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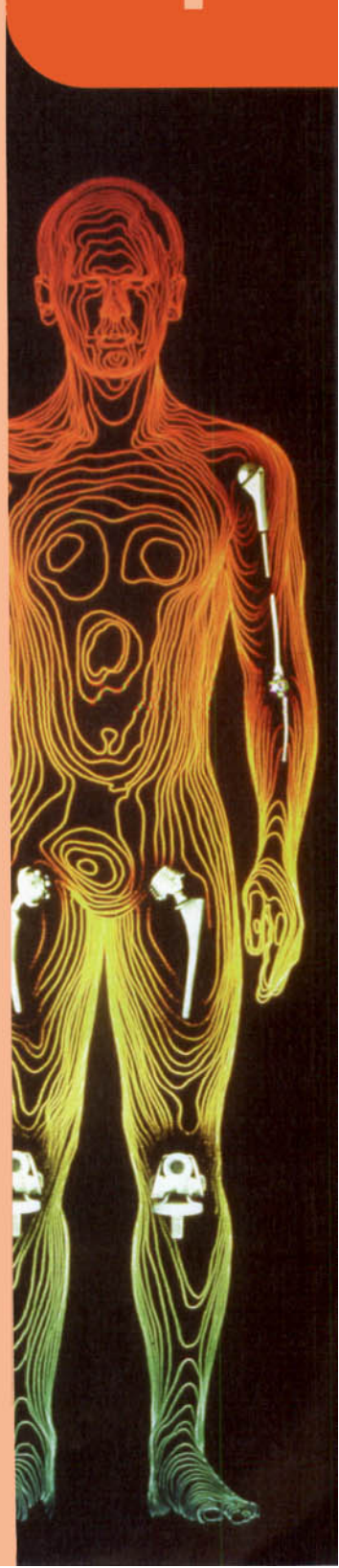
The body and its constituents



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1 Introduction to the human body

The human body is complex, like a highly technical and sophisticated machine. It operates as a single entity, but is made up of a number of operational parts that work interdependently. Each part is associated with a specific, and sometimes related, function that is essential for the well-being of the individual. The component parts do not operate independently, but rather in conjunction with all the others. Should one part fail, the consequences are likely to extend to other parts, and may reduce the ability of the body to function normally. Integrated working of the body parts ensures the ability of the individual to survive. The human body is therefore complex in both its structure and function, and the aim of this book is to explain the fundamental structures and processes involved.

Anatomy is the study of the structure of the body and the physical relationships involved between body parts. *Physiology* is the study of how the parts of the body work, and the ways in which they cooperate together to maintain life and health of the individual. *Pathology* is the study of abnormalities and how they affect body functions, often causing illness. Building on the normal anatomy and physiology, relevant illnesses are considered at the end of the later chapters.

LEVELS OF STRUCTURAL COMPLEXITY

Learning outcome

After studying this section you should be able to:

- state the levels of structural complexity within the body.

Within the body there are different levels of structural organisation and complexity (Fig. 1.1). The lowest level is chemical. *Atoms* combine to form *molecules*, of which there is a vast range in the body. The structures, properties and functions of important biological molecules are considered in Chapter 2. *Cells* are the smallest independent units of living matter and there are millions in the body. They are too small to be seen with the naked eye, but when magnified using a microscope different types can be distinguished by their size, shape and the dyes they absorb when stained in the laboratory. Each cell type has become *specialised*, and carries out a particular function that contributes to body needs. 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 up of a number of different types of tissue and carry out a specific function. *Systems* consist of a number of organs and tissues that together contribute to one or more survival needs of the body. The human body has several systems, which work interdependently carrying out specific functions. All are required for health. The body systems are considered in later chapters.

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* surrounds the body and provides the oxygen and nutrients required by all the cells of the body. Waste products of cellular activity are eventually excreted into the external environment. The skin provides a barrier between the dry external environment and the watery environment of most body cells.

The *internal environment* is the water-based medium in which body cells exist. Cells are bathed in fluid called *interstitial* or *tissue fluid*. Oxygen and other substances they require must pass from the internal transport systems through the interstitial fluid to reach them. Similarly, cell waste products must move through the interstitial fluid to the transport systems to be excreted.

Cells are surrounded by the *cell membrane*, which provides a potential barrier to substances entering or leaving. The structure of membranes (p. 30) confers certain properties, in particular *selective permeability* or *semipermeability*. This prevents large molecules moving between the cell and the interstitial fluid (Fig. 1.2). Smaller particles can usually pass through the membrane, some more readily than others, and therefore the chemical composition of the fluid inside is different from that outside the cell.

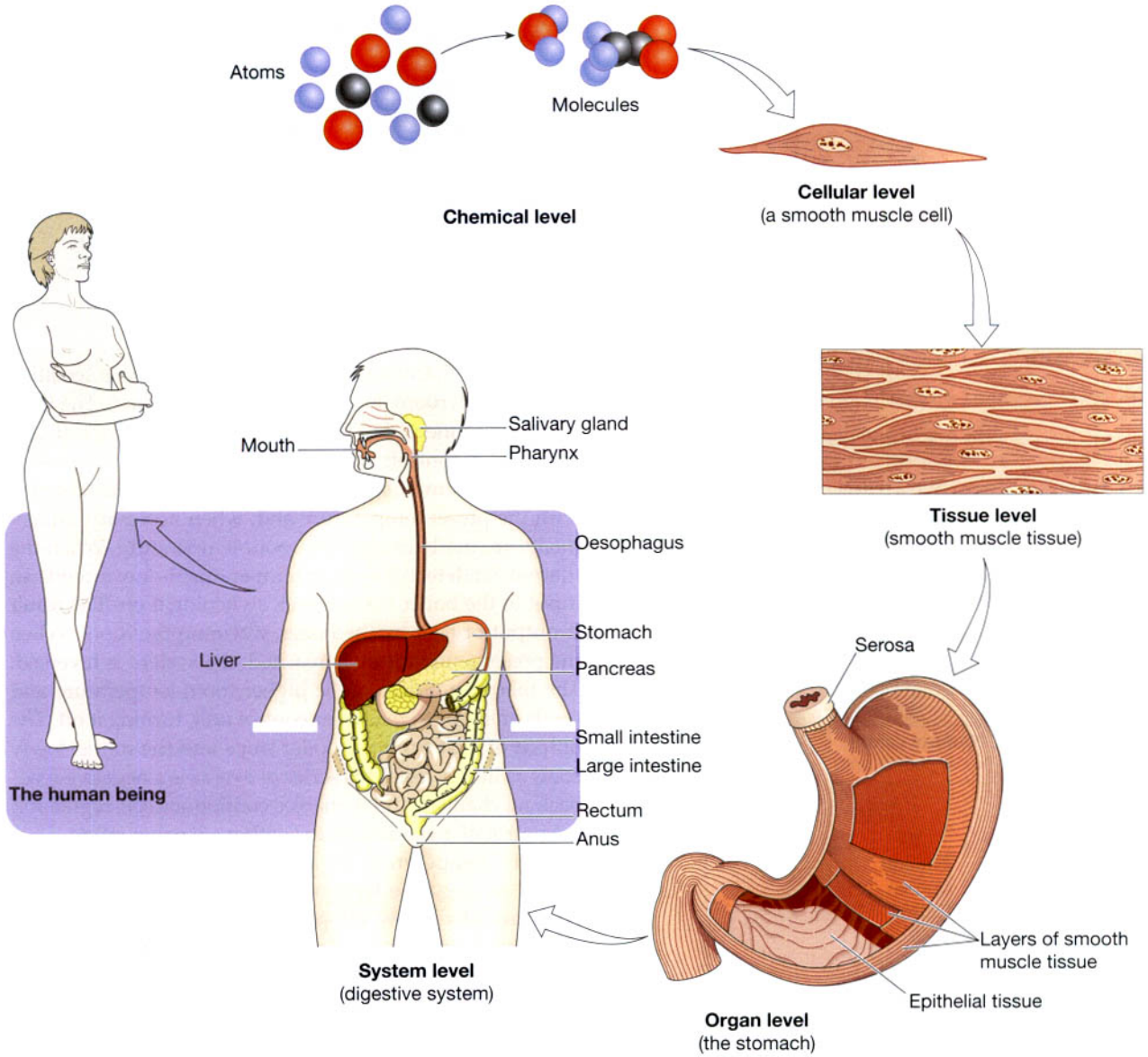

Figure 1.1 The levels of structural complexity.

Homeostasis

The composition of the internal environment is maintained within narrow limits, and this fairly constant state is called *homeostasis*. Literally, this term means 'unchanging', but in practice it describes a dynamic, ever-changing situation kept within narrow limits. When this balance is threatened or lost, there is a serious risk to the well-being of the individual. There are many factors in the internal environment which must be maintained within narrow limits and some of these are listed in Box 1.1.

Homeostasis is maintained by control systems which detect and respond to changes in the internal environment. A control system (Fig. 1.3) has three basic components: detector, control centre and effector. The *control centre* determines the limits within which the variable factor should be maintained. It receives an input from the *detector* or *sensor*, and integrates the incoming information. When the incoming signal indicates that an adjustment is needed the *control centre* responds and its output to the *effector* is changed. This is a dynamic process that maintains homeostasis.

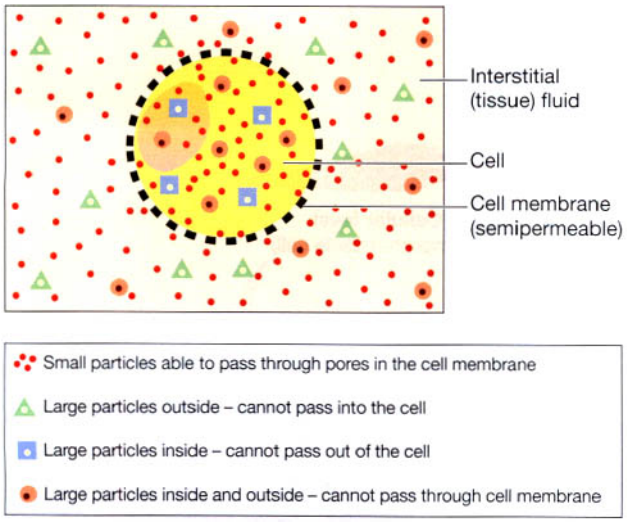

Figure 1.2 Diagram of a cell with a semipermeable membrane.

