic and parasympathetic (p. 190).

In summary, the CNS receives sensory information about its internal and external environments from afferent nerves. The CNS integrates and processes this input and responds, when appropriate, by sending nerve impulses through motor (efferent) nerves to the effector organs: muscles and glands. For example, responses to changes in the internal environment regulate essential involuntary body functions such as respiration and blood pressure; responses to changes in the external environment maintain body posture and other voluntary activities.

The first sections of this chapter explore the structure and functions of the components of the nervous system, including the impact of ageing, while the final ones consider the effects on body function when one or more of the components do not function normally.

Cells and tissues of the nervous system

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the structure and functions of myelinated and unmyelinated neurones
- state the functions of sensory and motor nerves
- explain the events that occur following release of a neurotransmitter at a synapse
- briefly describe the functions of four types of neuroglial cell
- outline the response of nervous tissue to injury.

There are two types of nervous tissue: neurones and neuroglia. Neurones (nerve cells) generate and transmit nerve impulses. Neurones are supported by connective tissue, collectively known as neuroglia, formed from different types of glial cell. There are vast numbers of both cell types: 1 trillion (10^{12}) glial cells and 10 times fewer (10^{11}) neurones.

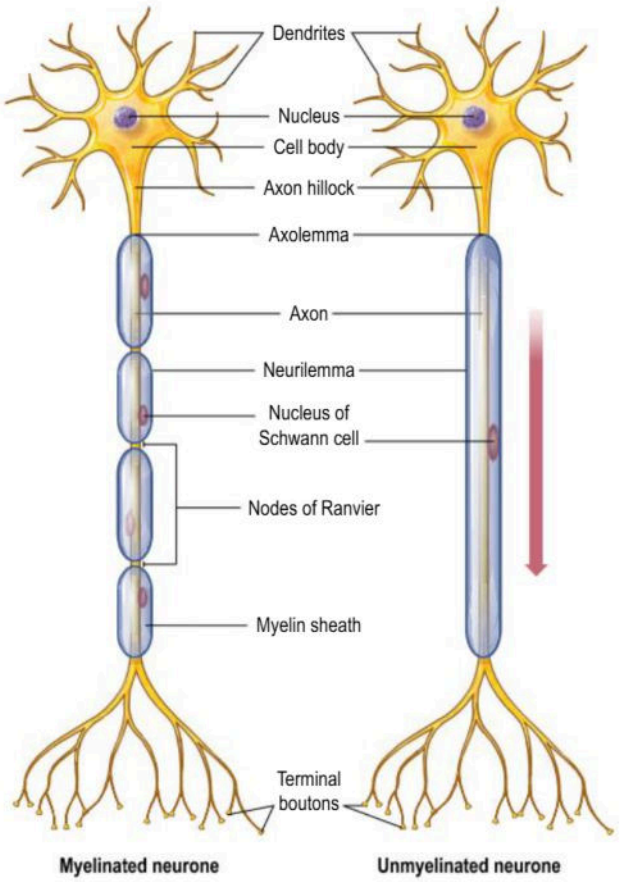

Figure 7.2 The structure of neurones. Red arrow indicates direction of impulse conduction.

Neurones

Neurones consist of a cell body and several processes: one axon and, usually, many dendrites (Fig. 7.2), all filled with cytoplasm. Bundles of axons bound together are called nerves. Neurones cannot divide, and for survival they need a continuous supply of oxygen and glucose. This is because neurones can normally synthesise chemical energy (adenosine triphosphate, or ATP) only from glucose, unlike many other cells.

Neurones generate and transmit electrical impulses called action potentials. Some neurones initiate action potentials while others act as 'relay stations' where they are passed on and sometimes redirected.

Action potentials can be initiated in response to stimuli from:

- outside the body (external stimuli), e.g. touch on the skin; light waves reaching the back of the eyeball
- inside the body (internal stimuli), e.g. a change in the concentration of carbon dioxide in the blood alters respiration; a thought may result in voluntary movement.

The initial strength of the action potential is maintained throughout the length of the neurone. Transmission of nerve signals is both electrical and chemical. The action potential travelling down the nerve axon is an electrical signal, but because nerves do not come into direct contact with each other, the signal between one nerve cell and the next is nearly always chemical (p. 163).

Cell bodies

The cell body contains the nucleus and the same organelles as other cell types. Cell bodies form the grey matter of the nervous system and are found at the periphery of the brain and in the centre of the spinal cord. Groups of cell bodies are called nuclei in the CNS and ganglia in the PNS. An important exception is the basal ganglia (nuclei) situated within the cerebrum (p. 172).

Axons and dendrites

Axons and dendrites are extensions of the cell body and form the white matter of the nervous system. Axons are found deep in the brain and in groups, called tracts, at the periphery of the spinal cord. Groups of axons outside the brain and spinal cord are referred to as nerves or nerve fibres.

Axons

Neurones have only one axon, which begins at a tapered area of the cell body, the axon hillock. Its outer membrane is called the axolemma. Axons carry action potentials away from the cell body and are usually much longer than the dendrites, sometimes as long as 100 cm. At its free end, the axon divides into many minute branches that end in small swellings called synaptic knobs, or terminal boutons.

Myelinated neurones. Large axons and those of peripheral nerves are surrounded by a myelin sheath (Figs 7.3A and C). This consists of a series of Schwann cells arranged along the length of the axon. Each one is wrapped around the axon so that it is covered by several concentric layers of Schwann cell plasma membrane. Between the layers of plasma membrane is a small amount of fatty substance called myelin. The outermost layer of the Schwann cell plasma membrane is the neurilemma. There are tiny areas of exposed axolemma between adjacent Schwann cells, called nodes of Ranvier (see Fig. 7.2). Myelin speeds up the transmission of action potentials in myelinated neurones making it faster than in unmyelinated neurones. Figure 7.4 shows a section through a nerve fibre at a node of Ranvier, where the area without myelin can be clearly seen.

Unmyelinated neurones. Postganglionic fibres (see below) and some small fibres in the CNS are unmyelinated, meaning that several axons are embedded in one Schwann cell (see Fig. 7.3B). The adjacent Schwann cells are in close association; there is no myelin sheath and no exposed axolemma.

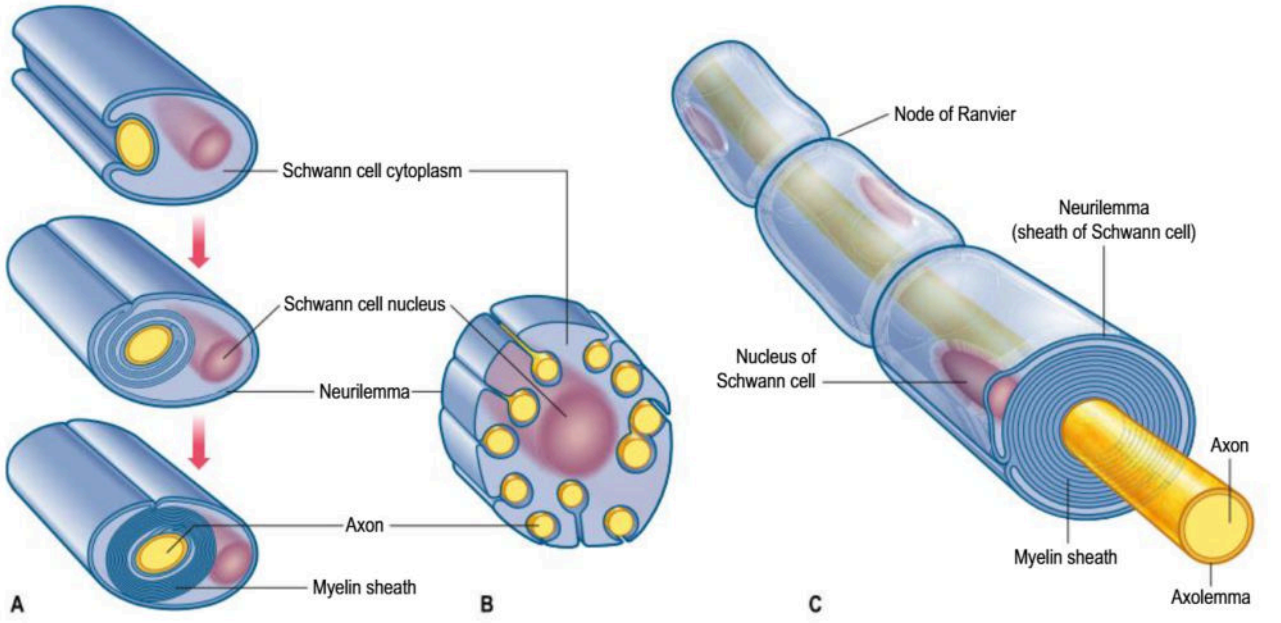

Figure 7.3 Arrangement of myelin. (A) Myelinated neurone. (B) Unmyelinated neurone. (C) Length of myelinated axon.

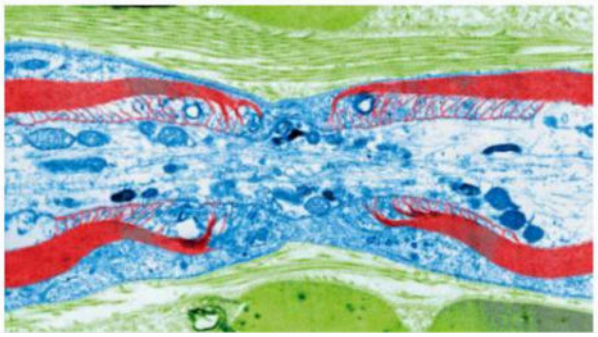

Figure 7.4 Node of Ranvier. Colour transmission electron micrograph of a longitudinal section of a myelinated nerve fibre. Nerve tissue is shown in blue and myelin in red. (CMEABG - UCBL1, ISM/Science Photo Library. Reproduced with permission.)

Conduction of action potentials is significantly slower in unmyelinated fibres than their myelinated counterparts.

Dendrites

These are the numerous short, branching extensions of the cell body that receive and transmit incoming action potentials towards the axon. In motor neurones, dendrites form part of synapses (see Fig. 7.7), and in sensory neurones they form the sensory receptors that respond to specific stimuli.

The action potential (nerve impulse)

An impulse is initiated by stimulation of sensory nerve endings or by the passage of an impulse from another nerve. Transmission of the action potential is carried out by movement of ions across the nerve cell membrane. In the resting state the nerve cell membrane is polarised due to differences in the concentrations of ions across the plasma membrane. This means that there is a different electrical charge on each side of the membrane, called the resting membrane potential. At rest, the charge on the outside is positive and inside it is negative. The principal ions involved are:

- sodium (Na^+), the main extracellular cation
- potassium (K^+), the main intracellular cation.

In the resting state there is a continual tendency for these ions to diffuse down their concentration gradients, i.e. K^+ outwards and Na^+ into cells. When stimulated, the permeability of the nerve cell membrane to these ions changes. Sodium channels in the membrane open and Na^+ floods into the neurone from the extracellular fluid. This is called depolarisation and triggers an action potential. Depolarisation is very rapid, enabling the conduction of a nerve impulse along the entire length of a neurone in a few milliseconds. Action potential transmission along a nerve is one-way because the membrane behind the travelling action potential is temporarily unexcitable (refractory) until repolarisation occurs.

Almost immediately following the entry of Na^+, K^+ channels open and K^+ floods out of the neurone. The movement of these ions returns the membrane potential to its resting state. This is called the refractory period, during which restimulation is not possible. The action of the sodium–potassium pump (see Ch. 3), which is in continual operation, expels Na^+ from the cell in exchange for K^+, returning levels of Na^+ and K^+ to the original resting state and repolarising the neurone.

In myelinated neurones, the insulating properties of the myelin sheath prevent the movement of ions. Therefore, electrical changes across the membrane can occur only at the gaps in the myelin sheath, i.e. at the nodes of Ranvier (see

Fig. 7.2). When an impulse occurs at one node, depolarisation passes along the myelin sheath to the next node, so that the flow of current appears to 'leap' from one node to the next. This is called 'saltatory conduction' (Fig. 7.5).

The speed of conduction depends on the diameter of the neurone: the larger the diameter, the faster the conduction. In addition, myelinated fibres conduct action potentials faster than unmyelinated fibres because saltatory conduction is faster than continuous conduction, or simple propagation (Fig. 7.6). The fastest fibres can conduct action potentials to, for example, skeletal muscles at a rate of 130 metres per second, while the slowest impulses travel at 0.5 metres per second.

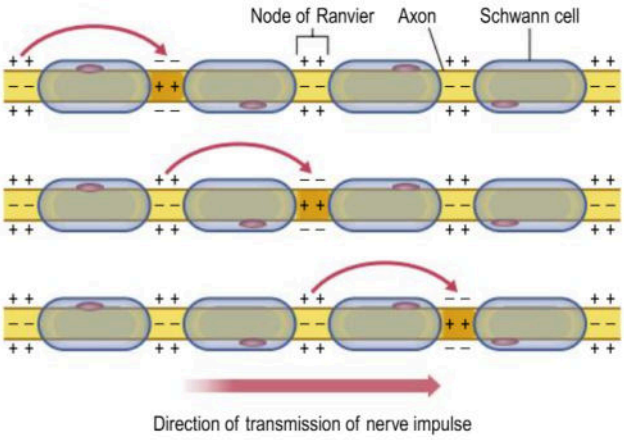

Figure 7.5 Saltatory conduction of an action potential in a myelinated nerve fibre. Red arrows indicate direction of impulse transmission.

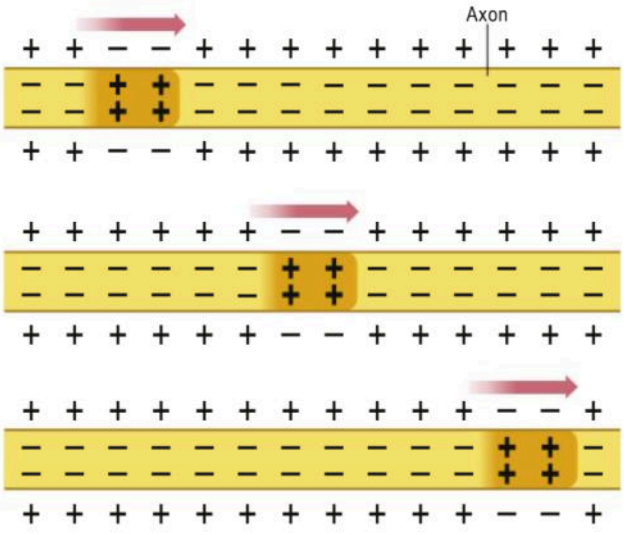

Figure 7.6 Simple propagation of an action potential in an unmyelinated nerve fibre. Red arrows indicate direction of impulse transmission.

The synapse and neurotransmitters

There is always more than one neurone involved in the chain of transmission of a nerve impulse from its origin to its destination, whether it is sensory or motor. There is no physical contact between any two neurones in the chain. The point at which the action potential passes from one neurone to the next is called the synapse (Fig. 7.7). The neurone that carries an action potential to the synapse is called the presynaptic neurone; the postsynaptic neurone carries the action potential away from the synapse. The terminal boutons of the presynaptic neurone lie very close to the dendrites on the cell body of the postsynaptic neurone. The space between them is the synaptic cleft. Synaptic knobs contain abundant spherical membrane-bound synaptic vesicles, which store the neurotransmitter. Neurotransmitters are chemicals synthesised by nerve cell bodies, actively transported along the axons and stored in the synaptic vesicles. They are released by exocytosis in response to an action potential in the presynaptic neurone and diffuse across the synaptic cleft, where they act on specific receptor sites on the postsynaptic membrane. Their

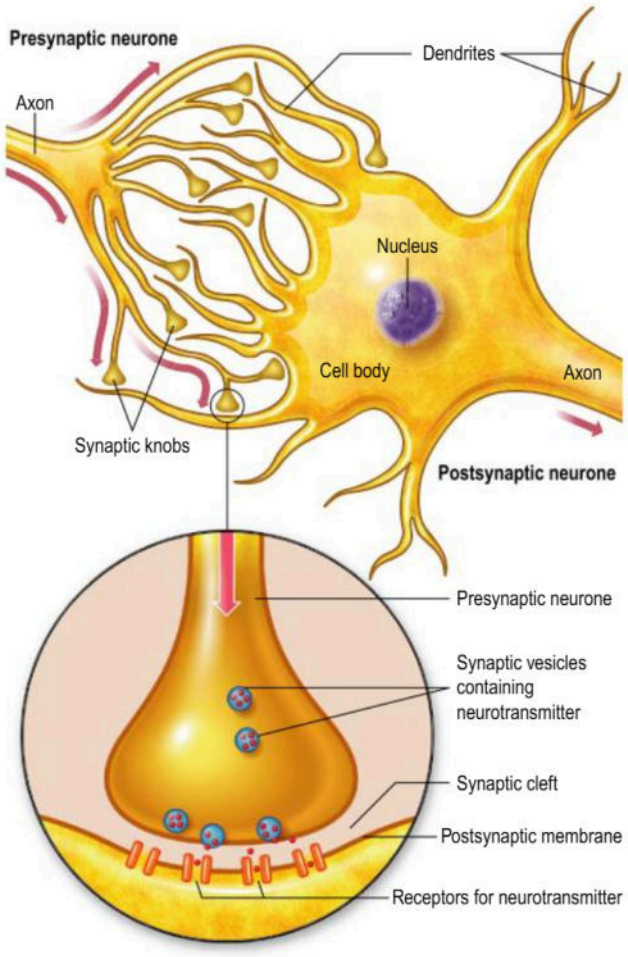

Figure 7.7 Synapse. Red arrows indicate direction of action potential.

action is short-lived because immediately after acting on the postsynaptic membrane, they are either inactivated by enzymes or taken back into the synaptic knob. Some important drugs act by mimicking, neutralising (antagonising) or prolonging normal actions of neurotransmitters. Neurotransmitters usually have an excitatory effect on postsynaptic receptors but are sometimes inhibitory.

There are more than 50 neurotransmitters in the brain and spinal cord, including noradrenaline (norepinephrine), adrenaline (epinephrine), dopamine, histamine, serotonin, gamma-aminobutyric acid (GABA) and acetylcholine. Other substances, such as enkephalins, endorphins and substance P, have specialised roles in, for example, transmission of pain signals.

Nerves

A nerve consists of numerous neurones bound together by connective tissue (bundles of nerve fibres in the CNS are known as tracts). For example, large nerves such as the sciatic nerves (p. 185) contain tens of thousands of axons. Each bundle has several coverings of protective connective tissue (Fig. 7.8):

- Endoneurium is a delicate tissue surrounding each individual fibre.
- Perineurium is a smooth connective tissue surrounding each bundle of fibres.
- Epineurium is the fibrous tissue surrounding and enclosing several bundles of nerve fibres. Most large nerves are covered by epineurium.

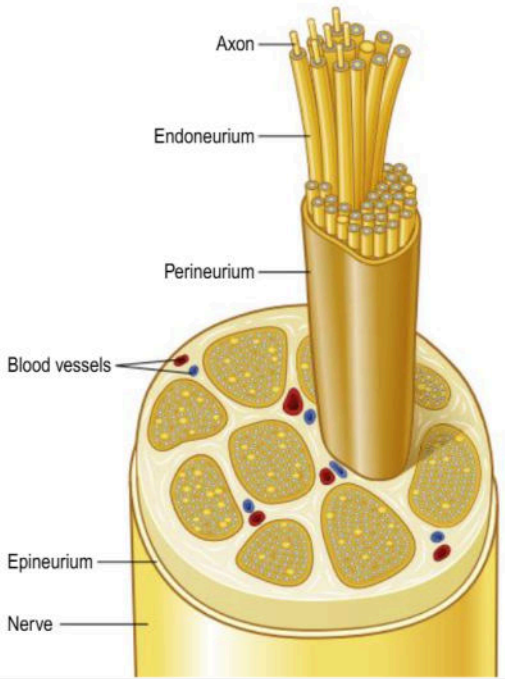

Figure 7.8 Transverse section of a peripheral nerve showing the connective tissue coverings.

Sensory or afferent nerves

Sensory nerves carry information from the body to the spinal cord (see Fig. 7.1). The impulses then pass either to the brain or to connector neurones of reflex arcs in the spinal cord (p. 179).

Sensory receptors

These are the specialised endings formed by the dendrites of sensory neurones; different types usually respond to different stimuli (changes) inside or outside the body.

Somatic, cutaneous or common senses

These originate in the skin and are stimulated by pain, touch, heat and cold. Sensory nerve endings in the skin are fine branching non-myelinated nerve endings (see Fig. 1.8). When stimulated, an action potential is generated and transmitted by the sensory nerves to the brain, where the sensation is perceived.

Proprioceptor senses

These originate in muscles and joints (Ch. 16). They send information to the brain about the position of the body and its parts in space, enabling maintenance of posture and balance.

Special senses

These are sight, hearing, balance, smell and taste, and are discussed in detail in Chapter 8.

Autonomic afferent nerves

These originate in internal organs, glands and tissues – e.g. the baroreceptors involved in the control of blood pressure (Ch. 5), and the chemoreceptors involved in the control of respiration (Ch. 10) – and are associated with reflex regulation of involuntary activity and visceral pain.

Motor or efferent nerves

Motor nerves originate in the brain, spinal cord and autonomic ganglia. They transmit impulses to the effector organs: muscles and glands (see Fig. 7.1). There are two types:

- somatic nerves – involved in voluntary and reflex skeletal muscle contraction
- autonomic nerves (sympathetic and parasympathetic) – involved in a range of involuntary functions, including cardiac and smooth muscle contraction and glandular secretion.

Motor pathways may contain one or two nerves (see Fig. 7.44). Somatic motor nerve pathways, which supply skeletal (voluntary) muscle, have only one neurone, which leaves the spinal cord and travels directly to the skeletal muscle. This nerve is called the lower motor neurone (p. 179); its synapse with the muscle is specifically named the neuromuscular junction (p. 467) and the neurotransmitter is always acetylcholine. Autonomic nerve pathways (p. 190) involve two nerves, the preganglionic neurone that leaves the spinal

cord and synapses with a second nerve, the postganglionic neurone, which in turn synapses with the effector tissue, i.e. cardiac muscle, smooth muscle or glands. The main neurotransmitters in these pathways are noradrenaline (norepinephrine) and acetylcholine.

Mixed nerves

In the spinal cord, sensory and motor nerves are arranged in separate groups, called tracts. Outside the spinal cord, when sensory and motor nerves are enclosed within the same sheath of connective tissue, they are called mixed nerves.

Neuroglia

The neurones of the CNS are supported by non-excitable glial cells, also called neuroglia (Fig. 7.9). Unlike nerve cells, which cannot divide, glial cells continue to replicate throughout life. There are four types: astrocytes, oligodendrocytes, ependymal cells and microglia.

Astrocytes

These cells are the most abundant neuroglia (Fig. 7.10). They are star-shaped with fine branching processes and they lie in a mucopolysaccharide ground substance. When these cells are damaged, their processes multiply, forming a mesh or 'scar', which inhibits the regrowth of damaged CNS neurones.

At the free ends of some of the processes are small swellings called foot processes. Astrocytes are found in large numbers adjacent to blood vessels, with their foot processes forming a sleeve round them. This means that the blood is separated from the neurones by the capillary wall and a layer of astrocyte foot processes, which together constitute the blood–brain barrier (Fig. 7.11).

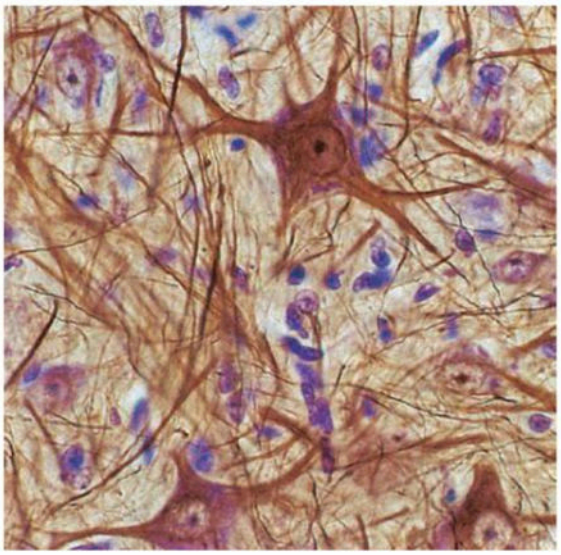

Figure 7.9 Neurones and glial cells. Stained light micrograph of neurones (gold) and nuclei of the more numerous glial cells (blue). (Young B, Lowe JS, Stevens A et al. 2006 Wheater's functional histology: a text and colour atlas. Edinburgh: Churchill Livingstone. Reproduced with permission.)

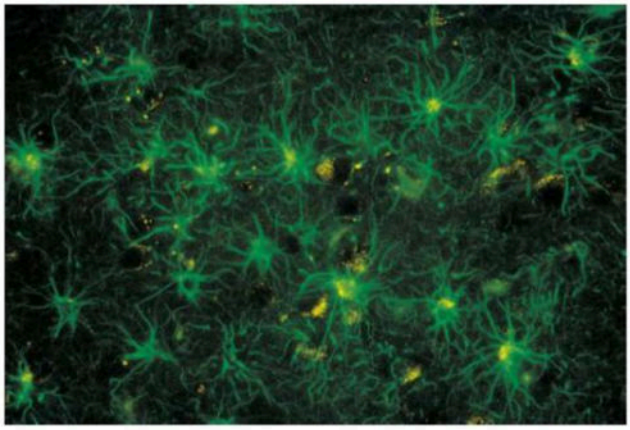

Figure 7.10 Star-shaped astrocytes in the cerebral cortex. (Standring S, 2004 Gray's anatomy: the anatomical basis of clinical practice, 39th edn. Edinburgh: Churchill Livingstone. Reproduced with permission.)

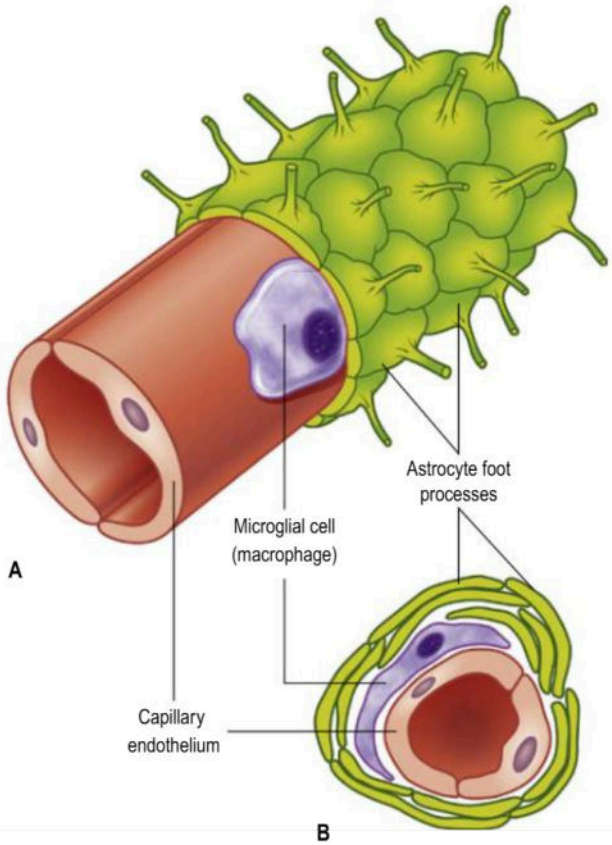

Figure 7.11 Blood–brain barrier. (A) Longitudinal section. (B) Transverse section.

Blood–brain barrier

The blood–brain barrier is a selective barrier that protects the brain from potentially toxic substances and chemical variations in the blood, e.g. after a meal. Oxygen, carbon dioxide, glucose and other small lipid-soluble substances, such as alcohol, quickly cross the barrier into the brain. Some large molecules, many drugs, inorganic ions and amino acids pass more slowly, or do not pass at all.

Oligodendrocytes

These cells are smaller than astrocytes. They are found in clusters round nerve cell bodies in grey matter and are located adjacent to, and along the length of, myelinated nerve fibres. Like Schwann cells in the PNS, oligodendrocytes form and maintain myelin in the CNS. They multiply around degenerating neurones and are destroyed in demyelinating diseases such as multiple sclerosis (p. 205).

Ependymal cells

These are ciliated cells that form the epithelial lining of the ventricles of the brain and the central canal of the spinal cord. The motile cilia assist the flow of CSF though the fluid-filled cavities within the brain. Some specialised ependymal cells form the choroid plexuses of the ventricles and secrete cerebrospinal fluid (CSF, see Fig. 7.16).

Microglia

The smallest and least numerous glial cells, these cells are derived from monocytes that migrate from the blood into the nervous system before birth and are part of the mononuclear phagocyte system (see Fig. 4.13). They are normally static cells dispersed throughout the brain. However when inflammation and cell damage or destruction occur they migrate to the site, where they enlarge and become phagocytic, removing microbes and damaged tissue.

Response of nervous tissue to injury

Unlike neuroglia, which have the capacity to reproduce, neurones reach maturity a few weeks after birth and cannot divide.

Damage to neurones can lead either to rapid necrosis with sudden acute functional failure, or to slow atrophy with gradually increasing dysfunction. These changes may result from:

- hypoxia and anoxia
- nutritional deficiencies
- poisons, e.g. organic lead
- trauma
- infections
- ageing
- hypoglycaemia.

Peripheral nerve regeneration

The axons of peripheral nerves can sometimes regenerate after a limited degree of damage if the cell body remains intact (Fig. 7.12). Distal to the damage, the axon and myelin sheath disintegrate and are removed by macrophages; the muscle supplied by the damaged fibre atrophies in the absence of nerve stimulation. Provided the two damaged ends are in close apposition, the neurilemma then slowly regenerates (about 1.5 mm per day) from the point of injury along its original track through what is called a regeneration tube (Fig. 7.12A). New Schwann cells develop within the neurilemma, providing a pathway within which the axon can regenerate.

Restoration of function depends on the re-establishment of functional connections with the effector organ. When the neurilemma is out of position or destroyed, the sprouting axons and Schwann cells may form a tumour-like cluster (traumatic neuroma), producing severe pain, for example, sometimes following fractures and amputation of limbs (Fig. 7.12B).

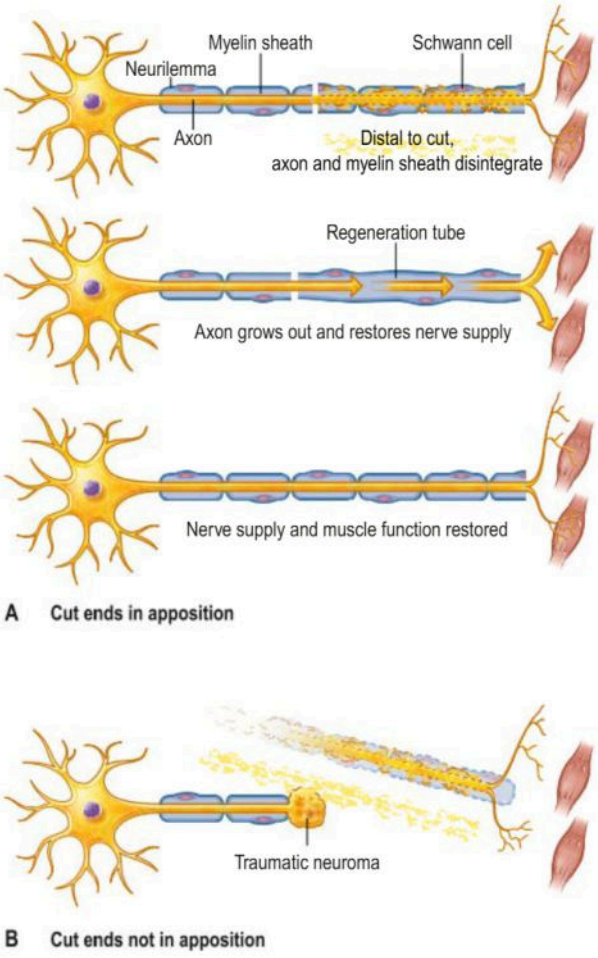

Figure 7.12 Regrowth of peripheral nerves following injury. (A) Cut ends in apposition. (B) Cut ends not in apposition.

SPOT CHECK

1. Describe transmission of an action potential.
2. Explain why the speed of nerve conduction is faster in myelinated neurones than in their unmyelinated counterparts.

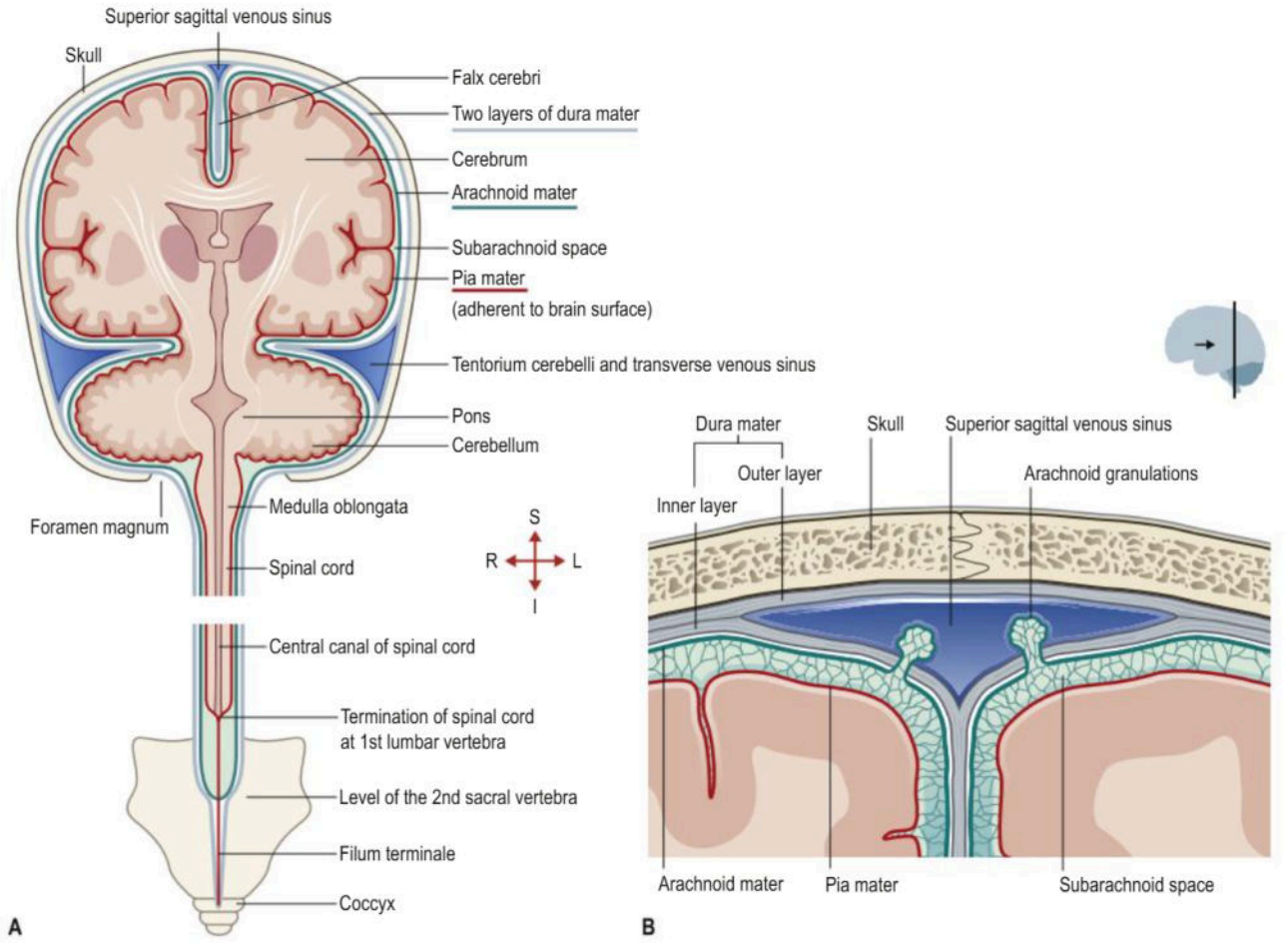

Figure 7.13 The meninges surrounding the brain and spinal cord. (A) Frontal section of the brain. (B) Arrangement at the superior sagittal sinus.

Central nervous system

The CNS consists of the brain and the spinal cord (see Fig. 7.1). These essential structures are both well protected from damage and injury: the brain is enclosed within the skull and the spinal cord by the vertebrae that form the spinal column. Membranous coverings, the meninges, provide further protection. The structure and functions of the meninges, brain and spinal cord are explored in this section.

Meninges and cerebrospinal fluid

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the meninges
- describe the flow of cerebrospinal fluid in the brain
- list the functions of cerebrospinal fluid.

Meninges

The brain and spinal cord are completely surrounded by three layers of tissue, the meninges (Fig. 7.13A), lying between the skull and the brain, and between the vertebral foramina and the spinal cord. Named from outside inwards, they are the:

- dura mater
- arachnoid mater
- pia mater.

In the brain, two spaces are associated with the meninges:

- the subdural space – this is a potential space between the dural and arachnoid maters, and contains a very small amount of serous fluid
- the subarachnoid space – this separates the arachnoid and pia maters and contains cerebrospinal fluid (CSF).

These continue into the spinal canal, which contains an additional space: the epidural space (see Figs 7.14 and 7.26).

Dura mater

The cerebral dura mater consists of two layers of dense fibrous tissue (Fig. 7.13B). The outer periosteal layer lines the

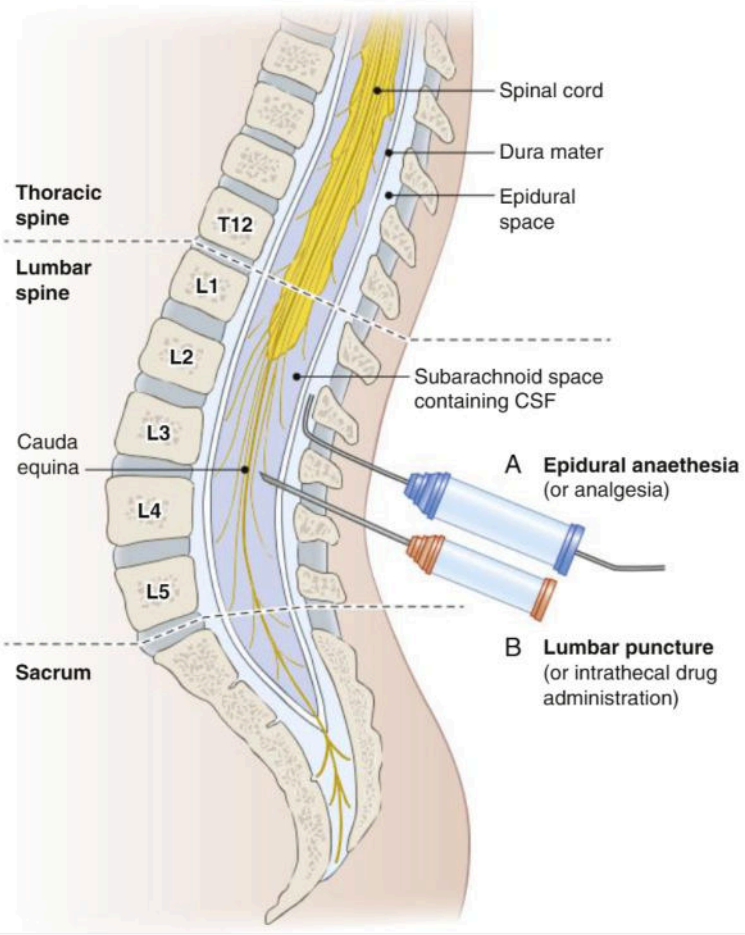

Figure 7.14 Longitudinal section of the lower vertebral canal showing cannula placement sites. (A) Epidural anaesthesia. B. Lumbar puncture.

inner surface of the skull bones and the inner (meningeal) layer provides a protective covering for the brain. There is only a potential space between the two layers, except where the inner layer sweeps inwards following the contours of the brain, forming membranous extensions that partially divide the cranial cavity:

- the falx cerebri, which separates the two cerebral hemispheres (see Fig. 7.13A).
- the falx cerebelli, which separates the two cerebellar hemispheres
- the tentorium (meaning 'tent-like') cerebelli, which separates the cerebrum and the cerebellum (see Fig. 7.13A).

Venous blood from the brain drains into venous sinuses between the two layers of dura mater. The superior sagittal sinus is formed by the falx cerebri, and the tentorium cerebelli forms the straight and transverse sinuses (see Fig. 5.36).

Spinal dura mater forms a loose sheath round the spinal cord, extending from the foramen magnum, the opening at the base of the skull through which the spinal cord passes, to the 2nd sacral vertebra. Thereafter it encloses the filum terminale, an extension of pia mater that anchors the spinal cord to the coccyx at the base of the vertebral column, and fuses with the periosteum of the coccyx. It is an extension of the inner layer of cerebral dura mater and is separated from the periosteum of the vertebrae and ligaments within the neural canal by the epidural space (see Fig. 7.26), containing blood vessels and areolar connective tissue. This space is not found within the skull; it is only present in the vertebral canal. Nerves entering and leaving the spinal cord pass through the epidural space. These attachments stabilise the spinal cord in the neural canal.

Figure 7.14 shows a cannula inserted into the epidural space at the lower end of the vertebral canal and also a needle in the subarachnoid space, which contains CSF. Dyes used for diagnostic purposes, and local anaesthetics or analgesics to relieve pain may be injected into the epidural space where they act on the nerve roots emerging from the vertebral column. Access to the subarachnoid space is used to sample CSF or measure its pressure, a procedure called lumbar puncture; when drugs are injected into this space, this is called intrathecal administration.

Arachnoid mater

This is a layer of fibrous tissue that lies between the dura and pia maters (Fig. 7.13). It is separated from the dura mater by

the subdural space, which contains a small amount of serous fluid, and from the pia mater by the subarachnoid space, which contains CSF. The arachnoid mater passes over the convolutions of the brain and accompanies the inner layer of dura mater in the formation of the falx cerebri, tentorium cerebelli and falx cerebelli. It continues downwards to envelop the spinal cord (see Fig. 7.25) and ends by merging with the dura mater at the level of the 2nd sacral vertebra.

Pia mater

This is a delicate layer of connective tissue containing many tiny blood vessels; it adheres to the brain, completely covering the convolutions and dipping into each fissure (Fig. 7.13). It continues downwards, surrounding the spinal cord (see Fig. 7.25). Beyond the end of the cord it continues as the filum terminale, and continues, with the dura mater, to fuse with the periosteum of the coccyx (see Fig. 7.26).

Ventricles of the brain and the cerebrospinal fluid

The brain contains four irregular-shaped cavities, or ventricles, containing CSF (Fig. 7.15). They are the:

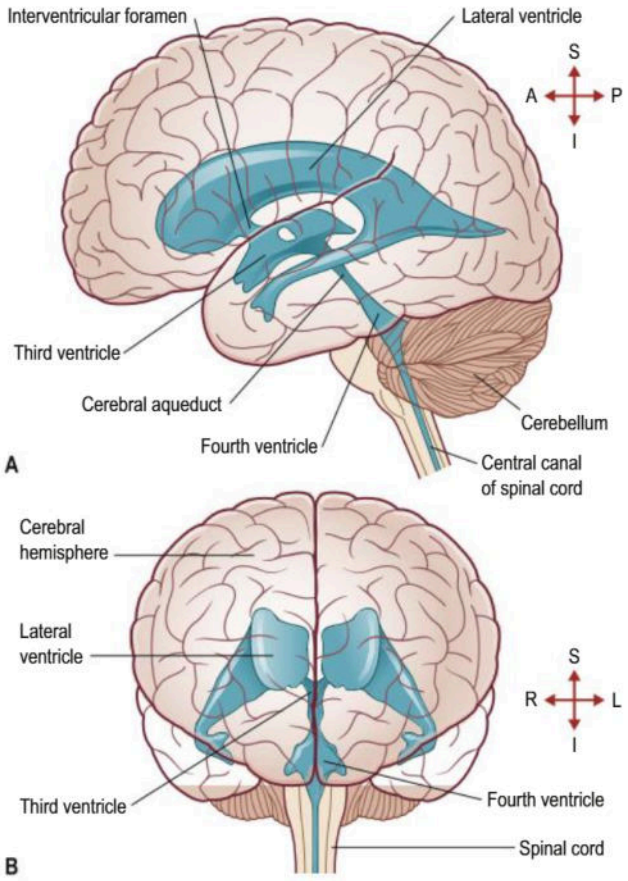

Figure 7.15 The ventricles of the brain. (A) Viewed from the left side. (B) Anterior view.

- right and left lateral ventricles
- third ventricle
- fourth ventricle.

Lateral ventricles

These cavities lie within the cerebral hemispheres, one on each side of the median plane just below the corpus callosum (see Fig. 7.17). They are separated by a narrow septum and lined with ciliated epithelium. Each communicates with the third ventricle by an interventricular foramen (Fig. 7.15).

Third ventricle

The third ventricle is a tube-shaped cavity situated below the lateral ventricles between the two parts of the thalamus. It communicates with the fourth ventricle by a canal, the cerebral aqueduct.

Fourth ventricle

The fourth ventricle is a small diamond-shaped cavity lying below and behind the third ventricle, between the cerebellum and pons. It is continuous below with the central canal of the spinal cord. It allows passage of CSF into the subarachnoid space through tiny foramina in its roof.

Cerebrospinal fluid

CSF circulates constantly from the ventricles through the subarachnoid space around the brain and spinal cord. CSF is a clear, slightly alkaline fluid with a specific gravity of 1.005, consisting of:

- water
- mineral salts
- glucose
- plasma proteins: small amounts of albumin and globulin
- a few leukocytes
- small amounts of creatinine
- small amounts of urea.

CSF is secreted into each ventricle of the brain by choroid plexuses. These are vascular areas that are rich in blood vessels and surrounded by ependymal cells in the lining of ventricle walls. CSF passes back into the blood through tiny finger-like projections of arachnoid mater, called arachnoid villi (arachnoid granulations, see Fig. 7.13B), which project into the venous sinuses. The movement of CSF from the subarachnoid space to venous sinuses depends on the difference in pressure on each side of the walls of the arachnoid villi, which act as one-way valves. When CSF pressure is higher than venous pressure, CSF is pushed into the blood, and when the venous pressure is higher, the arachnoid villi collapse, preventing the passage of blood constituents into the CSF. There may also be some reabsorption of CSF by cells in the walls of the ventricles.

From the roof of the fourth ventricle, CSF flows through foramina into the subarachnoid space completely surrounding the brain and spinal cord (Fig. 7.16). There is no discrete CSF pump, but its movement is aided by pulsating blood vessels, respiration and changes of posture.

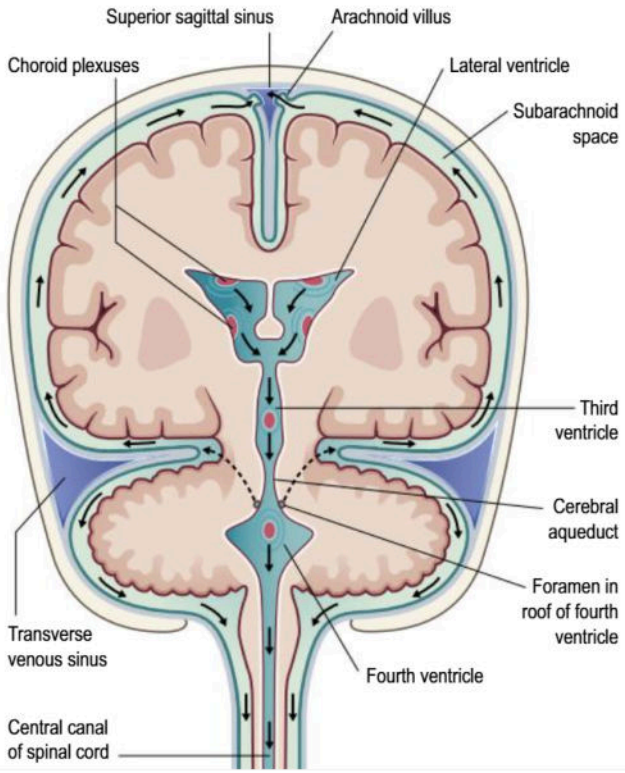

Figure 7.16 Frontal section of the skull. Black arrows indicate direction of CSF flow.

CSF is secreted continuously at a rate of about 0.5 mL per minute, i.e. 720 mL per day. The volume remains fairly constant at about 150 mL, because absorption keeps pace with secretion. CSF may be sampled by inserting a needle into the subarachnoid space above or below the 4th lumbar vertebra, which is about 2 cm below the end of the spinal cord. This procedure is known as a lumbar puncture (Fig. 7.14); CSF pressure can be measured by attaching a vertical tube to the needle. Normal CSF pressure is between 50 and 250 mmH_2O.

If the brain is enlarged by, for example, haemorrhage or a slow-growing tumour, some compensation is made by a reduction in the amount of CSF. When the volume of brain tissue is reduced, such as in degeneration or atrophy, the volume of CSF is increased.

Functions of cerebrospinal fluid

CSF supports and protects the brain and spinal cord by maintaining a uniform pressure around these vital structures and by acting as a cushion or shock absorber between the brain and the skull.

CSF keeps the brain and spinal cord moist and there may be exchange of nutrients and waste products between CSF and the interstitial fluid of the brain. CSF is involved in regulation of breathing, as it bathes the surface of the medulla where the central respiratory chemoreceptors are located (Ch. 10).

Brain

Learning outcomes

After studying this section, you should be able to:

- describe the blood supply to the brain
- name the lobes and principal sulci of the brain
- outline the functions of the cerebrum
- identify the main sensory and motor areas of the cerebrum
- outline the position and functions of the thalamus and hypothalamus
- describe the position and functions of the midbrain, pons, medulla oblongata and reticular activating system
- describe the structure and functions of the cerebellum.

The brain is a large organ weighing around 1.4 kg, which lies within the cranial cavity. Its parts are (Fig. 7.17) the:

- cerebrum
- thalamus
- hypothalamus

} the diencephalon

- midbrain
- pons
- medulla oblongata

} the brain stem

Blood supply and venous drainage

The circulus arteriosus and its contributing arteries (see Fig. 5.34) play a vital role in maintaining a constant supply of oxygen and glucose to the brain when the head is moved and also when a contributing artery is narrowed. The brain receives about 15% of the cardiac output, approximately 750 mL of blood per minute.

Autoregulation of cerebral arteriolar diameter maintains a constant blood flow to the brain, compensating for fluctuations in systemic blood pressure. This mechanism protects the brain, provided that mean systemic blood pressure remains between about 65 and 140 mmHg .

Venous blood from the brain drains into the dural venous sinuses and then downwards into the internal jugular veins (see Fig. 5.36).

Cerebrum

This is the largest part of the brain and it occupies the anterior and middle cranial fossae (see Fig. 16.15). It is divided by a deep cleft, the longitudinal cerebral fissure, into right and left cerebral hemispheres, each containing one of the lateral ventricles. Deep within the brain, the two hemispheres are connected by a mass of white matter (nerve fibres) called the corpus callosum. The falx cerebri (see Fig. 7.13) is formed by the dura mater; it separates the

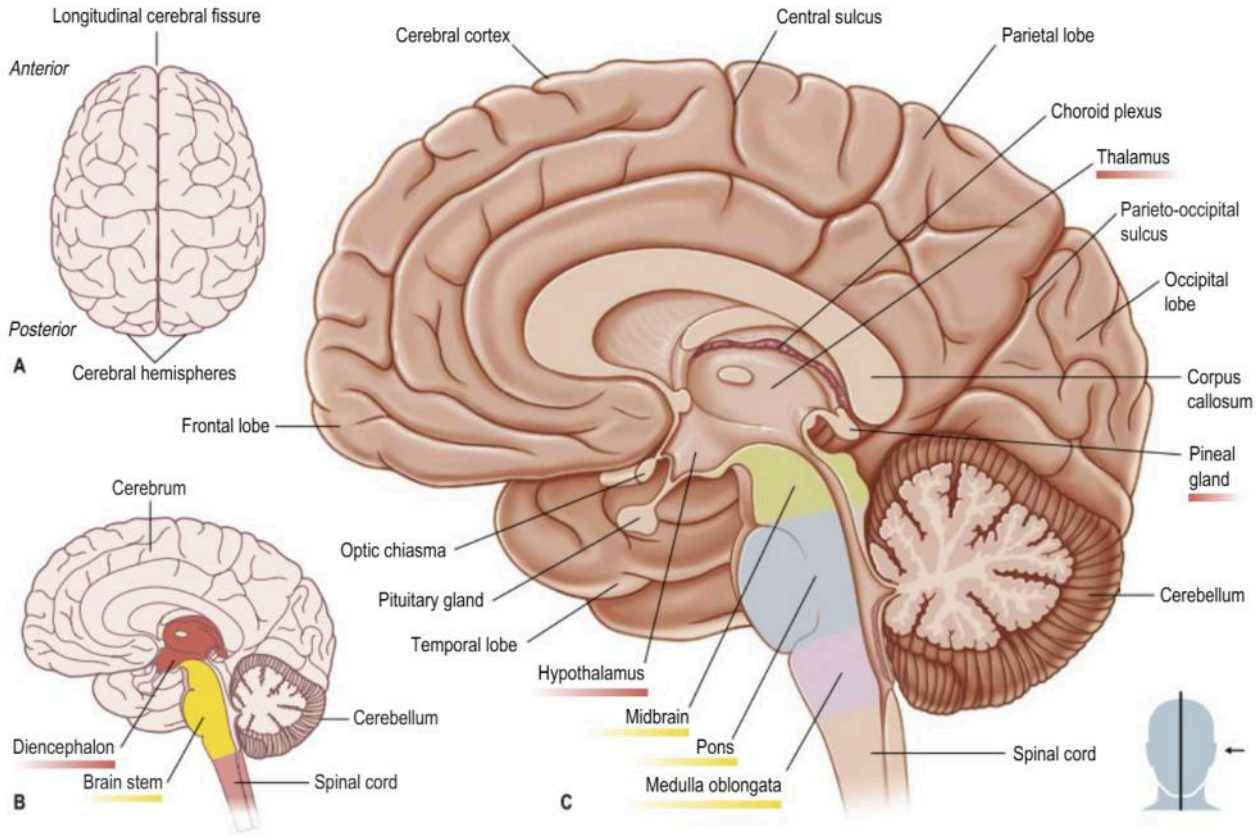

Figure 7.17 The brain. (A) The cerebrum viewed from above. (B) Regions of the brain. (C) The main structures.

two cerebral hemispheres and penetrates to the depth of the corpus callosum. The superficial part of the cerebrum, the cerebral cortex, is composed of nerve cell bodies (grey matter) and the deeper layers are composed of nerve fibres (axons, white matter).

The surface of the cerebral cortex shows many infoldings or furrows of varying depth. The exposed areas of the folds are the gyri (convolutions) and these are separated by sulci (fissures). These convolutions greatly increase the surface area of the cerebrum.

For descriptive purposes, each cerebral hemisphere is divided into lobes, which take the names of the bones of the cranium (see Fig. 16.14) above them:

- frontal
- parietal
- temporal
- occipital.

The boundaries of the lobes are marked by deep sulci. These are the central, lateral and parieto-occipital sulci (Fig. 7.18).

Cerebral tracts and basal ganglia

The surface of the cerebral cortex is composed of grey matter (nerve cell bodies). Within the cerebrum the lobes are connected by masses of nerve fibres, or tracts, which make up the white matter of the brain (Fig. 7.19). The afferent and efferent fibres linking the different parts of the brain and spinal cord are:

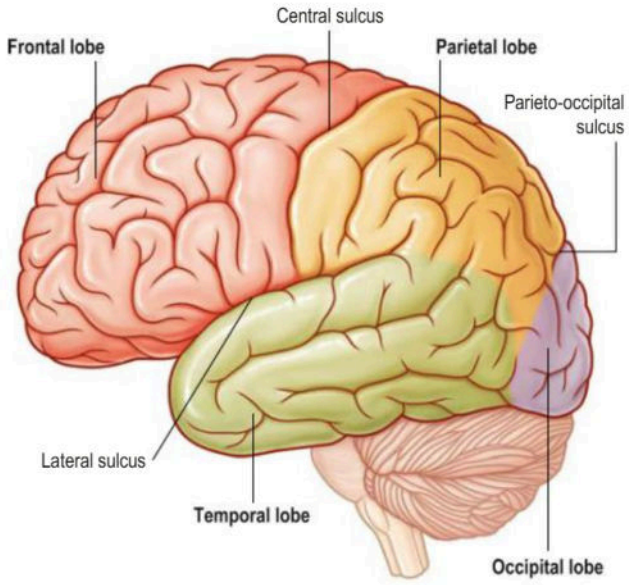

Figure 7.18 The lobes and principal sulci of the cerebrum. Viewed from the left side.

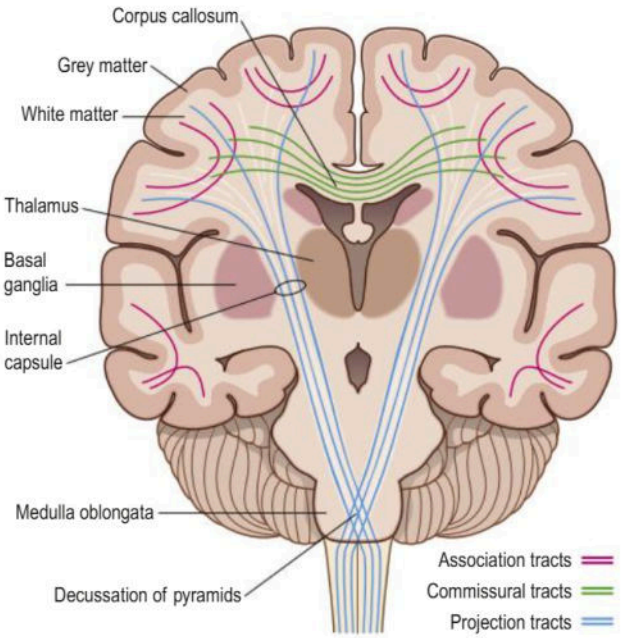

Figure 7.19 Frontal section of the brain showing the important tracts.

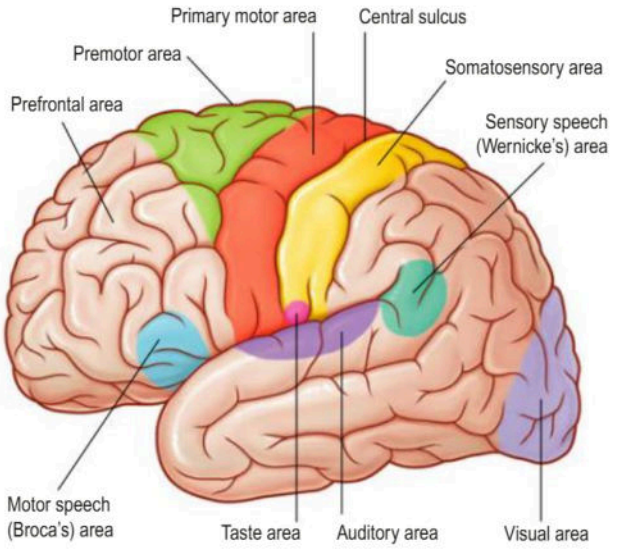

Figure 7.20 The cerebrum showing the main functional areas. Viewed from the left side.

- Association tracts, which are most numerous and connect different parts of the same cerebral hemisphere by extending from one gyrus to another, some that may be adjacent and some distant.
- Commissural tracts, which connect corresponding areas of the two cerebral hemispheres; the largest and most important commissure is the corpus callosum.
- Projection tracts, which connect the cerebral cortex with grey matter in lower parts of the brain and with the spinal cord, e.g. the internal capsule.

The internal capsule (Fig. 7.19) is an important projection tract linking the cerebral cortex to a number of other structures, including the thalamus and the brainstem. Motor fibres within the internal capsule form the pyramidal tracts (corticospinal tracts) that cross over (decussate) at the medulla oblongata and are the main pathway to skeletal muscles. Those motor fibres that do not pass through the internal capsule form the extrapyramidal tracts and have connections with many parts of the brain, including the basal ganglia, thalamus and cerebellum.

Basal ganglia

The basal ganglia (Fig. 7.19) are groups of cell bodies that lie deep within the brain and form part of the extrapyramidal tracts. They act as relay stations with connections to many parts of the brain, including motor areas of the cerebral cortex and the thalamus. Their functions include initiation and fine control of complex movement and learned coordinated activities, such as posture and walking; if control is inadequate or absent, movements are jerky, clumsy and uncoordinated (see Parkinson's disease, p. 203).

Functional areas of the cerebral cortex

The main functional areas of the cerebral cortex (Fig. 7.20) have been identified but it is unlikely that any area is associated exclusively with one function. Except where specially mentioned, the different areas are active in both hemispheres although there are variations between the sexes and between individuals. The different types of functional area are:

- motor areas, which initiate and control skeletal (voluntary) muscle movement
- sensory areas, which receive and decode sensory impulses, enabling perception of pain, temperature, touch, sight, hearing, taste and smell
- association areas, concerned with integration and processing of complex mental functions such as intelligence, memory, reasoning, judgement and emotions.

In general, areas of the cortex lying anterior to the central sulcus are associated with motor functions, and those lying posterior to it are involved in sensory functions.

Motor areas of the cerebral cortex

Primary motor area

This lies in the frontal lobe, immediately anterior to the central sulcus. These cell bodies control skeletal muscle activity. Two neurones are involved in the pathway to skeletal muscle. The first, is the upper motor neurone, which descends from the motor cortex through the internal capsule to the medulla oblongata. Here it crosses to the opposite side and descends in the spinal cord. At the appropriate level in the spinal cord it synapses with a second neurone (the lower motor neurone), which leaves the spinal cord and travels to the target muscle. It terminates at the motor

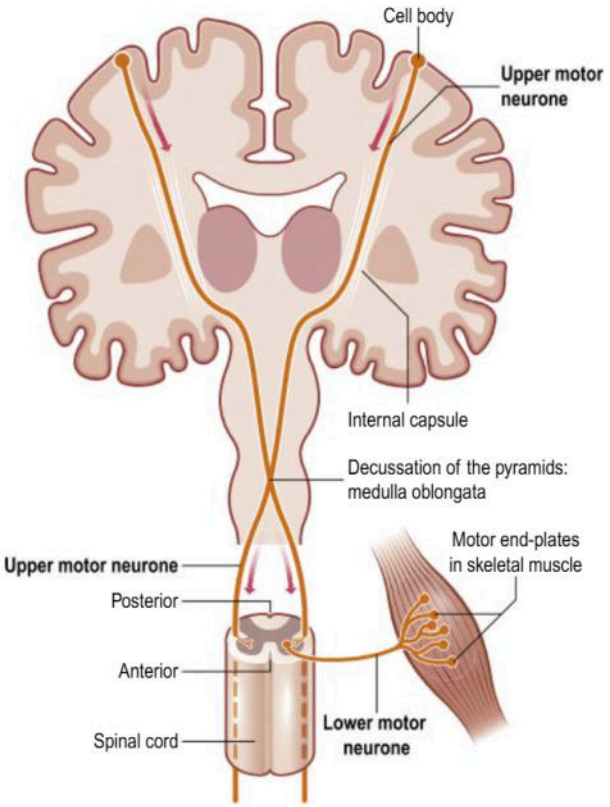

Figure 7.21 The motor nerve pathways. Upper and lower motor neurones.

end-plate of a muscle fibre (Fig. 7.21). The crossing over of nerve fibres in the spinal cord means that the motor area of the right hemisphere of the cerebrum controls voluntary muscle movement on the left side of the body and vice versa. Damage to either of these neurones may result in paralysis.

In the motor area of the cerebrum the body is represented upside down, i.e. the uppermost cells control the feet and those in the lowest part control the head, neck, face and fingers (Fig. 7.22A). The sizes of the areas of the cerebral cortex representing different parts of the body are proportional to the complexity of movement of the body part, not to its size. Figure 7.22A shows that – in comparison with the trunk – the hand, foot, tongue and lips are represented by large cortical areas, reflecting the greater degree of motor control associated with these areas.

Motor speech (Broca's) area

This is situated in the frontal lobe just above the lateral sulcus and controls the muscle movements needed for speech. It is dominant in the left hemisphere in right-handed people and vice versa.

Sensory areas of the cerebral cortex

Somatosensory area

This is the area immediately behind the central sulcus, where sensations of pain, temperature, pressure and touch, awareness of muscular movement and the position of joints (proprioception) are perceived. The somatosensory area of the right hemisphere receives impulses from the

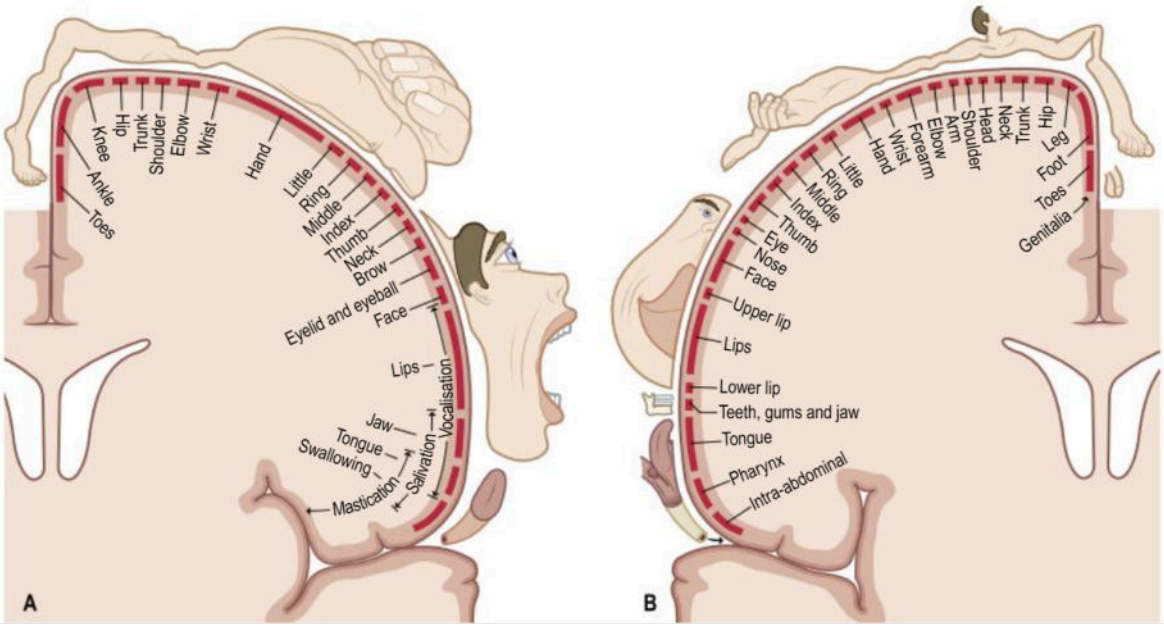

Figure 7.22 Functional areas of the cerebral cortex. (A) The motor homunculus, showing how the body is represented in the motor area of the cerebrum. (B) The sensory homunculus, showing how the body is represented in the sensory area of the cerebrum. (Penfield W, Rasmussen T 1950 The cerebral cortex of man. New York: Macmillan. © 1950 Macmillan Publishing Co., renewed 1978 Theodore Rasmussen. Reproduced with permission.)

left side of the body and vice versa. The size of the cortical areas representing different parts of the body (Fig. 7.22B) is proportional to the extent of sensory innervation; for example, the large area for the face is consistent with the extensive sensory nerve supply by the three branches of the trigeminal nerves (5th cranial nerves, see Fig. 7.41).

Auditory (hearing) area

This lies immediately below the lateral sulcus within the temporal lobe. The nerve cells receive and interpret impulses transmitted from the inner ear by the cochlear (auditory) part of the vestibulocochlear nerves (8th cranial nerves, see Fig. 8.4).

Olfactory (smell) area

This lies deep within the temporal lobe, where impulses from the olfactory epithelium of the nose, transmitted via the olfactory nerves (1st cranial nerves), are received and interpreted.

Taste area

This lies just above the lateral sulcus in the deep layers of the somatosensory area. Here, impulses from sensory receptors in taste buds are received and perceived as taste.

Visual area

This lies behind the parieto-occipital sulcus and includes the greater part of the occipital lobe. The optic nerves (2nd cranial nerves) pass from the eye to this area, which receives and interprets the impulses as images.

Association areas

These are connected to each other and other areas of the cerebral cortex by association tracts and some are outlined below. They receive, coordinate and interpret impulses from the sensory and motor cortices, permitting higher cognitive abilities. Although Figure 7.23 depicts some of the areas involved, their functions are much more complex.

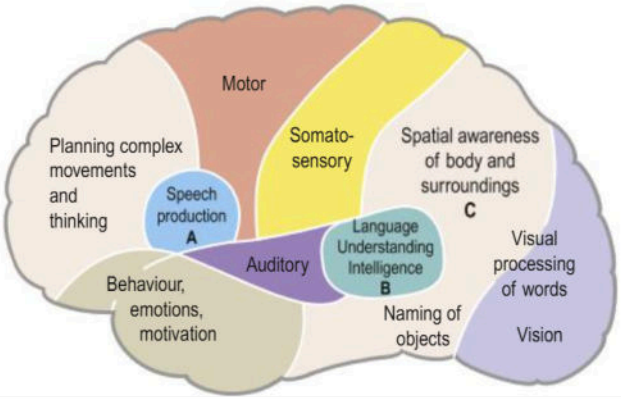

Figure 7.23 Areas of the cerebral cortex involved in higher mental functions. (A) Motor speech (Broca's) area. (B) Sensory speech (Wernicke's) area. (C) Parieto-occipital area.

Premotor area

Located in the frontal lobe immediately anterior to the motor area (Fig. 7.20), the neurones here coordinate movement initiated by the primary motor cortex. This means that learned patterns of movement can be repeated, e.g. when tying a shoelace or writing, many muscles contract but the movements must be coordinated and carried out in a particular sequence. Such a pattern of movement, when established, is described as manual dexterity.

Prefrontal area

This extends anteriorly from the premotor area to include the remainder of the frontal lobe. It is a large area and is more highly developed in humans than in other animals. Intellectual functions controlled here include perception and comprehension of the passage of time, the ability to anticipate consequences of events and the normal management of emotions.

Sensory speech (Wernicke's) area

Situated in the temporal lobe adjacent to the parieto-occipital area, it is here that language, both written and spoken, is perceived, and comprehension and intelligence are based. Understanding language is central to higher mental functions, as they too are language-based. This area is dominant in the left hemisphere in right-handed people and vice versa.

Parieto-occipital area

This lies behind the somatosensory area and includes most of the parietal lobe (including Wernicke's area). Its functions are thought to include spatial awareness, interpretation of language and the ability to name objects (Fig. 7.23). It has been suggested that objects can be recognised by touch alone because the knowledge gained from past experience (memory) is retained in this area.

Diencephalon

The diencephalon (see Fig. 7.17) connects the cerebrum and the midbrain. It consists of several structures situated around the third ventricle, the main ones being the thalamus and hypothalamus, which are considered here. The pineal gland (p. 252) and the optic chiasma (see Fig. 7.40) are also situated there.

Thalamus

This consists of two interconnected masses of grey and white matter situated within the cerebral hemispheres just below the corpus callosum, one on each side of the third ventricle (see Fig. 7.19). Sensory receptors in the skin and viscera send information about touch, pain and temperature, and input from the special sense organs travels to the thalamus, where there is recognition, although only in a basic form, as refined perception also involves other parts of the brain. The thalamus plays a role in arousal and the processing of some emotions and complex reflexes. It relays and redistributes impulses from most parts of the brain to the cerebral cortex.

Hypothalamus

The hypothalamus (see Fig. 7.17) is a small but highly important structure, which weighs around 7 g and consists of several nuclei. It is situated below and in front of the thalamus, immediately above the pituitary gland. The hypothalamus is linked to the posterior lobe of the pituitary gland by nerve fibres and to the anterior lobe by a complex system of blood vessels (see Figs 9.2 and 9.3). Through these connections the hypothalamus controls the output of hormones from both anterior and posterior lobes of the pituitary gland (p. 241).

Other functions of the hypothalamus include control of:

- effectors of the autonomic nervous system
- appetite and satiety
- thirst and water balance
- body temperature (p. 406)
- emotional reactions, e.g. pleasure, fear, rage, sexual arousal
- circadian rhythms, i.e. 24-hour body clocks, including the sleeping and waking cycle.

Brain stem

Its position within the brain is shown in Figs 7.17B & C.

Midbrain

The midbrain is the area of the brain situated around the cerebral aqueduct (see Fig. 7.15) lying between the cerebrum above and the pons below. It consists of nuclei and nerve fibres (tracts) that connect the cerebrum with lower parts of the brain and with the spinal cord. The nuclei act as relay stations for the ascending and descending nerve fibres and have important roles in auditory and visual reflexes.

Pons

The pons is situated in front of the cerebellum, below the midbrain and above the medulla oblongata. It consists mainly of nerve fibres (white matter) that form a bridge between the two cerebellar hemispheres, and of fibres passing between the higher levels of the brain and the spinal cord. The pons also processes information from some of the cranial nerves, including the 5th cranial nerve (sensory information from the face, scalp, mouth and nose, and motor control of chewing) and 8th cranial nerve (hearing and balance). In addition, the pons contains the pneumotaxic area that operates in conjunction with the respiratory centre in the medulla oblongata to control respiration (Ch. 10).

The anatomical structure of the pons is different to that of the cerebrum, in that the cell bodies (grey matter) lie deeply while the nerve fibres are superficial.

Medulla oblongata

The medulla oblongata, or simply the medulla, is the most inferior region of the brain stem (Fig. 7.24A; see also Fig. 7.17). Extending from the pons above, it is continuous with the spinal cord below. It is about 2.5 cm long and lies within the cranium, just above the foramen magnum. Its anterior and posterior surfaces are marked by central fissures. The outer aspect is composed of white matter, which passes between the brain and the spinal cord, and grey matter, which lies centrally. Some medullary nerves relay information from the special senses of hearing and balance to higher centres in the brain.

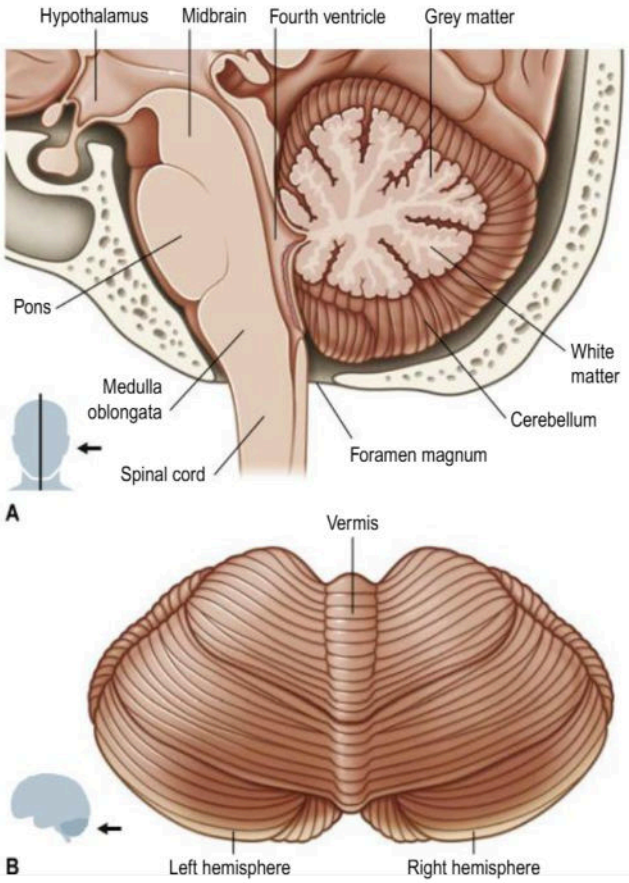

Figure 7.24 The cerebellum. (A) Showing associated structures. (B) Posterior view.

The vital centres consist of groups of cell bodies (nuclei) associated with autonomic reflex activity and lie deep within the medulla. They include the cardiovascular and respiratory centres and several reflex centres.

Cardiovascular centre

The cardiovascular centre (CVC) controls blood pressure and the rate and force of cardiac contraction (p. 101). Within the CVC, other groups of nerve cells forming the vasomotor centre control the diameter of the blood vessels, especially the small arteries and arterioles. The vasomotor centre is stimulated by the arterial baroreceptors, body temperature and emotions such as sexual arousal and anger. Pain usually causes vasoconstriction, although severe pain may cause vasodilation, a fall in blood pressure and fainting.

Respiratory centre

This area controls the rate and depth of respiration. From here, nerve impulses travel to the phrenic and intercostal nerves, which stimulate contraction of the diaphragm and intercostal muscles and initiate inspiration. It functions in close association with the pneumotaxic area in the pons (p. 288).

Reflex centres

Irritants in the stomach or respiratory tract stimulate the medulla oblongata, activating the reflex centres. Vomiting, coughing and sneezing are protective reflexes that attempt to expel irritants. The swallowing reflex ensures safe passage of ingested food to the stomach and avoids it being inhaled into the respiratory tract.

Decussation (crossing) of the pyramids

In the medulla, motor nerves descending from the motor area in the cerebrum to the spinal cord in the pyramidal (corticospinal) tracts cross from one side to the other. This means that the left hemisphere of the cerebrum controls the right half of the body and vice versa. These tracts are the main pathways to skeletal (voluntary) muscles.

Sensory decussation

Some of the sensory nerves ascending to the cerebrum from the spinal cord cross from one side to the other in the medulla. Others decussate lower down in the spinal cord.

Reticular formation

The reticular formation is a collection of neurones in the core of the brain stem, surrounded by numerous and diffuse neural pathways that conduct ascending and descending nerve impulses between the brain and the spinal cord. It has extensive synaptic connections with other parts of the brain and is therefore constantly receiving 'information' being transmitted in ascending and descending tracts.

Reticular activating system

The reticular activating system (RAS) consists of areas within the reticular formation that, when activated, bring about increased stimulation of the cerebral cortex, accompanied by consciousness, arousal and increased alertness, although the mechanisms involved are poorly understood. The RAS also mediates selective awareness, meaning that it selectively blocks or permits transmission of sensory information to the cerebral cortex; for example, the slightest noise made by a sick child moving in bed may arouse a sleeping mother but the noise of regularly passing trains does not disturb her.

Cerebellum

The cerebellum (Fig. 7.24) is situated behind the pons and immediately below the posterior part of the cerebrum occupying the posterior cranial fossa. It is ovoid in shape and has two hemispheres, separated by a narrow median strip called the vermis. Grey matter forms the surface of the cerebellum, and the white matter lies deeply.

Functions

The cerebellum controls and coordinates the movements of various groups of skeletal muscles, ensuring smooth, steady and precise actions. Cerebellar activity is not under voluntary control; it coordinates subconscious activities that maintain posture, balance and equilibrium. The sensory input for these functions is derived from the muscles, joints, eyes and ears. Proprioceptor impulses from the stretch receptors in the muscles and joints indicate their position in relation to the body as a whole and the eyes and the semicircular canals in the ears provide information about the position of the head in space. The cerebellum integrates all this information and regulates skeletal muscle activity to maintain balance and posture.

The cerebellum may also have a role in learning of voluntary and complex motor skills.

Damage to the cerebellum results in clumsy, uncoordinated muscular movement, staggering gait and inability to carry out smooth, steady and precise movements.

Spinal cord

Learning outcomes

After studying this section, you should be able to:

- describe the gross structure of the spinal cord
- state the functions of the sensory (afferent) and motor (efferent) nerve tracts in the spinal cord
- explain the events of a simple reflex arc.

The spinal cord is an elongated, almost cylindrical part of the CNS, which is suspended in the vertebral canal surrounded by the meninges and CSF (Fig. 7.25). The meninges are described on page 167. The spinal cord is continuous above

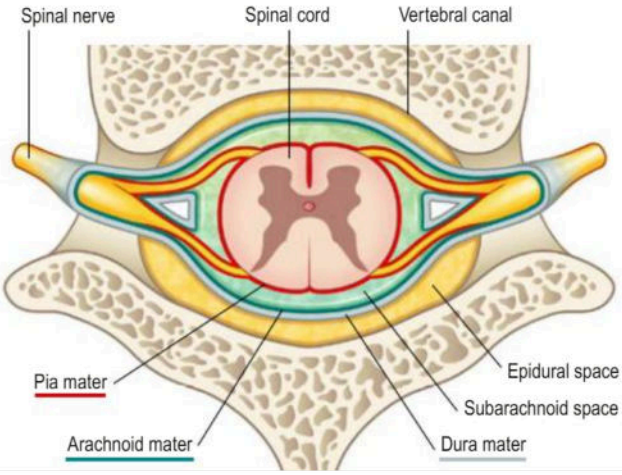

Figure 7.25 The meninges covering the spinal cord. Transverse section.

with the medulla oblongata and extends from the upper border of the atlas (first cervical vertebra) to the lower border of the 1st lumbar vertebra (Fig. 7.26). It is approximately 45 cm long in adult males and is about the thickness of the little finger.

Along with the cranial nerves (p. 188), the spinal cord is the nervous tissue link between the brain and the rest of the body (see Fig. 7.30). Motor nerves transmitting impulses from the brain to the body organs and tissues descend through the spinal cord. At the appropriate level they leave the cord between adjacent vertebrae and pass to the structure(s) they supply. Similarly, sensory nerves from organs and tissues enter and pass upwards in the spinal cord to the brain.

Some activities of the spinal cord are independent of the brain and are controlled at the level of the spinal cord by spinal reflexes. To facilitate these, there are extensive neurone connections between sensory and motor neurones at the same or different levels in the cord.

A cross-section of the spinal cord shows that it is almost completely divided into left and right parts by the deep, narrow anterior median fissure and the much shorter posterior median sulcus (Fig. 7.27). It consists of grey matter in the centre surrounded by white matter supported by neuroglia. Two bundles of nerve fibres called nerve roots merge into each side of the spinal cord. The dorsal (or posterior) nerve roots carry sensory nerve impulses into the spinal cord while the fibres of the ventral (or anterior) nerve root carry motor impulses away from the spinal cord. Figure 7.27 shows the structure of the spinal cord and the nerve roots.

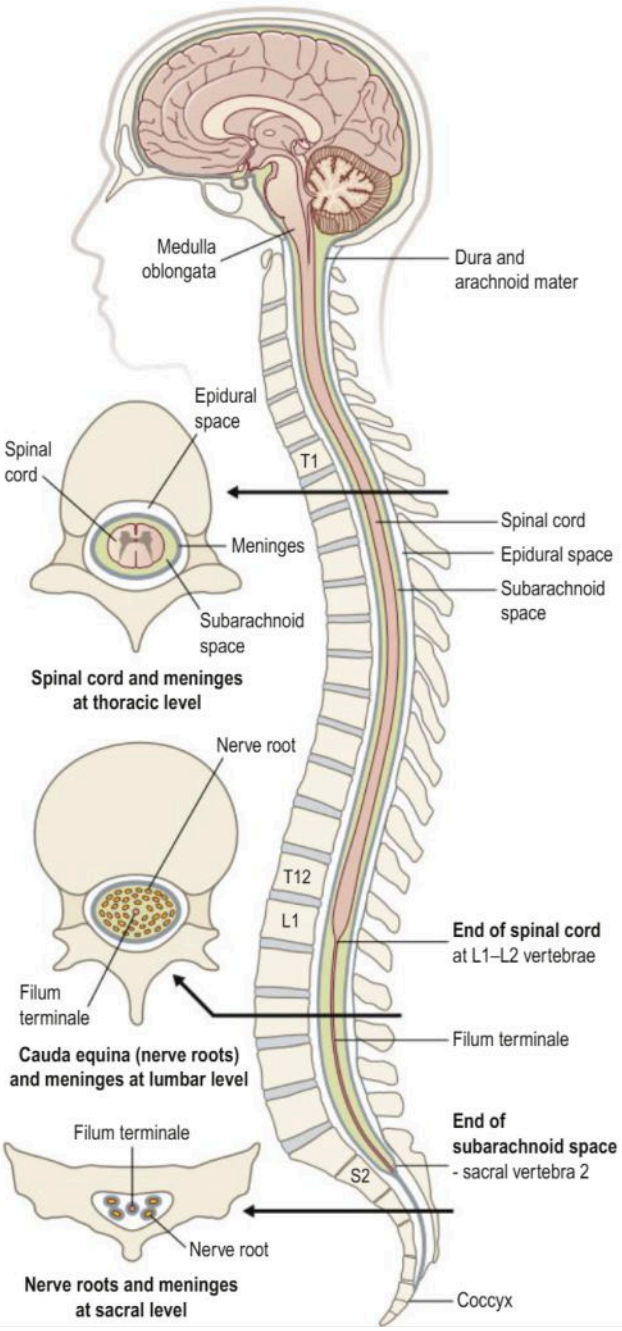

Figure 7.26 Sections of the vertebral canal showing the subarachnoid and epidural spaces.

Grey matter

The arrangement of grey matter in the spinal cord is roughly H-shaped on a transverse section, having two posterior, two anterior and two lateral columns (Fig. 7.27). The grey columns extend the length of the spinal cord, containing the cell bodies of the neurones that also run up and down its length. The area of grey matter lying transversely is the transverse commissure and it is pierced by the central canal, an extension from the fourth ventricle containing CSF. The nerve cell bodies may belong to:

- sensory neurones, which receive impulses from the periphery of the body
- lower motor neurones, which transmit impulses from the spinal cord to the skeletal muscles
- interneurones, which directly link a sensory and a motor neurone to form a reflex arc.

The sensory and motor nerves may enter and leave the spinal cord at the same or at different levels.

Posterior columns of grey matter

These are composed of the cell bodies of sensory nerves, which carry information from the body upwards to the brain. The nerve fibres of these cells contribute to the white matter of the cord and transmit the sensory impulses upwards to the brain. The posterior (dorsal) root ganglia (Fig. 7.28) are formed by the cell bodies of the sensory nerves.

Anterior columns of grey matter

These are composed of the cell bodies of the lower motor neurones, and are stimulated by upper motor neurones or the interneurones linking the anterior and posterior columns to form reflex arcs.

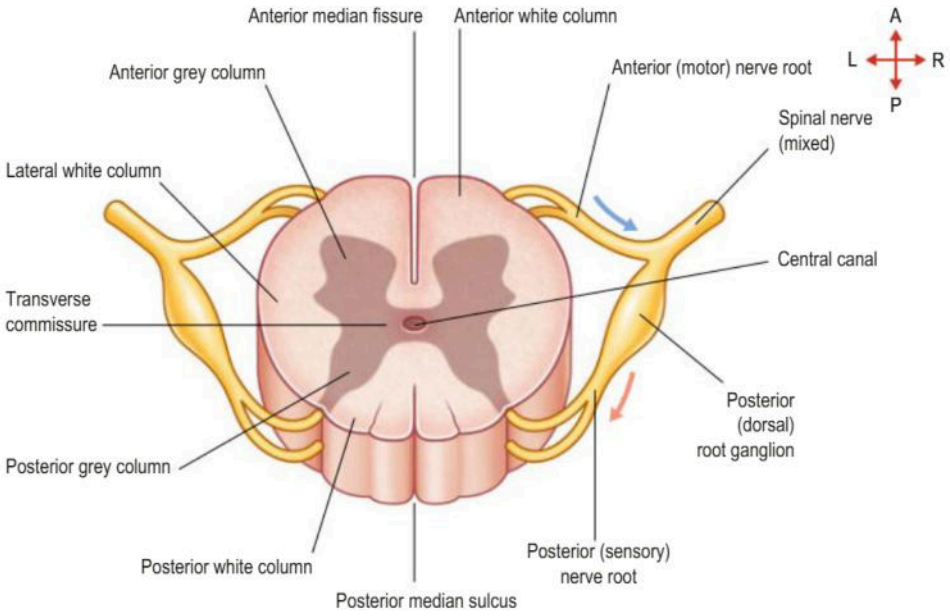

Figure 7.27 A transverse section of the spinal cord showing nerve roots.

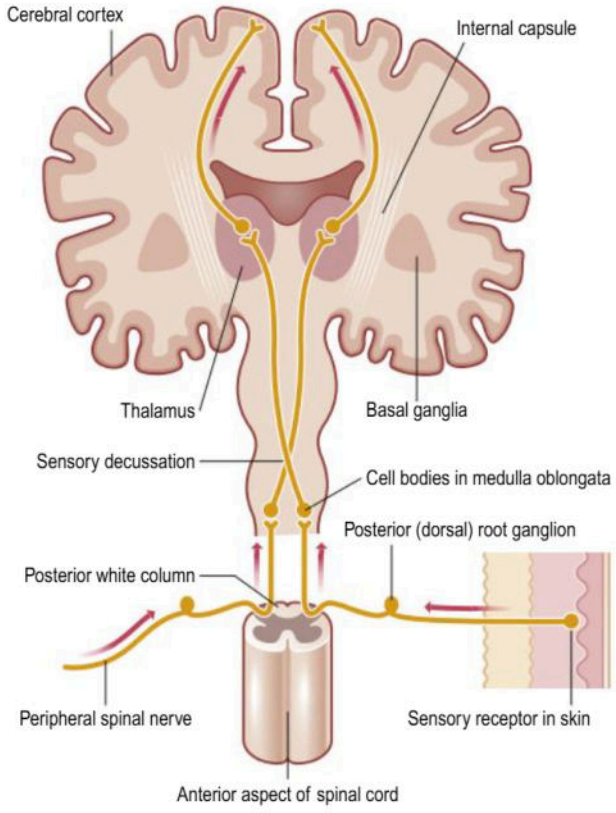

Figure 7.28 A sensory nerve pathway from the skin to the cerebrum.

White matter

The white matter of the spinal cord is arranged in three columns or tracts: anterior, posterior and lateral. These tracts are formed by sensory nerve fibres ascending to the brain, motor nerve fibres descending from the brain and fibres of interneurones.

Tracts are often named according to their points of origin and destination that also indicates their direction of travel in the spinal cord:

- Spinothalamic tracts – these originate in the spinal cord and transmit impulses upwards to the thalamus in the brain
- Corticospinal tracts – these originate in the cerebral cortex and transmit impulses downward to the spinal cord.

Sensory nerve tracts in the spinal cord

Neurones that transmit impulses towards the brain are called sensory (afferent, ascending). There are two main sources of sensory information transmitted to the brain via the spinal cord.

The skin

Sensory receptors (nerve endings) in the skin are stimulated by pain, heat, cold and touch (pressure) (Ch. 14). The nerve impulses generated in these receptors are conducted by three neurones to the sensory area in the cerebral hemisphere on the other side to that where the sensation and its location are perceived (Fig. 7.28). Crossing either occurs at the level at which impulses enter the cord or in the medulla.

The tendons, muscles and joints

Sensory receptors in these structures are specialised nerve endings called proprioceptors, and they are stimulated by stretch. Together with impulses from the eyes and the ears, they contribute to the maintenance of balance and posture,

Table 7.1 Sensory nerve pathways: origins, routes, destinations of impulses in sensory neurones

Receptor	Route	Destination
Pain, touch, temperature	Neurone 1 – by posterior root	Spinal cord
	Neurone 2 – decussation on entering spinal cord then in anterolateral spinothalamic tract	Thalamus
	Neurone 3	Parietal lobe of cerebrum
Touch, proprioceptors	Neurone 1 – in posterior spinothalamic tract	Medulla
	Neurone 2 – decussation in medulla, transmission	Thalamus
	Neurone 3	Parietal lobe of cerebrum
Proprioceptors	Neurone 1	Spinal cord
	Neurone 2 – no decussation, in posterior spinocerebellar tract	Cerebellum

and with perception of the position of the body in space. These nerve impulses have two destinations:

- By a three-neurone pathway, to the sensory area of the opposite hemisphere of the cerebrum.
- By a two-neurone pathway, to the cerebellar hemisphere on the same side.

Table 7.1 summarises the main sensory pathways.

Motor nerve tracts in the spinal cord

Neurones that transmit nerve impulses away from the brain are called motor (efferent or descending) neurones. Stimulation of motor neurones results in:

- contraction of muscle (skeletal, smooth or cardiac)
- glandular secretion.

Voluntary muscle movement

Muscle contraction that moves the joints is, in the main, under conscious (voluntary) control, which means that the stimulus to contract originates at the level of consciousness in the cerebrum. However, skeletal muscle activity is regulated by subconscious outputs from the midbrain, brain stem and cerebellum, which assist with its coordination, e.g. in very fine movement and in the maintenance of posture and balance.

Efferent nerve impulses are transmitted from the brain to other parts of the body via tracts in the spinal cord. The motor pathways from the brain to the muscles consist of two neurones (see Fig. 7.21). These are either pyramidal (corticospinal) or extrapyramidal (p. 193).

Upper motor neurones. The cell bodies of upper motor neurones are situated in the primary motor area of the cerebrum and their axons pass through the internal capsule, pons and medulla. In the spinal cord they form the lateral corticospinal tracts of white matter, and synapse with the cell bodies of the lower motor neurones in the anterior columns of grey matter. The axons of the upper motor neurones make up the pyramidal tracts and decussate in the medulla oblongata, forming the pyramids.

Lower motor neurones. These have their cell bodies in the anterior horn of grey matter in the spinal cord. The axons emerge from the spinal cord via the anterior root, join with the incoming sensory fibres and form the mixed spinal nerve that passes through the intervertebral foramen.

The lower motor neurone is the final common pathway for the transmission of nerve impulses to skeletal muscles. The cell body of this neurone is influenced by several upper motor neurones originating from various sites in the brain and by other neurones that begin and end within the spinal cord. Some of these neurones stimulate the lower motor neurone while others inhibit it. The outcome of these influences is smooth, coordinated muscle movement, some of which is voluntary and some involuntary.

Involuntary muscle movement

Upper motor neurones. The cell bodies of these neurones originate in the brain, but below the cerebrum, i.e. in the midbrain, brain stem, cerebellum or spinal cord. They influence muscle activity that maintains posture and balance, coordinates skeletal muscle movement and controls muscle tone. Table 7.2 summarises the area of origin of these neurones and the tracts that their axons form before reaching the cell body of the lower motor neurone in the spinal cord.

Reflexes

A reflex is a protective, predictable near-immediate involuntary motor response to a potentially dangerous stimulus (Fig. 7.29).

Withdrawal reflexes

These consist of three elements:

- a sensory neurone
- an interneurone in the spinal cord
- a lower motor neurone.

For example, the pain impulses initiated in a finger touching a very hot surface are transmitted to the spinal cord by sensory fibres in mixed nerves. These stimulate many interneurones and lower motor neurones in the spinal cord, resulting in the contraction of many skeletal muscles of the hand, arm and shoulder, and near-immediate removal of the finger. A reflex action happens very quickly; the motor response may occur simultaneously with the perception of the pain in the cerebrum. Protective reflexes can occasionally

Table 7.2 Extrapyramidal upper motor neurones: origins and tracts

Origin	Name of tract	Site in spinal cord		Functions
Midbrain and pons	Rubrospinal tract – decussates in brain stem	Lateral column		Control of skilled muscle movement
Reticular formation	Reticulospinal tract – does not decussate	Lateral column		
Midbrain and pons	Tactospinal tract – decussates in midbrain	Anterior column		Coordination of muscle movement
Midbrain and pons	Vestibulospinal tract – some fibres decussate in cord	Anterior column		Maintenance of posture and balance

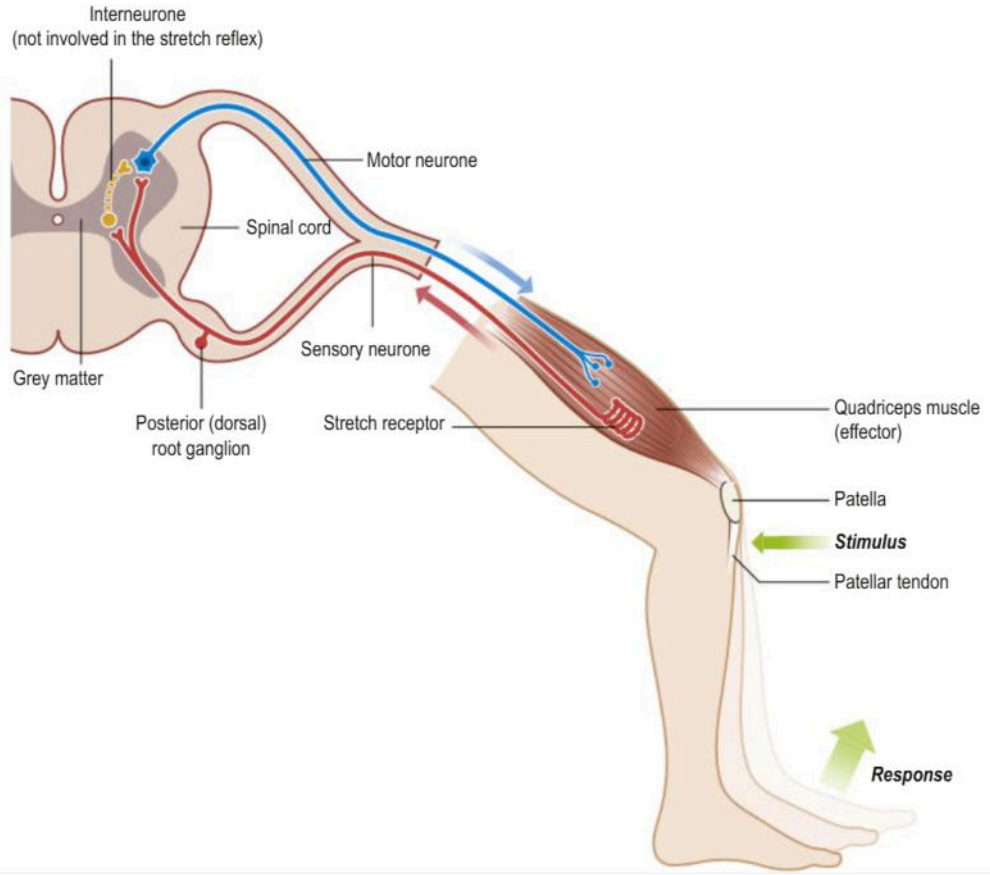

Figure 7.29 The knee jerk reflex. Left side.

be inhibited. For example, if a precious plate is very hot when lifted, every effort will be made to overcome the pain to prevent dropping it!

Stretch reflexes

These involve only two neurones. The cell body of the lower motor neurone is stimulated directly by the sensory neurone, with no interneurone in between (Fig. 7.29). The knee jerk is one example, but this type of reflex can be demonstrated at any point where a stretched tendon crosses a joint. If the patellar tendon is tapped briskly just below the bent knee, the sensory nerve endings in the tendon and the quadriceps muscles are suddenly stretched. This initiates a nerve impulse that passes into the spinal cord and synapses with the cell body of the lower motor neurone in the anterior column of grey matter on the same side. This in turn directly activates the motor neurone, which stimulates sudden contraction of the quadriceps muscle and the foot kicks forwards. This relieves the stretch on the quadriceps muscle and prevents it from being damaged by over-stretching. This is used clinically to test the integrity of the reflex arc. This type of reflex in general has a protective function because it prevents excessive joint movement that may damage tendons, ligaments and muscles.

Autonomic reflexes

These include the pupillary light reflex, when the pupil immediately constricts in response to bright light, preventing retinal damage.

SPOT CHECK

3. Describe the secretion and reabsorption of cerebrospinal fluid.
4. Functional areas of the cerebral cortex are described as motor, sensory or association. Outline the function of each type.

Peripheral nervous system

Learning outcomes

After studying this section, you should be able to:

- outline the function of a nerve plexus
- list the spinal nerves entering each plexus and the main nerves emerging from it
- describe the areas innervated by the thoracic nerves
- outline the functions of the 12 cranial nerves
- compare and contrast the structures and neurotransmitters of the divisions of the autonomic nervous system
- compare and contrast the effects of stimulation of the divisions of the autonomic nervous system on body function.

The peripheral nervous system (PNS) is made up of all nerves, belonging to both the somatic and the autonomic nervous systems, entering and leaving the CNS. These are the:

- spinal nerves
- cranial nerves, which originate in the base of the brain and flow out through foramina (tiny holes) in the base of the skull.

Peripheral nerves can be sensory (carrying input from the body to the brain), motor (carrying impulses from the brain to skeletal, smooth or cardiac muscle and glands) or mixed (containing both sensory and motor fibres).

Spinal nerves

Thirty-one pairs of spinal nerves leave the vertebral canal by passing through the intervertebral foramina, formed between adjacent vertebrae. They are named and grouped according to the vertebrae with which they are associated (Fig. 7.30):

- 8 cervical
- 12 thoracic
- 5 lumbar
- 5 sacral
- 1 coccygeal.

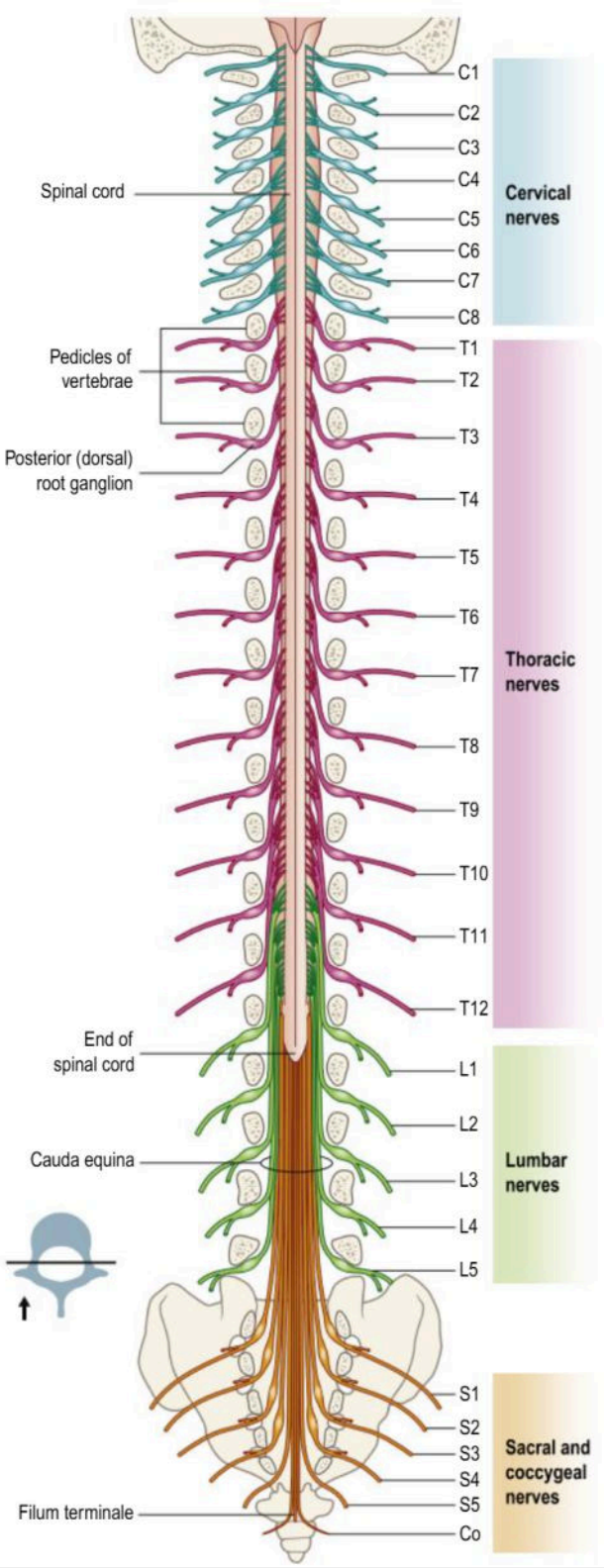

Figure 7.30 The spinal cord and spinal nerves.

Although there are only seven cervical vertebrae, there are eight nerves because the first pair leaves the vertebral canal between the occipital bone and the atlas (first cervical vertebra), and the eighth pair leaves below the last cervical vertebra. Thereafter, the nerves are given the name and number of the vertebra immediately above.

The lumbar, sacral and coccygeal nerves leave the spinal cord near its termination, at the level of the 1st lumbar vertebra, and extend downwards inside the vertebral canal in the subarachnoid space, forming a sheaf of nerves that resembles a horse's tail, the cauda equina (Fig. 7.30). These nerves leave the vertebral canal at the appropriate lumbar, sacral or coccygeal level, depending on their destination.

Nerve roots

The spinal nerves arise from both sides of the spinal cord and emerge through the intervertebral foramina (see Fig. 16.30). Each nerve is formed by the union of a motor (anterior) and a sensory (posterior) nerve root and is, therefore, a mixed nerve (Fig. 7.31). Thoracic and upper lumbar (L1 and L2) spinal nerves have a contribution from the sympathetic part of the autonomic nervous system in the form of a preganglionic neurone.

Chapter 16 describes specific bones and muscles mentioned in the following sections. Bones and joints are supplied by adjacent nerves.

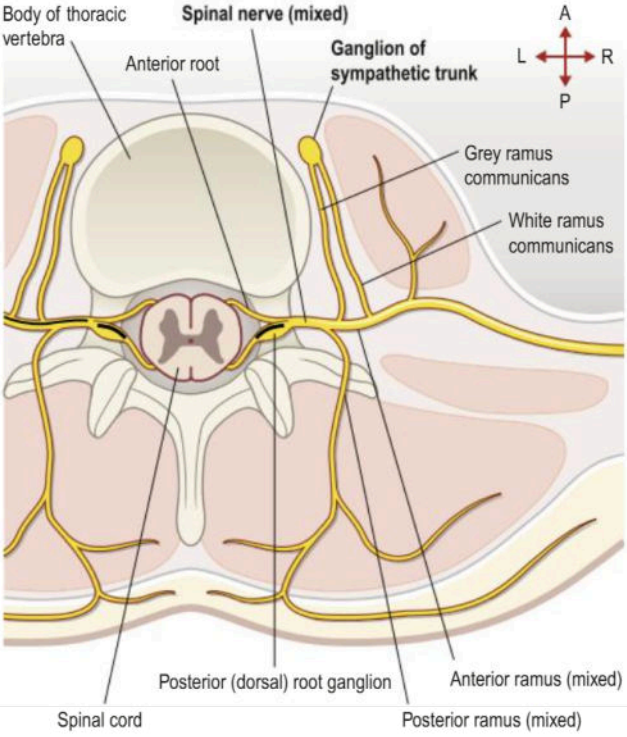

Figure 7.31 The relationship between sympathetic and mixed spinal nerves.

The anterior nerve root consists of motor nerve fibres, which are the axons of the lower motor neurones from the anterior column of grey matter in the spinal cord and, in the thoracic and lumbar regions, sympathetic nerve fibres, which are the axons of cells in the lateral columns of grey matter.

The posterior nerve root is comprised of sensory nerve fibres (see Fig. 7.27). Just outside the spinal cord there is a spinal ganglion (posterior, or dorsal, root ganglion), consisting of a cluster of cell bodies. Sensory nerve fibres pass through these ganglia before entering the spinal cord. The area of skin served by a particular nerve is called a dermatome (see Figs 7.36 and 7.39).

For a very short distance after leaving the spinal cord the nerve roots have a covering of dura and arachnoid maters. These terminate before the two roots join to form the mixed spinal nerve. The nerve roots have no covering of pia mater.

Branches

Immediately after emerging from the intervertebral foramen, spinal nerves divide into branches, or rami: a ramus communicans, a posterior ramus and an anterior ramus.

The rami communicantes are part of preganglionic sympathetic neurones of the autonomic nervous system (Fig. 7.31).

The posterior rami pass backwards and divide into smaller medial and lateral branches to supply skin and muscles of relatively small areas of the posterior aspect of the head, neck and trunk.

The anterior rami supply the anterior and lateral aspects of the neck, trunk and the upper and lower limbs.

Plexuses

In the cervical, lumbar and sacral regions the anterior rami unite near their origins to form large masses of nerves, or plexuses, where nerve fibres are regrouped and rearranged before proceeding to supply skin, bones, muscles and joints of a particular area (Fig. 7.32). This means that these structures have a nerve supply from more than one spinal nerve and therefore damage to one spinal nerve does not cause loss of function of a region. Moreover, they lie deep within the body, often under large muscles, and are therefore well protected from injury.

In the thoracic region the anterior rami do not form plexuses.

There are five large plexuses of mixed nerves formed on each side of the vertebral column. They are the:

- cervical plexuses
- brachial plexuses
- lumbar plexuses
- sacral plexuses
- coccygeal plexuses.

Cervical plexus

The cervical plexus (Fig. 7.33) is formed by the anterior rami of the first four cervical nerves. It lies protected by the

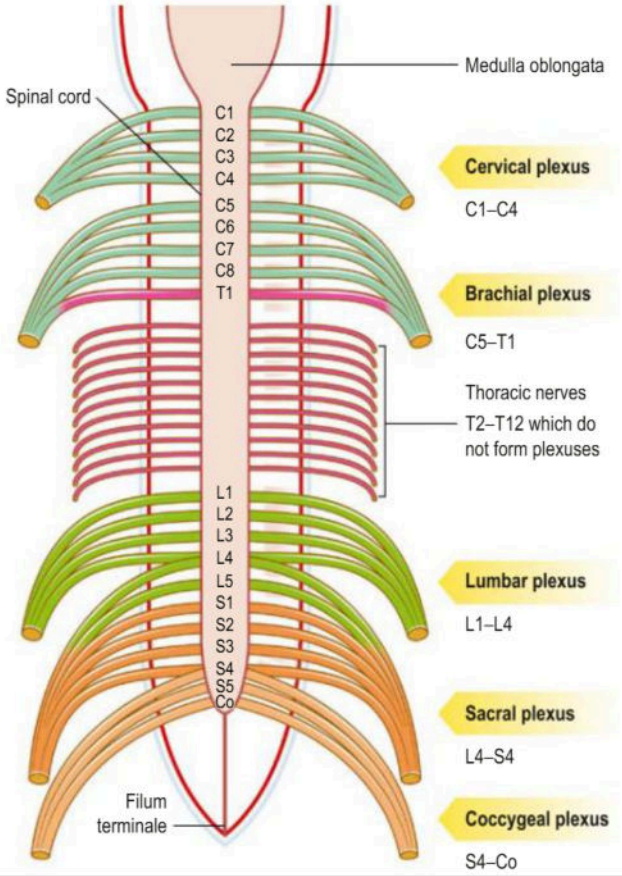

Figure 7.32 Plexuses formed by spinal nerves.

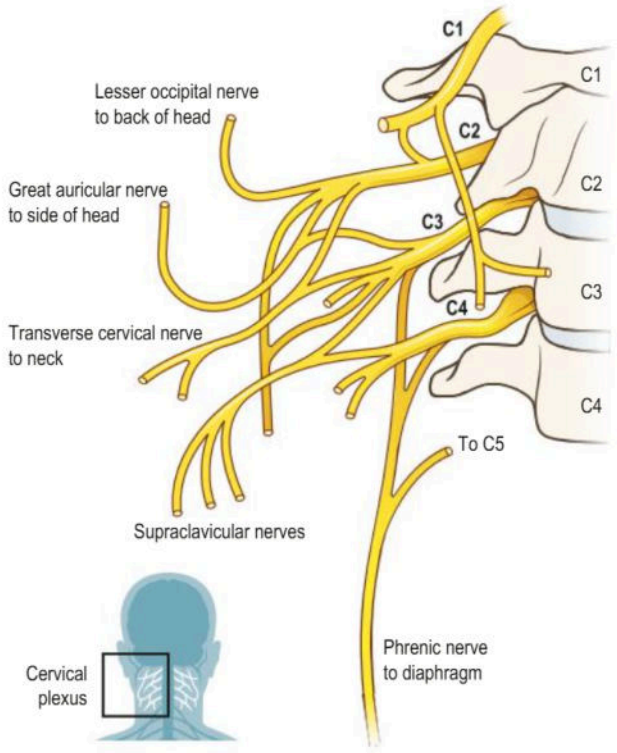

Figure 7.33 The cervical plexus.

sternocleidomastoid muscle deep within the neck opposite the 1st, 2nd, 3rd and 4th cervical vertebrae.

The superficial branches supply the structures at the back and side of the head, and the skin of the front of the neck to the level of the sternum.

The deep branches supply muscles of the neck, e.g. the sternocleidomastoid and the trapezius.

The phrenic nerve originates from cervical nerve roots 3, 4 and 5 and passes downwards through the thoracic cavity in front of the root of the lung to supply the diaphragm, initiating inspiration. Disease or spinal cord injury at this level is fatal, as spontaneous respiration is no longer possible.

Brachial plexus

The anterior rami of the lower four cervical nerves and a large part of the 1st thoracic nerve form the brachial plexus. Figure 7.34 shows its formation and the nerves that emerge from it. The plexus is situated deeply within the neck and shoulder above and behind the subclavian vessels and in the axilla.

The branches of the brachial plexus supply the skin and muscles of the upper limbs and some of the chest muscles. Five large nerves and several smaller ones emerge from this plexus, each with a contribution from more than one nerve root, containing sensory, motor and autonomic fibres:

- axillary (circumflex) nerve: C5, 6
- radial nerve: C5, 6, 7, 8, T1
- musculocutaneous nerve: C5, 6, 7
- median nerve: C5, 6, 7, 8, T1
- ulnar nerve: C7, 8, T1
- medial cutaneous nerve: C8, T1.

The axillary (circumflex) nerve winds round the upper part of the humerus. It then divides into branches that supply the deltoid muscle, shoulder joint and overlying skin.

The radial nerve is the largest branch of the brachial plexus. It supplies the triceps muscle behind the humerus, crosses in front of the elbow joint and then winds round to the back of the forearm to supply extensor muscles of the wrist and finger joints. The superficial branch continues into the back of the hand to supply the skin of the posterior aspect of the thumb, first two fingers and the lateral half of the third finger.

The musculocutaneous nerve passes downwards to the lateral aspect of the forearm. Its branches supply the muscles of the upper arm and, as cutaneous nerves, the skin of the forearm.

The median nerve passes down the midline of the arm in close association with the brachial artery. It passes in front of the elbow joint and then down to supply the muscles of the front of the forearm. It continues into the hand, where it supplies small muscles and the skin of the front (palmar

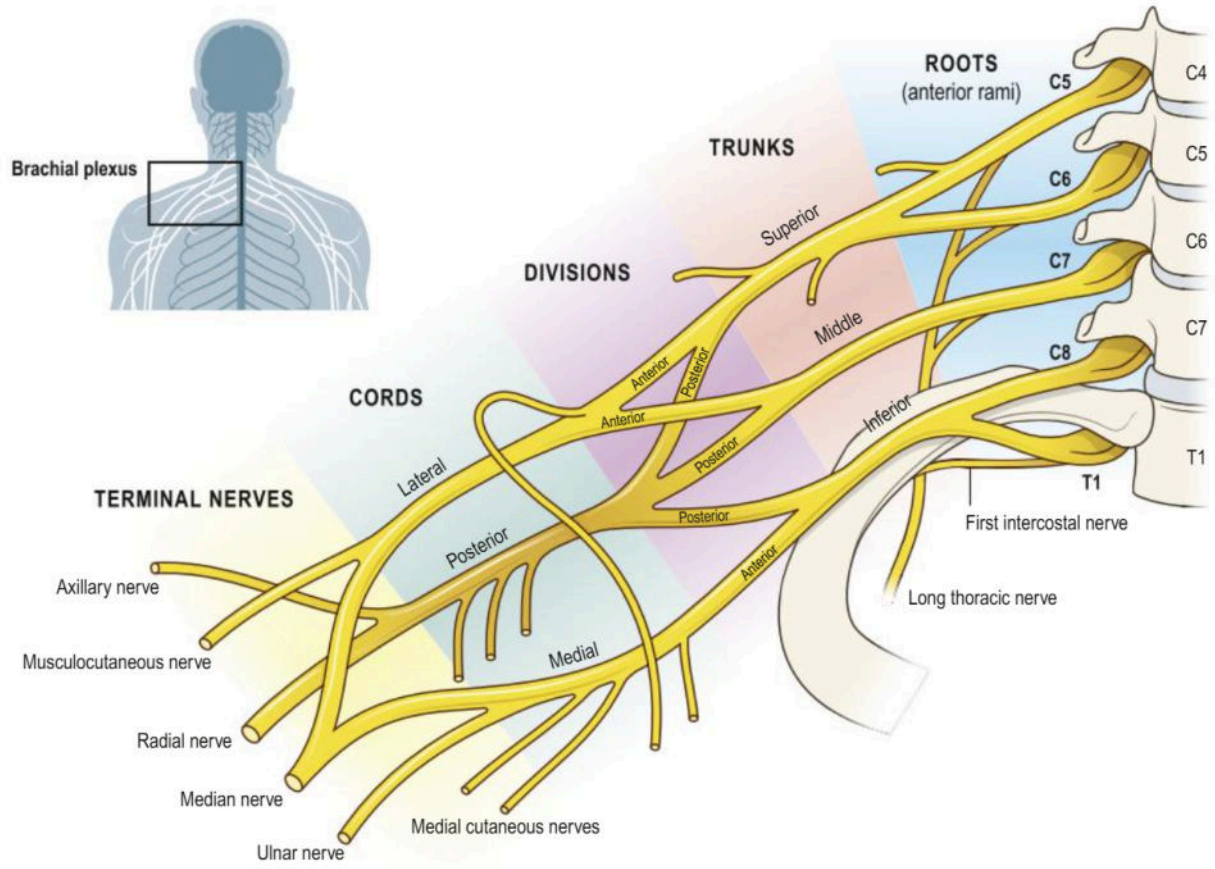

Figure 7.34 The brachial plexus.

aspect) of the thumb, first two fingers and the lateral half of the third finger. Its branches start below the elbow.

The ulnar nerve descends through the upper arm, lying medial to the brachial artery. It passes behind the medial epicondyle of the humerus to supply the muscles on the ulnar aspect of the forearm. It continues downwards to supply the muscles in the palm of the hand and the skin of the whole of the little finger and the medial half of the third finger. Its branches start below the elbow.

The main nerves of the arm are shown in Figure 7.35. The distribution and origins of the cutaneous sensory nerves of the arm, i.e. the dermatomes, are shown in Figure 7.36.

Lumbar plexus

The lumbar plexus (Figs 7.37–7.39) is formed by the anterior rami of the first three and part of the 4th lumbar nerves. The plexus is situated in front of the transverse processes of the lumbar vertebrae and behind the psoas muscle. The main branches and their nerve roots are the:

- iliohypogastric nerve: L1
- ilioinguinal nerve: L1
- genitofemoral nerve: L1, 2
- lateral femoral cutaneous nerve of thigh: L2, 3
- femoral nerve: L2, 3, 4
- obturator nerve: L2, 3, 4
- lumbosacral trunk: L4, 5.

The iliohypogastric, ilioinguinal and genitofemoral nerves supply muscles and the skin in the area of the lower abdomen, upper and medial aspects of the thigh and the inguinal region.

The lateral femoral cutaneous nerve of the thigh supplies the skin of the lateral aspect of the thigh, including part of the anterior and posterior surfaces.

The femoral nerve is one of the larger branches. It passes behind the inguinal ligament to enter the thigh in close association with the femoral artery. It divides into cutaneous and muscular branches to supply the skin and the muscles of the front of the thigh. Another branch, the saphenous nerve, supplies the medial aspect of the leg, ankle and foot.

The obturator nerve supplies the adductor muscles of the thigh and skin of the medial aspect of the thigh. It ends just above the level of the knee joint.

The lumbosacral trunk descends into the pelvis and contributes to the sacral plexus.

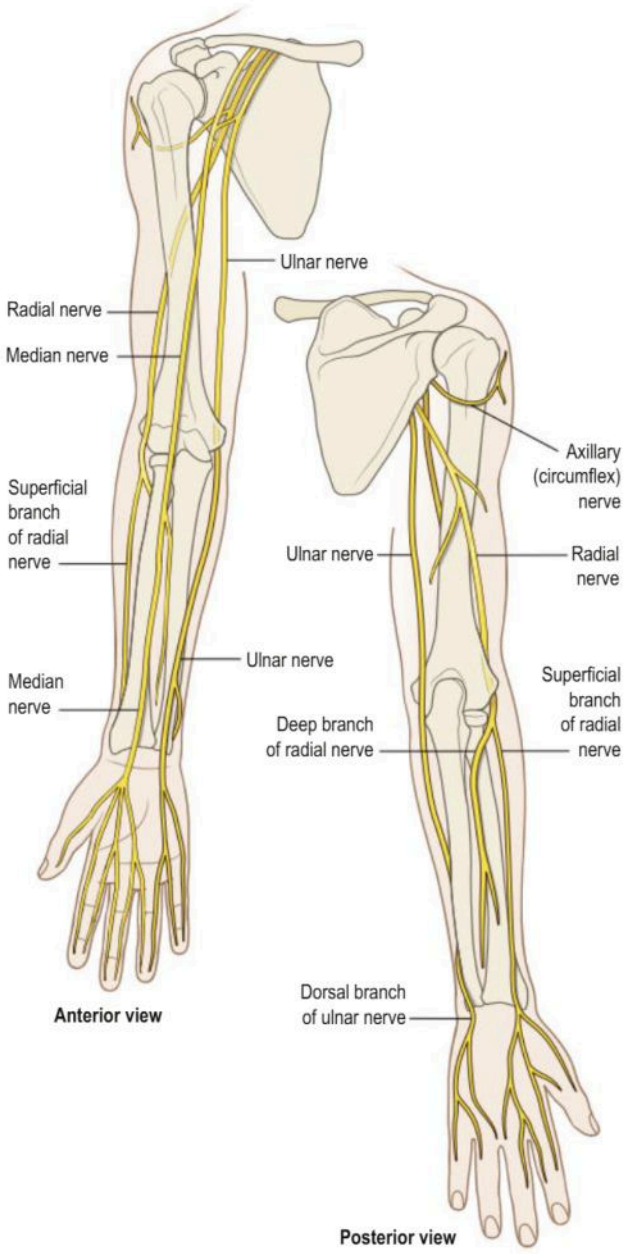

Figure 7.35 The main nerves of the arm.

Sacral plexus

The sacral plexus (Figs 7.37–7.39) is formed by the anterior rami of the lumbosacral trunk and the 1st, 2nd and 3rd sacral nerves. The lumbosacral trunk is formed by the 5th and part of the 4th lumbar nerves. It lies in the posterior wall of the pelvic cavity.

The sacral plexus divides into several branches, supplying the muscles and skin of the pelvic floor, muscles around the hip joint and the pelvic organs. It also gives rise to the sciatic nerve, which contains fibres from L4 and 5 and S1–3.

The sciatic nerve is the largest nerve in the body and is about 2cm wide at its origin. It passes into the buttock and descends through the posterior aspect of the thigh, supplying the hamstring muscles. At the level of the middle of the femur it divides to form the tibial and the common fibular (peroneal) nerves.

The tibial nerve descends through the popliteal fossa to the posterior aspect of the leg, where it supplies muscles and skin. It passes under the medial malleolus to supply muscles and skin of the sole of the foot and toes. One of the main branches is the sural nerve, which supplies the tissues in the area of the heel, the lateral aspect of the ankle and a part of the dorsum of the foot.

The common fibular (peroneal) nerve descends obliquely along the lateral aspect of the popliteal fossa and winds round the neck of the fibula into the front of the leg, where it divides into the deep fibular (anterior tibial) and the superficial fibular (musculocutaneous) nerves. These nerves supply the skin and muscles of the anterior aspect of the leg and the dorsum of the foot and toes.

The perineal branch of the pudendal nerve (S2, 3, 4) supplies the external anal sphincter, the external urethral sphincter and adjacent skin.

Figures 7.38 and 7.39 show the main nerves of the leg, the dermatomes and the origins of the main nerves.

Coccygeal plexus

The coccygeal plexus (see Fig. 7.37) is the smallest plexus. Formed by part of the 4th and 5th sacral and the coccygeal nerves, the nerves from this plexus supply the skin around the coccyx and anal area.

Thoracic nerves

There are 12 pairs of thoracic nerves; unlike the cervical, lumbar and sacral nerves, they do not intermingle to form plexuses. The first 11 are the intercostal nerves, which pass between the ribs, supplying them, the intercostal muscles and overlying skin. The 12th pair are the subcostal nerves. The 7th–12th thoracic nerves also supply the muscles and

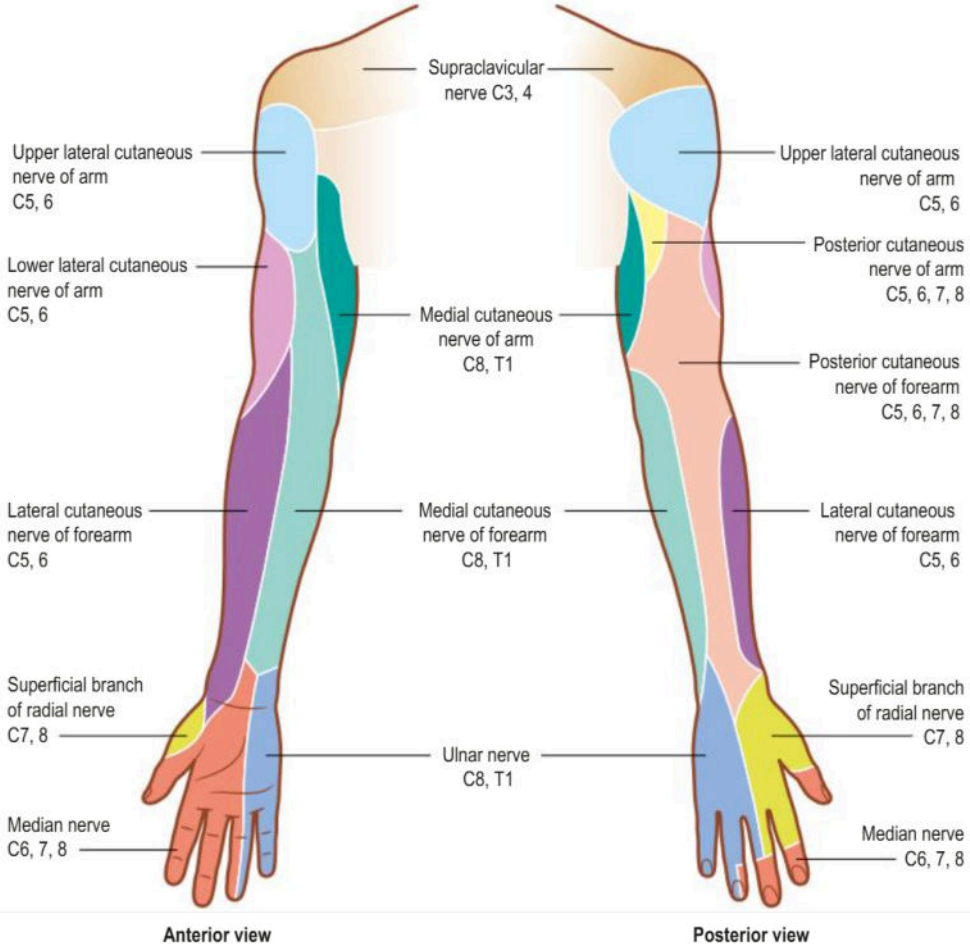

Figure 7.36 Distribution and origins of the cutaneous nerves of the arm. Colour distinguishes the dermatomes.

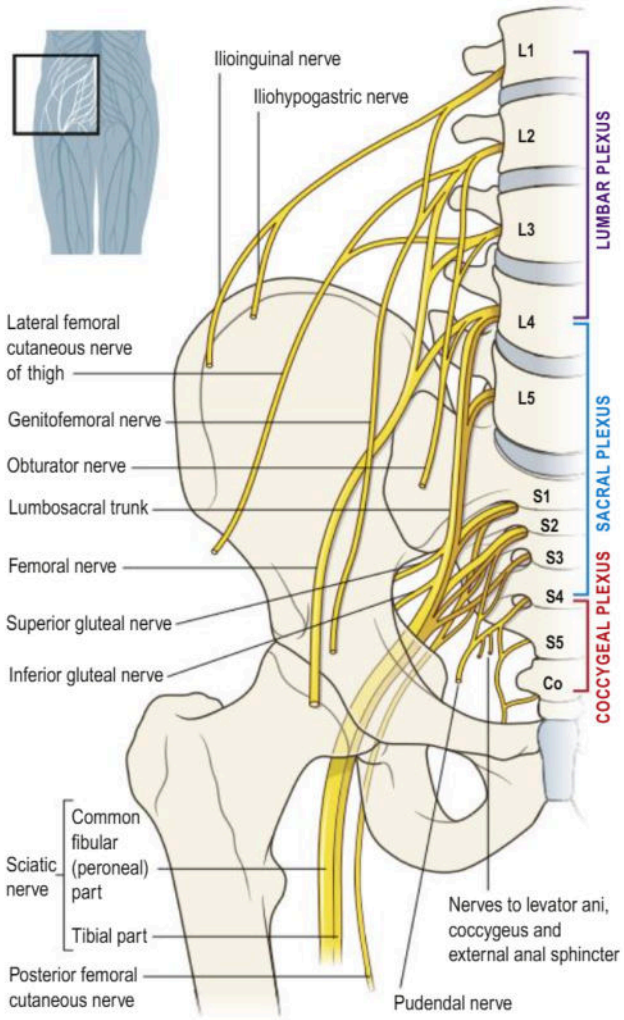

Figure 7.37 The lumbosacral and coccygeal plexuses. (Thibodeau GA, Patton KT 2007 Anthony's textbook of anatomy and physiology, 18th edn. St Louis: Mosby. Reproduced with permission.)

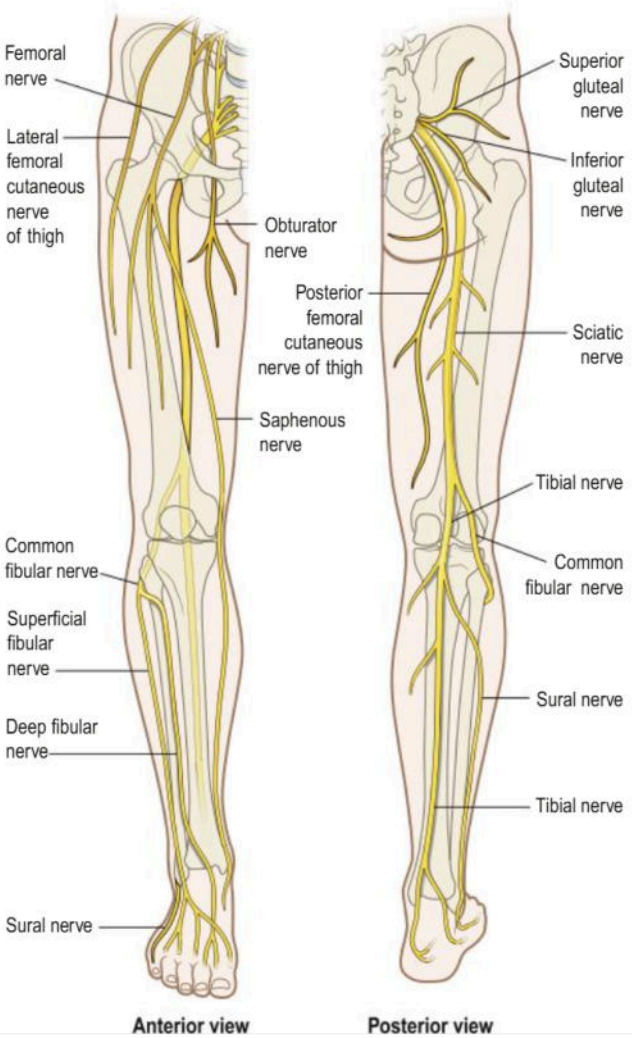

Figure 7.38 The main nerves of the leg.

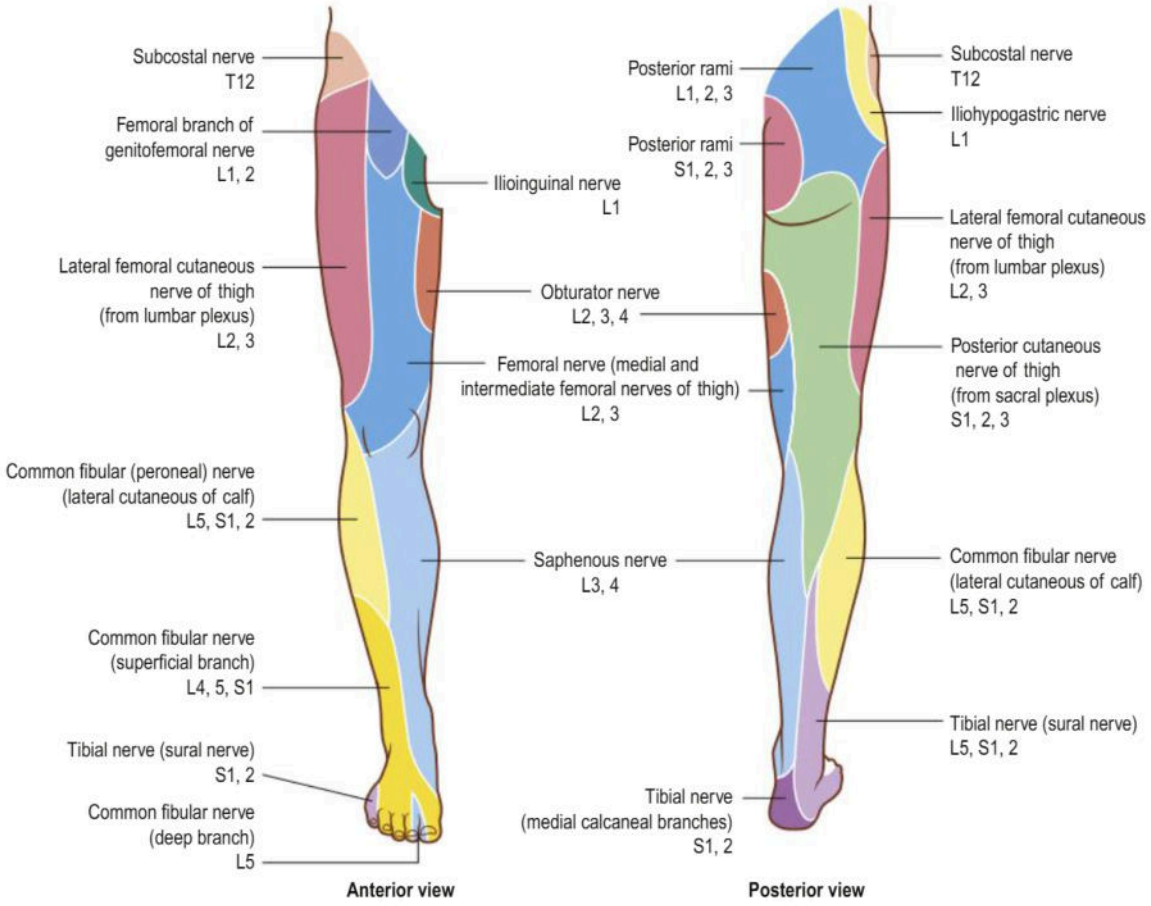

Figure 7.39 Distribution and origins of the cutaneous nerves of the leg. Colour distinguishes the dermatomes.

the skin of the posterior and anterior abdominal walls (see Fig. 7.30).

Cranial nerves

There are 12 pairs of cranial nerves (Fig. 7.40) originating from nuclei in the inferior surface of the brain, mainly from the brain stem. Some are sensory, some motor and some mixed. Their names suggest their distribution or function, which is generally related to the head and neck. They are numbered using Roman numerals according to the order in which they connect to the brain, starting anteriorly. They are:

I. Olfactory: sensory.
II. Optic: sensory.
III. Oculomotor: motor.
IV. Trochlear: motor.
V. Trigeminal: mixed.
VI. Abducent: motor.
VII. Facial: mixed.
VII. Vestibulocochlear (auditory): sensory.
IX. Glossopharyngeal: mixed.
X. Vagus: mixed.
XI. Accessory: motor.
XII. Hypoglossal: motor.

I. Olfactory nerves (sensory)

These are the nerves of smell. Their sensory receptors and nerve fibres originate in the olfactory epithelium of the nasal cavity, pass upwards through the cribriform plate of the ethmoid bone and then to the olfactory bulb (see Fig. 8.24). The nerves then proceed backwards as the olfactory tract, to the temporal lobe of the cerebrum, where smell is perceived (Ch. 8).

II. Optic nerves (sensory)

These are the nerves of sight. Their fibres originate in the retinae of the eyes and they combine to form the optic nerves (see Fig. 8.13). They run backwards and medially through the posterior part of the orbital cavity and then pass through the optic foramina of the sphenoid bone into the cranial cavity, where they join at the optic chiasma. The nerves proceed backwards as the optic tracts to the lateral geniculate bodies of the thalamus. Impulses pass from there to the visual areas in the occipital lobes of the cerebrum and to the cerebellum. Sight is perceived in the visual cortex, which lies in the occipital lobe of the cerebral cortex, and in the cerebellum the impulses from the eyes contribute to the maintenance of balance, posture and orientation of the head in space.

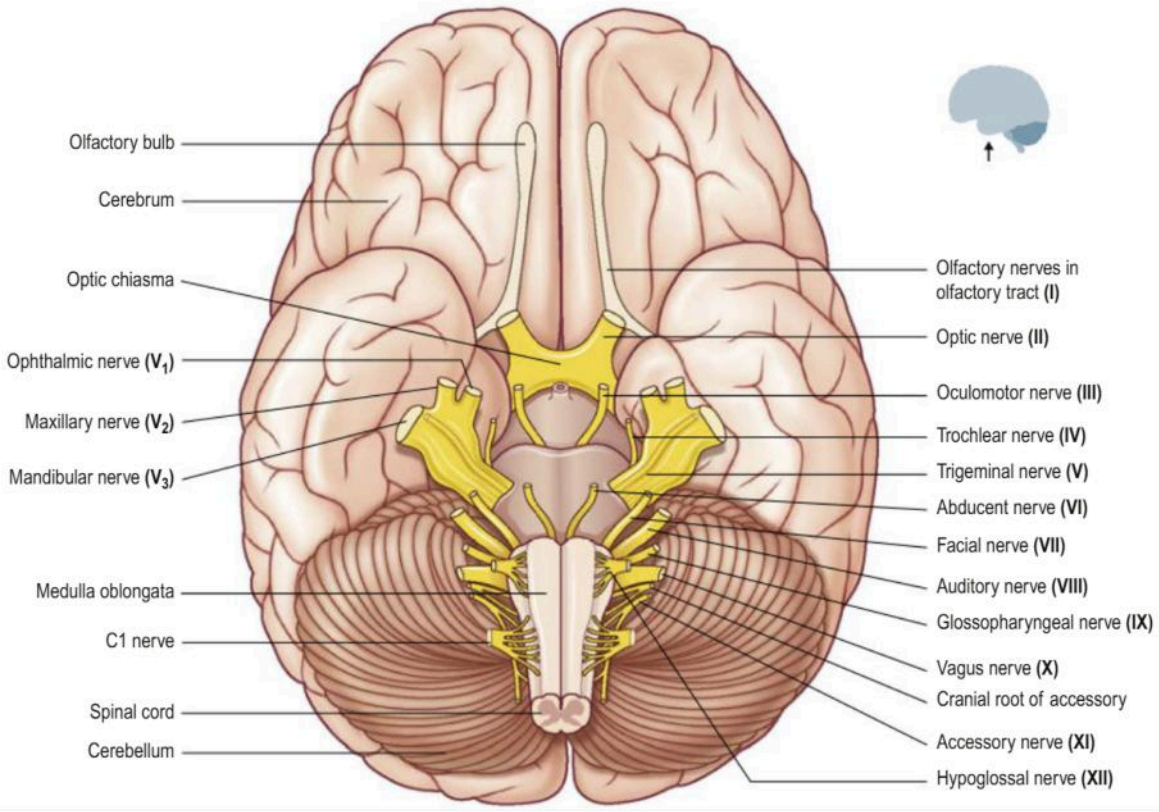

Figure 7.40 The inferior surface of the brain showing the cranial nerves and associated structures.

III. Oculomotor nerves (motor)

These nerves arise from nuclei near the cerebral aqueduct. They supply:

- four of the six extrinsic muscles that move the eyeball, namely the superior, medial and inferior recti and the inferior oblique muscle (see Table 8.1)
- the intrinsic (intraocular) muscles:
  - ciliary muscles, which alter the shape of the lens, changing its refractive power to focus images on the retina
  - circular muscles of the iris, which constrict the pupil
- the levator palpebrae muscles, which raise the upper eyelids.

IV. Trochlear nerves (motor)

These nerves arise from nuclei near the cerebral aqueduct. They supply the superior oblique (extrinsic) muscles of the eyes.

V. Trigeminal nerves (mixed)

These large nerves are the main sensory nerves for the face and head, including the teeth and oral and nasal cavities, and transmit sensory impulses, e.g. for pain, temperature and touch. The motor fibres stimulate the muscles for chewing (mastication). As the name suggests, there are three main branches of the trigeminal nerves. The dermatomes innervated by the sensory fibres are shown in Figure 7.41.

The ophthalmic nerves are sensory only and supply the lacrimal glands, conjunctiva of the eyes, forehead, eyelids, anterior aspect of the scalp and mucous membrane of the nose.

The maxillary nerves are sensory only and supply the cheeks, upper gums, upper teeth and lower eyelids.

The mandibular nerves contain both sensory and motor fibres. These are the largest of the three divisions and they supply the teeth and gums of the lower jaw, pinnae of the ears, lower lip and tongue. The motor fibres supply the muscles for chewing.

VI. Abducent nerves (motor)

These nerves arise from nuclei lying underneath the fourth ventricle. They supply the lateral rectus muscles, extrinsic muscles of the eyeballs that cause abduction, as the name suggests.

VII. Facial nerves (mixed)

These nerves arise from nuclei in the lower pons. The motor fibres supply the muscles of facial expression. The sensory fibres convey impulses from the taste buds in the anterior two-thirds of the tongue to the taste perception area in the cerebral cortex (see Fig. 7.20).

VIII. Vestibulocochlear (auditory) nerves (sensory)

These nerves have two discrete divisions: the vestibular nerves and cochlear nerves.

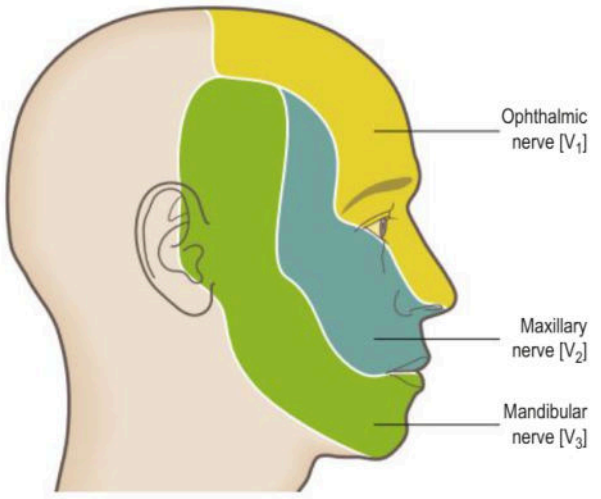

Figure 7.41 Cutaneous distribution of the main branches of the right trigeminal nerve. (5th cranial nerve)

The vestibular nerves arise from the semicircular canals of the inner ear and convey impulses to the cerebellum. They are associated with the maintenance of posture and balance.

The cochlear nerves originate in the spiral organ (of Corti) in the inner ear and convey impulses to the auditory area in the temporal lobe of the cerebral cortex, where sound is perceived.

IX. Glossopharyngeal nerves (mixed)

The motor fibres arise from nuclei in the medulla oblongata and stimulate the muscles of the tongue and pharynx and the secretory cells of the parotid (salivary) glands.

The sensory fibres convey impulses to the cerebral cortex from the posterior third of the tongue, the tonsils and pharynx, and taste buds in the tongue and pharynx. These nerves are essential for the swallowing and gag reflexes. Some fibres conduct impulses from the carotid sinus, which plays an important role in the control of blood pressure (p. 103).

X. Vagus nerves (mixed)

These nerves have many branches, giving them the most extensive distribution of the cranial nerves (Fig. 7.42); their name aptly means 'wanderer'. They pass downwards through the neck into the thorax and the abdomen. These nerves form an important part of the parasympathetic nervous system (see Fig. 7.46).

The motor fibres arise from nuclei in the medulla and supply the smooth muscle and secretory glands of the pharynx, larynx, trachea, bronchi, heart, carotid body, oesophagus, stomach, intestines, exocrine pancreas, gall bladder, bile ducts, spleen, kidneys, ureter and blood vessels in the thoracic and abdominal cavities.

The sensory fibres convey impulses from the membranes lining the same structures to the medulla and pons.

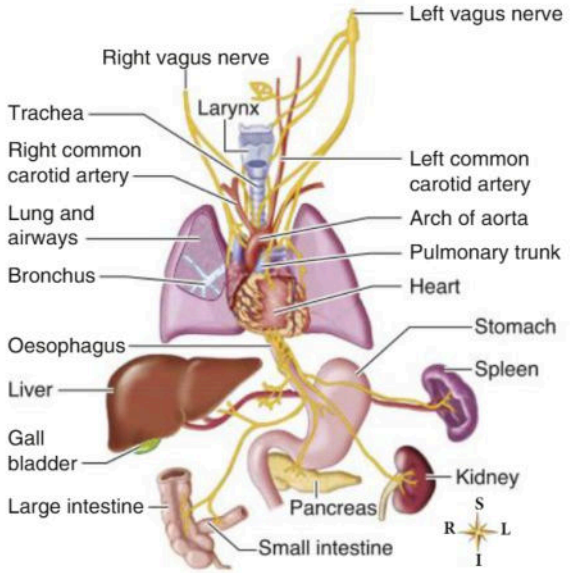

Figure 7.42 Structures supplied by the vagus nerves.

XI. Accessory nerves (motor)

These nerves arise from nuclei in the medulla oblongata and in the spinal cord. The fibres originating in the spinal cord supply the sternocleidomastoid and trapezius muscles in the neck, while those from the medulla join the vagus nerves and supply the pharyngeal and laryngeal muscles, also in the neck.

XII. Hypoglossal nerves (motor)

These nerves arise from nuclei in the medulla oblongata. They supply the muscles of the tongue and muscles surrounding the hyoid bone, and contribute to swallowing and speech.

Functions of the cranial nerves

The functions of the cranial nerves are summarised in Figure 7.43.

Autonomic nervous system

The autonomic or involuntary nervous system (see Fig. 7.1) controls involuntary body functions. Although control is not voluntary, the individual can sometimes be conscious of its effects, e.g. an increase in heart rate.

The autonomic nervous system is separated into two divisions:

- sympathetic (thoracolumbar outflow)
- parasympathetic (craniosacral outflow).

The two divisions work in an integrated and complementary manner to maintain involuntary functions and homeostasis. Most body organs have both sympathetic and parasympathetic supply, whose effects usually oppose one another. Such activities include coordination and control of breathing,

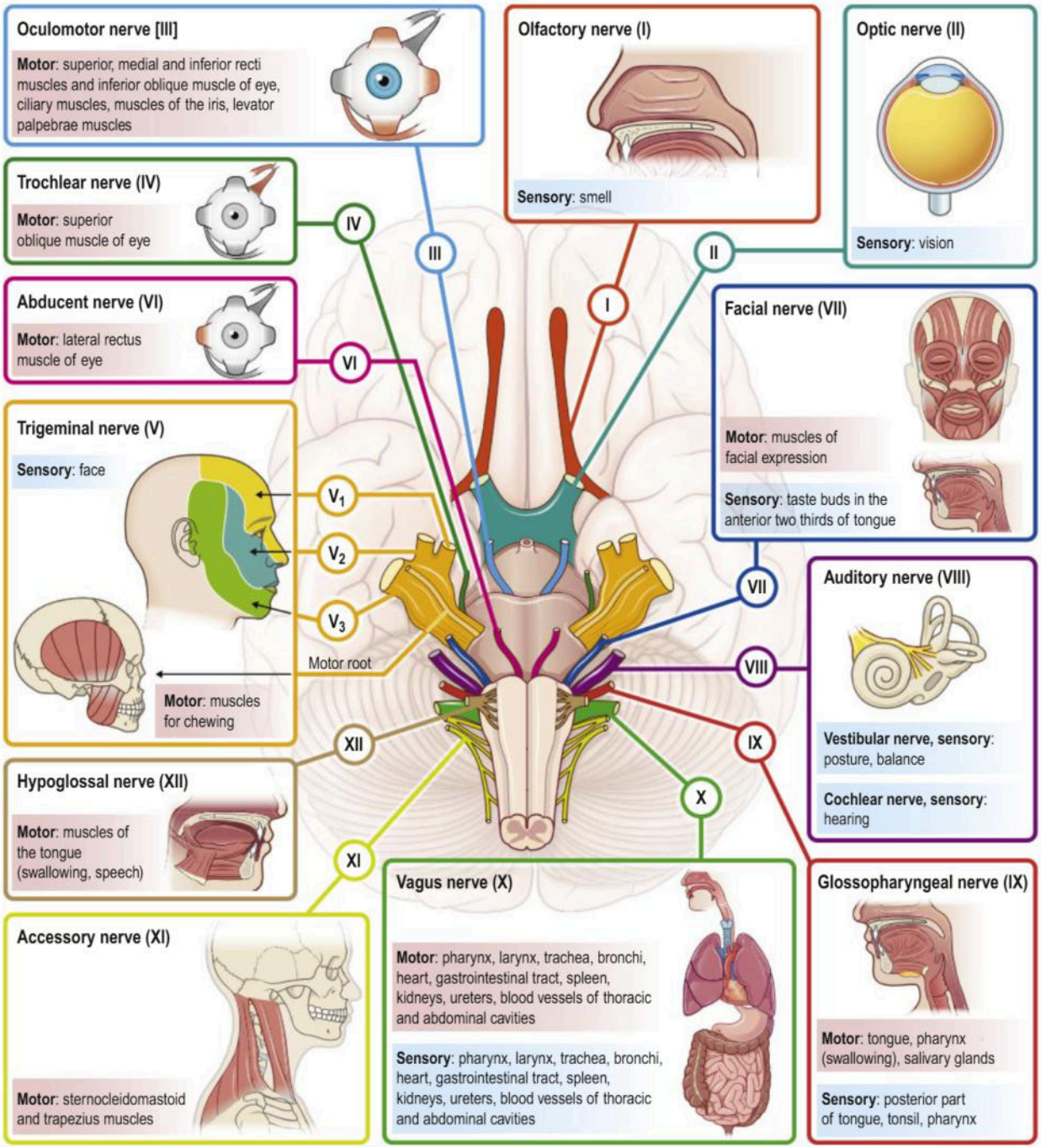

Figure 7.43 Functions of the cranial nerves.

blood pressure, water balance, digestion and metabolic rate. Sympathetic activity predominates in stressful situations, as it equips the body to respond when exertion and exercise are required. Parasympathetic activity is increased, and sympathetic activity is normally lessened, in calm, non-stressful situations. There are similarities and differences between the two divisions. Some similarities are outlined below.

As with other parts of the nervous system, the effects of autonomic activity are rapid. The effector organs are:

- smooth muscle, which controls the diameter of smaller airways and blood vessels
- cardiac muscle, which controls the rate and force of cardiac contraction
- glands, which control the volumes of gastrointestinal secretions.

The efferent (motor) nerves of the autonomic nervous system arise from the brain or spinal cord and emerge at various levels between the midbrain and the sacral region of

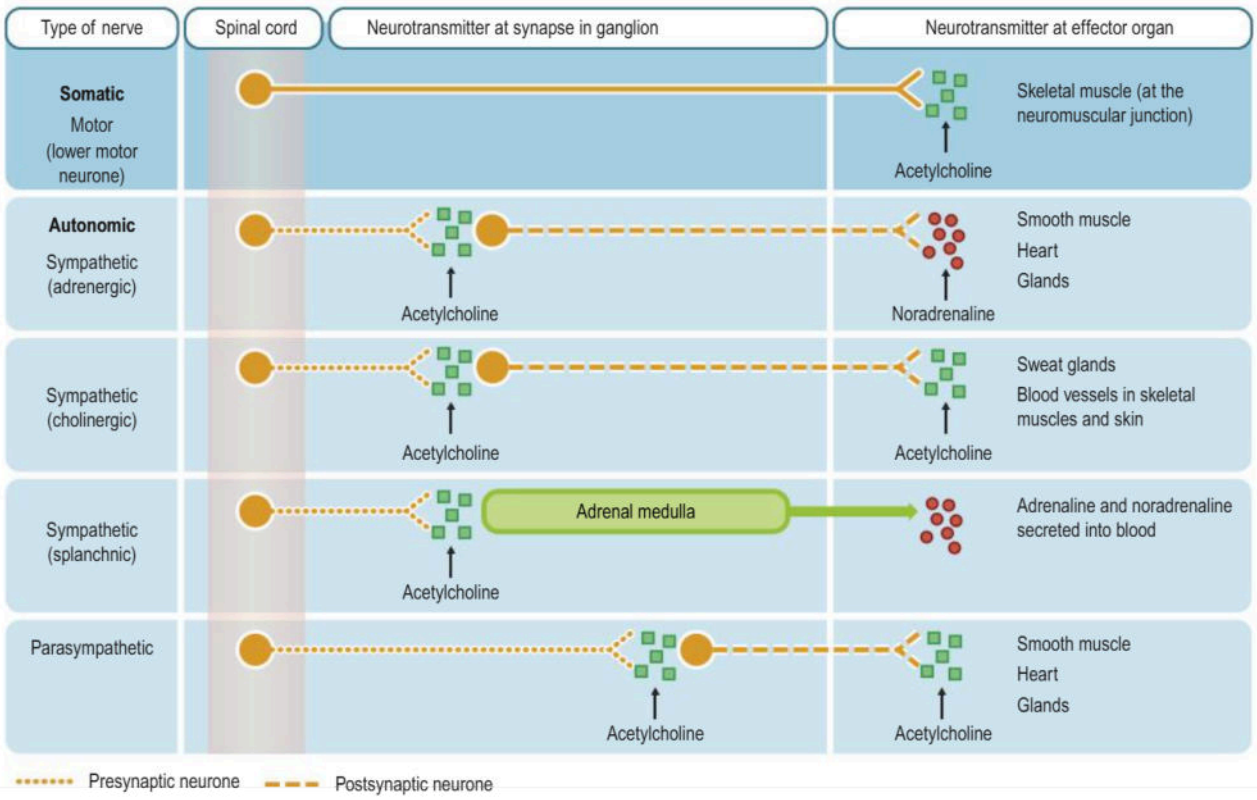

Figure 7.44 Main neurotransmitters at synapses in the peripheral nervous system.

the spinal cord. Many of them travel within the same nerve sheath as peripheral nerves to reach the organs they innervate.

Each division has two efferent neurones between the CNS and effector organs (Fig. 7.44). These are:

- the preganglionic neurone
- the postganglionic neurone.

The cell body of the preganglionic neurone lies in the brain or spinal cord. Its axon terminals synapse with the cell body of the postganglionic neurone in an autonomic ganglion outside the CNS. The postganglionic neurone conducts impulses to the effector organ. The neurotransmitter at the synapses in autonomic ganglia is always acetylcholine, but different neurotransmitters are used at effector organs (Fig. 7.44).

Sympathetic nervous system

This is summarised in Figure 7.45, along with the main structures supplied and the effects of stimulation. Since the preganglionic neurones originate in the spinal cord at the thoracic and lumbar levels, the alternative name of 'thoracolumbar outflow' is apt.

The preganglionic neurone

This has its cell body in the lateral column of grey matter in the spinal cord between the levels of the 1st thoracic and 2nd or 3rd lumbar vertebrae. The nerve fibre leaves the cord by the anterior root and ends at a synapse. This may be either in one of the ganglia in the lateral chain of sympathetic ganglia, or one of the prevertebral ganglia (see later). Acetylcholine is the neurotransmitter at sympathetic ganglia (Fig. 7.44).

The postganglionic neurone

This has its cell body in a sympathetic ganglion and terminates in the organ or tissue supplied. Noradrenaline (norepinephrine) is usually the neurotransmitter at sympathetic effector organs. The major exceptions are the sweat glands, skin and blood vessels of skeletal muscles, which are only supplied by sympathetic postganglionic neurones. These are known as sympathetic cholinergic nerves, and usually have acetylcholine as their neurotransmitter (see Fig. 7.44). There is no parasympathetic supply to these structures.

Sympathetic ganglia

The lateral chains of sympathetic ganglia

These chains extend from the upper cervical vertebrae to the sacrum, with one chain lying on each side of the vertebral bodies. The ganglia are connected to each other by nerve fibres. Preganglionic neurones that emerge from the cord may synapse with the cell body of the postganglionic neurone at the same level or they may pass up or down the chain through one or more ganglia before synapsing. For example, the nerve that dilates the pupil leaves the cord at the level of the 1st thoracic vertebra and passes up the chain to the superior cervical ganglion before it synapses with the cell body of the postsynaptic neurone. The postganglionic neurones then pass to the eyes.

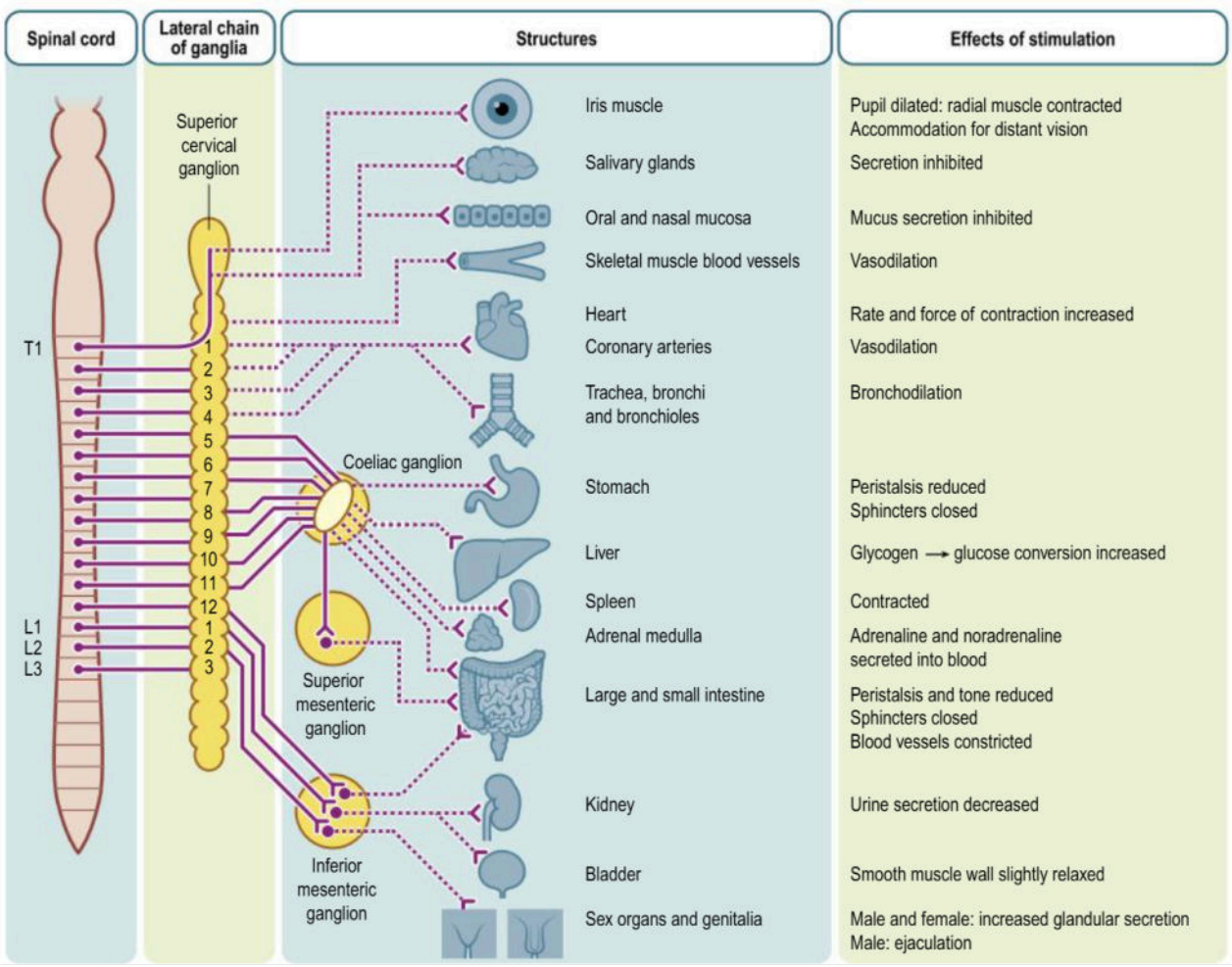

Figure 7.45 The sympathetic outflow, the main structures supplied and the effects of stimulation. Solid purple lines, preganglionic fibres; broken purple lines, postganglionic fibres. There are right and left lateral chains of ganglia.

The arrangement of the ganglia allows excitation of nerves at multiple levels very quickly, providing a rapid and widespread sympathetic response that enables the body to respond effectively when 'fight or flight' is urgently required.

Prevertebral ganglia

There are three prevertebral ganglia situated in the abdominal cavity close to the origins of arteries of the same names:

- coeliac ganglion
- superior mesenteric ganglion
- inferior mesenteric ganglion.

The ganglia consist of nerve cell bodies rather diffusely distributed among a network of nerve fibres that form plexuses. Preganglionic sympathetic fibres pass straight through the lateral chain to reach these ganglia.

Parasympathetic nervous system

This is summarised in Figure 7.46, together with the main structures supplied and the effects of stimulation. Like the sympathetic nervous system, two neurones (preganglionic and postganglionic) are involved in the transmission of impulses to the effector organs. The neurotransmitter at both synapses is acetylcholine.

The preganglionic neurone

This is usually long in comparison to its counterpart in the sympathetic nervous system and has its cell body either in the brain or the spinal cord. The cell bodies originating in the brain form the cranial outflow and their fibres are within cranial nerves III, VII, IX and X. The cell bodies of the sacral outflow lie within the lateral columns of grey matter at the distal end of the spinal cord. Their fibres leave the cord in sacral segments 2, 3 and 4.

The nerve fibres of parasympathetic preganglionic neurones usually synapse with their postganglionic counterparts at or near the effector organs.

The postganglionic neurone

This is usually very short and has its cell body either in a ganglion or, more often, in the wall of the organ supplied.

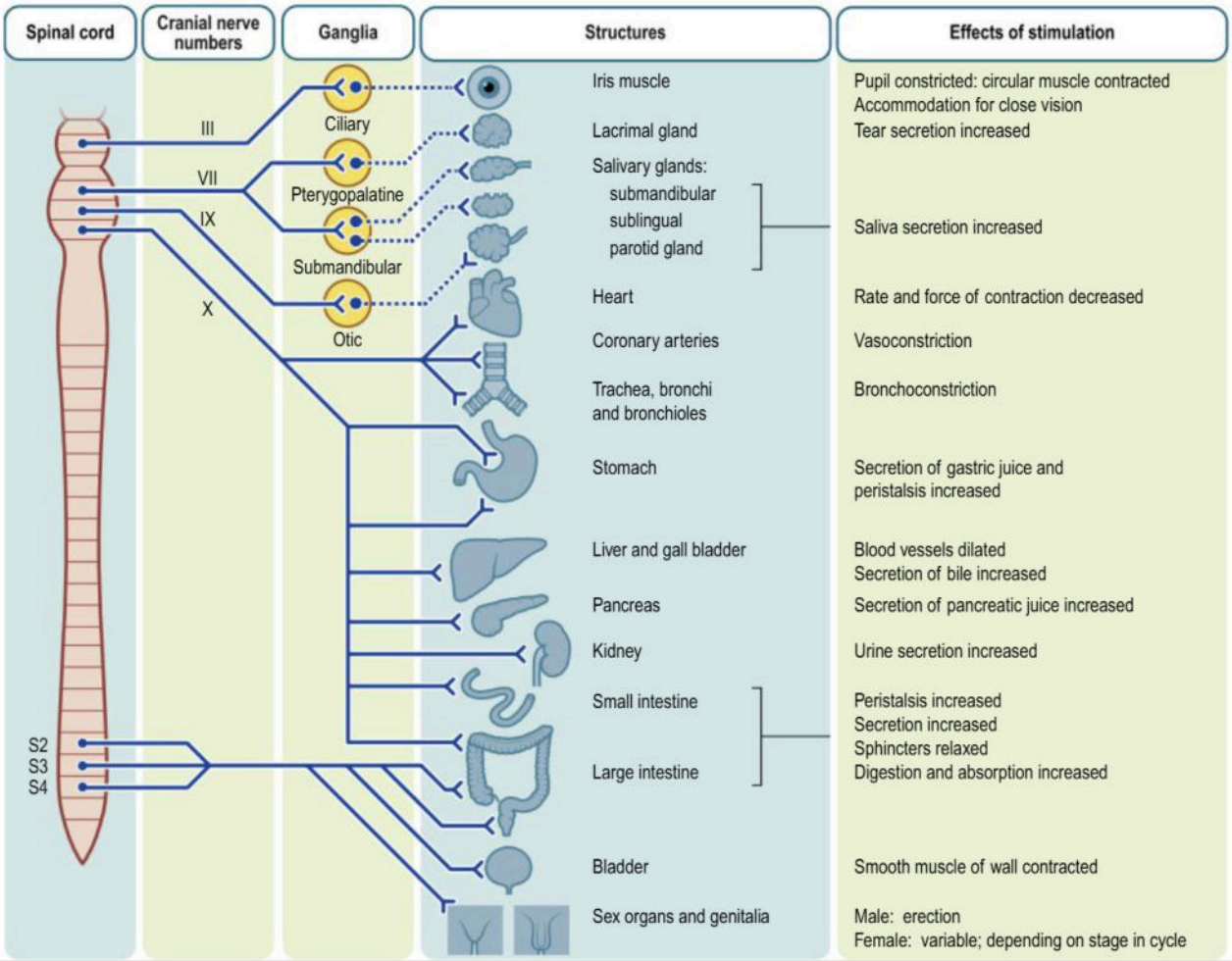

Figure 7.46 The parasympathetic outflow, the main structures supplied and the effects of stimulation. Solid blue lines, preganglionic fibres; broken blue lines, postganglionic fibres. Where there are no broken lines, the postganglionic neurone is in the wall of the structure.

Functions of the autonomic nervous system

The autonomic nervous system is involved in many complex involuntary reflex activities (Figs 7.45 and 7.46), which, like the reflexes described earlier, depend not only on sensory input to the brain or spinal cord but also on motor output. In this case the reflex action is rapid contraction, or inhibition of contraction, of involuntary (smooth and cardiac) muscle or glandular secretion. These activities are coordinated subconsciously. Sometimes sensory input does reach consciousness and may result in temporary inhibition of the reflex action, e.g. reflex micturition can be temporarily inhibited.

Most organs are supplied by both sympathetic and parasympathetic nerves, which have complementary, swift effects that are finely balanced to ensure that body function is optimised and meets its needs from moment to moment.

Functions of the sympathetic nervous system

Sympathetic stimulation prepares the body to deal with exciting and stressful situations, e.g. in times of danger and in extremes of environmental temperature, the so-called 'fight or flight' response. Emotional states, e.g. fear, embarrassment and anger also cause sympathetic stimulation.

The adrenal glands secrete noradrenaline (norepinephrine) and some adrenaline (epinephrine) into the bloodstream in response to sympathetic stimulation. These hormones act as neurotransmitters when they reach target organs of the sympathetic nervous system. Through this effect, they potentiate and sustain the effects of sympathetic nerve stimulation.

The effects of sympathetic stimulation on the heart, blood vessels and lungs (see below) prepare the body for exercise. Additional effects are an increase in the metabolic rate and increased conversion of glycogen to glucose. During exercise, e.g. fighting or running away, when oxygen and energy requirements of skeletal muscles are greatly increased, these changes enable the body to respond quickly to meet the increased energy demand.

Functions of the parasympathetic nervous system

Parasympathetic stimulation slows down cardiac and respiratory activity, but it stimulates digestion and

absorption of food and the functions of the genitourinary systems. Its general effect is that of 'rest and digest', allowing digestion and restorative processes to occur quietly when required.

Effects of autonomic stimulation

Normally the two systems function together, maintaining a regular heartbeat, normal temperature and an internal environment compatible with both physiological needs and the immediate external surroundings.

Cardiovascular system

Sympathetic stimulation

- Accelerates firing of the sinoatrial node in the heart, increasing the heart rate.
- Stimulates cardiac muscle increasing contractility (force of the heartbeat).
- Dilates the coronary arteries, increasing the blood supply to cardiac muscle increasing the supply of oxygen and nutrients and the removal of metabolic wastes, thus increasing the capacity of the muscle to work.
- Dilates the blood vessels supplying skeletal muscle, with the same effects as those on cardiac muscle, above.
- Raises peripheral resistance and blood pressure by constricting the small arteries and arterioles in the skin. In this way an increased blood supply is available for highly active tissue, such as skeletal muscle, heart and brain.
- Constricts the blood vessels to the secretory glands of the digestive system, raising the volume of blood available for circulation in dilated blood vessels, e.g. cardiac muscle, skeletal muscles.
- Accelerates blood coagulation because of vasoconstriction.

Parasympathetic stimulation

- Decreases the rate and force of the heartbeat.
- Constricts the coronary arteries, reducing the blood supply to cardiac muscle.

The parasympathetic nervous system exerts little or no effect on blood vessels except the coronary arteries.

Respiratory system

Sympathetic stimulation

This causes smooth muscle relaxation and therefore dilation of the airways (bronchodilation), especially the bronchioles, allowing more air to enter the lungs at each inspiration, and increases the respiratory rate. In conjunction with the increased heart rate, the oxygen intake and carbon dioxide output of the body are increased to deal with 'fight or flight' situations.

Parasympathetic stimulation

This causes contraction of the smooth muscle in the airway walls, leading to bronchoconstriction.

Digestive and urinary systems

Sympathetic stimulation

- Increases conversion of glycogen to glucose by the liver, making more fuel immediately available to provide energy.
- Inhibits smooth muscle contraction and secretion of digestive juices in the stomach and small intestine, delaying digestion, onward movement and absorption of food; increases the tone of sphincter muscles.
- Increases secretion of adrenaline (epinephrine) and noradrenaline (norepinephrine) from the adrenal glands; this potentiates and sustains the effects of sympathetic stimulation throughout the body.
- Increases the tone of the urethral and anal sphincters, and relaxes the bladder wall, inhibiting micturition and defaecation.
- Significantly increases metabolic rate.

Parasympathetic stimulation

- Increases secretion of bile by the liver.
- Increases motility and secretion of the stomach and small intestine, together with the rate of digestion and absorption.
- Increases the secretion of pancreatic juice.
- Stimulates micturition. This occurs when relaxation of the internal urethral sphincter is accompanied by contraction of the muscle of the bladder wall. Similarly, when relaxation of the internal anal sphincter is accompanied by contraction of the muscle of the rectum, defaecation occurs. In both cases, voluntary relaxation of the external sphincters is also required.

In contrast to sympathetic stimulation, parasympathetic stimulation has no effect on either the adrenal glands or metabolic rate.

Eye

Sympathetic stimulation

This contracts the radial muscle fibres of the iris, dilating the pupil (see Fig. 8.32). Retraction of the levator palpebrae muscles occurs, opening the eyes wide and giving the appearance of alertness and excitement. The ciliary muscle that adjusts the thickness of the lens is slightly relaxed, facilitating distant vision.

Parasympathetic stimulation

This contracts the circular muscle fibres of the iris, constricting the pupil. The eyelids tend to close, giving the appearance of sleepiness. The ciliary muscle contracts, facilitating near vision.

Skin

Sympathetic stimulation

- Increases sweat secretion, leading to more loss of heat generated by increased skeletal muscle activity.
- Contracts the arrector pili (the muscles in the hair follicles), giving the appearance of 'goose flesh'.

- Constricts the peripheral blood vessels, increasing blood supply available to active organs, e.g., the heart and skeletal muscle.

There is no parasympathetic nerve supply to the skin. Some sympathetic fibres are adrenergic, causing vasoconstriction, and some are cholinergic, causing vasodilation (see Fig. 7.44).

Afferent impulses from viscera

Sensory fibres from the viscera (internal organs) travel with autonomic fibres and are sometimes called autonomic afferents. The impulses they transmit are associated with:

- visceral reflexes, usually at an unconscious level, e.g. cough, blood pressure (baroreceptors)
- sensation, for example, of hunger, thirst, nausea, sexual sensation, rectal and bladder distension
- visceral pain.

Visceral pain

Normally the viscera are not sensitive to cutting, burning and crushing. However, a sensation of dull, poorly located pain is experienced when:

- visceral nerves are stretched
- many fibres are stimulated
- there is ischaemia and local accumulation of metabolites
- the sensitivity of sensory nerve endings to painful stimuli is increased, e.g. during inflammation.

If the cause of the pain, e.g. inflammation, affects the parietal layer of a serous membrane (pleura, peritoneum, p. 57), the pain is acute and easily located over the site of inflammation. This is because the peripheral spinal nerves that innervate the superficial tissues also innervate the parietal layer of serous membranes. They transmit the impulses to the cerebral cortex, where somatic pain is perceived and accurately located. Appendicitis is an example of this type of pain. Initially, it is dull and vaguely located around the midline of the abdomen. As the condition progresses the parietal peritoneum becomes involved and acute pain becomes clearly located in the right iliac fossa, i.e. over the appendix.

Referred pain

In some cases of visceral disease, pain may be felt in superficial tissues remote from its site of origin. This is called referred pain and occurs when sensory fibres from the affected organ enter the same segment of the spinal cord as somatic nerves, i.e. those from the superficial tissues (Fig. 7.47). It is believed that the sensory nerve from the damaged organ stimulates an adjacent nerve in the spinal cord and it transmits the impulses to the sensory area in the cerebral cortex, where the pain is perceived as originating in the area supplied by the somatic nerve. Examples of referred pain are given in Table 7.3.

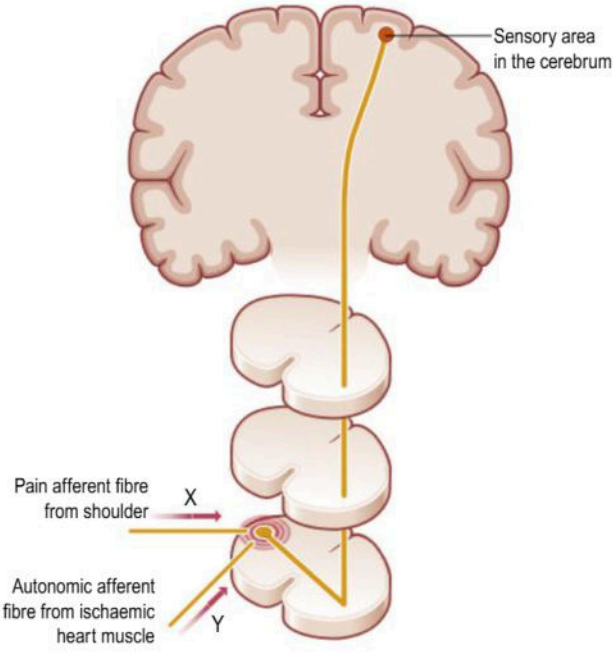

Figure 7.47 Referred pain. Ischaemic heart tissue generates impulses in nerve Y, which then stimulate nerve X, and pain is perceived in the shoulder.

Table 7.3 Referred pain

Tissue of origin of pain	Site of referred pain
Heart	Neck, left shoulder, arm and jaw
Liver, Biliary tract	Right shoulder
Kidney, Ureter	Loin and groin
Uterus	Low back
Male genitalia	Low abdomen
Prolapsed intervertebral disc	Buttock, leg

Effects of ageing on the nervous system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the nervous system.

As neurones are not replaced after birth, a natural decrease in numbers occurs with ageing; however, a considerable

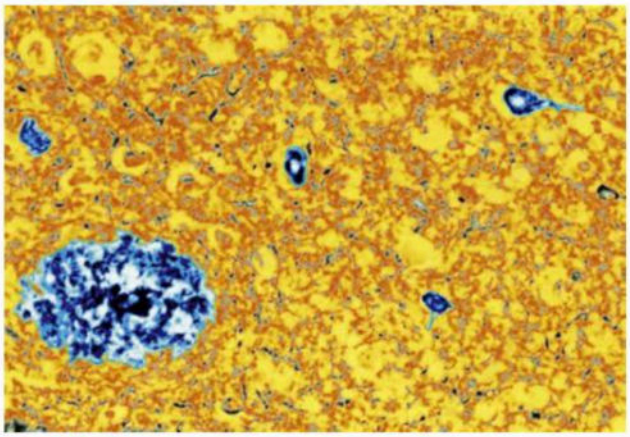

Figure 7.48 Age-associated brain changes. Coloured light micrograph of brain tissue showing an amyloid plaque (large blue area) and several neurofibrillary tangles (smaller blue areas). (From Science Photo Library. Reproduced with permission.)

reserve means that cognitive function is not necessarily impaired.

Characteristic features of brain tissue are seen at postmortem in most older adults. These include amyloid deposits called plaques which weaken blood vessel walls leaving them prone to rupture and neurofibrillary tangles formed by accumulation of abnormal proteins (Fig. 7.48). Their significance is not known although they are much more abundant in those who had dementia.

Gradual narrowing which decreases blood flow may develop in the arteries that supply the brain (atheroma and arteriosclerosis, see Ch. 4), making their walls more prone to rupture. Should this occur, bleeding into the surrounding brain tissue causes a stroke (p. 201).

Motor control of precise movement diminishes, meaning that older adults take longer to carry out motor actions than younger adults and they also become more prone to falls. The conduction rate of nerve impulses becomes slower, and this may contribute to less effective control of, for example, vasodilation, vasoconstriction and the baroreceptor reflex (Ch. 5).

Memory of the recent past typically becomes more difficult to access, although long-term memories, including problem-solving skills, remain intact and are generally still retrievable. For unknown reasons, some older adults are much more incapacitated by progressive CNS changes than others, e.g., dementia (p. 202).

Effects of ageing on the special senses are almost universal and are considered in Chapter 8. Thermoregulation is discussed in Chapter 14.

SPOT CHECK

5. Outline the impact of ageing on memory.

Disorders of the brain

Learning outcomes

After studying this section, you should be able to:

- list three causes of raised intracranial pressure
- relate the effects of raised intracranial pressure to the functions of the brain and changes in vital signs
- describe four complications of head injury
- outline the effects of intracranial tumours
- explain the effects of stroke
- outline the causes and effects of dementia
- relate the pathology of Parkinson's disease to its effects on body function.

Increased intracranial pressure

This is a serious complication of many conditions that affect the brain. The cranium forms a rigid cavity enclosing the brain, the cerebral blood vessels and CSF; an increase in volume of any one of these will lead to raised intracranial pressure (ICP).

Sometimes the effects of raised ICP are more serious than the condition causing it, e.g. disruption of the blood supply or distortion of the shape of the brain, especially if the ICP rises rapidly. A slow rise in ICP allows time for compensatory adjustment to be made, i.e. a slight reduction in the volume of circulating blood and of CSF. The slower the rise in ICP, the more effective the compensation.

Rising ICP is accompanied by bradycardia and hypertension. As it reaches its limit, a further small increase in pressure is followed by a sudden and usually serious reduction in the cerebral blood flow as autoregulation fails. The result is hypoxia and a rise in carbon dioxide levels, causing arteriolar dilation, which further increases ICP. This leads to rapid and progressive loss of cerebral function, which exacerbates bradycardia and hypertension. Without physiological compensation or medical intervention, rising ICP is usually fatal.

The causes of increased ICP include:

- cerebral oedema
- hydrocephalus, the accumulation of excess CSF (p. 200)
- expanding lesions, also known as space-occupying lesions, inside the skull, such as:
  - haemorrhage or haematoma (traumatic or spontaneous)
  - tumours (primary or secondary).

Expanding lesions may occur in either the brain or between the meninges, and they can damage the brain in various ways (Fig. 7.49).

Effects of increased intracranial pressure

Displacement of the brain

Lesions causing displacement are usually one-sided but may affect both sides. Such lesions may cause herniation (displacement of part of the brain from its usual compartment) of the cerebral hemisphere at different sites with serious consequences; protrusion

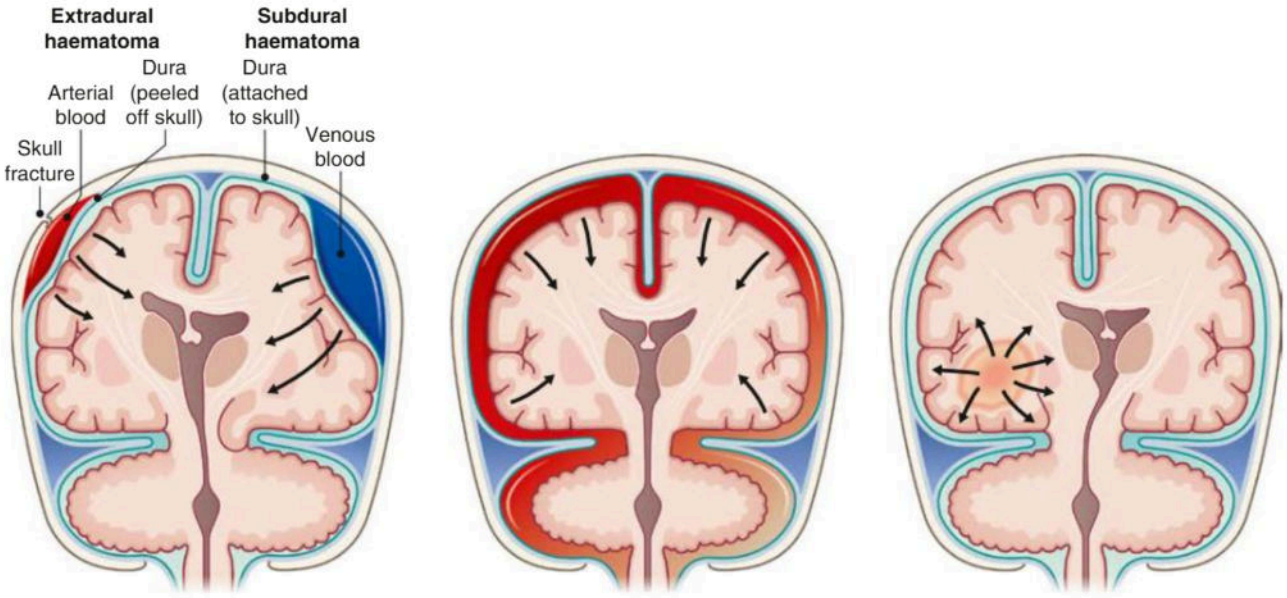

Figure 7.49 Effects of different types of expanding lesions inside the skull. (A) Subdural haematoma. (B) Subarachnoid haemorrhage. (C) Tumour or intracerebral haemorrhage.

of the medulla oblongata through the foramen magnum ('coning') compresses the vital centres and is rapidly fatal.

Obstruction of the flow of cerebrospinal fluid

Expanding lesions may displace the ventricles or their ducts and/or obstruct a duct (Fig. 7.49). The effects depend on the position of the lesion; for example, compression of the cerebral aqueduct causes dilation of the lateral ventricles and the third ventricle, further increasing the ICP.

Vascular damage

Blood vessels may be stretched or compressed, causing:

- haemorrhage when stretched blood vessels rupture
- intracranial ischaemia and infarction if blood vessels are compressed
- papilloedema (oedema round the optic disc) when there is compression of the retinal vein in the optic nerve sheath, where it crosses the subarachnoid space.

Neural damage

At its most serious, the vital centres in the medulla oblongata may be damaged when the increased ICP causes 'coning'. Stretching of the brain stem may damage cranial nerves, especially the oculomotor (III) and the abducent (VI), causing disturbances of eye movement and accommodation. Dilation of a pupil and loss of the light reflex (failure of the pupil to constrict in response to bright light) are caused by compression of the oculomotor nerve.

Cerebral oedema

Oedema (tissue swelling, see p. 134) occurs when there is excess fluid in tissue cells and/or interstitial spaces. In the brain, this is known as cerebral oedema and it increases ICP. It is associated with:

- traumatic head injury
- haemorrhage
- infections and abscesses
- hypoxia, local ischaemia or infarcts
- primary or secondary tumours (see Fig. 7.50)
- inflammation of the brain or meninges
- hypoglycaemia

Head injuries

Damage to the brain may be serious, even when there is no outward sign of injury although damage is often serious when associated with skull fractures.

Head injuries may be the result of direct trauma but this is not always the case. Because the brain floats relatively freely in a 'cushion' of CSF, sudden acceleration or deceleration has an inertia effect. For example, when a vehicle stops suddenly, passengers are thrown forwards: the head then moves forwards or backwards relative to the rest of the body, injuring the brain at the site of impact if it moves within the skull. In 'contre-coup' injuries, brain damage is more severe on the side opposite to the site of impact.

Complications of head injury

If the individual survives the immediate effects, complications may develop hours or days later. Sometimes they are the first indication of serious damage caused by a seemingly trivial injury. Their effects may increase ICP, damage brain tissue or provide a route of entry for infection. In the longer term, dementia (p. 202) is associated with a single moderate or severe head injury and increasingly with multiple mild episodes, in e.g. contact sports.

Traumatic intracranial haemorrhage

Haemorrhage may occur, causing secondary brain damage at the site of injury, on the opposite side of the brain or diffusely throughout the brain. If bleeding continues, the expanding haematoma increases the ICP, compressing the brain.

Extradural haemorrhage

This usually follows a fracture and is typically associated with rupture of the middle meningeal artery (Fig. 7.49A). The individual may recover quickly but rapidly deteriorates later with signs of increasing ICP as the haematoma rapidly expands, stripping the outer layer of dura mater (periosteum) off the bone. The haematoma usually remains localised. In children, fractures are rare because the skull bones are still soft and the joints (sutures) have not fused.

Subdural haemorrhage

This is normally due to bleeding from lacerated vessels, usually veins, on the surface of the brain and may be acute or chronic. There is often another more severe primary brain injury, e.g. extensive brain contusions and lacerations that cause concurrent bleeding into the subarachnoid space, subarachnoid haemorrhage (Fig. 7.49B).

An acute subdural haematoma usually remains localised but sometimes spreads in the subdural space (Fig. 7.49A). The growing haematoma causes neurological deterioration as ICP increases, typically over a longer period than an extradural haemorrhage (above).

Chronic subdural haemorrhage is so called because, despite an acute bleed, raised ICP only becomes apparent weeks or months after a minor injury. This may also occur spontaneously without any history of injury and anticoagulant therapy increases the risk. This situation usually arises because there is some pre-existing cerebral atrophy, e.g. in older adults and in alcohol misuse, in which case reduction in brain volume initially compensates for bleeding within the skull. Evidence of increased ICP may be delayed when brain volume is reduced. The haematoma gradually increases in size and causes mild chronic inflammation and accumulation of inflammatory exudate. In time, it becomes isolated within a wall of fibrous tissue.

Intracerebral haemorrhage and cerebral oedema

These occur following contusions, lacerations and shearing injuries to the brain associated with acceleration and deceleration, especially rotational movements as may happen in a traffic accident.

Cerebral oedema (see opposite is a common complication of contusions of the brain, leading to increased ICP, worsening hypoxia and further brain damage.

Meningitis

The term meningitis refers to inflammation of the meninges, usually due to infection (see p. 198). It normally affects the arachnoid mater but may affect the dura mater when microbes can enter directly, e.g. through a compound skull fracture. Sites that allow leakage of CSF and blood also provide a route of entry for microbes. These include the:

- scalp, in compound skull fractures
- middle ear, in fractures of the temporal bone (CSF otorrhoea)
- nose, in fractures of the sphenoid, ethmoid or frontal bones when air sinuses are involved (CSF rhinorrhoea).

Post-traumatic epilepsy

This is characterised by seizures (fits) and may present soon after the head injury but may not do so for several months. Early development is most common after severe injuries, although in children the injury itself may have appeared trivial. After depressed fractures or large haematomas, epilepsy tends to develop later.

Vegetative state

This is a consequence of severe cortical brain damage. The individual appears awake and is observed to undergo sleep–wake cycles; however, there are no signs of awareness or responses to the external environment. As the brain stem remains intact, the vital centres continue to function, i.e. cardiorespiratory function is maintained. It is considered permanent if there is no recovery 12 months after trauma or longer than 6 months after any other cause.

Hydrocephalus

In this condition the volume of CSF is abnormally high and when accompanied by increased ICP, it is called primary hydrocephalus; this can be either congenital or acquired. An obstruction to CSF flow is the most common cause. Hydrocephalus is described as communicating when there is free flow of CSF from the ventricular system to the subarachnoid space and non-communicating when there is not, i.e., there is obstruction in the system of ventricles, foramina or ducts (see Fig. 7.15).

Enlargement of the head occurs in children when ossification of the cranial bones is incomplete. Thereafter, primary hydrocephalus leads to increased ICP.

In secondary hydrocephalus, ICP remains normal as the CSF volume is raised to compensate for loss of brain tissue after e.g. cerebral infarction or atrophy.

Tumours

Primary tumours of the nervous system usually arise from the neuroglia, meninges or blood vessels; neurones are rarely involved because they do not multiply. Brain tumours typically arise from different cell types in adults and children and range from benign to highly malignant. In adults, the most common are glioblastomas and meningiomas, while astrocytomas and medulloblastomas account for most brain tumours in children.

Nervous tissue tumours rarely metastasise. Because of this, the rate of growth of an intracranial tumour is a more important prognostic indicator than the likelihood of spread outside the nervous system. In this context, 'benign' means slow growing and 'malignant' rapid growing. For instance, a small, benign, capsulated tumour can have massive and disproportionate consequences if it blocks CSF drainage or compresses critical functional areas in the brain.

Early signs typically include headache, vomiting, visual disturbances and papilloedema (swelling of the optic disc seen by ophthalmoscopy). Signs of raised ICP appear after the limits of compensation have been reached (p. 198). Within the confines of the skull, haemorrhage within a tumour exacerbates increased ICP caused by the tumour itself.

Slow-growing tumours

These allow time for compensation for increasing ICP, so the tumour may be quite large before its effects become evident. Compensation involves gradual reduction in the volume of CSF and circulating blood.

Rapidly growing tumours

These do not allow time for adjustment to compensate for the rapidly increasing ICP, so the effects quickly become apparent (see Fig. 7.49C). Complications include:

- neurological impairment, depending on tumour site and size
- effects of increased ICP (p. 198)
- necrosis of the tumour, causing haemorrhage and cerebral oedema.

Metastases in the brain

Some 50% of tumours in the brain are metastatic tumours spread via the blood from primary sites elsewhere, usually the bronchus (lung), breast or kidney. Distant spread of tumours generally carries a poor prognosis, which depends on the site(s) and rate of metastatic growth. As metastases grow larger, ICP increases. Their enlargement causes localised inflammation accompanied by cerebral oedema (swelling) that further exacerbates raised ICP (Fig. 7.50).

Cerebrovascular disease

Cerebrovascular disease is the underlying cause of most strokes and transient ischaemic attacks. Predisposing factors include:

- hypertension
- atheroma
- diabetes mellitus
- cigarette smoking.

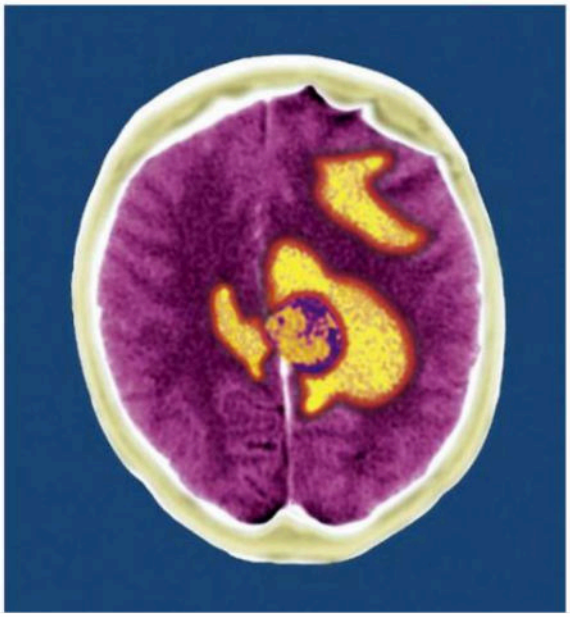

Figure 7.50 Metastatic brain tumours. Coloured computer tomography of brain tissue showing a secondary metastasis (blue, round) and associated cerebral oedema (yellow). (From Science Photo Library. Reproduced with permission.)

Stroke

Stroke is the third most common cause of death in the UK after heart attack and cancer. The incidence is greater in Asian and black African populations and increases steeply with age.

A stroke follows interruption of the blood supply to the brain. Effects appear in a few minutes and usually include paralysis of a limb or one side of the body (hemiparesis), often accompanied by disturbances of speech and vision. The nature and extent of damage depend on the location of the affected blood vessels. Around 80% of patients survive for at least a month following an acute stroke; gradual improvement of limb movement follows in about 50% of cases, which is sometimes accompanied by improved speech. Recurrence is common.

The vast majority of strokes are caused by cerebral infarction (about 85%), with spontaneous intracranial haemorrhage accounting for most of the remainder.

Cerebral infarction

This occurs when blood flow to the brain is suddenly interrupted by an embolus becoming lodged in a cerebral artery, blocking the blood supply to the distal brain tissue and resulting in cerebral hypoxia and tissue death. The main cause is atheroma affecting the carotid artery or aortic arch, which is complicated by thrombosis (p. 129), although a blocked artery supplying the brain can also arise from an embolus originating in the heart, e.g. infective endocarditis (p. 139).

Spontaneous intracranial haemorrhage

The haemorrhage may be intracerebral (into the brain tissue itself) or into the subarachnoid space (Fig. 7.51). It is commonly associated with an aneurysm or hypertension. In each case the escaped blood may cause arterial spasm, leading to ischaemia, infarction, fibrosis (gliosis) and hypoxic brain damage. A severe haemorrhage may be instantly fatal, while repeated small haemorrhages have a cumulative effect in extending brain damage as in multi-infarct (vascular) dementia.

Intracerebral haemorrhage

Prolonged hypertension leads to the formation of multiple microaneurysms in the walls of arterioles in the brain (Fig. 7.51). Rupture of one or more of these, due to a continuing rise in blood pressure, is usually the cause of intracerebral haemorrhage. The most common sites are branches of the middle cerebral artery in the region of the internal capsule and the basal ganglia (see Fig. 7.19).

Severe haemorrhage causes compression and destruction of brain tissue, a sudden increase in ICP and distortion and herniation of the brain with fatal consequences when the vital centres in the medulla oblongata are affected or if there is coning.

Less severe haemorrhage causes paralysis and loss of sensation of varying severity, affecting the side of the body opposite the haemorrhage. If the bleeding stops and does not recur, a fluid-filled cyst develops, i.e. the haematoma is walled off by gliosis, the blood clot is gradually absorbed and the cavity becomes filled with tissue exudate When the ICP returns to normal, some function may be restored, e.g., speech and movement of limbs.

Subarachnoid haemorrhage

This accounts for a small number of strokes and is usually due to rupture of a berry aneurysm of one of the major cerebral arteries (Fig. 7.51), most commonly in middle life; when younger people are affected this is usually due to rupture of a congenitally malformed blood vessel. This condition is often fatal or results in permanent disability.

The blood usually spreads in the subarachnoid space round the brain and spinal cord, causing a general increase in ICP without distortion of the brain (see Fig. 7.49B). The irritant effect of the blood may cause arterial spasm, leading to cerebral ischaemia, infarction, gliosis and the effects of localised brain damage.

Transient ischaemic attack

In contrast to a stroke, a transient ischaemic attack (TIA) is a brief period of reversible cerebral deficit. Typically, there is a short period (minutes or hours) where there is weakness

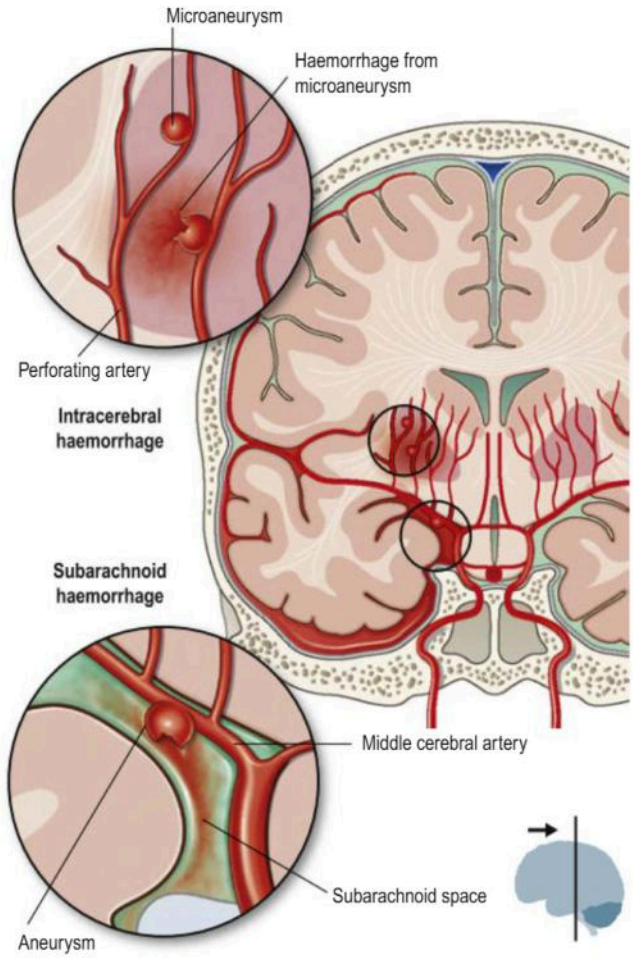

Figure 7.51 Types of spontaneous intracranial haemorrhage that cause stroke.

of a limb and/or loss of speech and/or vision, followed by complete recovery. A TIA may precede a stroke (about 30% in 5 years) or, less commonly, myocardial infarction (Ch. 5). The definition of a TIA lasting for less than 24 hours is no longer used.