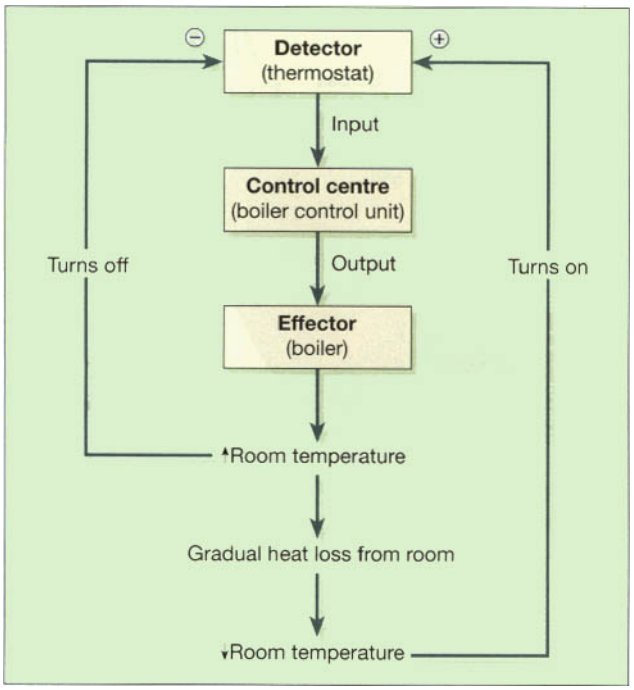

Figure 1.3 Example of a negative feedback mechanism: control of room temperature by a domestic boiler.

Negative feedback mechanisms

In systems controlled by negative feedback the effector response decreases or negates the effect of the original stimulus, restoring homeostasis (thus the term negative feedback). Control of body temperature is similar to the non-physiological example of a domestic central heating system. The thermostat (temperature detector) is sensitive to changes in room temperature (variable factor). The thermostat is connected to the boiler control unit (control centre), which controls the boiler (effector). The thermostat constantly compares the information from the detector with the preset temperature and, when necessary, adjustments are made to alter the room temperature. When the thermostat detects the room temperature is low it sends an input to the boiler control unit, switching it on. The result is output of heat by the boiler, warming the room. When the preset temperature is reached, the system is reversed. The thermostat detects the higher room temperature and sends an input to the boiler control unit, turning it off. The output of heat from the boiler stops and the room slowly cools as heat is lost. This series of events is a negative feedback mechanism and it enables continuous self-regulation or control of a variable factor within a narrow range.

Body temperature is a physiological variable controlled by negative feedback (Fig. 1.4). When body temperature falls below the preset level, this is detected by specialised temperature sensitive nerve endings. They transmit this information as an input to groups of cells in the hypothalamus of the brain which form the control centre. The output from the control centre activates mechanisms that raise body temperature (effectors). These include:

- stimulation of skeletal muscles causing shivering
- narrowing of the blood vessels in the skin reducing the blood flow to, and heat loss from, the peripheries
- behavioural changes, e.g. we put on more clothes or curl up.

When body temperature rises to within the normal range, the temperature sensitive nerve endings no longer stimulate the cells of the control centre and therefore the output of this centre to the effectors ceases.

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.

Box 1.1 Examples of physiological variables

- 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

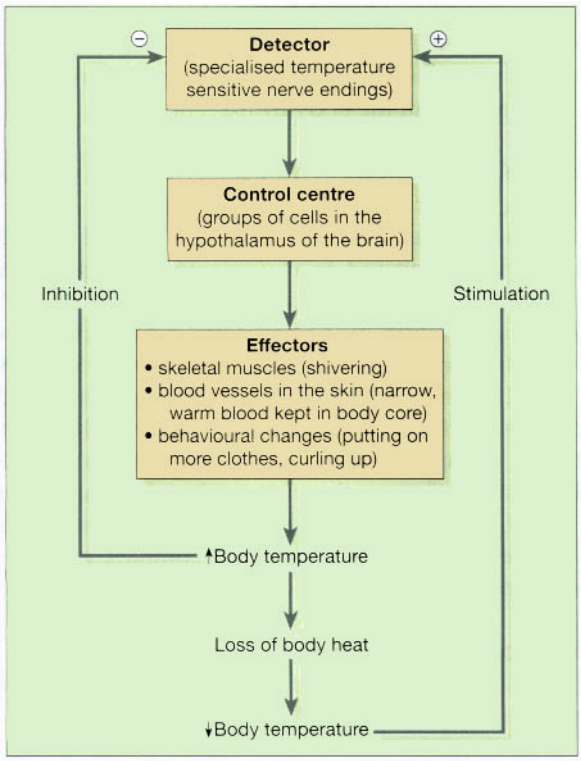

Figure 1.4 Example of a physiological negative feedback mechanism: control of body temperature.

Positive feedback mechanisms

There are only a few of these *amplifier* or *cascade 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 being 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 cervix of the uterus stimulating stretch receptors there. In response to this, more of the hormone oxytocin is released, further strengthening the contractions and maintaining labour. After the baby is born the stimulus (stretching of the cervix) is no longer present and the release of oxytocin stops (see Fig. 9.5, p. 219).

Homeostatic imbalance

This arises when the fine control of a factor in the internal environment is inadequate and the level of the factor falls outside the normal range. If control cannot achieve homeostasis, an abnormal state develops that may threaten health, or even life. Many of these situations are explained in later chapters.

SURVIVAL NEEDS OF THE BODY

Learning outcomes

After studying this section you should be able to:

- describe the role of the body transport systems
- outline the roles of the nervous and endocrine systems in internal communication
- outline how raw materials are absorbed by the body
- state the waste materials eliminated from the body
- outline activities undertaken by an individual for protection and survival.

By convention, the body systems are described separately in the study of anatomy and physiology, but in reality they are all interdependent. This section provides an introduction to body activities linking them to survival needs (Table 1.1). The later chapters build on this framework, exploring human structure and functions in health and illness using a systems approach.

Table 1.1 Survival needs and related body activities

Survival need	Body activities
Communication	Transport systems: blood, circulatory 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 Dietary intake Elimination of waste: carbon dioxide, urine, faeces
Protection and survival	Protection against the external environment: skin Resistance and immunity: non-specific and specific defence mechanisms Body movement Reproduction

Communication

In this section, transport and communication are considered. Transport systems ensure that all cells have access to the internal and external environments; the blood, the circulatory system and lymphatic system are involved. All communication systems involve receiving, collating and responding to appropriate information.

There are different systems for communicating with the internal and external environments. Internal communication involves mainly the nervous and endocrine systems; these are important in the maintenance of homeostasis and regulation of vital body functions. Communication with the external environment involves the special senses, and verbal and non-verbal activities, and all of these also depend on the nervous system.

Transport systems

Blood

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

Plasma. This is mainly water with a wide range of substances dissolved or suspended in it. These include:

- nutrients absorbed from the alimentary canal
- oxygen absorbed from the lungs
- chemical substances synthesised by body cells, e.g. hormones
- waste materials produced by body cells to be eliminated from the body by excretion.

Blood cells. There are three distinct groups, classified according to their functions (Fig. 1.5).

Erythrocytes (red blood cells) are concerned with the transport of oxygen and, to a lesser extent, carbon dioxide between the lungs and all body cells.

Leukocytes (white blood cells) are mainly concerned with protection of the body against microbes and other potentially damaging substances that gain entry to the body. There are several types of leukocytes which carry out their protective functions in different ways. These cells are larger than erythrocytes and are less numerous.

Thrombocytes (platelets) are tiny cell fragments which play an essential part in the very complex process of blood clotting.

Circulatory system (Ch. 5)

This consists of a network of blood vessels and the heart (Fig. 1.6).

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.

Capillaries are tiny blood vessels with very thin walls consisting of only one layer of cells. They are the site of

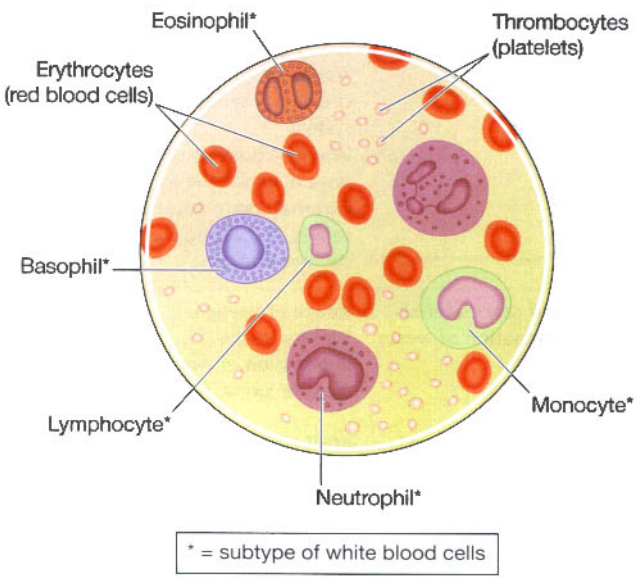

Figure 1.5 Blood cells after staining in the laboratory viewed through a microscope.

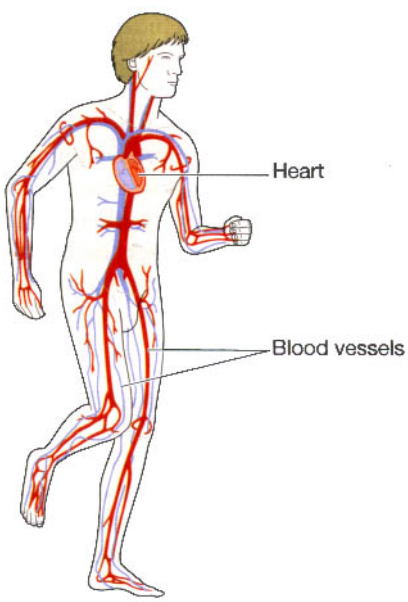

Figure 1.6 The circulatory system.

exchange of substances between the blood and body tissues, e.g. nutrients, oxygen and cellular waste products. Blood vessels form a network that transports blood to:

- the lungs (*pulmonary circulation*) where 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 parts of the body (*general* or *systemic circulation*).

Heart. The heart is a muscular sac. It pumps the blood round the body and maintains the blood pressure in the lungs and general circulation. This is essential for life.

The heart muscle is not under conscious (voluntary) control. At rest, the heart contracts between 65 and 75 times per minute. The rate may be greatly increased during physical exercise, when the oxygen and nutritional needs of the muscles moving the limbs are increased, and in some emotional states.

The rate at which the heart beats can be counted by taking the *pulse*. The pulse can be felt most easily where an artery lies close to the surface of the body and can be pressed gently against a bone. The wrist is the site most commonly used for this purpose.

Lymphatic system

The lymphatic system (Ch. 6) consists of a series of *lymph vessels*, which begin as blind-ended tubes in the spaces between the blood capillaries and tissue cells (Fig. 1.7). Structurally they are similar to veins and blood capillaries but the pores in the walls of the lymph capillaries are larger than those of the blood capillaries. *Lymph* is tissue fluid containing large molecules, e.g. proteins, fragments of damaged tissue cells and microbes. It is transported along lymph vessels and is returned to the bloodstream.

There are collections of *lymph nodes* situated at various points along the length of the lymph vessels. Lymph is filtered as it passes through the lymph nodes, and microbes, noxious substances and some waste materials are removed.

The lymphatic system provides the sites for formation and maturation of *lymphocytes*, the white blood cells involved in immunity.

Internal communication

Communication and the nervous system

The nervous system is a rapid communication system (Ch. 7). The main components are shown in Figure 1.8.

The central nervous system consists of:

- the *brain*, situated inside the skull
- the *spinal cord*, which extends from the base of the skull to the lumbar region and is protected from injury by the bones of the spinal column.

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

- *sensory* or *afferent*, providing the brain with 'input' from organs and tissues, or
- *motor* or *efferent*, which convey nerve impulses carrying 'output' from the brain to effector organs: the muscles and glands.

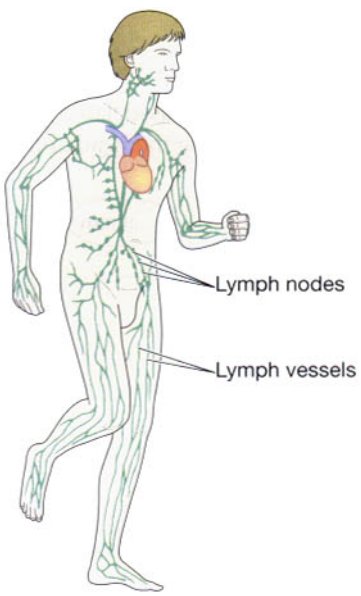

Figure 1.7 The lymphatic system: lymph nodes and vessels.

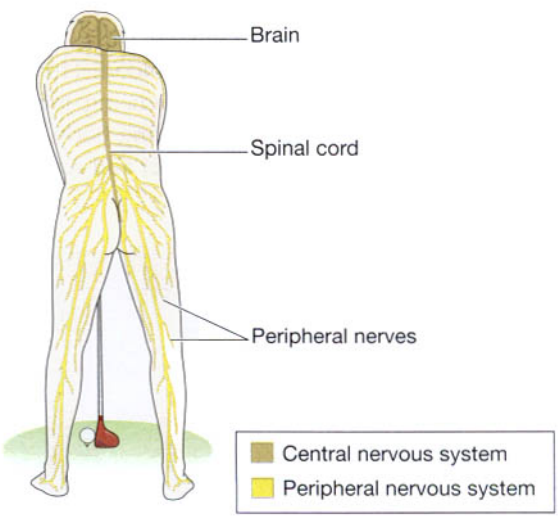

Figure 1.8 The nervous system.

The somatic (common) senses are pain, touch, heat and cold, and they arise following stimulation of specialised sensory receptors at nerve endings found throughout the skin. There are different receptors in muscles and joints that respond to changes in the position and orientation of the body, maintaining posture and balance. Yet other receptors are activated by stimuli in internal organs and maintain control of 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 nerve fibres (cells) is by electrical impulses that are generated when nerve endings are stimulated.

Communication between nerve cells is also required, since more than one nerve is involved in the chain of events occurring between the initial stimulus and the physiological reaction to it. Nerves communicate with each other by releasing a chemical (the *neurotransmitter*) into tiny gaps between them. The neurotransmitter quickly travels across the gap and either stimulates or inhibits the next nerve cell, thus ensuring the message is transmitted.

Sensory nerves and chemical substances circulating in the blood provide information to appropriate parts of the brain, which collates it and then responds via motor nerves to effector organs, often through a negative feedback mechanism (Fig. 1.3). Some of these activities are understood and perceived, e.g. pain, whereas others take place subconsciously, e.g. changes in blood pressure. Nerve impulses travel at great speed along nerve fibres leading to rapid responses; adjustments to many body functions occur within a few seconds.

Communication and the endocrine system

The endocrine system consists of a number of *endocrine glands* situated in different parts of the body. They synthesise and secrete chemical messengers called *hormones* that circulate round the body in the blood. Hormones stimulate *target glands* or *tissues*, influencing metabolic and other cellular activities and regulating 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 controlled by negative feedback mechanisms (Fig. 1.3). The endocrine system provides slower and more precise control of body functions than the nervous system.

Box 1.2 The senses and related sense organs

Sight – eyes

Hearing – ears

Balance – ears

Smell – nose

Taste – tongue

Communication with the external environment

Special senses

These senses arise following stimulation of specialised sensory receptor cells located in sensory organs or tissues in the head. The senses and the special organs involved are shown in Box 1.2.

Although these senses are usually considered separate and different from each other, one sense is rarely used alone (Fig. 1.9). For example, when the smell of smoke is perceived then other senses such as sight and sound are used to try and 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 the fire, or to prepare the digestive system for eating.

Verbal communication

Sound is a means of communication and is produced in the larynx as a result of blowing air through the space between the *vocal cords* during expiration. Speech is the manipulation of sound by contraction of the muscles of the throat and cheeks, and movements of the tongue and lower jaw.

Non-verbal communication

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

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

shoulders. The skeletal system provides the bony framework of the body (Ch. 16), and movement takes place at joints between bones. Skeletal muscles which move the bones lie between them and the skin. They are stimulated by the part of the nervous system under conscious (voluntary) control. Some non-verbal communication, e.g. changes in facial expression, may not involve the movement of bones.

Intake of raw materials and elimination of waste

This section considers the substances that must be taken into and excreted from the body. Oxygen, water and food are the substances the body needs to take in, and carbon dioxide, urine and faeces are those excreted.

Intake of oxygen

Oxygen is a gas that makes up about 21% of atmospheric air. A continuous supply is essential for human life because most chemical activities that take place in the body cells can occur only in its presence. Oxygen is needed in the series of chemical reactions that result in the release of energy from nutrients.

The respiratory system carries air between the nose and the lungs during breathing (Ch. 10). Air passes through a system of passages consisting of the pharynx (also part of the alimentary canal), the larynx (voice box), the trachea, two bronchi (one bronchus to each lung) and a large number of 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 the vital process of gas exchange between the lungs and the blood takes place (Fig. 1.11).

Nitrogen, which makes up about 80% of atmospheric air, is breathed in and out but, in this gaseous form, it cannot be used by the body. The nitrogen needed by the body is present in protein-containing foods, mainly meat and fish.

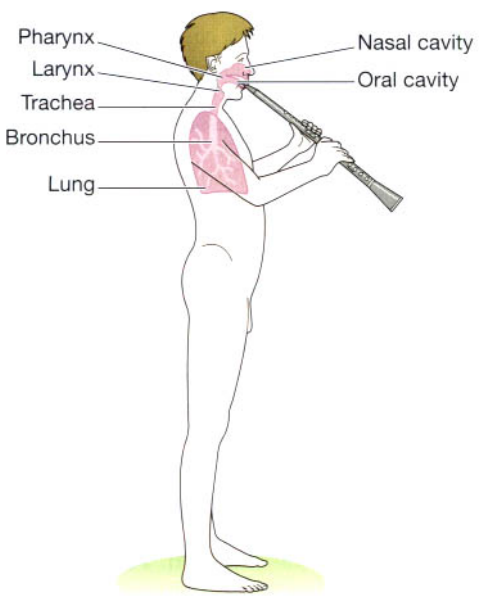

Figure 1.10 The respiratory system.

Dietary intake

Nutrition is considered in Chapter 11. A balanced diet is important for health and provides *nutrients*, substances that are absorbed, often following digestion, and promote body function. Nutrients include water, carbohydrates, proteins, fats, vitamins and mineral salts. They are required for:

- maintaining water balance within the body
- energy production, mainly carbohydrates and fats
- synthesis of large and complex molecules, using mineral salts, proteins, fats, carbohydrates and vitamins
- cell building, growth and repair, especially proteins.

Digestion

The digestive system has developed because the food eaten is chemically complex and seldom in a form the 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 tract and accessory glands (Fig. 1.12).

Alimentary canal. This is a tube that begins at the mouth and continues through the pharynx, oesophagus, stomach, small and large intestines, rectum and anus.

Glands. The accessory organs situated outside the alimentary canal with ducts leading into it are the *salivary*

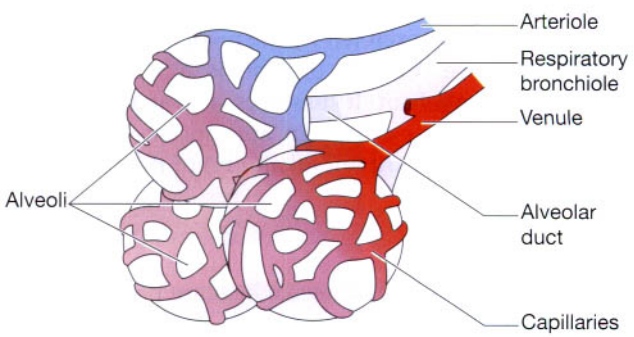

Figure 1.11 Alveoli: the site of gas exchange.