Dementia

Dementia is caused by progressive, irreversible degeneration of the cerebral cortex, usually over several years. There is gradual impairment of memory (especially short term), intellect, reasoning and language, although consciousness is not affected. Emotional lability and personality change may also occur. As dementia also impacts on the personal safety and independence of older adults and there is no cure irrespective of the cause, the associated healthcare burden is increasing as populations age.

Alzheimer's disease

Alzheimer's disease (AD) is the commonest form of dementia in developed countries, accounting for around two thirds of cases in the UK. Females are affected twice as often as males; it usually affects people over 60 years, the incidence increasing with age. AD commonly affects people with Down's syndrome by the age of 40. The aetiology is unknown. Several genetic mutations are known to be involved; most are sporadic but are occasionally inherited. Postmortem examination of brain tissue reveals an abundance of amyloid plaques and neurofibrillary tangles (see Fig. 7.48), a characteristic feature of AD. There is gradual and relentless atrophy of the cerebral cortex, accompanied by progressive cognitive impairment. After diagnosis, patients usually survive between 2 and 8 years.

Vascular dementia

This is the second commonest form of dementia in the UK, accounting for around a fifth of cases. Also known as multi-infarct dementia, because deterioration is sometimes 'stepwise' and associated with repeated small episodes with a cumulative effect, this is associated with widespread cerebrovascular disease and arteriosclerosis (p. 131).

Secondary dementia

Dementia also occurs in association with a wide range of other conditions. Those that collectively account for most of the remaining cases are shown in Table 7.4.

Table 7.4 Causes of secondary dementia

Cause	Examples
Parkinson's disease	Lewy body dementia
Inherited (genetic)	Huntington's disease, an inherited autosomal dominant disorder (p. 493) of the *huntingtin* gene, associated with deficiency of the neurotransmitter gamma-aminobutyric acid (GABA), onset usually between 30 and 50 years
Metabolic disorders	Uraemia, liver failure
Endocrine disorders	Congenital hypothyroidism
Infectious conditions	Creutzfeldt–Jakob disease (CJD), HIV, syphilis
Substance misuse	Alcohol, solvents
Intracranial tumours	Usually cerebral metastases, occasionally primary tumours
Trauma (head injury)	Single moderate or severe episode; repeated minor episodes such as concussion in contact sports, e.g. boxing, soccer, rugby

Figure 7.52 Typical posture of Parkinson's disease.

Parkinson's disease

In this condition there is gradual and progressive degeneration of dopamine-releasing neurones in the extrapyramidal system, especially at the basal ganglia. This leads to loss of control and coordination of muscle movement, resulting in:

- slowness of movement (bradykinesia) and difficulty initiating movements
- fixed muscle tone, causing expressionless facial features, and rigidity of voluntary muscles, causing the slow and characteristic stiff, shuffling gait and stooping posture (Fig. 7.52)
- muscle tremor of extremities that usually begins in one hand, e.g. 'pill-rolling' movement of the fingers
- speech problems, excessive salivation and, in advanced disease, dysphagia.

Onset is usually from 60 years and the incidence rises steeply with age; it affects more men than women. There is progressive physical disability but cognitive function is not impaired until the disease is advanced, when dementia may develop.

The cause is unknown in about 80% of cases. Parkinsonism (signs and symptoms of Parkinson's disease) is associated with some drugs such as phenothiazines, cerebrovascular disease and tumours causing midbrain compression.

Effects of neurotoxins

Many chemicals, including drugs, environmental toxins, microbial products and metabolic wastes, can damage nervous tissue. This may range from short-term reversible neurological disturbance, such as depression of cognitive and motor functions after drinking alcohol, through to long-term permanent neurological damage, such as heavy metal poisoning (e.g. lead) or hepatic encephalopathy (p. 370).

SPOT CHECK

6. Explain why hydrocephalus in children, but not adults, may be accompanied by enlargement of the skull.
7. Relate the pathology of Parkinson's disease to its common signs and symptoms.

Infections of the central nervous system

Learning outcome

After studying this section, you should be able to:

- describe common infections of the nervous system and their effects on body function.

The brain and spinal cord are relatively well protected from microbial infection by the blood–brain barrier. CNS infections are usually bacterial or viral but may also be protozoal or fungal. Infections may originate in the meninges (meningitis) or in the brain (encephalitis), then spread from one site to the other.

Bacterial infections

Entry of bacteria into the CNS is often blood-borne from a site of infection elsewhere, usually the upper respiratory tract (see below). Bacteria can also enter the CNS directly from a nearby site of infection, e.g. a compound skull fracture or infection of the middle ear or paranasal sinuses. If there is an extradural or subdural abscess, infection may spread further locally should it rupture. Occasionally infection is iatrogenic, occurring when bacteria are introduced during an invasive procedure, e.g., lumbar puncture.

Bacterial meningitis

The term 'meningitis' refers to inflammation of the meninges and usually affects the subarachnoid space. It is normally acquired by inhaling infected respiratory droplets from an infected individual. Bacterial meningitis is usually preceded by a mild upper respiratory tract infection, during which a few bacteria enter the bloodstream and are carried to the meninges.

Many bacteria can cause meningitis. Preschool children are mostly infected by *Haemophilus influenzae*. In older children and adults, the responsible bacteria are usually *Neisseria meningitidis* (meningococcus) or *Streptococcus pneumoniae*.

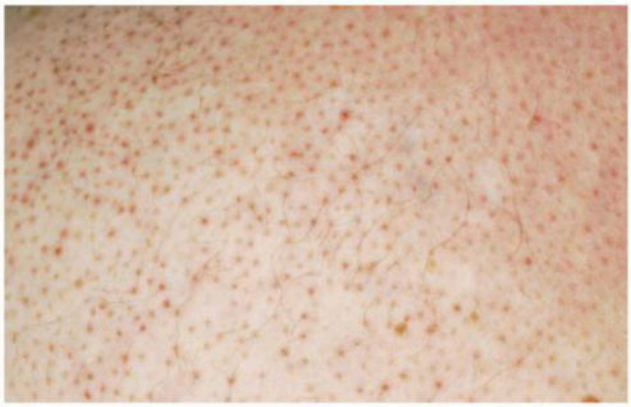

Figure 7.53 Petechial rash in meningitis. (From Science Photo Library. Reproduced with permission.)

Figure 7.54 Shingles. (From Feather A, Randall D, Waterhouse M, 2021 Kumar and Clark's Clinical Medicine, 10th ed. Elsevier.)

Other pathogenic bacteria can also cause meningitis, e.g., those involved in tuberculosis (p. 298) and syphilis (p. 519).

The onset is usually sudden with severe headache, neck stiffness, photophobia (intolerance of bright light) and fever. This is sometimes accompanied by a petechial rash that presents as round pinpoint spots due to tiny bleeds just under the skin, a serious sign associated with septicaemia and sepsis (Fig. 7.53). CSF appears cloudy owing to the presence of many bacteria and neutrophils in the subarachnoid space. Even with antibiotic treatment, mortality and morbidity are high.

Viral infections

Entry of viruses into the CNS is usually via the blood from viral infection elsewhere. Less commonly, transmission to the CNS is through the peripheral nervous system when invading neurotropic viruses, i.e. those with an affinity for nervous tissue, travel along peripheral nerves from a site elsewhere, e.g. poliovirus. They enter the body via:

- the alimentary tract, e.g. poliomyelitis
- the respiratory tract, e.g. shingles (Fig. 7.54)
- broken skin, e.g. rabies.

The effects of viral infections vary, according to the site and the amount of tissue destroyed. Viruses may damage neurones by multiplying within them or stimulating an immune reaction, which may explain why sometimes signs of infection do not appear until there is a high antibody titre, some 1–2 weeks after infection.

Viral meningitis

Affecting mainly children and young adults, this is the most common form of meningitis, which is usually relatively mild and followed by complete recovery within 4 to 10 days.

Viral encephalitis

Viral encephalitis, inflammation of the brain tissue, is rare and usually associated with a recent viral infection. Most cases are mild and recovery is complete. In Europe, serious cases are usually associated with herpes simplex viruses, while in South East Asia and the Far East the flavivirus causing Japanese encephalitis is usually responsible. Many different sites in the brain can be affected and, as neurones cannot be replaced, loss of function reflects the extent of damage, e.g. if vital centres in the medulla are damaged, the prognosis is very poor. Long-term consequences including cognitive impairment and epilepsy are common in those who survive.

Herpes zoster (shingles)

The herpes zoster virus causes two distinct diseases:

- chickenpox (varicella), mainly in children
- shingles (zoster) in adults.

Chickenpox is nearly always transmitted by infected respiratory droplets and usually affects children. Sometimes chickenpox is contracted from a person with shingles but the reverse is not true. Following recovery from chickenpox, viruses may remain dormant in posterior (dorsal) root ganglia of the spinal nerves and then become active decades later, causing shingles. Reactivation may be either spontaneous or associated with intercurrent illness or immunosuppression due to e.g. old age, cancer, diabetes mellitus or AIDS.

When shingles develops, the posterior root ganglion becomes acutely inflamed. From there the viruses travel along the sensory nerve(s) to the skin it supplies. The infection is usually unilateral and the most common sites are:

- the nerves supplying the trunk, sometimes two or three adjacent dermatomes
- the ophthalmic division of the trigeminal nerve (see Fig. 7.43), causing trigeminal neuralgia, and, if vesicles form on the cornea, there may be ulceration, scarring and residual interference with vision.

Affected tissues become inflamed and vesicles, containing serous fluid and viruses, develop along the course of the nerve (Fig. 7.54). This is accompanied by persistent pain and hypersensitivity to touch (hyperaesthesia). Recovery is

usually slow and there may be permanent loss of sensation, and impaired visual function when the eye is affected, depending on the severity of the disease.

Poliomyelitis

This disease is usually caused by polioviruses but occasionally by other enteroviruses. The infection is spread by the faeco–oral route (p. 361) and, after ingestion, viral multiplication initially occurs in the alimentary tract. The viruses then become blood-borne travelling to the central nervous system and invading anterior horn cells in the spinal cord.

Polio is usually asymptomatic but sometimes there is a mild febrile illness followed by complete recovery. In some 5% of cases the severity worsens; pyrexia, headache and signs of meningitis (p. 204) develop. Irreversible damage to lower motor neurones (Fig. 7.21) causes flaccid muscle paralysis, which, in the limbs, may lead to deformity and permanent disability because of the unopposed tonal contraction of antagonistic muscles. Respiratory paralysis (failure) may occur with fatal consequences when the intercostal muscles are affected. Where available, vaccination programmes have almost eradicated this disease.

Rabies

All warm-blooded animals are susceptible to the rabies virus, which is endemic in many countries but not in the UK. The main reservoirs are wild animals, some of which may be carriers; in regions where rabies is endemic, domestic pets may also become infected. The viruses multiply in the salivary glands of affected animals and are present in large numbers in saliva. Human infection nearly always occurs following a bite from an infected animal or carrier.

Once in the body the viruses travel to the brain along peripheral nerves; the incubation period varies from about 2 weeks to several months. On reaching the brain, the virus proliferates and later spreads along autonomic nerves to other sites including the salivary glands, lungs and kidneys. Initial signs include fever followed by increasing anxiety. Hydrophobia (hatred of water) and excessive salivation occur as attempts to eat or drink result in painful spasm of the throat muscles that inhibits swallowing. Spasm affecting other muscles and convulsions are common. Acute encephalomyelitis is accompanied by damage to many important functional areas of the brain.

Not all people exposed to the virus contract rabies, but in those who do, it is nearly always fatal. Death is usually due to respiratory muscle spasm or paralysis.

Human immunodeficiency virus

The brain is often affected in HIV-infected individuals with AIDS, who may develop opportunistic CNS infections, including meningitis, and dementia.

Creutzfeldt–Jakob disease

This condition is caused by a highly heat-resistant, transmissible distorted protein known as a prion. It is rare and usually occurs spontaneously but may also be iatrogenic if introduced during neurosurgical procedures. CJD is a rapidly progressive form of dementia (p. 202) affecting adults over 50 years old. There is no known treatment or cure and the condition is fatal within 6 months.

Variant Creutzfeldt–Jakob disease (vCJD) was discovered in the 1990s and is also caused by a prion. It develops after eating contaminated beef from cattle with bovine spongiform encephalopathy (BSE, or 'mad cow disease'). It affects people from about 20 years of age. The symptoms are progressive ataxia and dementia, although many people survive for several years.

Myalgic encephalitis

Myalgic encephalitis (ME) is also known as postviral syndrome or chronic fatigue syndrome and it generally affects females, mostly teenagers and young adults. The aetiology is unknown although it sometimes follows a viral illness. The effects include malaise, severe fatigue, poor concentration and myalgia. Gradual recovery is usually spontaneous but sometimes the outcome is chronic disability.

SPOT CHECK

8. Outline the relationship between chickenpox and shingles.

Demyelinating diseases

Learning outcome

After studying this section, you should be able to:

- explain how the signs and symptoms of demyelinating disease are related to pathological changes in the nervous system.

Multiple sclerosis (MS) is the most common demyelinating (or neuroinflammatory) disease.

Multiple sclerosis

Myelin forms a sheath around most CNS nerve axons and dendrites. In MS, areas of demyelinated white matter, called plaques, replace myelin and are found irregularly distributed throughout the brain and spinal cord. In the early stages there may be little damage to axons.

MS usually develops between 20 and 40 years of age and affects twice as many women as men; it is a common cause of disability in young adults throughout Europe and North America.

The actual cause(s) of MS are not known; it is an autoimmune inflammatory disorder that destroys myelin,

possibly triggered by environmental factors in a genetically susceptible individual. The environment before adolescence is implicated because the disease is most prevalent in people who spend their preadolescent years in temperate climates, and those who move to other climates after that age retain their susceptibility to MS. People from equatorial areas moving into a temperate climate during adolescence or later life appear not to be at increased risk. Genetic factors are also implicated, as there is an increased incidence of MS among siblings, especially in identical twins, and parents of patients.

Effects of multiple sclerosis

Symptoms depend on the size and location of the developing plaques, which impair impulse transmission in affected nerves. They include:

- Limb weakness and sometimes paralysis when the nerves suppling skeletal muscles are affected.
- Impaired coordination and movement.
- Paraesthesia (disturbed sensation), e.g. burning or pins and needles.
- Incontinence of urine.
- Visual disturbances, especially blurring and double vision. The optic nerves are commonly affected early in the disease.

Its pattern is usually one of relapses and remissions of widely varying duration. Typically, each relapse further damages nervous tissue causing progressive dysfunction. In some cases, there is chronic progression without remission and occasionally acute disease rapidly becomes fatal.

Acute disseminated encephalomyelitis

This rare but serious condition usually affects children and young adults. It typically occurs a week or so after a viral infection, e.g. measles or chickenpox, or follows immunisation against viral disease.

The cause of the acute diffuse demyelination is not known although an autoimmune response that destroys myelin may be triggered either by viruses during a viral infection such as measles, or by an immune response to a vaccine. The effects vary considerably, according to the distribution and degree of demyelination, and resemble those of MS. The early febrile state may progress to seizures, paralysis and coma. Most patients survive the initial phase and recover completely but around 20% have severe neurological impairment.

SPOT CHECK

9. Outline the pathological changes characteristic of multiple sclerosis.

Motor neurone disease

Learning outcome

After studying this section, you should be able to:

- Outline the effects of MND.

Motor neurone disease (MND) is a chronic progressive degenerative disorder that affects both upper and lower motor neurones with devastating consequences. It occurs more commonly in men over 50 years of age and the cause is seldom known, although occasionally it is inherited as an autosomal dominant disorder (p. 493).

Motor neurones in the cerebral cortex, brain stem and anterior horns of the spinal cord are destroyed and replaced by gliosis (scar tissue). Table 7.5 summarises the effects of damage to motor neurones. The parts of the body affected depend on which neurones have been damaged and their site in the brain, spinal cord or peripheral nerve.

Early signs of MND are usually weakness and twitching of the small muscles of the hand and the muscles of the arm and shoulder girdle. Speech becomes increasing slurred. Progressive weakness and paralysis affect the legs later. Most people with MND survive for only about 3–5 years, death is usually due to respiratory difficulties or complications of immobility.

Table 7.5 Summary of effects of damage to motor neurones

Upper motor neurone	Lower motor neurone
Muscle weakness and spastic paralysis	Muscle weakness and flaccid paralysis
Exaggerated tendon reflexes	Absence of tendon reflexes
Muscle twitching	Muscle wasting Contracture of muscles Impaired circulation

SPOT CHECK

10. What causes MND?

Disorders of the spinal cord

Learning outcome

After studying this section, you should be able to:

- explain how disorders of the spinal cord affect normal function.

Because space in the neural canal and intervertebral foramina is limited, any condition that distorts their shape or reduces the space may damage the spinal cord or peripheral nerve roots, or compress blood vessels, causing ischaemia. The effects of disease or injury depend on the severity of the damage, and the type and position of the neurones involved.

Injury to the spinal cord often impairs sensory and motor function of the limbs causing paralysis. When the cervical region is affected this may affect all four limbs causing tetraplegia, also known as quadriplegia. Additionally, respiratory paralysis occurs when the upper cervical nerves that innervate the diaphragm are involved. Injuries below the level of T1 affect the lower limbs causing paraplegia.

Compression of the spinal cord and nerve roots can affect both motor and sensory nerves. Causes include:

- prolapsed intervertebral disc
- syringomyelia
- tumours: metastatic, meningeal or arising from a nerve sheath
- vertebral fractures with displacement of bone fragments.

Prolapsed intervertebral disc

This is the most common cause of compression of the spinal cord and/or nerve roots. The vertebral bodies are separated by the intervertebral discs, each consisting of an outer rim of cartilage, the annulus fibrosus, and a central core of soft gelatinous material, the nucleus pulposus.

Prolapse of a disc is herniation of the nucleus pulposus, causing the annulus fibrosus and the posterior longitudinal ligament to protrude into the neural canal. It is most common in the lumbar region, usually below the level of the spinal cord, i.e. below L2, and therefore affects nerve roots only (Fig. 7.55). If it occurs in the cervical region the spinal cord may also be compressed. Herniation may occur suddenly, typically in young adults during strenuous exercise or exertion, or progressively in older people when there is bone disease or degeneration of the disc, which leads to rupture during minimal exercise. The prolapse is usually one-sided, compressing a nerve root. Occasionally it occurs on the midline, compressing the spinal cord, the anterior spinal artery and sometimes bilateral nerve roots causing ischaemia and possibly spinal cord damage (necrosis).

The outcome depends on the size and level of the prolapse, and the period of compression. Small herniations cause local pain due to pressure on the nerve endings in the posterior longitudinal ligament. Larger herniations may cause:

- acute or chronic pain, which may be severe, perceived by the patient to originate from the area supplied by the compressed sensory nerve, e.g. in the leg or foot
- severe local muscle spasm due to pressure on motor nerves

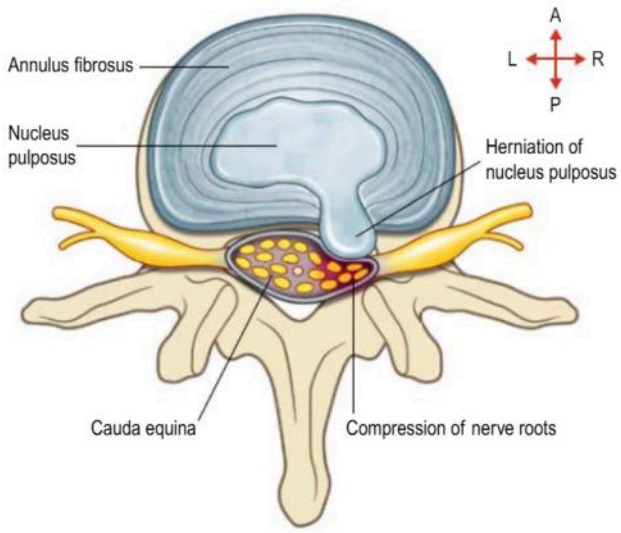

Figure 7.55 Prolapsed intervertebral disc.

- retention and incontinence of urine and/or faeces if sphincter function is affected.

Syringomyelia

This dilation (syrinx) of the central canal of the spinal cord occurs most commonly in the cervical region and is associated with congenital abnormality of the distal end of the fourth ventricle, spinal cord injury or a tumour. As the central canal dilates, pressure causes progressive damage to sensory and motor neurones. Effects include:

- dissociated anaesthesia, i.e. loss of pain and temperature sensation, due to compression of the sensory nerve fibres
- lower motor neurone damage (muscle weakness and atrophy) affecting only the upper limbs.

SPOT CHECK

11. Describe the changes in an intervertebral disc that has prolapsed.

Disorders of peripheral nerves

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the causes and effects of polyneuropathies and mononeuropathies
- describe the effects of Guillain–Barré syndrome and Bell's palsy.

Peripheral neuropathy

This is a group of diseases affecting peripheral nerves that may impair sensory and/or motor function. They are classified as:

- polyneuropathy: several nerves are affected
- mononeuropathy: a single nerve is usually affected.

Polyneuropathy

Many nerves and sometimes myelin sheaths are affected in association with other disorders such as:

- vitamin deficiencies, e.g. vitamins B_1, B_6, B_{12}
- metabolic disorders, commonly diabetes mellitus, also uraemia (in renal failure), hepatic failure, malignancy
- toxins, e.g. alcohol, aniline dyes and some drugs, such as phenytoin, isoniazid.

Long nerves are usually affected first, e.g. those supplying the feet and legs. The outcome depends on the cause of the neuropathy and the extent of the damage.

Mononeuropathy

Only one nerve is affected, usually by compression, causing tissue ischaemia and paresthaesia (tingling) and/or pain in the affected area. The resultant dysfunction depends on the site and extent of the injury. Examples include:

- compression of a nerve in a confined space caused by surrounding inflammation and oedema, e.g. the median nerve in carpal tunnel syndrome (p. 482)
- external pressure on a nerve, e.g. in an unconscious person lying with an arm hanging over the side of a bed or trolley
- trapping of a nerve between the broken ends of a bone.

Guillain–Barré syndrome

Also known as acute inflammatory polyneuropathy, this is sudden, acute, progressive, bilateral ascending muscular weakness or paralysis often accompanied by numbness. It begins in the lower limbs and spreads to the arms, trunk and cranial nerves. It usually occurs 1–3 weeks after an upper respiratory tract infection. There is widespread inflammation, accompanied by some demyelination of spinal, peripheral and cranial nerves and the spinal ganglia. Paralysis may affect all the limbs and the respiratory muscles. Many patients who survive the acute phase make a complete recovery. Recovery is typically slow, usually over many months; however fully independent mobility never returns in about a third of those with severe disease.

Bell's palsy

Compression of a facial nerve in the temporal bone foramen causes paralysis of facial muscles with drooping and loss of facial expression on the affected side. The immediate cause is inflammation and oedema of the nerve. The underlying cause is thought to be viral. The onset may be sudden or develop over several hours. Distortion of the features is due to loss of muscle tone on the affected side leaving it expressionless, while the unaffected side remains normal. Spontaneous recovery is usually complete within 12 weeks, although the effects are sometimes permanent.

SPOT CHECK

12. Describe Bell's palsy and its usual consequences.

Developmental abnormalities of the nervous system

Learning outcomes

After studying this section, you should be able to:

- describe developmental abnormalities of the nervous system
- relate their effects to abnormal body function.

Developmental disorders of the nervous system cause a range of congenital abnormalities. Common causes may be:

- genetic – e.g. Down's syndrome (p. 498)
- infective – e.g. maternal rubella before 18 weeks of pregnancy, which may result in fetal death and spontaneous abortion; in less severe cases there is brain damage with disabling consequences
- poor nutrition – e.g. folic acid deficiency at the time of conception and early pregnancy is associated with neural tube defects including spina bifida.

Spina bifida

This is a congenital malformation of the embryonic neural tube and spinal cord (Fig. 7.56). The vertebral (neural) arches are absent and the dura mater is abnormal, most commonly in the lumbosacral region. The causes are not known, although the condition is associated with dietary deficiency of folic acid at the time of conception. Anti-epilepsy drugs, e.g. sodium valproate have also been implicated. These defects may be of genetic origin or due to environmental factors, e.g. irradiation, or maternal infection (rubella) at a critical stage in development of the fetal vertebrae and spinal cord. The effects depend on the extent of the abnormality.

Occult spina bifida

In this 'hidden' condition the skin over the defect is intact and excessive growth of hair or a pit over the site may be the only sign of abnormality. This is sometimes associated with minor nerve defects that commonly affect the bladder.

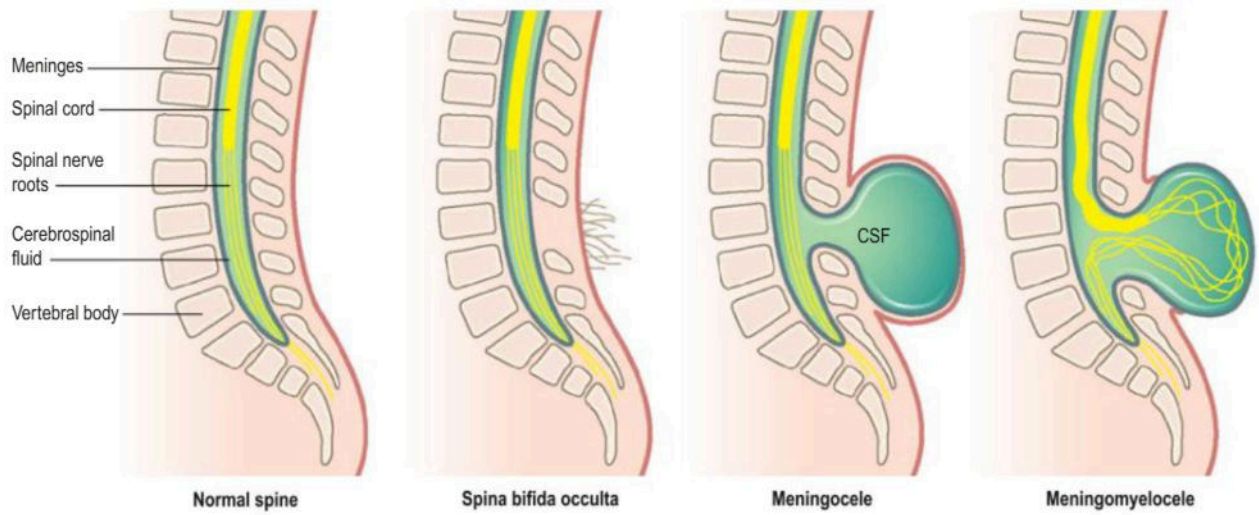

Figure 7.56 Spina bifida. Vertebrae viewed from the side.

Meningocele

The skin over the defect is very thin and may rupture after birth. There is dilation of the subarachnoid space posteriorly. The spinal cord is correctly positioned.

Meningomyelocele

The meninges and spinal cord are grossly abnormal. The skin may be absent or rupture. In either case, there is leakage of CSF and the meninges may become infected. Serious nerve defects result in paraplegia and lack of sphincter control, causing incontinence of urine and faeces. There may also be impaired cognitive development.

Hydrocephalus

This condition may be either congenital or acquired (see p. 200).

SPOT CHECK

13. Identify the factors thought to predispose to spina bifida.

Case study 1

Ashraf went to wash his hands under a running tap. He hadn't checked the water temperature and discovered it was piping hot as soon as he put his hands under it.

1. The impulses sending this information to his central nervous system travelled along:

   a. Afferent (motor) nerves
   b. Afferent (sensory) nerves
   c. Efferent (motor) nerves
   d. Efferent (sensory) nerves

He immediately withdrew his hand to prevent scalding.

2. Such withdrawal actions are called:

   a. Reflex responses
   b. Sensory responses
   c. Spinal responses
   d. Autonomic responses

Ashraf looked at his fingers to see if the hot water had caused any damage such as redness or blistering.

3. Information about location of the pain or signs of scalding is perceived in the:

   a. Medulla oblongata
   b. Cerebellum
   c. Spinal cord
   d. Cerebral cortex

4. Perception of sight takes place in the visual area of the cerebrum, located in the:

   a. Occipital lobe
   b. Temporal lobe
   c. Frontal lobe
   d. Parietal lobe

Case study 2

Jonny was driving to college and a child stepped off the pavement in front of him. He applied the brakes sharply and his car stopped short of the child. He felt relieved but quickly became aware of his heart pounding in his chest.

1. The reason for his heart beating faster was increased activity of:

   a. The somatic nervous system
   b. The sympathetic nervous system
   c. The central nervous system
   d. The parasympathetic nervous system

2. In what order does an impulse travel along a neurone?

   a. Terminal boutons, dendrites, axon, axon hillock
   b. Terminal boutons, axon, axon hillock, dendrites
   c. Dendrites, axon, axon hillock, terminal boutons
   d. Dendrites, axon hillock, axon, terminal boutons

3. The sympathetic neurotransmitter that increases the rate and force of the heartbeat is:

   a. Histamine
   b. Acetylcholine
   c. Noradrenaline
   d. Serotonin

4. As well as a raised heart rate, which of the following will also have occurred subconsciously after Jonny applied the brakes?

   a. Dilation of his large airways
   b. Constriction of his pupils
   c. Increased peristalsis in his alimentary tract
   d. Reduced hormone secretion from the adrenal medulla

Review and revise

Complete each of the following statements:

1. There are two types of nervous tissue. The cells that generate and transmit impulses are known as _____ and they are supported by connective tissue cells collectively called _____. There are four types of these cells, two of which are _____ and _____.

2. The region where an action potential passes from one nerve to the next is the _____. A chemical, the _____, is released from _____ _____ into the _____ _____, the space between the two neurones.

3. A _____ is an involuntary and immediate response to a sensory stimulus. The sensory neurone enters the spinal cord through the _____ nerve root and the impulse in the motor (effector) neurone leaves it by the _____ nerve root.

4. The peripheral nervous system consists of _____ pairs of spinal nerves and _____ pairs of cranial nerves.

5. The most common form of dementia in developed countries is _____ _____. The cause of this form is unknown but dementia can also be secondary to other conditions; cerebrovascular disease is associated with _____ dementia and infective causes include _____.

Choose one answer to complete each of the following statements:

6. The connective tissue that covers each bundle of nerve fibres within a nerve is the: _____
   a. Endoneurium
   b. Perineurium
   c. Epineurium
   d. Myelin sheath

7. The special senses do not include: _____
   a. Pain
   b. Balance
   c. Sight
   d. Taste

8. It is true that: ____
   a. The central nervous system consists of the brain, spinal cord and involuntary muscles.
   b. Afferent nerves carry impulses away from the central nervous system.
   c. The autonomic nervous system controls activity of voluntary muscle.
   d. Baroreceptors and chemoreceptors send information about the internal environment to the central nervous system.

9. A lumbar puncture is used to gain access to the cerebrospinal fluid, which is found in the: ___
   a. Subdural space
   b. Subarachnoid space
   c. Epidural space
   d. Central canal

10. The cause of poliomyelitis is: _____
    a. Bacterial
    b. Viral
    c. Genetic
    d. Idiopathic.

Indicate whether each of the following statements is true or false:

11. Afferent nerves carry impulses towards the central nervous system. _____

12. Skeletal muscles are the only effector organs of the somatic (voluntary) nervous system. ____

13. The dura mater is the fine innermost layer of the meninges that completely covers the brain. _____

14. The vestibulocochlear nerves are associated with hearing, posture and balance. _____

15. Herpes simplex viruses cause both chickenpox and, after a latent period, shingles. _____

16. Match each letter in List A to the appropriate number in List B:

List A
____ (a) Schwann cells
____ (b) Continuous propagation
____ (c) Ependymal cells
____ (d) White matter
____ (e) Oligodendrocytes
____ (f) Grey matter
____ (g) Microglia
____ (h) Astrocytes

List B
1. Cells whose foot processes form the blood–brain barrier
2. Cells that remove bacteria and damaged tissue in the central nervous system
3. Cells that secrete cerebrospinal fluid
4. Formed by the bodies of nerve cells
5. Nerve conduction used by unmyelinated nerves
6. Microglia that secrete and maintain myelin
7. Cells that secrete and maintain myelin in the peripheral nervous system
8. Formed by axons of nerve cells

17. Match each letter in List A to the appropriate number in List B:

List A
____ (a) Corpus callosum
____ (b) Gyri
____ (c) Decussation
____ (d) Tracts
____ (e) Cerebral cortex
____ (f) Diencephalon
____ (g) Sulci
____ (h) Nuclei

List B
1. Superficial part of the cerebrum
2. Mass of white matter that connects the two cerebral hemispheres
3. Part of the brain the includes the thalamus and hypothalamus
4. Groups of cell bodies in the central nervous system
5. Crossing over of nerve fibres in the central nervous system
6. Bundles of nerve fibres that make up the white matter of the brain
7. The many convolutions of the surface of the brain
8. The many furrows on the surface of the brain

18. Match each letter in List A to the appropriate number in List B:

List A
____ (a) Motor nerve
____ (b) Dermatome
____ (c) Plexus
____ (d) Phrenic nerve
____ (e) Pudendal nerve
____ (f) Sensory nerve
____ (g) Sciatic nerve
____ (h) Intercostal nerve

List B
1. Supplies the hamstring muscles
2. Carries impulses towards the central nervous system
3. Area where nerves converge and there is regrouping of the fibres
4. Supplies the external anal sphincter
5. Carries impulses away from the central nervous system
6. Supplies muscles of breathing that lie between the ribs
7. Area of skin whose sensory receptors are associated with a specific nerve
8. Supplies the diaphragm

19. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Papilloedema
____ (b) Spina bifida
____ (c) Hydrocephalus
____ (d) *Haemophilus influenzae*
____ (e) Neurotropic
____ (f) Herniation
____ (g) Transient ischaemic attack
____ (h) Hemiparesis

List B

1. Term used to describe microbes with an affinity for nervous tissue
2. Displacement of part of the brain from its normal compartment
3. A period of cerebral deficits that are restored but may precede a stroke
4. Swelling around the optic disc seen on ophthalmoscopy
5. Paralysis of a limb or one side of the body
6. Abnormally high volume of cerebrospinal fluid
7. A bacterium that causes meningitis in young children
8. A congenital condition that affects the spinal cord

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 8

The special senses

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The special senses are hearing, sight, smell, taste and balance; all use specialised sensory receptors to collect and transmit information to specific areas of the brain. Incoming nerve impulses from the ears, eyes, nose and mouth are integrated and coordinated within the brain, allowing perception of this information. Up to 80% of what we perceive comes from external sensory stimuli. The first sections of this chapter explore the special senses, while the later ones consider the effect of ageing and consequences of disorders affecting the ear and the eye.

Hearing and the ear

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the outer, middle and inner parts of the ear
- explain the physiology of hearing.

The ear is the organ of hearing and is also involved in balance. It is supplied by the cochlear branch of the 8th cranial (vestibulocochlear) nerve, which responds to the vibrations generated by sound waves and transmits this information to the brain.

Structure

The ear is divided into three distinct parts (Fig. 8.1): the outer ear, middle ear (tympanic cavity) and inner ear. The middle and inner ear are encased within the petrous part of the temporal bone.

The outer ear collects sound waves and directs them to the middle ear, which in turn transmits them to the inner ear. The inner ear converts the sound waves into nerve impulses, which are transmitted to the hearing area (auditory cortex) in the brain.

Outer ear

This consists of the auricle (pinna) and the external acoustic meatus (auditory canal).

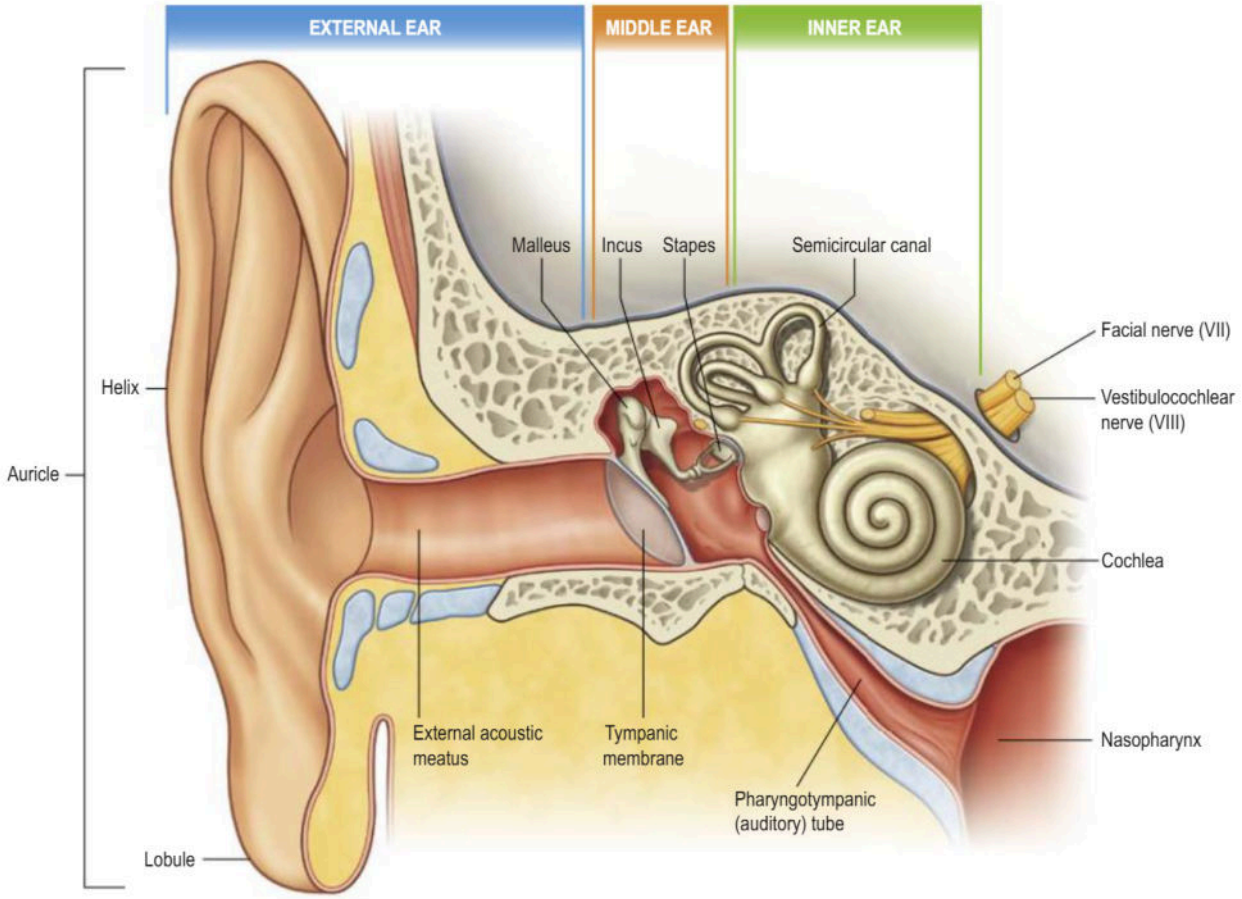

Figure 8.1 Structure of the ear.

Auricle (pinna)

The auricle is the visible part of the ear that projects from the side of the head. It is composed of fibroelastic cartilage and covered with skin. It is deeply grooved and ridged; the most prominent outer ridge is the helix.

The lobule (earlobe) is the soft pliable part at the lower extremity, composed of fibrous and adipose tissue richly supplied with blood.

External acoustic meatus (auditory canal)

This is a slightly 'S'-shaped tube about 2.5 cm long, extending from the auricle to the tympanic membrane (eardrum). The lateral third is embedded in cartilage and the remainder lies within the temporal bone. It is lined with skin continuous with that of the auricle. There are numerous ceruminous glands and hair follicles, with associated sebaceous glands in the skin of the lateral third. Ceruminous glands are modified sweat glands that secrete cerumen (earwax), a sticky material containing protective substances including the bactericidal enzyme lysozyme and immunoglobulins. Foreign materials, e.g. dust, insects and microbes, are prevented from reaching the tympanic membrane by wax, hairs and the curvature of the meatus. Movements of the temporomandibular joint during chewing and speaking 'massage' the cartilaginous meatus, moving wax towards the exterior.

The tympanic membrane (eardrum) (Fig. 8.2) completely separates the external acoustic meatus from the middle ear. It is oval-shaped with the slightly broader edge upwards and consists of three layers: an outer covering of hairless skin, a middle layer of fibrous tissue and an inner lining of mucous membrane continuous with that of the middle ear.

Middle ear (tympanic cavity)

This is an irregular-shaped air-filled cavity within the petrous part of the temporal bone (Fig. 8.3; see also Fig. 8.1). The cavity, its contents and the air sacs that open out of it are lined with either simple squamous or cuboidal epithelium.

The lateral wall of the middle ear is formed by the tympanic membrane.

The roof and floor are formed by the temporal bone.

The posterior wall is formed by the temporal bone with openings leading to the mastoid antrum, through which air passes to the air cells within the mastoid process.

Figure 8.2 The tympanic membrane. Coloured scanning electron micrograph showing the malleus and the incus. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

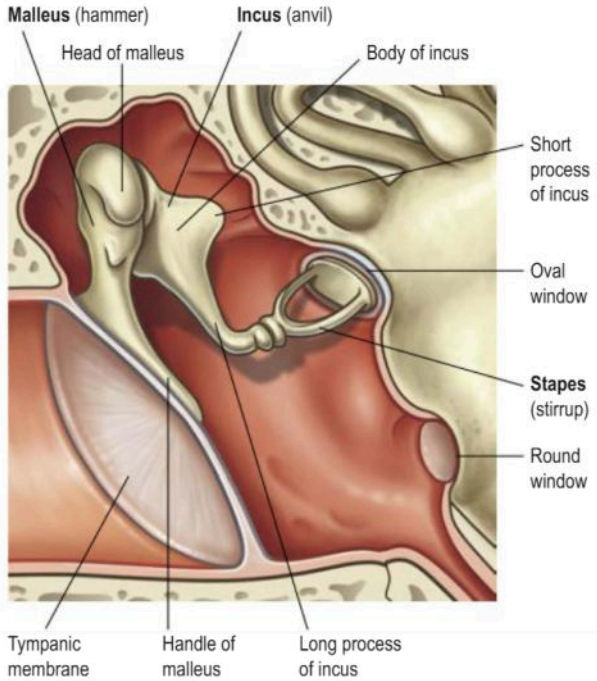

Figure 8.3 The auditory ossicles.

The medial wall is a thin layer of temporal bone in which there are two openings:

- oval window
- round window (see also Fig. 8.6).

The oval window is attached to one of the tiny bones in the middle ear, called the stapes and the round window by a fine sheet of fibrous tissue.

Air reaches the middle ear through the auditory (pharyngotympanic or Eustachian) tube, which links it to the nasopharynx. It is about 4 cm long and lined with ciliated columnar epithelium. The presence of air at atmospheric pressure on both sides of the tympanic membrane is maintained by the auditory tube and this enables the membrane to vibrate when sound waves strike it. The auditory tube is normally closed but when there is unequal pressure across the tympanic membrane, e.g. at high altitude, it is opened by swallowing or yawning and the ears 'pop', equalising the pressure again.

Auditory ossicles

These are three very small bones, only a few millimetres in size, that form a chain across the middle ear from the tympanic membrane to the oval window (Fig. 8.3; see also Fig. 8.1). Synovial joints between the ossicles allow them to vibrate within the air-filled tympanic cavity. The ossicles are held in place by fine ligaments and are named according to their shapes.

Malleus

This is the lateral hammer-shaped bone. The handle is in contact with the tympanic membrane, and the head forms a synovial joint with the incus.

Incus

This is the middle anvil-shaped bone. Its body articulates with the malleus, and the long process with the stapes; it is stabilised by the short process, fixed by fibrous tissue to the posterior wall of the tympanic cavity.

Stapes

This is the medial stirrup-shaped bone. Its head articulates with the incus and its footplate fits into the oval window.

Inner ear

The inner ear (Fig. 8.4) or labyrinth (meaning 'maze') contains the organs of hearing and balance. It has two structural parts: the bony labyrinth and the membranous labyrinth. It is divided into three main regions:

- the vestibule, containing the utricle and saccule
- three semicircular canals
- the cochlea.

The inner ear is formed from a network of channels and cavities in the temporal bone (the bony labyrinth). Within the bony labyrinth, like a tube within a tube, is the membranous labyrinth, a network of fluid-filled membranes that lines and fills the bony labyrinth (Fig. 8.4).

Bony labyrinth

This is lined with periosteum. Within the bony labyrinth lies the membranous labyrinth suspended in watery fluid called perilymph.

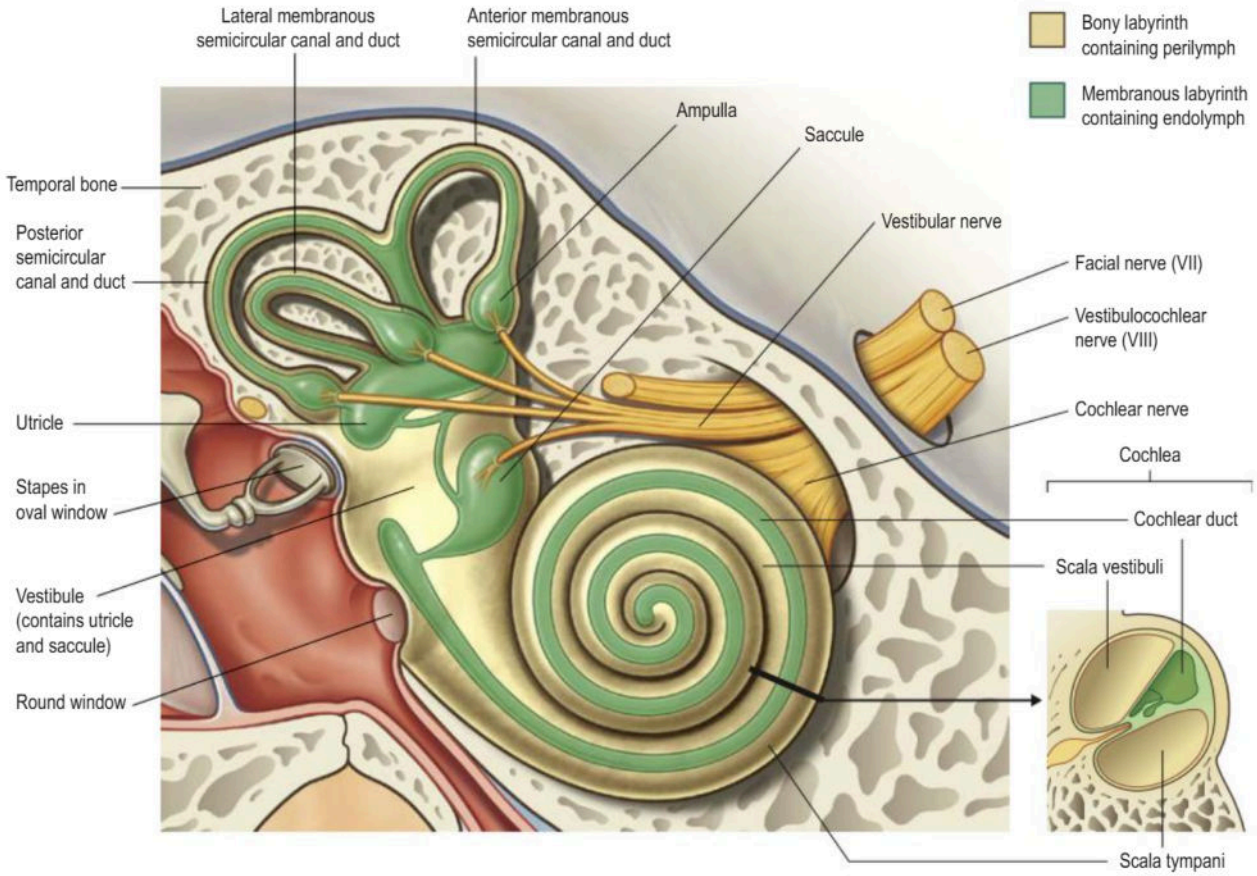

Figure 8.4 The inner ear. The membranous labyrinth within the bony labyrinth.

Membranous labyrinth

This is filled with endolymph.

Vestibule

This is the expanded region nearest the middle ear. The oval and round windows are located in its lateral wall. It contains two membranous sacs, the utricle and the saccule, which are important in balance (p. 218).

Semicircular canals

These are three tubes arranged so that one is situated in each of the three planes of space. They are continuous with the vestibule and are important in balance (p. 218).

Cochlea

This resembles a snail's shell in appearance. It has a broad base where it is continuous with the vestibule and a narrow apex, and it spirals round a central bony column.

A cross-section of the cochlea (Fig. 8.5) reveals its three compartments:

- the scala vestibuli
- the scala media, or cochlear duct
- the scala tympani.

Two of these compartments contain perilymph: the scala vestibuli, which originates at the oval window, and the scala tympani, which ends at the round window. These two compartments are continuous with each other and Figure 8.6A shows the relationship between them. The cochlear duct, which is an extension of the membranous labyrinth, lies between the scala vestibuli and the scala tympani, is triangular in cross-section and contains the organs of hearing. On the basilar membrane, the base of the triangle, are supporting cells and specialised cochlear hair cells containing auditory receptors. These cells form the spiral organ (of Corti), the sensory organ that responds to vibration by initiating nerve impulses which are then perceived as hearing within the brain. The auditory receptors are dendrites of afferent (sensory) nerves that combine, forming the cochlear (auditory) part of the vestibulocochlear (8th cranial) nerve, which passes through a foramen in the temporal bone to the hearing area in the temporal lobe of the cerebrum (see Fig. 7.20).

Physiology of hearing

Sound is carried as pressure (sound) waves in the air, which travel at about 340 metres per second. The shape of the auricle funnels and concentrates sound waves and directs them along the auditory canal, causing the tympanic membrane to vibrate.

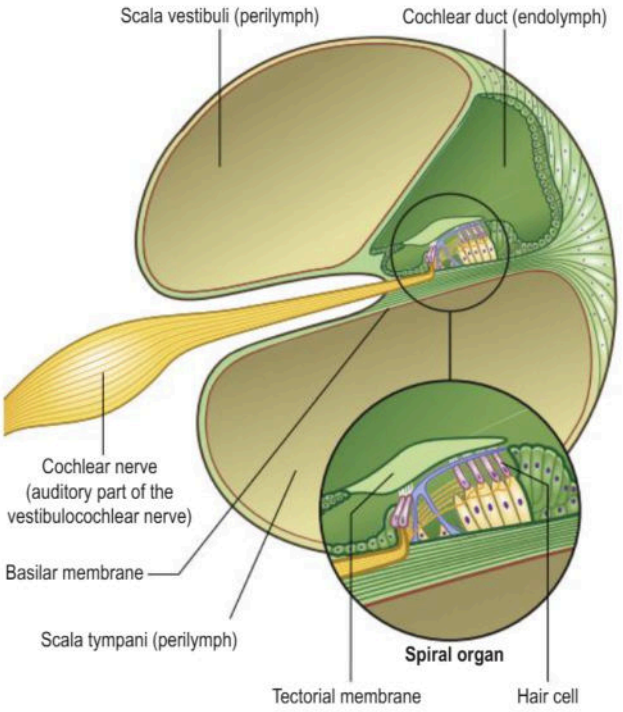

Figure 8.5 A cross-section of the cochlea showing the spiral organ (of Corti).

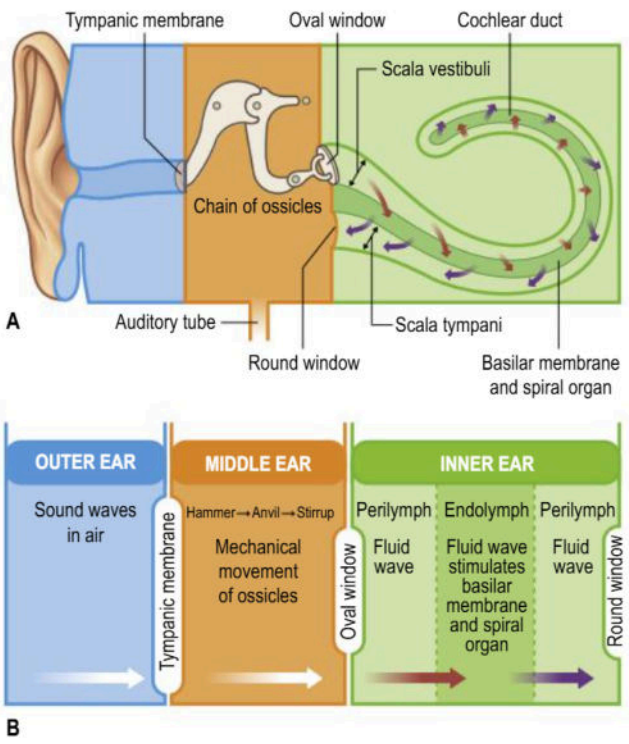

Figure 8.6 Passage of sound waves. (A) The ear with cochlea uncoiled. (B) Summary of transmission.

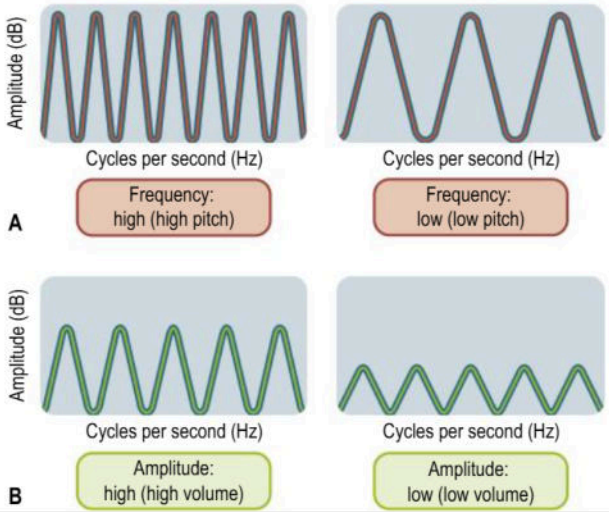

Figure 8.7 Behaviour of sound waves. (A) Difference in frequency but of the same amplitude. (B) Difference in amplitude but of the same frequency.

Tympanic membrane vibrations are transmitted and amplified through the middle ear by movement of the ossicles (Fig. 8.6).

At their medial end, the footplate of the stapes rocks to and fro in the oval window, setting up fluid waves in the perilymph of the scala vestibuli in the inner ear. Some of the force of these waves is transmitted along the length of the scala vestibuli and scala tympani, but most of the pressure is transmitted into the cochlear duct (Fig. 8.5). This causes a corresponding wave motion in the endolymph, resulting in vibration of the basilar membrane and stimulation of the auditory receptors in the hair cells of the spiral organ. The nerve impulses generated there are transmitted to the brain in the cochlear (auditory) branch of the vestibulocochlear nerve. The fluid wave is finally expended into the middle ear by vibration of the membrane of the round window.

The vestibulocochlear nerve transmits the impulses to the auditory nuclei in the medulla, where they synapse before they are conducted to the auditory area in the temporal lobe of the cerebrum (see Fig. 7.20). Because some fibres cross over in the medulla and others do not, the left and right auditory areas of the cerebrum receive impulses from both ears.

Sound waves have the properties of pitch and volume (Fig. 8.7). Pitch is determined by the frequency of the sound waves and is measured in hertz (Hz). Sounds of different frequencies stimulate the basilar membrane (see Fig. 8.6A) at different places along its length, allowing discrimination of pitch. The basilar membrane near the oval window is sensitive to high-pitched sounds, whereas the region towards the tip of the cochlea is responsive to lower-pitched sounds.

The volume depends on the magnitude of the sound waves and is measured in decibels (dB). The greater the amplitude of the wave created in the endolymph, the greater the stimulation of the auditory receptors in the hair cells in the spiral organ, and the louder the sound. Long-term exposure to excessive noise causes hearing impairment because it damages the sensitive hair cells of the spiral organ.

SPOT CHECK

1. Outline the features and functions of the external acoustic meatus.
2. Describe the role of the ossicles in hearing.

Balance and the ear

Learning outcome

After studying this section, you should be able to:

- describe the physiology of balance.

As well as its role in hearing, the ear is also the sense organ for balance, or equilibrium.

The semicircular canals and vestibule

The semicircular canals (see Fig. 8.4) have no auditory function, although they are associated with the cochlea. Instead, they provide information about the position of the head in space, contributing to maintenance of posture and balance.

There are three semicircular canals, one lying in each of the three planes of space. They are situated above, beside and behind the vestibule of the inner ear and open into it.

The semicircular canals, like the cochlea, are composed of an outer bony wall and inner membranous tubes or ducts. The membranous ducts contain endolymph and are separated from the bony wall by perilymph.

The utricle is a membranous sac that is part of the vestibule, and the three membranous ducts open into it at their dilated ends, the ampullae. The saccule is a part of the vestibule and communicates with the utricle and the cochlea.

In the walls of the utricle, saccule and ampullae are fine, specialised epithelial cells with minute projections, called hair cells. Among the hair cells there are receptors on sensory nerve endings, which combine, forming the vestibular branch of the vestibulocochlear nerve.

Physiology of balance

The semicircular canals and the vestibule (utricle and saccule) are concerned with balance, or equilibrium. The arrangement of the three semicircular canals, one in each plane, allows perception not only of the position of the head in space but also of the direction and rate of any movement. Any change of position of the head causes movement in the endolymph bathing the hair cells, which distorts them and stimulates the sensory receptors in the utricle, saccule and ampullae. The resultant nerve impulses are transmitted by the vestibular nerve, which joins the cochlear nerve to form the vestibulocochlear nerve. The vestibular branch passes first to the vestibular nucleus, then to the cerebellum.

The cerebellum also receives nerve impulses from the eyes and proprioceptors (sensory receptors) in the skeletal muscles and joints. The cerebellum coordinates incoming impulses from the vestibular nerve, the eyes and proprioceptors. Thereafter, impulses are transmitted to the cerebrum and skeletal muscles, enabling perception of body position and any adjustments needed to maintain posture and balance. This maintains upright posture and fixing of the eyes on the same point, independently of head movements.

SPOT CHECK

3. Outline the roles of the semicircular canals and vestibule in maintaining balance.

Sight and the eye

Learning outcomes

After studying this section, you should be able to:

- describe the gross structure of the eye
- describe the route taken by nerve impulses from the retina to the cerebrum
- explain how light entering the eye is focused on the retina
- state the functions of the extraocular eye muscles
- explain the functions of the accessory organs of the eye.

The eye is the organ of sight. It sits in the orbital cavity, a bony socket built into the bones of the face. The space between the eye and the orbital cavity is filled with adipose tissue. This together with the bony orbital cavity protects the eye from injury.

Structurally, the two eyes are separate but, unlike the ears, some of their activities are coordinated so that they normally function as a pair. It is possible to see with only one eye (monocular vision) but three-dimensional vision is impaired when only one eye is used, especially in relation to the judgement of speed and distance.

Structure

The eye is almost spherical in shape, about 2.5 cm in diameter and is supplied by the optic nerve (2nd cranial nerve).

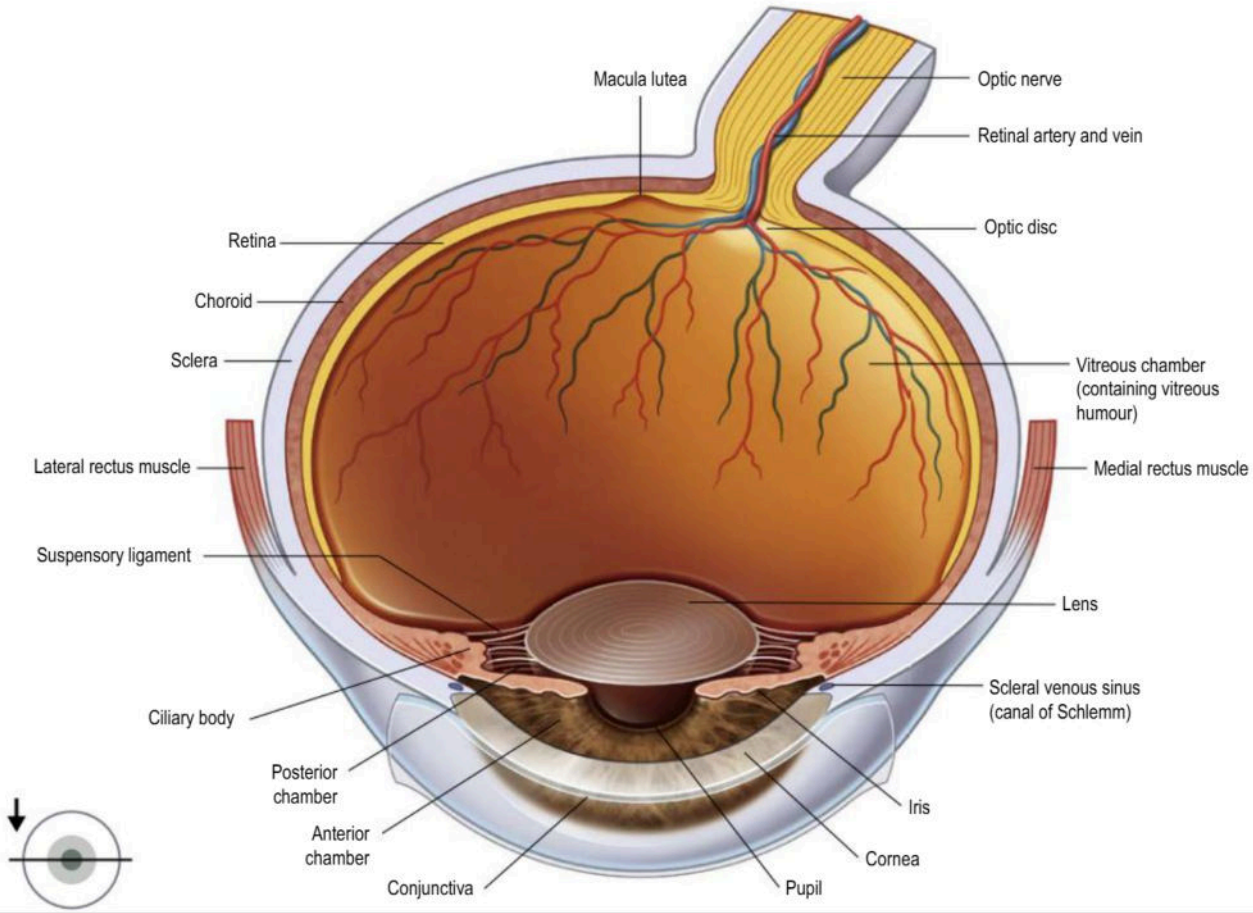

Figure 8.8 Transverse section of the right eye.

Chambers of the eye

Internally, the eye is divided into three chambers by the iris and the lens: the vitreous, anterior and posterior chambers (Fig. 8.8). The vitreous chamber is the largest chamber, and lies behind the lens, filling the eyeball. It contains vitreous humour (vitreous body), a soft, colourless, transparent, jelly-like substance composed of 99% water, mineral salts and mucoprotein and maintains sufficient pressure inside the eyeball to support the internal structures and prevent it from collapsing.

The posterior chamber lies between the lens and the iris, and the anterior chamber between the iris and the cornea (Figs 8.8 and 8.9). These two chambers are filled with a clear, watery fluid called aqueous humour.

Walls of the eye

These are made from three layers of tissue (Fig. 8.8):

- the outer fibrous layer: sclera and cornea
- the middle vascular layer or uveal tract: the choroid, ciliary body and iris
- the inner nervous tissue layer: the retina.

Sclera and cornea

The sclera, or white of the eye, forms the outermost layer of the posterior and lateral aspects of the eyeball and is continuous anteriorly with the cornea. It is a firm fibrous membrane that maintains the shape of the eye and gives attachment to the extrinsic muscles of the eye (see Table 8.1, p. 227).

Anteriorly the sclera continues as a clear transparent epithelial membrane, the cornea. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and, together with the lens, is involved in refracting (bending) light rays to focus them on the retina (Fig. 8.9). Neither structure has a blood supply; the aqueous humour supplies them with nutrients and removes wastes.

Choroid

The choroid (Figs 8.8 and 8.10) lines the posterior five-sixths of the inner surface of the sclera. It is rich in blood vessels and is deep chocolate brown in colour. Light enters the eye through the pupil, stimulates the sensory receptors in the retina (see below) and is then absorbed by the choroid.

Ciliary body

The ciliary body is the anterior continuation of the choroid, consisting of ciliary muscle (circular smooth muscle fibres) and secretory epithelial cells. The lens is attached to the ciliary body by radiating suspensory ligaments, like the spokes of a wheel (Fig. 8.10). Contraction and relaxation of the ciliary muscle fibres, which are attached to these ligaments, control the size and thickness of the lens.

The ciliary body is supplied by parasympathetic branches of the oculomotor nerve (3rd cranial nerve). Stimulation causes contraction of the ciliary muscle and accommodation of the eye for near vision (p. 223).

Aqueous humour and intraocular pressure

The epithelial cells secrete aqueous humour into the posterior chamber; it then circulates through the anterior chamber nourishing its contents, and drains into the venous system via the scleral venous sinus (canal of Schlemm, Fig. 8.8). This tiny sinus lies in the angle between the iris and cornea. Normally the rate of secretion of aqueous humour matches the rate of drainage, maintaining intraocular pressure between 1.3 and 2.6 kPa (10 and 20 mmHg). Rising intraocular pressure causes glaucoma (p. 234).

Iris

The iris is the visible coloured ring at the front of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. With the lens, it divides the anterior chamber of the eye into the anterior and posterior chambers (Fig. 8.8).

The iris is composed of pigment cells and two layers of smooth muscle fibres. In the centre is an aperture called the pupil. The iris is supplied by both divisions of the autonomic nervous system; parasympathetic stimulation constricts the pupil by contracting the circular fibres and sympathetic stimulation dilates it by contracting the radial (radiating) fibres (see Figs 8.19, 7.45 and 7.46).

The colour of the iris is genetically determined and depends on the number of pigment cells present. Albinos have no pigment cells and people with blue eyes have fewer than those with brown eyes.

Lens

The lens (Figs 8.9 and 8.10) is a highly elastic circular biconvex body, lying immediately behind the pupil. It consists of fibres enclosed within a capsule and is suspended from the ciliary body by the suspensory ligament. Its thickness is controlled

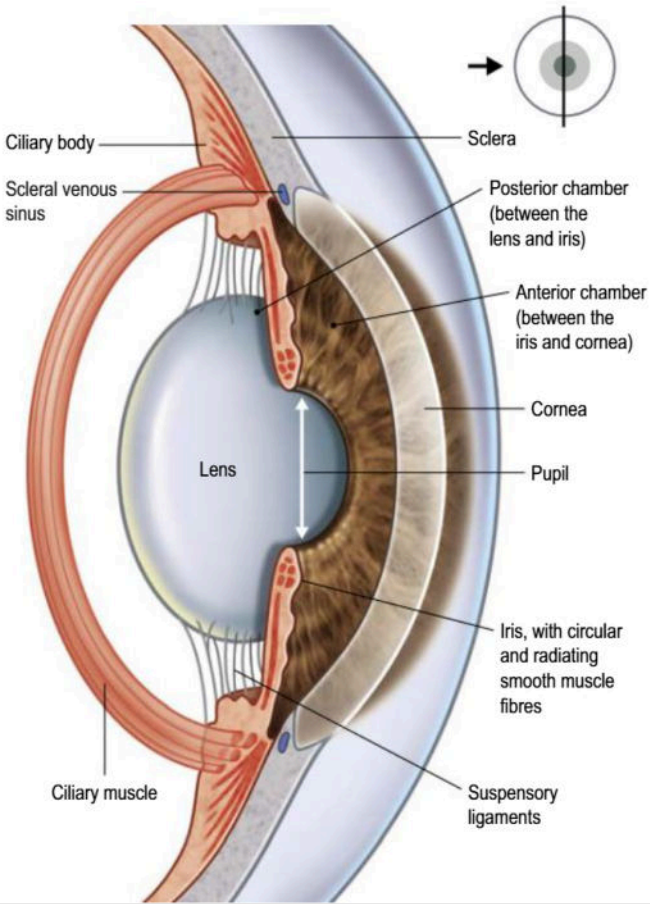

Figure 8.9 The choroid, ciliary body and iris. Viewed from the front.

by the ciliary muscle through the suspensory ligament. The lens bends (refracts) light rays reflected into the eye from objects in the visual field in order to focus them on the retina.

When the ciliary muscle contracts, it releases its pull on the lens, increasing its thickness. The nearer the object being viewed, the thicker the lens becomes to allow focusing (see Fig. 8.18).

Retina

The retina is the inner lining of the eye (Fig. 8.8). It is a delicate structure composed of several layers of nerve cell bodies and their axons, lying on a pigmented layer of epithelial cells. The light-sensitive layer consists of sensory receptor cells, called rods and cones, which contain photosensitive pigments that convert light rays into nerve impulses (Fig. 8.11).

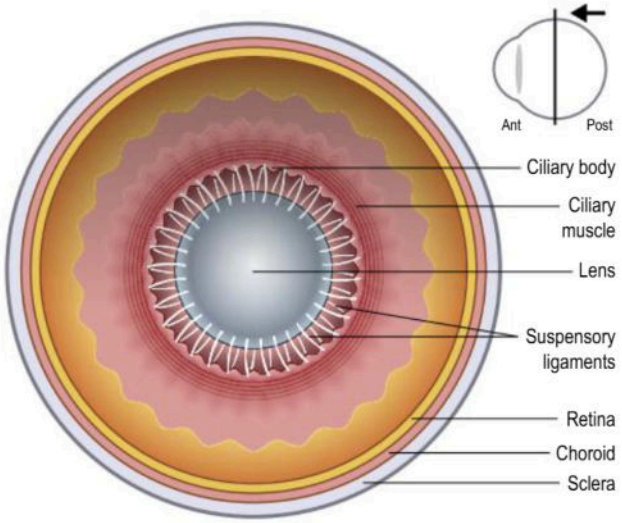

Figure 8.10 The lens and suspensory ligaments viewed from the front. The iris has been removed.

The retina lines about three-quarters of the eyeball and is thickest at the back. It thins out anteriorly ending just behind the ciliary body. Near the centre of the posterior retina is the macula lutea, or yellow spot (Figs 8.11A and 8.12). In the centre of the yellow spot is a little depression called the fovea centralis, consisting only of cones. Towards the anterior part of the retina there are fewer cones than rods.

About 0.5 cm to the nasal side of the macula lutea all the retinal nerve fibres converge to form the optic nerve. The area of retina where the optic nerve leaves the eye is the optic disc or blind spot. It has no rods and cones (light-sensitive cells).

Blood supply to the eye

Arterial supply is from the ciliary arteries and the central retinal artery. These are branches of the ophthalmic artery, a branch of the internal carotid artery.

Venous drainage is by several veins, including the central retinal vein, which eventually empty into a deep venous sinus.

The central retinal artery and vein are encased within the optic nerve, which enters the eye at the optic disc (Fig. 8.8).

Optic nerves (second cranial nerves)

The fibres of the optic nerve (Fig. 8.13) originate in the retina and converge to form the optic nerve about 0.5 cm to the nasal side of the macula lutea at the optic disc. The nerve pierces the choroid and sclera before passing backwards and medially through the orbital cavity. It then passes through the optic foramen of the sphenoid bone, backwards and medially to meet its counterpart from the other eye at the optic chiasma.

Optic chiasma

This is situated immediately in front of and above the pituitary gland, which lies in the hypophyseal fossa of the sphenoid bone (see Fig. 9.2). In the optic chiasma the nerve fibres of the optic nerve from the nasal side of each retina

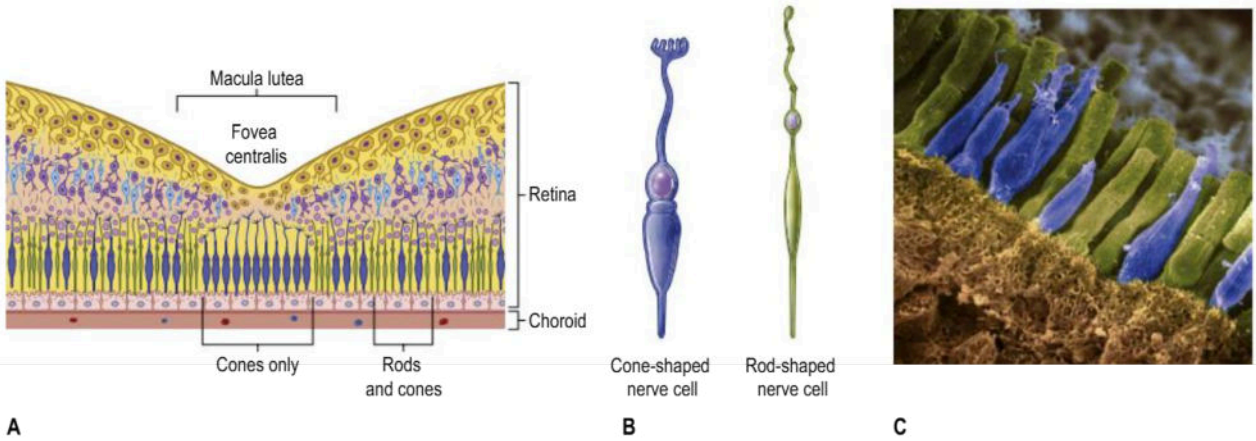

Figure 8.11 The retina. (A) Magnified section. (B) Light-sensitive nerve cells: rods and cones. (C) Coloured scanning electron micrograph of rods *(green)* and cones *(blue)*. (C, Omikron/Science Photo Library. Reproduced with permission.)

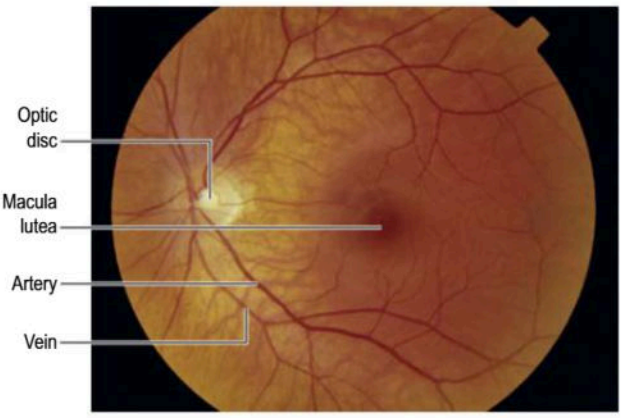

Figure 8.12 The retina. Viewed through the pupil with an ophthalmoscope. (Paul Barker/Science Photo Library. Reproduced with permission.)

cross over to the opposite side. The fibres from the temporal side do not cross but continue backwards on the same side. This crossing over provides both cerebral hemispheres with sensory input from each eye.

Optic tracts

These are the pathways of the optic nerves posterior to the optic chiasma (Fig. 8.13). Each tract consists of the nasal fibres from the retina of one eye and the temporal fibres from the retina of the other. The optic tracts pass backwards to synapse with nerve cells of the lateral geniculate bodies of the thalamus. From there the nerve fibres proceed backwards and medially as the optic radiations, to terminate in the visual area in the occipital lobes of the cerebral cortex (see Fig. 7.20). Other neurones originating in the lateral geniculate bodies transmit impulses from the eyes to the cerebellum. There, together with impulses from the semicircular canals of the inner ears and from the proprioceptors in skeletal muscles and joints, they are integrated enabling the maintenance of posture and balance.

Physiology of sight

Light waves travel at 300,000,000 metres per second (m/s), or about 186,000 miles per second. This is much greater than the speed of sound in air (about 340 m/s) and explains why we see lightning before hearing thunder.

Light is reflected into the eyes by objects within the field of vision. White light is a combination of all the colours of the visual spectrum (rainbow), i.e. red, orange, yellow, green, blue, indigo and violet. This is demonstrated by passing white light through a glass prism that refracts (bends) the rays of the different colours to a greater or lesser extent, depending on their wavelengths, and separates them (Fig. 8.14). Red light has the longest wavelength and violet the shortest.

This range of colour is the spectrum of visible light. In a rainbow, white light from the sun is broken up by raindrops, which act as prisms and reflectors.

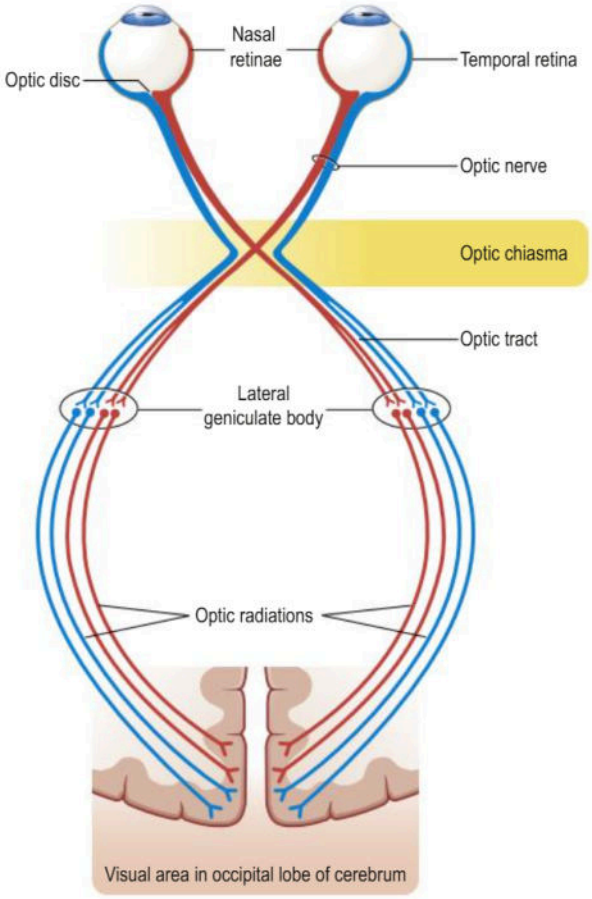

Figure 8.13 The optic nerves and their pathways.

The electromagnetic spectrum

The electromagnetic spectrum includes electromagnetic radiation (rays) of varying wavelengths and frequencies (Fig. 8.15), but only a small part is visible to the human eye. Beyond the red end of the visible spectrum are longer waves: infrared waves (heat), microwaves and radio waves. Beyond the violet end are shorter ultraviolet (UV) rays, X-rays and gamma rays. UV light is not normally visible because it is absorbed by a yellow pigment in the lens.

A specific colour is perceived when only one part of the visible spectrum is reflected by the object and all other wavelengths are absorbed, e.g. an object appears red when it reflects only red light. Objects appear white when they reflect all wavelengths of light into the eye, and black when they absorb all the light hitting them and so reflect nothing.

In sharp, clear vision, light reflected from objects in the visual field is focused onto the retina of each eye. The processes involved in producing a clear visual image are:

- refraction (bending) of light rays
- adjustment of pupil size
- accommodation (adjustment of the lens) for near vision. This is the ability of the eye to switch focus enabling clear vision of objects at different distances.

Each of these processes is explained below; effective vision is dependent on all three operating in a coordinated manner.

Refraction of light rays

When light rays pass from a medium of one density to another, they are refracted. Figure 8.14 shows how a glass prism separates a beam of white light into its constituent colours, because it refracts each wavelength to a different degree. A biconvex lens refracts and focuses light rays (Fig. 8.16A) and Figure 8.16B shows how the biconvex human lens focuses light on the retina.

Before reaching the retina, light rays pass successively through the conjunctiva, cornea, aqueous fluid, lens and vitreous chamber. These structures are all denser than air and except for the lens, have the same refractory power, similar to that of water. This means that only the lens can be adjusted to assist in focusing.

Light rays entering the eye need to be bent to focus them on the retina. Light rays reflected from an object are refracted by the lens when they enter the eye, as shown in Figure 8.16, although the image on the retina is actually upside down (Fig. 8.17). The brain adapts to this early in life so that objects are perceived the right way up.

Abnormal refraction within the eye is corrected using biconvex or biconcave lenses (see Fig. 8.30).

Refractory power of the lens

The lens is a biconvex elastic transparent body suspended behind the iris from the ciliary body by the suspensory ligaments (see Figs 8.9 and 8.10) and is the only structure in the eye able to change its refractive power. This is determined by the amount of pull the ciliary muscle places on the suspensory ligaments.

Distant objects

Light from distant objects needs least refraction and, as an object comes closer, the amount of refraction needed increases. To focus light rays from distant objects more than about 6 m away on the retina, the circular ciliary muscle relaxes, increasing its pull on the suspensory ligaments. This makes the lens thinner and focuses light rays from distant objects on the retina (Fig. 8.18A).

Near objects

To focus light rays from near objects on the retina, the refractory power of the lens must be increased. To do this, the ciliary muscle contracts, reducing the diameter of the ring formed by the ciliary muscle and reducing the pull on the suspensory ligaments. This allows the lens to bulge. This lessens the pull on the suspensory ligaments and allows the lens to bulge, increasing its convexity and focusing light rays on the retina (Fig. 8.18B).

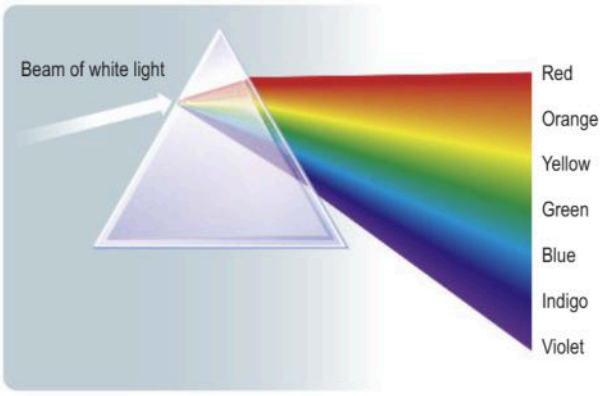

Figure 8.14 Refraction. White light is broken into the colours of the visible spectrum when it passes through a glass prism.

Size of the pupils

Pupil size contributes to clear vision by controlling the amount of light entering the eye. In bright light the pupils are constricted and in dim light they are dilated (Fig. 8.19).

If the pupils were dilated in bright light, too much light would enter the eye and damage the sensitive retina. In dim light, if the pupils were constricted, insufficient light would enter the eye to activate the light-sensitive pigments in the rods and cones.

Pupil size is controlled by the smooth muscle in the iris, which consists of two layers of smooth muscle fibres, one circular and one radial. These fibres are controlled by the autonomic nervous system. Sympathetic stimulation contracts the radial fibres, dilating the pupil, while parasympathetic stimulation contracts the circular smooth muscle and constricts the pupil.

Accommodation for near vision

In order to focus on near objects, i.e. within about 6 metres, the eye must make the following adjustments:

- constriction of the pupils
- convergence
- increase the refractory power of the lens.

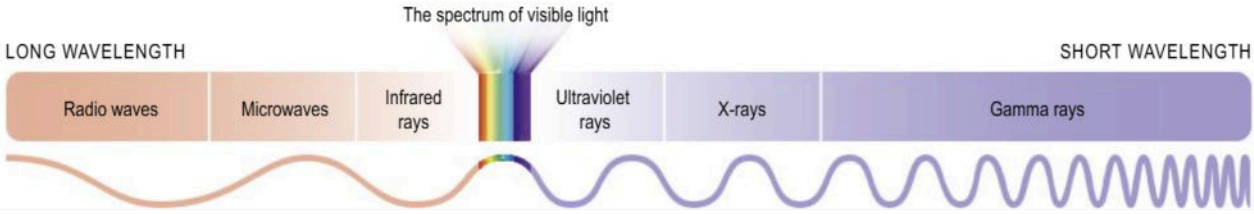

Figure 8.15 The electromagnetic spectrum.

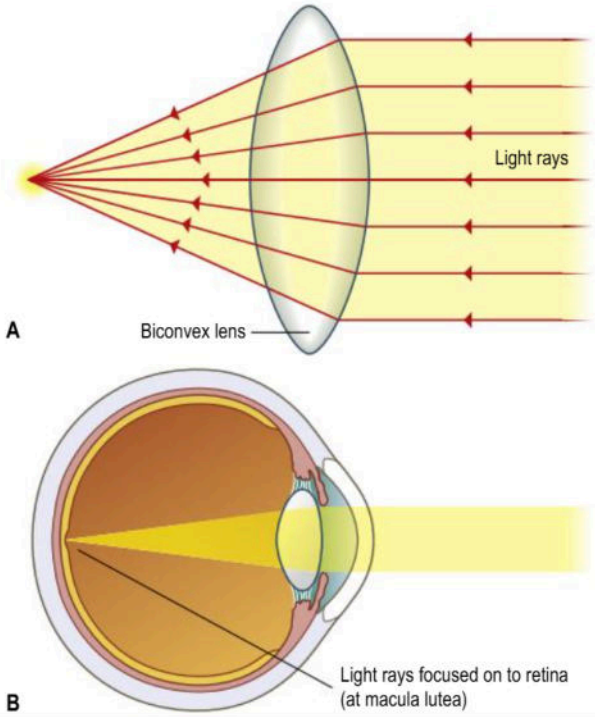

Figure 8.16 Refraction of light rays passing through a biconvex lens. (A) A glass lens. (B) The lens in the eye.

Constriction of the pupils

Pupil size is controlled by the iris (see above). Constriction assists accommodation by reducing the width of the beam of light entering the eye so that it passes through the central curved part of the lens (Fig. 8.18).

Convergence (movement of the eyeballs)

Light rays from nearby objects enter the two eyes at different angles and for clear vision they must stimulate corresponding areas of the two retinae. Extrinsic muscles move the eyes and to obtain a clear image they also rotate them so that they converge on the object viewed. This coordinated muscle activity is under autonomic control. When there is voluntary movement of the eyes, both eyes move and convergence is maintained. The nearer an object is to the eyes, the greater the eye rotation needed to achieve convergence; for example, focusing near the tip of one's nose gives the appearance of being 'cross-eyed'. If convergence is not complete, the eyes are focused on different objects or on different points of the same object. There are then two images sent to the brain and this can lead to double vision, or diplopia. If convergence is not possible, the brain tends to ignore the impulses received from the divergent eye (see squint, p. 234).

Change in the refractory power of the lens

The amount of adjustment depends on the distance of an object from the eyes, i.e. the lens is thicker for near vision and at its thinnest when focusing on objects more than 6 metres away (see above and Fig. 8.18). Looking at near objects tires the eyes more quickly, due to continuous use of the ciliary muscle.

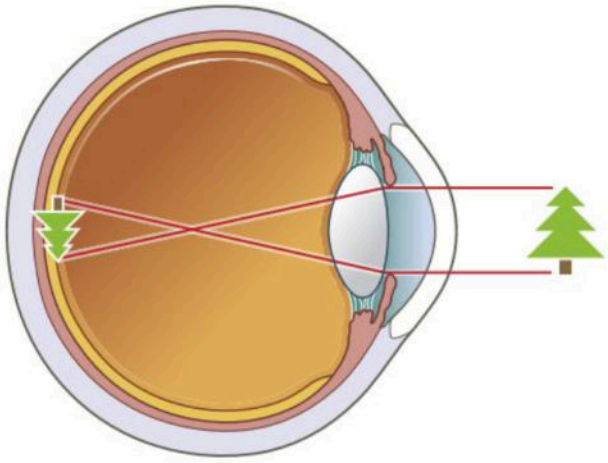

Figure 8.17 Section of the eye showing the focusing of light rays on the retina. Representation of light rays reaching the retina showing inverted image.

Accommodation for distant vision

When looking at objects further than about 6 m, the refractory power of the lens is decreased (Fig. 8.18A), the pupils dilate and convergence is no longer required.

Functions of the retina

The retina is the light-sensitive (photosensitive) part of the eye. The light-sensitive nerve cells are the rods and cones and their distribution in the retina is shown in Figure 8.11A. Light rays cause chemical changes in light-sensitive pigments in these cells, which generates nerve impulses, which are conducted to the occipital lobes of the cerebrum via the optic nerves (see Fig. 8.13).

Cones

The cones are sensitive to light and colour; bright light is required to activate them and give sharp, clear colour vision. Cones are concentrated at the macula lutea, the spot on the retina where light rays fall from an object in the direct field of vision. This means that whatever is being directly observed is seen in detail, brightly coloured and in sharp focus. Cone numbers fall sharply and rod numbers rise on the retina peripheral to the macula lutea.

Rods

The rods (see Fig. 8.11) are much more light-sensitive than the cones, so they are used when light levels are low. Stimulation of rods leads to monochromic (black and white) vision. Rods outnumber cones in the retina by about 16:1 and are much more numerous towards the periphery.

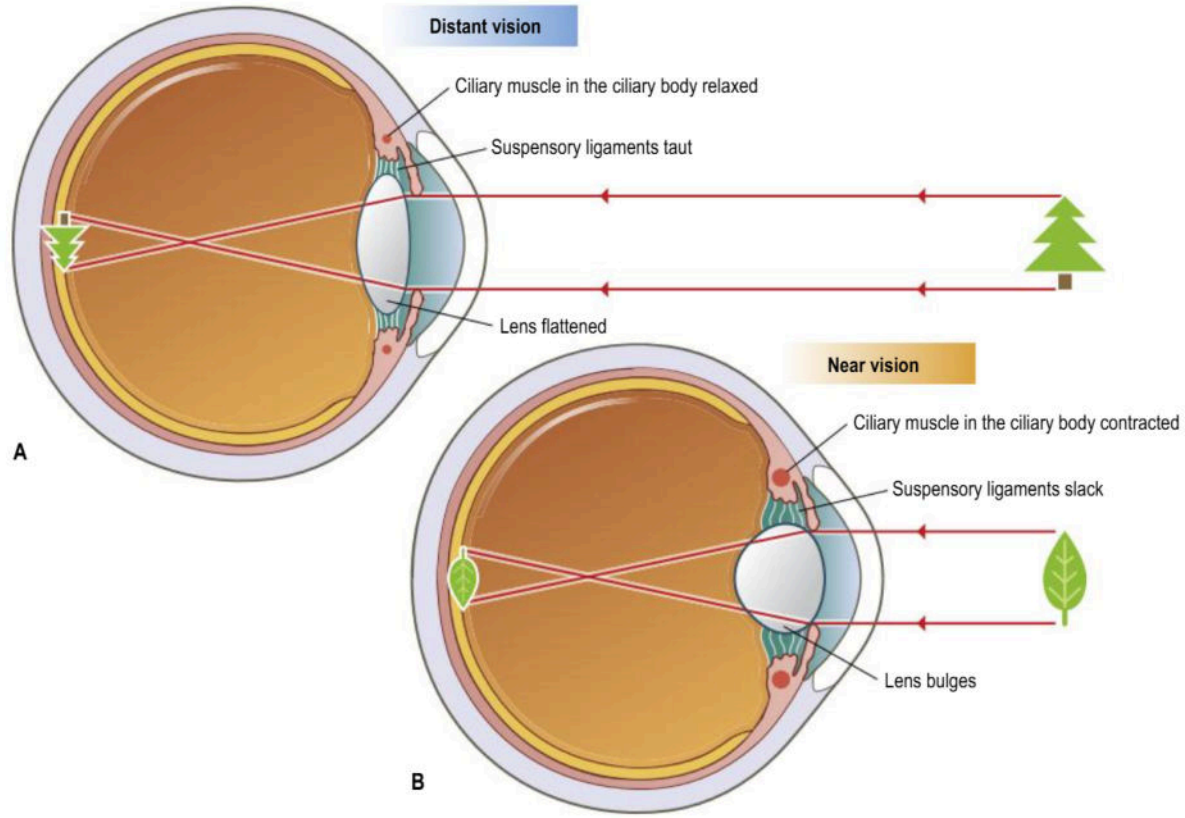

Figure 8.18 Accommodation: action of the ciliary muscle on the shape of the lens. (A) Distant vision. (B) Near vision.

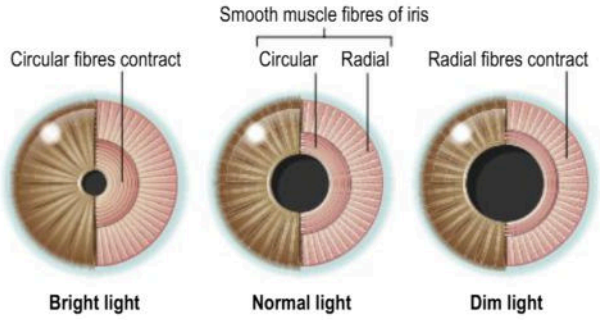

Figure 8.19 Changes in pupil size in response to intensity of light.

Rhodopsins

This is a family of light-sensitive pigments, found in both rods and cones, which are broken down (bleached) when they absorb light hitting the cell. Degradation of the rhodopsin molecule generates an action potential. Following bleaching, the rhodopsin molecule must be reassembled before it is functional again. There is only one type of rhodopsin in rods, absorbing at a single wavelength, which is why rods give monochromatic vision. Cones, however, have one of three different rhodopsins, absorbing at three different wavelengths and giving rise to red, blue and green cones. Colour perception depends on the combination of red, blue and green cones stimulated. A good supply of vitamin A is needed for adequate rhodopsin production.

Colour blindness

This is a common condition that affects more men than women. Although affected individuals see colours, they cannot always differentiate between them, because the rhodopsin in one or more cone types is abnormal. There are different forms but the most common is red–green colour blindness, which is transmitted by a sex-linked recessive gene (see Fig. 17.14); greens, oranges, pale reds and browns are all perceived as the same colour and can only be distinguished by their intensity.

Dark adaptation

When exposed to bright light, the rhodopsin within the sensitive rods is completely degraded. This does not affect vision in good light, when there is enough light to activate the cones. However, moving into a darkened area where the light intensity is insufficient to stimulate the cones causes temporary visual impairment while the rhodopsin is being regenerated within the rods: so called 'dark adaptation'. When regeneration of rhodopsin has occurred, normal sight returns.

Sudden exposure to bright light, e.g. a camera flash, causes immediate bleaching of rhodopsin in rods and cones, and temporary blindness until the rhodopsin is regenerated.

It is easier to see a dim star in the sky at night if the head is turned slightly away from it because light of low intensity is then focused on an area of the retina where there is a greater concentration of rods. If a dim star is looked at directly, the light intensity is not sufficient to stimulate the less sensitive cones in the area of the macula lutea. In dim evening light, colours cannot be distinguished because the light intensity is insufficient to stimulate colour-sensitive pigments in cones.

Binocular vision

Binocular or stereoscopic vision enables three-dimensional views, although each eye 'sees' a scene from a slightly different angle (Fig. 8.20). The visual fields overlap in the middle but the left eye sees more on the left than can be seen by the right eye and vice versa. The images from the two eyes are integrated in the cerebrum so that only one image is perceived.

Binocular vision provides a much more accurate assessment of one object relative to another, e.g. its distance, depth, height and width. People with monocular vision may find it difficult, for example, to judge the speed and distance of an approaching vehicle.

Extrinsic muscles of the eye

Six skeletal muscles move the eyeball. They are attached to the eyeball at one end and the wall of the orbital cavity at the other. There are four straight (rectus) muscles and two oblique muscles (Fig. 8.21).

Moving the eyes to look in a particular direction is under voluntary control but coordination of movement, needed for convergence (as part of accommodation for near or distant vision), is under autonomic (involuntary) control. Movements of the eyes made by these muscles are shown in Table 8.1.

Nerve supply to the muscles of the eye

Table 8.1 shows the nerves that supply the extrinsic muscles. The oculomotor nerves also supply the intrinsic eye muscles, i.e. those of the iris and ciliary body.

Accessory organs of the eye

The eye is a delicate organ, which is protected by several structures (Fig. 8.22):

- eyebrows
- eyelids and eyelashes
- lacrimal apparatus.

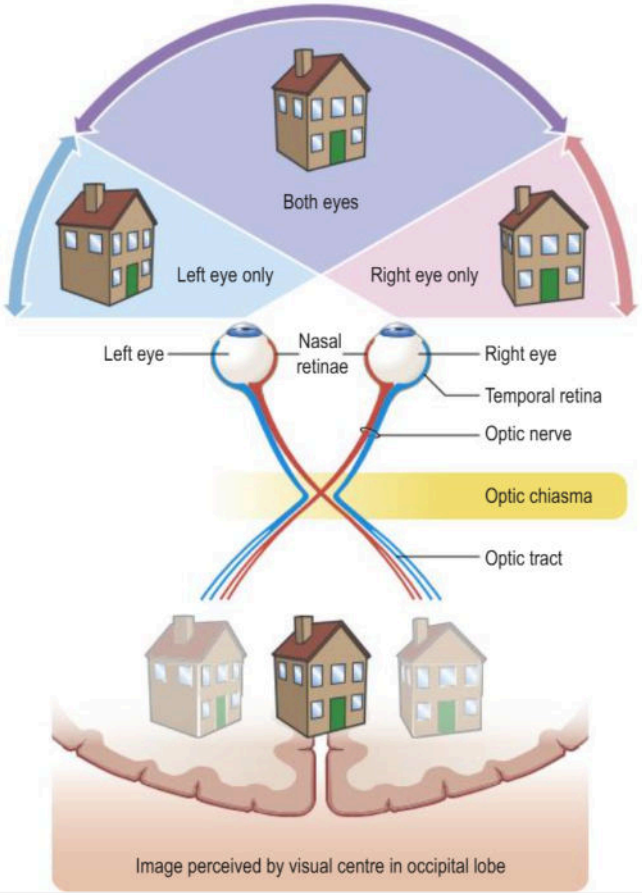

 Figure 8.20 Parts of the visual field. Monocular and binocular.

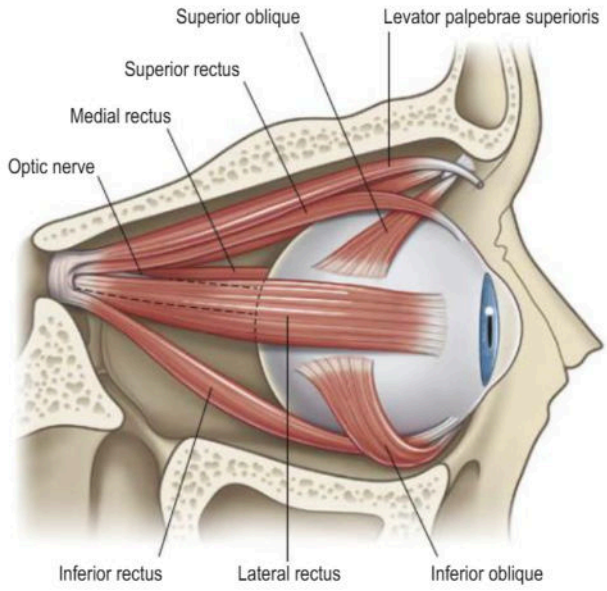

Figure 8.21 The extrinsic eye muscles.

Table 8.1 Extrinsic muscles of the eye: their actions and cranial nerve supply

Name	Action	Cranial nerve supply
Medial rectus	Rotates eyeball inwards	Oculomotor nerve (3rd cranial nerve)
Lateral rectus	Rotates eyeball outwards	Abducent nerve (6th cranial nerve)
Superior rectus	Rotates eyeball upwards	Oculomotor nerve (3rd cranial nerve)
Inferior rectus	Rotates eyeball downwards	Oculomotor nerve (3rd cranial nerve)
Superior oblique	Rotates eyeball downwards and outwards	Trochlear nerve (4th cranial nerve)
Inferior oblique	Rotates eyeball upwards and outwards	Oculomotor nerve (3rd cranial nerve)

Eyebrows

These are two arched ridges of the supraorbital margins of the frontal bone. Numerous hairs (eyebrows) project obliquely from the surface of the skin; they protect the eyeball from sweat, dust and other foreign bodies.

Eyelids (palpebrae)

The eyelids are two movable folds of tissue situated above and below the front of each eye. On their free edges are short, curved hairs, the eyelashes. The layers of tissue that form them are:

- a thin covering of skin
- a thin sheet of subcutaneous connective (loose areolar) tissue

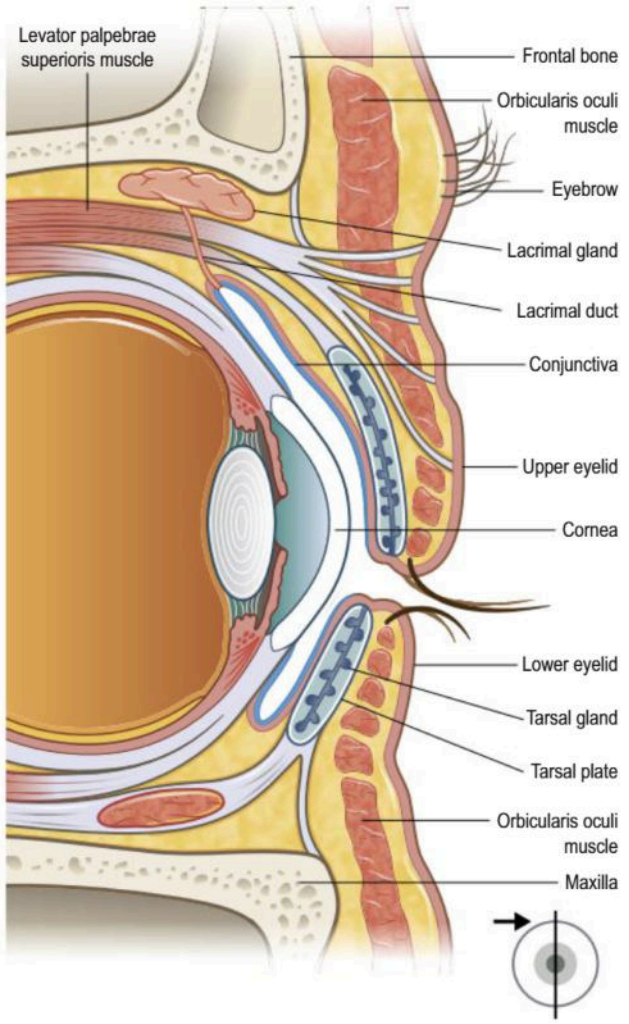

Figure 8.22 Section of the eye and its accessory structures.

- two muscles – the orbicularis oculi and levator palpebrae superioris
- a thin sheet of dense connective tissue – the tarsal plate, larger in the upper than the lower eyelid, which supports the other structures
- a membranous lining – the conjunctiva.

Conjunctiva

This is a fine transparent membrane that lines the eyelids and the front of the eyeball (Fig. 8.22). Where it lines the eyelids it consists of highly vascular columnar epithelium. Corneal conjunctiva consists of avascular stratified epithelium, i.e. epithelium without blood vessels. When the eyelids are closed the conjunctiva becomes a closed sac. It protects the delicate cornea and the front of the eye. When eyedrops are administered, they are placed in the lower conjunctival sac. The medial and lateral angles of the eye, where the upper and lower lids come together, are called the medial canthus and the lateral canthus, respectively.

Eyelid margins

Along the edges of the lids are numerous sebaceous glands, some with ducts opening into the hair follicles of the eyelashes and some on to the eyelid margins between the hairs. Tarsal glands are modified sebaceous glands embedded in the tarsal plates with ducts that open on to the inside of the free margins of the eyelids. They secrete an oily material, spread over the conjunctiva by blinking, which delays evaporation of tears.

Functions of the eyelids

The eyelids and eyelashes protect the eye from injury:

- Reflex closure of the lids occurs when the conjunctiva or eyelashes are touched, when an object comes close to the eye, if a bright light is shone into the eye (the pupillary reflex, see Fig. 8.19), or if anything comes into direct contact with the cornea itself (the corneal reflex).
- Blinking about every 3–7 seconds spreads tears and oily secretions over the cornea, preventing drying.

The eyelids close when the orbicularis oculi muscles contract, and open when the levator palpebrae muscles contract (see Fig. 16.64).

Lacrimal apparatus

The lacrimal apparatus (Fig. 8.23) consists of the structures that secrete tears and drain them from the front of the eyeball:

- 1 lacrimal gland and its ducts
- 2 lacrimal canaliculi
- 1 lacrimal sac
- 1 nasolacrimal duct.

The lacrimal glands are exocrine glands situated in recesses in the frontal bones on the lateral aspect of each eye, just behind the supraorbital margin. Each gland is approximately the size and shape of an almond and is composed of secretory epithelial cells. The glands secrete tears composed mainly of water, with small amounts of mineral salts, antibodies (immunoglobulins, Ch. 15) and lysozyme, a bactericidal enzyme.

The tears leave the lacrimal gland in several small ducts and spread over the front of the eye under the lids towards the medial canthus. They drain into the two lacrimal canaliculi, the opening of which is called the punctum. The two canaliculi lie one above the other, separated by a small red body, the caruncle. The tears then drain into the lacrimal sac, which is the upper expanded end of the nasolacrimal duct. This is a membranous canal approximately 2cm long, extending from the lower part of the lacrimal sac to the nasal cavity.

Normally, the rate of secretion of tears matches the rate of drainage. When a foreign body or other irritant enters the eye, and in emotional states, e.g. sorrow, laughing, secretion of tears is greatly increased and the conjunctival blood vessels dilate. When secretion is excessive, crying occurs as tears overflow directly from the eyes instead of draining into the nasal cavity.

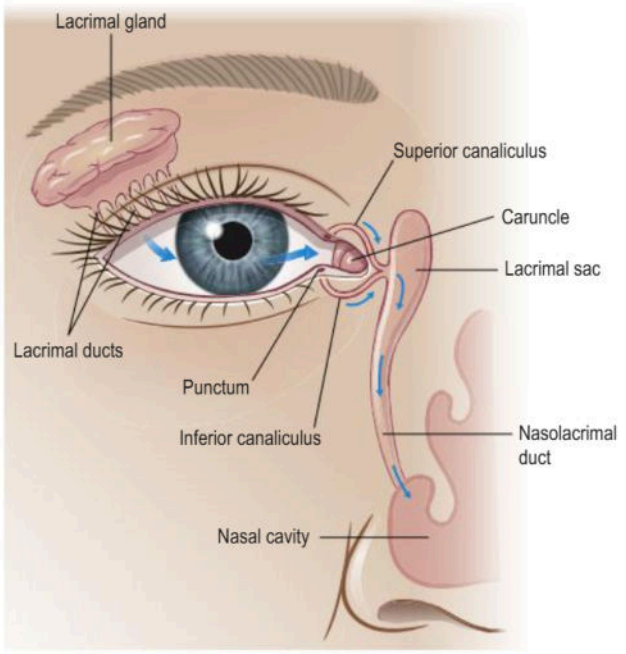

Figure 8.23 The lacrimal apparatus. Blue arrows indicate direction of the flow of tears.

Functions of the lacrimal apparatus

The fluid that fills the conjunctival sac is a mixture of tears and the oily secretion of tarsal glands, which is spread over the cornea by blinking. The functions of this fluid, the tear film, include:

- provision of oxygen and nutrients to the avascular corneal conjunctiva and drainage of its wastes
- washing away irritants, e.g. dust, grit
- preventing microbial infection by the bactericidal enzyme lysozyme
- delaying evaporation and prevention of friction or drying of the conjunctiva due to its oiliness.

SPOT CHECK

4. Name the adjustments made by the eye to focus on nearby objects.
5. Outline the functions of eyelids and eyelashes.

Sense of smell

Learning outcome

After studying this section, you should be able to:

- describe the physiology of smell.

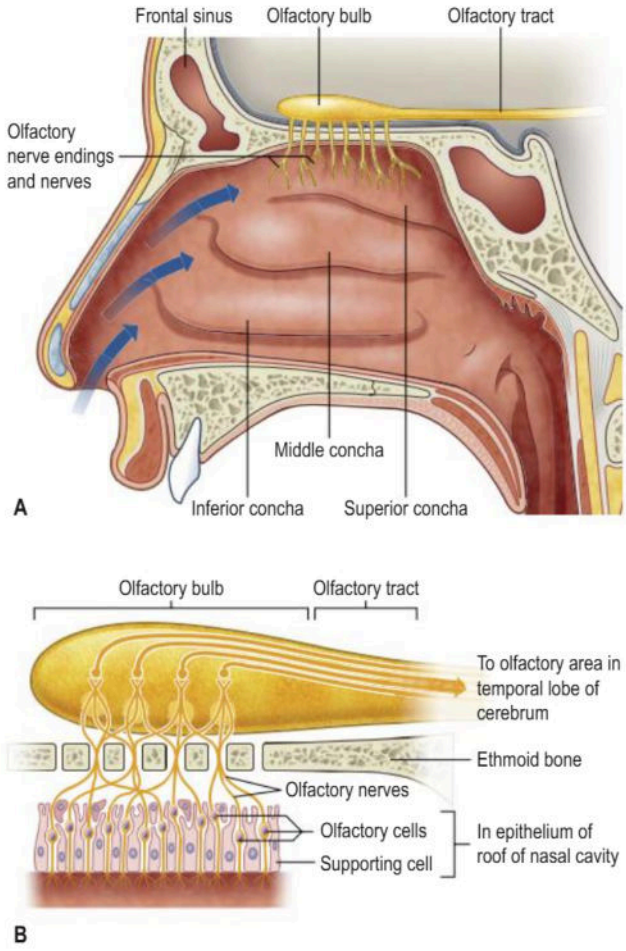

Figure 8.24 The sense of smell. (A) The olfactory structures. (B) An enlarged section of the olfactory apparatus in the nose and on the inferior surface of the cerebrum.

The sense of smell, or olfaction, originates in the nasal cavity. The human sense of smell is less acute than in other animals. Many animals secrete odorous chemicals called pheromones, which play an important part in chemical communication in, for example, territorial behaviour, mating and the bonding of mothers and their newborn. The role of pheromones in humans remains unclear.

Olfactory nerves (first cranial nerves)

These are the sensory nerves of smell (see Fig. 7.40). They originate as chemoreceptors, specialised olfactory nerve endings in the mucous membrane of the roof of the nasal cavity above the superior nasal conchae (Fig. 8.24). On each side of the nasal septum nerve fibres pass through the cribriform plate of the ethmoid bone to the olfactory bulb, where interconnections and synapses occur. From the bulb, bundles of nerve fibres form the olfactory tract, which passes backwards to the olfactory area in the temporal lobe of the cerebral cortex in each hemisphere, where the impulses are interpreted and odour perceived.

Physiology of smell

All odorous materials give off volatile molecules, which are carried into the nose with inhaled air, and even at very low concentrations, when dissolved in mucus, stimulate the olfactory chemoreceptors.

The air entering the nose is warmed and convection currents carry eddies of inspired air to the roof of the nasal cavity although most inspired air is drawn directly downwards through the nasal passageways. 'Sniffing' concentrates volatile molecules in the roof of the nose. This increases the number of olfactory receptors stimulated and thus perception of the smell. The sense of smell and the sense of taste are closely related; the sense of smell may affect the appetite. If the odours are pleasant the appetite may improve and vice versa. When accompanied by the sight of food, an appetising smell increases salivation and stimulates the digestive system (Ch. 12). The sense of smell may create powerful and long-lasting memories, especially for distinctive odours, e.g. hospital smells, or favourite or least-liked foods.

Inflammation of the nasal mucosa prevents odorous substances from reaching the olfactory area of the nose, causing loss of the sense of smell (anosmia). The usual cause is a cold.

Adaptation

When an individual is continuously exposed to a specific odour, perception of it decreases and stops within a few minutes; this loss of perception affects only that odour.

SPOT CHECK

6. Define the term olfaction.

Sense of taste

Learning outcome

After studying this section, you should be able to:

- describe the physiology of taste.

The sense of taste, or gustation, is closely linked to the sense of smell and, like smell, also involves stimulation of chemoreceptors by dissolved chemicals.

Taste buds contain chemoreceptors, sensory receptors, widely distributed in the epithelium of the papillae of the tongue. There are four types of papillae (Fig. 8.25A).

Circumvallate papillae are the largest, and are visible at the base of the tongue arranged in an inverted V shape. There are about 12 of this type and they contain multiple taste buds (Fig. 8.25B).

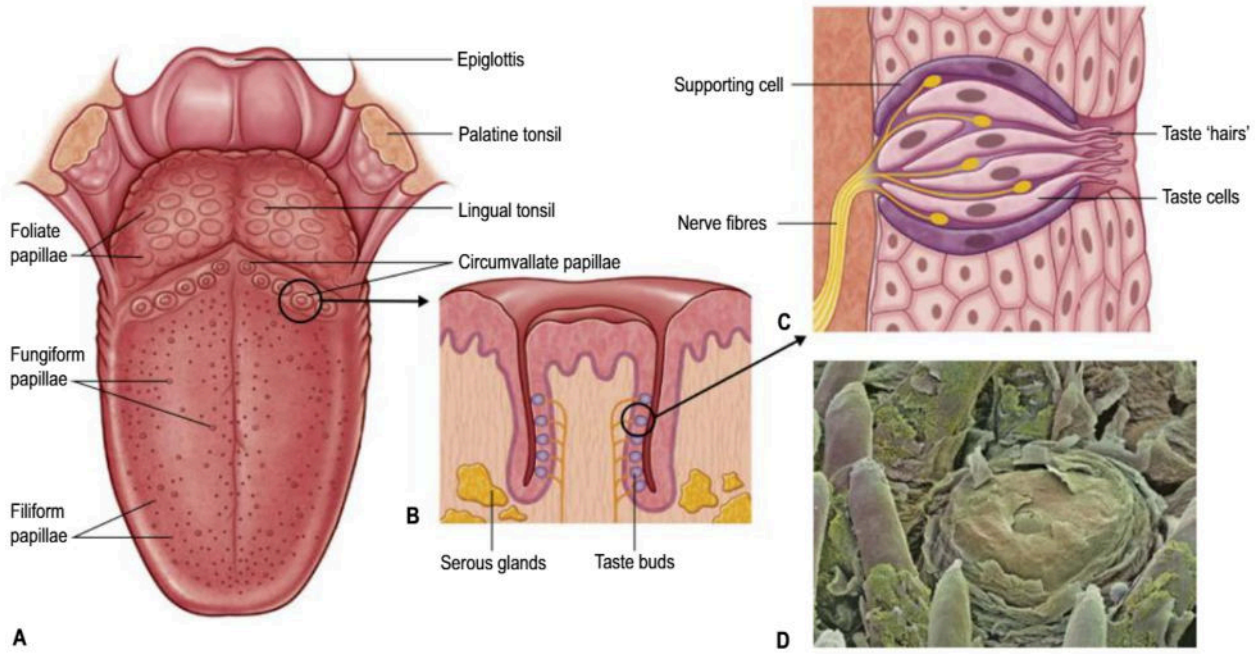

Figure 8.25 Structure of taste buds. (A) Diagram showing the papillae of the tongue. (B) A section of a papilla. (C) A taste bud, greatly magnified. (D) Coloured scanning electron micrograph of a taste bud (centre) on the tongue. (D, Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

Foliate papillae are found in two areas at each side of the tongue just behind the circumvallate papillae, and also contain several taste buds.

Fungiform papillae are located mainly around the tip and edges of the tongue and are more numerous than the circumvallate papillae.

Filiform papillae are the smallest and most numerous; they are situated on the anterior two-thirds of the tongue. These papillae do not contain taste buds, but they roughen the surface of the tongue and provide 'grip' as it pushes food around inside the mouth.

The taste cells within the taste buds have hair-like cilia on their free border, called taste hairs, projecting towards tiny pores in the epithelium (Fig. 8.25C). The taste hairs are highly sensitive and stimulated by tiny amounts of chemicals dissolved in saliva. Nerve impulses are generated and conducted along the glossopharyngeal, facial and vagus nerves (cranial nerves VII, IX and X) before synapsing in the medulla and thalamus. Their final destination is the taste area in the parietal lobe of the cerebral cortex, where taste is perceived (see Fig. 7.20).

Physiology of taste

Four fundamental sensations of taste have been described: sweet, sour, bitter and salt; however, others have also been suggested, including metallic and umami (a Japanese savoury taste). However, perception varies widely and many tastes cannot be easily classified. It is thought that all taste buds are stimulated by all tastes. Taste is impaired when the mouth is dry because substances can be tasted only when in solution.

The sense of taste is closely linked to the sense of smell. For example, when a person has a cold, it is common for food to taste bland and unappealing. In addition, taste triggers salivation and the secretion of gastric juice (Ch. 12). It also has a protective function, e.g. when foul-tasting food is eaten, reflex gagging or vomiting may be induced.

SPOT CHECK

7. Name the four fundamental tastes.

Effects of ageing on the special senses

Learning outcome

After studying this section, you should be able to:

- describe the impact of ageing on the special senses.

Changes in hearing and sight that occur as part of normal ageing are almost universal and often accompanied by diminished senses of taste and smell.

The number of olfactory receptors reduces around the age of 50, diminishing the sense of taste; older adults may complain of their food being bland while children can find the same food too spicy. In a similar way, older adults may not

smell (perceive) weak odours. The effect of changes associated with ageing on hearing and sight are considered here.

Hearing

The most common form of age-related hearing impairment is presbycusis.

Presbycusis

This form of hearing impairment accompanies the ageing process and is very common in older adults. Degenerative changes in the sensory cells of the spiral organ result in sensorineural hearing loss (p. 232). Perception of high-frequency sound diminishes first and later low-frequency sound may also be affected. Difficulty in discrimination develops, e.g. following a conversation, especially in the presence of background noise.

Sight

Presbyopia and cataracts are common consequences of normal ageing.

Presbyopia

Age-related changes in the lens lead to loss of accommodation as the lens loses its elasticity and becomes firmer. This prevents focusing of light on the retina, giving blurred vision. Nearly all older adults need this corrected and use glasses with convex lenses for near vision, e.g. reading (see Fig. 8.30).

Cataract

In cataract there is opacity of the lens (Fig. 8.26), present to some extent almost universally by the age of 70. Weak light rays cannot easily pass through a less transparent or cloudy lens and for this reason, many older adults need to use brighter light for reading and may also experience difficulty with night vision. It is believed to be the result of prolonged exposure to UV light, although X-rays and cigarette smoke are also implicated. There are other important causes of cataracts (p. 231).

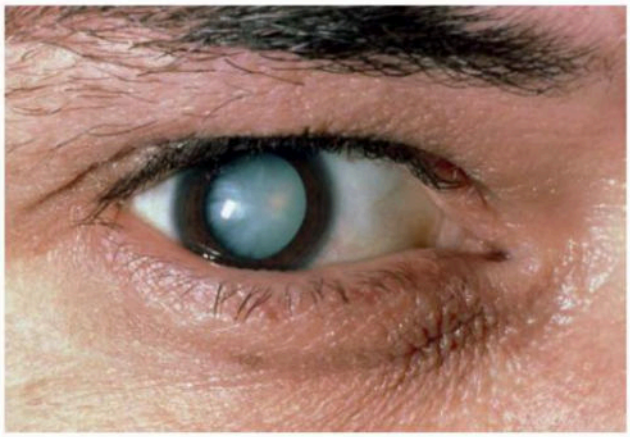

Figure 8.26 Cataract. (Sue Ford/Science Photo Library. Reproduced with permission.)

Age-related macular degeneration

This affects around a third of adults in the UK over the age of 75 and more women than men. In age-related macular degeneration (AMD) there is gradual degeneration of the retina around the macula (see Figs 8.8 and 8.9). Due to its location near the middle of the retina, only central vision is affected, both near and distant, while peripheral vision usually remains normal.

This sometimes progresses to a more serious form, called 'wet' AMD when abnormal blood vessels develop under the retina; these may become leaky causing local accumulation of exudates, scarring and permanent loss of central vision.

SPOT CHECK

8. Which age-related condition that affects the eyes leads to most people over the age of 40 requiring glasses for reading?

Disorders of the ear

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the features of conductive and sensorineural hearing loss
- describe the causes and effects of diseases of the ear.

Hearing loss

Hearing impairment can be classified in two main categories: conductive and sensorineural. Hearing impairment can also be mixed when there is a combination of conductive and sensorineural hearing loss in one ear.

Conductive hearing impairment

This occurs when an abnormality of the outer or middle ear impairs conduction of sound waves to the oval window; common examples are listed in Box 8.1.

Otosclerosis

This is a common cause of progressive conductive hearing loss in young adults, which may affect one ear but is more commonly bilateral. It is usually hereditary, and more common in females than males; it often worsens during pregnancy. Abnormal bone develops around the footplate of the stapes, fusing it to the oval window and reducing the ability to transmit sound waves across the tympanic cavity.

Box 8.1 Common causes of hearing loss

Conductive
Otosclerosis
Serous otitis media
Acute otitis media
Chronic otitis media
Barotrauma
External otitis
Injury of the tympanic membrane

Sensorineural
Long-term exposure to excessive noise
Congenital
Ménière's disease
Presbycusis
Impacted earwax or foreign body
Ototoxic drugs, e.g. aminoglycoside antibiotics, diuretics, chemotherapy
Infections, e.g. mumps, herpes zoster, meningitis, syphilis

Serous otitis media

Also known as 'glue ear', or secretory otitis media, this is a collection of fluid (effusion) in the middle ear cavity. Causes include:

- obstruction of the auditory tube by, for example, pharyngeal swelling, enlarged adenoids or tumour
- barotrauma (usually caused by descent in an aeroplane when suffering from a cold)
- untreated acute otitis media.

The air normally present in the middle ear is absorbed and negative pressure develops, causing retraction of the tympanic membrane. Thereafter, fluid is drawn into the low-pressure cavity from surrounding blood vessels, causing conductive hearing loss.

Adults experience hearing loss and blockage of the ear, which is usually painless. In preverbal children, however, this is a common cause of hearing impairment, which may manifest as delayed speech and/or achievement of developmental milestones. Secondary infection can complicate this condition in both adults and children.

Sensorineural hearing impairment

This is the more prevalent form of hearing impairment and, as the name suggests, affects the nerves of the inner ear or the central nervous system, e.g. the cochlea, cochlear branch of the vestibular nerve or the auditory area of the cerebrum. Common causes are listed in Box 8.1. Noise-induced hearing loss is a preventable cause of sensorineural hearing impairment, which may arise through:

- employment, e.g. construction work, manufacturing or the music industry
- social activities, e.g. listening to loud music on personal equipment or at nightclubs.

Risk factors for congenital sensorineural hearing impairment include family history, acute hypoxia at birth and exposure to intrauterine viruses, e.g. maternal rubella.

Ménière's disease

In this condition there is accumulation of endolymph, causing distension and increased pressure within the membranous labyrinth with destruction of the sensory cells in the ampulla and cochlea. It is usually unilateral at first but both ears may be affected later.

The cause is not known. Ménière's disease is associated with recurrent episodes of incapacitating dizziness (vertigo), nausea and vomiting, lasting for several hours. Periods of remission vary from days to months. During and between attacks there may be continuous ringing in the affected ear (tinnitus). Loss of hearing is experienced during episodes, which may gradually become permanent over a period of years as the spiral organ is destroyed.

Ear infections

External otitis

Infection by *Staphylococcus aureus* is the usual cause of localised inflammation (boils) in the auditory canal. More

generalised inflammation may be caused by prolonged exposure to bacteria or fungi or by an allergic reaction to, for example, soaps, hair sprays or hair dyes.

Acute otitis media

This is inflammation of the middle ear cavity, usually caused by upward spread of microbes from an upper respiratory tract infection via the auditory tube. It is very common in children and is accompanied by severe earache. Occasionally, it spreads inwards from the outer ear through a perforated tympanic membrane (eardrum).

Bacterial infection leads to the accumulation of pus and the outward bulging of the tympanic membrane. Sometimes it ruptures and pus discharges from the middle ear (otorrhoea). The spread of infection may cause mastoiditis and labyrinthitis. As the petrous part of the temporal bone is very thin, the infection may spread through the bone and cause meningitis (p. 203) and brain abscess.

Chronic otitis media

In this condition there is permanent perforation of the tympanic membrane following acute otitis media (especially when recurrent, persistent or untreated) and mechanical or blast injuries. As healing occurs, stratified epithelium from the outer ear sometimes grows into the middle ear, forming a cholesteatoma. This is a collection of desquamated epithelial cells and purulent material. Continued development of cholesteatoma may lead to destruction of the ossicles, tinnitus (ringing in the ears) and conductive hearing loss. Rarer complications include spread of infection to the inner ear, which may cause labyrinthitis and erosion of the roof of the middle ear causing meningitis.

Labyrinthitis

The cause often remains unclear, although it can be a complication of middle ear infection when a fistula develops from a cholesteatoma (see above). It is accompanied by vertigo, tinnitus, nausea and vomiting, and nystagmus. Recovery is generally spontaneous and usually takes a few days although this debilitating condition can also be recurrent. Sometimes the spiral organ is destroyed, causing sudden and profound sensorineural hearing loss in the affected ear.

Motion sickness

This occurs when the brain receives conflicting sensory information; the visual information received from the eye does not match the information from the semicircular canals of the inner ear about one's position in relation to the environment. It causes nausea and vomiting in affected people, and is usually associated with travel, e.g. by car, boat or aeroplane.

SPOT CHECK

9. What is 'glue ear'?
10. Describe sensorineural hearing impairment.

Disorders of the eye

Learning outcome

After studying this section, you should be able to:

- describe the pathological changes and effects of diseases of the eye.

Inflammatory conditions

Stye

Also known as hordeolum, this is an acute and painful bacterial infection of sebaceous or tarsal glands of the eyelid margin (Fig. 8.27). The most common cause is *Staphylococcus aureus*. A 'crop' of styes may occur due to localised spread to adjacent glands. Infection of tarsal glands may block their ducts, leading to cyst formation (chalazion), which may damage the cornea.

Blepharitis

This is chronic inflammation of the eyelid margins, usually caused by bacterial infection or allergy, e.g. staphylococcal infection or seborrhoea (excessive sebaceous gland secretion). If ulceration occurs, healing by fibrosis may distort the eyelid margins, preventing complete closure of the eye. This may lead to drying of the eye, conjunctivitis and sometimes corneal ulceration.

Conjunctivitis

Inflammation of the conjunctiva may be caused by irritants, such as smoke, dust, wind, cold or dry air, microbes or antigens. Both eyes are usually affected, and become red, sometimes gritty and may discharge (Fig. 8.28). This condition may be acute or chronic. Corneal ulceration (see below) is a rare complication.

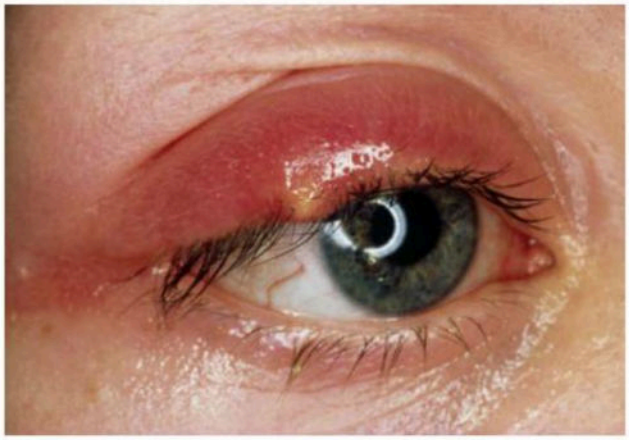

Figure 8.27 Stye on the upper eyelid. (From Science Photo Library. Reproduced with permission.)

Figure 8.28 Conjunctivitis. (Dr P Marazzi/Science Photo Library. Reproduced with permission.)

Acute bacterial conjunctivitis

Also known as 'pinkeye', this is highly contagious and in adults is usually caused by strains of staphylococci, streptococci or *Haemophilus*.

Neonatal conjunctivitis

Sexually transmitted disease in the mother, including chlamydia, and less frequently, gonorrhoea and genital herpes, can infect the newborn infant's eyes during vaginal delivery at childbirth.

Allergic conjunctivitis

This may be a complication of hay fever or be caused by a wide variety of airborne antigens, e.g. dust, pollen, fungus spores, animal dander, cosmetics, hair sprays or soaps. The condition sometimes becomes chronic.

Trachoma

This chronic inflammatory condition is caused by *Chlamydia trachomatis* and is the commonest preventable cause of blindness worldwide. Deposition of fibrous tissue in the conjunctiva and cornea leads to eyelid deformity and corneal scarring as distorted eyelashes rub against the surface of the eye. The microbes are spread by poor hygiene, e.g. communal use of contaminated washing water, cross-infection between mother and child, or contaminated towels and clothing.

Corneal ulcer

This is local necrosis of corneal tissue, usually associated with corneal infection (keratitis) following trauma (e.g. corneal abrasion), or infection spread from the conjunctiva or eyelids. Causative organisms include staphylococci, streptococci and herpes viruses. Acute pain, injection (redness of the cornea), photophobia and lacrimation interfere with sight during the acute phase. In severe cases, extensive ulceration or perforation and healing by fibrosis can cause opacity of the cornea, requiring corneal transplantation.

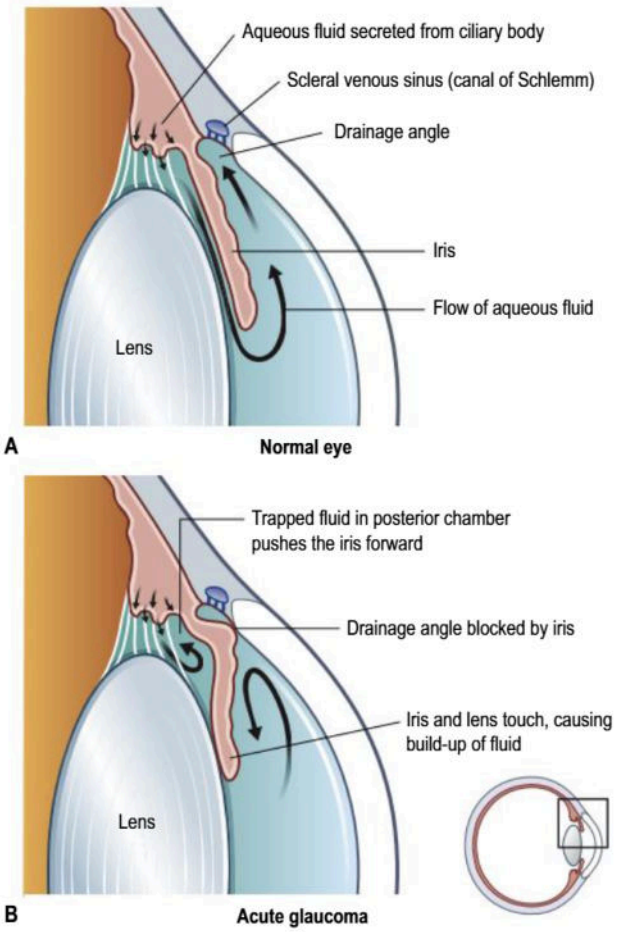

Figure 8.29 Glaucoma. (A) Normal eye. (B) Acute glaucoma.

Glaucoma

In this group of conditions, intraocular pressure (IOP) rises due to impaired drainage of aqueous fluid through the scleral venous sinus (canal of Schlemm) in the angle between the iris and cornea in the anterior chamber (Fig. 8.29). Persistently raised IOP may damage the optic nerve causing ischaemia. Damage to the optic nerve impairs vision, the extent of which varies from some visual impairment to complete loss of sight.

In addition to the commonest types described here, glaucoma can also be congenital or secondary to other causes, e.g. anterior uveitis or a tumour.

Primary open angle glaucoma

In primary open angle glaucoma (POAG) there is an insidious and painless rise in IOP with progressive loss of vision; this is also known as chronic open angle glaucoma. It is the commonest form in the UK, affecting about 1% of people at 40 years and 10% at 80 years.

Peripheral vision is lost first but the condition may remain asymptomatic until only central (tunnel) vision remains. As the condition progresses, atrophy of the optic disc occurs,

leading to irreversible loss of vision. It is commonly bilateral. The cause is not known but there is a familial tendency.

Angle closure glaucoma

This usually affects one eye. During life the lens gradually increases in size, pushing the iris forwards. In dim light, when the pupil dilates, the lax iris bulges still further forwards and may come into contact with the cornea, closing off the drainage angle to the scleral venous sinus. This blockage quickly leads to accumulation of aqueous fluid and suddenly raises the intraocular pressure.

Sudden severe pain, photophobia, headache, nausea and blurred vision accompany an acute attack. It may resolve spontaneously if the iris responds to bright light, constricting the pupil and releasing the pressure on the scleral venous sinus. After repeated attacks, spontaneous recovery may be incomplete and vision becomes progressively impaired. This condition sometimes becomes chronic.

Strabismus (squint, cross-eye)

In normal binocular vision, the eyes are aligned so that each eye sees the same image, meaning that both eyes send similar images to the brain (see Fig. 8.20). In strabismus, only one eye is directed at the observed object and the other diverges (is directed elsewhere). The result is that two quite different images are sent to the brain, one from each eye. It is caused by one-sided extrinsic muscle weakness or impairment of the cranial nerve (III, IV or VI) supply to the extrinsic muscles. In most cases the image from the squinting eye is suppressed by the brain; otherwise there is double vision (diplopia).

Cataract

The most common cause of visual impairment worldwide, cataracts can affect one or both eyes. Cataract is opacity of the lens, which impairs vision, especially in poor light and darkness when weak light rays can no longer pass through the cloudy lens to the retina (see Fig. 8.26). The extent of visual impairment depends on the location and extent of the opacity. Although most commonly age-related, this condition can also be congenital or secondary to other conditions, e.g. ocular trauma, uveitis or diabetes mellitus.

Congenital cataract may be idiopathic, or due to genetic abnormality including Down's syndrome, or maternal infection in early pregnancy, e.g. rubella. Early treatment is required to prevent permanent loss of sight.

Conditions affecting the retina

Occlusion of retinal vessels

Occlusion of the central retinal artery or vein causes sudden, painless unilateral loss of vision, because these vessels provide the sole arterial supply and venous drainage. Both are usually a consequence of systemic blood vessel disease.

- Arterial occlusion is usually due to embolism from an atheromatous plaque in the carotid artery.
- Venous occlusion is usually associated with thrombosis.

Diabetic retinopathy

This occurs in type 1 and type 2 diabetes mellitus, and has developed in most people 20 years after diagnosis although it often remains symptomatic. Changes in the small retinal blood vessels increase with the severity and duration of hyperglycaemia (microangiopathy, p. 264).

Retinopathy of prematurity

Retinopathy of prematurity (ROP) affects premature babies. Risk factors include birth before 32 weeks' gestation, birth weight under 1500 g, requirement for oxygen therapy and serious illness. Normal development of retinal blood vessels remains incomplete until the end of pregnancy (40 weeks' gestation). Maturation can be interrupted by premature delivery and is associated with abnormal growth of blood vessels into the vitreous chamber, causing varying degrees of interference with vision. The prognosis depends on the severity and many cases resolve spontaneously. In severe cases the abnormal blood vessels sometimes haemorrhage into the vitreous body and retinal detachment and blindness may occur.

Retinal detachment

This painless condition occurs when a tear or hole in the retina allows fluid to accumulate between the layers of retinal cells separating the upper layers from the wall of the eye. It is usually localised at first but as fluid collects the detachment spreads.

There are visual disturbances, often spots before the eyes or flashes of light due to abnormal stimulation of sensory nerves, and progressive loss of vision, sometimes described as a 'shadow' or 'curtain'. In many cases the cause is unknown but it may be associated with trauma to the eye or head, tumours, diabetes mellitus or as a complication of cataract surgery.

Retinitis pigmentosa

This is a group of hereditary diseases in which there is progressive degeneration of the retina that mainly affects the rods. Worsening impairment of peripheral vision, especially in dim light, usually becomes apparent in early childhood. Over time this leads to tunnel vision and, eventually, loss of sight.

Tumours

The main tumours that occur within the eye are melanomas and retinoblastomas. Metastatic tumours sometimes spread to the eye or orbit from the lung, breast or intestinal tract,

Choroidal melanoma

This is the most common ocular malignancy in adults, occurring between the ages of 40 and 70. There are several types, some more malignant than others. Vision is not normally affected until the tumour causes retinal detachment or secondary glaucoma, usually when well advanced. The tumour spreads locally in the choroid, and blood-borne metastases usually develop in the liver.

Retinoblastoma

This is the most common malignant tumour in children. A small number of cases are familial. It is normally evident before the age of 4 years and usually affects one side. The condition presents with a squint and enlargement of the eye. As this retinal tumour grows, visual impairment develops and the pupil looks pale. It spreads locally to the vitreous body and may grow along the optic nerve, invading the brain.

SPOT CHECK

11. What is a cataract?
12. Why does an embolus that occludes the central retinal artery cause sudden and irreversible loss of vision?

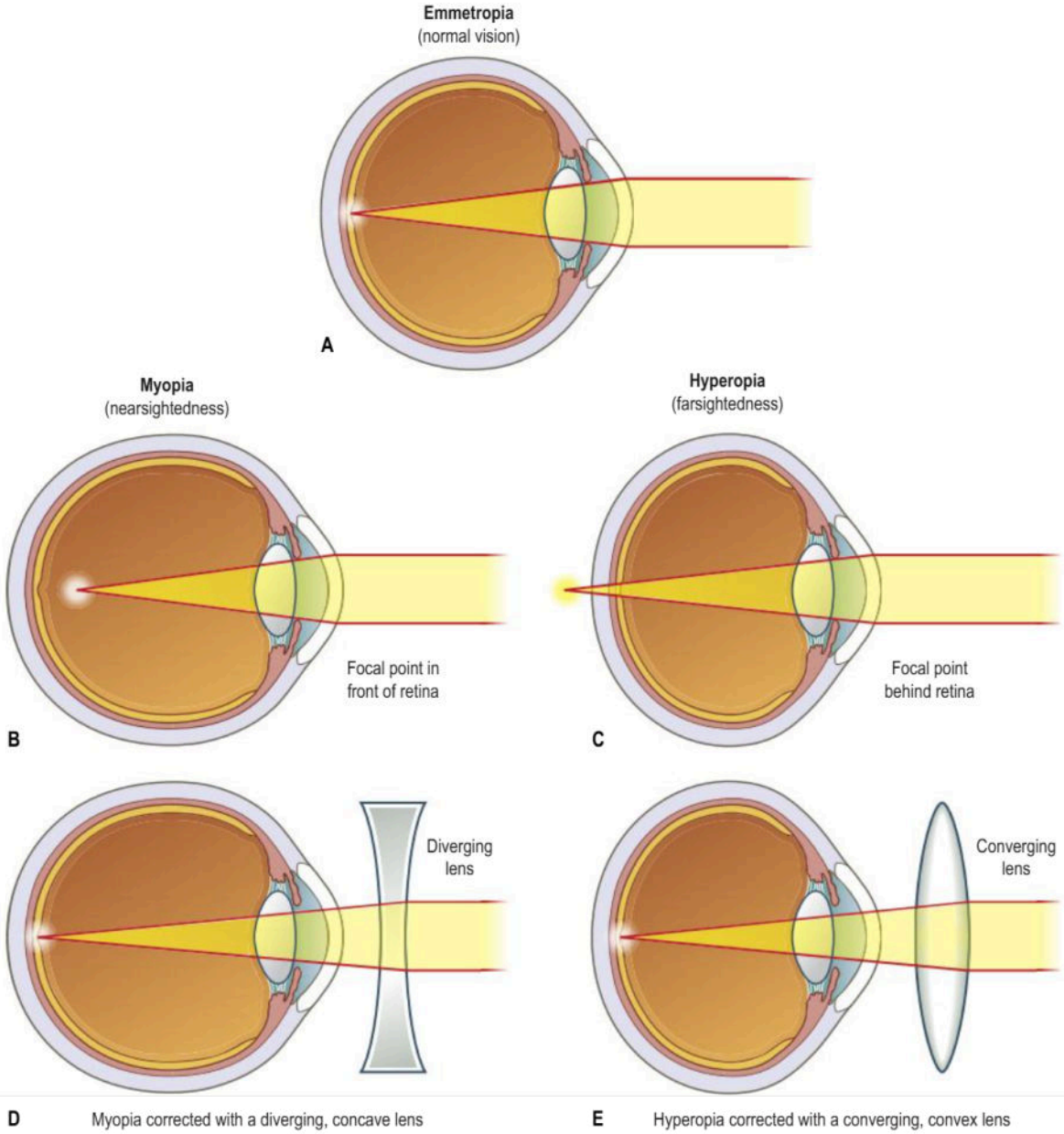

Figure 8.30 Common refractive errors of the eye and corrective lenses. (A) Normal eye. (B) Nearsightedness. (C) Farsightedness. (D) Correction of nearsightedness. (E) Correction of farsightedness.

Refractive errors of the eye

Learning outcome

After studying this section, you should be able to:

- explain how corrective lenses overcome refractive errors of the eye.

In the emmetropic or normal eye, light from near and distant objects is focused on the retina (Fig. 8.30A).

Myopia

This is also called nearsightedness or shortsightedness. Because the eyeball is too long, distant objects are focused in front of the retina (Fig. 8.30B). Close objects are focused normally but distant vision is blurred. Correction is achieved using a biconcave lens (Fig. 8.30D).

Hyperopia

Also called farsightedness or longsightedness, this abnormality causes a near image to be focused behind the retina because the eyeball is too short (Fig. 8.30C). Distant objects are focused normally but close vision is blurred. A convex lens corrects this (Fig. 8.30E).

Astigmatism

This is abnormal curvature of part of the cornea or lens. It interferes with the light path though the eye and prevents focusing of light on the retina, causing blurred vision. Correction requires cylindrical lenses. It is very common and may coexist with other refractive disorders.

SPOT CHECK

13. In which refractive error is the eyeball too long?

Case study

Tom is 80 years old and being assessed by the practice nurse for his annual health check.

The nurse notices he is finding it hard to hear the questions she's asking him.

1. Difficulty in hearing associated with ageing is called:

   a. Conductive hearing loss
   b. Labyrinthitis
   c. Presbyopia
   d. Presbycusis

2. Which of the statements about the structure of the ear is true?

   a. Three semi-circular canals lie at right angles to each other in the middle ear.
   b. The three ossicles are the malleus, hammer and stapes.
   c. The auditory tube connects the nasopharynx to the middle ear.
   d. The tympanic membrane forms the oval window.

Tom explains he needs to be in a well-lit area to be able to read these days and the nurse observes that he has some opacity of the lens of the eye. She reassures him that this is not uncommon in older adults.

3. This condition is known as:

   a. Cloudy eye
   b. Cataract
   c. Astigmatism
   d. Glaucoma

4. Light waves entering the eye pass through its structures in the following order:

   a. Conjunctiva, cornea, pupil, retina
   b. Retina, lens, pupil, cornea
   c. Iris, cornea, retina, pupil
   d. Conjunctiva, vitreous body, cornea, retina

References and further reading

Bradbury M, Murphy C, 2019. Ophthalmology: an illustrated colour text, 4th ed. Elsevier.

Gault JA, Vander JF, 2016. Ophthalmology Secrets in Colour, 4th ed. Elsevier.

Scholes MA, Ramakrishnan VR, 2016. ENT Secrets, 4th ed. Elsevier.

Review and revise

Complete each of the following statements:

1. The olfactory nerves arise as tiny nerve endings in the _____ of the nasal cavity. They pass through the ethmoid bone to the _____. After synapsing, the nerve fibres converge and pass backwards as the _____ to the olfactory area in the _____, where odour is perceived.

2. An acute middle ear infection is also known as acute _____. Microbes usually spread there through the _____. Accumulation of _____ in the middle ear leads to outward bulging of the _____.

Choose one answer to complete each of the following statements:

3. The characteristic property of a sound wave that is perceived as loud is: _____
   a. High amplitude
   b. Low amplitude
   c. High number of cycles per second
   d. Low number of cycles per second

4. The structure that causes the most significant refraction of light waves is the: _____
   a. Conjunctiva
   b. Cornea
   c. Lens
   d. Vitreous body

Indicate whether each of the following statements is true or false:

5. The membranous labyrinth encloses the bony labyrinth like a 'tube within a tube'. _____

6. The vestibular part of the vestibulocochlear nerve transmits impulses that maintain balance. _____

7. Match each letter in List A to the appropriate number in List B:

List A
- ____ (a) Cerumen
- ____ (b) Lobule
- ____ (c) Tympanum
- ____ (d) Stapes
- ____ (e) Malleus
- ____ (f) Incus
- ____ (g) Endolymph
- ____ (h) Perilymph

List B
1. Ossicle adjacent to the oval window
2. Fluid within the bony labyrinth
3. Earwax
4. Ossicle in contact with the tympanic membrane
5. Fluid within the membranous labyrinth
6. Earlobe
7. Anvil-shaped ossicle
8. Eardrum

8. Match each letter in List A to the appropriate number in List B:

List A
- ____ (a) Iris
- ____ (b) Optic disc
- ____ (c) Cornea
- ____ (d) Conjunctiva
- ____ (e) Pupil
- ____ (f) Vitreous body
- ____ (g) Rods
- ____ (h) Cones

List B
1. Jelly-like substance that fills the posterior chamber
2. Enable colour vision
3. Anterior part of the sclera
4. Area of the retina where the optic nerve leaves
5. Anterior aperture that controls the amount of light entering the eye
6. The visible coloured part of the anterior eye
7. Membranous lining of the eyelids
8. Contain the light-sensitive pigment rhodopsin

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/.

CHAPTER 9

The endocrine system

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The endocrine system is a collection of glands, which are widely separated and have no physical connections with each other. Endocrine glands are groups of secretory cells surrounded by extensive networks of capillaries that facilitate diffusion of hormones (chemical messengers) from the secretory cells into the bloodstream. They are also referred to as ductless glands because hormones diffuse directly into the bloodstream (see Fig. 3.27). Hormones are then carried in the bloodstream to distant target tissues and organs, where they influence cell growth and metabolism.

Homeostasis of the internal environment is maintained partly by the autonomic nervous system and partly by the endocrine system. The autonomic nervous system is concerned with rapid changes, while endocrine control is generally involved in slower and more precise adjustments.

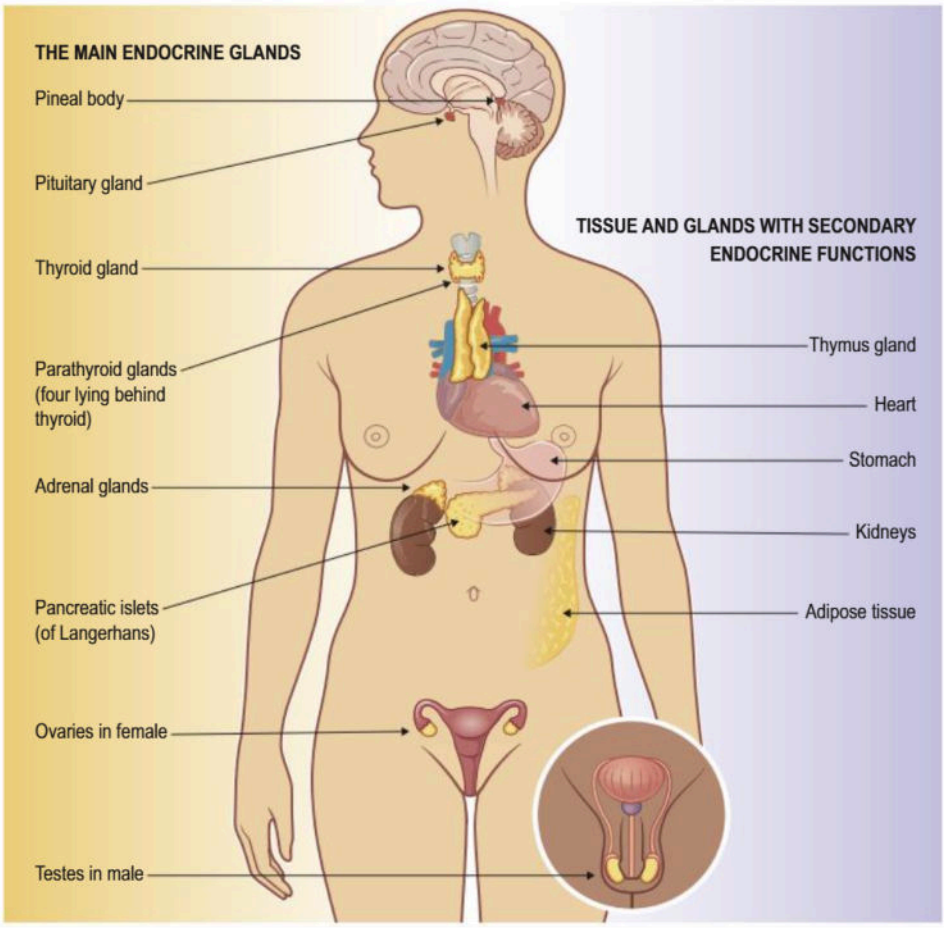

Figure 9.1 Positions of the endocrine glands.

The main endocrine glands are shown in Figure 9.1, although many other organs and tissues also secrete hormones as a secondary function. For example, Table 9.4 (p. 253) shows that adipose tissue produces leptin, which is involved in the regulation of appetite, and that the heart secretes atrial natriuretic peptide, which acts on the kidneys.

Although the hypothalamus is classified as a part of the brain rather than an endocrine gland, it secretes hormones that control the pituitary gland and indirectly influences many others.

The ovaries and the testes secrete hormones associated with the reproductive system after puberty; their functions are described in Chapter 18. The placenta, which develops to nourish the developing fetus during pregnancy, also has an endocrine function (see Ch. 5).

The most important endocrine glands are explored in the early sections of this chapter. Some hormones are secreted by tissues (rather than by discrete glands) and act locally, e.g. prostaglandins, and are considered briefly on page 253. Changes in endocrine functions that accompany ageing are explored. Problems that arise when abnormalities occur are caused by the over- or under-activity of endocrine glands and are explained in the final sections of the chapter.

Overview of hormone action

When a hormone arrives at its target cell, it binds to a specific receptor, where it acts as a switch influencing chemical or metabolic reactions inside the cell. Receptors for peptide hormones, e.g. noradrenaline (norepinephrine), insulin and glucagon are situated on the outer surface of the cell membrane and those for lipid-based hormones, e.g. cortisol, are located inside the body cells.

The level of a hormone in the blood is variable and self-regulating within its normal range. A hormone is released in response to a specific stimulus and usually its action reverses or negates the stimulus through a negative feedback mechanism (p. 37). This may be controlled either indirectly through the release of hormones by the hypothalamus and the anterior pituitary gland, e.g. steroid and thyroid hormones, or directly by blood levels of the stimulus, e.g. insulin and glucagon, which are determined by plasma glucose levels.

The effect of a positive feedback mechanism is amplification of the stimulus and increasing release of the hormone until a process is complete and the stimulus ceases, e.g. release of oxytocin during labour.

Pituitary gland and hypothalamus

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the hypothalamus and the pituitary gland
- explain the influence of the hypothalamus on the lobes of the pituitary gland
- outline the actions of the hormones secreted by the anterior and posterior lobes of the pituitary gland.

The pituitary gland and the hypothalamus act as a unit, regulating the activity of most of the other endocrine glands. The pituitary gland lies in the hypophyseal fossa of the sphenoid bone below the hypothalamus, to which it is attached by a stalk (Fig. 9.2). It is the size of a pea, weighs about 500 mg and consists of two main parts that originate from different types of cell. The anterior pituitary is composed of hormone-secreting glandular tissue because it is an upgrowth of glandular tissue from the pharynx, while the posterior pituitary is a downgrowth of nervous tissue from the brain and is therefore composed of nervous tissue. A network of nerve fibres connects the hypothalamus and the posterior pituitary (Fig. 9.3).

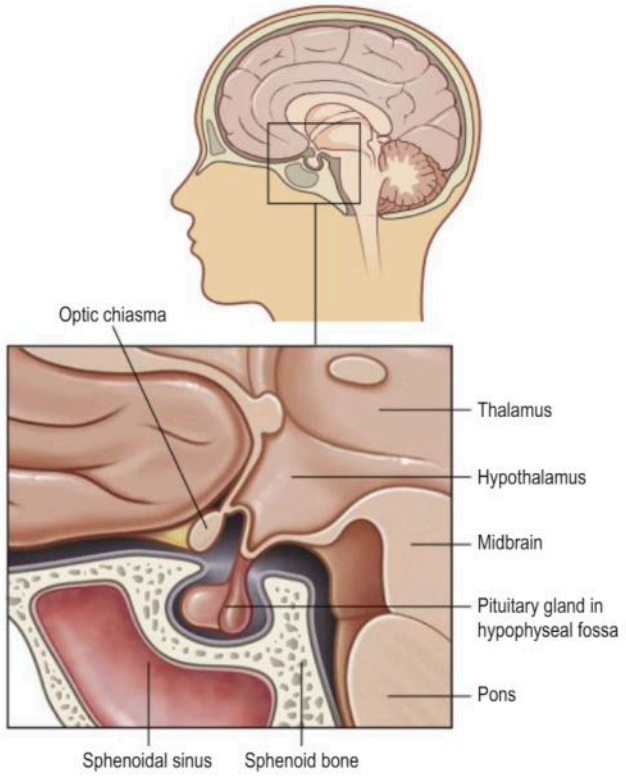

Figure 9.2 The pituitary gland. Median section showing its position and associated structures.

Blood supply

Arterial blood

Arterial supply is from branches of the internal carotid artery. The anterior lobe is supplied indirectly by blood that has already passed through a capillary bed in the hypothalamus (see later), and the posterior lobe is supplied directly.

Venous drainage

Venous blood, containing hormones from both lobes, leaves the gland in short veins that enter the venous sinuses between the layers of dura mater.

The influence of the hypothalamus on the pituitary gland

The hypothalamus controls release of hormones from both the anterior and posterior pituitary but in different ways that are explained in the next sections.

Anterior pituitary

The anterior pituitary is supplied with blood that has already passed through a capillary bed in the hypothalamus (Fig. 9.3A), where it collects hypothalamic hormones for transport to the pituitary. The network of capillaries linking the hypothalamus and anterior pituitary is called the pituitary portal system.

Pituitary portal system

This network of vessels transports blood from the hypothalamus to the anterior pituitary, where it enters a network of tiny sinusoids (p. 88) that are in close contact with the secretory cells, facilitating easy passage of hormones into the bloodstream. As well as providing oxygen and nutrients, this blood transports releasing and inhibiting hormones secreted by the hypothalamus. These hormones influence secretion and release of specific hormones formed in the anterior pituitary (Table 9.1).

Stimulation and inhibition of the anterior pituitary

Some of the hormones secreted by the anterior lobe stimulate or inhibit secretion by other endocrine glands (target glands) while others have a direct effect on target tissues. Table 9.1 summarises the main relationships between the hormones of the hypothalamus, the anterior pituitary and target glands or tissues.

Secretion of an anterior pituitary hormone follows stimulation of the gland by a specific releasing hormone produced by the hypothalamus and carried to the gland through the pituitary portal system. The whole system is controlled by a negative feedback mechanism: that is, when the level of a hormone in the blood supplying the hypothalamus (the sensor) is low it produces the appropriate releasing hormone, which stimulates release of a trophic hormone by the anterior pituitary. This in turn stimulates

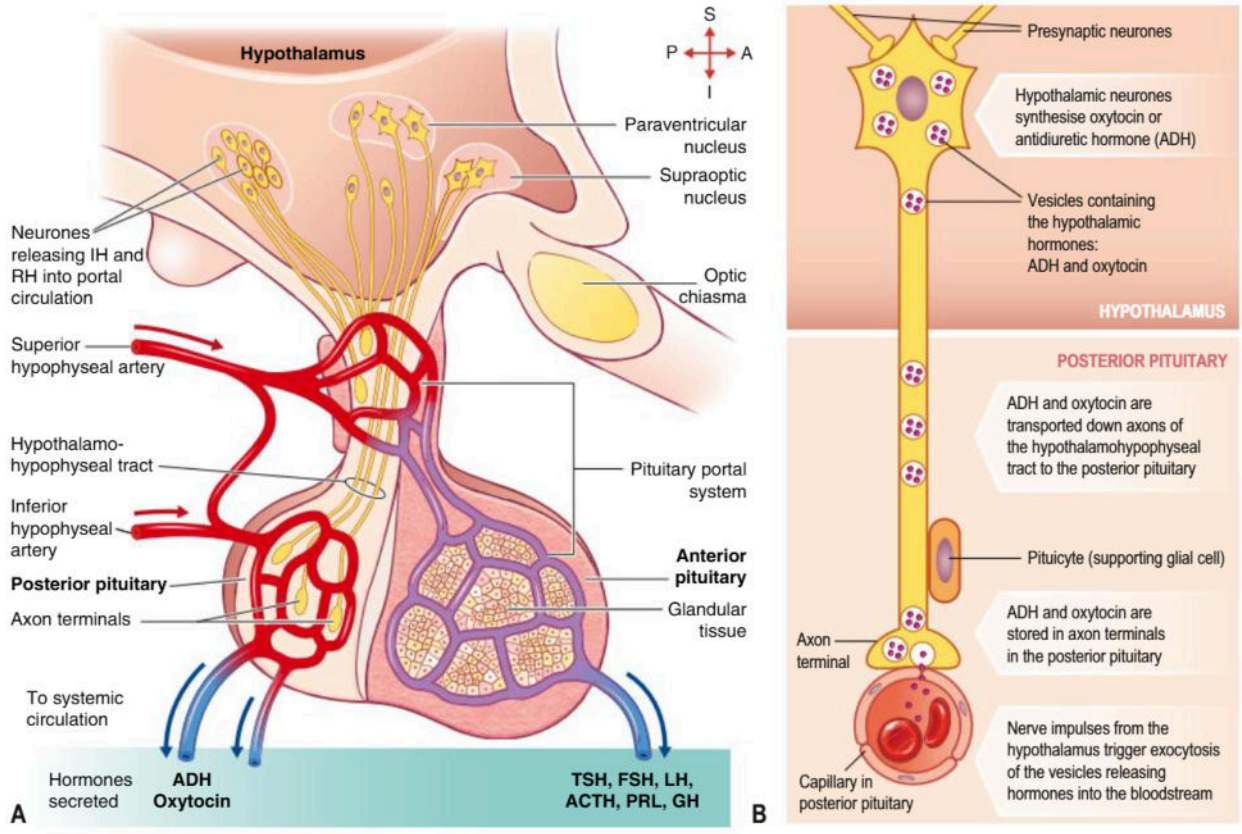

Figure 9.3 The pituitary gland. (A) The lobes of the pituitary gland and their relationship with the hypothalamus. (B) Synthesis and storage of antidiuretic hormone (ADH) and oxytocin. *ACTH*, adrenocorticotrophic hormone; *FSH*, follicle stimulating hormone; *GH*, growth hormone; *IH*, inhibiting hormone; *LH*, luteinising hormone; *PRL*, prolactin (lactogenic hormone); *RH*, releasing hormone; *TSH*, thyroid stimulating hormone.

the target gland (the effector) to produce and release its hormone. As a result, the blood level of that hormone rises and the hypothalamus responds to increased levels by stopping secretion of its releasing factor and hormone secretion is switched off (Fig. 9.4). Through this negative feedback mechanism, blood levels of hormones can be finely adjusted to meet changing body needs.

Anterior pituitary hormones

These have wide-ranging effects, described below.

Growth hormone

Growth hormone (GH) is the most abundant anterior pituitary hormone. It has anabolic effects and stimulates growth and division of most body cells especially in the bones and skeletal muscles. GH secretion is highest in childhood and adolescence, accelerating cell division, increasing tissue mass and driving the rapid body growth that takes place at this time. In adults, GH controls growth and regeneration of nearly all body tissues, especially skeletal muscle and bone. It stimulates protein synthesis, especially for tissue growth and repair, promotes breakdown of fats and increases blood glucose levels (Ch. 12). GH also regulates aspects of metabolism in many organs, e.g. liver, intestines and pancreas.

Its release is stimulated by growth hormone releasing hormone (GHRH) and suppressed by growth hormone release inhibiting hormone (GHRIH), also known as somatostatin, both of which are secreted by the hypothalamus. GH secretion is controlled by a negative feedback system; secretion is inhibited when the blood level rises and by GHRIH release from the hypothalamus. GHRIH also suppresses secretion of thyroid stimulating hormone and gastrointestinal secretions, e.g. gastric juice, gastrin and cholecystokinin (Ch. 12).

Secretion of GH is greater at night during deep sleep and is stimulated by hypoglycaemia (low blood glucose), exercise and anxiety. Ongoing sleep disturbances in children, e.g. in childhood asthma, can restrict normal growth.

GH is a stress hormone and, as such, is released during situations such as starvation and trauma.

Prolactin

This hormone, also known as lactogenic hormone, is secreted during pregnancy to prepare the breasts for lactation (milk production) after childbirth. The blood level of prolactin is increased by prolactin releasing

Table 9.1 Hormones of the hypothalamus, anterior pituitary and their target tissues

Hypothalamus	Anterior pituitary	Target gland or tissue
Growth hormone releasing hormone (GHRH)	Growth hormone (GH, somatotrophin)	Most tissues Many organs
Growth hormone release inhibiting hormone (GHRIH, somatostatin)	GH inhibition Thyroid stimulating hormone (TSH) inhibition	Thyroid gland Pancreatic islets Most tissues
Thyrotrophin releasing hormone (TRH)	TSH	Thyroid gland
Corticotrophin releasing hormone (CRH)	Adrenocorticotrophic hormone (ACTH)	Adrenal cortex
Prolactin releasing hormone (PRH)	Prolactin (lactogenic hormone, PRL)	Breast
Prolactin inhibiting hormone (dopamine, PIH)	PRL inhibition	Breast
Luteinising hormone releasing hormone (LHRH) *or*	Follicle stimulating hormone (FSH)	Ovaries and testes
Gonadotrophin releasing hormone (GnRH)	Luteinising hormone (LH)	Ovaries and testes

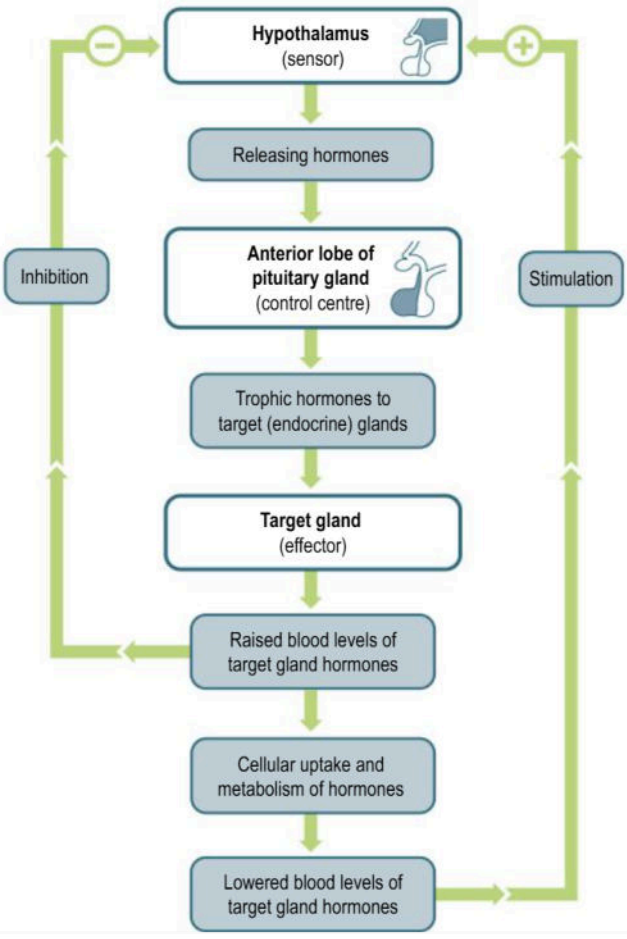

Figure 9.4 Negative feedback regulation of secretion of hormones by the anterior lobe of the pituitary gland.

hormone (PRH) released from the hypothalamus and lowered by prolactin inhibiting hormone (PIH, dopamine) and increased blood prolactin levels. Immediately after birth, suckling stimulates prolactin secretion and lactation (see Fig. 18.14). The resultant high blood level is a factor in reducing the incidence of conception during lactation because prolactin inhibits FSH secretion.

Other hormones that initiate and maintain lactation include oestrogens, corticosteroids, insulin and thyroxine. Prolactin secretion is related to sleep, rising during any period of sleep, night or day.

Thyroid stimulating hormone

Release of thyroid stimulating hormone (TSH, thyrotrophin) is stimulated by thyrotrophin releasing hormone (TRH) from the hypothalamus. It stimulates growth and activity of the thyroid gland, which secretes the hormones thyroxine (T_4) and tri-iodothyronine (T_3). Secretion is regulated by a negative feedback mechanism: i.e. when the blood level of thyroid hormones is high, secretion of TSH is reduced, and vice versa (see Fig. 9.9). Exposure to cold is a powerful stimulant of TSH secretion, leading to increased release of thyroid hormones and an increase in metabolic rate.

Adrenocorticotrophic hormone (corticotrophin)

Corticotrophin releasing hormone (CRH) from the hypothalamus promotes synthesis and release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary. ACTH stimulates growth and activity of the adrenal cortex, increasing the output of adrenocortical steroid hormones, especially cortisol.

ACTH levels fluctuate naturally during each 24-hour period, being highest about 8 a.m. and lowest about midnight, although high levels sometimes also occur around midday and 6 p.m. This circadian rhythm is maintained throughout life. It is associated with sleep patterns and adjustment to changes takes several days, e.g. following changing work shifts or travelling to a different time zone (jet lag).

Secretion is also regulated by a negative feedback mechanism, being suppressed when the blood level of ACTH rises (Fig. 9.4). Other factors that stimulate ACTH secretion

Table 9.2 Anterior pituitary hormones and their functions

Hormone	Function
Growth hormone (GH)	Regulates metabolism and promotes tissue growth, especially of bones and muscles
Thyroid stimulating hormone (TSH)	Stimulates growth and activity of the thyroid gland and secretion of T_3 and T_4
Adrenocorticotrophic hormone (ACTH)	Stimulates the adrenal cortex to secrete glucocorticoids
Prolactin (PRL)	Stimulates growth of breast tissue and milk production
Follicle stimulating hormone (FSH)	Stimulates production of sperm in the testes, stimulates secretion of oestrogen by the ovaries, maturation of ovarian follicles, ovulation
Luteinising hormone (LH)	Stimulates secretion of testosterone by the testes, stimulates secretion of progesterone by the corpus luteum

include hypoglycaemia, exercise and other stressors, e.g. emotional states and fever.

Gonadotrophins

Just before puberty, two gonadotrophins (sex hormones) are secreted in gradually increasing amounts by the anterior pituitary in response to hypothalamic release of luteinising hormone releasing hormone (LHRH), also known as gonadotrophin releasing hormone (GnRH). Rising levels of these hormones at puberty promotes maturation of the reproductive organs. In both males and females the hormones responsible are:

- follicle stimulating hormone (FSH)
- luteinising hormone (LH).

In both sexes

FSH stimulates production of gametes by the gonads, namely:

- ova in the female ovary
- spermatozoa in the male testis.

In females

LH and FSH control the secretion of the hormones oestrogen and progesterone during the reproductive cycle (see Figs 18.10 and 18.11). Rising levels of oestrogen alone stimulate the release of FSH and LH. When both oestrogen and progesterone levels rise however, secretion of LH and FSH is suppressed.

In males

LH, also called interstitial cell stimulating hormone (ICSH), stimulates the interstitial cells of the testes to secrete the hormone testosterone (Ch. 18).

Table 9.2 summarises the functions of the anterior pituitary hormones.

Posterior pituitary

The posterior pituitary is formed from nervous tissue and consists of nerve cells surrounded by supporting glial cells called pituicytes. The cell bodies of the posterior pituitary neurones lie within the supraoptic and paraventricular nuclei of the hypothalamus and their axons merge forming a bundle known as the hypothalamohypophyseal tract (see Fig. 9.3A). Posterior pituitary hormones are synthesised in the nerve cell bodies in the hypothalamus. They are transported in vesicles along the axons to the axon terminals in the posterior pituitary where they are stored until needed (see Fig. 9.3B).

Unlike in the anterior pituitary, where secretion is stimulated by hormones, nerve impulses from the hypothalamus trigger exocytosis of the hormone-containing vesicles from the axon terminals, releasing posterior pituitary hormones into the bloodstream.

Posterior pituitary hormones

The structure of the posterior pituitary gland and its relationship with the hypothalamus is explained above. Oxytocin and antidiuretic hormone (ADH, vasopressin) are the two posterior pituitary hormones and both act directly on non-endocrine tissue.

Oxytocin

Oxytocin stimulates two target tissues during and after childbirth (parturition): uterine smooth muscle and the muscle cells of the lactating breast.

During childbirth, the posterior pituitary releases increasing amounts of oxytocin into the bloodstream in response to increasing stimulation of sensory stretch receptors in the uterine cervix as the baby's head progressively dilates it. Sensory impulses are generated and transmitted to the hypothalamus, stimulating the posterior pituitary to release more oxytocin. In turn, this stimulates more forceful uterine contractions and greater stretching of the uterine cervix as the baby's head is forced further downwards. This is an example of a positive feedback mechanism, which stops soon after the baby is delivered and cervical stretching stops (Fig. 9.5).

Ejection of milk also involves a positive feedback mechanism. Suckling generates sensory impulses that are transmitted from the breast to the hypothalamus, triggering release of oxytocin from the posterior pituitary. On reaching the lactating breast, oxytocin stimulates contraction of the milk ducts and myoepithelial cells around the glandular cells, ejecting milk. Suckling also inhibits the release of prolactin inhibiting hormone (PIH), prolonging prolactin secretion and lactation.

Oxytocin levels rise during sexual arousal in both males and females. This increases smooth muscle contraction, which is associated with glandular secretion and ejaculation

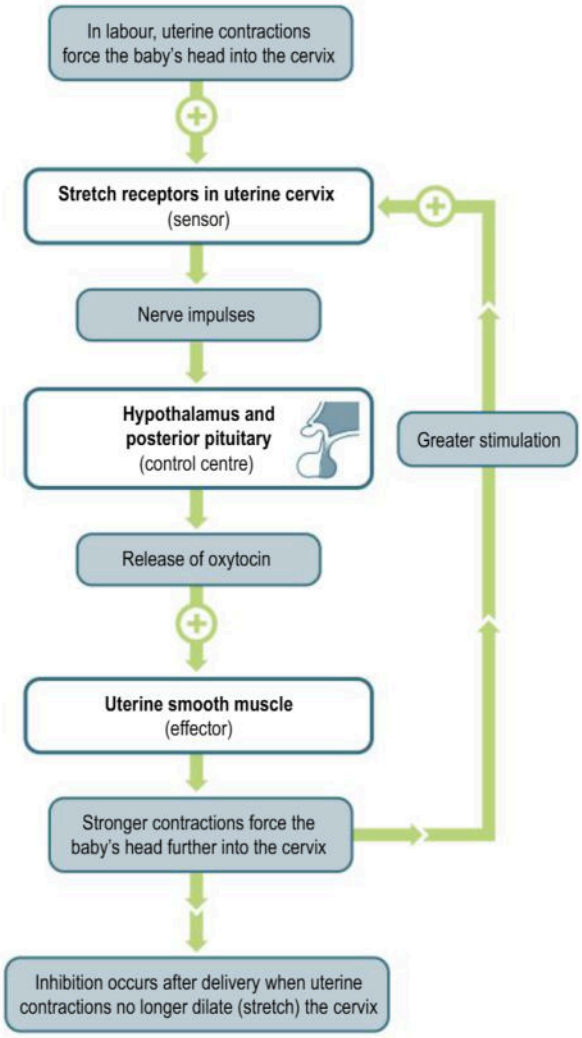

Figure 9.5 Positive feedback regulation of secretion of oxytocin.

in males. In females, contraction of smooth muscle in the vagina and uterus promotes movement of sperm towards the uterine tubes. It is believed that oxytocin may be involved in bonding between mother and newborn baby.

Antidiuretic hormone (vasopressin)

The main effect of antidiuretic hormone (ADH) is to reduce urine output (diuresis is the production of large volumes of urine). ADH acts on the distal convoluted tubules and collecting ducts of the kidneys, increasing their permeability to water (Ch. 13). This increases reabsorption of water from the glomerular filtrate and causes a consequent reduction in the volume of urine produced. ADH secretion is determined by the osmotic pressure of the blood circulating to the osmoreceptors, which lie in the hypothalamus close to the supraoptic nucleus (see Fig. 9.3A).

As osmotic pressure rises, e.g. as a result of dehydration, secretion of ADH increases. More water is therefore reabsorbed by the kidneys and the urine output is reduced. This means that the body retains more water and the rise in osmotic pressure is reversed. Conversely, when the osmotic

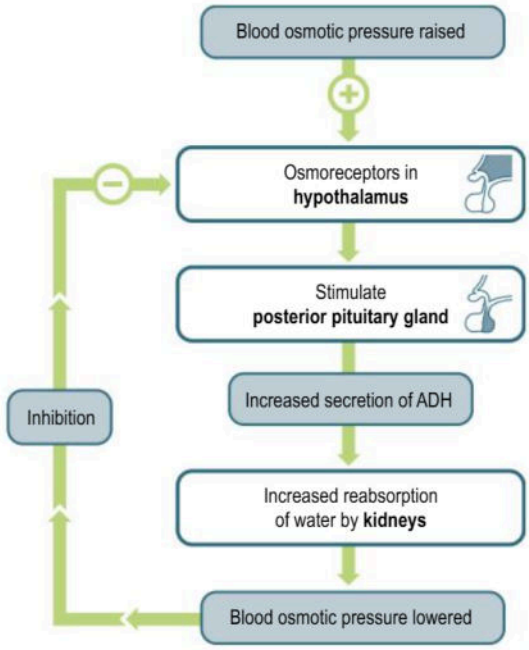

Figure 9.6 Negative feedback regulation of secretion of antidiuretic hormone (ADH).

pressure of the blood is low, e.g. after a large fluid intake, secretion of ADH is reduced, less water is reabsorbed and more urine is produced (Fig. 9.6).

When released in high concentrations, e.g. after severe blood loss, ADH causes smooth muscle contraction, especially vasoconstriction in small muscular arteries (arterioles). This has a pressor effect, raising systemic blood pressure; the alternative name of this hormone, vasopressin, reflects this effect.

SPOT CHECK

1. Outline the relationship between the hypothalamus and secretion of hormones by the anterior pituitary gland.

Thyroid gland

Learning outcomes

After studying this section, you should be able to:

- describe the position of the thyroid gland and its related structures
- describe the microscopic structure of the thyroid gland
- outline the actions of the thyroid hormones
- explain how blood levels of the thyroid hormones T_3 and T_4 are regulated.

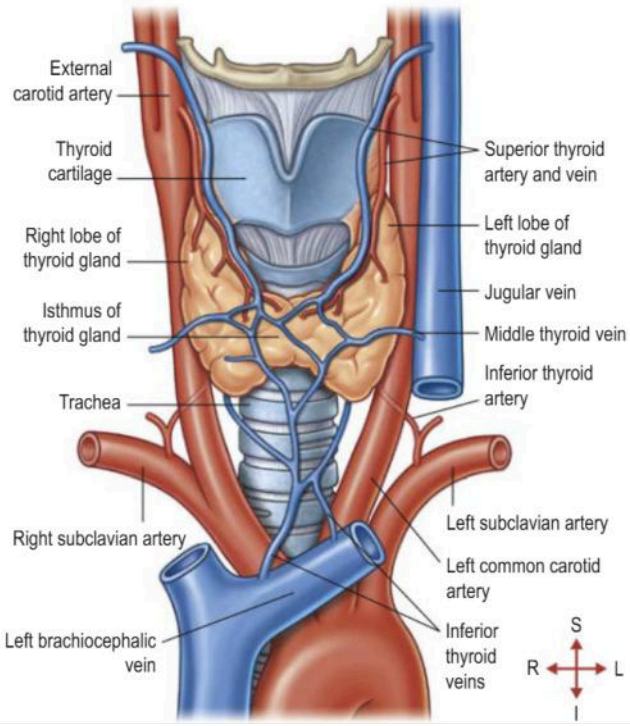

Figure 9.7 The thyroid gland. Anterior view showing position and associated structures.

The thyroid gland (Fig. 9.7) is situated in the neck in front of the larynx and trachea at the level of the 5th, 6th and 7th cervical and 1st thoracic vertebrae. It is a highly vascular gland that weighs about 25 g and is surrounded by a fibrous capsule. It is butterfly-shaped, consisting of two lobes, one on either side of the thyroid cartilage and upper cartilaginous rings of the trachea. Each is about 5 cm long and 3 cm wide and they are joined in front of the trachea by a narrow isthmus.

The gland is mainly composed of follicles whose walls are formed from cuboidal epithelial cells called follicular cells. Follicular cells secrete colloid, a thick, sticky protein material (Fig. 9.8). Between the follicles are parafollicular cells (sometimes called C-cells), found singly or in groups; they secrete the hormone calcitonin.

Blood and nerve supply

The arterial blood supply to the gland is through the superior and inferior thyroid arteries. The superior thyroid artery is a branch of the external carotid artery and the inferior thyroid artery is a branch of the subclavian artery.

The venous return is by the thyroid veins, which drain into the internal jugular veins.

The recurrent laryngeal nerves pass upwards, close to the posterior of the thyroid gland, and lie near the inferior thyroid artery, especially on the right side (see Fig. 9.10).

Thyroxine and tri-iodothyronine

Iodine is essential for the formation of the thyroid hormones, thyroxine (T_4) and tri-iodothyronine (T_3), so numbered

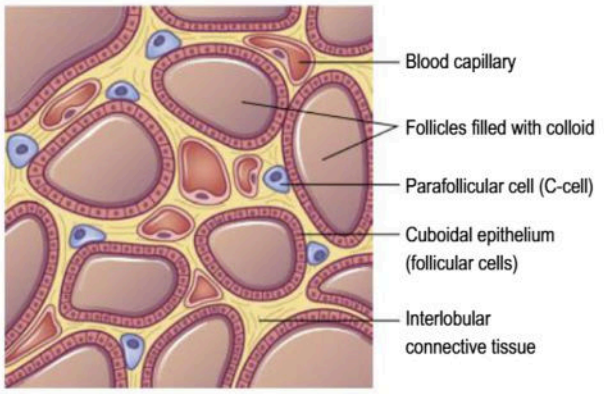

Figure 9.8 The microscopic structure of the thyroid gland.

because these molecules contain four and three atoms of iodine respectively. The main dietary sources of iodine are seafood, vegetables grown in iodine-rich soil and iodinated table salt. The thyroid gland selectively takes up iodine from the blood in a process called iodine trapping.

Thyroid hormones are synthesised as large precursor molecules called thyroglobulin, the major constituent of colloid. The release of T_3 and T_4 into the blood is stimulated by thyroid stimulating hormone (TSH) from the anterior pituitary.

Secretion of TSH is stimulated by thyrotrophin releasing hormone (TRH) from the hypothalamus and secretion of TRH is stimulated by exposure to cold, exercise, stress, malnutrition, low plasma glucose levels and sleep. TSH secretion depends on the plasma levels of T_3 and T_4 because these hormones control the sensitivity of the anterior pituitary to TRH. Through the negative feedback mechanism, increased levels of T_3 and T_4 decrease TSH secretion and vice versa (Fig. 9.9). Dietary iodine deficiency greatly increases TSH secretion causing proliferation of thyroid gland cells and enlargement of the gland (goitre, see Fig. 9.17).

Secretion of T_3 and T_4 begins in about the 3rd month of fetal life and increases at puberty and in women during the reproductive years, especially during pregnancy. Otherwise, it remains constant throughout life. Of the two thyroid hormones, T_4 is much more abundant. However, it is less potent than T_3, which is more physiologically important. Most T_4 is converted into T_3 inside target cells.

Thyroid hormones enter the cell nucleus and regulate gene expression, i.e. they increase or decrease synthesis of specific proteins (Ch. 17). They enhance the effects of other hormones, notably adrenaline (epinephrine) and noradrenaline (norepinephrine). T_3 and T_4 affect most cells of the body by:

- increasing metabolic rate and heat production
- regulating metabolism of carbohydrates, proteins and fats.

T_3 and T_4 are essential for normal growth and development, especially of the skeleton and nervous system. Most other organs and systems are also influenced by thyroid hormones. Effects of under-activity or over-activity of the thyroid gland can be profound, especially in childhood (Table 9.3).

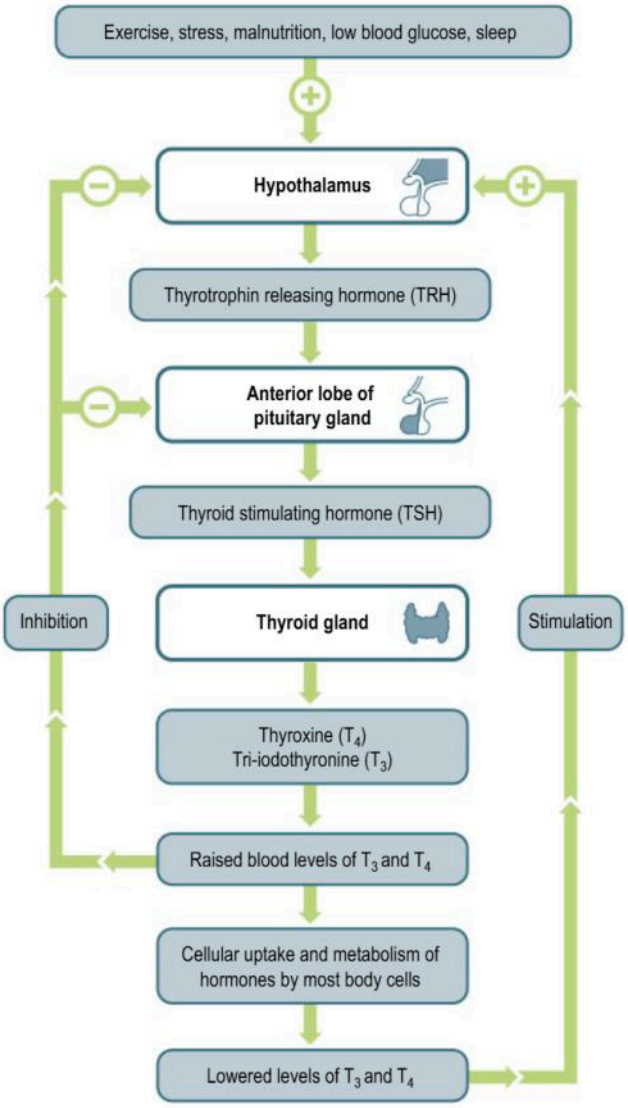

Figure 9.9 Negative feedback regulation of secretion of thyroxine (T_4) and tri-iodothyronine (T_3).

Calcitonin

This hormone is secreted by the parafollicular or C-cells in the thyroid gland (see Fig. 9.8). Calcitonin lowers blood calcium (Ca^{2+}) levels by acting on the bone-building cells, osteoblasts, promoting their uptake and storage of calcium into bone tissue (Ch. 16).

Its action opposes that of parathyroid hormone, secreted by the parathyroid glands. Release of calcitonin is stimulated by increased blood calcium levels.

This hormone may be important during childhood, when developing bones undergo considerable changes in size and shape.

SPOT CHECK

2. Which hormone involved in regulation of blood calcium levels is secreted by the thyroid gland?

Table 9.3 Common effects of abnormal secretion of thyroid hormones

Hyperthyroidism: increased T_3 and T_4 secretion	Hypothyroidism: decreased T_3 and T_4 secretion
Increased basal metabolic rate	Decreased basal metabolic rate
Weight loss, good appetite	Weight gain, anorexia
Anxiety, physical restlessness, mental excitability	Depression, psychosis, mental slowness, lethargy
Hair loss	Dry skin, brittle hair
Tachycardia, palpitations, atrial fibrillation	Bradycardia
Warm sweaty skin, heat intolerance	Dry, cold skin, prone to hypothermia
Diarrhoea	Constipation
Exophthalmos in Graves' disease (see Fig. 9.18)	

Parathyroid glands

Learning outcomes

After studying this section, you should be able to:

- describe the position and gross structure of the parathyroid glands
- outline the functions of parathyroid hormone and calcitonin
- explain how blood levels of parathyroid hormone and calcitonin are regulated.

There are four parathyroid glands, each weighing around 50 mg; two are embedded in the posterior surface of each lobe of the thyroid gland (Fig. 9.10). They are enclosed by fine connective tissue capsules and surrounded by a network of sinusoids (p. 88).

Function

These glands secrete parathyroid hormone (PTH, parathormone), which increases blood calcium levels. When these fall, secretion of PTH is increased and vice versa.

PTH secretion increases blood calcium levels by releasing calcium stored in bone via a dual action: it stimulates osteoclasts (bone-destroying cells) and, in association with vitamin D, increases calcium reabsorption from the renal tubules.

PTH and calcitonin from the thyroid gland act in a complementary manner to maintain blood calcium levels within the normal range. As well as being central to building and maintaining a healthy skeleton, calcium is essential for:

- muscle contraction
- transmission of nerve impulses

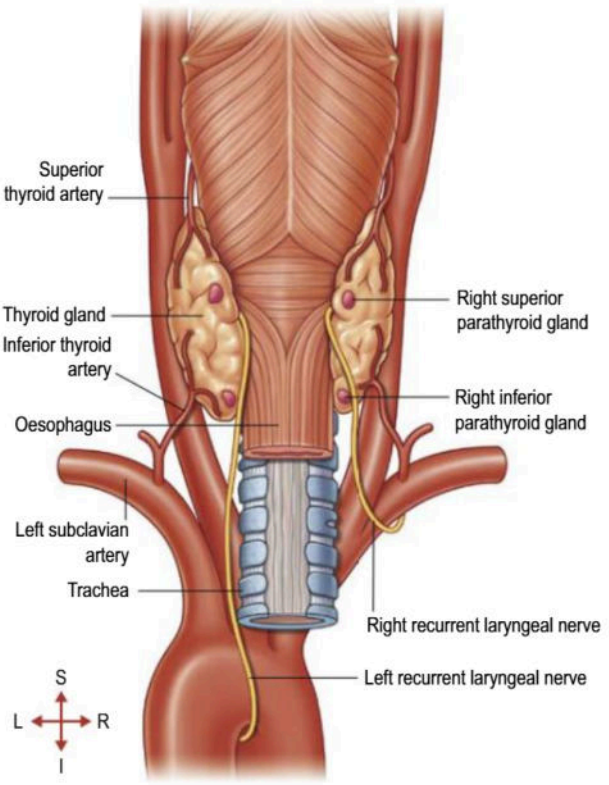

Figure 9.10 The parathyroid glands. Posterior view showing their position and associated structures.

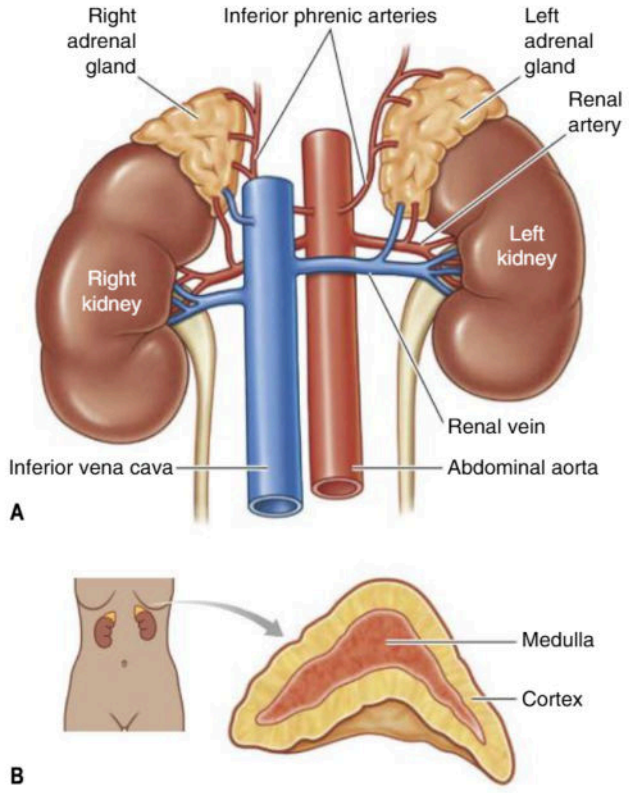

Figure 9.11 The adrenal glands. (A) Position in relation to the kidney. (B) Cross-section.

- blood clotting
- normal action of many enzymes.

SPOT CHECK

3. Describe the function of parathyroid hormone.

Adrenal glands

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the adrenal glands
- describe the actions of each of the three groups of adrenocorticoid hormones
- explain how blood levels of glucocorticoids are regulated
- describe the actions of adrenaline (epinephrine) and noradrenaline (norepinephrine)
- outline how the adrenal glands respond to stress.

The two adrenal (suprarenal) glands are situated on the upper pole of each kidney (Fig. 9.11), enclosed within the renal fascia. They are pyramid-shaped, about 5 cm wide and 3 cm high; each weighs around 5 g.

The glands are composed of two parts, which have different structures and functions. The outer layer is the cortex and the inner core the medulla. The adrenal cortex is essential to life but the medulla is not.

Blood supply

The arterial blood supply is by branches of the phrenic, renal and many suprarenal arteries.

The venous return is by suprarenal veins. The right gland drains into the inferior vena cava and the left into the left renal vein.

The adrenal glands and the stress response

A stressor is any effect, either internal or external, that disturbs or threatens to disturb homeostasis within the body. Stressors can be major or minor, and physical or psychological. They include infection, exercise, trauma, surgery, disease, emotional states, fasting, extremes of temperature and sleep deprivation.

Immediate responses to short-term stress include activation of the 'flight or fight' response (p. 192). This

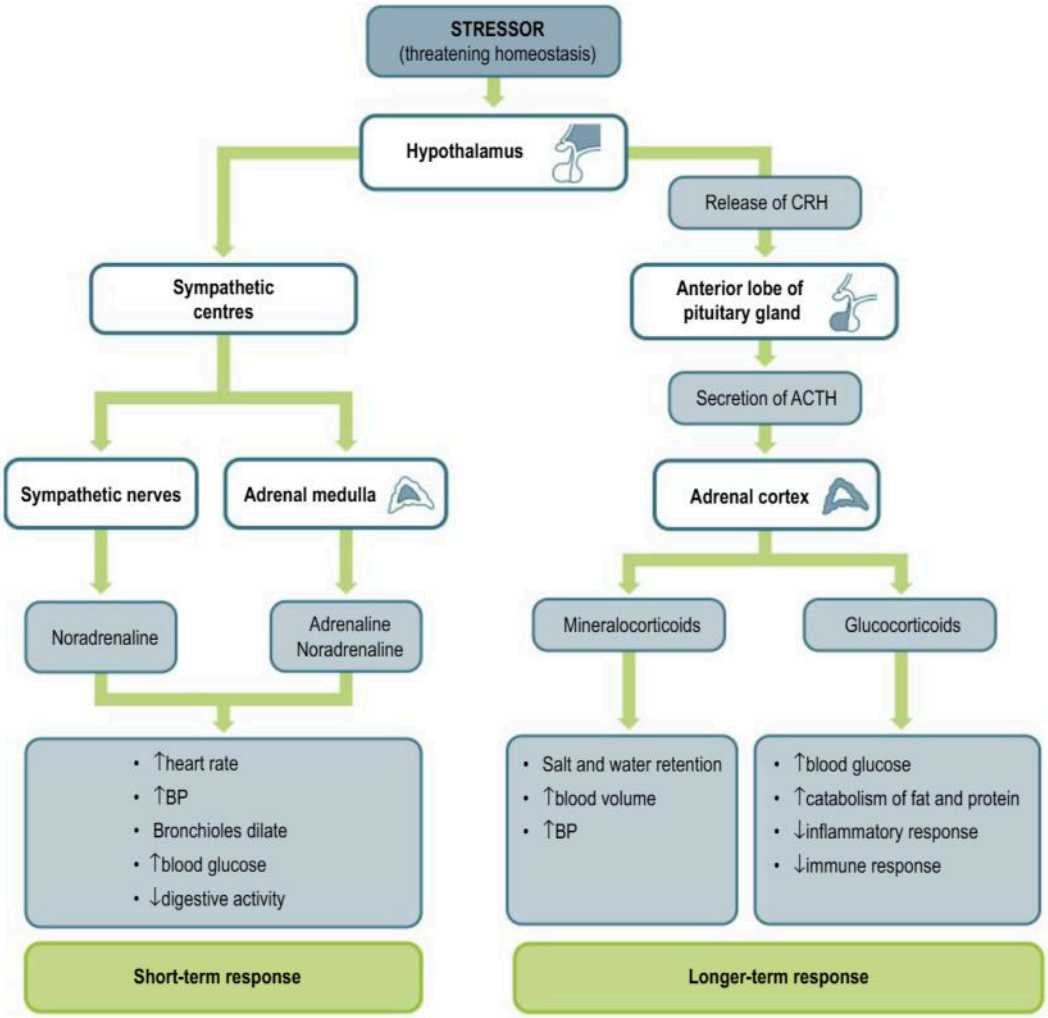

Figure 9.12 Endocrine responses to stress. *ACTH*, adrenocorticotrophic hormone; *BP*, blood pressure; *CRH*, corticotrophin releasing hormone.

is mediated by the sympathetic nervous system and the principal effects are shown in Figure 9.12.

Longer-term stress leads to release of ACTH from the anterior pituitary, which stimulates the release of glucocorticoids and mineralocorticoids from the adrenal cortex, providing a more prolonged response (Fig. 9.12).

Adrenal medulla

The medulla is surrounded by the adrenal cortex (Fig. 9.11B). It develops from nervous tissue in the embryo and is part of the sympathetic nervous system (Ch. 7).

Adrenaline (epinephrine) and noradrenaline (norepinephrine)

Noradrenaline is the postganglionic neurotransmitter of the sympathetic division of the autonomic nervous system (see Fig. 7.44). When stimulated by its extensive sympathetic nerve supply, the adrenal glands release the hormones adrenaline (epinephrine, 80%) and noradrenaline (norepinephrine, 20%) into the bloodstream. These hormones prolong and augment stimulation of the sympathetic nervous system by binding to the receptors of its effector organs (Fig. 7.45). Structurally, they are very similar, which explains their similar effects. They potentiate the fight or flight response by:

- increasing heart rate
- increasing blood pressure
- diverting blood to essential organs, including the heart, brain and skeletal muscles, by dilating their blood vessels and constricting those of less essential organs, such as the skin
- increasing metabolic rate
- dilating the pupils.

Adrenaline has a greater effect on the heart and metabolism, whereas noradrenaline has more influence on blood vessel diameter.

Adrenal cortex

The adrenal cortex produces three groups of steroid hormones from cholesterol, collectively called adrenocorticoids (corticosteroids):

- glucocorticoids
- mineralocorticoids
- sex hormones (gonadocorticoids).

The hormones in each group have different actions, but as they are structurally similar, their actions may overlap.

Glucocorticoids

Cortisol (hydrocortisone) is the main glucocorticoid but small amounts of corticosterone and cortisone are also produced. Glucocorticoids are essential for life, regulating metabolism, the inflammatory and immune responses, and responses to stress (Fig. 9.12).

Secretion is controlled through a negative feedback system involving the hypothalamus and anterior pituitary. It is stimulated by ACTH from the anterior pituitary and by stress (Fig. 9.13). Cortisol secretion shows marked circadian variation, peaking between 4 a.m. and 8 a.m. and being lowest between midnight and 3 a.m. When the sleep/wake pattern is changed, e.g. in night shift working, it takes several days for ACTH/cortisol secretion to readjust (p. 243). Glucocorticoid secretion increases in response to stress (Figs 9.12 and 9.13), including infection and surgery.

Glucocorticoids have widespread metabolic effects, generally concerned with catabolism (breakdown) of protein and fat that makes glucose and other substances available for use to help the body combat stress. These include:

- hyperglycaemia (raised blood glucose levels) caused by breakdown of glycogen and gluconeogenesis (formation of new sugar from, for example, protein)
- lipolysis (breakdown of triglycerides into fatty acids and glycerol for energy production), raising circulating levels of free fatty acids
- stimulation of protein breakdown, releasing amino acids and increasing blood levels; amino acids are then used for synthesis of other proteins, e.g. enzymes, or for energy production (Ch. 12)
- promoting absorption of sodium and water from renal tubules (a weak mineralocorticoid effect).

In pathological and pharmacological quantities, glucocorticoids also have other effects, including:

- anti-inflammatory actions
- suppression of immune responses
- delayed wound healing.

When corticosteroids are administered systemically to treat inflammatory disorders, e.g. asthma, the high circulating levels exert a negative feedback effect on the hypothalamus and pituitary, which can completely suppress natural secretion of CRH and ACTH, respectively.

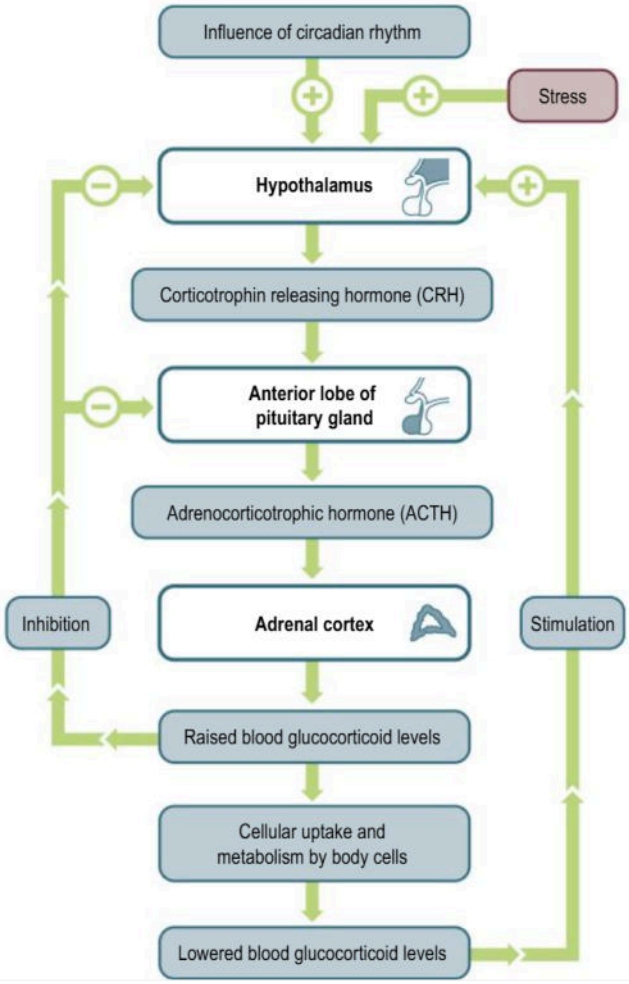

Figure 9.13 Negative feedback regulation of glucocorticoid secretion.