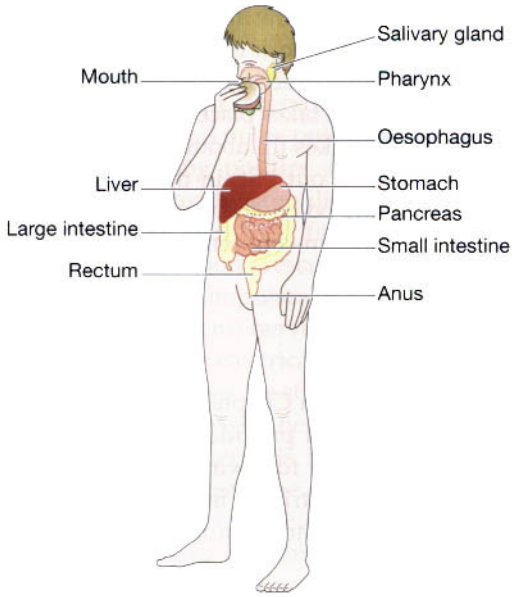

Figure 1.12 The digestive system.

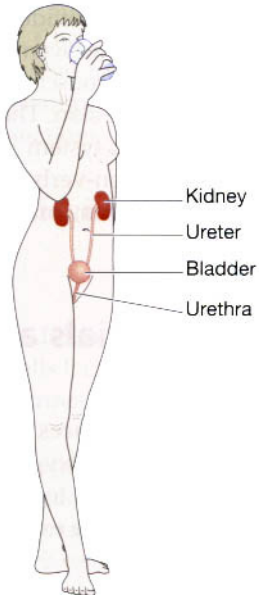

Figure 1.13 The urinary system.

glands, the *pancreas* and the *liver*. There are also many small glands situated in the walls of the alimentary canal. Most of these glands synthesise *digestive enzymes* that are involved in the chemical breakdown of food.

Metabolism

This is the sum total of the chemical activity in the body. It consists of two groups of processes:

- *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 the carbohydrates and fats provided by the diet. If these are in short supply, proteins are used.

Elimination of waste

Carbon dioxide

This is continually excreted by the respiratory system, as described above. Carbon dioxide is a waste product of cellular metabolism. It dissolves in water to form an acid that must be excreted in appropriate amounts to maintain the pH (acidity or alkalinity) of the blood in its normal range.

Urine

This is formed by the kidneys, which are part of the urinary system (Ch. 13). The organs of the urinary system are shown in Figure 1.13. Urine consists of water and waste products mainly of protein breakdown, e.g. urea. Under the influence of hormones from the endocrine system the kidneys regulate water balance within the body. They also play a role in maintaining blood pH within the normal range. The bladder stores urine until it is excreted during *micturition*. The process of micturition (passing urine) also involves the nervous system.

Faeces

The waste materials from the digestive system are excreted as faeces containing:

- indigestible food residue that remains in the alimentary canal because it cannot be absorbed
- bile from the liver, which contains the waste products from the breakdown of red blood cells
- large numbers of microbes.

Elimination of faeces (*defecation*) also involves the nervous system.

Protection and survival

In this section relevant activities will be outlined under the following headings: protection against the external environment, resistance and immunity, movement and reproduction.

Protection against the external environment

On the body surface, the skin (Ch. 14) mainly provides this. 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 surface layer consists of dead cells that are constantly being rubbed off and replaced from below. The epidermis constitutes the barrier between the moist environment of the living cells of the body and the dry atmosphere of the external environment.

The dermis contains tiny *sweat glands* that have little canals or ducts, leading to the surface. Hairs grow from follicles in the dermis. The layers of the skin form a barrier against:

- invasion by microbes
- chemicals
- dehydration.

Sensory nerve endings present in the dermis are stimulated by pain, temperature and touch. If the finger touches a very hot plate, it is removed immediately. This cycle of events is called a *reflex action* and is a very rapid motor response (contraction of muscles) to a sensory stimulus (stimulation of sensory nerve endings in the skin). This type of reflex action is an important protective mechanism that is mediated by the nervous system.

The skin also plays an important role in the regulation of body temperature.

Resistance and immunity

The body has many means of self-protection from invaders (Ch. 15). They are divided into two categories: specific and nonspecific defence mechanisms.

Nonspecific defence mechanisms

These are effective against any invaders. The protection provided by the skin is outlined above. In addition there are other protective features at body surfaces, e.g. mucus secreted by mucous membranes traps microbes and other foreign materials on its sticky surface. Some body fluids contain antimicrobial substances, e.g. gastric juice contains hydrochloric acid, which kills most ingested microbes. Following successful invasion other nonspecific processes may occur including the inflammatory response, which is also involved in tissue healing.

Specific defence mechanisms

The body generates a specific (immune) response against any substance it identifies as foreign. Such substances are called *antigens* and include:

- bacteria and other microbes
- cancer cells or transplanted tissue cells
- pollen from flowers and plants.

Following exposure to an antigen, lifelong immunity against further invasion by the same antigen usually develops. Over a lifetime, an individual gradually builds up immunity to millions of antigens. Allergic reactions are abnormally powerful immune responses to an antigen that usually poses no threat to the body.

Movement

Movement of the whole body or parts of it are essential for:

- obtaining food
- avoiding injury
- reproduction.

Most body movement is under conscious (voluntary) control. The exceptions include protective movements which are carried out before the individual is aware of them, e.g. the reflex action of removing the finger from a very hot surface.

The skeleton provides the bony framework of the body and movement takes place at joints between two or more bones. *Skeletal muscles* (Fig. 1.14) move the *joints* and they are stimulated to contract by the nervous system. A brief description of the skeleton is given in Chapter 3, and a more detailed account of bones, muscles and joints is presented in Chapters 16, 17 and 18.

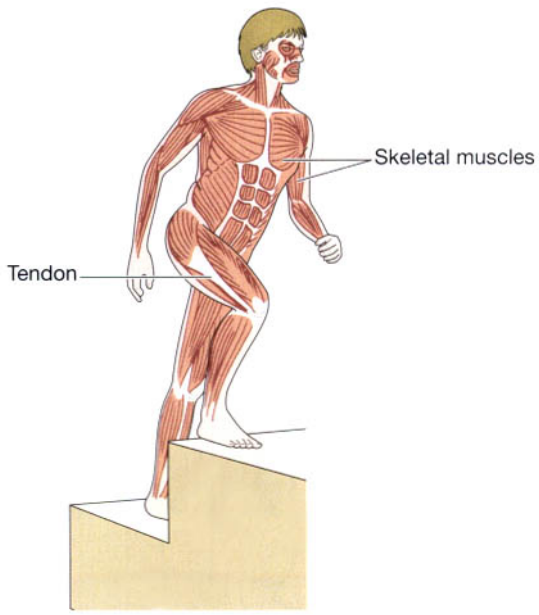

Figure 1.14 The skeletal muscles.

Reproduction (Ch. 19)

Successful reproduction is essential in order to ensure the continuation of a species from one generation to the next. *Bisexual reproduction* results from the fertilisation of a female egg cell or *ovum* by a male sperm cell or *spermatozoon*. Ova are produced by two *ovaries* situated in the female pelvis (Fig. 1.15). Usually only one ovum is released at a time and it travels towards the *uterus* in the *uterine tube*. The spermatozoa are produced in large numbers by the two *testes*, situated in the *scrotum*. From each testis spermatozoa pass through a duct called the *deferent duct (vas deferens)* to the *urethra*. During sexual intercourse (coitus) the spermatozoa are deposited in the female *vagina*.

They then pass upwards through the uterus and fertilise the ovum in the uterine tube. The fertilised ovum (*zygote*) then passes into the uterus, embeds itself in the uterine wall and grows to maturity during pregnancy or gestation, in about 40 weeks. The newborn baby is entirely dependent on others for food and protection that was provided by the mother's body before birth.

One ovum is produced about every 28 days during the child-bearing years between *puberty* and the *menopause*.

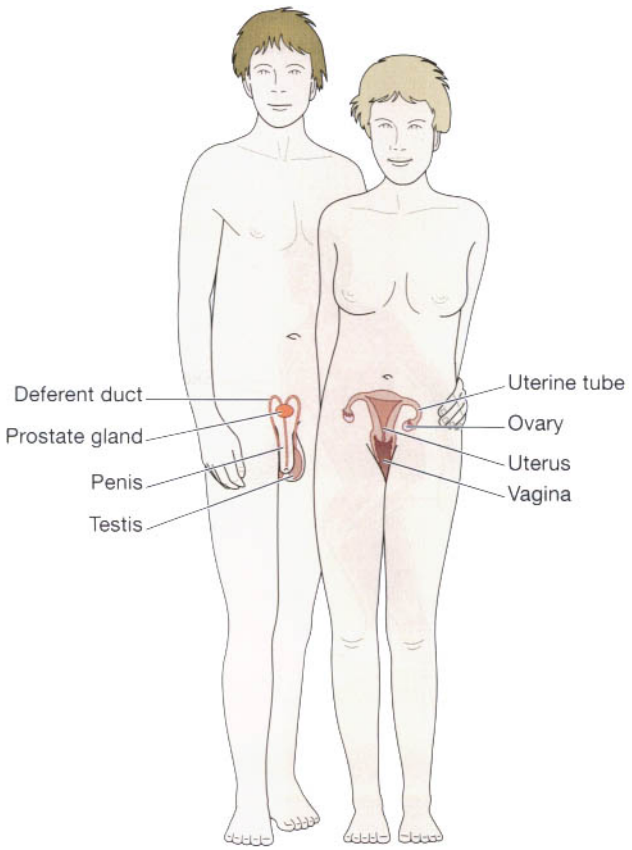

Figure 1.15 The reproductive systems: male and female.

When the ovum is not fertilised it passes out of the uterus accompanied by bleeding, called *menstruation*. The cycle in the female, called the *menstrual cycle*, has phases associated with changes in the concentration of hormones involving the endocrine system. There is no similar cycle in the male but hormones similar to those of the female are involved in the production and maturation of the spermatozoa.

INTRODUCTION TO THE STUDY OF ILLNESS

Learning outcomes

After studying this section you should be able to:

- list factors that commonly cause disease
- define the following terms: aetiology, pathogenesis and prognosis
- name some common disease processes that can affect many of the body systems.

In order to understand the specific diseases described in later chapters, a knowledge of the relevant anatomy and physiology is necessary, as well as familiarity with the pathological processes outlined below.

Many different illnesses, disorders and diseases are known, and these 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 1.3 will be used as a guide. Causes (*aetiology*) are outlined first when there are clear links between them and the effects of the abnormality (*pathogenesis*).

Box 1.3 Suggested framework for understanding diseases

Aetiology: cause of the disease

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

Complications: other consequences which might arise if the disease progresses

Prognosis: the likely outcome

Aetiology

Disease is usually caused by one or more of a limited number of factors including:

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

In some diseases more than one of the aetiological factors listed above is involved, while in others, no specific cause has been identified and these may be described as *essential, idiopathic* or *spontaneous*. For some diseases of which the precise cause is unknown, links may have been established with *predisposing factors*, or *risk factors*. *Iatrogenic* conditions are those that result from harm caused by members of the caring professions.

Pathogenesis

The main processes causing illness or disease are as follows.

- *Inflammation* (p. 375) – this is a tissue response to damage by, e.g. trauma, invasion of microbes*. Inflammatory conditions are recognised by the suffix -itis, e.g. appendicitis.
- *Tumours* (p. 53) – these arise when the rate of cell production exceeds that of normal cell destruction causing a mass to develop. Tumours are recognised by the suffix -oma, e.g. carcinoma.
- *Abnormal immune mechanisms* (p. 383) – these are a response of the normally protective immune system that causes undesirable effects.
- *Thrombosis, embolism* and *infarction* (p. 117) – these are the effects and consequences of abnormal changes in the blood and/or blood vessel walls.
- *Degeneration* – this is often associated with normal ageing but also arises prematurely when structures deteriorate causing impaired function.
- *Metabolic abnormalities* – cause undesirable effects (e.g. phenylketonuria (p. 185)).
- *Genetic abnormalities* – may be either inherited or caused by environmental factors such as exposure to ionising radiation.

Box 1.4 is a glossary of disease-associated terminology.

Box 1.4 Glossary of terminology associated with disease

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

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

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

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

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 which tend to occur together.

*The term **microbe**, used throughout the text, includes all types of organisms that can only be seen by using a microscope. Specific microbes are named where appropriate.

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2 Introduction to the chemistry of life

In all the following chapters, the cells, tissues and organs of the body will be studied in more depth. However, on a smaller scale even than the cell, all living matter is made up of chemical building blocks. The basis of anatomy and physiology is therefore a chemical one, and before launching into the study of the subject it is necessary to consider briefly some aspects of chemistry and biochemistry.

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 bonds that hold molecules together
- outline the concept of molar concentration
- discuss the importance of buffers in the maintenance of body pH.

The *atom* is the smallest particle of an element which can exist as a stable entity. An *element* is a chemical substance whose atoms are all of the same type; e.g. iron contains only iron atoms. *Compounds* contain more than one type of atom; for instance, water is a compound containing both hydrogen and oxygen atoms.

There are 92 naturally occurring elements. The body structures are made up of a great variety of combinations of four elements: carbon, hydrogen, oxygen and nitrogen. In addition small amounts of others are present, collectively described as *mineral salts* (p. 276).

Atomic structure

Atoms are made up of three main types of particles.

- *Protons* are particles present in the nucleus or central part of the atom. Each proton has *one unit of positive electrical charge* and *one atomic mass unit*.
- *Neutrons* are also found in the nucleus of the atom. They have *no electrical charge* and *one atomic mass unit*.
- *Electrons* are particles which revolve in orbit around the nucleus of the atom at a distance from it (Fig. 2.1), as the planets revolve round the sun. Each electron carries *one unit of negative electrical charge* and its mass is so small that it can be disregarded when compared with the mass of the other particles.

Table 2.1 Characteristics of subatomic particles

Particle	Mass	Electric charge
Proton	1 unit	1 positive
Neutron	1 unit	neutral
Electron	negligible	1 negative

Table 2.1 summarises the characteristics of these subatomic particles.

In all atoms the number of positively charged protons in the nucleus is *equal to* the number of negatively charged electrons in orbit around the nucleus and therefore an atom is electrically neutral.

Atomic number and atomic weight

What makes one element different from another is the number of protons in the nuclei of its atoms. For instance, hydrogen has only one proton per nucleus, oxygen has eight and sodium has 11. The number of protons in the nucleus of an atom is called the atomic number; the atomic numbers of hydrogen, oxygen and sodium are therefore 1, 8 and 11 respectively. It therefore follows that each element has its own atomic number (Fig. 2.2). The atomic weight of an element is the sum of the protons and neutrons in the atomic nucleus (Fig. 2.2).

The electrons are shown in Figure 2.1 to be in concentric rings round the nucleus. These shells diagrammatically represent the different energy levels of the electrons

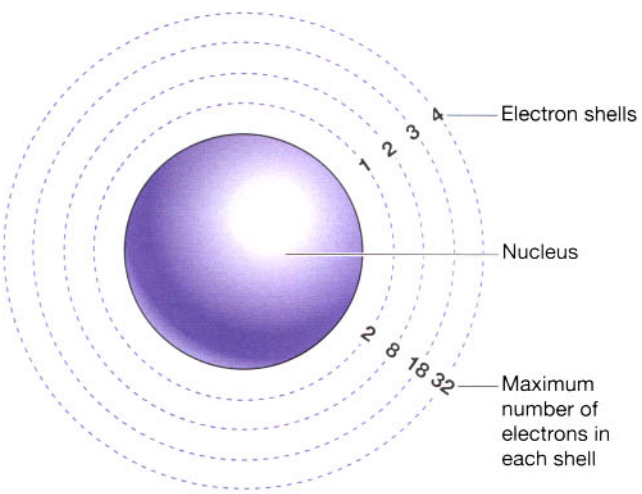
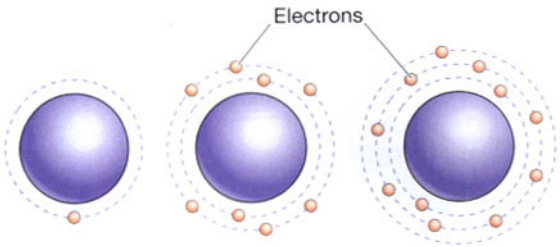


Figure 2.1 The atom showing the nucleus and four electron shells.



	Hydrogen	Oxygen	Sodium
Atomic number	1	8	11
Atomic weight	1	16	23

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

in relation to the nucleus, 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 subsequent energy levels hold increased numbers of electrons, each containing more than the preceding level.

The *electron configuration* denotes the distribution of the electrons in each element, e.g. sodium is 2 8 1 (Fig. 2.2).

An atom is most stable when its outermost electron shell is full. Once electrons have filled the first two shells, the atom can reach a level of stability by having either the full complement of 18, or exactly eight, electrons in its third shell. When the outermost shell does not have a stable number of electrons, the atom is reactive and will combine with other reactive atoms, forming the wide range of the complex molecules of life. This will be described more fully in the section discussing molecules and compounds.

Isotopes. These are atoms of an element in which there is 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 forms of the hydrogen atom. The most common form has one proton in the nucleus and one orbiting electron. Another form has one proton and *one neutron* in the nucleus. A third form has one proton and *two neutrons* in the nucleus and one orbiting electron. These three forms of hydrogen are called *isotopes* (Fig. 2.3).

Taking into account the isotopes of hydrogen and the proportions in which they occur, the atomic weight of hydrogen is 1.008, although for many practical purposes it can be taken as 1.

Chlorine has an atomic weight of 35.5, because it exists in two forms; one isotope has an atomic weight of

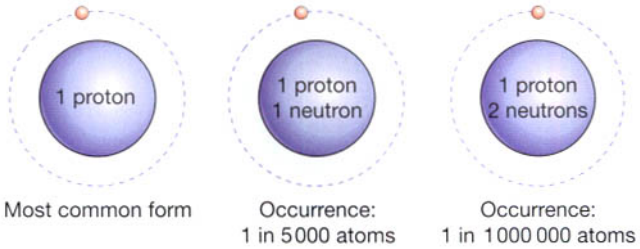


Figure 2.3 The isotopes of hydrogen.

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.

Molecules and compounds

It was mentioned earlier that 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 the optimum number (Fig. 2.1), the element is described as inert or chemically unreactive, i.e. it will not easily combine with other elements to form compounds. These elements are the inert or noble gases—helium, neon, argon, krypton, xenon and radon.

Molecules consist of two or more atoms which are chemically combined. The atoms may be of the same element, e.g. a molecule of atmospheric oxygen (O_2) consists of two oxygen atoms. Most molecules, however, contain two or more different elements; e.g. a water molecule (H_2O) contains two hydrogen atoms and an oxygen atom. As mentioned earlier, when two or more elements combine, the resulting molecule can also be referred to as a compound.

Compounds which contain the element carbon are classified as *organic*, and all others as *inorganic*. The body contains both.

Covalent and ionic bonds. The vast array of chemical processes on which body functioning is based is completely dependent upon the way atoms come together, bind and break apart. For example, the simple water molecule is a crucial foundation of all life on Earth. If water was a less stable compound, and the atoms came apart easily, human biology could never have evolved. On the other hand, the body is dependent upon 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 which is generally one of two types: *covalent* or *ionic*.