Mineralocorticoids (aldosterone)

Aldosterone is the main mineralocorticoid, and is involved in maintaining water and electrolyte balance. Through a negative feedback system it stimulates reabsorption of sodium (Na^+) by the renal tubules and excretion of potassium (K^+) in the urine. Sodium reabsorption is accompanied by water retention and therefore aldosterone is involved in the regulation of blood volume and blood pressure too.

Blood potassium levels regulate aldosterone secretion by the adrenal cortex. When blood potassium levels rise, more aldosterone is secreted (Fig. 9.14). Low blood potassium has the opposite effect. Angiotensin II (see below) also stimulates the release of aldosterone.

Renin–angiotensin–aldosterone system (RAAS)

When renal blood flow is reduced or blood sodium levels fall, the enzyme renin is secreted by kidney cells. Renin converts the plasma protein angiotensinogen, produced by the liver, to angiotensin I (one). Angiotensin converting enzyme (ACE), formed in small quantities mainly in the

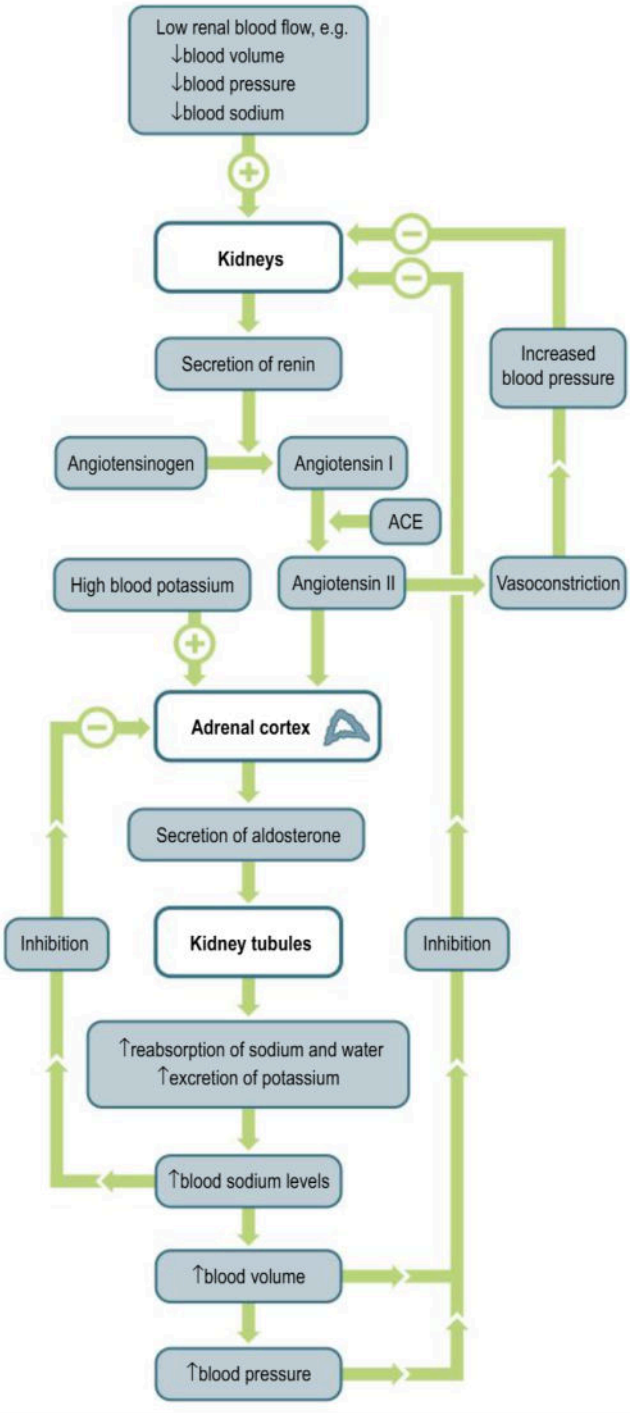

Figure 9.14 Negative feedback regulation of aldosterone secretion.

lungs, converts angiotensin I to angiotensin II (two), which stimulates secretion of aldosterone from the adrenal cortex. Angiotensin II causes vasoconstriction and increases blood pressure, closing the negative feedback loop (Fig. 9.14).

Sex hormones (gonadocorticoids)

Sex hormones secreted by the adrenal cortex are mainly androgens (male sex hormones), although the amounts produced are insignificant compared with those secreted by the testes and ovaries in late puberty and adulthood (Ch. 18).

SPOT CHECK

4. Name the three groups of adrenocorticoid hormones.

Pancreatic islets

Learning outcomes

After studying this section, you should be able to:

- list the hormones secreted by the endocrine pancreas
- describe the actions of insulin and glucagon
- explain how blood glucose levels are regulated.

The gross structure of the pancreas is described in Chapter 12. Only 2% of pancreatic tissue has an endocrine function and this consists of clusters of cells scattered throughout the gland; these are known as the pancreatic islets (islets of Langerhans). Pancreatic hormones are secreted directly into the bloodstream and circulate throughout the body. This is in marked contrast to the exocrine pancreas and its associated ducts (see Fig. 12.34).

There are some 1–2 million pancreatic islets, which contain three main types of hormone-secreting cell:

- α (alpha) cells, which secrete glucagon
- β (beta) cells, the most numerous accounting for about 75% of islet cells, and which secrete insulin
- δ (delta) cells, which secrete somatostatin (GHRIH)

The normal blood glucose level is between 3.5 and 8 mmol/L (63–144 mg/100 mL). Blood glucose levels are controlled within this range mainly by the opposing actions of insulin and glucagon:

- Glucagon increases blood glucose levels.
- Insulin reduces blood glucose levels.

Insulin

Insulin is a polypeptide hormone consisting of 51 amino acids. Body cells require glucose to fuel their metabolic activities but glucose does not freely cross the cell membrane. All body cells have insulin receptors on their plasma membranes, and in the presence of insulin can actively import glucose. Insulin also has an essential function in lowering raised blood nutrient levels, not only glucose but also

amino acids and fatty acids. These are anabolic effects, i.e. they promote storage of nutrients. The tissues most sensitive to the action of insulin are liver, skeletal muscle and adipose tissue. When blood levels of glucose and other nutrients are in excess of immediate needs, insulin promotes their storage by:

- activating glucose transport mechanisms in cell membranes, stimulating uptake and use of glucose by muscle and connective tissue cells
- increasing conversion of glucose to glycogen (glycogenesis), especially in the liver and skeletal muscles
- accelerating uptake of amino acids by cells, and their use in protein synthesis
- promoting synthesis of fatty acids and storage of fat in adipose tissue (lipogenesis)
- decreasing glycogenolysis (breakdown of glycogen into glucose)
- preventing the breakdown of protein and fat, and gluconeogenesis (formation of new sugar from, for example, protein).

Secretion of insulin is stimulated by increased blood glucose levels, e.g. after eating a meal, and to a lesser extent by parasympathetic stimulation, raised blood amino acid and fatty acid levels, and gastrointestinal hormones, e.g. gastrin, secretin and cholecystokinin. Secretion is decreased by sympathetic stimulation, glucagon, adrenaline (epinephrine), cortisol and somatostatin (GHRIH), which is secreted by the hypothalamus and pancreatic islets.

Glucagon

Glucagon increases blood glucose levels by stimulating:

- conversion of glycogen to glucose in the liver and skeletal muscles (glycogenolysis)
- gluconeogenesis.

Secretion of glucagon is stimulated by low blood glucose levels and exercise, and decreased by somatostatin and insulin.

Somatostatin

Somatostatin (GHRIH), also produced by the hypothalamus, inhibits secretion of both insulin and glucagon by the islet cells in addition to inhibiting the secretion of GH from the anterior pituitary (p. 242).

SPOT CHECK

5. Secretion of which hormone is stimulated by low blood sugar levels?

Pineal gland

Learning outcomes

After studying this section, you should be able to:

- state the position of the pineal gland
- outline the actions of melatonin.

The pineal gland is a small body attached to the roof of the third ventricle and is connected to it by a short stalk containing nerves, many of which terminate in the hypothalamus (see Fig. 7.17). The pineal gland is about 1 cm long, reddish brown in colour and surrounded by a capsule. It tends to atrophy after puberty and may become calcified in later life.

Melatonin

This is the main hormone secreted by the pineal gland. It is structurally similar to serotonin (see below). Secretion is suppressed by daylight and increased during darkness; levels fluctuate during each 24-hour period, being highest at night and the lowest around midday. Secretion is also influenced by the number of daylight hours, i.e. there may be seasonal variations. Although its functions are not fully understood, melatonin is believed to be associated with:

- coordination of the body's daily and seasonal circadian and diurnal rhythms
- mood, as melatonin has been implicated in seasonal affective disorder (SAD), also known as 'winter depression', a condition associated with low mood during winter when there are few hours of daylight
- possibly inducing sleepiness during darkness
- maturation of the sex organs at puberty.

SPOT CHECK

6. At what time of day are melatonin levels highest?

Organs with secondary endocrine functions

Learning outcome

After studying this section, you should be able to:

- outline the functions of other hormones secreted as a secondary function of some glands and tissues.

Table 9.4 Organs with secondary endocrine functions

Organ	Hormone	Site of action	Function
Kidney	Erythropoietin	Red bone marrow	Stimulation of red blood cell production (Ch. 4)
Gastrointestinal tract			
Gastric mucosa	Gastrin	Gastric glands	Stimulates secretion of gastric juice (Ch. 12)
Intestinal mucosa	Secretin	Stomach and pancreas	Stimulates secretion of pancreatic juice; slows emptying of the stomach (Ch. 12)
	Cholecystokinin (CCK)	Gallbladder and pancreas	Stimulates release of bile and pancreatic juice (Ch. 12)
Adipose tissue	Leptin	Hypothalamus and other tissues	Provides a feeling of fullness ('satiety') after eating (Ch. 11); needed for gonadotrophin releasing hormone and gonadotrophin synthesis (Ch. 18)
Ovary and testis	Inhibin	Anterior pituitary	Inhibits secretion of follicle stimulating hormone
Heart (atria)	Atrial natriuretic peptide (ANP)	Kidney tubules	Decreases reabsorption of sodium and water in renal tubules (Ch. 13)
Placenta	Human chorionic gonadotrophin (hCG)	Ovary	Stimulates secretion of oestrogen and progesterone during pregnancy (Ch. 5)
Thymus	Thymosin	White blood cells (T-lymphocytes)	Development of T-lymphocytes (Ch. 15)

In addition to the glands with primary endocrine functions already described, many other organs and tissues secrete hormones as a secondary function (see Fig. 9.1). Examples of such organs and the hormones they secrete are shown in Table 9.4.

SPOT CHECK

7. Which organs/tissues, respectively, secrete human chorionic gonadotrophin, secretin and erythropoietin as a secondary function?

Local hormones

Learning outcome

After studying this section, you should be able to:

- outline the actions of local hormones.

A number of body tissues not normally described as endocrine glands secrete substances that act on local tissues. Some of these are outlined here.

Histamine

This is synthesised and stored by mast cells in the tissues and basophils in blood. It is an important inflammatory mediator, especially in allergic inflammation (p. 426), increasing capillary permeability and causing vasodilation.

Serotonin (5-hydroxytryptamine)

This is present in platelets, and its role in haemostasis (blood clotting) is outlined in Chapter 4.

Prostaglandins

Prostaglandins (PGs) are a group of lipid-based substances found in most tissues. They act on neighbouring cells but their actions are short-lived as they are quickly metabolised and their blood levels are negligible. Prostaglandins have potent and wide-ranging physiological effects in:

- inflammatory responses
- potentiation of pain
- stimulation of gastric mucus production
- fever
- regulation of blood pressure
- blood clotting
- uterine contractions during labour.

Other chemically similar compounds include leukotrienes, which are involved in inflammatory and immune responses, and thromboxanes, e.g. thromboxane A_2, a potent aggregator of platelets. These substances are also found in only small amounts, as they are rapidly degraded.

SPOT CHECK

8. Which cells make histamine?

Effects of ageing on the endocrine system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the endocrine system.

Endocrine function often declines with age, although levels of some important hormones can remain unchanged well into old age.

Reduced secretion of aldosterone and renin may contribute to age-related postural hypotension and increase sodium and water loss.

In the pancreatic islets, β-cell function declines with age. Especially when associated with weight gain in middle life and older age, the risk of type 2 diabetes mellitus is increased (p. 262).

Ovarian secretion of female sex hormones declines after the menopause (see Ch. 18), although secretion of the male sex hormone testosterone often remains high well into old age.

Some hormone levels may rise with age, including PTH; this may contribute to osteoporosis (Ch. 16).

The risk of most endocrine cancers rises with age.

SPOT CHECK

9. What condition is associated with declining pancreatic function in older life?

Endocrine disorders are commonly caused by tumours or autoimmune diseases, and their effects are usually the result of:

- hypersecretion (over-production) of hormones, or
- hyposecretion (under-production) of hormones.

The effects of many conditions explained in this section can therefore be readily linked to the underlying abnormality.

Disorders of the pituitary gland

Learning outcomes

After studying this section, you should be able to:

- relate the features of conditions affecting the anterior pituitary to the actions of the hormones involved
- relate the features of diabetes insipidus to abnormal secretion of antidiuretic hormone.

Hypersecretion of anterior pituitary hormones

Gigantism and acromegaly

The most common cause is prolonged hypersecretion of growth hormone (GH), usually by a hormone-secreting pituitary tumour. The conditions are occasionally due to excess growth hormone-releasing hormone (GHRH) secreted by the hypothalamus.

As the tumour increases in size, compression of nearby structures may lead to hyposecretion of other pituitary hormones (from both lobes) and damage to the nearby optic nerves (see Fig. 9.2), causing visual disturbances. The effects of excess GH include:

- excessive growth of bones
- enlargement of internal organs
- formation of excess connective tissue
- enlargement of the heart, hypertension and atheroma (Ch. 5)
- reduced glucose tolerance and a predisposition to diabetes mellitus.

Gigantism

This occurs when GH levels are excessive in pre-pubescent children whose epiphyseal cartilages of long bones are still growing, i.e. before ossification of bones is complete. It is evident mainly in the bones of the limbs, and affected individuals may grow to heights of 2.1 to 2.4 m, although body proportions remain normal (Fig. 9.15).

Acromegaly

Meaning 'large extremities', this occurs in adults when there is excessive GH secretion, usually from a pituitary tumour, after ossification is complete.

Figure 9.15 Historical drawing showing the effects of normal and abnormal growth hormone secretion. From left to right: normal stature, gigantism (2.3 m tall) and restricted growth (dwarfism; 0.9 m tall). (George Bernard/Science Photo Library. Reproduced with permission.)

Figure 9.16 Facial features and large hands in acromegaly. (John Radcliffe Hospital/Science Photo Library. Reproduced with permission.)

The bones become abnormally thick and there is also thickening of the soft tissues. These changes are most noticeable as coarse facial features (especially excessive growth of the lower jaw), an enlarged tongue and excessively large hands and feet (Fig. 9.16).

Without treatment, life expectancy is shortened considerably. There is an increased incidence of premature death from consequences of heart failure, hypertension and coronary artery disease along with a predisposition to large bowel tumours.

Hyposecretion of anterior pituitary hormones

Panhypopituitarism is the absence of all anterior pituitary hormones. The number of hormones involved and the extent of hyposecretion vary. Most are the result of physical damage to the gland, including:

- tumours of the hypothalamus or pituitary or pituitary compression by an adjacent tumour
- trauma, usually caused by surgery or skull fractures
- infection, e.g. meningitis, encephalitis, syphilis
- ionising radiation or cytotoxic drugs.
- postpartum necrosis.

Postpartum necrosis

Also known as Sheehan's syndrome, this occurs following hypotensive shock associated with severe haemorrhage during or after childbirth. Improvements in obstetric care have greatly reduced the incidence in developed countries.

A portal blood supply, instead of a direct arterial supply, makes the anterior pituitary unusually susceptible to a fall in systemic blood pressure. Failure of lactation precedes the other effects, which include deficient anterior pituitary secretion and consequent hypofunction of all or some of the thyroid, adrenal cortex and gonads. The outcome depends on the extent of pituitary necrosis and hormone deficiency and in mild cases signs may not become evident for many months. In severe cases, glucocorticoid deficiency may be life-threatening or fatal.

Pituitary dwarfism

This is caused by deficiency of GH, and sometimes other hormones, in childhood. It may be due to genetic abnormality or a tumour. The individual is small in stature but normally proportioned, cognitive development is not affected (Fig. 9.15). Puberty is delayed and there may be episodes of hypoglycaemia.

Disorders of the posterior pituitary

Diabetes insipidus

In this rare condition there is hyposecretion of ADH. It is usually secondary to damage to the hypothalamus by, for example, head injury, tumour or encephalitis. Occasionally, it occurs when the renal tubules fail to respond to ADH.

Water reabsorption by the renal tubules is impaired, leading to excretion of excessive amounts of dilute urine, often more than 10 litres daily. This results in dehydration and extreme thirst (polydipsia). Greatly increasing fluid intake will compensate for excess losses, but when this is not possible, life-threatening dehydration develops.

SPOT CHECK

10. Excessive urine output is associated with which posterior pituitary condition?

Disorders of the thyroid gland

Learning outcome

After studying this section, you should be able to:

- compare and contrast the effects of hyperthyroidism and hypothyroidism, relating them to the actions of T_3 and T_4.

Disorders of the thyroid gland fall into three main categories:

- abnormal hormone secretion, causing hyperthyroidism or hypothyroidism
- enlargement of the entire gland – goitre
- tumours.

Abnormal thyroid function may arise not only from thyroid disease but also from disorders of the pituitary or hypothalamus; in addition, insufficient dietary iodine impairs synthesis of thyroid hormones. The main symptoms are caused by abnormal secretion of T_3 and T_4.

Hyperthyroidism

This syndrome, also known as thyrotoxicosis, arises as the body tissues are exposed to excessive levels of T_3 and T_4. The symptoms are due to increased basal metabolic rate (see Table 9.3).

In older adults, cardiac failure is another common consequence, as the ageing heart must work harder to deliver more blood and nutrients to the hyperactive body cells. The main causes of hyperthyroidism are:

- Graves' disease
- toxic nodular goitre
- adenoma (a benign tumour).

Graves' disease

Sometimes called Graves' thyroiditis, this accounts for 75% of cases of hyperthyroidism. It affects more women than men and may occur at any age, but most commonly people between the ages of 30 and 50. It is an organ-specific autoimmune disorder in which an antibody that mimics the effects of TSH is produced, causing:

- increased release of T_3 and T_4 and signs of hyperthyroidism (see Table 9.3)
- goitre (visible enlargement of the gland, Fig. 9.17) as the antibody stimulates thyroid growth
- exophthalmos in many cases.

Exophthalmos

This is protrusion of the eyeballs that gives the appearance of staring; it is due to the deposition of excess fat and fibrous tissue behind the eyes (Fig. 9.18), and is often present in Graves' disease. Effective treatment of hyperthyroidism

Figure 9.17 Enlarged thyroid gland in goitre. (Science Photo Library. Reproduced with permission.)

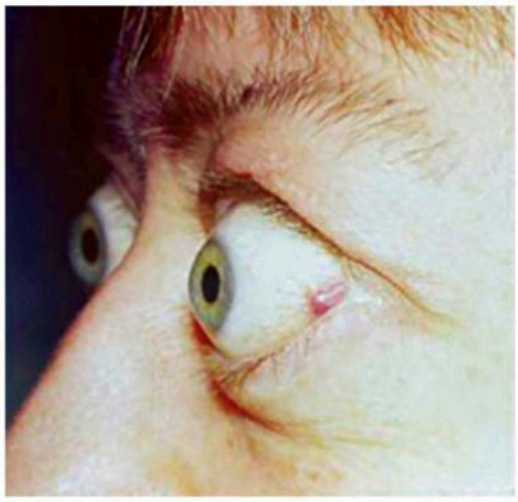

Figure 9.18 Abnormally bulging eyes in exophthalmos. (From Patton K, 2022. Anatomy & Physiology, 11th ed. Elsevier.)

does not completely reverse exophthalmos, although it may lessen after 2–3 years. In severe cases the eyelids become retracted and may not completely cover the eyes during blinking and sleep, leading to drying of the conjunctiva and predisposing to infection. It does not occur in other forms of hyperthyroidism.

Toxic nodular goitre

In this condition, one or two nodules of a gland that is already affected by goitre (see Fig. 9.17) become active and secrete excess T_3 and T_4, causing the effects of hyperthyroidism (see Table 9.3). It is more common in women than men and after middle age. As this condition affects an older age group than Graves' disease, arrhythmias and cardiac failure are more common. Exophthalmos does not occur.

Hypothyroidism

Prevalent in older adults, this condition is five times more common in females than males. Deficiency of T_3 and T_4 in adults results in an abnormally low metabolic rate and other effects shown in Table 9.3. There may be accumulation of mucopolysaccharides in the subcutaneous tissues, causing swelling (non-pitting oedema), especially of the face, hands, feet and eyelids (myxoedema). The most common causes are autoimmune thyroiditis, severe iodine deficiency (see goitre) and healthcare interventions, e.g. antithyroid drugs, surgical removal of thyroid tissue or ionising radiation.

Autoimmune thyroiditis

The most common cause of acquired hypothyroidism is Hashimoto's disease. It is more common in women than men and, like Graves' disease, is an organ-specific autoimmune condition. Autoantibodies that react with thyroglobulin and thyroid gland cells develop and prevent synthesis and release of thyroid hormones, causing hypothyroidism. Goitre is sometimes present.

Congenital hypothyroidism

This is a profound deficiency or absence of thyroid hormones that becomes evident a few weeks or months after birth. Hypothyroidism is endemic in parts of the world where the diet is severely deficient in iodine and contains insufficient for synthesis of T_3 and T_4. Absence of thyroid hormones results in profound impairment of growth and cognitive development. Unless treatment begins early in life, cognitive impairment is permanent and the individual typically has disproportionately short limbs, a large, protruding tongue, coarse, dry skin, poor abdominal muscle tone and, often, an umbilical hernia.

Simple goitre

This is enlargement of the thyroid gland without signs of hyperthyroidism. It is caused by a relative lack of T_3 and T_4 and low plasma levels of these hormones then stimulate pituitary secretion of TSH. This results in hyperplasia (see Fig. 3.27) and enlargement of the thyroid gland (see Fig. 9.17). Sometimes the extra thyroid tissue is able to maintain normal hormone levels, but if not, hypothyroidism develops. Causes may be:

- persistent iodine deficiency – in parts of the world where there is dietary iodine deficiency, this is a common condition and known as endemic goitre
- genetic – an abnormality affecting synthesis of T_3 and T_4
- iatrogenic – e.g. antithyroid drugs, surgical removal of excess thyroid tissue.

The enlarged gland may compress adjacent tissues, especially if it lies in an abnormally low position, i.e. behind the sternum. The most significantly affected structures are the

oesophagus, causing dysphagia, the trachea, causing dyspnoea, and the recurrent laryngeal nerve, causing hoarseness.

Tumours of the thyroid gland

Malignant tumours are rare.

Benign tumours

Single adenomas are fairly common and may become cystic. Sometimes the adenoma secretes hormones and hyperthyroidism may develop. These tumours may become malignant, especially in older adults.

SPOT CHECK

11. List six symptoms of thyrotoxicosis caused by raised levels of T_3 and T_4.

Disorders of the parathyroid glands

Learning outcome

After studying this section, you should be able to:

- explain how the diseases described here are related to abnormal secretion of parathyroid hormone.

Hyperparathyroidism

This condition is characterised by high blood calcium levels (hypercalcaemia) and is usually caused by a benign parathyroid tumour, which secretes high levels of parathormone (PTH). This increases release of calcium from bones, raising blood calcium levels. The effects may include:

- polyuria and polydipsia
- formation of renal calculi
- anorexia and constipation
- muscle weakness
- general fatigue.

Hypercalcaemia

This can be caused by bone malignancies, sarcoidosis and multiple myeloma as well as hyperparathyroidism.

Hypoparathyroidism

PTH deficiency causes hypocalcaemia, i.e. abnormally low blood calcium levels, and is much rarer than hyperparathyroidism. There is less reabsorption of calcium from bone and glomerular filtrate. Low blood calcium causes:

Figure 9.19 Characteristics of tetanic spasms.

- tetany (Fig. 9.19)
- anxiety
- paraesthesia
- grand mal seizures
- in some cases, cataracts (opacity of the lens, see Fig. 8.26) and brittle nails.

Causes of hypoparathyroidism include damage to or removal of the glands during thyroidectomy, ionising radiation, development of autoantibodies to PTH and parathyroid cells, and congenital abnormalities.

Tetany

This is caused by hypocalcaemia, because low blood calcium levels increase the excitability of peripheral nerves. There are very strong painful spasms of skeletal muscles, causing characteristic inward bending of the hands, forearms and feet (Fig. 9.19). In children there may also be laryngeal spasm and seizures.

Hypocalcaemia

In addition to hypoparathyroidism, this may be caused by:

- chronic kidney disease, as the failing kidney is unable to retain calcium and excretes large quantities in the urine; this is the commonest cause of hypocalcaemia
- deficiency of vitamin D or dietary deficiency of calcium
- alkalosis – metabolic or respiratory
- acute pancreatitis.

SPOT CHECK

12. What is the most common cause of hyperparathyroidism?

Disorders of the adrenal cortex

Learning outcomes

After studying this section, you should be able to:

- relate the features of Cushing's syndrome to the physiological actions of adrenocorticoids
- relate the features of Addison's disease to the physiological actions of adrenocorticoids.

Hypersecretion of glucocorticoids (Cushing's syndrome)

Cortisol is the main glucocorticoid hormone secreted by the adrenal cortex. Causes of hypersecretion include:

- most commonly, hypersecretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary
- prolonged systemic treatment with ACTH or glucocorticoids
- abnormal (ectopic) secretion of ACTH by a non-pituitary tumour, e.g. the bronchus or pancreas
- hormone-secreting adrenal tumours.

Hypersecretion of cortisol exaggerates its physiological effects (Fig. 9.20). These include:

- adiposity of the face ('moon face'), neck and abdomen
- excessive tissue protein breakdown, causing thinning of subcutaneous tissue and muscle wasting, especially of the limbs
- diminished protein synthesis
- suppression of GH secretion, impairing normal growth in children
- osteoporosis (p. 479), and kyphosis if vertebral bodies are affected
- pathological fractures caused by calcium loss from bones
- excessive gluconeogenesis, resulting in hyperglycaemia and glycosuria, which can induce diabetes mellitus (p. 261)
- atrophy of lymphoid tissue and suppression of immune responses
- susceptibility to infection due to impaired febrile response and suppressed immune and inflammatory responses

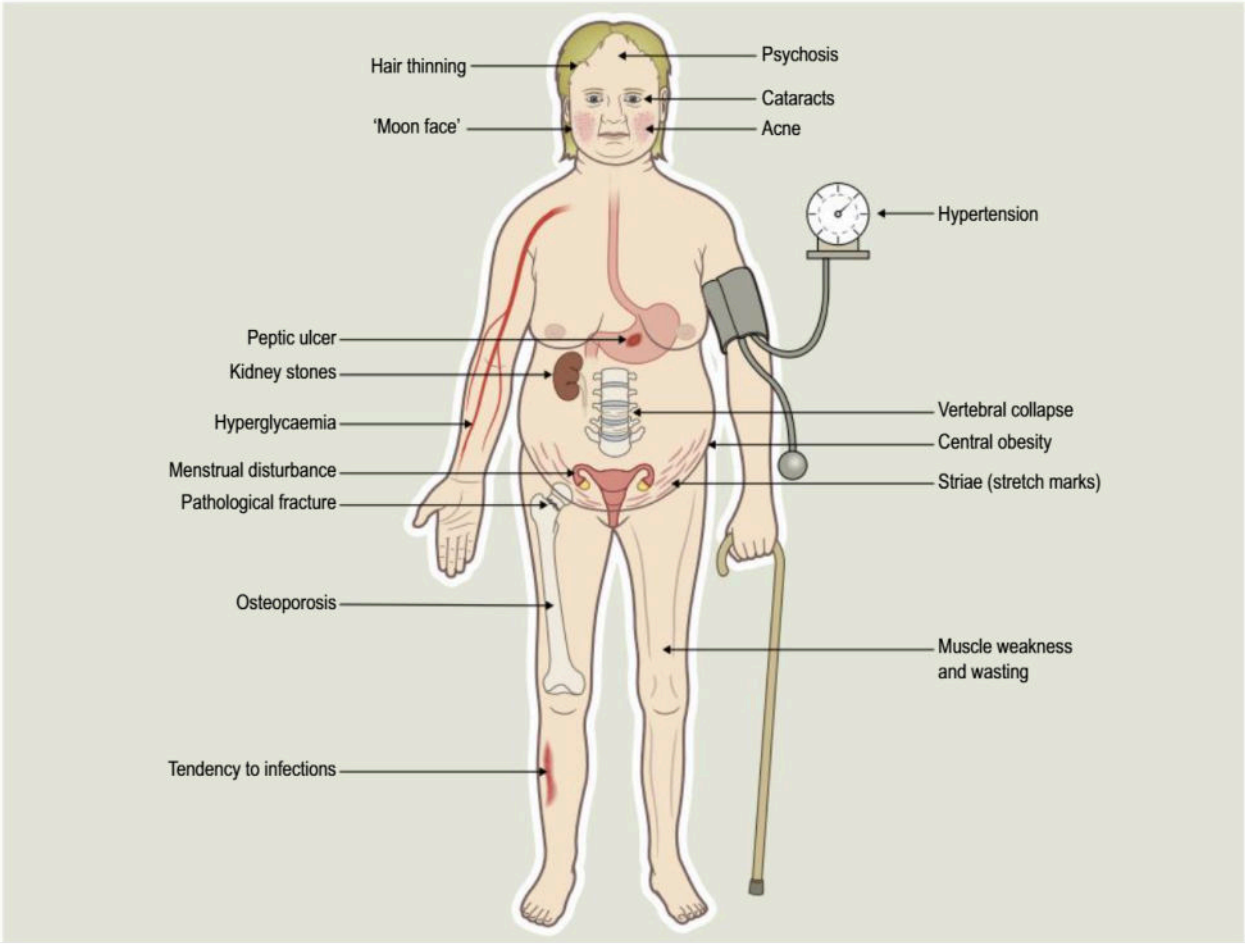

Figure 9.20 The systemic features of Cushing's syndrome.

- impaired collagen production, leading to capillary fragility, cataract (see Fig. 8.26) and striae (stretch marks)
- insomnia, excitability, euphoria, depression or psychosis
- hypertension due to salt and water retention
- menstrual disturbances
- renal calculi
- peptic ulceration.

Hyposecretion of glucocorticoids

Inadequate cortisol secretion causes diminished gluconeogenesis, low blood glucose levels, muscle weakness and pallor. This may be:

- primary – due to disease of the adrenal cortex; this is accompanied by hyposecretion of aldosterone (see below)
- secondary – due to deficiency of ACTH from the anterior pituitary. Aldosterone secretion is not usually affected because its release is controlled by the renin–angiotensin–aldosterone system (RAAS, see Fig. 9.14)

Hypersecretion of mineralocorticoids

Excess aldosterone secretion affects kidney function, with consequences elsewhere:

- excessive reabsorption of sodium chloride and water, causing increased blood volume and hypertension
- excessive excretion of potassium, causing hypokalaemia, which leads to cardiac arrhythmias, alkalosis, syncope, muscle weakness and, occasionally, paralysis or tetany (see Fig. 9.19).

Primary hyperaldosteronism

Also known as Conn's syndrome, this is due to excessive mineralocorticoid secretion, which occurs independently of the RAAS. It is usually caused by a tumour affecting only one adrenal gland.

Secondary hyperaldosteronism

This is more common than the primary form; it is a physiological response to low renal perfusion or low blood sodium levels that raises renin levels (see Fig. 9.14).

Hyposecretion of mineralocorticoids

Hypoaldosteronism results in failure of the kidneys to regulate sodium, potassium and water excretion, leading to:

- blood sodium deficiency (hyponatraemia) and potassium excess (hyperkalaemia)
- dehydration, low blood volume and low blood pressure.

There is usually hyposecretion of other adrenal cortical hormones, as in Addison's disease.

Chronic adrenocortical insufficiency (Addison's disease)

This is due to destruction of the adrenal cortex, which results in hyposecretion of glucocorticoids and mineralocorticoids. The most common causes are sudden withdrawal of systemic corticosteroid therapy, development of autoantibodies to adrenocortical cells, metastatic tumours and infections, e.g. tuberculosis or HIV. Autoimmune disease of other glands can also be associated with Addison's disease, e.g. diabetes mellitus, thyrotoxicosis and hypoparathyroidism. The most important effects are:

- muscle weakness and wasting
- gastrointestinal disturbances, e.g. vomiting, diarrhoea, anorexia
- increased skin pigmentation, especially of exposed areas
- listlessness and tiredness
- hypoglycaemia
- confusion
- menstrual disturbances and loss of body hair in women
- electrolyte imbalance, including hyponatraemia and hyperkalaemia
- chronic dehydration, low blood volume and hypotension.

The adrenal glands have a considerable tissue reserve and Addison's disease is not usually severely debilitating unless more than 90% of the adrenal cortex is destroyed, but this condition is fatal without treatment.

Acute adrenocortical insufficiency (Addisonian crisis)

This is characterised by sudden severe nausea, vomiting, diarrhoea, hypotension, electrolyte imbalance (hyponatraemia and hyperkalaemia) and, in severe cases, circulatory collapse. It is precipitated when an individual with chronic adrenocortical insufficiency is subjected to stress, e.g. by an acute infection.

SPOT CHECK

13. List the main features of Cushing's syndrome.

Disorders of the adrenal medulla

Learning outcome

After studying this section, you should be able to:

- explain how the features of phaeochromocytoma relate to excessive hormone secretion.

Tumours

Most tumours of the adrenal medulla are hormone-secreting. The predominant symptoms are therefore consequences of hypersecretion of adrenaline (epinephrine) and noradrenaline (norepinephrine), i.e. those of excessive sympathetic stimulation (see Fig. 7.45). These include:

- hypertension
- weight loss
- nervousness and anxiety
- headache
- excessive sweating and alternate flushing and blanching of the skin
- hyperglycaemia and glycosuria
- constipation.

Phaeochromocytoma

This is usually a benign condition although tumours can be multiple and occur in one or both glands. Hormone secretion may be constantly elevated or occur in intermittent bursts, often precipitated by raised intra-abdominal pressure, e.g. coughing or defaecation.

SPOT CHECK

14. Explain why tumours of the adrenal medulla cause symptoms including hypertension, weight loss, anxiety, nervousness and excessive sweating.

Disorders of the pancreatic islets

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the onset and features of types 1 and 2 diabetes mellitus
- relate the signs and symptoms of diabetes mellitus to deficiency of insulin
- explain how the causes and effects of the following conditions occur: diabetic ketoacidosis and hypoglycaemic coma
- describe the long-term complications of diabetes mellitus.

Diabetes mellitus

Diabetes mellitus (DM) is the most common endocrine disorder and the principal condition that affects the pancreatic islets. The primary sign is hyperglycaemia, which is accompanied by varying degrees of disruption of carbohydrate and fat metabolism. DM is caused by complete absence of, relative deficiency of or resistance to the hormone insulin.

Box 9.1 Classification of diabetes mellitus

Primary

Type 1 diabetes mellitus

Type 2 diabetes mellitus

Secondary

Due to other situations, e.g.:

- Acute or chronic pancreatitis (p. 368)
- Drug therapy, e.g. corticosteroids
- Other endocrine disorders involving hormones that increase plasma glucose levels, e.g. growth hormone, thyroid hormones, cortisol (Cushing's syndrome, p. 259)

Gestational diabetes

Develops during pregnancy and may disappear after delivery, but often recurs in later life

Associated with birth of heavier than normal and stillborn babies, and deaths shortly after birth

Table 9.5 Features of type 1 and type 2 diabetes mellitus (DM)

	Type 1 DM	Type 2 DM
Age of onset	Usually childhood	Adulthood and later life
Body weight at onset	Normal or low	Obese
Onset of symptoms	Weeks	Months/years
Main cause(s)	Autoimmune	Obesity, lack of exercise
Insulin requirement	100% of cases	Up to 20% of cases
Ketonuria	Yes	No
Complications at diagnosis	No	Up to 25%
Family history	Rare	Common

Box 9.1 shows the classification of diabetes. Primary DM is categorised as type 1 or type 2. In secondary DM, the disorder arises as a result of other conditions, and gestational diabetes develops in pregnancy. Some distinguishing features of types 1 and 2 DM are shown in Table 9.5; genetic predisposition and environmental factors, including viral infections, are implicated in both types.

The worldwide increase in DM over the past few decades has been described as an epidemic. The International Diabetes Foundation estimates that globally, some 463 million adults aged 20–79 years are currently living with diabetes (almost 10% of the world's population in this age group) and that around 20% of people over the age of 65 are affected. The prevalence continues to increase rapidly although there

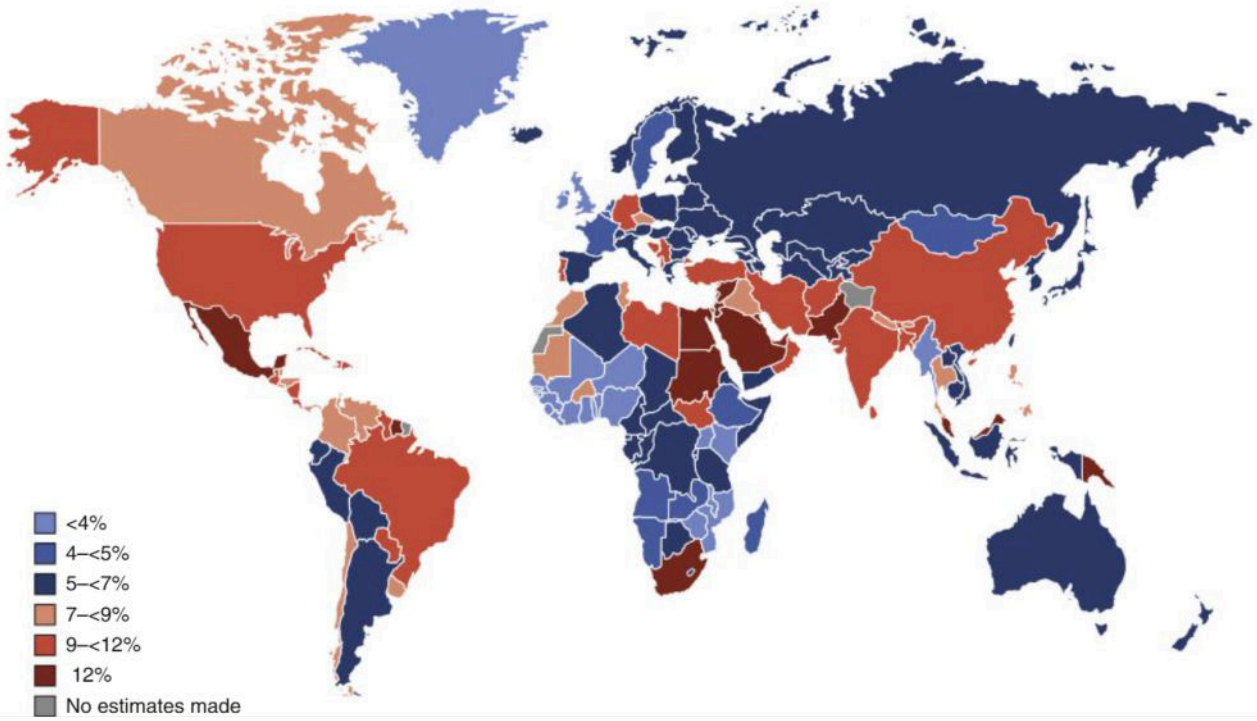

Figure 9.21 Estimated prevalence of diabetes in adults (aged 20–79) in 2019. (From International Diabetes Federation. https://diabetesatlas.org)

is significant variation across the world (Fig. 9.21). DM is a major cause of blindness, kidney failure, myocardial infarction, stroke and lower limb amputation worldwide.

Type 1 diabetes mellitus

Previously known as insulin-dependent diabetes mellitus (IDDM), this occurs mainly in children and young adults; the onset is usually sudden and can be life-threatening. It is of autoimmune origin, and there is severe deficiency or absence of insulin secretion due to destruction of β-islet cells by autoantibodies. Treatment with insulin is required.

Type 2 diabetes mellitus

Previously known as non-insulin-dependent diabetes mellitus (NIDDM), this is the most common form of diabetes, accounting for about 90% of cases. The causes are multifactorial and predisposing factors include:

- obesity
- sedentary lifestyle
- increasing age, predominantly affecting middle-aged and older adults
- ethnicity, increased risk in people from black African, African Caribbean and south Asian backgrounds
- environmental and genetic factors.

Its onset is gradual, often over many years, and it frequently goes undetected until signs are found on routine investigation or a complication occurs. Up to 25% of patients have evidence of one or more long-term complications at the time of diagnosis.

Insulin secretion may be below or above normal. Body cells are unable to extract glucose from the extracellular fluid, and there are two main reasons for this. Firstly, inadequate insulin levels means that activation of the insulin-mediated glucose transport mechanisms in the plasma membrane is deficient. Secondly, insulin receptors on the cell surface may become dysfunctional, known as insulin resistance, so that even in the presence of normal or elevated blood glucose and insulin levels, the cells cannot extract the insulin they require. Treatment involves diet and/or oral medication, although insulin injections are required in about 20% of patients.

Pathophysiology of diabetes mellitus

Raised plasma glucose level (hyperglycaemia)

After a carbohydrate-rich meal, the plasma glucose level remains high because:

- cells are unable to take up and use glucose from the bloodstream, despite high plasma levels
- conversion of glucose to glycogen in the liver and muscles is diminished
- there is gluconeogenesis from protein, in response to deficiency of intracellular glucose.

Hyperglycaemia causes long-term damage to blood vessels and nerves (see below).

Glycosuria and polyuria

The concentration of glucose in the glomerular filtrate is the same as in the blood and, although DM raises the renal threshold for glucose, it is not all reabsorbed by the kidney tubules. The glucose remaining in the filtrate raises its osmotic pressure, causing a reduction in water reabsorption and so increasing the volume of urine produced (polyuria). This results in electrolyte imbalance and excretion of urine of high specific gravity. Polyuria leads to dehydration, extreme thirst (polydipsia) and increased fluid intake.

Weight loss

This is fairly common in type 1 DM but rare in type 2. It happens as the cells are essentially starved of glucose because, in the absence of insulin, they are unable to extract it from the bloodstream. This leads to derangement of energy metabolism as cells must use alternative metabolic pathways to produce the energy they need. This results in weight loss due to:

- gluconeogenesis from amino acids and body protein, causing muscle wasting, tissue breakdown and further increases in blood glucose
- catabolism of body fat, releasing some of its energy and excess production of ketone bodies.

Ketosis and ketoacidosis

This is much more common in type 1 DM than in type 2.

In the absence of insulin to promote normal intracellular glucose metabolism, alternative energy sources must be used instead and increased breakdown of fat occurs (see Fig. 12.45). Ketones, including acetone and butyrate, are released as by-products. The liver has a limited capacity to metabolise these ketones, and normal buffering systems maintain pH balance so long as the levels of ketone bodies are not excessive. Ketosis (p. 352) develops as ketone bodies accumulate. Excretion of ketones is via the urine (ketonuria) and/or the lungs, giving the breath a characteristic smell of acetone or 'pear drops'.

Ketoacidosis is a medical emergency, indicating severely deranged cell metabolism secondary to insulin deficiency. It may be due to stressors such as pregnancy, infection or acute illness, or missed or inadequate doses of insulin, especially when requirements are increased. Severe and dangerous ketoacidosis may occur without loss of consciousness. When worsening ketosis swamps the compensatory buffer systems, control of acid–base balance is lost; the blood pH falls and ketoacidosis occurs. If this is untreated, the consequences are:

- worsening hyperglycaemia
- increasing acidosis (abnormally low blood pH) due to accumulation of keto acids
- hyperventilation as the lungs excrete excess hydrogen ions as CO_2 in an attempt to correct the acidosis
- acidification of urine – the result of kidney buffering to excrete excess H^+
- polyuria as the renal threshold for glucose is exceeded
- dehydration and hypovolaemia (characterised by hypotension and tachycardia) – caused by polyuria
- disturbances of electrolyte balance accompanying fluid loss – hyponatraemia (decreased plasma sodium) and hypokalaemia (decreased plasma potassium)
- confusion and coma
- death.

Acute complications of diabetes mellitus

Diabetic ketoacidosis

The effects and consequences of diabetic ketoacidosis are outlined above.

Hypoglycaemia and hypoglycaemic coma

In DM, hypoglycaemia is defined as plasma glucose under 4 mmol/L (70 mg/dL) and indicates that treatment is required to increase blood glucose levels. It usually occurs when insulin is administered in excess of that needed to balance the food intake and expenditure of energy. Hypoglycaemia is of sudden onset and may be the result of:

- accidental overdose of insulin
- delay in eating after administration of insulin
- drinking alcohol on an empty stomach
- strenuous exercise.

It may also arise from an insulin-secreting tumour, especially if it produces irregular bursts of secretion. Because neurones are more dependent on glucose for their energy needs than other cells, glucose deprivation causes disturbed neurological function, leading to coma and, if prolonged, irreversible brain damage.

Common signs and symptoms of hypoglycaemia include drowsiness, confusion, speech difficulty, sweating, trembling, anxiety and a rapid pulse. This can progress rapidly to hypoglyaemic coma without treatment. Treatment, e.g. a glucose drink or tablet, or sugary sweets usually facilitates rapid recovery. Most people quickly learn to recognise the symptoms of hypoglycaemia and can take appropriate action.

Long-term complications of diabetes mellitus

Over time, hyperglycaemia damages blood vessels and nerves, so poor control increases the risk of long-term complications; these represent significant causes of morbidity (poor health) and mortality (death) in people with both type 1 and type 2 DM.

Cardiovascular disturbances

DM is a significant risk factor for cardiovascular disorders, which account for about 80% of deaths. Blood vessel abnormalities (angiopathies) may still occur even when the disease is well controlled.

Diabetic macroangiopathy

Macroangiopathy means disorders of large blood vessels, mainly due to atheroma and calcification of the tunica media

of the large arteries. In type 1 DM these changes often occur at a relatively early age. The most common consequences are serious and often fatal:

- ischaemic heart disease, i.e. angina and myocardial infarction (p. 138)
- stroke (p. 201)
- peripheral vascular disease.

Diabetic microangiopathy

As the name suggests, this affects small blood vessels; there is thickening of the epithelial basement membrane of arterioles, capillaries and, sometimes, venules. These changes may lead to:

- peripheral vascular disease, progressing to gangrene and 'diabetic foot' (see below)
- diabetic retinopathy and visual impairment (p. 235)
- diabetic nephropathy and chronic kidney disease (p. 392)
- peripheral neuropathy, causing sensory deficits and motor weakness.

Peripheral neuropathy

Also called diabetic neuropathy, this affects more than half of those with DM. Its prevalence increases with poor diabetic control and the length of time since diagnosis. Impaired sensation, described variously as tingling, burning, aching, electric or shooting sensations or numbness develops. Initially the feet are affected and sometimes later the legs too; neuropathy may also develop in the hands and arms. In many people the condition is painless although in about a third, it is reported as painful. This is an important risk factor in diabetic foot (see below).

In some people motor function also becomes impaired; this can lead to difficulty walking normally and eventually abnormal gait. Neuropathy can affect other organs too, including the cardiovascular system causing postural hypotension and sometimes tachycardia at rest, and the gastrointestinal tract in many ways including dysphagia, dyspepsia, abdominal pain and altered bowel function.

Infection

DM predisposes to infection, especially by bacteria and fungi, possibly because phagocyte activity is depressed by insufficient intracellular glucose. Infection may cause:

- boils and carbuncles
- vaginal candidiasis (thrush, p. 520)
- pyelonephritis (p. 393)
- diabetic foot.

Renal failure

Chronic kidney disease is due to diabetic nephropathy (p. 392) and is a common cause of death.

Figure 9.22 Diabetic foot. A large heel ulcer. (Dr P Marazzi/Science Photo Library. Reproduced with permission.)

Visual impairment and blindness

Diabetic retinopathy (p. 235) is the most common cause of blindness in adults between 30 and 65 years in developed countries. DM also increases the risk of early development of cataracts (p. 235) and other visual disorders.

Diabetic foot

Many factors commonly present in DM contribute to the development of this serious situation. Disease of large and small blood vessels impairs blood supply to and around the extremities. If peripheral neuropathy is present, sensation is reduced and a small injury to the foot may go unnoticed, especially when there is visual impairment. In DM, healing is slower and injuries easily worsen if aggravated, e.g. by chafing shoes, and often become infected. An ulcer may form (Fig. 9.22) and the healing process is lengthy, if it occurs at all. In severe cases the injured area ulcerates and enlarges, and may become gangrenous, sometimes to the extent that amputation is required.

SPOT CHECK

15. Explain why the signs of polyuria and polydipsia occur in diabetes.

References and further reading

International Diabetes Federation, 2019. IDF Diabetes Atlas, ninth edition. Available online at: https://diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf.

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Case study

Stella has a disorder of her thyroid gland.

1. The thyroid gland secretes its hormones in response to raised blood levels of:

   a. Thyroid stimulating hormone
   b. Thyrotrophin releasing hormone
   c. Thyroxine
   d. Tri-iodothyronine

2. Which dietary constituent is essential for production of thyroid hormones?

   a. Calcium
   b. Iodine
   c. Vitamin A
   d. Vitamin D

The doctor explains that signs and symptoms of thyroid disorders are related to the physiological effects of over- or under-secretion of thyroid hormones and that she has an underactive thyroid gland.

3. The signs of an underactive thyroid gland include:

   a. Tachycardia and palpitations
   b. Increased metabolic rate
   c. Heat intolerance
   d. Weight gain

The parathyroid glands are closely associated with the thyroid gland.

4. Which statement describes them most accurately?

   a. They lie embedded in the posterior surface of the thyroid gland.
   b. They secrete calcitonin, which increases blood calcium levels.
   c. They secrete insulin which promotes storage of glucose.
   d. They atrophy after puberty.

Review and revise

Complete each of the following statements:

1. Endocrine glands are groups of secretory cells surrounded by networks of _____ that carry the chemical messengers, known as _____, to distant sites where they act on their _____.

2. Complications of diabetes that damage blood vessel walls are called _____. Changes to small blood vessels in the eyes can lead to _____ and cause _____ in the kidneys.

Choose one answer to complete each of the following statements:

3. The most abundant hormone secreted by the anterior pituitary gland is: _____
   a. Growth hormone
   b. Thyroid stimulating hormone
   c. Adrenocorticotrophic hormone
   d. Prolactin

4. Prostaglandins are: _____
   a. Cells in the prostate gland
   b. Involved in the cardiac cycle
   c. Involved in blood clotting
   d. Long-acting substances

Indicate whether each of the following statements is true or false:

5. Oxytocin secretion from the posterior pituitary is an example of a positive feedback control mechanism. _____

6. The thyroid gland has four lobes. _____

7. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Insulin
____ (b) Leptin
____ (c) Prolactin
____ (d) Oxytocin
____ (e) Cortisol
____ (f) Calcitonin
____ (g) Noradrenaline (norepinephrine)
____ (h) Glucagon

List B

1. Posterior pituitary
2. α-cells of the pancreatic islets
3. β-cells of the pancreatic islets
4. Adrenal cortex
5. Adrenal medulla
6. Adipose tissue
7. Thyroid
8. Anterior pituitary

8. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Acromegaly
____ (b) Tetany
____ (c) Phaeochromocytoma
____ (d) Graves' disease
____ (e) Diabetes insipidus
____ (f) Gestational diabetes
____ (g) Addison's disease
____ (h) Cushing's syndrome

List B

1. Insulin
2. Glucocorticoids
3. Adrenaline (epinephrine) and noradrenaline (norepinephrine)
4. Parathyroid hormone
5. Antidiuretic hormone
6. Growth hormone
7. T_3 and T_4
8. Glucocorticoids and mineralocorticoids

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

SECTION THREE

CHAPTER 10

The respiratory system

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Review and revise 302

The first part of this chapter describes the structure and functions of the respiratory system. Later sections consider the effects of ageing on respiratory function and discuss some important respiratory disorders.

Body cells need energy for all their metabolic activities. This energy is produced by chemical reactions, which can take place only in the presence of oxygen (O_2). The main waste product of these reactions is carbon dioxide (CO_2). The respiratory system provides the route by which atmospheric oxygen enters the body, and the route for carbon dioxide excretion.

The condition of the atmospheric air entering the respiratory tract varies considerably according to the external environment: it may be dry or moist, warm or cold,

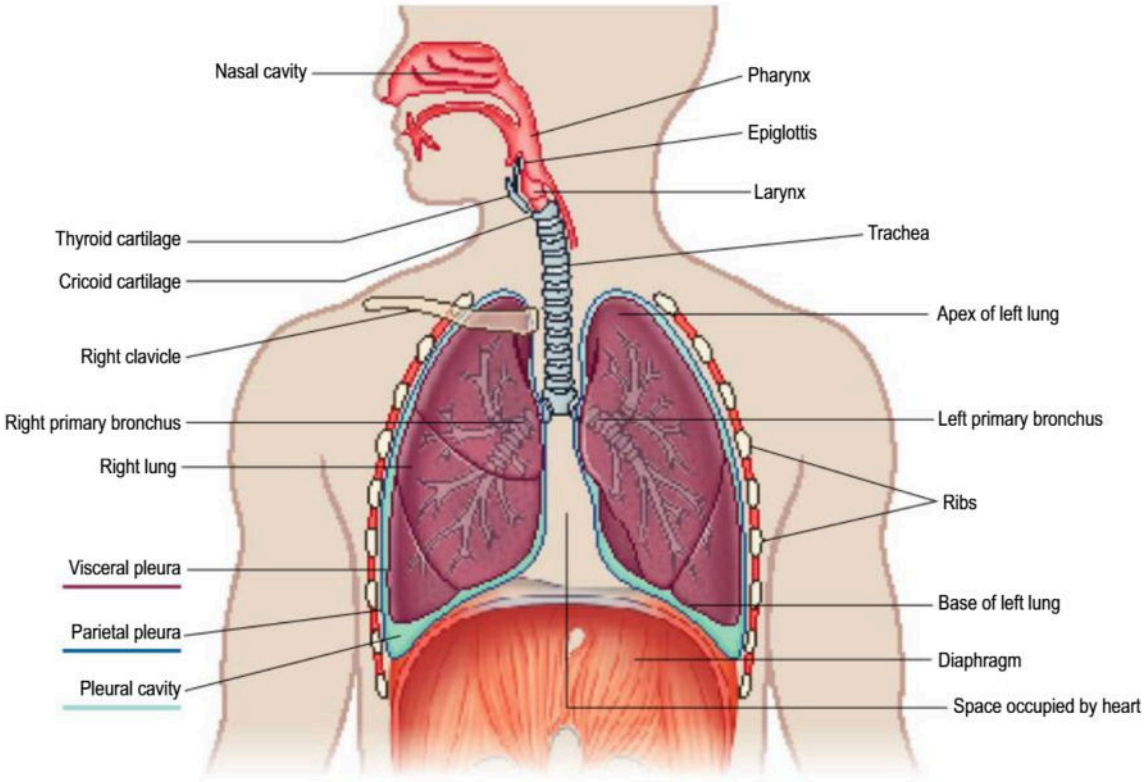


Figure 10.1 The respiratory system.

and carry varying quantities of pollutants, dust or dirt. As inhaled air flows through the air passages towards the lungs, it is warmed or cooled to body temperature, saturated with water vapour and 'cleaned' as particles of dust stick to the mucus that coats the epithelium lining the airways. Blood transports O_2 and CO_2 between the lungs and body tissues. Exchange of gases between the blood and the lungs is called external respiration and that between the blood and the cells internal respiration.

Figure 10.1 shows the organs of the respiratory system and associated structures.

Nose and nasal cavity

Learning outcomes

After studying this section, you should be able to:

- describe the location of the nasal cavities
- relate the structure of the nasal cavities to their function in respiration
- outline the physiology of smell.

Position and structure

The nostrils (nares) are the openings into the nose and are the main route of air entry into the respiratory system. Behind each nostril lies a large cavity, the walls of which are formed by several bones of the face. The right and left nasal cavities are separated by the nasal septum (Fig. 10.2).

Bones forming the nasal cavity

The roof is formed by the cribriform plate of the ethmoid bone and the sphenoid bone, frontal bone and nasal bones.

The floor is formed by the roof of the mouth and consists of the hard palate in front and the soft palate behind. The hard palate is composed of the maxilla and palatine bones, and the soft palate consists of smooth muscle.

The medial wall is formed by the septum, a perpendicular sheet of bone and cartilage formed from the vomer and ethmoid bones and also the cartilage forming the anterior part of the nose.

The lateral walls are formed by the maxilla, the ethmoid bone and the inferior conchae (Fig. 10.3). The posterior wall is formed by the posterior wall of the pharynx.

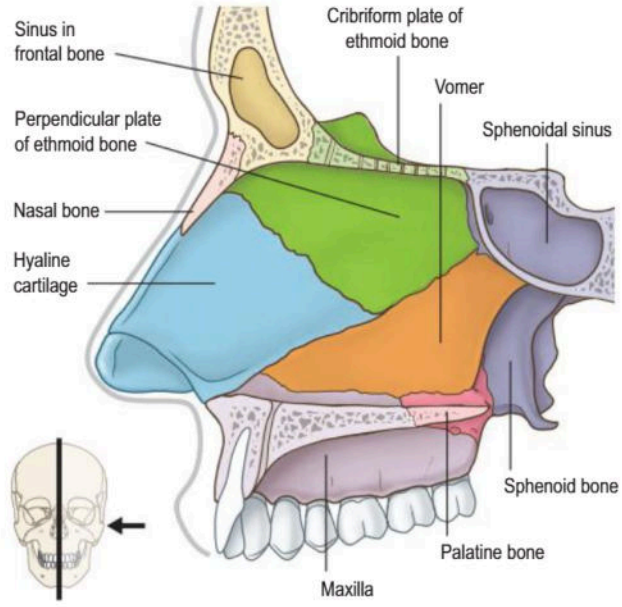


Figure 10.2 Structures forming the nasal septum.

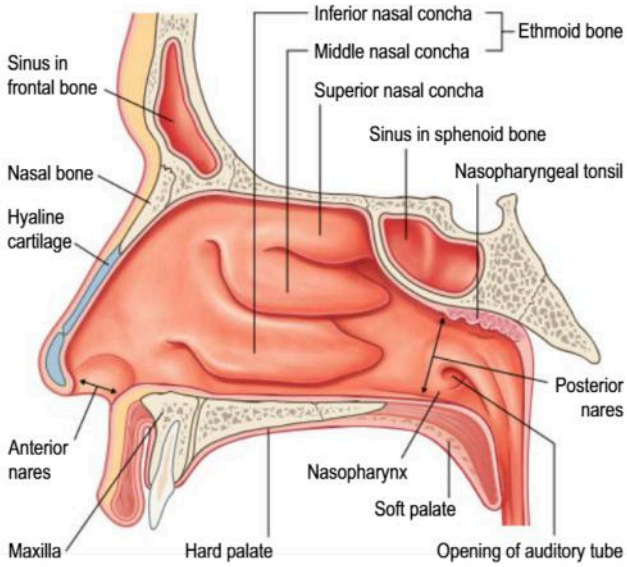


Figure 10.3 Lateral wall of right nasal cavity.

Lining of the nasal cavity

The nasal cavity is lined with very vascular ciliated columnar epithelium (ciliated mucous membrane, see Fig. 10.12), which contains mucus-secreting goblet cells. At the anterior nares this blends with the skin and posteriorly it extends into the nasal part of the pharynx (the nasopharynx). Here also, the epithelium has coarse hairs, covered in sticky mucus.

Openings into the nasal cavity

The anterior nares are the openings from the exterior into the nasal cavity. The posterior nares are the openings from the nasal cavity into the pharynx (Fig. 10.3).

The paranasal sinuses are four groups of tiny air-filled cavities in the bones of the face and the cranium. They open into the nasal cavity and are lined with ciliated mucous membrane, continuous with that of the nasal cavity. The main sinuses are:

- maxillary sinuses in the lateral walls
- frontal and sphenoidal sinuses in the roof
- ethmoidal sinuses in the upper part of the lateral walls.

The sinuses are involved in speech and lighten the skull. The nasolacrimal ducts extend from the lateral walls of the nose to the conjunctival sacs of the eye (p. 227). They drain tears from the eyes.

Functions

Respiratory function of the nose

The nose is the first of the respiratory passages through which inspired air passes. In the nasal cavity, air is warmed, moistened and filtered. The three projecting conchae (Figs 10.3 and 10.4) increase the surface area and cause turbulence, spreading inspired air over the whole nasal surface. The large surface area maximises warming, humidification and filtering.

Warming

The nasal mucosa is very vascular, and rapidly warms the air flowing over its surface. This also explains the large blood loss when a nosebleed (epistaxis) occurs.

Filtering and cleaning

Hairs at the anterior nares trap larger particles. Smaller particles such as dust and bacteria settle and adhere to the mucus. Mucus protects the underlying epithelium from irritation and prevents drying. Synchronous beating of the cilia wafts the mucus towards the throat, where it is swallowed or coughed up.

Humidification

As air travels over the moist mucosa, it becomes saturated with water vapour. Irritation of the nasal mucosa results in sneezing, a reflex action that forcibly expels an irritant.

The sense of smell

The nose is the organ of the sense of smell (olfaction). Specialised chemoreceptors that detect smell are located in the olfactory epithelium found in the roof of the nose in the area of the cribriform plate of the ethmoid bones and the superior conchae (Fig. 10.4 and see Fig. 8.24A). These chemoreceptors are stimulated by molecules of airborne odorous substances dissolved in the mucus lining the nasal cavity. The resultant

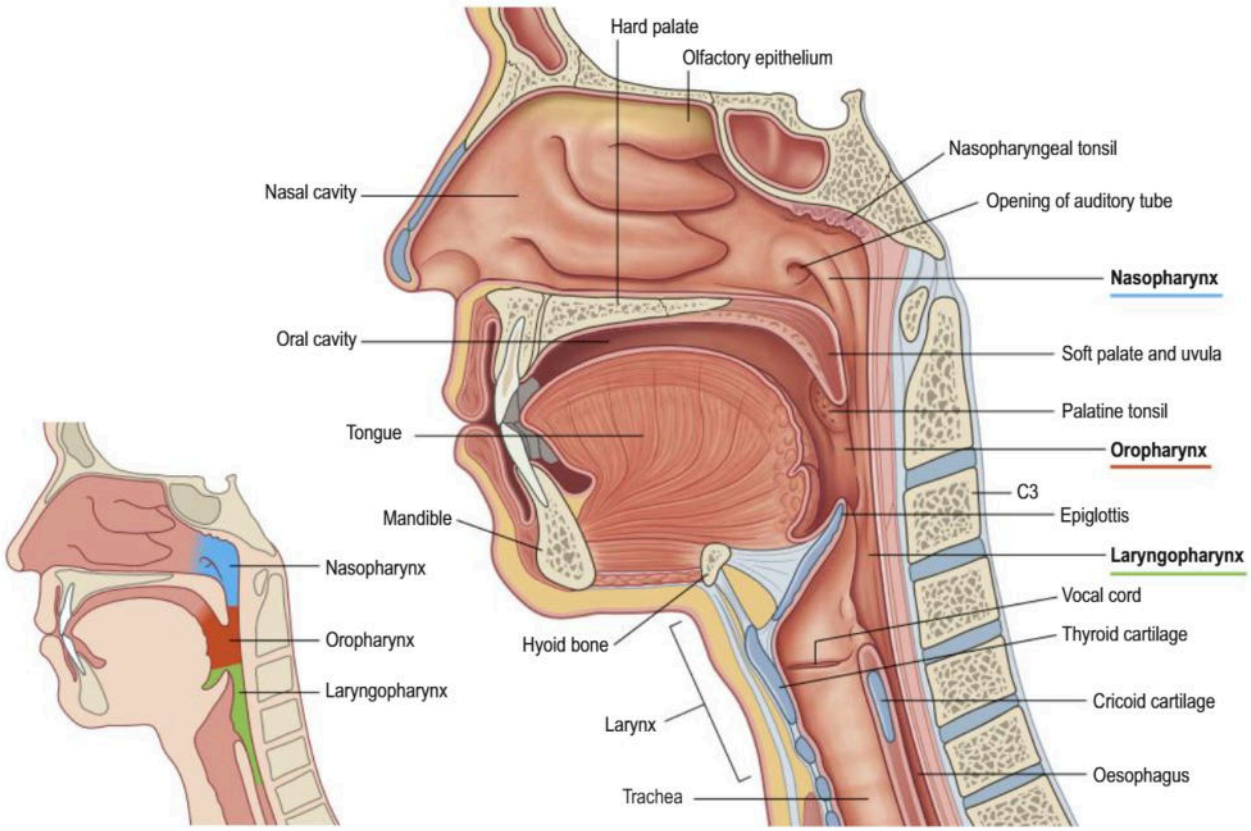


Figure 10.4 The upper respiratory tract.

nerve signals are carried by the olfactory nerves to the brain, where the sensation of smell is perceived (p. 228).

SPOT CHECK

1. Name the bones that form the walls of the nasal cavity.
2. Where is the olfactory epithelium and what is its function?

Pharynx

Learning outcomes

After studying this section, you should be able to:

- describe the location of the pharynx
- relate the structure of the pharynx to its function.

Position

The pharynx (throat) is a passageway about 12–14 cm long. It extends from the posterior nares and runs behind the mouth and the larynx to the level of the 6th cervical vertebra, where it becomes the oesophagus. The pharynx has a dual function as the passageway for air travelling to and from the lungs as well as swallowed food and drink heading into the oesophagus.

Structures associated with the pharynx

Superiorly – the inferior surface of the base of the skull.
Inferiorly – it opens into the trachea and the oesophagus.
Anteriorly – the wall is incomplete because of the openings into the nose and mouth.
Posteriorly – areolar tissue, smooth muscle and the bodies of the first six cervical vertebrae.

For descriptive purposes the pharynx is divided into three parts: nasopharynx, oropharynx and laryngopharynx.

The nasopharynx lies behind the nose above the level of the soft palate. On its lateral walls are the two openings of the auditory tubes (see Fig. 8.1), one leading to each middle ear. On the posterior wall is the pharyngeal tonsil (see Fig. 6.6), most prominent in children up to approximately 7 years of age. Thereafter it gradually atrophies.

The oropharynx lies behind the mouth, extending from below the level of the soft palate to the level of the upper part of the body of the 3rd cervical vertebra. The lateral walls of the pharynx blend with the soft palate to form two folds on each side. Between each pair of folds is the palatine tonsil (see Fig. 6.6).

During swallowing, the soft palate and uvula are pushed upwards, sealing off the nasal cavity and preventing the entry of food and fluids into the respiratory tract (see Fig. 12.16). The laryngopharynx extends from the oropharynx above and opens into the larynx at the top of the trachea. Behind the larynx, it continues as the oesophagus, the passageway to the stomach.

Structure

The walls of the pharynx contain several types of tissue.

Mucous membrane lining

The mucosa varies slightly in the different regions. In the nasopharynx it is continuous with the lining of the nose and consists of ciliated columnar epithelium. The oropharynx and laryngopharynx are lined with stratified squamous epithelium, which is continuous with the lining of the mouth and oesophagus. This thicker lining protects underlying tissues from abrasion by dry or rough foodstuffs passing through during swallowing, important because the pharynx is a passageway in both the respiratory and the digestive tracts.

Submucosa

The layer of tissue below the epithelium, the submucosa, is rich in mucosa-associated lymphoid tissue (MALT, p. 154), involved in immunity. Tonsils (p. 152) are masses of MALT that bulge through the epithelium. Some glandular tissue is also found here.

Smooth muscle

The pharyngeal muscles help to keep the pharynx permanently open so that breathing is not obstructed. Sometimes in sleep, and particularly after taking sedative drugs or alcohol, the tone of these muscles is reduced and the opening through the pharynx can become partially or totally blocked. This contributes to snoring and periodic wakenings, which disturb sleep.

Constrictor muscles close the pharynx during swallowing, pushing food and fluid into the oesophagus.

Blood and nerve supply

Blood supply to the pharynx is by several branches of the facial artery. The venous return is into the facial and internal jugular veins.

The nerve supply is from the pharyngeal plexus and includes both parasympathetic and sympathetic nerves. Parasympathetic supply is by the vagus and glossopharyngeal nerves. Sympathetic supply is by nerves from the superior cervical ganglia (see Fig. 7.45).

Functions

Passageway for air and food

The pharynx is involved in both the respiratory and the digestive systems: air passes through the nasal and oral sections into the larynx, and food through the oral and laryngeal sections into the oesophagus.

Warming and humidifying

As in the nose, the air is further warmed and moistened as it passes towards the lungs.

Hearing

The air-filled auditory tube connects the nasopharynx to the middle ear. This keeps the air in the middle ear at atmospheric pressure, so that the air pressures in the middle and outer ear are the same (see Fig. 8.1) and preventing damage to the tympanic membrane (eardrum) from any sudden changes in atmospheric pressure.

Protection from infection

Immune cells in the pharyngeal and laryngeal tonsils defend against swallowed or inhaled antigens (Ch. 15). The tonsils are larger in children and tend to atrophy in adults.

Speech

The pharynx functions in speech; by acting as a resonating chamber for sound ascending from the larynx, it helps (together with the sinuses) to give the voice its individual characteristics.

SPOT CHECK

3. Identify the locations of the main tonsils.
4. Which cavities are linked by the auditory tube?

Larynx

Learning outcomes

After studying this section, you should be able to:

- describe the structure and function of the larynx
- outline the physiology of speech generation.

Position

The larynx, or voice box, links the laryngopharynx and the trachea (Figs 10.1 and 10.4). It lies in front of the laryngopharynx and the 3rd, 4th, 5th and 6th cervical vertebrae. Until puberty there is little difference in the size of the larynx between the sexes. Thereafter, it grows larger in the male, giving men generally deeper voices than women.

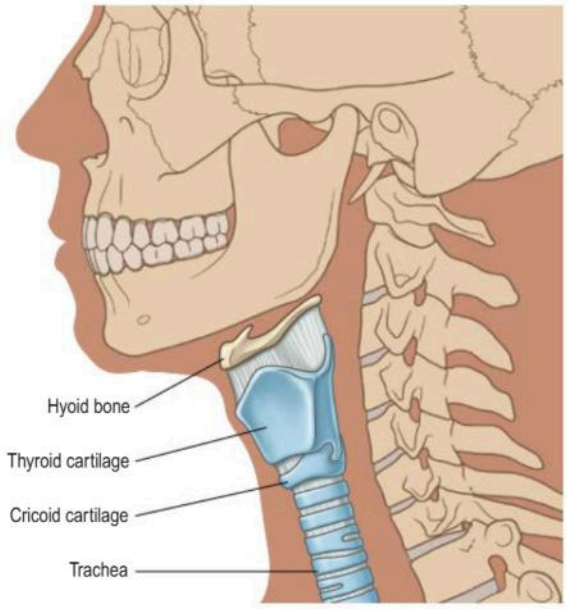


Figure 10.5 Larynx. Viewed from the side.

Structures associated with the larynx

Superiorly – the hyoid bone and the root of the tongue.
Inferiorly – it is continuous with the trachea.
Anteriorly – the muscles attached to the hyoid bone and the muscles of the neck.
Posteriorly – the laryngopharynx and 3rd–6th cervical vertebrae.
Laterally – the lobes of the thyroid gland.

Structure

Cartilages

The larynx is composed of nine irregularly shaped cartilages attached to each other by ligaments and membranes. The main cartilages are the epiglottis, the thyroid cartilage, the cricoid cartilage and two arytenoid cartilages. Several ligaments attach the cartilages to each other and to the hyoid bone (Figs 10.5 and 10.6; see also Fig. 10.8).

Thyroid cartilage

The thyroid cartilage (Figs 10.5 and 10.6), made of hyaline cartilage, is the most prominent of the laryngeal cartilages. It lies at the front of the neck and forms most of the anterior and lateral walls of the larynx. Its anterior wall projects into the soft tissues of the throat forming the laryngeal prominence (Adam's apple), easily palpated and often visible in adult males. The anterior wall is partially divided by the thyroid notch. It is incomplete posteriorly and is bound with ligaments to the hyoid bone above and the cricoid cartilage below.

The upper part of the thyroid cartilage is lined with stratified squamous epithelium like the larynx, and the lower part with ciliated columnar epithelium like the trachea.

Cricoid cartilage

The cricoid cartilage (Fig. 10.7) lies below the thyroid cartilage and is also composed of hyaline cartilage. It is shaped like a signet ring, completely encircling the larynx with the narrow part anteriorly and the broad part posteriorly. The broad posterior part articulates with the arytenoid cartilages and with the thyroid cartilage. It is lined with ciliated columnar epithelium and there are muscles and ligaments attached to

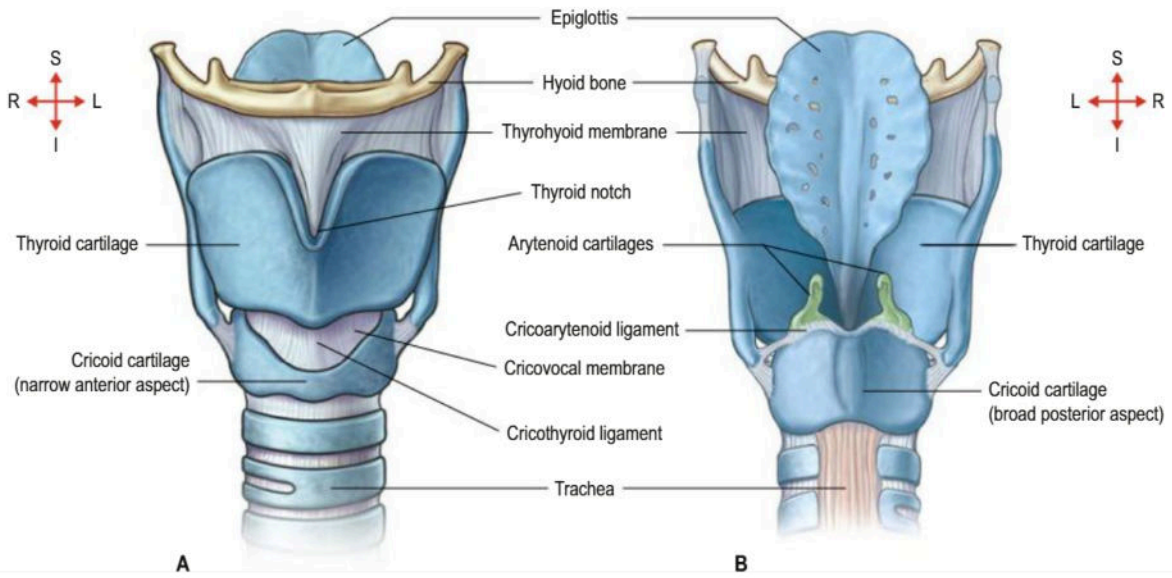


Figure 10.6 Larynx. (A) Viewed from the front. (B) Viewed from behind.

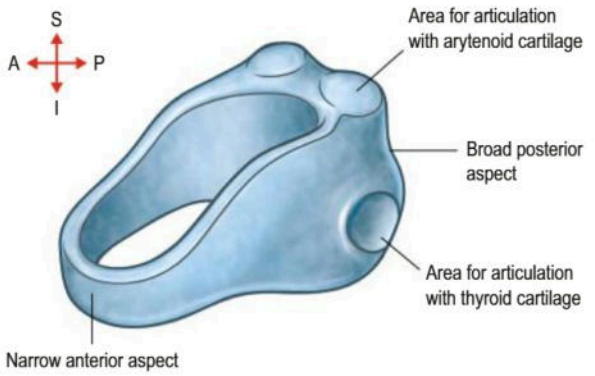


Figure 10.7 The cricoid cartilage.

its outer surface. The lower border of the cricoid cartilage marks the end of the upper respiratory tract.

Arytenoid cartilages

These are two roughly pyramid-shaped hyaline cartilages situated on top of the broad part of the cricoid cartilage, forming part of the posterior wall of the larynx (Fig. 10.6B). They give attachment to the vocal cords and to muscles and are lined with ciliated columnar epithelium.

Epiglottis

The epiglottis (Fig. 10.8; see also Figs 10.4 and 10.6) is a leaf-shaped fibroelastic cartilage covered with stratified squamous epithelium and attached by a flexible stalk of cartilage to the inner surface of the anterior wall of the thyroid cartilage, immediately below the thyroid notch. It rises obliquely upwards behind the tongue and the body of the hyoid bone. If the larynx is likened to a box, then the epiglottis acts as the lid; it closes off the larynx during swallowing, protecting the lungs from accidental inhalation of foreign objects.

Blood and nerve supply

Blood is supplied to the larynx by the superior and inferior laryngeal arteries and drained by the thyroid veins, which join the internal jugular vein.

The parasympathetic nerve supply is from the superior laryngeal and recurrent laryngeal nerves, which are branches of the vagus nerves. The sympathetic nerves are from the superior cervical ganglia, one on each side. These provide the motor nerve supply to the muscles of the larynx and sensory fibres to the lining membrane.

Interior of the larynx

The vocal cords (Fig. 10.8) are two pale folds of mucous membrane with cord-like free edges, stretched across the laryngeal opening. They extend from the inner wall of the thyroid prominence anteriorly to the arytenoid cartilages posteriorly. The space between the vocal cords is called the glottis.

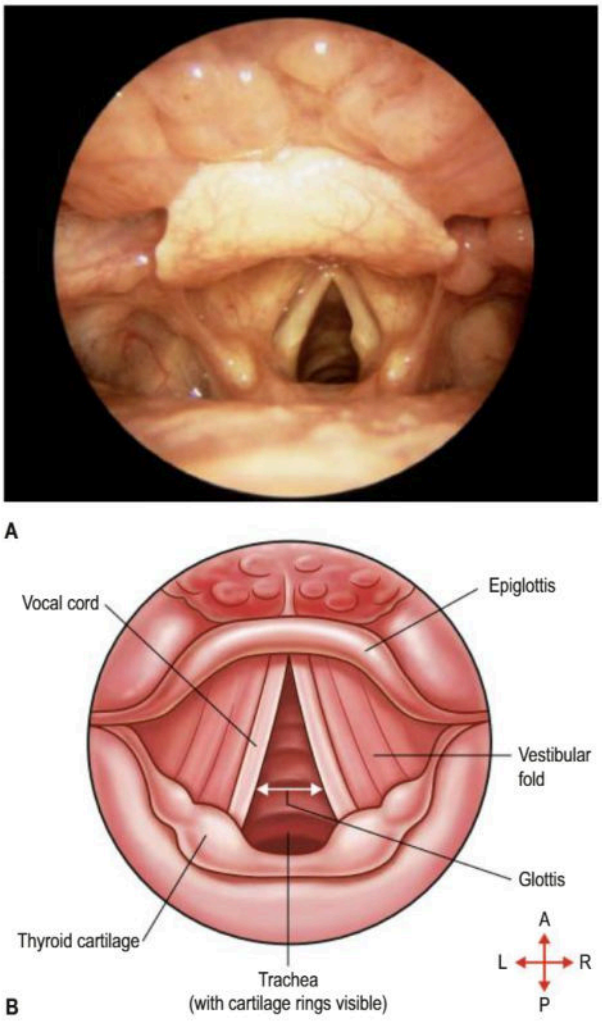


Figure 10.8 Vocal cords. (A) Bronchoscopic image of the open (abducted) vocal cords. (B) Diagram of the vocal cords showing the principal structures. (A, CNRI/Science Photo Library. Reproduced with permission.)

When the muscles controlling the vocal cords are relaxed, the vocal cords open and the passageway for air coming up through the larynx is clear; the vocal cords are said to be abducted (open, Fig. 10.9A). When the muscles controlling the vocal cords contract, the vocal cords are stretched out tightly and pulled across the glottis (Fig. 10.9B) and are said to be adducted (closed). When not in use, the vocal cords are abducted.

Functions

Production of sound

Sound is produced when the vocal cords are vibrated by air flowing upwards from the lungs, so speech, singing and other vocalisations occur during exhalation. Sound has the properties of pitch, volume and resonance.

- Pitch of the voice depends on the length and tightness of the vocal cords. The tightness is controlled by the muscles

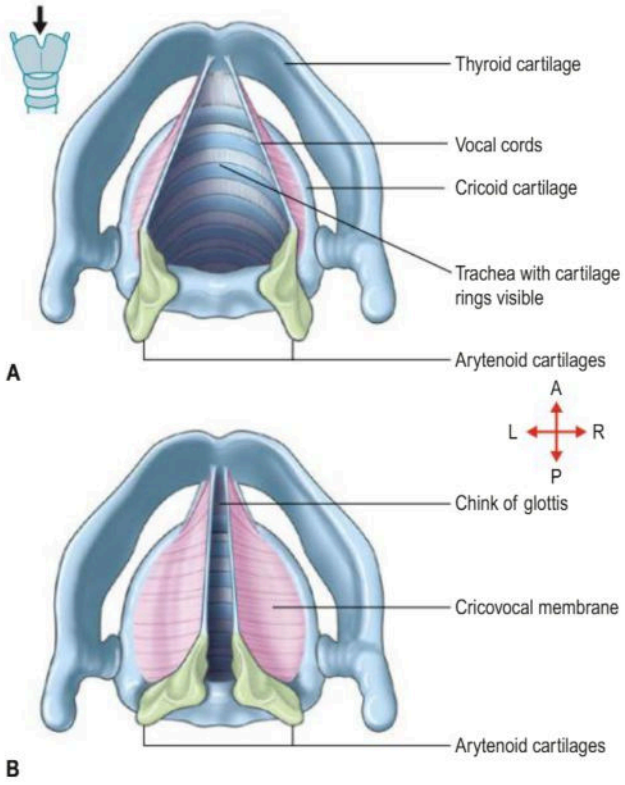


Figure 10.9 The extreme positions of the vocal cords. (A) Abducted (open). (B) Adducted (closed).

to which they attach. The cords are at their shortest and pulled most tightly in the adducted position, stretched across the glottis, and when they vibrate in this position they produce high-pitched sounds. Sounds produced when the cords are abducted and the glottis is wide are low-pitched. At puberty the male vocal cords begin to grow longer, giving adult males deeper voices than females.

- Volume of the voice depends on the force with which the cords vibrate. The greater the force of expired air, the more strongly the cords vibrate and the louder the sound produced.
- Resonance, or tone, depends on the shape of the mouth, the position of the tongue and the lips, the facial muscles and the air in the paranasal sinuses.

Speech

This is produced when the sounds produced by the vocal cords are amplified and manipulated by the tongue, cheeks and lips.

Protection of the lower respiratory tract

During swallowing (Fig. 12.16) the larynx lifts, blocking the opening into it from the oropharynx. In addition, the hinged epiglottis closes over the laryngeal opening. This ensures that food passes into the oesophagus and not the trachea.

Passageway for air

The larynx links the oropharynx above with the trachea below.

SPOT CHECK

5. Name the main cartilages of the larynx and state which ones are paired.
6. How are the pitch and volume of speech controlled?

Trachea

Learning outcomes

After studying this section, you should be able to:

- describe the location of the trachea
- outline the structure of the trachea
- explain the functions of the trachea in respiration.

Humidifying, filtering and warming

These processes continue as inspired air travels through the larynx.

Position

The trachea, or windpipe, is a continuation of the larynx and extends downwards to about the level of the 5th thoracic vertebra, where it divides at the carina into the right and left primary bronchi. The carina is rich in sensory nerve endings, and inhaled particles, irritant gases or physical contact, e.g. with an endotracheal tube, trigger a powerful and protective cough reflex. The trachea is approximately 10–11 cm long and lies in front of the oesophagus.

Structures associated with the trachea

These are shown in Figure 10.10.

Superiorly – the larynx.
Inferiorly – the right and left primary bronchi.
Anteriorly – upper part, the isthmus of the thyroid gland; lower part, the arch of the aorta and the sternum.
Posteriorly – the oesophagus, which separates the trachea from the vertebral column.
Laterally – the lungs and the lobes of the thyroid gland.

Structure

The trachea is held open by between 16 and 20 incomplete (C-shaped) rings of hyaline cartilage stacked one above the other. The rings are incomplete posteriorly, where the trachea lies against the oesophagus (Fig. 10.11). The cartilages are embedded in a sleeve of smooth muscle and connective tissue, which also forms the posterior wall where the rings are incomplete.

The tracheal wall is made up of three layers.

- The outer layer contains fibrous and elastic tissue. It is protective and supportive.

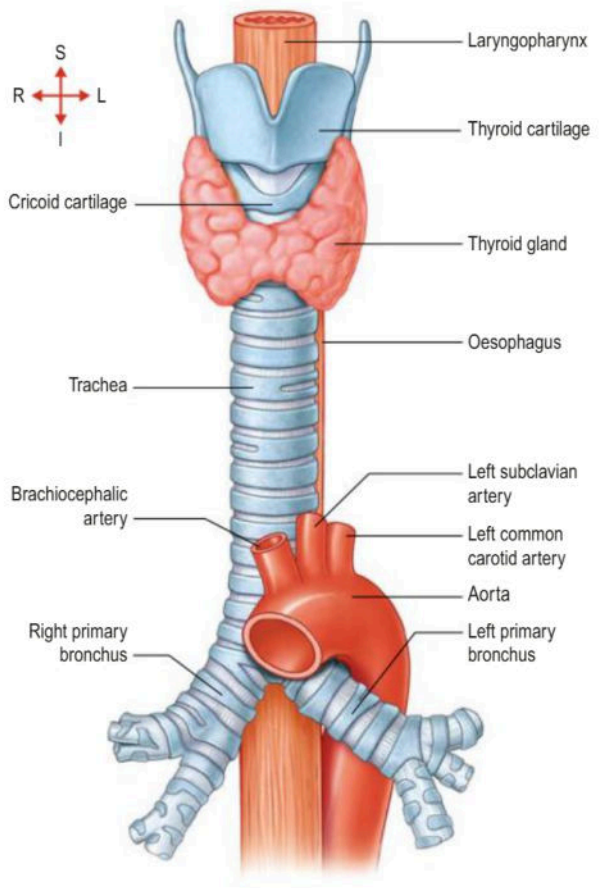


Figure 10.10 The trachea and some of its related structures.

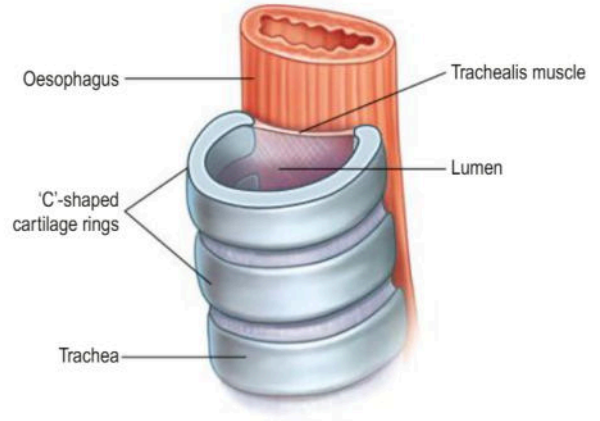


Figure 10.11 The relationship of the trachea to the oesophagus.

- The middle layer contains the C-shaped cartilages and bands of smooth muscle that wind round the trachea. There is some areolar tissue, containing blood and lymph vessels and autonomic nerves. The free ends of the incomplete cartilages are connected by the trachealis muscle (Fig. 10.11), which allows for limited adjustment of tracheal diameter.
- The mucosal lining is ciliated columnar epithelium, containing mucus-secreting goblet cells (Fig. 10.12A).

The submucosa, a thin layer of supporting tissue below the mucosa, also contains large numbers of glands producing respiratory secretions.

Blood and nerve supply, lymph drainage

Arterial blood supply is mainly by the inferior thyroid and bronchial arteries, and venous drainage is by the inferior thyroid veins into the brachiocephalic veins.

Parasympathetic nerve supply is by the recurrent laryngeal nerves and other branches of the vagus nerves. Sympathetic supply is by nerves from the sympathetic ganglia. Parasympathetic stimulation constricts the trachea, and sympathetic stimulation dilates it.

Lymph from the respiratory passages drains through lymph nodes situated around the trachea and in the carina, the area where it divides into the two bronchi.

Functions

Support and patency

Tracheal cartilages hold the trachea permanently open (patent), but the soft tissue bands between the cartilages allow flexibility so that the head and neck can move freely without obstructing or kinking the trachea. The absence of cartilage posteriorly permits the oesophagus to expand comfortably during swallowing. Contraction or relaxation of the trachealis muscle, which links the free ends of the C-shaped cartilages, helps to regulate the diameter of the trachea.

Mucociliary escalator

This is the synchronous and regular beating of the cilia of the mucous membrane lining (Fig. 10.12) that wafts mucus with adherent particles upwards towards the larynx, where it is either swallowed or coughed up.

Cough reflex

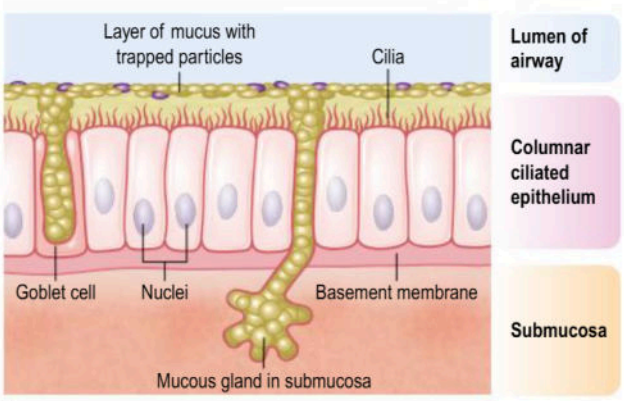
Nerve endings in the larynx, trachea and bronchi are highly sensitive to irritation, which generates nerve impulses conducted by the vagus nerves to the respiratory centre in the brain stem (p. 288). The reflex motor response is deep inspiration followed by closure of the glottis, i.e. closure of the vocal cords. The abdominal and respiratory muscles then contract, causing a sudden and rapid increase of pressure in the lungs. Then the glottis opens suddenly, forceably expelling air through the mouth and taking mucus and/or foreign material with it.

Warming, humidifying and filtering

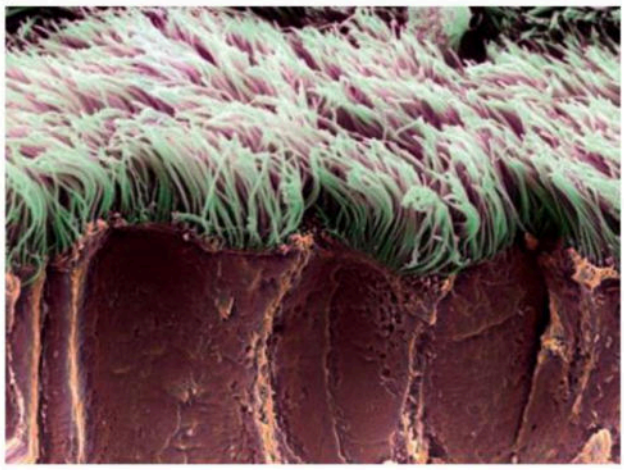
These continue as in the nose, although air is normally saturated and at body temperature when it reaches the trachea.

SPOT CHECK

7. Why does the cartilage-rich wall of the trachea not obstruct swallowing, since the soft oesophagus lies directly against the back of the trachea?
8. Describe the structure of the tracheal epithelium.



A



B

Figure 10.12 Cells lining the trachea. (A) Ciliated columnar epithelium and submucosa. (B) Coloured scanning electron micrograph of bronchial cilia. (B, Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

Lungs

Learning outcomes

After studying this section, you should be able to:

- name the air passages of the bronchial tree in descending order of size
- describe the structure and changing functions of the different levels of airway
- describe the location and gross anatomy of the lungs
- identify the functions of the pleura
- describe the pulmonary blood supply.

Position and gross structure

There are two cone-shaped lungs, one lying on each side of the midline in the thoracic cavity. Figure 10.13 shows the lungs in the thorax and their relationship to other thoracic organs and structures. The space between the lungs is called the mediastinum (Fig. 10.14), and contains the heart, great vessels, trachea, right and left primary bronchi, lymph nodes and vessels and nerves. The lungs are not symmetrical: the left lung is slightly smaller than the right because the heart occupies space left of the midline, and the right sits slightly higher in the thorax than the left because of the bulky liver in the abdominal cavity below. Each lung is divided into individual subunits called lobes, which are separated by fissures (Fig. 10.15). The right lung has three lobes, the superior (upper), medial (middle) and inferior (lower) lobe, and the left lung has only two, the superior and inferior lobes. The right lung therefore has two fissures: the horizontal fissure separates the superior and medial lobes, and the oblique fissure separates the medial and inferior lobes. The two lobes of the left lung are separated by the oblique fissure.

The main structures in the thorax can be seen on a plain chest X-ray (Fig. 10.16)

Each lung has an apex, a base, a costal surface and a medial surface.

Apex (Fig. 10.13)

This is the rounded tip of the lung and rises into the root of the neck, about 25 mm above the level of the middle third of the clavicle. It lies close to the first rib and the blood vessels and nerves in the root of the neck.

Base

This is the inferior surface of the lung (Fig. 10.17). It is concave and semilunar in shape and is attached to the upper (thoracic) surface of the diaphragm.

Costal surface

This is the broad outer surface of the lung that lies directly against the costal cartilages, the ribs and the intercostal muscles (Fig. 10.15).

Medial surface (Fig. 10.17)

The medial surface of each lung faces the other directly across the mediastinum. Each is concave and has a roughly triangular-shaped area, called the hilum, at the level of the 5th, 6th and 7th thoracic vertebrae. The primary bronchus, the pulmonary artery supplying the lung and the two pulmonary veins draining it, the bronchial artery and veins, and the lymphatic and nerve supply enter and leave the lung at the hilum.

Pleura and pleural cavity

The pleura consists of a closed sac of serous membrane, one for each lung, which contains a small amount of serous fluid, called pleural fluid. Figure 10.18 illustrates the arrangement, using a balloon partly filled with water to represent the pleural sac and a fist to represent the lung. The membrane of the balloon is a single membrane, but when the fist is pushed into the balloon, it is effectively coated in two membranes, with water in between. The fist can be slid around within the pouch it has

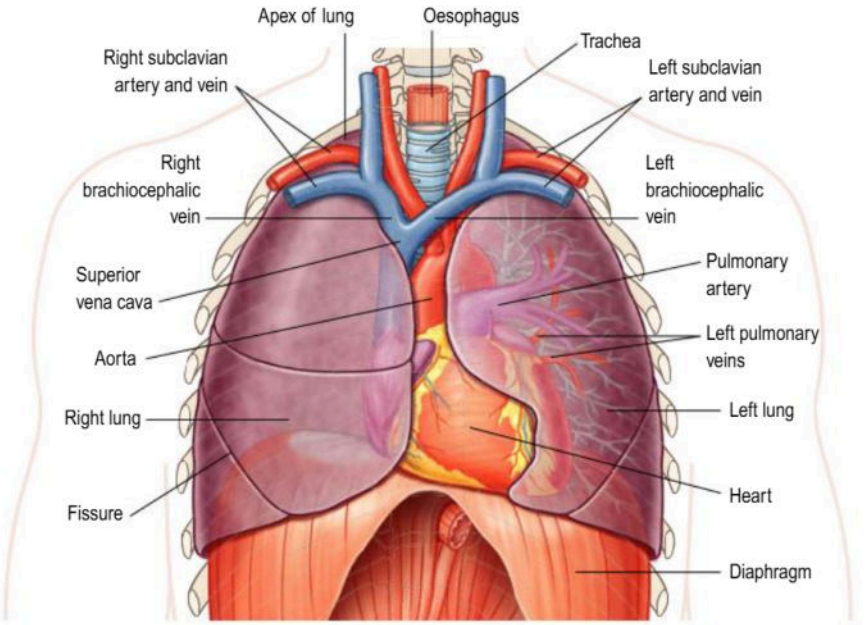


Figure 10.13 Organs associated with the lungs. Viewed from the front.

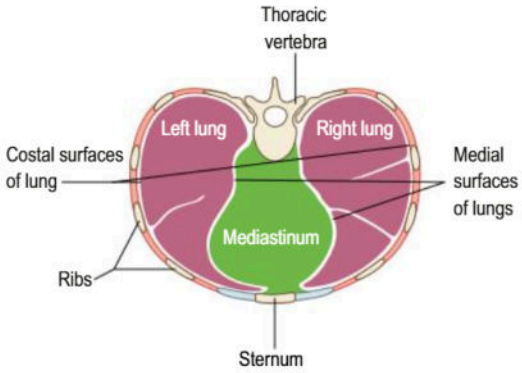


Figure 10.14 Transverse section of the thorax, showing the mediastinum.

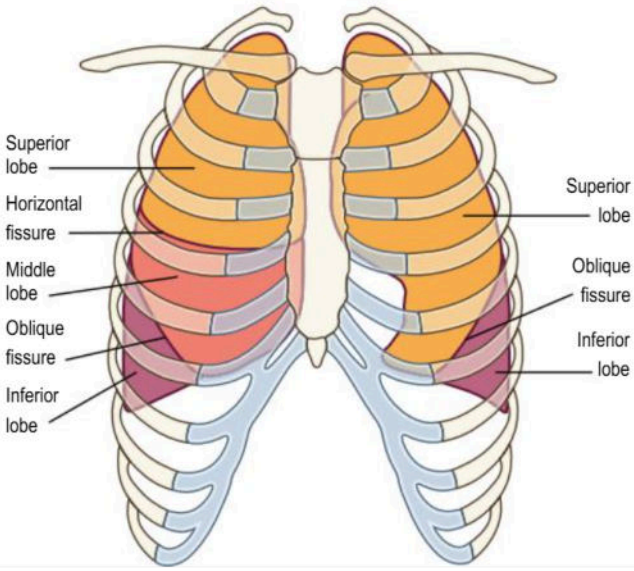


Figure 10.15 The relationship of the lobes of the lungs to the ribcage.

formed for itself but it does not get wet and the sac remains enclosed. In this way the lung can expand and recoil within the pleural sac, lubricated by the pleural fluid. Although the pleural membrane is described as two sheets, the visceral and the pleural membranes, the description refers to whether the layer is the outer or inner one: it is still all one membrane. The pericardium forms a similar arrangement around the heart (see Fig. 5.10), allowing it to beat without friction.

Visceral pleura

This adheres to the lung, covering each lobe and lining the fissures that separate them. It folds back on itself near the hilum to form the parietal pleura.

Parietal pleura

This adheres to the inside of the chest wall and the upper surface of the diaphragm. It is not attached to other structures in the mediastinum and simply folds back on itself in the region of the hilum to form the visceral pleura.

Pleural cavity

This is the enclosed space between the visceral and parietal layers of the folded pleural membrane. It contains no air, and the pressure within is negative relative to atmospheric pressure (negative intrapleural pressure). This generates a partial vacuum, which holds the two layers of the pleural membrane together. However, the two membranes slide easily over each other because the pleural cavity contains

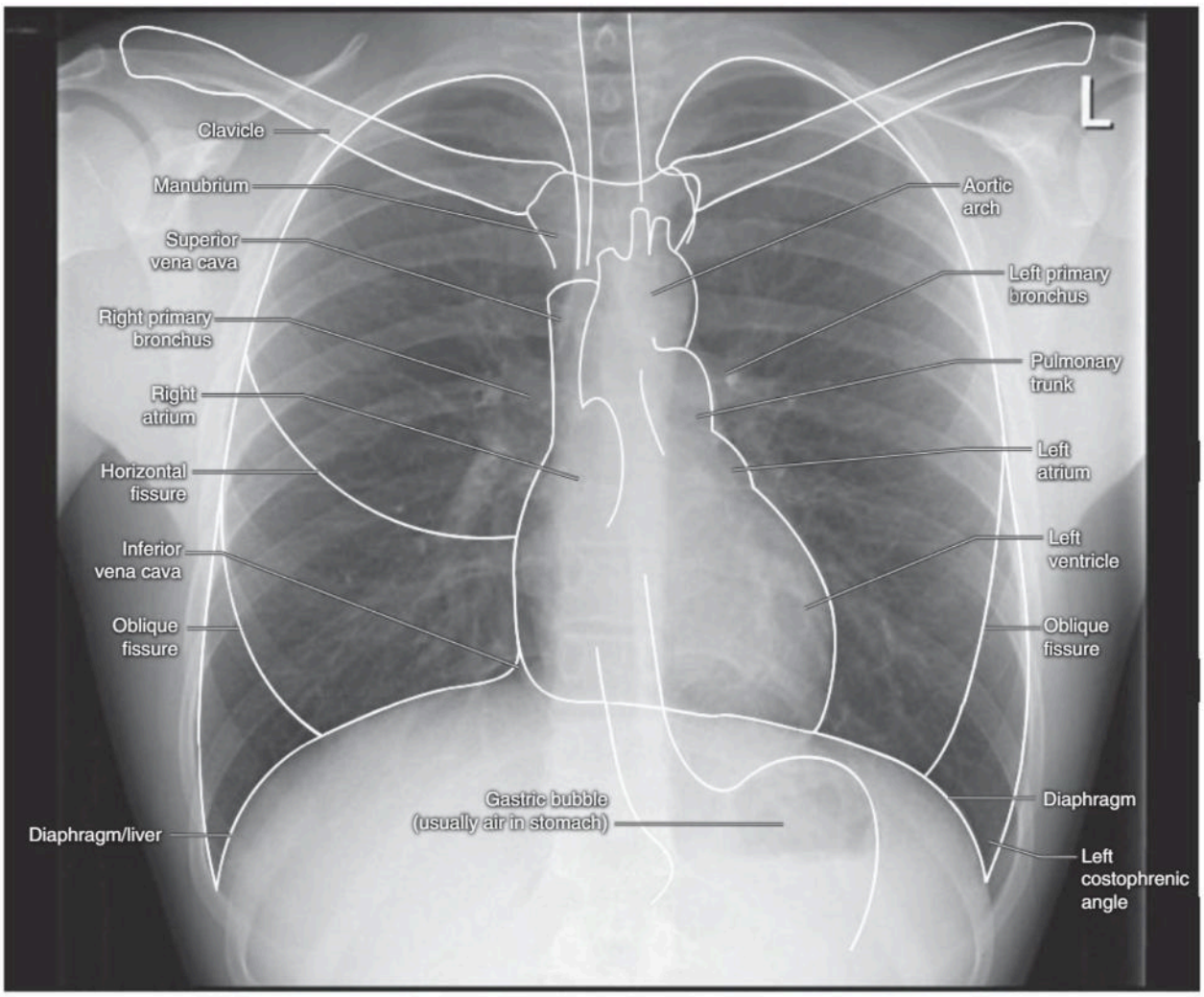


Figure 10.16 Normal chest X-ray. (Modified from Talley N, et al. 2021. Essentials of Internal Medicine, 4th ed. Elsevier.)

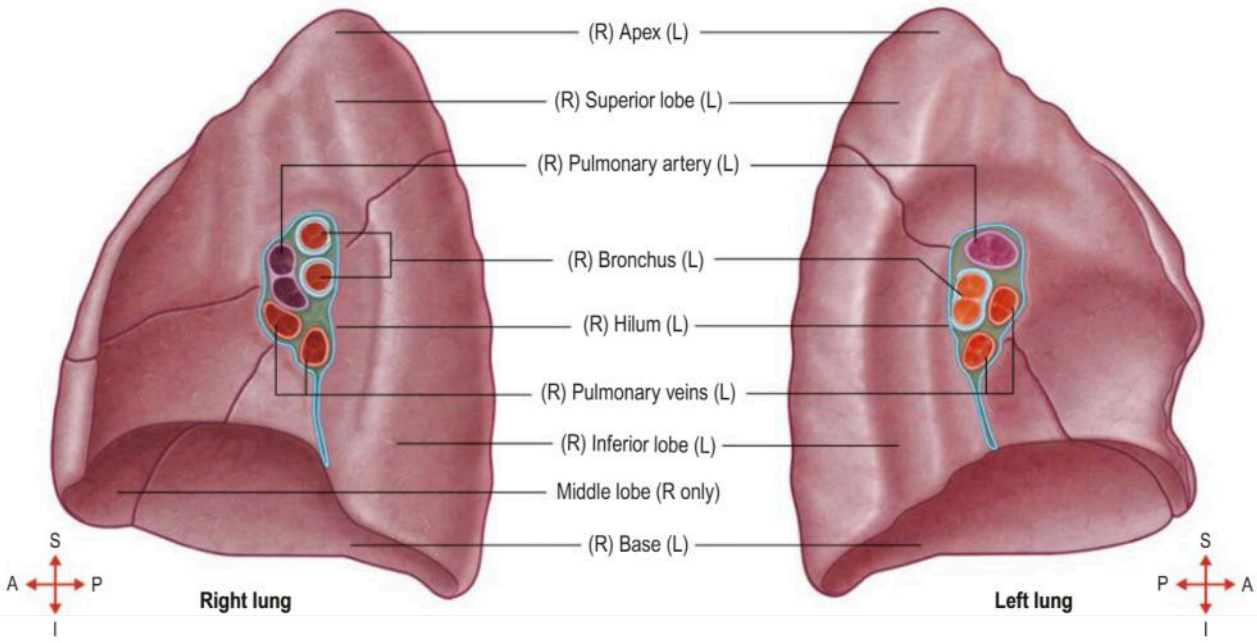


Figure 10.17 Medial surfaces of the lungs showing the hilum.

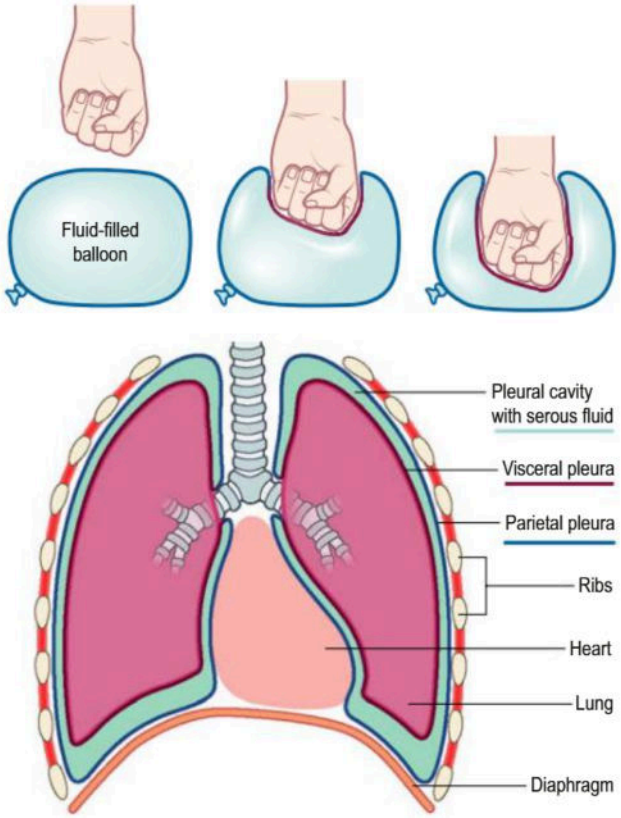


Figure 10.18 The relationship of the pleura to the lungs.

on average between 7 and 10 mL of pleural fluid, which lubricates lung movement during breathing.

Because the parietal pleura is attached firmly to the inside of the chest wall and to the upper surface of the diaphragm, the negative intrapleural pressure holds the visceral pleura with the underlying lung tissue closely against it. The negative intrapleural pressure is therefore essential for keeping the lung inflated against the inside of the chest wall. The airways and the alveoli of the lungs are embedded in elastic tissue, which constantly pulls the lung tissues towards the hilum, but because the negative intrapleural pressure holds the two pleura together the lung remains expanded. If either layer of pleura is punctured, air is sucked into the pleural space and part or all of the underlying lung collapses.

Interior of the lungs

The lungs are composed of the bronchi and smaller air passages, alveoli, connective tissue, blood vessels, lymph vessels and nerves, all embedded in an elastic connective tissue matrix. Each lobe is made up of many lobules.

Pulmonary blood supply

The pulmonary trunk divides into the right and left pulmonary arteries, carrying deoxygenated blood to each lung (Fig. 10.19). Within the lungs each pulmonary artery divides into many

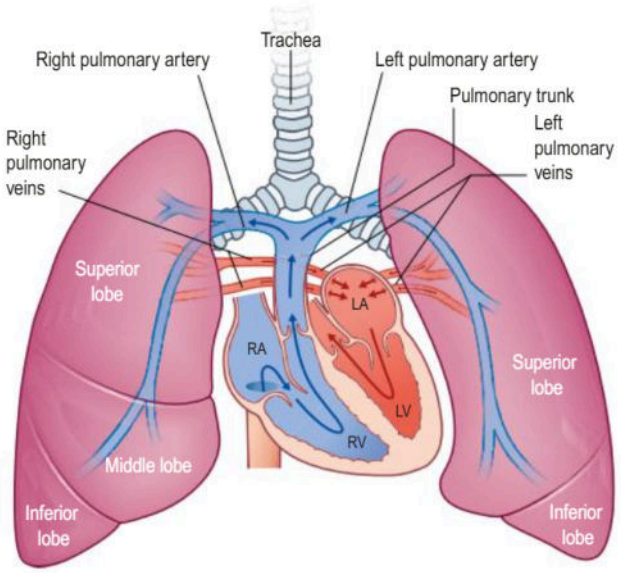


Figure 10.19 The flow of blood between the heart and the lungs. Arrows show direction of blood flow.

branches, which in turn subdivide and eventually produce dense capillary networks wrapped around the alveoli (see Fig. 10.21A). The alveolar and capillary walls each consist of only one layer of flattened epithelial cells on a thin basement membrane. The exchange of gases between air in the alveoli and blood in the capillaries takes place here. The pulmonary capillaries merge into a network of larger pulmonary venules, which in turn form two pulmonary veins carrying oxygenated blood from each lung back to the left atrium of the heart.

The blood supply to the respiratory passages, lymphatic drainage and nerve supply is described later.

Bronchi and bronchioles

The two primary bronchi are formed when the trachea divides (Fig. 10.20), at about the level of the 5th thoracic vertebra.

Right bronchus

This is wider, shorter and more vertical than the left bronchus and is therefore more likely to become obstructed by an inhaled foreign body. It is approximately 2.5 cm long. After entering the right lung at the hilum it divides into three branches, one to each lobe. Each branch then subdivides into numerous smaller branches.

Left bronchus

This is about 5 cm long and is narrower than the right. After entering the lung at the hilum it divides into two branches, one to each lobe. Each branch then subdivides into progressively smaller airways within the lung substance.

Structure

The bronchial walls contain the same three layers of tissue as the trachea and are lined with ciliated columnar epithelium. The bronchi progressively subdivide into bronchioles

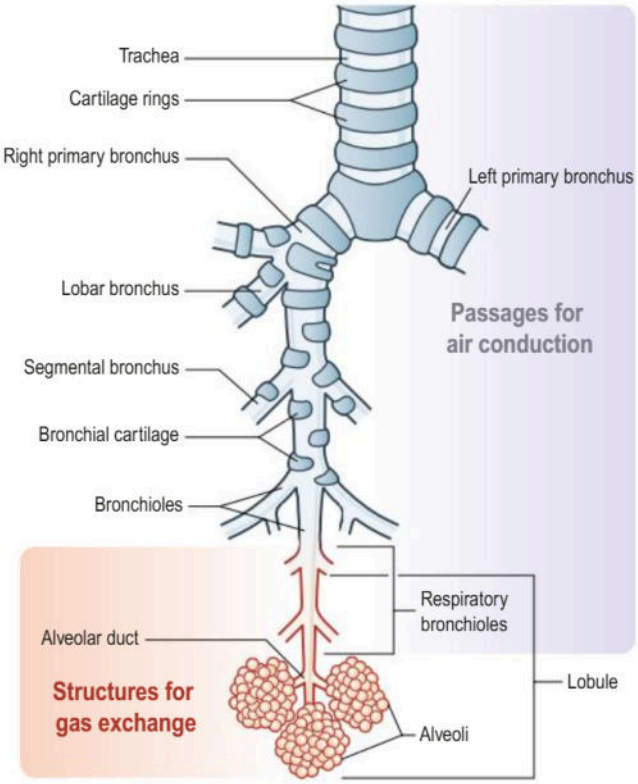


Figure 10.20 The lower respiratory tract.

(Fig. 10.20), terminal bronchioles, respiratory bronchioles, alveolar ducts and, finally, alveoli. The wider passages are called conducting airways because their function is to bring air into the lungs, and their walls are too thick to permit gas exchange.

Structural changes in the bronchial passages

As the bronchi divide and become progressively smaller, their structure changes to match their change in function.

Cartilage

Because rigid cartilage would interfere with expansion of lung tissue and the exchange of gases, it is present for support in the larger airways only. The bronchi contain cartilage rings like the trachea, but as the airways divide, these rings become much smaller plates, and at the bronchiolar level there is no cartilage in the airway walls at all.

Smooth muscle

As the cartilage disappears from airway walls, it is replaced by smooth muscle. This allows the diameter of the airways to be increased or decreased through the influence of the autonomic nervous system, regulating airflow within each lung.

Epithelial lining

The ciliated epithelium is gradually replaced with non-ciliated epithelium, and goblet cells disappear.

Blood and nerve supply, lymph drainage

The arterial supply to the walls of the bronchi and smaller air passages is through branches of the right and left bronchial arteries, and the venous drainage is mainly through the bronchial veins. On the right side they empty into the azygos vein, and on the left into the superior intercostal vein (see Fig. 5.29).

The nerve supply is from the autonomic nervous system. The vagus nerves (parasympathetic) stimulate contraction of smooth muscle in the bronchial tree, causing bronchoconstriction, and sympathetic stimulation causes bronchodilation (see later).

Lymph is drained from the walls of the air passages in a network of lymph vessels. It passes through lymph nodes situated around the trachea and bronchial tree, then into the thoracic duct on the left side and right lymphatic duct on the other.

Functions

Control of air entry

The capacity of the bronchi and other large airways to significantly affect air entry is limited because they are held open by cartilage and cannot adjust in diameter. Cartilage disappears with the progressive division of the respiratory tree and it is replaced with increasing amounts of smooth muscle. This means the diameter of the smaller respiratory passages can be altered considerably by contraction or relaxation of the smooth muscle in their walls, regulating the speed and volume of airflow into and within the lungs. These changes are controlled by the autonomic nerve supply: parasympathetic stimulation causes constriction and sympathetic stimulation causes dilation (see Figs 7.45 and 7.46).

Respiratory bronchioles and alveoli

Structure

Within each lobe the lung tissue is further divided by fine sheets of connective tissue into lobules. Each lobule is supplied with air by a terminal bronchiole, which further subdivides into respiratory bronchioles, alveolar ducts and large numbers of alveoli (air sacs). There are about 150 million alveoli in the adult lung. It is in these structures that gas exchange occurs. As airways progressively divide and become smaller and smaller, their walls gradually become thinner until muscle and connective tissue disappear, leaving a single layer of simple squamous epithelial cells in the alveolar ducts and alveoli. These distal respiratory passages are supported by a loose network of elastic connective tissue in which macrophages, fibroblasts, nerves, and blood and lymph vessels are embedded. The alveoli are surrounded by a dense network of capillaries (Fig. 10.21), and the capillary and alveolar walls are fused firmly together to form a thin membrane called the respiratory membrane. Exchange of gases between the alveoli and the bloodstream, called external respiration, takes place across the respiratory membrane.

On microscopic examination, the extensive air spaces are clearly seen and healthy lung tissue has a honeycomb appearance (Fig. 10.22).

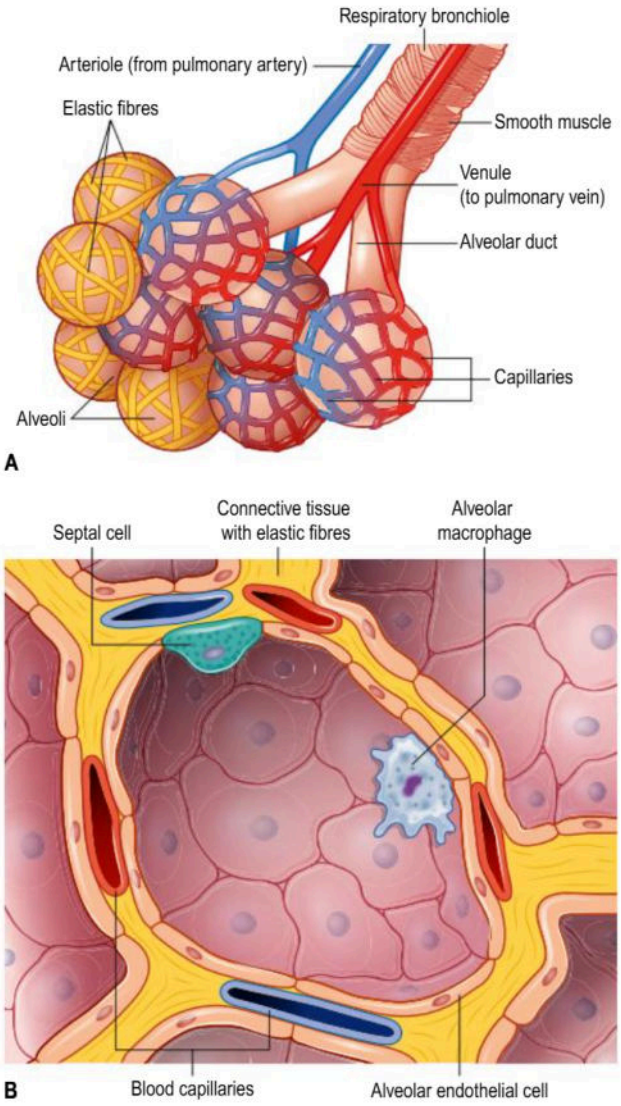


Figure 10.21 The alveoli and their capillary networks. (A) A group of alveoli. (B) Section through an alveolus.

Lying in the alveolar wall between the squamous cells are septal cells (Fig. 10.21B) that secrete surfactant, a phospholipid fluid that stops the alveoli drying out and reduces surface tension, preventing alveolar collapse during expiration. Secretion of surfactant into the distal air passages and alveoli begins in about the 35th week of fetal life. Its presence in newborn babies permits expansion of the lungs and the establishment of respiration immediately after birth. It may not be present in sufficient amounts in the immature lungs of premature babies, causing serious breathing problems.

Nerve supply to bronchioles

Parasympathetic stimulation, from the vagus nerve, contracts bronchiolar smooth muscle and causes bronchoconstriction. The absence of supporting cartilage means that small airways may be completely closed off by constriction of their smooth muscle. Conversely, sympathetic stimulation causes bronchodilation.

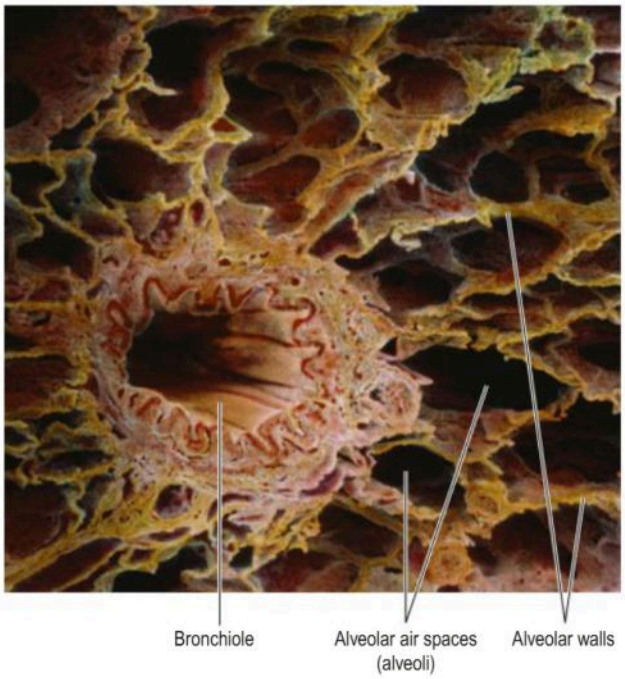


Figure 10.22 Coloured scanning electron micrograph of lung alveoli and a bronchiole. (Hossler, Custom Medical Stock Photo/ Science Photo Library. Reproduced with permission.)

Functions

External respiration

See page 286.

Defence against infection

At this level, ciliated epithelium, goblet cells and mucus are no longer present because they would impede gas exchange and encourage infection. By the time inspired air reaches the alveoli, it is usually clean. Defence relies on protective cells present within the lung tissue. These include lymphocytes and plasma cells, which produce antibodies, and phagocytes, including alveolar macrophages. These cells are most active in the distal air passages, where ciliated epithelium has been replaced by flat squamous cells.

SPOT CHECK

9. Describe the four main surfaces of the lungs.
10. What is the function of the elastic tissue of the lungs?
11. What is the function of smooth muscle in bronchioles?
12. Describe the structure of the alveolar wall.

Respiration

Learning outcomes

After studying this section, you should be able to:

- describe the actions of the main muscles involved in breathing
- compare and contrast the mechanical events occurring in inspiration and expiration
- define the terms 'compliance', 'elasticity' and 'airflow resistance'
- describe the principal lung volumes and capacities
- compare the processes of internal and external respiration, using the concept of diffusion of gases
- describe O_2 and CO_2 transport in the blood
- explain the main mechanisms by which respiration is controlled.

The term 'respiration' means the exchange of gases between body cells and the environment. This involves two main processes: breathing, the mechanical process of moving air in and out of the lungs, and gas exchange. Gas exchange between the alveolar air and the blood in the pulmonary capillaries is called external respiration. Gas exchange between the bloodstream and body tissues is called internal respiration.

Breathing

Breathing (pulmonary ventilation) supplies oxygen to the alveoli and excretes carbon dioxide.

Muscles of breathing

Chest expansion during inspiration occurs as a result of muscular activity, partly voluntary and partly involuntary. The main muscles used in normal quiet breathing are the external intercostal muscles and the diaphragm.

Intercostal muscles

There are 11 pairs of intercostal muscles occupying the spaces between the 12 pairs of ribs. They are arranged in two layers, the external and internal intercostal muscles (Fig. 10.23) and are supplied by the intercostal nerves.

External intercostal muscles

These extend downwards and forwards from the lower border of the rib above to the upper border of the rib below. They lift the ribcage upwards and outwards in inspiration.

Internal intercostal muscles

These extend downwards and backwards from the lower border of the rib above to the upper border of the rib below, crossing the external intercostal muscle fibres at right angles. They are used when expiration becomes active, as in exercise.

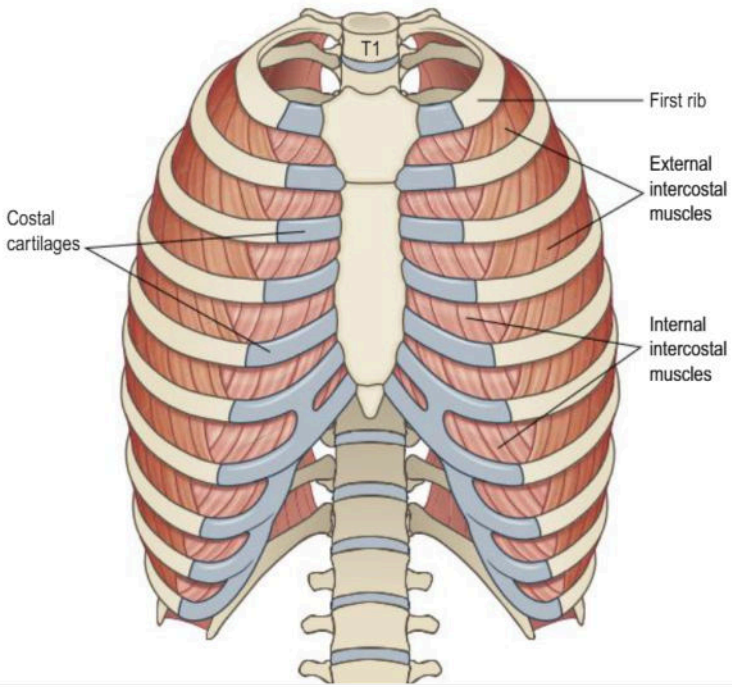


Figure 10.23 The thoracic cage, showing the intercostal muscles.

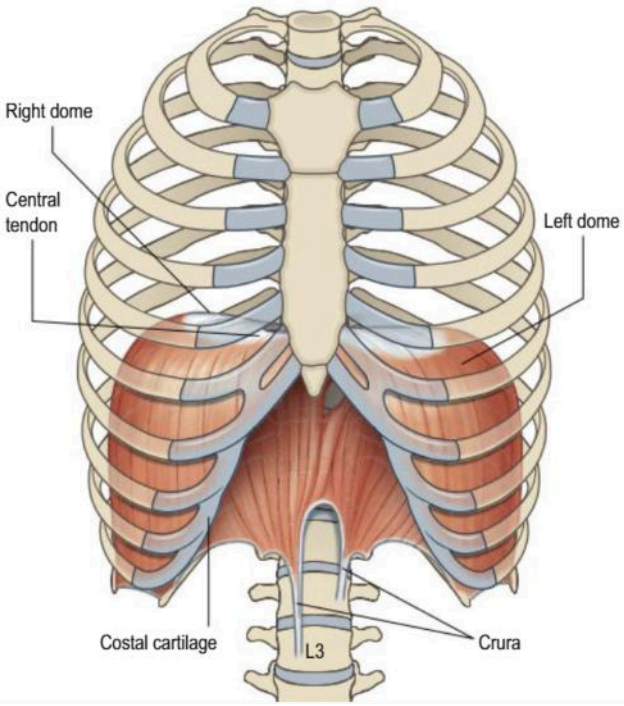


Figure 10.24 The diaphragm.

Diaphragm

The diaphragm is a dome-shaped muscular structure supplied by the phrenic nerve and separating the thoracic and abdominal cavities. It forms the floor of the thoracic cavity and the roof of the abdominal cavity and consists of a central tendon from which muscle fibres radiate to be attached to the lower ribs and sternum, and to the vertebral column by two crura (Fig. 10.24).

Quiet, restful breathing is sometimes called diaphragmatic breathing because 75% of the work is done by the diaphragm.

Accessory muscles of respiration

When extra respiratory effort is required, as in exercise or when respiratory function is restricted by disease, additional muscles are used (Fig. 10.25A). These are called the accessory muscles of respiration.

Accessory muscles of forced inspiration

Forced inspiration is assisted by the sternocleidomastoid muscles and the scalene muscles, which link the cervical vertebrae to the first two ribs and increase ribcage expansion. When these muscles contract, they pull the ribcage upwards, supplementing the action of the external intercostal muscles.

Accessory muscles of forced expiration

Quiet exhalation takes around 3 to 4 seconds. Recruiting accessory muscles of expiration shortens the expiration time, increases the speed and force of exhalation and allows respiratory rate to rise. Forced expiration is helped by contraction of the internal intercostal muscles, which pull the ribcage downwards and inwards, compressing the lungs and aiding exhalation. Sometimes the rectus abdominis muscle is also used, which compresses the abdominal organs, increasing the upward pressure on the diaphragm and helping to force air out of the lungs.

The 'sprung' ribcage

The respiratory muscles can expand the ribcage because of its cartilage content. If the ribcage were built entirely of bone, without costal cartilages, changing the lung volume would depend entirely on the diaphragm below rising and falling. This would allow the lungs to lengthen and shorten only. As cartilage is strong and inelastic but still slightly flexible, the costal cartilages (Fig. 10.23) permit enough movement between the sternum and ribs to allow lateral and anterior expansion too through the action of other muscles, including the intercostals. In addition, this arrangement gives the ribcage a 'sprung' structure, with the ribs under gentle outwards tension, meaning that the ribcage is constantly being pushed outwards, pulling gently on the lungs because of the arrangement of the pleura and helping to keep them expanded.

Cycle of breathing

The average respiratory rate is 12–15 breaths per minute. Each breath consists of three phases: inspiration, expiration and pause.

Breathing depends on changes in pressure and volume in the thoracic cavity. It follows the underlying physical principle that increasing the volume of a container decreases the pressure inside it, and that decreasing the volume of a container increases the pressure inside it. Since air flows from an area of high pressure to an area of low pressure, changing the pressure inside the lungs determines the direction of airflow.

Inspiration

During inspiration, the external intercostal muscles and the diaphragm contract simultaneously, enlarging the thoracic cavity in all directions (Fig. 10.25B). The ribcage is anchored at the first rib, which is fastened firmly to the sternum and the first thoracic vertebra (Fig. 10.23). Contraction of the external intercostal muscles lifts the ribcage as a unit upwards and outwards, expanding the thorax anteriorly and laterally. When the diaphragm contracts, its muscle fibres shorten and the central tendon is pulled downwards to the level of the 9th thoracic vertebra, lengthening the thoracic cavity. Because the parietal pleura adheres to the diaphragm and the inside of the ribcage, it is pulled outwards along with them. This pulls the visceral pleura outwards too, since the two pleura are held together by negative intrapleural pressure. Because the visceral pleura is firmly adherent to the lung, the lung tissue is therefore also pulled upwards and outwards with the ribs, and downwards with the diaphragm. This expands

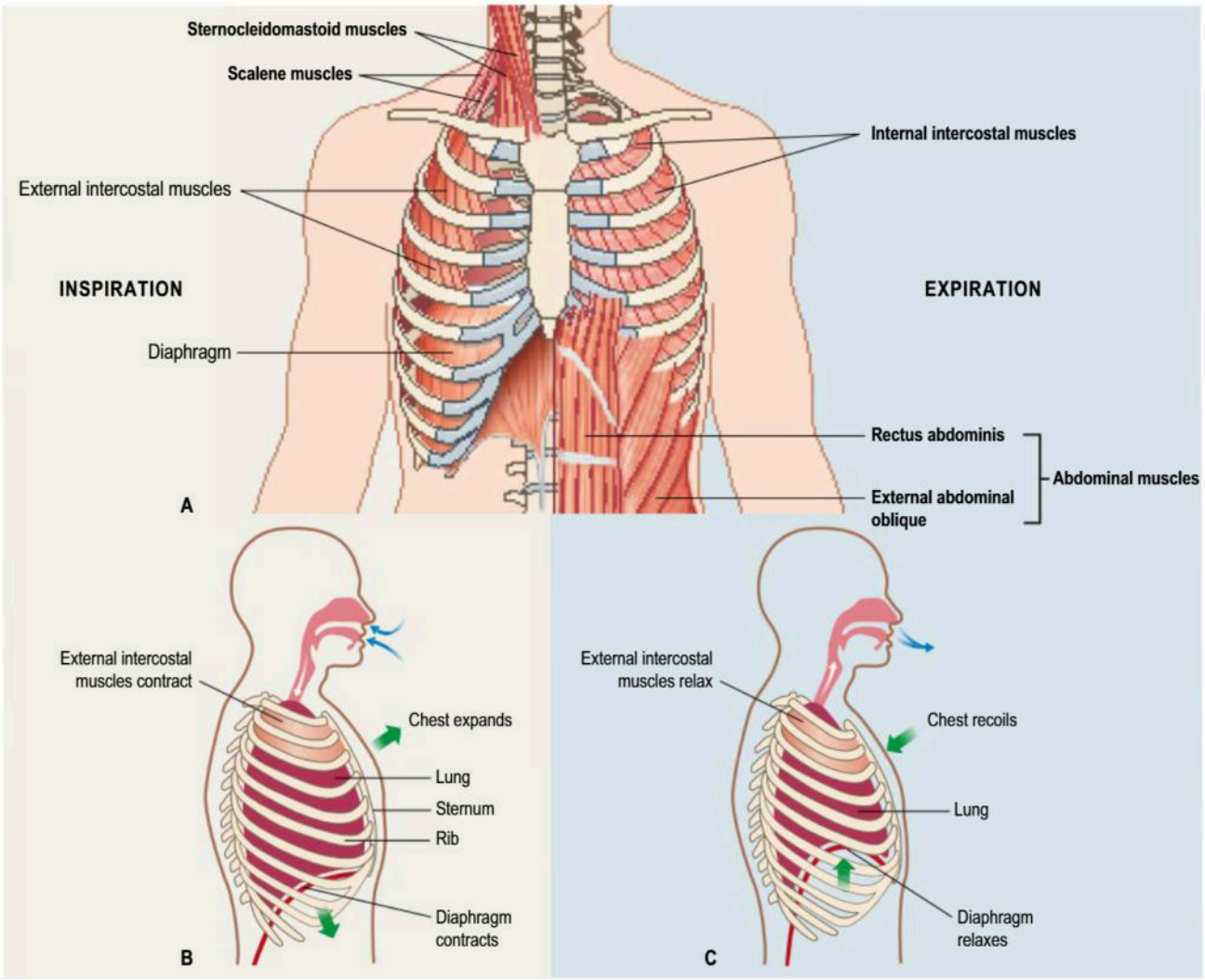


Figure 10.25 Changes in chest size during inspiration. (A) Muscles involved in respiration (accessory muscles labelled in bold). (B and C) Changes in chest volume.

the lungs, and the pressure within the alveoli and in the air passages falls, drawing air into the lungs in an attempt to equalise atmospheric and alveolar air pressures. The negative pressure created in the thoracic cavity aids venous return to the heart and is called the respiratory pump.

The process of inspiration is active, because it needs energy for muscle contraction. At rest, inspiration lasts about 2 seconds.

Expiration

Relaxation of the external intercostal muscles and the diaphragm results in downward and inward movement of the ribcage (Fig. 10.25C) and elastic recoil of the lungs. This action increases pressure inside the lungs and expels air from the respiratory tract. At the end of expiration, the lungs still contain some air, and are prevented from complete collapse by the intact pleura.

This process is passive, as it does not require the expenditure of energy. At rest, expiration lasts about 3 seconds.

Physiological variables affecting breathing

Elasticity

Elasticity is the ability of the lung to return to its normal shape after stretching during inspiration. Loss of elasticity of the connective tissue in the lungs, e.g. in emphysema (p. 293), necessitates forced expiration and increased effort on inspiration.

Compliance

This is the stretchability of the lungs, i.e. the effort required to inflate the alveoli. The healthy lung is very compliant and

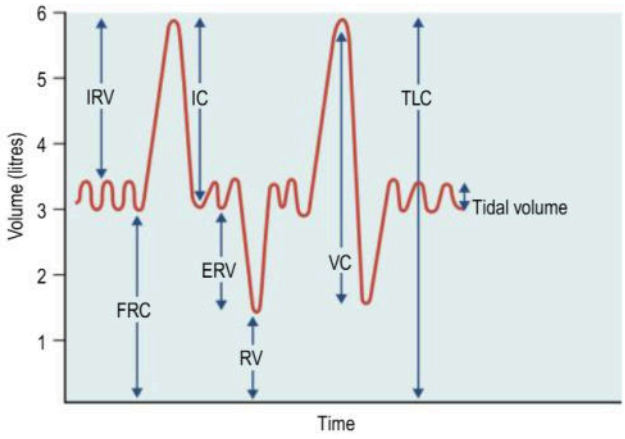


Figure 10.26 Lung volumes and capacities. *ERV*, expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *IRV*, inspiratory reserve volume; *RV*, residual volume; *TLC*, total lung capacity; *VC*, vital capacity.

inflates with very little effort. When compliance is low the effort needed to inflate the lungs is greater than normal, e.g. when insufficient surfactant is present. Note that compliance and elasticity are opposing forces.

Airway resistance

When this is increased, e.g. in bronchoconstriction or any other form of airway obstruction, more respiratory effort is required to inflate the lungs.

Spirometry

Spirometry is the general term used for the range of lung function tests that measure air flow in and out of the lung. Instruments used to make these measurements are called spirometers. Many of these measurements are the basis of lung function tests performed in clinical practice to assess and manage respiratory function (Fig. 10.26). Results of these tests can help in the diagnosis and monitoring of respiratory disorders.

Lung volumes and capacities

In normal quiet breathing there are about 15 complete respiratory cycles (respirations) per minute. The lungs and the air passages are never empty and, because the exchange of gases takes place only across the walls of the alveolar ducts and alveoli, the remaining capacity of the respiratory tract is called the anatomical dead space (about 150 mL).

Tidal volume

Tidal volume (TV) is the amount of air passing into and out of the lungs during each cycle of breathing (about 500 mL at rest).

Inspiratory reserve volume

Inspiratory reserve volume (IRV) is the extra volume of air over and above normal TV that can be inhaled into the lungs during maximal inspiration.

Inspiratory capacity

Inspiratory capacity (IC) is the amount of air that can be inspired with maximum effort. It consists of the tidal volume (500 mL) plus the inspiratory reserve volume.

Functional residual capacity

Functional residual capacity (FRC) is the amount of air remaining in the air passages and alveoli at the end of quiet expiration. Tidal air mixes with this air, causing relatively small changes in the composition of alveolar air. As blood flows continuously through the pulmonary capillaries, this means that the continual exchange of gases is not interrupted between breaths, preventing moment-to-moment changes in the concentration of blood gases. The functional residual volume also prevents collapse of the alveoli on expiration.

Expiratory reserve volume

Expiratory reserve volume (ERV) is the additional volume of air that can be expelled over and above normal TV during maximal expiration.

Residual volume

Residual volume (RV) cannot be directly measured but is the volume of air remaining in the lungs after forced expiration.

Vital capacity

Vital capacity (VC) is the maximum volume of air that can be moved into and out of the lungs:

$$\text{VC} = \text{Tidal volume} + \text{IRV} + \text{ERV}$$

Total lung capacity

Total lung capacity (TLC) is the maximum amount of air the lungs can hold. In an adult of average build, it is normally around 6 litres. Total lung capacity represents the sum of the VC and the RV. It cannot be directly measured in clinical tests because, even after forced expiration, the residual volume still remains in the lungs.

Alveolar ventilation

This is the volume of air that moves into and out of the alveoli per minute. It is equal to the tidal volume minus the anatomical dead space, multiplied by the respiratory rate:

$$\begin{aligned}\text{Alveolar ventilation} &= \text{TV} - \text{anatomical dead space} \\ &\quad \times \text{respiratory rate} \\ &= (500 - 150)\ \text{mL} \times 15\ \text{per minute} \\ &= 5.25\ \text{litres per minute}\end{aligned}$$

Peak expiratory flow (PEF, peak flow)

Peak expiratory flow is measured with a peak flow meter and records the maximum speed of air flow during forced expiration. It is measured in litres per minute and is only attained for a fraction of a second. Normal peak flow values vary significantly with age, sex and physical build, but the

normal range is generally between 400 and 700 L/min. Peak flow depends mainly on the diameter of the larger airways: if they are constricted or obstructed, peak flow decreases, and so regular measurements are most useful in assessing lung function in obstructive respiratory disorders such as asthma.

Exchange of gases

Although breathing involves the alternating processes of inspiration and expiration, gas exchange at the respiratory membrane and in the tissues is continuous and ongoing. Diffusion of oxygen and carbon dioxide depends on pressure differences between atmospheric air and the blood in external respiration, or blood and the body tissues in internal respiration.

Composition of air

Atmospheric pressure at sea level is 101.3 kilopascals (kPa) or 760 mmHg. With increasing height above sea level, atmospheric pressure progressively falls and at 5500 m, about two-thirds the height of Mount Everest (8850 m), it is about half that at sea level. Under water, pressure increases by approximately 1 atmosphere for every 10 m below sea level.

Air is a mixture of gases: nitrogen, oxygen, carbon dioxide, water vapour and small quantities of inert gases. The percentage of each in inspired and expired air is listed in Table 10.1. Each gas in the mixture contributes towards the total pressure in proportion to its concentration. This is called its partial pressure (Table 10.2). This is denoted as, for example, PO_2, PCO_2. For example, oxygen makes up 21% of atmospheric air. This means the PO_2 of atmospheric air is 21% of 760 mmHg, about 160 mmHg or 21.2 kPa.

Table 10.1 The composition of inspired and expired air

	Inspired air %	Expired air %
Oxygen	21	16
Carbon dioxide	0.04	4
Nitrogen	78	78
Water vapour	Variable	Saturated

Alveolar air

The composition of alveolar air remains fairly constant and is different from atmospheric air. It is saturated with water vapour and contains more carbon dioxide and less oxygen. Saturation with water vapour provides 6.3 kPa (47 mmHg), thus reducing the partial pressure of all the other gases present. Gas exchange between the alveoli and the bloodstream (external respiration) is a continuous process, as the alveoli are never empty, so it is independent of the respiratory cycle. During each inspiration only some of the alveolar gases are exchanged.

Diffusion of gases

Exchange of gases occurs when a difference in partial pressure exists across a semipermeable membrane. Gases diffuse from the higher concentration to the lower until equilibrium is established. Atmospheric nitrogen is not used by the body so its partial pressure remains unchanged and is the same in inspired and expired air, alveolar air and the blood.

These principles govern the diffusion of gases in and out of the alveoli across the respiratory membrane in external respiration and across capillary membranes in the tissues in internal respiration.

External respiration

External respiration (Fig. 10.27A) is exchange of gases by diffusion between the alveoli and the blood in the alveolar capillaries, across the respiratory membrane. Each alveolar wall is one cell thick and is surrounded by a network of tiny capillaries, the walls of which are also only one cell thick. The total area of respiratory membrane for gas exchange in the lungs is about 260 m^2, equivalent to the area of a tennis court. Venous blood arriving at the lungs in the pulmonary artery has travelled from all the tissues of the body and its PCO_2 is high and its PO_2 is low. Carbon dioxide diffuses from venous blood down its concentration gradient into the alveoli until equilibrium with alveolar air is reached. By the same process, oxygen diffuses from the alveoli into the blood. The relatively slow flow of blood through the pulmonary capillaries increases the time available for gas exchange. When blood leaves the alveolar capillaries, PO_2 and PCO_2 are in equilibrium with alveolar air.

Table 10.2 Partial pressures of gases

	Alveolar air		Deoxygenated blood		Oxygenated blood	
Gas	kPa	mmHg	kPa	mmHg	kPa	mmHg
Oxygen	13.3	100	5.3	40	13.3	100
Carbon dioxide	5.3	40	5.8	44	5.3	40
Nitrogen	76.4	573	76.4	573	76.4	573
Water vapour	6.3	47				
Total	101.3	760				

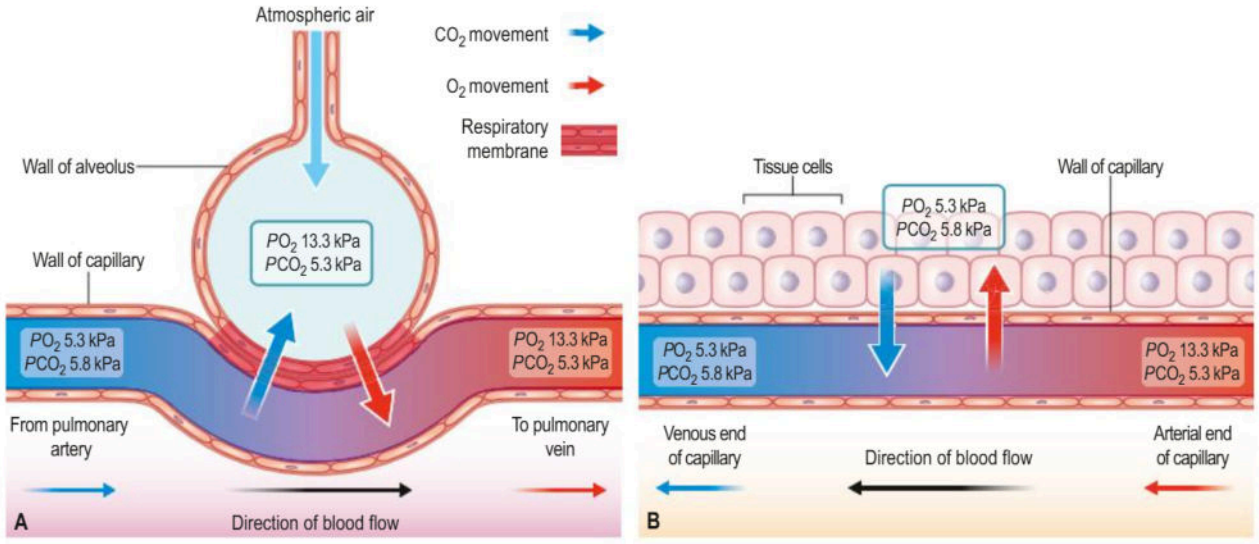


Figure 10.27 Respiration. (A) External respiration. (B) Internal respiration.

Internal respiration

Internal respiration (Fig. 10.27B) is exchange of gases by diffusion between blood in the capillaries and the body cells. Gas exchange does not occur across the walls of the arteries carrying blood from the heart to the tissues because their walls are too thick. PO_2 of blood arriving at the capillary bed is therefore the same as blood leaving the lungs. Blood arriving at the tissues has been cleansed of its excess CO_2 and saturated with O_2 during its passage through the lungs, and therefore has a higher PO_2 and a lower PCO_2 than the tissues. This creates concentration gradients between capillary blood and the tissues, and gas exchange therefore occurs. O_2 diffuses from the bloodstream through the capillary wall into the tissues. CO_2 diffuses from the cells into the extracellular fluid, then into the bloodstream towards the venous end of the capillary.

Figure 10.28 summarises the processes of internal and external respiration.

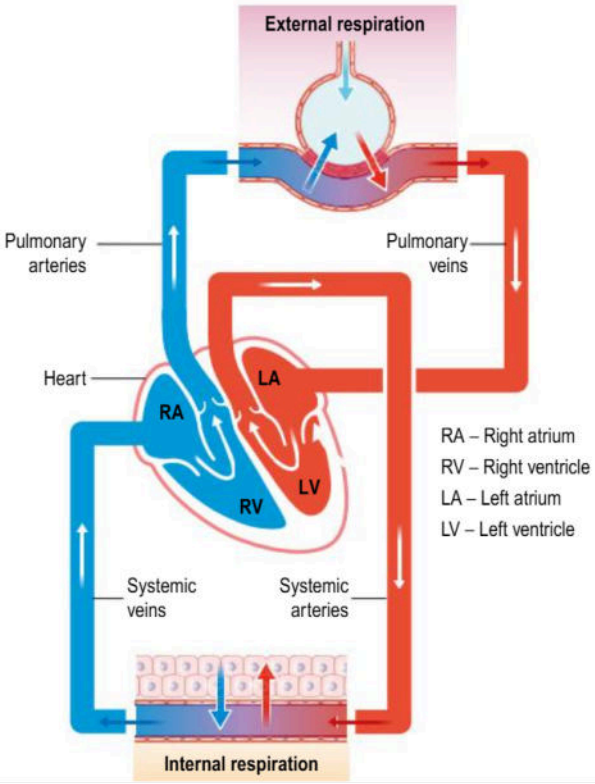


Figure 10.28 Summary of external and internal respiration.

Transport of gases in the bloodstream

Oxygen and carbon dioxide are carried in the blood in different ways.

Oxygen

Oxygen is carried in the blood:

- in chemical combination with haemoglobin (see Fig. 4.6) as oxyhaemoglobin (98.5%)
- dissolved in plasma water (1.5%).

Oxyhaemoglobin is unstable and under certain conditions readily dissociates, releasing oxygen. Factors that increase dissociation include low O_2 levels, low pH and raised temperature (Ch. 4). Active tissues produce increased quantities of CO_2 and heat, which leads to increased release of oxygen. In this way, oxygen is available to tissues in greatest need.

Carbon dioxide

CO_2 is one of the waste products of cellular metabolism. It is excreted by the lungs and is transported by three mechanisms:

- as bicarbonate ions (HCO_3^-) in the plasma (70%)
- combined with haemoglobin in erythrocytes as carbaminohaemoglobin (23%)
- dissolved in the plasma (7%).

Carbon dioxide levels must be finely controlled, as either an excess or a deficiency leads to significant disruption of acid–base balance. Sufficient CO_2 is essential for the bicarbonate buffering system that protects against a fall in body pH (Ch. 2). Excess CO_2, on the other hand, reduces blood pH because it dissolves in body water to form carbonic acid.

Regulation of airflow and blood flow in the lung

When at rest, with quiet breathing and a resting heart rate, only a small portion of the lung's total capacity is ventilated with each breath, and cardiac output is not high enough to perfuse all alveolar beds. This means that only a fraction of the total alveolar numbers are being ventilated, usually in the upper lobes, and much of the remaining lung is temporarily partially collapsed. In addition, only some of the alveoli are well perfused, i.e., receiving good blood flow. Airways supplying alveoli that are not well supplied with blood constrict, directing airflow into functioning well-perfused alveoli. In addition, the pulmonary arterioles bringing blood into the ventilated alveoli dilate, to maximise gas exchange, and blood flow past the non-functioning alveoli is reduced. This is called ventilation-perfusion matching.

When respiratory requirements are increased, e.g. in exercise, the increased tidal volume expands additional alveoli, and blood flow is redistributed to perfuse these too. In this way, airflow and blood flow are constantly adjusted to maximise the opportunity for gas exchange.

Control of respiration

Effective control of respiration enables the body to regulate blood gas levels over a wide range of physiological, environmental and pathological conditions, and is normally involuntary. Voluntary control is exerted during activities such as speaking and singing but is overridden if blood CO_2 rises (hypercapnia).

The respiratory centre

This is formed by groups of nerves in the medulla, the respiratory rhythmicity centre, which control the respiratory pattern, i.e. the rate and depth of breathing (Fig. 10.29). Three important groups of neurones here regulate breathing: an inspiratory group, an expiratory group, and neurones in the pneumotaxic area. Regular automatic firing of the inspiratory neurones sets the basic rhythm of breathing. Expiratory neurones control expiration, and neurones in the pneumotaxic area help to regulate the rate and depth of breathing.

Motor impulses leaving the respiratory centre pass in the phrenic and intercostal nerves to the diaphragm and intercostal muscles, respectively, to stimulate respiration.

Although the respiratory centre controls the pattern and rate of breathing, it is also influenced by information coming in from the periphery: most importantly, chemoreceptor input related to the CO_2 content and pH of body fluids.

Chemoreceptors

These receptors respond to changes in the PO_2 and PCO_2 of the blood and cerebrospinal fluid (CSF). They are located centrally and peripherally.

Central chemoreceptors

These are located on the surface of the medulla oblongata and are bathed in CSF. When arterial PCO_2 rises (hypercapnia), even slightly, this in turn increases PCO_2 in the CSF. The central chemoreceptors respond by stimulating the respiratory centre, increasing the rate and depth of breathing to reduce arterial PCO_2. The sensitivity of the central chemoreceptors to raised arterial PCO_2 is the most important factor in controlling normal blood gas levels. A small reduction in PO_2 (hypoxaemia) has the same effect, though less pronounced, but a substantial reduction depresses breathing.

Peripheral chemoreceptors

These are situated in the arch of the aorta and in the carotid bodies (Fig. 10.29). They respond to changes in blood CO_2 and O_2 levels but are much more sensitive to carbon dioxide than oxygen. Even a slight rise in PCO_2 activates these receptors, triggering nerve impulses to the respiratory centre via the glossopharyngeal and vagus nerves. This stimulates an immediate rise in the rate and depth of respiration. An increase in blood acidity (decreased pH or raised $[H^+]$) also stimulates the peripheral chemoreceptors, increasing ventilation to increase CO_2 excretion and increase blood pH. These chemoreceptors also help to regulate blood pressure (p. 101).

Exercise and respiration

Physical exercise increases the oxygen requirements of the exercising skeletal muscles and the heart. Accessory muscles are recruited to increase the rate and depth of breathing. Tidal volume increases, using both inspiratory and expiratory reserve volumes. Exercising muscle produces higher quantities of CO_2, which stimulates central and peripheral chemoreceptors. The increased respiratory effort persists even after exercise stops, in order to supply enough oxygen to repay the 'oxygen debt'. This represents mainly the oxygen needed to get rid of wastes, including lactic acid.

Other factors that influence respiration

Breathing may be modified via the higher centres in the brain by speech, singing, emotional displays (e.g. crying, laughing, fear), drugs (e.g. sedatives, alcohol) and sleep.

Body temperature influences breathing. In fever, respiration is increased to meet the increased oxygen requirements of a higher metabolic rate, while in hypothermia respiration and metabolism are depressed because tissue metabolism is slowed. Respiration is briefly inhibited when swallowing, to prevent inhalation of food or drink, and inspiration is also inhibited during sneezing and coughing, while irritants are expelled from the respiratory tract. There may be complete

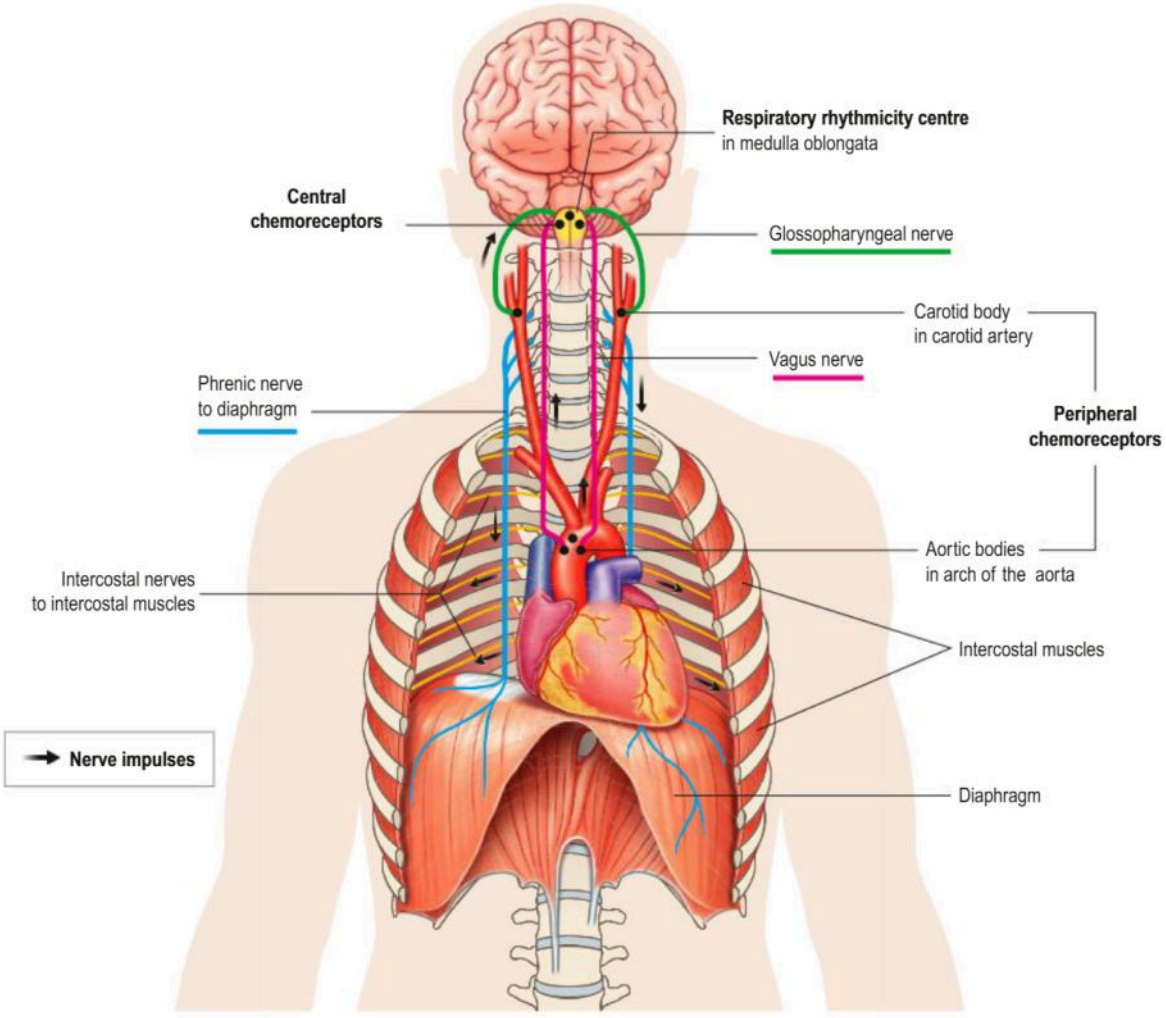


Figure 10.29 Some of the structures involved in control of respiration.

involuntary cessation of breathing (apnoea) for more extended periods, e.g. if the face is submerged in water or the air contains high concentrations of dust, smoke or other noxious substances; this has an obvious protective function.

The Hering–Breuer reflex prevents over-inflation of the lungs. Stretch receptors in the lung, linked to the respiratory centre by the vagus nerve, inhibit respiration when lung volume approaches maximum.

SPOT CHECK

13. Describe the muscular effort required for quiet inspiration.
14. The vital capacity can be calculated by adding together the tidal volume plus which two other lung volumes?
15. How do chemoreceptors in the blood vessels and central nervous system regulate breathing?

Effects of ageing on the respiratory system

Learning outcome

After studying this section, you should be able to:

- describe the main consequences of ageing on respiratory structure and function.

Respiratory performance declines with age, beginning in the mid-20s, although the substantial physiological reserve in the healthy respiratory system means that there is no significant loss of efficiency. As with the cardiovascular system, maintaining physical fitness into older age helps to maintain good respiratory function. General loss of elastic tissue in the lungs increases the likelihood that small airways will collapse during expiration and decreases the functional

lung volume. Varying degrees of emphysema (p. 293) are normal in older people, usually without symptoms.

Cartilage in general becomes less flexible with age and there is an increased risk of arthritic joint changes. The ribcage therefore becomes stiffer, which, along with the general age-related reduction in muscle function, reduces the respiratory minute volume.

The risk of respiratory infections rises because of age-related immune decline and decreased mucus production in the airways. The respiratory chemoreceptor reflexes that increase respiratory effort in response to rising blood CO_2/falling blood O_2 levels become less efficient, so older people may respond less well to adverse changes in blood gases.

Age-related respiratory compromise is much more significant in smokers.

SPOT CHECK

16. What are the two main factors that reduce minute volume in healthy older people?

Disorders of the upper respiratory tract

Learning outcome

After studying this section, you should be able to:

- describe the common inflammatory and infectious disorders of the upper respiratory tract.

Infectious and inflammatory disorders

Inflammation of the upper respiratory tract can be caused by inhaling irritants, such as cigarette smoke or air pollutants, but is commonly due to infection. Such infections are usually caused by viruses, which are often mild and self-limiting in themselves but that lower the resistance of the respiratory tract to other microbes. This can predispose to a secondary bacterial infection. Such infections are only life-threatening if they spread to the lungs or other organs, or if inflammatory swelling and exudate block the airways.

Pathogens are usually spread by droplet infection (tiny exhaled droplets containing infectious material suspended in the air), by dust or by contaminated equipment and dressings. If not completely resolved, acute infection may become chronic.

Viral infections cause acute inflammation of the mucous membrane, leading to tissue congestion and profuse exudate of watery fluid. This can predispose to secondary bacterial infection, particularly in vulnerable groups such as children and older adults.

Common cold and influenza

The common cold (coryza) is caused by a range of viruses. Most colds are due to a rhinovirus, but others include coronavirus and respiratory syncytial virus (RSV). A cold is a highly infectious, normally mild illness characterised mainly by a runny nose (rhinorrhoea), sneezing, sore throat and sometimes slight fever. Normally, a cold runs its course over a few days. Influenza is caused mainly by an influenza virus and produces far more severe symptoms than a cold, including very high temperatures and muscle pains; complete recovery can take weeks and secondary bacterial infections are more common than with a simple cold. In healthy adults, most strains of influenza are incapacitating but rarely fatal, unless infection spreads to the lungs. It can, however, be a lethal illness in the elderly or immunocompromised, who may succumb to secondary bacterial pneumonia.

COVID-19

Severe acute respiratory coronavirus 2 (SARS-CoV-2), a new and highly contagious member of the coronavirus family, emerged from China in late 2019 and swept across the globe in only a few months, with infections reported in every country. The WHO declared it a global pandemic in March 2020. In common with other coronavirus-mediated infections, e.g. Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), it causes a significant respiratory illness, called COVID-19. The main presenting symptoms include a persistent dry cough, headache and high fever. There may also be loss of the senses of taste and smell. More severe infections lead to pneumonia, severe acute respiratory syndrome, renal failure and death. Those most at risk of severe disease include the over-75 age group and individuals with underlying health conditions such as diabetes or asthma.

Sinusitis

This is usually caused by spread of microbes from the nose and pharynx to the mucous membrane lining the paranasal sinuses. The primary viral infection is usually followed by bacterial infection. The congested mucosa may block the openings between the nose and the sinuses, preventing drainage of mucopurulent discharge and causing facial pain and headache. If there are repeated attacks or if recovery is not complete, the infection may become chronic.

Tonsillitis

Viruses and *Streptococcus pyogenes* are common causes of inflammation of the palatine tonsils, palatine arches and walls of the pharynx (Fig. 10.30). Severe infection may lead to suppuration and abscess formation (quinsy). Occasionally the infection spreads into the neck, causing cellulitis. Following acute tonsillitis, swelling subsides and the tonsil returns to normal, but repeated infection may lead to chronic inflammation, fibrosis and permanent enlargement. Endotoxins from tonsillitis caused by *Streptococcus pyogenes* are associated with the development of rheumatic fever (p. 139) and glomerulonephritis (p. 391). Repeated infection of the nasopharyngeal tonsil (adenoids, Fig. 10.3) can leave them enlarged and fibrotic, and can cause airway obstruction, especially in children.

Pharyngitis, laryngitis and tracheitis

The pharynx, larynx and trachea may become infected secondary to other upper respiratory tract infections, e.g. the common cold or tonsillitis.

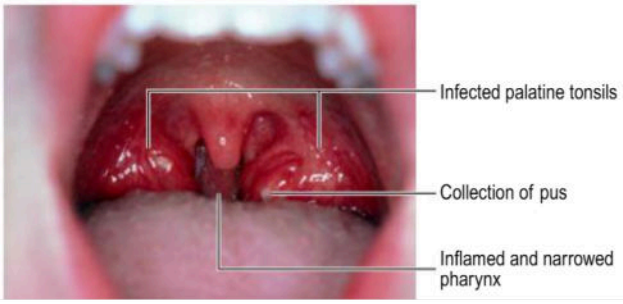


Figure 10.30 Streptococcal tonsillitis. (Dr P Marazzi/Science Photo Library. Reproduced with permission.)

Laryngotracheobronchitis (croup in children) is a rare but serious complication of upper respiratory tract infections. The airway is obstructed by marked swelling around the larynx and epiglottis, accompanied by wheeze and dyspnoea.

Diphtheria

This is a bacterial infection of the pharynx, which may extend to the nasopharynx and trachea; it is caused by *Corynebacterium diphtheriae*. A thick, fibrous membrane forms over the area and may obstruct the airway. The pathogen produces powerful exotoxins that may severely damage cardiac and skeletal muscle, the liver, kidneys and adrenal glands. In countries where immunisation is widespread, diphtheria is rare.

Hay fever (allergic rhinitis)

In this condition, atopic ('immediate') hypersensitivity (p. 426) develops to foreign proteins (antigens), e.g. pollen, mites in pillow feathers or animal dander. Acute inflammation of nasal mucosa and conjunctiva causes rhinorrhoea (excessive watery exudate from the nose), redness of the eyes and excessive tear production. Atopic hypersensitivity tends to run in families but no single genetic factor has yet been identified; it is likely to involve multiple genes. Other forms of atopic hypersensitivity include childhood-onset asthma (see next section), eczema (p. 411) in infants and young children, and food allergies.

SPOT CHECK

17. What is the difference between a cold and influenza?

Obstructive lung disorders

Learning outcomes

After studying this section, you should be able to:

- compare the causes and pathology of chronic and acute bronchitis
- discuss the pathologies of the main forms of emphysema
- discuss the causes and disordered physiology of asthma
- explain the main physiological abnormality in bronchiectasis
- describe the effect of cystic fibrosis on lung function.

Obstructive lung disorders are characterised by blockage of airflow through the airways. Obstruction may be acute or chronic.

Bronchitis

Acute bronchitis

This is usually a secondary bacterial infection of the bronchi, preceded by a common cold or influenza, and may also complicate measles and whooping cough in children. Viral infection depresses normal defence mechanisms, allowing pathogenic bacteria already present in the respiratory tract to multiply. Downward spread of infection may lead to bronchiolitis and/or bronchopneumonia, especially in children and in debilitated or older adults.

Chronic bronchitis

This common disorder becomes increasingly debilitating as it progresses. Chronic bronchitis is defined clinically when an individual has had a cough with sputum for 3 months in 2 successive years. It is a progressive inflammatory disease resulting from prolonged irritation of the bronchial epithelium, often worsened by damp or cold conditions. It is often a consequence of cigarette smoking but can also follow episodes of acute bronchitis (often caused by *Haemophilus influenzae* or *Streptococcus pneumoniae*) and chronic exposure to airborne irritants such as urban fog, vehicular exhaust fumes or industrial pollutants.

It develops mostly in middle-aged men who are chronic heavy smokers and may have a familial predisposition. Acute exacerbations are common, and often associated with infection. The changes occurring in the bronchi are described here.

Increased size and number of mucus glands

The increased volume of mucus may block small airways and overwhelm the ciliary escalator, leading to reduced clearance, a persistent cough and infection.

Oedema and other inflammatory changes

Swelling and thickening of the airway wall narrows the lumen and obstructs airflow.

Reduction in number and function of ciliated cells

Ciliated epithelium is progressively destroyed and replaced by non-ciliated epithelium. This may precede neoplastic (cancerous) change. As ciliary efficiency is reduced, mucus accumulation worsens, further increasing the risk of infection.

Fibrosis of the airways

Inflammatory changes lead to fibrosis and stiffening of airway walls, further reducing airflow.

Breathlessness (dyspnoea)

This is worse with physical exertion and increases the work of breathing.

Ventilation of the lungs becomes severely impaired, causing breathlessness and leading to hypoxia, pulmonary

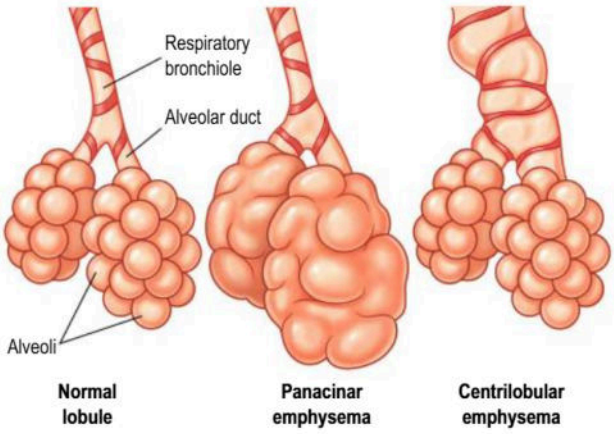


Figure 10.31 Emphysema.

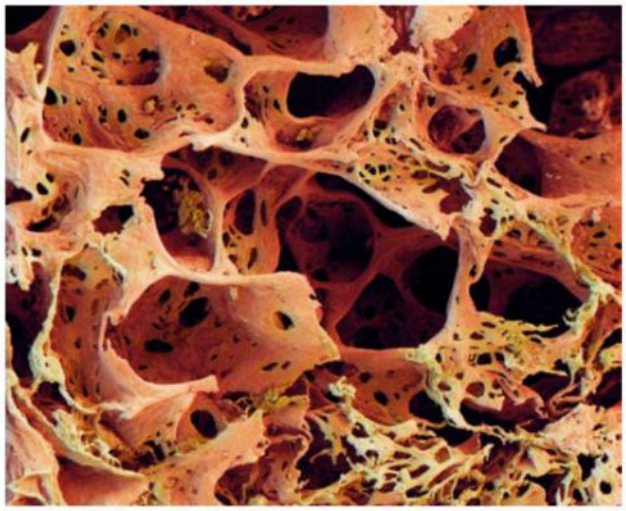


Figure 10.32 Coloured scanning electron micrograph of lung tissue with emphysema. (Dr Tony Britain/Science Photo Library. Reproduced with permission.)

hypertension and right-sided heart failure. As respiratory failure develops, arterial blood PO_2 is reduced (hypoxaemia) and is accompanied by a rise in arterial blood PCO_2 (hypercapnia). When the condition becomes more severe, the respiratory centre in the medulla responds to hypoxaemia rather than to hypercapnia. In the later stages, the inflammatory changes begin to affect the smallest bronchioles and the alveoli themselves, and emphysema develops (see next section). The term chronic obstructive pulmonary disease (COPD) is sometimes used to describe this situation.

Emphysema

The term emphysema means an abnormal accumulation of air. Two unrelated types are recognised: pulmonary emphysema and interstitial emphysema.

Pulmonary emphysema (Figs 10.31 and 10.32)

Pulmonary emphysema, generally referred to simply as emphysema, usually develops as a result of long-term inflammatory conditions or irritation of the airways, e.g. in smokers or coal miners. Occasionally, it may be due to a genetic deficiency in the lung of α_1-antitrypsin, which normally blocks the activity of enzymes that break down tissue proteins. These conditions lead to progressive destruction of supporting elastic tissue in the lung, and the lungs progressively expand (barrel chest) because without their elastic fibres they cannot recoil after expanding. In addition, the chronic inflammation causes irreversible distension and destruction of the respiratory bronchioles, alveolar ducts and alveoli, reducing the surface area for the exchange of gases.

On microscopic examination, the lung tissue is full of large, irregular cavities created by the destruction of alveolar walls (Fig. 10.32; compare with Fig. 10.22). There are two main types of pulmonary emphysema and both are usually present.

Panacinar emphysema

This affects alveoli and the tiny bronchioles throughout the lungs. The walls between adjacent alveoli break down, the alveolar ducts dilate and interstitial elastic tissue is lost. The lungs become distended and their capacity is increased. As the volume of air in each breath remains unchanged, it constitutes a smaller proportion of the total volume of air in the distended alveoli, reducing the partial pressure of oxygen. This reduces the concentration gradient of O_2 across the alveolar membrane, decreasing diffusion of O_2 into the blood. Merging of alveoli reduces the surface area for exchange of gases. In the early stages of the disease, normal arterial blood O_2 and CO_2 levels are maintained at rest by hyperventilation. As the disease progresses, the combined effect of these changes may lead to hypoxia, pulmonary hypertension and eventually right-sided heart failure.

Centrilobular emphysema

In this form there is irreversible dilation of the respiratory bronchioles supplying lung lobules and the distal alveoli beyond are relatively spared. When inspired air reaches the dilated area the pressure falls, reducing forward flow of air and the amount of oxygen-rich air getting to the alveoli. This reduces gas exchange and PO_2. As the disease progresses, the resultant hypoxia leads to pulmonary hypertension and right-sided heart failure.

Interstitial emphysema

Interstitial emphysema is the accumulation of small air bubbles in the thoracic interstitial tissues, and this may happen in one of the following ways:

- from the outside, by injury, e.g. fractured rib, stab wound

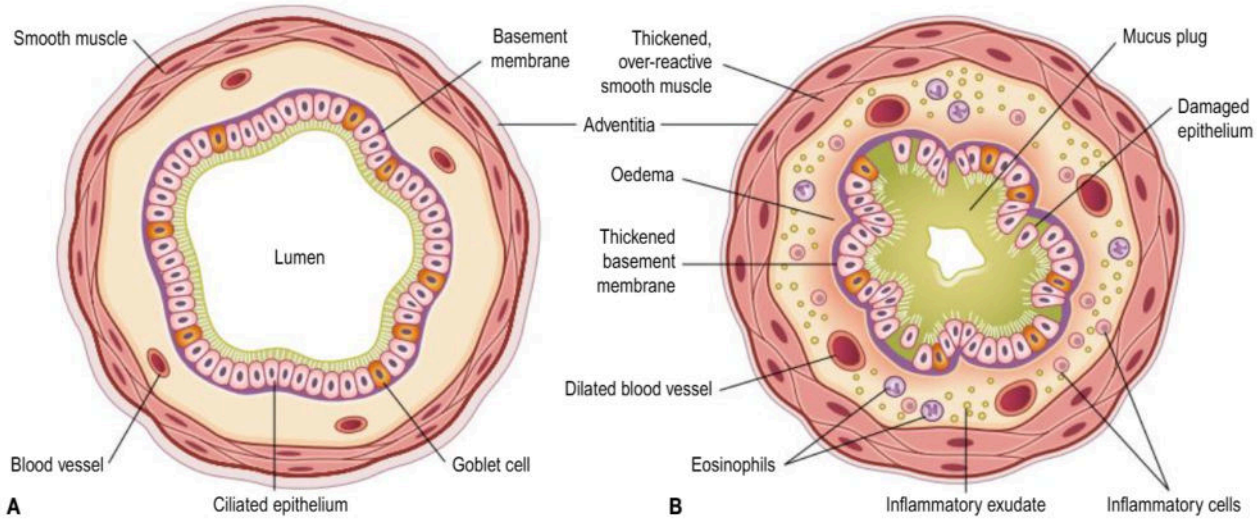


Figure 10.33 Cross-section of the airway wall in asthma. (A) Normal airway. (B) Asthmatic airway.

- from the inside, when alveoli rupture through the pleura, e.g. during an asthmatic attack, in bronchiolitis, or coughing as in whooping cough.

The air in the tissues usually tracks upwards to the soft tissues of the neck, where it is gradually absorbed, causing no damage. A large quantity in the mediastinum may, however, limit heart movement. It is important to distinguish between interstitial emphysema and pneumothorax (p. 300), where the air is trapped between the pleura.

Asthma

Asthma is a common inflammatory disease of the airways associated with episodes of reversible hyperreactivity of the airway smooth muscle (Fig. 10.33). The mucous membrane and muscle layers of the bronchi and bronchioles become inflamed, oedematous and swollen and the mucous glands enlarge, reducing airflow in the lower respiratory tract. The inflammatory exudate is rich in inflammatory cells, especially eosinophils. During an asthmatic attack, spasmodic contraction of bronchiolar muscle (bronchospasm) constricts the airways and there is excessive secretion of thick, sticky mucus, which further narrows the airway. Only partial expiration is achieved, so the lungs become hyperinflated and there is severe dyspnoea and wheezing. Peak expiratory flow (p. 285) is significantly reduced. Asthma attacks may last from a few minutes to several hours. In severe acute attacks larger bronchi may be completely obstructed by mucus plugs, blocking airflow and leading to acute respiratory failure, hypoxia and sometimes death even with treatment.

Non-specific factors that may precipitate asthma attacks include cold air, cigarette smoking, air pollution, upper respiratory tract infection, emotional stress and strenuous exercise.

There are two clinical categories of asthma, which give rise to similar symptoms and are treated in the same way. Whatever the aetiology, asthma can usually be well controlled with inhaled anti-inflammatory and bronchodilator agents, enabling people to live a normal life.

Atopic (allergic, childhood-onset, extrinsic) asthma

This occurs in children and young adults and is associated with atopic (type I) hypersensitivity (p. 426). A history of infantile eczema or food allergies is common and there are often close family members with a history of allergy. It is the most common chronic disease of childhood.

Antigens (allergens) are inhaled and absorbed by the bronchial mucosa. This stimulates the production of immunoglobulin E (IgE) antibodies, which bind to the surface of mast cells and basophils around the bronchial blood vessels. When the allergen is encountered again, the antigen/antibody reaction results in the release of histamine and other inflammatory mediators that stimulate mucus secretion and muscle contraction, narrowing the airways. Attacks tend to become less frequent and less severe with age.

Adult onset (late onset) asthma

This type occurs in adult life and there is no history of childhood allergic reactions. Risk factors include female sex, smoking, pre-existing respiratory conditions and obesity. Aspirin triggers an asthmatic reaction in some people. Attacks tend to increase in severity over time and lung damage may be irreversible. Eventually, impaired lung ventilation leads to hypoxia, pulmonary hypertension and right-sided heart failure.

Bronchiectasis

This is permanent abnormal dilation of bronchi and bronchioles. It is associated with chronic bacterial infection,

and sometimes with a history of childhood bronchiolitis and bronchopneumonia, cystic fibrosis or bronchial tumour. The bronchi become obstructed by mucus, pus and inflammatory exudate, and the alveoli distal to the blockage collapse as trapped air is absorbed. Interstitial elastic tissue degenerates and is replaced by fibrous adhesions that attach the bronchi to the parietal pleura. The pressure of inspired air in these damaged bronchi leads to dilation proximal to the blockage. The persistent severe coughing to remove copious purulent sputum causes intermittent increases in pressure in the blocked bronchi, leading to further dilation.

The lower lobe of the lung is usually affected. Suppuration is common. If a blood vessel is eroded, the individual may cough up blood (haemoptysis). Microbes may escape into the bloodstream, leading to abscess formation elsewhere in the body, commonly the brain. Progressive lung fibrosis leads to hypoxia, pulmonary hypertension and right-sided heart failure.

Cystic fibrosis (mucoviscidosis)

This is one of the most common inherited diseases, affecting 1 in 2500 babies. It is estimated that almost 5% of people carry the abnormal recessive gene, which must be present in both parents to cause the disease.

The secretions of all exocrine glands are abnormally thick because of impaired chloride transport across the secretory epithelia, but the most severely affected are those of the lungs, pancreas, intestines, biliary tract, and the male reproductive system. Sweat is abnormally salty. The pancreas secretes highly viscous mucus that obstructs the ducts that carry its digestive enzymes to the small intestine. The enzymes accumulate in the pancreas, causing inflammation and damage. In the newborn, intestinal obstruction may be caused by a plug of meconium (fetal faeces) and viscid mucus, leading to perforation of the alimentary canal wall and meconium peritonitis, which is often fatal. In less acute cases protein and fat digestion can be impaired, resulting in malabsorption, steatorrhoea and failure to thrive in infants.

The disease is life-limiting and the average lifespan of affected individuals is around 50 years, mainly because of impaired respiratory and gastrointestinal function, including:

- impaired digestion and malabsorption
- liver disease and cirrhosis, because of bile duct obstruction
- recurrent bronchitis and pneumonia because of thick respiratory secretions
- bronchiectasis.

The main treatments offered are aimed at maintaining effective respiratory function and preventing infection. Chronic lung and heart disease are common complications.

SPOT CHECK

18. Why do blood carbon dioxide levels rise in obstructive airways disease?
19. What does the term 'interstitial emphysema' mean?

Restrictive lung disorders

Learning outcomes

After studying this section, you should be able to:

- describe the main pneumoconioses
- outline the main causes and consequences of chemically induced lung disease.

Restrictive lung disorders are characterised by increasing stiffness (low compliance) of lung tissue, making it harder to inflate the lung and increasing the work of breathing. Chronic restrictive disease is often associated with progressive fibrosis caused by repeated and ongoing inflammation of the lungs.

Pneumoconioses

This group of lung diseases is caused by prolonged exposure to inhaled organic dusts, which trigger generalised inflammation and progressive fibrosis of lung tissues. Inhalation of work-related pollutants was a major cause of lung disease prior to the introduction of legislation that limits workers' exposure to them. To cause disease, particles must be so small that they are carried in inspired air to the level of the respiratory bronchioles and alveoli, where they can be cleared only by phagocytosis. Larger particles are trapped by mucus higher in the respiratory tract and expelled by ciliary action and coughing. The risk increases with cigarette smoking and the duration and concentration of exposure.

Coal worker's pneumoconiosis

Inhalation of coal dust over a prolonged period leads to varying degrees of respiratory impairment; many miners develop little or no disease but others suffer massive progressive fibrosis that is ultimately fatal. The inhaled dust collects in the lung and is phagocytosed by macrophages, which collect around airways and trigger varying degrees of fibrosis. If the fibrosis remains restricted to these small collections of macrophages and there is no significant reduction in lung function, the disorder is referred to as simple coal worker's pneumoconiosis and is unlikely to progress once exposure to dust stops. For reasons that are unclear, the fibrotic changes in the lungs progress much more aggressively in some people, with formation of large, dense fibrotic nodules, destruction and cavitation of lung tissue, and potentially fatal respiratory impairment.

Silicosis

This may be caused by long-term exposure to dust containing silicon compounds. High-risk industries include quarrying,

mining of minerals, stone masonry, sand blasting, glass making and pottery production.

Inhaled silica particles accumulate in the alveoli and are ingested by macrophages, to which silica is toxic. The inflammatory reaction triggered when the macrophages die causes significant fibrosis.

Silicosis appears to predispose to the development of tuberculosis, which rapidly progresses to tubercular bronchopneumonia and possibly miliary tuberculosis (p. 298). Gradual destruction of lung tissue progressively reduces pulmonary function, causing pulmonary hypertension and right-sided heart failure.

Asbestosis

Asbestosis, caused by inhaling asbestos fibres, usually develops after 10–20 years' exposure, but sometimes after only 2 years. Asbestos miners and workers involved in making and using some products containing asbestos are at risk. There are different types of asbestos but blue asbestos is associated with the most serious disease.

Despite their large size, asbestos particles penetrate to the level of respiratory bronchioles and alveoli. Macrophages accumulate in the alveoli and ingest shorter fibres. The larger fibres form asbestos bodies, consisting of fibres surrounded by macrophages, protein material and iron deposits. Macrophages containing fibres migrate out of the alveoli and accumulate around respiratory bronchioles and blood vessels, stimulating the formation of fibrous tissue. Lung tissue is progressively destroyed, with the development of dyspnoea, chronic hypoxia, pulmonary hypertension and right-sided heart failure. Asbestos is linked to the development of mesothelioma (p. 299).

Extrinsic allergic alveolitis

This group of conditions is caused by inhaling organic dusts, including those in Table 10.3. The contaminants act as antigens, causing a type III hypersensitivity reaction (p. 426) in the walls of the alveoli.

Initially, the allergy causes bronchiolitis, dyspnoea, cough, accumulation of inflammatory cells and formation of granulomas (collections of macrophages). If the exposure is brief the inflammatory response may resolve, but on repeated exposures pulmonary fibrosis develops.

Pulmonary toxins

Lung fibrosis can be triggered by a range of substances, including a range of drugs (Table 10.4) and high oxygen levels.

High-concentration oxygen therapy

Premature babies may require oxygen treatment while their lung function matures, but the high concentrations used can cause permanent fibrotic damage to the lungs, as well as to the retina of the eye (p. 221). People of any age who require high-concentration oxygen therapy may also develop pulmonary fibrosis.

Table 10.3 Conditions caused by organic dusts

Disease	Contaminant
Farmer's lung	Mouldy hay
Bagassosis	Mouldy sugar waste
Bird handler's lung	Moulds in bird droppings
Malt worker's lung	Mouldy barley
Byssinosis	Cotton fibres

Table 10.4 Drugs that may cause pulmonary fibrosis

Drug class	Examples
Opioids	Diamorphine (heroin)
Cardiovascular drugs	Amiodarone, hydralazine
Cytotoxic drugs used to treat cancer	Bleomycin, busulfan
Immunosuppressants	Methotrexate, cyclophosphamide
Antibiotics	Nitrofurantoin, sulphonamides

SPOT CHECK

20. Why do asbestos fibres cause permanent lung damage?

Lung infections

Learning outcome

After studying this section, you should be able to:

- describe the causes and effects of lung infection, including pneumonia, abscess and tuberculosis.

Pneumonia

Pneumonia means infection of the alveoli. This occurs when pulmonary defence mechanisms fail to prevent inhaled or blood-borne microbes reaching and colonising the lungs. Some predisposing factors are listed here.

Reduced respiratory tract defences

Coughing is an effective cleaning mechanism, but if it is impaired or lost by, for example, damage to respiratory muscles or the nerves supplying them, or by painful coughing, then respiratory secretions may accumulate and become infected.

Ciliary action may be impaired or the epithelium destroyed by smoking, inhaling noxious gases or infection.

Depressed pulmonary macrophage activity may be caused by smoking, alcohol or anoxia.

Hospitalisation

Hospitalisation can be a predisposing factor, especially when mechanically assisted ventilation is required, partly because of exposure to a wide range of potentially antibiotic-resistant and more virulent pathogenic organisms.

Other factors

The risk of pneumonia is increased in extremes of age, leukopenia, hypothermia, chronic disease (e.g. heart failure, cancer, chronic renal failure, alcoholism) or immunosuppression caused by, for example, ionising radiation or corticosteroid drugs.

Causative organisms

A wide variety of organisms, including bacteria, viruses, mycoplasma, protozoa and fungi, can cause pneumonia under appropriate conditions. The most common pathogen is the bacterium *Streptococcus pneumoniae*. Others include *Staphylococcus aureus* and *Haemophilus influenzae*. *Legionella pneumophila* spreads through water distribution systems, e.g. air conditioning systems, and is transmitted via droplet inhalation. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are common causes of hospital-acquired pneumonia.

Lobar pneumonia

This form of pneumonia is most common in previously healthy young adults. The infection is confined to one or more lobes of one lung, because the lobes are separated from each other by the lung fissures, preventing spread from one lobe to another (Fig. 10.34A). The most common causative organism is *Streptococcus pneumoniae*. Infection leads to production of watery inflammatory exudate in the alveoli, which accumulates and fills the lobule, and overflows into and infects adjacent lobules. It is of sudden onset and pleuritic pain accompanies inflammation of the visceral pleura. Antibiotic therapy is usually prescribed, but even if untreated it generally resolves within 2–3 weeks.

Bronchopneumonia

Bronchopneumonia (Fig. 10.34B) occurs most commonly in immunosuppressed people and in the very young and the very old, and death is fairly common, especially when the condition complicates debilitating diseases. Other predisposing factors include:

- debility due to, for example, cancer, uraemia, cerebral haemorrhage, congestive heart failure, malnutrition, hypothermia
- pre-existing lung disease, e.g. bronchiectasis, cystic fibrosis or acute viral infection
- recent general anaesthesia, which depresses respiratory and ciliary activity
- inhalation of gastric contents (aspiration pneumonia) in, for example, unconsciousness or very deep sleep, or following excessive alcohol consumption or drug overdose

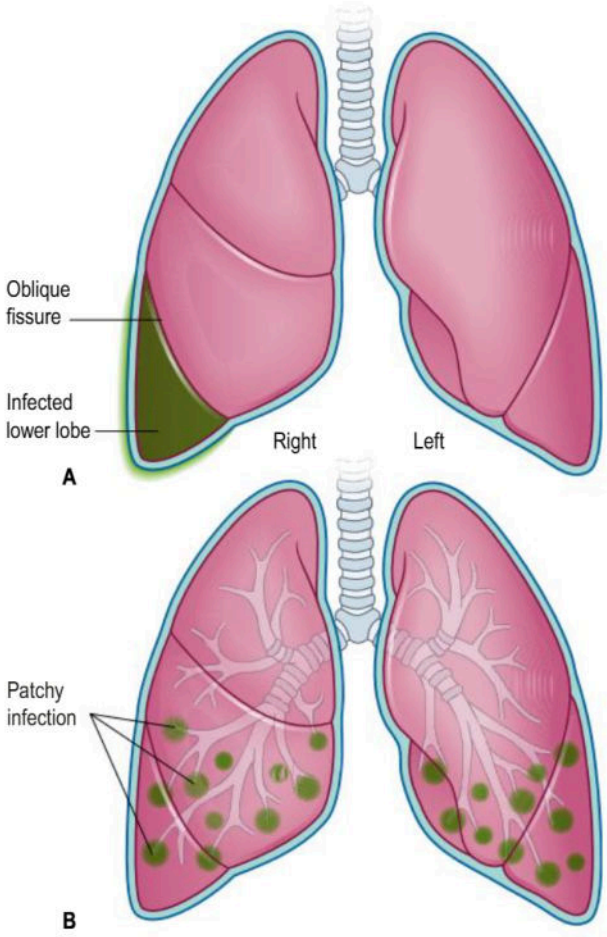


Figure 10.34 Distribution of infected tissue in pneumonia. (A) Lobar pneumonia. (B) Bronchopneumonia.

- inhalation of infected material from the paranasal sinuses or upper respiratory tract.

The infection is distributed throughout the lungs, involving the airways and the alveoli. It is usually bilateral and mainly affects the lung bases. As these become inflamed, fibrous exudate accumulates and there is an influx of leukocytes. Areas of consolidation (fluid-filled alveoli) develop. Figure 10.35 is a chest X-ray of an individual with bronchopneumonia, showing patches of consolidation throughout both lungs and particularly marked in the lateral areas of the lung encircled on the image. Even after resolution, the lung is frequently left with permanent fibrotic scarring. Bronchiectasis is a common complication, leading to further acute attacks, lung fibrosis and progressive destruction of lung substance.

Lung abscess

This is localised suppuration and necrosis within the lung substance. The abscess may develop from local infection:

- if pneumonia is inadequately treated
- as a result of trauma, e.g. rib fracture, stab wound or surgery

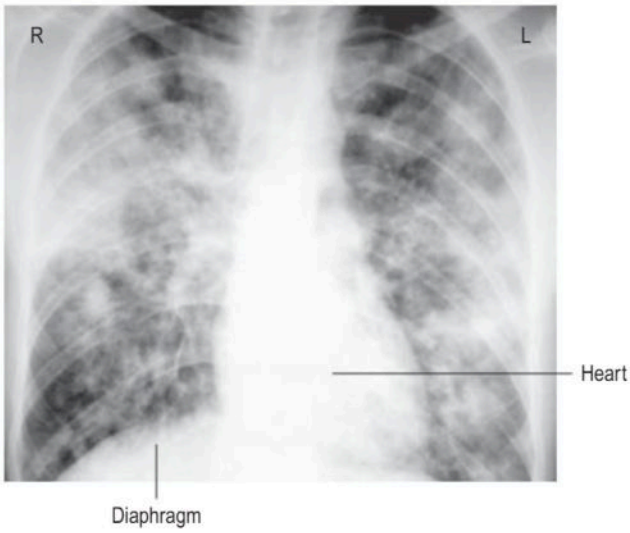


Figure 10.35 Chest X-ray showing bronchopneumonia. Patchy consolidation (white areas) present in both lungs. (From Franquet T, 2001. Imaging of pneumonia: trends and algorithms. Eur. Resp. J., 18: 196-208.)

- by spreading from infection in local structures, e.g., oesophagus, spine, pleural cavity, or a subphrenic abscess.

Occasionally, this develops when infected material travelling in the bloodstream, a septic embolus, arrives and lodges in the lung. Such material usually originates from thrombophlebitis (p. 132) or infective endocarditis (p. 139).

Outcomes

Recovery from lung abscess may either be complete or lead to complications, such as erosion of a pulmonary blood vessel, causing haemorrhage. Fragments of infected material can travel in the bloodstream to other tissues and cause infection there: for example, a cerebral abscess.

Tuberculosis

Tuberculosis (TB) is a major and increasing health problem worldwide, particularly in low-income countries that cannot afford effective prevention or treatment, and in countries where HIV infection is common. It is caused by one of two similar forms of mycobacteria, the main one being *Mycobacterium tuberculosis*. Humans are the main host. The microbes are spread by inhalation, either by aerosol droplet infection from an individual with active tuberculosis, or in dust contaminated by infected sputum. Mycobacteria are taken up by macrophages, but are protected from phagocytic digestion by their thick outer cell wall. This greatly reduces the ability of the immune system to destroy the microbes and contributes to the persistence of the microbe in the body following infection.

TB can be caused by *Mycobacterium bovis* from cows. Pasteurisation of milk prevents the spread of this form of the disease.

Pulmonary tuberculosis

Primary tuberculosis

Initial infection usually involves the apex of the lung. Inflammatory cells, including macrophages and lymphocytes, are recruited in defence, sealing off the infected lesions in Ghon foci. The centres of Ghon foci are filled with a cheese-like necrotic material that may contain significant numbers of active bacteria that have survived inside macrophages. If infection spreads to the regional lymph nodes, the Ghon foci and these infected nodes together are called the primary complex. At this stage, the disease is likely to have caused few, if any, clinical symptoms and in most people progresses no further, although calcified primary complexes are clearly identifiable on X-ray. Exposure to the bacterium causes sensitisation, which leads to a strong T-cell-mediated immune reaction (p. 421) if the infection becomes reactivated.

Secondary tuberculosis

This is usually due to reactivation of disease from latent bacteria surviving primary TB and can occur decades after the initial exposure in response to factors such as stress, ageing, immunocompromise or malnutrition. The infection is now much more likely to progress than it was at the primary stage, with significant destruction and cavitation of lung tissues. Symptoms include fever, cough, malaise, haemoptysis, weight loss and night sweats. Nearly half of patients with secondary TB develop non-pulmonary involvement.

Non-pulmonary tuberculosis

Primary TB rarely affects tissues other than the lung but non-pulmonary involvement in secondary TB is very common. Widely disseminated TB is nearly always fatal unless adequately treated.

Miliary tuberculosis

Blood-borne spread from the lungs leads to widespread dissemination of the bacilli throughout body tissues, and foci of infection can establish in any organ, including the bone marrow, liver, spleen, kidneys and central nervous system. Numerous tiny nodules develop in the lungs, which on X-ray look like sprinkled millet seeds (hence 'miliary'). Rapid treatment is essential to prevent further spread.

Lymph node tuberculosis

This is the second most common site of infection after the lung. Lymph nodes in the mediastinum, neck, axilla and groin are most likely to be affected. Infection causes swelling and central necrosis of the node. It is usually painless.

Joint and bone tuberculosis

The intervertebral, hip and knee joints are most commonly affected, and in children this is usually a consequence of primary TB. Infection of the intervertebral disc or synovial membrane of a synovial joint is followed by extensive

destruction of cartilage and adjacent bone, which in turn can progress to tuberculous osteomyelitis.

Other affected tissues

The pericardium, skin and gastrointestinal tract may all become involved. One in five people with extrapulmonary disease develop central nervous system infection, which requires urgent treatment; if it is not fatal, it can leave survivors with permanent neurological damage.

SPOT CHECK

21. What is the difference between lobar pneumonia and bronchopneumonia?
22. What is secondary tuberculosis?

Lung tumours

Learning outcome

After studying this section, you should be able to:

- describe the pathology of the common lung tumours.

Benign tumours of the lung are rare.

Bronchial carcinoma

Primary bronchial carcinoma is a very common malignancy. Up to 90% of cases occur in smokers or those who inhale other people's smoke (passive smokers). Other risk factors include exposure to airborne dusts and the presence of lung fibrosis. The primary tumour has usually spread by the time of diagnosis, and therefore the prognosis of this type of cancer is usually extremely poor.

The tumour usually develops in a main bronchus, forming a large friable mass projecting into the lumen, sometimes causing obstruction. Mucus then collects and predisposes to infection. As the tumour grows, it may erode a blood vessel, causing haemoptysis.

Spread of bronchial carcinoma

This does not follow any particular pattern or sequence. It infiltrates local tissues and tumour fragments are carried to distant tissues in blood and lymph. If blood or lymph vessels are eroded, fragments may spread while the tumour is still quite small. A metastatic tumour may, therefore, cause symptoms before the primary in the lung has been detected.

Local spread

This may be within the lung or to mediastinal structures, including blood vessels, nerves and the oesophagus.

Lymphatic spread

Tumour fragments spread along lymph vessels to successive lymph nodes, in which they may cause metastatic tumours. Fragments may enter lymph draining from a tumour or enter a larger vessel if its walls have been eroded by a growing tumour.

Blood spread

Tumour cells can enter the blood if a blood vessel is eroded by a growing tumour. The most common sites of blood-borne metastases are the liver, brain, adrenal glands, bones and kidneys.

Pleural mesothelioma

This malignant tumour of the pleura is usually associated with previous exposure to asbestos dust, e.g. asbestos workers and people living near asbestos mines and factories. Smoking multiplies the risk of mesothelioma several-fold in people exposed to asbestos. Mesothelioma may develop after a widely varying duration of asbestos exposure, from 3 months to 60 years, and is usually associated with crocidolite fibres (blue asbestos). The tumour involves both layers of pleura and, as it grows, it obliterates the pleural cavity, compressing the lung. Lymph- and blood-spread metastases are commonly found in the hilar and mesenteric lymph nodes, the other lung, liver, thyroid and adrenal glands, bone, skeletal muscle and the brain. The prognosis is usually very poor.

SPOT CHECK

23. Where is the most common site for the development of primary bronchial carcinoma?

Lung collapse

Learning outcomes

After studying this section, you should be able to:

- list the main causes of lung collapse
- describe the effects of lung collapse.

The clinical effects of collapse (atelectasis) of all or part of a lung (Fig. 10.36) depend on how much of the lung is affected. Fairly large sections of a single lung can be out of action without symptoms. There are four main causes of this condition:

- obstruction of an airway (absorption collapse)
- impaired surfactant function
- pressure collapse
- alveolar hypoventilation.