Covalent bonds are formed when atoms share their electrons with each other. Most atoms use this type of bond when they come together; it forms a strong and stable link between them, because atoms are most stable

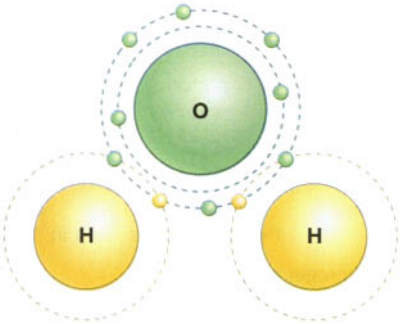


Figure 2.4 A water molecule, showing the covalent bonds between hydrogen (yellow) and oxygen (green).

when their outer electron shells are filled. 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 and thereby conferring stability. 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 are formed when electrons are transferred from one atom to another. For example, when sodium (Na) combines with chlorine (Cl) to form sodium chloride (NaCl) there is a transfer of the only electron in the outer shell of the sodium atom to the outer shell of the chlorine atom. (Fig. 2.5).

This leaves the sodium atom of the compound with eight electrons in its outer (second) shell, and therefore stable. The chlorine atom also has eight electrons in its outer shell, which, although not filling the shell, is a stable number.

The number of electrons is the only change which occurs in the atoms in this type of reaction. There is no change in the number of protons or neutrons in the nuclei of the atoms. The chloride atom now has *18 electrons*, each with one negative electrical charge, and *17 protons*, each with one positive charge. The sodium atom has lost one electron, leaving *10 electrons* orbiting round the nucleus with *11 protons*. When sodium chloride is dissolved in water the two atoms separate, i.e. they *ionise*, and the imbalance of protons and electrons leads to the formation of two *charged particles* called *ions*. Sodium, with the positive charge, is a *cation*, written Na^+, and 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.

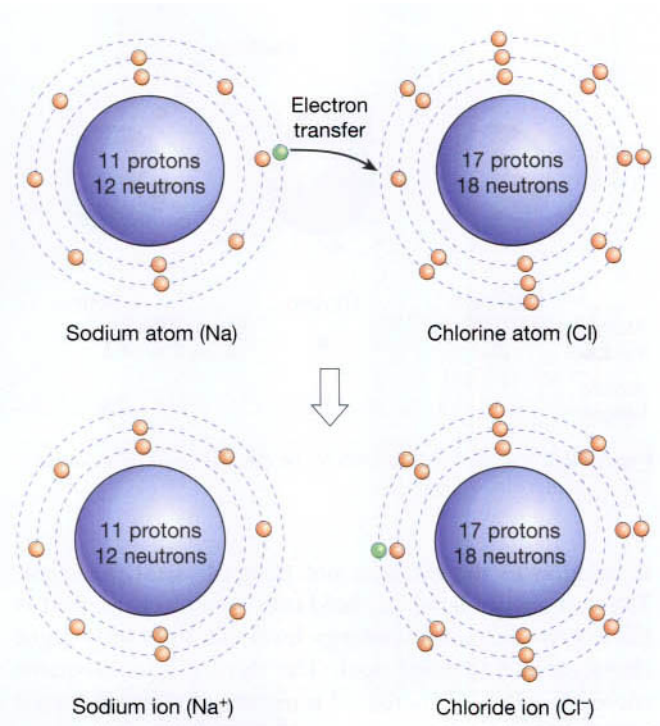


Figure 2.5 Formation of the ionic compound, sodium chloride.

Electrolytes

An ionic compound, e.g. sodium chloride, in solution in water is called an *electrolyte* because it can conduct electricity. Electrolytes are important body constituents because:

- some conduct electricity, essential for muscle and nerve function
- some exert osmotic pressure, keeping body fluids in their own compartments
- some function in acid–base balance, as buffers to resist pH changes in body fluids.

In this discussion, sodium chloride has been used as an example of the formation of an ionic compound and to illustrate electrolyte activity. There are, however, many other electrolytes within the human body which, though in relatively small quantities, are equally important. Although these substances may enter the body in the form of compounds, such as sodium bicarbonate, they are usually discussed in the ionic form, that is, as sodium ions (Na^+) and bicarbonate ions (HCO_3^-).

The bicarbonate part of sodium bicarbonate is derived from carbonic acid (H_2CO_3). All inorganic acids contain hydrogen combined with another element, or with a group of elements called a *radical* which acts like a single element. Hydrogen combines with chlorine to form hydrochloric acid (HCl) and with the *phosphate radical* to form phosphoric acid (H_3PO_4). When these two acids ionise they do so thus:

$HCl \rightarrow H^+ Cl^-$
$H_3PO_4 \rightarrow 3H^+ PO_4^{3-}$

In the second example, three atoms of hydrogen have each lost one electron, all of which have been taken up by one unit, the phosphate radical, making a phosphate ion with three negative charges.

A large number of compounds present in the body are not ionic and therefore have no electrical properties when dissolved in water, e.g. carbohydrates.

Molecular weight

The molecular weight of a molecule is the sum of the atomic weights of the elements which form its molecules, e.g.:

Water (H.OH)

2 hydrogen atoms	(atomic weight 1)	2
1 oxygen atom	(atomic weight 16)	16
	Molecular weight	= 18

Sodium bicarbonate ($NaHCO_3$)

1 sodium atom	(atomic weight 23)	23
1 hydrogen atom	(atomic weight 1)	1
1 carbon atom	(atomic weight 12)	12
3 oxygen atoms	(atomic weight 16)	48
	Molecular weight	= 84

Molecular weight, like atomic weight, is expressed simply as a figure until a scale of measurement of weight is applied.

Molar concentration

This is the term recommended in the *Système Internationale* for expressing the concentration of substances present in the body fluids (SI units).

The mole (mol) is the molecular weight in grams of a substance (formerly called 1 gram molecule). One mole of any substance contains 6.023×10^{23} molecules or atoms. For example, 1 mole of sodium bicarbonate (the example above) is 84 grams.

A molar solution is a solution in which 1 mole of a substance is dissolved in 1 litre of solvent. In the human body the solvent is water or fat. A molar solution of sodium bicarbonate is therefore prepared using 84 g of sodium bicarbonate dissolved in 1 litre of solvent.

Molar concentration may be used to measure quantities of electrolytes, non-electrolytes, ions and atoms, e.g. molar solutions of the following substances mean:

1 mole of sodium chloride molecules (NaCl)	= 58.5 g per litre
1 mole of sodium ions (Na^+)	= 23 g per litre
1 mole of carbon atoms (C)	= 12 g per litre
1 mole of atmospheric oxygen (O_2)	= 32 g per litre

Table 2.2 Examples of normal plasma levels

Substance	Amount in SI units	Amount 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 µmol/l	90–196 µg/100 ml

In physiology this system has the advantage of being a measure of the number of particles (molecules, atoms, ions) of substances present because molar solutions of different substances contain the same number of particles. It has the advantage over the measure milliequivalents per litre* because it can be used for non-electrolytes, in fact for any substance of known molecular weight.

Many of the chemical substances present in the body are in very low concentrations so it is more convenient to use smaller metric measures, e.g. *millimoles per litre* (mmol/l) or micromoles per litre (µmol/l) as a biological measure (Table 2.2).

For substances of unknown molecular weight, e.g. insulin, concentration may be expressed in International Units per millilitre (IU/ml).

Acids, alkalis and pH

The number of hydrogen ions present in a solution is a measure of the acidity of the solution. The maintenance of the normal hydrogen ion concentration ($[H^+]$) within the body is an important factor in maintaining a stable environment, i.e. homeostasis.

The pH scale

A standard scale for the measurement of the hydrogen ion concentration in solution has been developed: the pH scale. Not all acids ionise completely when dissolved in water. The hydrogen ion concentration is a measure, therefore, of the amount of *dissociated acid* (ionised acid) rather than of the total amount of acid present. Strong acids dissociate more freely than weak acids, e.g. hydrochloric acid

*Milliequivalents per litre (mEq/l)

$$\text{Equivalent weight} = \frac{\text{atomic weight}}{\text{number of electrical charges}}$$

Concentration is expressed:

$$\text{mEq/l} = \frac{\text{mg/l}}{\text{atomic weight}} \times \text{number of electrical charges}$$

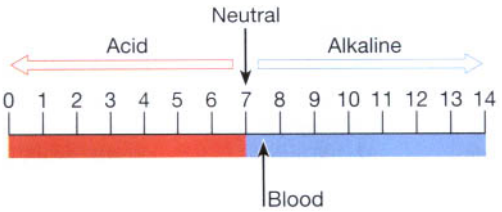


Figure 2.6 The pH scale.

dissociates freely into H^+ and Cl^-, while carbonic acid dissociates much less freely into H^+ and HCO_3^-. The number of *free hydrogen ions* in a solution is a *measure of its acidity* rather than an indication of the type of molecule from which the hydrogen ions originated.

The alkalinity of a solution depends on the number of hydroxyl ions (OH^-). Water is a neutral solution because every molecule contains one hydrogen ion and one hydroxyl radical. For every molecule of water (H.OH) which dissociates, one hydrogen ion (H^+) and one hydroxyl ion (OH^-) are formed, neutralising each other.

The scale for measurement of pH was developed taking water as the standard.

In a neutral solution such as water, where the number of hydrogen ions is balanced by the same number of hydroxyl ions, the pH = 7. The range of this scale is from 0 to 14.

A pH reading *below* 7 indicates an *acid solution*, while readings *above* 7 indicate *alkalinity* (Fig. 2.6). A change of one whole number on the pH scale indicates a tenfold change in $[H^+]$. Therefore, a solution of pH 5 contains ten times as many hydrogen ions as a solution of pH 6.

Ordinary litmus paper indicates whether a solution is acid or alkaline by colouring blue for alkaline and red for acid. Other specially treated absorbent papers give an approximate measure of pH by a colour change. When accurate measurements of pH are required, sensitive pH meters are used.

pH values of the body fluids

Body fluids have pH values that must be maintained within relatively narrow limits for normal cell activity. The pH values are not the same in all parts of the body; e.g. the normal range of pH values of certain body fluids are shown in Table 2.3.

The pH value in an organ is produced by its secretion of acids or alkalis which establishes the optimum level. 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 value in the stomach provides the environment best suited to the functioning of the enzyme pepsin that begins the digestion of dietary protein. Saliva has a pH of between 5.4 and 7.5 which is the optimum value for the action of salivary amylase, the enzyme present in saliva which initiates the digestion of carbohydrates. The action of salivary amylase is inhibited when food containing it reaches the stomach and is mixed with acid gastric juice.