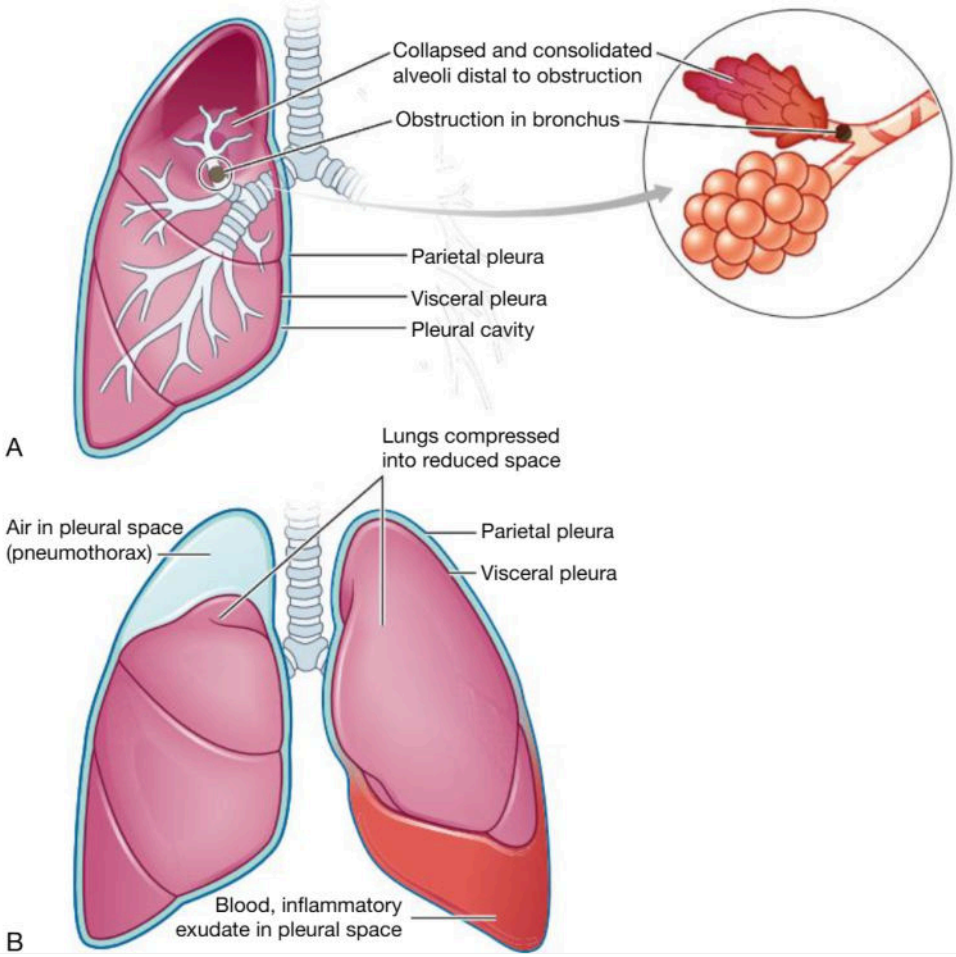


Figure 10.36 Collapse of a lung. (A) Absorption collapse. (B) Pressure collapse.

Obstruction of an airway (absorption collapse)

The amount of lung affected depends on the size of the obstructed air passage. Distal to the obstruction, air is trapped and absorbed, the lung collapses and secretions collect (Fig. 10.36A). These may cause infection and sometimes abscess formation. Short-term obstruction is usually followed by reinflation of the lung without lasting ill-effects. Prolonged obstruction leads to progressive fibrosis and permanent collapse. Sudden obstruction may be due to inhalation of a foreign body (usually into the right primary bronchus, which is wider and more steeply angled than the left) or to a mucus plug formed during an asthmatic attack or in chronic bronchitis. Gradual obstruction may be due to a bronchial tumour or pressure on a bronchus by, for example, enlarged mediastinal lymph nodes or aortic aneurysm.

Impaired surfactant function

Premature babies, born before the 34th week of pregnancy, may be unable to expand their lungs by their own respiratory effort because their lungs are too immature to produce surfactant (p. 280). These babies may need to be mechanically ventilated until their lungs begin to produce surfactant. This is called neonatal respiratory distress syndrome (NRDS).

In acute respiratory distress syndrome (ARDS), dilution of surfactant by fluid collecting in the alveoli (pulmonary oedema) leads to atelectasis. These patients are nearly always gravely ill already, and collapse of substantial areas of lung contributes to the mortality rate of around one-third.

Pressure collapse

When air or fluid enters the pleural cavity, the negative pressure becomes positive, preventing lung expansion. Fluids tend to settle in the lung bases because of the effect of gravity, whereas collections of air are usually found towards the lung apex (Fig. 10.36B). The collapse usually affects only one lung and may be partial or complete.

Pneumothorax

This is air in the pleural cavity. It may occur spontaneously or be the result of trauma.

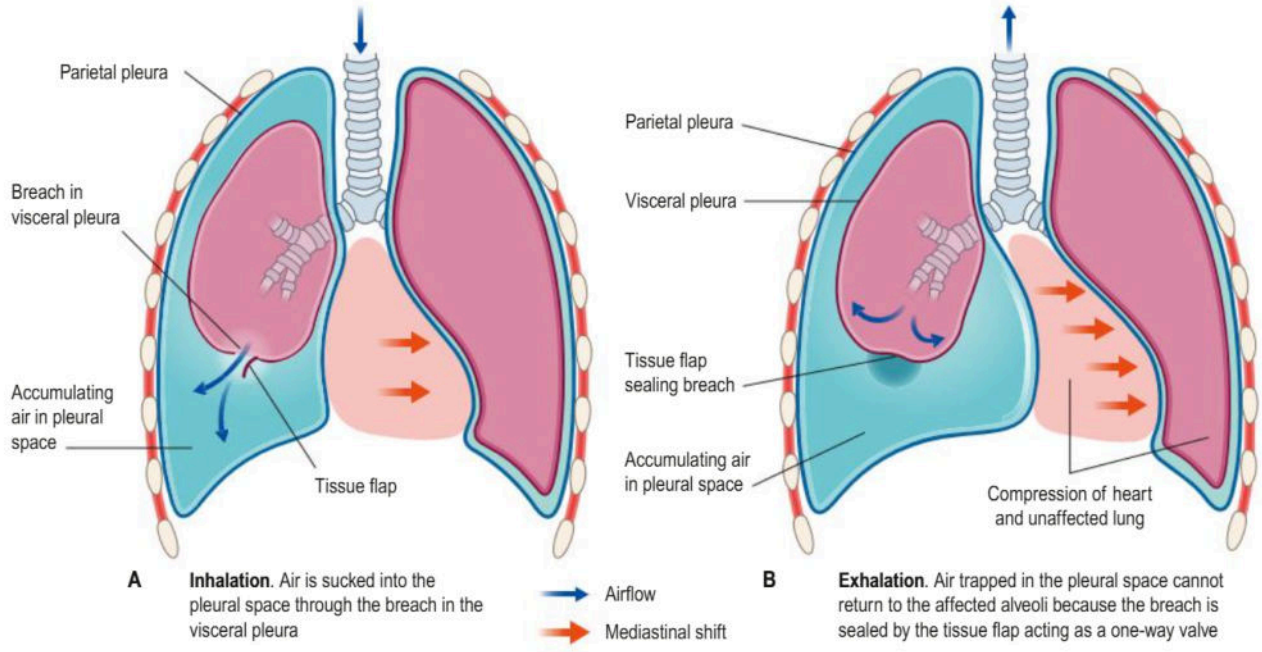


Figure 10.37 Tension pneumothorax. (A) Inhalation. (B) Exhalation.

Spontaneous pneumothorax

This may be either primary or secondary. Primary spontaneous pneumothorax is of unknown cause, is often recurrent, and occurs in fit and healthy people, usually males between 20 and 40 years of age. Secondary spontaneous pneumothorax occurs when air enters the pleural cavity after the visceral pleura ruptures due to lung disease, e.g. emphysema, asthma, pulmonary tuberculosis or bronchial cancer.

Traumatic pneumothorax

This is due to a penetrating injury that breaches the pleura, such as a compound rib fracture, a stab or gunshot wound, or surgery.

Tension pneumothorax

Tension pneumothorax (Fig. 10.37) is a life-threatening complication of a simple pneumothorax when a tissue flap that acts as a one-way valve develops between the lungs and the pleural cavity. Air enters the pleural cavity during inspiration but cannot escape on expiration because the flap is sucked across the breach in the visceral pleura, and steadily, sometimes rapidly, accumulates. The volume of air in the pleural space on the affected side increases steadily and sometimes very rapidly. This pushes the mediastinum towards the unaffected side, compressing the heart, the unaffected lung and the great vessels. This is a medical emergency and is fatal without prompt treatment.

Haemothorax

This is blood in the pleural cavity. It may be caused by a penetrating chest injury involving blood vessels, a ruptured aortic aneurysm or erosion of a blood vessel by a malignant tumour.

Pleural effusion

This is excess fluid in the pleural cavity. It may be caused by:

- increased hydrostatic pressure, e.g. heart failure (p. 136), increased blood volume
- increased capillary permeability due to local inflammation, e.g. lobar pneumonia, pulmonary TB, bronchial cancer, mesothelioma
- decreased plasma osmotic pressure, e.g. nephrotic syndrome (p. 392), liver cirrhosis (p. 369)
- obstructed lymphatic drainage, e.g. malignant tumour involving the pleura.

Following haemothorax and pleural effusion, fibrous adhesions that limit reinflation may form between the layers of pleura.

Alveolar hypoventilation

In the normal individual breathing quietly at rest, there are always some partially collapsed lobules within the lungs because of the low tidal volume. These lobules re-expand without difficulty at the next deep inspiration. Non-physiological causes of hypoventilation collapse include postoperative collapse, particularly after chest and upper abdominal surgery, when pain restricts thoracic expansion. This predisposes to chest infections because mucus collects in the under-ventilated airways and is not coughed up.

SPOT CHECK

24. Why does prematurity increase the risk of respiratory difficulty at birth?
25. What is traumatic pneumothorax?

Case study

Aadya has been feeling increasingly unwell over the past three days. This morning she wakes feeling awful, with a fever, a headache and profound fatigue. She also has a painful cough which is bringing up green sputum.

1. Which cranial nerve carries sensory information from the airways to the cough centre?

   a. Vagus (CN X)
   b. Trigeminal (CN V)
   c. Glossopharyngeal (CN IX)
   d. Accessory (CN XI)

2. Aadya's doctor diagnoses bacterial pneumonia, an infection of the alveoli. Which type of defence cell is found in alveolar walls?

   a. lymphocyte
   b. dendritic cell
   c. alveolar neutrophil
   d. macrophage

3. The infected alveoli fill with inflammatory exudate and debris from damaged lung tissue. This dilutes the normal fluid lining the inside of the alveoli. Which of the following is true in the healthy lung?

   a. This fluid is called pleural fluid and reduces surface tension in the alveoli.
   b. This fluid is called surfactant and reduces surface tension in the alveoli.
   c. This fluid is called pleural fluid and lubricates alveolar expansion.
   d. This fluid is called surfactant and lubricates alveolar expansion.

4. Aadya is finding it hard to fully expand her lungs with each breath. This is because pneumonia reduces which property of the lung?

   a. Elasticity
   b. Recoil
   c. Compliance
   d. Contractability

5. Aadya makes a complete recovery from her pneumonia, and full lung function is restored. Which of the following processes occurs across the wall of the healthy alveolus?

   a. Active transport of carbon dioxide out of the alveolar space
   b. Internal respiration
   c. Ciliary clearance of mucus
   d. Diffusion of oxygen down its concentration gradient

Review and revise

Complete each of the following statements:

1. In pneumonia, the _____ of the lungs are infected. Common organisms include _____ *pneumoniae* and *Haemophilus* _____. The form most common in young, otherwise healthy, adults is _____ pneumonia, whereas _____ is more common in older or immunocompromised people.

2. Each lung has a broad lower surface, called the _____, and a pointed _____. The lower surface rests on the _____. The area between the lungs is called the _____ and contains important structures such as the _____, the _____ and the _____. The right lung is composed of three _____ and is higher in the thorax than the left because of the _____ below.

Choose one answer to complete each of the following statements:

3. The epiglottis is composed of: _____
   a. Muscle
   b. Cartilage
   c. Bone
   d. Elastic connective tissue

4. Mesothelioma is associated with exposure to: _____
   a. Asbestos
   b. Cigarette smoke
   c. Industrial chemicals
   d. Silica dust

5. Rhinorrhoea is: _____
   a. Sneezing
   b. Breathlessness
   c. A runny nose
   d. A dry cough

6. The trachea is lined with: _____
   a. Stratified squamous epithelium
   b. Transitional epithelium
   c. Cuboidal epithelium
   d. Columnar ciliated epithelium

7. The structure/substance directly applied to the outer lung surface is: _____
   a. Visceral pleura
   b. Respiratory membrane
   c. Pleural fluid
   d. Surfactant

8. During quiet inspiration, the muscles that contract simultaneously with the diaphragm are: _____
   a. Both the external and internal intercostals
   b. External intercostals
   c. Internal intercostals
   d. External intercostals and scalenes

9. Tidal volume at rest is usually about: _____
   a. 1 litre
   b. 750 mL
   c. 500 mL
   d. 250 mL

10. Match each letter in List A to the appropriate number in List B. You may use each number more than once:

List A
- ____ (a) Percentage of carbon dioxide carried in solution in the plasma
- ____ (b) Percentage of carbon dioxide carried bound to haemoglobin in the plasma
- ____ (c) Percentage of oxygen carried bound to haemoglobin in the plasma
- ____ (d) Percentage content of oxygen in the atmosphere
- ____ (e) Percentage content of nitrogen in the atmosphere
- ____ (f) Average respiratory rate at rest
- ____ (g) Number of pairs of ribs
- ____ (h) Average number of cartilage rings in the trachea
- ____ (i) Number of cartilages forming the larynx

List B
1. 7
2. 9
3. 12
4. 18
5. 21
6. 23
7. 78
8. 98.5

11. Match each letter in List A to the appropriate number in List B:

List A
- ____ (a) Columnar ciliated epithelium
- ____ (b) Squamous epithelium
- ____ (c) Septal cell
- ____ (d) Alveolar macrophage
- ____ (e) Smooth muscle
- ____ (f) Skeletal muscle
- ____ (g) Cartilage

List B
1. Production of surfactant
2. Contraction of diaphragm
3. Cleaning of air in the upper airway
4. Control of airway diameter
5. Tracheal support
6. Exchange of gases in the alveoli
7. Defence in the air sacs

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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CHAPTER 11

Introduction to nutrition

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Before exploring the digestive system and its functions in Chapter 12, it is useful to understand the body's nutritional needs. The importance of healthy eating is increasingly recognised, as this provides the correct amounts of nutrients and confers many health benefits; it counteracts the increasing prevalence of obesity, and reduces the risk of other significant conditions, such as cardiovascular disease and some cancers.

Food provides nutrients, some of which are broken down to provide energy while others are needed for growth, repair and other cellular activities. The main nutrient groups are:

- carbohydrates
- proteins
- fats
- vitamins
- mineral salts, trace elements and water.

Food usually contains more than one nutrient group; for example, potatoes and bread are mainly carbohydrate but both also contain protein and some vitamins. An essential nutrient is a substance that cannot be made by the body and, for the maintenance of health, must therefore be eaten in the diet. Dietary fibre, more correctly known as non-starch polysaccharide (NSP), consists of largely indigestible material. Although it is not a nutrient, as it is neither a source of energy nor essential for cellular metabolism, fibre is an important dietary constituent that has many beneficial effects on the body.

The first parts of this chapter explore the balanced diet and its constituents. Later sections review nutrition in older adults and some nutritional disorders common in later life. The final section considers some consequences of poor nutrition and being overweight or obese.

The balanced diet

Learning outcomes

After studying this section, you should be able to:

- list the constituent food groups of a balanced diet
- calculate and interpret an individual's body mass index.

A balanced diet contains appropriate proportions of all the nutrients required for health. This is normally achieved by eating a variety of foods because no single food, except breast milk, contains all nutrients in the correct proportions. If any nutrient is eaten in excess or is deficient, health may be adversely affected. For example, a high-energy diet can lead to obesity, and an iron-deficient one to anaemia.

Healthy eating requires knowledge and planning. An important dietary consideration is the amount of energy required, as well as the amounts of each nutrient group needed to meet individual requirements. In the UK, labels (see Fig. 11.1) indicate the nutritional content of all packaged food

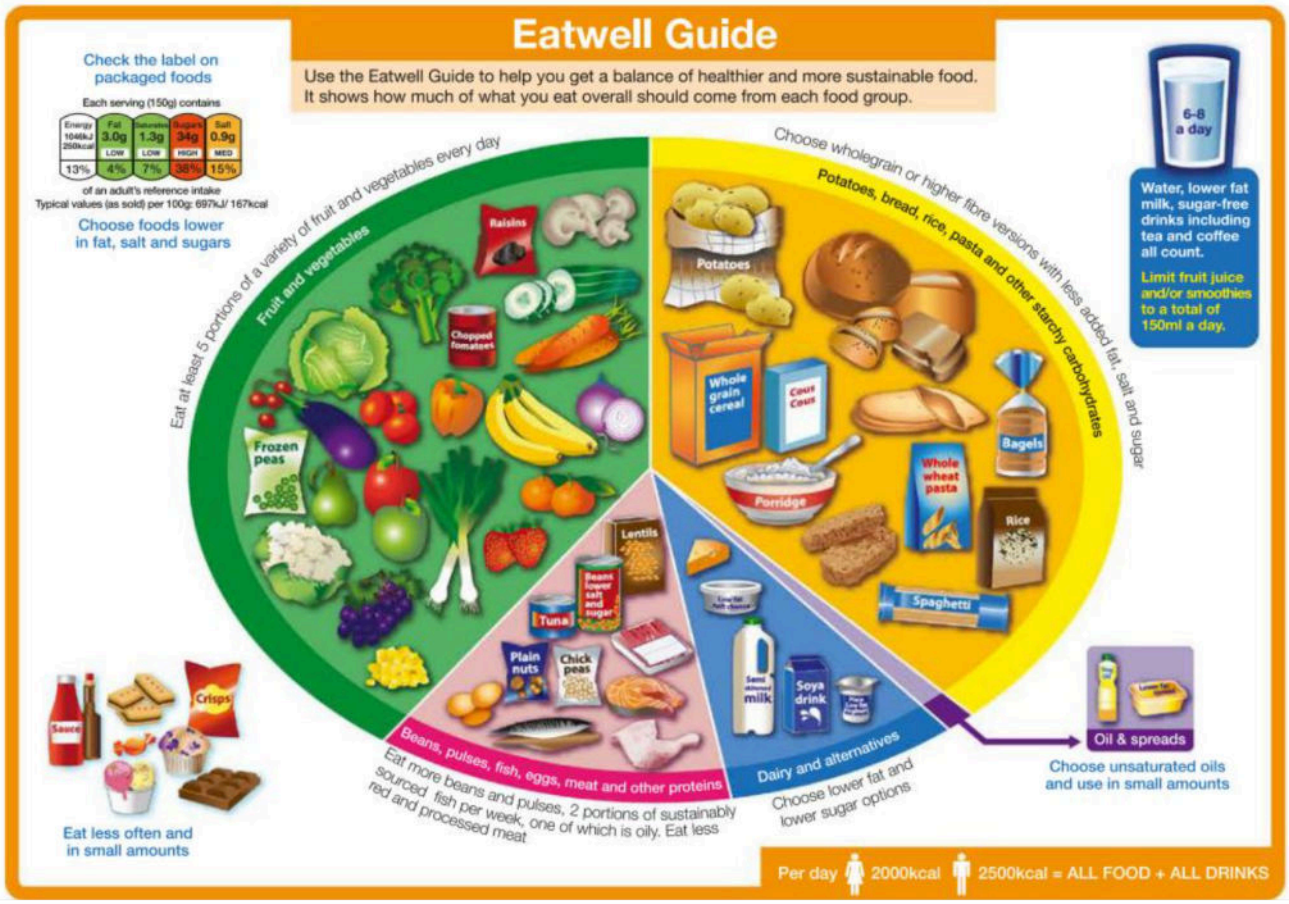

Figure 11.1 The Eatwell Guide. The main food groups and their recommended proportions within a balanced diet. (Public Health England in association with the Welsh Government, Food Standards Scotland and the Food Standards Agency in Northern Ireland. © Crown copyright 2016. Reproduced with permission.)

to guide decision making. This includes a traffic light system; the more green information boxes, the healthier the food.

Daily energy requirements

Daily energy requirements depend on several factors, including metabolic rate (p. 348), age, gender and activity levels. Certain groups of people have higher energy requirements than others. These include babies and children, who have relatively higher growth and metabolic rates, and pregnant and lactating women who additionally need to support the growing baby and milk production. For healthy adults, the recommended average daily energy intake is:

- women: 2000 kcal = 8400 kJ
- men: 2500 kcal = 10,500 kJ

Dietary carbohydrates, fats and proteins are the principal energy sources and fat is the most concentrated form. Dietary energy is correctly expressed in joules or kilojoules (kJ), although the older terms calories and kilocalories (kcal or Cal) are also still used in the UK.

Body mass index

A balanced diet is important in maintaining a healthy body weight relative to an individual's height; this indicator of nutritional status is calculated as the body mass index (BMI). BMI correlates well with health risks not only for individuals but also for populations. Box 11.1 shows how BMI is calculated and interpreted in adults aged over 20.

Healthy eating

This section is based on the recommendations of NHS England (2018) and the British Nutrition Foundation (2020). Recommendations for daily intake sort foods of similar origins and nutritional values into food groups and advise that from the age of 2 years a certain proportion from each group should be eaten daily (Fig. 11.1). Following this plan should ensure a healthy and well balanced diet. The five food groups are:

- fruit and vegetables
- potatoes, bread, rice, pasta and other starchy carbohydrates
- dairy and dairy alternatives
- beans, pulses, fish, eggs, meat and other proteins
- oils and spreads.

The first two groups listed above should form at least two thirds of the diet, with the other groups forming the remainder.

Box 11.1 Body mass index (WHO, 2021)

Calculation of BMI

$$\text{Body mass index} = \text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

International classification of BMI

BMI	Nutritional status
<18.5	Underweight
18.5–24.9	Normal weight
≥25.0	Overweight
25.0–29.9	Pre-obese
≥30	Obese
30.0–34.9	Obese class I
35.0–39.9	Obese class II
≥40	Obese class III

Fruit and vegetables

Fruit and vegetables should make up around a third of the diet (Fig. 11.1). This group includes fresh, frozen and canned products, and provides carbohydrate, fibre, vitamins A and C, and folic acid. At least five portions per day ('five a day') are recommended; one portion is 80 g and some equivalents are shown below:

1 piece of medium fruit, e.g. apple, orange, banana
3 tablespoons of cooked vegetables
1 bowl of mixed salad
150 mL of fruit juice or fruit smoothie (one portion irrespective of the volume consumed).

Potatoes, bread, rice, pasta and other starchy carbohydrates

This group should also make up about a third of the diet and each meal should be based around one food from this group (Fig. 11.1). Potatoes, yams and plantains are classified as starchy carbohydrates and are, therefore, considered within this group rather than as fruit and vegetables. Other foods in this group include breakfast cereals, rice and noodles. Healthier choices are the wholegrain or 'high fibre' options, which have a low glycaemic index (GI, see p. 308), are digested more slowly and provide sustained energy release. Some also contain iron and B-group vitamins, including folic acid (p. 311).

Dairy and dairy alternatives

Foods in this group provide protein and minerals, including calcium, iodine and zinc; some are also a source of vitamins and they often contain considerable amounts of fat. They include milk, cheese, fromage frais and yoghurt. Low-fat and unsweetened options are healthier choices. Non-dairy alternatives such as soy, almond or oat 'milk' are used in cases of cow's milk allergy, lactose intolerance or dietary preference, e.g. vegan diets. These are plant-based low calorie products; their vitamin and calcium content is variable, but generally less than dairy equivalents.

Beans, pulses, fish, eggs, meat and other proteins

In addition to the foods shown in Figure 11.1, this group includes processed meat products such as bacon, sausages, beefburgers, salami and pâté. Intake of red and processed meat should not exceed 70 g per day because many of these foods have a high fat content. Two portions of fish should be eaten weekly, including one portion (140 g) of oily fish such as salmon, trout, sardines or fresh tuna. This group provides protein, iron, vitamins, and sometimes minerals. Vegetarian alternatives include tofu, nuts, beans and pulses, e.g. lentils. Beans and pulses are also a good source of fibre, although only one 80-g portion counts as one of the 'five a day'.

Oils and spreads

Fat is an essential part of the diet because it provides essential fatty acids and enables absorption of the fat-soluble vitamins. As fats are high in energy, only very small amounts are required (Fig. 11.1). Fats are classified as saturated or unsaturated and the differences are explained on page 309. Low-fat and unsaturated products, which generally come from plants, are healthier options.

Snack foods

Examples are shown in the bottom left-hand corner of Figure 11.1; they include sugary soft drinks, syrup, chocolate and sweets, cakes, biscuits, ice cream and savoury snacks, e.g. crisps. They should be eaten only occasionally and in small amounts as, notably, they are not part of the Eatwell plate. This is because they are not required in the diet and can have adverse health consequences, as they are high in energy and have little additional nutritional value; low-salt and low-fat/sugar alternatives are recommended.

Additional recommendations

These include salt (see p. 312) and fluid intake. Fluid intake should be 1.5–2 litres per day, e.g. water, tea, coffee, squash and fruit juice (Fig. 11.1). Alcohol should not exceed 3–4 units per day for men and 2–3 units per day for women; alcoholic drinks and mixers are generally high in calories. Equivalents of 1 unit of alcohol are:

100 mL (small glass) of wine
300 mL (half-pint) of standard-strength beer, lager or cider
25 mL of spirits.

Groups of people with specific dietary requirements

Certain groups of people with higher energy requirements were identified above. Menstruating women need more iron in their diet than non-menstruating women to compensate for blood loss during menstruation. In some gastrointestinal

disorders, e.g. coeliac disease (p. 367), there is intolerance of certain foods, which restricts dietary choices. People with diabetes mellitus need to manage their diet to maintain normal plasma glucose levels and those with severe liver and kidney conditions and other disorders, e.g. phenylketonuria (p. 497), may also require modified diets. Some cultures and religions have specific dietary requirements and customs.

SPOT CHECK

1. What are the recommended daily energy intakes for healthy adults?
2. List the nutrient groups found in a balanced diet.

Nutrients

Learning outcomes

After studying this section, you should be able to:

- describe the functions of dietary carbohydrate, protein and fat
- outline the sources and functions of fat- and water-soluble vitamins
- outline the sources and functions of minerals, trace elements and water.

Carbohydrates

Carbohydrates are mainly sugars and starches, which are found in a wide variety of foods, e.g. sugar, jam, cereals, bread, biscuits, pasta, fruit and vegetables. Chemically, they consist of carbon, hydrogen and oxygen, the hydrogen and oxygen being in the same proportion as in water (Ch. 2). Carbohydrates are classified according to the complexity of the chemical units from which they are formed:

- monosaccharides, single sugar units, e.g. glucose (see Fig. 2.7)
- disaccharides, two sugar units joined together, e.g. sucrose (see Fig. 2.7)
- polysaccharides, complex molecules built from large numbers of monosaccharides, some of which are digestible, e.g. glycogen, while others are not, e.g. fibre.

Glycaemic index

The type of carbohydrate eaten is important in a healthy diet. The rate of carbohydrate absorption from the alimentary tract depends on the complexity of its structure. Monosaccharides such as glucose are quickly absorbed and cause blood glucose levels to rise sharply. Foods high in glucose and other monosaccharides therefore rapidly increase blood glucose levels and are said to have a high glycaemic index (GI). They tend not to satisfy hunger for long because the rapid rise in blood glucose stimulates insulin secretion, which quickly reduces blood glucose levels. More complex carbohydrates such as starches require digestion before absorption, and so cause a slower and more sustained rise in blood glucose levels. They are referred to as low-GI foodstuffs and include unprocessed wholegrain and high-fibre foods. They satisfy hunger for longer because they release carbohydrates over a more extended period. Low-GI foods are important in weight control and in managing diabetes mellitus.

Functions of digestible carbohydrates

These include:

- Provision of energy and heat: the breakdown of monosaccharides, preferably in the presence of oxygen, releases heat and chemical energy for metabolic work. Glucose is the main fuel molecule used by body cells.
- 'Protein sparing': when there is adequate carbohydrate in the diet, protein does not need to be used to provide energy and heat and is used for its main purpose of building new and replacement body proteins.
- Provision of energy stores when carbohydrate is eaten in excess of the body's needs, because it is converted to:
  - glycogen – a short-term energy store in the liver and skeletal muscles (see Fig. 12.41)
  - fat – long-term stores in adipose tissue, e.g. under the skin.

Proteins

During digestion, proteins are broken down into their constituent amino acids which are absorbed into the bloodstream; a constant supply of amino acids is needed to build new proteins.

Amino acids

Amino acids (see Fig. 2.8) are composed of the elements carbon, hydrogen, oxygen and nitrogen. Some contain minerals such as iron, copper, zinc, iodine, sulphur and phosphate. Amino acids are divided into two categories: essential and non-essential.

Essential amino acids cannot be synthesised in the body and so must be included in the diet. Non-essential amino acids can be synthesised in the body by transamination (see p. 351). The essential and non-essential amino acids after infancy are shown in Box 11.2.

Nitrogen balance

When in excess of body needs, amino acids are broken down; the amino group ($\sim NH_2$) is converted to the nitrogenous waste product urea and excreted by the kidneys. The remainder of the molecule is converted to either glucose or a ketone body (see ketosis, p. 263), depending on the amino acid. In this situation the body is in positive nitrogen balance. Conversely, negative nitrogen balance occurs when amino acid supply does not meet body needs. This may arise either when dietary protein intake is inadequate, or body protein

Box 11.2 Essential and non-essential amino acids

Essential amino acids	Non-essential amino acids
Isoleucine	Alanine
Leucine	Arginine
Lysine	Asparagine
Methionine	Aspartic acid
Phenylalanine	Cysteine
Threonine	Cystine
Tryptophan	Glutamic acid
Valine	Glutamine
	Glycine
	Histidine
	Hydroxyproline
	Proline
	Serine
	Tyrosine

requirement is increased, e.g. during growth spurts and following injury or surgery.

Biological value of protein

The nutritional value of a protein, its biological value, is determined by how well it meets the body's nutritional needs. Protein of high biological value is usually of animal origin; it is easily digested and contains all the essential amino acids in the proportions required by the body. A diet containing all the amino acids required may also be achieved by eating a range of foods containing proteins of lower biological values, if deficiencies in amino acid content of any of the constituent proteins is supplied by another. Vegetarian and vegan diets contain proteins with lower biological values, e.g. from vegetables, cereals and pulses. When proteins from different plant sources are combined, they complement each other, providing higher biological values than a single plant source. Through this complementary action the biological value of vegetarian and vegan diets can be similar to those based on animal protein.

Functions of proteins

Amino acids are used for:

- growth and repair of body cells and tissues
- synthesis of new proteins, e.g. enzymes, plasma proteins, antibodies (immunoglobulins) and some hormones
- provision of energy – normally a secondary function, this becomes important only when there is not enough carbohydrate in the diet and fat stores are depleted.

When protein is eaten in excess of the body's needs, the nitrogenous amino group is detached, i.e. it is deaminated, and excreted by the kidneys. The remainder is converted to fat for storage in adipose tissue.

Fats

Fats consist of carbon, hydrogen and oxygen, but they differ from carbohydrates in that the hydrogen and oxygen are not in the same proportions as in water. There are several groups of fats and lipids that are important in nutrition.

Fats (triglycerides)

Commonly known as fat, a triglyceride molecule consists of three fatty acids linked to a glycerol molecule (see Fig. 2.9). This is the form in which the body stores fats in adipose tissue. Depending on the type and relative amounts of fatty acids they contain, fats are classified as saturated or unsaturated. In general, saturated fats are solid at room temperature and originate from animal sources, while unsaturated fats are oils usually derived from vegetables or plants. A high intake of saturated fats may predispose to coronary heart disease (Ch. 5).

Linoleic, linolenic and arachidonic acids are essential fatty acids that cannot be synthesised by the body in significant amounts but are needed for synthesis of prostaglandins, phospholipids and leukotrienes. These fatty acids are found in oily fish.

Cholesterol

Unlike other lipids, whose molecules are composed of chains of atoms, this molecule contains four rings, which give it the characteristic steroid structure. About 20% is synthesised by the body with the remainder coming from dietary saturated fats in full-fat dairy products, fatty meat and egg yolk. Cholesterol is needed for synthesis of steroid hormones, e.g. glucocorticoids and mineralocorticoids (Ch. 9), and is an important constituent of cell membranes.

Cholesterol is transported in the blood combined with proteins, forming lipoproteins. Two examples are:

- Low-density lipoprotein (LDL): this carries cholesterol from the liver to the body cells. Excessive blood LDL levels are harmful to health, as LDL can build up in arterial walls, leading to atherosclerosis. LDL is sometimes known as 'bad cholesterol'.
- High-density lipoprotein (HDL): this carries cholesterol back from body cells to the liver, where it is either broken down or excreted. This may be referred to as 'good cholesterol' and raised HDL levels are cardioprotective.

High blood cholesterol levels are associated with an increased risk of atherosclerosis (p. 130), hypertension (high blood pressure, p. 141) and diabetes mellitus.

Functions of fats

These include:

- a concentrated source of chemical energy and heat
- support of some organs, e.g. the kidneys, the eyes
- absorption, transport and storage of the fat-soluble vitamins: A, D, E and K

- a constituent of myelin sheaths (p. 191) and of sebum (p. 404)
- formation of steroid hormones from cholesterol
- an energy store in adipose tissue under the skin and in the mesentery
- insulation – as a subcutaneous layer it reduces heat loss through the skin
- satiety value – the emptying time of the stomach is prolonged after eating food that is high in fat, postponing the return of hunger.

Because the body stores excess fat, it is important not to eat too much, as this contributes to weight gain and becoming overweight or obese (Box 11.1).

Vitamins

Vitamins are chemicals required in tiny quantities for essential metabolic processes. As most cannot be made by the body, they are an essential part of the diet and insufficiency may lead to a deficiency disease. They are found in a wide range of foods and there are two groups:

- fat-soluble vitamins: A, D, E and K
- water-soluble vitamins: B complex and C.

Fat-soluble vitamins

Bile is needed for absorption of these vitamins from the small intestine. The presence of mineral oils in the intestine and malabsorption impair their absorption.

Vitamin A (retinol)

This vitamin is found in foods such as cream, egg yolk, liver, fish oil, milk, cheese and butter. It is not found in vegetable fats and oils but is added to margarine during manufacture. In addition, vitamin A can be formed in the body from certain carotenes, the main dietary sources of which are green vegetables, orange-coloured fruit (e.g. mangoes, apricots) and carrots. The main functions of vitamin A are:

- generation of the light-sensitive pigment rhodopsin (visual purple) in the retina of the eye (Ch. 8)
- cell growth and differentiation, which is especially important in fast-growing cells, such as bone and the epithelial cells covering both internal and external body surfaces
- immunity and defence against infection.

The first sign of vitamin A deficiency is night blindness due to formation of abnormal retinal pigment. Other consequences include xerophthalmia (drying and thickening of the conjunctiva), which ultimately ulcerates and destroys the conjunctiva. This is a common cause of blindness in developing countries. Atrophy and keratinisation of other epithelial tissues lead to an increased incidence of infections of the ear and the respiratory, genitourinary and alimentary tracts. Immunity is compromised and bone development may be abnormal and delayed.

Vitamin D

Vitamin D is found mainly in animal fats such as eggs, butter, cheese and fish liver oils. Humans can synthesise this vitamin by the action of the ultraviolet rays in sunlight on a form of cholesterol (7-dehydrocholesterol) in the skin. Advice from Public Health England (2016) is that all UK residents should take vitamin D supplements (10 µg/day) in autumn and winter when sunlight is limited. People with darkly pigmented skin are at greater risk of deficiency because melanin absorbs UV light and prevents vitamin D synthesis. These people, together with those seldom exposed to sunlight, should consider taking vitamin D supplements throughout the year.

Vitamin D increases calcium and phosphate absorption from the gut and stimulates their retention by the kidneys. It therefore promotes the calcification of bones and teeth.

Deficiency causes rickets in children and osteomalacia in adults (p. 479), due to impaired absorption and use of calcium and phosphate.

Vitamin E

Also known as tocopherol, this is found in nuts, egg yolk, wheat germ, whole cereal, milk and butter.

Vitamin E is an antioxidant, which means that it protects body constituents such as membrane lipids from being destroyed in oxidative reactions caused by free radicals. Vitamin E has been shown to protect against coronary heart disease.

Deficiency is rare because this vitamin is present in many foods, and is usually seen only in premature babies and in conditions associated with impaired fat absorption, e.g. cystic fibrosis (p. 295).

Vitamin K

The sources of vitamin K are liver, some vegetable oils and leafy green vegetables. It is also synthesised by bacteria in the large intestine and significant amounts are absorbed. A small amount is stored in the liver. Vitamin K is required by the liver for synthesis of some blood clotting factors, including prothrombin and factors VII, IX and X (Box 4.1, p. 75). Deficiency therefore prevents normal blood coagulation and increases bleeding times. It may occur in adults if obstruction in the biliary tract prevents bile delivery into the duodenum, in severe liver damage and in malabsorption, e.g. in coeliac disease. Premature babies may be given vitamin K to prevent haemorrhagic disease of the newborn. This is because their intestines are sterile and require several weeks to become colonised with vitamin K-producing bacteria, during which time their synthesis of clotting factors is low.

Water-soluble vitamins

Water-soluble vitamins are lost in the urine, so body stores are usually limited.

Vitamin B complex

This group of water-soluble vitamins promotes activity of enzymes involved in the chemical breakdown (catabolism) of nutrients to release energy.

Vitamin B_1 (thiamin)

This is present in nuts, yeast, egg yolk, liver, legumes, meat and the germ of cereals. It is rapidly destroyed by heat. Thiamin is essential for the complete aerobic release of energy from carbohydrate. Absence or deficiency leads to anaerobic respiration (p. 351) and accumulation of lactic and pyruvic acids, which may cause vasodilation and eventually heart failure. Thiamin is also important for nervous system function because neurones are dependent on glucose for fuel.

Deficiency causes beriberi, which occurs mainly in countries where polished rice (rice with the outer coverings and germ removed) is the chief constituent of the diet. In beriberi there is:

- severe muscle wasting
- delayed growth in children
- polyneuropathy, causing degeneration of motor, sensory and some autonomic nerves.

If it is untreated, death from cardiac failure or severe microbial infection may occur.

The main cause of thiamin deficiency in developed countries is alcoholism, where the diet is usually poor. The central nervous system is affected, causing neurological symptoms; these are generally irreversible and include memory loss, ataxia and visual disturbances, collectively known as Wernicke–Korsakoff syndrome.

Vitamin B_2 (riboflavin)

Riboflavin is found in yeast, green vegetables, milk, liver, eggs, cheese and fish roe. Only small amounts are stored in the body and it is destroyed by light and alkalis. It is involved in carbohydrate and protein metabolism, especially in the eyes and skin. Deficiency leads to cracking of the skin, commonly around the mouth (angular stomatitis), and inflammation of the tongue (glossitis).

Vitamin B_3 (niacin)

This is present in liver, cheese, yeast, whole cereals, eggs and dairy products; in addition, the body can synthesise it from the amino acid tryptophan. It is central to energy release from carbohydrates in cells. In fat metabolism it inhibits the production of cholesterol and assists in fat breakdown.

Deficiency is rare in developed countries, where the main causes are alcoholism and conditions causing malabsorption. Elsewhere, it occurs where maize is the chief constituent of the diet because niacin in maize is in an unusable form. Pellagra develops within 6–8 weeks of severe deficiency. It is characterised by:

- dermatitis – severe sunburn-like skin sensitivity affecting areas exposed to sunlight
- diarrhoea, nausea and anorexia
- confusion and, in the longer term, dementia.

Vitamin B_6 (pyridoxine)

This stable vitamin is found in egg yolk, peas, beans, soya beans, yeast, poultry, white fish and peanuts. Dietary deficiency is very rare. Vitamin B_6 is needed for amino acid metabolism, including the synthesis of non-essential amino acids and important molecules such as haem and nucleic acids (Ch. 2).

Vitamin B_{12} (cobalamin)

This is a group of cobalt-containing compounds that are found in almost all foods of animal origin and are destroyed by heat.

Vitamin B_{12} is essential for DNA synthesis, including red blood cell production in the bone marrow; deficiency leads to megaloblastic anaemia (p. 78), which is correctable with supplements. However, vitamin B_{12} is also required for formation and maintenance of myelin, the fatty substance that surrounds and protects some nerves. Deficiency accordingly causes irreversible neurological damage, such as peripheral neuropathy and/or subacute spinal cord degeneration. The presence of intrinsic factor in the stomach is essential for absorption of vitamin B_{12} in the terminal ileum. Deficiency is usually associated with insufficient intrinsic factor, which is fairly common in older adults. Dietary deficiency is rare, but is sometimes associated with vegan diets.

Folic acid (folate)

This is found in liver, leafy green vegetables, brown rice, beans, nuts and milk. It is synthesised by bacteria in the large intestine, and much of it is absorbed. It is destroyed by heat and moisture. As only a small amount is stored in the body, deficiency quickly becomes evident. Like vitamin B_{12}, folic acid is also essential for DNA synthesis, and when it is lacking, mitosis (cell division) is impaired. This manifests particularly in rapidly dividing tissues such as blood, and folate deficiency therefore leads to megaloblastic anaemia (p. 78), which is reversible with folate supplements. It is involved in development of the embryonic neural tube, which later becomes the spinal cord and skull. Folate deficiency at conception and during early pregnancy is linked to spina bifida (p. 208).

Vitamin C (ascorbic acid)

This is found in fresh fruit, especially blackcurrants, oranges, grapefruit and lemons, and also in rosehips and green vegetables. Vitamin C is highly water soluble and easily destroyed by heat, ageing, chopping, salting and drying. These processes may predispose to the development of scurvy (deficiency), which becomes apparent after about 2 months without eating fresh fruit or vegetables.

Vitamin C is associated with protein metabolism, especially the laying down of collagen fibres in connective tissue. Vitamin C, like vitamin E, acts as an antioxidant, protecting body molecules from damaging oxidative reactions caused by free radicals. When scurvy affects collagen production, there is fragility of blood vessels, delayed wound healing and poor bone repair. Gums become swollen and spongy, and the teeth loosen in their sockets. Systemic effects include anaemia, fatigue, weakness and aching joints and muscles.

Minerals, trace elements and water

Minerals and trace elements

Minerals are inorganic substances needed in small amounts for normal cellular function. Some are needed in larger amounts than others, e.g. calcium, phosphate, sodium and potassium. Those required in only tiny quantities are known as trace elements or trace minerals, e.g. iron, iodine, zinc, copper, cobalt, selenium and fluoride. The main minerals and trace elements are outlined here.

Calcium

This is found in milk, cheese, eggs, green vegetables and some fish, e.g. sardines. An adequate supply should be obtained from a well-balanced diet, although requirements are higher in pregnant women and growing children. The most abundant of the minerals, 99% of calcium (about 1 kg in adults) is found in the bones and teeth, where it is an essential structural component. Calcium is also involved in blood clotting and in nerve and muscle function. Deficiency of calcium causes rickets in children and osteomalacia in adults (p. 479).

Phosphate

Sources include milk and dairy products, red meat, fish, poultry, bread and rice. If there is sufficient calcium in the diet, it is unlikely that there will be phosphate deficiency.

Phosphate contributes with calcium and vitamin D to the hardening of bones and teeth; 85% of body phosphate is found in these sites. Phosphates are also an essential part of nucleic acids (DNA and RNA, Ch. 17), cell membranes and energy storage molecules such as adenosine triphosphate (ATP, see Fig. 2.10).

Sodium

Sodium is found in most foods in the form of salt (sodium chloride), especially in processed foods and 'fast food'. It is also frequently added during cooking or as table salt. Salt intake should not exceed 6 g daily (about 1 teaspoon), although excess is normally excreted in the urine. High salt intake is associated with hypertension (p. 141), which is a risk factor for ischaemic heart disease (p. 137) and stroke (p. 201). In the UK, packaged food displays a coloured nutritional label that includes a value for salt (see Fig. 11.1); green indicates low salt and is therefore a healthier option than amber or red.

Sodium is the most common extracellular cation (see Fig. 2.19) and is essential for muscle contraction and transmission of nerve impulses.

Potassium

This is found widely distributed in almost all foods, especially in fruit and vegetables, and intake usually exceeds requirements.

It is the most common intracellular cation (see Fig. 2.19) and, like sodium, is involved in muscle contraction and transmission of nerve impulses.

Iron

Iron, as a soluble compound, is found in liver, red meat, pulses, nuts, eggs, dried fruit, wholemeal bread and leafy green vegetables. In adults about 1 mg of iron is lost from the body daily; a healthy diet contains more, i.e. 9–15 mg per day, but only 5%–15% of this is in a form that can be absorbed. Iron is essential for the formation of haemoglobin in red blood cells. It is also necessary for carbohydrate metabolism and synthesis of some hormones and neurotransmitters. Menstruating and pregnant women have increased iron requirements, as do young people experiencing growth spurts.

Iron deficiency anaemia (p. 77) is the most common nutritional deficiency worldwide and occurs when iron stores become depleted. Iron deficiency anaemia may also arise from chronic bleeding, e.g. in peptic ulcer disease.

Iodine

Iodine is found in seafoods and in vegetables especially those grown near the sea where the soil is rich in iodine. In parts of the world where soil is deficient in iodine, very small quantities are added to table salt to prevent goitre (p. 257).

It is essential for the formation of thyroxine and triiodothyronine, two hormones secreted by the thyroid gland, which regulate metabolic rate and physical and mental development.

Water

Water is the most abundant constituent of the human body, accounting for around 60% of the body weight in an adult (see Fig. 2.18).

A large amount of water is lost each day in urine, sweat and faeces. This is normally balanced by intake in food and fluids, to satisfy thirst. The recommended daily intake is about 1.5–2 litres (6–8 glasses, Fig. 11.1) for adults. Water requirement is increased by physical activity and high environmental temperatures. Dehydration, with serious consequences, may occur if intake does not balance loss. Water balance is finely regulated by the action of hormones on the kidney tubules (Ch. 13).

Functions of water

These include:

- providing the solvent and medium for all metabolic processes
- moistening food for swallowing (see saliva, p. 328)
- regulating body temperature – as a constituent of sweat, which is secreted on to the skin, it evaporates, cooling the body surface (Ch. 14)
- as the major constituent of blood and tissue fluid, transporting substances round the body and allowing exchange between the blood, tissue fluid and body cells
- diluting waste products and toxins in the body
- providing the medium for excretion of waste products, e.g. urine and faeces.

SPOT CHECK

3. What does the term 'essential amino acid' mean?
4. Name the fat-soluble vitamins.
5. Which is the most abundant mineral in the body?

Non-starch polysaccharide

Learning outcome

After studying this section, you should be able to:

- describe the sources and functions of non-starch polysaccharide.

Non-starch polysaccharide (NSP) is the correct term for dietary fibre, although the latter term continues to be more commonly used in the UK. It is the indigestible part of the diet and consists of bran, cellulose and other polysaccharides found in fruit, vegetables and cereals. Dietary fibre is partly digested by microbes in the large intestine and is associated with gas (flatus) formation. The recommended daily intake is contained within five portions of fruit or vegetables ('five a day', Fig. 11.1).

Functions of NSP (dietary fibre)

Dietary fibre:

- stimulates peristalsis (p. 323)
- attracts water, increasing faecal bulk

} prevents constipation

- protects against some gastrointestinal disorders, e.g. colorectal cancer and diverticular disease.

SPOT CHECK

6. List two functions of dietary fibre.

Ageing and nutrition

Learning outcome

After studying this section, you should be able to:

- describe the factors affecting diet and nutrition in older adults.

The importance of good nutrition to health and well-being at all stages of the lifespan is well established. The relationship between nutrition, diet and ageing is complex, as many diseases arise from longstanding poor diet. Good nutrition during early and middle life can significantly reduce the risk of problems in later life; for example, there is evidence that young women who limit their dairy intake when trying to lose weight, or drink lots of fizzy drinks (which impair calcium absorption), have an increased risk of osteoporosis (p. 479) in later life.

The senses of smell and taste decline with age (Ch. 8), which can reduce appetite and spoil the enjoyment of eating. Loss of teeth and/or ill-fitting dentures as the result of poor oral health in earlier years can make eating, especially chewing, difficult or nearly impossible.

Basal metabolic rate (BMR, p. 348) gradually declines with age from the fourth or fifth decade of life. This is mainly due to a reduction in muscle mass and a corresponding increase in body fat; BMR is higher in those with more muscle, as muscle is more metabolically active than adipose tissue. Physical activity generally lessens with age, further reducing BMR in older adults.

UK dietary recommendations for older adults are the same as those for other adults, although energy requirements gradually reduce as the BMR falls, especially when physical activity is limited. As for other age groups, it is important for older adults to eat a healthy, well-balanced diet with sufficient fibre and vitamins. Difficulty with activities related to eating may develop; for example mobility problems that prevent shopping, impaired cognitive function or loss of the manual dexterity required to prepare food and drinks can adversely affect nutritional status.

Nutritional disorders in older adults

Malnutrition and obesity are both prevalent in older adults, as well as other conditions considered here. Malnutrition is more prevalent in those living in institutions, whereas being overweight or obese tends to be more common in people living at home.

Malnutrition

Being underweight (BMI below 18.5) predisposes to health problems, e.g. development of pressure ulcers, which take longer to heal in older adults. In the oldest adults, anorexia and weight loss become increasingly common and the incidence of protein-energy malnutrition (PEM, p. 315) increases. After 65 years, a lower dietary intake may lead to weight loss accompanied by a decline in muscle mass and an increasing risk of malnutrition. Malnutrition in healthcare settings is briefly considered below.

Obesity

It is common for body weight to increase between the ages of 40 and 65 ('middle age spread'). This is generally attributed to a reduction in physical activity and BMR rather than increased dietary energy intake. Overweight is defined as BMI above 25 and obesity when BMI is above 30 (see Box 11.1). Being overweight or obese at any age carries many health risks (see Box 11.3).

Box 11.3 Conditions for which obesity is a predisposing factor

Cardiovascular diseases, e.g. hypertension (p. 141), ischaemic heart disease (p. 137)
Type 2 diabetes (p. 262)
Some cancers
Gallstones (p. 370)
Osteoarthritis (p. 482)
Varicose veins (p. 133)
Postoperative complications (increased risk)

Vitamin deficiency

Some vitamin deficiencies become more common in older adults. Vitamin D deficiency (p. 310) is more common in older adults because the skin becomes less able to synthesise it with age, a situation compounded in those who spend limited time outdoors, e.g. people who live in institutions or are housebound. It is recommended that vitamin D intake be maintained by eating oily fish and fortified cereals regularly, spending time outdoors in spring and summer months and that everyone over 65 years takes vitamin D supplements (10 µg per day) throughout the year.

Vitamin B_{12} deficiency, perhaps due to decreased absorption of intrinsic factor, is also more common in older adults and may result in pernicious anaemia (p. 78).

Constipation

Constipation becomes more common as muscle tone and peristaltic activity of the colon lessen with age. This is exacerbated by a lower fluid and/or fibre intake, taking less exercise and reduced mobility together with other difficulties related to eating described above.

SPOT CHECK

7. Which vitamin supplement is recommended year-round in all older adults living in the UK?

Disorders of nutrition

Learning outcome

After studying this section, you should be able to:

- describe the main consequences of malnutrition and obesity.

The importance of nutrition is increasingly recognised as essential for health, and illness often alters nutritional requirements.

Protein-energy malnutrition

Protein-energy malnutrition (PEM) is the result of inadequate intake of protein, carbohydrate and fat. It occurs during periods of starvation and when dietary intake is insufficient to meet increased requirements, e.g. in trauma, fever and illness. Malnutrition is relatively rare in high-income countries except when there is a serious underlying condition, e.g. sepsis, trauma, surgery or concurrent illness. Poor nutrition is generally seen where poverty is prevalent and is usually the result of a diet that is not adequately balanced.

In the UK, many older adults admitted to hospitals and care homes have signs of under-nutrition, which often worsens after admission. Anorexia (loss of appetite) from any cause may lead to malnutrition. People with advanced cancer or some chronic illnesses can experience loss of appetite accompanied by profound weight loss and muscle wasting as a symptom of cachexia (p. 63).

If dietary intake is inadequate, it is not uncommon for vitamin deficiency to develop at the same time. Poor nutrition reduces the ability to combat other illness and infection. The degree of malnutrition can be assessed from measurement of body mass index (see Box 11.1).

Infants and young children are particularly susceptible, as their nutritional requirements for normal growth and development are high. In low-income countries where people experience long periods of near-total starvation, the following two conditions are found in children under 5 years.

Kwashiorkor

This is malnutrition with oedema that typically occurs when breast feeding stops and is often precipitated by infections such as measles or gastroenteritis. Severe liver damage significantly reduces the production of plasma proteins, leading to ascites and oedema in the lower limbs that mask emaciation (Fig. 11.2A).

Growth stops and there is loss of weight and loss of pigmentation of skin and hair, accompanied by listlessness, apathy and irritability. There is susceptibility to infection, and recovery from injury and infection takes longer.

Marasmus

This type of malnutrition with severe muscle wasting is characterised by emaciation due to breakdown of muscle and fat (Fig. 11.2B). There is no oedema. Growth milestones are delayed, hair is lost and the skin becomes wrinkled due to absence of subcutaneous fat.

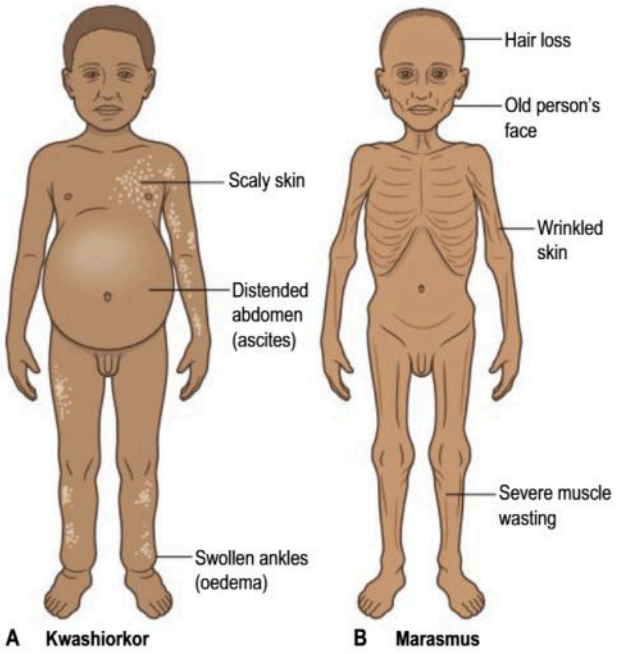

Figure 11.2 Features of protein-energy malnutrition. (A) Kwashiorkor. (B) Marasmus.

Malabsorption

The causes of malabsorption vary widely, from short-term problems such as gastrointestinal infections (p. 361) to chronic conditions such as cystic fibrosis (p. 295). Malabsorption may be specific for one nutrient, e.g. vitamin B_{12} in pernicious anaemia (p. 78), or it may apply to several nutrients, e.g. tropical sprue (p. 367).

Obesity

The WHO defines obesity as a BMI of 30 or above (see Box 11.1); it occurs when energy intake exceeds energy expenditure, e.g. in inactive individuals (Fig. 11.3).

Global obesity rates almost tripled between 1975 and 2016 (WHO, 2020); this represents a growing and preventable public health challenge worldwide that affects people of all ages and predisposes to many other conditions (Box 11.3). Worldwide, 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese (WHO, 2020); in the same year there were nearly 40 million children aged under 5 and 340 million children and young people aged between 5 and 19 who were overweight or obese. Childhood obesity is of particular concern, especially in low-income countries (where malnutrition can also be widespread), because this preventable condition is likely to continue into and during adulthood with its associated health risks, especially diabetes and cardiovascular disease.

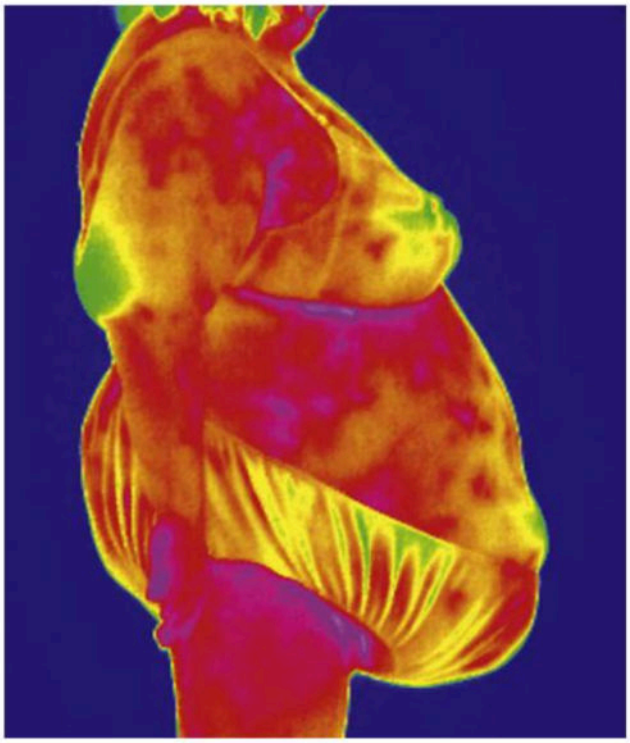

Figure 11.3 Obese woman (thermogram). (Tony McConnell/ Science Photo Library. Reproduced with permission.)

The hormone leptin is associated with obesity. It has several functions, one of which is control of appetite. After eating, this hormone is released by adipose tissue and acts on the hypothalamus, resulting in a feeling of satiety (fullness), which suppresses the appetite. In obesity, blood levels of leptin are raised and the negative feedback system, which usually suppresses the appetite, no longer operates normally.

Another function of leptin is involvement in the synthesis of gonadotrophin releasing hormone and gonadotrophins at puberty (Ch. 18). As it is secreted by fat tissue, levels are low in thin individuals, which explains why:

- thin girls with little body fat reach puberty later than their peers of normal weight
- very thin women may have difficulty in conceiving
- menstruation stops in females with very little body fat.

SPOT CHECK

8. What is the normal body mass index (BMI) range in adults?

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Case study

Increasing frailty has led to Albert, an eighty-year-old widower, moving into a care home. He finds it hard to mobilise and has recently become overweight.

1. He is described as overweight because his body mass index is between:

   a. 18–24.99
   b. 25–29.99
   c. 30–34.9
   d. 35–39.9

His key worker Sadek explains that adjustments to his diet may be helpful.

2. Eating more of which dietary constituent will minimise the risk of constipation?

   a. Fibre
   b. Vitamins
   c. Protein
   d. Carbohydrate

3. Reducing his intake of which nutrient will best avoid further weight gain?

   a. Carbohydrates
   b. Proteins
   c. Fats
   d. Water

4. As he is elderly and seldom goes outside, Sadek draws Albert's attention to UK Government advice about taking which dietary supplement:

   a. Vitamin A
   b. Vitamin D
   c. Vitamin E
   d. Vitamin K

Review and revise

Complete each of the following statements:

1. Fats are classified as _____ or _____. In general the former come from _____ sources and are solids at room temperature while the latter group come from _____ and are oils at room temperature.

2. Vitamin B_{12} is essential for synthesis of _____ and deficiency leads to _____ anaemia. It is absorbed in the _____, assisted by _____ secreted by the stomach.

Indicate whether each of the following statements is true or false:

3. High-density lipoproteins can build up in arterial walls, leading to atherosclerosis. _____

4. Deficiency of calcium in children can lead to rickets. _____

5. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Kwashiorkor
____ (b) Ascorbic acid
____ (c) Goitre
____ (d) Leptin
____ (e) Monosaccharide
____ (f) Marasmus
____ (g) Amino acid
____ (h) Folic acid

List B

1. The simplest form of carbohydrate
2. Malnutrition with oedema, e.g. ascites
3. Vitamin C
4. Hormone involved in control of appetite
5. Required for normal development of the neural tube in embryos
6. Malnutrition with extreme muscle wasting
7. Building block of proteins
8. Sign of iodine deficiency

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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CHAPTER 12

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The digestive system describes the alimentary canal, its accessory organs and the digestive processes they undertake. The alimentary canal begins at the mouth, passes through the thorax, abdomen and pelvis, and ends at the anus (Fig. 12.1). It has a basic structure that is modified in different organs to facilitate the processes occurring in each one. The walls of the alimentary canal contain smooth muscle to mix and propel food through its length. Breakdown of food is both mechanical, for example, mastication (chewing), and chemical (by digestive enzymes).

Chemical digestion gradually breaks down food eaten, or ingested, until it is in a form suitable for absorption. For example, meat, even when cooked, is chemically too complex to be absorbed from the alimentary canal. Digestion releases its constituents: amino acids, mineral salts, fat and vitamins. The digestive enzymes responsible for these changes are secreted into the canal by specialised glands, some of which are in the walls of the canal, and some outside the canal but with ducts leading into it.

Absorbed nutrients provide the building blocks for making new cells, hormones and enzymes. The chemical energy needed for these and other processes is also generated from the products of digestion. Waste material is eliminated from the alimentary canal as faeces.

The following sections explain the structure and functions of the digestive tract and its accessory organs. Thereafter the fate of absorbed nutrients and how they are used by the body are explored and the effects of ageing on the digestive system are considered. In the final section, common disorders of the digestive system are explained.

Organs of the digestive system

Learning outcomes

After studying this section, you should be able to:

- identify the organs of the alimentary canal
- list the accessory organs of digestion.

Alimentary canal

Also known as the gastrointestinal (GI) tract, this is essentially a long tube. It begins at the mouth and ends at the anus, and in adults is around 10 metres long (Fig. 12.1). The organs along its length have different functions, although structurally they are remarkably similar. The parts are:

- mouth
- pharynx
- oesophagus
- stomach
- small intestine
- large intestine
- rectum and anal canal.

Accessory organs

Various secretions are released into the alimentary tract, some by glands in the lining of certain organs, e.g. gastric

juice secreted by glands in the lining of the stomach, and others by glands outside the tract. The latter are the accessory organs of digestion and their secretions pass through ducts to enter the tract. They consist of:

- three pairs of salivary glands
- the pancreas
- the liver and biliary tract.

The organs and glands are linked physiologically as well as anatomically, in that digestion and absorption are coordinated and occur in stages, each being dependent on the previous stage or stages.

SPOT CHECK

1. Name the accessory organs of the alimentary canal.

Basic structure of the alimentary canal

Learning outcomes

After studying this section, you should be able to:

- describe the distribution of the peritoneum
- explain the function of smooth muscle in the walls of the alimentary canal
- discuss the structures of the alimentary mucosa
- outline the nerve supply of the alimentary canal.

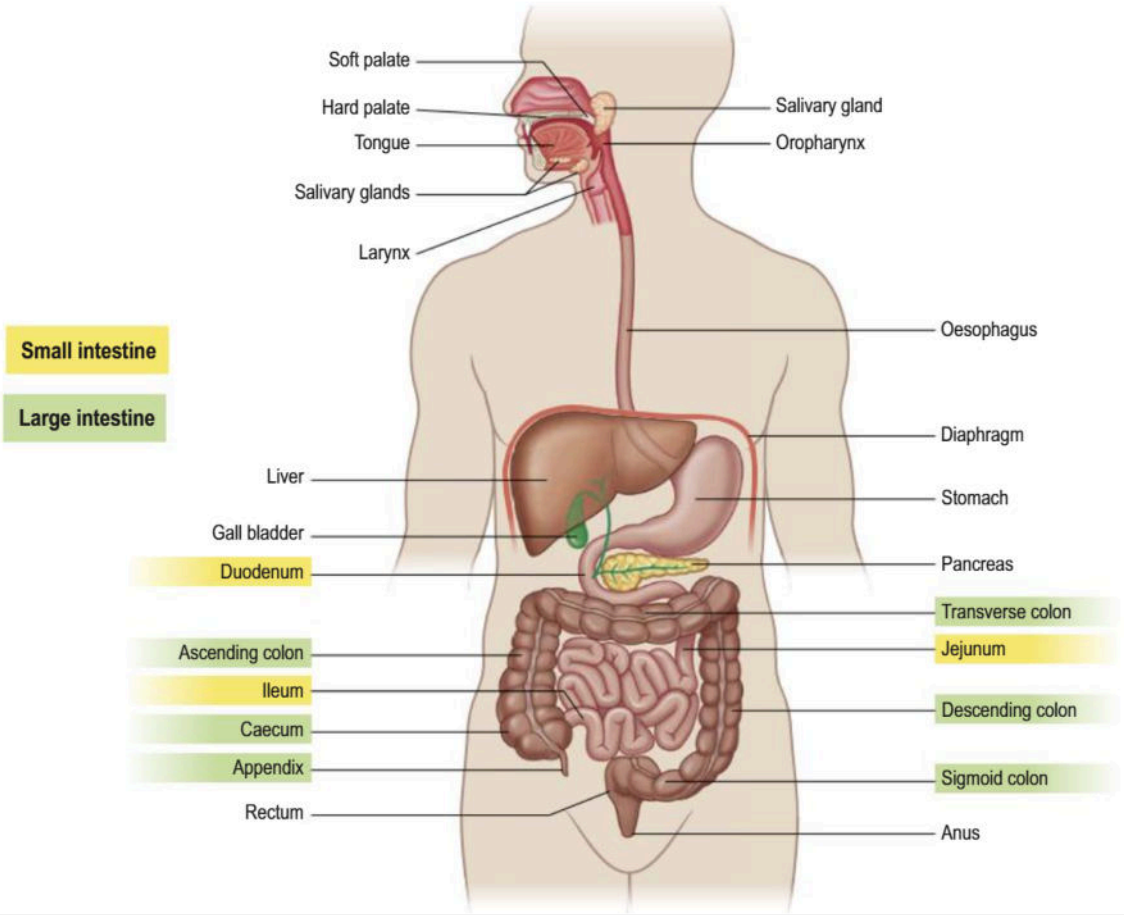

Figure 12.1 The digestive system.

The layers of the walls of the alimentary canal follow a consistent pattern from the oesophagus onwards (Fig. 12.2). The basic structure is described here and specific modifications in its structure and function are described in the appropriate sections.

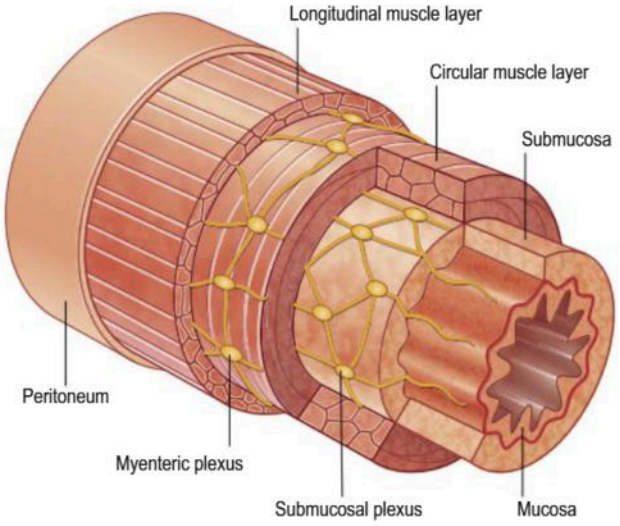

Figure 12.2 General structure of the alimentary canal.

The walls of the alimentary tract are formed by four layers of tissue:

- adventitia or serosa – outer covering
- smooth muscle
- submucosa
- mucosa – mucosal lining.

Adventitia or serosa

This is the outermost layer. In thoracic organs it consists of loose fibrous tissue, and in the abdomen the organs are covered by a serous membrane (serosa), the peritoneum.

Peritoneum

The peritoneum is the largest serous membrane of the body (Fig. 12.3A). It is a single membrane, forming a closed sac within the abdominal cavity and containing a small amount of serous fluid, called peritoneal fluid, secreted by the peritoneal cells. It is richly supplied with blood and lymph vessels and contains many lymph nodes. It provides a physical barrier to local spread of infection and can isolate an infective focus such as appendicitis, preventing involvement of other abdominal structures. It has two layers:

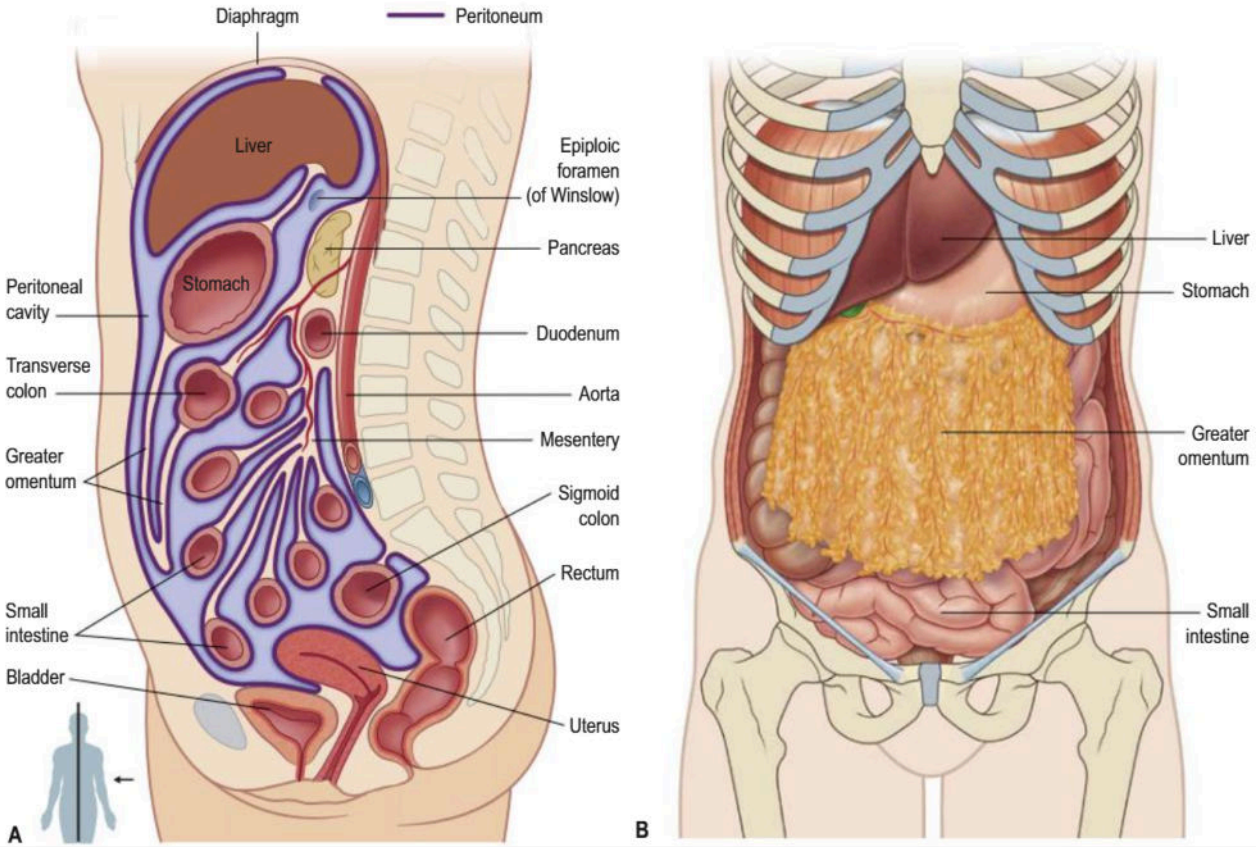

Figure 12.3 The peritoneum and associated structures. (A) The peritoneal cavity *(blue)*, the abdominal organs of the digestive system and the pelvic organs. (B) The greater omentum.

- the parietal peritoneum, which lines the anterior abdominal wall
- the visceral peritoneum, which covers the organs (viscera) within the abdominal and pelvic cavities.

The two layers of peritoneum are in close contact, and friction between them is prevented by the peritoneal fluid; the peritoneal cavity is only a potential cavity. A similar arrangement is seen with the membranes covering the lungs, the pleura (p. 276). The abdominal organs are covered to varying degrees by the loops and folds of the visceral peritoneum, which attaches them firmly to the abdominal wall. If an organ is almost completely covered by the visceral peritoneum, it is said to be intraperitoneal. If an organ is covered on its anterior side only, it is said to be retroperitoneal (meaning behind the peritoneum). The arrangement of peritoneum is such that:

- Pelvic organs are covered only on their superior surface.
- The stomach and intestines are almost completely surrounded by peritoneum and have a double fold (the mesentery) that attaches them to the posterior abdominal wall. The fold of peritoneum enclosing the stomach extends beyond the greater curvature of the stomach and hangs down in front of the abdominal organs like an apron (Fig. 12.3B). This is the greater omentum, which stores fat that provides both insulation and a long-term energy store.
- The kidneys, adrenal glands, pancreas and spleen are retroperitoneal organs (i.e. they lie behind the peritoneum) as they are only covered with peritoneum on their anterior surfaces.
- The liver is almost completely covered by peritoneum, which attaches it to the inferior surface of the diaphragm.
- The main blood vessels and nerves lie close to the posterior abdominal wall and send branches to the organs between folds of peritoneum.

Muscle layer

With some exceptions, this consists of two layers of smooth (involuntary) muscle. The muscle fibres of the outer layer are arranged longitudinally, and those of the inner layer are circular. Between these two muscle layers are blood vessels, lymph vessels and a plexus (network) of sympathetic and parasympathetic nerves, called the myenteric plexus (see Fig. 12.2). These nerves supply the adjacent smooth muscle and blood vessels.

Contraction and relaxation of the muscle layers occur in waves, which push the contents of the tract onwards. This type of rhythmical contraction of smooth muscle is called peristalsis (Fig. 12.4) and is under the influence of sympathetic and parasympathetic nerves. Muscle contraction also mixes food with the digestive juices.

Onward movement of the contents of the tract is controlled at various points by sphincters, which are thickened rings of circular muscle. They act as one-way valves, preventing backflow; this control allows time for digestion and absorption to take place.

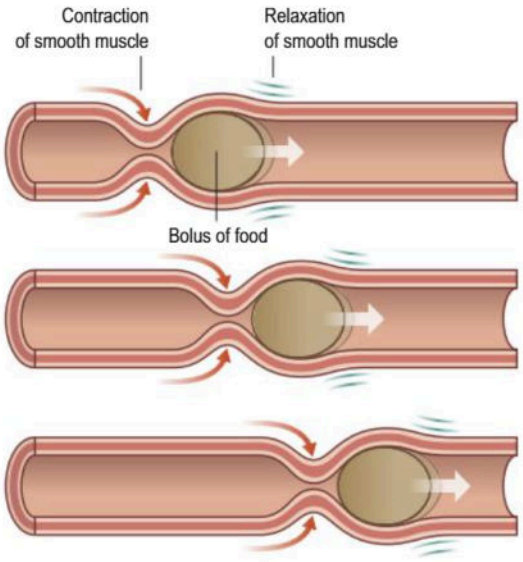

Figure 12.4 Movement of a bolus by peristalsis.

Submucosa

This layer consists of loose areolar connective tissue containing collagen and some elastic fibres, which binds the muscle layer to the mucosa. Within it are small blood vessels, nerves, lymph vessels and varying amounts of lymphoid tissue. The nerves here form the submucosal plexus (see Fig. 12.2), which contains sympathetic and parasympathetic nerves that supply the mucosal lining including the mucosal glands.

Mucosa

The mucosa lines the tract and has three layers. The most superficial layer is the mucous membrane, the epithelium. Below this lies a thin layer of loose connective tissue, which supports the blood vessels, and lymphoid tissue which protects against ingested microbes. The deepest layer is a thin layer of smooth muscle that provides features of the tract wall, e.g. gastric glands (p. 333) and villi (p. 337).

Mucous membrane

In parts of the tract subject to great wear and tear or mechanical injury, e.g., the pharynx, this superficial layer of the mucosa consists of protective stratified squamous epithelium with mucus-secreting glands just below the surface. In areas where the food is already soft and moist, and where secretion of digestive juices and absorption occur, e.g. the small intestine, the mucous membrane consists of columnar epithelial cells interspersed with mucus-secreting goblet cells (Fig. 12.5). Mucus lubricates the walls of the tract and provides a physical barrier that protects them from the corrosive effects of digestive enzymes.

At several points along the tract, specialised glands release secretions into the lumen, including:

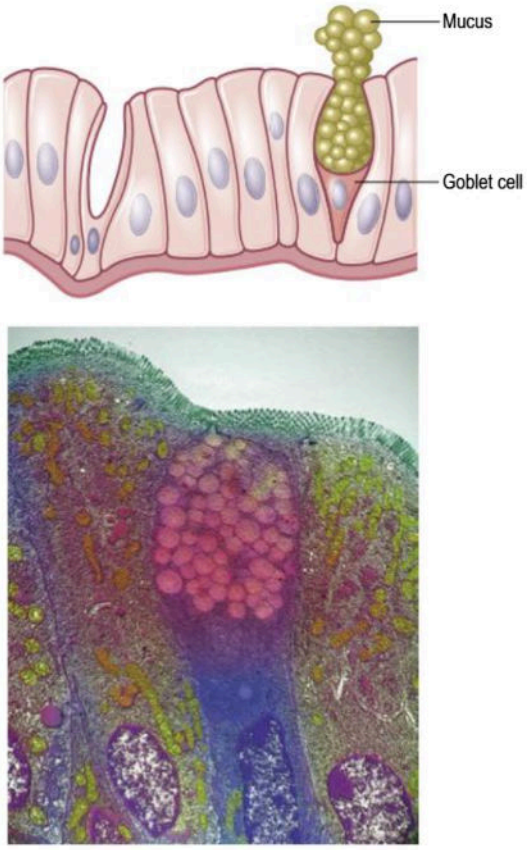

Figure 12.5 Columnar epithelium with a goblet cell. (A) Diagram. (B) Coloured transmission electron micrograph of a section through a goblet cell *(pink and blue)* of the small intestine. (B, Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

- saliva from the exocrine salivary glands
- gastric juice from the subepithelial gastric glands
- intestinal juice from the subepithelial intestinal glands
- pancreatic juice from the exocrine pancreas
- bile from the liver.

These secretions are the digestive juices and most contain enzymes that chemically break down food.

Nerve supply

The alimentary canal and its related accessory organs are supplied by nerves from both divisions of the autonomic nervous system, i.e. both parasympathetic and sympathetic parts (Fig. 12.6). As their actions are generally antagonistic, their activities adjust according to body needs at any particular time. Increased parasympathetic activity to the digestive organs promotes digestive processes, and increased sympathetic activity inhibits them.

The parasympathetic supply

One pair of cranial nerves, the vagus nerves, supplies most of the alimentary canal and the accessory organs. Sacral nerves supply the most distal part of the GI tract. The effects of parasympathetic stimulation on the digestive system are:

- increased smooth muscle activity, especially peristalsis, stimulated by increased activity of the myenteric plexus
- increased glandular secretion, through increased activity of the submucosal plexus (see Fig. 12.2).

The sympathetic supply

This is provided by numerous nerves that emerge from the spinal cord in the thoracic and lumbar regions. These form plexuses (ganglia) in the thorax, abdomen and pelvis, from which nerves pass to the organs of the alimentary tract. The effects of sympathetic stimulation on the digestive system are to:

- decrease smooth muscle activity, especially peristalsis, because stimulation of the myenteric plexus is reduced
- decrease glandular secretion, as there is less stimulation of the submucosal plexus.

SPOT CHECK

2. Identify the layers of the alimentary tract wall.

Mouth

Learning outcomes

After studying this section, you should be able to:

- list the principal structures associated with the mouth
- describe the structure of the mouth
- describe the structure and function of the tongue
- describe the structure and function of the teeth
- outline the arrangement of normal primary and secondary dentition.

The mouth (Fig. 12.7) is formed by the following structures:

Anteriorly – the lips
Posteriorly – it is continuous with the oropharynx
Laterally – the muscles of the cheeks
Superiorly – the bony hard palate and muscular soft palate
Inferiorly – the muscular tongue and the soft tissues of the floor of the mouth.

The mouth is lined with mucous membrane made of sturdy, stratified squamous epithelium containing small mucus-secreting glands. The part of the mouth between the gums and the cheeks is the vestibule, and the remainder is the oral cavity. The mucous membrane lining the cheeks and the lips is reflected on to the gums and is continuous with the skin of the face.

The palate forms the roof of the mouth and is divided into the anterior hard palate and the posterior soft palate (see

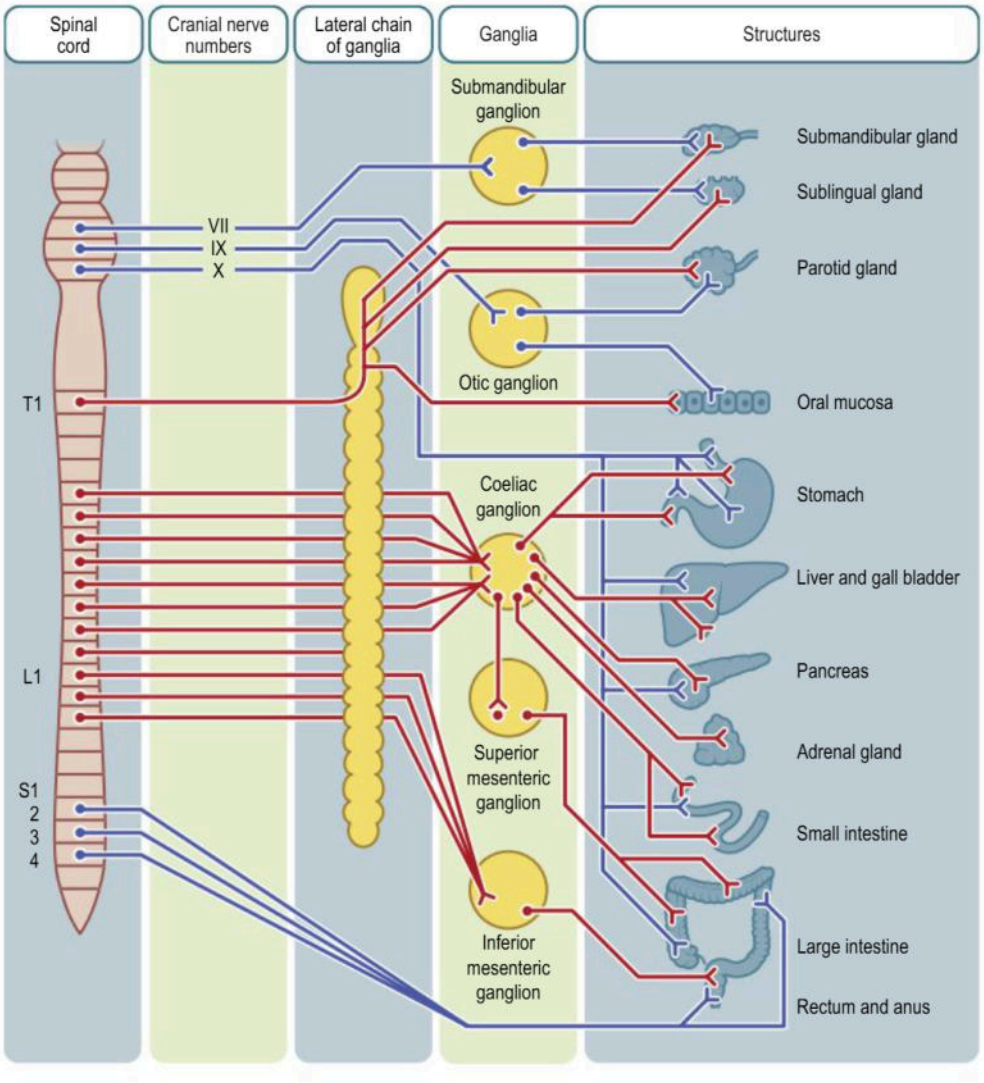

Figure 12.6 Autonomic nerve supply to the digestive system. *Blue*, parasympathetic; *red*, sympathetic.

Fig. 12.1). The hard palate is formed by the maxilla and the palatine bones. The soft palate, which is muscular, curves downwards from the posterior end of the hard palate and blends with the walls of the pharynx at the sides.

The uvula is a curved fold of muscle covered with mucous membrane, hanging down from the middle of the free border of the soft palate and visible at the back of the mouth when it is wide open (Fig. 12.7). Originating from the upper end of the uvula are four folds of mucous membrane, two passing downwards at each side to form membranous arches. The posterior folds, one on each side, are the palatopharyngeal arches, and the two anterior folds are the palatoglossal arches. On each side, between the arches, is a collection of lymphoid tissue called the palatine tonsil.

Tongue

The tongue is composed of voluntary muscle. It is attached by its base to the hyoid bone (see Fig. 10.4) and by a fold of its mucous membrane covering, called the frenulum, to the floor of the mouth (Fig. 12.8). The superior surface consists of stratified squamous epithelium, with numerous papillae (little projections). These contain the taste buds that house the taste receptors (specialised sensory nerve endings, see Fig. 8.25).

Blood supply

The main arterial blood supply to the tongue is by the lingual branch of the external carotid artery. Venous drainage is by the lingual vein, which joins the internal jugular vein.

Nerve supply

This involves:

- the hypoglossal nerves (12th cranial nerves), which supply the voluntary muscle
- the lingual branch of the mandibular nerves, which arise from the trigeminal nerves (5th cranial nerves), the somatic sensory nerves for pain, temperature and touch

- the facial and glossopharyngeal nerves (7th and 9th cranial nerves), the nerves for taste (see Fig. 7.43).

Functions

The tongue plays an important part in:
- chewing (mastication)
- swallowing (deglutition)
- speech (p. 273)
- taste (p. 269).

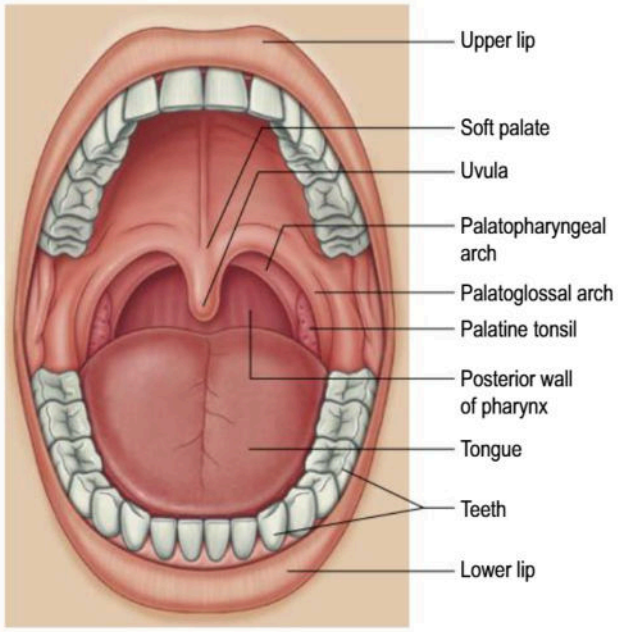

Figure 12.7 Structures seen in the wide-open mouth.

Teeth

The teeth are embedded in the alveoli, or sockets, of the alveolar ridges of the mandible (see Fig. 16.21) and the maxilla. Babies are born with two sets, or dentitions: the temporary or deciduous (baby) teeth and the permanent teeth (Fig. 12.9). The teeth of both dentitions are present, in immature form, in the mandible and maxilla at birth.

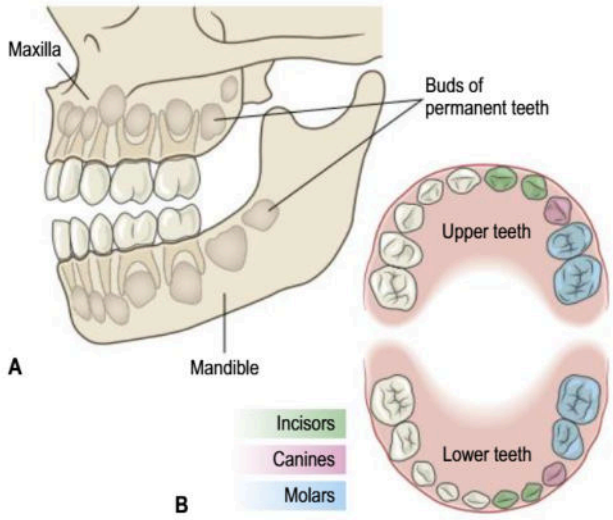

Figure 12.9 The deciduous teeth. (A) Lateral view. (B) Locations in the upper and lower jaw.

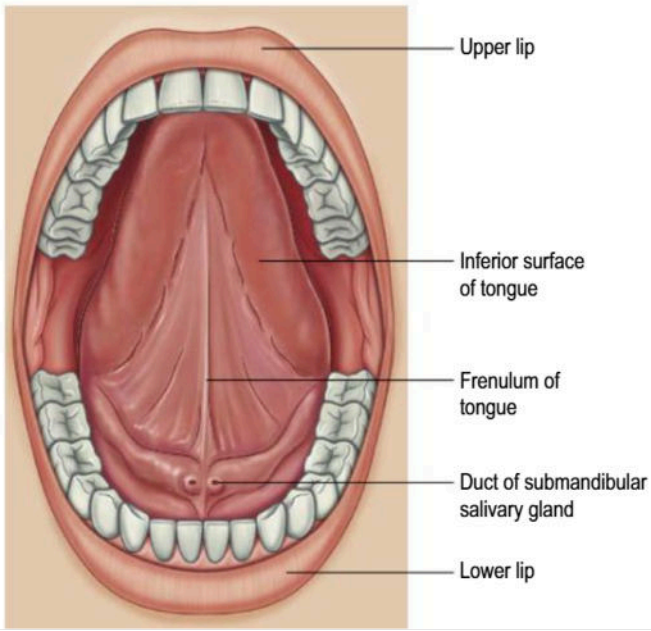

Figure 12.8 The inferior surface of the tongue.

Table 12.1 Deciduous and permanent dentitions

	Molars	Premolars	Canine	Incisors	Incisors	Canine	Premolars	Molars
Deciduous teeth								
Upper	2	–	1	2	2	1	–	2
Lower	2	–	1	2	2	1	–	2
Permanent teeth								
Upper	3	2	1	2	2	1	2	3
Lower	3	2	1	2	2	1	2	3

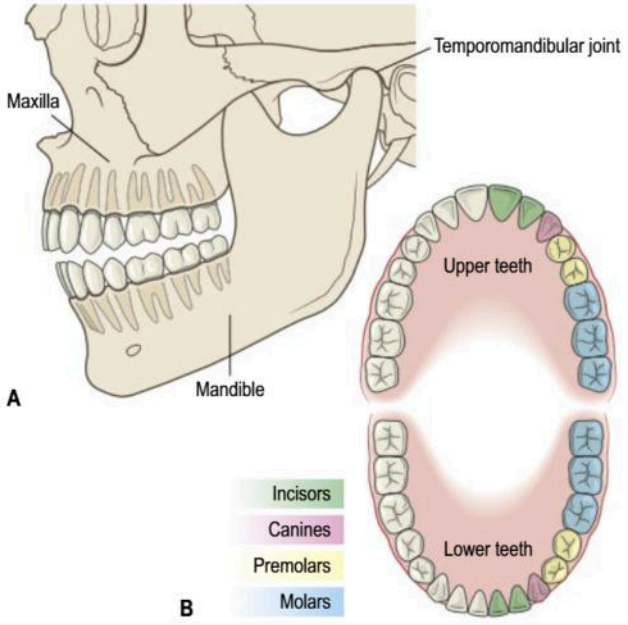

Figure 12.10 The permanent teeth. (A) Lateral view. (B) Locations in the upper and lower jaw.

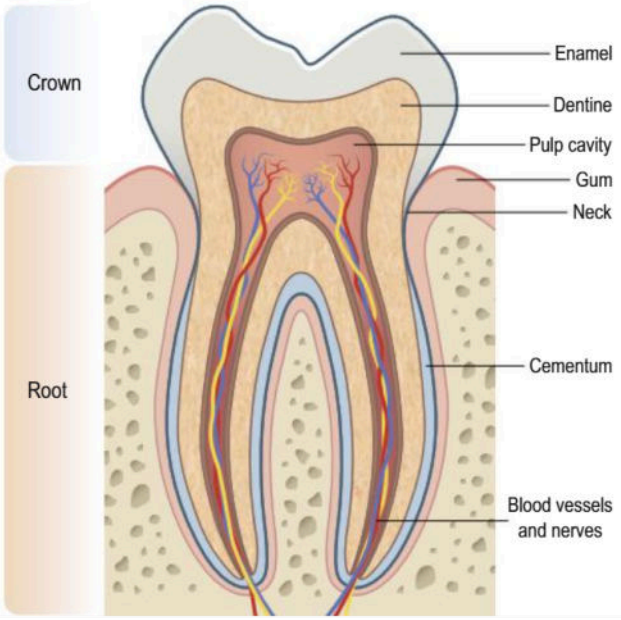

Figure 12.11 Section of a tooth.

There are 20 temporary teeth, 10 in each jaw. They begin to erupt at about 6 months of age and should all be present by 24 months (Table 12.1).

The permanent teeth (Fig. 12.10) begin to replace the deciduous teeth between the ages of 6 and 13. This dentition, consisting of 32 teeth, is usually complete by the age of 20. The third molars (wisdom teeth) are the last to erupt.

Structure

Although the shapes of the different teeth vary, the structure (Fig. 12.11) is the same and consists of:

- the crown – the part that protrudes from the gum
- the root – the part embedded in the bone
- the neck – the slightly narrowed region where the crown merges with the root.

In the centre of the tooth is the pulp cavity, containing blood vessels, lymph vessels and nerves, and surrounding this is a hard, ivory-like substance called dentine. The dentine of the crown is covered by a thin layer of very hard enamel. The root of the tooth is covered with a substance resembling bone, called cementum, which secures the tooth in its socket. Blood vessels and nerves pass to the tooth through a small foramen (hole) at the apex of each root.

Blood supply

Most of the arterial blood supply to the teeth is by branches of the maxillary arteries. The venous drainage is by several veins that empty into the internal jugular veins.

Nerve supply

The nerve supply to the upper teeth is by branches of the maxillary nerves and that to the lower teeth by branches of the mandibular nerves. These are both branches of the trigeminal nerves (5th cranial nerves; see Fig. 7.41).

Functions

Teeth have different shapes, depending on their functions. Incisors and canine teeth are the cutting teeth and used for

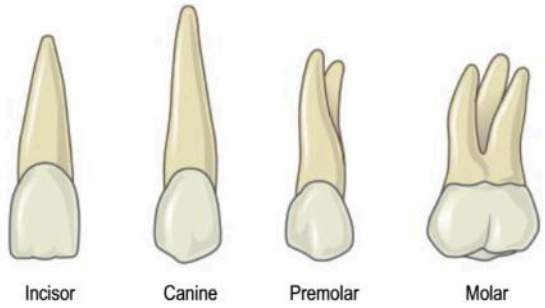

Figure 12.12 The shapes of the permanent teeth.

biting off pieces of food, whereas the premolar and molar teeth, with broad, flat surfaces, are used for grinding or chewing food (Fig. 12.12).

SPOT CHECK

3. Outline the functions of the tongue.

Salivary glands

Learning outcomes

After studying this section, you should be able to:

- describe the structure and functions of the principal salivary glands
- explain the role of saliva in digestion.

The salivary glands (Fig. 12.13) are exocrine glands that release saliva into ducts, which lead into the mouth. There are three pairs: the parotid glands, the submandibular glands and the sublingual glands. There are also numerous smaller salivary glands widely scattered around the mouth.

Parotid glands

These are situated one on each side of the face, just below the auditory canal. Each has a duct opening into the mouth at the level of the second upper molar tooth.

Submandibular glands

These lie one on each side of the face under the angle of the jaw. The two submandibular ducts open on the floor of the mouth, one on each side of the frenulum of the tongue (Fig. 12.8).

Sublingual glands

These glands lie under the mucous membrane of the floor of the mouth in front of the submandibular glands. They have numerous small ducts that open into the floor of the mouth.

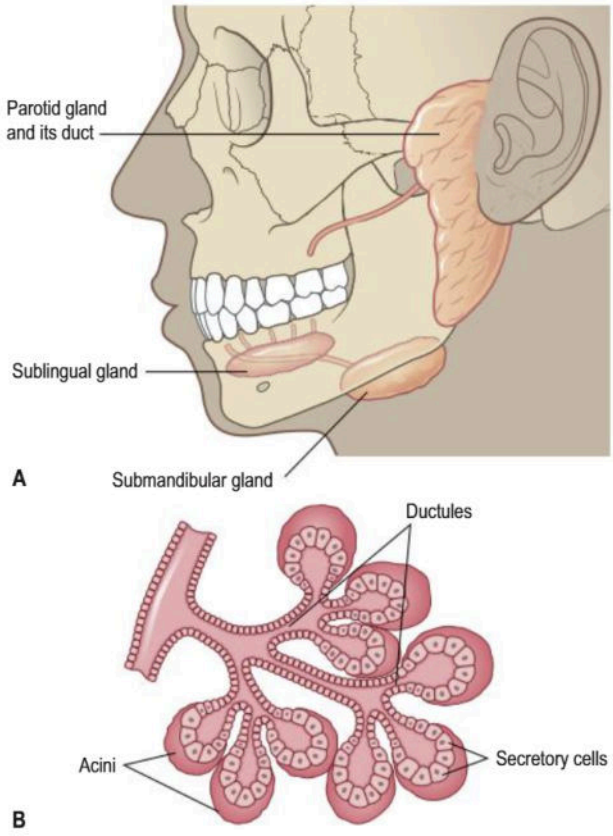

Figure 12.13 Salivary glands. (A) The position of the salivary glands. (B) Enlargement of part of a gland.

Structure

Salivary glands are surrounded by a fibrous capsule. They consist of many lobules made from small grape-like acini lined with secretory cells (Fig. 12.13B). Saliva is released into ductules that merge forming larger ducts that lead into the mouth.

Blood supply

Arterial supply is by various branches from the external carotid arteries, and venous drainage is into the external jugular veins.

Saliva

Saliva is the combined secretions from the salivary glands and the small mucus-secreting glands of the oral mucosa. About 1.5 litres of saliva is produced daily and it consists of:

- water
- mineral salts
- salivary amylase – a digestive enzyme
- mucus
- antimicrobial substances – immunoglobulins (antibodies) and the enzyme lysozyme.

Secretion of saliva

This is controlled by the autonomic nervous system. Parasympathetic stimulation causes profuse secretion of watery saliva with a relatively low content of enzymes and other organic substances. Sympathetic stimulation results in secretion of small amounts of saliva rich in organic material, especially from the submandibular glands. Reflex secretion occurs when there is food in the mouth and the reflex becomes conditioned so that the sight, smell and even thought of food stimulate the flow of saliva.

Functions of saliva

Chemical digestion of polysaccharides

Saliva contains the enzyme amylase, which begins the breakdown of complex sugars, including starches, reducing them to the disaccharide maltose. The optimum pH for the action of salivary amylase is 6.8 (slightly acid). Salivary pH ranges from 5.8 to 7.4, depending on the rate of flow; the higher the flow rate, the higher the pH. The action of amylase continues until it reaches the stomach where it is inactivated by the strongly acidic gastric juice.

Lubrication of food

Its high water content means that saliva moistens and lubricates dry food to form a semi-solid bolus ready for swallowing.

Cleaning and lubrication of the mouth

An adequate flow of saliva is necessary to keep the mouth clean, moist and pliable. This also helps to prevent damage to the mucous membrane by rough or abrasive food.

Non-specific defence

Lysozyme and immunoglobulins (antibodies) present in saliva help to combat invading microbes.

Taste

The taste buds are stimulated only by chemicals in solution and therefore dry foods stimulate the sense of taste only after thorough mixing with saliva. The senses of taste and smell (Ch. 8) are closely linked and involved in the enjoyment, or otherwise, of food (see Fig 1.8).

SPOT CHECK

4. Outline the functions of the two enzymes in saliva.

Pharynx

Learning outcome

After studying this section, you should be able to:

- describe the structure of the pharynx.

The pharynx is divided for descriptive purpose into three parts: the nasopharynx, oropharynx and laryngopharynx (p. 270). The nasopharynx is important in respiration. The oropharynx and laryngopharynx are passages common to both the respiratory and the digestive systems. Food passes from the oral cavity into the pharynx and then to the oesophagus below, with which it is continuous. The walls of the pharynx consist of three layers of tissue.

The superficial mucosa is stratified squamous epithelium, continuous with the lining of the mouth at one end and the oesophagus at the other. This provides a thick, sturdy lining well suited to the wear and tear of swallowing ingested food.

The middle layer consists of connective tissue, which becomes thinner towards the lower end and contains blood and lymph vessels and nerves.

The deepest layer consists of involuntary muscles that are involved in swallowing. When food reaches the pharynx, swallowing is no longer under voluntary control (see below).

Blood supply

The blood supply to the pharynx is from several branches of the facial arteries. Venous drainage is into the facial veins and the internal jugular veins.

Nerve supply

This is from the pharyngeal plexus and consists of parasympathetic and sympathetic nerves. Parasympathetic supply is mainly by the glossopharyngeal and vagus nerves (9th and 10th cranial nerves), and sympathetic supply is from the cervical ganglia.

SPOT CHECK

5. Name the regions of the pharynx that form part of the digestive tract.

Oesophagus

Learning outcomes

After studying this section, you should be able to:

- outline the structure of the oesophagus
- explain the mechanisms involved in swallowing, and the route taken by a bolus.

The oesophagus (Fig. 12.14) is about 25 cm long and about 2 cm in diameter; it runs centrally through the thorax in front of the vertebral column and behind the trachea and the heart. It is continuous with the pharynx above and joins the stomach just below the diaphragm. It passes between muscle fibres of the diaphragm behind the central tendon at the level of the 10th thoracic vertebra and immediately curves upwards

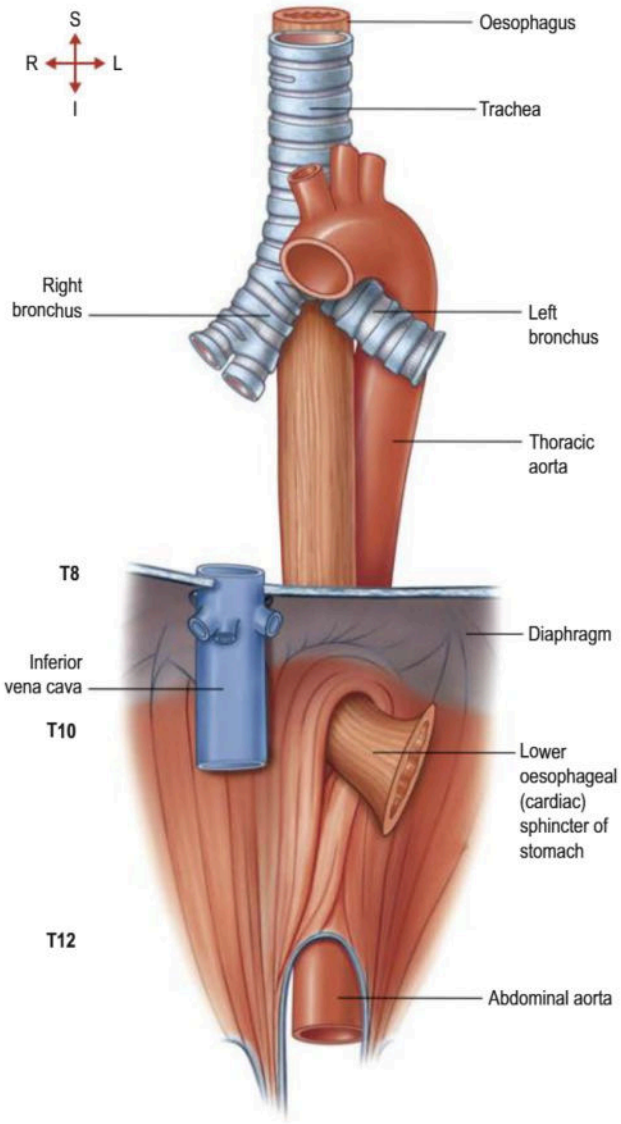

Figure 12.14 The oesophagus and some related structures.

before opening into the stomach. This sharp angle is believed to be one of the factors that prevents regurgitation (backflow) of gastric contents into the oesophagus. The upper and lower ends of the oesophagus are closed by sphincters. The upper oesophageal sphincter prevents air entering the oesophagus during inspiration, and the aspiration of oesophageal contents. The lower oesophageal (cardiac) sphincter (see Figs 12.14 and 12.18) prevents the reflux of acid gastric contents into the oesophagus.

Structure

There are four layers of tissue, as shown in Figure 12.2. The oesophagus lies almost entirely in the thorax, and the deepest adventitia consists of elastic fibrous tissue that attaches it to the surrounding structures. The proximal third is lined by stratified squamous epithelium for protection during swallowing, and the distal third by columnar epithelium. The middle third is lined by a mixture of the two.

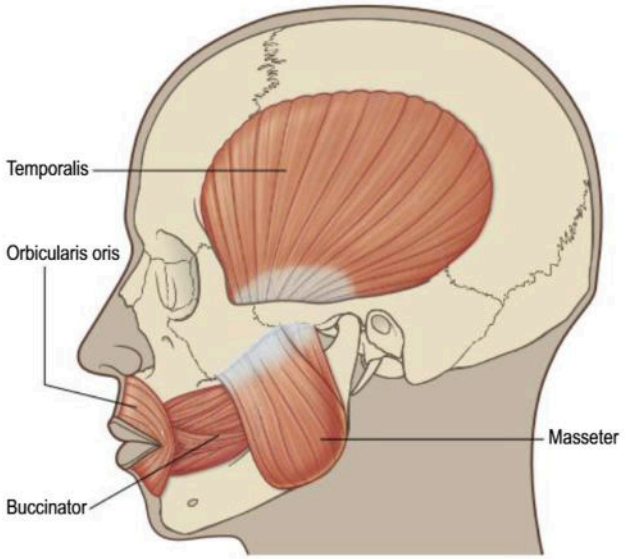

Figure 12.15 The muscles used in chewing.

Blood supply

Arterial supply

The thoracic region is supplied mainly by the paired oesophageal arteries, branches from the thoracic aorta. The abdominal region is supplied by branches from the inferior phrenic arteries and the left gastric branch of the coeliac artery.

Venous drainage

From the thoracic region venous drainage is into the azygos and hemiazygos veins. The abdominal part drains into the left gastric vein. There is a plexus of anastomotic veins at the distal end that links the upward and downward venous drainage, i.e. the general and portal circulations (see Fig. 12.49).

Functions of the mouth, pharynx and oesophagus

Formation of a bolus

Ingested food is chewed and moved around the mouth by the tongue and muscles of the cheeks (Fig. 12.15). It is mixed with saliva until it is sufficiently moist to be formed into a soft mass, or bolus, ready for swallowing; some foods need to be chewed longer than others.

Swallowing (deglutition)

Swallowing the bolus (Fig. 12.16) occurs in three stages. It is initiated voluntarily but completed by reflex (involuntary) action.

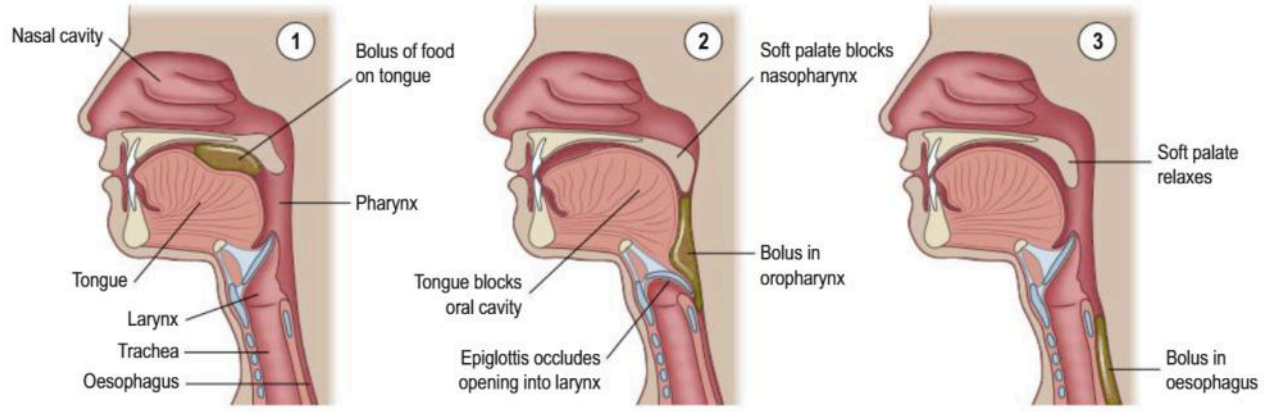

Figure 12.16 The three stages of swallowing. 1. Oral. 2. Pharyngeal. 3. Oesophageal.

1. Oral stage

With the mouth closed, the voluntary muscles of the tongue and cheeks push the bolus backwards into the pharynx.

2. Pharyngeal stage

The muscles of the pharynx are stimulated by a reflex initiated in the walls of the oropharynx and coordinated by the swallowing centre in the medulla. Involuntary contraction of these muscles propels the bolus down into the oesophagus as all other routes that the bolus could take are closed. The soft palate rises up closing off the nasopharynx, the tongue and the pharyngeal folds block the way back into the mouth, and the larynx is lifted up and forwards so that its opening is occluded by the overhanging epiglottis, preventing entry into the trachea.

3. Oesophageal stage

Once in the pharynx, the bolus stimulates a wave of involuntary peristalsis that propels it through the oesophagus to the stomach.

Peristaltic waves (see Fig. 12.4) pass along the oesophagus only after swallowing begins. At other times, the walls are relaxed. Ahead of a peristaltic wave, the lower oesophageal sphincter guarding the entrance to the stomach relaxes to allow the descending bolus to pass into the stomach. Usually, constriction of the lower oesophageal sphincter prevents reflux of gastric acid into the oesophagus. Other factors preventing gastric reflux include:

- the attachment of the stomach to the diaphragm by the peritoneum
- the acute angle formed by the position of the oesophagus as it enters the fundus of the stomach, i.e. an acute gastro-oesophageal angle (see Fig. 12.18)
- increased tone of the lower oesophageal sphincter when intra-abdominal pressure is increased together with a pinching effect when the diaphragm muscle fibres contract, e.g. during swallowing and defaecation.

The walls of the oesophagus are lubricated by mucus, which assists the passage of the bolus during swallowing.

SPOT CHECK

6. List the stages of swallowing and indicate whether each is voluntary or involuntary.

Stomach

Learning outcomes

After studying this section, you should be able to:

- describe the location of the stomach with reference to surrounding structures
- explain the physiological significance of the layers of the stomach wall
- discuss the digestive functions of the stomach.

The stomach is a J-shaped organ that lies in the epigastric, umbilical and left hypochondriac regions of the abdominal cavity (Fig. 12.17).

Organs associated with the stomach

Anteriorly – left lobe of liver and anterior abdominal wall.
Posteriorly – abdominal aorta, pancreas, spleen, left kidney and adrenal gland.
Superiorly – diaphragm, oesophagus and left lobe of liver.
Inferiorly – transverse colon and small intestine.
To the left – diaphragm and spleen.
To the right – liver and duodenum.

Structure

The stomach is continuous with the oesophagus at the lower oesophageal sphincter and the duodenum at the pyloric

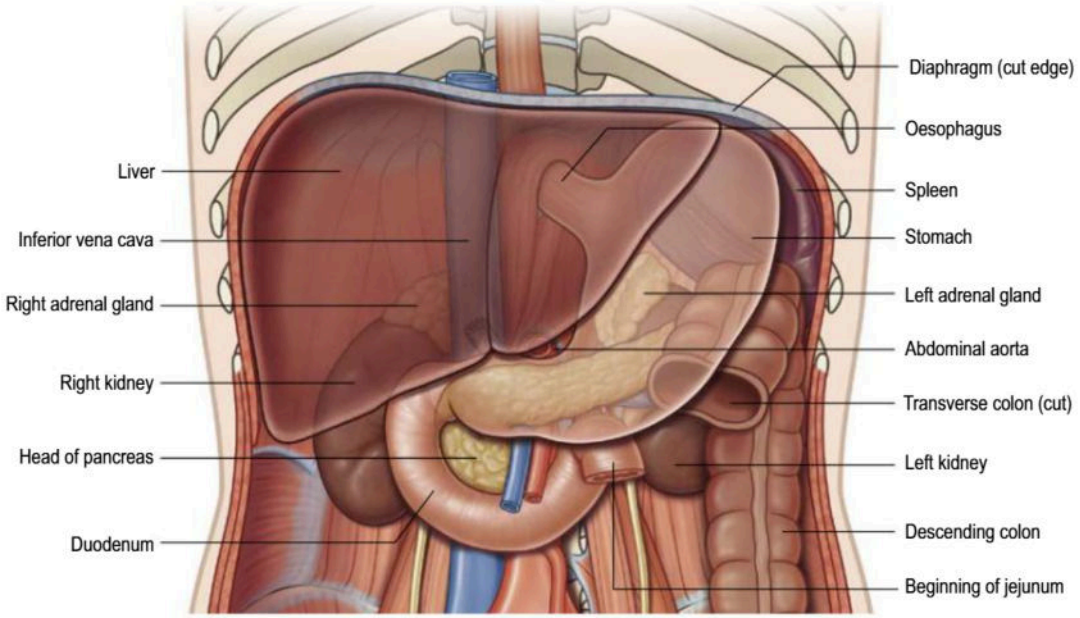

Figure 12.17 The stomach and its associated structures.

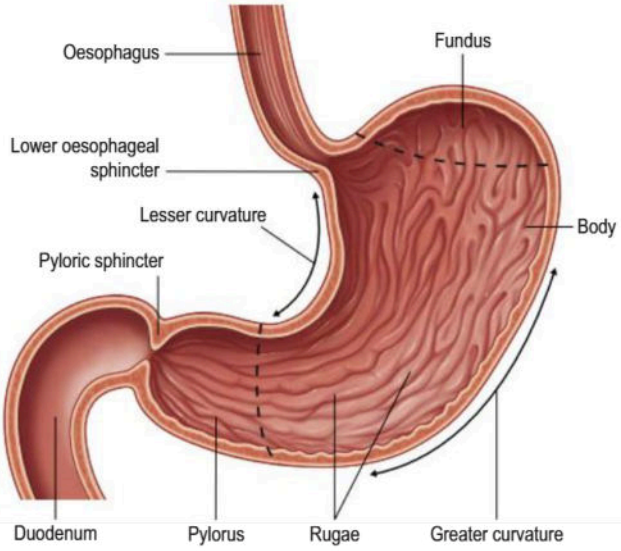

Figure 12.18 Longitudinal section of the stomach.

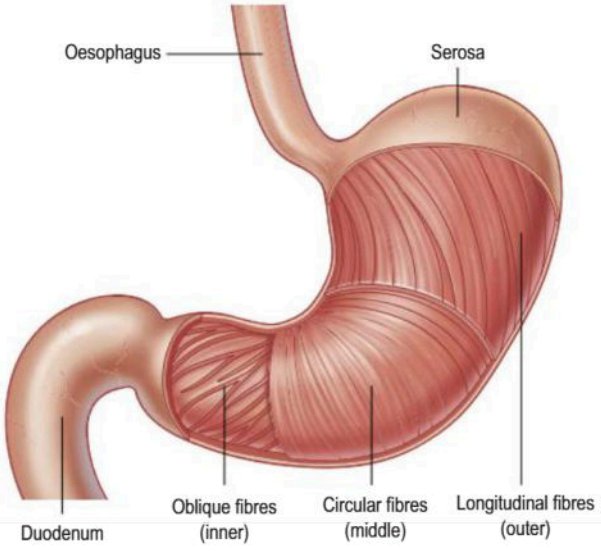

Figure 12.19 Muscle layers of the stomach wall.

sphincter (Fig. 12.18). It has two curvatures. The lesser curvature is short, lies on the posterior surface of the stomach and is the downward continuation of the posterior wall of the oesophagus. Just before the pyloric sphincter it curves upwards to complete the J shape. Where the oesophagus joins the stomach, the anterior region angles acutely upwards then curves downwards forming the much longer greater curvature; it curves slightly upwards towards the pyloric sphincter.

The stomach is divided into three regions:

- the fundus
- the body
- the pylorus.

At the distal end of the pylorus is the pyloric sphincter, guarding the opening between the stomach and the duodenum.

Walls of the stomach

The four layers of tissue that comprise the basic structure of the alimentary canal (see Fig. 12.2) are found in the stomach but with some modifications.

Muscle layer

This consists of three layers of smooth muscle fibres (Fig. 12.19):

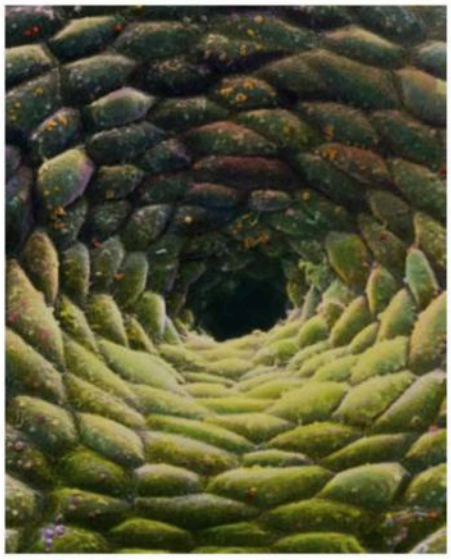

Figure 12.20 The entrance to a gastric gland. Coloured scanning electron micrograph of the mucous membrane lining the stomach. (Professors PM Motta, KR Porter and PM Andrews/Science Photo Library. Reproduced with permission.)

- an outer layer of longitudinal fibres
- a middle layer of circular fibres
- an inner layer of oblique fibres.

In this respect the stomach is different from other regions of the alimentary tract, as it has three layers of muscle instead of two. This arrangement allows for the powerful churning action characteristic of gastric activity, as well as peristaltic movement. Circular muscle is strongest between the pylorus and the pyloric sphincter.

Mucosa

When the stomach is empty the mucous membrane lining is thrown into longitudinal folds or rugae (Fig. 12.18), and as it fills the rugae are stretched out, giving the surface a smooth, velvety appearance. Numerous gastric glands are situated below the surface of the mucous membrane and open on to it (Fig. 12.20). They contain specialised cells, including chief cells and parietal cells which secrete constituents of gastric juice into the stomach, as well as enteroendocrine cells (see below).

Blood supply

Arterial supply to the stomach is by the left gastric artery, a branch of the coeliac artery, the right gastric artery and the gastroepiploic arteries. Venous drainage is through veins of corresponding names into the portal vein (see Figs 5.41 and 5.42).

Gastric juice and functions of the stomach

Stomach size varies with the volume of its contents, which may be 1.5 litres or more in adults after a heavy meal. Food accumulates in the stomach in layers, the last part of the meal remaining in the fundus for longest. Mixing with the gastric juice takes place gradually and it may be some time before the food is sufficiently acidified to inactivate the salivary amylase.

Contraction of the gastric smooth muscle generates a churning action that breaks down the bolus and mixes it with gastric juice to produce a thick, highly acidic, semifluid mass called chyme. Peristaltic waves in the stomach wall propel the chyme towards the pylorus. When the stomach is active the pyloric sphincter closes to retain the food in the stomach until it is sufficiently mixed and ready to be passed into the small intestine. Strong peristaltic contraction of the pylorus forces chyme through the pyloric sphincter into the duodenum in small spurts. Parasympathetic stimulation increases the motility of the stomach and secretion of gastric juice; sympathetic stimulation has the opposite effects.

Gastric juice

About 2 litres of gastric juice are secreted daily by specialised secretory glands in the mucosa (Fig. 12.21). It consists of:

- water
- mineral salts
- mucus secreted by both mucous neck cells in the glands and mucous cells on the stomach surface
- hydrochloric acid, intrinsic factor — secreted by parietal cells in the gastric glands
- inactive enzyme precursors – pepsinogens secreted by chief cells in the glands.

Functions of gastric juice

- Water further liquefies the food swallowed.
- Hydrochloric acid:
  - acidifies the food and inactivates salivary amylase
  - kills ingested microbes
- Pepsinogens are activated to pepsins by both hydrochloric acid and pepsins already present in the stomach. These enzymes begin the digestion of proteins, breaking them into smaller peptide molecules. Pepsins have evolved to act most effectively at a very low pH, between 1.5 and 3.5.
- Intrinsic factor is necessary for the absorption of vitamin B_{12} from the ileum.
- Mucus prevents mechanical injury to the stomach wall by lubricating the contents. It also prevents chemical injury by acting as a barrier between the gastric mucosa and the highly corrosive gastric juice; hydrochloric acid is present in potentially damaging concentrations and pepsins would digest the gastric tissues.

Secretion of gastric juice

There is always a small quantity of gastric juice present in the stomach, even when it contains no food. This is called fasting

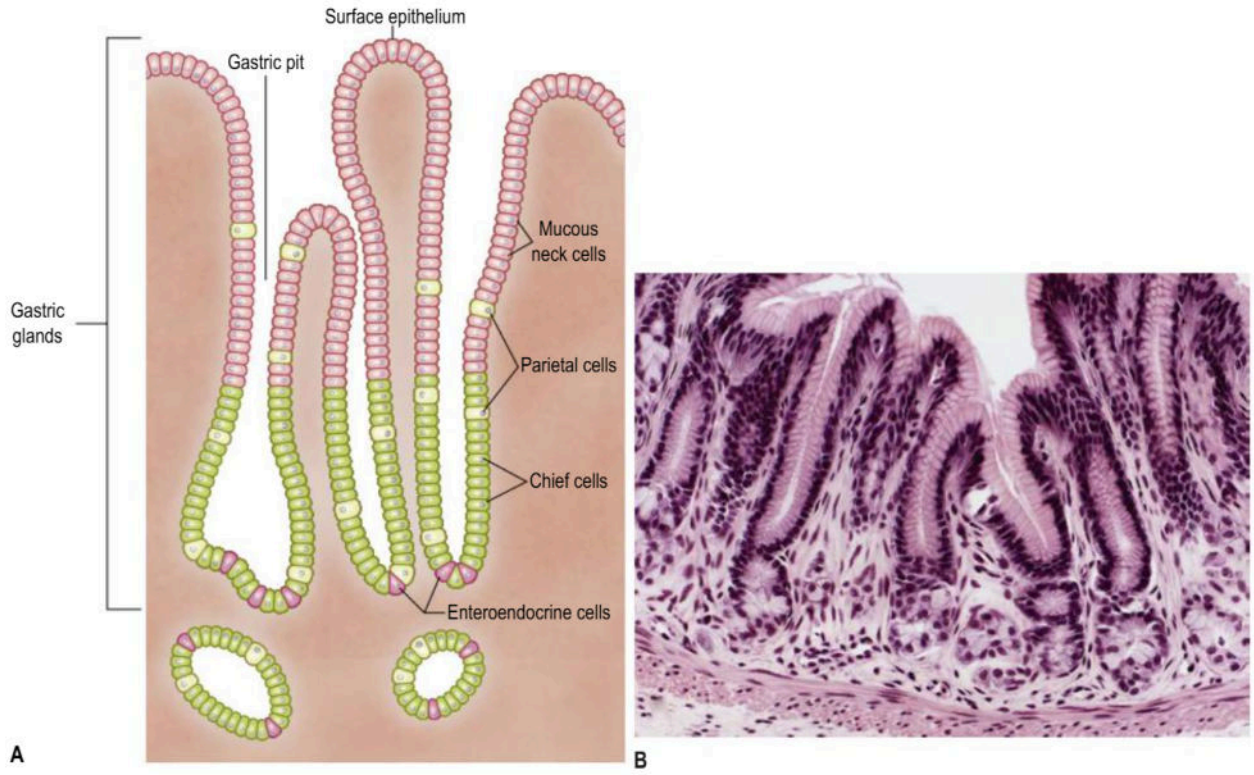

Figure 12.21 Structure of the gastric mucosa showing gastric glands. (A) Diagram. (B) Stained section of the pyloric region of the stomach (magnified × 150). (B, Telser AG, Young JK, Baldwin KM 2007 Elsevier's integrated histology. Edinburgh: Mosby. Reproduced with permission.)

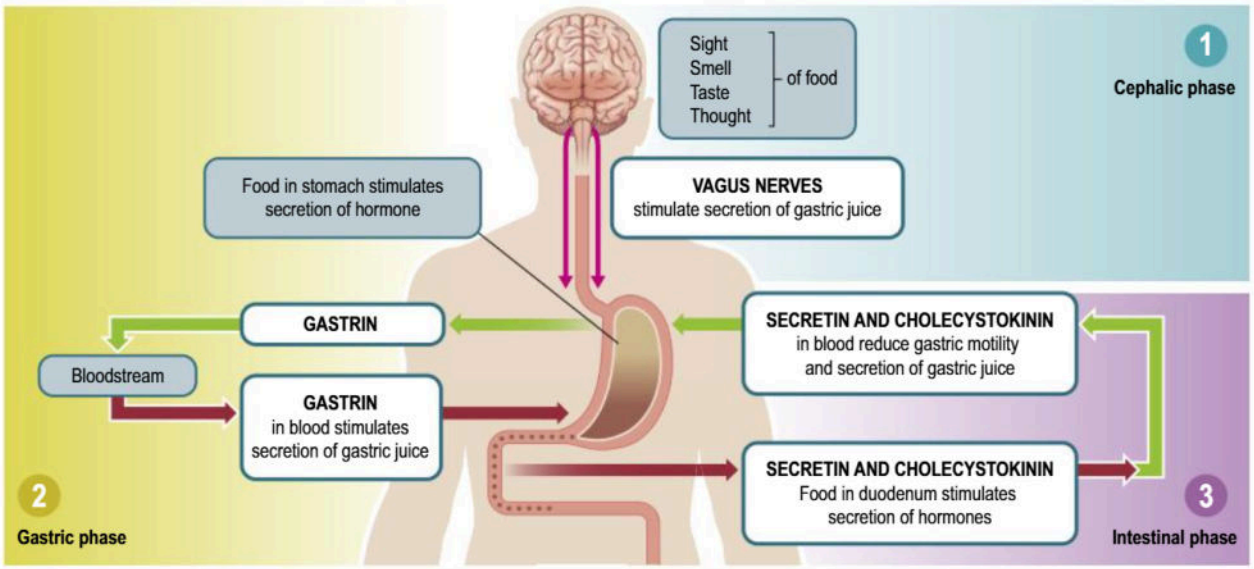

Figure 12.22 The three phases of secretion of gastric juice.

juice. Secretion reaches its maximum level about 1 hour after a meal, then declines to the fasting level after about 4 hours.

There are three phases of secretion of gastric juice (Fig. 12.22).

1. Cephalic phase

Secretion occurs before food reaches the stomach and is due to reflex stimulation of the vagus nerve, initiated by the sight, smell, taste or thought of appealing food. Sympathetic

stimulation, e.g. during emotional states, inhibits gastric activity.

2. Gastric phase

When stimulated by the presence of food, the enteroendocrine cells in the gastric glands (see Fig. 12.21) secrete the hormone gastrin directly into the circulating blood. Gastrin, circulating in the blood that supplies the stomach, stimulates the gastric glands to produce more gastric juice. In this way, secretion of digestive juice continues after eating is finished and the cephalic phase is past. Gastrin secretion is suppressed when the pH in the pylorus falls to about 1.5.

3. Intestinal phase

When the partially digested contents of the stomach reach the small intestine, two hormones, secretin and cholecystokinin (CCK), are produced by enteroendocrine cells in the intestinal mucosa. They slow down the secretion of gastric juice and reduce gastric motility. By slowing the emptying rate of the stomach, the chyme in the duodenum becomes more thoroughly mixed with bile and pancreatic juice. This phase of gastric secretion is most marked following a high fat meal.

The rate at which the stomach empties depends largely on the type of food eaten. A carbohydrate meal leaves the stomach in 2–3 hours, a protein meal remains for longer and a fatty meal remains there longest.

Functions of the stomach

These include:

- Temporary storage – allows time for the digestive enzymes, pepsins, to act.
- Chemical digestion – pepsins split proteins into polypeptides.
- Mechanical breakdown – the three smooth muscle layers enable the stomach to act as a powerful churn, gastric juice is added and the contents are liquefied to chyme. Gastric motility and secretion are increased by parasympathetic nerve stimulation.
- Limited absorption – water, alcohol and some lipid-soluble drugs.
- Non-specific defence against microbes – provided by hydrochloric acid in gastric juice. Vomiting (see Table 12.4) may occur as a protective response to e.g. the presence of gastric irritants or circulating toxins.
- Preparation of iron for absorption – the acid environment of the stomach solubilises iron salts, essential for its absorption in the small intestine.
- Production and secretion of intrinsic factor, a protein needed for absorption of vitamin B_{12} in the terminal ileum. Deficiency leads to pernicious anaemia (p. 78).
- Regulation of the passage of gastric contents into the duodenum – when the chyme is sufficiently acidified and liquefied, the pylorus forces it in small jets through the pyloric sphincter into the duodenum. The sphincter is normally closed, preventing backflow of chyme into the stomach.
- Secretion of the hormone gastrin (see above).

SPOT CHECK

7. Outline the functions of mucus secreted by mucous neck cells in the gastric glands.

Small intestine

Learning outcomes

After studying this section, you should be able to:

- describe the location of the small intestine, with reference to surrounding structures
- sketch a villus, labelling its component parts
- discuss the digestive functions of the small intestine and its secretions
- explain how nutrients are absorbed in the small intestine.

The small intestine (see Fig. 12.24) is continuous with the stomach at the pyloric sphincter; it is about 2.5 cm in diameter and a little over 5 metres long, and joins the large intestine at the ileocaecal valve. Chemical digestion of food is completed in the small intestine and absorption of most nutrients also takes place here. It is comprised of three continuous parts.

Duodenum

This is about 25 cm long and curves around the head of the pancreas (Fig. 12.23). Secretions from the gall bladder and pancreas merge in a common structure – the hepatopancreatic ampulla – and enter the duodenum at the duodenal papilla. The duodenal papilla is guarded by a ring of smooth muscle, the hepatopancreatic sphincter (of Oddi) (see Fig. 12.40).

Jejunum

This is the middle section of the small intestine and is about 2 metres long (Fig. 12.24).

Ileum

This terminal section is about 3 metres long and ends at the ileocaecal valve, which controls the flow of material

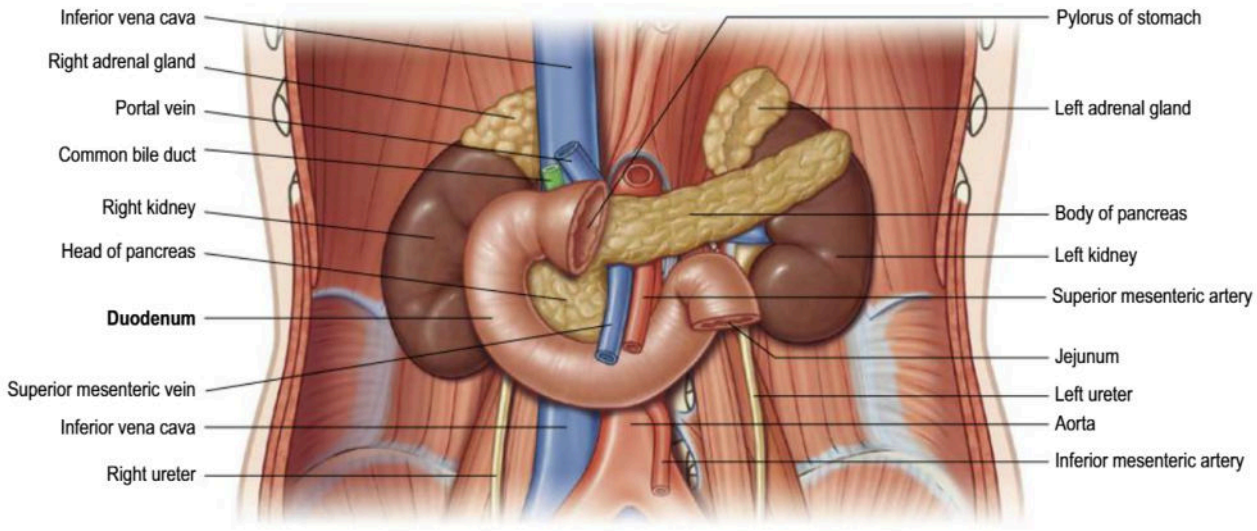

Figure 12.23 The duodenum and its associated structures.

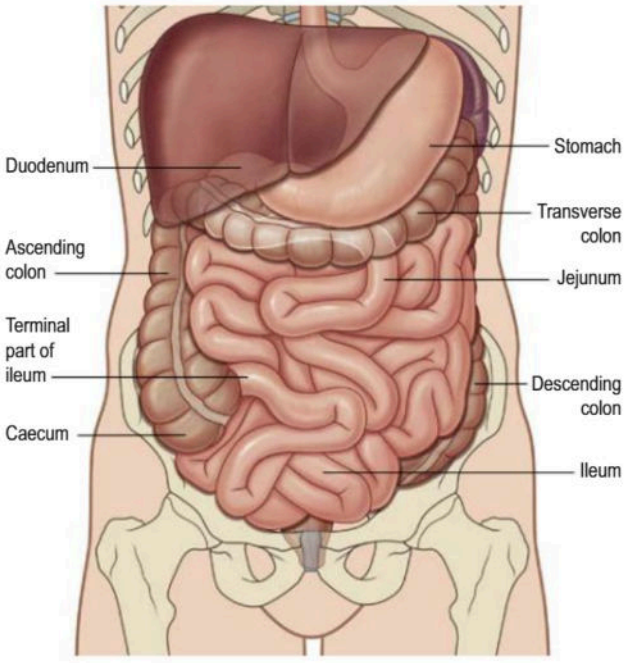

Figure 12.24 The jejunum and ileum and their related structures.

from the ileum into the caecum, the first part of the large intestine.

Structure

The walls of the small intestine are composed of the four layers of tissue shown in Figure 12.2. Some modifications of the peritoneum and mucosa (mucous membrane lining) are described below.

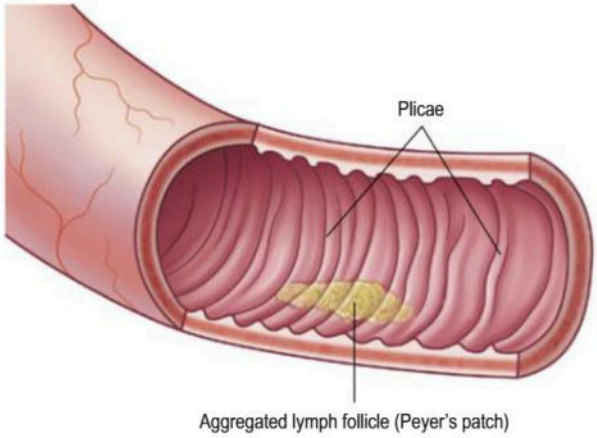

Figure 12.25 Section of a small piece of small intestine (opened out), showing the permanent circular folds.

Peritoneum

The mesentery, a double layer of peritoneum, attaches the jejunum and ileum to the posterior abdominal wall (see Fig. 12.3A). The attachment is quite short in comparison with the length of the small intestine; it is therefore fan-shaped. The large blood vessels and nerves lie on the posterior abdominal wall and the branches to the small intestine pass between the two layers of the mesentery.

Mucosa

The surface area of the small intestine mucosa is greatly increased by permanent circular folds called plicae, as well as villi and microvilli.

The plicae, unlike the rugae of the stomach, are not smoothed out when the small intestine is distended (Fig. 12.25). They promote mixing of chyme as it passes along.

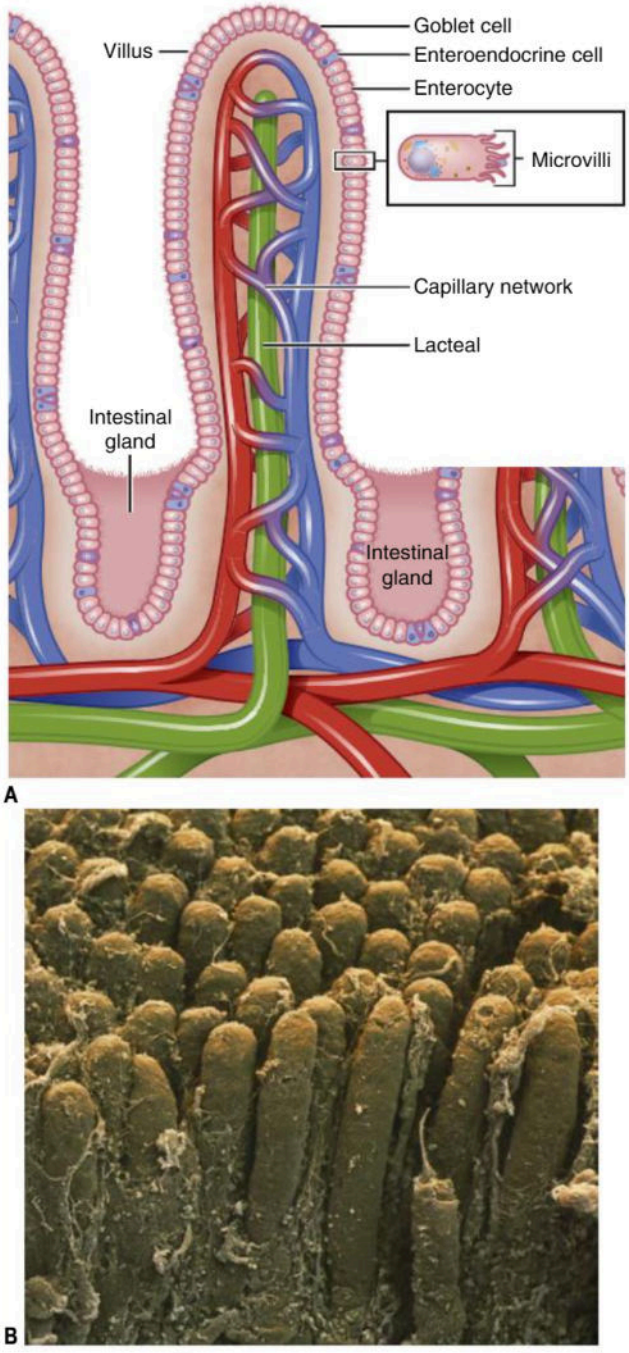

Figure 12.26 Villi. (A) A highly magnified diagram of one complete villus in the small intestine. (B) Coloured scanning electron micrograph showing many villi. (B, Eye of Science/Science Photo Library. Reproduced with permission.)

The villi are very small finger-like projections of the mucosal layer into the intestinal lumen, about 0.5–1 mm long (Fig. 12.26). Their covering consists of columnar epithelial cells, or enterocytes, with tiny microvilli (1 μm long) on their free border. Hormone-secreting enteroendocrine cells and mucus-secreting goblet cells are interspersed between the enterocytes. The villi contain a network of blood capillaries and a central lymph capillary. Lymph capillaries are called lacteals because absorbed fat gives the lymph a milky appearance. Absorption and some final stages of digestion of nutrients take place in the enterocytes before entering the blood and lymph capillaries.

The intestinal glands, also known as intestinal crypts, are simple tubular glands situated below the surface between the villi (Fig. 12.26A). As the epithelial cells of these glands mature, they migrate upwards as enterocytes that form the outer surface of the villi, replacing those at the tips as they are rubbed off by the passage of intestinal contents. The entire epithelium is replaced every 3–5 days. During migration, epithelial cells produce digestive enzymes that lodge in the microvilli and, together with intestinal juice, complete the chemical digestion of carbohydrates, protein and fats.

Numerous lymph nodes are found in the mucosa at irregular intervals throughout the length of the small intestine. The smaller ones are called solitary lymph follicles, and collections of about 20–30 larger nodes situated towards the distal end of the ileum are called aggregated lymph follicles (Peyer's patches, Fig. 12.25). These lymphoid tissues are packed with defensive cells and strategically located to neutralise ingested antigens (Ch. 15).

Blood supply

The superior mesenteric artery supplies the whole of the small intestine. Venous drainage is via the superior mesenteric vein, which joins other veins to form the portal vein (see Figs 5.41 and 5.42). The blood in the portal vein contains a high concentration of absorbed nutrients; this blood passes through the liver before entering the hepatic veins and, ultimately, the inferior vena cava (see Fig. 12.38).

Functions of the small intestine

These are:

- onward movement of its contents by peristalsis, which is increased by parasympathetic stimulation
- secretion of intestinal juice, also increased by parasympathetic stimulation
- completion of chemical digestion of carbohydrates, protein and fats in the enterocytes of the villi
- protection against infection by microbes that have survived the antimicrobial action of the hydrochloric acid in the stomach, by both solitary and aggregated lymph follicles
- secretion of the hormones CCK and secretin by enteroendocrine cells of the villi
- absorption of nutrients.

Chemical digestion in the small intestine

When acid chyme passes into the small intestine it is mixed with intestinal juice, pancreatic juice and bile, and is in contact

with the absorptive enterocytes of the villi. The digestion of all nutrients is completed:

- carbohydrates are broken down to monosaccharides
- proteins are broken down to amino acids
- fats are broken down to fatty acids and glycerol.

Intestinal juice

About 1500 mL of intestinal juice are secreted daily by the glands of the small intestine. It is slightly alkaline and consists of water, lubricating mucus and bicarbonate to neutralise gastric acid. Alkaline intestinal juice (pH 7.8–8.0) assists in raising the pH of the intestinal contents to between 6.5 and 7.5. Unlike other parts of the digestive tract, the intestinal juice does not contain digestive enzymes, which are instead found within the enterocytes themselves.

Control of its secretion is poorly understood. Mechanical stimulation of the intestinal glands is believed to be the main stimulus, although hormones may also be involved.

Pancreatic juice

Pancreatic juice is secreted by the exocrine pancreas (p. 343), and about 1500 mL enters the duodenum at the duodenal papilla daily. It consists of:

- water
- mineral salts
- enzymes:
  - amylase
  - lipase
  - nucleases that digest the nucleic acids, DNA and RNA
- inactive enzyme precursors including:
  - trypsinogen
  - chymotrypsinogen.

Pancreatic juice is alkaline, with a pH of 8 because it contains significant quantities of bicarbonate ions, which are alkaline in solution. When acid stomach contents enter the duodenum they are mixed with pancreatic juice and bile from the liver, raising the pH to between 6 and 8. This is the pH at which the pancreatic enzymes, amylase and lipase, act most effectively.

Secretion of pancreatic juice

The secretion of pancreatic juice is stimulated by secretin and CCK, produced by enteroendocrine cells in the walls of the villi. When acid chyme from the stomach enters the duodenum, it stimulates the release of these hormones (see Fig. 12.22).

Bile

Bile, secreted by the liver, is unable to enter the duodenum when the hepatopancreatic sphincter is closed; it therefore passes from the hepatic duct along the cystic duct to the gall bladder, where it is stored (see Fig. 12.40).

Bile has a pH of around 8 and about 500 mL is secreted daily. It consists of:

- water
- mineral salts
- mucus
- bile salts
- bile pigments, mainly bilirubin
- cholesterol.

Functions of bile

The functions of bile are explained further on page 348. In summary, these are:

- emulsification of fats in the small intestine – bile salts
- making cholesterol and fatty acids soluble, enabling their absorption along with the fat-soluble vitamins – bile salts
- excretion of bilirubin (a waste product from the breakdown of red blood cells), most of which is in the form of stercobilin.

Release from the gall bladder

After a meal, the enteroendocrine cells of the villi release the hormones secretin and CCK during the intestinal phase of gastric secretion (p. 335). They stimulate contraction of the gall bladder and relaxation of the hepatopancreatic sphincter, expelling both bile and pancreatic juice through the duodenal papilla into the duodenum. Secretion is markedly increased when chyme entering the duodenum contains a high proportion of fat.

Enzymatic digestion in the small intestine

Most of the digestive enzymes in the small intestine are contained in the enterocytes of the epithelium that covers the villi. Digestion of carbohydrate, protein and fat is completed by direct contact between these nutrients and the microvilli and within the enterocytes.

The enzymes that complete chemical digestion of food at the surface of the enterocytes are:

- peptidases
- lipase
- sucrase, maltase and lactase.

Digestion of proteins

Pancreatic trypsinogen and chymotrypsinogen are inactive enzyme precursors that are activated only on their arrival in the duodenum, because otherwise they would digest the pancreas. They are activated by enterokinase, an enzyme in the microvilli, which converts them into the active peptidases: trypsin and chymotrypsin. Other peptidases are found in the enterocytes, and along with pancreatic trypsin and chymotrypsin they break polypeptides down into tripeptides, dipeptides and amino acids.

Digestion of carbohydrates

Pancreatic amylase converts all digestible polysaccharides (starches) not acted on by salivary amylase to disaccharides. Sucrase, maltase and lactase complete the digestion of carbohydrates by splitting disaccharides such as sucrose,

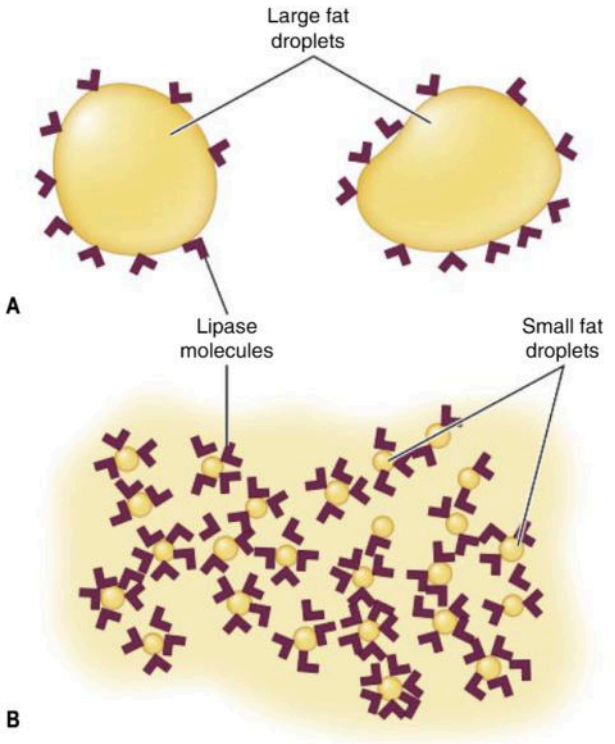

Figure 12.27 Emulsification of fats. (A) In the absence of bile fat is present as large droplets. (B) In the presence of bile the large droplets are dispersed into small droplets, greatly increasing the surface area for lipase action.

maltose and lactose into monosaccharides at the surface of the enterocytes.

Digestion of fats

Fat enters the small intestine as relatively large droplets which each have a small surface area (Fig. 12.27A); in this form they are not easily absorbed and action of lipase would be difficult. Bile salts are released into the duodenum and emulsify fats; this means that they disperse the large fat droplets into many much smaller ones, greatly increasing the surface area available for lipase to act (Fig. 12. 27B). Lipase in the pancreatic juice and the enterocytes can then complete the digestion of fats by converting the small droplets into their constituent fatty acids and glycerol.

Absorption of nutrients

Absorption of nutrients from the small intestine through the enterocytes occurs by several processes (Fig. 12.28), including diffusion, osmosis, facilitated diffusion and active transport. Water moves by osmosis; small fat-soluble substances, e.g. fatty acids and glycerol, are able to diffuse through cell membranes; and others are generally transported inside the villi by other mechanisms.

Monosaccharides and amino acids are actively co-transported with sodium ions into the blood capillaries in

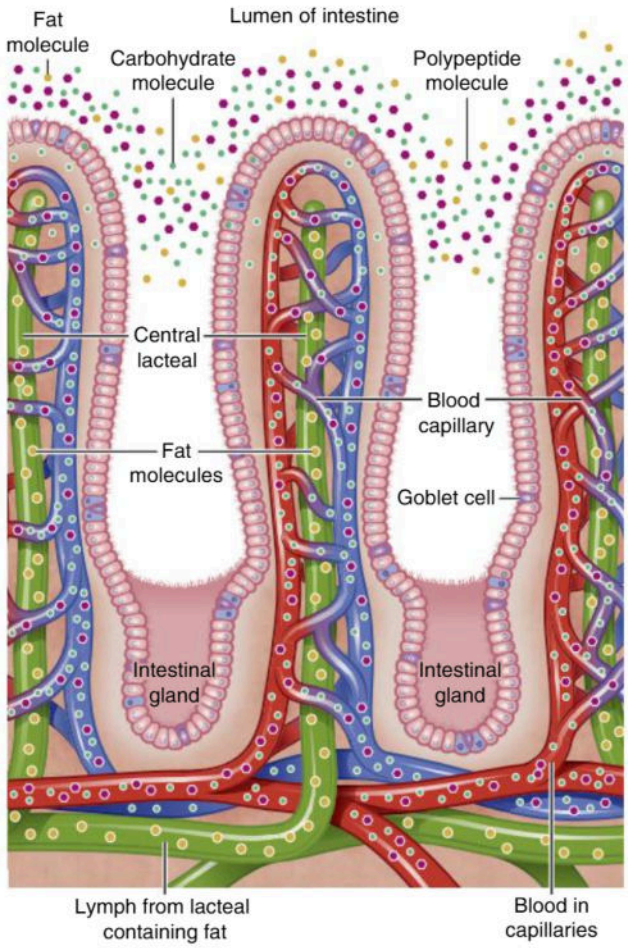

Figure 12.28 The absorption of nutrients into villi.

the villi. Fatty acids and glycerol diffuse into the lacteals and travel along lymph vessels to the thoracic duct, where they enter the circulation (Ch. 6).

A small number of proteins and other large substances are absorbed unchanged, e.g. antibodies present in breast milk and oral vaccines, such as poliomyelitis vaccine.

Other nutrients, such as vitamins, mineral salts and water, are also absorbed from the small intestine into the blood capillaries. Fat-soluble vitamins are absorbed into the lacteals along with fatty acids and glycerol. Vitamin B_{12} combines with intrinsic factor in the stomach and is actively absorbed in the terminal ileum.

The surface area through which absorption takes place in the small intestine is greatly increased by the circular folds of mucous membrane and by the very large number of villi and microvilli present (see Fig. 12.26). It has been calculated that the surface area of the small intestine is about five times that of the whole body surface.

Large amounts of fluid enter the alimentary tract each day (Fig. 12.29). Of this, only about 1500 mL is not absorbed by the small intestine and passes into the large intestine.

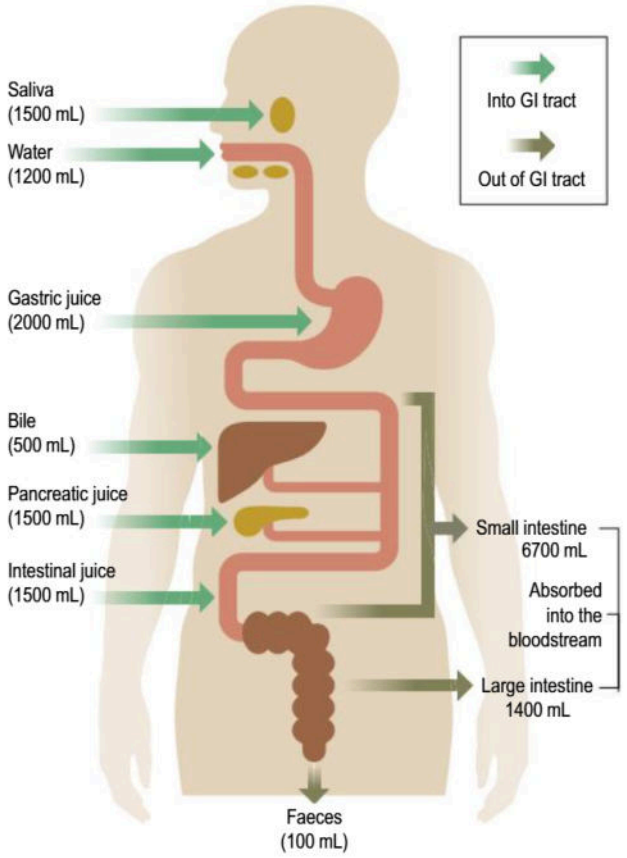

Figure 12.29 Average volumes of fluid ingested, secreted, absorbed and eliminated from the gastrointestinal (GI) tract daily.

SPOT CHECK

8. Name the valves at each end of the small intestine.
9. Relate the structure of the villus to its functions.

Large intestine, rectum and anal canal

Learning outcomes

After studying this section, you should be able to:

- identify the different sections of the large intestine
- describe the structure and functions of the large intestine, the rectum and the anal canal.

The large intestine is about 1.5 metres long, beginning at the caecum in the right iliac fossa and terminating at the rectum and anal canal. It is about 6.5 cm in diameter, considerably larger than the small intestine. It forms an arch around the coiled-up small intestine (Fig. 12.30). For descriptive purposes the large intestine is divided into the caecum, colon, rectum and anal canal.

Caecum

This is the first part of the large intestine; it is a dilated region about 6 cm long with a blind lower end (Fig. 12.31). The ileocaecal valve connects the terminal ileum to the large intestine where the caecum merges with the ascending colon above.

Appendix

The appendix is a fine tube, closed at one end, which opens from the caecum about 3 cm below the ileocaecal valve. It is about 8–9 cm long and has the same structure as the walls of the large intestine but contains more lymphoid tissue. The appendix has no digestive function but is believed to play a role in maintaining the normal flora of the healthy colon, which keeps potentially pathogenic microbes at bay. Inflammation of the appendix can cause significant problems (see appendicitis, p. 364).

Colon

The colon has four continuous parts, which have the same structure and functions.

- The ascending colon passes upwards from the caecum to the level of the liver, where it curves acutely to the left at the hepatic flexure.
- The transverse colon extends across the abdominal cavity from the hepatic flexure in front of the duodenum and the stomach to the area of the spleen, where it curves acutely downwards at the splenic flexure.
- The descending colon passes down the left side of the abdominal cavity, then curves towards the midline. At the level of the iliac crest it becomes the sigmoid colon.
- The sigmoid colon is an S-shaped curve in the pelvic cavity that continues downwards to become the rectum.

Rectum

This is a slightly dilated section of the large intestine. It is about 15 cm long and links the sigmoid colon to the anal canal.

Anal canal

This is a short passage about 2.5 cm long in adults and connects the rectum to the exterior. Two muscular sphincters control the anus:

- the internal sphincter, consisting of smooth muscle, is under the control of the autonomic nervous system
- the external sphincter, formed by skeletal muscle, is under voluntary control (Fig. 12.32).

Structure

The four layers of tissue described in the basic structure of the gastrointestinal tract (see Fig. 12.2) are present in the caecum, colon, rectum and anal canal. The arrangement of

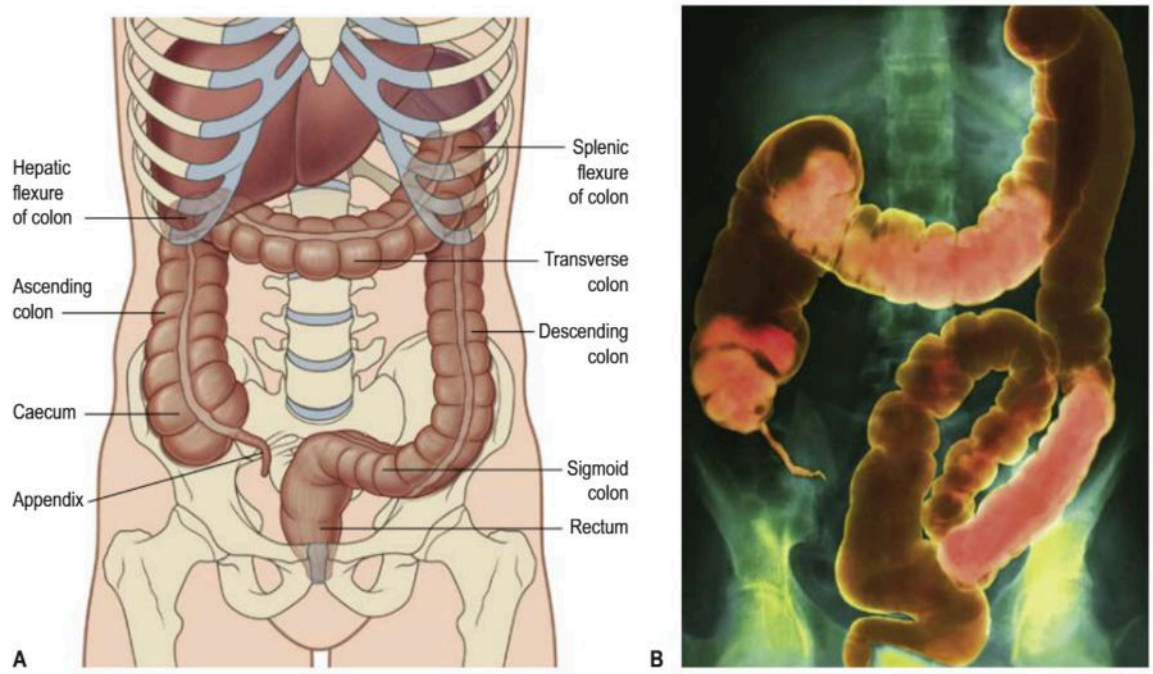

Figure 12.30 The large intestine. (A) Its position in the abdominal cavity. (B) Visualised with barium (false colour X-ray image). (B, Alain Pol, ISM/Science Photo Library. Reproduced with permission.)

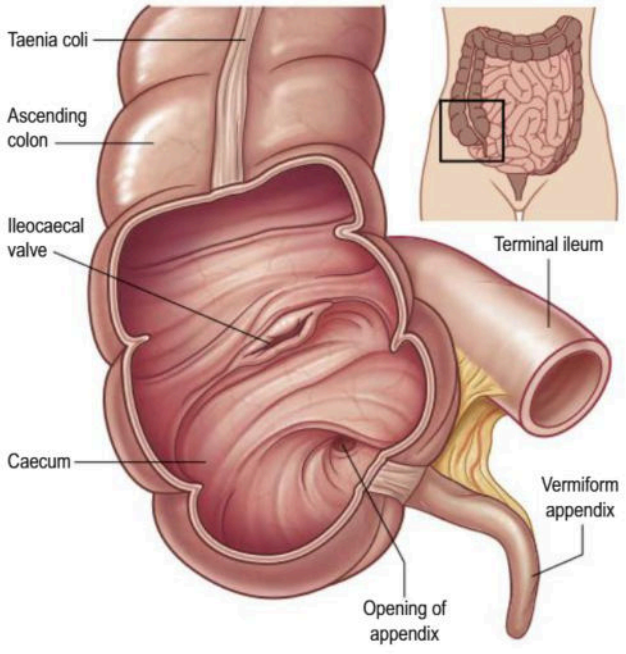

Figure 12.31 Interior of the caecum.

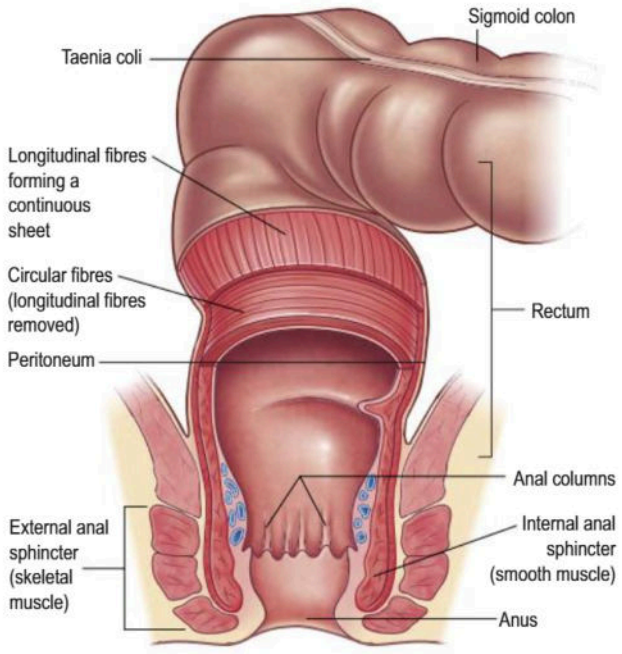

Figure 12.32 Arrangement of muscle fibres in the large intestine, rectum and anus. Sections have been removed to show the layers.

the longitudinal muscle fibres is modified in the caecum and colon. They do not form a continuous layer of tissue but are instead collected into three strips, called taeniae coli, which run lengthways along the caecum and colon to its junction with the rectum. As these longitudinal strips of muscle tissue are slightly shorter than the total length of the caecum and colon, they give it a puckered appearance (see Fig. 12.32).

In the rectum and anal canal the longitudinal muscle fibres form a continuous layer as in the basic structure. The

anal sphincters are formed by thickened rings of circular muscle.

In the submucosal layer there is more lymphoid tissue than in any other part of the alimentary tract, protecting against infection, by either resident (commensal) or invading bacteria.

The mucosal lining of the colon and the upper rectum contains large numbers of mucus-secreting goblet cells (see Fig. 12.5) within simple tubular glands. They are not present beyond the junction between the rectum and the anal canal. The mucus produced here lubricates the faeces as they pass through the remainder of the tract.

The lining of the anal canal consists of stratified squamous epithelium continuous with the mucous membrane lining of the rectum above and which merges with the skin beyond the external anal sphincter. In the upper section of the anal canal the mucous membrane is arranged in 6–10 vertical folds, the anal columns. Each column contains a terminal branch of the superior rectal artery and vein.

Blood supply

Arterial supply

This is mainly by the superior and inferior mesenteric arteries (see Fig. 5.40). The superior mesenteric artery supplies the caecum, ascending colon and most of the transverse colon. The inferior mesenteric artery supplies the remainder of the colon and the proximal part of the rectum. The middle and inferior rectal arteries, branches of the internal iliac arteries, supply the distal section of the rectum and the anus.

Venous drainage

This is mainly by the superior and inferior mesenteric veins which drain blood from the parts supplied by arteries of the same names. These veins join the splenic and gastric veins to form the portal vein (see Fig. 5.41).

Veins draining the distal part of the rectum and the anus join the internal iliac veins, meaning that blood from this region returns directly to the inferior vena cava, bypassing the liver and portal circulation.

Functions of the large intestine

Absorption

The contents of the ileum that pass through the ileocaecal valve into the caecum are still fluid, even though a large amount of water has been absorbed in the small intestine. Water continues to be absorbed by osmosis in the large intestine until the normal semisolid consistency of faeces is achieved. Mineral salts, vitamins and some drugs are also absorbed into blood capillaries from the large intestine.

Microbial activity

The large intestine is heavily colonised by certain types of bacteria, which synthesise vitamin K and folic acid. They include *Escherichia coli*, *Enterobacter aerogenes*, *Streptococcus faecalis* and *Clostridium perfringens*. These microbes are commensals, i.e. are normally harmless, in humans. However, they may become pathogenic if transferred to another part of the body; for example, *E. coli* may cause cystitis (p. 396) if introduced into the urinary bladder.

Gases in the bowel include air swallowed with food and drink. Additionally, hydrogen, carbon dioxide and methane are produced by bacterial fermentation of unabsorbed dietary constituents, especially fibre. Gases pass out of the anus as flatus (wind).

Mass movement

The large intestine does not exhibit peristaltic movement as do other parts of the digestive tract. At fairly long intervals (4–6 times a day in adults) a wave of strong peristalsis sweeps along the transverse colon, forcing its contents into the descending and sigmoid colons. This is known as mass movement and it is often precipitated by the entry of food into the stomach. This combination of stimulus and response is called the gastrocolic reflex.

Defaecation

The rectum is usually empty, but when a mass movement forces the contents of the sigmoid colon into the rectum the nerve endings in its walls are stimulated by stretch. In infants, defaecation occurs by reflex (involuntary) action. However, during the second or third year of life, children develop voluntary control of bowel function and learn to inhibit the reflex until it is convenient to defaecate. The external anal sphincter is under conscious control through the pudendal nerve. Thus, defaecation involves involuntary contraction of the muscle of the rectum and relaxation of the internal anal sphincter. Contraction of the abdominal muscles and lowering of the diaphragm during a forced expiration (Valsalva's manœuvre) increase the intra-abdominal pressure and assist defaecation. When the need to pass faeces is voluntarily postponed, it tends to fade until the next mass movement occurs and the reflex is initiated again. Repeated suppression of the reflex may lead to constipation (hard faeces) as water continues to be absorbed.

Constituents of faeces

The faeces consist of a semisolid brown mass. The brown colour is due to the presence of stercobilin (p. 346 and see Fig. 12.39).

Although much is absorbed in the small and large intestines, water still makes up about 60%–70% of the weight of the faeces. The remainder consists of:

- fibre (indigestible cellular plant and animal material)
- dead and live microbes
- epithelial cells shed from the walls of the tract
- fatty acids
- mucus secreted by the epithelial lining of the large intestine.

Mucus helps to lubricate the faeces, and an adequate amount of dietary fibre, mainly non-starch polysaccharides (NSPs) and commonly known as 'roughage', ensures that the contents of the large intestine are sufficiently bulky to stimulate defaecation.

SPOT CHECK

10. Name the parts of the large intestine.

Pancreas

Learning outcome

After studying this section, you should be able to:

- differentiate between the structures and functions of the exocrine and endocrine pancreas.

The pancreas (Fig. 12.33) is a creamy pink gland weighing about 60 g. It is about 12–15 cm long and is situated in the epigastric and left hypochondriac regions of the abdominal cavity (see Figs 1.25 and 1.26). It lies in front of the abdominal aorta and the inferior vena cava, and consists of a broad head, a body and a narrow tail. The head lies in the curve of the duodenum, the body behind the stomach, and the tail in front of the left kidney, just reaching the spleen.

The pancreas is both an exocrine and an endocrine gland.

Exocrine pancreas

This consists of multiple lobules made from many small, grape-like acini, whose walls are composed of secretory cells (Fig. 12.34). Each lobule is drained by a tiny duct and these eventually unite to form the pancreatic duct, which extends along the whole length of the gland and opens into the duodenum (Fig. 12.33). Just before entering the duodenum the pancreatic duct joins the common bile duct to form the hepatopancreatic ampulla. The duodenal opening of the ampulla is controlled by the hepatopancreatic sphincter (of Oddi) at the duodenal papilla.

The function of the exocrine pancreas is to produce pancreatic juice containing enzymes, some in the form of inactive precursors, which digest carbohydrates, proteins and fats. As in the alimentary canal, parasympathetic stimulation increases secretion of pancreatic juice and sympathetic stimulation suppresses it.

Endocrine pancreas

Distributed throughout the gland, lying alongside the capillary networks, are groups of specialised cells called the pancreatic islets (of Langerhans). The islets have no ducts, and the hormones diffuse directly into the bloodstream (Fig. 12.34). The endocrine pancreas secretes the hormones insulin and glucagon, which are mainly concerned with control of blood glucose levels (Ch. 9).

Blood supply

The splenic and mesenteric arteries supply the pancreas, and venous drainage is by veins of the same names that join other veins to form the portal vein.

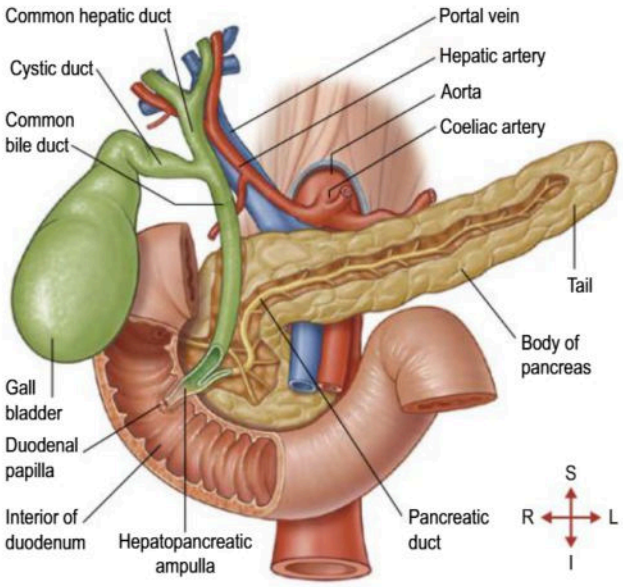

Figure 12.33 The pancreas in relation to the duodenum and biliary tract.

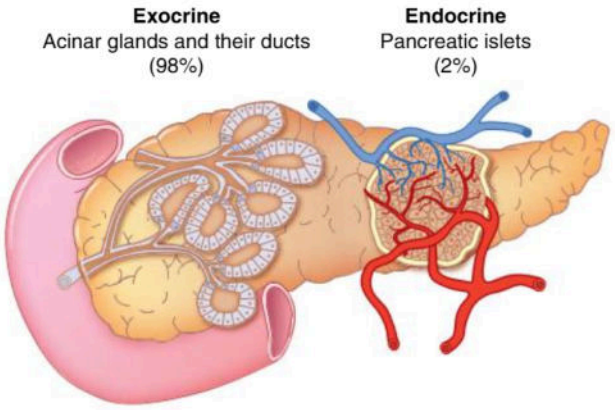

Figure 12.34 The exocrine and endocrine glands of the pancreas.

SPOT CHECK

11. How is secretion of pancreatic juice stimulated?

Liver

Learning outcomes

After studying this section, you should be able to:

- describe the location of the liver
- describe the structure of a liver lobule
- outline the functions of the liver.

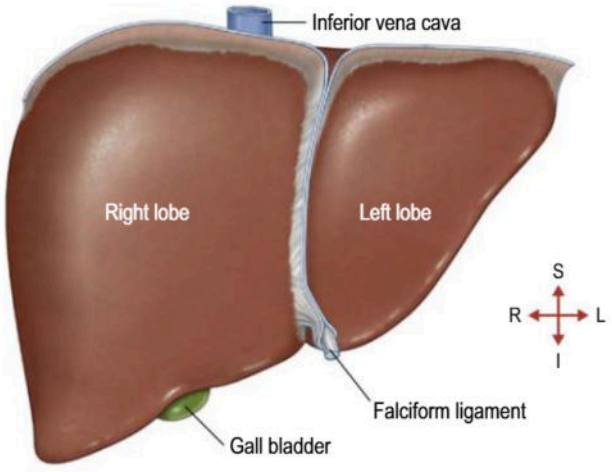

Figure 12.35 The liver. Anterior view.

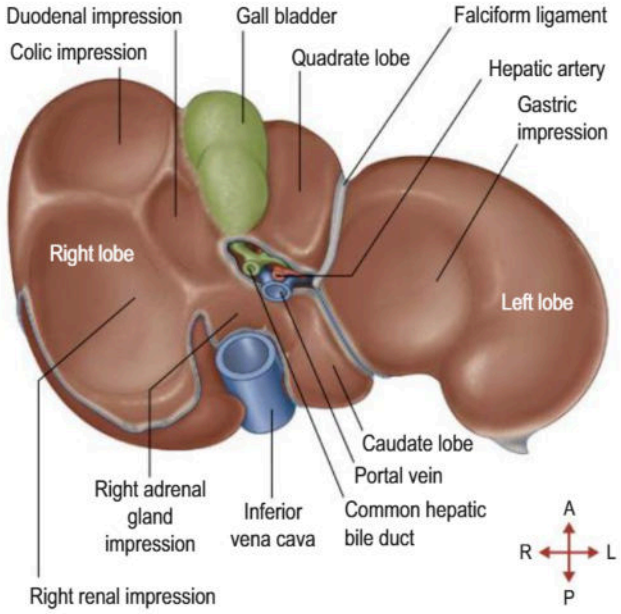

Figure 12.36 The liver. Inferior view (turned up to show the posterior surface).

Gross structure

The liver is the largest gland in the body; it is reddish brown in colour and weighs between 1 and 2.3 kg. Situated in the upper part of the abdominal cavity, it occupies the greater part of the right hypochondriac region and part of the epigastric region and extends into the left hypochondriac region. Its upper and anterior surfaces lie just under the diaphragm (Fig. 12.35); its posterior surface is irregular in outline (Fig. 12.36).

Organs associated with the liver

Superiorly and anteriorly – diaphragm and anterior abdominal wall.

Inferiorly – stomach, bile ducts, duodenum, hepatic flexure of the colon, right kidney and adrenal gland.

Posteriorly – oesophagus, inferior vena cava, aorta, gall bladder, vertebral column and diaphragm.

Laterally – lower ribs and diaphragm.

The liver is enclosed in a thin inelastic capsule and incompletely enclosed by a layer of peritoneum. Folds of peritoneum form supporting ligaments that attach the liver to the inferior surface of the diaphragm. It is held in position partly by these ligaments and partly by the pressure of the organs in the abdominal cavity.

The liver has four lobes. The two most obvious are the large right lobe and the smaller, wedge-shaped left lobe. The other two, the caudate and quadrate lobes, are areas on the posterior surface (Fig. 12.36).

Portal fissure

This is the region on the posterior surface of the liver where various structures enter and leave the organ:

- The portal vein (Fig. 5.41) enters, carrying blood from the stomach, spleen, pancreas and small and large intestines.
- The hepatic artery (Fig. 5.39) enters, carrying arterial blood. It is a branch from the coeliac artery, which branches from the abdominal aorta.
- Sympathetic and parasympathetic nerve fibres enter here.
- The right and left hepatic ducts leave, merging into the common hepatic duct just outside the portal fissure, carrying bile from the liver.
- Lymph vessels leave the liver, draining lymph to abdominal and thoracic nodes.

Blood supply

The hepatic artery and the portal vein take blood to the liver (see Fig. 12.38). Venous return is by a variable number of hepatic veins that leave the posterior surface and immediately enter the inferior vena cava just below the diaphragm.

Microscopic structure

The lobes of the liver are made up of tiny functional units called lobules, which are just visible to the naked eye (Fig. 12.37A). Liver lobules are hexagonal in outline and are formed by cuboidal liver cells, called hepatocytes, arranged in pairs of columns radiating from a central vein. Between two pairs of columns of cells are sinusoids (large capillaries with incomplete walls) containing a mixture of blood from the tiny branches of the portal vein and hepatic artery (Fig. 12.37B). This arrangement allows the arterial blood and portal venous blood, with its high concentration of nutrients, to mix and come into close contact with the hepatocytes. Among the cells lining the sinusoids are hepatic macrophages (Kupffer cells), part of the fixed mononuclear phagocyte system (see Fig. 4.13). These cells ingest and destroy microbes, other foreign particles and worn-out blood cells in the blood passing through the liver lobules.

Blood drains from the sinusoids into central or centrilobular veins. These then merge with veins from other

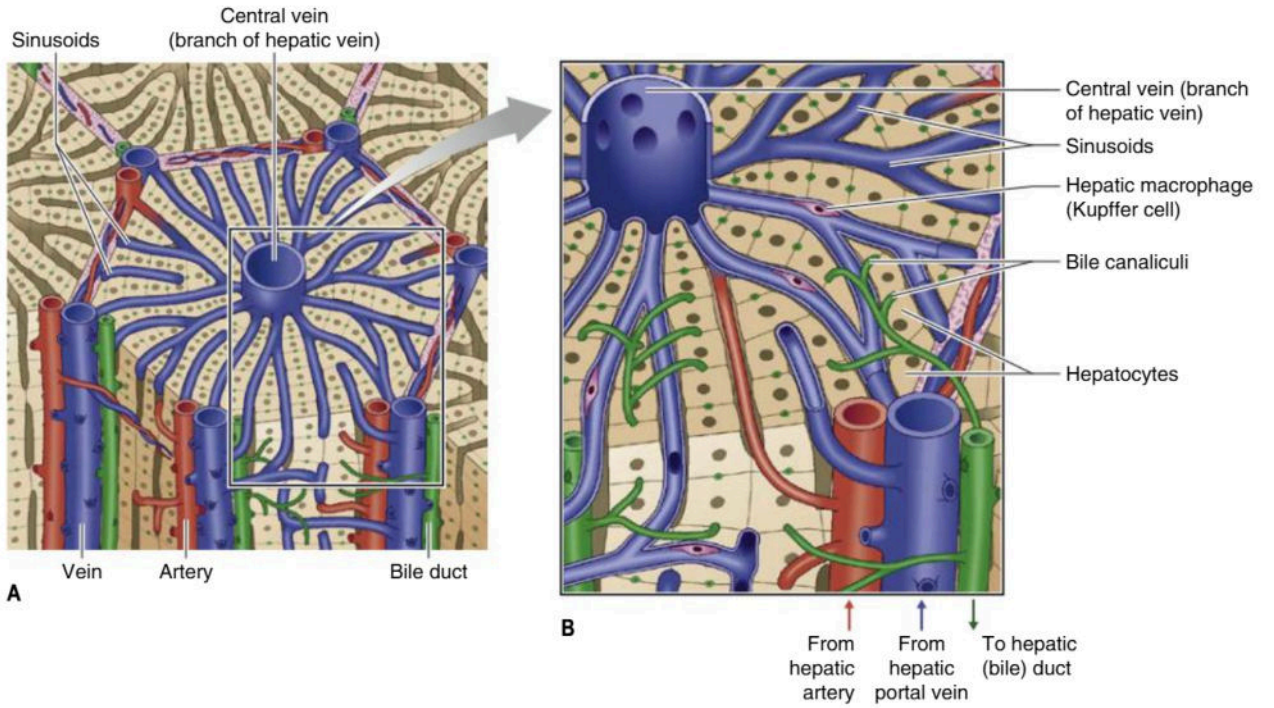

Figure 12.37 Microscopic structure of the liver. (A) A liver lobule. (B) A highly magnified tranverse section of a liver lobule (Modified from Standring S (ed.) 2020. Gray's Anatomy: The Anatomical Basis of Clinical Practice, 42nd ed., Elsevier.)

lobules, forming progressively larger veins, until eventually they become the hepatic veins, which leave the liver and empty into the inferior vena cava. Figure 12.38 shows the system of blood flow through the liver. One of the functions of the liver is to secrete bile. In Figure 12.37B bile canaliculi (tiny bile channels) can be seen running between the columns of liver cells. This means that each column of hepatocytes has a blood sinusoid on one side and a bile canaliculus on the other, so that there is no mixing of bile and blood; they are drained from the liver lobules separately. The canaliculi join up to form larger bile channels until eventually they form the right and left hepatic ducts, which drain bile from the liver.

Lymphoid tissue and a network of lymph vessels are also present in each lobule.

Functions of the liver

The liver is very metabolically active, with multiple interrelated functions, including metabolism of key nutrients, synthesis of many essential proteins, detoxification of harmful chemicals and production of bile.

Carbohydrate metabolism

The liver has an important role in maintaining normal plasma glucose levels. After a meal, when levels rise, the hormone insulin stimulates the uptake of glucose by the liver and converts it to glycogen for storage. Later, when glucose levels fall, the hormone glucagon stimulates conversion of stored glycogen into glucose again, keeping levels within the normal range (see Fig. 12.41).

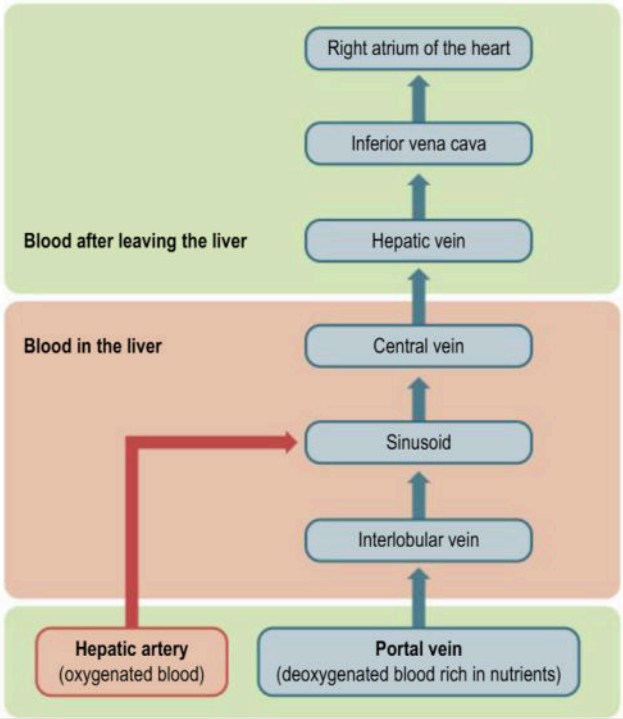

Figure 12.38 Scheme of blood flow through the liver.

Fat metabolism

Stored fat can be converted to a form in which it can be used by the tissues to provide energy (see Fig. 12.45).

Protein metabolism

Deamination of amino acids

This process removes the nitrogenous amino group from excess amino acids; amino groups are combined and modified before being excreted as urea in the urine.

Transamination

This process removes the amino group from amino acids and attaches it to other molecules, forming new non-essential amino acids (see Fig. 12.44).

Synthesis of plasma proteins

The liver produces 90% of the plasma proteins circulating in the bloodstream, including albumins, globulins and blood clotting factors (see Box. 4.1).

Breakdown of erythrocytes and defence against microbes

These processes are carried out by phagocytic hepatic macrophages (Kupffer cells) in the sinusoids, although breakdown of red blood cells also takes place in the spleen (see Fig. 12. 39).

Detoxification of drugs and toxic substances

Substances including ethanol (alcohol), waste products and microbial toxins are inactivated by the liver. Some drugs are extensively inactivated by the liver and are therefore not very effective when given by mouth (orally), e.g. glyceryl trinitrate. This is because, after absorption from the alimentary tract, they travel in the hepatic portal vein to the liver, where they are largely metabolised, so that levels in the blood leaving the liver and then entering the systemic circulation are inadequate to achieve therapeutic effects. This is called first-pass metabolism.

Inactivation of hormones

Examples include insulin, glucagon, cortisol, aldosterone, thyroid and sex hormones.

Production of heat

The liver uses a substantial amount of energy to fuel its intense metabolic activity, which in turn produces a great deal of CO_2, H_2O and heat as by-products. The liver is the main heat-producing organ of the body. Distribution of this heat around the body helps to maintain core body temperature.

Secretion of bile

The hepatocytes synthesise bile from the mixed arterial and venous blood flowing through the sinusoids; its constituents include bile salts, bile pigments and cholesterol (see below).

Storage

Stored substances include:

- glycogen (see Fig. 12.41)
- fat-soluble vitamins: A, D, E, K
- iron, copper
- some water-soluble vitamins, e.g. vitamin B_{12}.

Functions of bile

Fat digestion

The composition of bile is described above. The bile acids, cholic and chenodeoxycholic acid, are synthesised by hepatocytes from cholesterol, then secreted into bile as sodium or potassium salts. In the small intestine they emulsify fats by dispersing them into tiny droplets, thus aiding their digestion by lipases (Fig. 12.27). Fatty acids are insoluble in water, which makes them difficult to absorb through the intestinal wall. Bile salts make cholesterol and fatty acids more water-soluble, enabling both these and the fat-soluble vitamins (vitamins A, D, E and K) to be readily absorbed.

In the terminal ileum most of the bile salts are reabsorbed and returned to the liver in the portal vein. This enterohepatic circulation preserves and recycles bile salts, ensuring adequate levels in the small intestine despite a relatively small pool (Fig. 12.39).

Excretion of bilirubin

Bilirubin is one of the products of haemolysis of erythrocytes by hepatic macrophages (see above). Bilirubin is insoluble in water and is carried in the blood bound to the plasma protein albumin. It is conjugated (combined) with glucuronic acid by hepatocytes in the liver and becomes water-soluble enough to be excreted in bile. Microbes in the large intestine convert bilirubin into stercobilin, which is excreted in the faeces and gives them their brown colour. A small amount is reabsorbed and excreted in urine as urobilinogen (Fig. 12.39). Jaundice is yellow pigmentation of the tissues, seen in the skin and conjunctiva, caused by excessive blood bilirubin levels (p. 372).

SPOT CHECK

12. Which vessels enter and leave the liver at the portal fissure and what do they transport?

Biliary tract

Learning outcomes

After studying this section, you should be able to:

- describe the route taken by bile from the liver to the gall bladder, and then to the duodenum
- outline the structure and functions of the gall bladder.

Bile ducts

The right and left hepatic ducts join to form the common hepatic duct just outside the portal fissure (Fig. 12.40). The hepatic duct passes downwards for about 3 cm and is joined by the cystic duct from the gall bladder. The

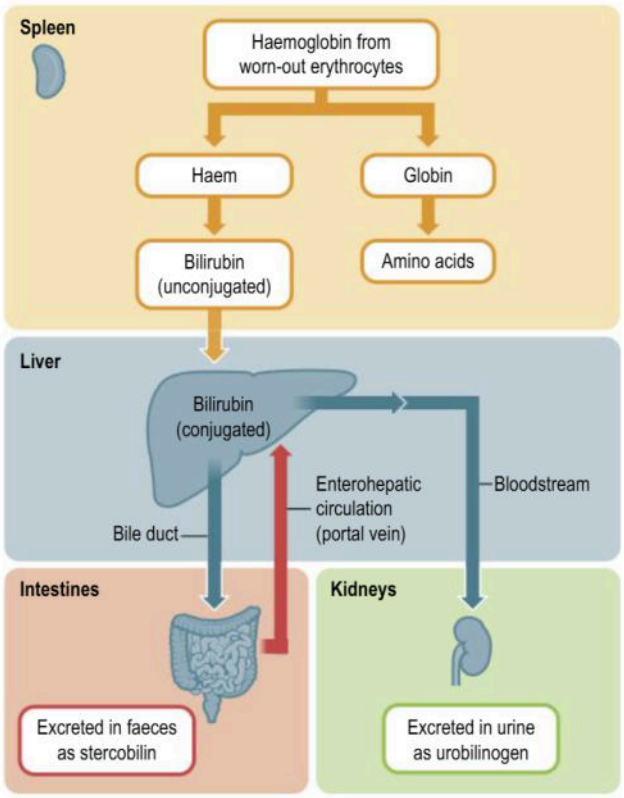

Figure 12.39 Fate of bilirubin from breakdown of worn-out erythrocytes.

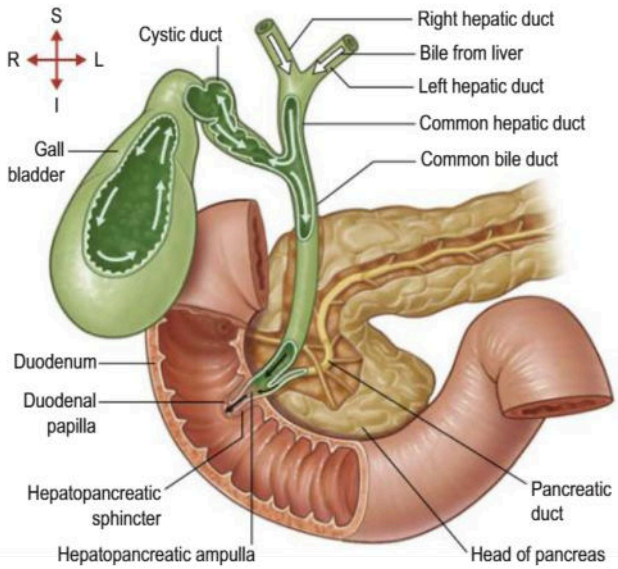

Figure 12.40 Direction of the flow of bile from the liver to the duodenum.

cystic and hepatic ducts merge, forming the common bile duct, which passes downwards behind the head of the pancreas and which is about 7.5 cm long and about 6 mm in diameter. It merges with the main pancreatic duct at the hepatopancreatic ampulla and opens into the duodenum at the duodenal papilla, which is controlled by the hepatopancreatic sphincter (of Oddi).

Structure of the bile ducts

The walls of the bile ducts have the same layers of tissue as those of the basic structure of the alimentary canal (see Fig. 12.2). In the cystic duct the mucous membrane lining is arranged in irregular circular folds, which have the effect of a spiral valve. Bile passes through the cystic duct twice: once on its way into the gall bladder, and again when it is expelled from the gall bladder into the common bile duct and then on to the duodenum.

Gall bladder

The gall bladder is a pear-shaped sac attached to the posterior surface of the liver by connective tissue. It is about 7–10 cm long and has a fundus or expanded end, a body or main part, and a neck, which is continuous with the cystic duct. Its capacity is around 50 mL.

Structure of the gall bladder

The wall of the gall bladder has the same layers of tissue as those of the basic structure of the alimentary canal, with some modifications.

Peritoneum

This covers only the inferior surface because the upper surface of the gall bladder is in direct contact with the liver and held in place by the visceral peritoneum that covers the liver.

Muscle layer

There is a layer of oblique smooth muscle fibres in addition to the longitudinal and circular layers.

Mucous membrane

This displays small rugae when the gall bladder is empty, which disappear as it fills with bile.

Blood supply

The cystic artery, a branch of the hepatic artery, supplies the gall bladder. Venous drainage is via the cystic vein, which joins the portal vein.

Functions

These include:

- storage of bile
- concentration of the bile by up to 10- or 15-fold, by absorption of water through the walls of the gall bladder
- release of stored bile.

When the muscular wall of the gall bladder contracts, bile is expelled into the bile ducts and enters the duodenum. Contraction is stimulated by the hormone CCK, secreted by the enterocytes of the villi (Fig. 12.26), and by the presence of fat and acid chyme in the duodenum.

Relaxation of the hepatopancreatic sphincter (of Oddi) is caused by CCK and is a reflex response to contraction of the gall bladder.

SPOT CHECK

13. Outline the pathway taken by bile, from leaving the liver to entering the small intestine.

Summary of digestion and absorption of nutrients

Learning outcomes

After studying this section, you should be able to:

- list the principal digestive enzymes, their sites of action, their substrates and their products
- describe the sites of absorption of the main nutrients.

Table 12.2 summarises the main digestive processes of the principal nutrient groups, the locations where these processes occur and the enzymes involved.

SPOT CHECK

14. Describe the functions of hydrochloric acid in the stomach.

Metabolism

Learning outcomes

After studying this section, you should be able to:

- discuss general principles of metabolism, including units of energy, metabolic rate, catabolism and anabolism
- compare and contrast the metabolic fates of the body's main energy sources (carbohydrate, protein and fat)
- describe in simple terms the central metabolic pathways – glycolysis, the citric acid cycle and oxidative phosphorylation.

Metabolism constitutes all the chemical reactions that occur in the body to provide the chemical energy essential for all cellular activities. Units of energy, energy balance and metabolic rate are briefly outlined below before considering the metabolic pathways used to release energy from absorbed nutrients. Metabolism involves two types of processes:

$$\text{large molecules} \underset{\text{anabolism}}{\overset{\text{catabolism}}{\rightleftharpoons}} \text{small molecules}$$

Catabolism

Catabolic processes break down large molecules into smaller ones, releasing chemical energy, which is stored as adenosine triphosphate (ATP), and heat. The heat generated maintains core body temperature at the optimum level for chemical activity (36.8°C). Excess heat is dissipated, mainly through the skin (Ch. 14).

Anabolism

This is synthesis of large molecules from smaller ones and requires a source of energy, usually ATP.

Energy

All body cells need energy to carry out their metabolic processes, including cell division, tissue repair, muscle contraction and synthesis of glandular secretions.

The energy produced in the body may be measured and expressed in either units of work (joules) or units of heat (kilocalories).

A kilocalorie (kcal) is the amount of heat required to raise the temperature of 1 litre of water by 1 degree Celsius (1°C). The body's collective metabolic processes generate a total of about 3 million kilocalories daily.

$$1\ \text{kcal} = 4184\ \text{joules (J)} = 4.184\ \text{kilojoules (kJ)}$$

The nutritional value of carbohydrates, protein and fats eaten in the diet can be expressed in either kJ per gram or kcal per gram.

1 g of carbohydrate provides 17 kJ (4 kcal)
1 g of protein provides 17 kJ (4 kcal)
1 g of fat provides 38 kJ (9 kcal)

Energy balance is important, as it determines changes in body weight. Body weight remains constant when energy intake is equal to energy use. When intake exceeds requirement, body weight increases, which, when continual, will lead to obesity (Ch. 11). Conversely, body weight decreases when nutrient intake is less than energy requirements.

Metabolic rate

The metabolic rate is the rate at which energy is released from the fuel molecules inside cells. Because most metabolic processes use oxygen and produce carbon dioxide as waste, the metabolic rate can be estimated by measuring oxygen uptake or carbon dioxide excretion.

The basal metabolic rate (BMR) is the rate of metabolism when the individual is at rest in a warm environment and

Table 12.2 Summary of the sites of digestion and absorption of nutrients

	Mouth	Stomach	Small intestine		Large intestine
			Digestion	Absorption	
Carbohydrates	*Salivary amylase:* digestible starches to disaccharides	*Hydrochloric acid*: denatures and stops action of salivary amylase	*Pancreatic amylase*: digestible starches to disaccharides *Sucrase*, *maltase*, *lactase* (in enterocytes): disaccharides to monosaccharides (mainly glucose)	Into blood capillaries of villi	–
Proteins	–	*Hydrochloric acid*: pepsinogen to pepsin *Pepsin*: proteins to polypeptides	*Enterokinase* (in enterocytes): chymotrypsinogen and trypsinogen (from pancreas) to chymotrypsin and trypsin *Chymotrypsin and trypsin*: polypeptides to di- and tripeptides *Peptidases* (in enterocytes): di- and tripeptides to amino acids	Into blood capillaries of villi	–
Fats	–	–	*Bile* (from liver): bile salts emulsify fats *Pancreatic lipase*: fats to fatty acids and glycerol *Lipases* (in enterocytes): fats to fatty acids and glycerol	Into lacteals of villi	–
Water	–	Small amount absorbed here	–	Most absorbed here into lacteals of villi	Remainder absorbed here
Vitamins	–	Intrinsic factor secreted for vitamin B_{12} absorption	–	Water-soluble vitamins absorbed into capillaries; fat-soluble ones into lacteals of villi	Bacteria synthesise vitamin K in colon; absorbed here

is in the postabsorptive state, i.e. has not had a meal for at least 12 hours. In this state the release of energy is sufficient to meet only the essential (basal) needs of vital organs, such as the heart, lungs, nervous system and kidneys. Some of the many factors that affect metabolic rate are shown in Table 12.3.

Metabolic pathways

Anabolism and catabolism (see above) usually involve a series of chemical reactions, called metabolic pathways. These are linked sequences of small steps that permit controlled, efficient and gradual transfer of energy from ATP rather than large intracellular 'explosions'. Each step is catalysed (speeded up) by a specific enzyme. Metabolic pathways are switched on and off by hormones, providing fine control of metabolism that is adjusted to meet individual requirements at any given time.

Both catabolic and anabolic processes occur continually in all cells. Very active tissues, such as muscle and liver, need a large energy supply to support their metabolic requirements.

Central metabolic pathways

Much of the metabolic effort of cells is concerned with energy production to fuel cellular activities. Certain common pathways are central to this function. Fuel molecules enter these central energy-producing pathways, and their breakdown involves a series of steps. At each step an intermediate molecule is formed and energy is released; the end results of these processes are production of energy, carbon dioxide and water (called metabolic water). Much of the energy is stored as ATP, although some is lost as heat.

The preferred fuel molecule is glucose but alternatives, should glucose not be available, include amino acids, fatty acids, glycerol and occasionally nucleic acids. Each of these may enter the central energy-producing pathways and be converted to energy, carbon dioxide and water. There are three central metabolic pathways (see Fig. 12.46):

- glycolysis
- the citric acid (Krebs) cycle
- oxidative phosphorylation.

Products from glycolysis enter the citric acid cycle, and products from the citric acid cycle proceed to oxidative phosphorylation. The fates of the different fuel molecules entering the central metabolic pathways are discussed in the following sections.

Carbohydrate metabolism

Glucose is the preferred fuel source for most body cells. Digested carbohydrate, mainly glucose, is absorbed into

Table 12.3 Factors affecting metabolic rate

Factor	Effect on metabolic rate
Age	Gradually reduced with age
Sex	Higher in men than women
Height, weight	Relatively higher in larger people
Pregnancy, menstruation, lactation	Increased
Ingestion of food	Increased
Muscular activity, physical exertion	Increased
Elevated body temperature (fever)	Increased
Excess thyroid hormones	Increased
Emotional states	Increased
Starvation	Decreased

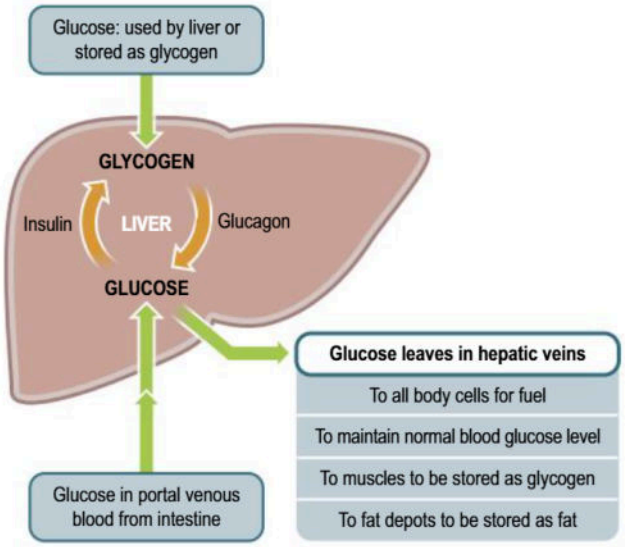

Figure 12.41 Summary of the source, distribution and use of glucose.

the blood capillaries in the villi of the small intestine. It is then transported by the portal circulation to the liver, where it is dealt with in several ways (Fig. 12.41):

- Glucose may be oxidised to provide the chemical energy, in the form of ATP, that is necessary for the intense metabolic activity that takes place in the liver itself (see functions of the liver, p. 345).
- Some glucose may remain in the circulating blood to maintain normal blood glucose levels between 3.5 and 8 mmol/L (63–144 mg/100 mL).
- Glucose in excess of the above requirements may be converted by the hormone insulin to the insoluble polysaccharide glycogen in the liver and skeletal muscle. The formation of glycogen inside cells is a means of storing carbohydrate without upsetting the osmotic equilibrium. Before it can be used to maintain blood levels or to generate ATP, it must be broken down again into its constituent glucose units. Liver glycogen is a store of glucose used for liver activity and for maintenance of blood glucose levels, while skeletal muscle glycogen stores generally provide the glucose required for physical activity. Glucagon, adrenaline (epinephrine) and thyroxine are the main hormones associated with the breakdown of glycogen to glucose. These processes can be summarised:

$$\text{glucose} \underset{\text{glucagon}}{\overset{\text{insulin}}{\rightleftharpoons}} \text{glycogen}$$

- Carbohydrate in excess of that required to maintain the blood glucose level and glycogen stores in liver and muscle is converted to fat and stored in adipose tissue.