Table 2.3 pH values of body fluids

Body fluid	pH
Blood	7.35 to 7.45
Saliva	5.4 to 7.5
Gastric juice	1.5 to 3.5
Bile	6 to 8.5
Urine	4.5 to 8.0

Blood has a pH value between 7.35 and 7.45. The pH range of blood compatible with life is 7.0 to 7.8. The metabolic activity of the body cells produces certain acids and alkalis which alter the pH of the tissue fluid and blood. To maintain the pH within the normal range, there are substances present in blood that act as *buffers*.

Buffers

The optimum pH level is maintained by the balance between acids and bases produced by cells. Bases are substances that accept (or bind) hydrogen ions and when dissolved in water they produce an alkaline solution. Buffers are substances such as phosphates, bicarbonates and some proteins that maintain the $[H^+]$ within normal, but narrow, limits. Some buffers 'bind' hydrogen ions and others 'bind' hydroxyl ions, reducing their circulating levels and preventing damaging changes. For example, if there is sodium hydroxide (NaOH) and carbonic acid (H_2CO_3) present, both will ionise to some extent, but they will also react together to form sodium bicarbonate ($NaHCO_3$) and water (H.OH). One of the hydrogen ions from the acid has been 'bound' in the formation of the bicarbonate radical and the other by combining with the hydroxyl radical to form water.

NaOH	+	H_2CO_3	→	$NaHCO_3$	+ H.OH
sodium hydroxide		carbonic acid		sodium bicarbonate	water

Acidosis and alkalosis

The substances in the complex buffer system that 'bind' hydrogen ions are called the *alkali reserve* of the blood. When the pH is below 7.35, and all the reserves of alkaline buffer are used up, the condition of *acidosis* exists. When the reverse situation pertains and the pH is above 7.45, and the increased alkali uses up all the *acid reserve*, the state of *alkalosis* exists.

The buffer systems maintain *homeostasis* by preventing dramatic changes in the pH values in the blood, but can only function effectively if there is some means by which excess acid or alkali can be excreted from the body. The organs most active in this way 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.

CO_2	$+ H_2O$	$\rightarrow H_2CO_3$	$\rightarrow H^+$	$+$	HCO_3^-
carbon dioxide	water	carbonic acid	hydrogen ion		bicarbonate ion

In acidosis, the brain detects the rising $[H^+]$ in the blood and stimulates breathing, causing increased CO_2 loss and a fall in $[H^+]$. Conversely, in alkalosis, the brain can reduce the respiration rate to increase CO_2 levels and increase $[H^+]$, restoring pH towards normal.

The kidneys have the ability to form ammonia, an alkali, which combines with the acid products of protein metabolism which are then excreted in the urine.

The buffer and excretory systems of the body together maintain the *acid–base balance* so that the pH range of the blood remains within normal, but narrow, limits.

IMPORTANT BIOLOGICAL MOLECULES

Learning outcomes

After studying this section, you should be able to:

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

Carbohydrates

The carbohydrates are the sugars. Carbohydrates are composed of carbon, oxygen and hydrogen and the carbon atoms are normally arranged in a ring, with the oxygen and hydrogen atoms linked to them. The structures of glucose, fructose and sucrose are shown in Figure 2.7. When two sugars link up, the reaction occurring expels a molecule of water and the resulting bond is called a *glycosidic linkage*.

Simple sugars, like glucose, can exist as single units, and are referred to as *monosaccharides*. Glucose is the main form in which sugar is used by cells, and blood levels are tightly controlled. Frequently, the monosaccharides are linked together, the resultant molecule ranging from two sugars or *disaccharides*, e.g. sucrose (table sugar), to long chains containing many thousands of sugars. Such complex carbohydrates are called *polysaccharides*, e.g. starch.

Glucose can be broken down (metabolised) 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. 315) This family of molecules:

- serves as a ready source of energy to fuel cellular activities (p. 272)
- provides a form of energy storage, e.g. glycogen (p. 315)
- forms an integral part of the structure of DNA and RNA (p. 25)
- can act as receptors on the cell surface, allowing the cell to recognise other molecules and cells.

Amino acids and proteins

Amino acids always contain carbon, hydrogen, oxygen and nitrogen, and many in addition carry sulphur. In human biochemistry, 20 amino acids are used as the principal building blocks of protein, although there are

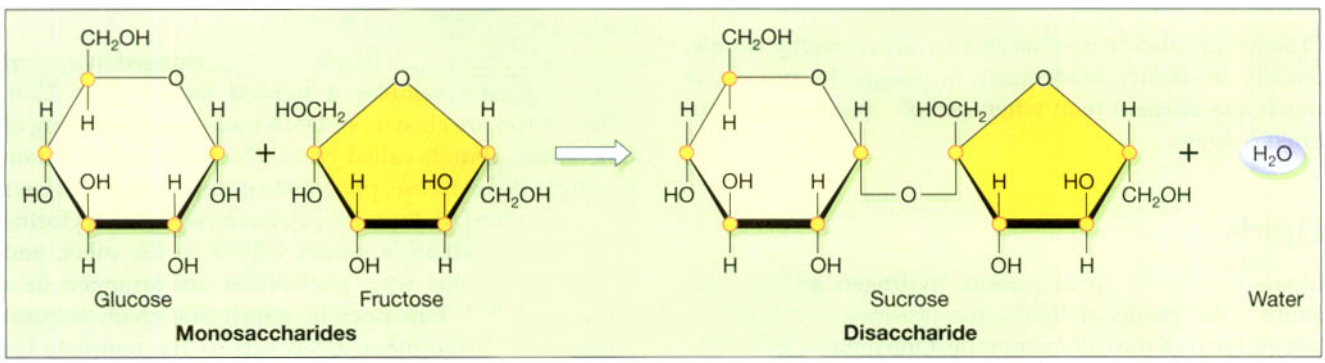


Figure 2.7 The combination of glucose and fructose to make sucrose.

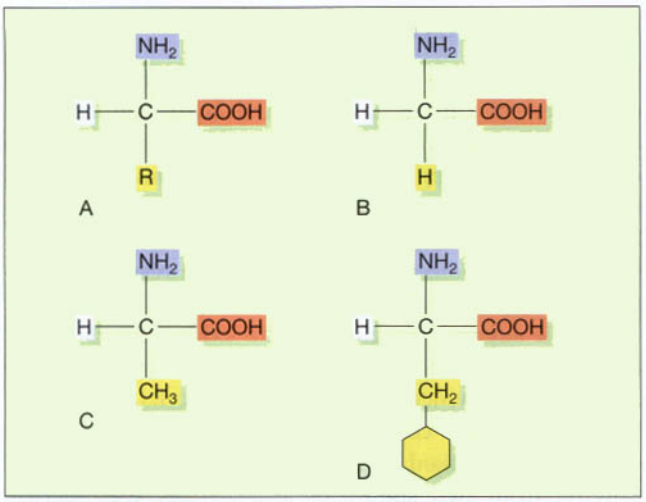


Figure 2.8 Amino acid structures: A. Common structure, R = variable side chain. B. Glycine, the simplest amino acid. C. Alanine. D. Phenylalanine.

others; for instance, there are some amino acids used only in certain proteins, and some seen only in microbial products. Of the amino acids used in human protein synthesis, there is a basic common structure, including an amino group (NH_2), a carboxy group (COOH) and a hydrogen atom. What makes one amino acid different from the next is a variable side chain. The basic structure and three common amino acids are shown in Figure 2.8. As in formation of glycosidic linkages, when two amino acids join up the reaction expels a molecule of water and the resulting bond is called a *peptide bond*.

Proteins are made from amino acids joined together, and are the main family of molecules from which the human body is built. Protein molecules vary enormously in size, shape, chemical constituents and function. Many important groups of biologically active substances are proteins, e.g.:

- carrier molecules, e.g. haemoglobin (p. 63)
- enzymes (p. 26)
- many hormones, e.g. insulin (p. 225)
- antibodies (p. 380).

Proteins can also be used as an alternative energy source, usually in dietary inadequacy, although the process is much less efficient than when carbohydrates or fats are broken down.

Lipids

Lipids are made up of carbon, hydrogen and oxygen atoms. One group of lipids, the *phospholipids*, form an integral part of the cell membrane. One notable feature of lipid molecules is that they are strongly hydrophobic

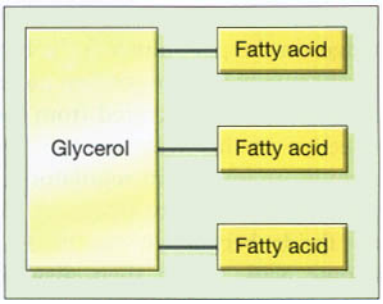


Figure 2.9 Core structure of the fats.

(water hating) and therefore lipids do not mix with water. This is important in their function in the cell membrane (p. 30).

Other types of lipids include certain vitamins (e.g. E and K), an important group of hormones called *steroids*, and the *fats*. A molecule of fat consists of three fatty acids, each linked to a molecule of glycerol (Fig. 2.9). Fats are a source of energy, and provide a convenient form in which to store excess calorific intake. When fats are broken down, they release energy, but the process is less efficient than when carbohydrates are used, since it requires more energy for the breakdown reaction to take place. They are used in the body for:

- insulation
- protection of body parts
- energy storage.

Nucleotides

Nucleic acids

These are the largest molecules in the body and are built from components called nucleotides, which consist of three subunits:

- a sugar unit
- a base
- one or more phosphate groups linked together.

Deoxyribonucleic acid (DNA)

This is a double strand of nucleotides arranged in a spiral (helix) which resembles a twisted ladder (Fig. 2.10). *Chromosomes* are clusters of DNA molecules consisting of functional subunits called *genes*. The nucleotides contain the sugar deoxyribose, phosphate groups and one of four bases: adenine [A], thymine [T], guanine [G] and cytosine [C]. A in one chain is paired with T in the other, and G with C. In this way, nucleotides are arranged in a precisely ordered manner in which one chain is complementary to the other. DNA acts as the template for protein synthesis and is stored safely in the nucleus.