Oxidation of carbohydrate and fat provides most of the energy required by the body. When glycogen stores are low and more glucose is needed, the body can make glucose from non-carbohydrate sources, e.g. amino acids, glycerol. This is called gluconeogenesis (formation of new glucose).

Carbohydrate and energy release

This is shown in Figure 12.41. Catabolism of glucose releases energy, carbon dioxide and metabolic water; it occurs in a series of steps, with a little energy released at each stage. The total number of ATP molecules that may be generated from the complete breakdown of 1 molecule of glucose is 38, but for this to be achieved the process must occur in the presence of oxygen (aerobic respiration). In the absence of oxygen, an anaerobic pathway must be used instead; ATP production is greatly reduced and so anaerobic respiration is much less efficient.

Aerobic respiration

Aerobic catabolism of glucose can occur only when the oxygen supply is adequate and is the process by which energy is released during prolonged, manageable exercise. When exercise levels become very intense, the energy requirements of muscles outstrip the oxygen supply, making anaerobic breakdown necessary. Such high levels of activity can be sustained for only short periods because, in addition to being less efficient, anaerobic respiration leads to accumulation of wastes, mainly lactate (the physiological form of lactic acid).

The first stage of glucose catabolism is glycolysis (Fig. 12.42), an anaerobic pathway that takes place in the cytoplasm of the cell. Through some intermediate steps, 1 glucose molecule is converted to 2 molecules of pyruvate, with the net production of 2 molecules of ATP.

The remainder of the considerable energy stores locked up within the original molecule of glucose is released only if there is enough oxygen to allow the pyruvate molecules to enter the biochemical roundabout called the citric acid cycle (Fig. 12.42). This takes place in the mitochondria of the cell

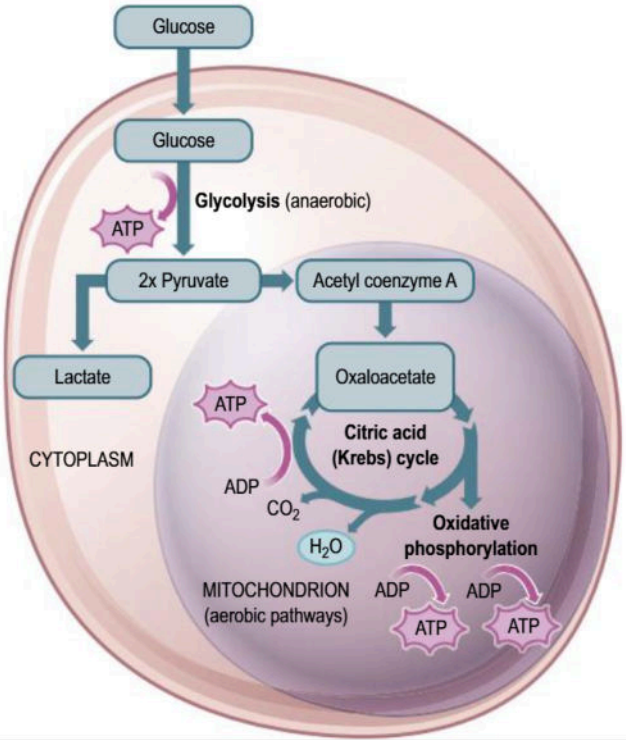

Figure 12.42 Oxidation of glucose. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

and is oxygen-dependent. For every 2 molecules of pyruvate entering the citric acid cycle, a further 2 molecules of ATP are formed, but this is still far short of the maximum possible 38 ATP molecules.

The remaining 34 molecules of ATP come from the third energy-generating process, oxidative phosphorylation (Fig. 12.42), which depends on hydrogen atoms released during earlier stages of glucose breakdown. Oxidative phosphorylation, like the citric acid cycle, can occur only in the presence of oxygen and takes place in the mitochondria.

Anaerobic respiration

When oxygen levels in the cell are low, the molecule of glucose still undergoes glycolysis and is split into 2 molecules of pyruvate because glycolysis is an anaerobic pathway. However, the pyruvate does not enter the citric acid cycle or progress to oxidative phosphorylation; instead, it is converted anaerobically to lactate. Build-up of lactate causes the pain and cramps typical of over-exercised muscles. When oxygen levels are restored, lactate is converted back to pyruvate, which may then enter the citric acid cycle.

Fate of the end products of carbohydrate metabolism

Lactate

Some of the lactate produced by anaerobic catabolism of glucose may be oxidised in the cells to carbon dioxide and water but first it must be changed back to pyruvate. If complete oxidation does not take place, lactate is converted in the liver to glucose and may then take any of the pathways open to glucose (see Fig. 12.41).

Carbon dioxide

This is excreted in expired air by the lungs.

Metabolic water

This is added to the water already present in the body, and excess is excreted in the urine by the kidneys.

Protein metabolism

Proteins are built from amino acids. About 20 amino acids have been named and 9 of these are described as essential because they cannot be synthesised in the body. The others are non-essential amino acids, so called, because they can be synthesised by many tissues. This process is called transamination and the enzymes involved are called transaminases (see Fig. 12.44).

In the small intestine, digestive enzymes break down dietary protein into its constituent amino acids ready for absorption into the blood capillaries of the villi. Amino acids are transported in the portal circulation from the small intestine to the liver and then into the general circulation, thus making them available to all body cells. From the amino acids available, different cells choose from the particular ones required for their own needs.

Amino acid pool

The body's capacity for storing amino acids is very limited and excess amino acids are deaminated in the liver. A small pool of amino acids (Fig. 12.43) is available to body cells to draw on when they need to synthesise their own materials, e.g. new cells or cell components, secretions such as enzymes, hormones, antibodies and plasma proteins.

Sources of amino acids

Exogenous

These are derived from dietary protein.

Endogenous

These are obtained from the breakdown of existing body proteins. In adults, about 80–100 g of protein are broken down and replaced each day.

Loss of amino acids

Deamination

Amino acids not needed by the body are broken down, or deaminated, mainly in the liver. The nitrogenous part, the amino group (NH_2), is converted to ammonia (NH_3) and then combined with carbon dioxide, forming urea, which is excreted in the urine. The remaining non-nitrogenous part

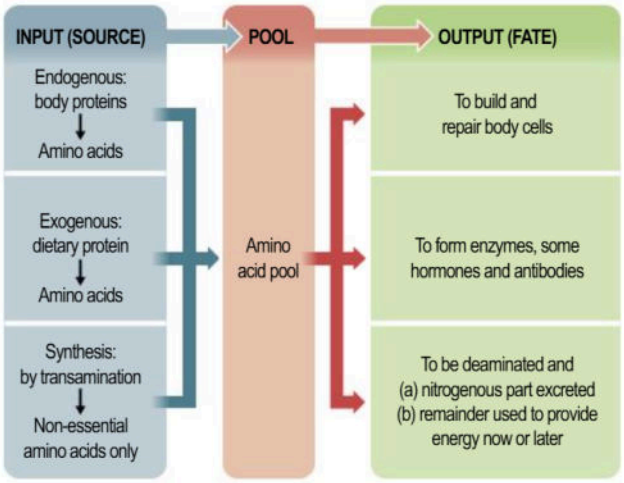

Figure 12.43 Sources and use of amino acids in the body.

is used to provide energy, as glucose by gluconeogenesis, or stored as fat, if in excess of immediate requirements.

Excretion

The faeces contain a considerable amount of protein within cells shed from the lining of the alimentary tract.

Nitrogen balance

Endogenous and exogenous amino acids are mixed in the pool; the body is said to be in nitrogen balance when the rate of removal from the pool is equal to the rate of addition to it. Unlike carbohydrates, the body cannot store amino acids except for this relatively small pool. Figure 12.44 summarises what happens to amino acids in the body.

Amino acids and energy release

Amino acids are potential fuel molecules but are only used for this purpose when other energy sources are low, e.g. in starvation. To supply the amino acids for use as fuel, in extreme situations, the body breaks down muscle, its main source of protein. Some amino acids can be converted directly to glucose, which enters glycolysis. Other amino acids are metabolised to intermediate compounds of the central metabolic pathways, e.g. acetyl coenzyme A or oxaloacetate, and therefore enter the system at a later stage (see Fig. 12.46).

Fat metabolism

This is shown in Figure 12.45. Fat is synthesised from excess dietary carbohydrates and proteins, and stored in the fat depots, i.e. under the skin, in the omentum or around the kidneys.

Fats that have been digested and absorbed as fatty acids and glycerol into the lacteals are transported by the lymphatic system via the cisterna chyli and the thoracic

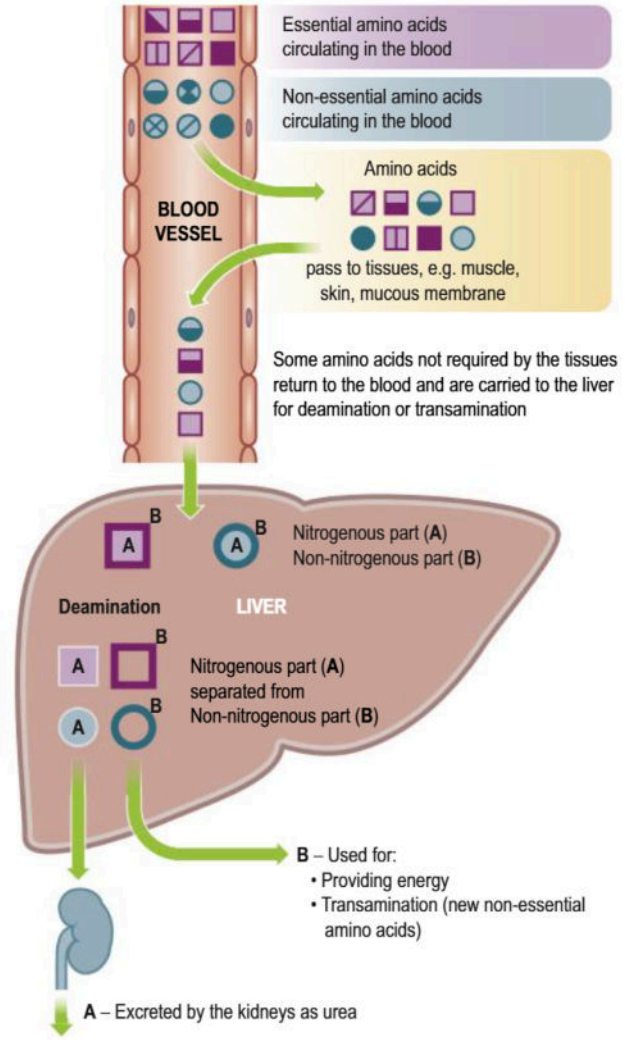

Figure 12.44 The fate of amino acids in the body.

duct (Ch. 6) to the bloodstream and to the liver. Fatty acids and glycerol circulating in the blood are used by the cells to provide energy and to synthesise some of their secretions. In the liver, some fatty acids and glycerol are metabolised to provide energy and heat, and some are recombined, forming triglycerides, the form in which fat is stored. A triglyceride consists of three fatty acids chemically combined with a glycerol molecule (see Fig. 2.9). When required, triglycerides are converted back to fatty acids and glycerol, and catabolised to provide energy. The end products of fat metabolism are chemical energy, heat, carbon dioxide and metabolic water.

Fatty acids and energy release

When body tissues are deprived of glucose, as in prolonged fasting, starvation, energy-restricted diets or strenuous exercise, the body uses alternative energy sources, mainly fat stores. Fatty acids may be converted to acetyl coenzyme A

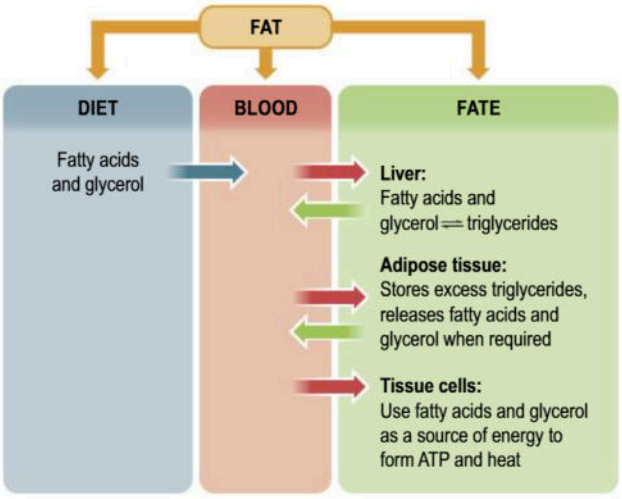

Figure 12.45 Sources, distribution and use of fats in the body. ATP, adenosine triphosphate.

and enter the central metabolic pathways in that form. One consequence of this is accumulation of ketone bodies, which are produced in the liver from acetyl coenzyme A when levels are too high for processing through the citric acid cycle (Fig. 12.46). Ketone bodies then enter the blood and can be used by other body tissues, including the brain, which is usually glucose-dependent, as a source of fuel. However, at high concentrations, ketone bodies are toxic, particularly to the brain. Ketone bodies include acetone and some weak organic acids. Normally, blood levels are low because they are used as soon as they are produced. When production exceeds use, in the situations mentioned earlier, levels rise, causing ketosis. Ketosis is associated with acidosis, which can lead to coma or even death if severe. Excretion of excess ketone bodies is via:

- the urine (ketonuria)
- the lungs, giving the breath a characteristic sweet smell of acetone (nail varnish remover).

In ketosis, compensation is required to maintain acid–base balance. This is achieved by buffer systems that excrete excess acid (hydrogen ions) either by the lungs, through hyperventilation, or kidneys. In health, ketosis is self-limiting and ketone body production stops when fasting or exercise ceases. Ketoacidosis is associated with uncontrolled type 1 diabetes mellitus (p. 261).

Glycerol and energy release

The body converts glycerol from the degradation of fats into one of the intermediary compounds produced during glycolysis, and in this form it enters the central metabolic pathways (Fig. 12.46).

SPOT CHECK

15. Define the terms 'anabolism' and 'catabolism'.
16. Name the three central metabolic pathways.

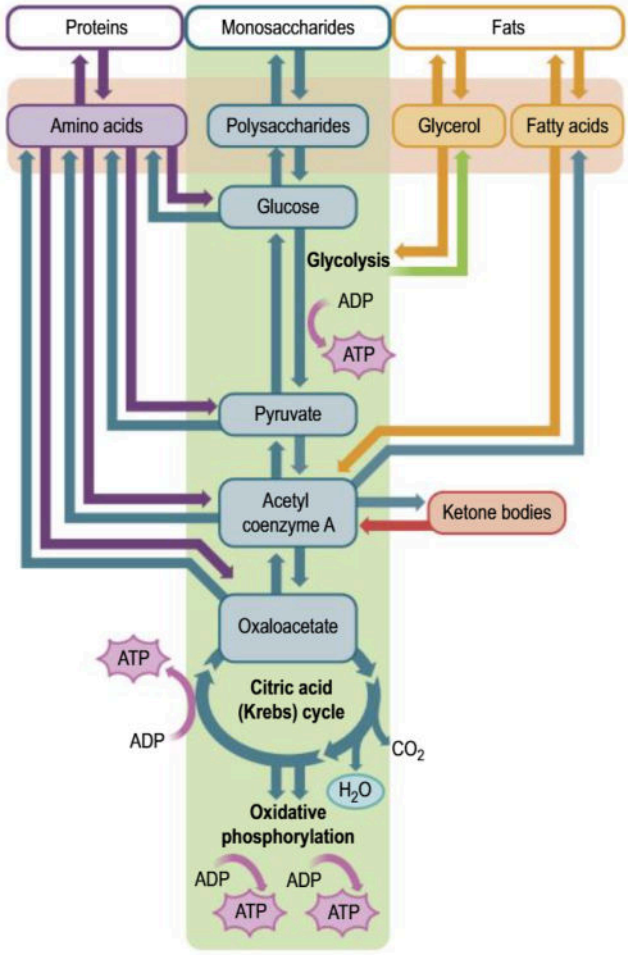

Figure 12.46 Summary of the fates of the three main energy sources in the central metabolic pathways. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Effects of ageing on the digestive system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the digestive system.

Tooth loss, e.g. through periodontal disease, may cause difficulty chewing, which in turn restricts dietary choices. A reduction in the muscle mass of the tongue and lessened salivation can exacerbate this. The sensitivity and number of taste buds decline with age, and can make food taste bland.

Peristalsis within the alimentary canal reduces, which predisposes to constipation (Ch. 11). Other features of ageing, such as lessened mobility or poor cognitive function, also contribute to constipation (see Fig. 12.47)

unless dietary fibre is increased and an adequate fluid intake is maintained.

Liver mass decreases with age and this is accompanied by a variable decline in its reserve capacity, which can impair metabolism, including breakdown of drugs; this in turn may lead to toxicity.

In older adults there is a reduction in skeletal muscle mass and its responsiveness to hormones, including adrenaline (epinephrine), noradrenaline (norepinephrine) and thyroid hormones. Together, these lower BMR. Limited physical activity or inactivity also reduces BMR. A reduction in BMR that is not accompanied by a lower dietary intake predisposes to obesity and its consequences (Ch. 11).

SPOT CHECK

17. Explain briefly why older adults are at increasing risk of drug toxicity.

This section considers disorders of the digestive system. Table 12.4 and Figure 12.47 list some common signs and symptoms of gastrointestinal disorders.

Diseases of the mouth

Learning outcomes

After studying this section, you should be able to:

- discuss the main inflammatory and infectious conditions of the mouth
- outline the sites and effects of oral squamous cell carcinoma
- compare and contrast the anatomical abnormalities in cleft lip and cleft palate.

Inflammatory and infectious conditions

Injury may be caused to tissues in and around the mouth by food and other ingested substances, if they are corrosive, abrasive or excessively hot or cold. The mouth contains a large number and variety of normally harmless commensal microorganisms. The antibacterial action of saliva helps to limit their growth, but the presence of dental plaque and residual foodstuffs, especially sugars, in the mouth can promote infection. Inflammation of the mouth is known as stomatitis, and inflammation of the gums as gingivitis.

Figure 12.47 Bristol Stool Form Scale. (Distributed with the kind permission of Dr K. W. Heaton; formerly reader in Medicine at the University of Bristol. Reproduced as a service to the medical profession by Norgine Ltd. ©2017 Norgine group of companies.)

Table 12.4 Common signs and symptoms of gastrointestinal disorders

Sign/symptom	Definition and description
Abdominal pain	Caused by stretching of smooth muscle or organ capsules. The location is described with reference to the regions of the abdomen (see Fig. 1.26)
Anorexia	Loss of appetite that prevents or markedly reduces eating. When severe and ongoing, it is accompanied by weight loss
Constipation	Passage of faeces less frequently than normal and/or passage of hard faeces (Fig. 12.47). Normal frequency varies greatly between individuals, ranging between 3 times daily to 3 times per week
Diarrhoea	Unusually frequent passage of loose or watery faeces. Normally, most fluid in the gastrointestinal tract is reabsorbed (see Fig. 12.29). Diarrhoea (Fig. 12.47) arises when water reabsorption from the intestines is reduced and/or intestinal motility is increased
Dysphagia	Difficulty swallowing
Haematemesis	Vomiting of blood, either fresh (red or purplish) or black when partly digested (described as 'coffee grounds')
Melaena	Passing blood in the faeces which are black and tarry. Very small amounts are found only by testing for faecal occult (hidden) blood (FOB)
Nausea	A feeling of sickness, which usually precedes vomiting. It may be accompanied by profuse salivation and tachycardia
Steatorrhoea	Passing fatty faeces; foul smelling, pale and bulky; typically float and difficult to flush
Vomiting	An (involuntary) reflex that forcefully ejects stomach contents through the mouth. Vomiting follows stimulation of, for example, the pharynx, oesophagus, stomach or the vomiting centre in the medulla, e.g. by drugs. Coordinated by the medulla; the glottis closes, the diaphragm contracts, the upper oesophageal sphincter relaxes; strong waves of reverse peristalsis in the stomach then expel its contents upwards. If severe, consequences include disturbance of fluid, electrolyte and acid–base balance (metabolic alkalosis, as excessive H^+ is lost)

Oral candidiasis

Also known as thrush, this acute fungal infection is caused by the commensal yeast-like fungus *Candida albicans*, which grows in white patches on the tongue and oral mucosa. In adults it causes opportunistic infection, mainly in debilitated people and in those whose immunity is suppressed, e.g. by antibiotics, oral steroids, or cytotoxic drugs. In children it mostly affects babies when oral abrasions from a bottle teat or a dummy become colonised with *Candida albicans*.

Chronic thrush may affect the roof of the mouth in people who wear dentures. The fungus survives in fine grooves on the upper surface of the denture and repeatedly reinfects the oral mucosa. The same fungus is also a vaginal commensal (see Ch. 18).

Gingivitis

This is inflammation of the gums, which may be acute or, much more commonly, chronic. Chronic gingivitis is a common condition caused by accumulation of bacterial plaque around the teeth. The gums bleed easily and ongoing inflammation gradually destroys the tissues that support the teeth, which eventually loosen and may fall out.

Aphthous ulceration

This common and often recurrent condition affects up to 25% of the population. Extremely painful mucosal ulcers develop, either singly or in crops anywhere in the mouth. They usually resolve spontaneously in 7–10 days. The cause is unknown but is sometimes associated with inflammatory bowel disease or coeliac disease.

Viral infections

These are usually caused by the herpes simplex virus, HSV-1.

Acute herpetic gingivostomatitis

Inflammation of the mouth and gums is caused by HSV-1, the most common oral viral infection. It is characterised by extensive and very painful ulceration.

Secondary or recurrent herpes lesions (cold sores)

These lesions, also caused by HSV-1, occur around the nose and on the lips. After an outbreak, the viruses remain dormant within local nerves. Later outbreaks, usually at the same site, are precipitated by a variety of stimuli, including exposure to ultraviolet rays (strong sunlight) and impaired immunity.

Tumours of the mouth

Squamous cell carcinoma

This accounts for 95% of malignant oral tumours and mainly affects older adults. The usual sites are the floor of the mouth and the edge of the tongue. Ulceration occurs frequently and there is early spread to surrounding tissues and cervical lymph nodes, in which case the prognosis is poor.

Congenital disorders

Cleft palate and cleft lip (harelip)

During embryonic development, the roof of the mouth (hard palate) develops as two separate (right and left) halves; this occurs from the lips anteriorly to the uvula posteriorly. Before birth, these two halves normally fuse along the midline (Fig. 12.48A). If fusion is incomplete, a cleft (division) remains, which may be either very minor or substantial.

Cleft lip (Fig. 12.48B) ranges from a minor notch in the upper lip to a more extensive condition when the lip is completely split in one or two places and the nose is also involved.

In cleft palate, incomplete fusion leaves a gap between the two halves of the palate, which creates a channel of communication between the mouth and the nasal cavity (Fig. 12.48C).

Contributing factors include genetic abnormalities, some anticonvulsant drugs or poor nutrition before week 10 of pregnancy. In severe cases, surgical repair is needed to enable infant feeding and speech development.

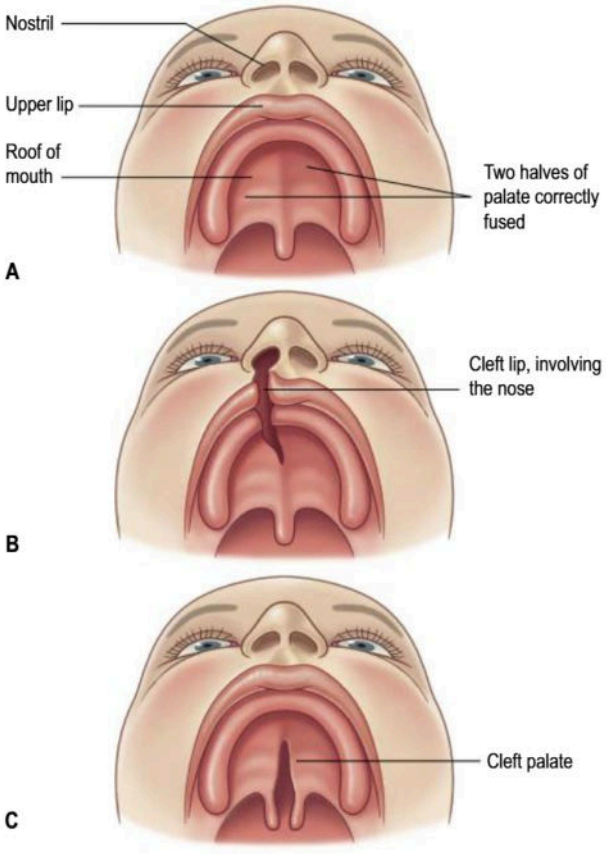

Figure 12.48 Cleft lip and cleft palate. (A) Normal hard palate. (B) Cleft lip. (C) Cleft palate.

Dental caries

Tooth decay starts with discoloration and then formation of cavities (caries). It arises when bacteria present in plaque on the teeth act on sugars, forming acid, which may eventually destroy the hard parts of the teeth. Caries can be prevented by good oral hygiene.

Without treatment, infection, inflammation of the soft tissues of the mouth and loss of teeth can occur.

SPOT CHECK

18. Which organism causes oral thrush?

Diseases of the pharynx

See tonsillitis (p. 291) and diphtheria (p. 292).

Diseases of the salivary glands

Learning outcomes

After studying this section, you should be able to:

- outline the pathophysiology of mumps
- describe the most common tumours of the salivary glands.

Mumps (parotitis)

This is an acute inflammatory condition of the salivary glands, especially the parotids. It is caused by the mumps virus, one of the parainfluenza group. The virus is spread by inhalation of infected droplets. Viruses multiply elsewhere in the body before spreading to the salivary glands. The virus is most infectious for 1–2 days before and 5 days after symptoms appear. Although most common between 5 and 15 years, mumps also affects adults and is often a more serious infection; about 25% of adult males suffer from testicular inflammation (orchitis), which can result in atrophy and occasionally sterility. Complications that affect the brain, including meningitis and meningoencephalitis (Ch. 7), may arise at any age.

In high-income countries, preschool children are routinely vaccinated against mumps.

Tumours of the salivary glands

These are rare and 80% affect the parotid glands. There are many types, both benign and malignant; about 75% are benign.

SPOT CHECK

19. Which infection of the salivary glands forms part of childhood immunisation programmes in many countries?

Diseases of the oesophagus

Learning outcomes

After studying this section, you should be able to:

- explain how oesophageal varices develop
- discuss the main inflammatory conditions of the oesophagus
- describe the main oesophageal tumours.

Oesophageal varices

In conditions such as cirrhosis (p. 369) or venous thrombosis, blood flow into the liver via the portal vein is impeded and blood pressure within the portal system rises; this is called portal hypertension. This forces blood from the portal vein into anastomotic veins, which shunt blood into the systemic venous circulation, bypassing the liver (Fig. 12.49). Fifty per cent or more of the portal blood may be shunted into anastomotic veins, increasing the pressure in these veins too. One route taken by the shunted blood is into veins of the lower oesophagus, which then become distended and weakened by the abnormally high volume of blood.

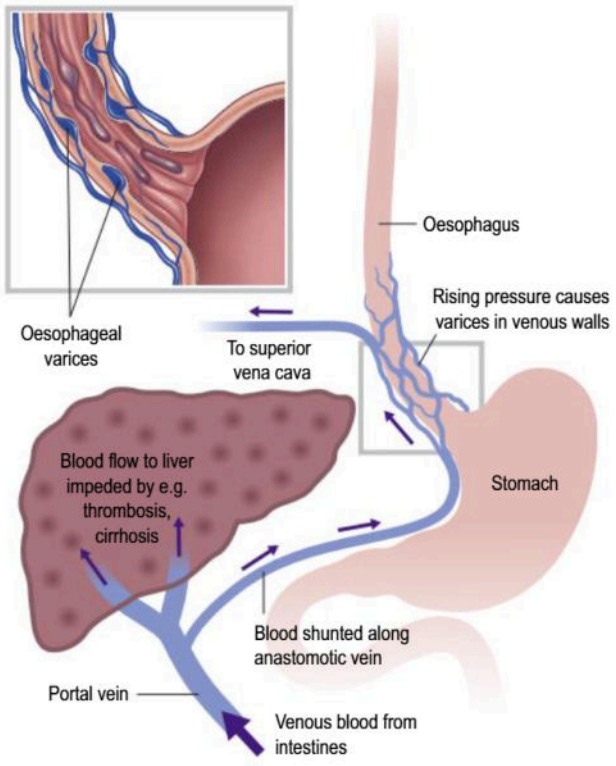

Figure 12.49 Oesophageal varices.

Varices (localised dilations of veins) develop when the weakest regions of the vessel wall bulge outwards into the lumen of the oesophagus; being thin-walled and fragile, they are easily eroded or traumatised by swallowed food. Bleeding may be minor but chronic, leading to iron deficiency anaemia (p. 77); however, sudden rupture can cause life-threatening haemorrhage.

Inflammatory and infectious conditions

Acute oesophagitis

This may be due to swallowing of caustic substances, or by infections. Immunocompromised people may acquire severe fungal infections, typically candidiasis see above, or viral infections such as herpes simplex. Dysphagia (difficulty in swallowing) is usually present. Following severe injury, healing often causes fibrosis, and as the fibrous tissue shrinks, there is a risk of oesophageal stricture.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD), the most common cause of indigestion (heartburn), is caused by persistent regurgitation of acidic gastric juice into the oesophagus, causing irritation, inflammation and painful ulceration. Haemorrhage occurs when blood vessels are eroded. Persistent reflux leads to chronic inflammation, and if damage is extensive, secondary healing with fibrosis occurs. As fibrous tissue matures, it shrinks and may cause stricture of the oesophagus. When chronic, GORD can lead to Barrett's oesophagus (see below). Reflux of gastric contents is associated with:

- an increase in intra-abdominal pressure, e.g. in pregnancy, constipation and obesity
- low levels of the hormone gastrin, which reduce the activity of the lower oesophageal sphincter
- hiatus hernia (Fig. 12.54C).

Barrett's oesophagus

This is a premalignant condition usually associated with long-standing GORD; it is sometimes accompanied by a hiatus hernia (Fig. 12.54C). Columnar epithelial cells resembling those found in the stomach replace the squamous epithelium of the lower oesophagus. This is a protective response to the continual acid reflux and its associated inflammation.

Tumours of the oesophagus

Benign tumours are rare, accounting for only 5% of oesophageal tumours.

Malignant tumours

These occur more often in males than in females. They are most common in the lower oesophagus, but can arise at any level. There are two types:

- Squamous cell carcinoma is the more prevalent form worldwide accounting for about 80% of oesophageal cancers and predominant in Asia and Africa. It is associated with excessive alcohol intake, obesity and cigarette smoking.
- Adenocarcinoma is the more common type in Europe and North America and is usually associated with GORD and/or Barrett's oesophagus (see above).

Both types begin as an ulcer that spreads round the circumference, causing an oesophageal stricture that results in dysphagia. By the time of diagnosis, local spread has occurred in some 66% of patients and the prognosis is very poor with under 10% surviving for two years.

Achalasia

In this condition, peristalsis of the lower oesophagus is impaired and the lower oesophageal sphincter fails to relax during swallowing. This leads to accumulation of food and drink in the oesophagus, dysphagia, regurgitation of gastric contents and aspiration pneumonia. The oesophagus becomes dilated and the muscle layer hypertrophies. The autonomic nerve supply to the oesophageal muscle is abnormal but the cause is not known. Achalasia may occur at any age but is most common in middle life.

Congenital disorders

The most common congenital disorders of the oesophagus are:

- oesophageal atresia, in which the lumen is narrow or blocked
- tracheo-oesophageal fistula, in which there is an opening (fistula) between the oesophagus and the trachea through which milk or regurgitated gastric contents are aspirated.

One or both abnormalities may be present. The causes are unknown.

SPOT CHECK

20. Identify two congenital abnormalities of the oesophagus.

Diseases of the stomach

Learning outcomes

After studying this section, you should be able to:

- compare the main features of chronic and acute gastritis
- discuss the pathophysiology of peptic ulcer disease
- describe the main tumours of the stomach and their consequences
- define the term 'congenital pyloric stenosis'.

Gastritis

Inflammation of the stomach can be an acute or chronic condition.

Acute gastritis

This is usually a response to irritant drugs or alcohol, especially binge drinking. The most commonly implicated drugs are non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin. Other causes include ingestion of corrosive substances and severe physiological stress, e.g. extensive burns and multiple organ failure.

There are varying degrees of severity. Mild cases can be asymptomatic or may present with nausea and vomiting associated with inflammatory changes of the gastric mucosa. Erosions are areas of tissue loss affecting the superficial layers of the gastric mucosa. These may lead to mild bleeding, which can become chronic; the situation is worsened when the mucus-secreting mucosal cells are also affected and the normally protective effect of mucus is lost. In more serious cases, multiple erosions may result in life-threatening haemorrhage, causing haematemesis (see Table 12.4) and melaena (see Table 12.4), especially in older adults.

The outcome depends on the extent of the damage. In many cases, recovery is speedy and uneventful after the cause is removed. Where there has been extensive tissue damage, healing is by fibrosis, causing reduced elasticity and peristalsis.

Chronic gastritis

Chronic gastritis is a milder but longer-lasting condition. Haematemesis is rare but otherwise, the signs and symptoms are less severe but longer lasting than in acute cases. It is usually associated with *Helicobacter pylori* infection but is sometimes due to autoimmune disease or chemical injury. It is more common in later life.

Helicobacter-associated gastritis

H. pylori is an acid-resistant bacterium that colonises the gastric mucosa and is commonly associated with chronic gastritis and peptic ulcer disease (see below).

Autoimmune chronic gastritis

This is a progressive autoimmune disease; the causes are not known but there is a familial predisposition and an association with autoimmune thyroid disorders. Destructive inflammatory changes that begin on the surface of the mucous membrane may extend to affect its whole thickness, including the gastric glands. At this stage, secretion of hydrochloric acid and intrinsic factor is markedly reduced because the target antigens are the gastric parietal cells and sometimes intrinsic factor too. Consequences include development of pernicious anaemia due to deficiency of intrinsic factor (p. 78) and increased risk of stomach cancer.

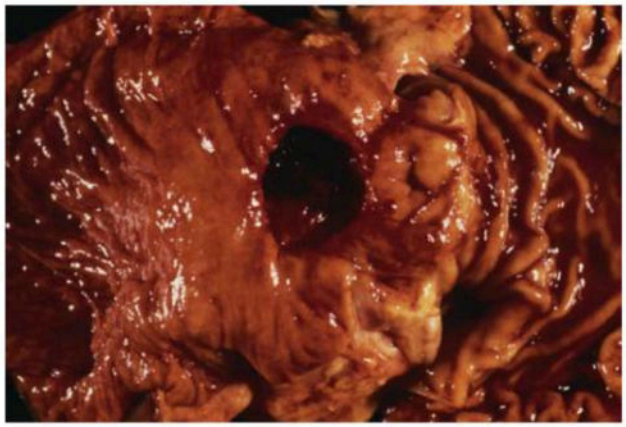

Figure 12.50 Peptic ulceration. A large duodenal ulcer. (CNRI/Science Photo Library. Reproduced with permission.)

Peptic ulcer disease

Peptic ulcers involve the full thickness of the gastrointestinal mucosa and often also penetrate the submucosa and muscle layer of the stomach or duodenum (Fig. 12.50). They may be viewed as an extension of the superficial gastric erosions found in acute gastritis. The duodenum is affected 2–3 times more often than the stomach. Burning epigastric pain is a classic symptom of peptic ulceration and is sometimes accompanied by nausea.

H. pylori infection is very common and is thought to be acquired during childhood. It affects up to 50% of adults aged over 50 in Western countries although in low-income countries up to 90% are infected. The incidence has markedly reduced in countries where antibiotic eradication therapy is widespread. Most people remain healthy and asymptomatic and only a minority develop symptoms. *H. pylori* is strongly associated with peptic ulcer disease, being found in 90% of people with duodenal ulcers and 70% of those with gastric ulcers. Most other gastric ulcers are attributed to the use of non-steroidal anti-inflammatory drugs (NSAIDs). Smoking predisposes to peptic ulceration and delays healing. The incidence of peptic ulcers is greater in men than in women and increases with age.

Pathophysiology

Peptic ulcers are caused by disruption of the normal balance between the corrosive effect of gastric juice and the protective effect of mucus on the gastric epithelial cells. If gastric mucosal protection is impaired, the epithelium can be exposed to gastric acid, causing the initial damage that leads to ulceration. The main mechanisms that protect against peptic ulceration are a good blood supply, adequate mucus secretion and efficient epithelial cell replacement.

Blood supply. Reduced blood flow and ischaemia may be caused by cigarette smoking and severe stress, either physical

or mental. The sympathetic nerve activity that accompanies stress causes vasoconstriction reducing the blood supply to the alimentary tract.

Secretion of mucus. The composition and the amount of mucus may be altered, for example:

- by regular and prolonged use of aspirin and other anti-inflammatory drugs
- by the reflux of bile acids and salts from the duodenum
- in chronic gastritis.

Epithelial cell replacement. There is normally a rapid turnover of gastric and intestinal epithelial cells. This may be reduced:

- by raised levels of steroid hormones, e.g. in response to stress or when used as therapeutic treatment
- in chronic gastritis
- by radiotherapy and cytotoxic drugs.

Acute peptic ulcers

These are found in many sites in the stomach and in the first few centimetres of the duodenum and may be single or multiple. Their development is often associated with acute gastritis, severe stress, e.g. severe illness, shock, burns, severe emotional disturbance and following major surgery. Healing without the formation of fibrous tissue usually occurs when the stressor is removed. Haemorrhage and perforation may be life-threatening complications (see below).

Chronic peptic ulcers

These ulcers are 2–3 times more common in the duodenum than in the stomach; occasionally they affect the lower oesophagus or a surgical anastomosis anywhere between the oesophagus and small intestine, e.g. after partial gastrectomy. They are often recurrent and usually occur singly in the pylorus of the stomach or in the duodenum. Healing occurs with the formation of fibrous tissue which may shrink and cause:

- stricture of the lumen of the stomach
- gastric outflow obstruction or stenosis of the pyloric sphincter
- adhesions to adjacent structures, e.g. pancreas, liver or transverse colon.

Complications of peptic ulcers

Perforation. When an ulcer erodes through the full thickness of the wall of the stomach or duodenum, GI contents enter the peritoneal cavity, causing acute peritonitis (p. 365).

Infected inflammatory material may collect under the diaphragm, forming a subphrenic abscess (see Fig. 12.53), and the infection may spread through the diaphragm to the pleural cavity.

Haemorrhage. When a major artery is eroded, a serious and potentially life-threatening haemorrhage may occur, causing shock (p. 127), haematemesis and/or melaena.

Anaemia. Chronic, persistent, low-grade bleeding from an ulcer may lead to development of iron deficiency anaemia (p. 77).

Gastric outflow obstruction. Also known as pyloric stenosis, fibrous tissue formed as an ulcer in the pyloric region heals and gradually shrinks as it matures, narrowing the pylorus. This obstructs outflow from the stomach, and results in persistent vomiting.

Malignancy. See below.

Tumours of the stomach

Benign tumours of the stomach are rare.

Malignant tumours of the stomach

Gastric cancer accounts for the third highest number of cancer-related deaths worldwide. Adenocarcinoma is the commonest gastric malignancy. It occurs twice as frequently in men than in women and the incidence peaks between 50 and 70 years of age. The causes remain unclear but 60%–70% of cases are associated with *H. pylori* infection. Smoking, alcohol and diets high in salted, smoked and pickled food have also been implicated.

Local growth of the tumour gradually destroys the normal tissue so that achlorhydria (reduced hydrochloric acid secretion) and pernicious anaemia are common secondary features. As the tumour grows, the surface may ulcerate and become infected, especially when achlorhydria develops.

This condition usually carries a poor prognosis because it is asymptomatic until at an advanced stage, by which time it has already spread. Local spread is to adjacent organs, e.g. the oesophagus, duodenum and pancreas, and also to the peritoneal cavity when the outermost layer, the serosa, is affected. Spread via the blood is by the hepatic portal vein to the liver, where tumour cells may lodge, causing metastases. Lymphatic spread is initially to nearby nodes and later to more distant ones.

Congenital pyloric stenosis

In this condition there is spasmodic constriction of the pyloric sphincter, characteristic projectile vomiting and failure to put on weight. In an attempt to overcome the spasms, hypertrophy of the muscle of the pylorus develops, causing pyloric obstruction with projectile vomiting 2–3 weeks after birth. The cause is unknown but there is a familial tendency and the condition is much more common in boys.

SPOT CHECK

21. Name the two most common causes of peptic ulceration.

Diseases of the intestines

Learning outcomes

After studying this section, you should be able to:

- discuss the principal infectious disease of the intestines
- compare and contrast the features of Crohn's disease and ulcerative colitis
- distinguish between diverticulitis and diverticulosis
- describe the main intestinal tumours
- describe appendicitis and its consequences
- describe the abnormalities present in hernia, volvulus and intussusception.

Diseases of the small and large intestines are described together because they have certain characteristics in common and some conditions affect both.

Gastrointestinal infections

The incidence of these diseases varies considerably but they represent a major cause of morbidity and mortality worldwide; many are highly contagious. Public health measures, including clean, safe drinking water and effective sewage disposal, and safe food hygiene practices greatly reduce their transmission. As most of these infections are spread by the faeco-oral route, meticulous handwashing after defaecation and contact with any potentially contaminated material is essential, especially in healthcare facilities. Contaminated drinking water causes diarrhoeal diseases that are a major cause of illness in all age groups and of infant death in low-income countries.

Typhoid and paratyphoid (enteric) fever

Typhoid and paratyphoid fevers are caused by *Salmonella typhi* and *S. paratyphi* A or B, respectively. Their only hosts are humans. Both are common in some tropical countries and both are spread by the faeco-oral route from food, water or any items contaminated by individuals who either have the illness or are carriers (see below).

Typhoid fever

The incubation period is about 10–14 days, during which time ingested bacteria invade the lymphoid tissue of the small intestine, especially the aggregated lymph follicles (Peyer's patches). Thereafter, the bacteria spread via the blood to the liver, spleen and gall bladder. A fever follows, accompanied by malaise, headache, drowsiness and aching limbs. The intestinal lymphoid tissue becomes acutely inflamed and ulcerated, although healing usually follows.

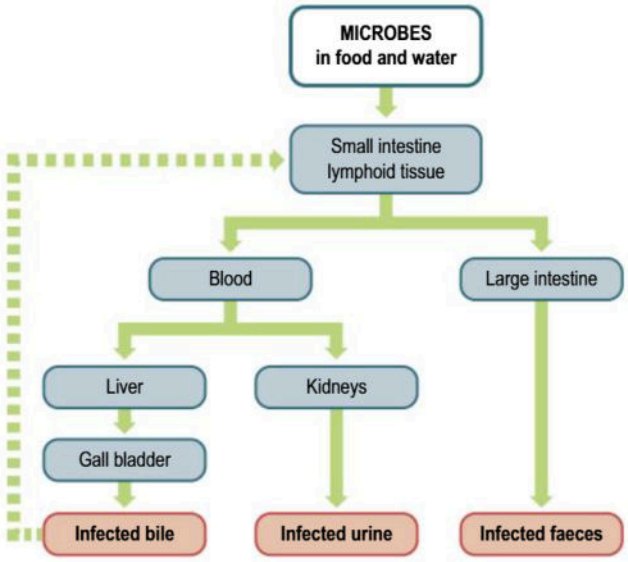

Figure 12.51 The routes of excretion of microbes in typhoid and paratyphoid (enteric) fever.

The spleen becomes enlarged (splenomegaly) and red spots are typically seen on the skin, especially on the chest and back.

Typhoid fever is serious and often fatal without treatment. Complications due to spread of microbes during the febrile phase include pneumonia, meningitis and typhoid cholecystitis, in which microbes multiply in the gall bladder and are secreted in the bile, reinfecting the intestine (Fig. 12.51). Bacterial toxins can cause disorders of the heart and kidneys (nephritis, Ch. 13). In the bowel, ulcers may perforate a blood vessel wall, resulting in severe haemorrhage, or erode the intestinal wall, causing acute peritonitis.

Up to 5% of cases become carriers with asymptomatic but chronic infection of the gall bladder. Continued multiplication and release of microbes into the bile for months or years after recovery leads to ongoing infection of the faeces (Fig. 12.51). Occasionally, the urinary system is also involved and microbes are released into the urine. Carriers may transmit the infection through their infected faeces or urine.

Paratyphoid fever

This follows a similar course but is usually milder and shorter-lasting. The onset can be more sudden although complications are less frequent. Some people may become carriers, but fewer than in typhoid fever.

Other *Salmonella* infections

Salmonella typhimurium and *S. enteritidis* are the most common bacteria in this group and cause infection worldwide. Hosts include domestic animals and birds in addition to humans. The microbes may be present in meat, poultry, eggs and milk, causing infection if food is not sterilised by cooking.

Mice and rats also carry the organisms and may contaminate food before or after cooking.

Generally, the effects are confined to the gastrointestinal tract, unlike the *Salmonella* infections described above. The incubation period is 12–72 hours; enteritis is usually short-lived and accompanied by acute abdominal pain, diarrhoea and sometimes vomiting, which may cause dehydration and electrolyte imbalance. In children, immunosuppressed people and debilitated older adults the infection may be severe and occasionally fatal.

Escherichia coli food poisoning

The severity of the disease depends on the strain of *E. coli* responsible. Certain strains of *E. coli* are commensal flora (normally present) in the healthy gastrointestinal tract; other strains are pathogenic, some being more virulent than others. Common sources of pathogenic strains include under-cooked meat and unpasteurised milk; adequate cooking of meat and pasteurisation of milk kill *E. coli*. Outbreaks of *E. coli* food poisoning can cause fatalities, particularly in young children and older adults.

Staphylococcal food poisoning

This is transmitted from the hands of those preparing food; the risk of food poisoning increases when inappropriate storage then supports rapid bacterial multiplication. When consumed in contaminated food, *S. aureus* releases enterotoxins that cause acute gastroenteritis. Although cooking kills the bacteria, the enterotoxins are heat-resistant.

The enterotoxins cause acute but short-lived gastroenteritis with violent vomiting occurring 2–4 hours after ingestion, which may lead to dehydration and electrolyte imbalance. Diarrhoea is often insignificant. In most cases, complete recovery occurs within 24 hours.

Clostridium perfringens food poisoning

These commensal anaerobic, spore-forming bacteria are normally present in the intestines of humans and animals but can cause food poisoning when ingested in large numbers. Bacterial spores may become a source of food poisoning; large outbreaks are generally associated with industrial catering, e.g. in schools and hospitals. When meat or poultry is cooled slowly and/or stored in unrefrigerated conditions and/or prepared in advance and kept warm for several hours before serving, dormant microbial spores germinate into viable bacteria, which then multiply very rapidly. When the ingested bacteria reach the intestines, they release powerful enterotoxins that cause watery diarrhoea and severe abdominal pain. The illness is usually self-limiting.

Antibiotic-associated diarrhoea

The bacterium *Clostridium difficile* is commonly present in the large intestine without causing symptoms. However, after antibiotic therapy many other commensal intestinal bacteria die. This allows *C. difficile* to proliferate, releasing toxins that damage the mucosa of the large intestine and causing profound diarrhoea. Hospitalised older adults are most affected and are highly susceptible to severe and life-threatening colitis.

Campylobacter food poisoning

These Gram-negative bacilli are a common cause of gastroenteritis, which affects mainly young adults and children under 5 years, especially in low-income countries. These bacteria are commensals present in the intestines of birds and animals, and transmitted to humans in under-cooked poultry and meat. They may also be spread in contaminated water and milk. After an incubation period of 2–4 days, nausea, vomiting and acute abdominal cramps develop; this is usually followed by spontaneous recovery within a few days.

Cholera

Cholera is caused by *Vibrio cholerae*, which is spread by the faeco-oral route. The only known hosts are humans. Most infected people are asymptomatic, but they can transmit the condition to others for 1–10 days after infection. A powerful enterotoxin released by ingested bacteria stimulates the intestinal glands to secrete large quantities of water, bicarbonate and chloride. When symptomatic, cholera is usually mild and self-limiting but sometimes watery diarrhoea, severe dehydration and electrolyte imbalance develop rapidly, and subsequent hypovolaemic shock can be fatal, especially in children.

Dysentery

Bacillary dysentery

This infection of the large intestine is caused by bacteria of the *Shigella* group, which are closely related to *E. coli*. Children and older debilitated adults are particularly susceptible. Humans are the only host and transmission is by the faeco-oral route (see above).

The severity depends on the organism involved. In the UK it is usually a relatively mild condition caused by *Shigella sonnei*. *S. dysenteriae* causes the most severe infection; it occurs mainly in the tropics and causes significant mortality in children. The intestinal mucosa becomes inflamed, ulcerated and oedematous with excessive mucus secretion. In severe infections, the acute diarrhoea, which contains blood and excessive mucus, causes dehydration, electrolyte imbalance and anaemia.

Intestinal amoebiasis (amoebic dysentery)

This disease is caused by the protozoan *Entamoeba histolytica*, which is found worldwide but is more common in the tropics. The only known hosts are humans and infection is spread by the faeco-oral route (see above). Many infected people do not develop symptoms, i.e. are asymptomatic carriers.

The amoebae grow, divide and invade the mucosal cells, causing inflammation of the colon (colitis). Without

treatment the condition frequently becomes chronic with mild, intermittent diarrhoea and abdominal pain. This may progress with ulceration of the colon, and persistent and debilitating diarrhoea that contains mucus and blood. Complications are rare but include severe haemorrhage from ulcers and liver abscesses.

Viral gastroenteritis

Several highly transmissible viruses, including rotavirus and norovirus, are known to cause outbreaks of debilitating vomiting and/or diarrhoea.

Rotavirus

This was a major cause of diarrhoea in young children worldwide until its prevalence was greatly reduced by the introduction of vaccination programmes. It is highly contagious, and outbreaks often affect childcare and healthcare facilities. Self-limiting diarrhoea lasts about 5 days although faeces may remain mildly infected for longer.

Norovirus

Also known as the winter vomiting virus, this is responsible for outbreaks of acute but self-limiting enteritis with vomiting as the main symptom. Most common in the winter months, it affects all age groups and spreads easily in families and in closed communities, e.g. prisons, cruise ships, childcare and healthcare facilities. Spread is generally by the faeco-oral route but may also be by inhalation of infected airborne droplets. Symptoms usually resolve spontaneously within 2–3 days although faeces may remain mildly infected for several weeks.

Inflammatory bowel disease

The term inflammatory bowel disease (IBD) includes two chronic conditions: Crohn's disease and ulcerative colitis. A comparison of the main features is shown in Table 12.5, although it is not always possible to distinguish them in practice. Their aetiology is unknown but is thought to involve environmental and immune factors in genetically susceptible individuals. Both conditions typically affect young adults and have a pattern of relapse and remission.

Crohn's disease

The terminal ileum and the rectum are usually affected although any part of the tract may be involved. There is chronic patchy inflammation with oedema of the full thickness of the intestinal wall, sometimes described as skip lesions, causing partial obstruction of the lumen. There are variable periods of relapse and remission. The main symptoms are diarrhoea, abdominal pain and weight loss. Complications include:

- secondary infections, occurring when inflamed areas ulcerate
- fibrous adhesions and subsequent intestinal obstruction, caused when fibrous tissue from previous flare ups shrinks as it matures
- formation of fistulae between intestinal lesions and adjacent structures, e.g. the skin surface (see Fig. 14.11) and loops of bowel; when large lengths of bowel are bypassed, malabsorption (p. 367) develops
- perianal fistulae, fissures and skin tags
- cancer of the small or large intestine (lower risk than ulcerative colitis).

Ulcerative colitis

This is a chronic inflammatory disease of the mucosa of the colon and rectum, which ulcerates and may become infected. It begins in the rectum and from there spreads proximally to a variable proportion of the colon. Sometimes the entire colon becomes involved. The main symptom is bloody diarrhoea. There are variable periods of remission lasting weeks, months or years. Long-standing disease carries an increased risk of colonic cancer (2%). Individuals may develop systemic problems affecting, for example, the joints (ankylosing spondylitis, p. 481), skin and liver.

Toxic megacolon is a rare but acute complication in which the colon loses its muscle tone and dilates. There is a high risk of electrolyte imbalance, perforation and hypovolaemic shock, which may be fatal if untreated.

Table 12.5 Comparison of the main features of Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
Incidence	Usually between 20 and 40 years of age (mean 26 years); both sexes affected equally; smokers at higher risk	Usually between 20 and 40 years of age (mean 34 years); both sexes affected equally; smoking not a risk factor
Main symptoms	Any or all of: abdominal pain, diarrhoea, weight loss	Bloody diarrhoea
Main sites of lesions	Anywhere in digestive tract from mouth to anus; common in terminal ileum	Rectum always involved, with variable spread along colon
Tissue involved	Entire thickness of wall affected; ulcers and fistulae common	Only mucosa involved
Nature of lesions	'Skip' lesions, i.e. diseased areas interspersed with regions of normal tissue; ulcers and fistulae common	Continuous lesion that spreads proximally from rectum; mucosa is red and inflamed
Prognosis	In severe cases, surgery may improve condition but relapse rate very high; slightly increased risk of cancer	Surgical removal of entire colon is curative; significantly increased risk of cancer

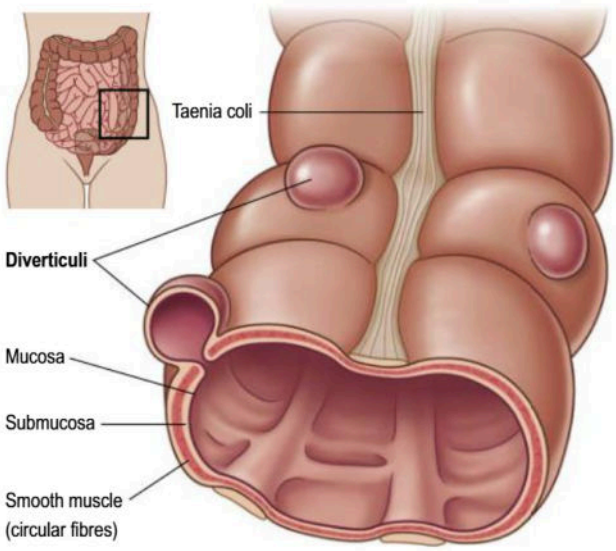

Figure 12.52 Diverticular disease. Cross-section of bowel showing diverticuli.

Diverticular disease

Diverticula are small pouches of mucosa that protrude (herniate) into the peritoneal cavity through the circular muscle fibres of the colon between the taeniae coli (Fig. 12.52). The walls consist of mucous membrane with a covering of visceral peritoneum. They occur at the weakest points of the intestinal wall, i.e. where the blood vessels enter, most commonly in the sigmoid colon.

The causes of diverticulosis (presence of diverticula) are not known but it is associated with deficiency of dietary fibre. In Western countries, diverticulosis is present in about 50% of people over 60 years of age but is usually asymptomatic.

Diverticulitis arises when faeces become trapped in the diverticula. The walls become inflamed and oedematous as secondary infection develops. This reduces the blood supply, causing ischaemic abdominal pain. Occasionally, perforation occurs, resulting in peritonitis (p. 365).

Tumours of the small and large intestines

Perhaps surprisingly, given the vast surface area and high rate of cell multiplication, tumours of the small intestine are rare, especially in comparison with the stomach, large intestine and rectum.

Benign tumours

Benign neoplasms may form a broad-based mass or polyp, i.e. develop a pedicle. Occasionally, polyps twist on themselves, causing ischaemia, necrosis and sometimes gangrene.

Adenomas are very common in Western countries; they are present in 50% of people over 60 years and are often multiple. They are usually asymptomatic but occasionally bleed and cause anaemia. Sometimes malignant changes transform adenomas into adenocarcinomas.

Colorectal cancer

This is the most common malignancy in high-income countries and in the UK is second only to lung cancer as a cause of cancer-related death (see Fig. 3.30).

The most important predisposing factor for colorectal cancer is thought to be diet. In cultures eating a high-fibre, low-fat diet the disease is virtually unknown, whereas in countries where large quantities of red meat and saturated animal fat and insufficient fibre are eaten, the disease is much more common. Slow movement of bowel contents may result in conversion of unknown substances present into carcinogenic agents which also spend longer in contact with the intestinal wall. Genetic factors are also implicated. Predisposing diseases include ulcerative colitis and some benign intestinal tumours (usually adenomas).

The tumours are adenocarcinomas with about half arising in the rectum, one-third in the sigmoid colon and the remainder elsewhere in the colon. The tumour may be:

- a soft polypoid mass, projecting into the lumen of the colon or rectum with a tendency to ulceration, infection and bleeding
- a hard fibrous mass encircling the colon or rectum, narrowing and eventually obstructing the lumen.

Local spread occurs early but may not be evident until there is severe ulceration and haemorrhage or intestinal obstruction. Spread can also be outwards through the wall into the peritoneal cavity and adjacent structures.

Lymph-spread metastases affect lymph nodes in the mesentery, peritoneum and other abdominal and pelvic organs. Enlarged lymph nodes may compress other structures causing intestinal obstruction or ascites (accumulation of fluid in the peritoneal cavity) if drainage of lymph is blocked (see Fig. 5.58C).

Blood-spread metastases are most commonly to the liver, brain and bones.

Appendicitis

The lumen of the appendix is very narrow with little room for swelling when it becomes inflamed. The initial cause of inflammation is not always clear. Microbial infection commonly follows obstruction by, for example, hard faecal matter (faecoliths), kinking or a foreign body. Inflammatory exudate causes swelling and ulceration of its mucous membrane lining. In the initial stages the pain of appendicitis is usually located in the central area of the abdomen. After a few hours the pain typically shifts and becomes localised to the region above the appendix (the right iliac fossa). In mild cases the inflammation

resolves spontaneously and healing takes place. In more severe cases, microbial growth progresses, leading to suppuration, abscess formation and further congestion. The rising pressure inside the appendix occludes local veins first and then the arteries, causing ischaemia; this may be followed by gangrene and perforation.

Complications of appendicitis

Peritonitis

The peritoneum becomes acutely inflamed, the blood vessels dilate and excess serous fluid is secreted. Peritonitis occurs as a serious complication of appendicitis when:

- microbes spread through the wall of the appendix and infect the peritoneum
- an appendix abscess (Fig. 12.53) perforates and pus enters the peritoneal cavity
- the appendix becomes gangrenous and perforates, discharging its contents into the peritoneal cavity.

Abscess formation

The most common types are:

- subphrenic abscess, between the liver and diaphragm, from which infection may spread upwards to the pleura, pericardium and mediastinal structures
- pelvic abscess, around the bladder or rectum, from which infection may spread to adjacent structures (Fig. 12.53).

Adhesions

When healing takes place, bands of fibrous scar tissue (adhesions) form and later shrinkage may cause:

- stricture or obstruction of the bowel
- limitation of the movement of a loop of bowel, which may twist around the adhesion, causing a type of obstruction called a volvulus (see below).

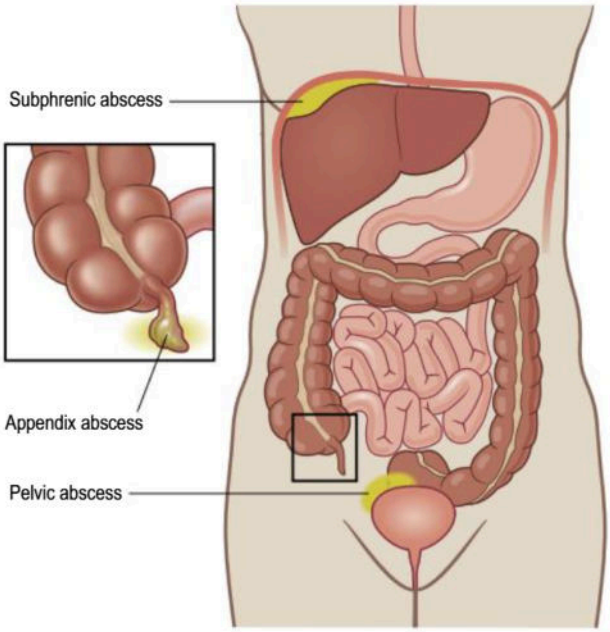

Figure 12.53 Abscess formation. This is a complication of appendicitis.

Hernias

A hernia is a protrusion of an organ or part of an organ through a weak point or aperture in the surrounding structures. In hernias affecting the digestive system, a piece of bowel protrudes through a weak point in either the musculature of the anterior abdominal wall or an existing opening (Fig. 12.54A). Many sites may be affected, and several are described below.

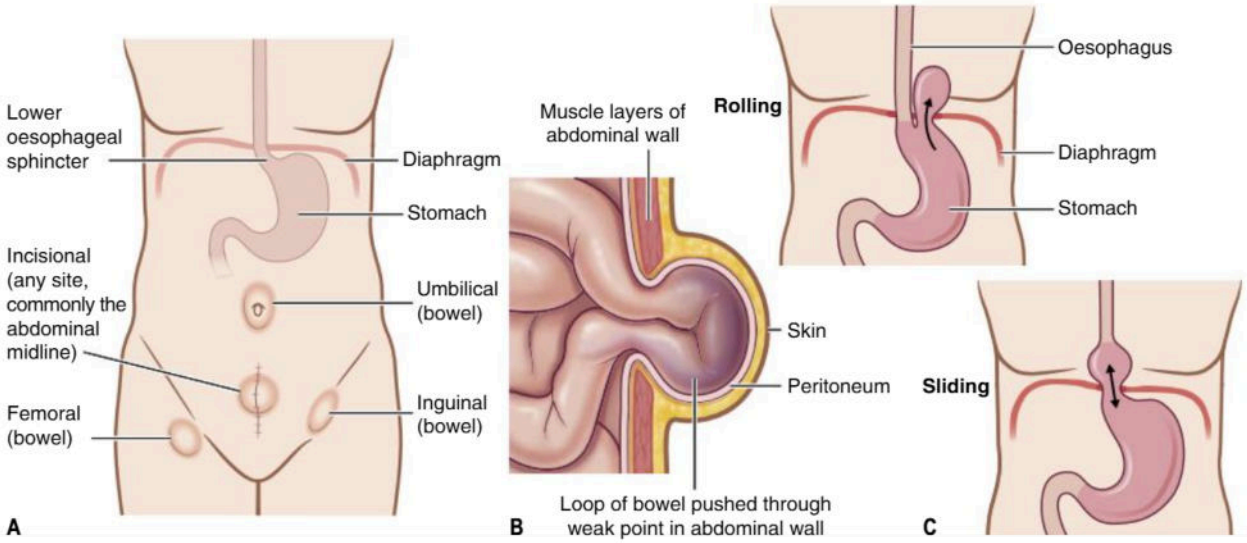

Figure 12.54 Hernias. (A) Common sites of herniation. (B) Strangulated hernia. (C) Hiatus hernia.

Inguinal hernia

The weak point is the inguinal canal, which contains the spermatic cord in the male (see Fig. 18.16) and the round ligament in the female. They are more common in males than females. The cause is regular, repeated increases in intra-abdominal pressure, usually in men who lift heavy loads at work or by frequent coughing associated with chronic lung disease. Outcomes include:

- Spontaneous reduction, when the loop of bowel slips back to its correct place once the intra-abdominal pressure returns to normal.
- Manual reduction, when gentle pressure is applied over the abdominal swelling.
- Strangulation (Fig. 12.54B), when reduction is not possible and the venous drainage from the herniated loop of bowel is impaired, causing congestion and ischaemia; this may lead to gangrene and intestinal obstruction (p. 366).

Femoral hernia

The weakness is the femoral canal, through which the femoral artery, vein and lymph vessels pass from the pelvis to the thigh.

Umbilical hernia

This affects the umbilicus, where the umbilical blood vessels from the placenta entered the fetus before birth.

Incisional hernia

This is caused by repeated stretching of fibrous (scar) tissue formed after abdominal surgery and affects about 5% of patients in the first five years postoperatively.

Hiatus hernia

This is protrusion of a part of the fundus of the stomach through the oesophageal opening in the diaphragm (Fig. 12.54C). Although it is often asymptomatic, irritation of the oesophagus occurs, but only when there is reflux of acid gastric juice, especially when lying flat or bending down. They are common after middle age and are often associated with GORD (p. 358); they are present in most people diagnosed with oesophageal stricture or Barrett's oesophagus (p. 358). Strangulation does not occur.

Rolling hiatus hernia. An abnormally large opening in the diaphragm allows a pouch of stomach to 'roll' upwards into the thorax beside the oesophagus. This is associated with obesity and increased intra-abdominal pressure.

Sliding hiatus hernia. Part of the stomach is pulled upwards into the thorax through the oesophageal opening in the diaphragm. This may be caused by shrinkage of fibrous tissue formed during healing of previous oesophageal damage that shortens it; further shortening occurs causing herniation when the oesophageal muscle contracts during swallowing.

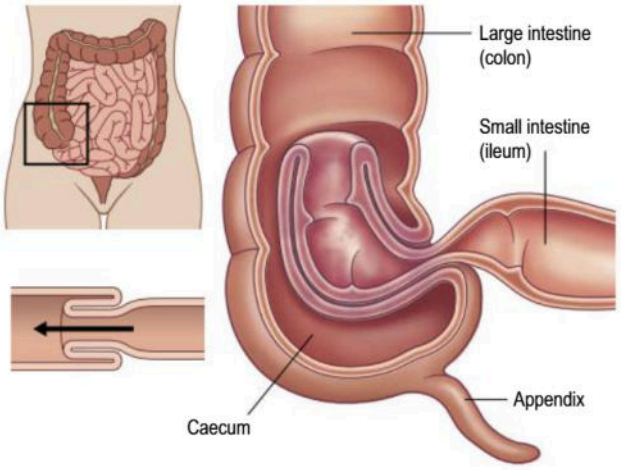

Figure 12.55 Intussusception.

Congenital diaphragmatic hernia

Incomplete formation of the diaphragm, usually on the left side, allows abdominal organs such as the stomach and loops of intestine into the thoracic cavity, preventing normal development of the fetal lungs.

Volvulus

This rare condition occurs when a loop of bowel twists, occluding both its lumen and its blood supply (strangulation, Fig. 12.54B) resulting in intestinal obstruction and gangrene respectively. The most common site in adults is the sigmoid colon and in children it is the small intestine.

Intussusception

This develops when a length of intestine becomes invaginated, or 'telescopes' into itself, causing intestinal obstruction (Fig. 12.55). It usually affects children, especially those under 2 years, when a piece of terminal ileum is pushed through the ileocaecal valve. This creates a partial obstruction and a rise in pressure inside the intestine proximal to the swelling. Strong peristaltic waves develop in an attempt to overcome the partial obstruction. These propel the invaginated section further, creating the intussusception. The pressure on the veins in the invaginated area increases, causing congestion, further swelling, ischaemia and, in severe cases, intestinal obstruction and gangrene. In adults, thickening of the intestinal wall by e.g. a tumour growing into the lumen, or polyp is usually responsible.

Intestinal obstruction

This is not a disease in itself but arises as a consequence of many other conditions; either or both the small and large intestines may be affected. The cause is usually a mechanical blockage although different conditions may affect the small

Table 12.6 Common causes of intestinal obstruction

Small intestine	Large intestine
Adhesions (80% of obstructions in adults) Hernias (Fig. 12.54) Crohn's disease Intussusception (Fig. 12.55) Compression by a nearby tumour	Cancer of the large intestine Volvulus of the sigmoid colon Diverticular disease

and large intestines (Table 12.6). Other causes and effects are summarised below.

Effects of intestinal obstruction

Symptoms include abdominal pain, vomiting and constipation. When the upper gastrointestinal tract is affected, vomiting may be profuse, although it may be absent in lower bowel obstruction. Bowel sounds are absent and flatus (wind) is not passed because peristalsis stops. Secretion of water and electrolytes continues, although intestinal motility is lost and absorption impaired. This causes distension of the bowel proximal to the affected area, electrolyte imbalance, and hypovolaemic shock. Without treatment, irrespective of the cause, this condition is fatal.

Paralytic ileus

This is partial or complete loss of peristaltic activity, which is mediated by the autonomic nervous system and produces the effects of intestinal obstruction (see above). The main causes are major abdominal surgery and peritonitis (see above).

Intestinal ischaemia

When the blood supply to part of the bowel is interrupted, the affected area becomes ischaemic. This is usually caused by atheroma, thrombosis or embolism (p. 129) of mesenteric blood vessels and affects older adults.

Sometimes there is adequate collateral circulation to minimise the effects if only a small area of bowel is affected. Otherwise, ischaemia is followed by infarction and gangrene of the damaged area of bowel, which rapidly becomes unable to function.

Malabsorption

Impaired absorption of nutrients and water from the intestines is not a specific disease, but the result of factors that impair digestion of nutrients or their transport across the intestinal wall. Intestinal conditions that may cause malabsorption include extensive resection of the small intestine, which greatly reduces surface area for absorption of adequate nutrients or lymphatic obstruction by e.g. compressed lymphatic vessels or diseased lymph nodes that prevent adequate absorption of fatty acids and glycerol.

Symptoms of malabsorption typically include diarrhoea, steatorrhoea (see Table 12.4), bloating and indigestion; in more severe cases fatigue, anaemia, abdominal pain and weight loss are also common.

Coeliac disease

This is the main cause of malabsorption in high-income countries. It is due to an abnormal, genetically determined autoimmune reaction to the protein gluten, present in wheat, barley and rye. Ingested gluten leads to marked villous atrophy, especially in the jejunum causing malabsorption and its associated symptoms (see above) in affected people. When it is removed from the diet, there is usually complete remission.

It often presents in infants after weaning or in adults during the third or fourth decades, more commonly in women. Sometimes other autoimmune conditions are also present.

Tropical sprue

This disease is endemic in many subtropical and tropical countries except Africa. The disease may become chronic and progressive in indigenous populations. After returning from an endemic area most travellers suffering from sprue recover, but others may not develop symptoms until months or even years later.

There is partial villous atrophy with malabsorption, chronic diarrhoea, a variable degree of weight loss and pernicious anaemia due to deficient absorption of vitamin B_{12} and folic acid. The cause is unknown but microbial infection is a likely factor, as occasional epidemics occur.

SPOT CHECK

22. Gastrointestinal infections are often highly contagious. Describe how their transmission can be minimised.
23. What is a hernia?

Diseases of the pancreas

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the causes and effects of acute and chronic pancreatitis
- outline the main pancreatic tumours and their consequences.

Pancreatitis

Proteolytic enzymes produced by the pancreas are secreted in inactive forms, which are not activated until they reach the intestine; this protects the pancreas from digestion by its own enzymes. If these precursor enzymes are activated while still in the pancreas, pancreatitis results.

Acute pancreatitis

The severity of acute pancreatitis is directly related to the amount of pancreatic tissue involved. Mild disease accounts for about 80% of cases and damages only those cells near the ducts; recovery is usually complete.

Severe disease causes widespread damage with necrosis and haemorrhage. Common complications include infection, suppuration and local venous thrombosis. Pancreatic enzymes, especially amylase, enter and circulate in the bloodstream, damaging structures elsewhere. In severe cases mortality is high.

Gallstones and excessive alcohol are responsible for over 75% of cases. Less common causes include trauma, viral infections, notably mumps, hypercalcaemia and drugs, e.g. azathioprine.

Chronic pancreatitis

This either is due to repeated attacks of acute pancreatitis or may arise gradually without a previous history of pancreatic disease. It is more common in men.

Chronic pancreatitis is associated with irreversible structural changes and is frequently associated with fibrosis and distortion of the main pancreatic duct. Protein plugs block the tiny acinar ductules (see Fig. 12.34). This eventually leads to the formation of encapsulated cysts, a feature of both acute and chronic pancreatitis. Malabsorption (p. 367) develops when pancreatic secretions are reduced, and diabetes mellitus (p. 261) when the β-islet cells are damaged.

The commonest cause in high-income countries is excessive alcohol consumption. In low-income countries, dietary factors and malnutrition have been implicated. Chronic pancreatitis is also associated with cystic fibrosis (p. 295) and chronic kidney disease.

Tumours of the pancreas

Benign tumours are very rare.

Malignant tumours

These are relatively common and feature in the top 10 causes of cancer deaths in the UK (see Fig. 3.30). The incidence increases with age and they affect more men than women. There is an association with smoking, excessive alcohol intake, use of aspirin and coexisting conditions, including diabetes mellitus and chronic pancreatitis.

Tumours usually affect the exocrine ducts in the head of the pancreas where, over time, local invasion obstructs the flow of bile and pancreatic juice into the duodenum. Jaundice, sometimes accompanied by intense itching, develops. Impaired digestion and absorption of fat cause weight loss, although anorexia and metabolic effects of the tumour may also play a role.

The condition typically remains asymptomatic until at an advanced stage and therefore the prognosis is very poor.

SPOT CHECK

24. Where do most pancreatic tumours originate and what are the common local consequences?

Diseases of the liver

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the causes, forms and effects of chronic and acute hepatitis
- discuss the causes and consequences of liver failure
- describe the main liver tumours.

Liver tissue has a remarkable capacity for regeneration and therefore damage is usually extensive before it is evident. The effects of disease or toxic agents are seen when:

- regeneration of hepatocytes (liver cells) does not keep pace with damage, leading to hepatocellular failure
- there is gradual replacement of damaged cells by fibrous tissue, leading to portal hypertension.

In most liver disease both changes are present.

Hepatitis

Areas of necrosis develop as groups of hepatocytes die; the eventual outcome depends on the size and number of these areas. The causes include viral infections and hepatotoxic substances including drugs. Hepatitis may be acute or chronic (lasting over 6 months).

Viral hepatitis

Viral infections are the most common cause of acute liver dysfunction; the different types are distinguished serologically, i.e. by the antibodies produced to combat the infection. Although the severity of the disease caused by the different viruses varies, their effects on the liver are similar. The viruses invade the liver cells, causing degenerative changes. An inflammatory reaction follows with the release of an exudate that contains lymphocytes, plasma cells and granulocytes. There is reactive hyperplasia of the hepatic macrophages (Kupffer cells) in the walls of the sinusoids.

Chronic hepatitis sometimes follows hepatitis B, C and D virus infections (see below).

Hepatitis A virus

Hepatitis A virus (HAV) is common worldwide and often occurs in epidemics. It is highly infectious and spread by the faeco-oral route, usually indirectly via contaminated hands, food, water and fomites. HAV mainly affects children and young adults but is often asymptomatic (subclinical disease). In both situations, antibodies develop, conferring lifelong immunity; up to 30% of adults have antibodies to this virus without any history of the disease. There is no carrier state. Viruses are excreted in the faeces for around 2 weeks before symptoms appear and for about 7 days after.

Symptoms include general malaise, followed by a period of jaundice (p. 372), which is accompanied by the passing of dark urine and pale faeces. This is usually a mild and self-limiting illness, and complications are rare.

Hepatitis B virus

Hepatitis B virus (HBV) infection occurs at any age but mostly in adults. Spread of HBV is blood-borne and the incubation period is between 50 and 180 days. People at greatest risk of infection are those in contact with blood and blood products in the course of their work, e.g. healthcare workers, tattooists and acupuncturists. HBV is also spread by body fluids, i.e. saliva, semen and vaginal secretions, and from mother to fetus, usually during or shortly after childbirth (vertical transmission). Other at-risk groups include men who have sex with men and those in contact with potentially contaminated needles, e.g. intravenous drug users.

This infection is often asymptomatic and when symptomatic, varies greatly in severity. Antibodies are formed and immunity persists after recovery. Carriers may or may not have been symptomatic.

Most cases are mild and recovery is complete. In about 1% of cases, HBV causes severe illness lasting between 2 and 6 weeks. This is usually followed by a protracted convalescence, but sometimes the outcome is massive necrosis that causes acute liver failure, which is often fatal.

In up to 10% of cases chronic hepatitis develops; viable virus continues to circulate in the blood and other body fluids. The infection predisposes to cirrhosis (see below) and liver cancer.

Hepatitis D. This virus contains no RNA and can replicate only in the presence of HBV. It superinfects people who already have HBV, typically intravenous drug users. Its presence accelerates the progression of chronic hepatitis.

Hepatitis C

Spread of hepatitis C virus (HCV) is blood-borne. Since the introduction of routine screening of blood and blood products, iatrogenic HCV infection is rare and intravenous drug users now account for 95% of cases in the UK. Most HCV infection is asymptomatic, although many infected people become carriers. HCV is usually diagnosed later in life when resultant cirrhosis or chronic liver failure becomes evident.

Hepatitis E

This is clinically similar to HAV infection, being typically mild and spread by the faeco-oral route. However, if HEV is contracted during pregnancy, 20% of people develop acute liver failure that is often fatal.

Hepatotoxic substances

Many substances including drugs are metabolised in the liver before excretion. Both the substance and its metabolites may damage liver cells. Some drugs always cause liver damage in a dose-dependent manner (i.e. are predictably toxic), e.g. paracetamol. Others only do so in certain individuals and even at small doses, meaning that reactions are unpredictable or idiosyncratic, e.g. methyldopa.

Chronic hepatitis

This is defined as any form of hepatitis that persists for more than 6 months. It may be caused by viruses, alcohol or idiosyncratic drug reactions but is sometimes idiopathic (of unknown cause). Mild, persistent inflammation may follow acute viral hepatitis. Initially, there may be little or no fibrosis.

Continuing progressive inflammation leads to necrosis. As groups of hepatocytes die, necrotic areas develop, phagocytes remove the necrotic tissue and the lobules collapse. The basic lobule framework (see Fig. 12.37) including its blood vessels becomes distorted. These changes impair the blood supply to the remaining hepatocytes and the resultant hypoxia causes further local damage. Fibrous tissue develops in the damaged area and compensatory proliferation of hepatocytes in adjacent lobules follows. The effect on liver function depends on the size of the necrotic areas, the amount of fibrous tissue formed and the extent to which the blood and bile channels are distorted. Cirrhosis of the liver may follow.

Cirrhosis of the liver

This is the result of long-term diffuse liver injury, usually caused by excessive alcohol consumption, HBV and HBC infection and other forms of hepatitis.

Chronic liver inflammation causes necrosis, and in time, affected tissue is replaced with fibrous tissue. Compensatory hyperplasia of hepatocytes occurs in areas adjacent to the damaged tissue leads to formation of nodules characteristic of cirrhosis. The liver may become enlarged (hepatomegaly) and sometimes jaundice (p. 372) develops. Liver function becomes progressively impaired, usually over several years, as the structure of the liver lobules becomes increasingly abnormal; this impedes blood flow in the portal vein causing portal hypertension and, in most cases, oesophageal varices (Fig. 12.49).

Cirrhosis increases the risk of liver cancer and liver failure (see below).

Liver failure

The liver has a remarkable capacity for regeneration and is central to metabolism and other essential processes; its functions are explained on page 345. Failure occurs when liver function is no longer able to support physiological requirements. It can be acute or, more commonly, chronic. Causes are diverse and include acute viral hepatitis, hepatotoxic substances including drugs, adverse drug reactions and cirrhosis of the liver.

The effects of liver failure are serious and widespread, and some are considered below.

Hepatic encephalopathy

Blood levels of ammonia and other nitrogenous metabolites, which are normally detoxified in the liver, rise as liver function worsens. These chemicals are thought to damage astrocytes of the normally protective blood–brain barrier (p. 165) by making it more permeable to toxic substances.

The onset may either be acute or insidious if it develops alongside advancing and chronic liver disease. Early signs of the mild form include irritability, disorientation, confusion and cognitive impairment, which may progress to coma.

Blood coagulation defects

The liver fails to synthesise adequate supplies of blood clotting factors, i.e. prothrombin, fibrinogen and factors II, V, VII, IX and X, predisposing to purpura, bruising and bleeding (Ch. 4).

Portal hypertension and oesophageal varices

Portal hypertension often leads to oesophageal varices (p. 357). If varices rupture, severe haemorrhage may cause a fall in blood pressure that renal autoregulation cannot compensate for. This reduces renal blood flow and may result in progressive oliguria and acute kidney injury (AKI, p. 393).

Oedema and ascites

These may arise from portal hypertension which raises the capillary hydrostatic pressure in the organs drained by the tributaries of the portal vein (see p. 357 and Fig. 5.41) and/or diminished production of serum albumin and clotting factors, which reduces the plasma osmotic pressure. Together, these changes increase fluid movement into the interstitial spaces, where excess causes oedema (p. 134).

Ascites develops in the peritoneal cavity as free fluid accumulates, causing abdominal distension after the volume exceeds about 1L.

Jaundice

As liver failure develops, jaundice (p. 372) may be caused by the diminishing ability of the hepatocytes to conjugate and excrete bilirubin and/or blockage of bile flow through the bile channels that have become distorted by fibrous tissue in diseased lobules.

Tumours of the liver

Benign tumours are rarely significant.

Malignant tumours

Cancer of the liver usually arises from hepatocytes. Worldwide, the incidence is greatest in countries where HBV and HCV infections are prevalent; most people have evidence of these infections or are carriers. In Western countries it is frequently associated with alcohol-related cirrhosis. There is thought to be a link between chronic liver disease and liver cancer but the relationship between them is unclear. It may be that both cirrhosis and cancer are caused by the same agents or that the carcinogenic action of an agent is promoted by cirrhotic changes. Metastatic spread is usually to the abdominal lymph nodes or the lungs.

Secondary malignant tumours (metastases) in the liver are much more common than primary liver tumours. They usually spread there from primary tumours in the gastrointestinal tract (via the tributaries of the portal vein), the lungs or the breast. These tumours are often multiple, tend to grow rapidly and are often the cause of death.

SPOT CHECK

25. Compare and contrast the routes of transmission of hepatitis A and B infection.

Diseases of the gall bladder and bile ducts

Learning outcomes

After studying this section, you should be able to:

- describe the causes and consequences of gallstones
- compare and contrast cholecystitis and cholangitis
- outline the common sites and consequences of biliary tract tumours
- discuss the main causes and effects of jaundice.

Gallstones

Cholelithiasis is the presence of stones in the gall bladder; this is a very common and generally asymptomatic condition. Many small stones (Fig. 12.56) or one or more large stones form when the composition of bile changes, decreasing the

solubility of its constituents. Gallstones consist mainly of cholesterol or sometimes bile pigments (both constituents of bile). Predisposing factors include:

- increasing age
- female sex, especially before 60 years of age
- obesity
- several pregnancies in young women, especially when accompanied by obesity
- diabetes mellitus.

Cholecystitis

Inflammation of the gall bladder is usually associated with the presence of gallstones.

Acute cholecystitis

Acute inflammation occurs when a gallstone becomes impacted (stuck) in the gall bladder neck or cystic duct (Fig. 12.57), often after a fatty meal. Strong peristaltic contractions of the smooth muscle wall of the cystic duct develop in an attempt to move the stone onwards; this causes biliary colic, severe acute pain in the epigastrium or right hypochondrium (Fig. 1.27). There is no jaundice because bile from the liver can still pass directly into the duodenum, but bile is unable to leave the gall bladder and an inflammatory reaction follows. Nausea and vomiting may accompany severe attacks.

This is occasionally complicated by bacterial infection and distension of the gall bladder, which carries the risk of perforation and peritonitis (p. 365).

Chronic cholecystitis

This is usually associated with gallstones and thickening of the gall bladder wall (Fig. 12.56). It often follows several episodes of acute cholecystitis. The symptoms are similar to the acute condition but tend to be milder and recurrent although gallstones are not always present.

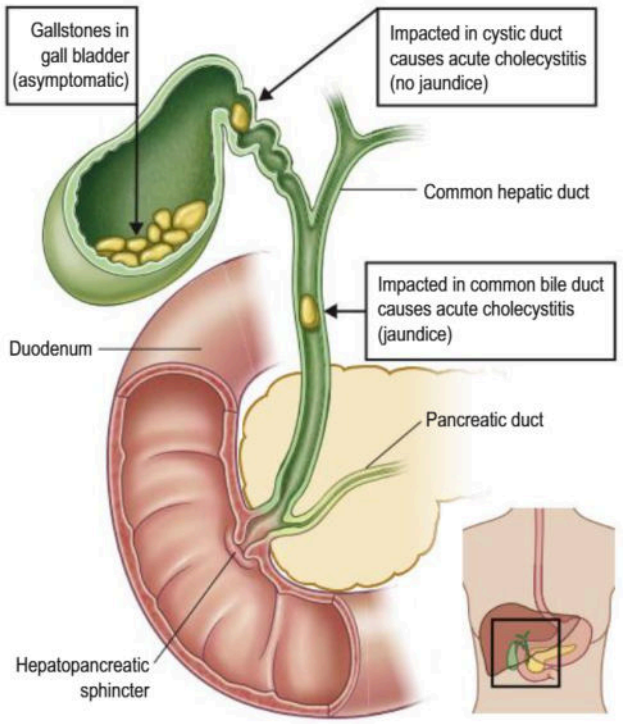

Figure 12.57 Effects of gallstones in different locations.

Cholangitis

This is inflammation of bile ducts caused by bacterial infection and is typically accompanied by abdominal pain, fever and jaundice (because the flow of bile into the duodenum is

Figure 12.56 Cholesterol gallstones. The gall bladder wall is thickened and fibrotic due to chronic cholecystitis. (From Kumar V et al. 2021. Robbins and Cotran Pathologic Basis of Disease, 10th ed. Elsevier.)

blocked). It accompanies existing gall bladder disease, e.g. stones in the common bile duct, biliary stricture or tumour. Infection can spread upwards in the biliary tree to the liver (ascending cholangitis), causing liver abscesses.

Tumours of the biliary tract

Benign tumours are rare.

Malignant tumours

These may originate in either the gall bladder or biliary tract: both are rare and gallstones are nearly always present. Local spread to the liver, the pancreas and other adjacent organs is common. Lymph and blood spread leads to widespread metastases. In both situations, spread has often occurred before diagnosis and the prognosis is poor.

Jaundice

This is yellowing of the skin and mucous membranes. It is not a disease in itself, but a sign of abnormal bilirubin metabolism and excretion. Bilirubin, produced from the breakdown of haemoglobin, is normally conjugated in the liver and excreted in the bile (see Fig. 12.39). Conjugation makes bilirubin water-soluble and greatly enhances its removal from the blood, an essential step in excretion. Its normal range in plasma is 3–13 μmol/L.

Unconjugated bilirubin, which is fat-soluble, has a toxic effect on brain cells. It is unable to cross the blood–brain barrier until the plasma level rises above 340 μmol/L, but when it does, it may cause neurological damage, seizures and cognitive impairment. Serum bilirubin may rise to 40–50 μmol/L before the yellow colouration of jaundice becomes evident in the skin and conjunctiva. Jaundice is often accompanied by pruritus (itching), caused by the irritating effects of bile salts on the skin. Different types are considered here.

Types of jaundice

Whatever stage in bilirubin processing is affected, the end result is rising blood bilirubin levels.

Prehepatic jaundice

This is due to increased haemolysis of red blood cells (see Fig. 12.39), which produces unconjugated bilirubin at a rate that exceeds the liver's capacity to conjugate it for excretion. Although blood bilirubin levels rise, because the excess bilirubin is unconjugated it cannot be excreted in the urine, which therefore remains normal in colour.

Neonatal haemolytic jaundice

This occurs in many babies, especially in those born prematurely, because before birth the baby has a high erythrocyte count in order to ensure its blood oxygen levels are adequate. After birth, when the baby is breathing for itself and its blood oxygen levels rise, the excess erythrocytes are rapidly haemolysed, producing large quantities of bilirubin. In addition, the immature liver has a shortage of conjugating enzymes which limits the rate of bilirubin clearance.

Intrahepatic jaundice

This is the result of damage to the liver itself by, for example:

- viral hepatitis (p. 368)
- toxic substances, such as drugs
- intestinal amoebiasis (amoebic dysentery, p. 362)
- cirrhosis (p. 369).

Excess bilirubin accumulates in the liver. Because it is mainly in the conjugated form, it is water-soluble and excreted in the urine, making it dark in colour.

Posthepatic jaundice

This is due to obstruction of the biliary tract, blocking the flow of bile into the duodenum. Causes include:

- gallstones in the common bile duct (Fig. 12.56)
- tumour affecting the head of the pancreas
- fibrosis of the bile ducts, following cholangitis or injury by the passage of gallstones.

The effects of raised serum bilirubin in this situation include:

- pale faeces due to the absence of stercobilin (see Fig. 12.39)
- dark urine due to the presence of increased amounts of conjugated bilirubin
- pruritus (itching).

SPOT CHECK

26. Gallstones lodged in which part(s) of the biliary tract may lead to jaundice?

Case study 1

Jasmine has recently started attending nursery. The teacher makes sure all the children wash their hands carefully after using the toilet and before eating.

1. Which type of microbial transmission will this minimise?

   a. Droplet
   b. Faeco-oral
   c. Direct
   d. Vertical

Before lunch the children also brush their teeth under supervision.

Case study 1—*cont'd*

2. The teeth at the front of the mouth are:

   a. Molars
   b. Canine
   c. Premolars
   d. Incisors

   Jasmine has a full complement of deciduous teeth.

3. These are usually all present by the age of:

   a. 1 year
   b. 2 years
   c. 3 years
   d. 4 years

4. How many teeth does she have altogether?

   a. 16
   b. 18
   c. 20
   d. 22

Case study 2

Capsule endoscopy

(From Science Photo Library. Reproduced with permission.)

Capsule endoscopy is a relatively new investigation used to visualise parts of the alimentary tract not accessible by traditional fibre optic endoscopy examinations such as gastroscopy and colonoscopy. The patient swallows a capsule (or 'pill cam') only slightly larger than a standard medicinal capsule. It contains a minute camera and lights powered by a battery. After a preset time, photographs are taken as it passes along the alimentary canal and sent wirelessly to a receiver worn around the patient's waist. In time, the capsule leaves the body in the faeces.

Donald was given this investigation after several episodes of abdominal pain.

Case study 2—*cont'd*

1. In what order will the capsule pass through the following structures?

   a. Lower oesophageal sphincter, pyloric sphincter, hepatic flexure, ileocaecal valve
   b. Hepatic flexure, lower oesophageal sphincter, pyloric sphincter, ileocaecal valve
   c. Ileocaecal valve, hepatic flexure, lower oesophageal sphincter, pyloric sphincter
   d. Pyloric sphincter, ileocaecal valve, hepatic flexure, lower oesophageal sphincter

2. Which part of the alimentary tract will subject the capsule to a highly acidic environment?

   a. Stomach
   b. Small intestine
   c. Large intestine
   d. Rectum

3. In the small intestine abundant tiny finger-like projections are captured on camera. These are called:

   a. Peyer's patches
   b. Plicae
   c. Villi
   d. Diverticuli

4. Where in the alimentary canal will the capsule be moved along by mass movement?

   a. Duodenum
   b. Jejunum
   c. Ileum
   d. Colon

5. In what order will the capsule pass though the large intestine?

   a. Ascending colon, transverse colon, descending colon, sigmoid colon
   b. Descending colon, transverse colon, ascending colon, sigmoid colon
   c. Sigmoid colon, ascending colon, transverse colon, descending colon
   d. Sigmoid colon, transverse colon, descending colon, ascending colon

6. Where might aggregated lymph follicles (Peyer's patches) be viewed?

   a. Stomach
   b. Small intestine
   c. Large intestine
   d. Rectum

Review and revise

Complete each of the following statements:

1. Secretions released into the gastrointestinal tract include _____ from the parotid glands, _____ from the chief cells in the gastric glands and _____ from the liver.

2. The shape and position of teeth depend on their function. The cutting teeth used for biting are the _____ and _____, while those involved in chewing are the _____ and _____.

3. The tiny functional units of the liver are known as _____. They are formed from cuboidal cells called _____. These are situated next to _____, which are capillaries with incomplete walls that contain a mixture of blood, some from branches of the _____ vein and some from the _____ artery.

4. The three central metabolic pathways that generate most of the body's energy are _____, the _____ and _____.

5. Peptic ulcer disease is strongly associated with the bacterium _____, which more commonly affects the _____ gender; ulcers most commonly affect the _____ and _____.

Choose one answer to complete each of the following statements:

6. In parts of the digestive tract subject to considerable wear and tear, the mucosa is formed from: _____
   a. Stratified squamous epithelium
   b. Simple squamous epithelium
   c. Columnar epithelium
   d. Smooth muscle

7. In parts of the digestive tract responsible for secretion and absorption, the mucosa is formed from: _____
   a. Stratified squamous epithelium
   b. Simple squamous epithelium
   c. Cuboidal epithelium
   d. Columnar epithelium

8. An accurate description of gastric function would be: ____
   a. Two layers of smooth muscle enable the stomach to act as a churn that breaks food down
   b. Peristaltic waves propel the contents of the stomach towards the pylorus
   c. Salivary amylase is inactivated by chyme in the stomach
   d. Sympathetic stimulation increases peristalsis and secretion of gastric juice

9. After bile is released from the liver, its route to the duodenum is: ____
   a. Hepatic duct, common bile duct, duodenum
   b. Hepatic duct, cystic duct, gall bladder, common bile duct, duodenum
   c. Hepatic duct, cystic duct, gall bladder, cystic duct, common bile duct, duodenum
   d. Hepatic duct, common bile duct, gall bladder, common bile duct, cystic duct, duodenum

10. Gastro-oesophageal reflux disease (GORD) is best described as: _____
    a. A common tumour of the gastrointestinal tract
    b. A congenital abnormality of the gastrointestinal tract
    c. A gastrointestinal infection
    d. The most common cause of indigestion or 'heartburn'

Indicate whether each of the following statements is true or false:

11. The accessory organs of digestion are three pairs of salivary glands, the pancreas, the liver and the biliary tract. _____

12. The visceral peritoneum is attached to the abdominal wall. _____

13. The submucosal layer of the alimentary tract propels the contents along it by peristalsis. _____

14. Saliva contains antimicrobial substances. _____

15. Intrinsic factor is essential for absorption of vitamin B_{12} in the terminal ileum. _____

16. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Bilirubin
____ (b) Glycogen
____ (c) Uric acid
____ (d) Triglyceride
____ (e) Amino acids
____ (f) Glucagon
____ (g) Lactate
____ (h) Adenosine triphosphate

List B

1. The building blocks of proteins
2. A storage form for fats
3. A storage form of glucose
4. A breakdown product of haem in erythrocytes
5. An anaerobic breakdown product of glucose
6. A molecule that stores chemical energy
7. A breakdown product of nucleic acids
8. A hormone that leads to breakdown of glycogen

17. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Peristalsis
____ (b) Ingestion
____ (c) Anabolism
____ (d) Gluconeogenesis
____ (e) Mastication
____ (f) Metabolism
____ (g) Deglutition
____ (h) First-pass metabolism

List B

1. Swallowing
2. Eating and drinking
3. Chewing
4. Chemical reactions that build larger substances from smaller ones
5. All the chemical reactions occurring in the body
6. The extensive breakdown of some drugs by the liver immediately after their absorption from the gastrointestinal tract
7. Manufacture of new glucose from other sources
8. Contractions of smooth muscle that propel the contents along the gastrointestinal tract

18. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Canaliculi
____ (b) Taeniae coli
____ (c) Jejunum
____ (d) Papillae
____ (e) Peritoneum
____ (f) Villi
____ (g) Caecum
____ (h) Sphincter

List B

1. The first part of the large intestine
2. Tiny finger-like projections of the mucosa layer of the small intestine
3. A ring of circular muscle that enables the area to act as a valve that controls passage of intestinal contents through it
4. Tiny bile channels in liver lobules
5. Tiny projections on the tongue that contain the taste buds
6. The largest serous membrane
7. Strips of smooth muscle in the large intestine that give it its puckered appearance
8. The middle section of the small intestine

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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CHAPTER 13

The urinary system

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The urinary system is important in excreting wastes and plays a vital part in maintaining homeostasis of water and electrolytes. The kidneys produce urine, which is mainly water but also contains waste products, including urea, uric acid and excess ions. The volume and composition of urine are continually adjusted to maintain water and electrolyte balance according to body requirements. Figure 13.1 shows an overview of the urinary system. It consists of two kidneys, which produce urine and two ureters that carry urine from the kidneys to the urinary bladder. The bladder collects and stores urine before it is excreted through the urethra during micturition (urination).

The kidney also plays an important role in red blood cell production and the control of blood pressure. It secretes two important substances:

- erythropoietin, the hormone that stimulates formation of red blood cells (erythropoiesis, p. 70)
- renin, an important enzyme in the long-term control of blood pressure (p. 385).

The first sections of this chapter explore the structures and functions of the organs of the urinary system and the impact of ageing on its function. In the final sections disorders of the urinary system are considered.

Kidneys

Learning outcomes

After studying this section, you should be able to:

- identify the organs associated with the kidneys
- outline the gross structure of the kidneys
- describe the structure of a nephron
- explain the processes involved in the formation of urine
- explain how body water and electrolyte balance is maintained.

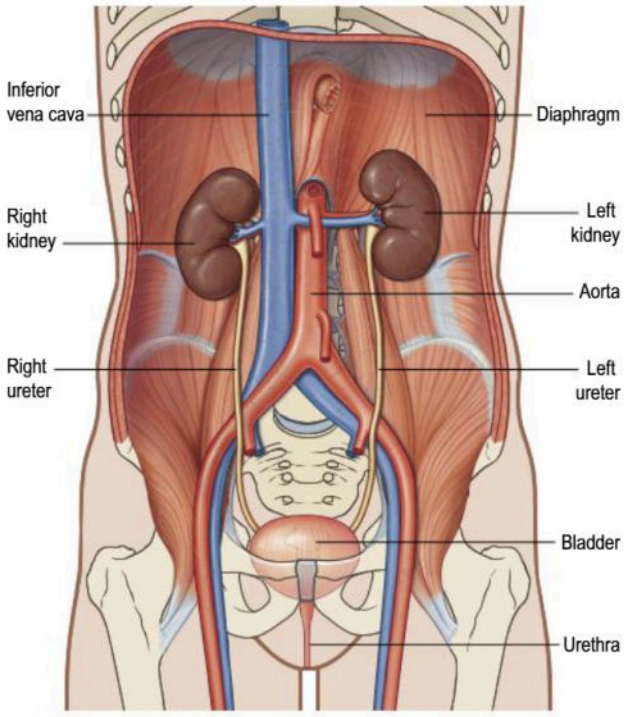

Figure 13.1 The urinary system and some associated structures.

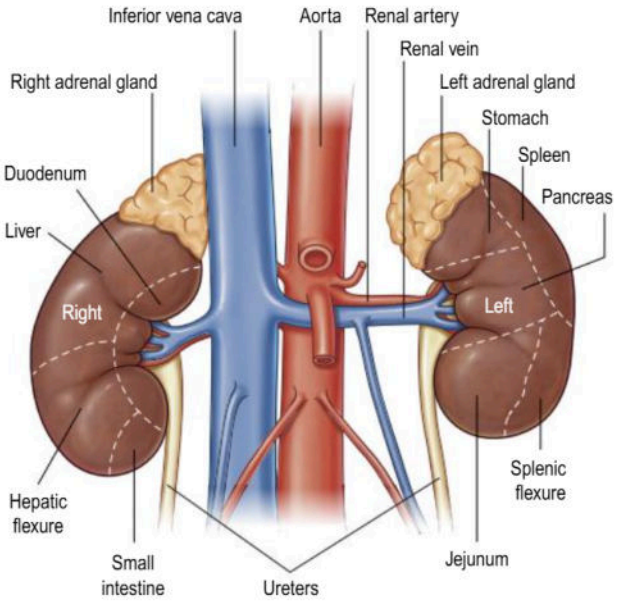

Figure 13.2 Anterior view of the kidneys showing the areas of contact with associated structures.

The kidneys (Fig. 13.2) lie on the posterior abdominal wall, one on each side of the vertebral column, below the diaphragm and behind the peritoneum, i.e. they are retroperitoneal. They extend from the level of the 12th thoracic vertebra to the 3rd lumbar vertebra, receiving some protection from the lower ribcage. The right kidney is usually slightly lower than the left, due to the considerable space occupied by the liver in that area.

Kidneys are bean-shaped organs, about 11 cm long, 6 cm wide and 3 cm thick; they weigh around 150 g. They are embedded in, and held in position by, a mass of fat. A sheath of fibrous connective tissue, the renal fascia, encloses the kidney and the renal fat.

Organs associated with the kidneys

The kidneys lie on either side of the vertebral column and so each is associated with different structures (Fig. 13.2).

Right kidney

Superiorly – the right adrenal gland.
Anteriorly – the right lobe of the liver, the duodenum and the hepatic flexure of the colon.
Posteriorly – the diaphragm, and muscles of the posterior abdominal wall.

Left kidney

Superiorly – the left adrenal gland.
Anteriorly – the spleen, stomach, pancreas, jejunum and splenic flexure of the colon.
Posteriorly – the diaphragm, and muscles of the posterior abdominal wall.

Gross structure

Three different areas of tissue are clearly distinguishable to the naked eye when viewing a longitudinal section (Fig. 13.3):

- an outer fibrous capsule, enclosing the kidney
- the cortex, a reddish-brown layer immediately below the capsule and dipping in between the renal pyramids
- the medulla, the innermost layer, consisting of pale, conical-shaped, striated structures, the renal pyramids. Each pyramid has a pointed proximal end called the papilla.

The hilum is the concave medial border of the kidney, where the renal blood and lymph vessels, the ureter and nerves enter and leave.

Urine formed in the kidney passes through one of several openings in a renal papilla into the drainage system that begins at a minor calyx (Fig. 13.3). Several minor calyces merge into a major calyx, and two or three major calyces combine, forming the renal pelvis, a hollow funnel-shaped structure that narrows when it leaves the kidney as the ureter. The walls of the calyces and renal pelvis are lined with transitional epithelium and contain smooth muscle. Peristalsis, intrinsic contraction of smooth muscle, propels urine through the calyces, renal pelvis and ureter to the bladder.

The blood supply to the kidney is via the renal artery, a large branch of the abdominal aorta. Together, these arteries

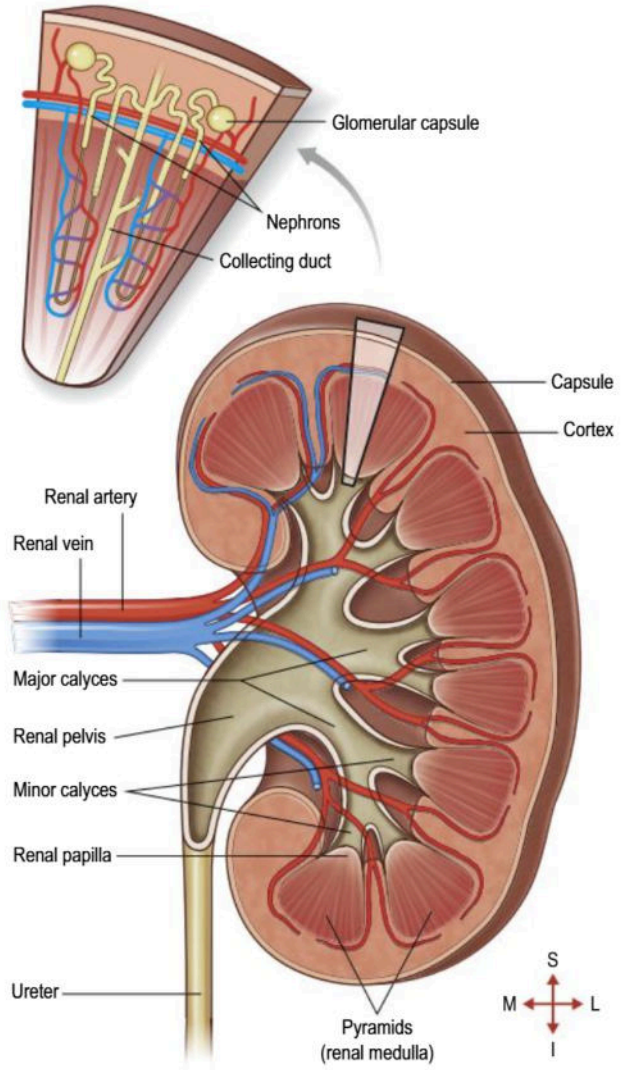

Figure 13.3 A longitudinal section of the kidney.

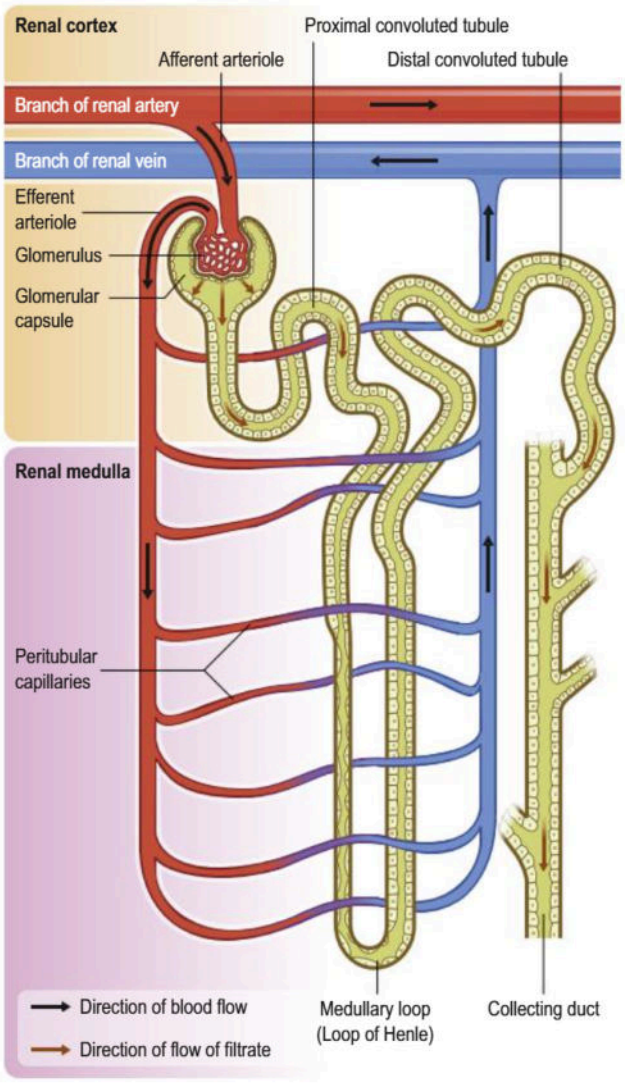

Figure 13.4 A nephron and associated blood vessels.

deliver about 20% of the cardiac output to the kidneys (about 1200 mL per minute). Venous drainage is through the renal vein.

Microscopic structure

The kidney contains 1–2 million functional units, the nephrons, and a much smaller number of collecting ducts. The collecting ducts transport urine through the pyramids to the calyces, giving the pyramids their striped appearance (Fig. 13.3). The collecting ducts are supported by connective tissue, containing blood vessels, nerves and lymph vessels.

The nephron

The nephron (Fig. 13.4) is essentially a tubule that is closed at one end and opens into a collecting duct at the other. The closed or blind end forms the cup-shaped glomerular (Bowman's) capsule, which almost completely encloses a coiled tuft of capillaries, the glomerulus (Fig. 13.5).

Continuing from the glomerular capsule, the remainder of the nephron is about 3 cm long and described in three parts:

- the proximal convoluted tubule
- the medullary loop (loop of Henle)
- the distal convoluted tubule, leading into a collecting duct.

After entering the kidney at the hilum, the renal artery divides into smaller arteries and arterioles. In the cortex a tiny arteriole, the afferent arteriole, enters the glomerular capsule and then subdivides into a cluster of tiny arterial capillaries, forming the glomerulus. Between these capillaries are fixed phagocytic mesangial cells, which are part of the mononuclear phagocyte system (see Fig. 4.13); these play an important role in protecting the kidneys from invading

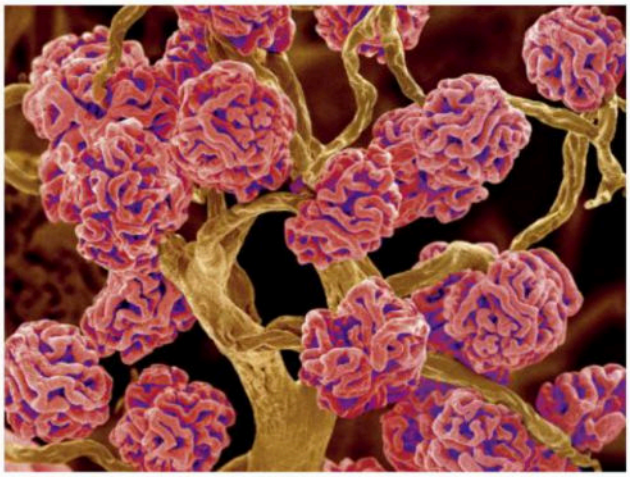

Figure 13.5 Coloured scanning electron micrograph of glomerular capillary tufts. (Susumi Nishinaga/Science Photo Library. Reproduced with permission.)

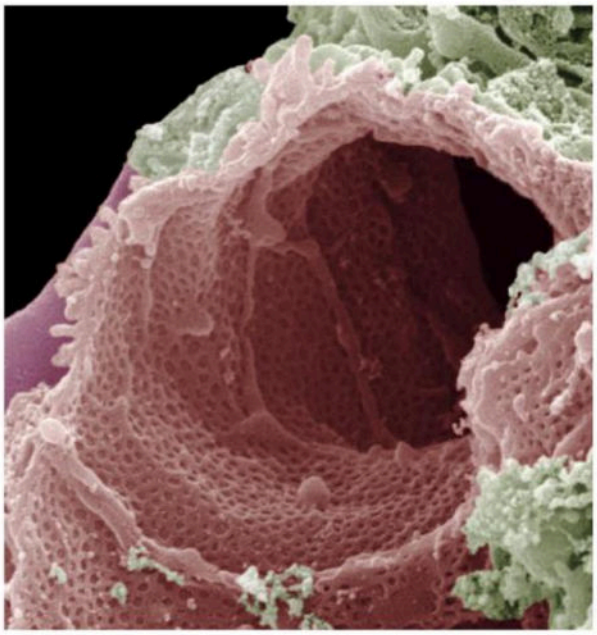

Figure 13.6 Coloured scanning electron micrograph of a glomerular capillary. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

microorganisms. Blood leaves the glomerulus in the efferent arteriole. The afferent arteriole has a larger diameter than the efferent arteriole, which increases blood pressure inside the glomerular capillaries and drives filtration outwards through the glomerular capillary walls into the glomerular capsule (Fig. 13.6). The fluid that has left the blood and entered the glomerular capsule is called the filtrate.

The efferent arteriole divides into the peritubular (meaning 'around tubules') capillary network, which wraps around the

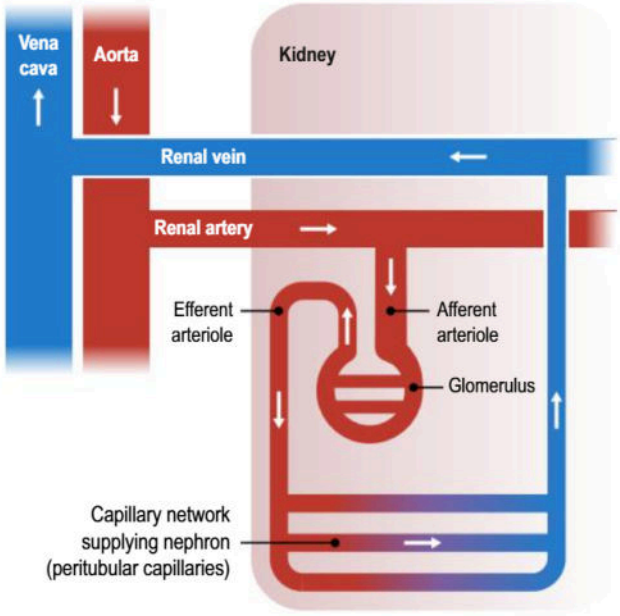

Figure 13.7 The series of blood vessels in the kidney.

remainder of the nephron, allowing exchange of substances between the filtrate and the bloodstream (Fig. 13.7; see also Fig. 13.4). This supplies tubular tissues with oxygen and nutrients and removes waste products. Venous blood drained from this capillary bed eventually leaves the kidney in the renal vein, which empties into the inferior vena cava.

The walls of the glomerulus and the glomerular capsule consist of a single layer of flat, highly permeable epithelial cells to facilitate filtration. The walls of the remainder of the nephron and the collecting duct are formed by a single layer of simple squamous epithelium (Fig. 13.8).

Renal blood vessels are supplied by both sympathetic and parasympathetic nerves. The presence of both divisions of the autonomic nervous system controls renal blood vessel diameter and renal blood flow independently of autoregulation (p. 382).

Functions

Formation of urine

The kidneys form urine; its composition reflects the exchange of substances between the filtrate in the nephron and the blood in the renal capillaries. Waste products of protein metabolism are excreted, and the balance of essential body constituents is maintained by adjusting the amounts of other substances excreted; these include water, electrolytes and hydrogen ions (to maintain acid–base balance). Three processes are involved:

- filtration
- selective reabsorption
- secretion.

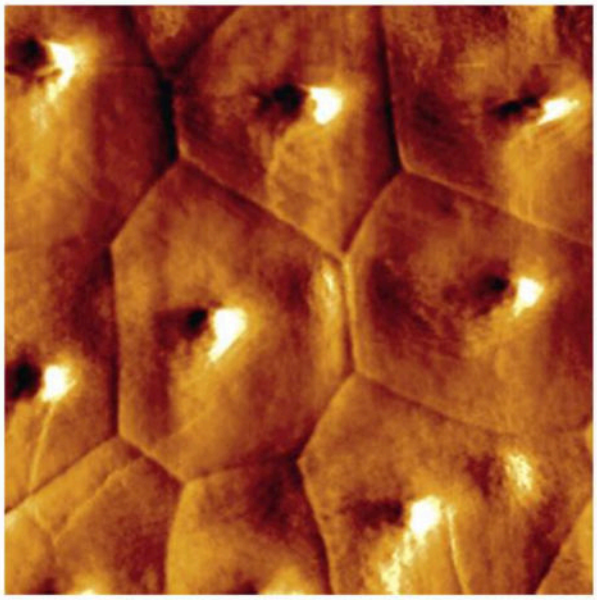

Figure 13.8 Simple squamous epithelium of the collecting ducts. Coloured atomic force micrograph. (Christopher Riethmuller, Prof. Dr H Oberleithner, University Hospital of Münster/Science Photo Library. Reproduced with permission.)

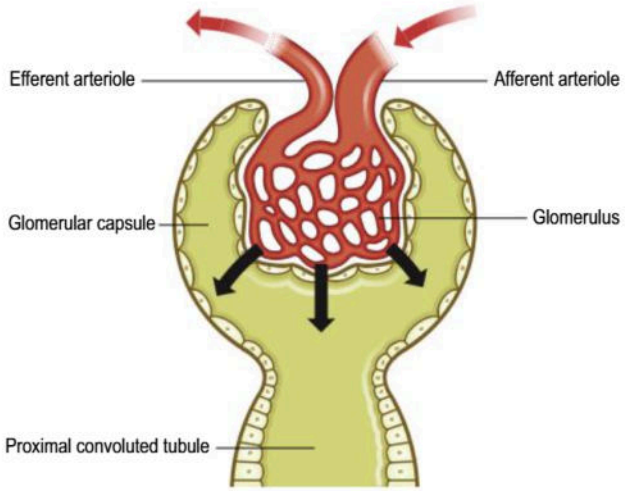

Figure 13.9 The glomerulus and glomerular capsule. Red arrows – direction of blood flow. Black arrows – direction of filtration.

Filtration

Filtration takes place through the semipermeable walls of the glomerular capillaries and glomerular capsule (Fig. 13.9). Water and other small molecules readily pass through, although some are reabsorbed later. The fluid filtered from the blood into the glomerular capsule (filtrate) is very similar in composition to plasma but is notably without blood cells, plasma proteins and other large molecules that are too large to be filtered through the glomerulus and which therefore remain in the blood (Table 13.1).

Filtration takes place because there is a difference between the blood pressure in the glomerulus and the pressure of the filtrate in the glomerular capsule (Fig. 13.10). The efferent arteriole is narrower than the afferent arteriole, and so a capillary hydrostatic pressure (outward pressure) of about 7.3 kPa (55 mmHg) builds up in the glomerulus. This pressure is opposed by the osmotic pressure of the blood (inward pressure), provided mainly by plasma proteins, about 4 kPa (30 mmHg), and by filtrate hydrostatic pressure of about 2 kPa (15 mmHg) in the glomerular capsule, both of which tend to pull fluid back into the bloodstream from the filtrate.

The net filtration pressure is, therefore:

$$7.3 - (4 + 2) = 1.3\ \text{KPa, or}$$

$$55 - (30 + 15) = 10\ \text{mmHg}$$

The volume of filtrate formed by both kidneys each minute is called the glomerular filtration rate (GFR). In a healthy adult the GFR is about 125 mL/min, i.e. 180 litres of filtrate are formed each day by the two kidneys. Nearly all the filtrate is later reabsorbed from the kidney tubules, with less than 1%, i.e. 1–1.5 litres, excreted as urine. The differences in volume and concentration are due to selective reabsorption of some filtrate constituents and tubular secretion of others and are explained below.

Table 13.1 Comparison of the composition of blood in glomerular capillaries and glomerular filtrate

Constituent	Present in glomerular capillary (plasma)	Present in glomerular filtrate
Water	√	√
Mineral salts	√	√
Amino acids	√	√
Ketoacids	√	√
Glucose	√	√
Some hormones	√	√
Creatinine	√	√
Urea	√	√
Uric acid	√	√
Some drugs (small molecules)	√	√
Leukocytes	√	
Erythrocytes	√	
Platelets	√	
Plasma proteins	√	
Some drugs (large molecules)	√	

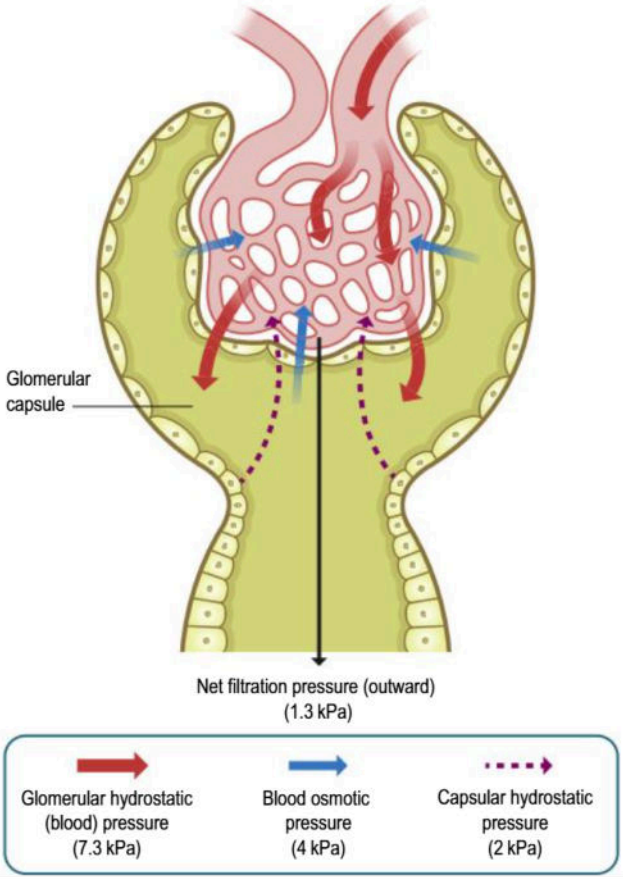

Figure 13.10 Filtration in the glomerulus.

Autoregulation

Renal blood flow, and therefore glomerular filtration, is protected by autoregulation, a mechanism whereby renal blood flow is maintained at a constant pressure across a wide range of systolic blood pressures (from around 80 to 200 mmHg). Because GFR depends on glomerular blood pressure, the glomerular blood pressure must be controlled independently of systemic blood pressure, which fluctuates significantly during normal daily activities. For this reason, renal blood flow is controlled locally. For example, in strenuous exercise when blood pressure rises, autoregulation constricts afferent arterioles to protect the delicate glomerular capillaries and enables the kidney to maintain constant blood flow through the glomeruli. Autoregulation is a property inherent in the smooth muscle in the walls of renal blood vessels and the mesangial cells; it operates independently of nervous control: i.e. if the nerve supply to the renal blood vessels is interrupted, autoregulation continues. It may be stimulated by changes in blood pressure in the renal arteries or by fluctuating levels of certain metabolites, e.g. prostaglandins.

In severe shock, when the systolic blood pressure falls below 80 mmHg, autoregulation fails and renal blood flow and the hydrostatic pressure decrease, impairing filtration

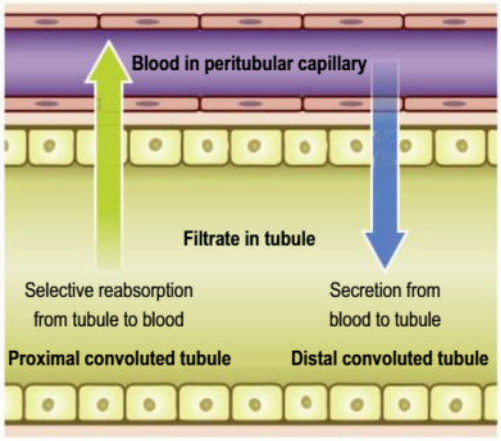

Figure 13.11 Directions and principal sites of selective reabsorption and secretion in the nephron.

within the glomeruli. Damage to the kidneys caused by such impairment may not be reversible (see acute kidney injury, p. 393).

Selective reabsorption

Most reabsorption from the filtrate back into the blood takes place in the proximal convoluted tubule (Fig. 13.11), whose epithelial lining possesses microvilli to increase surface area for absorption. Many substances are reabsorbed here, including water, electrolytes and nutrients including glucose and amino acids. Some reabsorption is passive but some substances, e.g. glucose, are actively transported. Only 60%–70% of filtrate reaches the medullary loop. Further reabsorption takes place in the loop, especially of water, sodium and chloride, so that only 15%–20% of the original filtrate reaches the distal convoluted tubule, and the composition of the filtrate is now very different. More electrolytes are reabsorbed in the distal convoluted tubule, especially sodium, so the filtrate entering the collecting ducts has become quite dilute. The main function of the collecting ducts is to reabsorb as much water as necessary to meet body needs (see below).

Active transport takes place at carrier sites in the epithelial membrane, using chemical energy to transport substances against their concentration gradients (p. 45).

Some ions, e.g. sodium and chloride, can be absorbed by both active and passive mechanisms, depending on the site in the nephron.

Some constituents of glomerular filtrate (e.g. glucose, amino acids) do not normally appear in urine because they are completely reabsorbed, unless blood levels are excessive. Reabsorption of nitrogenous waste products, such as urea, uric acid and creatinine, is very limited.

The kidneys' maximum capacity for reabsorption of a substance is called the transport maximum, or renal threshold. For example, the normal blood glucose level is 3.5–8 mmol/L (63–144 mg/100 mL); if this rises above the transport maximum of about 9 mmol/L (160 mg/100 mL),

glucose appears in the urine. This occurs because all the carrier sites in the nephron wall for glucose reabsorption are occupied and the mechanism for active transport out of the tubules is overloaded. Other substances reabsorbed by active transport include sodium, calcium, potassium, phosphate and chloride.

The renal threshold of some substances varies according to body need at a particular time, and in some cases reabsorption is regulated by hormones.

Hormones that influence selective reabsorption

Several hormones play such a role, each being regulated by a negative feedback mechanism.

Parathyroid hormone. This is secreted by the parathyroid glands and, together with calcitonin from the thyroid gland, regulates the reabsorption of calcium and phosphate to maintain normal blood levels (see Ch. 9). Parathyroid hormone increases the blood calcium level and calcitonin lowers it.

Antidiuretic hormone. Antidiuretic hormone (ADH) is secreted by the posterior pituitary. It increases the permeability of the distal convoluted tubules and collecting ducts to water, increasing water reabsorption. Osmoreceptors in the hypothalamus monitor the water content of the blood, and ADH secretion is adjusted accordingly (see Fig. 13.14).

Aldosterone. Secreted by the adrenal cortex, this hormone increases the reabsorption of sodium and water, and the excretion of potassium (see below).

Atrial natriuretic peptide. Atrial natriuretic peptide (ANP) is a hormone secreted by the atria of the heart in response to stretching of the atrial wall when blood volume is increased. It decreases reabsorption of sodium and water from the proximal convoluted tubules and collecting ducts (Fig. 13.12). This increases urinary volume and decreases blood volume; in turn, stimulation of the atrial stretch receptors is reduced and switches off ANP secretion.

Secretion

Filtration occurs as blood flows through the glomerulus. Some unwanted substances may not be entirely filtered out of the blood because of the short time spent passing through the glomerulus or because they are too large to pass through the filtration pores, e.g. some drugs including penicillin and aspirin. Such substances are cleared from the blood into the filtrate by secretion from the peritubular capillaries in the convoluted tubules (Fig. 13.11). Tubular secretion of hydrogen ions (H^+) is important in maintaining normal blood pH.

Summary of urine formation

The three processes involved – filtration, selective reabsorption and secretion – are summarised in Figure 13.13.

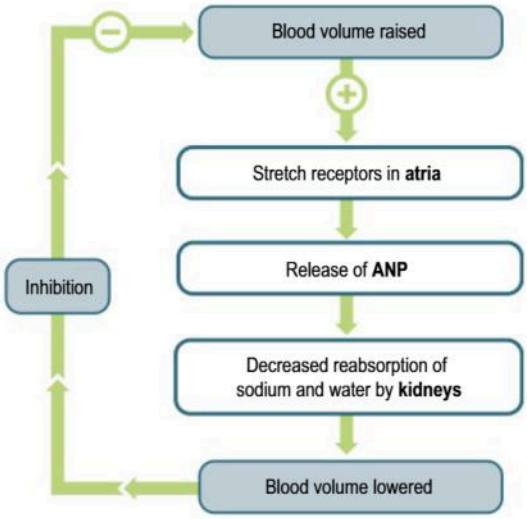

Figure 13.12 Negative feedback regulation of secretion of atrial natriuretic peptide (ANP).

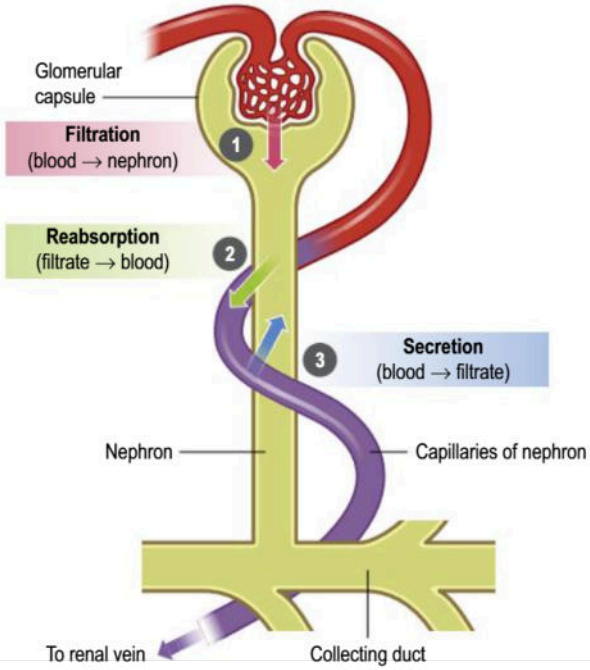

Figure 13.13 Summary of the three processes that form urine.

Composition of urine

Urine is clear and amber in colour due to the presence of the pigmented substance urobilin. This is generated following haemolysis when some of the urobilinogen produced in the kidneys is converted to urobilin (see Fig. 12.39). The specific gravity is between 1020 and 1030, and the pH is around 6 (normal range 4.5–8). A healthy adult passes 1000 to 1500 mL per day. The volume of urine produced and the specific

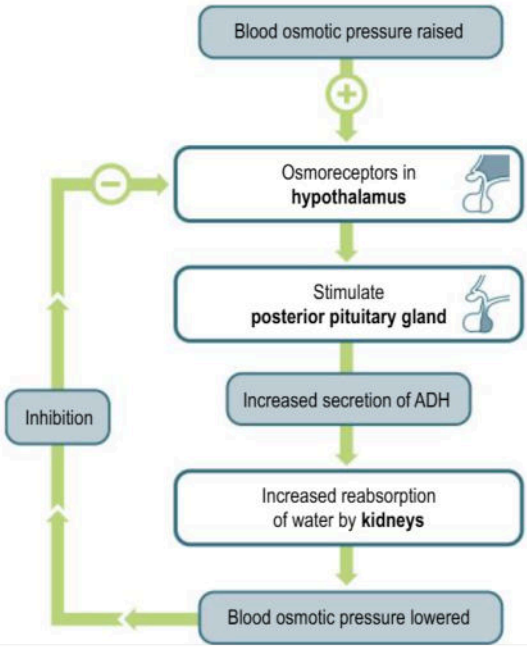

Figure 13.14 Negative feedback regulation of antidiuretic hormone (ADH) secretion.

gravity vary, according to fluid intake and the amount of solute excreted. Normal constituents of urine include:

- Water 96%
- Urea 2%
- Uric acid
- Creatinine
- Ammonia
- Sodium
- Potassium
- Chlorides
- Phosphates
- Sulphates
- Oxalates

} 2%

Water balance and urine output

Most body water comes from ingested food and fluid, although a small amount, called 'metabolic water', is formed as a byproduct of cellular metabolism. Water is excreted not only as the main constituent of urine but also in expired air and faeces, and through the skin as sweat. The amount lost in expired air and faeces is fairly constant; the amount of sweat produced is adjusted according to environmental and body temperatures (Ch. 14).

The kidneys control the balance between fluid intake and output. The minimum urinary output, i.e. the smallest volume required to excrete body waste products, is about 500 mL per day. Urinary volume in excess of this is controlled mainly by antidiuretic hormone (ADH) from the posterior pituitary gland.

Sensory nerve cells in the hypothalamus (osmoreceptors) respond to changes in the osmotic pressure of the blood. Nerve impulses from the osmoreceptors control the posterior pituitary release of ADH. When the osmotic pressure is raised, i.e. the blood is becoming more concentrated, ADH output is increased, and as a result, water reabsorption by the distal convoluted tubules and collecting ducts is increased, reducing the blood osmotic pressure and ADH output. This negative feedback mechanism maintains the blood osmotic pressure (and therefore sodium and water concentrations) within normal limits (Fig. 13.14).

At times, this negative feedback mechanism may be inadequate. For example, in diabetes mellitus, when blood glucose levels exceed the transport maximum of the renal tubules, the excess glucose remains in the filtrate, passively drawing water with it. Large volumes of urine are passed (polyuria), which may lead to dehydration despite increased ADH secretion. However, acute thirst and increased fluid intake usually compensate at least to some extent for the polyuria.

When blood volume is increased, stretch receptors in the atria of the heart are stimulated and cardiac muscle cells release atrial natriuretic peptide (ANP). This hormone travels in the bloodstream to the kidneys, where it reduces reabsorption of sodium and water by the proximal convoluted tubules and collecting ducts, meaning that more sodium and water are excreted. In turn, this lowers blood volume and reduces atrial stretching, and through the negative feedback mechanism ANP secretion is switched off (see Fig. 13.12). Raised ANP levels also inhibit secretion of ADH and aldosterone, further promoting loss of sodium and water.

Electrolyte balance

Changes in the concentration of electrolytes in the body fluids may be due to changes in the body water content, and/or electrolyte levels. The concentration of a fluid can be increased by reducing the water content and/or increasing amount of a solute it contains. Several mechanisms maintain the balance between water and electrolyte concentration.

Sodium and potassium balance

Sodium is the most common cation (positively charged ion) in extracellular fluid, and potassium is the most common intracellular cation. Sodium is a constituent of almost all foods and salt (sodium chloride) is often added during cooking. This means that intake usually exceeds body needs; excess is excreted mainly in urine and sweat.

The amount of sodium excreted in sweat is usually insignificant unless sweating is excessive. This may occur when there is pyrexia (fever), a high environmental temperature or during sustained physical exercise. Normally, the renin–angiotensin–aldosterone system (see below) maintains the concentration of sodium and potassium within physiological

limits. When excessive sweating is sustained, e.g. visiting a hot country or working in a hot environment, acclimatisation occurs in approximately 7–10 days and electrolyte secretion in sweat is reduced.

Digestive juices contain high concentrations of sodium and potassium: sodium in gastric juice and potassium in pancreatic and intestinal juice. Normally, these ions are reabsorbed by the large intestine, but following acute and prolonged diarrhoea they may be lost in large quantities; excessive loss of either causes electrolyte imbalance.

Renin–angiotensin–aldosterone system

Sodium is a normal constituent of urine and its excretion is regulated by the hormone aldosterone, secreted by the adrenal cortex. The renin–angiotensin–aldosterone system (RAAS) is summarised in Figure 13.15. Cells in the afferent arteriole of the nephron release the enzyme renin in response to sympathetic stimulation, low blood volume or low arterial blood pressure. Renin converts the plasma protein angiotensinogen, produced by the liver, to angiotensin I. Angiotensin converting enzyme (ACE), formed in small quantities in the lungs, proximal convoluted tubules and other tissues, converts angiotensin I into angiotensin II, which is a very potent vasoconstrictor and increases blood pressure. Angiotensin II and raised blood potassium levels also stimulate the adrenal gland to secrete aldosterone. Aldosterone in turn stimulates sodium and water absorption in the kidney, increasing blood volume and blood pressure. As blood volume rises, this reduces renin secretion through a negative feedback mechanism. When sodium reabsorption is increased, potassium excretion is increased, indirectly reducing intracellular potassium. Profound diuresis may lead to hypokalaemia (low blood potassium levels).

ANP

This hormone is also involved in the regulation of sodium levels (p. 383 and Fig. 13.12).

Calcium balance

Calcium levels are regulated by secretion of parathyroid hormone and calcitonin (Ch. 9).

pH balance

Hydrogen ions (H^+) are constantly produced as part of normal cellular metabolism and production increases during exercise. In order to maintain acid–base balance (and normal blood pH) they must be continuously excreted and the kidney is largely responsible. In the proximal convoluted tubules, hydrogen ions are secreted into the filtrate according to blood levels; they combine there with buffers (p. 33):

- bicarbonate, forming carbonic acid

$$H^+ + HCO_3^- \rightarrow H_2CO_3$$

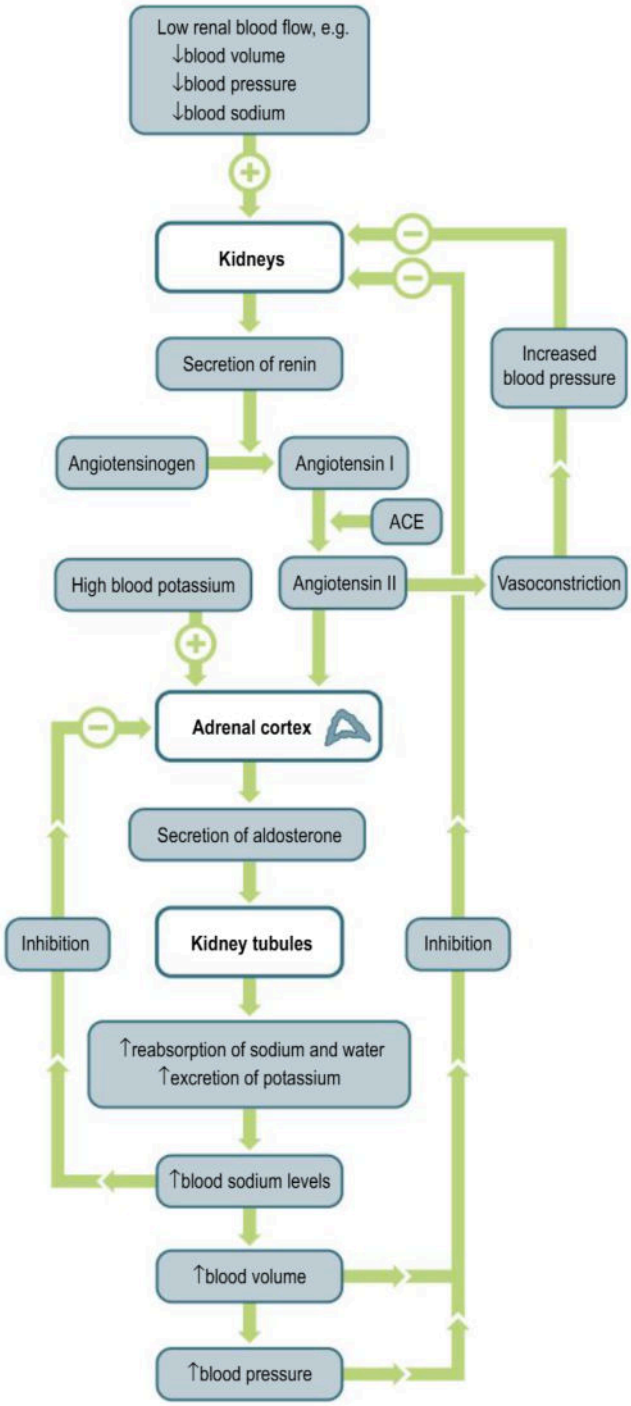

Figure 13.15 Negative feedback regulation of aldosterone secretion. ACE: angiotensin converting enzyme.

- ammonia, forming ammonium ions

$$H^+ + NH_3 \rightarrow NH_4^+$$

- hydrogen phosphate, forming dihydrogen phosphate

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$$

Carbonic acid is converted to carbon dioxide (CO_2) and water (H_2O), and the CO_2 is reabsorbed, maintaining the buffering capacity of the blood. Hydrogen ions are excreted in the urine as ammonium salts and hydrogen phosphate.

The normal pH of urine varies from 4.5 to 8, depending on diet, time of day and other factors. Individuals whose diet contains a large amount of animal protein tend to produce more acidic urine (lower pH) than vegetarians.

SPOT CHECK

1. Name the three processes involved in the formation of urine.
2. Glomerular filtration is maintained by autoregulation. Briefly explain autoregulation.

Ureters

Learning outcome

After studying this section, you should be able to:

- outline the structure and function of the ureters.

The ureters carry urine from the kidneys to the urinary bladder (Fig. 13.16). They are hollow muscular tubes about 25–30 cm long with a diameter of approximately 3 mm. The ureter is continuous with the funnel-shaped renal pelvis (plural: pelves) above. It passes downwards through the abdominal cavity, behind the peritoneum in front of the psoas muscle into the pelvic cavity, and passes obliquely through the posterior wall of the bladder (Fig. 13.17).

This arrangement means that, as urine accumulates and the pressure in the bladder rises, the ureters become compressed, occluding the openings into the bladder. This prevents backflow (reflux) of urine into the ureters (towards the kidneys) as the bladder fills and during micturition, when pressure increases as the muscular bladder wall contracts.

Structure

The walls of the ureters consist of three layers of tissue (Fig. 13.18):

- an outer covering of fibrous connective tissue, continuous with the fibrous capsule of the kidney
- a middle muscular layer consisting of interlacing smooth muscle fibres that form a functional unit around the ureter
- an inner layer, the mucosa, composed of transitional epithelium (see Fig. 3.16).

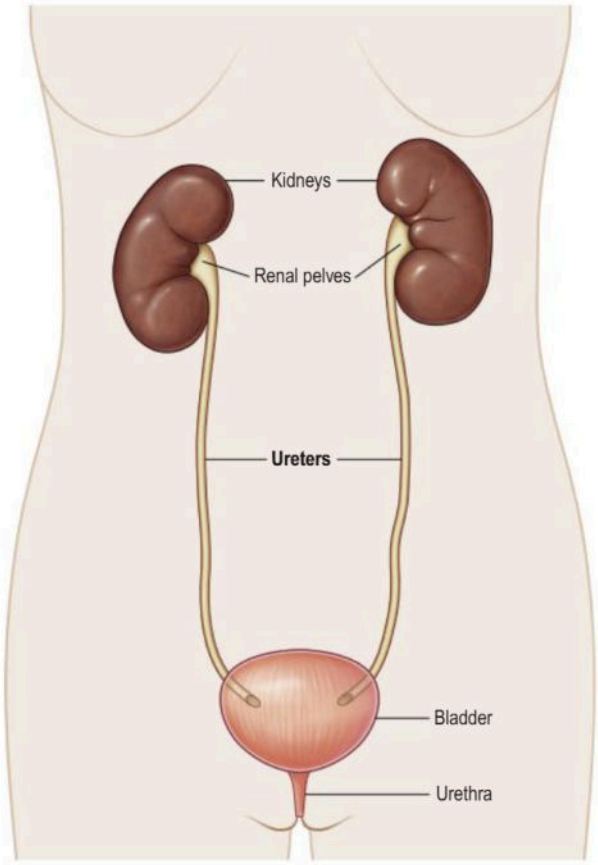

Figure 13.16 The ureters and their relationship to the kidneys and bladder.

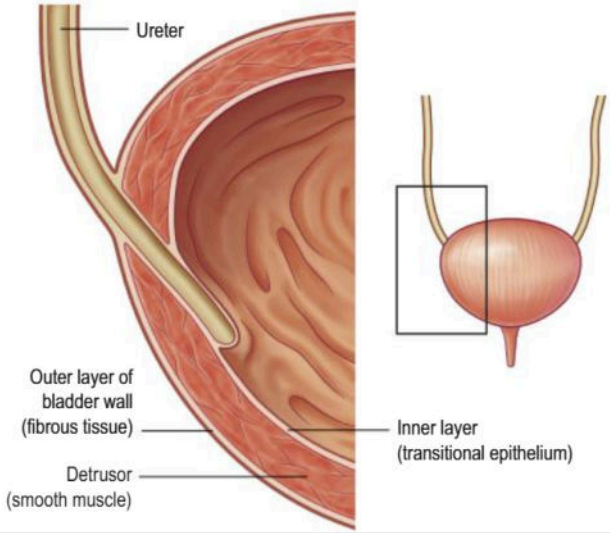

Figure 13.17 The position of the ureter where it passes through the bladder wall.

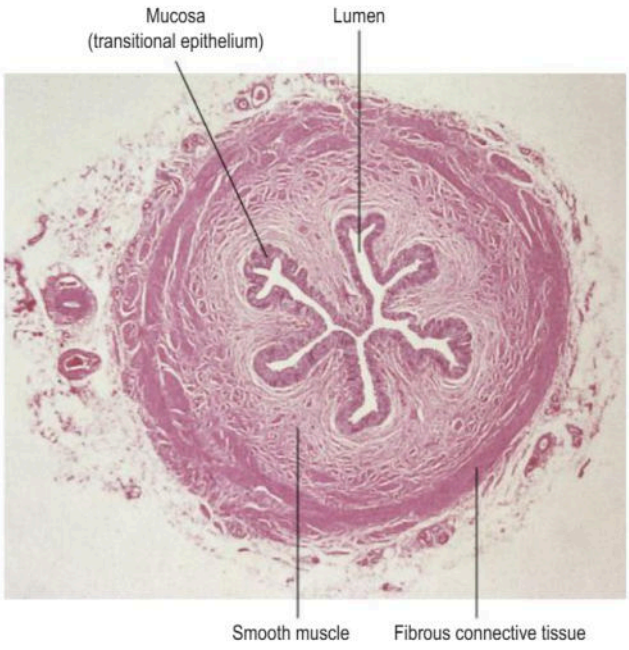

Figure 13.18 Cross-section of the ureter. (Young B, Lowe JS, Stevens A et al. 2006 Wheater's functional histology: a text and colour atlas. Edinburgh: Churchill Livingstone. Reproduced with permission.)

Function

Peristalsis is an intrinsic property of the smooth muscle layer. Peristaltic waves occur several times per minute, increasing in strength and frequency with the volume of urine produced propelling urine along the ureter towards the bladder.

SPOT CHECK

3. Describe the anatomical feature at the junction of the ureters and the bladder that prevents backflow of urine into the ureters.

Urinary bladder

Learning outcome

After studying this section, you should be able to:

- describe the structure of the bladder.

The urinary bladder is a highly distensible reservoir for urine that lies in the pelvic cavity. Its size and position vary, depending on the volume of urine it contains; when distended, the bladder rises into the abdominal cavity.

Organs associated with the bladder

These are shown in Figure 13.19.

Structure

The bladder (Fig. 13.20) is roughly pear-shaped, but becomes more balloon-shaped as it fills. It opens into the urethra at the neck, its lowest point.

The peritoneum covers only the superior surface of the bladder before it turns upwards as the parietal peritoneum, lining the anterior abdominal wall (see Fig. 12.3). Posteriorly, the peritoneum surrounds the uterus in the female and the rectum in the male. The bladder wall is composed of three layers:

- The outer layer of loose connective tissue, containing blood and lymphatic vessels and nerves, covered on the upper surface by the peritoneum.
- The middle layer, consisting of interlacing smooth muscle fibres and elastic tissue loosely arranged in layers. This is called the detrusor muscle; it allows distension of the bladder as it fills and when it contracts, the bladder empties.
- The inner layer, the mucosa, composed of transitional epithelium (see Fig. 3.16) that readily permits distension of the bladder as it fills.

When the bladder is empty the inner lining is arranged in folds, or rugae, which gradually disappear as it fills. When filling distends the bladder, awareness of the need to pass urine develops. The total capacity is rarely more than about 600 mL.

The three orifices in the bladder wall form a triangle, the trigone (Fig. 13.20). The upper two on the posterior wall are the openings of the ureters; the lower orifice is the opening into the urethra at the bladder neck. The internal urethral sphincter, a thickening of the urethral smooth muscle layer in the upper part of the urethra, controls outflow of urine from the bladder. This sphincter is not under voluntary control (see Fig. 13.21).

SPOT CHECK

4. Outline the structure and function of the detrusor muscle.

Urethra

Learning outcome

After studying this section, you should be able to:

- outline the structure and function of the urethra in males and females.

The urethra is a passageway extending from the neck of the bladder to the exterior, at the external urethral orifice. The

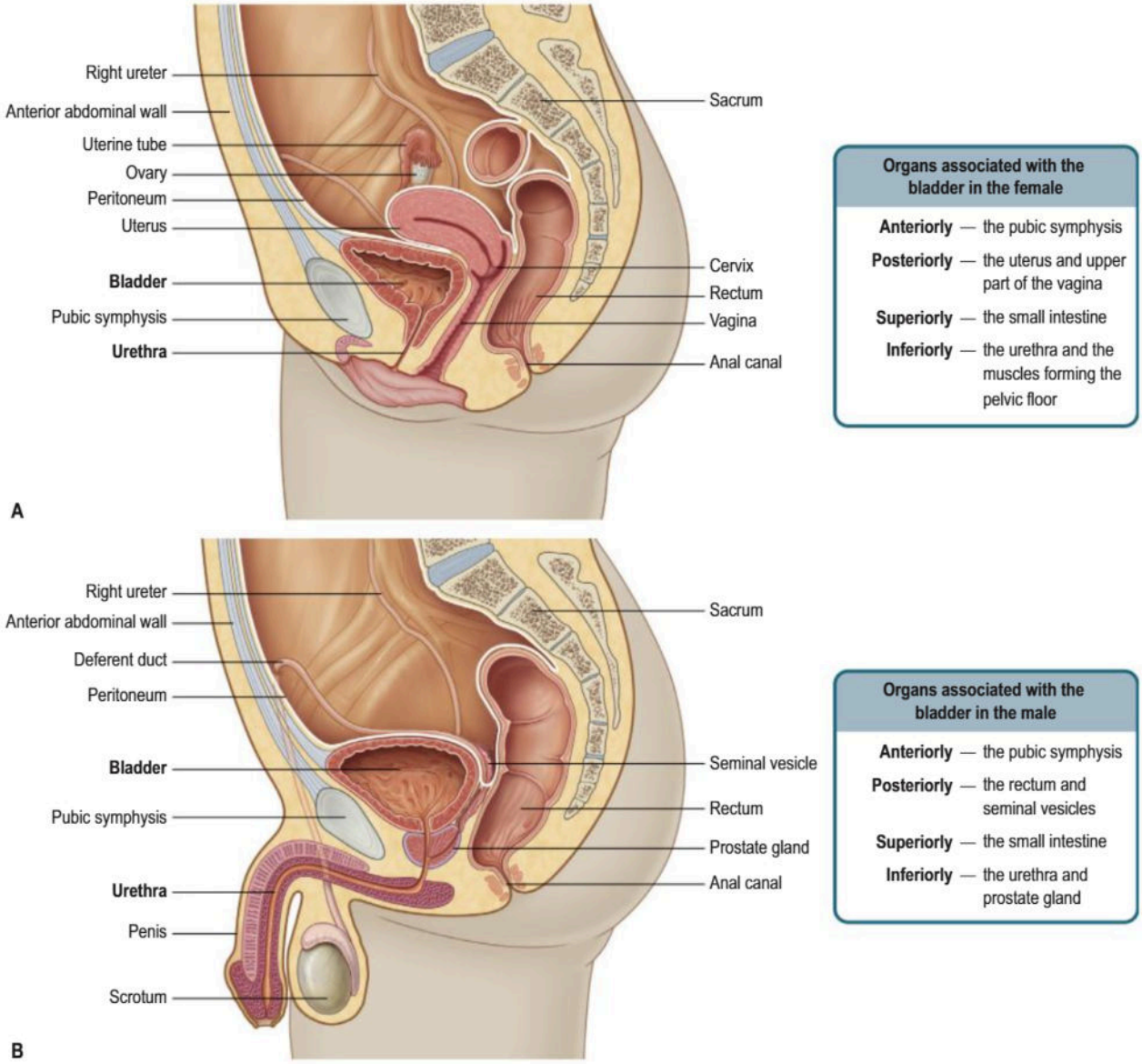

Figure 13.19 The pelvic organs associated with the bladder and the urethra. (A) The female. (B) The male.

male urethra is longer than in the female and is associated with both the urinary and the reproductive systems. It is described in detail in Chapter 18.

The female urethra is approximately 4 cm long and 6 mm in diameter. It runs downwards and forwards behind the symphysis pubis and opens at the external urethral orifice just in front of the vagina. The external urethral orifice is guarded by the external urethral sphincter, which is under voluntary control (Fig. 13.21).

The wall of the female urethra has two main layers: an outer muscle layer and an inner lining of mucosa, which is continuous with that of the bladder. The muscle layer has two parts: an inner layer of smooth muscle under autonomic nerve control, surrounded by an outer layer of striated (voluntary) muscle. The striated muscle forms the external urethral sphincter and is under voluntary control. The mucosa is supported by loose fibroelastic connective tissue containing blood vessels and nerves. Proximally it consists of transitional epithelium, while distally it is composed of stratified epithelium.

SPOT CHECK

5. Which structure controls the external urethral orifice in adults, allowing continence?

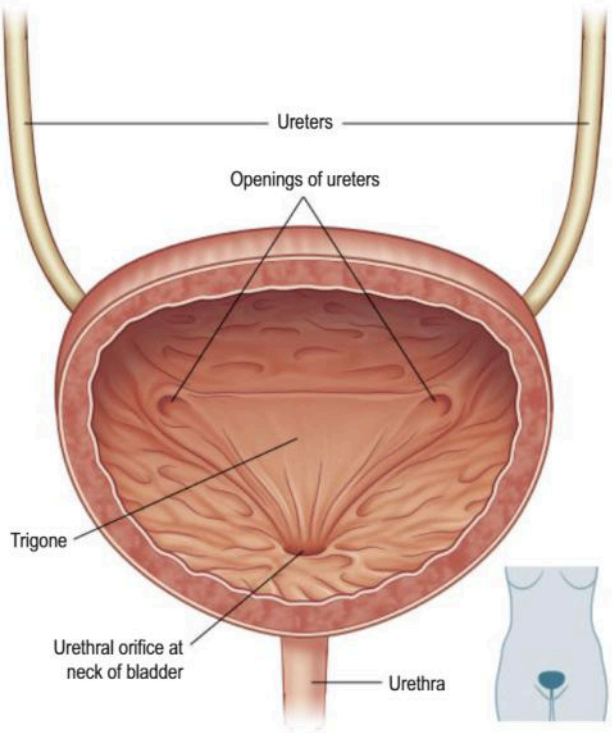

Figure 13.20 Section of the bladder showing the trigone.

Micturition

Learning outcome

After studying this section, you should be able to:

- compare and contrast the process of micturition in infants and adults.

Accumulation of urine in the bladder activates stretch receptors in the bladder wall, generating sensory (afferent) impulses that are transmitted to the spinal cord, where a spinal reflex (p. 179) is initiated. This reflex, the micturition reflex, stimulates involuntary contraction of the detrusor muscle and relaxation of the internal urethral sphincter (Fig. 13.21), and expels urine from the bladder: this is called micturition, urination or voiding of urine. The reflex leads to involuntary micturition in infants and young children until voluntary bladder control is established, usually between 18 months and 3 years of age.

After voluntary bladder control is established sensory impulses also pass upwards to the brain and awareness of the need to pass urine develops as the bladder fills (around 300–400 mL in adults). By learned and conscious effort, contraction of the external urethral sphincter and muscles of

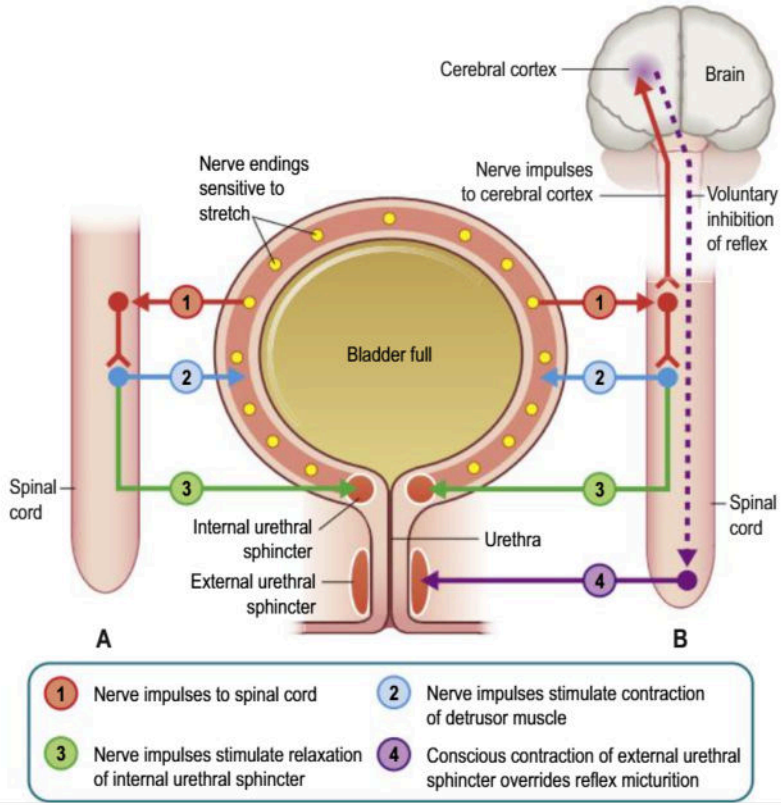

Figure 13.21 Control of micturition. (A) The involuntary micturition reflex in babies and young children. (B) Learned control of micturition: higher centres in the brain inhibit the reflex providing voluntary bladder control.

the pelvic floor are used to inhibit the micturition reflex until it is convenient to pass urine (Fig. 13.21).

Urination can be assisted by increasing the pressure within the pelvic cavity, achieved by lowering the diaphragm and contracting the abdominal muscles. Over-distension of the bladder is extremely painful, and when this occurs there is a tendency for involuntary relaxation of the external sphincter to occur, allowing a small amount of urine to escape, provided there is no mechanical obstruction. Incontinence is the involuntary leakage of urine after bladder control has been established.

SPOT CHECK

6. Briefly explain the changes needed during childhood to establish bladder control and urinary continence.

Effects of ageing on the urinary system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the urinary system.

The kidneys have a substantial functional reserve; the loss of one kidney does not cause problems in an otherwise healthy individual. The number of nephrons declines with age, glomerular filtration rate falls and the renal tubules function less efficiently; the kidneys become less able to concentrate urine.

These changes mean that older adults become more sensitive to alterations in fluid balance, and problems associated with fluid overload or dehydration are more prevalent. Elimination of drugs also becomes less efficient with declining kidney function, increasing the risk of accumulation, side effects and toxicity.

The ability to inhibit contraction of the detrusor muscle declines and may result in the urgent need to pass urine (urgency) and urinary frequency. Nocturia becomes increasingly common in older adults. Incontinence (p. 397) is more prevalent too, affecting 15% of women and 10% of men over 65, figures that double by 85 years of age.

Enlargement of the prostate gland is common in older men and may cause retention of urine and problems with micturition (see Ch. 18).

SPOT CHECK

7. Identify a common cause of urinary retention in older men.

Kidney disorders

Learning outcomes

After studying this section, you should be able to:

- outline the principal effects of glomerulonephritis and nephrotic syndrome
- describe the effects of diabetes mellitus and hypertension on kidney function
- discuss the sources and consequences of kidney infections
- explain the causes and implications of acute kidney injury and chronic kidney disease
- describe the pathogenesis of kidney stones
- list common congenital abnormalities of the kidney
- outline the development and spread of kidney tumours.

Because the kidneys have considerable functional reserve, impairment of renal function does not become evident until the equivalent of more than one kidney is lost. This is why it is possible for a person with healthy kidneys to donate one for transplantation. Table 13.2 lists common signs and symptoms of renal disorders.

Table 13.2 Common signs and symptoms of disorders of the urinary system

Sign/symptom	Definition and description
Oliguria	Urine output of less than 400 mL per day
Haematuria	Presence of blood in the urine. Leaky glomeruli allow red blood cells to escape from the glomerular capillaries and they cannot be reabsorbed from the filtrate, as they are too large. Bleeding in the urinary tract also causes haematuria
Proteinuria	Presence of protein in the urine. This is abnormal and occurs when leaky glomeruli allow plasma proteins to escape into the filtrate but they are too large to be reabsorbed
Anuria	Absence of urine
Dysuria	Pain on passing urine, often described as a burning sensation
Glycosuria	Presence of sugar glucose in the urine. This is abnormal and occurs in diabetes mellitus (p. 263)
Ketonuria	Presence of ketones in the urine. This is abnormal and occurs in, for example, starvation and diabetes mellitus
Nocturia	Passing urine during the night
Polyuria	Passing unusually large amounts of urine
Frequency of micturition	Passing urine frequently, often in small amounts
Incontinence	Involuntary leakage of urine (p. 397)

Glomerulonephritis

This term suggests inflammatory conditions of the glomerulus, but there are several types of glomerulonephritis (GN) and inflammatory changes are not always present. In many cases, GN has an autoimmune component, which leads to production of immune complexes that may lodge in the glomerular capillaries, causing inflammation and impairment of glomerular filtration. The generous arterial blood supply and filtering of the blood there both predispose to immune complexes becoming lodged in the glomeruli. Other immune mechanisms are also implicated in GN.

Classification of GN is based on several features: the cause, immunological characteristics and findings on microscopy. Microscopic distinction is based on:

- extent of damage:
  - diffuse: affecting all glomeruli
  - focal: affecting some glomeruli
- appearance:
  - proliferative: increased number of cells in the glomeruli
  - membranous: thickening of the basement membrane of the glomerular epithelium.

Examples of different types of GN, with their causes, features and prognoses, are shown in Table 13.3.

Effects of glomerulonephritis

These depend on the type.

Haematuria

This is usually painless and occurs when red blood cells are able to pass through damaged glomerular walls into the filtrate. When microscopic, it may be found only on routine urinalysis. Overt haematuria occurs when there is considerable escape of red blood cells from the glomeruli into the renal tubules, reddening the urine, while smaller amounts give urine a smoky appearance.

Asymptomatic proteinuria

Damaged glomeruli may allow protein to escape from the blood into the filtrate, which may be asymptomatic and found only during routine urinalysis. There are also other causes of asymptomatic proteinuria, including urinary tract infection. Significant proteinuria is associated with nephrotic syndrome (see below).

Acute nephritis

This is characterised by the presence of:

- oliguria (less than 400 mL urine/day in adults)
- hypertension
- haematuria
- uraemia (p. 397).

Loin pain, headache and malaise are also common.

Nephrotic syndrome

See below.

Table 13.3 Glomerulonephritis: features and prognosis of different types

Type	Cause	Presenting features	Prognosis
Diffuse proliferative	Usually follows a transient infection, especially β-haemolytic streptococcus	Acute nephritis Haematuria Proteinuria	Good in children; less good in adults, up to 40% develop hypertension or chronic kidney disease
Focal proliferative	Associated with other systemic conditions, e.g. systemic lupus erythematosus (p. 482), infective endocarditis (p. 139)	Acute nephritis Haematuria Proteinuria	Variable
Membranous	Sometimes cause is identified including infections, e.g. malaria, hepatitis B; drugs, e.g. penicillamine, diamorphine; tumours	Nephrotic syndrome Haematuria Proteinuria	Variable, but usually progresses to chronic kidney disease
Minimal-change	Unknown	Nephrotic syndrome Haematuria Proteinuria	Good in children but recurrences are common in adults

Chronic kidney disease

Chronic kidney disease (CKD, p. 394) occurs when nephrons are progressively and irreversibly damaged after the renal reserve is lost.

Nephrotic syndrome

This is not a disease in itself but is an important feature of several others. The main characteristics are:

- marked proteinuria
- hypoalbuminaemia
- generalised oedema
- hyperlipidaemia.

When glomeruli are damaged, the basement membrane of the glomerular epithelium becomes permeable, allowing plasma proteins to pass through it into the filtrate. Albumin is the main plasma protein lost because it is the most common and smallest. When the daily loss exceeds the rate of production by the liver, there is a significant fall in the total plasma protein level. The consequent low plasma osmotic pressure leads to widespread oedema and reduced plasma volume (see Fig. 5.58). This reduces renal blood flow and stimulates the renin–angiotensin–aldosterone system (Fig. 13.15), increasing reabsorption of water and sodium from the renal tubules. The reabsorbed water further reduces the blood osmotic pressure and increases the oedema. The key factor is the loss of albumin across the glomerular membrane, and as long as this continues, the vicious circle is perpetuated (Fig. 13.22). Levels of nitrogenous waste products, i.e. uric acid, urea and creatinine, usually remain normal. Hyperlipidaemia, especially hypercholesterolaemia, also occurs but the cause is unknown.

Nephrotic syndrome is associated with several diseases. In children the most common cause is minimal-change glomerulonephritis. In adults it may complicate:

- most forms of glomerulonephritis
- diabetic nephropathy (see below)
- systemic lupus erythematosus (p. 482)
- infections, e.g. malaria, hepatitis B
- drug treatment, e.g. penicillamine, captopril, phenytoin.

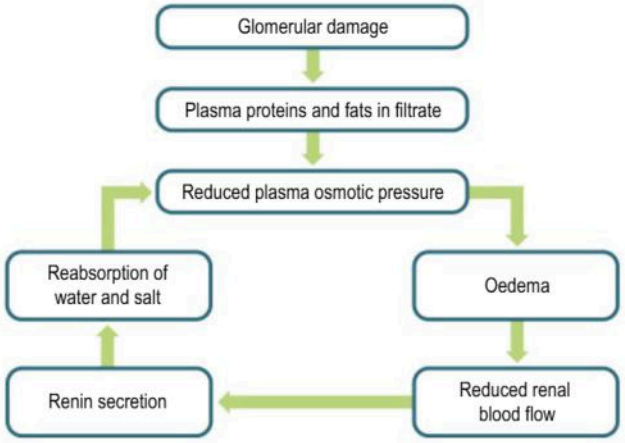

Figure 13.22 Stages of development of nephrotic syndrome.

Diabetic nephropathy

This is the commonest cause of end-stage kidney disease (see below) in the Western world and is associated with diabetes mellitus (DM, usually type 2) especially when hypertension and severe, long-standing hyperglycaemia are present. DM damages large and small blood vessels throughout the body, and in the kidney, the effects are known collectively as diabetic nephropathy. They include:

- progressive glomerular, proteinuria and nephrotic syndrome
- ascending infection, leading to acute pyelonephritis (see below)
- arteriosclerosis (Ch. 5) of the renal arteries and their branches, leading to renal ischaemia and hypertension
- chronic kidney disease (p. 394).

Hypertension and the kidneys

Hypertension can be the cause or the result of renal disease. Hypertension of any aetiology (p. 141) disrupts renal

function if renal blood vessel damage causes ischaemia. The reduced blood flow stimulates the renin–angiotensin–aldosterone system (see Fig. 13.15), raising the blood pressure still further.

Rising blood pressure is common in older adults and can cause gradual and progressive damage to the glomeruli, which may lead to chronic kidney disease after the renal reserve has been lost, or to malignant hypertension.

Malignant hypertension

Systemic damage to arterioles spreads to the glomeruli with subsequent destruction of nephrons that worsens hypertension and causes a variable degree of renal impairment. Sometimes there are more serious effects; increased permeability of the glomeruli allows escape of plasma proteins and red blood cells into the filtrate, causing proteinuria and haematuria, which may progress to renal failure.

Acute pyelonephritis

This is acute bacterial infection of the renal pelvis and calyces, which spreads to the kidney substance, causing small abscesses. Bacteria usually reach the kidney by travelling up the urinary tract from the exterior but are sometimes blood-borne. This condition is accompanied by fever, malaise and loin pain.

Ascending infection

Upward spread of bacteria from the bladder (see cystitis, p. 396) is the most common cause of this condition. Reflux of infected urine into the ureters when the bladder contracts during micturition predisposes to upward spread of infection to the renal pelves and the kidneys themselves. Normally, this is not possible because the relative positions of the ureters and bladder (see Fig. 13.16) prevent reflux.

Blood-borne infection

The kidneys are susceptible to blood-borne infection due to their large blood supply (20% of cardiac output) and its subsequent filtration there. Blood-borne bacteria may reach the kidney from infections elsewhere, e.g. the respiratory tract or an abscess.

Pathophysiology

Bacterial infection of the kidney tissue causes suppuration and occasionally papillary necrosis. Symptoms are fever, loin pain and tenderness over the kidneys. The prognosis depends on the amount of healthy kidney tissue remaining after the infection subsides. During healing, necrotic tissue is gradually replaced by fibrous tissue and there may be some hypertrophy of healthy nephrons, as a normal compensatory response. The outcomes are healing, recurrence – especially if there is a structural abnormality of the urinary tract – and reflux nephropathy.

Reflux nephropathy

Previously known as chronic pyelonephritis, this is almost always caused by reflux of urine from the bladder to the ureter, allowing upward spread of infection to the kidneys. A congenital abnormality of the angle of insertion of the ureter into the bladder predisposes to this; when the angle of insertion is less acute, the ureter is not sufficiently compressed to prevent urinary reflux as the bladder fills. It can also be acquired if an obstruction develops later in life. Progressive damage to the renal papillae and collecting ducts may lead to chronic kidney disease (see below) and concurrent hypertension is common.

Acute kidney injury

This occurs as a complication of many conditions not necessarily associated with the kidneys. The causes of acute kidney injury (AKI), previously known as acute renal failure, are classified as:

- prerenal: the result of reduced renal blood flow, e.g. in severe and prolonged shock
- renal: due to damage to the kidney itself, e.g. acute tubular necrosis, glomerulonephritis
- postrenal: arises from obstruction to the outflow of urine, e.g. prostate enlargement, tumours of the bladder, uterus or cervix or a large calculus (stone) in the renal pelvis.

There is a sudden and severe reduction in the glomerular filtration rate and kidney function that is often reversible over days or weeks with treatment. Oliguria or anuria is accompanied by metabolic acidosis due to retention of H^+, electrolyte imbalance and accumulation of mainly nitrogenous waste products.

Acute tubular necrosis

Acute tubular necrosis (ATN) is the most common cause of acute kidney injury. There is severe damage to the tubular epithelial cells, caused by ischaemia or, less often, by nephrotoxic substances (Box 13.1).

Box 13.1 Causes of acute tubular necrosis

Ischaemia – severe shock, dehydration, haemorrhage, trauma; extensive burns; myocardial infarction; prolonged and complex surgery, especially in older people

Drugs – e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, lithium compounds, paracetamol overdose

Haemoglobinaemia – accumulation of haemoglobin, released by haemolysis of red blood cells, e.g. incompatible blood transfusion, malaria

Myoglobinaemia – accumulation of myoglobin released from damaged muscle that raises blood levels, e.g. following crush injury

Oliguria, severe oliguria (less than 100 mL of urine per day in adults) or anuria (see Table 13.2) may last for a few weeks, followed by profound diuresis. There is a reduction in glomerular filtration, selective reabsorption and secretion by the tubules, leading to:

- heart failure due to fluid overload
- generalised and pulmonary oedema
- accumulation of urea and other metabolic wastes
- electrolyte imbalance, which may be exacerbated by the retention of potassium (hyperkalaemia) released from damaged cells anywhere in the body
- acidosis due to retention of hydrogen ions.

Profound diuresis (the diuretic phase) often occurs over several days at the start of recovery, when the tubular epithelial cells have regenerated but are still incapable of selective reabsorption and secretion. Diuresis may lead to acute dehydration, complicating the existing high plasma urea, acidosis and electrolyte imbalance. If the patient survives the initial acute phase, considerable renal function is usually restored during the recovery phase, which generally lasts between 1 and 3 weeks.

Chronic kidney disease

Previously known as chronic renal failure, chronic kidney disease (CKD) is insidious and asymptomatic in onset. It progresses irreversibly over several years. The main causes are diabetes mellitus, glomerulonephritis and hypertension.

The effects on GFR, selective reabsorption and tubular secretion become increasingly significant. GFR and filtrate volumes are greatly reduced and reabsorption of water is seriously impaired. This results in production of up to 10 L of urine per day (Table 13.4). Reduced glomerular filtration leads to accumulation of wastes in the blood, notably urea and creatinine.

When renal failure becomes evident, blood urea levels are raised (uraemia). Some of the signs and symptoms that may accompany this include nausea, vomiting, gastrointestinal bleeding and pruritus (itching). Others are explained here.

Polyuria

Large volumes of dilute urine with a low specific gravity are passed because water reabsorption is impaired. Nocturia is a common presenting symptom.

Table 13.4 Polyuria in chronic kidney disease

	Normal kidney	End-stage kidney disease
Glomerular filtration rate	125 mL/min or 180 L/day	10 mL/min or 14 L/day
Reabsorption of water	Over 99%	Approx. 30%
Urine output	Less than 1 mL/min or 1.5 L/day	Approx. 7 mL/min or 10 L/day

Acidosis

As the kidney buffer system that normally controls the pH of body fluids fails, hydrogen ions accumulate.

Electrolyte imbalance

This, especially hyperkalaemia, is also the result of impaired tubular reabsorption and secretion.

Anaemia

Erythropoietin (p. 70) deficiency occurs after a few months, causing anaemia that is exacerbated by haemodialysis, which damages red blood cells. If untreated, anaemia results in fatigue and possibly dyspnoea and heart failure (p. 136). Tiredness and breathlessness are sometimes the initial symptoms of chronic kidney disease.

Hypertension

This is often a consequence, if not a cause, of chronic kidney disease.

End-stage kidney disease

When death is likely without renal replacement therapy such as haemodialysis, peritoneal dialysis or a kidney transplant, the condition is referred to as end-stage kidney disease (ESKD), or sometimes end-stage renal disease. The excretory functions of the kidneys are lost, acid–base balance cannot be maintained and endocrine functions of the kidney are disrupted.

Towards the end of life, anorexia, nausea and very deep (Kussmaul's) respirations occur as uraemia progresses. In the final stages there may be hiccoughs, itching, vomiting, muscle twitching, seizures, drowsiness and coma.

Renal calculi

Calculi (stones) form in the kidneys and bladder when constituents normally dissolved in urine are precipitated, usually calcium oxalate and calcium phosphate. Stones are often recurrent and are more common in males and after 30 years of age. Most originate in the collecting tubules or renal papillae, and travel into the renal pelvis, where they may continue to grow. Some become too large to pass through the ureter and may obstruct the outflow of urine, causing kidney damage. Others travel to the bladder and either are excreted or continue to grow, obstructing the urethra (Fig. 13.23). In developing countries and often in children, stones sometimes originate in the bladder. Predisposing factors include:

- Dehydration: this increases water reabsorption from the tubules but does not change solute reabsorption, resulting in a low volume of highly concentrated filtrate in the collecting tubules.
- Raised urinary pH: when the normally acid filtrate becomes alkaline, some substances may be precipitated, e.g. phosphates. This occurs when the kidney buffering system is impaired and in some infections.

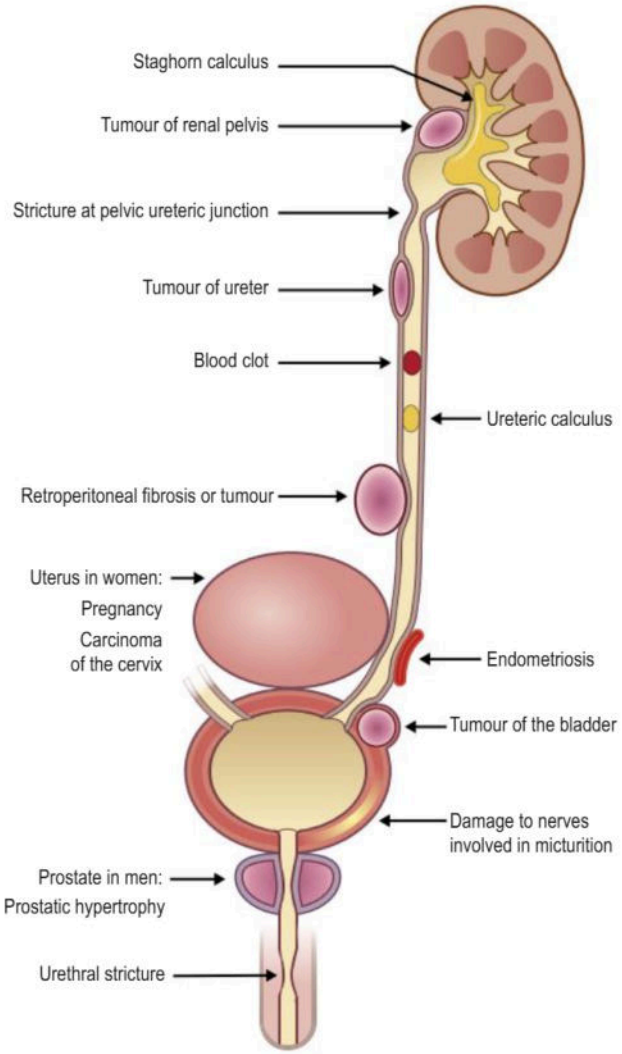

Figure 13.23 Summary of obstructions of the urinary tract.

- Infection: necrotic material and pus provide foci on which solutes in the filtrate may be deposited and the products of infection may alter the pH of the urine. Infection sometimes leads to alkaline urine (see above).
- Metabolic disorders: these include hyperparathyroidism (p. 258) and gout (p. 482).

Small calculi

These may pass through or become impacted in a ureter and damage the epithelium, leading to haematuria and, after healing, fibrosis and stricture. In ureteric obstruction, which is usually unilateral, there is spasmodic contraction of the ureter, causing acute intermittent ischaemic pain (renal colic) as the smooth muscle of the ureter contracts over the stone in an attempt to move it. Stones reaching the bladder may be passed in urine or increase in size and eventually obstruct the urethra causing retention of urine and bilateral hydronephrosis (p. 396), pyelonephritis and severe kidney damage.

Large calculi (staghorn calculus)

One large stone may form, usually over many years, filling the renal pelvis and the calyces (see Fig. 13.23), causing stagnation of urine. Large calculi predispose to infection, hydronephrosis (p. 396) and, occasionally, kidney tumours and chronic kidney disease.

Congenital abnormalities of the kidneys

Abnormal development of the urinary tract is common, affecting up to 10% of children although, many abnormalities are of little consequence.

Misplaced (ectopic) kidney

One or both kidneys may develop in abnormally low positions. Misplaced kidneys function normally if the blood vessels are long enough to provide an adequate blood supply, but a kidney in the pelvic cavity may cause problems, especially during pregnancy as the expanding uterus compresses renal blood vessels or the ureters. If the ureters become kinked, there is increased risk of infection, as there is a tendency for reflux and backflow to the kidney.

Polycystic disease

Autosomal recessive polycystic kidney disease (ARPKD)

Also known as infantile polycystic kidney disease, this is a rare inherited condition in which there is abnormal development of the kidneys and liver. It usually presents as renal failure soon after birth.

Autosomal dominant polycystic kidney disease (ADPKD)

This is inherited as an autosomal dominant condition (Ch. 17) which may become apparent any time between childhood and late adult life. Both kidneys are affected. Dilations (cysts) form at the junction of the distal convoluted tubules and collecting ducts. The cysts slowly enlarge and pressure causes ischaemia and destruction of nephrons. The disease is progressive and secondary hypertension is common. Over time, chronic kidney disease (CKD) develops in most patients. Cysts may also develop in the liver, spleen and pancreas but are not associated with dysfunction of these organs. Death may be due to CKD, cardiac failure and complications of hypertension including subarachnoid haemorrhage from a berry aneurysm (see Fig. 7.51) which is associated with this condition.

Tumours of the kidney

Benign tumours are rare.

Renal cell carcinoma

This malignant tumour of tubular epithelium is more common in males. The cause is unknown, although predisposing

factors include cigarette smoking and obesity. Clinical features include haematuria, back or loin pain, anaemia, weight loss and fever. Local spread involves the renal vein and leads to early blood spread of tumour fragments, most commonly to the lungs and bones.

Nephroblastoma (Wilms' tumour)

This is one of the most common malignant tumours in children, usually occurring in the first 4 years. Clinical features include haematuria, hypertension, abdominal pain and, sometimes, intestinal obstruction. It is usually unilateral but rapidly becomes very large and invades the renal blood vessels, causing early blood spread to the lungs.

SPOT CHECK

8. Define the terms 'oliguria', 'anuria' and 'dysuria'.

Disorders of the renal pelvis, ureter, bladder and urethra

Learning outcomes

After studying this section, you should be able to:

- describe the causes and implications of urinary obstruction
- explain the pathological features of urinary tract infections
- outline the characteristics of the main bladder tumours
- discuss the principal causes of urinary incontinence.

These structures are considered together; obstruction and infection are the main problems (Fig. 13.23).

Obstruction to the outflow of urine

This may occur anywhere between the renal pelvis and the urethra. Accumulation of urine above an obstruction may involve one or both kidneys, depending on the cause and site. When there is an abnormality of the bladder or urethra, both kidneys are affected, whereas an obstruction above the bladder is more common and affects only the kidney on that side.

Hydronephrosis

This is dilation of the renal pelvis and calyces, caused by accumulation of urine above an obstruction (Fig. 13.24). In time, it leads to destruction of the nephrons and fibrosis and atrophy of the kidney. Urinary stasis predisposes to infection.

In complete urinary tract obstruction, hydronephrosis develops quickly, pressure in the nephrons rises and urine production stops. The most common causes are a large calculus or compression by a tumour. The outcome depends on whether one or both kidneys are involved, because adequate renal function can be maintained by one kidney.

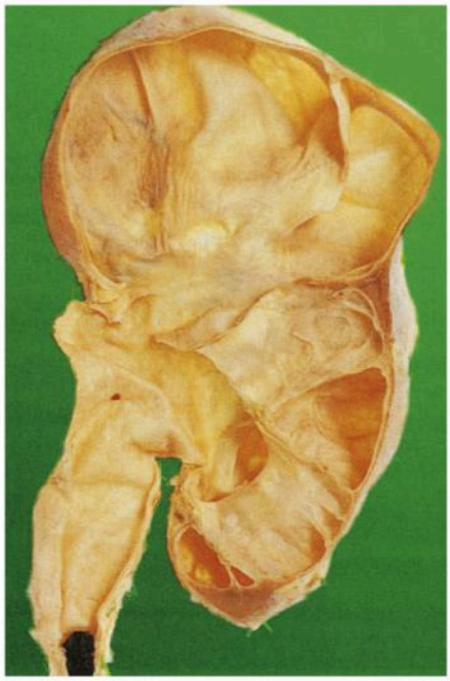

Figure 13.24 Hydronephrosis. Photograph showing dilation of the renal pelvis and calyces. From Cross S, 2019. Underwood's Pathology: a clinical approach, 7th ed. Elsevier.)

Partial or intermittent obstruction may progress undetected for many years and lead to progressive hydronephrosis. Causes include:

- recurrent renal calculi in a ureter, eventually moved onwards by peristalsis
- constriction of a ureter or the urethra by fibrous tissue, following epithelial inflammation caused by the passage of a stone or by infection
- a tumour in the urinary tract or in the abdominal or pelvic cavity
- an enlarged prostate gland in the male.

Urinary tract infections

Infection of any part of the urinary tract (a UTI) may spread upwards, causing acute pyelonephritis (p. 393) and kidney damage.

Ureteritis

Inflammation of a ureter is usually due to the upward spread of infection in cystitis.

Cystitis

This is inflammation of the bladder and may be due to:

- upward spread of commensal bacteria of the bowel (*Escherichia coli* and *Streptococcus faecalis*) from the perineum via the urethra, especially in women
- trauma, with or without infection, following healthcare interventions, e.g. radiotherapy, insertion of a urinary catheter or instrument into the bladder.

Predisposing factors include stasis of urine in the bladder and/or the shorter female urethra, which is close to the anus (see Fig. 13.19A); the moist perineal conditions there may harbour commensal microbes. Sexual intercourse may cause trauma to the urethra and transfer of microbes from the perineum, especially in the female. Hormones associated with pregnancy relax perineal muscle and cause relaxation and kinking of the ureters. Towards the end of pregnancy, pressure caused by the fetus may obstruct the outflow of urine. In the male, prostatitis provides a focus of local infection, or an enlarged prostate gland may cause progressive urethral obstruction.

The effects of inflammation include oedema and small haemorrhages of the mucosa that may cause haematuria. The sensory nerve endings in the bladder wall become hypersensitive and are stimulated even when the bladder contains only small volumes of urine, leading to frequency of micturition and dysuria. The urine may appear cloudy and have an unpleasant smell. Lower abdominal pain often accompanies cystitis. If untreated, upward spread may cause acute pyelonephritis (p. 393), which may develop into sepsis.

Cystitis is uncomplicated when it occurs in otherwise healthy individuals with a normal urinary tract. When it affects people with structural or functional abnormalities of the urinary tract or those with pre-existing conditions, such as diabetes mellitus or urinary outflow obstruction, it is described as complicated. Complicated UTIs sometimes cause permanent renal damage, whereas this is rare in uncomplicated infections. Recurrence is fairly common, especially in women, either when the original infection is not eradicated or when reinfection occurs.

Urethritis

This is inflammation of the urethra and is described in Chapter 18.

Tumours of the bladder

There is wide variation in the rates of progression and recurrence of these tumours. Most are superficial and highly amenable to treatment. Tumours are often multiple and recurrence is common. Predisposing factors include cigarette smoking, prolonged use of certain analgesics and occupational exposure to some chemicals, e.g. aniline dyes used in the textile and printing industries.

Transitional cell carcinomas

These tumours, also known as papillomas, arise from transitional epithelium, are often benign and account for 90% of bladder cancers in Europe and North America. They consist of a stalk with fine-branching fronds, which tend to break off, causing painless haematuria. Papillomas commonly recur, even when benign. Sometimes tumour cells are well differentiated and non-invasive but in other cases they behave as carcinomas and invade surrounding blood and lymph vessels.

Solid tumours

These are all malignant to some degree. The more malignant and solid tumours tend to rapidly invade the bladder wall and spread in lymph and blood to other parts of the body. If the tumour surface ulcerates, there may be haemorrhage and necrosis.

Urinary incontinence

This is involuntary leakage of urine; its prevalence increases with age.

Stress incontinence

This is leakage of urine when intra-abdominal pressure is raised, e.g. on coughing, laughing, sneezing or lifting. It usually affects women with weakness of the pelvic floor muscles or pelvic ligaments, e.g. after childbirth or as part of the ageing process. It occurs physiologically in young children before bladder control is established.

Urge incontinence

Leakage of urine follows a sudden and intense urge to void and there is inability to delay passing urine. This may be due to a urinary tract infection, calculus, tumour or hypersensitivity of the detrusor muscle.

Overflow incontinence

This occurs when there is chronic overfilling of the bladder and may be caused by retention of urine due to incomplete voiding because of obstruction, e.g. enlarged prostate gland or urethral stricture and/or impaired contraction of the detrusor muscle during micturition. It may also arise as a complication of pelvic nerve damage caused by, for example, surgery or trauma, or when the cauda equina is compressed by a tumour, spina bifida or prolapsed intervertebral disc.

The bladder becomes distended, and when the pressure inside overcomes the resistance of the external urethral sphincter, urine escapes from the urethra. There may be difficulty initiating and/or maintaining micturition. Larger than normal residual volumes of urine in the bladder (over 50–100 mL) predispose to infection.

SPOT CHECK

9. List three factors that predispose to renal calculi.

Case study

Billy has mild flu. He has been in bed for two days with a temperature and not feeling like eating or drinking much.

1. What abnormal constituent of urine is not unexpected in Billy's circumstances?

   a. White blood cells because Billy has an infection
   b. Red blood cells because GI bleeding is common in 'flu
   c. Bilirubin because increased red blood cell destruction often accompanies illness
   d. Ketones because his dietary intake is poor and Billy is metabolising body protein for energy.

2. Which of the following is an abnormal constituent of urine?

   a. Urobilin
   b. Urea
   c. Glucose
   d. Creatinine.

Having a fever has meant that Billy hasn't been passing much urine.

3. Which hormone is secreted by the posterior pituitary gland?

   a. Antidiuretic hormone
   b. Aldosterone
   c. Renin
   d. Atrial natriuretic peptide.

After drinking more fluid, Billy's kidneys produce larger volumes of urine.

4. Where in the nephron does filtration take place?

   a. Glomerulus
   b. Medullary loop
   c. Peritubular capillaries
   d. The efferent arteriole

5. After leaving the nephron, which part of the urinary system does the urine enter next?

   a. Ureter
   b. Bladder
   c. Minor calyx
   d. Renal pelvis

Review and revise

Complete each of the following statements:

1. Several hormones influence selective reabsorption in the kidneys by increasing the permeability of parts of the nephron to water. These include _____, secreted by the posterior pituitary; _____, secreted by the adrenal cortex; and _____, secreted by the atria of the heart.

2. There are different types of urinary incontinence. _____ incontinence occurs when intra-abdominal pressure is raised, e.g. during coughing. _____ incontinence follows a sudden and intense desire to void. _____ incontinence is associated with overfilling of the bladder.

Choose one answer to complete each of the following statements:

3. The proportion of glomerular filtrate that is normally reabsorbed is around: _____.
   a. 1%
   b. 10%
   c. 50%
   d. 99%

4. The ureters are lined with: _____.
   a. Transitional epithelium
   b. Stratified epithelium
   c. Adipose tissue
   d. Connective tissue

Indicate whether each of the following statements is true or false:

5. The urethra carries urine from the kidneys to the bladder. _____

6. Proteinuria can be normal. ____

7. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Erythropoietin
____ (b) Parathyroid hormone
____ (c) Renin
____ (d) Urea
____ (e) Angiotensinogen
____ (f) Bicarbonate
____ (g) Urobilin

List B

1. Bile pigment that gives urine its normal amber colour
2. Hormone secreted by the kidneys that stimulates formation of red blood cells
3. Substrate for renin
4. Bonds with H^+ to form carbonic acid
5. Hormone secreted by the parathyroid glands that influences reabsorption of calcium in the kidneys
6. Enzyme secreted by the kidneys that is involved in control of blood pressure
7. Main nitrogenous waste product found in urine

8. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Pyelonephritis
____ (b) Calculi
____ (c) Ectopic kidney
____ (d) Nephroblastoma
____ (e) Nephrotic syndrome
____ (f) Renal adenocarcinoma
____ (g) Acute tubular necrosis
____ (h) Cystitis

List B

1. Malignant kidney tumour more common after middle age
2. Presence of generalised oedema, severe proteinuria, hyperlipidaemia and hypoalbuminaemia
3. Infection of the kidney substance
4. Inflammation or infection of the bladder
5. Kidney stones
6. Most common cause of acute kidney injury
7. Common childhood malignant tumour affecting the kidney
8. Development of a kidney in an abnormally low position

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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SECTION FOUR

CHAPTER 14

The skin

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The skin completely covers the body and is continuous with the membranes lining the body orifices. It has a largely protective function but also plays a central role in the regulation of body temperature and in receiving information from the external environment.

The first parts of this chapter explore the structure and functions of the skin (the integumentary system) and the process of wound healing. The effects of ageing on the skin are discussed in the following section. The chapter concludes with a review of common skin conditions.

Structure of the skin

Learning outcome

After studying this section, you should be able to:

- describe the structure of the skin

The skin is the largest organ in the body and has a surface area of about 1.5–2 square metres in adults. In many places, the skin contains accessory structures: glands, hair and nails. It varies in thickness, being thickest on the palms of the hands and the soles of the feet. There are two main layers: the superficial layer is called the epidermis, and the deeper layer is the dermis. Beneath the dermis is a subcutaneous layer composed of areolar tissue and adipose (fat) tissue which covers and protects the underlying structures.

Epidermis

This is composed of stratified keratinised squamous epithelium (see Fig. 3.14). There are no blood vessels or nerve endings in the epidermis, but its deeper layers are bathed in interstitial fluid from the dermis, which provides oxygen and nutrients, and drains away as lymph.

There are several layers (strata) of cells in the epidermis, which extend from the deepest basal layer to the most superficial stratum corneum (a thick horny layer) (Fig. 14.1). The cells of the epidermis originate in the basal layer, which is made up of cuboidal, nucleated, highly active epithelial cells that are constantly dividing. As new cells are formed, they are pushed upwards, away from the basal layer and further from their blood and nutrient supply. As they progress towards the skin surface, their shape and structure gradually change. By the time they reach the surface, skin cells are flat, thin, non-nucleated, dead cells called squames, in which the cytoplasm has been replaced by the fibrous protein keratin. The surface squames are constantly rubbed off and replaced

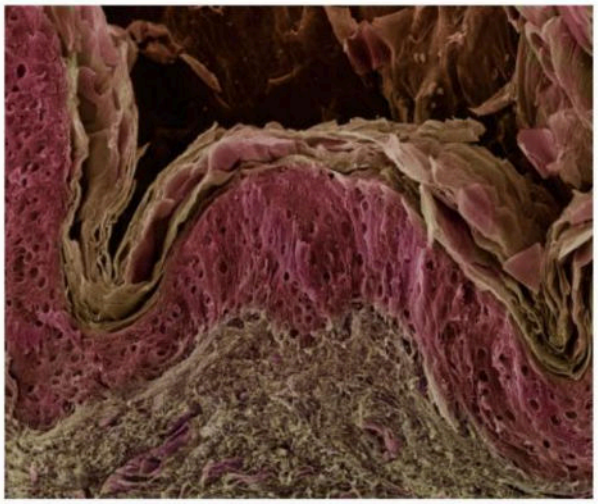

Figure 14.1 The skin. Coloured scanning electron micrograph showing the superficial stratum corneum *(pale brown)*, above the lower layers of the epidermis *(pink)* and the dermis *(grey–brown)*. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

by those beneath (see Fig. 14.4). Complete replacement of the epidermis takes about a month.

Hairs, secretions from sebaceous glands and ducts of sweat glands pass through the epidermis to reach the skin surface.

Upward projections of the dermal layer, the dermal papillae (Fig. 14.2), anchor the dermis securely to the epidermis and allow passage and exchange of nutrients and wastes to the lower part of the epidermis. This arrangement stabilises the two layers, preventing separation when the skin is subjected to shearing forces. When trauma separates the dermis and epidermis, serous fluid collects in blisters between the two layers.

Where the skin is subject to greater wear and tear, e.g. the palms and fingers of the hands and soles of the feet, the epidermis is thicker and hairs are absent. In these areas the dermal papillae are arranged in parallel lines, giving the skin surface a ridged appearance. The pattern of ridges on the fingertips is unique to every individual and the impression made by them is the fingerprint.

Skin colour is affected by various factors.

- Melanin, a dark pigment derived from the amino acid tyrosine and secreted by melanocytes in the

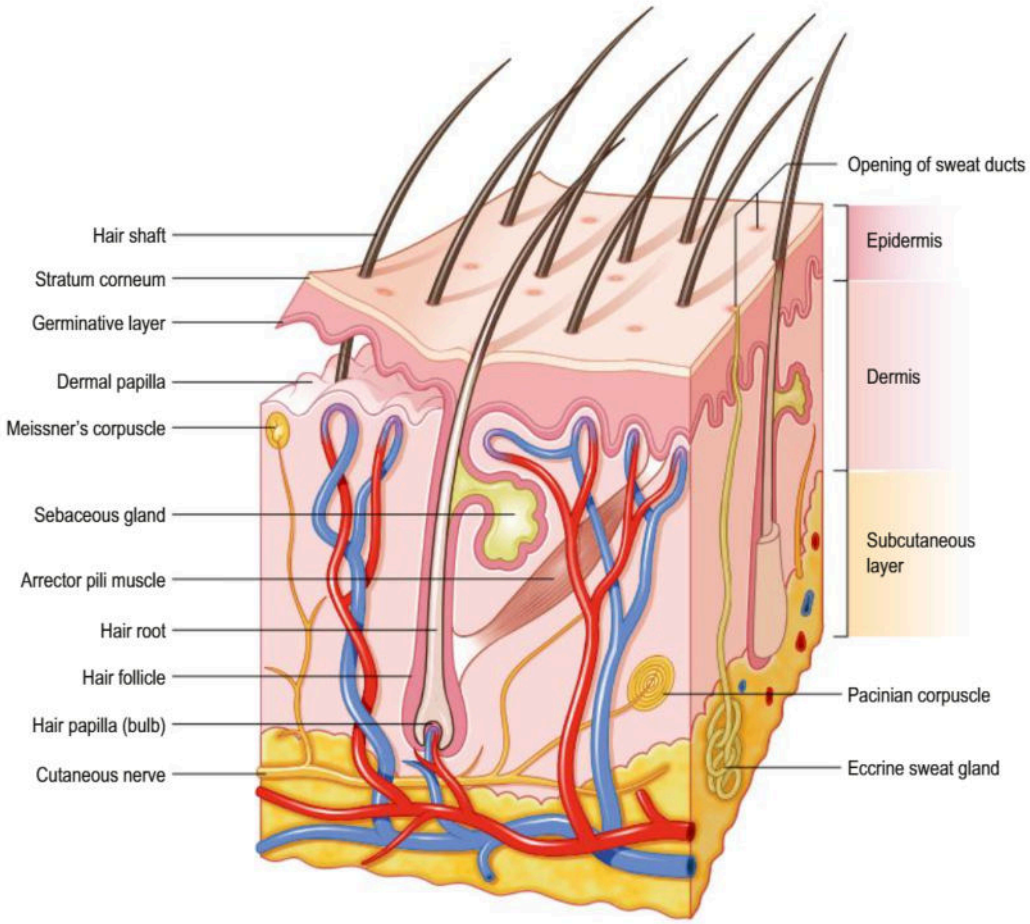

Figure 14.2 The layers of the skin and its main structures.

deep germinative layer (see Fig. 14.4), is absorbed by surrounding epithelial cells. The amount is genetically determined and varies between different parts of the body, between people of the same ethnic origin and between ethnic groups. The number of melanocytes is fairly constant, so the differences in colour depend on the amount of melanin secreted. Melanin protects the skin from the harmful effects of ultraviolet rays in sunlight; exposure to sunlight stimulates melanin synthesis.

- Normal oxygen saturation of haemoglobin and the amount of blood circulating in the dermis give white skin its pink colour. When oxygen saturation is very low, the skin in white people may appear paler or bluish (cyanosis).
- Excessive amounts of bile pigments in blood and carotenes in subcutaneous fat both give the skin a yellowish colour.

Dermis

The dermis (Fig. 14.2) is a tough and elastic layer. It is formed from connective tissue, and the matrix contains collagen fibres (see Fig. 3.17) interlaced with elastic fibres. Rupture of elastic fibres occurs when the skin is overstretched, resulting in permanent striae, or stretch marks, which are typically caused by pregnancy and obesity. Collagen fibres bind water and give the skin its tensile strength, but as this ability declines with age, wrinkles develop. Fibroblasts (see Fig. 3.8), Langerhans cells (fixed macrophages, see below) and mast cells (see Fig. 3.18) are the main cells found in the dermis. The deeper subcutaneous layer, containing areolar tissue and varying amounts of adipose (fat) tissue, lies under the dermis.

Structures found in the dermis include:

- small blood and lymph vessels
- sensory nerve endings
- sweat glands and their ducts
- hairs, arrector pili muscles and sebaceous glands.

Blood and lymph vessels

Arterioles form a fine network with capillary branches supplying sweat glands, sebaceous glands, hair follicles and the dermis. A network of lymph vessels drains the dermis.

Sensory nerve endings

Sensory receptors (specialised nerve endings) sensitive to touch, temperature, pressure and pain are widely distributed in the dermis. Incoming stimuli activate different types of sensory receptors (Fig. 14.2 and Table 14.1); for example, the Pacinian corpuscle (Fig. 14.3) is sensitive to deep pressure. Nerve impulses, generated in the sensory receptors in the dermis, are transmitted to the spinal cord by sensory nerves (Fig. 14.4). From there, impulses are conducted to the sensory area of the cerebrum, where the sensations are perceived (see Fig. 7.22B).

Table 14.1 Sensory receptors in the skin

Sensory receptor	Stimulus
Merkel cell	Light touch
Meissner's corpuscle	Light pressure
Pacinian corpuscle	Deep pressure
Free nerve ending	Pain

Sweat glands

These are widely distributed throughout the skin and are most numerous in the palms of the hands, soles of the feet, axillae and groins. These are exocrine glands, formed from epithelial cells. There are two types: eccrine and apocrine.

Eccrine sweat glands are much more numerous and are widely distributed. Their bodies lie coiled in the subcutaneous layer and their ducts open onto the skin surface through tiny pores. The sweat they produce is a clear, watery fluid important in regulating body temperature.

Apocrine sweat glands have ducts that open into hair follicles. They become active at puberty and may play a role in sexual arousal. These glands are found for example in the axilla and genital area; their secretions are more viscous and bacterial decomposition causes an unpleasant odour. A specialised type of apocrine sweat gland is the ceruminous gland of the outer ear, which secretes a brown waxy substance called cerumen (earwax, Ch. 8).

The most important function of sweat is in the regulation of body temperature (p. 405). Excessive sweating may lead to dehydration and serious depletion of sodium chloride unless intake of water and salt is appropriately increased to compensate for increased losses. After 7–10 days' exposure to high environmental temperatures the amount of salt lost is substantially reduced, although water loss remains high.

Figure 14.3 Pacinian corpuscle. (Anatomical Travelogue/Science Photo Library. Reproduced with permission.)

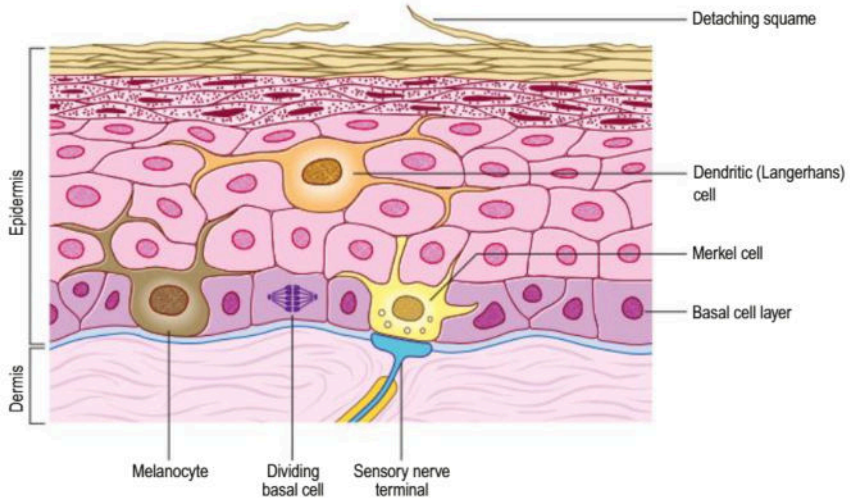

Figure 14.4 Specialised cells of the dermis. Modified from Standring S, 2021. Gray's Anatomy, 42nd ed. Elsevier.)

Figure 14.5 Coloured scanning electron micrograph of hair shafts growing through the skin. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

Hairs

These grow outwards from hair follicles, downgrowths of epidermal cells into the dermis or subcutaneous tissue. At the base of the follicle is a cluster of cells called the hair papilla or bulb. A hair is formed by multiplication of cells of the bulb and as the hairs are pushed upwards, away from their source of nutrition, the cells die and become keratinised. The part of the hair above the skin is the shaft, and the remainder the root (see Fig. 14.2). Figure 14.5 shows hair growing through the skin and also desquamation, which roughens the skin surface; the roughened surface may harbour microbial growth, although many microbes are removed by the constant rubbing off of the most superficial layers.

Hair colour is genetically determined and depends on the amount and type of melanin present. Hair turns white when melanin production by the follicle stops.

Arrector pili

Arrector pili (see Fig. 14.2) are little bundles of smooth muscle fibres attached to the hair follicles. Contraction of the muscle fibres makes the hair stand erect and raises the skin around the hair, causing 'gooseflesh'. This is stimulated by sympathetic nerve fibres in response to fear and cold. Erect hairs trap air, which acts as an insulating layer, providing an efficient warming mechanism, especially when accompanied by shivering, i.e. involuntary contraction of skeletal muscles.

Sebaceous glands

Sebaceous glands (see Fig. 14.2) consist of secretory epithelial cells. They secrete sebum, an oily antimicrobial substance, into the hair follicles and are present in the skin of all parts of the body except the palms of the hands and the soles of the feet. They are most numerous in the scalp, face, axillae and groins. In regions of transition from one type of superficial epithelium to another, such as lips, eyelids, nipple, labia minora and glans penis, there are sebaceous glands that are independent of hair follicles, secreting sebum directly on to the skin surface.

As an oily substance, sebum keeps the hair soft and pliable, gives it a shiny appearance and waterproofs the skin. It prevents drying and cracking of skin, especially on exposure to heat and sunlight. Sebum also acts as a bactericidal and fungicidal agent, preventing infection. The activity of these glands increases at puberty and is less at the extremes of age, rendering the skin of infants and older adults prone to the effects of excessive moisture (maceration).

Nails

Human nails (Fig. 14.6) are equivalent to the claws, horns and hooves of animals. Derived from the same cells as epidermis

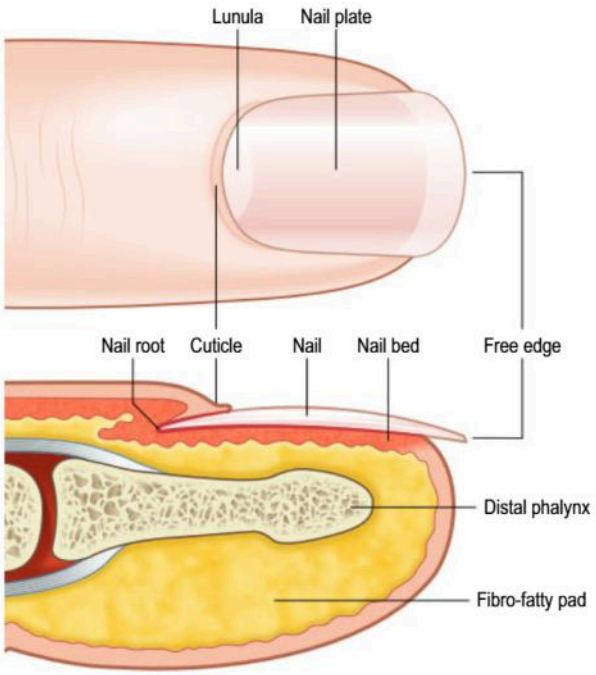

Figure 14.6 The nail and related structures.

and hair, these are hard, horny keratin plates that protect the tips of the fingers and toes.

The root of the nail is embedded in the skin and covered by the cuticle, which forms the hemispherical pale area called the lunula. The nail plate is the exposed part that has grown out from the nail bed, the basal layer of the epidermis.

Finger nails grow more quickly than toe nails and growth is faster when the environmental temperature is high.

Functions of the skin

Learning outcome

After studying this section, you should be able to:

- explain the principal functions of the skin

The skin has several important and varied functions that are explored below.

Protection

The skin forms a relatively waterproof layer, provided mainly by its superficial keratinised layer, which protects the deeper, more delicate structures. As an important non-specific defence mechanism it acts as a barrier against:

- invasion by microorganisms
- physical agents, e.g. mild trauma, ultraviolet
- chemicals
- dehydration.

The dermis contains melanocytes and specialised immune cells called dendritic (Langerhans) cells (Fig. 14.4).

Melanocytes secrete the pigment melanin, which protects against harmful ultraviolet rays in sunlight (see above).

Langerhans cells are a type of fixed macrophage (see Fig. 4.13), which phagocytose intruding antigens and present antigen to T-lymphocytes, thus stimulating an immune response against invading microorganisms (Ch. 15).

Abundant sensory nerve endings in the dermis enable very accurate perception, discrimination and location of internal and external stimuli. This allows responses to changes in the environment, e.g. by reflex action (withdrawal) to unpleasant or painful stimuli, protecting it from further injury.

Regulation of body temperature

Core body temperature remains fairly constant at around 36.8°C across a wide range of environmental temperatures, ensuring that the optimal range for enzyme activity required for metabolism is maintained. In health, variations are usually limited to between 0.5 and 0.75°C, although temperature rises slightly in the evening, during exercise and in women just after ovulation. To maintain this constant temperature, a negative feedback system regulates the balance between heat produced in the body and heat lost to the environment.

Heat production

When metabolic rate increases, body temperature rises; when it decreases, body temperature falls. Some of the energy released during metabolic activity is in the form of heat; the most active organs produce most heat. The principal organs involved are:

- Skeletal muscle contraction produces a large amount of heat; the more strenuous the muscular exercise, the greater the heat produced. Shivering, a rapid repetitive cycle of skeletal muscle contraction and relaxation, is initiated if there is a risk of body temperature falling below normal, and generates heat to keep the body warm.
- The liver is intensely active metabolically, and so generates considerable heat as a by-product. Metabolic rate and heat production are increased after eating.

In addition, the digestive organs generate smaller amounts of heat during peristalsis and the chemical reactions involved in digestion.

Heat loss

Most heat loss occurs through the skin. Small amounts are lost in expired air, urine and faeces. Heat loss through the skin but not the other routes can be regulated.

Heat loss through the skin is affected by the difference between body and environmental temperatures, the amount of the body surface exposed and the type of clothes worn. Air insulates against heat loss when trapped in layers of clothing and between the skin and clothing. For this reason, several layers of lightweight clothes provide more effective

insulation against low environmental temperatures than one heavy garment.

Mechanisms of heat loss

There are four mechanisms of heat loss (Fig. 14.7):

- Radiation, the main mechanism, when exposed parts of the body radiate heat away from the body.
- Evaporation, when the body is cooled as body heat converts the water in sweat to water vapour.
- Conduction, when clothes and other objects in direct contact with the skin take up heat.
- Convection, when air passing over exposed parts of the body is heated and rises, and cool air replaces it, setting up convection currents. Convection also cools the body when clothes are worn, except when they are windproof.

Control of body temperature

The temperature regulating centre in the hypothalamus is sensitive to the temperature of circulating blood. This centre responds to decreasing temperature by sending nerve impulses to:

- arterioles in the dermis, which constrict, decreasing blood flow to the skin
- skeletal muscles, stimulating shivering.

As heat is conserved, body temperature rises; when it returns to the normal range, the negative feedback mechanism is switched off (see Fig. 2.13).

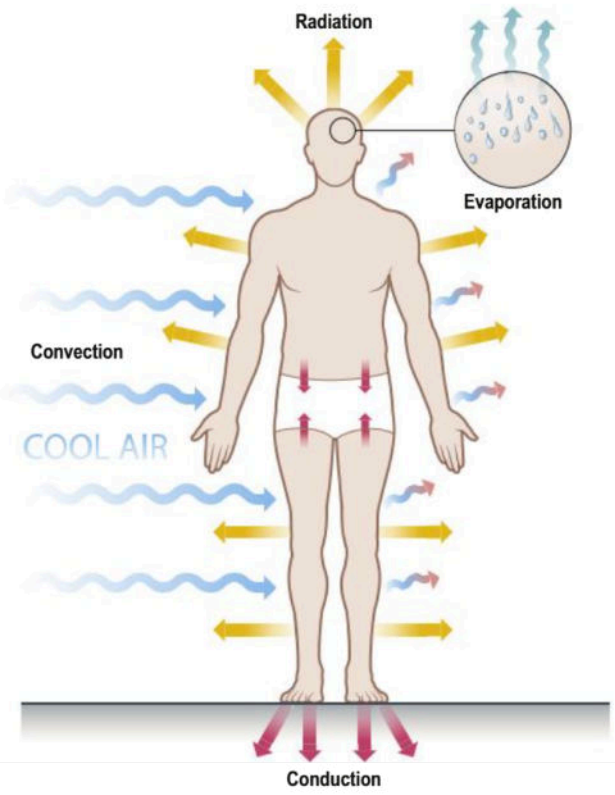

Figure 14.7 Mechanisms of heat loss.

Conversely, when body temperature rises, heat loss is increased by dilation of arterioles in the dermis, increasing blood flow to the skin, and stimulation of the sweat glands, causing sweating; this continues until body temperature falls into the normal range again, when the negative feedback mechanism is switched off.

Activity of the sweat glands

When body temperature is increased by 0.25–0.5°C the sweat glands secrete sweat onto the skin surface. Evaporation of sweat cools the body, but more slowly in humid conditions.

Loss of heat from the body by evaporation of water through the skin and expired air still occurs even when the environmental temperature is low. This is called insensible water loss (around 500 mL per day) and is accompanied by insensible heat loss.

Regulation of blood flow through the skin

The amount of heat lost from the skin depends largely on blood flow through dermal capillaries. As body temperature rises, the arterioles dilate and more blood enters the capillary network in the skin. The skin becomes warm and pink in colour. In addition to increasing the amount of sweat produced, the temperature of the skin rises and more heat is lost by radiation, conduction and convection.

If the environmental temperature is low or if heat production is decreased, the arterioles in the dermis are constricted. This reduces blood flow to the body surface, conserving heat. The skin appears paler and feels cool.

Fever

This is often the result of infection and is caused by release of chemicals (called pyrogens) from inflammatory cells and invading bacteria. Pyrogens, e.g. interleukin 1 (p. 418), act on the hypothalamus, which releases prostaglandins that reset the hypothalamic thermostat to a higher temperature (see Fig. 15.3). The body responds by activating heat-generating mechanisms, e.g. shivering and vasoconstriction, until the new higher temperature is reached. When the thermostat is reset to the normal level, heat-loss mechanisms are activated. There is profuse sweating and vasodilation, accompanied by warm, pink (flushed) skin, until body temperature falls to the normal range again. This shivering (sometimes referred to as a 'chill'), followed by profuse sweating, is known as a rigor.

Hypothermia

This is defined as a core (e.g. rectal) temperature below 35°C. At a core temperature below 32°C, compensatory mechanisms that normally restore body temperature fail, e.g. shivering is replaced by muscle rigidity and cramps, vasoconstriction fails and blood pressure, pulse and respiration rates fall. There is confusion and disorientation. Death usually occurs when the temperature falls below 25°C.

Individuals at the extremes of age are prone to hypothermia, because temperature regulation is less effective in babies, young people and older adults.

Formation of vitamin D

A lipid-based substance present in the skin, called 7-dehydrocholesterol, is converted to vitamin D by sunlight; this is discussed further in Chapter 11. This vitamin is used with calcium and phosphate in the mineralisation and maintenance of bone.

Cutaneous sensation

Sensory receptors including some specialised structures, e.g. Pacinian corpuscles, in the dermis can be sensitive to touch, pressure, temperature or pain (see Table 14.1). Stimulation generates impulses in sensory nerves, which are transmitted to the cerebral cortex where they are perceived (see Fig. 7.22B). Some areas have more abundant sensory receptors than others, causing them to be especially sensitive, e.g. the lips and fingertips. Collectively the sensory receptors enable fine discrimination between wide-ranging sensations on very specific areas of the skin.

Absorption

This property is limited but substances that can be absorbed include:

- some drugs when applied as transdermal patches, e.g. nicotine as an aid to smoking cessation, hormone replacement therapy during the menopause
- some toxic chemicals, e.g. mercury.

Excretion

The skin is a minor excretory organ for some substances, including:

- sodium chloride in sweat; excess sweating may lead to low blood sodium levels (hyponatraemia)
- urea, especially when kidney function is impaired
- aromatic substances, e.g. garlic and other spices.

SPOT CHECK

1. Outline four ways in which the skin protects the structures underneath it.
2. Define hypothermia.

Wound healing

Learning outcome

After studying this section, you should be able to:

- compare and contrast the processes of primary and secondary wound healing.

Conditions required for wound healing

Wound healing is affected by many factors, some of which can be modified. In wound management, those that support healing should be promoted, while those that impair it avoided or minimised when possible.

Systemic factors

These include good nutritional status and general health. Infection, impaired immunity, poor blood supply and systemic conditions, e.g. diabetes mellitus and cancer, all reduce the rate of wound healing.

Local factors

Local factors that facilitate wound healing include a good blood supply to provide oxygen and nutrients and remove waste products, and freedom from contamination by, for example, microbes, foreign bodies or toxic chemicals.

Primary healing (healing by first intention)

This type of healing follows minimal destruction of tissue when the damaged edges of a wound are in close apposition, e.g. a surgical incision (Fig. 14.8). There are several overlapping stages in the repair process.

Inflammation

In the first few hours the cut surfaces become inflamed, and blood clot (mainly fibrin, see Fig. 4.16) and cell debris fill the gap between them. Phagocytes, including macrophages, and fibroblasts migrate into the blood clot:

- Phagocytes begin to remove the clot and cell debris, stimulating fibroblast activity.
- Fibroblasts secrete collagen fibres, which begin to bind the wound margins together.

Proliferation

Epithelial cells proliferate across the wound, through the clot. The epidermis meets and grows upwards until full thickness is restored. The clot above the new tissue becomes the scab, which separates after 3–10 days.

Granulation tissue, consisting of new capillary buds, phagocytes and fibroblasts, develops, invading the clot and restoring blood supply to the wound. Fibroblasts continue to secrete collagen fibres as the clot and any bacteria are removed by phagocytosis. This is closely regulated by several locally released growth factors and is usually complete about 3 weeks after the injury.

Maturation

The granulation tissue is gradually replaced by fibrous scar tissue. Rearrangement of collagen fibres occurs and the strength of the wound increases. In time the scar fades as it becomes less vascular, appearing after a few months as a fine line.

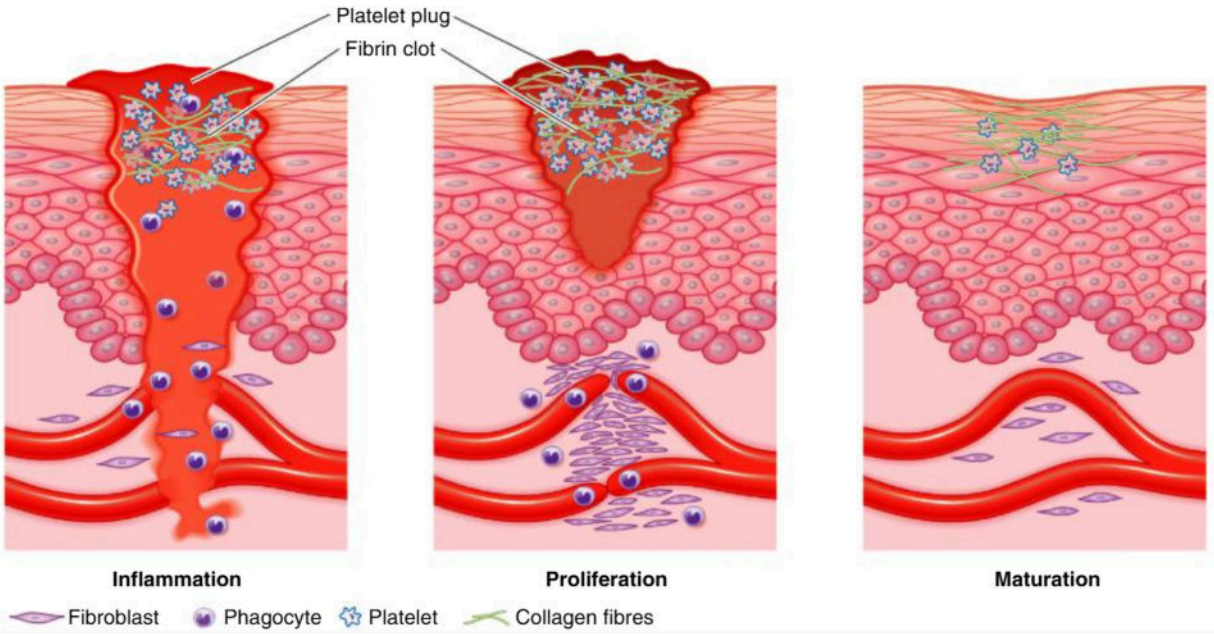

Figure 14.8 Stages in primary wound healing.

The channels left when stitches are removed heal by the same process.

Secondary healing (healing by second intention)

This type of healing occurs when there is extensive tissue destruction or when the edges of a wound cannot be brought into apposition, e.g. varicose ulcers and pressure ulcers. The stages of secondary healing (Fig. 14.9) are the same as those in primary healing (described above) and is also controlled by growth factors. Healing time depends on effective removal of the cause and on the size of the wound.

Inflammation

This develops on the surface of the healthy tissue and separation of necrotic tissue (slough) begins, due mainly to the action of phagocytes in the inflammatory exudate. The inflammatory process is described on page 417.

Proliferation

This begins as granulation tissue, consisting of capillary buds, phagocytes and fibroblasts, develops at the base of the cavity. Granulation tissue grows towards the surface, stimulated by macrophages and a range of locally released chemicals although the process remains poorly understood. Phagocytes in the plentiful blood supply reduce or prevent infection of the wound by ingesting bacteria after separation of the slough. Some fibroblasts in the wound, called myofibroblasts, develop a limited ability to contract, reducing the size of the wound and healing time. When granulation tissue reaches the level of the dermis, epithelial cells at the edges proliferate and grow towards the centre.

Maturation

This occurs by fibrosis (see below), in which scar tissue replaces granulation tissue, usually over several months, until the full thickness of the skin is restored. Scar tissue is inelastic and does not contain sweat glands, hair follicles or sebaceous glands.

Fibrosis (scar formation)

Fibrous tissue is formed during healing by secondary intention, e.g. following chronic inflammation, persistent ischaemia, suppuration or extensive trauma. The process begins with formation of granulation tissue; then, over time, the inflammatory material is removed, leaving only the collagen fibres secreted by the fibroblasts. Fibrous tissue may have long-lasting damaging effects.

Fibrosis of infarctions

Blockage of a blood vessel by a thrombus or an embolus causes an infarction (p. 129). Fibrosis of one large or numerous small infarctions may follow, leading to varying degrees of structural damage causing organ dysfunction, e.g. in the heart, brain, kidneys or liver.

Tissue shrinkage

This occurs as fibrous tissue shrinks as it matures. The effects depend on the site and extent of the fibrosis, e.g.:

- Small tubular structures, such as blood vessels, air passages, ureters, the urethra and ducts of glands may become narrow or obstructed and lose their elasticity.
- Contractures (bands of shrunken fibrous tissue) may extend across joints, e.g. in a limb or digit, and limit movement.

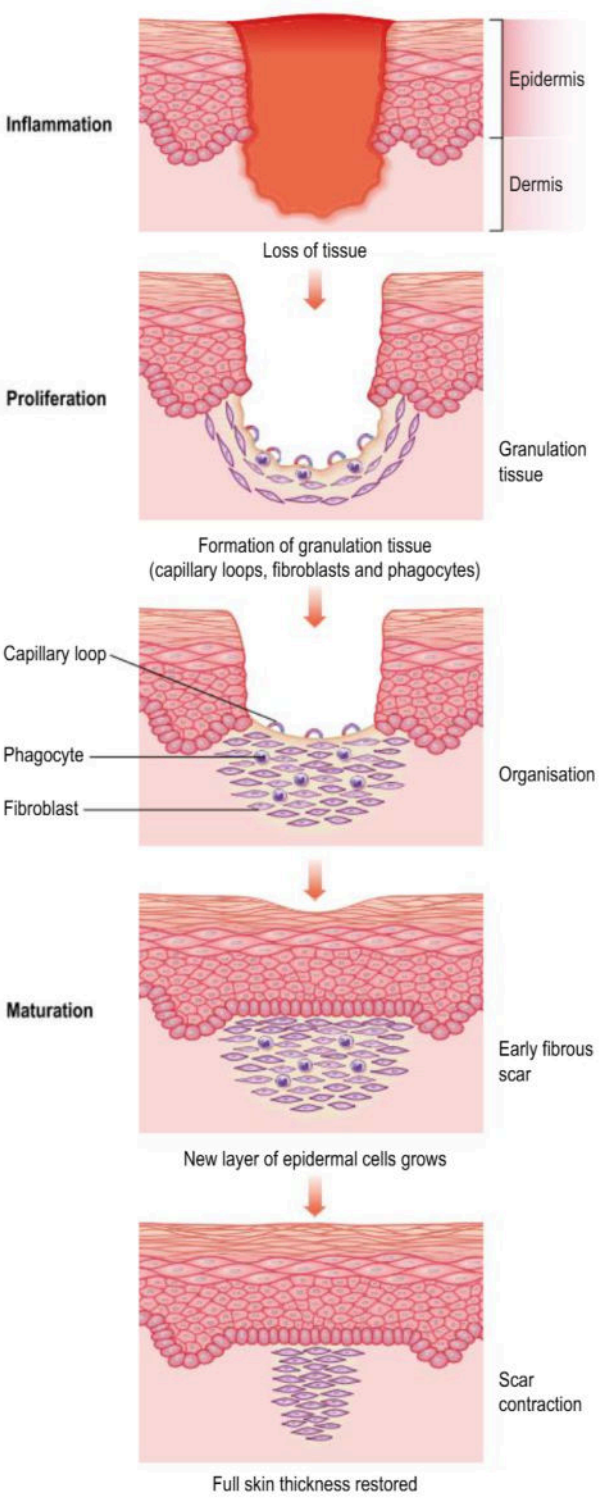

Figure 14.9 Stages in secondary wound healing.

Adhesions

These develop as shrinkage of fibrous tissue causes adjacent structures to stick together. This may limit movement, e.g. between the layers of pleura, preventing inflation of the lungs, or between loops of bowel, interfering with peristalsis.

Complications of wound healing

In addition to the effects of fibrosis of infarctions and tissue shrinkage including adhesions, others are outlined here.

Infection

This arises from microbial contamination, usually by bacteria, and results in formation of pus (suppuration).

Pus consists of dead phagocytes, other dead cells, cell debris, fibrin, inflammatory exudate and living and dead microbes. The most common pyogenic (pus-forming) pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes*. Small amounts of pus form boils and larger collections form abscesses. *S. aureus* produces the enzyme coagulase, which converts fibrinogen to fibrin, localising the pus. *S. pyogenes* produces toxins that break down tissue, spreading the infection. Healing following pus formation is by secondary intention (see above).

Superficial abscesses tend to rupture and discharge pus through the skin. Healing is usually complete unless tissue damage is extensive.

Deep abscesses have a variety of outcomes, which include:

- early rupture with complete discharge of pus onto the surface, followed by healing
- rupture and limited discharge of pus onto the surface, followed by the development of a chronic abscess with an open channel, called a sinus (Fig. 14.10)
- rupture and discharge of pus into an adjacent organ or cavity, forming an infected channel open at both ends, a fistula (Fig. 14.11)
- eventual removal of pus by phagocytes, followed by healing

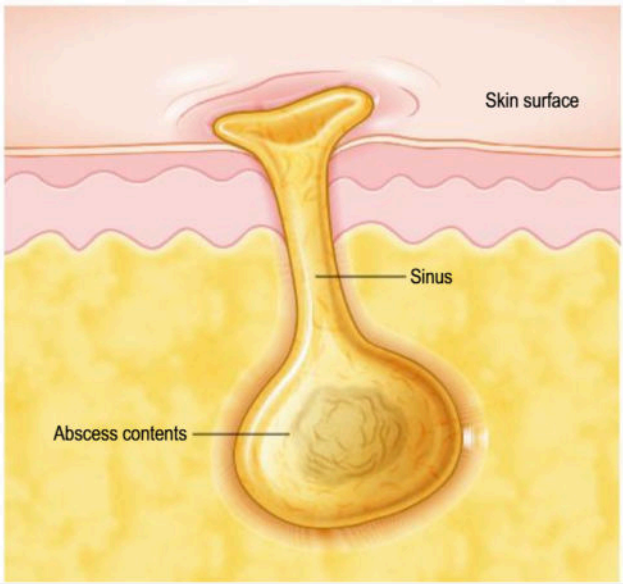

Figure 14.10 Sinus between a deep abscess and the body surface.

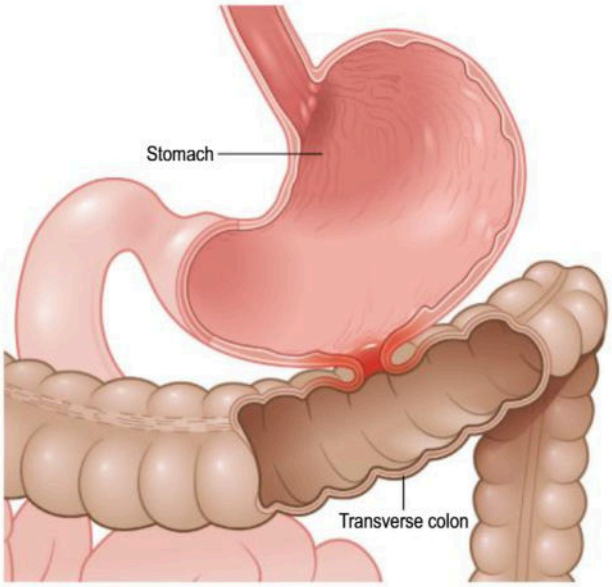

Figure 14.11 Fistula between the stomach and the colon.

- enclosure of pus by fibrous tissue that may become calcified, harbouring live organisms that may become a source of future infection, e.g. tuberculosis (Ch. 10)
- formation of adhesions (see above) between adjacent membranes, e.g. pleura, peritoneum
- shrinkage of fibrous tissue (see above), which may constrict the lumen or obstruct a tube, e.g. oesophagus, bowel, blood vessel.

SPOT CHECK

3. List the stages of wound healing.

Effects of ageing on the skin

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the structure and function of the skin.

From the third decade, there are gradual changes in the structure and function of the skin, which become increasingly prominent with age. As the basal layer becomes less active, the epidermis thins. The dermis also thins and there are fewer elastic and collagen fibres, which causes wrinkling and sagging. These changes may be accelerated by chronic and/or repeated exposure to strong sunlight, which is also associated with the development of malignant changes.

Sweat gland activity and temperature regulation become less efficient, putting older adults at greater risk in extreme temperatures because they are more prone to heatstroke and hypothermia. Less sebum is secreted, making the skin dry and more susceptible to damage from continual exposure to moisture (maceration).

Production of vitamin D decreases, predisposing older adults to deficiency and reduction in bone strength, especially when exposure to sunlight is limited.

Melanocytes become less active, causing older adults to be more sensitive to sunlight and prone to sunburn. In hair, loss of the pigment melanin causes greying. There are fewer active hair follicles and therefore hair thins, although in some areas this is not the case: notably, the eyebrows, nose and ears in males, and the face and upper lip in females.

SPOT CHECK

4. Why are older adults prone to macerated skin?

Disorders of the skin

Learning outcomes

After studying this section, you should be able to:

- list the causes of the diseases described here
- explain the pathological features and effects of common skin conditions.

Infections

Viral infections

Human papilloma virus

Warts and verrucae (singular: verruca) are caused by human papilloma virus (HPV). They commonly affect the hands, the face and the soles of the feet and are spread by direct contact, e.g. from another lesion or another infected individual. The epidermis proliferates and a small, firm growth develops, which is nearly always benign. Another strain of HPV is largely responsible for cervical cancer (see Ch. 18).

Herpes viruses

Rashes seen in chickenpox and shingles (p. 204) are caused by the herpes zoster virus. Other types of herpesvirus cause cold sores (herpes simplex virus 1, p. 356) and genital herpes (herpes simplex virus 2, p. 519).

Bacterial infections

Impetigo

This highly infectious condition is usually caused by *Staphylococcus aureus*. Superficial pustules develop, usually round the nose and mouth. It is spread by direct contact and affects mainly children and immunosuppressed individuals. When caused by *Streptococcus pyogenes* (a group A β-haemolytic streptococcus) the infection may be complicated by an immune reaction, causing glomerulonephritis (p. 391) a few weeks later.

Cellulitis

This is a spreading infection caused by some anaerobic bacteria, including *Streptococcus pyogenes* and *Clostridium perfringens*, which enter through a break in the skin. Their spread is facilitated by the formation of enzymes, which break down the connective tissue that normally isolates an area of inflammation. If the infection is untreated, the bacteria may enter the blood, causing bacteraemia.

In severe cases, necrotising fasciitis may occur. There is rapid and progressive necrosis of subcutaneous tissue that usually includes the fascia in the affected area. Multiple organ failure is common and mortality is high.

Fungal infections (mycoses)

Fungal infections are more common in warm, moist, unwashed areas of skin, such as skin folds and between the toes, and also in immunocompromised individuals.

Ringworm and tinea pedis

These are superficial skin infections. In ringworm there is an outward spreading ring of inflammation with a clear patch of apparently normal skin in the centre. It most commonly affects the scalp, feet and groin and is easily spread to others. Tinea pedis (athlete's foot) affects the skin between the toes. Both infections are spread by direct contact.

Non-infective inflammatory conditions

Dermatitis (eczema)

Dermatitis is a common inflammatory skin condition that may be either acute or chronic. In acute dermatitis there is redness, swelling and exudation of serous fluid, usually accompanied by pruritus (itching). This is often followed by crusting and scaling. If the condition becomes chronic, the skin thickens and may become leathery due to long-term scratching, which may also cause infection.

Atopic dermatitis

This is associated with allergy and commonly affects atopic individuals, i.e. those prone to hypersensitivity disorders (p. 426). Children, who may also suffer from hay fever or asthma (pp. 292 and 294), are often affected.

Contact dermatitis

This may be caused by direct contact with irritants, e.g. cosmetics, soap, detergent, strong acids or alkalis, industrial chemicals or a hypersensitivity reaction (see Fig. 15.11) to latex, nickel, dyes and other chemicals.

Psoriasis

Genetic and environmental factors are implicated in the development of this common condition, which is characterised by exacerbations and periods of remission of varying duration. Trigger factors that worsen the condition include trauma, infection, sunburn and some drugs. It is thought that anxiety and stress may also contribute in some individuals. Psoriasis is sometimes associated with rheumatoid arthritis (p. 481).

Cell division in the basal layer of the epidermis increases, so that new cells are pushed more quickly towards the surface. Transit time from the basal to the superficial layer may be as little as 5 days (instead of the normal 28 days), so that cells arriving at the surface have not had time to mature into keratinised squames.

Psoriasis is characterised by red, scaly plaques with a silvery surface (Fig. 14.12). Bleeding may occur when scales are scratched or rubbed off. The elbows, knees and scalp are common sites.

Figure 14.12 Psoriasis. (Biophoto Associates/Science Photo Library. Reproduced with permission.)

Acne vulgaris

This most frequently affects adolescent males and is thought to be caused by increased levels of testosterone after puberty. Sebaceous glands (in hair follicles) become blocked and then infected, leading to inflammation and pustule formation. In severe cases permanent scarring may result. The most common sites are the face, chest and upper back.

Vitiligo

This common and chronic condition affects about 1%–2% of the global population and about 30% of cases start in childhood. It is an autoimmune disorder and often associated with other autoimmune conditions, especially those of the thyroid. There is patchy loss of melanocytes that causes corresponding irregular areas of very pale skin (Fig. 14.13). Depigmentation is more apparent on darker skin; large areas and any part of the body may be affected.

Figure 14.13 Vitiligo. (From Science Photo Library. Reproduced with permission.)

Pressure ulcers

Also known as decubitus ulcers or bedsores, these occur over pressure points, areas where the skin may be compressed for long periods between a bony prominence and a hard surface, e.g. a bed or chair. When this occurs, blood flow to the affected area is impaired and ischaemia develops. Initially, the skin reddens and later, as ischaemia and necrosis occur, the skin sloughs and an ulcer forms; this may then enlarge into a cavity. If infection occurs, this can result in sepsis. Healing takes place by secondary intention (p. 408).

Predisposing factors may be:

- extrinsic, e.g. pressure, shearing forces, trauma, immobility, moisture
- intrinsic, e.g. poor nutritional status, emaciation, incontinence, infection, concurrent illness, sensory impairment, poor local circulation.

Burns

Burns may be caused by many types of trauma, including heat, cold, electricity, ionising radiation and corrosive chemicals, such as strong acids or alkalis (bases). Local damage disrupts the structure and functions of the skin.

Burns are classified according to their depth:

- Superficial (epidermal), involving only the epidermis. The surface is moist and there are signs of inflammation, including redness, swelling and pain. Tissue damage is minimal.
- Partial thickness when the epidermis and upper dermis are affected. In addition to the signs and symptoms listed above, blistering is also present.
- Full thickness when both the epidermis and dermis are damaged. These burns are usually relatively painless, as the sensory nerve endings in the dermis are destroyed. After a few days the destroyed tissue coagulates and forms an eschar, or thick scab, which sloughs off after 2–3 weeks.In circumferential burns, which encircle any area of the body, complications may arise from constriction of the part by eschar, e.g. respiratory impairment may follow circumferential burns of the chest, or the circulation to the distal part of an affected limb may be seriously impaired. Skin grafting is required except for small injuries. Healing, which is prolonged, occurs by secondary intention (p. 408) and there is no regeneration of sweat glands, hair follicles or sebaceous glands. Resultant scar tissue often limits movement of affected joints.

The extent of burns in adults is roughly estimated using the 'rule of nines' (Fig. 14.14). In adults, hypovolaemic shock usually develops when 15% of the surface area is affected. Mortality is high in adults with full-thickness burns if the surface area affected is added to the patient's age and the total exceeds 100.

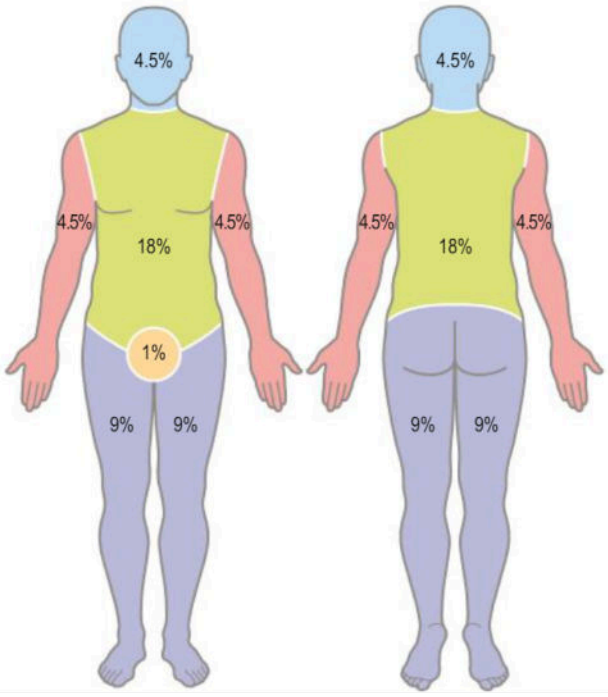

Figure 14.14 The 'rule of nines' for estimating the extent of burns in adults.

Complications of burns

Although burns primarily affect the skin, the systemic consequences of extensive burns can also be life-threatening or fatal.

Dehydration, hypovolaemia and shock

These may occur in extensive burns when excessive leakage of water and plasma proteins from the damaged skin surface results in dehydration. Ongoing losses lead to hypovolaemia and, without treatment, development of shock.

Hypothermia

This develops because heat is continually lost in leakage from burns.

Infection

When subcutaneous tissue is exposed to the environment, microbes can contaminate the wound causing local infection. If severe, this may progress to sepsis.

Acute kidney injury

Acute tubular necrosis (p. 393) occurs after severe burns when the nephrons are damaged by the large amounts of waste circulating in the bloodstream from haemolysed erythrocytes and inflamed and degenerating burn tissue.

Contractures

These are long-term complications that develop later. Fibrous scar tissue contracts as it matures, and significant contraction may distort joints such as the hands and restrict their range of movement.

Figure 14.15 Malignant melanoma. (James Stevenson/Science Photo Library. Reproduced with permission.)

Malignant tumours

Basal cell carcinoma

This is the least malignant and most common type of skin cancer. It is associated with long-term exposure to sunlight and is therefore most likely to occur in older adults on sun-exposed sites, usually the head or neck. It appears as a shiny nodule which later breaks down, becoming an ulcer with irregular edges, commonly called a rodent ulcer. Although this tumour is locally invasive, it seldom metastasises.

Malignant melanoma

This is malignant proliferation of melanocytes; it accounts for only 4% of skin cancers but 80% of skin cancer deaths. It usually originates in an enlarging mole that may have an irregular outline (Fig. 14.15) and typically ulcerates and bleeds. The incidence is increasing and it commonly affects young and middle-aged adults. Predisposing factors are a fair skin and recurrent episodes of intensive exposure to sunlight, including repeated episodes of sunburn, especially in childhood. Sites for this tumour show a gender bias, with the lower leg being the most common site in females and the upper back in males. Metastases usually develop early and are associated with a poor prognosis. Initial spread is usually to nearby lymph nodes and followed by blood-spread metastases in the liver, brain, lungs, bowel and bone marrow.

Kaposi's sarcoma

This malignant tumour arises from the walls of blood and lymphatic vessels. It is associated with human herpesvirus 8 and is usually AIDS-related. A small red–blue patch or nodule develops, usually on the lower limbs but the mouth, oesophagus, stomach and intestines can also be affected. Without treatment, skin lesions enlarge and become more numerous.

SPOT CHECK

5. Which skin cancer usually starts as a dark, enlarging mole with an irregular outline?

Case study

Billy, who has been in bed with flu, also featured in the previous case study (p. 398). He experienced episodes of sweating when his temperature was high.

1. Sweating helps to cool the body by which mechanism?

   a. Conduction
   b. Convection
   c. Radiation
   d. Evaporation

Profuse sweating leads to loss of water and electrolytes, especially sodium.

2. This would be evident in a blood sample as:

   a. Hypernatraemia
   b. Hyponatraemia
   c. Hyperkalaemia
   d. Hypokalaemia

3. Which part of the brain acts as the body thermostat and controls body temperature?

   a. Hypothalamus
   b. Thalamus
   c. Cerebellum
   d. Pons

As he continued to feel hot, Billy pushed back the blankets.

4. This led to further heat loss primarily by:

   a. Conduction
   b. Convection
   c. Radiation
   d. Evaporation

Review and revise

Complete each of the following statements:

1. When the body needs to cool down, the blood vessels called _____ dilate to divert more blood to the skin. Use of a fan generates currents and heat is lost by _____. This also assists in conversion of sweat into water vapour, a process known as _____.
2. A burn that involves only the epidermis is defined as _____. If it also involves the upper dermis and there is blistering of the skin, it is described as _____. Deeper burns are called _____ burns.

Choose one answer to complete each of the following statements:

3. The healthy epidermis is formed from: _____
   a. One layer of columnar epithelium
   b. Several layers of connective tissue
   c. Division of epithelial cells in the basal layer, which are pushed upwards
   d. Blood vessels, nerve endings, sebaceous glands and sweat glands

4. The skin condition that is characterised by red, scaly skin that often affects the elbows, knees and scalp is called: _____
   a. Atopic dermatitis
   b. Contact dermatitis
   c. Impetigo
   d. Psoriasis

5. Match each letter in List A to the appropriate number in List B:

List A

____ (a) Melanin
____ (b) Fistula
____ (c) Fibroblast
____ (d) Sebum
____ (e) Arrector pili
____ (f) Macrophage
____ (g) Interleukin 1
____ (h) Keratin

List B

1. Secretory product of sebaceous glands
2. A pyrogen
3. Fibrous protein of hair, nails and outer epidermis
4. An abnormal channel between two body structures
5. Collagen-secreting cell
6. Phagocytic cell
7. Bundles of smooth muscle cells attached to hair follicles
8. Pigment that protects against sunlight

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 15

Defence and immunity

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Review and revise 430

From the months spent in the womb to the end of life, the individual is under constant attack from an enormous range of potentially harmful entities. These threats include bacteria, viruses, parasites, chemicals, mutated body cells and foreign (non-self) cells, e.g. in tissue transplant. The body has developed a wide selection of protective measures, which can be divided into two categories.

Non-specific (innate) defence mechanisms

This is a collection of cells, defensive chemicals and physical barriers that protect against an enormous range of infections and harmful chemicals and are present at birth, hence the term 'innate'. They can be considered as the body's first line of defence.

Specific defence mechanisms (immunity)

Specific (adaptive) immunity can be considered the body's second line of defence, activated when required by the innate defence system or by the presence of microbes or microbial products in body tissues. The immune system is a collection of organs, cells and chemicals that generates defence cells and antibodies to eliminate a specific target. Any cell or substance that stimulates an immune response is called an antigen.

Immunity is sometimes called adaptive immunity because it adapts, refines and strengthens its response when repeatedly exposed to the same antigen. This ability to 'learn' is responsible for the development of immunological memory, giving long-term immunity to specific infections. The key defenc e cells providing immunity are two types of lymphocyte, called T-lymphocytes (T-cells) and B-lymphocytes (B-cells).

The later sections of the chapter describe the effects of ageing on the immune system and consider some disorders of immune function.

Non-specific (innate) defence mechanisms

Learning outcomes

After studying this section, you should be able to:

- identify the body's main non-specific defence cells
- describe the functions and features of the inflammatory response
- explain the process of phagocytosis
- list the main antimicrobial substances in the body.

Non-specific defence mechanisms are the first lines of general defence; they prevent entry and minimise further passage

of microbes and other foreign material into the body. They offer a rapid response system, permanently mobilised and providing constant protection.

There are five broad categories:

- epithelial barriers
- phagocytes and phagocytosis
- antimicrobial chemicals
- the inflammatory response
- immunological surveillance.

Epithelial barriers

Healthy, intact skin and mucous membranes provide an efficient physical barrier protecting the body's exposed surfaces. The skin carries a rich population of bacteria, called commensals, that do not normally cause infections, but which discourage the growth of other, potentially pathogenic organisms. This means that few pathogens can establish themselves on healthy skin. Sebum and sweat secreted on to the skin surface contain antibacterial and antifungal substances.

Epithelial membranes lining body cavities and passageways exposed to the external environment (e.g. the respiratory, genitourinary and digestive tracts) are more delicate but are also well defended. Epithelia produce antibacterial secretions, often acidic, containing antibodies and enzymes, as well as sticky mucus for trapping passing microbes.

Hairs in the nose act as a coarse filter, and the sweeping action of cilia in the respiratory tract (see Fig. 10.12) moves mucus and inhaled foreign materials towards the throat to be coughed up or swallowed.

The one-way flow of urine from the bladder minimises the risk of infection ascending through the urethra into the bladder. In the female the acidity of vaginal secretions discourages microbial growth.

Phagocytes and phagocytosis

The process of phagocytosis ('cell eating') is shown in Figure 4.11. Phagocytic defence cells, including neutrophils and macrophages, are the body's first line of cellular defence. Phagocytes actively migrate to sites of inflammation and infection (chemotaxis, see below) and indiscriminately engulf, digest and destroy foreign cells, antigenic material and damaged body cells and debris (Fig. 15.1).

Neutrophils are very short-lived once activated and destroy themselves as well as their targets when actively phagocytosing antigen.

Macrophages are specialised defence cells with a range of key functions in inflammation and immunity. They are effective phagocytes with a much longer lifespan than neutrophils, and also have an important role in activating the immune system in response to infection. After phagocytosis of an antigen, they display fragments of that antigen on their own cell surface to stimulate T-cells and activate the adaptive immune response (see later). Macrophages also produce a range of substances that promote key aspects of the inflammatory response, including production and recruitment of neutrophils, the induction of fever and healing.

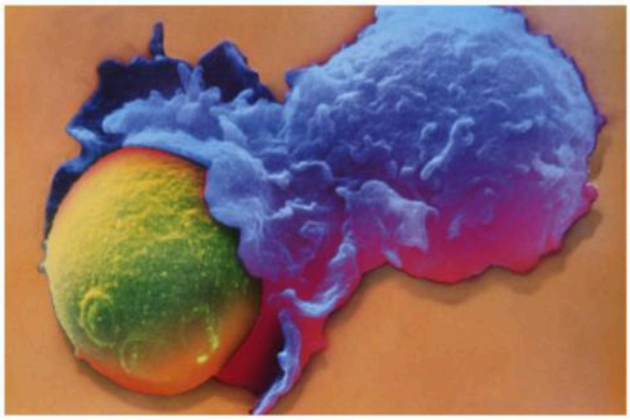

Figure 15.1 Phagocytosis. A white blood cell *(blue)* phagocytosing a yeast cell *(yellow)*. (Biology Media/Science Photo Library. Reproduced with permission.)

The body's population of fixed and roaming macrophages (the mononuclear phagocyte system, see Fig. 4.13) is discussed in Chapter 4. Other important populations of phagocytes include glial cells in the nervous system (p. 165) and osteoclasts in bone tissue (p. 433).

Antimicrobial chemicals

Hydrochloric acid

This is present in high concentrations in gastric juice and kills the majority of swallowed microbes. The pH of gastric fluids is between 1 and 2. Disorders and drugs that reduce gastric acidity increase susceptibility to gastrointestinal infection.

Lysozyme

This antibacterial enzyme is present in granulocytes, tears and other body secretions but not in sweat, urine or cerebrospinal fluid. It destroys bacterial cell walls but does not affect viruses or other pathogens.

Antibodies

These protective proteins synthesised by plasma cells (see Fig. 15.6) bind to and destroy antigens. They distribute into all body fluids, and coat membranes exposed to the external environment, e.g. those of the genitourinary, respiratory and gastrointestinal tracts.

Saliva

This is secreted into the mouth and washes away food debris that may otherwise encourage bacterial growth. It contains antibodies, lysozyme and buffers to neutralise bacterial acids that promote dental decay.

Interferons

These chemicals are produced and released into local tissues by T-cells, macrophages and body cells infected with a virus. They activate immune cells, including killer T-cells, prevent viral replication within infected cells, and reduce the spread of viruses to healthy cells.

Complement

Complement is a system of about 20 proteins found in the blood and tissues. It is activated by the presence of immune complexes (an antigen and antibody bound together) and by foreign sugars present on bacterial cell walls. Complement:

- binds to and damages bacterial cell walls, destroying the microbe
- binds to bacterial cell walls, stimulating phagocytosis by neutrophils and macrophages
- acts as a chemoattractant, recruiting phagocytic cells such as neutrophils into an area of infection.

The inflammatory response

This is the physiological response to tissue damage and is accompanied by a characteristic series of local changes (Fig. 15.2). Its purpose is protective: to isolate, inactivate and remove both the causative agent and damaged tissue, so that healing can take place. The cardinal signs of inflammation are:

- redness
- heat
- swelling
- pain.

Inflammatory conditions are recognised by their Latin suffix '-itis'; for example, appendicitis is inflammation of the appendix and laryngitis is inflammation of the larynx.

Causes of inflammation

Any form of tissue damage stimulates the inflammatory response, even in the absence of infection. The wide range of triggers includes extremes of temperature, the presence of foreign bodies, trauma, corrosive chemicals including extremes of pH, abrasion, immune reactions including autoimmunity, and infection.

Acute inflammation

Acute inflammation is typically of short duration, e.g. days to a few weeks, and may range from mild to very severe, depending on the extent of tissue damage. Most aspects of the inflammatory response are hugely beneficial, promoting removal of the harmful agent and optimising conditions for healing to follow.

The acute inflammatory response is described here as a collection of separate events: increased blood flow, accumulation of tissue fluid, migration of leukocytes, increased core temperature, pain and suppuration. In reality, these events significantly overlap and develop together. Even

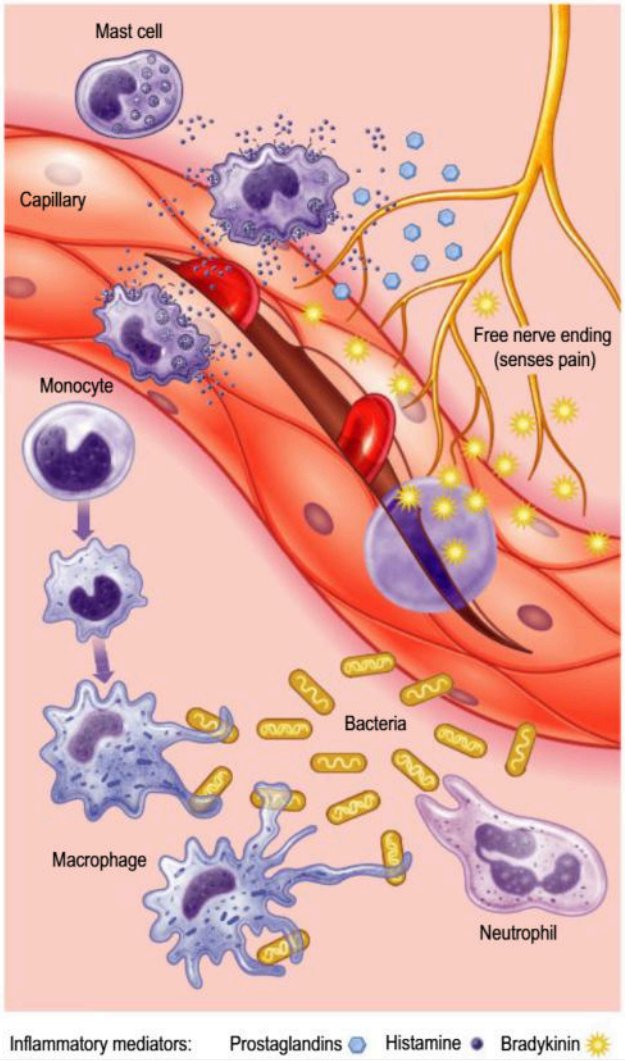

Figure 15.2 The inflammatory response.

when inflammation is localised, the release of inflammatory mediators into the blood leads to systemic effects. This is called the acute phase response, and systemic changes such as fever and elevated white blood cell count are important indicators of inflammation, with or without infection, somewhere in the body.

Some of the most important inflammatory mediators are summarised in Table 15.1.

Increased blood flow

Following injury, the arterioles supplying the damaged area dilate and the local capillaries expand, increasing blood flow to the site.

This is caused mainly by the local release of a number of chemical mediators from damaged cells, including histamine and serotonin. Increased blood flow to the area of tissue damage provides more oxygen and nutrients for the increased cellular activity that accompanies inflammation.

Table 15.1 Summary of the principal substances released in inflammation

Substance	Made by	Trigger for release	Main pro-inflammatory actions
Histamine	Mast cells (in most tissues), basophils (blood); stored in cytoplasmic granules	Binding of antibody to mast cells and basophils	Vasodilation, itching, increased vascular permeability, degranulation, smooth muscle contraction (e.g. bronchoconstriction)
Serotonin (5-hydroxytryptamine, 5-HT)	Platelets Mast cells and basophils (stored in granules) Also in central nervous system (acts as neurotransmitter)	Platelet activation and mast cell/basophil degranulation	Vasoconstriction, increased vascular permeability
Prostaglandins (PGs)	Nearly all cells; not stored, but made from cell membranes as required	Many different stimuli, e.g. drugs, toxins, other inflammatory mediators, hormones, trauma	Diverse, sometimes opposing, e.g. fever, pain, vasodilation or vasoconstriction, increased vascular permeability
Heparin	Liver, mast cells, basophils (stored in cytoplasmic granules)	Cell degranulation	Anticoagulant (prevents blood clotting), which maintains blood supply (nutrients, O_2) to injured tissue and washes away microbes and wastes
Bradykinin	Most body tissues produce bradykinin	Blood clotting, in trauma and inflammation	Pain, vasodilation

Increased blood flow causes the increased temperature and reddening of an inflamed area and contributes to the swelling associated with inflammation.

Increased tissue fluid formation

One of the cardinal signs of inflammation is swelling, caused by fluid leaving local blood vessels and entering the interstitial spaces (oedema).

This is partly due to increased capillary permeability caused by inflammatory mediators such as histamine, serotonin and prostaglandins, and partly due to elevated pressure inside small blood vessels because of increased blood flow. Most of the excess tissue fluid drains away in the lymphatic vessels, taking damaged tissue, dead and dying cells, and toxins with it.

Plasma proteins, normally retained within the bloodstream, also escape into the tissues through the leaky capillary walls; this increases the osmotic pressure of the tissue fluid and draws more fluid out of the blood (see Fig. 5.6). These proteins include antibodies, which combat infection, and fibrinogen, a clotting protein. Fibrinogen in the tissues is converted by thromboplastin to fibrin, which forms an insoluble mesh within the interstitial space, walling off the inflamed area and helping to limit the spread of infection. Some pathogens, e.g. *Streptococcus pyogenes*, which causes throat and skin infections, release toxins that break down this fibrin network and promote spread of infection into adjacent, healthy tissue.

Sometimes tissue oedema can be harmful. For instance, swelling around respiratory passages can obstruct breathing, and significant swelling often causes pain. On the other hand, the swelling around a painful, inflamed joint cushions it and limits movement, which encourages healing.

Migration of leukocytes

Loss of fluid from the blood thickens it, slowing flow and allowing the normally fast-flowing white blood cells to make contact with, and adhere to, the vessel wall. In the acute stages, the most important leukocyte is the neutrophil, which adheres to the blood vessel lining, squeezes between the endothelial cells and enters the tissues (diapedesis, see Fig. 4.10), where its main function is in phagocytosis of antigens. Phagocyte activity is promoted by the raised temperatures (local and systemic) associated with inflammation.

After about 24 hours, macrophages become the predominant cell type at the inflamed site, and they persist in the tissues if the situation is not resolved, leading to chronic inflammation. They phagocytose dead/dying tissue, microbes and other antigenic material, and dead/dying neutrophils. Some microbes resist digestion and provide a possible source of future infection, e.g. *Mycobacterium tuberculosis* (p. 298).

Chemotaxis

This is the chemical attraction of leukocytes, including neutrophils and macrophages, to an area of inflammation. Chemoattractants include microbial toxins, chemicals released from leukocytes, prostaglandins from damaged cells and complement proteins.

Increased temperature

The increased temperature of inflamed tissues has the twin benefits of inhibiting the growth and division of microbes while promoting the activity of phagocytes.

The inflammatory response may also be accompanied by a rise in core body temperature (fever, or pyrexia), especially if there is bacterial infection. The body's temperature control centre is located in the hypothalamus and adjusts metabolic

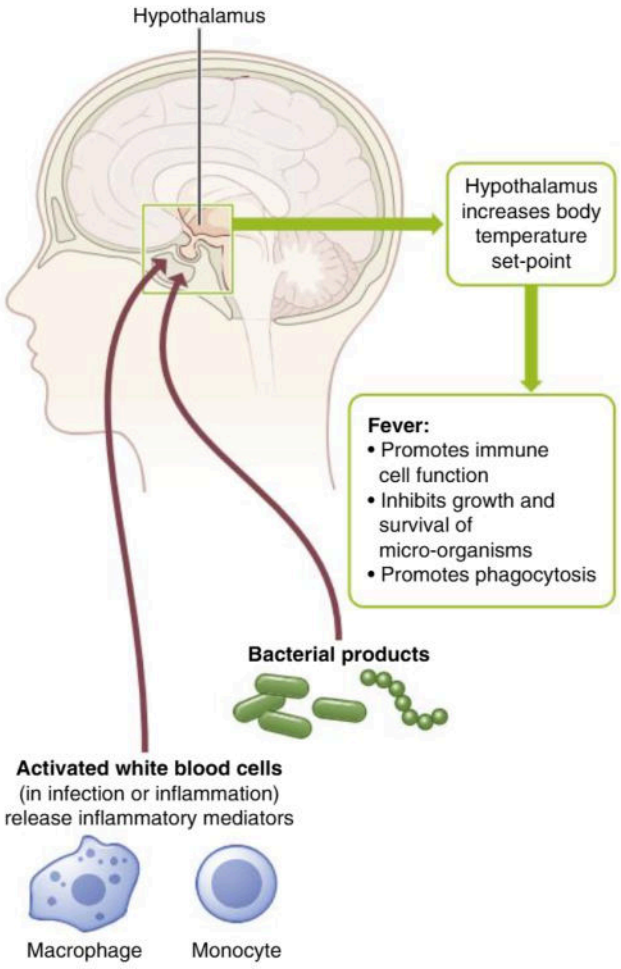

Figure 15.3 The pathogenesis of fever.

and physiological activities to maintain core temperature at around 98.6°F (37°C). In infection or inflammation it can be reset to a higher temperature by circulating microbial products or a number of inflammatory mediators including interleukin 1 (IL-1) released by activated macrophages and monocytes (Fig. 15.3). This causes pyrexia and other symptoms associated with systemic inflammation, e.g. fatigue and loss of appetite. Fever is an unpleasant experience, but is beneficial to the body in infection, because it enhances immune cell and phagocyte function and discourages microbial growth. Pyrexia increases the metabolic rate of cells in the inflamed area, increasing their oxygen and nutrient requirements. Any substance causing fever is called a pyrogen.

Pain

Pain occurs when local swelling compresses sensory nerve endings. It is exacerbated by key chemical mediators of the inflammatory process, including bradykinin and prostaglandins, which increase the sensitivity of the sensory nerve endings to painful stimuli. Although pain is an unpleasant experience, it may indirectly promote healing because it encourages protection of the damaged site.

Suppuration (pus formation)

Pus consists of dead phagocytes, dead cells, fibrin, inflammatory exudate, and living and dead microbes. A localised collection of pus in the tissues is called an abscess (see Fig. 14.10). The most common pyogenic (pus-forming) bacteria are *Staphylococcus aureus* and *Streptococcus pyogenes*.

Outcomes of acute inflammation

Resolution

This occurs when the cause has been successfully overcome, damaged cells and residual fibrin removed and healing is complete. There may be a degree of scarring, especially if the tissue damage was extensive or complicated by, for example, infection. Scar formation (fibrosis) is discussed in Chapter 14.

Development of chronic inflammation

Acute inflammation may become chronic if resolution is not complete if the area infected is not readily accessible to body defences, as in some deep-seated abscesses, wound infections and bone infections.

In addition, some organisms are more resistant to body defences than others, and so survive in the tissues. For example, members of the *mycobacteria* family, which cause tuberculosis, live inside host cells rather than in the extracellular fluids, and so are protected against host defences.

Persistent tissue irritation, repeated exposure to an allergen or ongoing pathological processes also cause chronic inflammation. For example, cigarette smoking causes chronic inflammation of the airways, hypersensitivity reactions to, e.g. laundry products, persist as long as the product is used and autoimmune destruction of the synovial membrane of synovial joints causes progressive inflammatory joint damage.

Chronic inflammation

The processes involved are very similar to those of acute inflammation but, because the processes are of longer duration, considerably more tissue damage is likely. The inflammatory cells are mainly lymphocytes instead of neutrophils, and fibroblasts are activated, leading to collagen production and fibrosis. If body defences are unable to clear the infection, they may try to wall it off instead, forming nodules called granulomas, nodules of inflamed tissues containing defensive cells and often viable bacteria. Tuberculosis is an example of an infection that frequently becomes chronic, leading to granuloma formation. The causative bacterium, *Mycobacterium tuberculosis*, has a thick outer coat resistant to phagocytic enzymes. The microbes survive and replicate within phagocytes, and so pockets of organisms are sealed up in granulomas (Ghon foci, p. 298) within the lungs.

Immunological surveillance

A population of lymphocytes, called natural killer (NK) cells, constantly patrol the body searching for abnormal host cells.

Cells which have been infected with a virus, or mutated cells that might become malignant, frequently display unusual markers on their cell membranes, which are recognised as abnormal/foreign by NK cells. Having detected an abnormal cell, the NK cell immediately kills it. NK cells are therefore particularly effective in clearing pre-cancerous body cells and in certain viral infections, including herpes virus. Although NK cells are lymphocytes, they are much less selective about their targets than the other two types discussed later in this chapter (T- and B-cells).

SPOT CHECK

1. Explain the relationship between chemotaxis and phagocytosis.
2. In what ways is increased temperature beneficial to the inflammatory response?

Immunity

Learning outcomes

After studying this section, you should be able to:

- discuss the roles of the different types of T-cell in providing cell-mediated immunity
- describe the process of antibody-mediated immunity
- distinguish between artificially and naturally acquired immunity, giving examples of each
- distinguish between active and passive immunity, giving examples of each.

The body's first line of defence is its collection of non-specific innate defences, including phagocytes such as macrophages. If these are overwhelmed, activation of the powerful immune system follows. Immunity possesses three key attributes not seen with non-specific defences: specificity, memory and tolerance.

Specificity

Unlike mechanisms such as the inflammatory response and the phagocytic action of macrophages, which are triggered by a wide range of threats, an immune response targets only one antigen. The two key immune cells are T-cells and B-cells. Each individual cell is programmed to recognise one specific receptor pattern and respond only to that stimulus.

Memory

Again, unlike general defence mechanisms, an immune response to a particular antigen will usually generate immunological memory of that antigen. This means that the immune response on subsequent exposures to the same antigen is generally faster and more powerful.

Tolerance

The cells of the immune system are aggressive and potentially extremely destructive. Control of their activity is essential to protect healthy body tissues. As immune cells travel around the body, they check the marker proteins that cells show on their cell membranes. Healthy body cells display the expected 'self' markers and are ignored by the patrolling immune cells: this is called immunological tolerance. However, non-self cells, including cancer cells, foreign (transplanted) cells or pathogens possess different patterns of surface markers, immediately activating the immune cell, which usually responds by destroying the target cell.

Immunological tolerance develops during fetal development, when any lymphocyte in the embryonic bone marrow, thymus gland or peripheral tissues that shows any tendency to react against self-antigens is deleted. This process is not infallible, and failure to delete all self-reacting lymphocytes is associated with an inappropriate immune response against self-cells. This is called autoimmunity (p. 426).

Lymphocytes

Lymphocytes (p. 74) make up 20%–30% of circulating white blood cells but at any one time most of them are found in lymphoid and other tissues rather than in the bloodstream. They include natural killer cells (see above), involved in immunological surveillance, T-cells (the majority) and B-cells. T- and B-cells are responsible for immunity (specific defence) and are produced in the bone marrow and some lymphoid tissues, although T-cells migrate to the thymus gland for final maturation.

Each individual T- and B-cell carries antigen recognition molecules on its plasma membrane, allowing it to detect and respond to only one specific antigen. The range of antigen recognition molecules is genetically determined, i.e. inherited from the parents. A healthy immune system has the capacity to recognise and respond to millions of different antigens; i.e. it can produce millions of different populations of T- and B-cells.

T-cells

The hormone thymosin, produced by the thymus gland, promotes T-cell maturation, which leads to the formation of fully specialised (differentiated), mature, functional T-cells. It is important to recognise that a mature T-cell has been programmed to recognise only one type of antigen, and during its subsequent travels through the body will react to no other antigen. Thus, a T-cell manufactured to recognise the chickenpox virus will not react to a measles virus, a cancer cell or a tuberculosis bacterium.

T-cells provide cell-mediated immunity, discussed later.

B-cells

B-cells are both produced and matured in the bone marrow. They produce antibodies (immunoglobulins), proteins that

are designed to bind to and destroy antigens. As with T-cells, each B-cell targets one specific antigen and produces antibodies targeted against that antigen alone. B-cells provide antibody-mediated immunity, discussed later.

Cell-mediated immunity

After maturation in the thymus gland, T-cells are released into the circulation, to patrol the body and detect and destroy their antigen should it enter body tissues. They cannot however detect free antigen directly in body fluids. To recognise and be activated by antigen, the T-cell must be 'presented' with it on the membrane of another cell. These cells are called antigen-presenting cells (APCs). Many different cell types present antigen to T-cells, and so are important in activating the adaptive immune system when antigen is present. Dendritic cells in the skin, for example, defend the body surface; they phagocytose invading organisms and present their antigens to T-cells. Macrophages are very important APCs. They are part of the non-specific defences because they engulf and digest antigens indiscriminately, but they are a crucial 'link' cell between initial non-specific defences and the adaptive immune system. After digesting the antigen, they transport the most antigenic fragment to their own cell membrane and display it on their surface (Fig. 15.4). They display (present) this antigen to the T-cell that recognises that particular antigen, activating it. In addition, abnormal body cells, e.g. those infected with a virus or with a mutation in their DNA, express abnormal proteins, which the cell displays on its cell membrane. In this way, the abnormal cell is also acting as an APC and marking itself for destruction.

T-cell activation triggers it to divide and proliferate (clonal expansion) (Fig. 15.4). Four main types of specialised T-cell are produced, each of which is still directed against the original antigen but will tackle it in different ways.

Cytotoxic T-cells

These directly inactivate any cells carrying antigens. They attach themselves to the target cell and release powerful toxins, which are very effective because the two cells are so close together. The main role of cytotoxic T-cells is in destruction of abnormal body cells, e.g. infected cells and cancer cells.

Helper T-cells

These are essential not only for cell-mediated immunity but also for antibody-mediated immunity. Their central role in immunity is emphasised in situations where they are destroyed, as by the human immunodeficiency virus (HIV). When helper T-cell numbers fall significantly, the whole immune system is compromised. T-helpers are the most common of the T-cells and their main functions include:

- Production of chemicals called cytokines, e.g. interleukins and interferons, which support and promote cytotoxic T-cells and macrophages.
- Cooperation with B-cells to produce antibodies; although B-cells are responsible for antibody manufacture, they need to be stimulated by a helper T-cell first.

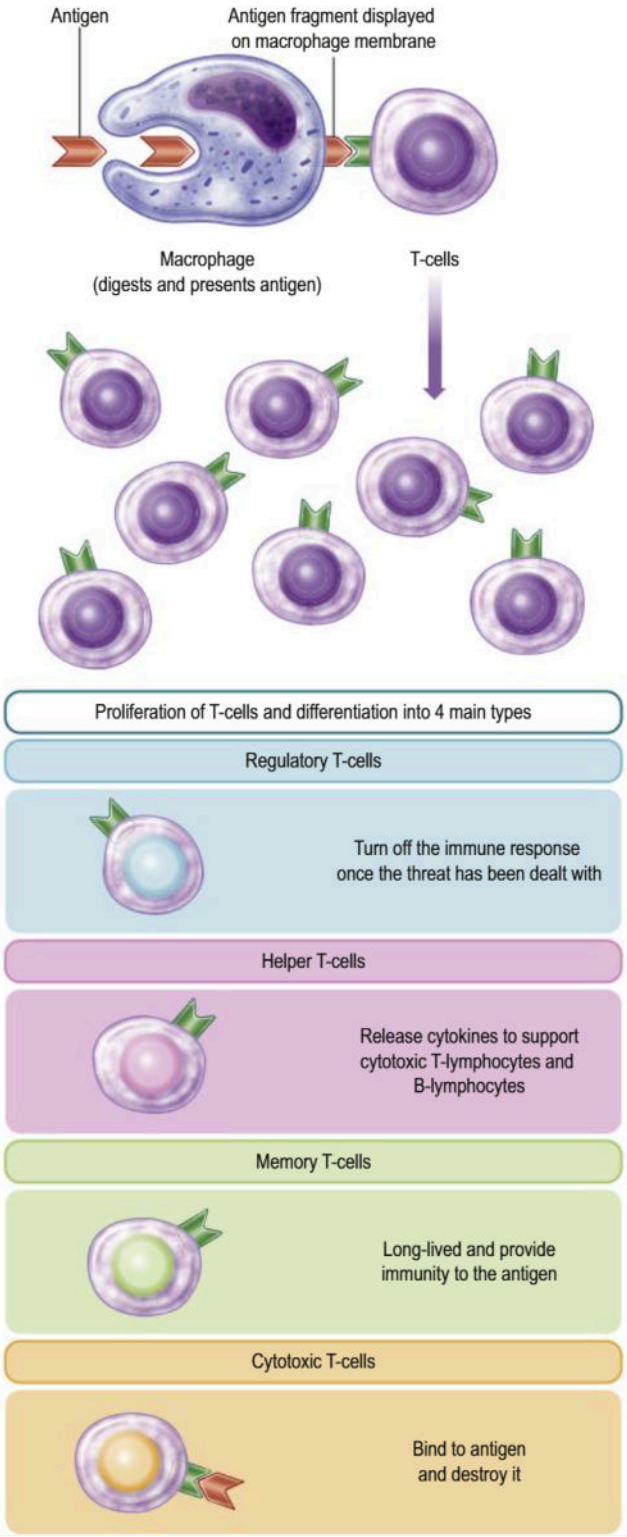

Figure 15.4 Clonal expansion of T-cells

Regulatory T-cells (Tregs)

These cells act as 'brakes', turning off activated T- and B-cells. This limits the powerful and potentially damaging effects of the immune response. Tregs are involved in immunological tolerance; they help prevent the development of autoimmunity (p. 426) and protect the fetus in pregnancy.

Memory T-cells

These long-lived cells survive after the threat has been neutralised and provide cell-mediated immunity by responding rapidly to another encounter with the same antigen.

Antibody-mediated (humoral) immunity

B-cells are much less mobile than T-cells and spend much of their time in lymphoid tissue, e.g. the spleen and lymph nodes. Unlike T-cells, B-cells recognise and bind antigen directly, without having to be presented with them by an antigen-presenting cell. Activated B-cells transform into plasma cells, which make antibodies. Each B-cell displays the antibody that it makes on its cell membrane. These bound antibodies act as antigen receptors. Once its antigen has been detected and bound, and with the help of an activated helper T-cell, the B-cell enlarges and begins to divide (clonal expansion, Fig. 15.5). It produces two functionally distinct types of cell, plasma cells and memory B-cells.

Plasma cells

Plasma cells secrete massive quantities of antibodies (immunoglobulin, Ig) into the blood. Antibodies comprise about 20% of plasma proteins, and they also distribute throughout the tissues and into body fluids. Plasma cells live no longer than a day and produce millions of molecules of only one type of antibody, which targets the specific antigen that originally activated the B-cell.

Antibodies

Antibodies:

- bind to antigens, labelling them as targets for other defence cells such as cytotoxic T-cells and macrophages
- bind to and neutralise bacterial toxins
- activate complement (p. 417).

There are five main types of antibody, summarised in Table 15.2.

Memory B-cells

Like memory T-cells, these cells remain in the body long after the initial episode has been dealt with, and rapidly respond to another encounter with the same antigen by stimulating the production of antibody-secreting plasma cells. The interdependence of the two parts of the immune system is summarised in Figure 15.6.

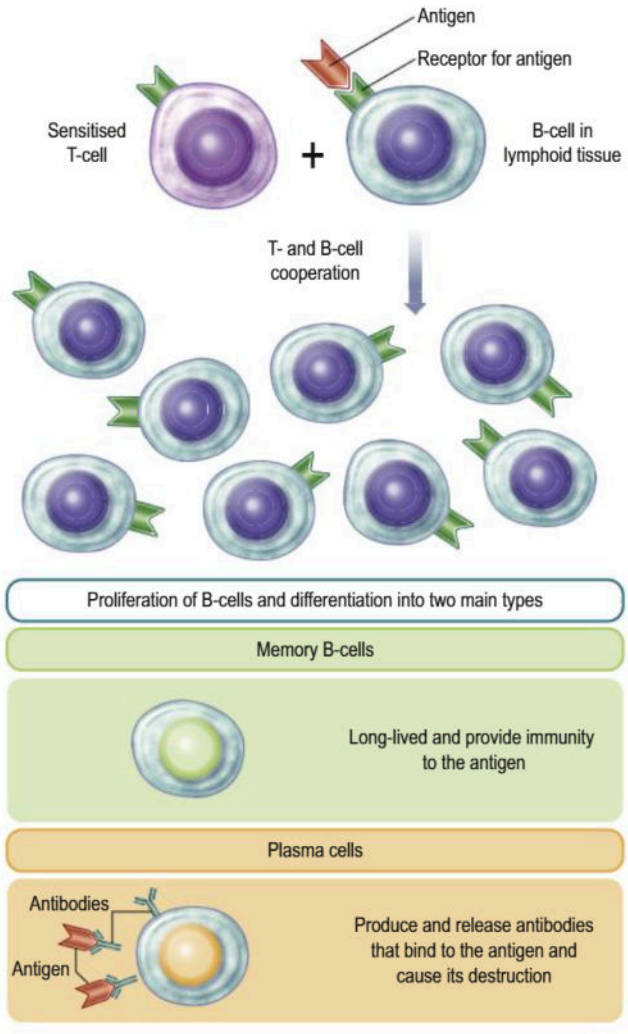

Figure 15.5 Clonal expansion of B-cells.

Acquired immunity

The immune response to an antigen following the first exposure (primary immunisation) is called the primary response. Second and subsequent exposures give rise to a secondary response (Fig. 15.7).

The primary response

Exposure of the immune system to an antigen for the first time leads to a slow and delayed rise in antibody levels, peaking 2–3 weeks after infection. The antibody produced is mainly IgM. This delayed response reflects the time required to activate the T-cell system, which then stimulates B-cell division. Antibody levels start to fall once the infection is cleared, but if the immune system has responded effectively, it will have generated a population of long-lived memory B-cells, making the individual immune to future infection.

Table 15.2 The five types of antibody

Type of antibody	Function
Immunoglobulin A (IgA)	Found in body secretions including breast milk and saliva, coats epithelial membranes and prevents antigens crossing them and invading deeper tissues
IgD	Made by B-cells and displayed on their surfaces. Antigens bind here to activate B-cells
IgE	Found on cell membranes of, for example, basophils and mast cells; if it binds its antigen, it activates the inflammatory response. This antibody is often found in excess in allergy
IgG	Is the largest, longest-lived and most common antibody type. It attacks many different pathogens and crosses the placenta to protect the fetus
IgM	Produced in large quantities in the primary immune response and is a potent activator of complement

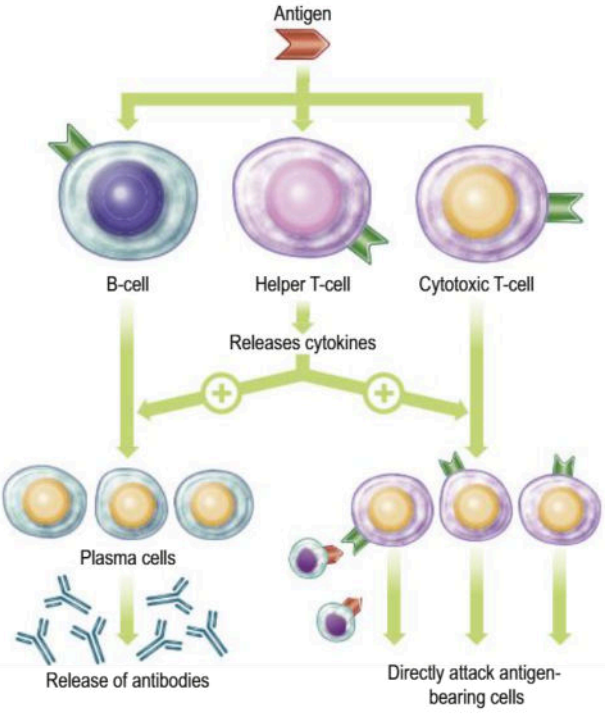

Figure 15.6 Interdependence of the T- and B-cell systems in the immune response.

The secondary response

On subsequent exposures to the same antigen, the immune response is much faster and 10–15 times more powerful because the memory T- and B-cells generated after the first infection rapidly divide and antibody production begins almost immediately. Repeated exposure to the same antigen usually reinforces and prolongs the immune response by increasing the pool of memory cells: this is the rationale behind booster vaccinations. Antibody produced is mainly IgG, which is more effective than IgM, and is characteristic of a secondary rather than a primary immune response.

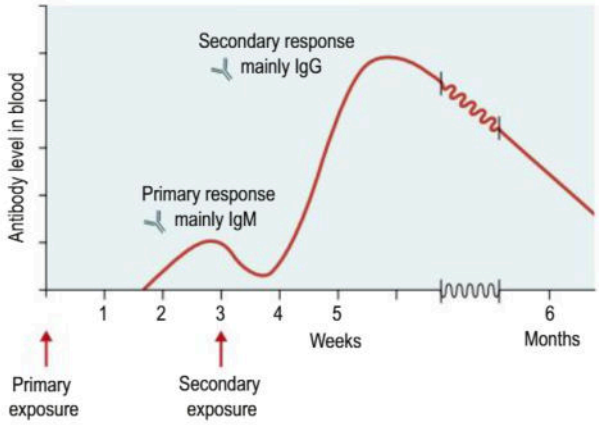

Figure 15.7 The primary and secondary immune responses. *Ig*, immunoglobulin.

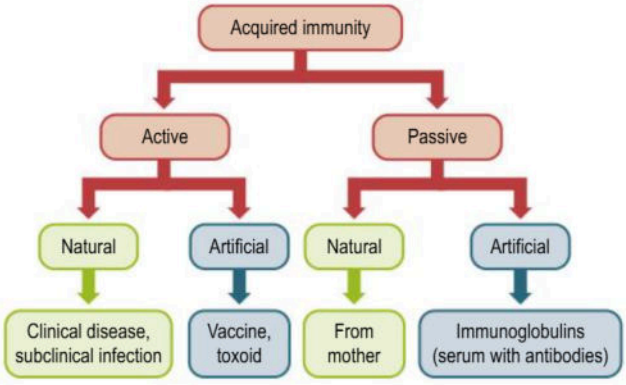

Figure 15.8 Summary of the types of acquired immunity.

Immunity may be acquired naturally or artificially and both forms may be active or passive (Fig. 15.8). Active immunity follows exposure to an antigen, with activation of T- and B-cells and antibody production. The memory cells formed provide extended immunity. In passive immunity the individual is given antibodies produced by someone else. The antibodies break down with time, so passive immunity is relatively short-lasting.

Active naturally acquired immunity

Active immunity to an infection may develop following natural exposure to the infection in the course of daily life. The first exposure may cause an episode of illness because the primary response to an infection takes 2–3 weeks to fully develop. Development of a healthy T- and B-cell

Box 15.1 Diseases preventable by vaccination

Anthrax
Cholera
Diphtheria
Hepatitis B
Measles
Mumps
Poliomyelitis
Rubella
Smallpox
Tetanus
Tuberculosis
Typhoid
Whooping cough

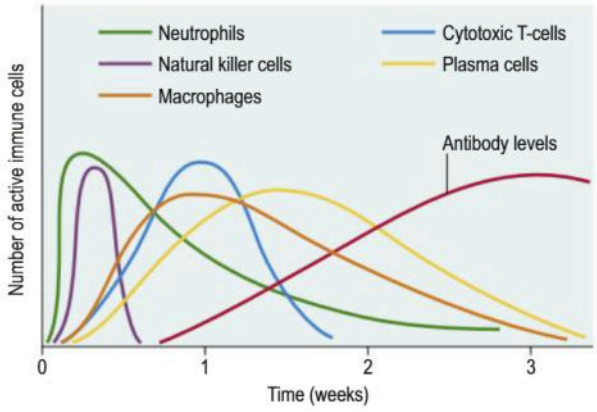

Figure 15.9 Summary of the defensive response to bacterial infection.

response clears the infection and leaves the individual with a population of memory cells.

Sometimes the infection is not sufficiently severe to cause clinical disease (subclinical infection) but still stimulates sufficient memory B-cells to establish immunity, e.g. to hepatitis A (p. 369). In other cases, subclinical infection may be too mild to stimulate an adequate response and for immunity to develop.

Active artificially acquired immunity

This type of immunity develops in response to the administration of a vaccine, a specially prepared substance designed to stimulate an immune response against a specific infection. Vaccines may contain live but weakened organisms or a killed organism, but most current vaccines are prepared using fragments from the pathogen and do not contain whole organisms. They usually contain key antigenic 'flags' from the pathogen surface, which are recognised by the body's immune system and trigger an immune response. Many infectious diseases can be prevented by artificial immunisation. Examples are shown in Box 15.1.

Active immunisation against some infectious disorders gives lifelong immunity, e.g. diphtheria, whooping cough or mumps. In other infections the immunity may last for a number of years or for only a few weeks before revaccination is necessary. Booster doses are used in a range of immunisation programmes, including tetanus, measles and rubella, to maximise protection. Apparent loss of immunity may be due to infection with a different strain of the same pathogen, which has different antigenic properties but causes the same clinical illness, e.g. viruses that cause the common cold and influenza. In older or poorly nourished individuals, lymphocyte production is reduced, especially B-cells, and the primary and secondary response may be inadequate.

Passive naturally acquired immunity

This type of immunity is acquired before birth when maternal antibodies cross the placenta to the fetus, and to the baby in breast milk. The range of antibodies provided depends on the mother's active immunity, i.e. the mother will produce antibodies to infections that she has been exposed to, which in turn protect her baby as well. The baby's own immune mechanisms are not stimulated and protection lasts only as long as the antibody supply from the mother continues.

Passive artificially acquired immunity

In this type of immunity, ready-made antibodies are injected into the recipient. The source of the antibodies may be the serum of an individual who has recovered from the infection or an animal that has been artificially immunised. Increasingly, antibodies are also manufactured using recombinant DNA technology, in which the gene coding for the desired antibody is inserted into a host cell, often a bacterium or yeast. Host cell division produces a large cell population, all containing the gene and synthesising large quantities of antibody that can be harvested for therapeutic use. Antibodies may be administered prophylactically to prevent the development of disease in people who have been exposed to a specific infection, e.g. rabies, or therapeutically after the disease has developed. Antibodies are available against a range of infectious agents, including cytomegalovirus, measles virus, hepatitis viruses and *Clostridium botulinum*.

Summary of the immune response to a bacterial infection

Figure 15.9 shows the main events contributing to the body's integrated response to infection. Initially, non-specific defence cells (neutrophils, natural killer cells and macrophages) accumulate at the site of infection and attempt to limit bacterial expansion. If the threat is strong enough and many macrophages are involved, arriving T-cells are activated, producing populations of cytotoxic and helper T-cells, which in turn activate B-cells. As B-cells proliferate and differentiate into plasma cells, antibody levels progressively rise.

SPOT CHECK

3. What is meant by the term 'immunological specificity'?
4. Outline the role of regulatory and cytotoxic T-cells in immunity.

Ageing and immunity

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on immunity.

Immunity declines with advancing age, increasing the risk of infection in older adults and lengthening recovery times. The thymus gland progressively shrinks from its maximum size at puberty and may be only a quarter of that by age 50. This is linked to decreased T-cell responsiveness, and as the B-cell response is dependent on T-cell function, antibody levels also fall with age. Levels of autoantibodies and incidence of autoimmunity increase in later life, and reduced function of natural killer cells is associated with increasing incidence of most types of cancer.

Abnormal immune function

Learning outcomes

After studying this section, you should be able to:

- describe, with examples, the four types of allergic response
- outline the basis of autoimmune disease
- discuss specific examples of autoimmune disease
- list the cause and effects of acquired immune deficiency syndrome (AIDS).

Hypersensitivity (allergy)

Allergy is an inappropriate, powerful immune response to an antigen (allergen) that is usually harmless. Examples include the faeces of the house dust mite, animal dander and plant pollens. It is therefore usually the immune response that causes the damage to the body, not the allergen itself. On initial exposure to the allergen the individual becomes sensitised to it, and on second and subsequent exposures the immune system mounts a response entirely out of proportion to the perceived threat. It is important to note that these responses are exaggerated versions of normal immune function (secondary response, see Fig. 15.7). Sometimes symptoms are mild, although annoying, e.g. the running nose and streaming eyes of hay fever. Occasionally, the reaction can be extreme, overwhelming body systems and causing death, e.g. anaphylactic shock, described later.

There are four mechanisms of hypersensitivity, which are classified according to the parts of the immune system that are involved.

Type I, anaphylactic hypersensitivity

Type I is usually called allergy and happens very quickly when a sensitised individual is exposed to an allergen, such as animal fur, pollen or insect stings. There is a strong hereditable factor in allergy, and a tendency to have higher than normal levels of IgE (atopy). The allergen binds to mast cells and basophils, which degranulate and release large amounts of histamine. Histamine contracts airway smooth muscle, restricting air flow, but relaxes smooth muscle in blood vessel walls, causing vasodilation and a drop in blood pressure. Additionally, it increases vascular permeability, leading to movement of fluid and proteins into the tissues from the bloodstream, which further reduces blood pressure. Examples of type I reactions include the serious situation of anaphylaxis. There is profound bronchoconstriction and shock (p. 127) due to extensive vasodilation. Anaphylaxis can be fatal.

Type II, antibody-mediated hypersensitivity

When an antibody reacts with an antigen on a cell surface, that cell is marked for destruction by the body's defence cells. This is the usual procedure in the elimination of, for example, bacteria, but if the antibodies are mistakenly directed against self-antigens, i.e. proteins of the body's own cells, it leads to destruction of the body's own tissues (autoimmune disease). Type II mechanisms cause other conditions, e.g. haemolytic disease of the newborn (p. 79) and transfusion reactions (p. 80).

Type III, immune complex-mediated hypersensitivity

Antibody–antigen complexes (immune complexes) are usually cleared efficiently from the blood by phagocytosis. If they are not, e.g. when there is phagocyte failure or excessive immune complex production (as in chronic infections), they can be deposited in tissues such as the kidneys, skin, joints and eye, where they set up an inflammatory reaction. The kidney is a common site of deposition because it not only receives a large proportion of the cardiac output but also filters the blood. Immune complexes collecting here lodge in and block the glomerular capillaries, impairing kidney function and causing glomerulonephritis (p. 391). Penicillin allergy is also a type III reaction: antibodies bind to penicillin, the antigen, forming large quantities of immune complexes. Deposition of the immune complexes in tissues causes the characteristic symptoms: skin rashes, joint pains and sometimes haematuria.

Type IV, delayed type (cell-mediated) hypersensitivity

Unlike types I–III, type IV hypersensitivity does not involve antibodies but is an over-reaction of T-cells to an antigen. When an antigen is detected by memory T-cells, it provokes clonal expansion of the T-cell (see Fig. 15.4), and large numbers of cytotoxic T-cells are released to eliminate the antigen. Usually, this system is controlled and the T-cell response is appropriate. If not, the actively aggressive cytotoxic T-cells trigger chronic and prolonged inflammation, which damages normal tissues.

An example of this is contact dermatitis (p. 411). Graft and transplant rejection is also caused by T-cells; an incompatible skin graft, for instance, will become necrotic and slough off in the days following application of the graft (Fig. 15.10).

The four mechanisms of hypersensitivity are summarised in Figure 15.11.

Autoimmune disease

Normally, an immune response is mounted only against foreign (non-self) antigens, but occasionally the body fails to recognise its own tissues and attacks itself. Autoimmune diseases have a strong genetic component and tend to be chronic and progressive in nature. They can involve self-directed antibodies (type II) or misdirected T-cells (type IV), and

Figure 15.10 Type IV-mediated hypersensitivity-mediated tissue graft rejection. The rejected ear tissue is black and necrotic. (From Getty images. Used with permission.)

some disorders, e.g. type 1 diabetes mellitus (p. 261), may have both components. The resulting autoimmune disorders include a number of relatively common conditions (Table 15.3).

Immunodeficiency

When the immune system is compromised, there is an increased risk of recurrent infections, often by microbes not normally pathogenic in humans (opportunistic infections). Immunodeficiency is classified as primary, usually genetically mediated and arising in infancy, or secondary, acquired in later life as the result of another disease, e.g. cancers and cancer treatments, protein deficiency, acute infection, chronic kidney disease, bone marrow diseases and acquired immune deficiency syndrome (AIDS), or following splenectomy.

Acquired immune deficiency syndrome

This condition is caused by the human immunodeficiency virus (HIV), an RNA retrovirus that produces the enzyme reverse transcriptase inside the cells of the infected person (host cells). This enzyme transforms viral RNA to DNA and this new DNA, called the provirus, is incorporated into the host cell DNA. The host cell then produces new copies of the virus that infect other host cells. When infected host cells divide, copies of the provirus are integrated into the DNA of daughter cells, spreading the disease within the body.

HIV infection particularly affects the immune and nervous systems, reflected in the clinical signs and symptoms. The virus has an affinity for cells that have a protein receptor called CD_4 in their membrane, including some T-cells, monocytes, macrophages, some B-cells and, possibly, cells in the gastrointestinal tract and neuroglial cells in the brain. CD_4 helper T-cells (see Fig. 15.4) are the main cells involved. HIV establishes itself within the body's CD_4 cell populations and gradually destroys them, while at the same time it is protected from other body defence mechanisms. CD_4 helper T-cells are central to a functional immune response, because they support cytotoxic T-cells and activate B-cells. Consequently, both cell-mediated immunity and antibody-mediated immunity are progressively impaired, with the development of widespread opportunistic infections, often by microbes of relatively low pathogenicity, and cancers. Current antiviral treatment is highly effective, preventing viral replication and reducing viral load in the body to undetectable levels. With appropriate treatment, life expectancy in HIV infection is normal.

HIV has been isolated from semen, cervical secretions, lymphocytes, plasma, cerebrospinal fluid, tears, saliva, urine and breast milk. The secretions known to be especially infectious are semen, cervical secretions, blood and untreated blood products.

Infection is spread by vaginal and anal sexual intercourse and by needles contaminated with infected blood. Mother-to-child transmission may occur during pregnancy, because the virus crosses the placenta, or during childbirth as the baby comes into contact with infected maternal fluids. Infection may also be transmitted in breast milk.

Stages of HIV infection

A few weeks after initial infection there may be an acute influenza-like illness with no specific features, followed by a period of two or more years without symptoms. Chronic HIV infection may cause persistent generalised lymphadenopathy (Ch. 6). Some patients may then develop AIDS-related complex and experience chronic low-grade fever, diarrhoea, weight loss, anaemia and leukopenia (Ch. 4).

AIDS is the most advanced stage of HIV infection and in untreated individuals develops between two and ten years after infection. It is associated with a low CD_4 count and the presence of one or more characteristic infections, tumours or presentations:

- pneumonia, commonly caused by *Pneumocystis jirovecii* although many other microbes may be involved
- persistent nausea, diarrhoea and weight loss due to recurrent infections of the alimentary tract by a wide variety of microbes
- meningitis, encephalitis and brain abscesses, which may be recurrent and are caused either by opportunistic microbes or possibly by HIV

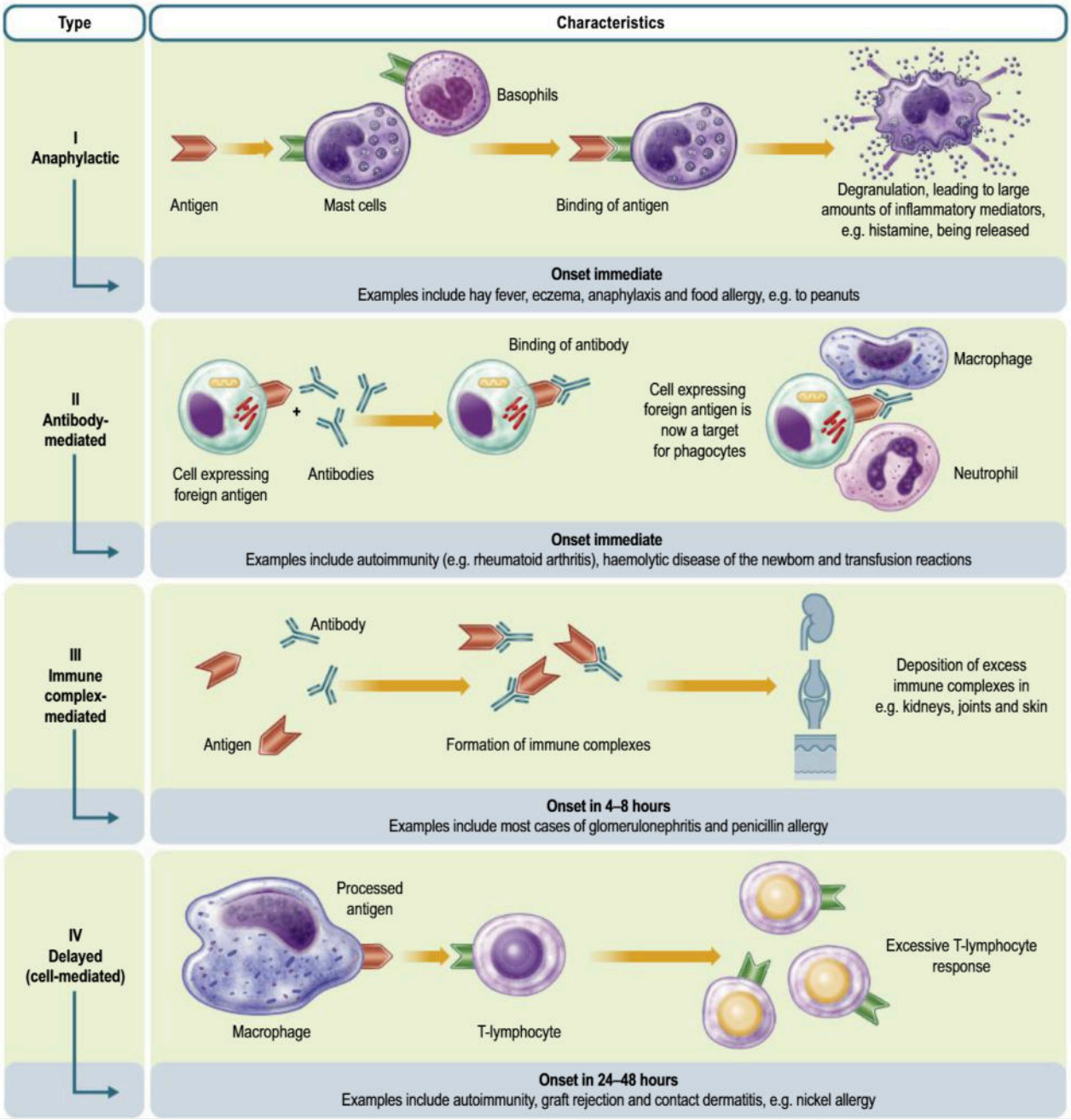

Figure 15.11 The four types of hypersensitivity.

- deteriorating neurological function, characterised by forgetfulness, loss of concentration, confusion, apathy, dementia, limb weakness, ataxia and incontinence
- skin conditions, often extensive, e.g. eczema, psoriasis, cellulitis, impetigo, warts, shingles and cold sores (Ch. 14)
- generalised lymphadenopathy (see Table 6.1)
- development of malignant tumours, which is not uncommon because of the progressive failure of immunological surveillance as the virus destroys the T-cell population. Typical cancers include:
  - lymphoma (p. 156)
  - Kaposi's sarcoma, manifesting as tumours under the skin and in internal organs (p. 413).

Table 15.3 Important autoimmune disorders

Condition	Autoantibodies/autoreactive T-cells made against
Rheumatoid arthritis (p. 481)	Synovial membrane of joints
Autoimmune thyroiditis (Hashimoto's disease) (p. 257)	Thyroglobulin
Graves' disease (p. 256)	Thyroid stimulating hormone receptors on thyroid cells
Myasthenia gravis (p. 483)	Acetylcholine receptors of skeletal muscle
Glomerulonephritis (p. 391)	Glomerular membrane
Type 1 diabetes (p. 261)	β-cells of the pancreas

SPOT CHECK

5. What are the main differences between type I and type IV hypersensitivity?
6. Why are those with HIV prone to opportunistic infections?

Case study

Anna has just had her first baby, Mai, and on the advice of her midwife has chosen to breastfeed.

1. Which kind of immunity does this give baby Mai?

   a. Active natural
   b. Passive natural
   c. Active artificial
   d. Passive artificial

2. In her first year of life, Mai will receive several important vaccines. What kind of immunity does this give her?

   a. Active natural
   b. Passive natural
   c. Active artificial
   d. Passive artificial

3. Mai goes to school when she is five and catches chickenpox from another child in her class. She is unwell for a week or two with the itchy rash that chickenpox causes but recovers quickly. In later life she is in contact on several occasions with infected individuals, but Mai never again catches chickenpox. This is because she now has which kind of immunity?

   a. Active natural
   b. Passive natural
   c. Active artificial
   d. Passive artificial

4. Which type of immune cell specific to the chickenpox virus appears for the first time in Mai's tissues after she has recovered from chickenpox?

   a. Cytotoxic T-cell
   b. Plasma cell
   c. Antibodies
   d. Memory B-cells

Review and revise

Complete the following statement:

1. Complement is a collection of about _____ proteins found in body tissues and fluids. It is activated in the presence of _____ or _____. It has three main defensive actions: it _____, _____ and _____.

Choose one answer to complete each of the following statements:

2. Non-specific defence mechanisms are also called: _____
   a. Innate
   b. Acquired
   c. Adaptive
   d. Secondary

3. Phagocytes belong to this type of defence mechanism: _____
   a. Innate
   b. Acquired
   c. Adaptive
   d. Secondary

4. Passive immunity is characterised by: _____
   a. Long-term protection
   b. Antibody production
   c. Absence of memory cells
   d. Large numbers of regulatory T-cells

5. Match the inflammatory mediators in List A to the relevant item in List B. You may use the items in List B more than once:

List A

_____ (a) Histamine
_____ (b) Bradykinin
_____ (c) Prostaglandins

List B

1. Formed as required
2. Stored in mast cells
3. Increase(s) vascular permeability
4. Cause(s) itch
5. Cause(s) pain
6. Released from basophils
7. Cause(s) vasodilation

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 16

The musculoskeletal system

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The musculoskeletal system consists of the bones of the skeleton, their joints and the skeletal (voluntary) muscles that move the body. The characteristics and properties of joints and of bone and muscle tissue are discussed in this chapter. The effects of ageing on the musculoskeletal system are listed, and the illnesses section at the end of the chapter describes some musculoskeletal disorders.

Bone

Learning outcomes

After studying this section, you should be able to:

- state the functions of bones
- list five types of bone and give an example of each
- outline the general structure of a long bone
- describe the structure of compact and spongy bone tissue
- describe the development of bone
- explain the process of bone healing and the factors that complicate it
- outline the factors that determine bone growth.

Bone tissue is a specialised connective tissue formed mainly from a heavily mineralised collagen matrix. The bones of the skeleton are laid down during embryonic development as rods and plates of cartilage, which are then converted to bone by specialised bone building cells. Conversion of connective tissue to bone is called ossification. Bones are strong, highly vascular and metabolically active and are constantly being renewed and remodelled. The functions of bones include:

- providing the structural framework of the body
- giving attachment to muscles and tendons
- allowing movement of the body as a whole and of parts of the body, at joints (articulations) that are moved by muscles
- forming the bony boundaries of the cranium, thorax and pelvis, and protecting the organs they contain
- haemopoiesis, blood cell production, which takes place in red bone marrow (see Fig. 4.3)
- mineral storage, especially calcium phosphate. The mineral reservoir within bone is essential for maintaining blood calcium levels, which must be tightly controlled.

Bone shape and structure

Bones are classified by shape as long, short, irregular, flat and sesamoid (Fig. 16.1). Irrespective of shape, all bones contain two types of bone tissue: compact and spongy. Compact bone is dense and strong, and forms the outer shell of bones, whereas spongy bone fills all or part of the bone interior. The microscopic structure of bone tissue is described later. Bones are wrapped in a tough, protective outer membrane called the periosteum, which has two layers. The outer (superficial) fibrous layer is tough and protects the bone underneath. The inner (deep) layer is rich in blood vessels and in osteoblasts and osteoclasts, the cells responsible for bone production and breakdown (see below). Periosteum is not present on bone surfaces that form joints, and muscles and tendons attached to the bone are anchored to it by the periosteum.

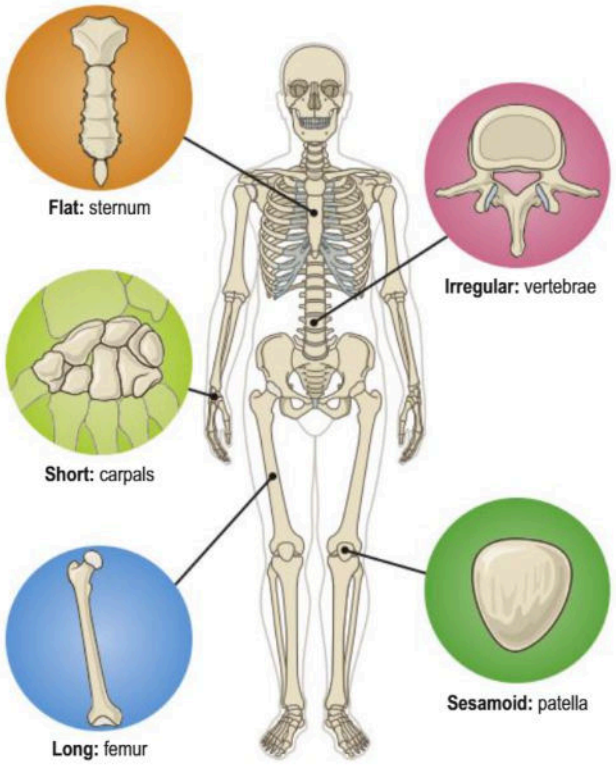


Fig. 16.1 Types of bone.

Long bones

Long bones are elongated, slender bones found mainly in the limbs. They have a diaphysis (shaft) and two epiphyses (extremities) (Fig. 16.2). The diaphysis is composed mainly of compact bone, with a central medullary canal containing fatty yellow bone marrow. The epiphyses consist of an outer covering of compact bone with spongy bone inside. The bone surfaces that participate in synovial joint formation (see below) are coated in hyaline cartilage to prevent damaging bone–bone contact.

Blood and nerve supply

One or more nutrient arteries supply the bone shaft; the epiphyses have their own blood supply, although in mature bones the capillary networks arising from the two are heavily interconnected. The sensory nerve supply usually enters the bone at the same site as the nutrient artery, and branches extensively throughout the bone. Bone injury is therefore usually very painful.

Short, flat, irregular and sesamoid bones

Short bones are chunky and boxy in shape. Examples include the carpals (wrist bones) and tarsals (ankle bones).

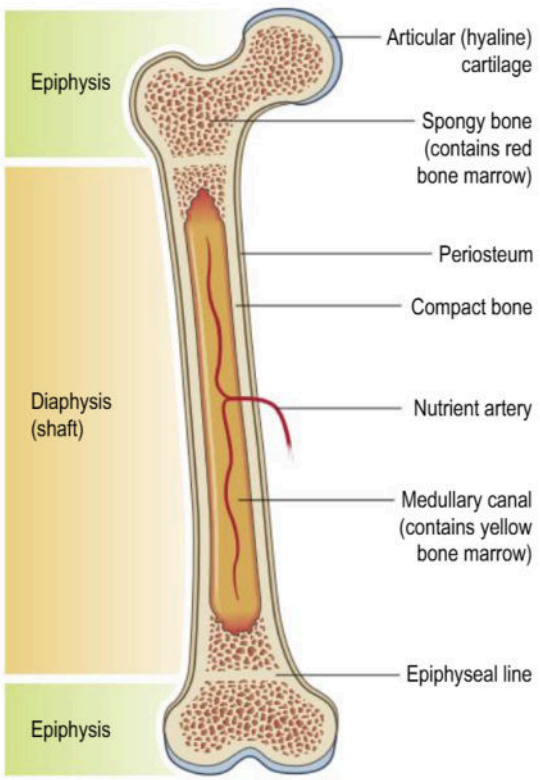


Fig. 16.2 The interior of a mature long bone.

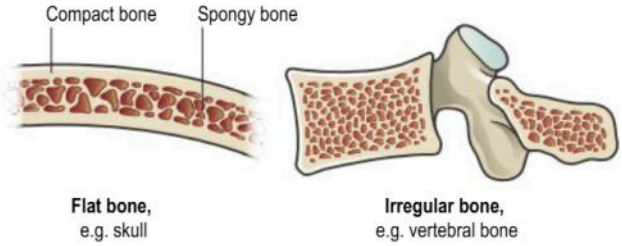


Fig. 16.3 The interiors of flat and irregular bones.

Flat bones are actually curved, not flat; they are thin with parallel surfaces, e.g. skull bones (Fig. 16.3), ribs and the sternum. Irregular bones have complex shapes with multiple processes and projections, e.g. vertebrae (Fig. 16.3). Sesamoid bones form within a tendon. The most common example is the patella (kneecap), which forms within the patellar tendon (see Fig. 16.71) and is partially enclosed within it.

Microscopic structure of bone

About two-thirds of bone mass is composed of calcium salts, mainly calcium phosphate. This inorganic matrix gives bone great hardness but alone would be brittle and prone to shattering. The remaining third is organic material called osteoid, composed mainly of collagen fibres (see Fig. 3.17) forming the framework on which the calcium salts are deposited. Collagen is very strong and gives bone slight flexibility. Bone cells contribute less than 2% of bone mass.

Bone cells

There are three types of bone cell:
- osteoblasts, bone-building cells
- osteocytes, mature bone cells
- osteoclasts, bone-reabsorbing cells.

Osteoblasts

These bone-building cells deposit both osteoid and inorganic salts in bone tissue. They are therefore present at sites where bone is growing, repairing or remodelling, e.g.:
- in the periosteum
- in the centres of ossification of developing bone
- at each end of the diaphysis of long bones, adjacent to the epiphyseal cartilages, where they ossify growing cartilage
- at fracture sites.

As they deposit new bone tissue around themselves, they eventually become trapped in tiny pockets called lacunae (Fig. 16.4) in the growing bone and differentiate into osteocytes.

Osteocytes

These mature bone cells do not divide. They monitor and maintain mature bone tissue. In the event of bone damage or disease, they de-differentiate into osteoblasts to rebuild or repair the bone.

Osteoclasts

These cells break bone down, releasing calcium and phosphate. They are giant cells with up to 50 nuclei, formed from the fusion of many monocytes (p. 73). The continuous remodelling of healthy bone tissue is the result of balanced activity of its osteoblast and osteoclast populations. Like osteoblasts, osteoclasts are found in areas of the bone where there is active growth, repair or remodelling, e.g.:
- in the periosteum, maintaining bone shape during growth and removing excess callus (see Fig. 16.12) formed during fracture healing
- on the internal surfaces of the medullary canal during growth and canalising the bone during healing.

Compact bone

Compact (cortical) bone makes up about 80% of the body's total bone mass. Its microscopic structure is shown in Figure 16.4. It is formed of a large number of parallel tube-shaped units called osteons (Haversian systems), each of which is made up of a central canal surrounded by a series of expanding rings, similar to the growth rings of a tree. Osteons tend to be aligned the same way that force is naturally applied to the bone; for example, in the femur (thigh bone), they run from one epiphysis to the other. This gives the bone great strength.

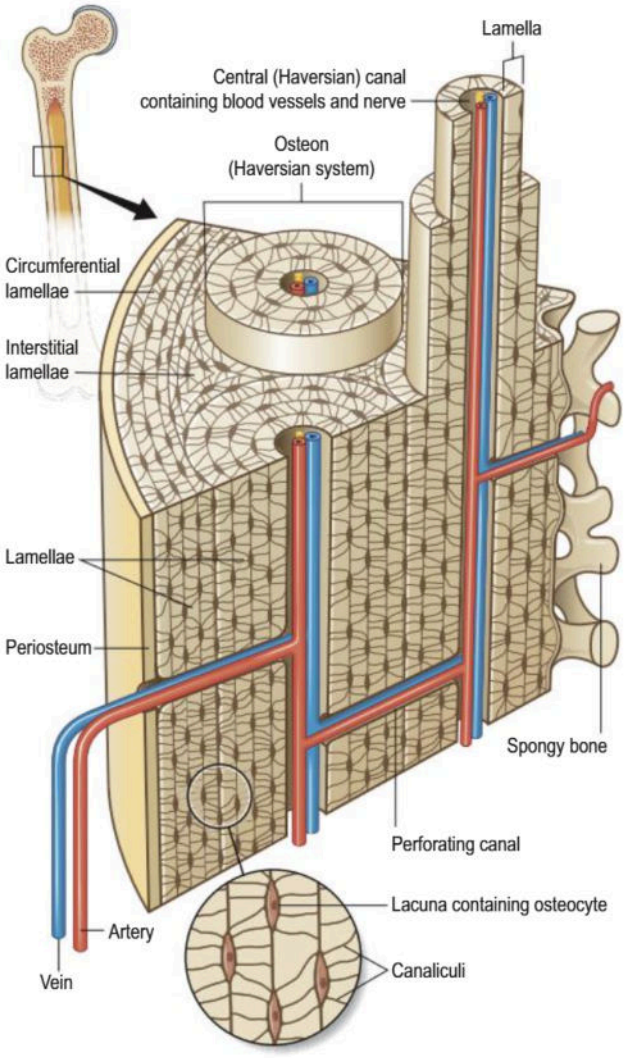


Fig. 16.4 Microscopic structure of compact bone.

The central canal contains nerves, lymphatics and blood vessels, and each is linked with neighbouring canals by tunnels called perforating canals running at right angles between them. The cylindrical layers of the osteon are called lamellae. Between adjacent lamellae of the osteon are strings of little cavities called lacunae, in each of which lives an osteocyte. Osteocytes communicate with each other through a network of tiny channels called canaliculi, which allows interstitial fluid to circulate through the bone, and permits direct contact between the osteocytes, which extend fine processes into them (Fig. 16.5).

Between the osteons are interstitial lamellae, the remnants of older systems partially broken down during bone remodelling or growth. The outer layer of bone, lying immediately below the periosteum, is made up of circumferential lamellae, which encircle the whole bone.

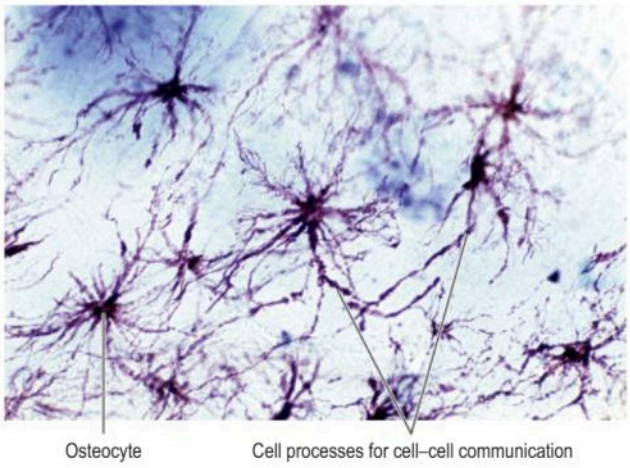


Fig. 16.5 Light micrograph of osteocytes. Multiple fine processes extend through bone canaliculi and allow each cell to communicate directly with its neighbours. (Jean-Claude Revy, ISM/Science Photo Library. Reproduced with permission.)

Spongy bone

About 20% of the body's total bone mass is spongy (cancellous, trabecular) bone. To the naked eye, spongy bone resembles a honeycomb (Fig. 16.6A). This honeycomb arrangement has two main functions. The spaces contain red bone marrow, which produces blood cells, and also makes spongy bone much lighter than compact bone, reducing the weight of the skeleton. Microscopic examination reveals a bony framework formed from trabeculae (meaning 'little beams') (Fig. 16.6B). Like compact bone, spongy bone is organised into osteons, with osteocytes living in lacunae and communicating with each other via canaliculi. However, because of the trabecular structure of spongy bone, individual osteocytes are never very far away from an internal bone surface. Canaliculi open onto the surface of the trabeculae, allowing rapid diffusion of nutrients, gases and wastes between osteocytes and the blood supplying the red bone marrow. There is therefore no need for a central canal. The branching framework of pillars and plates in spongy bone is not arranged randomly. Rather, the bony honeycomb develops maximum strength along the directions from which maximum stress comes, so that even though it is not solid bone, it can absorb its share of applied force.

Development of bone tissue

Also called osteogenesis or ossification, this begins before birth but is not complete until about the 21st year of life. Long, short and irregular bones develop in the fetus from rods of cartilage, called cartilage models. Flat bones develop from membrane models and sesamoid bones from tendon models.

During ossification, osteoblasts secrete osteoid, which gradually replaces the original cartilage model; then they

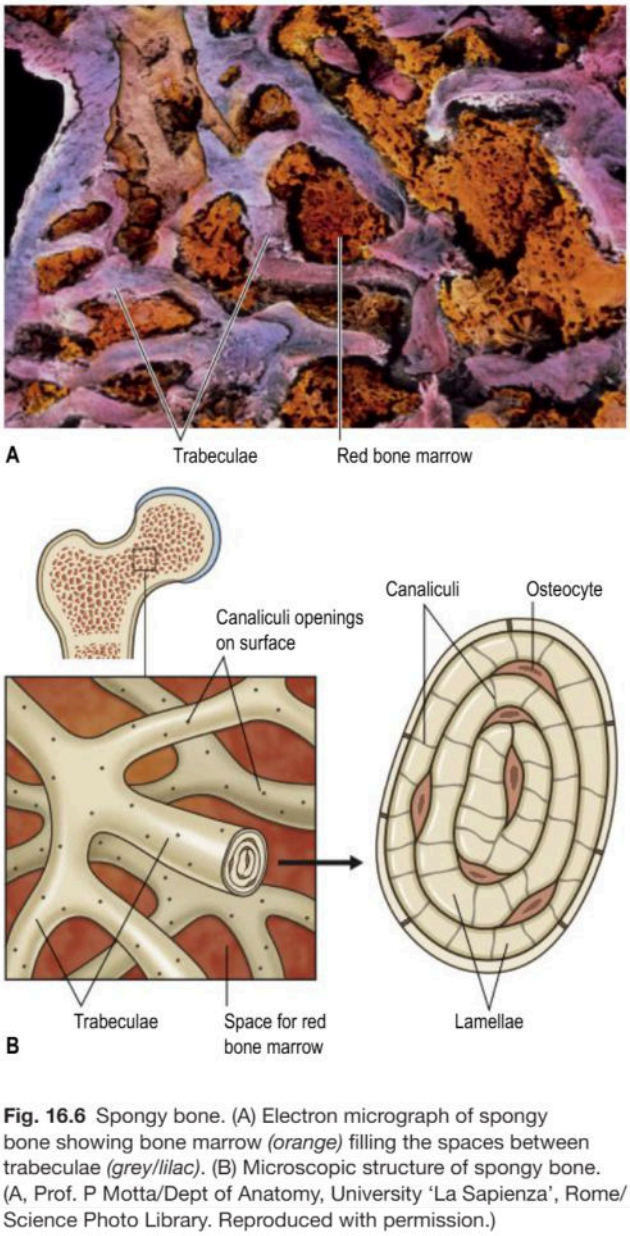


Fig. 16.6 Spongy bone. (A) Electron micrograph of spongy bone showing bone marrow *(orange)* filling the spaces between trabeculae *(grey/lilac)*. (B) Microscopic structure of spongy bone. (A, Prof. P Motta/Dept of Anatomy, University 'La Sapienza', Rome/ Science Photo Library. Reproduced with permission.)

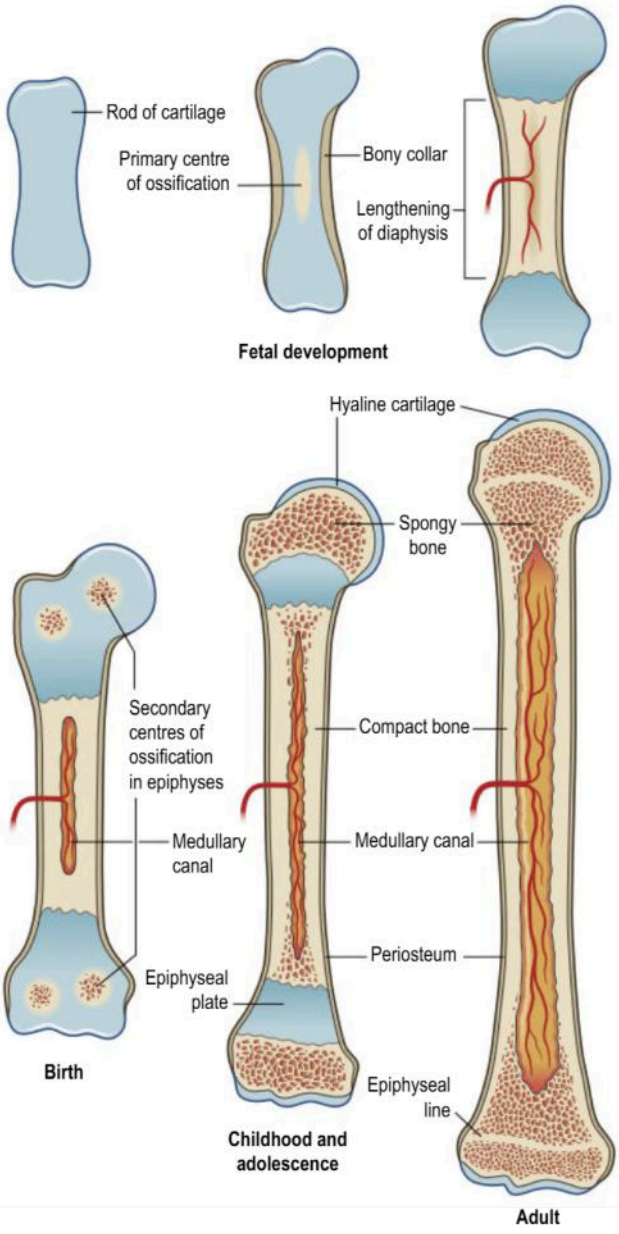


Fig. 16.7 Development of a long bone.

deposit calcium and phosphate salts through the cartilaginous osteoid, progressively calcifying it and converting it to the hard, rigid structure of mature bone. As the bone grows, the osteoblasts become trapped in the matrix of their own making and become osteocytes.

Development of long bones

In long bones the focal points from which ossification begins are small nests of osteogenic cells, called centres of ossification (Fig. 16.7). Ossification proceeds with development of a bony collar at about 8 weeks of gestation. Later the blood supply develops and bone tissue replaces cartilage as osteoblasts secrete osteoid in the shaft. The bone lengthens as ossification continues and spreads to the epiphyses. Around birth, secondary centres of ossification develop in the epiphyses, and the medullary canal forms when osteoclasts break down the bone tissue in the middle of the shaft.

During childhood, long bones continue to lengthen because there is a plate of cartilage called the epiphyseal (growth) plate at each end of the bone, separating each epiphysis from the diaphysis. The growth plate continues to produce new cartilage on its diaphyseal surface (the surface facing the shaft of the bone, Fig. 16.8). This cartilage, the location of which is clearly visible on X-ray (Fig. 16.9A), is then turned to bone. As long as cartilage production matches the rate of ossification, the bone continues to lengthen. At puberty, under the influence of sex hormones, cartilage growth in the epiphyseal plate slows and is overtaken by

bone deposition. Once the whole epiphyseal plate is turned to bone, no further lengthening of the bone is possible. In adult bones, its location is visible as the epiphyseal line (Fig. 16.9B and see Fig. 16.2).

A bone fracture damaging the epiphyseal growth plate in children can arrest growth of the bone, which may lead to that bone being shorter than its counterpart in the other limb. There is also a risk of deformity.

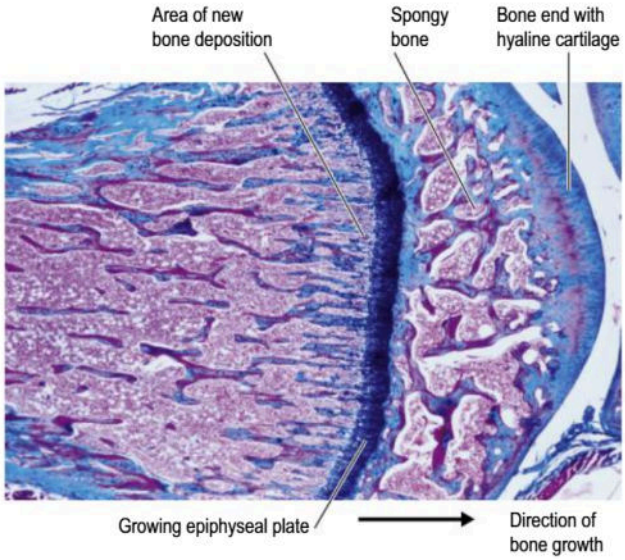


Fig. 16.8 Light micrograph of the end of a growing bone, showing the epiphyseal plate. (Innerspace Imaging/Science Photo Library. Reproduced with permission.)

Hormonal regulation of bone growth

Growth hormone and the thyroid hormones thyroxine and tri-iodothyronine are especially important during infancy and childhood; deficient or excessive secretion results in abnormal development of the skeleton, e.g. growth hormone deficiency causes dwarfism (p. 256).

Testosterone and oestrogen influence the physical changes that occur at puberty and help maintain bone structure throughout life. Rising levels of these hormones trigger the growth spurt of puberty but later stimulate closure of the epiphyseal plates so that bone growth lengthways stops, although bones can grow in thickness throughout life. Average adult male height is usually greater than female because male puberty tends to occur at a later age than female puberty, giving a male child's bones longer to keep growing. Oestrogen is responsible for the wider female pelvis that develops during puberty, and for maintaining bone mass in the adult female. Reduced oestrogen levels after the menopause puts postmenopausal women at higher risk of osteoporosis (p. 479).

Calcitonin and parathyroid hormone (p. 247) control blood calcium levels by regulating calcium uptake into and release from bone. Calcitonin increases calcium uptake into bone, reducing blood calcium, and parathyroid hormone decreases it, increasing blood calcium.

Exercise and bone health

Although bone growth lengthways ceases permanently once the epiphyseal plates have ossified, thickening of bone is possible throughout life. This involves the laying down of new osteons around the bone periphery by osteoblasts in the

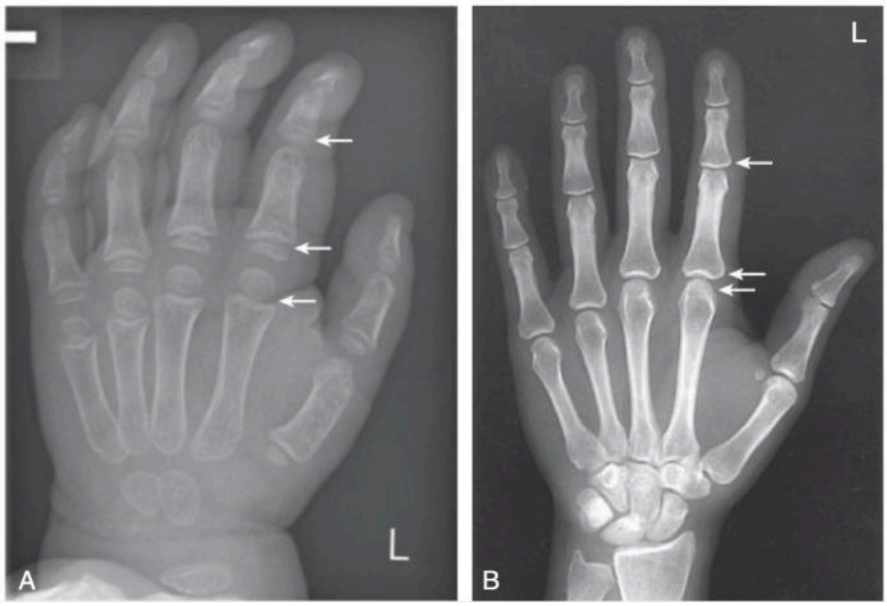


Fig. 16.9 (A) X-ray of a child's hand, showing epiphyseal plates (arrowed) at the ends of long bones. (B) Hand of an adult. The locations of the epiphyseal plates (arrowed) are marked with a fine epiphyseal line. (A, From Adam A, et al: Grainger & Allison's Diagnostic Radiology, ed 7, © 2021, Elsevier Limited. B, From Long BW, et al: Merrill's atlas of radiographic positioning & procedures, ed 14, St. Louis, 2019, Elsevier.)

periosteum. Weight-bearing exercise stimulates thickening of bone, strengthening it and making it less liable to fracture. Lack of exercise reverses these changes, leading to lighter, weaker bones.

Diet and bone health

Healthy bone tissue requires adequate dietary calcium and vitamins A, C and D. Calcium, and smaller amounts of other minerals such as phosphate, iron and manganese, are essential for adequate mineralisation of bone. Vitamin A is needed for osteoblast activity. Vitamin C is used in collagen synthesis, and vitamin D is required for calcium and phosphate absorption from the gastrointestinal tract.

Bone remodelling

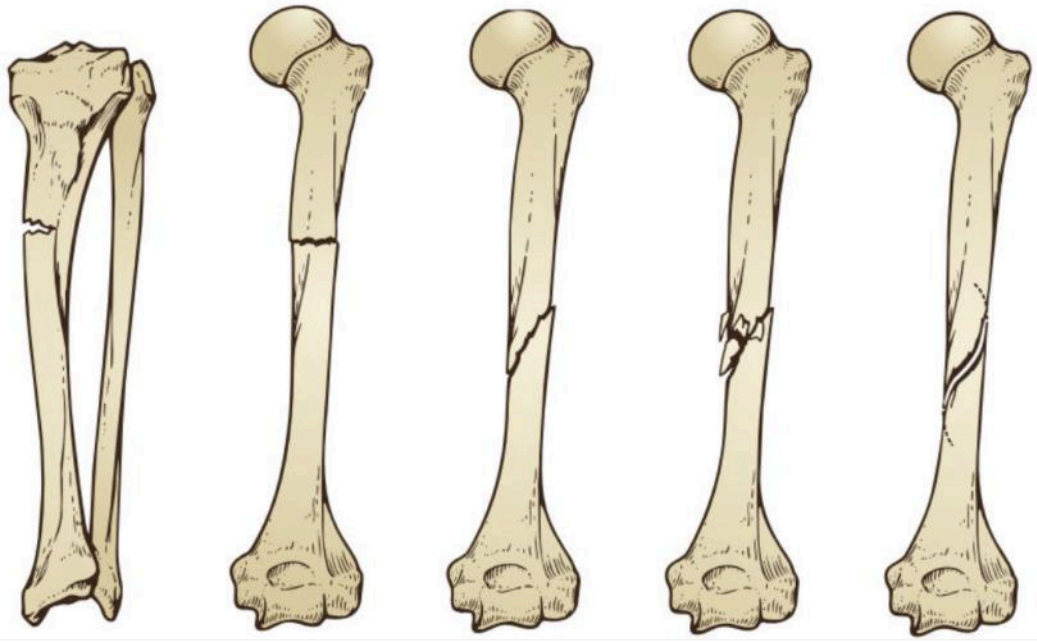
Bone is subject to constant mechanical stresses that damage, crack and weaken it over time. To combat this, there is a constant turnover of bone tissue, mediated by osteoblast and osteoclast activity. On average, about 10% of bone is replaced each year, but the rate at which individual bones are remodelled varies. Bones subject to high stress are remodelled faster than others. The distal part of the femur, for example, is generally renewed every 3–6 months. The process is not merely a replacement but reflects adjustment of bone to the stresses to which it is regularly exposed. For example, remodelling of lower limb bones in regular runners strengthens the bones along the lines of regularly applied stress.

Bone fractures and bone healing

A number of terms are used to classify fractures, including:

- simple (closed) – the bone ends do not protrude through the skin
- compound (open) – the bone ends protrude through the skin
- pathological – fracture of a bone weakened by disease, e.g. osteoporosis.

Other terms used to describe fractures indicate the direction of the fracture line, how cleanly the bone has broken and the alignment of the bone ends (Fig. 16.10). A transverse fracture runs across the bone roughly perpendicular to its long axis, whereas an oblique fracture runs at an angle. A spiral fracture follows a spiral line and results from rotational force applied to the bone. If the bone breaks into



Greenstick Fracture
The bone remains intact on one side, but broken on the other, in much the same way that a "green stick" bends; common in children, whose bones are more flexible than those of adults.

Transverse Fracture
The break occurs perpendicular to the long axis of the bone.

Oblique Fracture
The break occurs diagonally across the bone; generally the result of a twisting force.

Comminuted Fracture
The bone is splintered or shattered into three or more fragments; usually caused by an extremely traumatic direct force.

Spiral Fracture
The bone is broken into a spiral or S-shape; caused by a twisting force.

Fig. 16.10 Types of fracture. (From Bonewit-West K, Hunt S, Applegate E: Today's medical assistant: clinical & administrative procedures, ed. 2, St. Louis, 2013, Saunders.)

Fig. 16.11 X-ray showing a displaced oblique fracture of the humerus. (From Drake R, et al: Gray's Anatomy for Students, ed 4, 2020, Elsevier, Inc.)

three or more pieces, the fracture is said to be comminuted. A greenstick fracture is usually seen in children, whose bones contain proportionately more collagen than adults' bones. The collagen fibres tend to hold the bone tissue together, so the bone tends to split apart on the side opposite the site of applied force but is less likely to break completely.

Figure 16.11 shows an X-ray of an oblique, displaced fracture of the humerus.

Healing of fractures

Following a fracture, the broken bone ends are joined by the deposition of new bone. This occurs in several overlapping stages (Fig. 16.12):

1. A haematoma (collection of clotted blood) forms rapidly between the bone ends and the surrounding soft tissues.

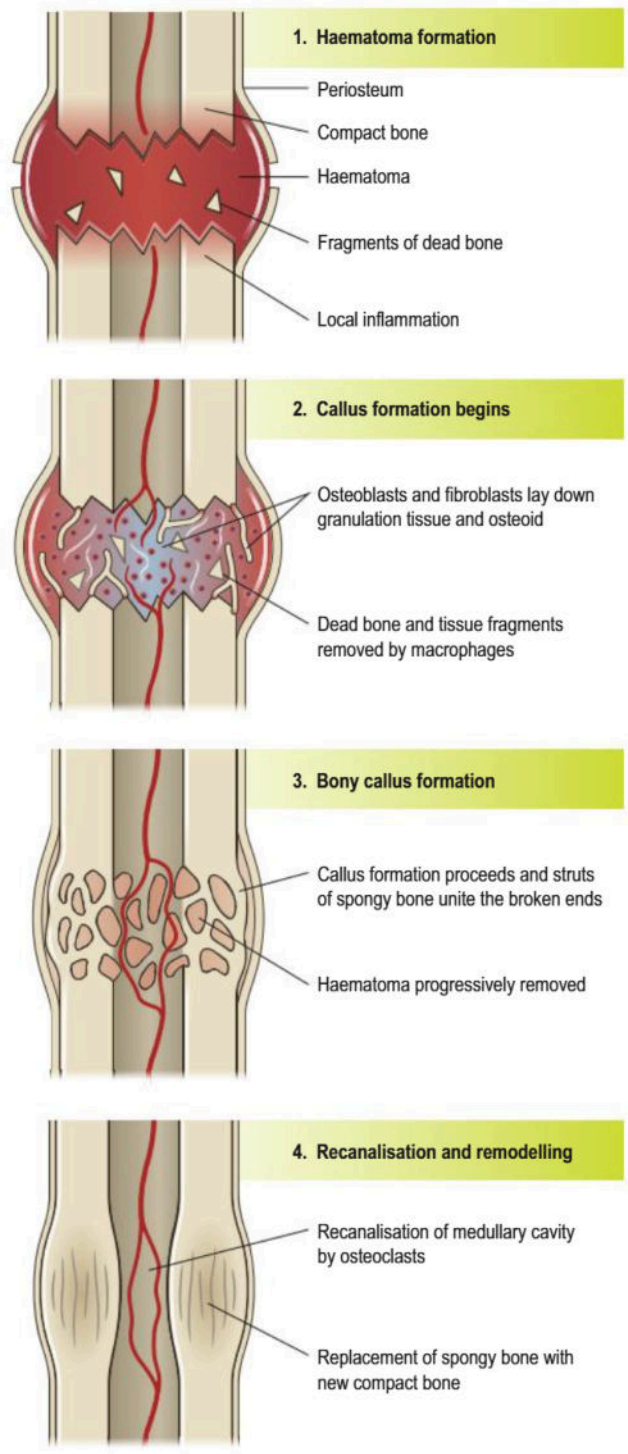


Fig. 16.12 Stages in bone healing.

An acute inflammatory response causes swelling and attracts inflammatory cells, including macrophages. This stage may be very painful, as the periosteum contains many sensory nerve endings.

2. The repair process begins as the haematoma is stabilised with large amounts of fibrin and becomes the framework

for the formation of granulation tissue (p. 407). Fibroblasts migrate to the site to lay down collagen fibres and other repair materials. Osteoblasts begin laying down new osteoid and the bone ends are joined with these soft tissues. Macrophages phagocytose dead bone and other tissues, to clear the way for new bone, and new capillaries begin to grow into the granulation tissue, restoring blood supply.

3. After about 2 weeks, bony callus forms as osteoblasts begin to calcify the osteoid. Callus is laid down as spongy bone and unites, supports and splints the fracture.
4. A period of remodelling converts the external callus to compact bone and recanalises the bone. Assuming healing has proceeded normally, bone structure is back to normal, and the bone at the site of the original callus may even be slightly thicker than before. The whole process can take months, depending on the degree of damage.

Factors that delay fracture healing

Tissue fragments between bone ends

Splinters of dead bone (sequestrae) and soft tissue fragments not removed by phagocytosis delay healing.

Deficient blood supply

Poor blood supply provides inadequate oxygen and other nutrients needed for healing. This impairs the activity of repair cells, including osteoblasts, so that the cartilage laid down in the early stages of repair might not be converted to bone fast enough. This can ultimately lead to the healed tissue at the fracture site being too rich in inadequately calcified cartilage, giving a weaker repair called a cartilaginous union. The most vulnerable sites, because of their normally poor blood supply, are the neck of femur, the scaphoid and the shaft of tibia.

Poor alignment of bone ends

The bone ends must be very closely aligned for good healing to take place. If they are displaced, it may result in the formation of a large and irregular callus that heals slowly and results in permanent deformity or disability.

Continued mobility of bone ends

Continuous movement disrupts normal granulation tissue formation and results in fibrosis of the granulation tissue, followed by fibrous rather than bony union of the fracture.

Miscellaneous

These include infection, systemic illness, poor nutrition, drugs such as corticosteroids and increasing age.

Complications of fractures

Infection

Compound fractures are more likely to become infected than simple fractures because pathogens may enter through broken skin, although they may occasionally be blood-borne. Healing will not occur until the infection (osteomyelitis, p. 480) resolves.

Fat embolism

Fat emboli from the bone marrow in the medullary canal may enter the circulation through torn veins. They are most likely to lodge in the lungs and block blood flow through the pulmonary capillaries.

Bone markings

Most bones have rough surfaces, raised protuberances and ridges that give attachment to muscle tendons and ligaments. These are not included in the descriptions of individual bones unless they are of particular note, but many are marked on illustrations of the individual bones discussed in the following sections. Bone markings and related terminology are defined in Table 16.1.

Bony landmarks

A bony landmark is an area on the body surface where a bony feature lies directly underneath the skin and is easily palpable. They are important orientation features for locating deeper structures, e.g. for correct stethoscope placement for auscultation, and for identifying safe sites for insertion of

Table 16.1 Anatomical terminology related to bones

Term	Meaning
Articulating surface	An area of bone involved in the formation of a joint
Articulation	A joint between two or more bones
Bony sinus	A hollow cavity within a bone
Border	A ridge of bone separating two surfaces
Condyle	A smooth, rounded projection of bone that forms part of a joint
Facet	A small, generally rather flat, articulating surface
Fissure or cleft	A narrow slit
Foramen (plural: foramina)	A hole in a structure
Fossa (plural: fossae)	A hollow or depression
Meatus	A tube-shaped cavity within a bone
Septum	A partition separating two cavities
Spine, spinous process or crest	A sharp ridge of bone
Styloid process	A sharp downward projection of bone that gives attachment to muscles and ligaments
Suture	An immovable fibrous joint between the bones of the skull
Trochanter, tuberosity or tubercle	Roughened bony projections, usually for attachment of muscles or ligaments. The different names are used according to the size of the projection. Trochanters are the largest and tubercles the smallest

cannulae, chest drains, spinal needles and other invasive healthcare interventions.

SPOT CHECK

1. Compare the living environment and functions of osteocytes and osteoblasts.
2. In terms of closure of epiphyseal plates, why are males generally taller than females?

Axial skeleton

Learning outcomes

After studying this section, you should be able to:

- identify the bones of the skull (face and cranium)
- list the functions of the sinuses and fontanelles of the skull
- outline the characteristics of a typical vertebra
- describe the structure of the vertebral column
- explain the movements and functions of the vertebral column
- identify the bones forming the thoracic cage.

The bones of the skeleton are divided into two groups: the axial skeleton and the appendicular skeleton (Fig. 16.13).

The axial skeleton, so-called because it is the axis or central core of the skeleton, consists of the skull, vertebral column, ribs and sternum. The appendicular skeleton consists of the shoulder and pelvic girdles and the limb bones.

Skull

The skull (Figs 16.14 and 16.15) rests on the upper end of the vertebral column and its bony structure is divided into two parts: the cranium and the face.

Sinuses

The sphenoid, ethmoid, maxillary and frontal bones contain air-filled cavities called sinuses lined with ciliated mucous membrane. They all communicate with the nasal cavity and upper respiratory tract infections can ascend and cause sinusitis (p. 291). They give resonance to the voice and reduce the weight of the skull.

Cranium

The cranium is formed by several flat and irregular bones that protect the brain. The brain rests on the base of the skull (Fig. 16.15) and is enclosed in the cranial cavity. The periosteum lining the inner surface of the skull bones forms the outer layer of dura mater (p. 167). In the mature skull the joints (sutures) between the bones are immovable. The bones have numerous perforations (e.g. foramina, fissures) through which nerves, blood and lymph vessels pass. The bones of the cranium are:

- 1 frontal bone
- 2 parietal bones
- 2 temporal bones
- 1 occipital bone
- 1 sphenoid bone
- 1 ethmoid bone.

Frontal bone

This bone forms the forehead, part of the orbital cavities (eye sockets) and the prominent ridges above the eyes, the supraorbital margins. The eye and muscles that move it are protected within the orbital cavity. The two frontal sinuses lie just above the supraorbital margins (see Fig. 16.19).

The frontal bone forms sutures with the parietal, sphenoid, zygomatic, lacrimal, nasal and ethmoid bones (Fig. 16.14). It originates in the fetus in two parts, joined in the midline by the frontal suture (see Fig. 16.22C), and converted entirely to bone shortly after birth.

Parietal bones

These bones form the sides and roof of the skull. They articulate with each other at the sagittal suture (Fig. 16.14B), with the frontal bone at the coronal suture, with the occipital bone at the lambdoidal suture and with the temporal bones at the squamous sutures.

Temporal bones

The temporal bones (Fig. 16.16) lie one on each side of the head and form sutures with the parietal, occipital, sphenoid and zygomatic bones. The squamous part is the thin fan-shaped area that articulates with the parietal bone. The zygomatic process articulates with the zygomatic bone to form the zygomatic arch (cheekbone).

The mastoid part contains the mastoid process, a thickened region easily felt behind the ear. It contains a large number of very small air sinuses that communicate with the middle ear.

The petrous portion forms part of the base of the skull and contains and protects the organs of hearing (the spiral organ of Corti) and balance (the semicircular canals).

The temporal bone articulates with the mandible at the temporomandibular joint, the only movable joint of the skull. Immediately behind this articulating surface is the external acoustic meatus (auditory canal), which passes inwards towards the petrous portion of the bone.

The styloid process projects from the lower process of the temporal bone and supports the hyoid bone and gives attachment to muscles associated with the tongue and pharynx.

Occipital bone

The occipital bone (Fig. 16.17) forms the back of the head and part of the base of the skull. It forms sutures with the parietal,

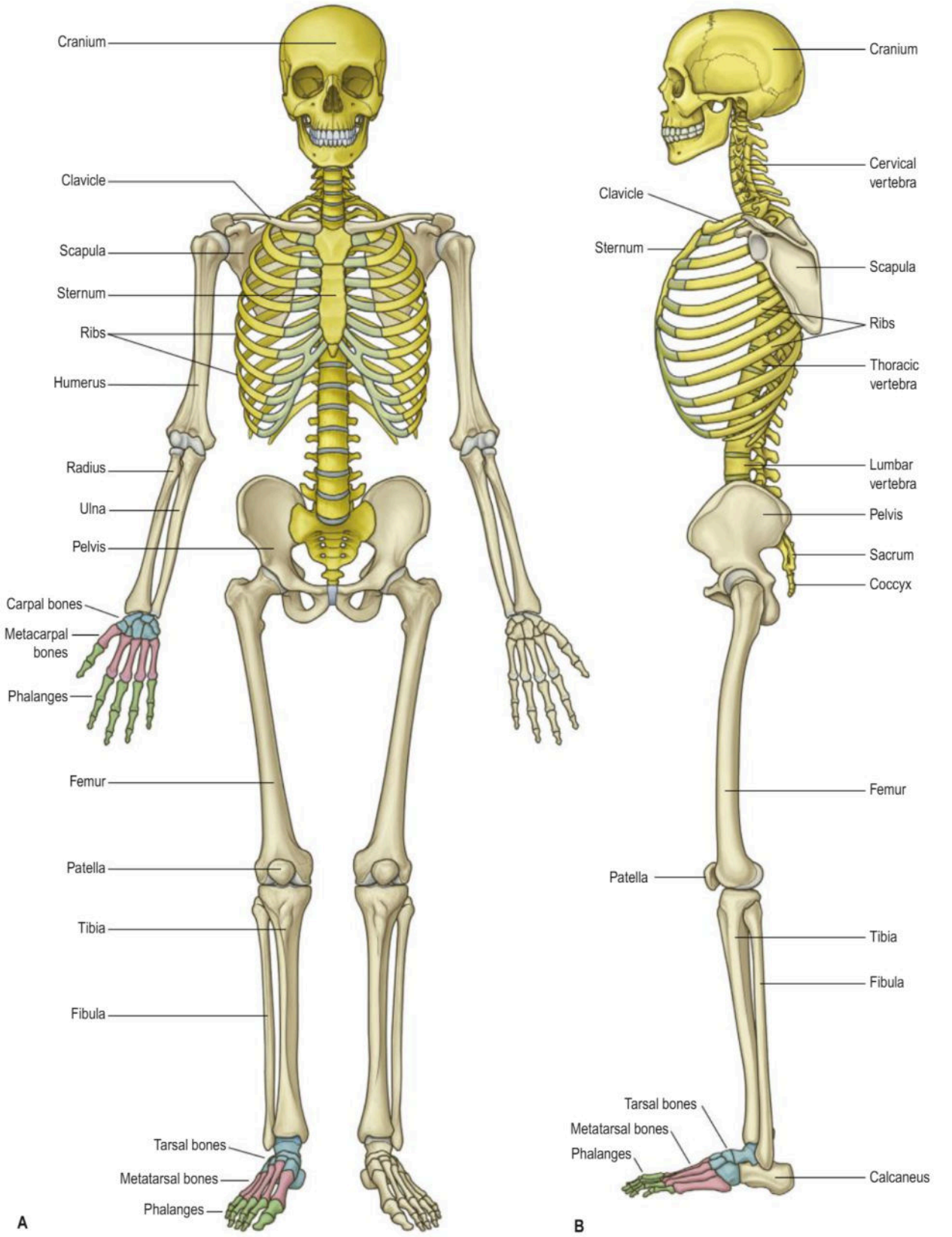


Fig. 16.13 The skeleton. *Gold,* axial skeleton; *brown,* appendicular skeleton. The bones of the right wrist, hand, ankle and foot are coloured separately for clarity. (A) Anterior view. (B) Lateral view.

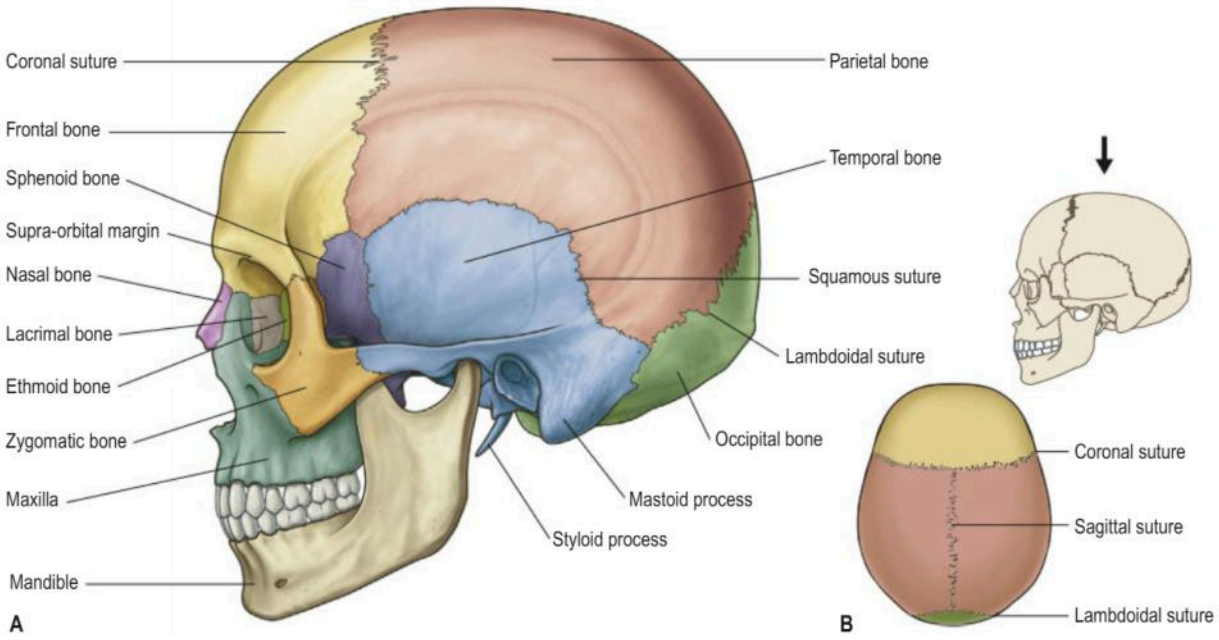


Fig. 16.14 The bones of the skull and their sutures (joints). (A) Lateral view. (B) Viewed from above.

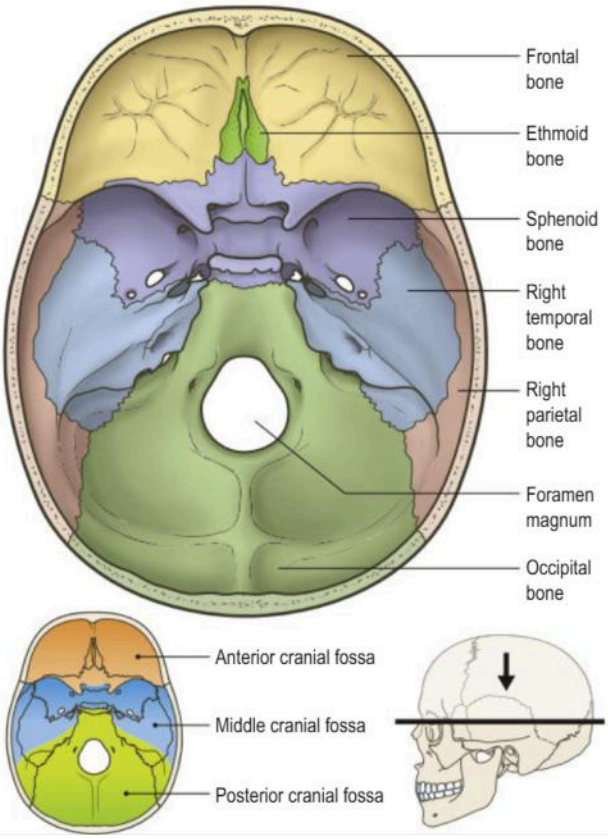


Fig. 16.15 The bones forming the base of the skull and the cranial fossae. Viewed from above.

temporal and sphenoid bones. Its inner surface is deeply concave to accommodate the occipital lobes of the cerebrum and the cerebellum. The occiput (the lower back part of the skull) has two articular condyles that form condyloid joints (p. 458) with the first bone of the vertebral column, the atlas. Between the condyles is the foramen magnum (meaning 'large hole'), through which the spinal cord passes from the cranial cavity.

Sphenoid bone

The sphenoid bone (Fig. 16.18) forms the middle part of the base of the skull and articulates with the occipital, temporal, parietal and frontal bones (Fig. 16.15). It links the cranial and facial bones, and cross-braces the skull. On the superior surface in the middle of the bone is a little saddle-shaped depression, the hypophyseal fossa (sella turcica), in which the pituitary gland rests. The body of the bone contains some fairly large air sinuses that open into the nasal cavity. The optic nerves pass through the optic foramina on their way to the brain.

Ethmoid bone

The delicate ethmoid bone (Fig. 16.19) occupies the anterior part of the base of the skull and helps to form the orbital cavity, the upper part of the nasal septum and the lateral walls of the nasal cavity. On each side it has two projections into the nasal cavity: the superior and middle conchae or turbinated processes. It contains numerous sinuses that open into the nasal cavity. The horizontal flattened part, the cribriform plate, forms the roof of the nasal cavity and has

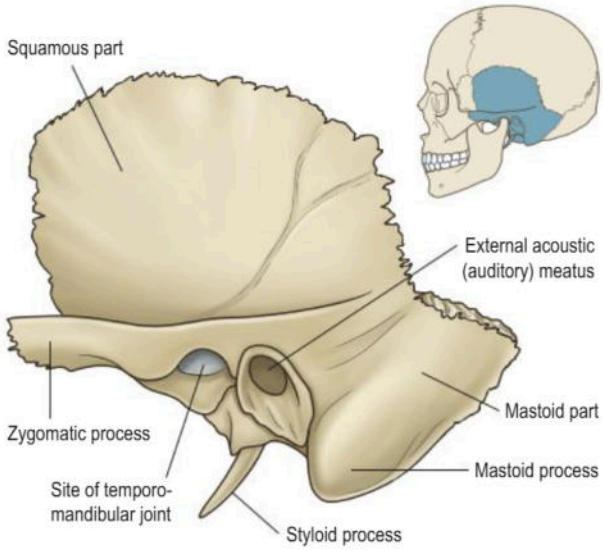


Fig. 16.16 The right temporal bone. Lateral view.

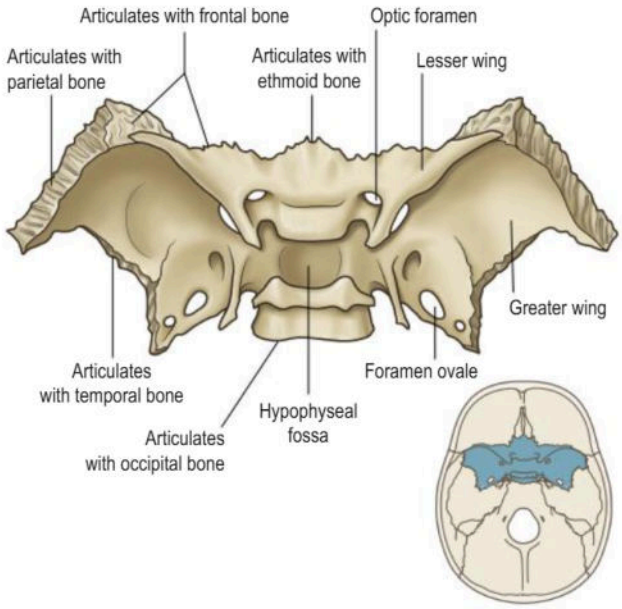


Fig. 16.18 The sphenoid bone. Viewed from above.

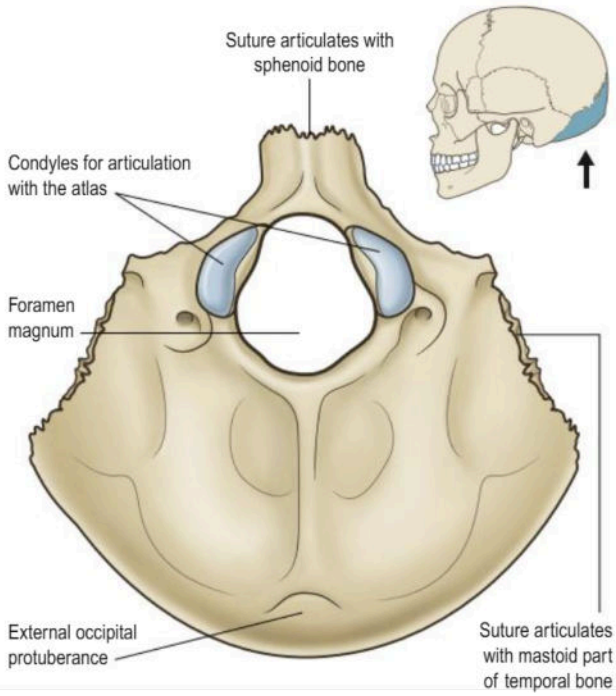


Fig. 16.17 The occipital bone. Viewed from below.

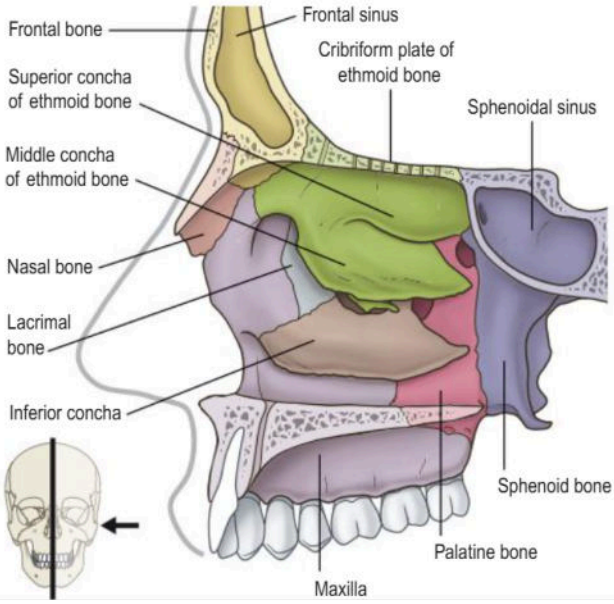


Fig. 16.19 Lateral view of the right nasal cavity. Viewed from the left.

numerous small foramina, through which nerve fibres of the olfactory nerve (sense of smell) pass upwards from the nasal cavity to the brain (see Fig. 8.24).

Face

The skeleton of the face is formed by 13 bones in addition to the frontal bone already described. They fit together like an intricate, three-dimensional jigsaw puzzle, forming the internal cavities of the face (e.g. the nasal and orbital cavities) and articulating with the bones of the cranium.

Figure 16.20 shows the relationships between the bones:

- 2 zygomatic (cheek) bones
- 1 maxilla
- 2 nasal bones
- 2 lacrimal bones
- 1 vomer

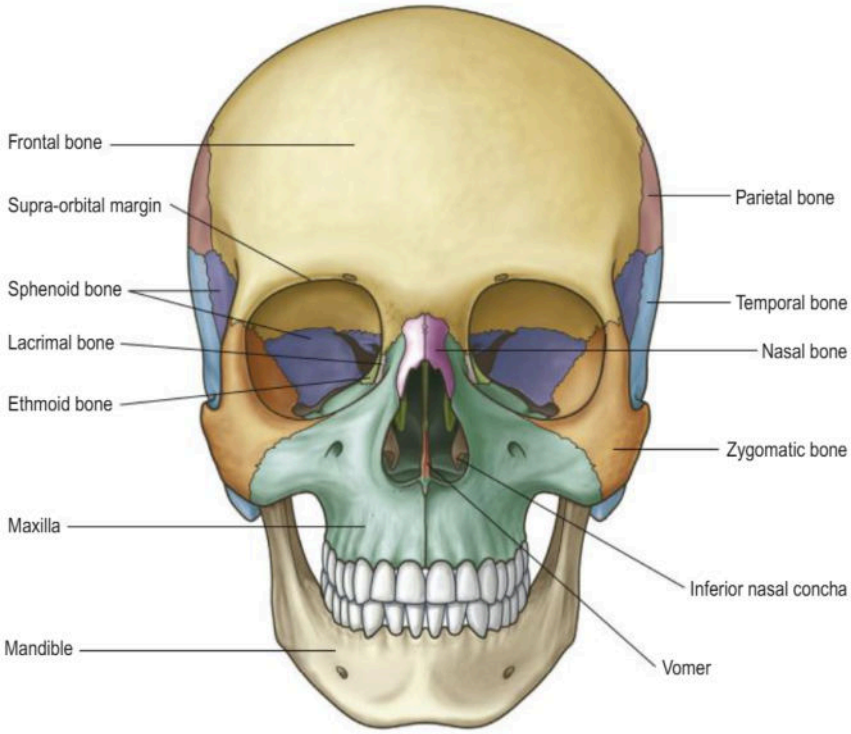


Fig. 16.20 The bones of the face. Anterior view.

- 2 palatine bones
- 2 inferior conchae
- 1 mandible.

Zygomatic bones

These bones form the prominences of the cheeks (the cheekbones) and part of the floor and lateral walls of the orbital cavities.

Maxilla

The maxilla forms the upper jaw, the anterior part of the roof of the mouth, the lateral walls of the nasal cavity and part of the floor of the orbital cavities. The alveolar ridge, or process, projects downwards and carries the upper teeth. On each side is the largest of the sinuses, the maxillary sinus, which opens into the nasal cavity.

Nasal bones

These two small flat bones form most of the lateral and superior surfaces of the bridge of the nose.

Lacrimal bones

These two small bones are posterior and lateral to the nasal bones and form part of the medial walls of the orbital cavities. Each is pierced by a foramen through which the nasolacrimal duct passes, carrying tears from the medial canthus of the eye to the nasal cavity.

Vomer

The vomer is a thin, flat bone that extends upwards from the middle of the hard palate to form most of the inferior part of the nasal septum. Superiorly, it articulates with the perpendicular plate of the ethmoid bone.

Palatine bones

These are two small, L-shaped bones. The horizontal parts unite to form the posterior part of the hard palate and the perpendicular parts project upwards to form part of the lateral walls of the nasal cavity. At their upper extremities they form part of the orbital cavities.

Inferior conchae

Each concha is a scroll-shaped bone which forms part of the lateral wall of the nasal cavity and projects into it below the middle concha. The superior and middle conchae are parts of the ethmoid bone. The conchae collectively increase the surface area in the nasal cavity, allowing inspired air to be warmed and humidified more effectively.

Mandible

This is the lower jaw bone (Fig. 16.21), the only movable bone of the skull, permitting opening and closing of the mouth and chewing. The anterior part, the body, is curved and features the alveolar ridge, which anchors the lower teeth. On each side the bone curves sharply upwards almost

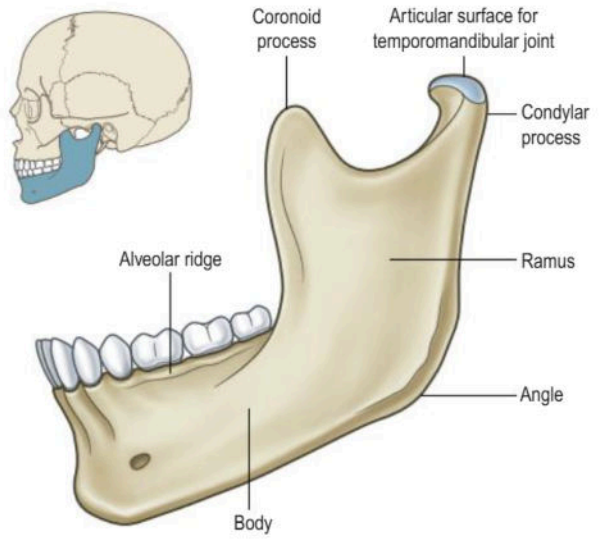


Fig. 16.21 The left mandible. Lateral view.

at right angles to the posterior end of the body: this part is called the ramus.

At its upper end the ramus divides into the condylar process, which articulates with the temporal bone to form the temporomandibular joint (Fig. 16.16), and the coronoid process, which gives attachment to muscles and ligaments that close the jaw. The point where the ramus joins the body is the angle of the jaw, easily felt through the skin.

Hyoid bone

This isolated horseshoe-shaped bone lies in the soft tissues of the neck just above the larynx and below the mandible (see Fig. 10.4). It does not articulate with any other bone but is attached to the styloid process of the temporal bone by ligaments. It supports the larynx and gives attachment to the base of the tongue.

Fontanelles of the skull

At birth, ossification of the cranial sutures is incomplete. The skull bones do not fuse earlier to allow for moulding of the baby's head during childbirth. Where three or more bones do not completely meet there are distinct membranous areas, called fontanelles ('soft spots', Fig. 16.22). The two largest are the anterior fontanelle, which does not fully ossify until the child is between 12 and 18 months old, and the posterior fontanelle, usually ossified 2–3 months after birth.

Vertebral column

The vertebral column, also called the spine or backbone, is the central axis of the body, providing direct and indirect support for the entire skeleton and the skeletal muscles that move it. It contains 26 interlocking bones stacked on top of

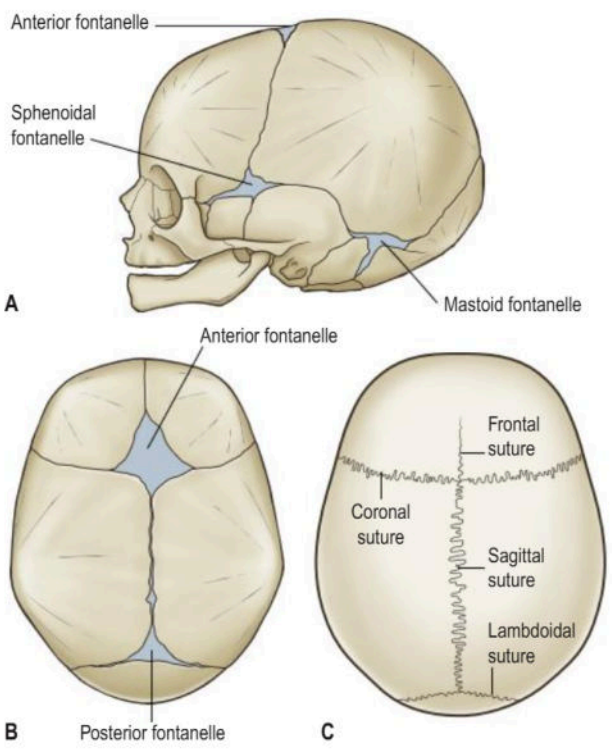


Fig. 16.22 The skull showing the fontanelles and sutures. (A) Fontanelles viewed from the side. (B) Fontanelles viewed from above. (C) Main sutures viewed from above when ossification is complete.

one another (Fig. 16.23), and encloses the vertebral canal, through which the spinal cord descends from the brain. The vertebral column is divided into different regions. The first 7 vertebrae, in the neck, form the cervical spine; the next 12 vertebrae are the thoracic spine, and the next 5 the lumbar spine, the lowest vertebra of which articulates with the sacrum. The sacrum is formed from five fused vertebrae, and articulates with the coccyx ('tail'), also formed from between three and five fused small vertebrae. Each vertebra is identified by the first letter of its region in the spine, followed by a number indicating its position. For example, the topmost vertebra is C1 and the third lumbar vertebra is L3.

The non-fused vertebrae have many characteristics in common but some groups have distinguishing features.

Characteristics of a typical vertebra (Fig. 16.24)

Body

This is the broad, flattened, largest part of the vertebra. When the vertebrae are stacked in the vertebral column, the flattened surfaces of the body of each vertebra articulate with the corresponding surfaces of the vertebrae above and below. However, there is no direct bone-to-bone contact

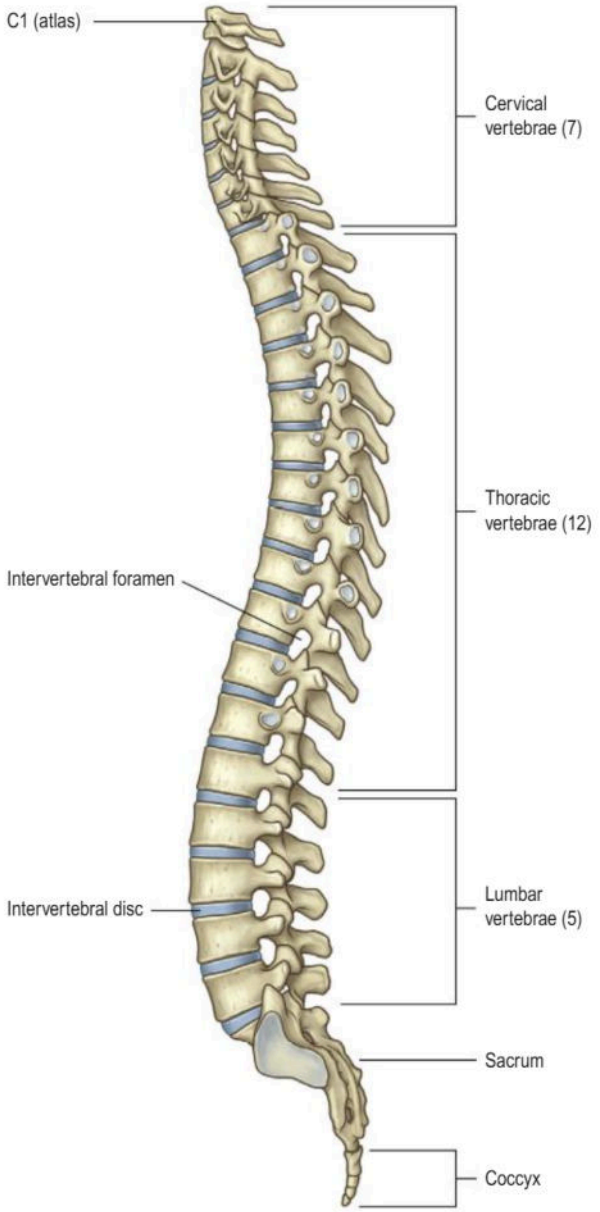


Fig. 16.23 The vertebral column. Lateral view.

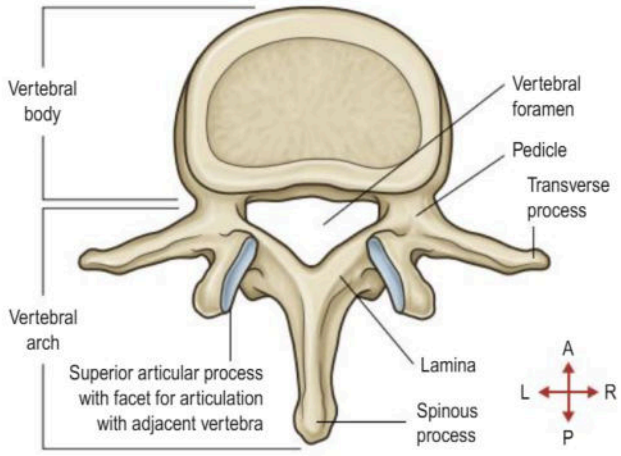


Fig. 16.24 A lumbar vertebra showing the features of a typical vertebra. Viewed from above.

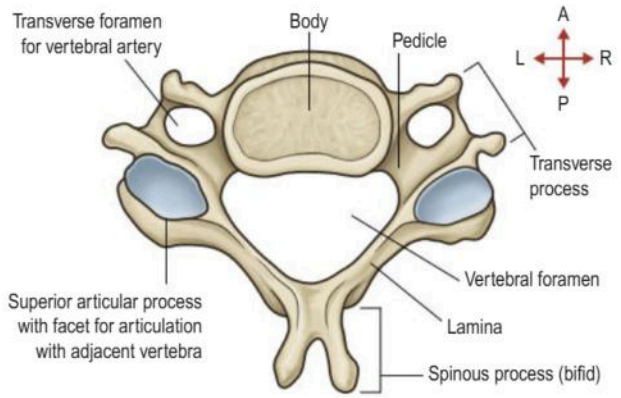


Fig. 16.25 A cervical vertebra, showing typical features. Viewed from above.

because between one vertebra and the next is a tough pad of fibrocartilage called the intervertebral disc. The bodies of the vertebrae lie to the front of the vertebral column, increasing greatly in size towards the base of the spine, because the lower spine has to support much more weight than the upper regions.

Vertebral (neural) arch

This is the bony structure forming the back of the vertebra; with the vertebral body it forms a channel called the vertebral (neural) foramen (Fig. 16.24). When the vertebrae are stacked on top of each other in the spinal column, the vertebral foramina align and form a channel that runs the length of the spine and through which the spinal cord passes, well protected from injury. The vertebral arch is formed from two lateral walls called pedicles, and two posterior walls called laminae. Projecting from the regions where the pedicle meets the lamina is a lateral prominence, the transverse process, and where the two laminae meet at the back is a process called the spinous process. These bony prominences can be felt through the skin along the length of the spine. The vertebral arch has four articular surfaces: two articulate with the vertebra above and two with the one below.

Region-specific vertebral characteristics

Cervical vertebrae

These are the smallest vertebrae (Fig. 16.25) because they only have to support the head. The transverse processes have a foramen through which a vertebral artery passes upwards to the brain. The first two cervical vertebrae, the atlas and the axis, are atypical.

The first cervical vertebra (C1), the atlas, is the bone on which the occipital bone of the skull rests. Below the atlas is the axis, the second cervical vertebra (C2).

The atlas (Fig. 16.26A) is essentially a ring of bone, with no distinct body or spinous process, although it has two short transverse processes. It has two flattened facets that articulate with the occipital bone; these are condyloid joints (p. 458) and they permit nodding of the head.

The axis (Fig. 16.26B and C) sits below the atlas and has a small body with a small superior projection called the dens (meaning tooth) or odontoid process. This fits into the posterior foramen of the atlas above and is held securely within it by the transverse ligament (Fig. 16.26D). The head pivots (i.e. turns from side to side) on this joint.

The 7th cervical vertebra, C7, is also called the vertebra prominens. It has a long spinous prominence terminating in a swollen tubercle, which is easily felt at the base of the neck.

Thoracic vertebrae

The 12 thoracic vertebrae (Fig. 16.27) are larger than the cervical vertebrae because this section of the vertebral column supports more body weight. The bodies and transverse processes have facets for articulation with the ribs.

Lumbar vertebrae

These are the largest of the vertebrae (see Fig. 16.24) because they support the weight of the entire upper body. They have substantial spinous processes for attachment of the muscles of the lower back.

Sacrum

This consists of five rudimentary vertebrae fused to form a triangular or wedge-shaped bone with a concave anterior surface (Fig. 16.28). The upper part, the base, articulates with the 5th lumbar vertebra. On each side it articulates with the ilium to form the sacroiliac joint, and at its inferior tip it articulates with the coccyx. The anterior edge of the base, the promontory, protrudes into the pelvic cavity. On each side of the bone is a series of foramina for the passage of sacral spinal nerves.

Coccyx

This consists of the four terminal vertebrae, fused to form a very small triangular bone (Fig. 16.28), the broad base of which articulates with the tip of the sacrum.

Features of the vertebral column

Intervertebral discs

The bodies of adjacent vertebrae are separated by intervertebral discs consisting of an outer rim of fibrocartilage (annulus fibrosus) and a central core of soft gelatinous material (nucleus pulposus) (Fig. 16.29). The discs are thinnest in the cervical region of the spine and become progressively thicker towards the lumbar region as spinal loading increases. The posterior longitudinal ligament in the vertebral canal helps to keep them in place. They act as shock absorbers, and the cartilaginous joints they form contribute to the flexibility of the vertebral column as a whole.

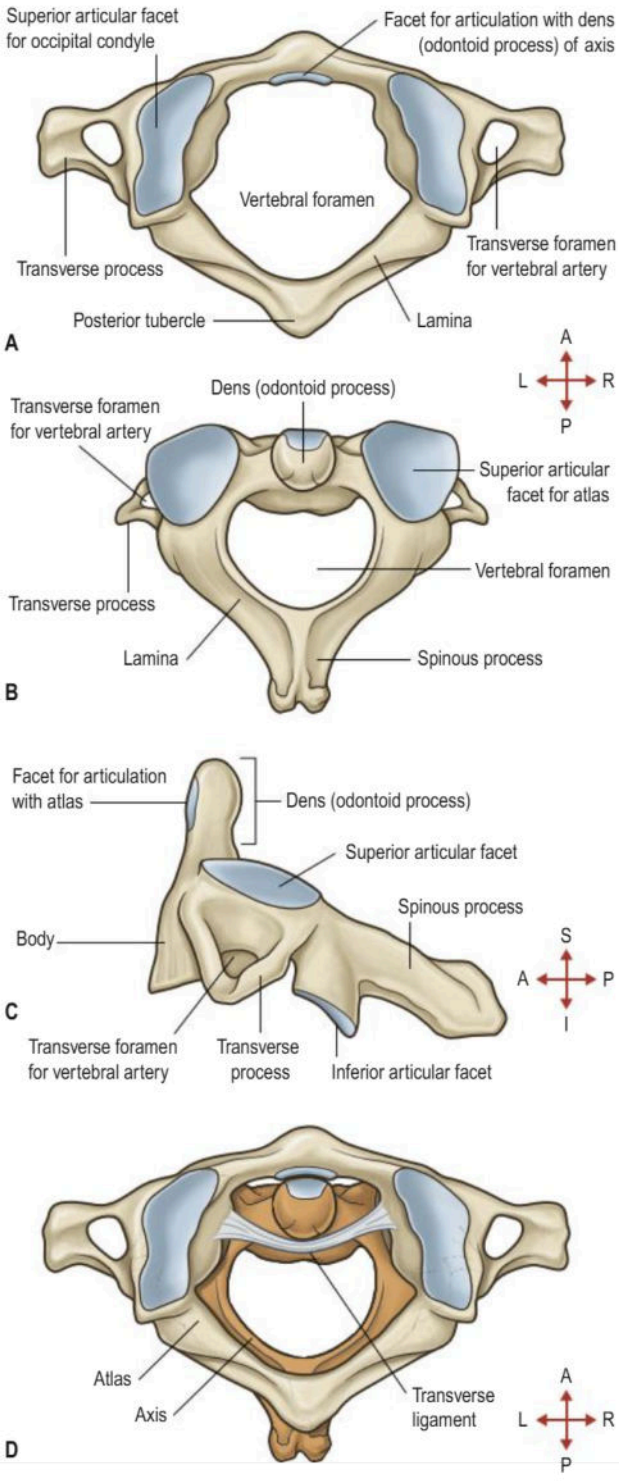


Fig. 16.26 The upper cervical vertebrae. (A) The atlas viewed from above. (B) The axis viewed from above. (C) The axis, lateral view. (D) The atlas and axis in position, showing the transverse ligament.

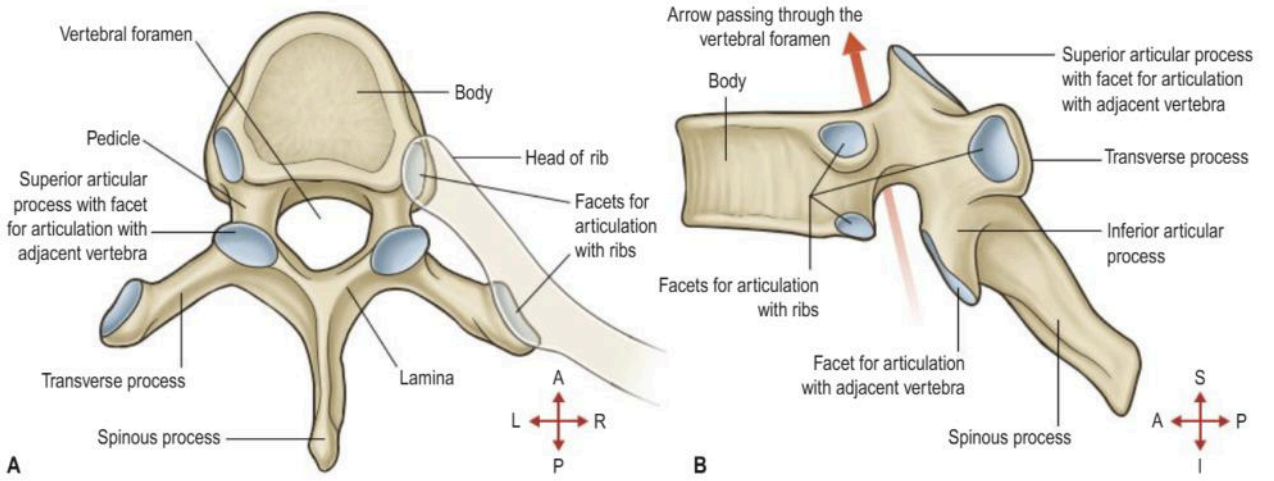


Fig. 16.27 A thoracic vertebra. (A) Viewed from above. (B) Viewed from the side.

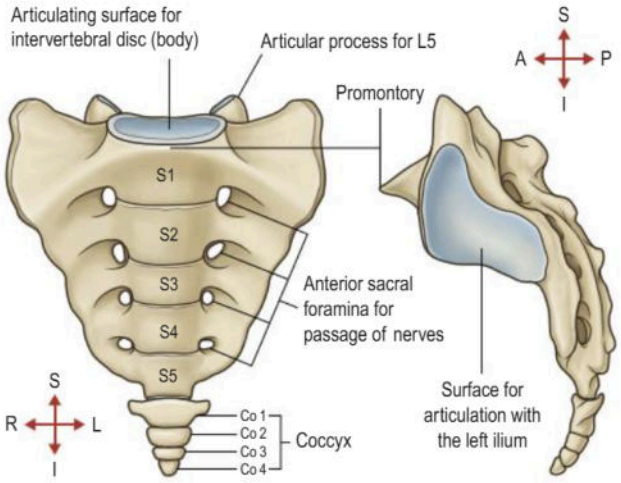


Fig. 16.28 The sacrum and coccyx. Anterior and lateral views.

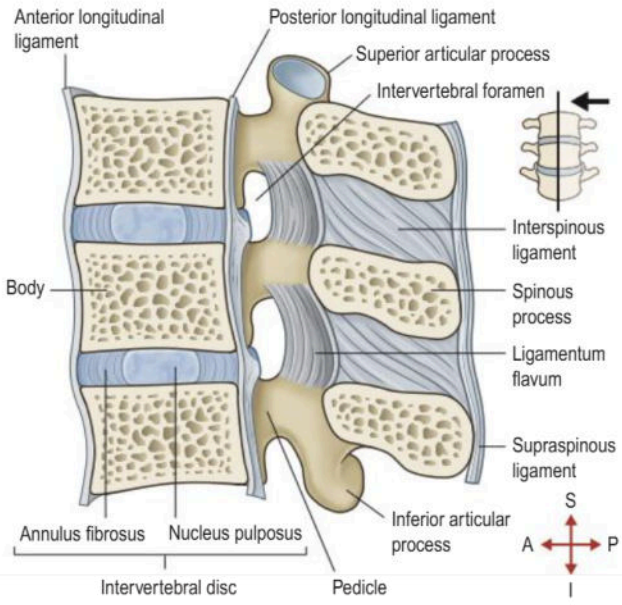


Fig. 16.29 Section of the vertebral column showing the ligaments, intervertebral discs and intervertebral foramina.

Intervertebral foramina

On each side of the vertebral column an intervertebral foramen is formed between the pedicles of every pair of vertebrae, through which the spinal nerves, blood vessels and lymph vessels pass (Fig. 16.30).

Ligaments of the vertebral column

Collectively, these ligaments (Fig. 16.29) hold the vertebrae together and keep the intervertebral discs in position.

The transverse ligament holds the dens of the axis in the correct position in relation to the atlas (Fig. 16.26D).

The anterior longitudinal ligament (Fig. 16.29) runs the whole length of the column in front of the vertebral bodies.

The posterior longitudinal ligament (Fig. 16.29) lies inside the vertebral canal and extends the whole length of the vertebral column in close contact with the posterior surface of the vertebral bodies.

The ligamentum flavum (Fig. 16.29) connects the laminae of adjacent vertebrae.

The ligamentum nuchae (see Fig. 16.65) and the supraspinous ligament connect the spinous processes, extending from the occiput to the sacrum.

Curvatures of the vertebral column

When viewed from the side, the vertebral column presents two primary and two secondary curvatures (curves) (Fig. 16.31).

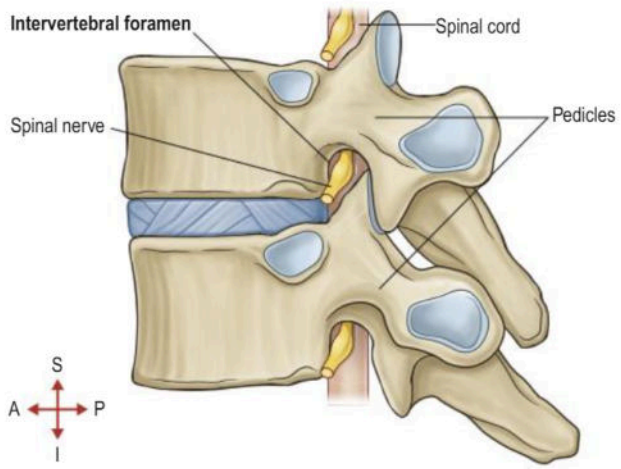


Fig. 16.30 Lower cervical vertebrae showing the spinal nerves emerging through the intervertebral foramina. Lateral view.

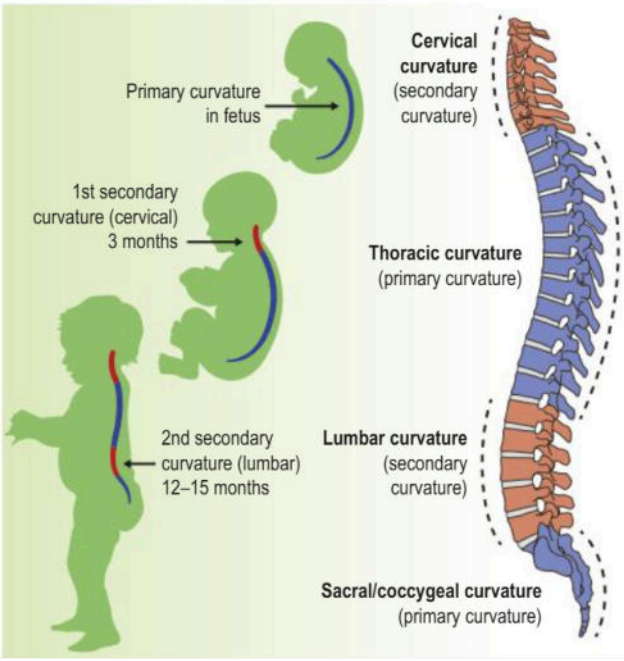


Fig. 16.31 Development of the spinal curvatures.

The fetus lies curled up in the uterus so that the head and the knees are almost touching. This position shows the primary curvature. The secondary cervical curvature develops when the child can hold up his head (after about 3 months) and the secondary lumbar curvature develops when he is able to stand (after 12–15 months). The primary thoracic and sacral curvatures are retained, now separated by the secondary lumbar curvature.

Movement of the vertebral column

Movement between adjacent vertebrae is very limited because the bones interlock and are held together with the supporting ligaments described above. However, the movements of the column as a unit are quite extensive and include flexion (bending forwards), extension (bending backwards), lateral flexion (bending to the side) and rotation. There is more movement in the cervical and lumbar regions than elsewhere.

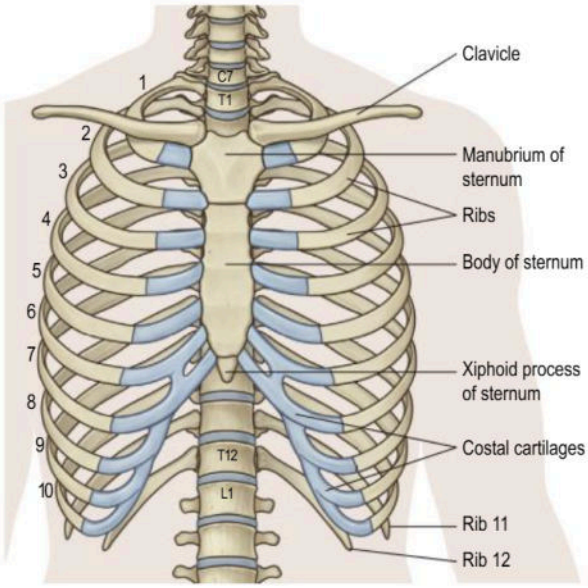


Fig. 16.32 The thoracic cage. Anterior view.

Thoracic cage

The thoracic cage (Fig. 16.32) is made up of the sternum anteriorly, 12 pairs of ribs and the 12 thoracic vertebrae posteriorly.

Sternum (breast bone)

This flat bone (Fig. 16.33) can be felt just under the skin in the middle of the front of the chest and is formed of three sections. The manubrium, the uppermost section, forms the sternoclavicular joint at the clavicular notch. It also forms joints with the first two pairs of ribs. The jugular (suprasternal) notch can be felt under the skin on its superior border. The manubrium articulates with the body, the middle part of the sternum, at the sternal angle (manubriosternal joint), which can be felt as a bony ridge about 5 cm below the jugular notch. The sternal body forms cartilaginous joints with the ribs.

The xiphoid process is the inferior tip of the bone. It gives attachment to the diaphragm, muscles of the anterior abdominal wall and the linea alba (literally 'white line'; see Fig. 16.68).

Ribs

The 12 pairs of ribs form the lateral walls of the thoracic cage (Fig. 16.32). They are elongated, curved bones which articulate posteriorly with the vertebral column (Fig. 16.33).

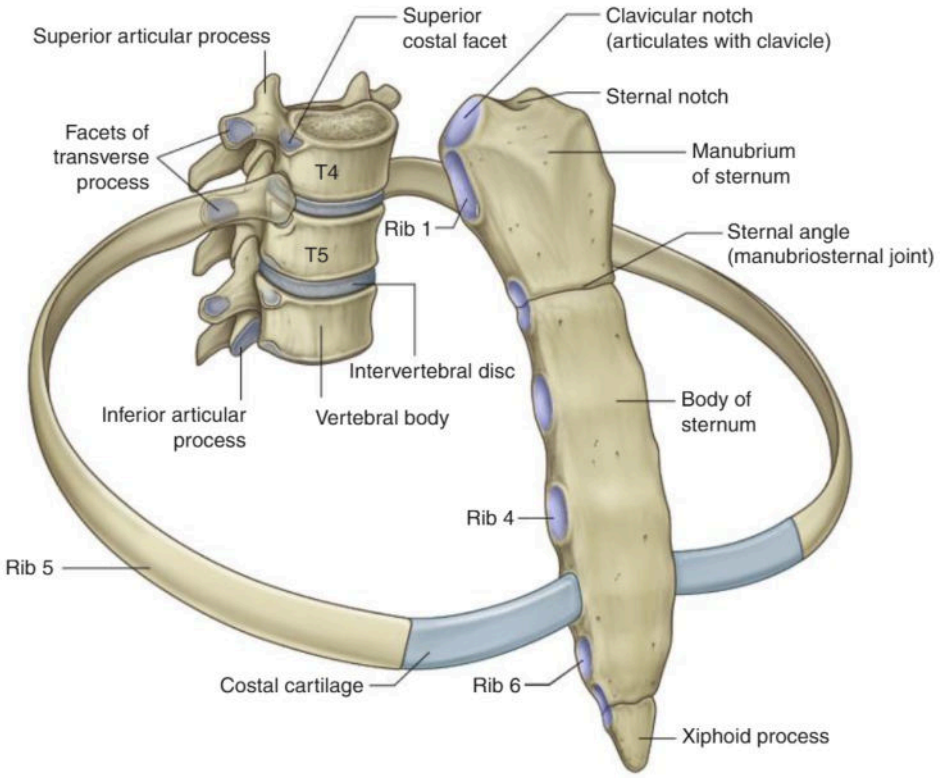


Fig. 16.33 The sternum and associated bones. Facets for articulation are shown in blue. (Modified from Drake R, et al. 2020. Gray's Anatomy for Students, 4th ed. Elsevier.)

The main features of a typical rib are shown in Figure 16.34. Anteriorly, the first seven pairs of ribs connect directly to the sternum by costal cartilages and are called true ribs. The costal cartilages of ribs 8–10 fuse with the costal cartilage of the ribs above, and so are said to articulate indirectly. The lowest two pairs of ribs (11–12), referred to as floating ribs, do not join the sternum at all and their anterior tips are free.

Each rib forms up to three joints with the vertebral column. Two of these joints are formed between facets on the head of the rib and facets on the bodies of two vertebrae, the one above the rib and the one below. Ten of the ribs also form joints between the tubercle of the rib and the transverse process of (usually) the lower vertebra. Showing the fifth rib as an example, these joints, and the articulation of the rib with the sternum, are shown on Figure 16.33.

The inferior surface of the rib is deeply grooved, providing a channel along which the intercostal nerves and blood vessels run. Between each rib and the one below are the intercostal muscles (see Fig. 10.25), which move the ribcage during breathing.

Due to the arrangement of the ribs and the quantity of cartilage present, the ribcage is a flexible structure that changes in shape and size during breathing. The first rib is firmly fixed to the sternum and to the 1st thoracic vertebra and does not move during breathing. It is a fixed point, so when the intercostal muscles contract, they pull the entire ribcage upwards as a unit towards the first rib during inspiration (see p. 282).

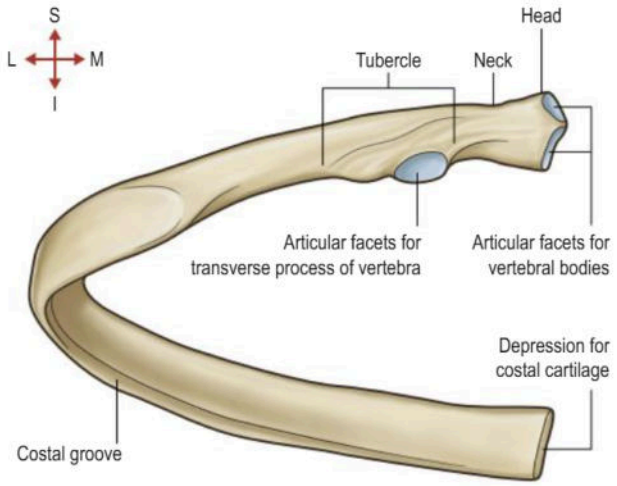


Fig. 16.34 A typical rib. Viewed from below.

SPOT CHECK

3. Which sutures are formed at the edges of the parietal bone?
4. Describe the position and structure of the vertebra prominens.

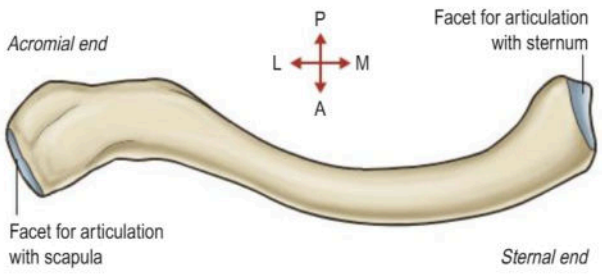


Fig. 16.35 The right clavicle. Viewed from above.

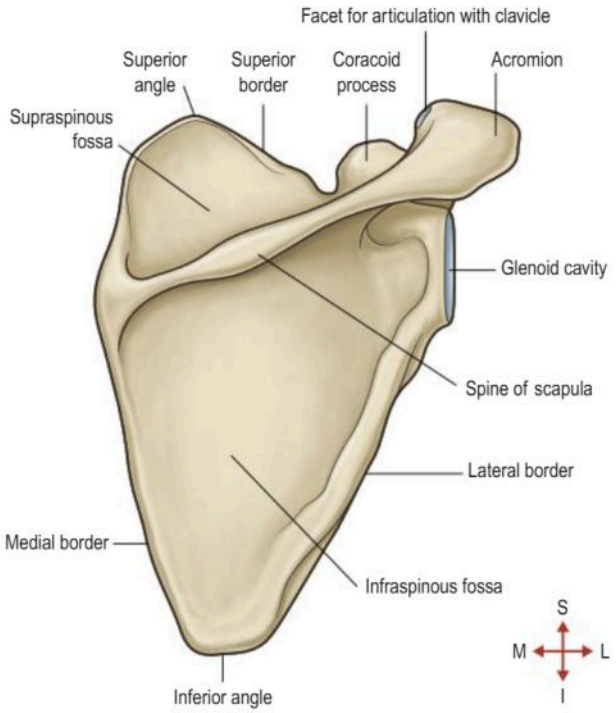


Fig. 16.36 The right scapula. Posterior view.

Appendicular skeleton

Learning outcomes

After studying this section, you should be able to:

- identify the bones forming the appendicular skeleton
- state the characteristics of the bones forming the appendicular skeleton
- outline the differences in structure between the male and female pelves.

The appendicular skeleton (see Fig. 16.13) consists of the:

- shoulder girdle and the upper limbs
- pelvic girdle and the lower limbs.

Shoulder girdle and upper limb

The upper limb, which consists of the hand, the forearm and the upper arm, forms the shoulder joint with the trunk via the shoulder (pectoral) girdle.

Shoulder girdle

The shoulder girdle consists of two clavicles and two scapulae.

Clavicle (collar bone)

The clavicle (Fig. 16.35) is a slender S-shaped bone. It articulates with the manubrium of the sternum at the sternoclavicular joint and forms the acromioclavicular joint with the acromion of the scapula. The clavicle is the only bony link between the upper limb and the axial skeleton.

Scapula (shoulder blade)

The scapula (Fig. 16.36) is a flat, triangular-shaped bone lying on the posterior chest wall, superficial to the ribs and separated from them by muscles.

At the lateral angle is a shallow articular surface, the glenoid cavity, which, with the head of the humerus, forms the shoulder joint.

On the posterior surface runs a rough ridge called the spine, which extends beyond the lateral border of the scapula and overhangs the glenoid cavity. The prominent overhang, which can be felt through the skin as the highest point of the shoulder, is called the acromion and forms a joint with the clavicle; this is the acromioclavicular joint, a slightly movable synovial joint that contributes to the mobility of the shoulder girdle. The coracoid process projects from the superior border of the bone and gives attachment to muscles that move the shoulder joint.

The upper limb

Humerus

The humerus (Fig. 16.37) is the bone of the upper arm. The head sits in the glenoid cavity of the scapula, forming the shoulder joint. Distal to the head are two roughened projections of bone, the greater and lesser tubercles, and between them is a deep groove, the bicipital groove, occupied by one of the tendons of the biceps muscle. The distal end of the bone has two surfaces that articulate with the radius and ulna to form the elbow joint.

Ulna and radius

These are the two bones of the forearm (Fig. 16.38). The ulna is longer than and medial to the radius, and when

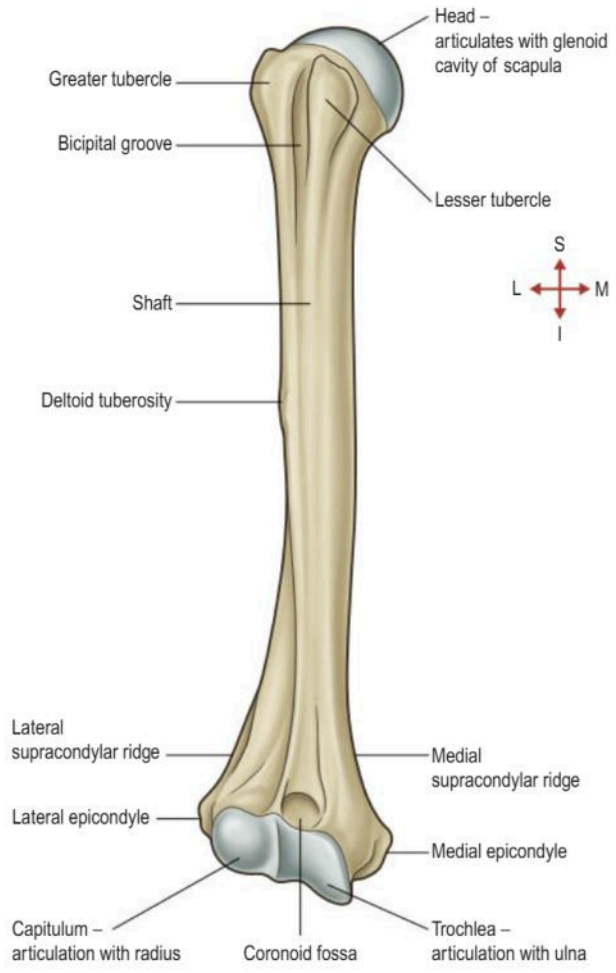


Fig. 16.37 The right humerus. Anterior view.

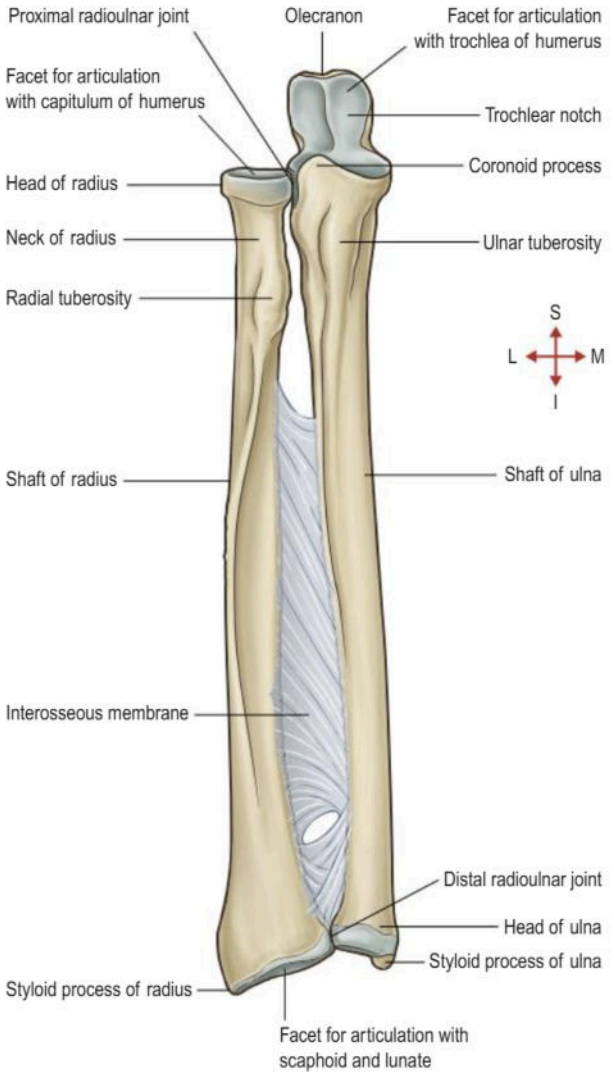


Fig. 16.38 The right radius and ulna with the interosseous membrane. Anterior view.

the arm is in the anatomical position, i.e. with the palm of the hand facing forwards, the two bones are parallel. They articulate with the humerus at the elbow joint, with the carpal bones at the wrist joint, and with each other at the proximal and distal radioulnar joints. In addition, an interosseous membrane, a fibrous joint, connects the bones along their shafts, stabilising their alignment and preventing them from separating when force is applied from the elbow or wrist.

Carpal (wrist) bones

There are eight carpal bones arranged in two rows of four (Fig. 16.39). From outside inwards, they are:

- proximal row: scaphoid, lunate, triquetrum, pisiform
- distal row: trapezium, trapezoid, capitate, hamate.

These bones fit closely together (see Fig. 16.9B) and are held in position by ligaments that allow a limited amount of movement between them. The bones of the proximal row are part of the wrist joint and those of the distal row form joints with the metacarpal bones. Tendons of muscles lying in the forearm cross the wrist and are held close to the bones by strong fibrous bands called retinacula (see Fig. 16.55).

Metacarpal bones

These five bones form the palm of the hand. They are numbered 1–5 from the thumb side inwards. The proximal ends articulate with the carpal bones and the distal ends with the phalanges.

Phalanges (finger bones)

There are 14 phalanges (singular: phalanx), 3 in each finger and 2 in the thumb. They articulate with the metacarpal bones and with each other by hinge joints.

Pelvic girdle and lower limb

The lower limb forms a joint with the trunk at the pelvic girdle. The lower limb consists of the foot, the lower leg and the thigh.

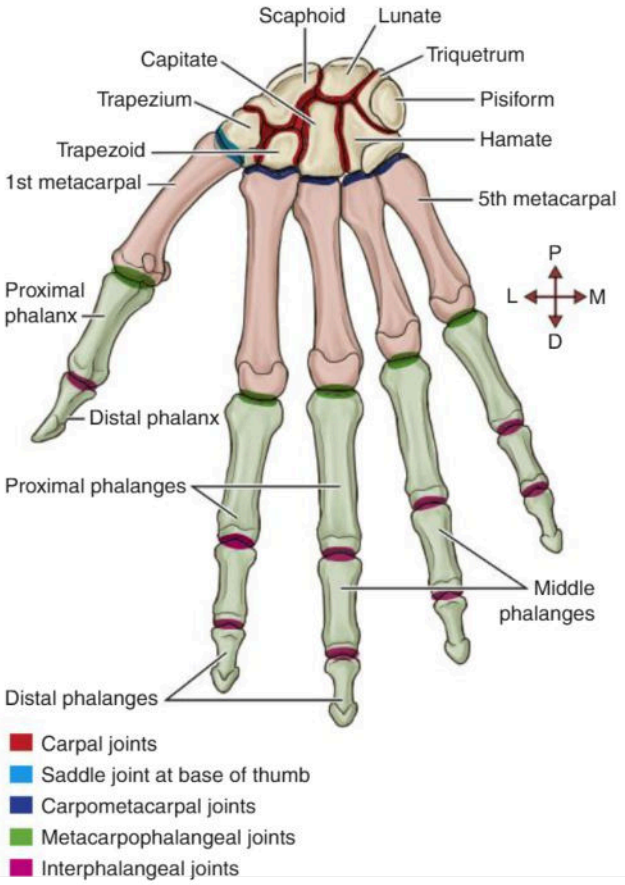


Fig. 16.39 The bones and joints of the right hand, wrist and fingers. Anterior view.

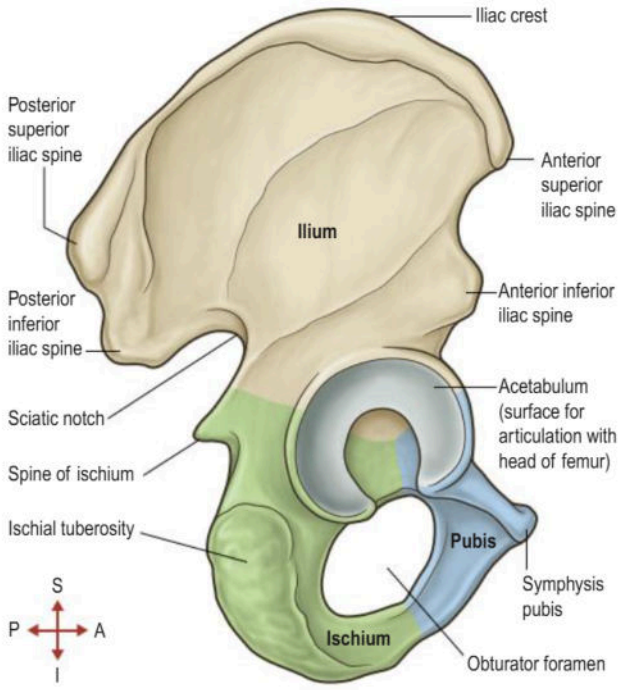


Fig. 16.40 The right hip bone. Lateral view.

Pelvic girdle

The pelvic girdle is formed from two innominate (hip) bones. The pelvis is the basin-shaped structure formed by the pelvic girdle and the sacrum.

Innominate (hip) bones

Each hip bone (Fig. 16.40) consists of three fused bones, the ilium, ischium and pubis. These fuse on its lateral surface to form a deep depression, the acetabulum, which forms the hip joint with the almost-spherical head of femur.

The ilium forms the upper flattened 'wings' of the hip bone. Its superior border is called the iliac crest, the anterior curve of which is called the anterior superior iliac spine. Both the iliac crest and the anterior superior iliac spine are easily felt through the skin and are important bony landmarks of the pelvis. The ilium forms a synovial joint with the sacrum; this is the sacroiliac joint, a strong joint capable of absorbing the stresses of weight bearing and which tends to become fibrosed in later life.

The pubis is the anterior part of the bone and it articulates with the pubis of the other hip bone at a cartilaginous joint, the symphysis pubis (also called the pubic symphysis).

The ischium is the inferior and posterior part. The rough inferior projections of the ischia, the ischial tuberosities, the so-called 'sitting bones', bear the weight of the body when the individual is seated.

The pelvis

The pelvis (Fig. 16.41) is formed by the hip bones, the sacrum and the coccyx. It is divided into upper and lower parts at the pelvic inlet by the brim of the pelvis, an imaginary line drawn round the interior of the pelvis through the sacral promontory and the iliopectineal lines of the innominate bones. The greater (false) pelvis lies above the brim and the lesser (true) pelvis is below.

Differences between male and female pelves

The female pelvis is generally roomier to allow for the passage of the baby during childbirth (Fig. 16.42). Compared to the male pelvis, it is lighter, shallower and more rounded.

Lower limb

Femur (thigh bone)

The femur (Fig. 16.43) is the longest, heaviest bone of the body. The head is almost spherical and fits into the acetabulum of the hip bone to form the hip joint. The neck extends outwards and slightly downwards from the head to the shaft and most of it lies within the capsule of the hip joint. The neck of femur is susceptible to fracture, especially in older people, and can heal poorly because fracture can seriously damage its blood supply.

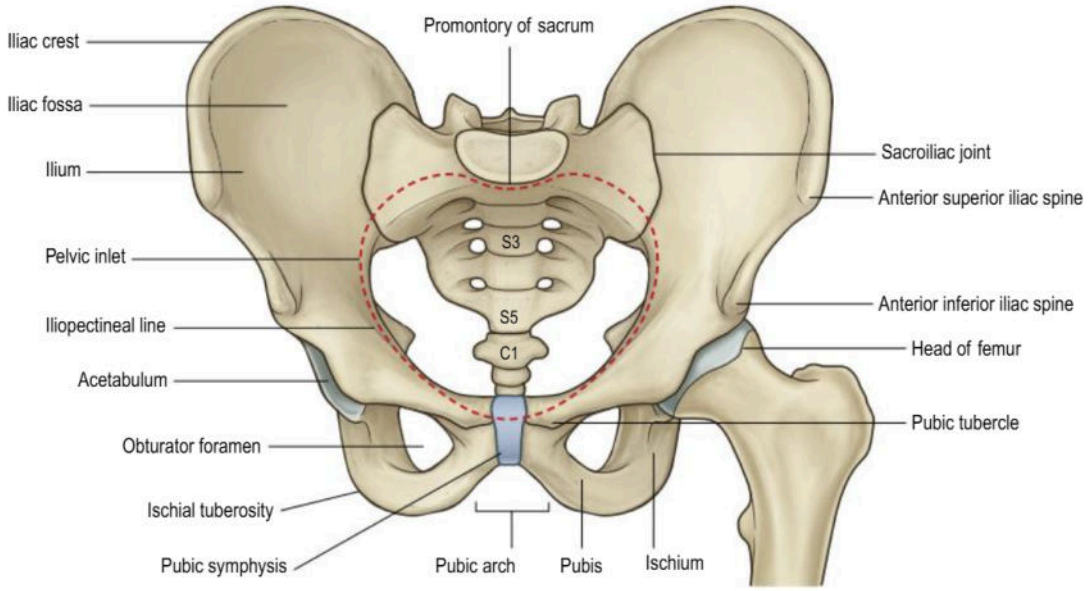


Fig. 16.41 The bones of the pelvis and the upper part of the left femur.

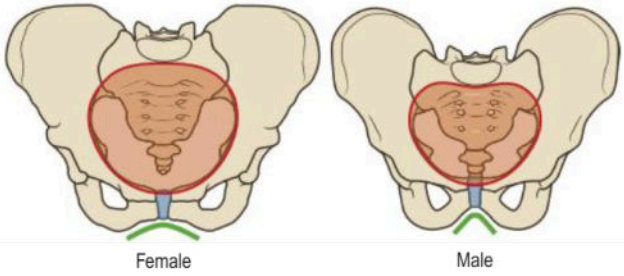


Fig. 16.42 The difference in shape of the male and female pelves.

The posterior surface of the lower third of the femur forms a flat triangular area called the popliteal surface, which forms a joint with the patella. The distal end has two articular condyles, which, with the tibia and patella, form the knee joint. The femur transmits the weight of the body through the bones below the knee to the foot.

Tibia (shin bone)

The tibia (Fig. 16.44) is the medial of the two bones of the lower leg. The proximal end is broad and flat and has two condyles for articulation with the femur at the knee joint. The head of the fibula articulates with the lateral condyle, forming the proximal tibiofibular joint.

The distal end of the tibia forms the ankle joint with the talus and the fibula. The medial malleolus is a downward projection of bone medial to the ankle joint, easily felt through the skin at the inner ankle.

Fibula

The fibula (Fig. 16.44) is the slender lateral bone in the lower leg. The head articulates with the lateral condyle of the tibia, forming the proximal tibiofibular joint, and the lower end articulates with the tibia, projecting beyond it to form the lateral malleolus. This is easily felt through the skin at the outer ankle and helps to stabilise the ankle joint.

Patella (knee cap)

This roughly triangular-shaped sesamoid bone forms part of the anterior wall of the knee joint. It is embedded in the patellar tendon, i.e. the tendon of the quadriceps femoris muscle (see Fig. 16.57B), and its posterior surface articulates with the patellar surface of the femur in the knee joint.

Tarsal (ankle) bones

The seven tarsal bones (Fig. 16.45A) forming the posterior part of the foot (ankle) are the talus, calcaneus, navicular, cuboid and three cuneiform bones. The talus articulates with the tibia and fibula at the ankle joint. The calcaneus forms the heel of the foot. The other bones articulate with each other and with the metatarsal bones.

Metatarsals (bones of the foot)

These are five bones (Fig. 16.45A), numbered from inside out, which form most of the sole (dorsum) of the foot. At their proximal ends they articulate with the tarsal bones, and at their distal ends with the phalanges. The enlarged distal head of the 1st metatarsal bone forms the ball of the foot.

Phalanges (toe bones)

There are 14 phalanges (Fig. 16.45A), arranged in a similar manner to those in the fingers, i.e. two in the great toe (the hallux) and three in each of the other toes.

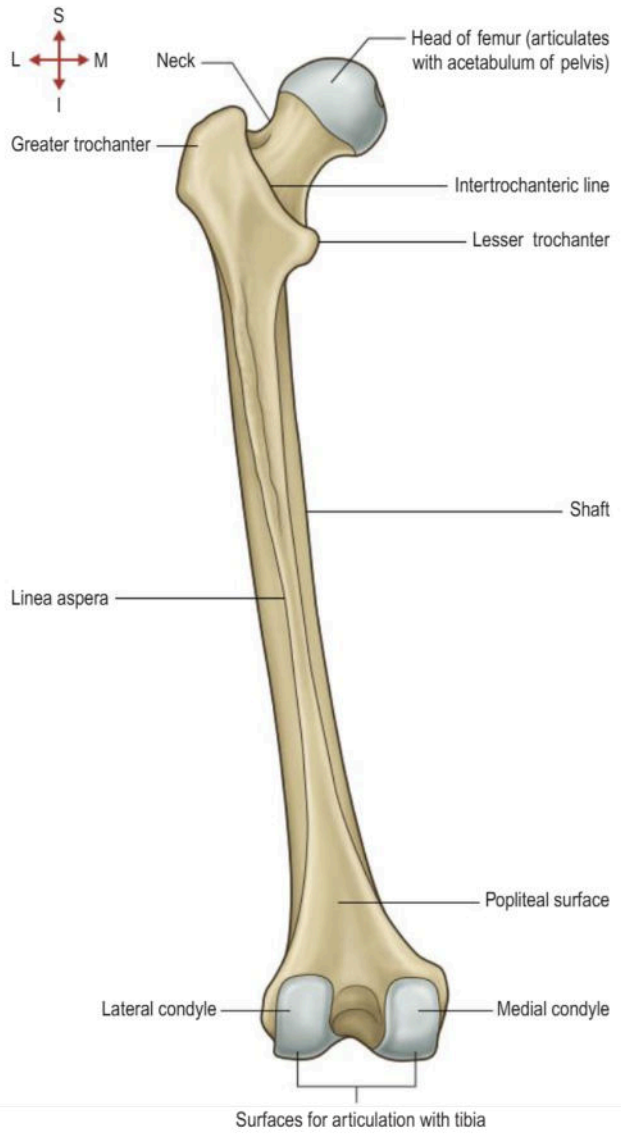


Fig. 16.43 The left femur. Posterior view.

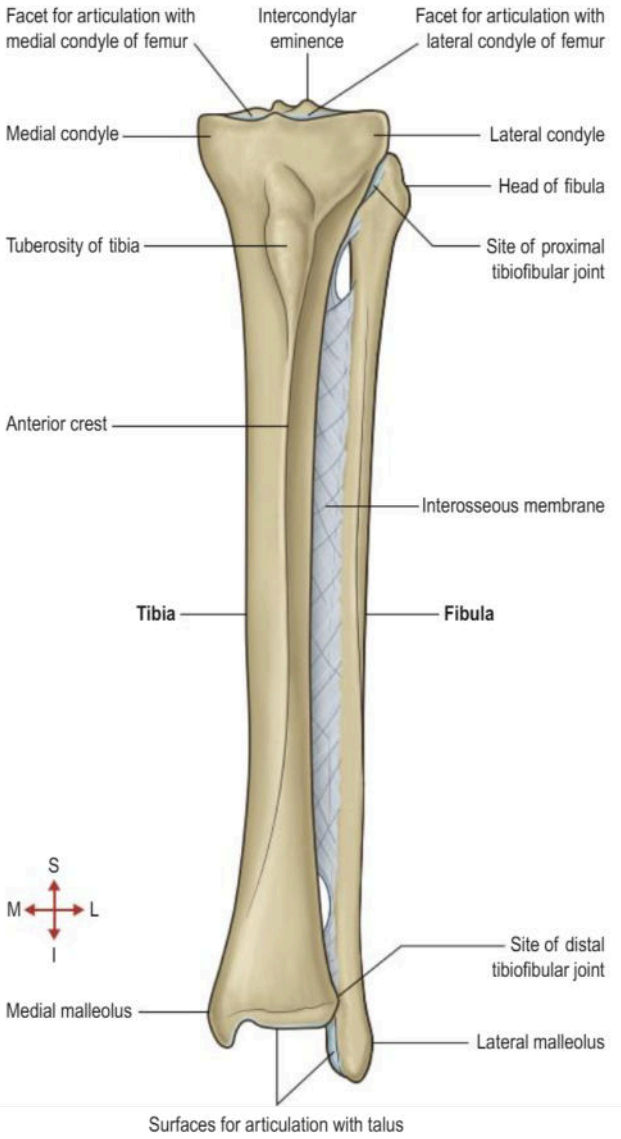


Fig. 16.44 The left tibia and fibula with the interosseous membrane. Anterior view.

Arches of the foot

The arrangement of bones in the foot, supported by associated ligaments and the action of associated muscles, gives the sole of the foot an arched or curved shape (Figs 16.45B and 16.46). The curve running from heel to toe is called the longitudinal arch, and the curve running across the foot is the transverse arch. Because there are movable joints between all the bones of the foot, very strong muscles and ligaments are needed to maintain the strength, resilience and stability of the foot during walking, running and jumping.

In the normal longitudinal arch, only the calcaneus and the distal ends of the metatarsals touch the ground, the bones in between being lifted clear. This gives the conventional footprint shape. If, however, the concavity of the sole is lost because of sagging ligaments or tendons, the arch sinks and much more of the sole of the foot is in contact with the ground: this is called flat foot. The arched design is an effective shock absorber and allows the foot to lever the body forwards in walking and running. The arches of the foot are also important in distributing body weight evenly while upright, whether stationary or moving. The flat foot loses the springiness and support of normal foot structure, leading to sore feet when standing, walking or running for long periods.

Posterior tibialis muscle. This is the most important muscular support of the longitudinal arch (Fig. 16.46). It lies on the posterior aspect of the lower leg and originates from the middle third of the tibia and fibula; its tendon passes behind the medial malleolus to be inserted into the navicular, cuneiform, cuboid and metatarsal bones. It acts as a sling or suspension apparatus for the arch.

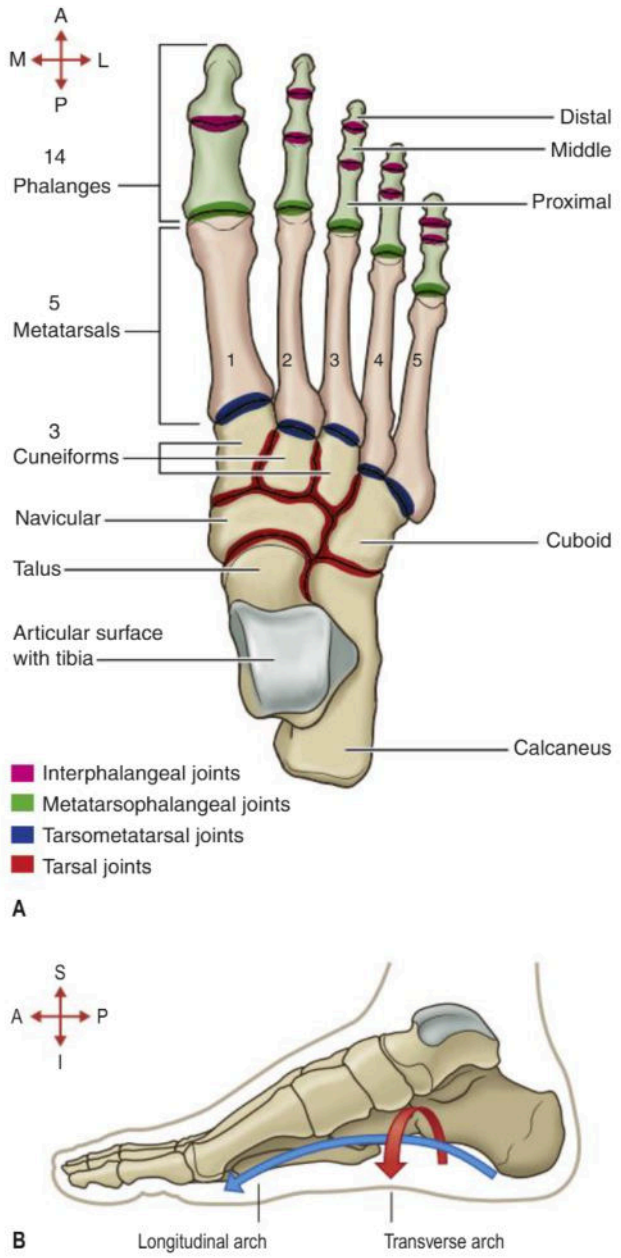


Fig. 16.45 The right foot. (A) Bones and joints viewed from above. (B) Medial view showing arches.

Short muscles of the foot. This group of muscles is mainly concerned with the maintenance of the longitudinal and transverse arches. They form the fleshy part of the sole of the foot.

Plantar calcaneonavicular (spring) ligament. This very strong thick ligament stretches from the calcaneus to the navicular bone (Fig. 16.46). It plays an important part in supporting the medial longitudinal arch.

Plantar ligaments and interosseous membranes. These structures support the lateral longitudinal and transverse arches.

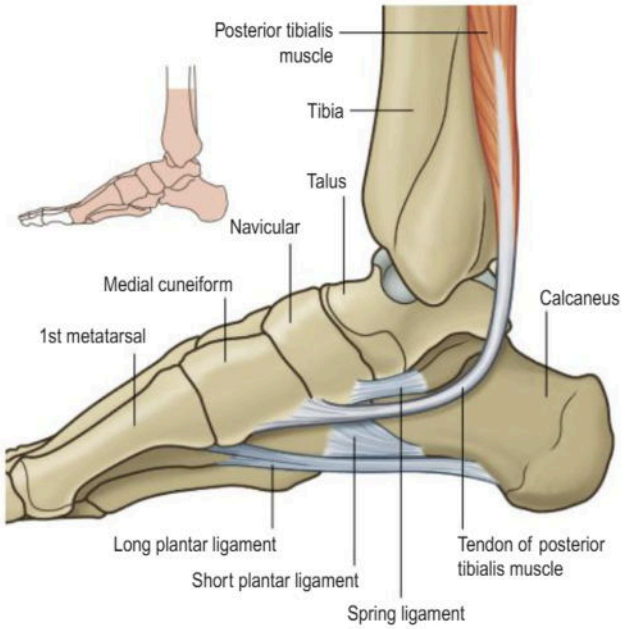


Fig. 16.46 The tendons and ligaments supporting the arches of the right foot. Medial view.

SPOT CHECK

5. On which bone would you find the acromion and how would you locate this on the body?
6. What is meant by the arches of the foot and why are they important to its function?

Joints

Learning outcomes

After studying this section, you should be able to:

- outline the characteristics of fibrous and cartilaginous joints
- list the different types of synovial joint
- outline the movements possible at six types of synovial joint
- describe the structure and functions of a typical synovial joint
- describe the structure and movements of the following synovial joints: shoulder, elbow, wrist, hip, knee and ankle.

A joint is the site at which two or more bones articulate with each other, and the ends or edges of the bones are held together by connective tissues. Joints may allow flexibility and movement of the participating bones. In some joints,

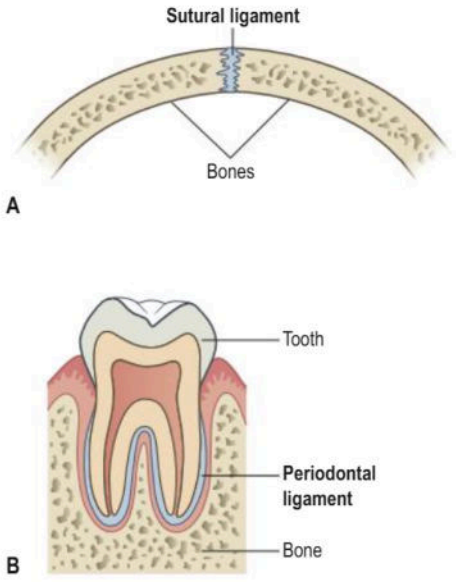


Fig. 16.47 Fibrous joints. (A) Suture of the skull. (B) The periodontal ligament.

however, the participating bones are fastened together so firmly that no movement between them is possible.

Fibrous joints

The bones forming these joints are linked with tough, fibrous material. This often permits no movement. For example, the sutures, the joints between the skull bones, are completely immovable (Fig. 16.47A), and the healthy tooth is anchored to the mandible by the periodontal ligament (Fig. 16.47B). The tibia and fibula in the leg are held together along their shafts by the interosseous membrane (Fig. 16.44). This fibrous joint allows a limited amount of movement and stabilises the alignment of the bones.

Cartilaginous joints

In these joints, a pad of tough fibrocartilage binds the bones together. The joint may be immovable, as in the cartilaginous epiphyseal plates (Fig. 16.48A), which in the growing child link the diaphysis of a long bone to the epiphysis. Some cartilaginous joints permit limited movement, for example the intervertebral discs between the vertebrae (Fig. 16.48B), or at the pubic symphysis (Fig. 16.48B), which is softened by circulating hormones during pregnancy to allow for expansion during childbirth.

Synovial joints

Synovial joints are characterised by the presence of a joint cavity between the articulating bones. The bone ends are held closely together by a sleeve of fibrous tissue and lubricated with a small amount of fluid. Synovial joints are the most movable of the body.

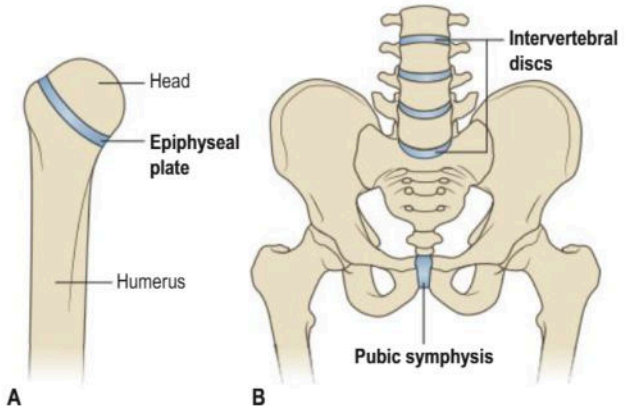


Fig. 16.48 Cartilaginous joints. (A) The epiphyseal plate. (B) Intervertebral discs and the pubic symphysis.

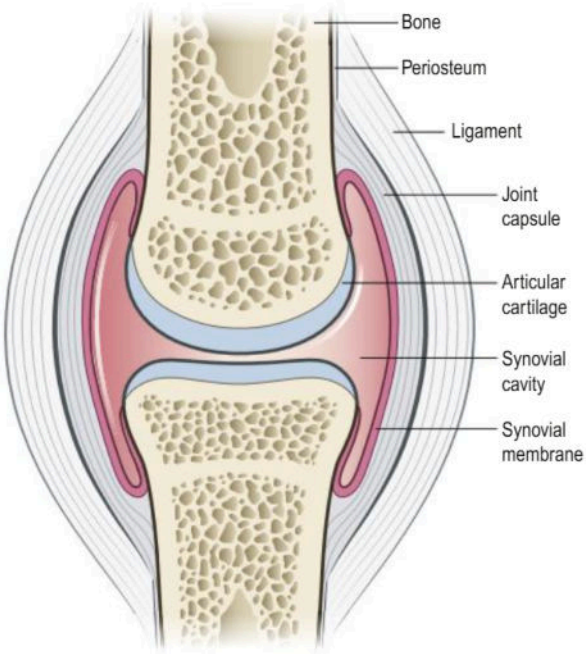


Fig. 16.49 The basic structure of a synovial joint.

Characteristics of a synovial joint

Figure 16.49 shows the general structure of a synovial joint.

Articular or hyaline cartilage

The bone surfaces in contact with each other are coated with hyaline cartilage (see Fig. 3.23A). This provides a smooth articular surface, reduces friction, distributes weight and prevents damaging bone-to-bone contact. The cartilage lining is up to 7 mm thick in young people, but becomes thinner and less compressible with age, increasing stress on other structures in the joint. Cartilage has no blood supply and receives its nourishment from synovial fluid.

Joint capsule

The joint is wrapped in a sleeve of fibrous tissue holding the bones together, which is sufficiently loose to allow freedom of movement but strong enough to protect from injury. The capsule is formed by an extension of the periosteum covering the participating bones.

Synovial membrane

This delicate epithelial layer lines the capsule and covers all non-articulating surfaces inside the joint. It secretes synovial fluid.

Synovial fluid

This thick, sticky fluid of egg-white consistency fills the synovial cavity. Its main function is to lubricate the joint, but it also:

- nourishes the structures within the joint cavity
- contains phagocytes, which remove microbes and cellular debris
- resists separation of the bone ends, like a little water between two glass surfaces.

Synovial membrane also forms little sacs of synovial fluid (bursae) found in or around some joints, including the knee and shoulder. Bursae act as cushions that prevent friction between a bone and a ligament or tendon, or skin where a bone in a joint is near the surface.

Other intracapsular structures

Some joints have structures within the capsule to pad and stabilise the joint, e.g. fat pads and menisci (see Fig. 16.57) in the knee joint. Any structures that do not bear weight are covered by synovial membrane.

Extracapsular structures

Ligaments that blend with the capsule stabilise the joint. In addition, muscles or their tendons stretch across the joints they move and stabilise and support it.

Nerve and blood supply

Nerves and blood vessels crossing a joint usually supply the capsule and the muscles that move it.

Movements at synovial joints

Movement at any given joint depends on various factors, such as the tightness of the ligaments holding the joint together, how well the bones interlock and the presence of intracapsular structures. Generally, the more stable the joint, the less mobile it is. The main movements possible are summarised in Table 16.2 and Figure 16.50.

Types of synovial joint

Synovial joints are classified according to the range of movement possible (Fig. 16.50 and Table 16.2) or the shape of the articulating parts of the bones involved (Fig. 16.51).

Ball and socket joints

The head of one bone is ball-shaped and fits into a cup-shaped socket of another. These joints allow a wide range of movement, including flexion, extension, adduction, abduction, rotation and circumduction. Examples include the shoulder and hip.

Hinge joints

The articulating ends of the bones fit together like a hinge on a door, and movement is therefore restricted to flexion and extension. For example. the elbow joint allows only flexion and extension of the forearm. Other hinge joints include the knee, ankle and the joints between the phalanges of the fingers and toes (interphalangeal joints, Fig. 16.39).

Gliding joints

The articular surfaces are flat or very slightly curved and glide over one another but the amount of movement possible is very restricted; gliding joints are the least movable of all the synovial joints. Examples include the joints between the carpal bones in the wrist, the tarsal bones in the foot, and the processes of the spinal vertebrae (note that the joints between the vertebral bodies are the cartilaginous discs).

Pivot joints

These joints allow a bone or a limb to rotate. One bone fits into a hoop-shaped ligament that holds it close to another bone and allows it to rotate in the ring thus formed. For example, the head rotates on the pivot joint formed by the dens of the axis held within the ring formed by the transverse ligament of the atlas (see Fig. 16.26D).

Condyloid joints

A condyle is a smooth, rounded projection on a bone and in a condyloid joint it sits within a cup-shaped depression on the other bone. Examples include the joint between the condylar process of the mandible and the temporal bone of the skull, allowing the mouth to open and close. Other examples include joints between the metacarpal and phalangeal bones of the hand, and between the metatarsal and phalangeal bones of the foot. These joints permit flexion, extension, abduction, adduction and circumduction.

Saddle joints

The articulating bones fit together like a person sitting on a saddle. The most important saddle joint is at the base of the thumb, between the trapezium of the wrist and the first metacarpal bone (Fig. 16.39). The range of movement is similar to that at a condyloid joint but with additional flexibility; opposition of the thumb, the ability to touch each of the fingertips on the same hand, is due to the nature of the thumb joint.

Principal synovial joints of the limbs

All synovial joints have the characteristics described above, so only their distinctive features are included in this section.

Table 16.2 Movements possible at synovial joints

Movement	Definition
Flexion	Bending at a joint to pull the bones forming the joint closer together (decreasing the angle between them)
Extension	Straightening at a joint to pull the bones forming the joint further away from each other
Abduction	Movement away from the midline of the body
Adduction	Movement towards the midline of the body
Circumduction	Movement of a limb or digit so that it describes the shape of a cone
Rotation	Movement round the long axis of a bone
Pronation	Turning the palm of the hand down (writing position)
Supination	Turning the palm of the hand up
Inversion	Turning the sole of the foot inwards
Eversion	Turning the sole of the foot outwards

Shoulder joint

This ball and socket joint (Fig. 16.52) is the most mobile in the body and consequently is the least stable and most likely to dislocate, especially in children. It is formed by the head of the humerus sitting in the shallow glenoid cavity of the scapula and is well padded with protective bursae. The capsular ligament is very loose inferiorly to allow for free shoulder movement. The shallow glenoid cavity is deepened by a rim of fibrocartilage, the glenoidal labrum, which provides additional stability without limiting movement (Fig. 16.52B). The tendon of the long head of the biceps muscle is held in the bicipital groove of the humerus by the transverse humeral ligament. It extends through the joint cavity and attaches to the upper rim of the glenoid cavity. Repeated dislocations can stretch the tendons and ligaments supporting the shoulder joint, making it less stable.

Synovial membrane forms a sleeve round the part of the tendon of the long head of the biceps muscles within the capsular ligament and covers the glenoidal labrum.

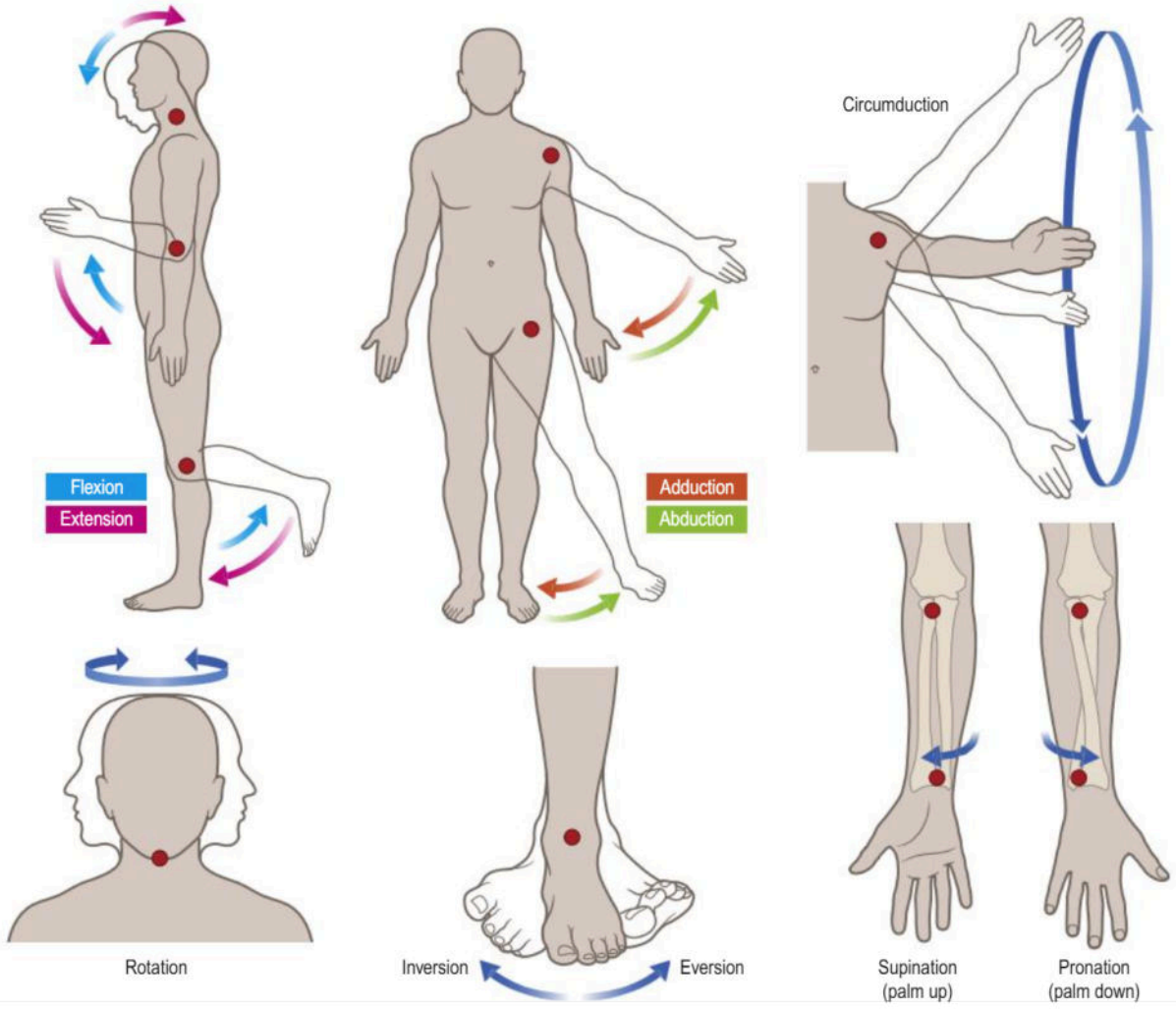


Fig. 16.50 The main movements possible at synovial joints.

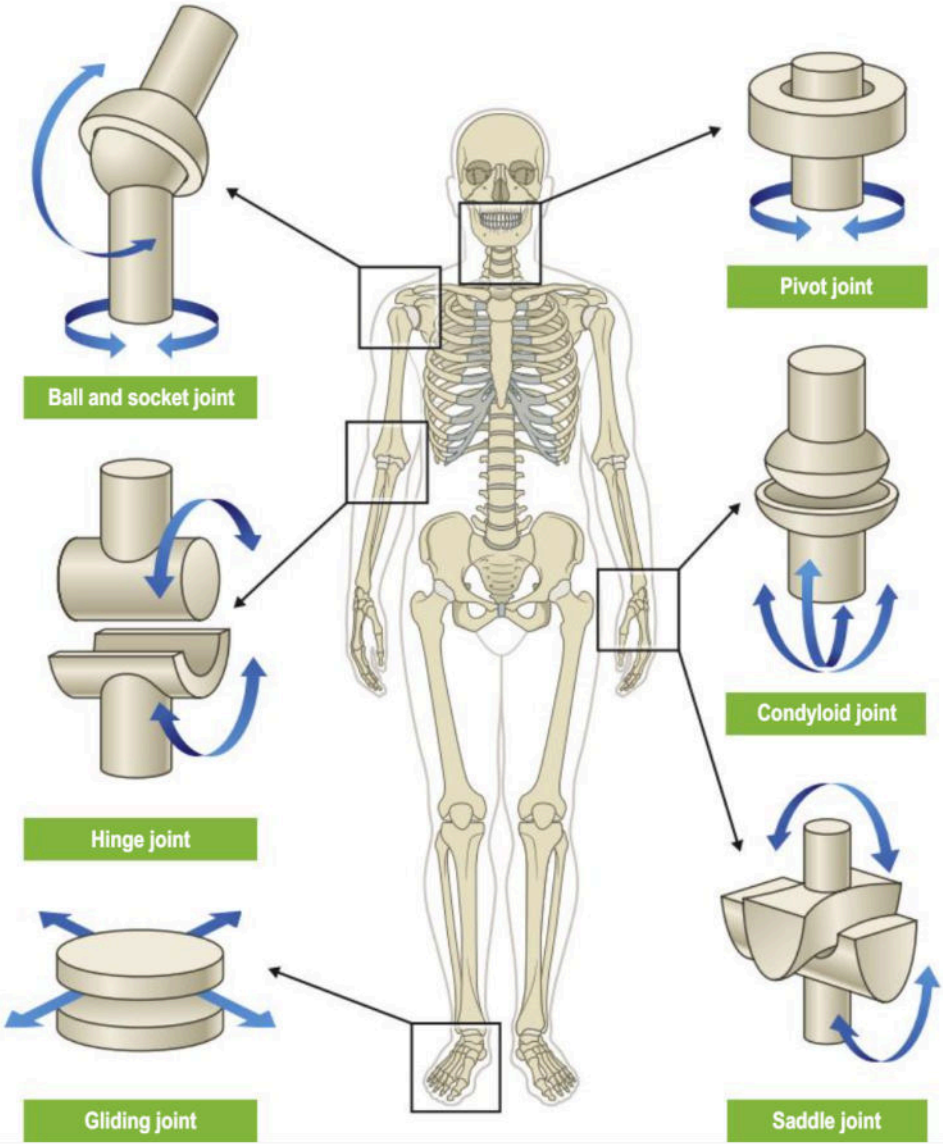


Fig. 16.51 Types of synovial joint with examples of their locations in the skeleton.

The joint is stabilised partly by the glenohumoral, coracohumeral and transverse humeral ligaments (Fig. 16.52C), but mainly by the muscles and their tendons crossing the shoulder. Four of these muscles are collectively called the rotator cuff, and rotator cuff injury is a common cause of shoulder pain.

Muscles and movements

The muscles that move the arm (see Fig. 16.70) are described on page 474, and Table 16.3 summarises the muscles and movements possible at the shoulder joint.

Elbow joint

The elbow joint (Fig. 16.53A) involves three bones: the humerus of the upper arm, and the radius and ulna of the forearm. The elbow joint actually contains two joints. The capitulum of the humerus is a rounded projection that fits against the head of the radius, forming the humero-radial joint. The trochlea is a grooved projection on the humerus which fits very closely into the trochlear notch of the ulna, forming the humero-ulnar joint. Because the bones fit together very closely and the whole joint is wrapped in a number of strong ligaments (Fig. 16.53B), the elbow joint is very stable.

The ulnar nerve runs superficially at the back of the elbow joint, along a shallow groove on the medial epicondyle. This area is referred to colloquially as the 'funny bone' and if it is bumped or struck, it produces a tingling sensation in the forearm.

Muscles and movements

The structure of the elbow joint allows only flexion and extension. The biceps is the main flexor of the forearm, aided by the brachialis; the triceps extends it (see Fig. 16.70).

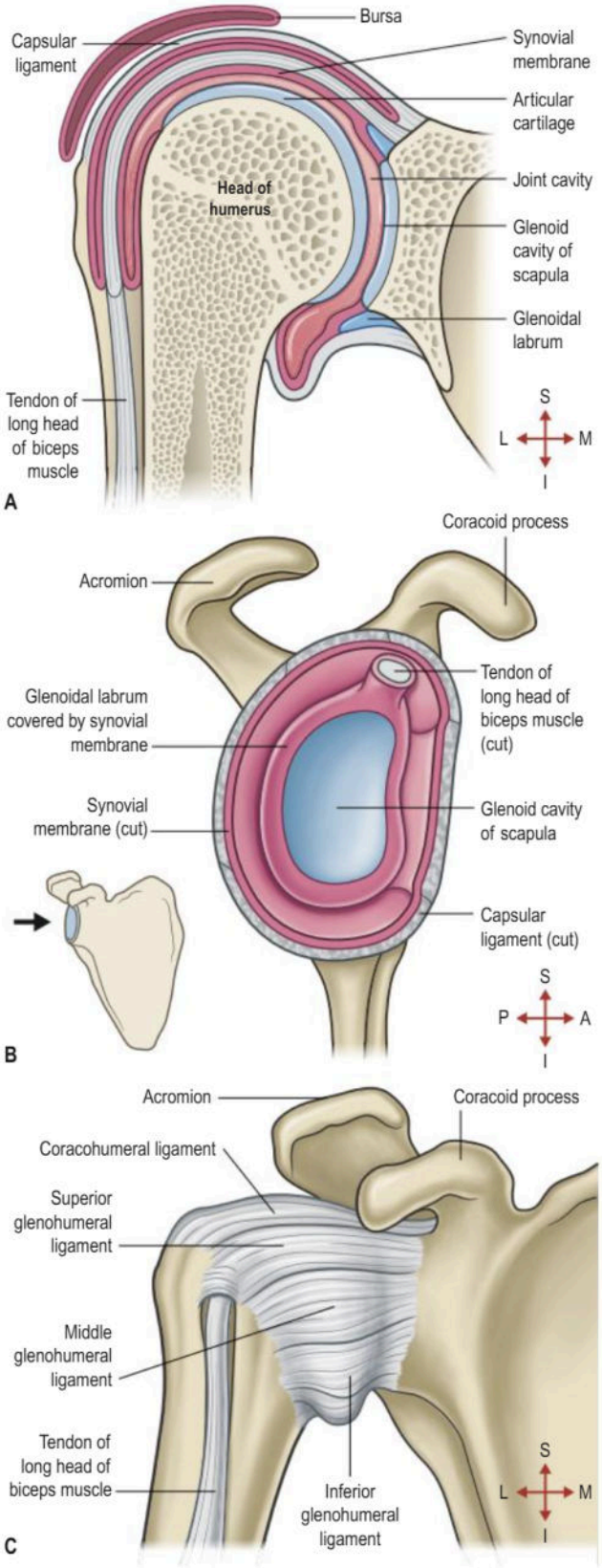


Fig. 16.52 The right shoulder joint. (A) Section viewed from the front. (B) The position of the glenoidal labrum with the humerus removed, viewed from the side. (C) The supporting ligaments viewed from the front.

Table 16.3 Muscles and movements at the shoulder joint

Movement	Muscles involved
Extension	Latissimus dorsi, teres major
Flexion	Coracobrachialis, pectoralis major
Abduction	Deltoid
Adduction	Latissimus dorsi, pectoralis major
Lateral rotation	Teres minor, posterior part of deltoid
Medial rotation	Latissimus dorsi, pectoralis major, teres major and anterior part of deltoid
Circumduction	Combination of actions of above muscles

Proximal and distal radioulnar joints

The proximal radioulnar joint is a pivot joint formed by the rim of the head of the radius rotating in the radial notch of the ulna, and is enclosed in the elbow joint capsule. The annular ligament is a strong extracapsular ligament that encircles the head of the radius and holds it against the radial notch of the ulna (Fig. 16.53B). The distal radioulnar joint is a pivot joint between the distal end of the radius and the head of the ulna (Fig. 16.38).

The two joints between each end of the radius and ulna are essential to allow pronation and supination of the forearm, in which the radius rotates relative to the ulna. In forearm supination, with the palm up and thumb lying laterally, the radius and ulna are parallel, but when the hand is turned through 180 degrees so that the thumb is lying medially, the radius crosses over the ulna, rotating in the ring formed by the annular ligament.

The interosseous membrane (see Fig. 16.38) is a fibrous joint that prevents separation of the bones when force is applied at either end, i.e. at the wrist or elbow.

Muscles and movements

Forearm pronation is caused by contraction of pronator teres (p. 476) and supination by the supinator and biceps muscles (p. 474 and see Fig. 16.70).

Wrist joint

This condyloid joint is formed between the distal end of the radius and the proximal surfaces of the scaphoid, lunate and triquetrum (Fig. 16.54). A disc of white fibrocartilage separates the ulna from the joint cavity and articulates with the carpal bones. It also separates the distal radioulnar joint from the wrist joint.

Medial and lateral ligaments and anterior and posterior radiocarpal ligaments stabilise the wrist joint.

Muscles and movements

The wrist can be flexed, extended, abducted and adducted. The muscles that perform these movements are described on page 474 (see Fig. 16.70). Table 16.4 summarises the main muscles that move the wrist.

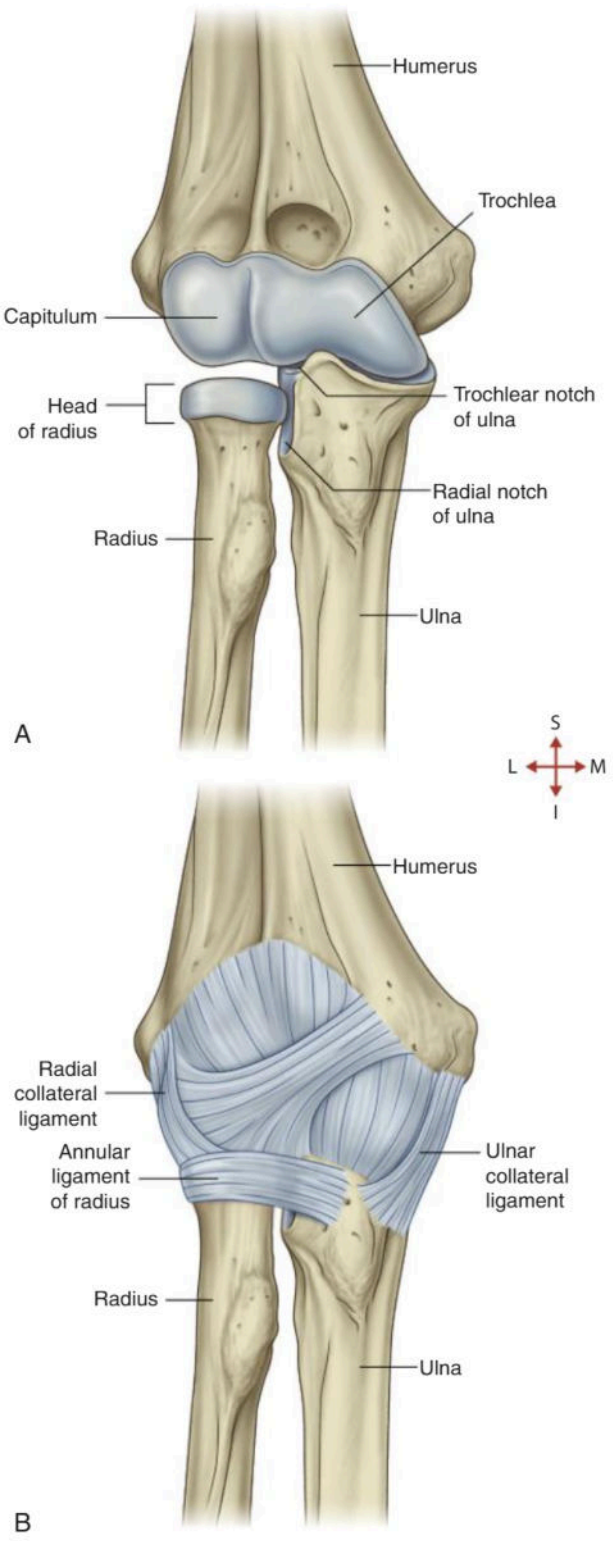


Fig. 16.53 The right elbow joint, viewed from the front. (A) The bones and articulating surfaces. (B) The supporting ligaments of the joint, including the annular ligament of the proximal radioulnar joint. (Modified from Drake R, et al. 2020. Gray's Anatomy for Students, 4th ed. Elsevier.)

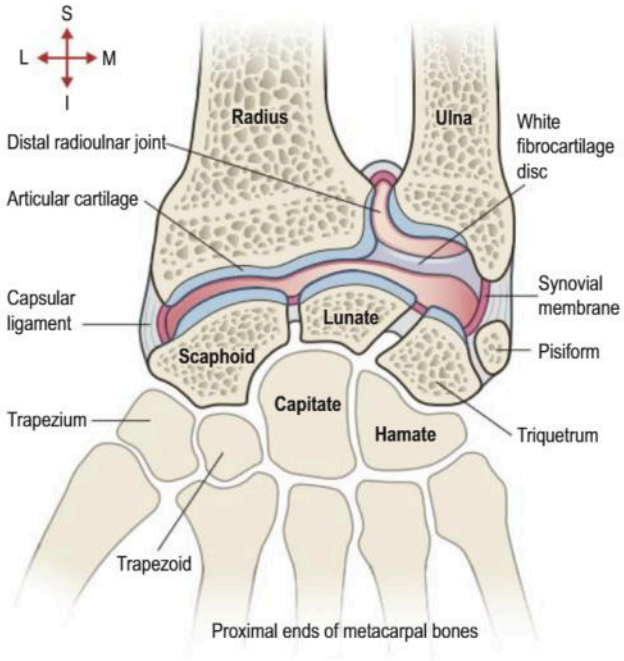


Fig. 16.54 The right wrist and distal radioulnar joints: anterior view.

Table 16.4 Muscles and movements at the wrist joint

Movement	Muscles involved
Flexion	Flexor carpi radialis, flexor carpi ulnaris
Extension	Extensors carpi radialis (longus and brevis), extensor carpi ulnaris
Abduction	Flexor carpi radialis, extensor carpi radialis
Adduction	Flexor carpi ulnaris, extensor carpi ulnaris

Joints of the hands and fingers

The carpal bones are held firmly together by several ligaments. All the wrist and hand joints are synovial for mobility. Movement at the hand and finger joints is controlled by muscles in the forearm and smaller muscles in the hand. There are no muscles in the fingers; finger movements are produced by tendons extending from muscles in the forearm and the hand (Fig. 16.55A).

The joints between the carpal bones and the metacarpals of the palm are called carpometacarpal joints (see Fig. 16.39). The joint at the base of the thumb, the first carpometacarpal joint, is a saddle joint, unlike the carpometacarpal joints of the other fingers, which are condyloid. This means that the thumb is more mobile than the fingers and the thumb can be flexed, extended, circumducted, abducted and adducted. In addition the thumb can be moved across the palm to touch each fingertip on the same hand (opposition), giving great manual dexterity and allowing, for example,

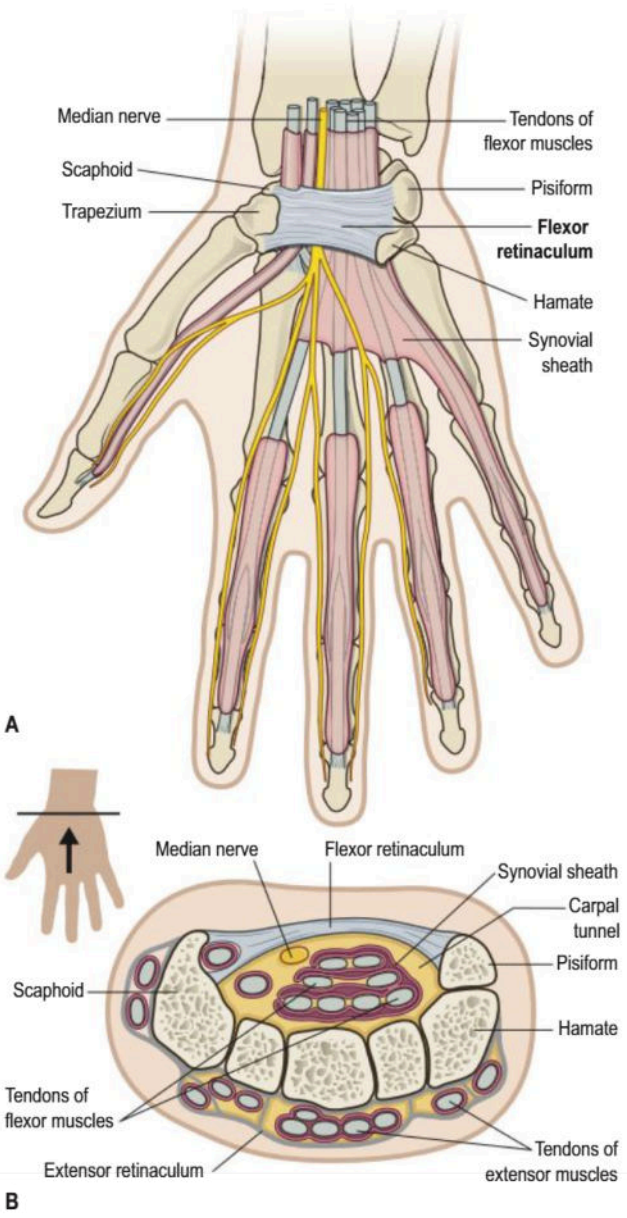


Fig. 16.55 The carpal tunnel and synovial sheaths in the right wrist and hand *(pink)*, with tendons *(white)*. (A) Palmar view. (B) Transverse section.

the holding of a pen and the fine manipulation of objects held in the hand.

The joints between each metacarpal and its first phalanx are called metacarpophalangeal joints (see Fig. 16.39). They allow flexion, extension, adduction, abduction and circumduction of each finger. The first finger is more flexible than the others. The interphalangeal joints between the phalanges are hinge joints and allow only flexion and extension.

The flexor retinaculum is a strong fibrous band stretched across the front of the carpal bones, forming the carpal tunnel (Fig. 16.55B). The tendons of flexor muscles of the wrist joint and the fingers and the median nerve pass through the carpal tunnel, the flexor retinaculum holding them close to the bones. Synovial membrane forms sleeves around these tendons in the carpal tunnel and extends some way into the palm of the hand (Fig. 16.55A). Synovial sheaths also enclose the tendons on the flexor surfaces of the fingers. Their synovial fluid prevents friction that might damage the tendons as they move over the bones.

The extensor retinaculum is a strong fibrous band stretched across the back of the wrist. Tendons of muscles that extend the wrist and finger joints are enclosed in synovial membrane under the extensor retinaculum.

Hip joint

This strong ball and socket joint is formed by the cup-shaped acetabulum of the innominate (hip) bone and the almost spherical head of the femur (Fig. 16.56A). The capsular ligament encloses the head and most of the neck of the femur. The cavity of the acetabulum is deepened by the acetabular labrum, a ring of fibrocartilage attached around the rim of the acetabulum, which stabilises the joint without limiting its range of movement. The hip joint needs to be sturdy and powerful, because it bears all the body weight when upright. It is stabilised by its surrounding muscles but its ligaments are also important. The three main external ligaments are the iliofemoral, pubofemoral and ischiofemoral ligaments (Fig. 16.56B). Within the joint, the ligament of the head of the femur (ligamentum teres) attaches the femoral head to the acetabulum (Fig. 16.56A and C).

Muscles and movements

The lower limb can be extended, flexed, abducted, adducted, rotated and circumducted at the hip joint (Table 16.5 and see Fig. 16.71).

Knee joint

This very stable hinge joint is the body's largest and most complex joint. The joint capsule contains two joints: one between the condyles of the femur and the tibia (Fig. 16.57A), and one between the femur and posterior surface of the patella (Fig. 16.57B). The anterior part of the capsule is formed by the tendon of the quadriceps femoris muscle, which also supports the patella. Intracapsular structures include two cruciate ligaments covered with synovial membrane which cross each other (Fig. 16.57C), extending from the intercondylar notch of the femur to the intercondylar eminence of the tibia and hold the femur and tibia together. This helps to stabilise the joint.

Semilunar cartilages or menisci are wedge-shaped pads of white fibrocartilage lying on top of the articular condyles of the tibia. They prevent lateral displacement of the bones and cushion and stabilise the moving joint by shifting within the joint space according to the relative positions of the articulating bones. Because they are weight-bearing, they are not covered in synovial membrane.

The joint is cushioned with numerous bursae and pads of fat, which prevent friction between a bone and a ligament

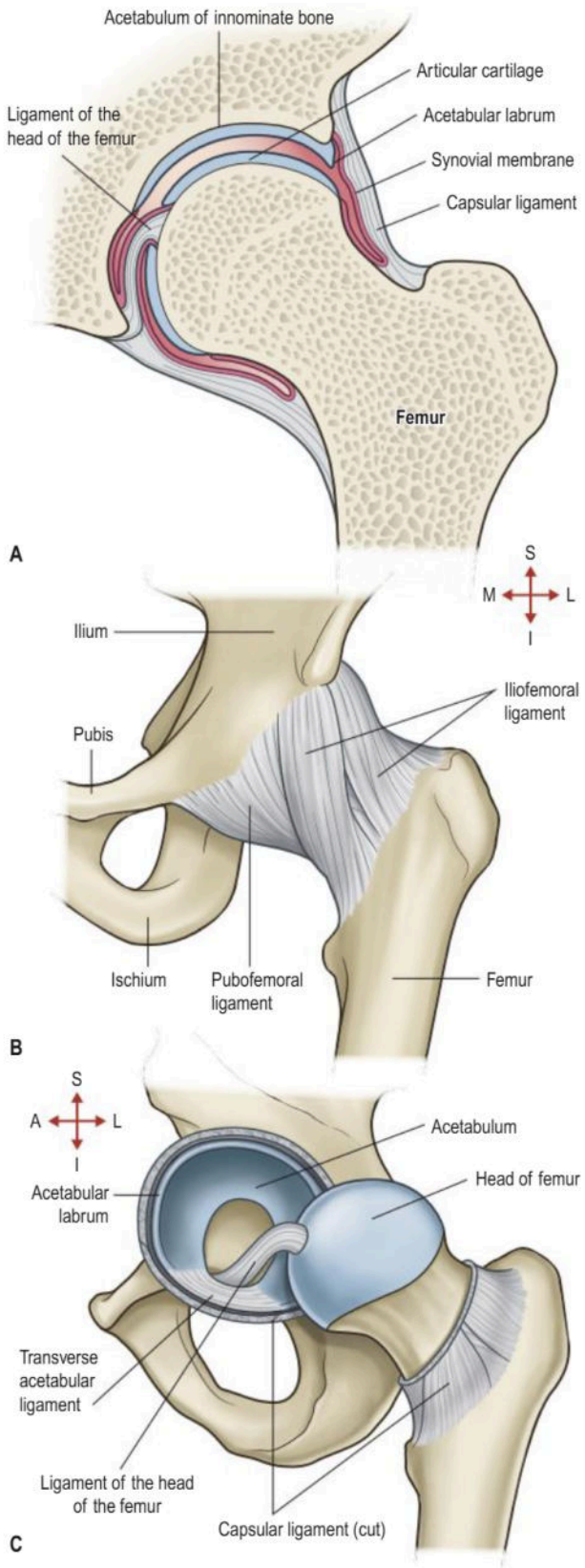


Fig. 16.56 The left hip joint: anterior view. (A) Section. (B) Supporting ligaments. (C) Head of femur and acetabulum separated to show acetabular labrum and ligament of head of femur.

Table 16.5 Muscles and movements at the hip joint

Movement	Muscles involved
Flexion	Psoas, iliacus, sartorius
Extension	Gluteus maximus, hamstrings
Abduction	Gluteus medius and minimus, sartorius
Adduction	Adductor group (longus, brevis and magnus)
Medial rotation	Gluteus medius and minimus, adductor group
Lateral rotation	Gluteus maximus, quadratus femoris, obturators

or tendon, and between the skin and the patella. External ligaments provide further support, making it a hard joint to dislocate. The main ligaments are the patellar ligament, an extension of the quadriceps tendon, the popliteal ligaments at the back of the knee and the collateral ligaments to each side.

Muscles and movements

The knee joint flexes and extends, and also permits a small amount of rotation, which locks the joint when fully extended. This makes it possible to stand upright for long periods of time without tiring the knee extensors. The main muscles extending the knee are the quadriceps femoris, and the principal flexors are the gastrocnemius and hamstrings (see Fig. 16.71).

Ankle joint

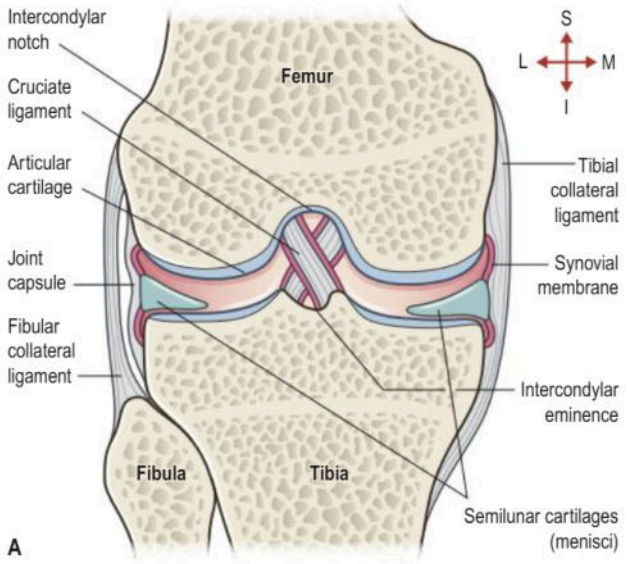
This hinge joint is formed between the distal end of the tibia and its malleolus (medial malleolus), the distal end of the fibula (lateral malleolus) and the talus (Fig. 16.58A). Several important ligaments strengthen this joint, including the deltoid and the anterior, posterior, medial and lateral ligaments (Fig. 16.58B and C).

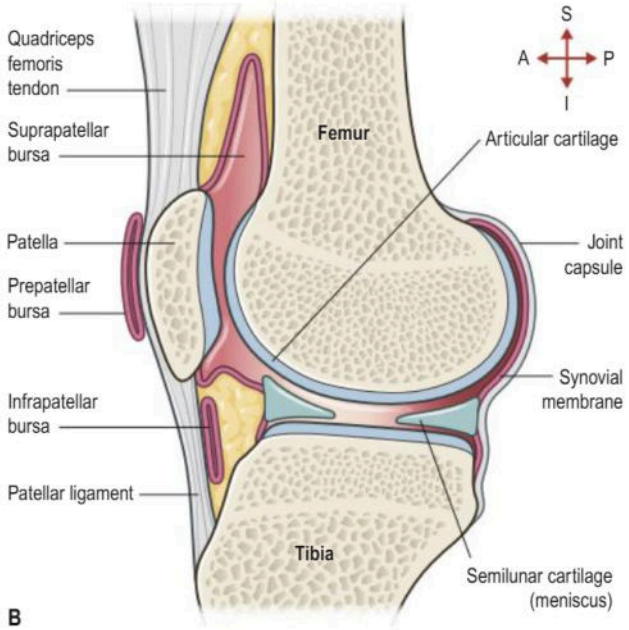
Muscles and movements

Ankle joint movements and the related muscles are shown in Table 16.6 and Fig. 16.71. The movements of inversion and eversion (Fig. 16.50) occur between the tarsal bones and not at the ankle joint.

Joints of the feet and toes

All the joints between the bones of the ankle and feet are synovial joints (see Fig. 16.45A). Movements are produced by muscles in the leg with long tendons that cross the ankle joint, and by muscles of the foot. The tendons crossing the ankle joint are wrapped in synovial sheaths and held close to the bones by strong transverse ligaments. They move smoothly within their sheaths as the joints move. In addition to moving the joints of the foot, these muscles support the arches of the foot and help to maintain balance.





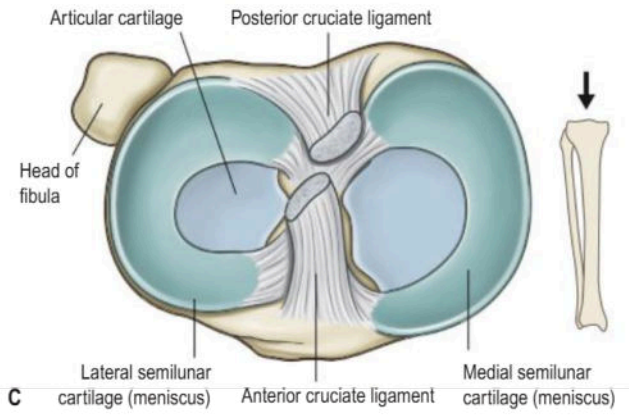
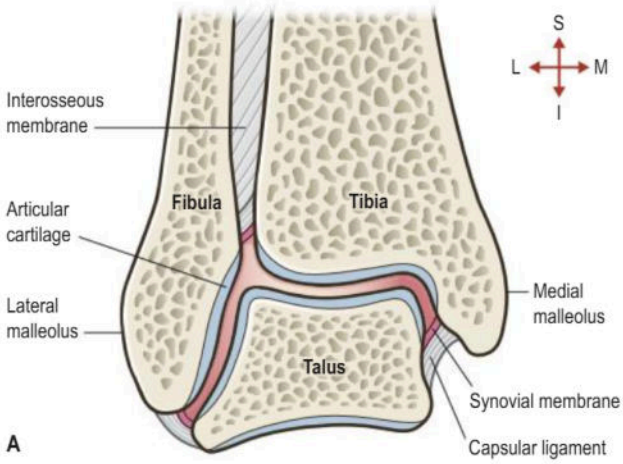
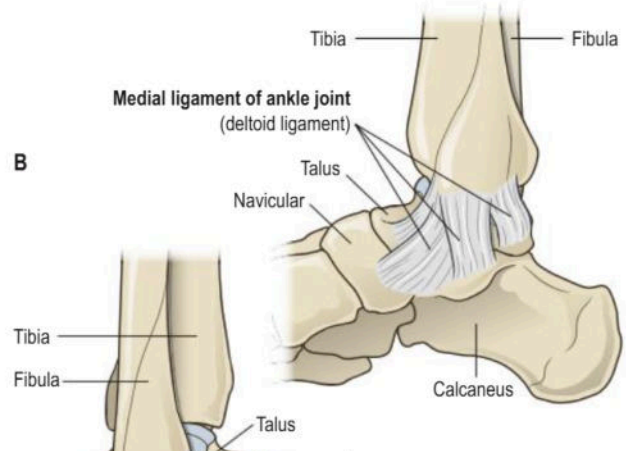


Fig. 16.57 The left knee joint. (A) Section viewed from the front. (B) Section viewed from the side. (C) The superior surface of the tibia, showing the semilunar cartilages and the cruciate ligaments.

Table 16.6 Muscles and movements at the ankle joint

Movement	Muscles involved
Dorsiflexion (lifting toes towards calf)	Anterior tibialis and toe extensors
Plantar flexion (rising on tiptoe)	Gastrocnemius, soleus and toe flexors





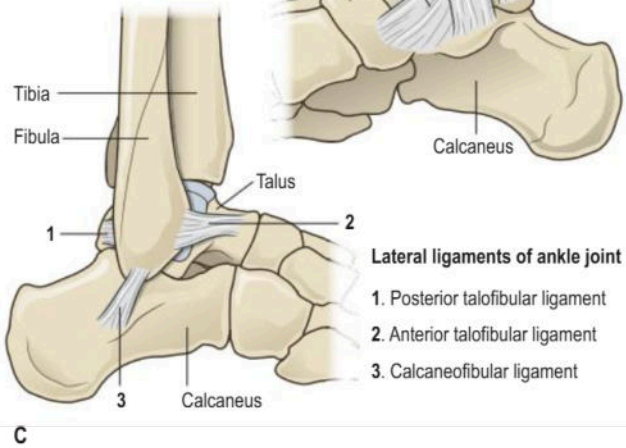


Fig. 16.58 The right ankle joint. (A) Section viewed from the front. (B) Supporting ligaments: medial view. (C) Supporting ligaments: lateral view.

SPOT CHECK

7. What is the difference between rotation and circumduction?
8. The glenoid cavity of the scapula is very shallow. How is the head of the humerus held firmly in such a shallow cup?

Skeletal muscle

Learning outcomes

After studying this section, you should be able to:

- identify the main characteristics of skeletal muscle
- relate the structure of skeletal muscle fibres to their contractile activity
- describe the nature of muscle tone and fatigue
- discuss the factors that affect the performance of skeletal muscle
- name the main muscles of the body regions described in this section
- outline the functions of the main muscles described in this section.

Muscle cells (also called muscle fibres) are specialised contractile cells. The three types of muscle tissue, smooth, cardiac and skeletal, differ in structure, location and physiological function. Smooth muscle and cardiac muscle are not under voluntary control and are discussed elsewhere (pp. 55 and 56). Skeletal muscles, which are under voluntary control, are attached to bones via their tendons (Fig. 16.59A) and move the skeleton. Like cardiac but not smooth muscle, skeletal muscle is striated (striped), and the stripes are seen in a characteristic banded pattern when the cells are viewed under the microscope (Fig. 16.59B and Fig. 16.60).

Organisation of skeletal muscle

A skeletal muscle can contain hundreds of thousands of muscle fibres as well as blood vessels and nerves. Throughout the muscle, providing internal structure and scaffolding, is an extensive network of connective tissue. The entire muscle is covered in a connective tissue sheath called the epimysium. Within the muscle the fibres are collected into separate bundles called fascicles, and each fascicle is covered in its own connective tissue sheath called the perimysium. Within the fascicles individual muscle fibres are wrapped in a fine connective tissue layer called the endomysium. Each of these connective tissue layers runs the length of the muscle. They bind the fibres into a highly organised structure and blend together at each end of the muscle to form the tendon, which secures the muscle to bone. Often the tendon

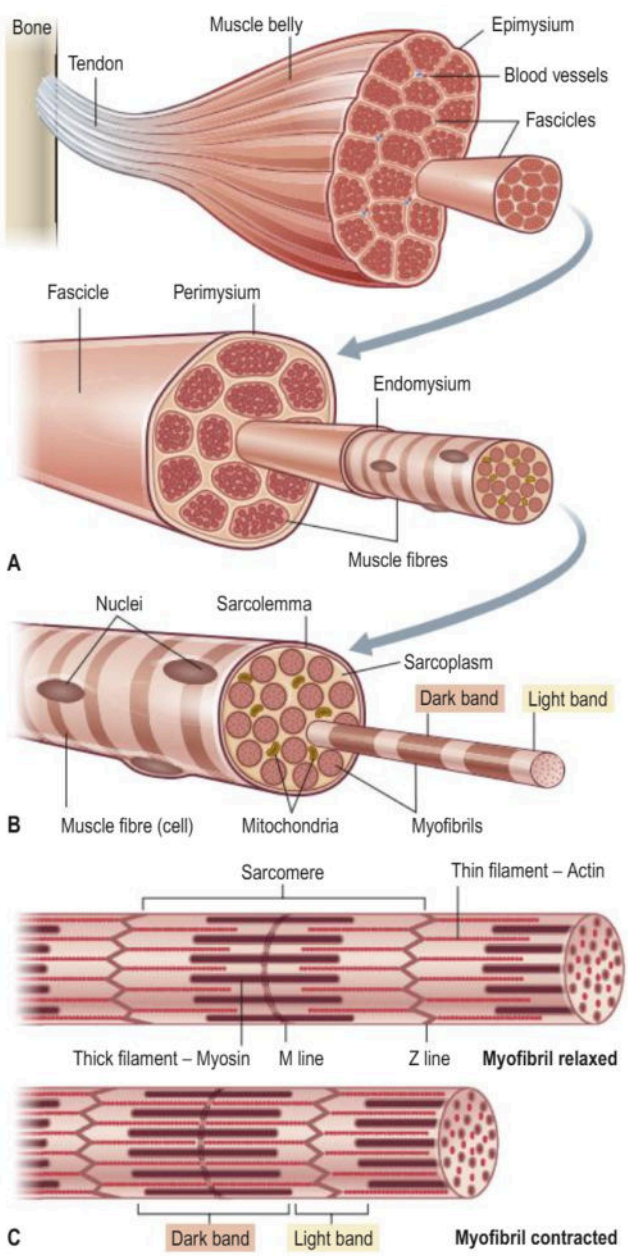


Fig. 16.59 Organisation within a skeletal muscle. (A) A skeletal muscle and its connective tissue. (B) A muscle fibre (cell). (C) A myofibril, relaxed and contracted.

is rope-like but sometimes it forms a broad sheet called an aponeurosis, e.g. the occipitofrontalis muscle (see Fig. 16.64). The multiple connective tissue layers throughout the muscle are important for transmitting the force of contraction from each individual muscle fibre to its points of attachment to the skeleton.

The fleshy part of the muscle is called the belly.

Skeletal muscle cells (fibres)

Contraction of a whole skeletal muscle occurs because there is coordinated contraction of its individual fibres.

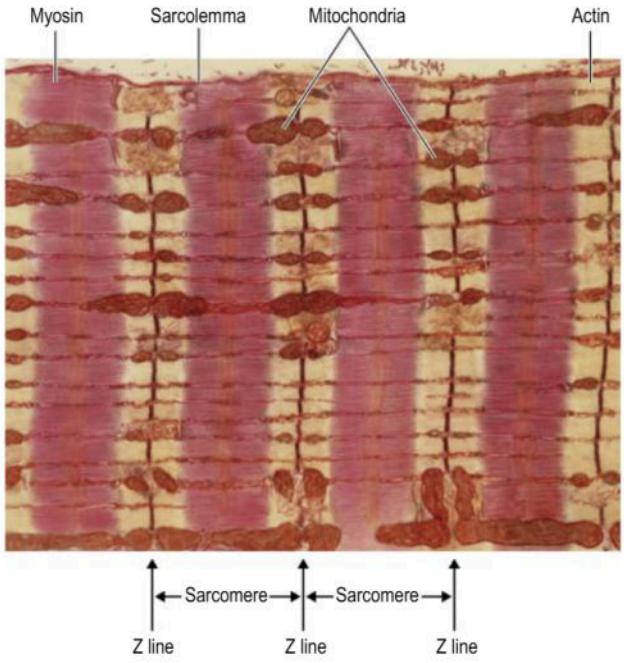


Fig. 16.60 Coloured transmission electron micrograph of part of a skeletal muscle fibre, showing the characteristic banding pattern and multiple mitochondria. (Steve G Schmeissner/Science Photo Library. Reproduced with permission.)

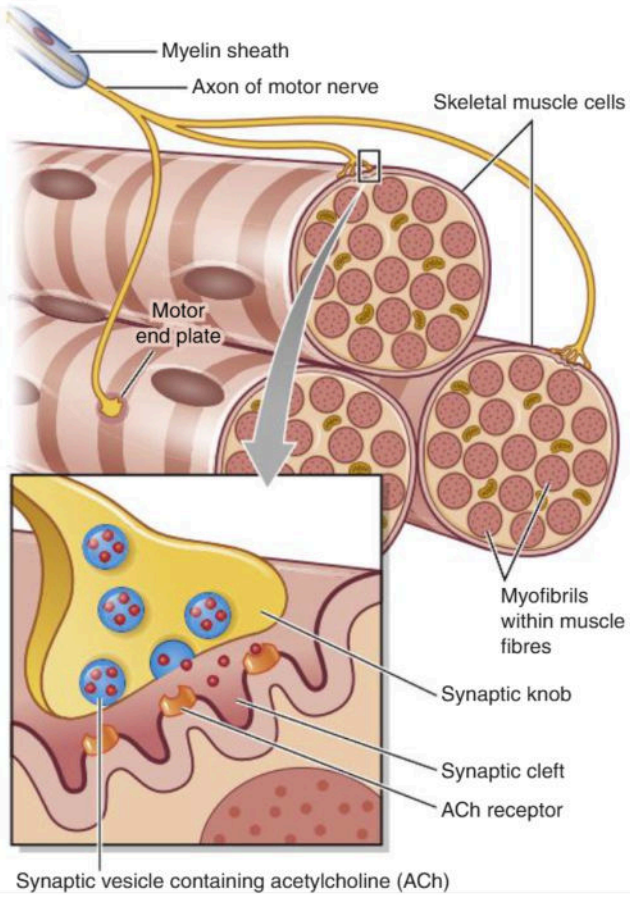


Fig. 16.61 The neuromuscular junction.

Structure

Under the microscope, skeletal muscle fibres are roughly cylindrical in shape, lying parallel to one another, with a distinctive banded appearance of alternate dark and light stripes (Figs 16.59B and 16.60). Muscle fibres run the length of the muscle, from one end to the other, and so individual fibres may be very long, up to 35 cm in the longest muscles. Because they are so large, each fibre has multiple nuclei, located just under the cell membrane (the sarcolemma). The cytoplasm of muscle cells, also called sarcoplasm, is packed with tiny thread-like filaments called myofibrils running longitudinally along the length of the fibre. They also have many mitochondria (Fig. 16.60), essential for producing adenosine triphosphate (ATP) from glucose and oxygen to power the contractile mechanism. Also present is a specialised oxygen-binding substance called myoglobin, which is similar to the haemoglobin of red blood cells and stores oxygen within the muscle. In addition, there are extensive intracellular stores of calcium, which is released into the sarcoplasm when the muscle is stimulated by its motor nerve and is essential for the contractile activity of the myofilaments.

Actin, myosin and sarcomeres

The myofibrils inside the muscle fibre contain two types of contractile proteins, called actin (thin) filaments and myosin (thick) filaments, arranged in repeating units called sarcomeres (Figs 16.59C and 16.60), giving the muscle cell its striped appearance. Because the myosin filaments are thick, they show up as dark bands under the microscope. The light bands contain only thin actin filaments.

Sarcomeres are divided from each other by a dense stripe, the Z line, to which the actin fibres are attached, pointing into the middle of the sarcomere. Running up the middle of the sarcomere is the M line, with the myosin filaments projecting out from each side of it. The ends of the myosin filaments overlap with the ends of the actin filaments. This overlap allows them to attach and slide over each other during muscle contraction.

The neuromuscular junction

The skeletal muscle cell contracts in response to stimulation from a motor nerve fibre, which usually synapses with the muscle cell about halfway along its length. The synapse between a motor nerve ending and its skeletal muscle cell is called the neuromuscular junction and the transmitter here is acetylcholine (ACh) (Figs 16.61 and 16.62). Drugs that block ACh receptors at the neuromuscular junction are called neuromuscular blockers and are used as adjuncts in anaesthesia and surgery, to paralyse the skeletal muscles and facilitate

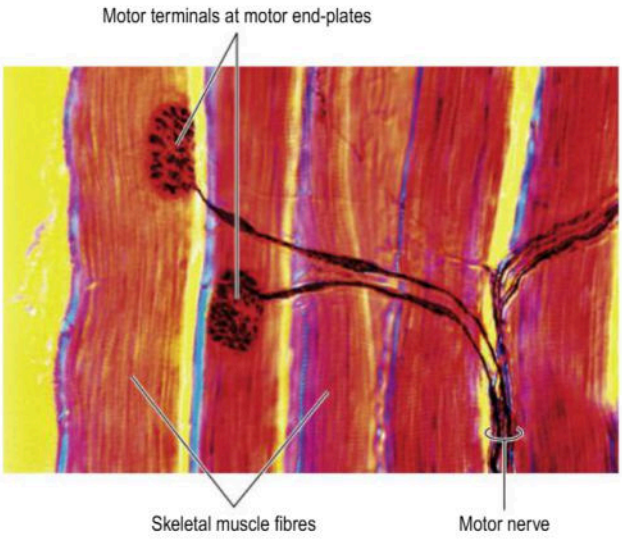


Fig. 16.62 Colour transmission electron micrograph of a motor neurone and two of its motor end-plates. (Kent Wood/Science Photo Library. Reproduced with permission.)

access to deeper structures. However, as the diaphragm is also composed of skeletal muscle, patients treated with neuromuscular blocking drugs must be artificially ventilated.

When it is very close to the muscle cell, the motor nerve fibre splits into a sheaf of very fine synaptic knobs, which come into very close proximity to, but do not actually make direct contact with, the sarcolemma (for a general description of synaptic physiology see p. 163). This area is called the motor end-plate (Fig. 16.62). Each individual synaptic knob forms a synapse between the motor nerve and the muscle fibre.

Skeletal muscle contraction

ACh release at the neuromuscular junction generates an action potential that spreads rapidly along the muscle cell membrane. However, in order to activate the contractile machinery inside the muscle fibre, the action potential is also conducted throughout its interior through a specialised network of channels running through the sarcoplasm. This releases calcium from the intracellular stores, which triggers the binding of actin and myosin to each other, forming so-called cross-bridges between them. ATP is split to provide the energy for actin and myosin filaments to slide over each other, pulling the Z lines at each end of the sarcomere closer to one another and shortening it (Fig. 16.59C). This is called the sliding filament theory. If enough fibres in the muscle are simultaneously stimulated, the whole muscle undergoes a degree of contraction. The more individual fibres that are stimulated, the greater the degree of contraction.

The muscle relaxes when motor nerve stimulation stops. Calcium is pumped back into its intracellular stores, breaking the cross-bridges between the actin and myosin filaments. They slide back into their resting positions, lengthening the sarcomere and returning the muscle to its original length.

Motor units

Each muscle cell is stimulated at only one motor end-plate, but each motor nerve can divide into multiple branches and so can stimulate several muscle fibres. Figure 16.62 shows an electron micrograph of a motor nerve and two of its motor end-plates.

One nerve fibre and all the muscle cells it supplies constitute a motor unit. The force of muscle contraction depends on how many motor units are in action at a particular time. The more motor units that are simultaneously stimulated, the greater the force of contraction.

Some motor units contain large numbers of muscle cells, i.e. one nerve stimulates many muscle cells. This arrangement is associated with large-scale, powerful movements, such as in the legs or upper arms. Fine, delicate control of muscle movement is achieved when one motor unit contains very few muscle fibres, as in the muscles controlling eye movement.

Action of skeletal muscle

When individual muscle cells in a muscle shorten, they pull on the connective tissue framework running through the whole muscle and the muscle develops a degree of tension (tone).

Muscle tone

When a muscle fibre contracts, it obeys the all-or-none law, i.e. it either contracts completely or does not contract at all. The degree of contraction achieved by a whole muscle therefore depends on the number of its fibres that are contracting at any one time, as well as how frequently they are stimulated. This means that in order to increase the strength of a muscle contraction, more motor units must be activated; to lift a heavy weight, more active muscle fibres are required than to lift a lighter one. Muscle tone is a sustained, partial muscle contraction that allows maintenance of posture without tiring the muscles involved. For instance, keeping the head upright requires constant activity of the muscles of the neck and shoulders. Motor units within these muscles take it in turns to contract, so that at any one time some muscle cells are contracted and others are resting. This allows the effort required to hold the head upright to be distributed throughout the muscles involved. Good muscle tone, promoted by regular exercise, protects joints and gives a muscle firmness and shape, even when relaxed.

Muscle fatigue

To work at sustained levels, muscles need an adequate supply of oxygen and fuel such as glucose. The muscle fatigues when it works at a level that exceeds these supplies, and its performance declines.

The chemical energy (ATP) that muscles need is usually generated from the breakdown of carbohydrate and fat; protein may be used if supplies of fat and carbohydrate are exhausted. An adequate oxygen supply is needed to fully release all the energy stored within these fuel molecules; without it, the body uses less efficient anaerobic metabolic pathways that produce lactate (the physiological form of lactic acid). Lactate accumulation in strenuously working muscles

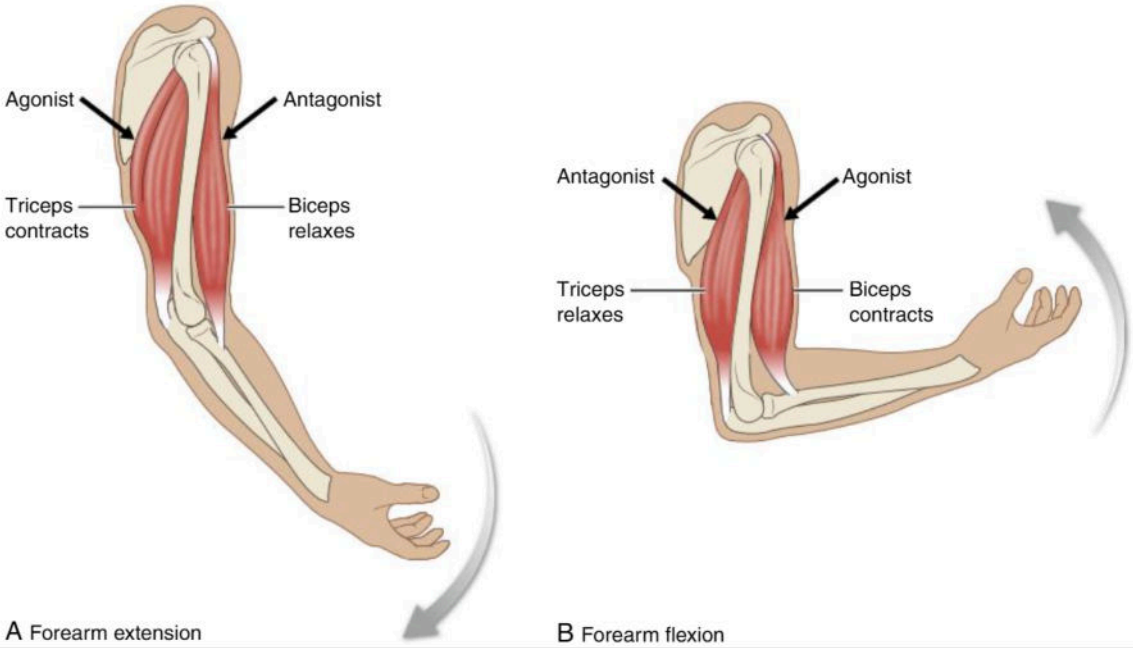


Fig. 16.63 The action of antagonistic muscle pairs: the biceps and triceps. (A) Forearm extension. (B) Forearm flexion.

causes muscle pain and fatigue. Fatigue may also be due to physical muscle injury, which may follow prolonged episodes of strenuous activity, e.g. marathon running.

Muscle recovery

After exercise, muscle needs a period of time to recover, to replenish its ATP and glycogen stores and to repair any damage. For some time following exercise, depending on the degree of exertion, the oxygen debt, an extended period of increased oxygen demand, remains as the body converts lactate to pyruvate and replaces its energy stores.

Factors affecting skeletal muscle performance

Skeletal muscle performs better when it is regularly exercised. Training improves endurance and power. Anaerobic training, such as weightlifting, increases muscle bulk because it increases the size of individual muscle fibres (hypertrophy, see Fig. 3.29).

The action of skeletal muscles

In order to move a body part, the muscle or its tendon must stretch across at least one joint. When it contracts, the muscle then pulls one bone towards another. The origin of a muscle is usually its proximal attachment and is generally on the bone that remains still when the muscle contracts, providing an anchor for it to pull against. The insertion of a muscle is usually its distal attachment site and is generally on the bone that moves when the muscle contracts. For example, the deltoid muscle of the shoulder (see Fig. 16.65) originates on the clavicle and scapula of the shoulder girdle and inserts on the humerus. When it contracts, the upper arm moves relative to the shoulder girdle, which remains stable.

Skeletal muscles and groups of skeletal muscles performing the same action generally work in antagonistic pairs. This ensures that for a given movement, there is an opposing muscle group that can perform the opposing action. The muscle or muscles performing a movement are called the agonist(s) or prime mover(s), and the opposing muscle(s) are called the antagonist(s). Antagonist muscles must be relaxed during muscle movement, to permit the movement to take place and to prevent injuring it during forced stretching.

For example, when the elbow is bent during flexion of the forearm, the agonist is biceps brachii, which is anchored on the scapula at one end and on the radius at the other (Fig. 16.63A). When it contracts, it pulls on the radius, moving the forearm up towards the upper arm and bending the elbow. The muscle opposing this movement is the triceps, which must be actively relaxed to allow flexion to take place. For the opposing movement, extension of the forearm (Fig. 16.63B), the triceps becomes the agonist and the biceps the antagonist.

Isometric and isotonic contraction

Contraction of a muscle usually shortens it, as happens for instance to the biceps muscle if the forearm is used to pick up a cup. The power generated by the muscle is used to lift the manageable weight, and tension in the muscle remains constant. In this situation the contraction is said to be isotonic (iso = same, tonic = tension). However, imagine trying to lift an 80-kg man with one hand. Most people would be unable to perform this task, but the muscles of the arm and shoulder would still work hard as they attempted it. In this situation, because the resistance from the man's weight is too great for him to be moved by the efforts of the

Table 16.7 Muscle terminology

Characteristic	Example	Comment
Shape	Trapezius	Trapezium-shaped
Fibre direction	Oblique muscles of abdomen	Fibres run obliquely (at an angle)
Muscle position	Tibialis	Found close to the tibia in the leg
Movement produced	Extensor carpi ulnaris	Attached to the carpal bones of the wrist and the ulna, and extends the wrist
Number of points of attachment	Biceps brachii	Bi- means two; this muscle has two points of attachment at the shoulder
Bones to which muscle is attached	Carpi radialis muscles	Attached to the carpal bones of the wrist and the radius of the forearm

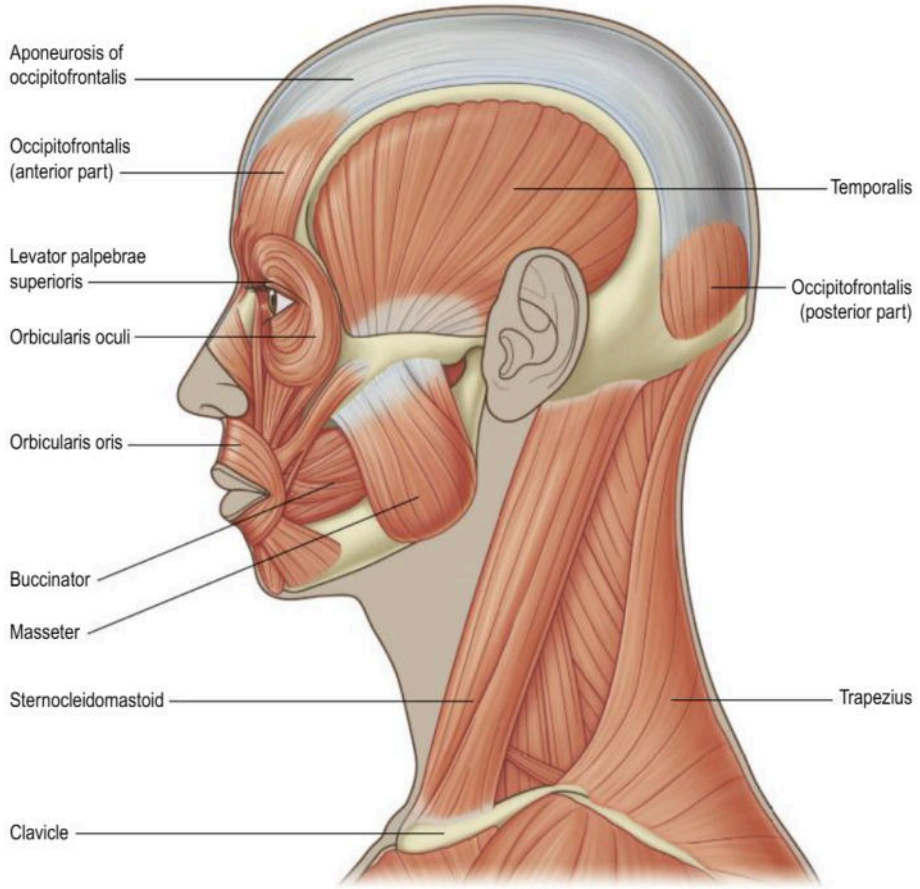


Fig. 16.64 The main muscles on the left side of the face, head and neck.

lifter, the muscles would be unable to shorten, but the work they are doing increases the muscle tension instead. This is isometric contraction (iso = same, metric = length).

Principal skeletal muscles

Muscles are named according to various characteristics (Table 16.7) and becoming familiar with the main ones makes it much easier to identify unfamiliar muscles. This section considers the main muscles that move the limbs, as well as the major muscles of the face and neck, back, chest, pelvic floor and abdominal wall.

Muscles of the face and neck

These are shown in Figure 16.64.

Muscles of the face

Facial muscles change facial expression and move the lower jaw during chewing and speaking. Only the main muscles

are described here. Except where indicated, the muscles are present in pairs, one on each side.

Occipitofrontalis (unpaired)
This has a posterior muscular part over the occipital bone (occipitalis), an anterior part over the frontal bone (frontalis) and an extensive flat tendon or aponeurosis that stretches over the dome of the skull and joins the two muscular parts. It raises the eyebrows.

Levator palpebrae superioris
This muscle extends from the posterior part of the orbital cavity to the upper eyelid. It raises the eyelid.

Orbicularis oculi
This muscle surrounds the eye, eyelid and orbital cavity. It closes the eye and, when strongly contracted, screws up the eyes.

Buccinator
This flat muscle draws the cheeks in towards the teeth in chewing and in forcible expulsion of air from the mouth (the 'trumpeter's muscle').

Orbicularis oris (unpaired)
This muscle surrounds the mouth and blends with the muscles of the cheeks. It closes the lips and, when strongly contracted, shapes the mouth for whistling.

Masseter
This broad muscle originates from the zygomatic arch and inserts on the angle of the jaw. In chewing, it draws the mandible up to the maxilla, closing the jaw and exerting considerable pressure on the food.

Temporalis
This muscle covers the squamous part of the temporal bone. It passes behind the zygomatic arch and inserts into the coronoid process of the mandible. It closes the mouth and helps with chewing.

Pterygoid
This muscle extends from the sphenoid bone to the mandible. It closes the mouth and pulls the lower jaw forwards.

Muscles of the neck
There are many muscles in the neck but only the two largest are considered here.

Sternocleidomastoid
This muscle originates from the manubrium of the sternum and the clavicle and extends upwards to insert on the mastoid process of the temporal bone. It turns the head from side to side, and when the muscle on one side contracts, it draws the head towards that shoulder. It is an accessory muscle of respiration, and in forced inspiration, pulls the sternum and clavicles upwards to help expand the ribcage.

Trapezius
This large muscle covers the shoulder and the back of the neck. It has multiple origins on the occipital bone and the transverse processes of the cervical and thoracic vertebrae, and it inserts on the clavicle and the spinous processes and acromion of the scapula. It pulls the head backwards, squares the shoulders and controls the movements of the scapula when the shoulder joint is in use.

Muscles of the trunk
These muscles of the back, abdominal wall and thorax stabilise the association between the appendicular and axial skeletons at the pectoral girdle. They also stabilise and allow movement of the shoulders and upper arms.

Muscles of the back
There are six pairs of large muscles in the back, in addition to those forming the posterior abdominal wall. The arrangement of these muscles is symmetrical on each side of the vertebral column. They include the trapezius (see above) and the psoas (see later) and the remaining four are described below.

Latissimus dorsi
This muscle (Figs 16.65 and 16.67) originates on the posterior part of the iliac crest and the spinous processes of the lumbar and lower thoracic vertebrae. It passes upwards across the back, under the arm and inserts into the bicipital groove of the humerus. It adducts, medially rotates and extends the arm.

Teres major
This muscle (Fig. 16.65) originates from the inferior angle of the scapula and inserts into the humerus just below the shoulder joint. It extends, adducts and medially rotates the arm.

Quadratus lumborum
This muscle originates from the iliac crest and passes upwards, parallel and close to the vertebral column, and inserts into the 12th rib (Figs 16.66 and 16.67). Together the two muscles fix the lower rib during respiration and extend the spine (bending backwards). If one muscle contracts, it causes lateral flexion of the lumbar region of the spine.

Sacrospinalis (erector spinae)
These muscles lie between the spinous and transverse processes of the vertebrae (Figs 16.65 and 16.67). They originate from the sacrum and insert into the occipital bone. They extend the vertebral column.

Muscles of the anterior abdominal wall
Five pairs of muscles form the strong muscular anterior abdominal wall (Figs 16.67 and 16.68). They include the quadratus lumborum (see above) and the remaining four are described below. When the muscles contract together they

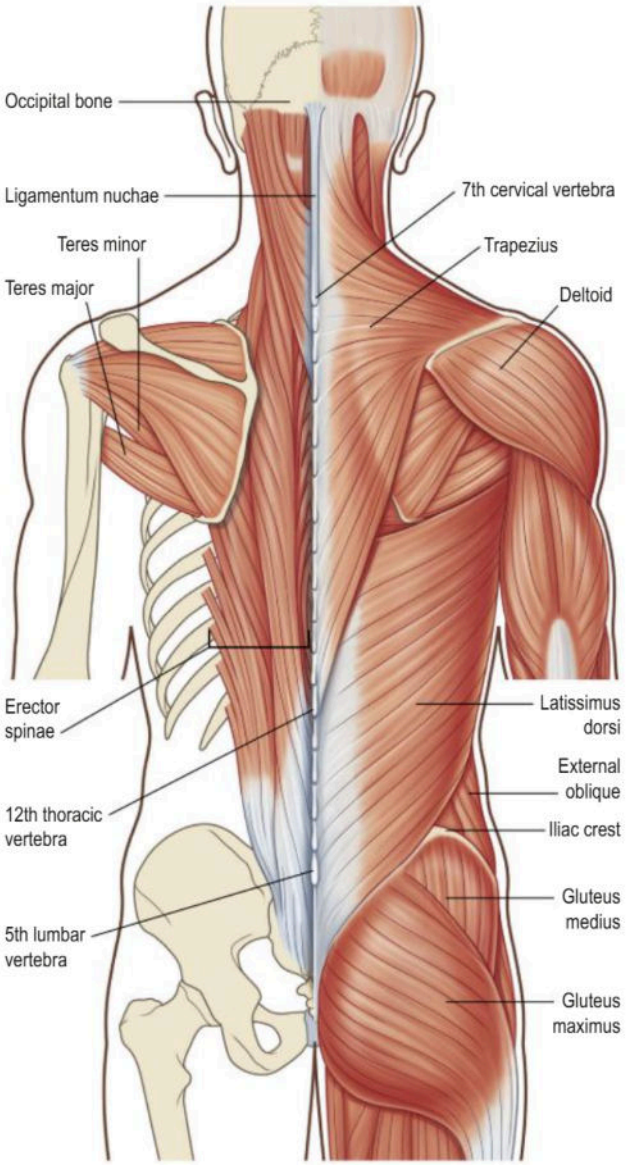


Fig. 16.65 The main muscles of the back. Right side.

compress the abdominal organs and flex the lumbar spine. Contraction of the muscles on one side bends the trunk towards that side. Contraction of the oblique muscles on one side rotates the trunk.

The anterior abdominal wall is divided longitudinally by a strong midline tendinous cord, the linea alba (meaning 'white cord'), which extends from the xiphoid process of the sternum to the pubic symphysis.

Rectus abdominis

This is the most superficial muscle. It is broad and flat, originating from the transverse part of the pubic bone and passing upwards to insert into the lower ribs and the xiphoid process of the sternum. There are two, separated down the midline by the linea alba. The rectus abdominis is the so-called 'six-pack' muscle. It curls the trunk and supports the abdominal wall when straining, e.g. in forced expiration or defaecation.

External oblique

This muscle lies deep to the rectus abdominis. It extends from the lower ribs downwards and forwards to insert into the iliac crest and, by an aponeurosis, to the linea alba.

Internal oblique

This muscle lies deep to the external oblique. It originates from the iliac crest and a broad band of fascia from the spinous processes of the lumbar vertebrae. Its fibres pass upwards towards the midline to insert into the lower ribs and, by an aponeurosis, into the linea alba. The fibres are at right angles to those of the external oblique.

Transversus abdominis

This is the deepest muscle of the abdominal wall. It originates from the iliac crest and the lumbar vertebrae and passes across the abdominal wall to insert into the linea alba by an aponeurosis. Its fibres are at right angles to those of rectus abdominis.

Inguinal canal

This canal is 2.5–4cm long and passes obliquely through the abdominal wall. It runs parallel to and immediately in front of the transversalis fascia and part of the inguinal ligament (Fig. 16.66). In the male it contains the spermatic cord, and in the female the round ligament. It constitutes a weak point in the otherwise strong abdominal wall through which herniation may occur.

Muscles of the thorax

These muscles are concerned with respiration and are discussed in Chapter 10.

Muscles of the pelvic floor

The pelvic floor (Fig. 16.69), formed from muscle and fascia, is divided into two identical halves that unite along the midline. It forms a hammock-type support for the pelvic organs and maintains continence. The weight of the developing baby and associated structures during pregnancy can stretch and weaken the pelvic floor muscles, and childbirth can tear them. This may cause stress incontinence after delivery (p. 397). The two muscles forming the pelvic floor are the levator ani and coccygeus.

Levator ani

This group of broad, flat muscles forms the anterior part of the pelvic floor. They originate from the inner surface of the true pelvis and unite in the midline.

Coccygeus

This is a paired triangular sheet of muscle and tendinous fibres situated behind levator ani. They originate from the medial surface of the ischium and insert into the sacrum and coccyx. They complete the formation of the pelvic floor,

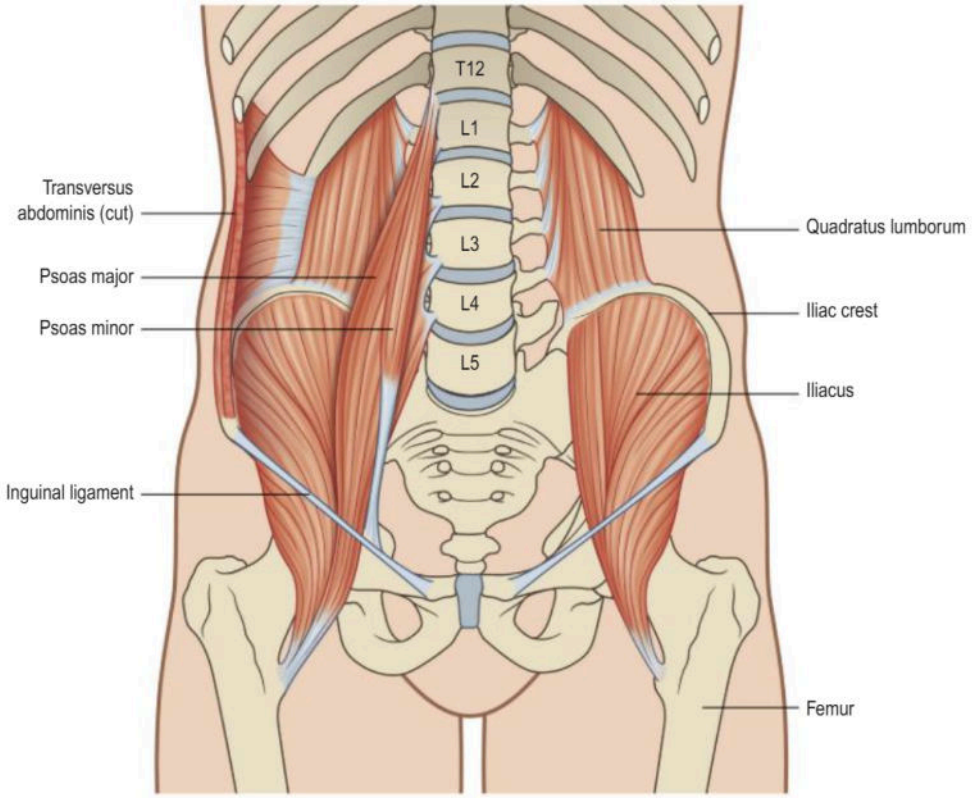


Fig. 16.66 The deep muscles of the posterior abdominal wall. Anterior view.

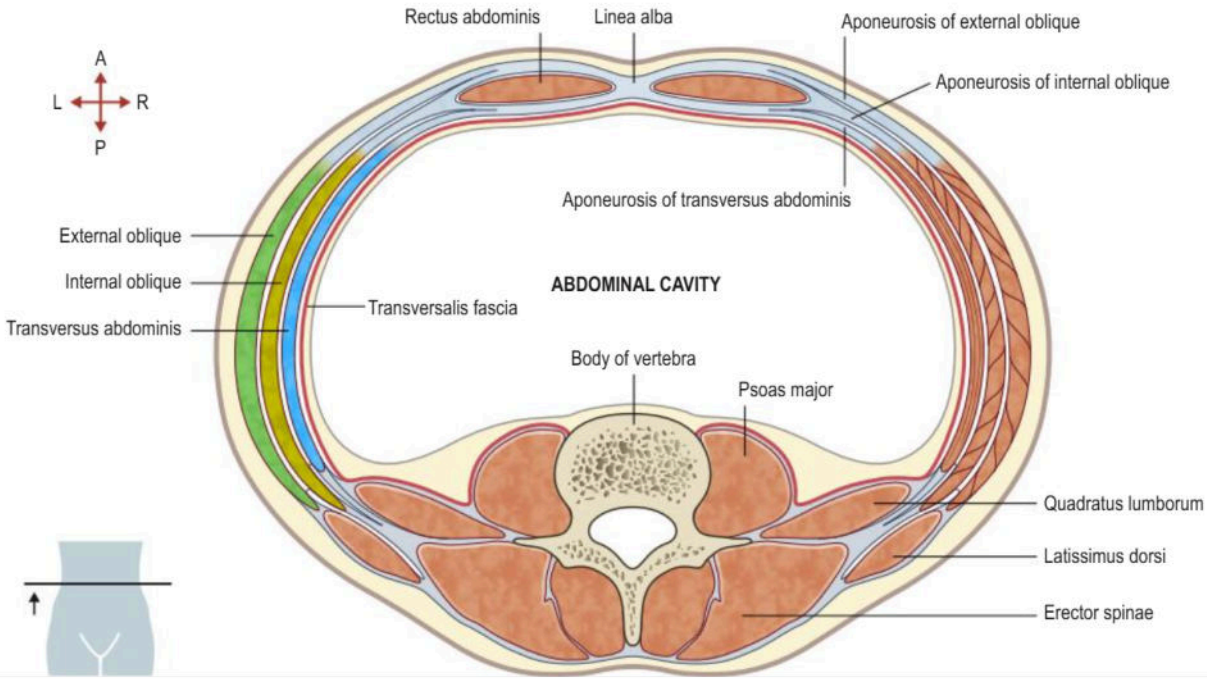


Fig. 16.67 Transverse section through the abdomen showing the muscles and fascia of the body wall. Viewed from below.

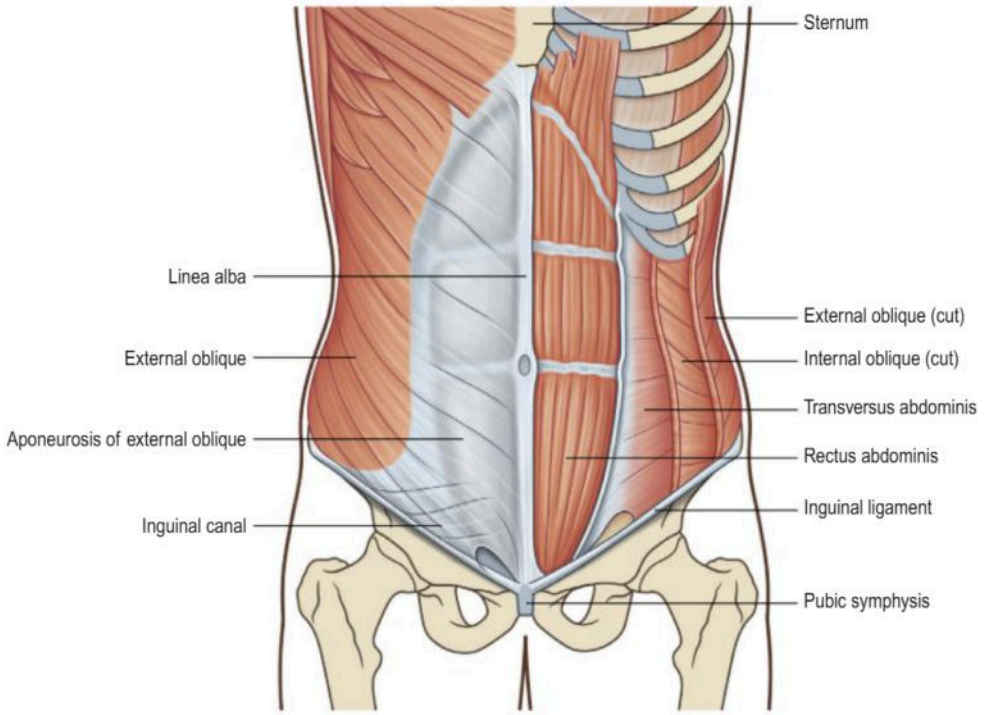


Fig. 16.68 The muscles of the anterior abdominal wall.

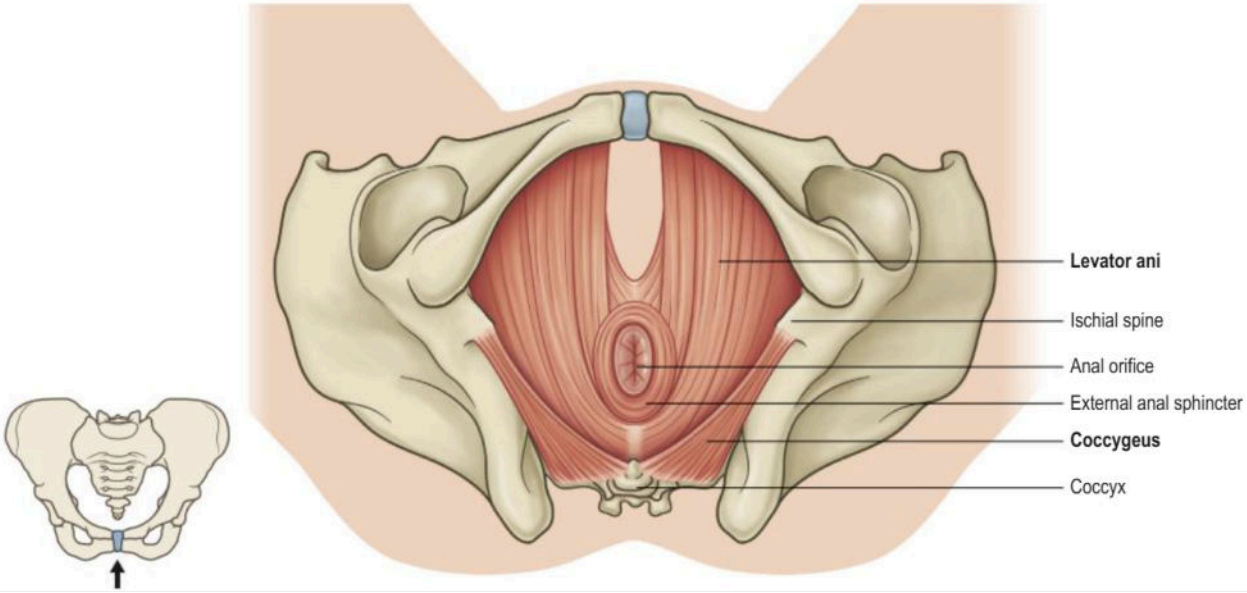


Fig. 16.69 The muscles of the female pelvic floor.

which is perforated in the male by the urethra and anus, and in the female by the urethra, vagina and anus.

Muscles of the shoulder and upper limb

These muscles (Fig. 16.70) stabilise the association between the appendicular and axial skeletons at the pectoral girdle, and they stabilise and allow movement of the shoulders and upper arms.

Deltoid

This muscle originates from the clavicle, acromion process and spine of scapula and passes over the shoulder joint to insert into the deltoid tuberosity of the humerus. It forms

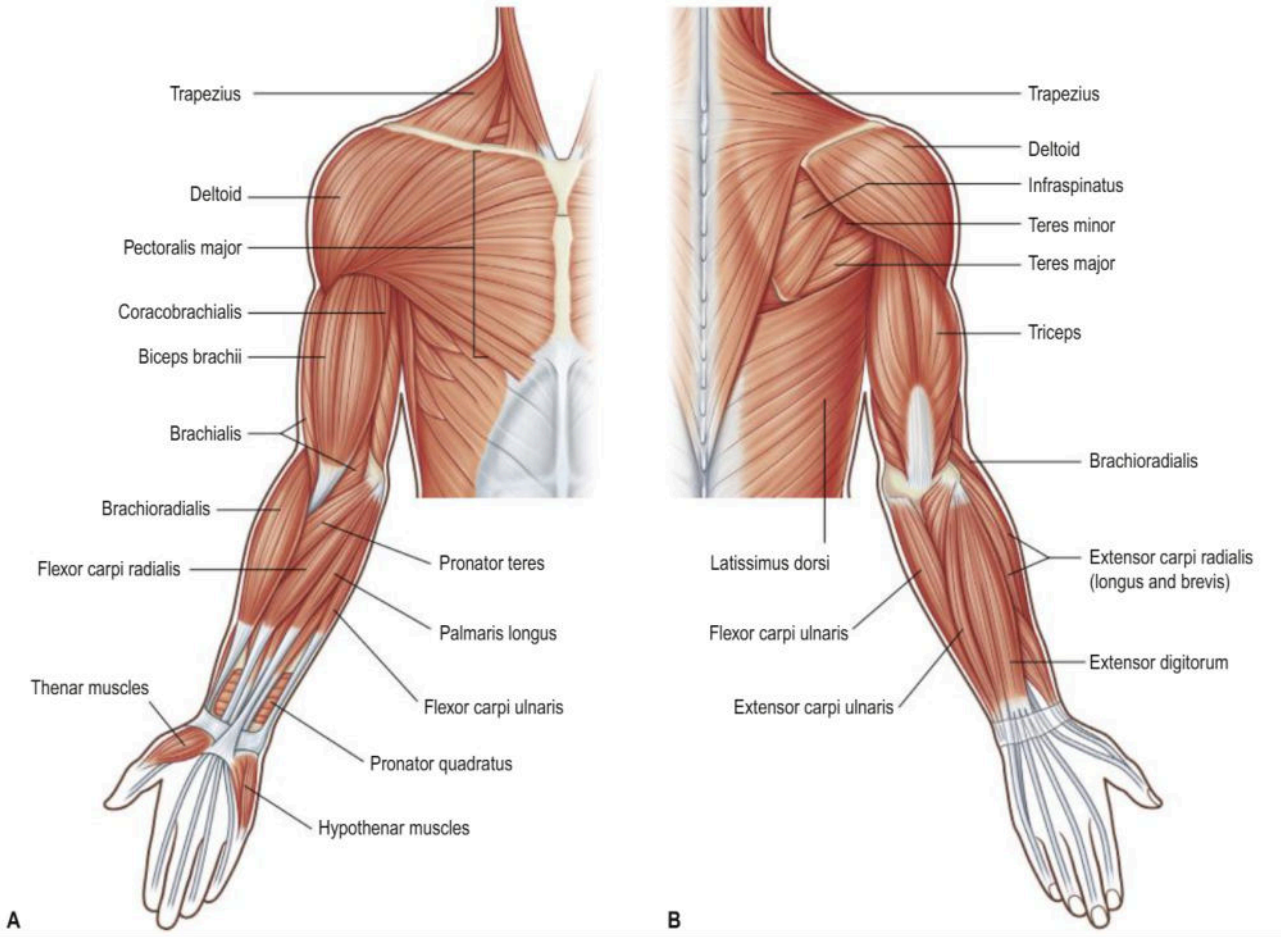


Fig. 16.70 The main muscles of the right shoulder and upper limb. (A) Anterior view. (B) Posterior view.

the fleshy and rounded contour of the shoulder and its main function is movement of the arm. The anterior part causes flexion, the middle or main part causes abduction, and the posterior part extends and laterally rotates the shoulder joint.

Pectoralis major

This muscle lies on the anterior thoracic wall. It originates from the middle third of the clavicle and from the sternum and inserts into the upper part of the humerus. It flexes and adducts the arm.

Coracobrachialis

This muscle lies on the upper medial aspect of the arm. It originates from the coracoid process of the scapula, stretches across in front of the shoulder joint and inserts into the middle third of the humerus. It flexes the shoulder joint.

Biceps brachii

This muscle lies on the anterior aspect of the upper arm. Its proximal end is divided into two parts (heads), each of which has its own tendon. The short head originates from the coracoid process of the scapula and passes in front of the shoulder joint to the arm. The long head originates from the rim of the glenoid cavity and its tendon passes through the joint cavity and the bicipital groove of the humerus (see Fig. 16.37) to the arm. The distal tendon crosses the elbow joint and inserts into the radial tuberosity. It helps to stabilise and flex the shoulder joint, and at the elbow joint it assists with flexion and supination.

Brachialis

This muscle lies on the anterior aspect of the upper arm deep to the biceps. It originates from the shaft of the humerus, extends across the elbow joint and inserts into the ulna just distal to the joint capsule. It is the main flexor of the elbow joint.

Triceps

This muscle lies on the posterior aspect of the humerus. It arises from three heads, one from the scapula and two from the posterior surface of the humerus. It inserts by a single tendon on the olecranon of the ulna. It helps to stabilise the shoulder joint, assists in adduction of the arm and extends the elbow joint.

Brachioradialis
The brachioradialis spans the elbow joint, originating on the distal end of the humerus, and inserts on the lateral epicondyle of the radius. Contraction flexes the elbow joint.

Pronator quadratus
This square-shaped muscle is the main muscle causing pronation of the hand and inserts on the lower sections of both the radius and the ulna.

Pronator teres
This muscle lies obliquely across the upper third of the front of the forearm. It arises from the medial epicondyle of the humerus and the coronoid process of the ulna and passes obliquely across the forearm to insert into the lateral surface of the shaft of the radius. It rotates the radioulnar joints, changing the hand from the anatomical to the writing position, i.e. pronation.

Supinator
This muscle lies obliquely across the posterior and lateral aspects of the forearm. It originates from the lateral epicondyle of the humerus and the upper part of the ulna and inserts into the lateral surface of the upper third of the radius. It rotates the radioulnar joints, often with help from the biceps, changing the hand from the writing to the anatomical position, i.e. supination. It lies deep to the muscles shown in Figure 16.70.

Flexor carpi radialis
This muscle lies on the anterior surface of the forearm. It originates from the medial epicondyle of the humerus and inserts into the second and third metacarpal bones. It flexes the wrist joint and, when acting with the extensor carpi radialis, abducts the joint.

Flexor carpi ulnaris
This muscle lies on the medial aspect of the forearm. It originates from the medial epicondyle of the humerus and the upper parts of the ulna, and inserts into the pisiform, the hamate and the fifth metacarpal bones. It flexes the wrist and, when acting with the extensor carpi ulnaris, adducts the joint.

Extensor carpi radialis longus and brevis
These muscles lie on the posterior aspect of the forearm. The fibres originate from the lateral epicondyle of the humerus and are inserted by a long tendon into the second and third metacarpal bones. They extend and abduct the wrist.

Extensor carpi ulnaris
This muscle lies on the posterior surface of the forearm. It originates from the lateral epicondyle of the humerus and inserts into the fifth metacarpal bone. It extends and adducts the wrist.

Palmaris longus
This muscle resists shearing forces that might pull the skin and fascia of the palm away from the underlying structures and flexes the wrist. It originates on the medial epicondyle of the humerus, and it inserts on tendons on the palm of the hand.

Extensor digitorum
This muscle originates on the lateral epicondyle of the humerus and spans both the elbow and wrist joints; in the wrist it divides into four tendons, one for each finger. Contraction of this muscle can extend any of the joints across which it passes, i.e. the elbow, wrist or finger joints.

Muscles that control finger movements
Large muscles in the forearm that extend to the hand give power to the hand and fingers, but not the delicate movements needed for fine and dexterous finger control. Smaller muscles, which originate on the carpal and metacarpal bones, control tiny and precise finger movements via tendinous attachments on the phalanges; muscle fibres do not extend into the fingers.

Muscles of the hip and lower limb

Most of these are shown in Figure 16.71. The biggest muscles of the body are found here, since their function is largely in weight bearing. The lower parts of the body are designed to transmit the force of body weight evenly through weight-bearing structures when walking or running and to act as shock absorbers.

Psoas
This muscle originates from the transverse processes and bodies of the lumbar vertebrae (Fig. 16.66). It passes across the flat part of the ilium and behind the inguinal ligament to insert into the femur. Together with iliacus, it flexes the hip joint.

Iliacus
This muscle lies in the iliac fossa of the innominate bone. It originates from the iliac crest, passes over the iliac fossa and joins the tendon of the psoas muscle to insert into the lesser trochanter of the femur. The combined action of iliacus and psoas flexes the hip joint.

Quadriceps femoris
This group of four muscles lies on the front and sides of the thigh. They are rectus femoris and three vasti: lateralis, medialis and intermedius (this last muscle is not shown in Figure 16.71 because it lies deep to the other two). Rectus femoris originates from the ilium and the three vasti from the upper end of the femur. Together they pass over the front of the knee joint to insert into the tibia by the patellar tendon. Only rectus femoris flexes the hip joint. Together, the group is a powerful extensor of the knee joint.

Obturators
The obturators, deep muscles of the buttock, originate from the rim of the obturator foramen of the pelvis and insert into the proximal femur. They laterally rotate the hip joint.

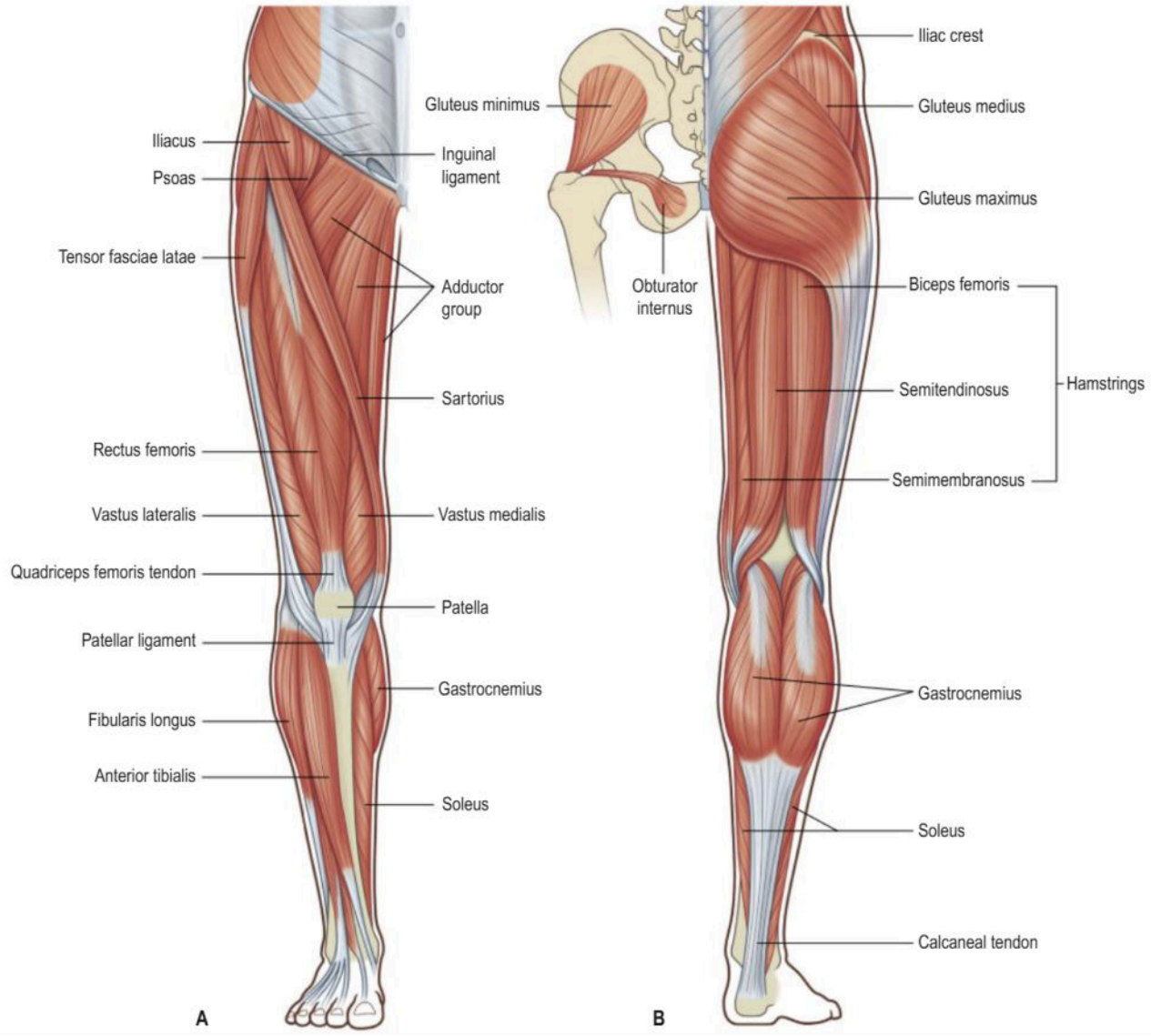


Fig. 16.71 The main muscles of the right lower limb. (A) Anterior view. (B) Posterior view.

Gluteal muscles

These are the gluteus maximus, medius and minimus, which together form the fleshy part of the buttock. They originate from the ilium and sacrum and insert into the femur. They extend, abduct and medially rotate the hip joint.

Sartorius

This is the longest muscle in the body and crosses both the hip and knee joints. It originates from the anterior superior iliac spine and passes obliquely across the hip joint, thigh and knee joint to insert into the medial surface of the upper part of the tibia. It assists with flexion and abduction at the hip joint and knee flexion.

Adductor group

These muscles, on the medial aspect of the thigh, originate from the pubic bone and insert into the linea aspera of the femur. They adduct and medially rotate the thigh.

Hamstrings

The hamstrings comprise the biceps femoris, semimembranosus and semitendinosus muscles and lie on the posterior aspect of the thigh. They originate from the ischium and insert into the upper end of the tibia. They flex the knee joint.

Gastrocnemius

This muscle forms the bulk of the calf of the leg. It arises by two heads, one from each condyle of the femur, and passes

down behind the tibia to insert into the calcaneus by the calcanean tendon (Achilles tendon). It crosses both knee and ankle joints, flexes the knee and plantarflexes (rising on to the ball of the foot) the ankle.

Anterior tibialis

This muscle originates from the upper end of the tibia, lies on the anterior surface of the leg and inserts into the middle cuneiform bone by a long tendon. It assists with dorsiflexion of the foot.

Soleus

This is one of the main muscles of the calf of the leg, lying immediately deep to gastrocnemius. It originates from the heads and upper parts of the fibula and the tibia. Its tendon joins that of gastrocnemius so that they have a common insertion into the calcaneus by the calcanean (Achilles) tendon. It plantarflexes the ankle and helps to stabilise the joint when standing.

SPOT CHECK

9. Define the term 'motor unit'.
10. What is the difference between the origin and the insertion of a skeletal muscle?

Effects of ageing on the musculoskeletal system

Learning outcome

After studying this section, you should be able to:

- describe the effects of ageing on the structure and function of the musculoskeletal system.

Bone tissue in old age becomes lighter and less dense, so fractures are more likely. This natural process is called osteopenia and begins between the ages of 30 and 40. It is due to a shift of the osteoblast–osteoclast balance towards osteoclast activity, meaning that bone is reabsorbed faster than new bone is laid down to replace it. Osteopenia does not cause symptoms but can progress to osteoporosis (see below). Oestrogen maintains bone mass, so pre-menopausal women have a degree of protection against osteopenic changes compared to age-matched men.

Compaction of the intervertebral discs reduces the length of the spinal column and leads to loss of height.

Cartilage and other connective tissues stiffen and may degenerate with age, reducing joint flexibility and mobility and predisposing to osteoarthritis (p. 482). Skeletal muscle cells become smaller and less elastic and take longer to repair following injury. Damaged muscle may be replaced with fibrous tissue, which is inelastic and reduces the strength of contraction. Exercise tolerance reduces because each muscle cell stores less glucose and myoglobin, and as cardiovascular function declines, regulation of blood supply to muscle becomes less efficient. In addition, older adults cannot lose the heat generated by working muscle as effectively as younger people, reducing exercise tolerance.

Regular exercise throughout life can significantly slow these age-related changes.

Diseases of bone

Learning outcomes

After studying this section, you should be able to:

- explain the pathological features of osteoporosis, Paget's disease, rickets and osteomalacia
- outline the causes and effects of osteomyelitis
- describe abnormalities of bone development
- explain the effects of bone tumours.

Osteoporosis

In this condition, bone density (the amount of bone tissue) is reduced because its deposition does not keep pace with resorption (see osteopenia above) and the risk of fracture is increased. The diagnosis may not be made until a fracture occurs. Although the bone is adequately mineralised, it is fragile, porous and microscopically abnormal, with loss of internal structure (Fig. 16.72). A range of environmental factors and diseases increase the risk of osteoporosis (Box 16.1). Some can be influenced by changes in lifestyle. Exercise and calcium intake during childhood and adolescence are thought to be important in determining a person's eventual bone mass, and therefore the risk of osteoporosis in later life. Reduced mobility causes reversible osteoporosis, the extent of which corresponds to its duration and degree. For instance, during prolonged unconsciousness, osteoporotic changes are uniform throughout the skeleton, but immobilisation of a particular joint following fracture leads to local osteoporotic changes in involved bones only.

Fig. 16.72 Osteoporosis. Scanning electron micrograph of spongy bone. (Prof. P Motta, Dept of Anatomy, University 'La Sapienza', Rome/Science Photo Library. Reproduced with permission.)

Common features of osteoporosis include:

- skeletal deformity – gradual loss of height with age, caused by vertebral compression
- bone pain
- fractures – especially of the neck of femur, wrist (Colles' fracture) and vertebrae.

Paget's disease

Paget's disease is a disorder of bone remodelling, where the normal balance between bone building and bone breakdown becomes disorganised and both osteoblasts and osteoclasts become abnormally active. The bone deposited is undermineralised and structurally abnormal. This predisposes to deformities (Fig. 16.73) and fractures, commonly of the pelvis, femur, tibia and skull. The cause is unknown and the disease often goes undetected until complications arise. Age is a risk factor; the average age at diagnosis is 70 years. Both genetic and environmental factors are probably also important. The disease increases the risk of osteoarthritis (p. 482) and development of benign or malignant bone tumours.

Rickets and osteomalacia

In both conditions, bone is inadequately mineralised, usually because of vitamin D deficiency, or sometimes because of defective vitamin D metabolism. Rickets occurs in children,

Box 16.1 Causes of decreased bone mass

Risk factors
Female sex, especially post-menopause
Increasing age
White ethnic origin
Family history
Lack of exercise/immobility
Diet (low calcium)
Smoking
Excess alcohol intake
Early menopause/oophorectomy
Thin build (small bones)

Drugs
Corticosteroids

Diseases
Cushing's syndrome
Hyperparathyroidism
Type 1 diabetes mellitus
Rheumatoid arthritis
Chronic renal failure
Chronic liver disease
Anorexia nervosa
Certain cancers

Fig. 16.73 Severe leg deformity in Paget's disease. (Biophoto Associates/Science Photo Library. Reproduced with permission.)

whose bones are still growing, causing characteristic bowing and deformity of the lower limbs. Adults need vitamin D for normal bone turnover, and deficiency causes osteomalacia, which is associated with increased risk of fracture and bone pain.

Deficiency may be due to poor diet, malabsorption or limited exposure to sunlight (needed for normal vitamin D metabolism).

Osteomyelitis

This is bacterial infection of bone and may follow an open fracture or surgical procedures, which allow microbial contamination through broken skin. It may also result from blood-borne infection from infection elsewhere, e.g. the ear, throat or skin; this is most common in children. If promptly and adequately treated, the infection can resolve without permanent damage, but if not, it may become chronic, with fever, pain and sinus formation draining pus to the skin (see Fig. 14.10).

Developmental abnormalities of bone

Achondroplasia

This is caused by a genetic abnormality that prevents normal ossification of bones that develop from cartilage models (Fig. 16.7), such as the long bones of the limbs, producing short limbs and characteristic dwarfism.

Osteogenesis imperfecta ('brittle bone syndrome')

This group of conditions involves a congenital defect of collagen synthesis and results in failure of ossification. The bones are brittle and fracture easily, either spontaneously or following even slight trauma.

Tumours of bone and cartilage

Benign tumours

These may cause pathological fractures or pressure damage to soft tissues, e.g. a benign vertebral tumour may damage the spinal cord or a spinal nerve. Benign tumours of cartilage tend to become malignant.

Malignant tumours

Metastatic tumours

The most common malignancies of bone are metastases (secondary growths) of primary carcinomas of the breast, lungs, thyroid, kidneys and prostate gland. The usual sites are those with the best blood supply, i.e. spongy bone, especially the bodies of the lumbar vertebrae and the epiphyses of the humerus and femur. Tumour growth destroys normal bone architecture, is usually painful and can cause pathological fractures.

Primary tumours

Primary malignant bone tumours are relatively rare. Osteosarcoma is rapidly growing and often highly malignant. It is most common in adolescence and usually develops in the medullary canal of long bones, especially the femur. It occasionally occurs in elderly people, generally in association with Paget's disease, and involving the vertebrae, skull and pelvis.

SPOT CHECK

11. Which vitamin is deficient in rickets in children, and why does this deficiency lead to different symptoms in adults?
12. What is osteosarcoma?

Disorders of joints

Learning outcomes

After studying this section, you should be able to:

- relate the features of the diseases in this section to abnormal anatomy and physiology
- compare and contrast the features of rheumatoid arthritis and osteoarthritis.

The tissues involved in diseases of the synovial joints are synovial membrane, hyaline cartilage and bone.

Inflammatory joint disease (arthritis)

Rheumatoid arthritis (rheumatoid disease)

Rheumatoid arthritis (RA) is a chronic progressive inflammatory autoimmune disease. It is a systemic disorder in which inflammatory changes affect not only joints but also many other sites, including the heart, blood vessels and skin.

It is more common in females than males; premenopausal women are affected three times more often than men. It can affect all ages, including children (Still's disease), although risk increases with age and it usually develops between 35 and 55 years of age. The cause is not clearly understood but there is sometimes a clear familial link, and autoimmunity may be initiated by microbial infection, possibly by viruses, in genetically susceptible people.

Up to 90% of affected individuals have rheumatoid factor (RF-autoantibodies) in their body fluids. High levels of RF, especially early in the disease, are strongly associated with accelerated and more severe disease.

Acute exacerbations of RA are usually accompanied by fever and are interspersed with periods of remission. Symptoms include joint pain and stiffness, particularly in the morning and after rest. Affected joints can be visibly swollen, hot and tender. The joints most commonly affected are those of the hands (Fig. 16.74) and feet, but in severe cases most synovial joints may be involved. With each flare-up there is additional and cumulative joint damage, leading to increasing deformity, pain and loss of function. The early changes, which may be reversible, include hypertrophy and hyperplasia of synovial cells and inflammatory effusion into the joint. Disease progression usually causes permanent tissue damage. Growth of inflammatory granulation tissue, called pannus, distorts the joint and destroys articular cartilage, exposing the bone below and causing further damage. Fibrosis of the pannus reduces joint mobility. Pain, stiffness and deformity severely restrict the use of affected joints, and as a result the associated muscles start to waste. About a third of patients, usually those with the most aggressive form of the disease, develop nodules of connective tissue (rheumatoid nodules), usually in the forearm or elbow. Extra-articular symptoms can include anaemia, peripheral neuropathy, cardiac abnormalities, pleurisy and vasculitis.

In the later stages of the disease inflammation and fever are less marked. The extent of disability varies from slight to severe. Table 16.8 highlights differences between osteoarthritis and rheumatoid arthritis.

Other types of polyarthritis

Polyarthritis means inflammation of more than one joint. This group of autoimmune inflammatory arthritic diseases has many characteristics similar to those of RA but rheumatoid factor is absent. The causes are not known but genetic features may be involved.

Fig. 16.74 Severe deformity of the hands in rheumatoid arthritis. (Alain Pol, ISM/Science Photo Library. Reproduced with permission.)

Table 16.8 Features of the two main types of arthritis

	Osteoarthritis	Rheumatoid arthritis
Type of disease	Degenerative	Inflammatory and autoimmune
Tissue affected	Articular cartilage	Synovial membrane
Age of onset	Late middle age	Any age, mainly 30–55 years, occasionally children
Joints affected	Weight bearing, e.g. hip, knee; often only a single joint	Small, e.g. hands, feet; often many joints

Ankylosing spondylitis

This tends to occur in young adults and affects the joints of the spine, including the sacroiliac joint (Fig. 16.28). Calcification of the intervertebral joints and laying down of new bone reduce spinal flexibility and cause permanent deformity.

Psoriatic arthritis

5%–10% of people with psoriasis (p. 411) develop psoriatic arthritis, more likely if the nails are involved. The finger and toe joints are most commonly affected.

Rheumatic fever

Rheumatic fever is a diffuse inflammatory condition that affects many connective tissues. Polyarthritis is a common presenting feature, often involving the wrists, elbows, knees and ankles. Unlike the cardiac effects, which are permanent (rheumatic heart disease, p. 139), arthritis usually resolves spontaneously without complications.

Infective arthritis

Joint infection (septic arthritis) usually results from a blood-borne bacterial infection, usually staphylococcal, although it may also be caused by a penetrating joint injury. Often the joint has been damaged by pre-existing disease, making it more susceptible to infection, and it becomes acutely inflamed. Complete resolution is possible if treatment is prompt but permanent joint damage usually occurs early in the disease.

Osteoarthritis (osteoarthrosis)

Osteoarthritis (OA) is a degenerative non-inflammatory disease that causes pain and restricted movement of affected joints. In its early stages, OA is often asymptomatic. It is very common, and most people over 65 show some degree of osteoarthritic changes. Articular cartilage gradually becomes thinner because its renewal no longer keeps pace with its breakdown. Eventually, the bony articular surfaces come in contact and the bones begin to degenerate. Bone repair is abnormal and the articular surfaces become misshapen, reducing joint mobility. Chronic inflammation develops with effusion (collection of fluid) in the joint. Sometimes there is abnormal outgrowth of cartilage at the edges of bones which ossifies, forming osteophytes.

In most cases, the cause is unknown (primary OA), but risk factors include excessive repetitive use of the affected joints, female sex, increasing age, obesity and heredity. Secondary OA occurs when the joint is already affected by disease or abnormality, e.g. trauma or gout. OA usually develops in late middle age and affects large weight-bearing joints, i.e. the hips, knees and joints of the cervical and lower lumbar spine. In many cases only one joint is involved.

Traumatic injury to joints

Sprains, strains and dislocations

These damage the soft tissues, tendons and ligaments round the joint without penetrating the joint capsule. In dislocations there may be additional damage to intracapsular structures by stretching, e.g. to the long head of biceps muscle in the shoulder joint, the cruciate ligaments in the knee joint or the ligament of head of femur in the hip joint. If repair is incomplete, there may be some loss of stability, which increases the risk of repeated injury.

Penetrating injuries

These may be caused by a compound fracture of one of the articulating bones or by trauma. Healing may be uneventful or delayed by the presence of fragments of damaged or torn joint tissue (bone, cartilage or ligaments), which cannot be removed or repaired by normal body mechanisms and prevent full joint recovery. Infection is another risk. Chronic inflammation can lead to permanent degenerative changes in the joint.

Gout

This condition is caused by the deposition of sodium urate crystals in joints and tendons, provoking an acute inflammatory response. Risk factors include male sex, obesity, family history, hyperuricaemia and high alcohol intake. Primary gout, the most common form, occurs almost always in men and is associated with reduced urate excretion or increased urate production. Secondary gout is usually caused by diuretic treatment or kidney failure, both of which reduce urate excretion.

In many cases only one joint is involved (monoarthritis), which is typically red, hot and extremely painful. The sites most commonly affected are the metatarsophalangeal joint of the big toe and the ankle, knee, wrist and elbow joints. Episodes of arthritis lasting days or weeks are interspersed with periods of remission. Repeated acute attacks can cause permanent deformity and loss of function of the affected joints. Gout is sometimes complicated by the development of renal calculi.

Connective tissue diseases

This group of chronic autoimmune disorders has common features. They affect many body tissues, especially the joints, skin and subcutaneous tissues and tend to occur in early adult life, affecting more women than men. They include the following:

- Systemic lupus erythematosus (SLE) – the affected joints are usually the hands, knees and ankles. A characteristic red 'butterfly' rash may occur on the face. Kidney involvement is common and can result in glomerulonephritis that may be complicated by chronic kidney disease.
- Systemic sclerosis (scleroderma) – in this group of disorders there is progressive thickening of connective tissue. There is increased collagen production within many organs. In the skin there is dermal fibrosis and tightness that impairs joint function, especially of the hands. It also affects the walls of blood vessels, the intestinal tract and other organs.
- Rheumatoid arthritis (p. 481).
- Ankylosing spondylitis (p. 481).
- Reiter's syndrome. Signs and symptoms include polyarthritis, urethritis and conjunctivitis); it may be precipitated by *Chlamydia trachomatis* infection. The lower limb joints are the most commonly affected.

Carpal tunnel syndrome

This occurs when the median nerve is compressed in the wrist as it passes through the carpal tunnel (see Fig. 16.55B). It is most common in women aged between 30 and 50 years. Pain and numbness in the hand and wrist affects the thumb, index and middle fingers, and half of the ring finger, the areas supplied by the median nerve. Many cases are idiopathic or secondary to other conditions, e.g. RA, diabetes mellitus, acromegaly and

hypothyroidism. Repetitive flexion and extension of the wrist joint also cause the condition, e.g. prolonged keyboard use.

SPOT CHECK

13. Why does gout affect the joints?
14. Which nerve is compressed in carpal tunnel syndrome, and by what?

Diseases of muscle

Learning outcomes

After studying this section, you should be able to:

- list the causes of the diseases in this section
- compare and contrast the characteristics of different types of muscular dystrophy.

Myasthenia gravis

This autoimmune condition of unknown origin affects more women than men, usually between 20 and 40 years of age. Circulating autoantibodies bind to and block the acetylcholine receptors of the neuromuscular junction (Fig. 16.61). The transmission of nerve impulses to skeletal muscle is therefore blocked, causing progressive and extensive muscle weakness, although the muscles themselves are normal. Muscles moving the eyeballs and the eyelids are usually affected first, causing ptosis (drooping of the eyelid) or diplopia (double vision), followed by those of the neck, possibly affecting chewing, swallowing and speech, and limb muscles. There are periods of remission, relapses being precipitated by, for example, strenuous exercise, infections or pregnancy.

Muscular dystrophies

In this group of inherited diseases there is progressive degeneration of groups of muscles. The main differences in the types are age of onset, rate of progression and muscles involved.

Duchenne muscular dystrophy

Inheritance of this condition is sex-linked (p. 495). Signs and symptoms may not appear until about 5 years of age. Wasting and weakness begin in lower limb muscles, then spread to the upper limbs, progressing rapidly without remission. Death usually occurs in adolescence, often from respiratory failure, cardiac arrhythmias or cardiomyopathy.

Facioscapulohumeral dystrophy

This disease affects both sexes. It usually begins in adolescence, and the younger the age of onset, the more rapidly it progresses. Muscles of the face and shoulders are affected first. It is a chronic condition which usually progresses slowly and may not cause complete disability. Life expectancy is normal.

Myotonic dystrophy

This inherited disease usually begins in adult life and affects both sexes. Muscle contraction is prolonged and relaxation can be slow, so that sufferers have difficulty in releasing an object held in the hand. Muscles of the tongue and the face are affected first, then limb muscles. Other effects of this condition include cataract (p. 235), abnormalities of cardiac conduction and increased risk of diabetes mellitus (p. 261).

The disease progresses without remission and with increasing disability. Death usually occurs in middle age from respiratory or cardiac failure.

SPOT CHECK

15. In myasthenia gravis, against which structure are the autoantibodies directed?

Case study 1

Edward has decided to improve his general fitness and joined a gym. His trainer has listed sit-ups and running on the treadmill among other exercises in his training programme.

1. Which muscles are strengthened by sit-ups?

   a. Psoas
   b. Rectus abdominis
   c. Quadratus lumborum
   d. Latissimus dorsi

2. Skeletal muscles tend to work in antagonistic pairs. Which of the following pairs of muscles is NOT an example of an antagonistic pair?

   a. Biceps brachii and triceps
   b. Rectus abdominis and erector spinae
   c. Rectus femoris and the hamstrings
   d. Biceps brachii and brachioradialis

3. After a particularly strenuous workout, Edward is very breathless, and his muscles are sore and tired. His muscle discomfort is the result of the accumulation of:

   a. Lactate
   b. Carbon dioxide
   c. Pyruvate
   d. Glycogen

4. Edward has overdone it on the treadmill and has injured his Achilles tendon. This tendon attaches which muscle to which bone?

   a. Soleus muscle and talus
   b. Gastrocnemius muscle and calcaneus
   c. Anterior tibialis muscle and navicular bone
   d. Fibularis longus and fibula

5. As part of rehabilitation from the Achilles tendon injury, the physiotherapist prescribes a range of exercises. Which of the following movements is NOT possible at the ankle joint?

   a. Flexion
   b. Circumduction
   c. Rotation
   d. Eversion

Case study 2

Lindsay, aged 8, is cycling to school and hits a pothole in the road. She goes over the handlebars and lands hard on the kerb. She feels searing pain in her right arm and feels a bone break. Passers-by call an ambulance and Lindsay is taken to hospital.

1. Lindsay has fractured the bone of her upper limb. This bone is the:

   a. Radius
   b. Scaphoid
   c. Humerus
   d. Ulna

2. The paramedic in attendance notes that Lindsay's fracture is a compound fracture. This means:

   a. The bone has broken into more than two pieces
   b. Fragments of bone are protruding through the skin
   c. The arm is badly deformed, indicating the bone ends have separated from each other
   d. More than one bone in the arm has been broken

3. An important step in the healing of Lindsay's fracture is:

   a. Dedifferentiation of osteocytes into osteoblasts to synthesise new bone
   b. Formation of callus, a large collection of clotted blood
   c. Calcification of new bone tissue by fibroblasts
   d. Recanalisation of the new bone by macrophages.

4. In a child of Lindsay's age, a fracture to which area of the bone could impair its ability to continue growing lengthways?

   a. Periosteum, which contains bone-building osteoblasts
   b. Medullary cavity, which contains red bone marrow in children
   c. The network of perforating canals, which bring the blood supply to the bone
   d. The epiphyseal plate, which contains dividing cartilage

5. Lindsay's fractured bone is stabilised under anaesthetic. During rehabilitation, the physiotherapist gives her exercises to do to improve shoulder strength. The shoulder joint is formed from which structures?

   a. Scapula and humerus
   b. Scapula and glenoid cavity
   c. Clavicle, scapula and humerus
   d. Humerus and clavicle

Review and revise

Complete each of the following statements:

1. The face is made up of a total of _____ bones. The _____ bones form the prominences of the cheeks and the floor of the bony _____. The only movable bone of the face is the _____ and its alveolar ridge contains the _____. The extended portion of this bone is called the _____, and it articulates with the _____ bone to form the _____ joint. Lying below this bone is the only bone of the body that does not articulate with any other bone. This bone is called the _____ bone and it supports the _____.

2. The most superficial muscles of the anterior abdominal wall are the _____, which are attached to each other lengthways by the _____. They attach superiorly to the _____ and the _____, and inferiorly to the _____. When these muscles contract, the trunk _____.

3. This is a fibrous joint: _____
   a. Shoulder
   b. Knee
   c. Intervertebral joint
   d. Suture

4. This muscle or muscle group lifts the ribcage during inspiration: _____
   a. Diaphragm
   b. External intercostals
   c. Internal obliques
   d. Pectoral group

5. The calcaneus is found: _____
   a. In the skull
   b. In the wrist
   c. At the top of the vertebral column
   d. In the foot

6. In the sarcomere, the Z line: _____
   a. Is the boundary between adjacent sarcomeres
   b. Runs down the centre of each sarcomere
   c. Gives attachment to myosin filaments
   d. Stores calcium

7. Myasthenia gravis: _____
   a. Is a sex-linked disorder
   b. Affects transmission at the neuromuscular junction
   c. Is caused by autoantibodies destroying skeletal muscle
   d. Generally manifests before the age of 5.

8. This movement is made by the thumb but not the other fingers: _____
   a. Flexion
   b. Adduction
   c. Circumduction
   d. Opposition

9. This skull bone lies most posteriorly: _____
   a. Occipital
   b. Parietal
   c. Temporal
   d. Sphenoid

10. Match the joints in List A with the bones that form them in List B. You may use the bones in List B more than once:

List A

____ (a) Knee joint
____ (b) Elbow joint
____ (c) Ankle joint
____ (d) Wrist joint

List B

1. Tibia
2. Femur
3. Fibula
4. Scaphoid
5. Patella
6. Humerus
7. Radius
8. Lunate
9. Ulna
10. Triquetrum
11. Talus

11. Match the musculoskeletal disorders in List A with the relevant statement in List B:

List A

____ (a) Rheumatoid arthritis
____ (b) Gout
____ (c) Osteosarcoma
____ (d) Achondroplasia
____ (e) Osteoarthritis
____ (f) Osteoporosis
____ (g) Rickets

List B

1. The primary form occurs almost exclusively in males
2. Associated with deficient vitamin D
3. A non-inflammatory degeneration of joints
4. Commonly associated with autoantibodies
5. Inadequate ossification of a developing bone
6. Rare, but may occur in conjunction with Paget's disease
7. Age-related loss of bone mass

12. Match the items in List A to the relevant hip bone in List B. You may use the items from List B more than once and each item in List A may match more than one item in List B:

List A

____ (a) The 'sitting bones' are part of this bone
____ (b) Helps to form the acetabulum
____ (c) Forms a synovial joint with the sacrum
____ (d) The anterior bone
____ (e) The posterior bone
____ (f) Helps to form the obturator foramen

List B

1. Ischium
2. Ilium
3. Pubis

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 17

Genetics and inheritance

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All living organisms, including human beings, need to reproduce, so that by the end of their lifespan they have produced one or more offspring to ensure the continuation of their species. Human beings reproduce sexually, meaning that at conception a new human being receives a random combination of genetic material from both parents. Sexual reproduction is complex and prone to error, but it favours the continuation of a species because it generates variation, which in turn allows a population of organisms to adapt to changing environments (survival of the fittest).

Genetics is the study of heredity and inherited characteristics, and advancing knowledge in this area has had a profound effect on many aspects of human society and health, e.g. for genetic counselling in families carrying inherited diseases, drug production from genetically engineered microorganisms and targeting specific anticancer therapies against the genetic profile of individual cancers.

The first part of the chapter explains the fundamental processes involved in protein synthesis and transmission of inherited characteristics from parent to child. At the end of the chapter the effects of ageing on chromosomes, cell division and heredity are considered, and the final section describes some common genetic abnormalities.

DNA, chromosomes and genes

Learning outcomes

After studying this section, you should be able to:

- explain the structural relationship between DNA, chromosomes and genes
- describe the molecular structure of DNA
- explain the terms 'autosome' and 'sex chromosome'
- define the terms 'mutation', 'genome', 'haploid', 'diploid' and 'karyotype'.

DNA

DNA (deoxyribonucleic acid) is the key genetic material of every living organism on Earth. It carries the information that allows living cells to produce all the proteins required for life, and passes this information from one generation to the next (heredity). DNA forms very long molecules wrapped up

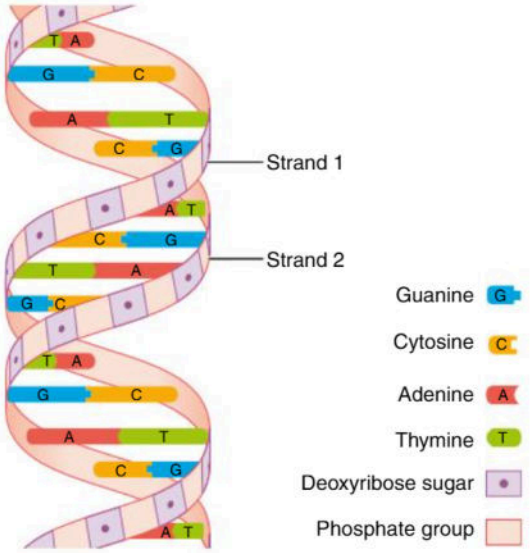

Figure 17.1 Deoxyribonucleic acid (DNA).

tightly in the cell nucleus with specialised supporting proteins into discrete thread-like structures called chromosomes (see Fig. 17.3). It is a double-stranded molecule, made up of two chains of nucleotides. Nucleotides consist of three subunits: a sugar, a phosphate group and a base.

The DNA molecule is sometimes compared to a twisted ladder, with the uprights formed by chains of alternating sugar (deoxyribose) and phosphate units (Fig. 17.1). Each sugar unit is linked to a base, and each base binds to another base on the other sugar/phosphate chain, forming the rungs of the ladder. The two chains are twisted around one another, forming a double helix. The double helix itself is further twisted and wrapped in a highly organised way around histones, the structural proteins important in maintaining the heavily coiled three-dimensional shape of the DNA. The DNA–histone material, called chromatin, is supercoiled and packaged into 46 chromosomes shortly before the cell divides (Fig. 17.2).

The genetic code

DNA carries a huge amount of coded information written in its base sequence. There are four bases:

- adenine (A)
- guanine (G)
- thymine (T)
- cytosine (C).

Bases are arranged in a precise order along the DNA molecule, making a code that can be read when protein synthesis is required. Each base along one strand of DNA pairs with a base on the other strand in a precise and predictable way. This is called complementary base pairing. Adenine and thymine always pair, and so do cytosine and guanine (Fig. 17.1).

Mitochondrial DNA

Each body cell has, on average, 5000 mitochondria (p. 46) that hold a small quantity of DNA (mitochondrial DNA), which codes mainly for enzymes important in energy production. This DNA is passed from one generation to the next via the ovum, so the offspring's complement of mitochondrial DNA is always inherited from the mother. Certain rare inherited disorders caused by faulty mitochondrial DNA are therefore passed through generations via the maternal line.

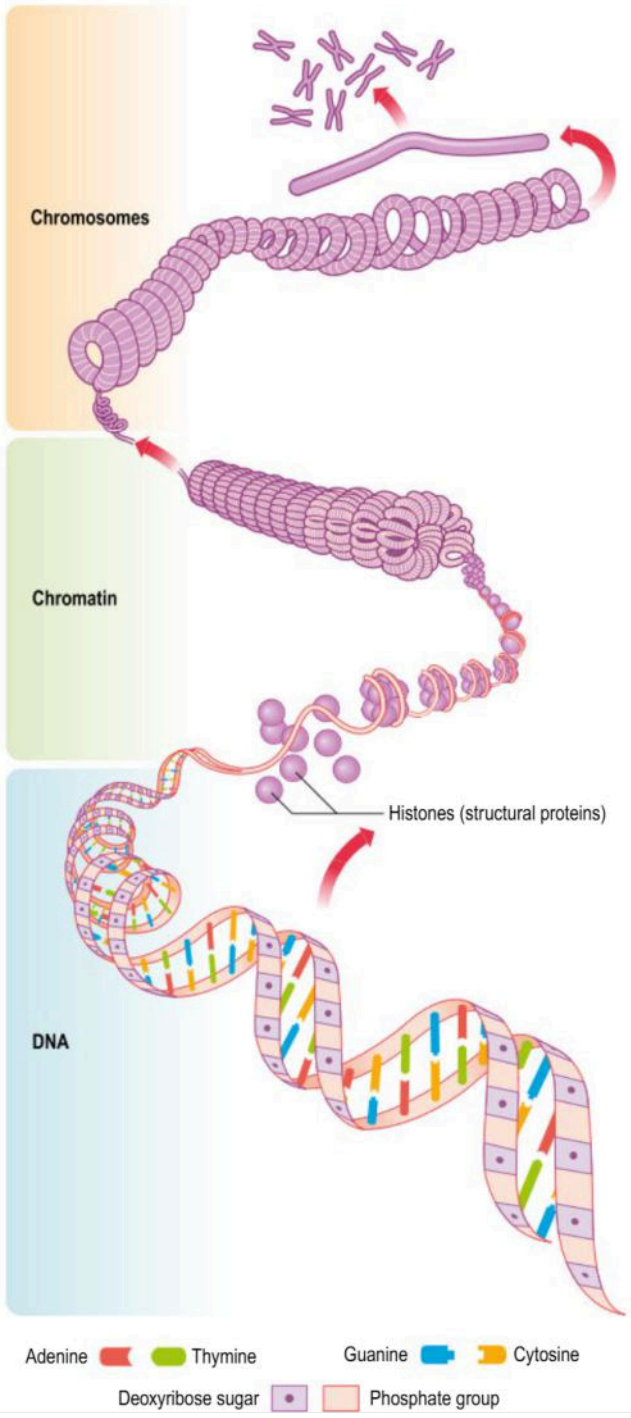

Figure 17.2 The structural relationship between DNA, chromatin and chromosomes.

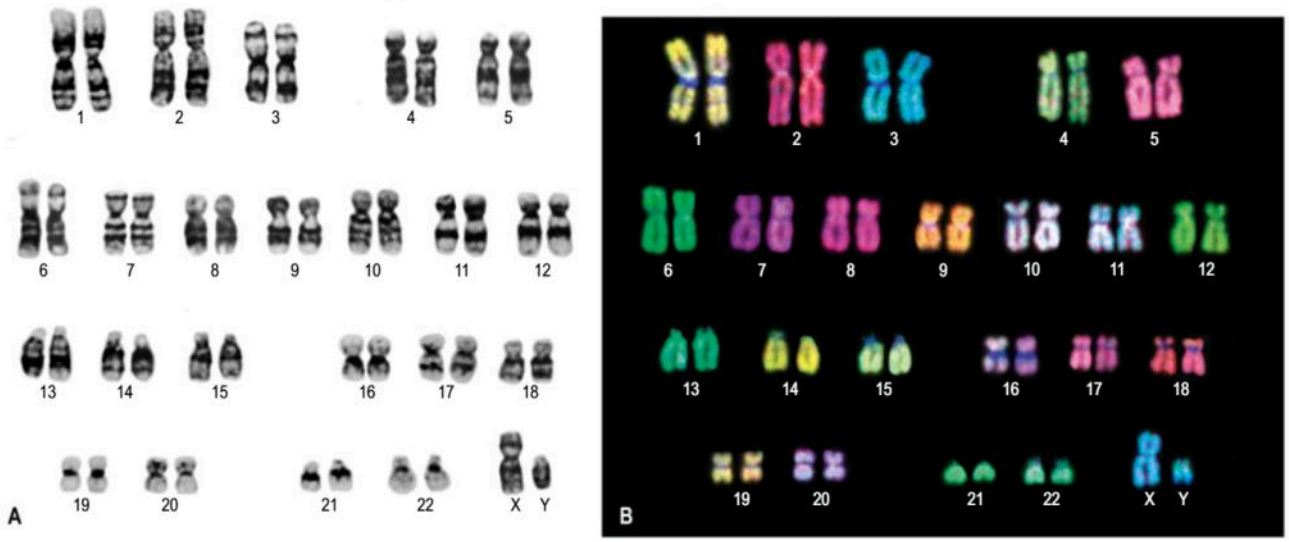

Figure 17.3 (A) Chromosomal complement (karyotype) of a normal human male. There are 22 pairs of autosomes and 1 pair of sex chromosomes (XY, pair 23). (B) The same karyotype, shown after coloured fluorescence staining. (Standring S 2004 Gray's anatomy: the anatomical basis of clinical practice, 39th edn. Edinburgh: Churchill Livingstone. Reproduced with permission.)

Chromosomes

Chromosomes are made of a tightly coiled strand of DNA, wrapped around histones. Uncoiled, there is a total length of about 2 metres of DNA in each body cell. It is an incredible feat, packaging such a large quantity of material into such a tiny space. Each chromosome has a narrow 'waist' called the constriction point that divides it unequally into two sections referred to as the short arm and the long arm (see Fig. 17.9)

All the genetic material contained within an organism is collectively called its genome.

Every nucleated body cell possesses an identical copy of the individual's 46 chromosomes, located in the nucleus. Important exceptions are red blood cells (which have no nucleus) and sperm cells and ova, the gametes, which have only 23 chromosomes (explained later). Chromosomes are only clearly visible when the cell is about to divide, because at other times the chromatin is dispersed in the nucleus. Each chromosome is one of a pair, one inherited from the mother and one from the father, so the 46 chromosomes can be arranged as 23 pairs. A cell with 23 pairs of chromosomes is termed diploid. Gametes, with only half of the normal complement, i.e. 23 chromosomes instead of 46, are described as haploid. Chromosomes belonging to the same pair are called homologous chromosomes. The complete set of chromosomes from a cell is its karyotype (Fig. 17.3).

Each pair of chromosomes is numbered, the largest pair being number 1. The first 22 pairs are collectively known as autosomes, and the chromosomes of each pair contain the same amount of genetic material. The chromosomes of pair 23 are called the sex chromosomes (Fig. 17.4) because they determine the individual's biological sex. There are two different sex chromosomes, the X and the Y and they are not the same size; the Y chromosome is much shorter than the X and is carried only by males. A child inheriting two X chromosomes (XX), one from each parent, is female, and a child inheriting an X from his mother and a Y from his father (XY) is male.

Figure 17.4 Coloured scanning electron micrograph of replicated human sex chromosomes. *Upper left*, Y chromosome; *centre*, X chromosome. (Power and Syred/Science Photo Library. Reproduced with permission.)

Each end of the chromosome is capped with a length of DNA called a telomere, which acts like a protective tip sealing the chromosome end and maintains chromosomal stability. Every time the DNA is copied for cell division, the telomere is shortened, eventually becoming so short that cell

suicide mechanisms (apoptosis) are activated and the cell is destroyed. This limits the number of times body cells can divide and is a significant contributor to the ageing process. Short or faulty telomeres lead to chromosomal damage and are associated with some cancers and the process of normal healthy cell ageing (senescence, p. 496).

Genes

A gene is a length of DNA carrying a code to make a specific protein, and genes are found along the length of the DNA, interspersed with sections of non-coding DNA. Non-coding DNA makes up about 99% of the total and although much of it seems to be redundant, some is essential for normal gene function, for example as start and stop signals to clearly mark the beginning and the end of genes. The protein that is made from the gene code is called the gene product and the process by which the gene code is converted into the gene product is called gene expression; for example, expression of the insulin gene leads to insulin synthesis. The human genome contains about 20,500 genes, and has now been completely mapped, with the location of every gene on its chromosome accurately identified. For example, the gene that codes for insulin is located on chromosome 11 (see Fig. 17.10).

Genes are normally present in pairs because the gene on one chromosome is matched at the equivalent site (locus) on the other chromosome of the pair. The exception to this is in males, whose sex chromosomes comprise one X and one Y, and are not of equal length (Fig. 17.4). This is explored further on page 493 ('The genetic basis of inheritance').

Mutation

Mutation is a hereditable alteration in the base sequence in a gene. It may be due to loss of a section of DNA, addition of extra bases into a gene sequence or a rearrangement of the bases in a particular section of DNA. This changes the gene code, and therefore changes the protein product, which may be completely nonfunctional. Most mutations occur spontaneously because of the countless millions of DNA replications and cell divisions that occur normally throughout life. Others may be caused by external factors, such as X-rays, ultraviolet rays or exposure to certain chemicals. Any factor capable of mutating DNA is called a mutagen. Most mutations are immediately repaired by an army of enzymes present in the cell nucleus, and therefore cause no permanent problems.

Sometimes the mutation is lethal because loss of the normal protein product interferes with an essential cellular process. The cell dies, and the mutation is destroyed along with the cell. Often, the mutated cell survives, but is identified as abnormal by immune cells and destroyed. Other mutations do not kill the cell but alter its function in some way that may cause disease, e.g. in cancer (p. 59). Non-lethal mutations in the ova or sperm can be passed from parent to child and cause inherited disease, e.g. phenylketonuria (p. 497) or cystic fibrosis (p. 295).

SPOT CHECK

1. What are histones?
2. Which base always pairs with cytosine in DNA?

Protein synthesis

Learning outcomes

After studying this section, you should be able to:

- describe the origin and structure of mRNA
- explain the mechanism of transcription
- outline the mechanism of translation.

Each gene codes for synthesis of a specific protein. Proteins are essential to all aspects of body function, forming the major structural elements of the body, as well as the enzymes essential for all biochemical processes within it. Protein synthesis involves two key steps: transcription and translation. An intermediary molecule is needed to carry the genetic instructions from the gene in the nucleus to the cytoplasm, where protein synthesis takes place. This intermediary is called messenger ribonucleic acid (mRNA), and mRNA production is called transcription. The process by which the mRNA information is then converted into the final protein is called translation. Protein synthesis is summarised in Figure 17.5.

Messenger ribonucleic acid

Like DNA, RNA is made of nucleotides but is structurally different to DNA in three main ways:

- It is single-stranded instead of double-stranded.
- It contains the sugar ribose instead of deoxyribose.
- It contains the base uracil instead of thymine.

To initiate protein synthesis, a piece of mRNA is transcribed from the appropriate gene. It then leaves the nucleus through the nuclear pores and attaches to a ribosome (p. 46) in the cytoplasm, where translation and production of the new protein take place.

Transcription (Fig. 17.6)

The base code is buried within the tightly folded DNA molecule and so the first step is to unfold the DNA and separate the strands to expose the bases. Only the gene to be transcribed is unzipped; the remainder of the chromosome remains coiled. Opening up the helix exposes both base strands, but the enzyme that makes the mRNA uses only one of them, which is why the mRNA molecule is single not double-stranded. As the enzyme moves along the opened DNA strand, reading its code, it adds the complementary base to the mRNA. Therefore, if the DNA base is cytosine,

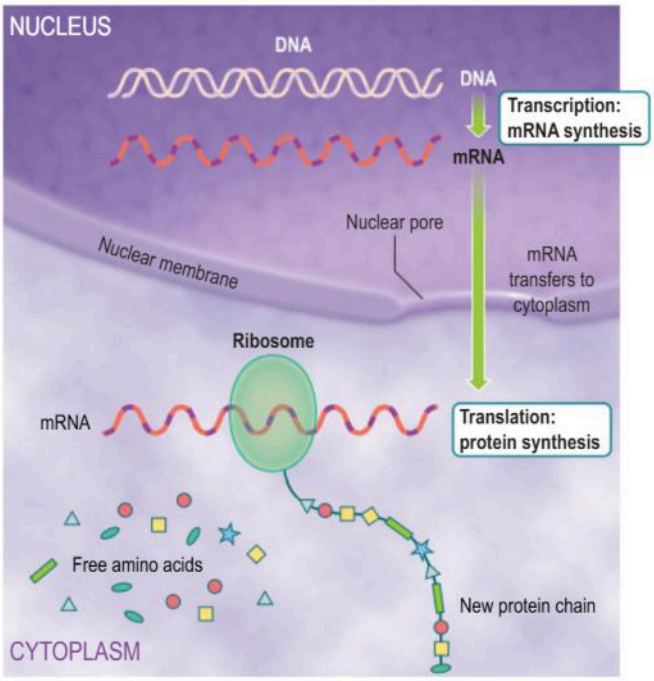

Figure 17.5 The relationship between DNA, RNA and protein synthesis.

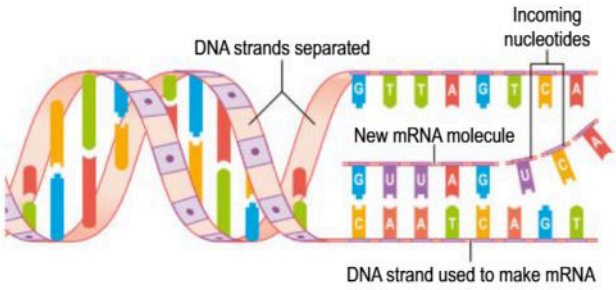

Figure 17.6 Transcription: mRNA synthesis in the nucleus.

guanine is added to the mRNA molecule (and vice versa); if it is thymine, adenine is added; if it is adenine, uracil is added (remember there is no thymine in RNA, but uracil instead). When the enzyme reaches a 'stop' signal on the gene, it stops synthesis of the mRNA molecule, and the mRNA is released. The DNA is zipped up again and recoiled by other enzymes and the mRNA leaves the nucleus.

Translation (Fig. 17.7)

Translation is synthesis of the final protein using the information carried on mRNA. It takes place on free ribosomes in the cytoplasm and those attached to rough endoplasmic reticulum. First, the mRNA attaches to the ribosome. The ribosome then 'reads' the base sequence of the mRNA.

Proteins are built from up to 20 different amino acids and so it is not possible to use the four bases individually in a simple one-to-one code. To give enough options, the

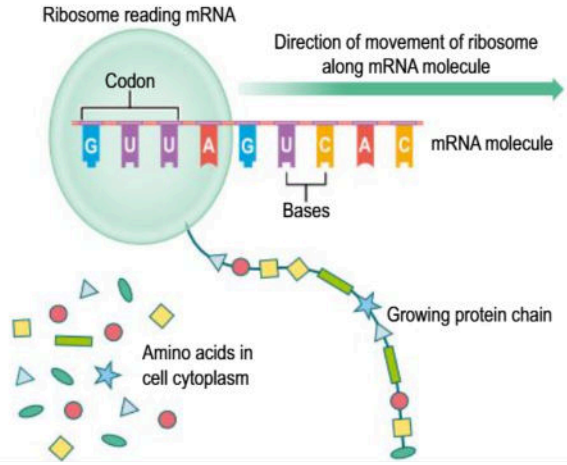

Figure 17.7 Translation: protein synthesis in the cytoplasm.

base code in RNA is read in triplets, giving a possible 64 base combinations, which allows a coded instruction for each amino acid as well as other codes, e.g. stop and start instructions. Each of these specific triplet sequences is called a codon; e.g. the base sequence ACA (adenine, cytosine, adenine) codes for the amino acid cysteine.

The first codon is a start codon, which initiates protein synthesis. The ribosome slides along the mRNA, reading the codons and adding the appropriate amino acids to the growing protein molecule as it goes. The ribosome continues assembling the new protein molecule until it arrives at a stop

codon, at which point it stops synthesis and releases the new protein. Some new proteins are used within the cell itself and others are exported, e.g. insulin synthesised by pancreatic β-islet cells is released into the bloodstream.

Gene expression in different tissues

Although all nucleated cells (except gametes) have an identical set of genes, each cell type uses only those genes related directly to its own particular function. For example, the only cell type containing haemoglobin is the red blood cell, although all body cells carry the haemoglobin gene. This selective gene expression ensures cells only produce the proteins required for their own specialised function, and the genes not needed are kept switched off.

SPOT CHECK

3. If the base sequence of a portion of DNA is ATTGAC, what will the base sequence be on the corresponding RNA?
4. What is the name given to a triplet sequence of three bases on an RNA molecule, which codes for a specific amino acid?

Cell division

Learning outcomes

After studying this section, you should be able to:

- explain the mechanism of DNA replication
- compare and contrast the processes of mitosis and meiosis
- describe the basis of genetic diversity from generation to generation.

Most body cells are capable of division, even in adulthood. Cell division usually produces two identical diploid daughter cells by the process of mitosis and is important in body growth and repair. Production of gametes, the ova in the female and sperm cells in the male, is different in that the daughter cells have only half the normal chromosome number: 23 instead of 46, i.e. they are haploid. Gametes are produced by a form of cell division called meiosis. DNA replication takes place before mitosis and meiosis.

DNA replication

DNA is the only biological molecule capable of self-replication. Mistakes in copying may lead to production of non-functioning or poorly functional cells, or cells that do not respond to normal cell controls (this could lead to the development of a tumour). Accurate copying of DNA is therefore essential.

The initial step in DNA replication is the unfolding of the double helix and the unzipping of the two strands to expose the bases, as happens in transcription (see above). Both strands of the parent DNA molecule are copied. The enzyme responsible for DNA replication moves along the base sequence on each strand, reading the genetic code and adding the complementary base to the newly forming chain. This means that each strand of opened bases becomes a double strand and the end result is two identical DNA molecules (Fig. 17.8). As each new double strand is formed, other enzymes twist and coil it back into its normal highly folded form.

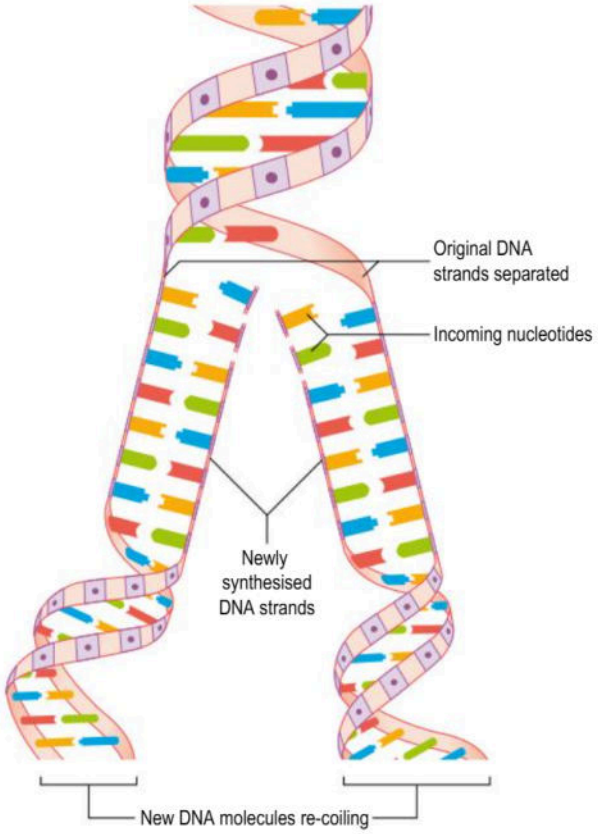

Figure 17.8 DNA replication.

Mitosis

This is described on page 48.

Meiosis

Meiosis produces sperm cells and ova, which carry the haploid number of 23 chromosomes. On fertilisation, when the sperm cell and the ovum unite, the resulting zygote is therefore diploid with 46 chromosomes.

Unlike mitosis, meiosis involves two distinct cell divisions rather than one (Fig. 17.9). Additionally, meiosis produces four daughter cells, not two, all different from the parent cells and from each other. This is the basis of genetic diversity and the uniqueness of each human individual.

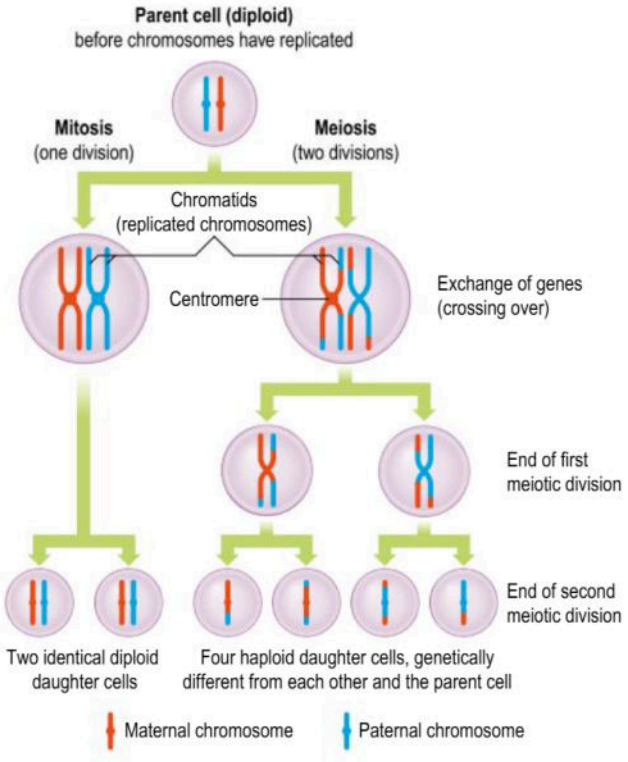

Figure 17.9 Mitosis and meiosis. For clarity, only one pair of chromosomes is shown.

First meiotic division

This stage (Fig. 17.9) produces two genetically different daughter cells.

DNA replication occurred beforehand, so there are now 92 chromosomes instead of the usual 46, and each pair of chromosomes is now four chromatids (a chromatid is a replicated chromosome). The four chromatids gather together into a tight bundle, making it possible for them to exchange genes. This process is called crossing over, and results in the four chromatids acquiring different combinations of genes. Following crossing over, the pairs of chromosomes then separate in preparation for the first meiotic division, and transfer of maternal and paternal chromosomes to either daughter cell is random. This means that the two daughter cells have an unpredictable assortment of maternal and paternal DNA, giving rise to a huge number of possible combinations of chromosomes. This explains why a child inherits a combination of the mother's and father's characteristics and why children of the same parents can be very different from one another.

Guided by spindle fibres, the homologous pairs of chromosomes now travel to one or other end of the cell, so that each half of the cell now has 23 chromosomes. When this cell divides, it, produces two genetically unique haploid daughter cells.

Second meiotic division

For a gamete to be produced, the amount of genetic material present in the two daughter cells following the first meiotic division must be halved. This is accomplished by the second division (Fig. 17.9). The centromeres separate and, guided by a cell spindle, the two sister chromatids of each replicated chromosome travel to opposite ends of the cell, which then divides. Each of the four haploid daughter cells now has only one chromosome from each original pair, and they are all different from the original parent cell. Fusion with a gamete from the opposite sex creates a zygote (fertilised ovum), a diploid cell that can go on to grow and develop into a human being by mitosis.

SPOT CHECK

5. Why are gametes haploid?
6. What is crossing over in genetics?

The genetic basis of inheritance

Learning outcomes

After studying this section, you should be able to:

- describe the basis of autosomal inheritance, including the relevance of recessive and dominant genes
- explain how sex-linked characteristics are passed from one generation to the next.

Mixing up of parental genes during meiosis leads to the huge genetic variety of the human race. It is important to understand how genes interact to produce inherited characteristics. The set of genes carried by an individual is their genotype, and the physical, behavioural, physiological and biochemical characteristics they produce, e.g. hair colour, finger length or blood group is called the phenotype. Most phenotypic traits are determined by the interaction of several genes: for example, around 16 different genes are thought to be involved in determining eye colour.

Autosomal inheritance

Each one of a pair of autosomal chromosomes (i.e. pairs 1–22) contains a matching sequence of genes along their length. This means that every nucleated body cell (except gametes) has two copies of every gene. For example, the gene that codes for insulin is found on the short arm of chromosome 11 on both chromosomes of the pair (Fig. 17.10). Such paired genes are called alleles. Corresponding alleles contain genes concerned with the same trait, but they need not be identical. An individual may have:

- two identical alleles (homozygous)
- two different alleles (heterozygous).

Not all alleles are equally likely to be expressed, i.e. used to synthesise the gene protein. An allele that is preferentially

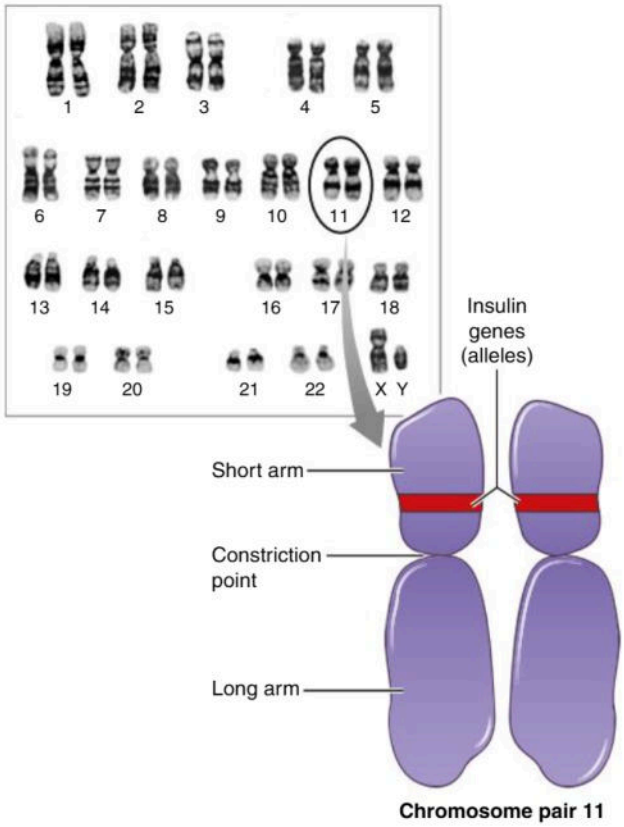

Figure 17.10 Chromosome pair 11, showing the paired genes (alleles) for insulin.

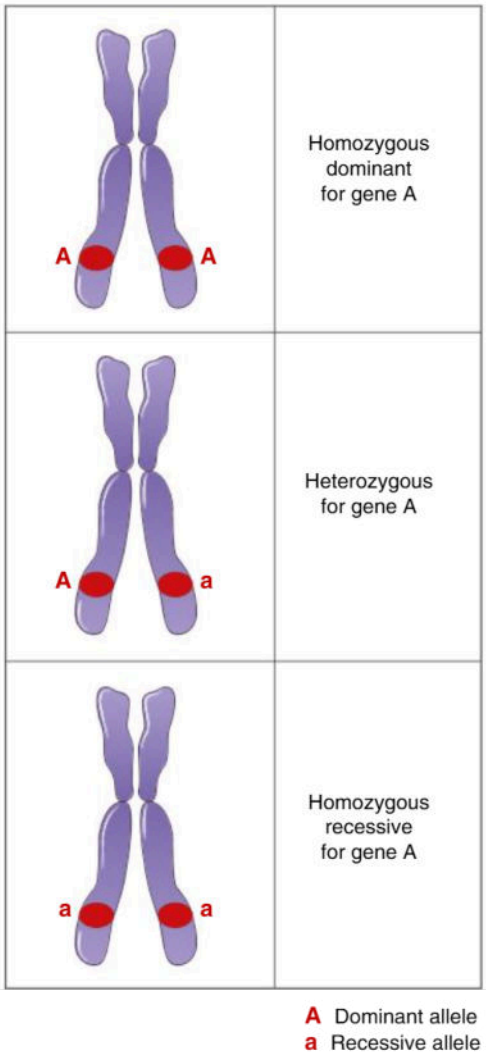

Figure 17.11 Genetic terminology for a hypothetical gene A. A: dominant allele; a: recessive allele.

expressed over another is called dominant, and an allele that is not expressed is called recessive. Individuals homozygous for a gene have two identical copies, of either the dominant or the recessive form. Heterozygous individuals have one dominant and one recessive gene. In genetic notation, dominant genes are represented by a capital letter and recessive genes with a lower-case letter. Figure 17.11 illustrates this terminology for a hypothetical gene A.

Because a dominant gene is always expressed over a recessive one, only one copy is needed for its characteristic to be expressed. Dominant genes are usually more common than their recessive forms, and usually code for normal, healthy protein products. Recessive genes are generally less common, and their characteristics can only be expressed in an individual if both alleles are of the recessive form (homozygous recessive). Recessive genes may be harmless, but may also be mutant forms of a gene associated with inherited disease.

Punnett squares

The probability of a child inheriting either form of a gene depends on the genotypes of the parents. Simple autosomal inheritance can be illustrated using a Punnett square. Punnett squares show all possible genotype combinations of offspring from two parents whose genotypes are known. To construct a Punnett square, the parents' genotypes are written down two sides of the square and the possible combinations of these genes then written inside the square. Figure 17.12 shows all the possible combinations of gene A in children whose parents are heterozygous for the gene, meaning both parents have a copy of each of the dominant (A) and recessive (a) alleles. Using this example, there is a 1 in 4 (25%) chance that a child of these parents will be homozygous dominant (AA), a 50% chance that they will be heterozygous (Aa) and a 1 in 4 chance that they will be homozygous recessive (aa).

Some important genetic diseases, e.g. cystic fibrosis (p. 295) and sickle cell anaemia (p. 79) are inherited via a single mutant recessive gene, and understanding the inheritance patterns of such disorders is essential in genetic counselling.

Co-dominance

For some traits, there can be more than two alleles that code for it, and more than one allele can be dominant. An example of this is the inheritance of A and B type antigens

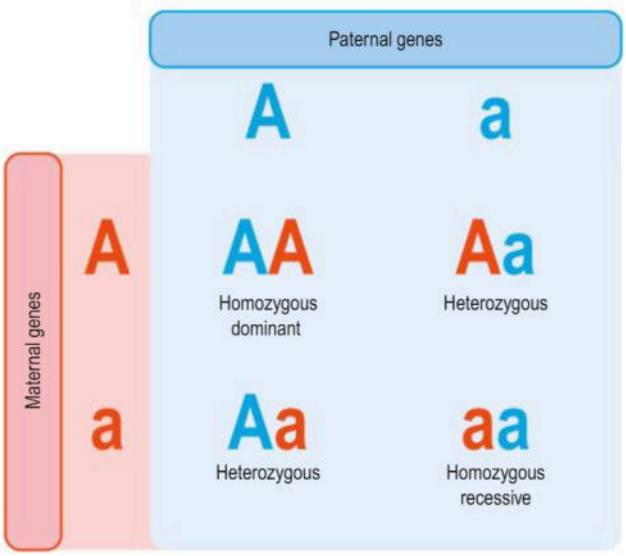

Figure 17.12 Autosomal inheritance. All possible combinations of gene A in children of parents heterozygous for the gene are shown.

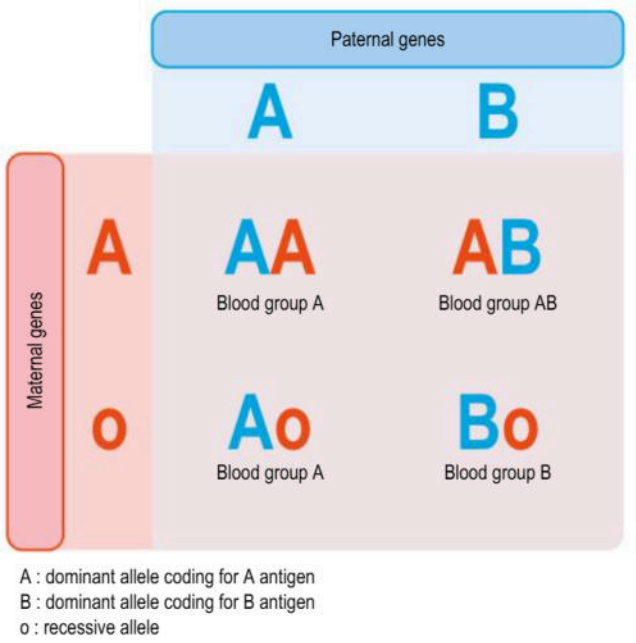

Figure 17.13 Co-dominant inheritance of ABO blood groups

on the surface of red blood cells, determined clinically as the ABO system of blood grouping (p. 70). There are three possible alleles here: one allele codes for production of A type antigens (A), one allele codes for production of B type antigens (B) and a third allele codes for no antigen at all (O). An individual may have any combination of two of these three alleles: AA, AB, BB, AO, BO or OO. Both A and B are dominant, and both express themselves wherever they are present. This is called co-dominance. O is recessive, and so only expresses itself in a homozygous recessive genotype. This means that individuals with an OO genotype have neither A nor B antigens on their red cell surface and are blood group O. An individual with genotype AB has both A and B and is blood group AB. An individual with genotype AO or AA has only A type antigens and is blood group A; someone with genotype BO or BB has only B type antigens and is blood group B.

Figure 17.13 shows a Punnett square illustrating the possible blood types of children produced by a mother with genotype AO (phenotype blood group A) and a father with genotype AB (phenotype blood group AB).

Sex-linked inheritance

Figure 17.4 shows clearly that the Y chromosome is much smaller than the X chromosome. It is not surprising, then, to find that the Y chromosome carries only 55 genes compared with the X chromosome's 900. Most of the genes on the Y chromosome are involved in the development of male-specific characteristics. Because it is so much longer than the Y chromosome, the vast majority of genes on the X chromosome do not have a corresponding allele on the Y. This means that a male has only one copy of most of the genes on his sex chromosomes. Traits coded for on the section of the X chromosome that has no corresponding material on the Y are said to be sex-linked. The gene that codes for normal colour vision is one example and is carried on X chromosomes only. It is the dominant form of the gene. There is a rare, recessive form of this gene, which is faulty and codes for red–green colour blindness. If a female inherits a faulty, recessive copy of the gene, she is statistically likely to have a normal, dominant gene on her other X chromosome, giving normal colour vision. A female carrying the colour blindness gene, even though she is not colour-blind, may pass the faulty gene on to her children and is said to be a carrier. If a male inherits the recessive gene on the X chromosome he inherits from his mother, he will be colour-blind because there is no corresponding allele on his Y chromosome and so the recessive gene expresses itself. Inheritance of colour blindness is shown in Figure 17.14. This illustrates the possible genetic combinations of the children of a carrier mother (one normal dominant gene and one faulty recessive gene) and a normal father (one normal dominant gene). In this example, sons have a 50% chance of being colour-blind and a 50% chance of having normal vision, and daughters have a 50% chance of being a carrier (with normal vision) and a 50% chance of being normal.

SPOT CHECK

7. If the father is homozygous for the tongue-rolling gene and the mother is heterozygous, what is the chance that their child will be able to roll their tongue?
8. If a child's parents are both blood group O, what is the child's chance of being blood group A?

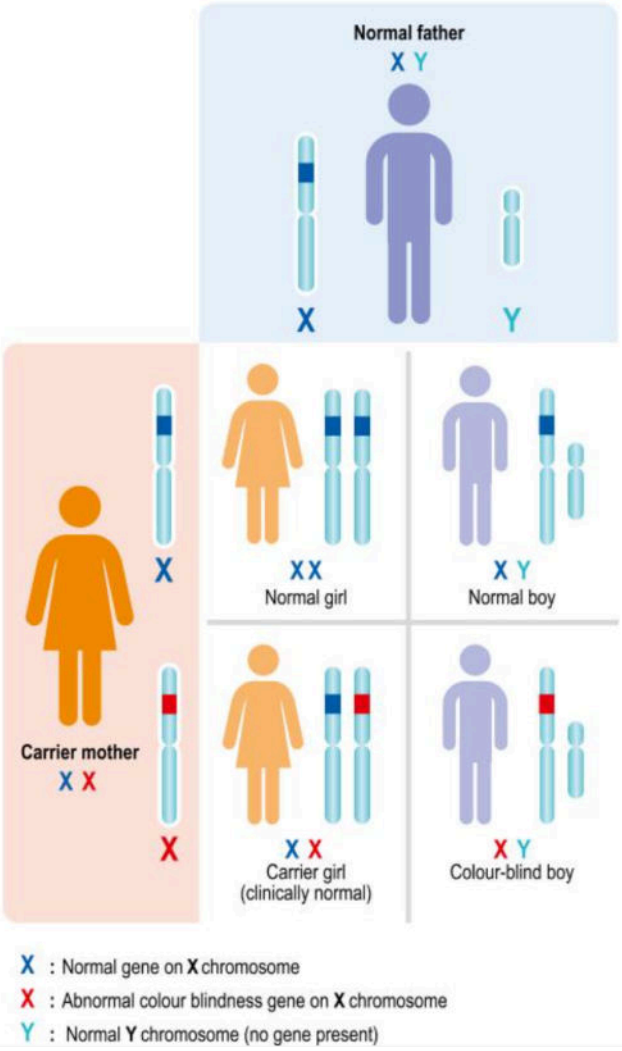

Figure 17.14 Inheritance of sex-linked red–green colour blindness

Ageing and genetics

Learning outcomes

After studying this section, you should be able to:

- describe the main effects of ageing on the genetic material of cells
- outline the genetic mechanisms of senescence.

Ageing and DNA

Cumulative exposure over a lifetime to potential mutagens, as well as a diminishing ability to repair DNA, means a cell's genome gradually accumulates mutations, which can lead to impaired function and increased risk of disease, e.g. cancer. Mitochondrial DNA is more prone to mutations than nuclear DNA and as it ages and develops 'wear and tear' damage, cell function progressively declines, contributing significantly to the ageing process.

Cell senescence (ageing)

The number of times a cell can divide is somewhere between 50 and 60 divisions. One important factor in this is thought to relate to the effects of ageing on telomerase function. Telomerase is the enzyme that repairs the telomeres (chromosome tips) following DNA replication. It declines in function with age. This restricts the number of cell replications possible, since without effective telomerase activity the chromosomes become progressively shorter with each division; they eventually become too short to be replicated and the cell can no longer divide.

Genetic basis of disease

Learning outcomes

After studying this section, you should be able to:

- outline the link between cancer and cell mutation
- distinguish between genetic disorders caused by gene mutation and chromosomal abnormalities, giving examples of each.

An individual's genetic makeup is one of the major determinants of health. In some cases, a particular genotype has inevitable or major consequences: for example, trisomy 21 (three copies of chromosome 21 instead of the normal 2) is the direct cause of Down's syndrome (see below). In many cases, however, although inheritance contributes to the risk of disease, it is impacted by a wide range of other factors, including social, behavioural and environmental influences. Genetic abnormalities may involve one or more individual genes or may be due to faults at the chromosomal level, for example inheriting more or fewer than the normal complement of 46 chromosomes.

Cancer

Cancer (malignant growth of new tissue, p. 59) is caused by mutation of cellular DNA, causing its growth pattern to become disorganised and uncontrolled.

Cells acquire increasing numbers of mutations as they get older, which explains why the incidence of cancer rises sharply with increasing age (see Fig. 3.31). The more mutations a cell suffers, the more likely it is to develop the characteristics of a tumour cell, including failure to respond to normal growth controls and acquisition of immortality. Some mutations are inherited, increasing the risk of some cancers in families, but most cancer is due to acquired mutations caused by ageing or other risk factors, such as irradiation or exposure to mutagenic chemicals (see also p. 60). Mutated genes capable of triggering the abnormal cell growth of cancer are called oncogenes.

Inherited disease

Box 17.1 lists a number of diseases with an inherited component.

Gene mutations

Many diseases, such as cystic fibrosis (p. 295) and haemophilia (p. 83), are passed directly from parent to child via a single faulty gene. Many of these genes have been located by mapping of the human genome, e.g. the gene for cystic fibrosis is carried on chromosome 7. Other diseases, e.g. asthma, some cancers and cardiovascular disease, have a genetic component (run in the family). In these cases, multiple faulty genes are likely to contribute to the disease process, and inheritance is not as predictable as when a single gene is responsible. The likelihood of an individual developing the disease depends not only on their genetic make-up but also on the influence of other factors, such as lifestyle and environment.

Box 17.1 Some disorders with an inherited component

Single gene disorders

- Phenylketonuria
- Duchenne muscular dystrophy (p. 483)
- Huntington disease
- Haemophilia (p. 83)
- Achondroplasia (p. 480)
- Some cancers, including a proportion of breast, ovarian and bowel cancers
- Myotonic dystrophy
- Cystic fibrosis (p. 295)
- Polycystic kidney disease (p. 395)

More complex inheritance

More than one gene is likely to be involved, leading to increased susceptibility and 'running in families'. Lifestyle and other factors are also involved in determining risk.

- Asthma (p. 294)
- Cleft lip (p. 356)
- Hypertension (p. 141)
- Atheroma (p. 130)
- Some cancers, e.g. some breast and gastric cancers
- Types 1 and 2 diabetes mellitus (p. 261)
- Epilepsy
- Schizophrenia
- Neural tube defects, e.g. spina bifida (p. 208)

Phenylketonuria

This is an example of an inborn error of metabolism. The gene responsible for producing the enzyme phenylalanine hydroxylase is faulty and the enzyme is absent. Phenylalanine hydroxylase normally converts the amino acid phenylalanine to tyrosine in the liver, but in its absence phenylalanine accumulates in the liver and overflows into the blood (Fig. 17.15). In high quantities, phenylalanine is toxic to the central nervous system and, if the condition is untreated, rising phenylalanine levels lead to brain damage and impaired cognitive development, obvious within a few months of birth when the child fails to meet developmental milestones. Tyrosine levels are low, and because tyrosine is needed to make melanin, depigmentation occurs and affected children are fair-skinned and blond. The incidence of this disease is now low in developed countries because screening of newborn babies detects the condition and treatment is provided.

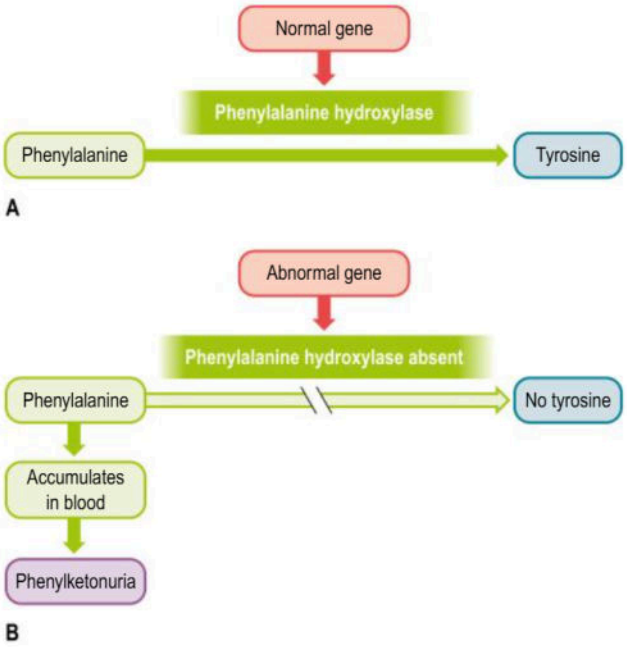

Figure 17.15 Phenylketonuria. (A) Gene function normal. (B) Abnormal gene.

Mitochondrial abnormalities

Mitochondrial DNA contains only 37 genes but defects in these genes can cause potentially fatal inherited disorders with a very wide range of signs and symptoms, most commonly involving the central nervous system and skeletal or cardiac muscle. Spontaneous mutations in this DNA can also occur in maturity, leading to onset of disease in adults. There is evidence that mitochondrial mutations may be associated with some forms of important diseases, e.g. diabetes mellitus, Parkinson's disease and Alzheimer's disease.

Chromosomal abnormalities

Sometimes a fault in separation of chromosomes during meiosis produces a gamete carrying abnormal chromosomes: too many, too few, abnormally shaped or with segments missing. Often, these aberrations are lethal and a pregnancy involving such a gamete miscarries in the early stages. Non-lethal conditions include Down's syndrome and cri-du-chat syndrome.

Down's syndrome

In this disorder, there are three copies of chromosome 21 (trisomy 21), meaning that an extra chromosome is present, caused by failure of chromosomes to separate normally during meiosis. Individuals with Down's syndrome are usually short of stature, with pronounced eyelid folds and flat, round faces. The tongue may be too large for the mouth and protrude. Learning disability is present, ranging from mild to severe. Life expectancy is shorter than normal, with an above average incidence of cardiovascular and respiratory disease, and a high incidence of early dementia. Down's syndrome is associated with increasing maternal age, especially over 35 years.

Cri-du-chat syndrome

Cri-du-chat (cat's cry) refers to the characteristic meowing cry of an affected child. This syndrome is caused when part of chromosome 5 is missing, and is associated with learning disabilities and anatomical abnormalities, including gastrointestinal and cardiovascular problems.

Abnormalities of the sex chromosomes

If the sex chromosomes fail to separate normally during meiosis, the daughter cells will have an incorrect number: either too many or too few. A child born with such an abnormality will not follow normal sexual development without treatment and may have additional problems such as learning disability.

Turner's syndrome

This is usually associated with having only one sex chromosome, an X, as well as 22 normal pairs of autosomes. The karyotype is therefore usually XO and affected individuals are female. They have female external genitalia and ovaries but are infertile because the ovaries fail to develop during fetal life, and secondary sexual characteristics do not develop at puberty unless oestrogen treatment is given. Other features include short stature and sometimes coarctation of the aorta (in 15%, p. 141). Intelligence is usually normal.

Klinefelter's syndrome

The karyotype in this condition is XXY, so affected individuals are male, with 47 chromosomes instead of 46. This condition is more common than Turner's syndrome and is associated with a greater than average height and mild learning disability. The genitalia are male but the testes are underdeveloped and affected individuals are infertile. At puberty, development of feminine characteristics such as enlarged breasts (gynaecomastia) and rounded hips is common, and there is no development of male secondary sexual characteristics unless testosterone treatment is given.

SPOT CHECK

9. What is an oncogene?
10. Describe the genetic basis of phenylketonuria.

References and further reading

Turnpenny P, Ellard S, 2017. Emery's Elements of Medical Genetics, 15th ed. Elsevier.

Case study

Calum is a genetic counsellor in a busy city hospital. Today he has an appointment with Susanna and Ismail, who are planning to start a family. Susanna has an aunt with the inherited disorder cystic fibrosis and wants to know what the risk is of any of their children having this disease.

1. Cystic fibrosis is an autosomal recessive disease. Which of the following is true?

   a. The disease is much more common in boys than girls.
   b. The faulty gene is carried on one of the chromosome pairs 1–22.
   c. An individual needs to carry only one copy of the faulty gene to have the disease.
   d. Cystic fibrosis can only be inherited from the mother.

2. Calum has drawn up the Punnett square below to explain the genetics of the situation to Susanna and Ismail. *C*, normal gene; *c*, faulty gene coding for cystic fibrosis. Which term describes Ismail's genotype?

		Ismail	
		C	C
Susanna	C		
	c		

   a. Homozygous recessive
   b. Heterozygous
   c. Homozygous dominant
   d. Carrier

3. Which term(s) describes Susanna's genotype?

   a. Homozygous recessive
   b. Heterozygous
   c. Homozygous dominant
   d. Carrier

4. Complete the Punnett square to show all possible genotypes for the cystic fibrosis gene in children of this couple. Which of the following statements would be correct advice for Calum to give Susanna and Ismail?

   a. There is no chance of any child of theirs having cystic fibrosis.
   b. There is a 50% chance of a child having cystic fibrosis.
   c. There is a 25% chance of a child having cystic fibrosis.
   d. There is a 75% chance of a child having cystic fibrosis.

Review and revise

Complete the following statement:

1. The disorder phenylketonuria is inherited as a _____ _____ disorder and is characterised by a lack of the enzyme _____ _____. This enzyme converts _____ to _____, and in its absence the former substance accumulates in the blood and is toxic to the _____ system.

Choose one answer to complete each of the following statements:

2. This cell type is haploid: _____
   a. Erythrocyte
   b. Ovum
   c. Nerve cell
   d. Cancer cell

3. A codon is: _____
   a. Any sequence of DNA that codes for a protein
   b. The region of DNA being unzipped for replication
   c. An RNA molecule carrying information to a ribosome for protein synthesis
   d. A sequence of three DNA bases corresponding to a particular amino acid

4. The first meiotic division produces: _____
   a. Four genetically identical daughter cells
   b. Four genetically different daughter cells
   c. Two genetically different daughter cells
   d. Two genetically identical daughter cells

5. Match the items in List A with the relevant definition in List B.

List A

_____ (a) Allele
_____ (b) Gene
_____ (c) Chromosome
_____ (d) Chromatin
_____ (e) Genome
_____ (f) Chromatid

List B

1. All the genetic material within a cell
2. One form of a gene
3. The single strand of a replicated chromosome
4. A sequence of DNA coding for a specific protein
5. The cell's genetic material, dispersed between cell divisions
6. A long stretch of DNA carrying multiple genes and packaged around histones

6. Which of the following descriptions apply to DNA, which to RNA and which to both?
   1. Single-stranded _____
   2. Double-stranded _____
   3. Contains adenine _____
   4. Contains uracil _____
   5. Contains guanine _____
   6. Contains thymine _____
   7. Stored in the cell nucleus _____
   8. Translated on the ribosome _____
   9. Used for transcription _____
   10. Contains ribose _____

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

CHAPTER 18

The reproductive systems

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Review and revise 525

The ability to reproduce is one of the properties distinguishing living from non-living matter. The more primitive the animal, the simpler the process of reproduction. Mammals, including humans, reproduce sexually. The male and female reproductive organs differ anatomically and physiologically, and the new individual develops from the fusion of one male and one female sex cell (gamete). The male gametes are called spermatozoa (singular: spermatozoon) and the female gametes are called ova (singular: ovum).

The first sections of this chapter explain the structure and functions of the female and male reproductive systems, including the production of gametes. The next sections give a brief overview of fetal development at the different stages of pregnancy, and the effects of ageing on reproductive function. Finally, some significant reproductive disorders are described.

Female reproductive system

Learning outcomes

After studying this section, you should be able to:

- describe the main structures of the external genitalia
- explain the structure and function of the vagina
- describe the location, structure and function of the uterus and the uterine tubes
- discuss the process of ovulation and the hormones that control it
- outline the changes that occur in the female at puberty, including the physiology of menstruation
- describe the structure and function of the female breast.

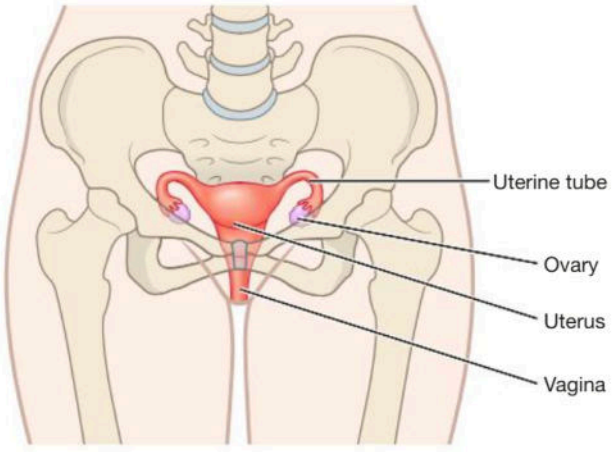

Figure 18.1 The female reproductive organs in the pelvis.

The functions of the female reproductive system are:

- formation of ova
- reception of spermatozoa
- provision of suitable environments for fertilisation and fetal development
- parturition (childbirth)
- lactation, the production of breast milk, which provides complete nourishment for the baby in its early life.

The female reproductive system is shown in Figure 18.1. The reproductive organs in the pelvis are called the genitalia and include both external and internal structures. Additionally, the female breast is considered an accessory organ of reproduction.

External genitalia (vulva)

The external genitalia (Fig. 18.2) are collectively called the vulva, and include the labia majora and labia minora, the clitoris, the vaginal orifice, the vestibule, the hymen and the vestibular glands (Bartholin's glands).

Labia majora

These two large folds form the boundary of the vulva. They are composed of fibrous tissue and fat, covered in skin, and contain large numbers of sebaceous and eccrine sweat glands (Ch. 14). Anteriorly they join in front of the symphysis pubis, and posteriorly they merge with the skin of the perineum.

Labia minora

These are two smaller folds of skin between the labia majora, also containing numerous sebaceous and eccrine sweat glands. The cleft between the labia minora is the vestibule. The vagina, urethra and ducts of the greater vestibular glands open into the vestibule.

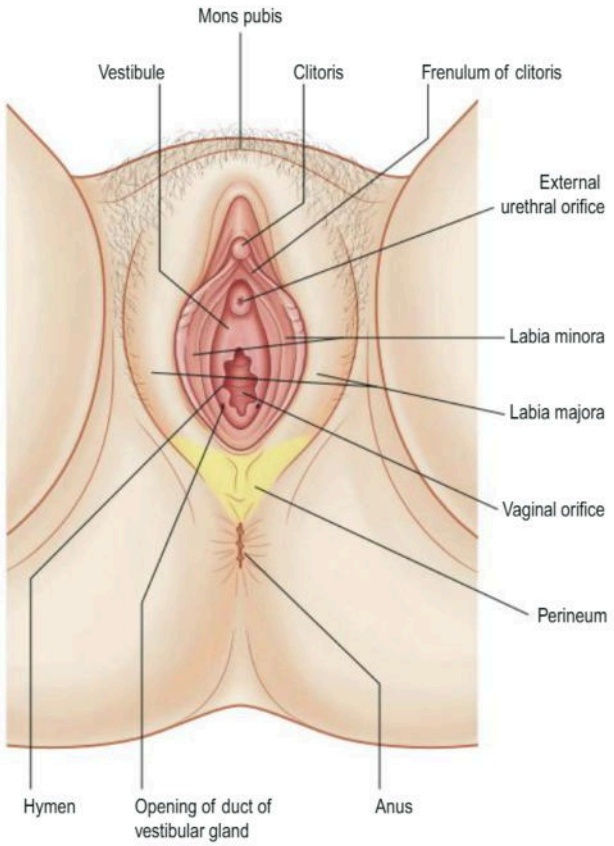

Figure 18.2 The female external genitalia.

Clitoris

The clitoris corresponds to the penis in the male and contains erectile tissue and sensitive sensory nerve endings important in female sexual pleasure.

Vestibular glands

The vestibular (Bartholin's) glands are situated one on each side near the vaginal opening. They are about the size of a small pea and their ducts open into the vestibule immediately lateral to the attachment of the hymen. They secrete mucus that keeps the vulva moist.

Perineum

The perineum is a roughly triangular area extending from the base of the labia minora to the anal canal. It consists of connective tissue, muscle and fat, and gives attachment to the muscles of the pelvic floor (see Fig. 16.69).

Blood supply, lymph drainage and nerve supply

The arteries supplying the external genitalia are branches of the internal pudendal arteries, arising from the internal iliac arteries, and by the external pudendal arteries, which branch

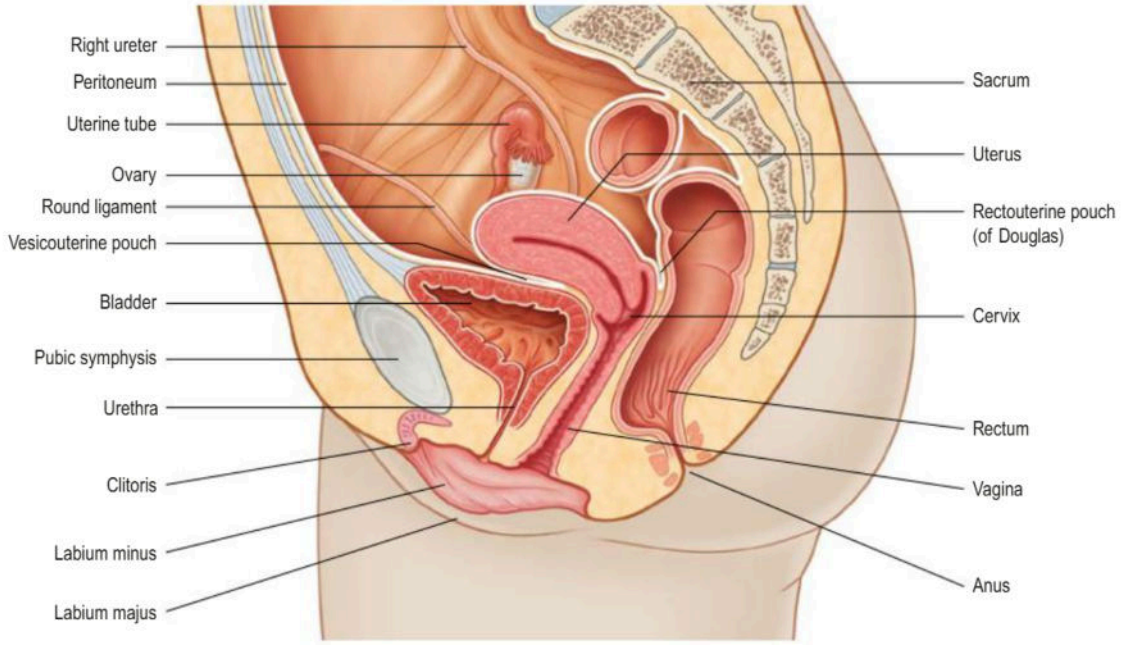

Figure 18.3 Lateral view of the female reproductive organs and their associated structures.

from the femoral arteries. Venous blood eventually drains into the internal iliac veins. Lymphatic drainage is through the superficial inguinal nodes (see Fig. 6.1), and nerve supply is by branches of the pudendal nerves.

Internal genitalia

The internal female reproductive organs (Figs 18.3 and 18.4) lie in the pelvic cavity and include the vagina, uterus, two uterine tubes and two ovaries.

Vagina

The distal end of the vagina opens into the vestibule, and the uterine cervix protrudes into its proximal end. It runs obliquely upwards and backwards at an angle of about 45 degrees between the bladder in front and the rectum and anus behind. In the adult, the anterior wall is about 7.5 cm long and the posterior wall about 9 cm long. The difference is because the cervix inserts at an angle through the anterior wall.

Hymen

The hymen is a thin layer of mucous membrane stretched across the vaginal lumen, just inside the external opening. It is normally incomplete to allow for passage of menstrual flow and is stretched or torn away by sexual intercourse, insertion of a tampon or childbirth.

Structure

The vagina is a fibromuscular tube lined with stratified squamous epithelium. Its wall has three layers: an outer covering of areolar tissue, a middle layer of smooth muscle and an inner lining of stratified squamous epithelium forming ridges or rugae, which allow the vagina to expand during childbirth. It has no secretory glands but the surface is kept moist by cervical secretions. Between puberty and the menopause, *Lactobacillus acidophilus*, a bacterium that secretes lactic acid, is normally present, maintaining vaginal pH between 4.9 and 3.5. The acidity inhibits the growth of most other microorganisms that may contaminate the vagina from the perineum or during sexual intercourse.

Blood supply, lymph drainage and nerve supply

Arterial blood to the vagina is supplied by the uterine and vaginal arteries, which branch from the internal iliac arteries. Venous blood drains into the internal iliac veins. Lymph drainage is through the deep and superficial iliac nodes (see Fig. 6.1). Its nerve supply consists of parasympathetic fibres from the sacral outflow, sympathetic fibres from the lumbar outflow and somatic sensory fibres from the pudendal nerves.

Functions

The vagina receives the penis during sexual intercourse (coitus) and provides an elastic passageway through which the baby passes during childbirth.

Uterus

The uterus is a hollow, muscular, pear-shaped organ lying in the pelvic cavity between the urinary bladder and the rectum (Fig. 18.3). It is about 7.5 cm long and 5 cm wide, and its walls are about 2.5 cm thick. It weighs between 30 and 40 g.

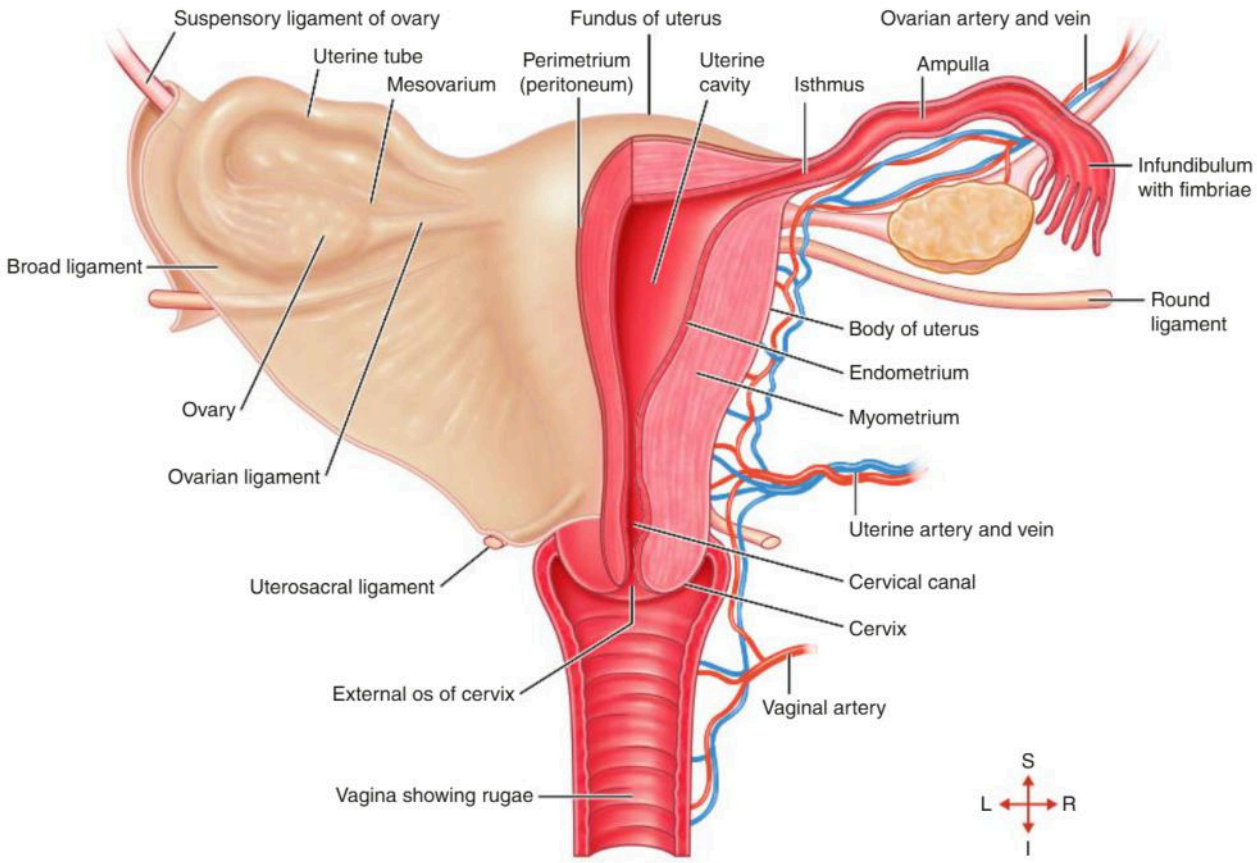

Figure 18.4 The female reproductive organs in the pelvis: anterior view.

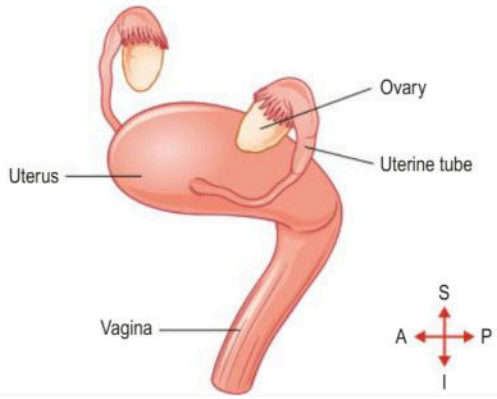

Figure 18.5 Normal positions of the female reproductive organs, showing anteversion and anteflexion of the uterus.

In most women the uterus lies almost horizontally. It leans forwards (anteversion) and is bent forwards (anteflexion) almost at right angles to the vagina (Fig. 18.5), so that its anterior wall rests partly against the bladder below, forming the vesicouterine pouch between the two organs. The three main parts are the fundus, body and cervix (Fig. 18.4). The fundus is the dome-shaped part above the openings of the uterine tubes. The body occupies the upper two-thirds of the uterus. It is pear-shaped, and narrowest inferiorly at the internal os, where it is continuous with the cervix. The cervix (neck) is the narrowest portion and is usually about 2.5 cm long. It protrudes through the anterior wall of the vagina, opening into it at the external os.

Structure

The walls of the uterus are composed of three layers of tissue: perimetrium, myometrium and endometrium (Fig. 18.6).

Perimetrium

This is peritoneum, which is distributed differently on the various surfaces of the uterus (Fig. 18.4). It can be imagined as a blanket draped over the uterus, uterine tubes and ovaries from above, so it mainly covers the anterior, upper and posterior surfaces of the uterus.

Anteriorly, it lies over the fundus and the body, where it folds on to the upper surface of the urinary bladder. This fold of peritoneum forms the vesicouterine pouch.

Posteriorly, the peritoneum covers the fundus, the body and the cervix, then it folds back on to the rectum to form the rectouterine pouch (of Douglas).

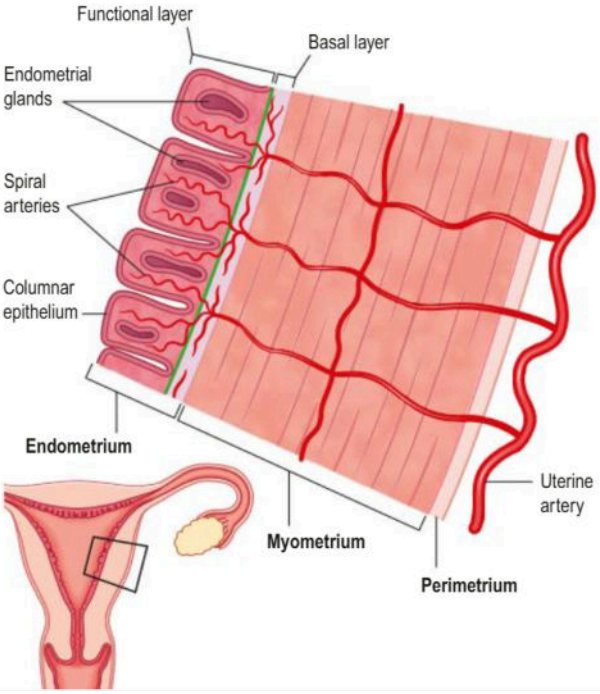

Figure 18.6 Layers of the uterine wall. Green line represents the boundary between the functional and basal layers of the endometrium.

Laterally, only the fundus is covered because the peritoneum forms a double fold with the uterine tubes in the upper free border. This double fold is the broad ligament, which, at its lateral ends, attaches the uterus to the sides of the pelvis.

Myometrium

This is the thickest layer of tissue in the uterine wall. It is a mass of smooth muscle fibres interlaced with areolar tissue, blood vessels and nerves.

Endometrium

This is columnar epithelium covering a layer of connective tissue containing abundant mucus-secreting tubular glands. It is richly supplied with blood by spiral arteries, branches of the uterine artery. It is divided into two layers:

- The superficial functional layer thickens and becomes rich in blood vessels in the first half of the menstrual cycle. If the ovum is not fertilised and does not implant, this layer is shed during menstruation.
- The deeper basal layer is the permanent layer and lies between the functional layer and the myometrium. It is not lost during menstruation and regenerates a fresh functional layer during each cycle.

The upper two-thirds of the cervical canal is lined with the same mucous membrane that lines the uterus. Lower down, however, the mucosa changes, becoming stratified squamous epithelium, which merges with the lining of the vagina itself.

Blood supply, lymph drainage and nerve supply

Arterial supply is by the uterine arteries, branches of the internal iliac arteries. They pass up the lateral aspects of the uterus between the two layers of the broad ligaments and supply the uterus and uterine tubes. They then join with the ovarian arteries to supply the ovaries. Corresponding veins follow the same route as the arteries and eventually drain venous blood into the internal iliac veins. Lymphatic drainage is by deep and superficial vessels from the uterus and the uterine tubes, and then to the aortic lymph nodes and groups of nodes associated with the iliac blood vessels. The nerves supplying the uterus and the uterine tubes consist of parasympathetic fibres from the sacral outflow and sympathetic fibres from the lumbar outflow.

Supporting structures

The uterus is supported in the pelvic cavity by surrounding organs, muscles of the pelvic floor and ligaments that suspend it from the walls of the pelvis (Fig. 18.7).

Broad ligaments

These are formed by a double fold of peritoneum, one on each side of the uterus. They hang down from the uterine tubes as though draped over them and their lateral ends are attached to the sides of the pelvis. The uterine tubes are enclosed in the upper free border and near the lateral ends they penetrate the posterior wall of the broad ligament and open into the peritoneal cavity. The ovaries are attached to the posterior wall, one on each side. Blood and lymph vessels and nerves pass to the uterus and uterine tubes between the layers of the broad ligaments.

Round ligaments

These are bands of muscular and fibrous tissue between the two layers of broad ligament, one on each side of the uterus. They pass to the sides of the pelvis, then through the inguinal canal, and fuse with the labia majora.

Uterosacral ligaments

These originate from the posterior walls of the cervix and vagina and extend backwards, one on each side of the rectum, to the sacrum.

Transverse cervical (cardinal) ligaments

These extend one from each side of the cervix and vagina to the side walls of the pelvis.

Pubocervical ligament

This extends forward from the transverse cervical ligaments on each side of the bladder and is attached to the posterior surface of the pubic bones.

Functions

After puberty, the endometrium goes through a regular monthly cycle of changes, the menstrual cycle, under the control of hypothalamic and anterior pituitary hormones

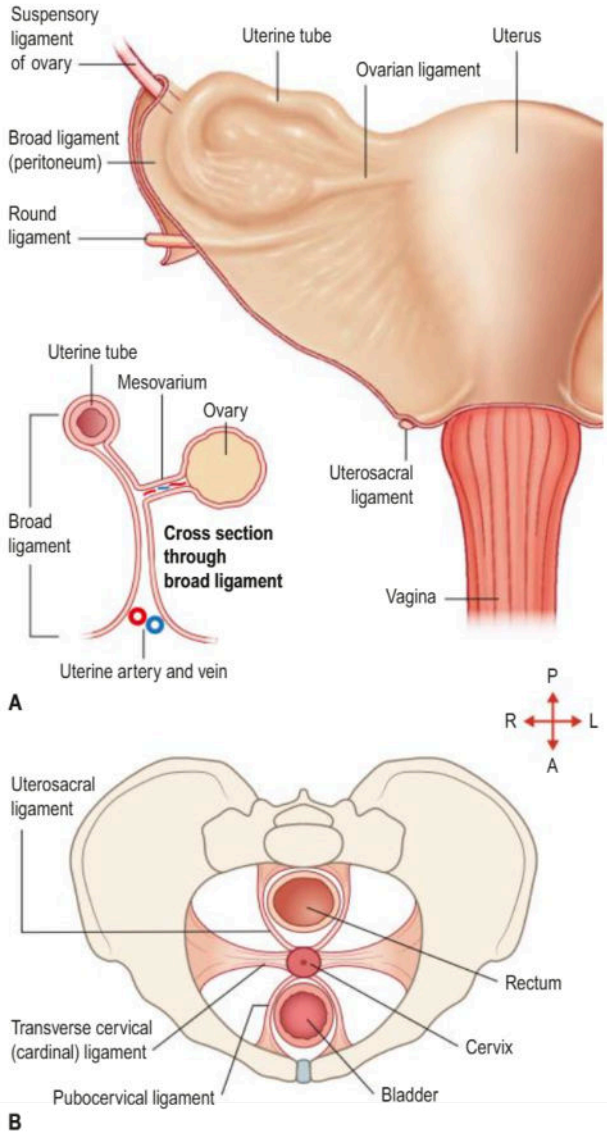

Figure 18.7 The main ligaments supporting the uterus. (A) Anterior and lateral views. (B) The pelvic floor, viewed from above.

(Ch. 9). The menstrual cycle prepares the uterus to receive, nourish and protect a fertilised ovum. If the ovum is not fertilised, the functional layer of the uterine lining is shed, and a new cycle begins with a short period of vaginal bleeding (menstruation).

If the ovum is fertilised, the zygote (p. 516) embeds itself in the uterine wall. The role of the uterus in a developing pregnancy is described below.

Uterine tubes

The uterine (Fallopian) tubes (Fig. 18.4) are about 10 cm long and extend from the sides of the uterus between the body and the fundus. They lie in the upper free border of the broad ligament and their trumpet-shaped lateral ends penetrate the posterior wall, opening into the peritoneal cavity close to the ovaries. The end of each tube has finger-like projections called fimbriae which extend around the ovary, but do not make direct contact.

Structure

The uterine tubes are covered with peritoneum (broad ligament), have a middle layer of smooth muscle and are lined with ciliated epithelium. Blood and nerve supply and lymphatic drainage are the same as for the uterus.

Functions

The fimbriae of the uterine tube ensure the ovum released at ovulation is channeled into the uterine tube, where it travels towards the uterus by peristalsis and ciliary action. The secretions of the uterine tube nourish both ovum and spermatozoa. Fertilisation of the ovum usually takes place in the uterine tube, and the zygote is propelled into the uterus for implantation.

Ovaries

The ovaries (Fig. 18.4) are the female gonads (glands producing sex hormones and the ova), and they lie in a shallow fossa on the lateral walls of the pelvis. They are 2.5–3.5 cm long, 2 cm wide and 1 cm thick. Each is attached to the upper part of the uterus by the ovarian ligament and to the back of the broad ligament by a broad band of tissue, the mesovarium. Blood vessels and nerves pass to the ovary through the mesovarium (Fig. 18.8).

Structure

The ovaries have two layers of tissue, the medulla and the cortex. The medulla is the inner part of the ovary and consists of fibrous tissue, blood vessels and nerves. The cortex surrounds the medulla. It has a framework of connective tissue called stroma covered by germinal epithelium. At birth, the stroma contains millions of ovarian follicles, each containing an immature ovum. During the childbearing years, about every 28 days, one or more ovarian follicle matures, ruptures and releases its ovum into the peritoneal cavity. This is called ovulation and it occurs during most menstrual cycles (Figs 18.8 and 18.9). Following ovulation the ruptured follicle develops into the corpus luteum (meaning 'yellow body'), which in turn leaves a small permanent scar of fibrous tissue called the corpus albicans (meaning 'white body') on the surface of the ovary.

Blood supply, lymph drainage and nerve supply

Arterial supply is by the ovarian arteries, which branch from the abdominal aorta just below the renal arteries. Venous blood drains into a plexus of veins behind the uterus, from which the ovarian veins arise. The right ovarian vein opens into the inferior vena cava and the left into the left renal vein. Lymph

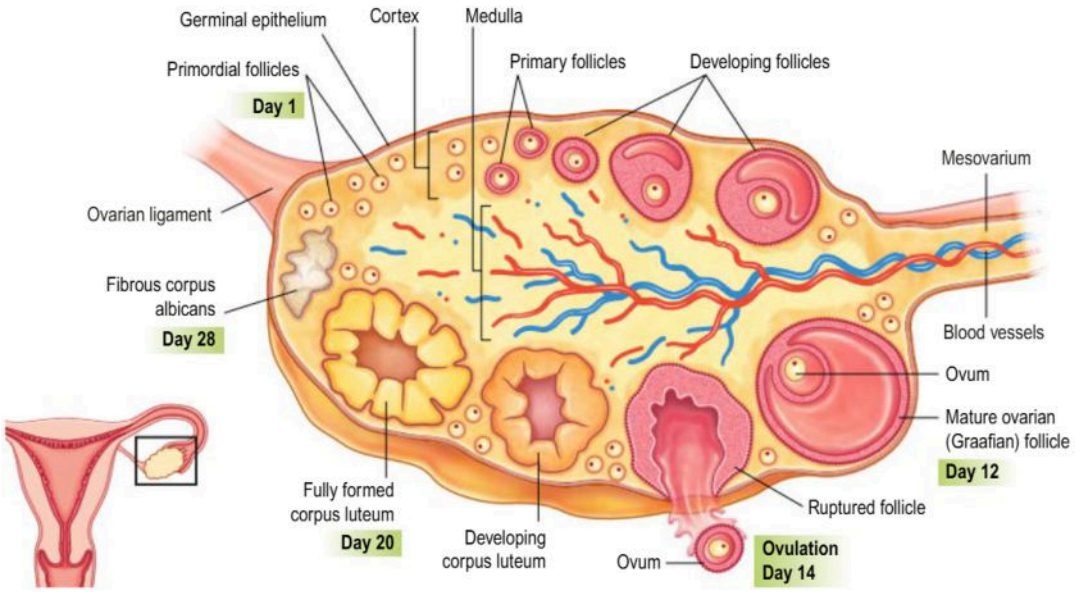

Figure 18.8 A section of an ovary showing the stages of development of one ovarian follicle.

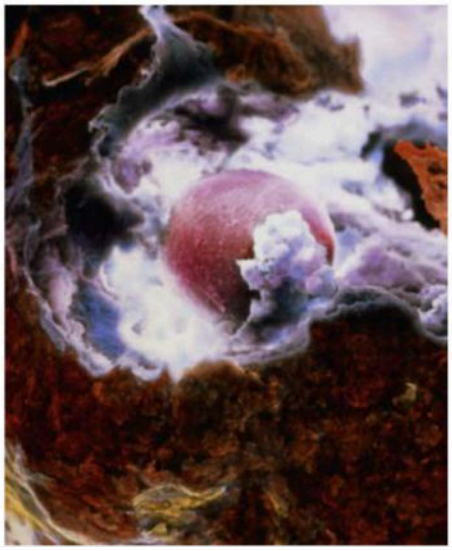

Figure 18.9 Ovulation. Scanning electron micrograph of an ovum (pink) emerging through the surface of the ovary (brown). (Professors PM Motta and J Van Blerkom/Science Photo Library. Reproduced with permission.)

drainage is to the lateral aortic and preaortic lymph nodes. Nerve supply is by parasympathetic nerves from the sacral outflow and sympathetic nerves from the lumbar outflow.

Functions

At puberty, about 400,000 of the original ovarian follicles remain, the others having degenerated. Their maturation is controlled by the hypothalamus and the anterior pituitary gland. The latter releases gonadotrophins (follicle stimulating hormone, FSH, and luteinising hormone, LH), both of which act on the ovary. In addition, the ovary has endocrine functions and releases hormones essential to the physiological changes during the reproductive cycle. The source of these hormones – oestrogen, progesterone and inhibin – is the follicle itself. During the first half of the cycle, while the ovum is developing within the follicle, the follicle secretes increasing amounts of oestrogen. However, after ovulation, the corpus luteum secretes primarily progesterone, with some oestrogen and inhibin (Fig. 18.10). The significance of this is discussed under the menstrual cycle (see later).

Puberty in the female

The hormonal changes at puberty, which usually occurs between the ages of 10 and 14, initiate the onset of the female reproductive cycle and reproductive capability. Puberty is characterised by a rise in the production of reproductive hormones, the onset of menstruation and maturation of the reproductive organs. Ovarian activity is controlled by the gonadotrophins FSH and LH from the anterior pituitary. Under the influence of the gonadotrophins, the ovaries begin to secrete oestrogen, the main stimulus for the development of the physical changes associated with puberty. These changes are also called the secondary sexual characteristics and include:

- maturation of the uterus, uterine tubes and ovaries
- increased secretion of labial and vestibular glands
- development and enlargement of the breasts
- growth of pubic and axillary hair
- increase in height and widening of the pelvis
- increased fat deposition in the subcutaneous tissue, especially at the hips and breasts.

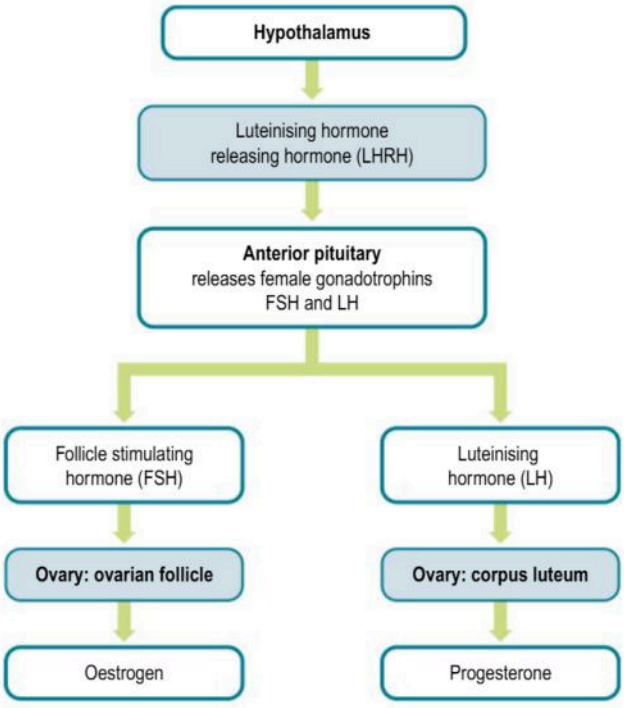

Figure 18.10 Female reproductive hormones and target tissues.

The reproductive cycle

This is a series of events, occurring regularly in females every 26–30 days throughout the childbearing period between the first menstrual period (menarche) and menopause (Fig. 18.11). The cycle consists of a series of changes taking place concurrently in the ovaries and uterine lining, controlled by oestrogen, progesterone, LH and FSH.

The hypothalamus secretes luteinising hormone releasing hormone (LHRH, see Table 9.1), which stimulates the anterior pituitary to secrete:

- FSH, which promotes the maturation of ovarian follicles and the secretion of oestrogen, leading to ovulation. FSH is therefore predominantly active in the first half of the cycle. Its secretion is suppressed once ovulation has taken place, to prevent other follicles maturing during the current cycle
- LH, which triggers ovulation, and stimulates the development of the corpus luteum and the secretion of progesterone.

The hypothalamus responds to changes in the blood levels of oestrogen and progesterone. It is stimulated by high levels of oestrogen alone (as happens in the first half of the cycle) but suppressed by oestrogen and progesterone together (as happens in the second half of the cycle).

The average length of the reproductive cycle is about 28 days. By convention, the days of the cycle are numbered from the beginning of the menstrual phase, which usually lasts about 4 days. This is followed by the proliferative phase (approximately 10 days), then by the secretory phase (about 14 days).

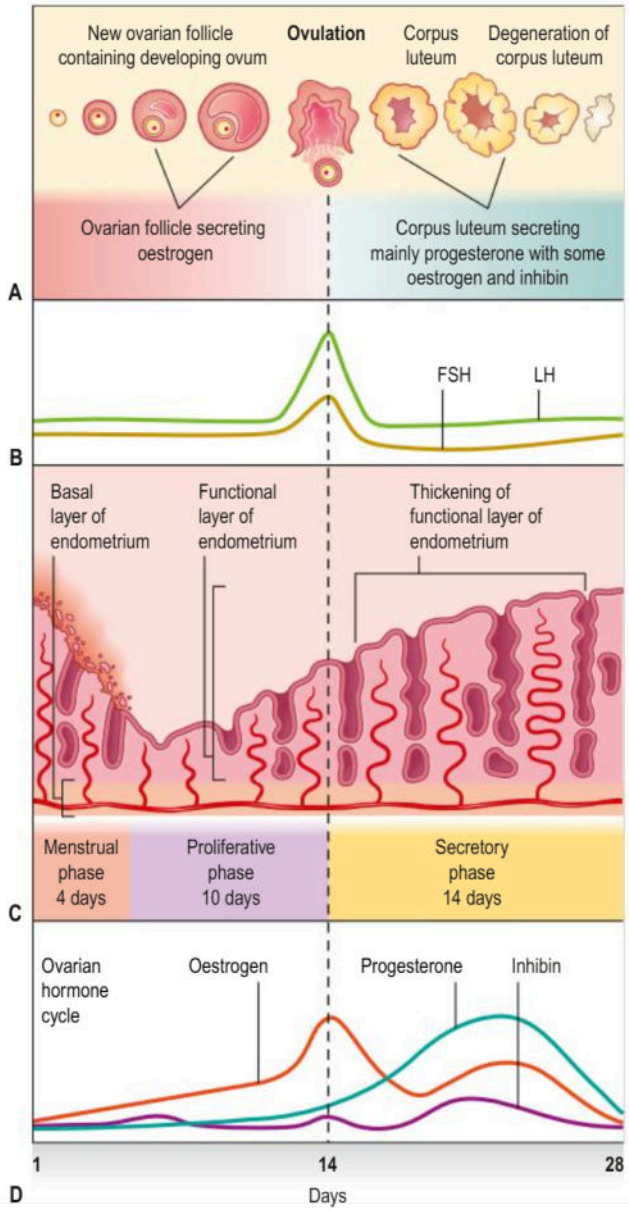

Figure 18.11 Summary of one female reproductive cycle. (A) Ovarian cycle: maturation of follicle and development of corpus luteum. (B) Anterior pituitary cycle: luteinising hormone (LH) and follicle stimulating hormone (FSH) levels. (C) Uterine cycle: menstrual, proliferative and secretory phases. (D) Ovarian hormone cycle: oestrogen, progesterone and inhibin levels.

Menstrual phase

If the ovum is not fertilised, the corpus luteum starts to degenerate. Because the corpus luteum is the source of progesterone and oestrogen, the levels of these hormones in

the blood fall, and the functional layer of the endometrium, dependent on high levels of these ovarian hormones, is shed in menstruation (Fig. 18.11C). Menstrual flow consists of the secretions from endometrial glands, endometrial cells, blood from the degenerating capillaries and the unfertilised ovum.

During the menstrual phase, levels of oestrogen and progesterone are very low because the corpus luteum has degenerated. This means the hypothalamus and anterior pituitary can resume their cyclical activity, and levels of FSH begin to rise, initiating a new cycle.

Proliferative phase

At this stage, one or more ovarian follicles, stimulated by FSH, grow towards maturity and produce increasing amounts of oestrogen, which stimulates proliferation of the functional layer of the endometrium in preparation for receiving a fertilised ovum. The endometrium thickens, becoming very vascular and rich in mucus-secreting glands. Rising levels of oestrogen are responsible for triggering a surge of LH approximately mid-cycle. This LH surge triggers ovulation. Usually one follicle ruptures and releases its ovum, marking the end of the proliferative phase.

Secretory phase

After ovulation, LH from the anterior pituitary stimulates development of the corpus luteum from the ruptured follicle, which produces progesterone, some oestrogen and inhibin. Under the influence of progesterone the endometrium becomes oedematous and the secretory glands produce increased amounts of watery mucus. This assists the motile spermatozoa through the uterus to the uterine tubes, where the ovum is usually fertilised. There is a similar increase in secretion of watery mucus by the glands of the uterine tubes and by cervical glands that lubricate the vagina.

The ovum may remain viable for only a very short time after ovulation, probably as little as 8 hours. The spermatozoa, deposited in the vagina during intercourse, may be capable of fertilising the ovum for only about 24 hours, although they can survive for several days. This means that the period in each cycle during which fertilisation can occur is relatively short. Observable changes in the woman's body occur around the time of ovulation. Cervical mucus, normally thick and dry, becomes thin, elastic and watery, and body temperature rises by about 1°C immediately following ovulation. Some women experience abdominal discomfort in the middle of the cycle, thought to correspond to rupture of the follicle and release of its contents into the abdominal cavity.

After ovulation the combination of progesterone, oestrogen and inhibin from the corpus luteum suppresses the hypothalamus and anterior pituitary, so FSH and LH levels fall. Low FSH levels in the second half of the cycle prevent further follicular development in case a pregnancy results from the current cycle. If the ovum is not fertilised, falling LH levels lead to degeneration and death of the corpus luteum, which is dependent on LH for survival. The resultant steady decline in circulating oestrogen, progesterone and inhibin leads to degeneration of the uterine lining and menstruation, with the initiation of a new cycle. This is summarised in Figure 18.12. Box 18.1 summarises the reproductive functions of oestrogen and progesterone.

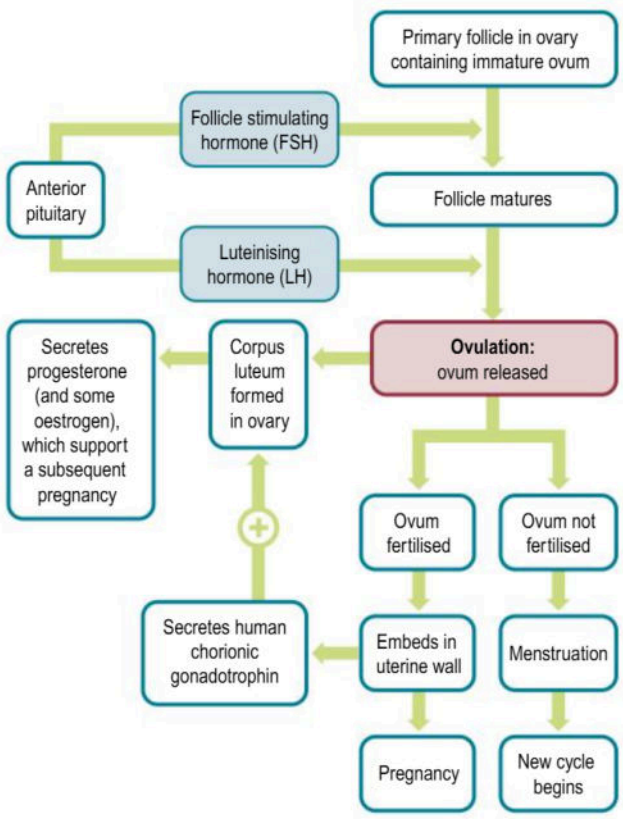

Figure 18.12 Summary of the stages of development of the ovum.

If the ovum is fertilized and successfully implants in the uterine wall, there is no breakdown of the endometrium and no menstruation. The stages of pregnancy are described below. Cessation of the reproductive cycles occurs at menopause (p. 517) when ovarian failure leads to falling oestrogen levels and loss of fertility.

Breasts

The breasts or mammary glands are accessory glands of the female reproductive system. They exist in the male in a rudimentary form.

Structure

The breasts (Fig. 18.13) contain varying amounts of glandular tissue, supported by fat and fibrous connective tissue which anchor the breast to the chest wall.

Box 18.1 Reproductive functions of oestrogen and progesterone

Oestrogen

Stimulates development of secondary sexual characteristics at puberty

Stimulates and supports thickening of uterine lining during proliferative phase of uterine cycle

Triggers luteinising hormone (LH) surge mid-cycle, stimulating ovulation

Stimulates anterior pituitary secretion of follicle stimulating hormone (FSH) and LH in first half of cycle

Progesterone

Stimulates and supports thickening and increased glandular development of uterine lining during secretory phase of the uterine cycle

With oestrogen, inhibits secretion of FSH and LH from anterior pituitary in second half of cycle

The breast contains about 20 lobes, each of which contains a number of glandular structures called lobules, which produce milk after childbirth. Lobules open into tiny lactiferous ducts, which drain milk towards the nipple. Fatty and connective tissues run through the breast, surrounding and supporting the lobules, and the breast itself is covered in subcutaneous fat. In the lactating breast, glandular tissue hypertrophies to support milk production, and atrophies again after lactation stops.

The nipple is a small conical projection at the centre of the breast surrounded by a pigmented area, the areola. On the surface of the areola are numerous sebaceous glands (Montgomery's tubercles), which lubricate the nipple during lactation.

Blood supply, lymph drainage and nerve supply

The breasts are supplied with arterial blood from the thoracic branches of the axillary arteries and from the internal mammary and intercostal arteries. Venous blood drains into an anastomotic circle round the base of the nipple, from which branches carry the venous blood to the circumference, and end in the axillary and mammary veins. Lymph drains mainly into the superficial axillary lymph vessels and nodes. Lymph may drain through the internal mammary nodes if the superficial route is obstructed. The nerve supply to the breasts is by branches from the 4th, 5th and 6th thoracic nerves, which contain sympathetic fibres. There are numerous somatic sensory nerve endings in the breast, especially around the nipple. When these touch receptors are stimulated by suckling, impulses pass to the hypothalamus and secretion of the hormone oxytocin is increased, promoting the release of milk.

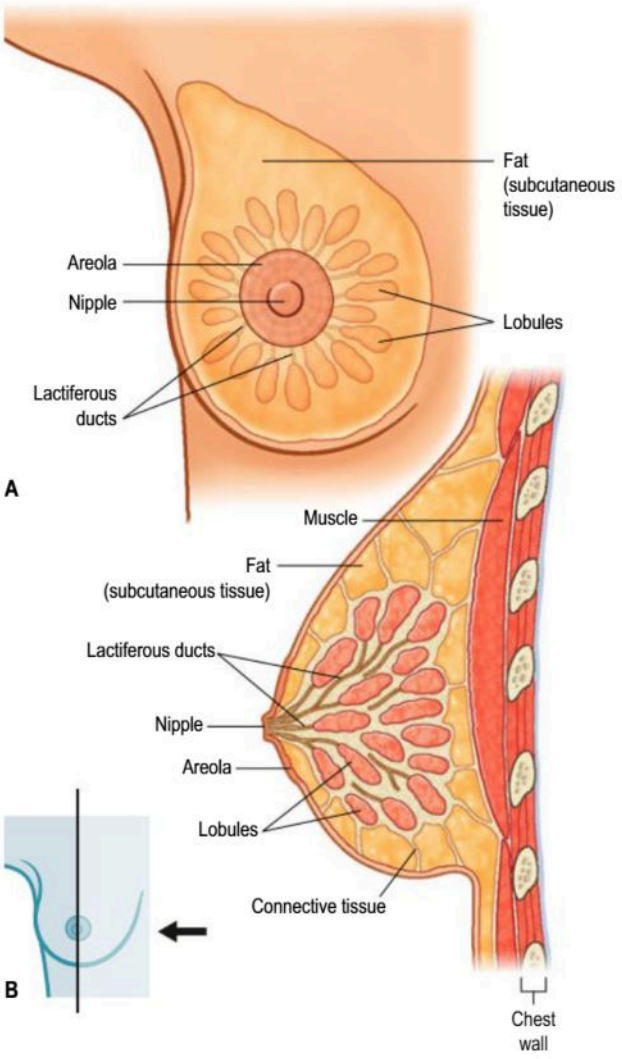

Figure 18.13 Structure of the breast. (A) Anterior view. (B) Lateral view.

Functions

The female breast is small and immature until puberty. Thereafter it grows and develops under the influence of oestrogen and progesterone. During pregnancy, these hormones stimulate further growth. After childbirth, the hormone prolactin (p. 242) from the anterior pituitary stimulates milk production (lactation). Oxytocin (p. 244) from the posterior pituitary stimulates milk ejection in response to nipple stimulation by the suckling baby (the let-down reflex, Fig. 18.14), by a positive feedback mechanism.

SPOT CHECK

1. What is the function of the rugae in the vaginal wall?
2. What is the function of the middle layer of tissue in the uterine wall?

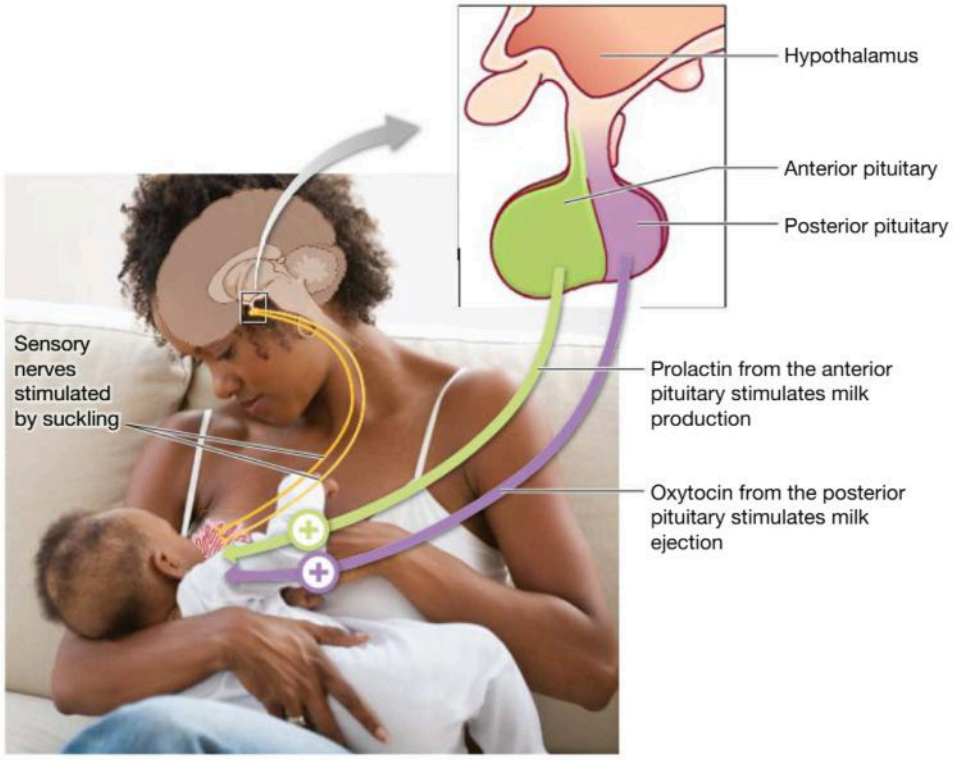

Figure 18.14 The suckling (let-down) reflex. (Photo from istock.com/)

Male reproductive system

Learning outcomes

After studying this section, you should be able to:

- describe the structure and function of the testes
- outline the structure and function of the spermatic cords
- describe the secretions that pass into the spermatic fluid
- explain the process of ejaculation
- list the main changes occurring at puberty in the male.

The male reproductive system is shown in Figure 18.15. In addition to its reproductive function, the urethra is also the passageway for the excretion of urine. The functions of the male reproductive organs are:

- production, maturation and storage of spermatozoa
- delivery of spermatozoa in semen into the female reproductive tract.

Scrotum

The scrotum is a pouch of pigmented skin, fibrous and connective tissue and smooth muscle. It is divided into two compartments, each of which contains one testis, one epididymis and the testicular end of a spermatic cord. It lies below the symphysis pubis, in front of the upper parts of the thighs and behind the penis.

Testes

The testes (Fig. 18.16) are the male reproductive glands and are the equivalent of the female ovary. They are about 4.5 cm long, 2.5 cm wide and 3 cm thick and are suspended in the scrotum by the spermatic cords. Each testis is surrounded by three layers of tissue.

Tunica vaginalis

This double membrane forms the outer covering of the testes and is a downgrowth of the abdominal and pelvic peritoneum. During early fetal life the testes develop in the lumbar region of the abdominal cavity just below the kidneys. They then descend into the scrotum, taking with them coverings of peritoneum, blood and lymph vessels, nerves and the deferent duct. The peritoneum eventually surrounds the testes in the scrotum and becomes detached from the abdominal peritoneum. Descent of the testes into the scrotum should be complete by the 8th month of fetal life.

Tunica albuginea

This is a fibrous covering beneath the tunica vaginalis. Ingrowths form septa, dividing the testes into lobules.

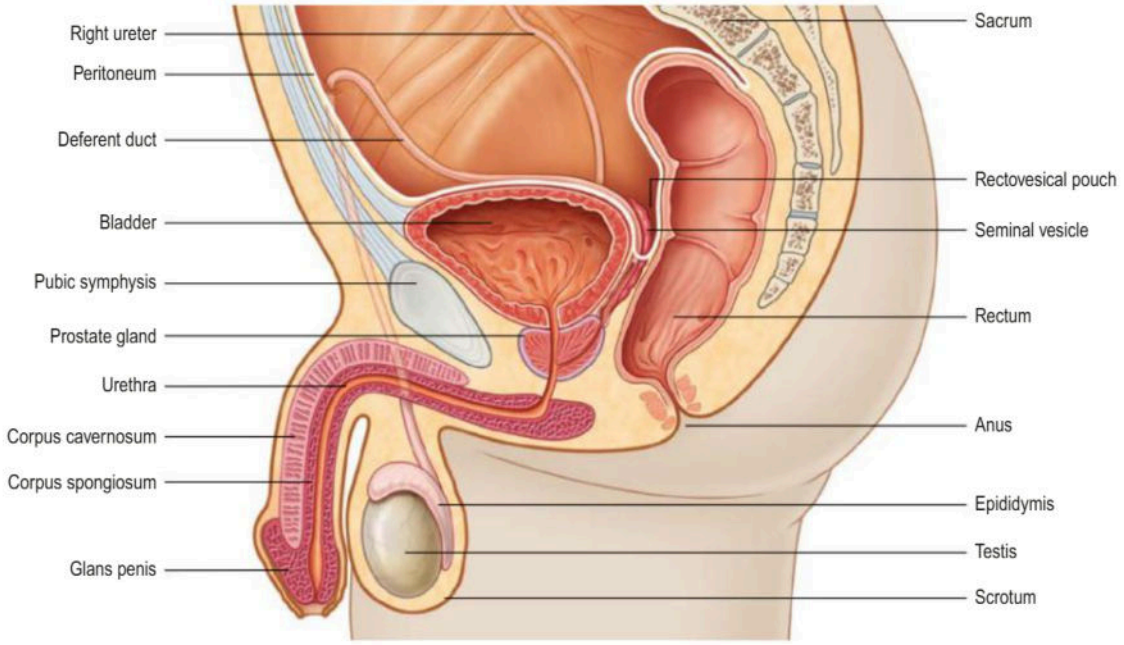

Figure 18.15 The male reproductive organs and their associated structures. Lateral view.

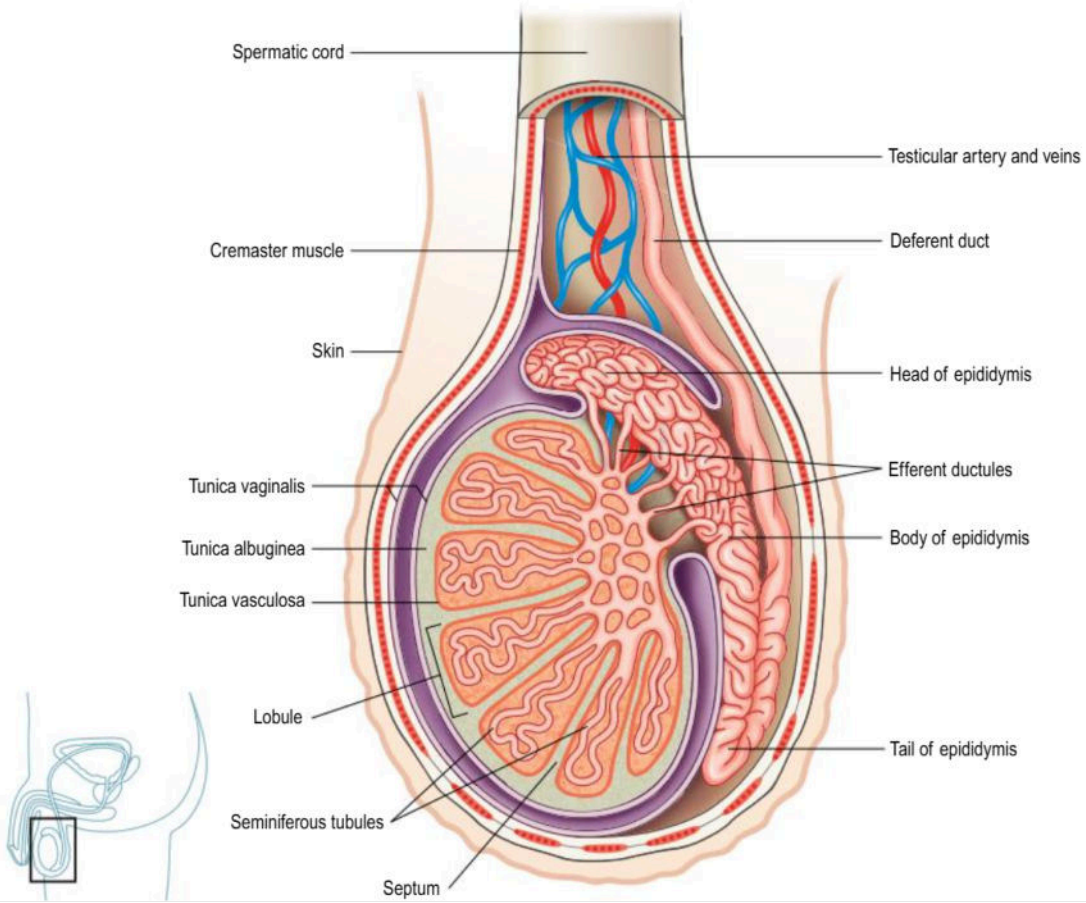

Figure 18.16 The testis.

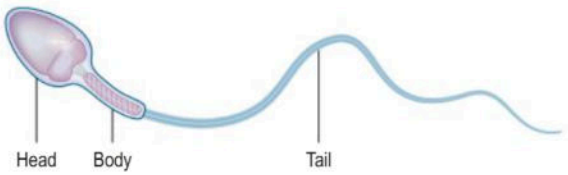

Figure 18.17 A spermatozoon.

Tunica vasculosa

This is a network of capillaries supported by delicate connective tissue.

Structure

Each testis contains 200–300 lobules, and within each lobule are 1–4 convoluted loops of germinal epithelial cells, called seminiferous tubules. Between the tubules are groups of interstitial cells (of Leydig) that secrete the hormone testosterone after puberty. At the upper pole of the testis the seminiferous tubules combine to form a single tubule. This tubule, about 6 m in length, is repeatedly folded and tightly packed into a mass called the epididymis. It leaves the scrotum as the deferent duct (vas deferens) in the spermatic cord.

Functions

Spermatozoa (sperm) are produced by the process of spermatogenesis in the seminiferous tubules of the testes, and mature as they pass through the long and convoluted epididymis, where they are stored. FSH from the anterior pituitary stimulates sperm production. A mature spermatozoon (Fig. 18.17) has a head, a body, and a long whip-like tail used for motility. The head is almost completely filled by the nucleus, containing its DNA. It also contains the enzymes required to penetrate the outer layers of the ovum to reach, and fuse with, its nucleus. The body of the spermatozoon is packed with mitochondria, to fuel the propelling action of the tail that powers it along the female reproductive tract.

Successful spermatogenesis takes place at a temperature about 3°C below normal body temperature. The testes are cooled by their position outside the abdominal cavity, and the thin outer covering of the scrotum has very little insulating fat. This exposed position does, however, leave the testes vulnerable to damage and to excessive cold, so a pouch of smooth muscle, the cremaster muscle, wraps around the tunica vaginalis; it extends upwards around the spermatic cord and attaches to structures in the groin. When it contracts, it pulls the scrotum towards the body for protection.

Unlike females, who produce no new gametes after birth, sperm production in males begins at puberty and continues throughout life, often into old age, under the influence of testosterone.

Spermatic cords

The spermatic cords suspend the testes in the scrotum. Each cord contains a testicular artery, testicular veins, lymphatics, a deferent duct and testicular nerves, which come together from their various origins in the abdomen to form the cord. The cord, wrapped in a sheath formed of the cremaster muscle and connective and fibrous tissues, extends through the inguinal canal (p. 472) and is attached to the testis on the posterior wall.

Blood supply, lymph drainage and nerve supply

The testicular artery branches from the abdominal aorta, just below the renal arteries. Venous blood drains through the testicular veins. The left testicular vein opens into the left renal vein and the right into the inferior vena cava. Lymphatic drainage is through lymph nodes around the aorta. The nerve supply is provided by branches from the 10th and 11th thoracic nerves.

Deferent duct

Also called the vas deferens, this is about 45 cm long. It passes upwards from the testis through the inguinal canal and ascends medially towards the posterior wall of the bladder, where it is joined by the duct from the seminal vesicle to form the ejaculatory duct (Fig. 18.18). Sperm may remain viable in the deferent duct for several weeks.

Seminal vesicles

The seminal vesicles are two small fibromuscular pouches, 5 cm long, lined with columnar epithelium and lying immediately behind the bladder (Fig. 18.18). At its lower end, each seminal vesicle opens into a short duct, which joins with the corresponding deferent duct to form an ejaculatory duct.

Seminal fluid

Seminal fluid forms 60% of the volume of semen and is viscous and alkaline to protect the sperm in the acidic environment of the vagina. It contains fructose to fuel the sperm during their journey through the female reproductive tract.

Ejaculatory ducts

The ejaculatory ducts are two tubes each about 2 cm long and formed by the union of the duct from a seminal vesicle and a deferent duct. They pass through the prostate gland and join the prostatic urethra, carrying seminal fluid and spermatozoa to the urethra (Fig. 18.18).

The walls of the ejaculatory ducts are composed of the same layers of tissue as the seminal vesicles.

Prostate gland

The prostate gland (Fig. 18.18) lies in the pelvic cavity in front of the rectum and behind the symphysis pubis, completely surrounding the male urethra as it emerges from the bladder. It has an outer fibrous covering, enclosing glandular tissue wrapped in smooth muscle. The gland weighs about 8 g in youth but progressively enlarges (hypertrophies) with age, commonly weighing about 40 g by the age of 50.

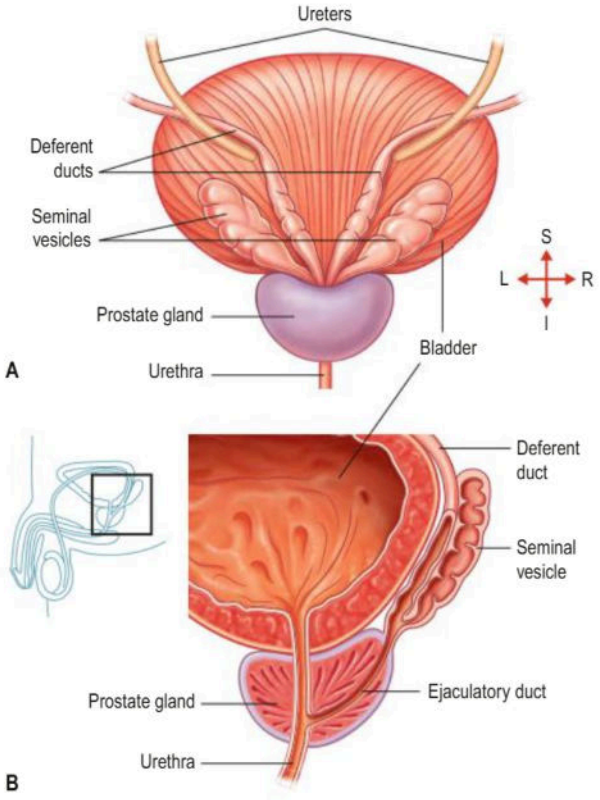

Figure 18.18 The prostate gland. (A) Viewed from the front. (B) Viewed in section from the front.

Prostatic fluid

Prostatic fluid makes up about 30% of the volume of semen. It is thin and milky in appearance, giving semen its white colour. It contains a clotting enzyme, which thickens the semen in the vagina, increasing the likelihood of semen being retained close to the cervix and spermatozoa successfully swimming into the uterus.

Urethra

The male urethra provides a common pathway for the flow of urine and semen and runs from the bladder to the tip of the penis. It is about 19–20 cm long and consists of three parts. The prostatic urethra opens from the bladder and passes through the prostate gland. The membranous urethra is the shortest and narrowest part and extends from the prostate gland to the bulb of the penis, after passing through the perineal membrane. The penile urethra lies within the corpus spongiosum of the penis and terminates at the external urethral orifice in the glans penis.

There are two urethral sphincters (Fig. 18.19B). The internal sphincter is a ring of smooth muscle at the neck of the bladder above the prostate gland. The external sphincter is a ring of skeletal muscle surrounding the membranous urethra. It is under voluntary control and allows conscious control of urination.

Penis

The penis (Fig. 18.19) has a root and a shaft. The root anchors the penis in the perineum and the shaft is the externally visible, movable portion of the organ. It is formed by three cylindrical masses of erectile tissue and smooth muscle. The erectile tissue is supported by fibrous tissue covered with skin and has a rich blood supply.

The two lateral columns are called the corpora cavernosa and the column between them, containing the urethra, is the corpus spongiosum (Figs 18.19A and 18.20). The penile tip is expanded into a triangular structure called the glans penis.

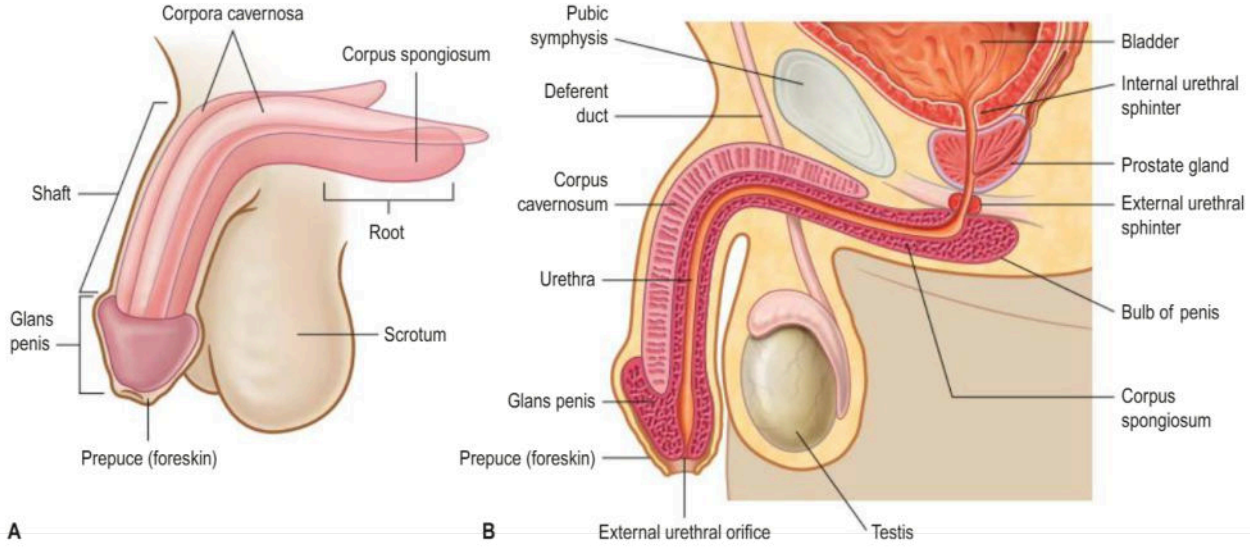

Figure 18.19 The penis. (A) Showing the erectile tissues. (B) Lateral view, showing associated structures.

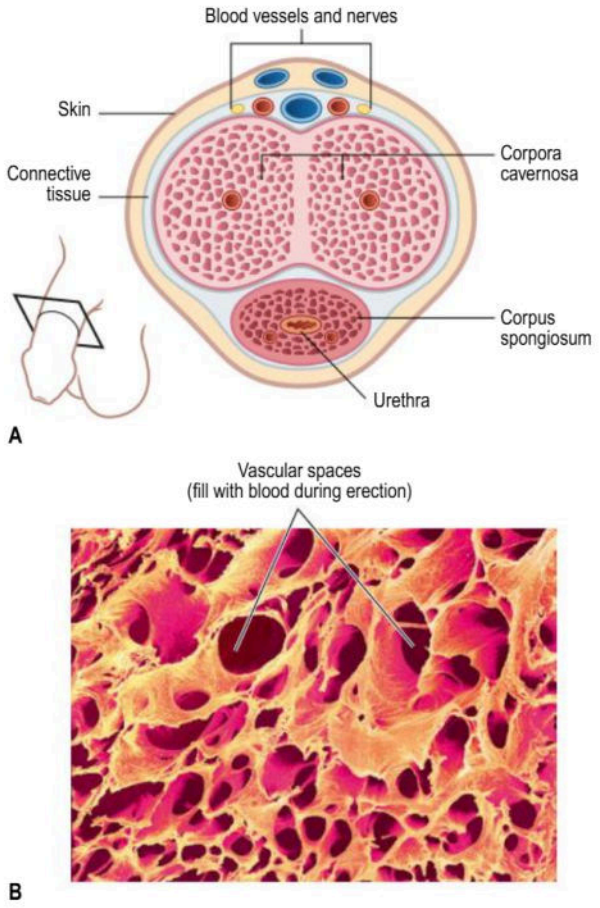

Figure 18.20 The penis. (A) Transverse section, showing the erectile tissues. (B) Erectile tissue (scanning electron micrograph). (B, Susumu Nishinaga/Science Photo Library. Reproduced with permission.)

Just above the glans the skin is folded on itself and forms a movable double layer, the foreskin or prepuce. Arterial blood is supplied by deep, dorsal and bulbar arteries of the penis, which are branches from the internal pudendal arteries. A series of veins drain blood to the internal pudendal and internal iliac veins. The penis is supplied by autonomic and somatic nerves.

Erection of the penis is facilitated by its rich sensory innervation. The diameter of blood vessels supplying and draining it regulates the filling of its erectile tissue and is controlled by the autonomic nervous system. Parasympathetic stimulation leads to filling of the spongy erectile tissue (Fig. 18.20) with blood, caused by arteriolar dilation and venoconstriction, which increases blood flow into the penis and obstructs outflow. The penis therefore becomes engorged and erect, essential for sexual intercourse.

Ejaculation

During ejaculation, which occurs at male orgasm, spermatozoa are expelled from the epididymis and pass through the deferent duct, the ejaculatory duct and the urethra. This route is shown in Figure 18.21. The semen is propelled by powerful rhythmical contraction of the smooth muscle in the walls of the deferent duct; the muscular contractions are sympathetically mediated. Muscle in the walls of the seminal vesicles and prostate gland also contracts, adding their contents to the fluid passing through the genital ducts. The force generated by these combined processes leads to emission of the semen through the external urethral sphincter.

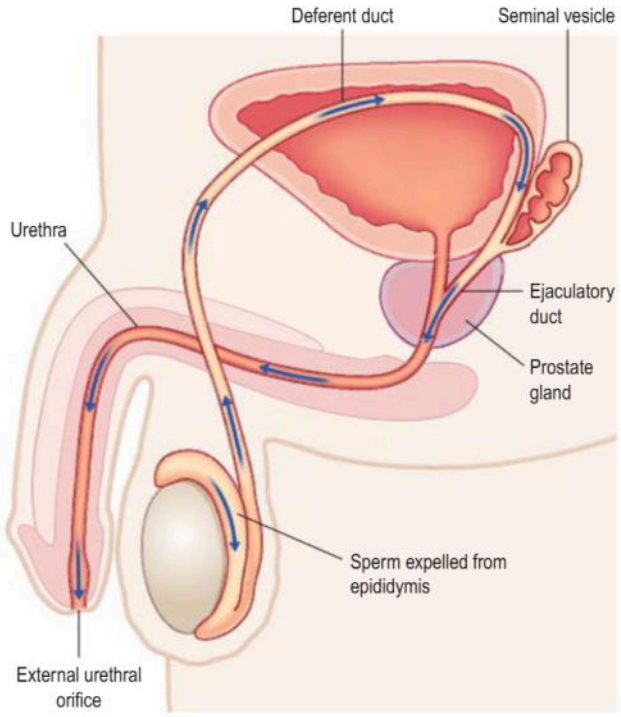

Figure 18.21 The route taken through the male reproductive tract by spermatozoa during ejaculation.

Sperm comprise only 10% of the final ejaculate, the remainder being made up mainly of seminal (60%) and prostatic fluids (30%), which are added to the sperm during male orgasm, as well as mucus produced in the urethra. Semen is slightly alkaline, to neutralise the acidity of the vagina. Between 2 and 5 mL of semen are produced in a normal ejaculate and contain between 40 and 100 million spermatozoa per mL. If not ejaculated, sperm gradually lose their fertility after several months and are reabsorbed by the epididymis.

Puberty in the male

This occurs between the ages of 10 and 14. LH from the anterior pituitary stimulates the interstitial cells of the testes to increase the production of testosterone. Under the influence of testosterone, sexual maturation and development of male secondary sexual characteristics take place, including:

- growth of muscle and bone and a marked increase in height and weight

- enlargement of the larynx and deepening of the voice, which 'breaks'
- growth of hair on the face, axillae, chest, abdomen and pubis
- enlargement of the penis, scrotum and prostate gland
- maturation of the seminiferous tubules and production of spermatozoa
- thickening of the skin, which also becomes oilier.

SPOT CHECK

3. Male reproductive fluids pass through the deferent duct and the urethra. What is the main difference in composition of these fluids?
4. Which compartment in the penis contains the urethra?

Fetal development and pregnancy

Learning outcomes

After studying this section, you should be able to:

- define the terms 'blastocyst', 'zygote', 'embryo' and 'fetus'
- outline the main stages of embryonic and fetal development.

Growth of a new human being begins when an ovum is fertilised by a spermatozoon (see Fig. 1.16), usually in the uterine tube. The resulting cell is called a zygote. Because the ovum and spermatozoon each had 23 chromosomes, the zygote has the full complement of 46 chromosomes. The period between fertilisation and birth (gestation) lasts about 40 weeks and is conventionally described in three stages called trimesters, each lasting about three months. The first 8 weeks of development are called the embryonic period and the developing baby is described as an embryo; thereafter it is called a fetus.

Pregnancy

Aided by peristalsis of the uterine tube, the zygote travels towards the uterus, a journey that takes about a week, and by 10 days after fertilisation it is firmly embedded in the uterine lining, signalling the beginning of pregnancy. During this period, it undergoes rapid and repeated cell divisions, and by the time it implants in the endometrium it has become a blastocyst, a hollow ball of 70–100 cells. The blastocyst contains an inner mass of cells, which develops into the fetus and its amniotic sac, a bag of membranes enclosing it. The outer layer, the trophoblast, becomes an important layer of the placenta.

Once embedded in the uterine wall, the zygote produces human chorionic gonadotrophin (hCG), a hormone similar to anterior pituitary luteinising hormone. This hormone supports the corpus luteum, which continues secreting progesterone and oestrogen for the first 3–4 months of the pregnancy, inhibiting the maturation of further ovarian follicles (Fig. 18.12). This gives the placenta time to grow and develop. After the first trimester, the placenta takes over the secretion of the hormones essential for the maintenance of pregnancy: oestrogen, progesterone and gonadotrophins. In particular, placental progesterone suppresses the contractility of the uterine muscle, and prevents it from contracting in response to being stretched as the baby grows.

Nourishment during intrauterine growth

In the early stages, the embryo is small enough for uterine secretions and simple diffusion to supply the dividing cells with nutrients and oxygen but, because embryonic growth is so rapid, this quickly becomes unsustainable and between the 3rd and 10th weeks of pregnancy the placenta (see Fig. 5.47) develops, attached firmly to the uterine wall. The fetus is attached to the placenta by the umbilical cord and absorbs oxygen and nutrients from the maternal bloodstream, as well as excreting its waste products.

The first trimester

A newborn baby is made up of trillions of cells and many different tissues, all of which have developed from the single-celled zygote formed at fertilisation. Differentiation of cells into specialised tissues, and the organisation of these specialised tissues into the body systems, is largely completed in the first 12 weeks of gestation. The first trimester is therefore the most critical for the development of all body organs and carries the highest risk for the development of a fetal abnormality. A range of agents, including infection, chemicals and irradiation can interfere with fetal development and cause a permanent deficit. Such agents are called teratogens. Significant disruption of fetal development, especially in the early weeks of gestation, usually leads to spontaneous loss of the pregnancy.

At the end of the first trimester, all the main body systems have been laid down and the baby is fully formed.

Later pregnancy

The final 6 months of pregnancy (the second and third trimesters) are devoted primarily to the rapid growth of the fetus and maturation of all body systems in preparation for birth and independent life. At term (the end of pregnancy), circulating oestrogen and oxytocin stimulate strong uterine contractions, initiating labour and delivery of the baby (a positive feedback system, see Fig. 9.5).

Table 18.1 summarises some of the main landmarks in embryonic/fetal development.

SPOT CHECK

5. What is a blastocyst?
6. By which stage of embryonic development would you expect to see a beating heart: 1, 3 or 5 months?

Table 18.1 Some landmarks in embryonic/fetal development

Month	Length	Weight	Main developmental features
1	5 mm	0.02 g	Heart is beating
			Main respiratory and gastrointestinal organs appear
			Neural tube appears (from which the nervous system develops)
			Limb buds apparent
2	28 mm	2.7 g	Endocrine glands appear
			Respiratory tree in place
			Vascular system laid down
			Heart development complete
			Skin, nails and sweat glands present in skin
			Cartilage models for bones appear
			Face has human profile
3	78 mm	26 g	Blood cells produced in bone marrow
			Basic brain and spinal cord structure in place
			Ossification of bones begins and muscles form
			Gonads appear (ovaries in females, testes in males)
4	133 mm	150 g	Formation of hair
			Eyes and ears in place
			Rapid central nervous system development
			Joints formed
9	346 mm	3.2 kg	At birth, many systems immature but functional. Some important adaptations to independent life required, e.g. in cardiovascular and respiratory function (p. 125)

Effects of ageing on the reproductive systems

Learning outcomes

After studying this section, you should be able to:

- describe the effects of ageing on female reproduction
- describe the effects of ageing on male reproduction.

Ageing and reproduction in the female

The menopause is the term given to the point in a woman's life when her reproductive cycles stop. This is usually due to increasing age, although it can be induced artificially by e.g. surgical removal of the ovaries or by ovarian failure.

The menopause

Usually between the ages of 45 and 55 years, the ovarian supply of viable oocytes runs out because they have degenerated with age, and the oestrogen they release therefore declines, at which point the reproductive cycle is disrupted and fertility declines towards zero. This period of declining fertility is called the menopause, and its onset may be abrupt or extend over months or years. On average, it lasts around four years although in some women it is much shorter and in others much longer.

Because of falling oestrogen levels, in the early stages of the menopause there is a rapid and sustained rise in FSH and LH secretion as the anterior pituitary and hypothalamus attempt to maintain activity in the failing ovaries. The ageing ovaries gradually become less responsive to FSH and LH, and ovulation and the menstrual cycle become irregular, eventually ceasing. Other signs and symptoms may include:

- short-term unpredictable vasodilation with flushing, sweating and feelings of intense warmth (hot flushes), which can cause significant discomfort and disrupt sleep
- episodes of uncharacteristic behaviour, e.g. irritability, mood changes
- loss of bone mass, predisposing to osteoporosis (p. 479)
- thinning of skin
- slow increase in blood cholesterol levels, which raises the risk of cardiovascular disease in postmenopausal women to that in males of the same age.

From menopause through to old age, the female reproductive organs, including the breasts, progressively shrink in size. The vulva atrophies and becomes more fibrous, which may predispose to infection and malignant change. Pubic and axillary hair becomes sparse. The walls of

the vagina become thin and smooth with loss of rugae and glandular secretions.

Ageing and reproduction in the male

There is no equivalent of the female menopause in the older male. Although testosterone secretion tends to decline after age 50, leading to a relative reduction in fertility and sexual desire, it is usually sufficient to maintain sperm production and a man may still be able to father a child until extreme old age.

Enlargement of the prostate gland (benign prostatic hyperplasia, p. 523) is common in older men.

Infections of the reproductive tract

Learning outcomes

After studying this section, you should be able to:

- list the principal causes of sexually transmitted infections
- explain the effects of sexually transmitted infections
- describe the circumstances associated with the development of candidiasis (thrush).

Many, but not all, infections of the reproductive tract are sexually transmitted.

Sexually transmitted infections

Sexually transmitted infections (STIs) are common in all cultures and an increasing problem in many countries. Microorganisms responsible for STIs are unable to survive outside the body for long periods and have no intermediate host.

Chlamydia

The bacterium *Chlamydia trachomatis* causes inflammation of the female cervix. Infection may ascend through the reproductive tract and cause pelvic inflammatory disease (see below). In the male, it may cause urethritis, which may also ascend and lead to epididymitis. In both sexes, it is an important cause of subfertility. Chlamydia infection is often present in conjunction with other STIs. The same organism causes trachoma, an eye infection that is the primary cause of blindness worldwide (p. 234).

Gonorrhoea

This is caused by the bacterium *Neisseria gonorrhoeae*, which infects the mucosa of the reproductive and urinary tracts. In the female, the infection may spread from the cervix to the body of the uterus, uterine tubes, ovaries and peritoneum. Healing by fibrosis may obstruct the uterine tubes, causing infertility. In the male, suppurative urethritis occurs (Fig. 18.22) and the infection may spread to the prostate gland, epididymis and testes. It may also cause urethral stricture. However, only 50% of females and 90% of males experience any symptoms, often leading to a delay in seeking treatment.

Gonorrhoea may cause neonatal ophthalmia in babies born to infected mothers. The eyes become infected as the baby passes through the birth canal. The disease can also be spread via unprotected oral or anal sex, leading to throat and rectal infections, respectively.

Syphilis

This disease is caused by the bacterium *Treponema pallidum*. There are three distinct stages. After an incubation period of several weeks the primary sore (chancre) appears at the site of infection, e.g. the vulva, vagina, perineum or penis, or round the mouth. In the female the primary sore may be undetected if it is internal. After several weeks the chancre subsides spontaneously. The secondary stage, 3–4 months after infection, involves systemic symptoms including lymphadenopathy, rashes and mucosal ulceration of the mouth and genital tract. There may then be a latent period of between 3 and 10 years. If untreated, about one-third of patients eventually develop late-stage disease, which has widespread and devastating effects. Tertiary lesions (gummas) develop in many organs, including skin, bone and mucous membranes, and may involve the nervous system, leading to general paralysis and dementia.

Sexual transmission occurs during the primary and secondary stages when discharge from lesions is highly infectious. Congenital transmission from mother to fetus carries a high risk of stillbirth.

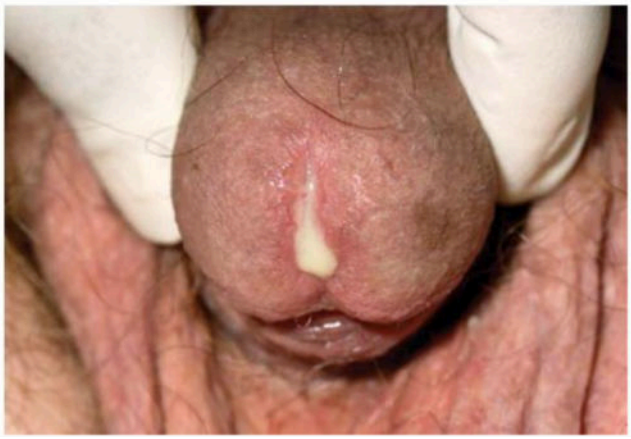

Figure 18.22 Gonorrhoea. (Dr P Marazzi/Photo Library. Reproduced with permission.)

Trichomonas vaginalis

This protozoan causes acute vulvovaginitis with irritating, offensive discharge. The infection is usually sexually transmitted and is commonly present in women with gonorrhoea. Males are often asymptomatic.

Acquired immune deficiency syndrome and hepatitis B infection

These viral conditions may be sexually transmitted but there are no local signs of infection. For a description of AIDS and HIV see page 427, and for hepatitis B see page 369.

Genital herpes

The term 'herpes' comes from the Greek word meaning 'to creep'. Eight types of herpes virus infect humans, but the main ones associated with genital infections are herpes simplex virus 1 and 2 (HSV1 and HSV2). HSV can infect most

body cells, including those in the genital tract, and can then establish itself and become latent in the nerves supplying the area. This means that even when the initial infection has subsided, the latent virus can be reactivated and cause repeated episodes of recurrent infection. Initial infection tends to present as clusters of small, painful ulcers on the external genitalia, often with fever and headache. Patients remain infectious even during symptom-free periods. Babies born to infected mothers can contract HSV, which is a very serious and sometimes fatal illness in the neonate.

Candidiasis

The yeast *Candida albicans* (see also p. 356) is frequently a commensal in the vagina, as well as other body sites, and normally causes no problems. It is prevented from flourishing in the healthy vagina by the acidic vaginal secretions but in certain circumstances it proliferates, causing candidiasis (thrush). Common precipitating factors include:

- antibiotic therapy, which kills the lactobacilli that keep vaginal pH low
- pregnancy, because of elevated oestrogen levels
- reduced immune function
- diabetes mellitus, because elevated blood sugar encourages microbial growth.

In women, the main symptom of vaginal candidiasis is persistent itch, with discharge, swelling and erythema of the vulvar area. It is important to note that *Candida* can infect almost any body site, given suitable conditions.

SPOT CHECK

7. Which organism causes syphilis?
8. Why is genital thrush associated with broad-spectrum antibiotic treatment?

Diseases of the female reproductive system

Learning outcomes

After studying this section, you should be able to:

- describe the causes and consequences of pelvic inflammatory disease
- outline the causes and effects of cervical carcinoma
- discuss the main pathologies of the uterus and uterine tubes
- describe the causes and effects of ovarian disease
- explain the causes of female infertility
- discuss the principal disorders of the female breast.

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is usually a consequence of STIs and is most common in young sexually active women. It usually begins as vulvovaginitis and spreads upwards to the cervix, uterus, uterine tubes and ovaries. It can also result from a surgical procedure, childbirth or miscarriage, especially if some of the products of conception are retained. Complications of PID include:

- infertility due to obstruction of the uterine tubes
- peritonitis
- intestinal obstruction due to adhesions between the bowel and the uterus and/or uterine tubes
- bacteraemia, which may lead to meningitis, endocarditis or septic arthritis.

Disorders of the uterus

Cervical carcinoma

Dysplastic changes, referred to as cervical intraepithelial neoplasia (CIN), begin in the deepest layer of cervical epithelium, usually where the stratified squamous epithelium of the lower third of the cervical canal meets the secretory epithelium of the upper two-thirds. Dysplasia (see Fig. 3.32) may progress to involve the full thickness of epithelium. Not all dysplasias develop into malignant disease but it is not possible to predict how far development will go and whether it will remain static or regress. Early detection using screening programmes can allow abnormal tissue to be removed before it becomes malignant. Established malignancy is staged according to how extensive the tumour is. Stage I is disease confined to the cervix. Stages II–IV reflect increasing spread, including involvement of the rectum, bladder and structures outside the pelvis. Early spread is via lymph nodes and local spread is commonly to the uterus, vagina, bladder and rectum. In the late stages, spread via the blood to the liver, lungs and bones may occur.

The disease takes 15–20 years to develop and mostly occurs between 35 and 50 years of age.

Over 90% of cases are caused by the sexually transmitted human papilloma virus (HPV), which also causes a large proportion of cancers of the penis and vulva. The risk is therefore greatest in women who are sexually active from an early age with multiple partners and who do not use barrier methods of contraception. HPV vaccines protect against HPV infection, and in countries that have instituted HPV vaccination programmes for young teenagers, the incidence of HPV-related cancers is significantly falling.

Disorders of the endometrium

The general term for inflammation of the endometrium is endometritis, caused by a range of pathogens following, for example, childbirth or miscarriage, or by an infected intra-uterine contraceptive device. Other more specific

conditions include endometriosis, endometrial hyperplasia and endometrial carcinoma.

Endometriosis

This is the growth of endometrial tissue outside the uterus (ectopic tissue), usually in the ovaries, uterine tubes and other pelvic structures. Like the uterine endometrium, ectopic tissue responds to fluctuations in sex hormone levels during the menstrual cycle. This causes menstrual-type bleeding into the lower abdomen and in the ovaries, the formation of coloured cysts called chocolate cysts. There is intermittent pain due to swelling and inflammation, and recurrent haemorrhage causes fibrous tissue formation. Ovarian endometriosis may lead to pelvic inflammation, infertility and extensive pelvic adhesions involving the ovaries, uterus, uterine ligaments and the bowel. The condition may also increase the risk of certain cancers, including ovarian cancer.

Endometrial hyperplasia

Hyperplasia of the endometrium is associated with high blood oestrogen levels, e.g. in obesity, oestrogen therapy or an ovarian tumour, and may increase the risk of malignant change.

Endometrial carcinoma

This occurs mainly in postmenopausal women between 50 and 60 years of age. Oestrogen exposure is the main risk factor, so women who have never been pregnant (nulliparous) or who had an early menarche and/or late menopause have an increased risk because they experience a greater number of reproductive cycles with the associated oestrogen surges. Obesity is associated with high circulating oestrogen levels and therefore obese people with or without the related conditions of diabetes and hypertension are also at increased risk of endometrial cancer.

As the tumour grows, there is often ulceration and vaginal bleeding. Endometrium has no lymphatics, so lymph spread is delayed until extensive local spread involves other pelvic structures. Distant metastases, spread in blood or lymph, develop later, usually in the liver, lungs and bones. Invasion of the ureters leads to hydronephrosis and uraemia, commonly the cause of death.

Disorders of the myometrium

Adenomyosis

This is the growth of endometrium within the myometrium, usually beginning between 40 and 50 years of age. The ectopic tissue may cause general or localised uterine enlargement. The lesions may cause dysmenorrhoea (painful menstrual periods) and menorrhagia (irregular excessive bleeding).

Leiomyoma (fibroid, myoma)

These are very common, often multiple, benign tumours of myometrium (Fig. 18.23). They are firm masses of smooth muscle encapsulated in compressed muscle fibres and they vary greatly in size. Large tumours may degenerate if they outgrow their blood supply, leading to necrosis, fibrosis and calcification. They are more common in black race women than in other racial groups, develop during the reproductive period and may be hormone-dependent, enlarging during pregnancy and when oral contraceptives are used. They tend to regress after the menopause. Large tumours may cause pelvic discomfort, urinary frequency, menorrhagia, irregular periods, dysmenorrhoea and reduced fertility. Malignant change is rare.

Figure 18.23 Uterine fibroid (shown in orange). False colour magnetic resonance imaging scan. (Simon Fraser/Newcastle Hospitals NHS Trust/Science Photo Library. Reproduced with permission.)

Disorders of the uterine tubes and ovaries

Acute salpingitis

Salpingitis is inflammation of the uterine tubes. It is usually due to infection spreading from the uterus, and occasionally from the peritoneal cavity. The uterine tubes may be permanently damaged by fibrous scar tissue, which can cause obstruction and infertility. Infection may spread into the peritoneum and involve the ovaries.

Ectopic pregnancy

This is the implantation of a fertilised ovum outside the uterus, usually in a uterine tube. As the fetus grows, the tube may rupture and its contents enter the peritoneal cavity, causing acute inflammation (peritonitis) and potentially fatal haemorrhage.

Ovarian tumours

Most ovarian tumours are benign, usually occurring between 20 and 45 years of age. The rest occur mostly between 45 and 65 years and are divided between borderline malignancy (low-grade cancer) and frank malignancy.

Ovarian cancer is associated with developed societies, higher socioeconomic groups and sometimes a genetic susceptibility. Pregnancy or use of the contraceptive pill has a protective effect. Most malignancies of the ovary arise from epithelium but some arise from the germ cells of the ovary or from stromal cells.

Metastatic ovarian tumours

The ovaries are common sites of metastatic spread from primary tumours in other pelvic organs, the breast, stomach, pancreas and biliary tract.

Female infertility

This common condition may be due to:

- blockage of uterine tubes, often the consequence of PID and/or STIs
- anatomical abnormalities, e.g. retroversion (backward tilting) of the uterus
- endocrine factors – any abnormalities of the glands and hormones regulating the menstrual cycle can interfere with fertility
- low body weight, e.g. in anorexia nervosa, or severe malnourishment; this may be associated with low leptin levels (see Table 9.4)
- endometriosis.

Disorders of the breast

Mastitis (inflammation of the breast)

This is usually associated with lactation and breast feeding and may or may not involve infection. It usually affects only one breast. Non-infective mastitis is caused by milk stasis in the breast and causes swelling and pain. Infection (usually by *Staphylococcus aureus*) can occur if the nipple is damaged during suckling, allowing bacteria to enter and spread into the system of milk ducts. The condition generally responds well to treatment but can progress to more serious complications such as abscess formation.

Tumours of the breast

Benign tumours

Most breast tumours (90%) are benign. Fibroadenomas are the most common type and occur any time after puberty; incidence peaks in the third decade. Other benign tumours may be cystic or solid and these usually occur in women nearing the menopause. They may originate from secretory cells, fibrous tissue or ducts.

Breast cancer

Breast cancer is the most common cancer worldwide in women and the incidence is increasing. Important risk factors include increasing age (up to about 70 years, after which the incidence declines), high alcohol consumption and obesity. Oestrogen exposure is an important risk factor so risk is increased in women with an early menarche, late menopause and no pregnancies because they experience more reproductive cycles with the monthly oestrogen surge associated with ovulation. A genetic component is also likely, with close relatives of breast cancer sufferers having an elevated risk of developing the disease. In 5%–10% of cases the disease is linked to the presence of one of two faulty genes, *BRCA1* and *BRCA2*. Women carrying one of these genes have a very high (80%–90%) chance of developing breast cancer, and there is also increased risk of ovarian and bowel cancer. The average age at which the disease appears in women carrying these genes is significantly lower than in those without the gene.

The tumour most commonly occurs in the upper outer quadrant of the breast. There is fibrosis around the tumour and this may cause retraction of the nipple, and necrosis and ulceration of the overlying skin (Fig. 18.24).

Early spread beyond the breast is via lymph to the axillary and internal mammary nodes. Local invasion involves the pectoral muscles and the pleura. Blood-spread metastases may occur later in many organs and bones, especially lumbar and thoracic vertebrae.

SPOT CHECK

9. What is a leiomyoma?
10. Why do women with a large number of sexual partners have an increased risk of cervical cancer?

Figure 18.24 Breast cancer. (Mid-Essex Hospital Services NHS Trust/Science Photo Library. Reproduced with permission.)

Diseases of the male reproductive system

Learning outcomes

After studying this section, you should be able to:

- outline the causes and effects of penile and urethral infections
- describe the main pathologies of the testis
- discuss the principal disorders of the prostate gland
- list the main causes of male infertility.

Infections of the penis

Inflammation of the glans and prepuce may be caused by a specific or non-specific infection. In non-specific infections, or balanitis, lack of personal hygiene is an important predisposing factor, especially if phimosis is present, i.e. the foreskin is tight and does not retract properly. If the infection becomes chronic, it can cause fibrosis of the foreskin, which increases the phimosis.

Infections of the urethra

Gonococcal urethritis is the most common specific infection. Non-specific infection may be spread from the bladder (cystitis) or be introduced during urinary catheterisation, cystoscopy or surgery. Both types may spread directly to the prostate, seminal vesicles, epididymis and testes. If infection becomes chronic, fibrosis may cause urethral stricture or obstruction, leading to retention of urine.

Disorders of the epididymis and testes

Infections

Non-specific epididymitis and orchitis are usually due to spread of infection from the urethra, often after prostatectomy. The microbes may spread either through the deferent duct or via lymph. Specific epididymitis is usually caused by gonorrhoea spread from the urethra.

Orchitis (inflammation of the testis)

This can be caused by a number of bacteria and viruses, but is usually caused by mumps virus, which is blood-borne from the parotid glands. Acute inflammation with oedema occurs about 1 week after the appearance of parotid swelling (parotitis, p. 357). The infection is usually unilateral but, if bilateral, severe damage to germinal epithelium of the seminiferous tubules may cause infertility.

Undescended testis (cryptorchidism)

During embryonic life the testes develop within the abdominal cavity, and normally descend into the scrotum before birth. If they fail to do this and the condition is not corrected, infertility is likely to follow because the temperature in the undescended testis is too warm for sperm production. The risk of testicular cancer is increased.

Hydrocele

This is the most common form of scrotal swelling and is accumulation of serous fluid in the tunica vaginalis. The onset may be acute and painful or chronic. It may be congenital or be secondary to another disorder of the testis or epididymis.

Testicular tumours

Most testicular tumours are malignant and are the most common malignancies in young men. Undescended testis is the most significant risk factor. The tumour tends to remain localised for a considerable time but eventually spreads in lymph to pelvic and abdominal lymph nodes, and more widely in the blood. If the tumour secretes testosterone, it may cause precocious development in boys.

Disorders of the prostate gland

Infections

Acute prostatitis is usually caused by non-specific infection, spread from the urethra or bladder, and often iatrogenic following e.g. urinary catheterisation, cystoscopy or prostate surgery. Chronic infection may follow an acute attack. Fibrosis of the gland may occur during healing, causing urethral stricture or obstruction.

Benign prostatic enlargement

The prostate gland surrounds the urethra (see Fig. 18.18) and so hyperplasia of the gland obstructs urine flow, causing urinary retention. There may be urgency and frequency of urination, difficulty starting to urinate and a weak or spurting urine stream. Incomplete emptying of the bladder predisposes to infection, which may spread upwards, causing pyelonephritis and other complications. Prostatic enlargement is common in men over 50, affecting up to 70% of men aged over 70. The cause is not clear.

Malignant prostatic tumours

Seven per cent of all cancers in men are prostatic carcinomas. The cause is not known, although increasing age, obesity and a family history of the disease are known risk factors. Initially, the growing tumour usually causes symptoms of urinary obstruction, but it spreads quickly and sometimes

presents with symptoms of secondary spread, e.g. back pain from bone metastases, weight loss or anaemia.

Disorders of the male breast

Gynaecomastia

This is proliferation of breast tissue in men. It usually affects only one breast and is benign. It is common in adolescents and older men, and is often associated with:

- endocrine disorders, especially those associated with high oestrogen levels
- cirrhosis of the liver (p. 369)
- malnutrition
- some drugs, e.g. chlorpromazine, spironolactone, digoxin
- Klinefelter's syndrome (p. 498), a genetic disorder with testicular atrophy and absence of spermatogenesis.

Malignant tumours

These sometimes develop in men, usually in the older age groups. One per cent of all breast cancers occur in men.

Male infertility

This may be due to endocrine disorders, obstruction of the deferent duct, failure of erection or ejaculation during intercourse, vasectomy, or suppression of spermatogenesis by, for example, ionising radiation, chemotherapy and other drugs.

SPOT CHECK

11. What is a hydrocele?
12. What is the name given to benign breast enlargement in men?

Case study

Sally has been trying to conceive for eight months. Despite regular sexual intercourse with her partner, she has not yet become pregnant. The nurse advises her to keep a diary of her menstrual periods.

1. Sally begins her diary on day 1 of her next menstrual period. Which layer of the uterine wall is shed during menstruation?

   a. The basal layer
   b. The luteal layer
   c. The functional layer
   d. The germinal layer

2. The nurse explains that further tests may include measurement of serum progesterone levels. This is because:

   a. High circulating progesterone levels in the first half of the cycle stimulate the uterine lining
   b. Rising progesterone levels in the second half of the cycle indicate that ovulation has occurred
   c. A progesterone spike mid-cycle triggers ovulation
   d. Unless progesterone levels are low in the second half of the cycle, implantation cannot occur

3. Two months later, Sally is delighted to find herself pregnant. A routine scan suggests she is nine weeks into the pregnancy. At this stage the developing baby is called a:

   a. Blastocyst
   b. Fetus
   c. Embryo
   d. Zygote

4. Which hormone ensures the myometrium relaxes and stretches as the pregnancy develops, rather than contracting and expelling the uterine contents?

   a. Progesterone
   b. Oestrogen
   c. Human chorionic gonadotrophin
   d. Inhibin

Review and revise

Complete the following statement:

1. The vaginal wall has three layers. The inner lining is made of _____ squamous _____; the middle layer is made of _____; and the outer layer is _____ tissue. The walls of the vagina form _____, folds that allow it to expand during sexual intercourse and childbirth. At its superior end the _____ projects into the vagina.

Choose one answer to complete each of the following statements:

2. Leiomyomas are also called: _____
   a. Adenomyomas
   b. Fibroids
   c. Uterine cysts
   d. Hydroceles

3. The corpus cavernosum surrounds the: _____
   a. Penis
   b. Corpus spongiosum
   c. Epididymis
   d. Urethra

4. The ejaculatory ducts are formed by the union of: _____
   a. Ureter and urethra
   b. Deferent duct and duct from seminal vesicle
   c. Prostatic duct and seminal vesicle
   d. Prostatic duct and urethra

5. Benign prostatic hypertrophy: _____
   a. Obstructs the urethra
   b. Predisposes to malignancy
   c. Is rare in older men
   d. Is the result of a viral infection

6. Classify the structures in the following list into internal or external genitalia:
   Labia majora _____
   Vagina _____
   Labia minora _____
   Uterus_____
   Uterine tubes _____
   Clitoris _____
   Hymen _____
   Ovary _____
   Vestibule _____

For a range of further self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/

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Answers to self-assessment and case study questions

Chapter 1

Spot check

1. Differentiation is the specialisation of cell structure and function to carry out particular functions. For example, nerve cells transmit electrical impulses; muscle cells contract.
2. Arteries carry blood away from the heart.
3. A neurotransmitter is a chemical released by a nerve ending that enables it to transmit electrical impulses to the next nerve or an effector organ.
4. The body is upright with the head facing forward, the arms at the side with the palms facing forward, and the feet together. Using the anatomical position enables consistent description of body parts and their interrelationships.
5. The axial skeleton consists of the skull, vertebral column, sternum and ribs.
6. The liver is situated in the right hypochondriac region.
7. At maturity, many organs, including the heart and kidneys, have 'spare capacity' that gradually declines in later life, meaning that significant tissue loss is needed to impair body function.
8. Congenital conditions are present at birth; acquired conditions develop after birth.

Case study

1. c.
2. b.
3. a.
4. d.

Review and revise

1. Arteries, veins, capillaries.
2. Puberty, menopause.
3. b.
4. d.
5. F.
6. T.
7. (a) 4, (b) 8, (c) 7, (d) 3, (e) 2, (f) 6, (g) 9, (h) 10, (i) 5, (j) 1.
8. (a) 7, (b) 5, (c) 2, (d) 1, (e) 6, (f) 8, (g) 3, (h) 4.

Chapter 2

Spot check

1. There are three isotopes of hydrogen. Isotopes of the same element have the same number of protons but different numbers of neutrons in their atomic nuclei. The most common isotope of hydrogen has one proton in its nucleus (all atoms with one proton in the nucleus are, by definition, hydrogen atoms) and one orbiting electron. Deuterium has one proton, one electron and one neutron. Tritium has one proton, one electron and two neutrons.
2. The body fluids contain buffers, which resist changes in pH by mopping up excess H^+ or OH^- ions. These excess ions are then disposed of by the organs of excretion, most significantly the lungs and the kidneys.
3. Amino acids contain a hydrogen ion, an amino group (NH_2), a carboxyl group (COOH) and a variable side chain, and so contain nitrogen, carbon, oxygen, hydrogen and sometimes other atoms such as sulphur. Monosaccharides, on the other hand, contain only carbon, hydrogen and oxygen, usually in the fixed ratio of 1:2:1 and arranged in a ring.
4. Enzymes are biological catalysts that speed up chemical reactions in the body. The enzyme molecule contains an active site, to which the reactants bind. In catabolic reactions the reactants are bound together into a larger product, whereas anabolic reactions break the substrate into smaller molecules.
5. When body temperature starts to fall, the temperature regulatory centre in the hypothalamus detects the change and responds in several ways. One response involves activating shivering to generate extra heat. The skeletal muscles are the effectors, as they are responsible for generating the heat to reverse the fall in body temperature. When body temperature returns to within the normal range, this too is detected by the hypothalamus, which then turns the shivering response off (negative feedback).

6. This process is osmosis. A hypotonic solution has more water molecules (i.e. is more dilute) than the contents of the red blood cell. To equalise water concentrations on either side of the red blood cell membrane, water enters the cell, which swells and may burst.

Case study

1. b.
2. a.
3. d.
4. b.
5. c.

Review and revise

1. Nucleus, protons, neutrons, electrons, negative.
2. ATP, ribose, phosphate, adenine.
3. a.
4. d.
5. (a) 1, (b) 2, (c) 5, (d) 4, (e) 3, (f) 5, (g) 1, 3.
6. (a) 6, (b) 3, (c) 1, (d) 1, (e) 5, (f) 2, (g) 4.

Chapter 3

Spot check

1. Particles too large to cross the plasma membrane are engulfed by cytoplasmic extensions, forming a membrane-bound vacuole inside the cell. Lysosomes then adhere to this and release enzymes that digest the contents of the vacuole.
2. Interphase is the period between two cell divisions and has three separate stages: the first gap phase (G_1), the synthesis (S) phase and the second gap phase (G_2). This is followed by the M phase: mitosis, which has four stages: prophase, metaphase, anaphase and telophase, and cytokinesis.
3. Mucous membrane is made from epithelial cells interspersed with mucus-secreting goblet cells. Mucus keeps the surface moist, protects it from mechanical and chemical damage and traps invading microbes.
4. Secretions from exocrine glands are released into hollow organs either directly or through a duct. Secretions from endocrine glands are called hormones; they are released into the capillaries surrounding the gland and travel to their target tissue in the bloodstream.
5. Hypertrophy describes cells that are larger than normal, often in response to changing demands whereas hyperplasia refers to increased cell numbers. Both processes increase the overall size of the tissue or organ.
6. Apoptosis.
7. Avoiding or stopping smoking, maintaining a healthy diet and normal body weight, taking regular exercise.
8. Local spread may occur when surrounding tissues are invaded by a tumour. Cells escaped from a tumour in a body cavity may migrate to another area of the cavity and divide forming a new tumour. If a vessel wall is eroded by a tumour, cells may escape into the blood and lymph and be transported to a distant site where they become lodged and divide forming metastases.

Case study

1. b.
2. c.
3. d.
4. a.
5. a.

Review and revise

1. Receptors, immunological identity (or 'self recognition' sites), pumps.
2. Centrioles, mitotic spindle.
3. Epithelial (epithelium), connective, muscle, nervous.
4. c.
5. b.
6. F.
7. T.
8. F.
9. (a) 5, (b) 1, (c) 2, (d) 4, (e) 8, (f) 7, (g) 6, (h) 3.
10. (a) 7, (b) 6, (c) 5, (d) 2, (e) 1, (f) 8, (g) 3, (h) 4.

Chapter 4

Spot check

1. As immunoglobulins (antibodies), transport – e.g. of hormones in the plasma, and as enzyme inhibitors in the regulation of enzyme activity.
2. Water (90%).
3. The red blood cell is flexible to squeeze through narrow capillaries. Nearly all of the internal space is packed with haemoglobin for gas transport. Biconcave discs increase the surface area to volume ratio for efficient gas diffusion. The flattened disc shape allows stacking in the bloodstream for smooth blood flow.
4. The ability of a cell to migrate actively through an intact capillary wall.
5. A platelet plug is a soft, temporary mass of platelets formed in rapid response (within a few minutes) to blood vessel injury. As clotting proceeds, it is converted into a sturdier, more stable clot, mainly by the deposition of fibrin strands.
6. This autoimmune condition is a form of anaemia caused by autoantibodies against intrinsic factor (IF) and the gastric parietal cells that produce it. Without adequate IF, vitamin B_{12}, essential for red blood cell production, cannot be absorbed.

7. In this inherited disorder, abnormal haemoglobin molecules change shape when bound to oxygen, which in turn distorts the red blood cell. The irregular shape of sickled cells greatly increases turbulence in the bloodstream and damages them, leading to early haemolysis and anaemia.
8. Leukaemia is a malignant proliferation of white blood cell precursors in the bone marrow, crowding out erythrocyte and thrombocyte precursors and leading to anaemia and also prolonged clotting times.
9. Chronic myeloid leukaemia.
10. Fat absorption is reduced in coeliac disease; this can lead to deficiency of the fat-soluble vitamins, including vitamin K, which is required for clotting factor synthesis.

Case study

1. b.
2. d.
3. a.
4. d.

Review and revise

1. Haem, four, iron, oxygen, 280, liver, bilirubin.
2. d.
3. b.
4. c.
5. (a) 3, (b) 5, (c) 4, (d) 2, (e) 6, (f) 1.
6. (a) 3, (b) 8, (c) 6, (d) 1, (e) 5, (f) 9, (g) 2, (h) 7, (i) 4.

Chapter 5

Spot check

1. From outside to inside: the tunica externa supports, protects and isolates the vessel from adjacent structures; the tunica media contains mainly elastic tissue in larger arteries, but mainly muscle in small arteries (arterioles) for control of blood flow and blood pressure; the tunica intima (endothelium) is a smooth, low-friction lining a single cell thick, which minimises blood turbulence, and releases important chemical factors to reduce the risk of inappropriate blood clotting.
2. Both are permeable vessels whose thin walls consist of a layer of endothelium a single cell thick sitting on a basement membrane; they are important in the exchange of substances between the blood and the tissues. Sinusoids are more permeable than capillaries, though, and are found in organs such as the liver, where it is important that the blood comes directly into contact with the local tissues.
3. The heart sits immediately behind the sternum, occupying the lower part of the mediastinum, with its lower portion (the apex) tilted to the left. The apex sits directly on the diaphragm. Running behind the heart are the aorta, the trachea, the oesophagus and the vertebral column. Laterally lie the lungs and the pulmonary arteries and veins. The superior and inferior venae cavae are also immediately adjacent.
4. The sinoatrial node acts as the heart's pacemaker and generates the electrical signal that triggers each heartbeat. When it fails, its pacemaker function can be taken over by another area of the heart, usually the atrioventricular node, which will keep the heart beating but at a significantly lower rate.
5. Systolic blood pressure is the peak pressure produced in the vascular system by ventricular contraction. Diastolic pressure is the lowest pressure, when the heart is actually resting, but pressure is maintained by vascular tone (i.e. the degree of constriction of the blood vessels).
6. When blood pressure rises, stretch receptors (baroreceptors) in the walls of the aorta and carotid arteries are stimulated, increasing their input to the cardiovascular centre in the brain stem. The cardiovascular centre responds by slowing the heart down and dilating blood vessels (increased parasympathetic and decreased sympathetic activity), which lowers blood pressure.
7. Obstruction to or limitation of blood flow in the lower limb, e.g. peripheral vascular disease, can block the pressure wave from some heartbeats from reaching the most distal blood vessels; so a pulse rate counted close to the heart, e.g. the carotid pulse, can be higher than a distal pulse rate, e.g. at the dorsalis pedis artery.
8. Ascending aorta, arch and descending aorta.
9. The blood travels through two separate capillary beds between the arterial and venous circulations. In the hepatic portal system, blood flows through the gastrointestinal capillaries, absorbing products of digestion, then through the hepatic portal vein, which breaks up into capillaries in the liver before finally returning to the venous circulation in the hepatic vein.
10. The placenta is a pancake-shaped organ, weighing about 500 g at maturity; it is about 20 cm wide and 2.5 cm thick. One of its flat faces is firmly anchored to the wall of the uterus, and extending from the other face is the umbilical cord containing the umbilical arteries and vein, which circulate the fetal blood through the placental villi. As the fetal blood passes through the placenta, it picks up oxygen, glucose and other nutrients from the maternal blood, and excretes wastes.
11. The ductus venosus is a short vessel linking the umbilical vein, carrying oxygenated blood from the placenta to the fetus, and the inferior vena cava; it bypasses the fetal liver.
12. Age-related reduction in heart muscle strength and blood flow can be minimised by lifestyle factors such as regular exercise and healthy diet.

13. Compensation refers to the compensatory mechanisms activated when blood flow to body organs falls in the early stages of shock. These help to maintain blood pressure and flow, and include sympathetic stimulation, increased heart rate and contractility, increased respiratory effort and vasoconstriction in non-essential organs. As long as these measures maintain adequate circulation to the tissues, the shock is said to be compensated.
14. Anaphylaxis leads to the release of large amounts of inflammatory mediators such as histamine and bradykinin into the bloodstream. These chemicals cause widespread vasodilation and increased vascular permeability, and so can drastically reduce blood pressure very quickly. They also cause bronchoconstriction, preventing adequate gas exchange in the lungs.
15. A thrombus is a static blood clot. An embolism is a solid mass of material, such as a fragment of a blood clot or a globule of fat, travelling in the bloodstream.
16. Ischaemia is impaired cell function caused by inadequate oxygen supply and the accumulation of wastes, and it may be reversible if not too severe or too prolonged. Infarction means cell death due to inadequate blood supply.
17. A fatty streak is the initial stage of a plaque, in which fatty material is deposited along the wall of an artery. As it grows into a mature plaque, it becomes much thicker, accumulating additional fatty material infiltrated with fat-laden macrophages (foam cells) and smooth muscle cells. Its cover (cap) is rough and can rupture, causing thrombosis.
18. A varicose vein is a stretched and bulging section of vein, usually in the leg, in which the valves have failed to prevent backflow of blood. The pooling blood stretches the vein, so the valves become less and less effective and the veins progressively more and more distended.
19. If the left ventricle is not pumping out the blood being delivered to it, the pressure inside the left ventricle will start to rise, backing up through the left atrium and the pulmonary veins, and finally into the low-pressure pulmonary capillaries. When pressure rises here, fluid is forced into the alveoli, causing pulmonary oedema.
20. The liver produces most plasma proteins, which maintain the osmotic pressure of the blood. If the liver fails and plasma protein production falls, the osmotic pressure also falls and fluid moves out of the bloodstream into the tissues and body cavities, including the abdominal cavity.
21. A heart murmur is an abnormal heart sound made by a faulty heart valve, commonly an atrioventricular valve.
22. The antibodies to the bacterium produced in response to the throat infection can attack and damage heart tissue, including the valves and the myocardium, leading to rheumatic heart disease.
23. Primary hypertension (about 90% of cases) has no single identified cause, whereas secondary hypertension is due to another condition.
24. Retinal capillaries can be viewed directly through an ophthalmoscope.

Case study 1

1. d.
2. a.
3. c.
4. b.

Case study 2

1. c.
2. a.
3. d.
4. b.

Review and revise

1. Four, atria, ventricles, septum, atrioventricular, endocardium, myocardium.
2. Right subclavian; right axillary; right brachial; right radial, right ulnar; right palmar; right digital arteries.
3. b.
4. d.
5. c.
6. a.
7. c.
8. d.
9. b.
10. Right atrium, right atrioventricular valve, right ventricle, pulmonary artery, pulmonary capillaries, pulmonary vein, left atrium, left atrioventricular valve, left ventricle, aortic valve, aorta, systemic arteries, systemic capillaries, systemic veins, right atrium.
11. (a) 4, 5, 7, 8; (b) 1, 3, 6; (c) 2.

Chapter 6

Spot check

1. The right lymphatic duct.
2. Three of: valves; compression from adjacent skeletal muscle; fall in pressure in the thoracic cavity during inspiration; action of smooth muscle within lymph vessel walls.
3. A lymph node is roughly bean-shaped, and somewhere in size between a pinhead and an almond. Each node is contained within a capsule; lymph enters through multiple afferent lymph vessels but drains away through only one efferent vessel. The interior of the node is made up mainly of lymphatic tissue, subdivided by trabeculae.

4. As sinusoids are very permeable, this allows the blood cells to come into contact with the splenic pulp, which can then extract old or damaged cells and destroy them.
5. Surgical removal of the breast (mastectomy) usually includes adjacent lymph nodes, which interrupts lymph drainage and causes lymphoedema of the arm.
6. Pathogens draining from the site of infection enter the lymph and are carried to local lymph nodes, where they can establish themselves and cause a degree of inflammation (lymphadenitis).
7. Poorly differentiated cells mean faster development of the disease and a poorer prognosis.

Case study

1. b.
2. d.
3. c.
4. a.

Review and revise

1. Oval, 200, capsule, hilum, splenic, stomach/pancreas/large intestine and left kidney.
2. Cervical, axillary, inguinal.
3. d.
4. c.
5. a.
6. (a) 3, 4, 7, 8; (b) 2, 5, 6; (c) 1, 2, 3.

Chapter 7

Spot check

1. Movement of ions (principally Na^+ and K^+) across nerve cell membranes enables generation of the action potential. At rest the nerve cell membrane is polarised, i.e. it has a different charge on each side of the plasma membrane. When the membrane is stimulated, the permeability to Na^+ immediately increases and Na^+ floods into the cell, causing depolarisation, which generates the action potential. The wave of depolarisation quickly spreads distally, transmitting the impulse. K^+ floods out of the cell, restoring the original charge of the membrane. The original levels of Na^+ and K^+ inside and outside the cell are then restored by the action of the sodium–potassium pump.
2. The nodes of Ranvier, present in myelinated nerves, allow 'saltatory conduction' of action potentials, where the action potential leaps from one node to the next. Saltatory conduction is faster than simple propagation, also known as continuous conduction, the method of conduction used in unmyelinated nerves.
3. Cerebrospinal fluid (CSF) is continually secreted by ependymal cells in the choroid plexuses into the ventricles of the brain. The arachnoid villi in the venous sinuses act as valves, pushing CSF back into the blood when the CSF pressure is higher than the venous pressure so that CSF volume remains fairly constant.
4. Motor areas direct movement of the skeletal muscles; sensory areas receive and interpret impulses, enabling sensory perception; and association areas are involved in higher mental functioning, e.g. reasoning, judgement and emotional responses.
5. The brain has considerable cognitive reserve and memory may not be affected, although commonly it becomes harder to access more recent memories. Some older adults are susceptible to severe and progressive cognitive impairment, e.g. dementia.
6. A child's skull is not completely ossified to allow for growth of the brain, so accumulation of fluid can force the skull bones apart and enlarge the cranium. In the adult ossified skull, this is not possible and an increase in cerebrospinal fluid volume (hydrocephalus) will increase intracranial pressure.
7. There is progressive degeneration of neurones that use dopamine as their neurotransmitter, especially around the basal ganglia. The lack of dopamine, which gives fine control to muscle movement, causes the signs and symptoms of Parkinson's disease, such as slow movements and difficulty initiating them, shuffling gait and stooping posture, lack of facial expression and muscle tremors of the extremities.
8. Both are caused by the herpes zoster virus. Chickenpox is usually contracted in childhood and can be reactivated as shingles throughout life. Chickenpox can be contracted from someone with shingles but not vice versa. After the infection has resolved, the virus may remain dormant in the posterior root ganglia and become active again, causing shingles years later.
9. Myelin in central nervous system nerve fibres is progressively and irreversibly lost (demyelination). Typically, there are periods of relapse, interspersed with remission. Ongoing loss of nervous tissue impairs vision (blurring and double vision are common), causes weakness (sometimes paralysis) of skeletal muscles and incontinence, and disrupts sensation.
10. Usually no cause is identified although it is sometimes inherited.
11. An intervertebral disc has a soft core called the nucleus pulposus, which is surrounded by an outer layer of cartilage, the annulus fibrosus. When a disc prolapses, there is herniation of the nucleus pulposus, which causes the annulus fibrosus to protrude into the neural canal and compress the spinal cord.

12. Compression of a facial nerve causes unilateral drooping and loss of facial expression. Bell's palsy is thought to be caused by viral inflammation and usually resolves spontaneously in a couple of months.
13. Dietary deficiency of folic acid at the time of conception is associated with spina bifida. It may also be associated with exposure to X-rays and maternal rubella during fetal development.

Case study 1

1. b.
2. a.
3. d.
4. a.

Case study 2

1. b.
2. d.
3. c.
4. a.

Review and revise

1. Neurones; neuroglia; any two of: astrocytes, oligodendrocytes, ependymal cells, microglia.
2. Synapse, neurotransmitter, synaptic vesicles, synaptic cleft.
3. Reflex, posterior (dorsal), anterior (ventral).
4. 31, 12.
5. Alzheimer's disease; multi-infarct (or vascular); [any one of] syphilis, HIV, Creutzfeldt–Jakob disease.
6. b.
7. a.
8. d.
9. b.
10. b.
11. T.
12. T.
13. F.
14. T.
15. F.
16. (a) 7, (b) 5, (c) 3, (d) 8, (e) 6, (f) 4, (g) 2, (h) 1.
17. (a) 2, (b) 7, (c) 5, (d) 6, (e) 1, (f) 3, (g) 8, (h) 4.
18. (a) 5, (b) 7, (c) 3, (d) 8, (e) 4, (f) 2, (g) 1, (h) 6.
19. (a) 4, (b) 8, (c) 6, (d) 7, (e) 1, (f) 2, (g) 3, (h) 5.

Chapter 8

Spot check

1. Also known as the auditory canal, this S-shaped tube collects, funnels and transmits sound waves to the middle ear. The lateral third contains hairs that trap foreign bodies and ceruminous glands (modified sweat glands) that secrete earwax, which contains lysozyme (a bactericidal enzyme).
2. The vibrations generated by the tympanic membrane (eardrum) when sound waves strike it are amplified and transmitted across the middle ear by movement of the chain of three ossicles.
3. The walls of the fluid-filled utricle, saccule and ampulla of the semicircular canals contain hair cells that are the sensory receptors of balance. As the head moves, resultant movement of the perilymph and endolymph in the vestibule and semicircular canals stimulates the hair cells, generating nerve impulses in the vestibulocochlear nerve. These impulses are conducted to the cerebellum, where they are integrated and processed with visual and proprioceptor impulses so that balance is maintained.
4. Constriction of the pupils, convergence of the eyes and increase of the refractory power of the lens.
5. Reflex closure when touched or when bright light shines into the eyes protects the internal structures, while blinking spreads tears and oily secretions over the cornea, keeping the anterior structures moist.
6. The sense of smell.
7. Sweet, sour, bitter and salt.
8. Presbyopia.
9. Also known as serous otitis media, glue ear is a collection of serous fluid in the middle ear cavity.
10. This type of hearing impairment arises from abnormality of the nerves of the inner ear, cochlear nerve or auditory area of the cerebrum (compare with conductive hearing impairment).
11. Opacity of the lens that impairs passage of light waves thorough it, especially when it is dark or the light is poor.
12. It is the only source of arterial blood to the eye.
13. Myopia.

Case study

1. d.
2. c
3. b
4. a.

Review and revise

1. Roof, olfactory bulb, olfactory tract, cerebral cortex/cerebrum.
2. Otitis media, auditory tube, pus, tympanum/tympanic membrane.
3. a.
4. c.
5. F.
6. T.
7. (a) 3, (b) 6, (c) 8, (d) 1, (e) 4, (f) 7, (g) 5, (h) 2.
8. (a) 6, (b) 4, (c) 3, (d) 7, (e) 5, (f) 1, (g) 8, (h) 2.

Chapter 9

Spot check

1. The anterior pituitary is supplied with blood from the pituitary portal system, which contains releasing and inhibiting hormones secreted by the hypothalamus. These influence secretion of other specific anterior pituitary hormones into the bloodstream.
2. Calcitonin.
3. When blood calcium levels are low, parathyroid hormone (PTH) secretion is stimulated. PTH increases blood calcium levels by releasing calcium stored in bone by stimulating osteoclasts (bone-destroying cells) to release calcium from bone tissue, and by increasing its reabsorption from the renal tubules.
4. Glucocorticoids, mineralocorticoids and sex hormones (gonadocorticoids).
5. Glucagon.
6. Night time.
7. Placenta, intestinal mucosa, kidney.
8. Mast cells in the tissues and basophils in blood.
9. Type 2 diabetes.
10. Diabetes insipidus.
11. Any six of: high metabolic rate, weight loss with good appetite, anxiety, restlessness, tachycardia, palpitations, atrial fibrillation, feeling warm, heat intolerance and exophthalmos in Graves' disease.
12. A benign parathyroid tumour.
13. Hypertension, adiposity of the face, neck and abdomen, muscle wasting, osteoporosis and pathological fractures, hyperglycaemia and glycosuria, thinning of the skin, peptic ulceration.
14. They secrete the sympathetic hormones adrenaline (epinephrine) and noradrenaline (norepinephrine), which cause these effects.
15. Glucose is not normally present in urine, as it is all absorbed by the renal tubules. In DM, some glucose remains in the renal filtrate, increasing the osmotic pressure. Less water is reabsorbed and the volume of urine is therefore increased (polyuria). Polyuria leads to dehydration and thirst (polydipsia), which is quenched by increasing fluid intake.

Case study

1. a.
2. b.
3. d.
4. a.

Review and revise

1. Capillaries, hormones, target tissue/organs.
2. Angiopathies, diabetic retinopathy, diabetic nephropathy.
3. a.
4. c.
5. T.
6. F.
7. (a) 3, (b) 6, (c) 8, (d) 1, (e) 4, (f) 7, (g) 5, (h) 2.
8. (a) 6, (b) 4, (c) 3, (d) 7, (e) 5, (f) 1, (g) 8, (h) 2.

Chapter 10

Spot check

1. Ethmoid (septum, lateral wall and roof), vomer (septum), maxilla (floor), sphenoid (roof), nasal (roof), frontal (roof), palatine (floor), inferior concha (wall).
2. This area of specialised epithelium is found in the lining of the roof of the nose. It detects molecules of odorous materials and transmits nerve signals along the olfactory nerve to the brain, where the sensation of smell is perceived.
3. The lingual tonsils are found on either side of the base of the tongue (see also Fig. 6.6), the pharyngeal tonsils lie in the nasopharynx and the palatine tonsils are in the oropharynx.
4. The middle ear and the nasopharynx.
5. The epiglottis, thyroid, cricoid cartilages (all single) and the arytenoid cartilages (paired).
6. Sound, including speech, is generated by vibrations of the true vocal cords. Pitch is determined by the length and tightness of the cords. Volume is determined by the strength of vibration of the cords, so the more forceful the air flow, the louder the sound.
7. The tracheal cartilages are C-shaped, with the oesophagus sitting against the gap at the back, allowing the oesophagus to expand comfortably when swallowing.
8. This is ciliated columnar epithelium containing goblet cells for mucus production. The cilia sweep the blanket of mucus along with adherent particles towards the mouth for swallowing.
9. The apical surface covers the lung tips and the base is the inferior surface, which sits on the diaphragm. The medial surfaces face into the mediastinum, and the hilum of the lung is found here. The costal surfaces are the broad outer surfaces of the lungs that lie immediately below the ribcage.
10. It allows the lungs to expand during inspiration, and also to return to their original size by elastic recoil during expiration.
11. It allows for adjustment of bronchiolar diameter, to regulate airflow through different areas of the lungs.

12. The main cell type is squamous epithelium, which is only one cell thick. The outer surface of each alveolus is wrapped in a dense network of blood capillaries to maximise gas exchange. Macrophages are also found in the alveolar wall, for defence, as well as septal cells, which produce surfactant.
13. Contraction (and descent) of the diaphragm, and contraction of the external intercostal muscles, which lifts and expands the ribcage.
14. The inspiratory and expiratory reserve volumes.
15. Found on the surface of the brain, and also in the aorta and carotid arteries, these chemoreceptors are very sensitive to even slight increases in carbon dioxide levels and stimulate breathing in response. They also respond to falling oxygen levels, but oxygen levels have to fall significantly before this triggers these chemoreceptors.
16. The cartilages associated with the ribcage, e.g. the costal cartilages, become stiffer and the respiratory musculature becomes weaker with age, in line with a general decline in age-related muscle strength.
17. Both are viral but caused by different groups of viruses. Influenza is much more severe and runs a longer course than a cold; it is associated with muscle pain, high temperature and an increased risk of secondary bacterial chest infections.
18. Airflow through obstructed airways is reduced or even stopped altogether, meaning that the volume of fresh air reaching the alveoli falls. This leads to accumulation of carbon dioxide in the distal airways and alveoli, and a reduction in the pressure gradient between the air in the alveoli and the bloodstream. As the pressure gradient reduces, diffusion also reduces and less carbon dioxide passes into the bloodstream for excretion.
19. This is air in the tissues of the chest; air can leak into the tissues from damaged alveoli or from the external environment if the chest wall is damaged, e.g. by a broken rib.
20. Asbestos, especially blue asbestos, fibres are so tiny that they can travel all the way through the respiratory tree to the alveoli, where they trigger a protective inflammatory response, mediated by alveolar macrophages. This can lead to progressive fibrotic changes that destroy lung tissue and increase the risk of a certain form of lung cancer, mesothelioma.
21. Lobar pneumonia refers to disease restricted to a discrete lung lobe or lobes, whereas bronchopneumonia is diffuse infection spread throughout lung tissue.
22. This is reactivation, after a variable period, of latent tuberculosis that has not been resolved from the initial (primary) infection.
23. Usually centrally, in a main bronchus.
24. The lungs of a premature baby may not have developed sufficiently to produce surfactant in sufficient quantities to keep the alveoli open, so large sections of the lung can fail to expand at birth.
25. This is due to penetrating injury that damages the pleura and opens up the pleural space, sucking air into the pleural space (because the intrapleural pressure is lower than atmospheric pressure) and collapsing all or part of the soft lung in the region of the breach.

Case study

1. a.
2. d.
3. b.
4. c.
5. d.

Review and revise

1. Alveoli, *Streptococcus*, *influenzae*, lobar, bronchopneumonia.
2. Base, apex, diaphragm, mediastinum, aorta/bronchi/heart/venae cavae/oesophagus/trachea, lobes, liver.
3. b.
4. a.
5. c.
6. d.
7. a.
8. b.
9. c.
10. (a) 1, (b) 6, (c) 8, (d) 5, (e) 7, (f) 3, (g) 3, (h) 4, (i) 2.
11. (a) 3, (b) 6, (c) 1, (d) 7, (e) 4, (f) 2, (g) 5.

Chapter 11

Spot check

1. Women 2000 kcal (8400 kJ), men 2500 kcal (10,500 kJ).
2. Carbohydrates, proteins, fats, vitamins and mineral salts, trace elements and water.
3. Essential amino acids (or other essential nutrients) must be included in the diet, as they cannot be made in the body.
4. A, D, E and K.
5. Calcium.
6. Any two of: bulking up the diet, which satisfies the appetite; preventing constipation by stimulating peristalsis and increasing faecal volume; protecting against some gastrointestinal conditions, including colorectal cancer and diverticular disease.
7. Vitamin D.
8. 18.5–24.9.

Case study

1. b.
2. a.
3. c.
4. b.

Review and revise

1. Saturated, unsaturated, animal, plants/vegetables.
2. DNA, megaloblastic, terminal ileum (small intestine), intrinsic factor.
3. F.
4. T.
5. (a) 2, (b) 3, (c) 8, (d) 4, (e) 1, (f) 6, (g) 7, (h) 5.

Chapter 12

Spot check

1. Three pairs of salivary glands, the pancreas and the liver.
2. Adventitia (serosa), muscle layer, submucosa and mucosa.
3. Chewing, swallowing, speech and taste.
4. Salivary amylase digests complex sugars to the disaccharide maltose; lysozyme is an antimicrobial enzyme.
5. Oropharynx, laryngopharynx.
6. Oral (voluntary), pharyngeal (involuntary), oesophageal (involuntary).
7. The mucus prevents mechanical injury by lubricating stomach contents, and prevents chemical injury by forming a barrier between the stomach wall and the corrosive gastric juice.
8. The pyloric sphincter guards the opening into the small intestine from the stomach, and the ileocaecal valve controls passage into the large intestine.
9. The extensive capillary network in the villus facilitates absorption of the water-soluble carbohydrates and polypeptides, and the central lymph channel (lacteal) facilitates diffusion of fatty acids and glycerol from the alimentary tract for use by the body.
10. Caecum, colon, rectum and anal canal.
11. Secretion is stimulated by parasympathetic activity and suppressed by sympathetic stimulation.
12. The portal vein enters, carrying blood from the stomach, spleen, pancreas and small and large intestines through the liver on its way back to the heart. The hepatic artery enters, carrying oxygenated blood. (Venous drainage of the liver is through the hepatic veins, which do not leave via the portal fissure.) The left and right hepatic ducts leave the liver, transporting bile to the gall bladder, and lymph vessels leave, draining lymph to the abdominal and thoracic lymph nodes.
13. Left/right hepatic duct, hepatic duct, cystic duct, gall bladder (storage until required), cystic duct, common bile duct, hepatopancreatic ampulla, duodenum.
14. It inactivates salivary amylase and converts pepsinogen into the proteolytic enzyme pepsin.
15. Anabolism means synthesis of larger molecules from smaller ones and usually requires adenosine triphosphate (ATP). Catabolism involves the breakdown of large molecules into smaller ones, often releasing energy that can be used to synthesise ATP.
16. Glycolysis, the citric acid cycle and oxidative phosphorylation.
17. The reserve capacity typically declines with age and this may lead to impaired liver function. This is likely to include detoxification of many substances such as drugs, whose blood levels may then become toxic.
18. *Candida albicans.*
19. Mumps.
20. Oesophageal atresia, tracheo-oesophageal fistula.
21. *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs).
22. Public health measures, including uncontaminated drinking water, effective disposal of sewage and safe food hygiene practices; education of individuals about spread by the faeco–oral route and an emphasis on handwashing after defaecation and handling of potentially contaminated items.
23. Protrusion of an organ or part of it through an aperture or weak point in surrounding structures.
24. Most tumours arise in the head of the pancreas, and as they grow they obstruct the flow of bile, causing jaundice.
25. Hepatitis A is spread via the faeco–oral route; it may be asymptomatic and there is no carrier state. Hepatitis B is transmitted by contaminated blood and body fluids, e.g. saliva and semen of both carriers and actively infected people.
26. The common bile duct.

Case study 1

1. b.
2. d.
3. b.
4. c.

Case study 2

1. a.
2. a.
3. c.
4. d.
5. a.
6. b.

Review and revise

1. Saliva, pepsinogens, bile.
2. Incisors, canines, premolars, molars.
3. Lobules, hepatocytes, sinusoids, portal, hepatic.
4. Glycolysis, citric acid (Krebs) cycle, oxidative phosphorylation.
5. *Helicobacter pylori*, male, stomach, duodenum.
6. a.
7. d.
8. b.
9. c.
10. d.
11. T.
12. F.
13. F.
14. T.
15. T.
16. (a) 4, (b) 3, (c) 7, (d) 2, (e) 1, (f) 8, (g) 5, (h) 6
17. (a) 8, (b) 2, (c) 4, (d) 7, (e) 3, (f) 5, (g) 1, (h) 6.
18. (a) 4, (b) 7, (c) 8, (d) 5, (e) 6, (f) 2, (g) 1, (h) 3.

Chapter 13

Spot check

1. Filtration, selective reabsorption, secretion.
2. Autoregulation is independent of nervous control and maintains renal blood flow at a fairly constant level across a wide range of systolic blood pressure (80–200 mmHg). Renal blood flow (and glomerular filtration) only becomes impaired when systolic pressure drops profoundly, below about 80 mmHg, e.g. in severe shock.
3. As urine accumulates, the ureters, which are inserted obliquely into the posterior wall of the bladder, are compressed, preventing backflow.
4. The detrusor muscle forms the middle layer of the bladder wall. It consists of smooth muscle fibres and elastic tissue, and when the muscle contracts, the bladder empties.
5. External urethral sphincter.
6. To establish continence (conscious bladder control), it is necessary to learn to control the external urethral sphincter and override the innate spinal reflex until it is convenient to pass urine.
7. Enlargement of the prostate gland.
8. Oliguria – urine output under 400 mL per day, anuria – no urine output, dysuria – pain on voiding.
9. Any three of: ongoing dehydration, alkaline pH of urine, infection of the urinary tract, metabolic conditions, e.g. gout, hyperparathyroidism.

Case study

1. d.
2. c.
3. a.
4. a.
5. c.

Review and revise

1. Antidiuretic hormone (ADH), aldosterone, atrial natriuretic peptide (ANP).
2. Stress, urge, overflow.
3. d.
4. a.
5. F.
6. F.
7. (a) 2, (b) 5, (c) 6, (d) 7, (e) 3, (f) 4, (g) 1.
8. (a) 3, (b) 5, (c) 8, (d) 7, (e) 2, (f) 1, (g) 6, (h) 4.

Chapter 14

Spot check

1. It provides a physical, fairly waterproof barrier against entry of microbes and damage by, for example, chemicals and physical agents; specialised immune dendritic (Langerhans) cells phagocytose invading microbes that do enter through the skin; abundant sensory nerve endings enable reflex withdrawal from harmful stimuli, e.g. heat; and the pigment melanin protects against ultraviolet rays in sunlight.
2. Core temperature below 35°C.
3. Inflammation, proliferation, maturation.
4. Sebaceous glands secrete sebum, which provides some waterproofing. They become more active at puberty but their activity declines with ageing, so that the skin of older individuals is less able to tolerate excessive moisture.
5. Malignant melanoma.

Case study

1. d.
2. b.
3. a.
4. c.

Review and revise

1. Arterioles, convection, evaporation.
2. Superficial (epidermal), partial thickness, full thickness.
3. c.
4. d.
5. (a) 8, (b) 4, (c) 5, (d) 1, (e) 7, (f) 6, (g) 2, (h) 3.

Chapter 15

Spot check

1. Chemotaxis is the active movement of defence cells like neutrophils towards a target such as a bacterium, so that it can attack and destroy it by phagocytosis.
2. Increased temperature tends to inhibit bacterial growth and activity, and enhances the activity of phagocytes.
3. Each immune cell or antibody is designed to target one specific antigen.
4. Regulatory T-cells mediate immunological tolerance, i.e. make sure that the immune response does not direct itself against host tissues. Cytotoxic T-cells are the soldiers of the immune system and directly kill target cells.
5. Type I hypersensitivity (allergy) is an immediate response to an allergen, involving the release of large amounts of histamine. Type IV hypersensitivity is a much slower-onset response and involves abnormally active T-cells, which cause chronic inflammation and tissue damage.
6. HIV targets the immune system, particularly CD_4 T-cells, which means that infected individuals are at increased risk of other infections. Their immunocompromised state allows normally non-pathogenic organisms to establish themselves and cause opportunistic infection.

Case study

1. b.
2. c.
3. a.
4. d.

Review and revise

1. 20, immune complexes, bacteria, binds to and damages bacterial cell walls, binds to bacteria and stimulates phagocytosis, stimulates chemotaxis.
2. a.
3. a.
4. c.
5. (a) 2, 3, 4, 6, 7; (b) 1, 3, 5, 7; (c) 1, 3, 5, 7.

Chapter 16

Spot check

1. Osteoblasts are found in the membranes covering and lining bone and are active in bone building and repair. As they lay down new bone and become encased within it, they differentiate into osteocytes. Osteocytes are mature bone cells that monitor and repair bone and live individually in pockets called lacunae within the bone. If bone is damaged they de-differentiate into osteoblasts again to participate in the repair process.
2. Lengthening of long bones stops when the cartilaginous epiphyseal plates at either end convert to bone. This happens at puberty when levels of the sex hormones (testosterone and oestrogen) rise. Puberty occurs later in males than females and so bones generally have more time to keep lengthening; therefore male adult height is, on average, greater.
3. Squamous suture (with the temporal bone), coronal suture (with the frontal bone), sagittal suture (with the other parietal bone) and the lambdoidal suture (with the occipital bone).
4. This is C7. In common with other vertebrae, it has a rounded body and two transverse processes, and a foramen for passage of the spinal cord. The posterior (spinous) process is large and prominent, and is easily felt through the skin at the base of the neck.
5. On the scapula; the acromion process is the highest point of the shoulder, easily felt under the skin.
6. The two arches of the foot, the transverse and longitudinal arches, are the curved shapes formed by the bones of the foot. They are held in these curves by the ligaments and muscles of the foot. The arched design of the foot allows it to act as a lever to propel the body forwards in walking and running, and absorb the shocks associated with these movements.
7. In rotation the whole structure turns around a central axis, like a pencil being rolled between the palms. In circumduction one end of the structure is fixed and the other end draws a circle.
8. The glenoid cavity also has a rim of fibrocartilage, which makes it deeper, but the shoulder joint depends heavily on a sturdy sleeve of ligaments and muscles to keep the joint in place. Important structures include the glenohumeral and coracohumeral ligaments and the rotator cuff muscles.
9. A motor unit is a motor nerve and all the skeletal muscle fibres it supplies. It can be small (nerve and a few muscle fibres), giving fine control, or large (nerve and thousands of muscle fibres), giving large-scale, powerful movements.
10. The origin of the muscle is the attachment closest to the midline, and is usually the end of the muscle that is fixed (kept stationary) when the muscle contracts. The insertion is the attachment farthest from the midline, and is usually the end that moves when the muscle contracts.
11. Vitamin D. Lack of this vitamin leads to poor bone mineralisation. In children, this leads to bowing of the lower limbs because the bone contains a higher proportion of collagen and is unable to support the weight of the upper body. In adults, whose bones have reached their full length, poor mineralisation leads to osteomalacia, with increased risk of fracture.

12. A malignant bone tumour.
13. Deposition of urate crystals in the joints leads to acute inflammation, which can cause permanent damage if prolonged.
14. The median nerve, as it passes through the carpal tunnel in the wrist, formed by the flexor retinaculum stretched across the front of the carpal bones. Compression of the nerve causes tingling, pain and paraesthesia of the fingers.
15. Acetylcholine (ACh) receptors at the neuromuscular junction. This means a loss of function of skeletal muscles because the ACh released by the motor nerve cannot activate contraction of the muscle.

Case study 1

1. b.
2. d.
3. a.
4. b.
5. c.

Case study 2

1. c.
2. b.
3. a.
4. d.
5. a.

Review and revise

1. 14; zygomatic; orbits; mandible; teeth; ramus; temporal; temporomandibular; hyoid; larynx.
2. Recti abdomini; linea alba; lower ribs; sternum; pubic bone; curls.
3. d.
4. b.
5. d.
6. a.
7. b.
8. d.
9. a.
10. (a) 1, 2, 5; (b) 6, 7, 9; (c) 1, 3, 11; (d) 4, 7, 8, 10.
11. (a) 4, (b) 1, (c) 6, (d) 5, (e) 3, (f) 7, (g) 2.
12. (a) 1; (b) 1, 2, 3; (c) 2; (d) 3; (e) 1; (f) 1, 3.

Chapter 17

Spot check

1. Histones are support proteins incorporated into the highly folded DNA molecule.
2. Guanine.
3. UAACUG.
4. Codon.
5. Because the two gametes (a sperm and an ovum) that fuse at fertilisation to make a new cell, which will develop into a new human being, must each contain only half the normal number of chromosomes (23 instead of 46).
6. Prior to the first meiotic division the replicated chromosomes exchange genes between themselves. This means that the four chromatids now have a new combination of genes and are all different from each other.
7. The chance is 100% because, although the child may receive the recessive non-tongue-rolling gene from the mother, they are also guaranteed to receive a dominant tongue-rolling gene from the father.
8. The chance is 0% because both parents must have two copies each of the recessive O gene, so do not have an A gene to pass to a child.
9. A mutated gene that promotes cell growth and prevents cell death, but can cause cancerous changes in the cell.
10. The gene that produces phenylalanine hydroxylase is faulty and the affected individual does not produce the enzyme, meaning they cannot metabolise phenylalanine, which accumulates in the bloodstream and causes a range of problems including nervous system damage.

Case study

1. b.
2. c.
3. b and d.
4. a.

Review and revise

1. Single gene, phenylalanine hydroxylase, phenylalanine, tyrosine, nervous.
2. b.
3. d.
4. c.
5. (a) 2, (b) 4, (c) 6, (d) 5, (e) 1, (f) 3.
6. 1. RNA; 2. DNA; 3. Both; 4. RNA; 5. Both; 6. DNA; 7. DNA; 8. RNA; 9. DNA; 10. RNA.

Chapter 18

Spot check

1. Rugae are folds in the vaginal wall that expand during childbirth to accommodate delivery of the baby.
2. The myometrium, the uterine muscle, which contracts during childbirth to expel the baby.
3. The deferent duct carries sperm from the testes. The seminal vesicle and prostate gland add their secretions as it passes into the urethra.

4. Corpus spongiosum.
5. The stage of fetal development when the zygote is a hollow ball of 70–100 cells.
6. One month.
7. *Treponema pallidum*.
8. Antibiotics kill the natural bacterial flora of the vagina, allowing other organisms, including *Candida albicans* (which causes thrush), to proliferate.
9. A benign tumour of muscle. When it is found in the uterus, it is called a fibroid.
10. Up to 90% of cases of cervical cancer are due to infection with human papilloma virus, which is sexually transmitted.
11. Accumulated fluid within the tunica vaginalis of the scrotum.
12. Gynaecomastia.

Case study

1. c.
2. b.
3. b.
4. a.

Review and revise

1. Stratified, epithelium, smooth muscle, areolar, rugae, uterine cervix.
2. b.
3. d.
4. b.
5. a.
6. Internal: vagina, uterus, uterine tubes, ovary. External: labia majora, labia minora, clitoris, hymen, vestibule.

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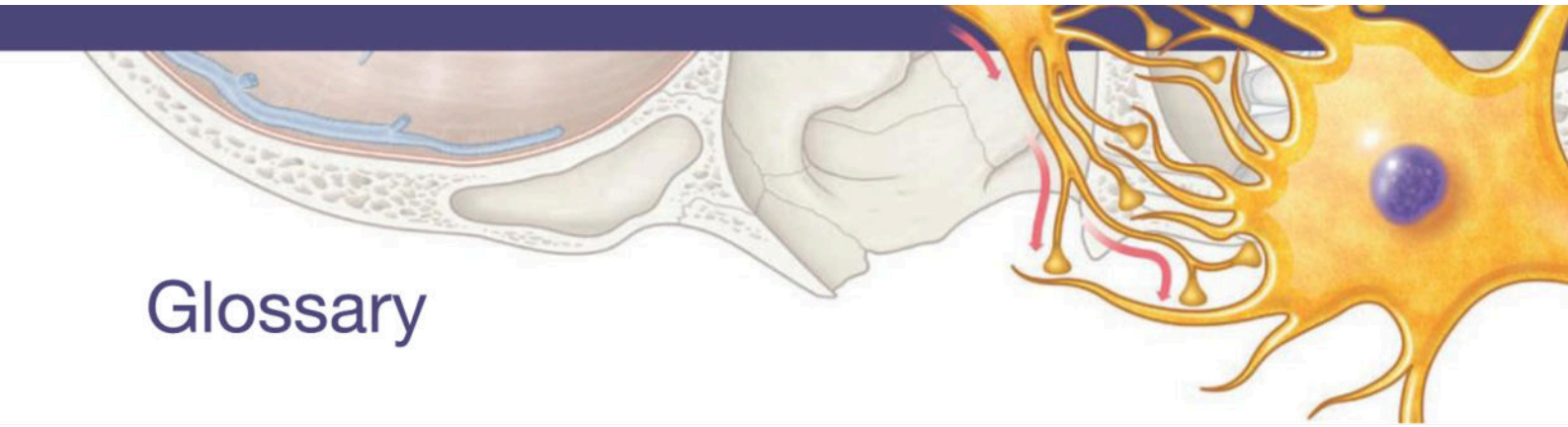


Glossary

Abduction Movement of a body part away from the midline of the body
Abscess Pus-filled cavity within tissue
Accommodation Focusing adjustment of the eyes to view close objects
Acid Substance that releases hydrogen ions in solution
Acidosis Situation when blood pH falls below the normal pH range
Action potential Electrical current (impulse) conducted along a nerve cell (neurone)
Active transport Movement of substances across a cell membrane, up the concentration gradient, and requiring energy
Acute Of sudden onset
Adaptation Lessening of response by sensory receptors to prolonged stimulation
Adduction Movement of a body part towards the midline of the body
Adenosine triphosphate (ATP) Molecular store of chemical energy for chemical reactions
Adhesions Fusion of two separate tissue layers with fibrous tissue, usually following inflammation
Adipose tissue Fat tissue
Aerobic Requiring oxygen
Aetiology Cause of a disease
Afferent Carrying or travelling towards an organ
Afterload Resistance to blood flow from the heart, determined mainly by the diameter of the arteries
Agranulocyte White blood cell with no granules in its cytoplasm (i.e. lymphocytes and monocytes)
Alkali Substance that accepts hydrogen ions in water or solution
Alkalosis Situation when blood pH rises above the normal pH range
Allele Form of a gene carried on a chromosome
Allergy Targeting and destruction of harmless antigens by the immune system, often with detrimental effects on normal body tissues
Alveolar ventilation Amount of air reaching the alveoli with each breath
Alveolus (pl. alveoli) Air sac in the lungs; also, milk-secreting sac in the mammary glands
Amino acid Building block of protein
Anabolism Synthesis of larger molecules from smaller ones
Anaerobic Not requiring oxygen
Anaphase Third phase of mitosis
Anaphylaxis Severest form of allergy, with multiple, potentially fatal, systemic effects
Anastomosis Joining of two tubes, e.g. (i) in blood vessels where there are no capillary beds, (ii) following surgery
Anatomical position Position in which the body is upright, with the head facing forwards, the arms at the sides with the palms of the hands facing forwards, and the feet together; term used to maintain consistency of anatomical descriptions
Aneurysm Weakness in the wall of an artery
Anion Negatively charged ion
Anterior (ventral) Describes a body part or structure lying to the front
Antibody Defensive protein synthesised by B-lymphocytes in response to the presence of antigen
Antigen Protein that stimulates the body's immunological defences
Antimicrobial Substance or mechanism that kills or inhibits growth of microorganisms
Appendicular skeleton (cf. axial skeleton) Shoulder girdle, upper limbs, pelvic girdle and lower limbs
Arrhythmia Abnormal heart rhythm
Arteriole Small artery
Artery Blood vessel that carries blood away from the heart
Articulation Joint
Atrophy Decrease in cell size resulting in shrinkage of an organ or body part
Auditory Related to hearing
Autoimmunity Targeting and sometimes destruction of one's own or 'self' tissues by the immune system
Autoregulation Ability of a tissue to control its own blood supply independently
Autorhythmicity Ability of a tissue to generate its own electrical signals
Autosome Any one of the chromosomes in pairs 1–22 (i.e. all but the sex chromosomes)
Axial skeleton (cf. appendicular skeleton) Skull, vertebral column, sternum (breastbone) and ribs
Bacterium (pl. bacteria) Single-celled microorganism, common in the external environment; some bacteria can cause disease
Baroreceptor Sensory receptor sensitive to pressure (stretch)
Basal metabolic rate Energy use of the body when at rest in a warm environment, without having eaten for 12 hours
Benign Non-cancerous or non-serious condition for which treatment may be required
Blastocyst Hollow ball of cells that embeds in the uterine wall during fetal development
Blood–brain barrier Collective term given to the physiological adaptations in the central nervous system that prevent many blood-borne substances from accessing it
Bradycardia Abnormally slow heart rate
Bronchoconstriction Narrowing of the larger airways and bronchioles

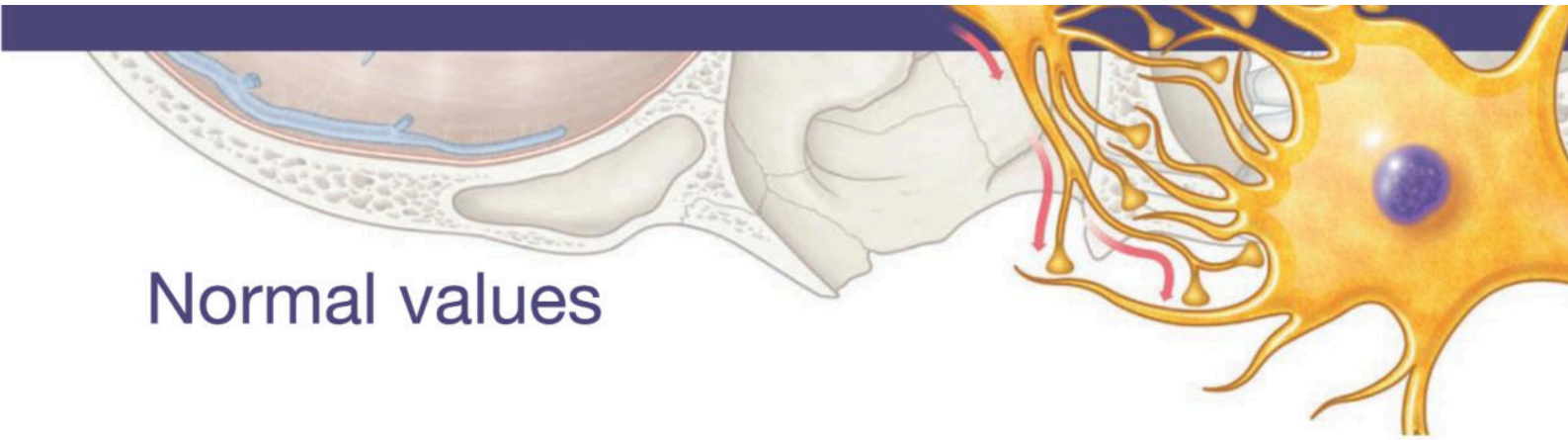
Bronchodilation Widening of the larger airways and bronchioles
Buffer Substance that resists a shift in the pH of body fluids
Capacitance vessel Vessel that can expand to contain large quantities of blood at low pressure (veins)
Capillary Tiny blood vessel between an arteriole and a venule, which has leaky walls to allow exchange of substances between the blood and tissues
Carbohydrate Any of a group of organic compounds that includes the sugars and starches
Carcinogen Cancer-causing substance
Carcinoma Tumour arising from epithelial tissue
Cardiac Of the heart
Cardiac output (CO) Amount of blood ejected by one ventricle every minute: CO = heart rate (HR) × stroke volume (SV)
Catabolism Breaking down of larger molecules into smaller ones
Catalyst Substance that speeds up a biochemical reaction without taking part in it
Cation Positively charged ion
Central nervous system Brain and spinal cord
Cerebrospinal fluid (CSF) Fluid bathing the brain and spinal cord
Chemoreceptor Sensory receptor sensitive to chemicals in solution
Chemotaxis Movement of a cell towards a chemical attractant
Chondrocyte Mature cartilage cell
Chromatin Uncoiled state of chromosomes during interphase
Chromosome Sausage-shaped structure consisting of a tightly coiled molecule of DNA visible at the end of interphase
Chronic Long-standing or recurring
Cilia (sing. cilium) Microscopic cell extensions for moving materials through the lumen of a tube
Circadian rhythm Regular, predictable fluctuation of a physiological function over a 24-hour period
Circumduction Movement of a body part to describe a cone shape
Citric acid cycle (Krebs) Important sequence of aerobic metabolic reactions in cellular energy production
Coagulation Blood clotting
Co-dominance Situation when more than one form of a gene is dominant
Coitus Act of sexual intercourse
Commensal Harmless microorganism that lives in the body or on its surfaces, which may bring advantages to its host, e.g. by producing vitamins or by preventing the growth of pathogens
Communicable Describes a disease that is transferable from one person to another
Compliance Stretchability of a tissue
Compound Molecule containing more than one element
Concentration gradient Situation where two areas of, for example, liquid have different concentrations of a solute
Congenital Inherited
Constriction Narrowing of a tube or vessel due to contraction of circular muscle in its wall
Convergence Turning of the eyes inwards to focus on a close object
Cortex Outer layer of a gland or structure
Costal Related to the ribs
Cytoplasm Contents of a cell except the nucleus (i.e. cytosol plus organelles)
Deamination Removal of the amine group from an amino acid
Deep Describes a body structure or part that is not close to the body surface
Defaecation Expulsion of faeces from the rectum
Deglutition Swallowing
Dehydration Excessive loss of body water
Deoxyribonucleic acid (DNA) Molecule in which the genetic code is written, and packaged into chromosomes in the nucleus
Diapedesis Movement of an independently motile cell from one place to another
Diaphysis Shaft of a long bone
Diastole Resting period of the heart or its individual chambers
Diastolic blood pressure Pressure recorded in the systemic circulation (often at the arm) when the pressure is at its lowest, corresponding to relaxation of the myocardium; the lower of the two measurements used to denote a blood pressure recording
Differentiation Process of cell specialisation
Diffusion Movement of substances down a concentration gradient, which does not require energy or the presence of a membrane
Dilation Widening of a tube or vessel due to relaxation of circular muscle in its wall
Diploid Describes a cell with 46 chromosomes, the whole complement of 23 pairs
Distal Further from the origin of a body part or point of attachment of a limb
Diuresis Passing of urine
Dominant In genetics, the preferential expression of one form of a gene over another
Dysplasia The appearance of abnormal cells within a tissue which may sometimes precede malignant change
Efferent Carrying or travelling away from an organ
Elasticity Ability of a tissue to stretch and recoil to its original length or shape
Electrolyte Inorganic ion in body fluids, which conducts electricity
Element Chemical whose atoms are all of the same type
Embolus Blood clot or other substance that travels in a blood vessel and may lodge there, blocking a smaller vessel
Embryo In humans, the developing offspring in the first eight weeks of development after fertilisation, following which it is referred to as the fetus
Endocrine gland Ductless gland that secretes a hormone that travels to its target organ in the bloodstream
Endogenous Internal, produced by the body
Endothelium Epithelium lining blood vessels
Enzyme Protein substance that speeds up (catalyses) chemical reactions
Epidermis Outermost layer of the skin
Epinephrine Another term for adrenaline
Epiphysis Each end of a long bone
Epithelium Tissue that lines and covers most body organs

Equilibrium State of physiological balance or equivalence
Erythropoiesis Production of red blood cells
Essential nutrient Nutrient that must be eaten in the diet
Eversion Turning the soles of the feet outwards
Exocrine gland Gland that secretes its product into ducts for transport
Exocytosis Process by which materials are expelled from a cell
Exogenous External; not produced by the body
Expiration (cf. inspiration) Physical process of breathing out
Extension Increase in the angle between two bones, straightening a limb
External respiration Exchange of gases in the lungs
Extracellular Outside a cell
Extrinsic pathway Clotting process triggered by damaged extravascular tissues
Facilitated diffusion Form of diffusion that requires carrier proteins for transfer of substances across cell membranes
Faeces Waste product of digestion excreted through the anus
Fascia Fibrous membrane that supports, covers and separates muscles
Fertilisation Penetration of an ovum by a spermatozoon to form a zygote that can grow into a fetus
Fibre Muscle cell; in nutrition, the indigestible part of the diet also known as non-starch polysaccharide
Fibrinolysis Breakdown of a blood clot
Fibroblast Connective tissue cell that produces collagen fibres
Filtration Movement of small molecules, by hydrostatic pressure, through a selectively permeable membrane
Fistula Abnormal passageway between two organs or an organ and the body surface
Flagella (sing. flagellum) Long cell extensions used for cellular propulsion
Flexion Reduction of the angle between two bones, bending a limb
Follicle Small secretory gland
Gamete Ovum or spermatozoon (reproductive cell)
Gastric Of the stomach
Gene Area on a chromosome that codes for one particular protein
Genome All the genes in a cell
Genotype Genetic make-up of an individual
Gestation The process of intrauterine development, between conception and birth
Glia Nervous tissue that supports neurones
Globulin One class of plasma protein, including antibodies
Glucocorticoids Group of steroid (fat-based) adrenal cortex hormones essential for life
Gluconeogenesis Production of glucose from non-carbohydrate molecules
Glucose Simple sugar used by cells for energy
Glycogen Very high molecular weight form of glucose used for storage
Glycolysis Anaerobic breakdown of glucose to release some of its stored energy
Granulation tissue Newly formed repair tissue following tissue damage
Granulocyte General term for a white blood cell without cytoplasmic granules
Gustation Taste
Haematemesis Vomiting of blood
Haemolysis Breakdown of red blood cells
Haemopoiesis Production of blood cells
Haemorrhage Profuse blood loss
Haemostasis Cessation of blood flow
Haploid Describes a cell with 23 chromosomes (half the total chromosome complement)
Hemiplegia Paralysis of a whole side of the body
Hepatic Of the liver
Heterozygous In genetics, describes a form of a gene on one chromosome that is different to the form of the same gene on the other chromosome of the pair
High-density lipoprotein Lipid/protein complex in the bloodstream that is important in transporting cholesterol to the liver for disposal
Hilum Indented area of an organ where blood vessels, nerves and ducts enter and leave
Homeostasis Maintenance of a stable internal environment
Homozygous In genetics, describes a form of a gene on one chromosome that is the same as the form of the same gene on the other chromosome of the pair
Hormone Substance secreted by an endocrine gland that is transported in the blood and acts on specific target cells elsewhere in the body
Hydrophilic Water-loving
Hydrophobic Water-hating
Hydrostatic pressure Pressure exerted by a fluid on the walls of its container, e.g. by blood on the walls of blood vessels
Hypersecretion Abnormally high secretion of a body product, e.g. a hormone
Hypersensitivity Abnormal immune response directed against either a harmless antigen (allergy) or a 'self' antigen (autoimmunity)
Hypertension Abnormally high blood pressure
Hypertonic Describes a solution with a solute concentration higher than body fluids
Hypertrophy Increase in cell size resulting in enlargement of an organ or body part
Hyperventilation Abnormally high respiratory effort, associated with loss of excessive amounts of carbon dioxide
Hyposecretion Abnormally low secretion of a body product, e.g. a hormone
Hypotension Abnormally low blood pressure
Hypothermia Abnormally low body temperature (core temperature <35°C)
Hypotonic Describes a solution with a solute concentration lower than body fluids
Hypoventilation Abnormally low respiratory effort, associated with retention of carbon dioxide
Hypoxia Inadequate levels of oxygen in the tissues
Iatrogenic Describes a condition resulting from a healthcare intervention
Idiopathic Describes a condition of unknown cause
Immunity Body defence mechanisms against a specific disease
Incontinence Inability to control the voiding of urine
Infarction Death of a region of tissue due to interruption of its blood supply
Infection Invasion of body tissues by pathogenic organisms

Inferior Describes a body part or structure that is closer to the soles of the feet
Inflammation Non-specific tissue response to damage
Ingestion Taking in of substances orally, i.e. through the mouth
Insensible water loss Loss of water through the skin and respiratory tract
Insertion (cf. origin) Point where a muscle is attached to the bone it moves
Inspiration (cf. expiration) Physical process of breathing in
Integumentary Of the skin
Internal respiration Exchange of gases in the tissues
Interphase Phase of the cell cycle when there is no division
Interstitial fluid Fluid situated between body cells, also known as tissue fluid
Intracellular Inside a cell
Intrinsic factor Protein secreted by the stomach required for absorption of vitamin B_{12}
Intrinsic pathway Clotting process triggered by damaged blood vessels
Inversion Turning of the soles of the feet to face each other
Involuntary Not under conscious control
Ion Charged atom (which has either lost or acquired electrons)
Ionising radiation Radiation that generates ions when it passes through atoms, and can damage cells by changing the atoms in the molecules that make up living tissue, e.g. X-rays
Ischaemia Impaired blood supply to a body part
Isometric Describes muscle work where the tension in the muscle rises but the muscle does not shorten, e.g. if trying to lift a weight that is too heavy to move
Isotonic Describes muscle work where the muscle shortens as the tension rises, allowing, for example, a load to be lifted by the arm; in chemistry, solutions with a solute concentration the same as body tissues
Isotope Form of an element that has a different number of neutrons from the principal form
Karyotype Photographic presentation of a cell's chromosomes as matched pairs in descending order of size
Lactation Production of breast milk
Lateral Describes a structure further from the midline or at the side of the body
Leukocyte General term for a white blood cell
Leukopenia Low blood white cell count
Leukopoeisis Formation of white blood cells
Ligament Band of connective tissue that binds one bone to another
Lipase Enzyme that breaks down fat
Lipid General term for any substance that does not dissolve in water but dissolves in non-polar solvents like alcohol
Lipolysis Breakdown of fat
Low-density lipoprotein Lipid/protein complex in the bloodstream that is associated with deposition of cholesterol in arterial walls
Lumen Central passageway within an internal tube or duct
Lymph Watery fluid drained by the lymphatic system from the tissue spaces
Lysis Destruction of a cell, e.g. haemolysis
Lysozyme Antimicrobial enzyme present in some body fluids
Macrophage Phagocytic cell usually found in connective tissue
Malignant Cancerous
Mastication Chewing
Meatus Opening into a passage
Medial Describes a structure that is nearer to the midline
Median plane Imaginary line that divides the body longitudinally into right and left halves
Mediastinum Region between the lungs, containing the heart, great vessels, trachea and other important structures
Medulla Inner layer of a gland or structure
Meiosis Process of cell division by which gametes are formed
Melaena Blood in the faeces
Menarche Onset of puberty in females, marked by the start of menstruation
Menopause Time of the female lifespan when reproductive function ceases
Menstruation (menses) Regular shedding of the uterine lining, usually monthly, during the reproductive period of the female lifespan
Metabolic pathway Sequence of metabolic steps in cellular biochemistry
Metabolism All the chemical reactions that take place within the body
Metaphase Second phase of mitosis
Metastasis (pl. metastases) Secondary deposit from a primary malignant tumour
Microbe Microorganism, e.g. a fungus, bacterium or virus
Micturition Passing urine
Mitosis Process of cell division giving two identical daughter cells
Mole In chemistry, the quantity of a substance representing its molecular weight in grams
Motor nerve or neurone Efferent nerve that carries impulses from the central nervous system to muscles or glands
Mucosa or mucous membrane Lining of body tracts
Mutagen Any substance that causes mutation
Mutation Genetic change that arises during cell division
Myelin Fatty substance that surrounds the axons of myelinated nerves
Myofilaments Intracellular protein threads within muscle cells, made of either actin or myosin, responsible for muscle cell contraction
Necrosis Cell death caused by an injury or a pathological condition
Negative feedback (cf. positive feedback) Control mechanism that resists and reverses any change from normal in a physiological system
Neoplasm New growth, which may be benign or malignant
Nephron Structure in the kidneys responsible for the formation of urine
Neuromuscular junction Synapse between a motor nerve and a skeletal muscle cell
Neurone Nerve cell
Neurotransmitter Chemical that transmits an impulse between one nerve and the next, or between a nerve and the neuromuscular junction

Non-specific defence Defence mechanisms of the body that are effective against different types of threat, e.g. the skin, inflammation, complement
Norepinephrine Alternative name for noradrenaline
Nucleotide Building block of nucleic acids
Nutrient Any substance that is digested, absorbed and used to promote body function
Oedema Tissue swelling due to collection of fluid in the intercellular spaces
Olfaction Sense of smell
Oncogenic Cancer-causing
Organ Body part, composed of different tissues, that carries out a specific body function
Organelle Intracellular structure that carries out a specific function
Organic Molecule or substance containing carbon
Origin Point of attachment of a muscle to a bone that moves least during muscle contraction
Osmoreceptors Specialised sensory receptors sensitive to solute concentration
Osmosis Movement of water down its concentration gradient across a semipermeable membrane
Osmotic pressure Pressure exerted by water in a solution
Ossicles Bones of the middle ear: hammer, anvil and stirrup
Ossification Production of bone tissue
Osteoid Organic constituent of bone tissue
Osteon Structural unit of compact bone
Osteopenia Age-related bone degeneration
Ovulation Release of a mature ovum from the ovary
Oxidative phosphorylation Aerobic, high energy-generating metabolic process of cellular respiration
Oxyhaemoglobin Oxygenated form of haemoglobin
Paraplegia Paralysis affecting the lower body including both lower limbs
Parasympathetic nervous system Division of the autonomic nervous system that prepares the body for 'rest and repair'
Parietal layer (cf. visceral layer) Layer of serous membrane lining a body cavity
Parturition Childbirth
Passive transport Any form of transport within the body that does not require the use of energy
Pathogen Microorganism capable of causing disease
Peptidase Enzyme that breaks down protein
Peripheral nervous system Nervous tissue that is not part of the brain or spinal cord
Peripheral resistance Force against which the blood has to push to move through the arterial circulation, determined mainly by the diameter of the arterioles
Peristalsis Rhythmical contraction of smooth muscle in the walls of hollow organs and tubes, e.g. the alimentary canal
Phagocytosis Defence mechanism by which body cells consume and destroy foreign materials; 'cell eating'
Phenotype Expression of the genes in an individual, e.g. hair colour, height, etc.
Phospholipid Fat-based molecule containing phosphate, essential to the structure of the cell membrane
pH scale Scale of measurement of acidity or alkalinity
Pinocytosis Ingestion of small vacuoles into a cell; 'cell drinking'
Plasma Clear, straw-coloured liquid portion of the blood
Plasma protein Any one of a group of important proteins synthesised by the liver and carried in the plasma, with diverse physiological functions, e.g. as antibodies or clotting proteins
Platelet (thrombocyte) Small cell fragment involved in blood clotting
Pleural Related to the lungs
Plexus Network formed by a collection of nerves or blood vessels
Polymorphonuclear leukocyte General term for a white blood cell with an irregular nucleus (i.e. basophils, eosinophils and neutrophils)
Polyuria Production of large quantities of urine
Positive feedback (cf. negative feedback) Control mechanism that increases and accelerates any change from normal in a physiological system; much rarer than negative feedback control
Posterior (dorsal) Describes a body part or structure lying to the back
Preload Amount of blood in the ventricle just prior to ventricular contraction, determined mainly by venous return
Presbycusis Irreversible hearing loss, usually due to ageing, which results from degeneration of the cochlea and begins with an inability to hear high-pitched sounds
Presbyopia Stiffening of the lens, usually due to ageing, which impairs the ability of the eye to change focus (accommodate)
Pressure ulcer Damage to superficial tissues caused by prolonged pressure and interrupted blood supply, usually over a bony prominence
Primary wound healing Simple repair of relatively minor tissue damage
Prognosis Likely outcome of a disease
Prophase First phase of mitosis
Pronation Turning the palm to face backwards
Protein Large polypeptide
Proximal Nearer the origin of a body part or point of attachment of a limb
Puberty Stage of life in males or females when reproductive maturity is achieved
Pulmonary Of the lungs
Pulse Pressure wave generated by the heart, felt along an arterial wall where that artery lies close to the body surface
Pulse pressure Diastolic blood pressure subtracted from the systolic value
Pyrexia Fever
Pyrogen Substance that causes fever
Radiation Transmission of energy in waves
Receptor Molecule, usually on the cell surface, that detects and responds to chemicals in the cell's external environment, e.g. a neurotransmitter. Also, a sensory nerve ending that detects physical changes in the local environment, e.g. a baroreceptor measuring pressure
Recessive In genetics, a form of a gene that can only be expressed if it is present as two identical forms on the chromosome pair
Refraction Bending of light rays as they pass through a lens, e.g. the lens of the eye
Renal Of the kidneys

Resistance vessel Blood vessel, usually an arteriole, with a thick layer of smooth muscle in its tunica media, which constricts or dilates to regulate blood flow and blood pressure
Reticulocyte Immature red blood cell
Retroperitoneal Lying behind the peritoneum
Ribonucleic acid (RNA) Molecule used to transfer genetic instructions from DNA to cytoplasmic ribosomes
Rotation Movement of a body part around its long axis
Rugae Folds in the internal surface of a hollow organ when the organ is relaxed
Sagittal plane Imaginary vertical line dividing the body into right and left halves, either down the midline (midsagittal) or on either side of the midline (sagittal)
Salt Product of a reaction between an acid and a base
Saltatory conduction 'Jumping' of a nerve impulse along a myelinated nerve axon, from one node of Ranvier to the next
Scar tissue Non-functional tissue that replaces damaged tissue
Secondary wound healing Repair of tissue after extensive damage; a more complex and intense process than primary wound healing
Semipermeability (selective permeability) Property of cell membranes that allows passage of some substances but not others
Senescence Cell ageing and the decline in function that accompanies it
Sensory nerve or neurone Afferent nerve that carries impulses to the central nervous system
Serous fluid General term for protein-containing fluid secreted by certain membranes, e.g. serous pericardium and visceral pleura
Sex chromosome X or Y chromosome (pair 23)
Sign Abnormality observed by people other than a patient
Simple propagation Continuous conduction of an impulse along a non-myelinated nerve fibre
Sliding filament theory Accepted mechanism by which actin and myosin filaments within muscle cells slide over one another to permit muscle shortening (contraction)
Specific defence mechanisms Immunity; the body's protective mechanisms raised against a specific threat or antigen
Sphincter Circle of muscle surrounding an internal passageway or orifice, used to regulate passage through the opening
Spinal reflex Involuntary, usually protective, action controlled at the level of the spinal cord (i.e. independent of the brain)
Squamous Flattened (epithelial cells)
Stratified Describes tissues that have several cell layers
Striated Describes the microscopic appearance of a striped pattern on skeletal and cardiac muscle cells
Stroke volume Volume of blood ejected by the ventricle when it contracts
Superficial Describes a body part or structure that is near the body surface
Superior Describes a body part or structure that is closer to the top of the head
Supination Turning the palm to face forwards
Sympathetic nervous system Division of the autonomic nervous system that prepares the body for 'fight or flight'
Symptom Abnormality described by a patient
Synapse Junction between a nerve and the cell it supplies
Syndrome Collection of signs and symptoms that tend to occur together
Systemic circulation Blood supply to all body organs except for the pulmonary arteries and veins
Systole Contraction period of the heart or its individual chambers
Systolic blood pressure Pressure recorded in the systemic circulation (often at the arm) when the pressure is at its highest, immediately following ventricular contraction; the higher of the two measurements used to denote a blood pressure recording
Tachycardia Abnormally fast heart rate
Telophase Fourth (final) phase of mitosis
Telomere Non-coding section of DNA that caps and protects the ends of each chromosome
Tendon Band of fibrous tissue connecting muscle to bone
Teratogen Any substance or agent known to cause abnormal fetal development
Thrombosis Inappropriate, pathological formation of stationary blood clots within blood vessels
Thrombus (pl. thrombi) Stationary blood clot
Tissue fluid Fluid between body cells, also known as interstitial fluid
Tolerance Ability of the immune system and its defensive cells and mechanisms to identify, and not attack, 'self' tissues
Tract Bundle of axons in the central nervous system
Transcription Production of messenger RNA from DNA
Translation Production of protein from messenger RNA
Transverse plane Imaginary line slicing the body into an upper and a lower part
Trophic hormone Hormone released that causes the release of a second hormone
Trophoblast Outer cell layer of the blastocyst that forms the placenta
Tumour Mass of cells growing outside the body's normal control mechanisms
Tunica adventitia Outer, supportive lining of blood vessels
Tunica intima Lining of blood vessels (also called endothelium)
Tunica media Middle layer of tissue in larger blood vessels
Urine Liquid waste product made in the kidneys
Vasoconstriction Decrease in diameter (narrowing) of a blood vessel
Vasodilation Increase in diameter (widening) of a blood vessel
Vein Blood vessel that carries blood towards the heart
Venule Small vein
Virus Non-living particle, which may be capable of causing disease
Viscera The internal body organs
Visceral layer Layer of serous membrane covering a body organ
Voluntary control Conscious control of a body function
Zygote Fertilised egg formed by fusion of an ovum and spermatozoon



Normal values

Note. *Some biological measures have been extracted from the text and listed here for easy reference. In some cases, slightly different normal values may be found in other texts and used by different medical practitioners.*

Metric measures, units and SI symbols

Name	SI unit	Symbol
Length	metre	m
Mass	kilogram	kg
Amount of substance	mole	mol
Pressure	pascal	Pa
Energy	joule	J

Decimal multiples and submultiples of the units are formed by the use of standard prefixes:

	Prefix	Symbol
10^{6}	mega-	M
10^{3}	kilo-	k
10^{2}	hecto-	h
10^{1}	deca-	da
10^{-1}	deci-	d
10^{-2}	centi-	c
10^{-3}	milli-	m
10^{-6}	micro-	μ
10^{-9}	nano-	n
10^{-12}	pico-	p
10^{-15}	femto-	f

Conversion of kPa and mmHg (e.g. for capillary pressures)

mmHg	kPa
1	0.13
7.5	1
35	4.7
25	3.3
15	2.0
10	1.3

Hydrogen ion concentration (pH)

Body fluid	Normal pH
Bile	6.0–8.5
Blood	7.35–7.45
Gastric juice	1.5–3.5
Saliva	5.8–7.4
Urine	4.5–8.0

Neutral = 7
Acid = 0–7
Alkaline = 7–14

Some normal plasma levels in adults

Analyte	SI unit	Non-SI unit
Calcium	2.12–2.62 mmol/L	8.5–10.5 mg/100 mL
Chloride	97–106 mmol/L	97–106 mEq/L
Cholesterol	3.6–6.7 mmol/L	140–260 mg/100 mL
Glucose	3.5–8 mmol/L	63–144 mg/100 mL
Fasting glucose	3.6–5.8 mmol/L	65–105 mg/100 mL
Potassium	3.3–4.7 mmol/L	3.3–4.7 mEq/L
Sodium	135–143 mmol/L	135–143 mEq/L
Urea	2.5–6.6 mmol/L	15–44 mg/100 mL

Arterial blood gases

Analyte	SI unit	Non-SI unit
PO_2	12–15 kPa	90–110 mmHg
PCO_2	4.5–6 kPa	34–46 mmHg
Bicarbonate	21–27.5 mmol/L	21–27.5 mEq/L
H^+ ions	36–44 nmol/L	7.35–7.45 pH units

Blood pressure (adult)

Status	mmHg
Normal	120/80
Generally considered high	>140/90

Normal values

Heart rate

Status	Beats/min
At rest	60–80
Sinus bradycardia	<60
Sinus tachycardia	>100

Respiratory parameters (adults)

Parameter	Normal value at rest
Tidal volume	500 mL
Dead space	150 mL
Alveolar ventilation	15 (500–150) mL = 5.25 L/min

Respiratory rate: 15–18 breaths/min

Blood count

Cell type	SI units
Leukocytes	$4–11 \times 10^9$/L
Neutrophils	$2.5–7.5 \times 10^9$/L
Eosinophils	$0.04–0.44 \times 10^9$/L
Basophils	$0.015–0.1 \times 10^9$/L
Monocytes	$0.2–0.8 \times 10^9$/L
Lymphocytes	$1.5–3.5 \times 10^9$/L
Erythrocytes	
Female	$3.8–5 \times 10^{12}$/L
Male	$4.5–6.5 \times 10^{12}$/L
Thrombocytes	$200–350 \times 10^9$/L

Energy sources in the diet

Energy source	Energy released
Carbohydrate	1 g = 17 kJ = 4 kcal
Protein	1 g = 17 kJ = 4 kcal
Fat	1 g = 38 kJ = 9 kcal

1 kilocalorie (kcal) = 4.182 kilojoules (kJ)
1 kilojoule = 0.24 kilocalories

Urine

Specific gravity: 1.020–1.030
Volume excreted: 1000–1500 mL/day
Glucose: normally absent, but appears in urine when blood glucose levels are > 9 mmol/L

Body temperatures

Status	Temperature
Normal	36.8°C: axillary
Hypothermia	≤35°C: core temperature
Death when below	25°C

Cerebrospinal fluid pressure

Lying on the side: 60–180 mm H_2O

Intraocular pressure

1.3–2.6 kPa (10–20 mmHg)

Common prefixes, suffixes and roots

Prefix/suffix/root	To do with	Examples in the text
a-/an-	lack of	agranulocyte, anaemia, anuria, asystole
ab-	away from	abduct
ad-	towards	adduct
-aemia	of the blood	anaemia, hypovolaemia, hypoxaemia, uraemia
angio-	vessel	angiotensin, haemangioma
ante-	before, in front of	anterior
anti-	against	anticoagulant, antidiuretic, antigen, antimicrobial
-ase	enzyme	amylase, lipase, peptidase
baro-	pressure	baroreceptor
-blast	germ, bud	osteoblast, fibroblast
brady-	slow	bradycardia
broncho-	bronchus	bronchiole, bronchitis, bronchus
card-	heart	cardiac, myocardium, tachycardia
chole-	bile	cholangitis, cholecystitis, cholecystokinin
circum-	around	circumduction
cyto-/-cyte	cell	cytoplasm, cytosol, cytotoxic, erythrocyte
derm-	skin	dermatitis, dermatome, dermis
di-	two	diencephalon, disaccharide
dys-	difficult	dysmenorrhoea, dysplasia, dyspnoea, dysuria
-ema	swelling	emphysema, lymphoedema, oedema
endo-	inner	endocrine, endocytosis, endothelium
enter-	intestine	enterokinase, gastroenteritis, enteric
epi-	on, upon	epicardium, epimysium
erythro-	red	erythrocyte, erythropoiesis, erythropoietin
exo-	outside	exocytosis, exophthalmos
extra-	outside	extracellular, extrapyramidal
-fferent	carrying	afferent, efferent

Common prefixes, suffixes and roots

Prefix/suffix/root	To do with	Examples in the text
gast-	stomach	gastric, gastrin, gastritis, gastrointestinal
-gen-	origin/production	allergen, antigen, gene, genetic, genome, pathogen
-globin	protein	haemoglobin, myoglobin
haem-	blood	haemolytic, haemorrhage, haemostasis
hepat-	liver	hepatic, hepatitis, hepatocyte, hepatomegaly
hetero-	different	heterozygous
homo-	the same, steady	homologous, homozygous
-hydr-	water	dehydration, hydrocephalus, hydrostatic
hyper-	excess/above	hypercapnia, hypertension, hypertrophy
hypo-	below/under	hypoglycaemia, hypotension, hypovolaemia
intra-	within	intracellular, intracranial, intraocular
-ism	condition	embolism, hyperthyroidism, rheumatism
-itis	inflammation	appendicitis, cystitis, gastritis, hepatitis
lact-	milk	lactation, lacteal, lactic
lymph-	lymph tissue	lymphatic, lymphocyte, lymphoedema
lyso-/-lysis	breaking down	glycolysis, lysosome, lysozyme
-mega-	large	acromegaly, hepatomegaly, megaloblast, splenomegaly
meta-	to change from one state to another	metabolism, metaplasia
micro-	small	microbe, microtubule, microvilli
myo-	muscle	myocardium, myoglobin, myopathy, myosin
neo-	new	gluconeogenesis, neonate, neoplasm
nephro-	kidney	nephroblastoma, nephron, nephrosis, nephrotic
neuro-	nerve	neuralgia, neurone, neuropathy
-oid	resembling	myeloid, sesamoid, sigmoid, sarcoid
olig-	small	oliguria
-ology	study of	cardiology, neurology, physiology
-oma	tumour	carcinoma, osteoma, melanoma
-ophth-	eye	exophthalmos, ophthalmic, xerophthalmia
-ory	referring to	auditory, gustatory, secretory, sensory
os-/osteo-	bone	osteoarthritis, osteocyte, osteoporosis
-osis	state or condition, usually pathological	alkalosis, fibrosis, stenosis, thrombosis
-path-	disease	nephropathy, neuropathy, pathogenesis

Prefix/suffix/root	To do with	Examples in the text
-penia	deficiency of	leukopenia, thrombocytopenia
peri-	around, near	pericardium, perineurium, periosteum
phag(o)-	eating	phagocyte, phagocytic
-plasm	substance	cytoplasm, neoplasm
pneumo-	lung/air	pneumonia, pneumothorax
poly-	many	polycythaemia, polypeptide, polyuria
-rrhagia	excessive flow	menorrhagia
-rrhoea	discharge	diarrhoea, dysmenorrhoea, rhinorrhoea
sarco-	muscle	sarcomere, sarcoplasm
-scler	hard	arteriosclerosis, scleroderma
sub-	under	subarachnoid, sublingual, subphrenic
tachy-	excessively fast	tachycardia, tachypnoea
thrombo-	clot	thrombin, thrombocyte, thrombosis, thrombus
-tox-	poison	cytotoxic, hepatotoxic, toxin
tri-	three	trigeminal, tripeptide, trisaccharide
-uria	urine	anuria, haematuria, nocturia, polyuria, oliguria
vas, vaso-	vessel	vascular, vasoconstriction, deferent duct

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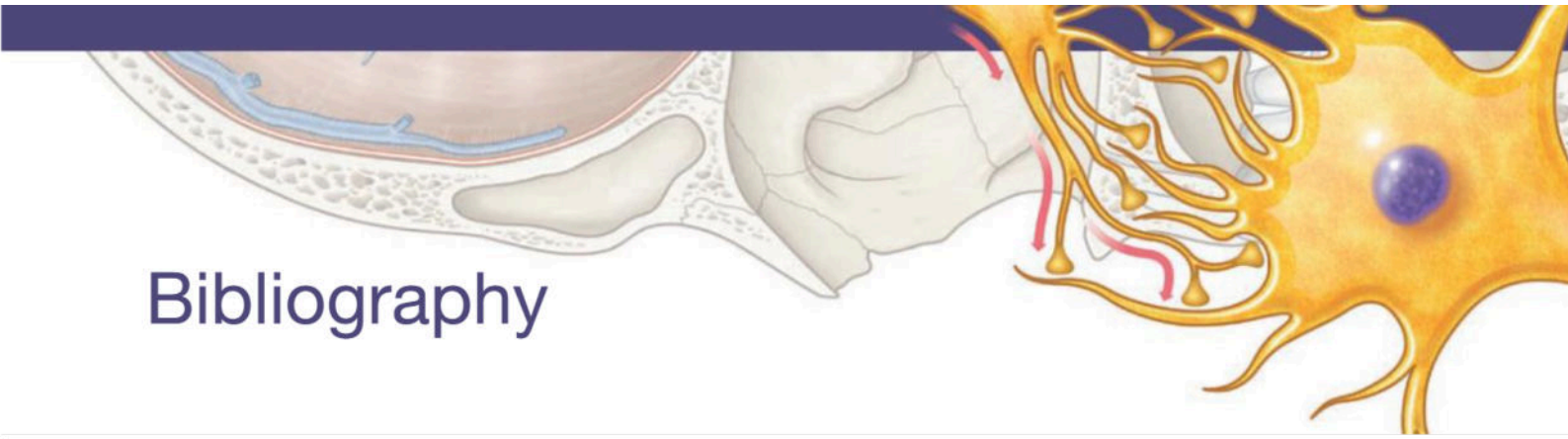

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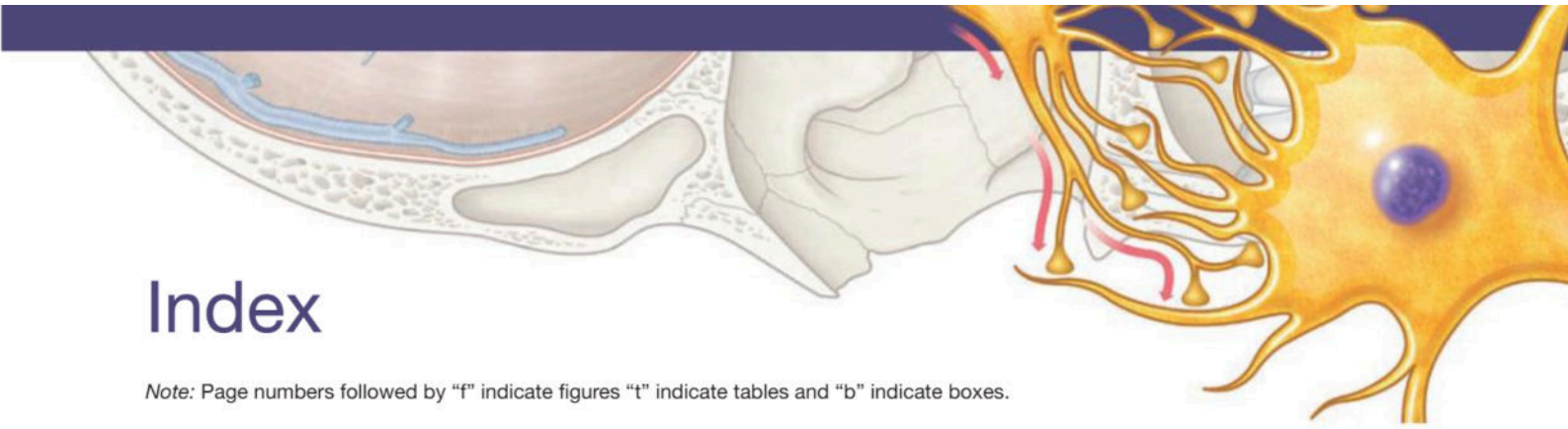

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