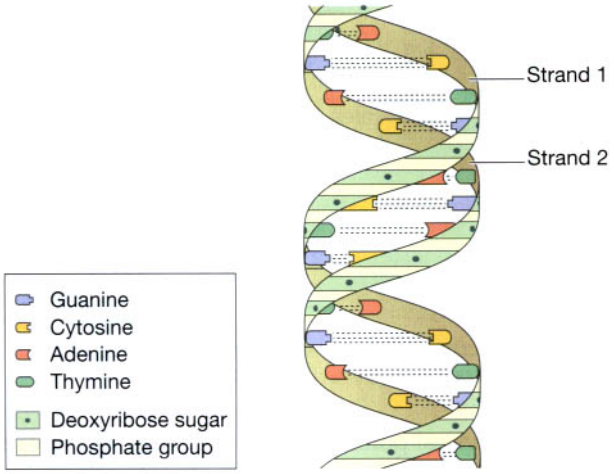


Figure 2.10 Deoxyribonucleic acid (DNA).

Ribonucleic acid (RNA)

This is a single-stranded chain of nucleotides which contains the sugar ribose instead of the deoxyribose found in DNA. It contains no thymine, but uses uracil [U] instead. It is synthesised in the nucleus from the DNA template, and carries the message instructing synthesis of a new protein from the DNA (which cannot leave the nucleus) to the protein-synthesising apparatus in the cell cytoplasm.

Protein synthesis. When cells require new protein, a single strand of RNA is made using DNA as the template; the RNA leaves the nucleus. RNA acts as the messenger which carries the instructions for the assembly of the new protein to tiny structures in the cytoplasm called ribosomes (p. 32). Ribosomes read the message and, following the instructions, assemble the new protein from amino acids in the cell cytoplasm (Fig. 2.11). New chains of protein are often large molecules which coil up in a particular way to maintain stability of the molecule.

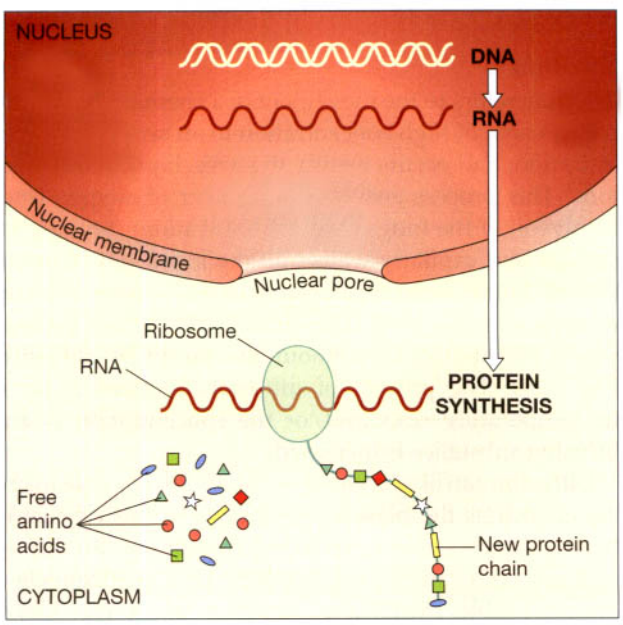


Figure 2.11 The relationship between DNA, RNA and protein synthesis.

Adenosine triphosphate (ATP)

ATP is a nucleotide which contains ribose (the sugar unit), adenine (the base) and three phosphate groups attached to the ribose (Fig. 2.12A). It is sometimes known as the energy currency of the body, which implies that the body has to 'earn' (synthesise) it before it can 'spend' it. Many of the body's huge number of reactions release energy, e.g. the breakdown of sugars in the presence of O_2. The body captures the energy released by these reactions, using it to make ATP from adenosine diphosphate (ADP). When the body needs chemical energy to fuel cellular activities, ATP releases its stored energy, water and a phosphate group through the splitting of a high-energy phosphate bond, and reverts to ADP (Fig. 2.12B).

The body needs chemical energy to:

- drive synthetic reactions (i.e. building biological molecules)
- fuel movement
- transport substances across membranes.

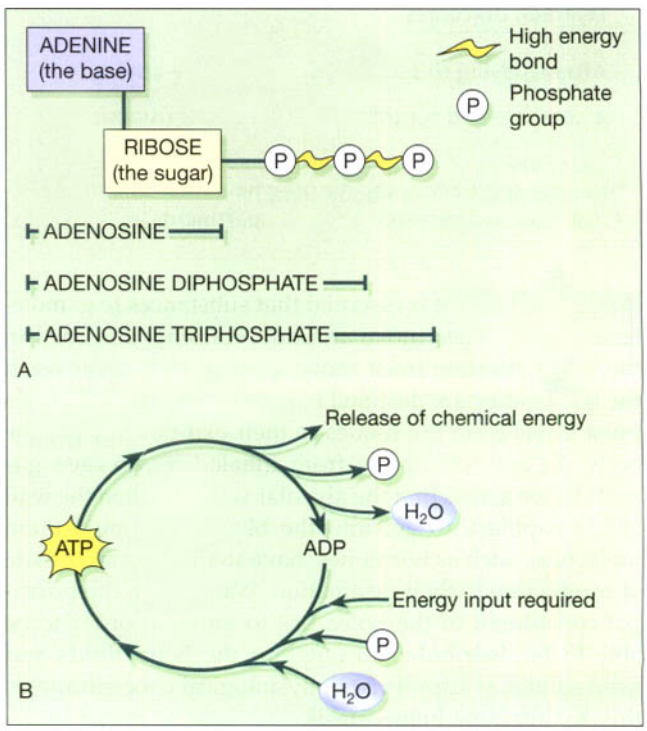


Figure 2.12 ATP and ADP: A. Structures. B. Conversion cycle.

Enzymes

Many of the body's chemical reactions can be reproduced in a test-tube. Surprisingly, the rate at which the reactions then occur usually plummets to the extent that, for all practical purposes, chemical activity ceases. The cells of the body have developed a solution to this apparent problem—they are equipped with a huge array of enzymes. Enzymes are proteins which act as *catalysts* for biochemical reactions—that is, they speed the reaction up but are not themselves changed by it, and therefore can be used over and over again. Enzymes are very selective and will usually catalyse only one specific reaction. The molecule(s) entering the reaction is called the *substrate* and it binds to a very specific site on the enzyme, called the *active site*. Whilst the substrate(s) is bound to the active site the reaction proceeds, and once it is complete the product(s) of the reaction breaks away from the enzyme and the active site is ready for use again (Fig. 2.13).

Enzymes can catalyse both synthesis and breakdown reactions, and their names (almost always!) end in ~ase.

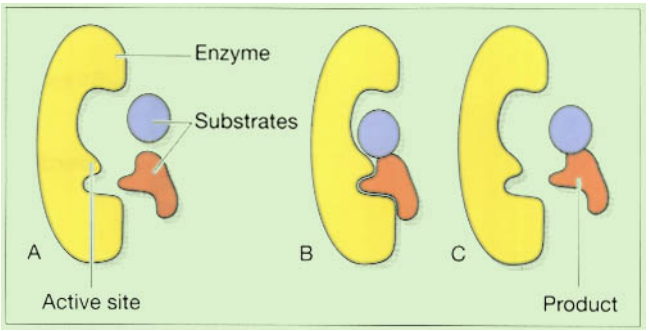


Figure 2.13 Action of an enzyme: A. Enzyme and substrates. B. Enzyme–substrate complex. C. Enzyme and product.

MOVEMENT OF SUBSTANCES WITHIN THE BODY

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the processes of osmosis and diffusion
- using these concepts, describe how molecules move within and between body compartments.

Within the body, it is essential that substances (e.g. molecules, electrolytes) move around. Nutrients absorbed in the small intestine must move, or they will never reach the tissues they are destined to nourish. Waste substances must travel from the tissues to their exit points from the body. To enter the body from inhaled air, oxygen gas must move across first the alveolar wall and then the wall of the capillary to get into the blood. Communication molecules, such as hormones, have to travel from the site of production to their destination. Water itself, the principal constituent of the body, has to move in order to be able to be distributed throughout the body fluids and keep solutes at appropriate physiological concentrations, thus maintaining homeostasis.

From a physical point of view, substances will always travel from an area of high concentration to one of low concentration, assuming that there is no barrier in the way. Between two such areas, there exists a *concentration gradient* and movement of substances occurs *down* the concentration gradient, or downhill. No energy is required for such movement; this process is therefore described as *passive*.

$$\text{high concentration} \xrightarrow{\text{Net movement of substance}} \text{low concentration}$$

There are many examples in the body of substances moving *uphill*, i.e. against the concentration gradient; in this case, chemical energy is required, usually in the form of ATP. These processes are described as *active*. Movement of substances across cell membranes by active transport is described on page 34.

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

Diffusion

Diffusion refers to the movement of a chemical substance from an area of high concentration to an area of low concentration, and occurs mainly in gases, liquids and solutions. This process enables the transfer of oxygen from the alveoli of the lungs (high concentration) through the alveolar and capillary walls into the blood (low concentration). Sugar molecules heaped at the bottom of a cup of coffee which 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 plasma membrane; in this case, only those molecules able to cross the membrane can diffuse through. For example, the capillary wall is effectively a semipermeable membrane; whereas water can travel freely in either direction across it, large proteins in the

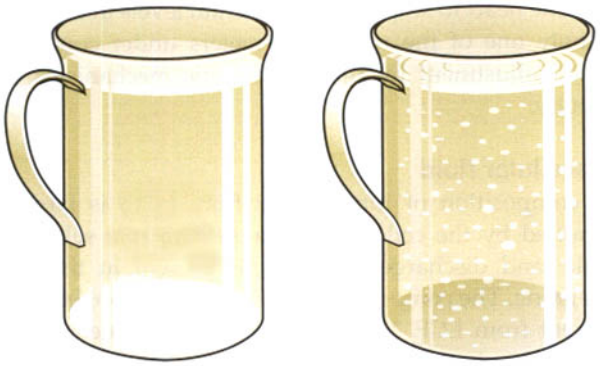


Figure 2.14 The process of diffusion: a spoonful of sugar in a cup of coffee.

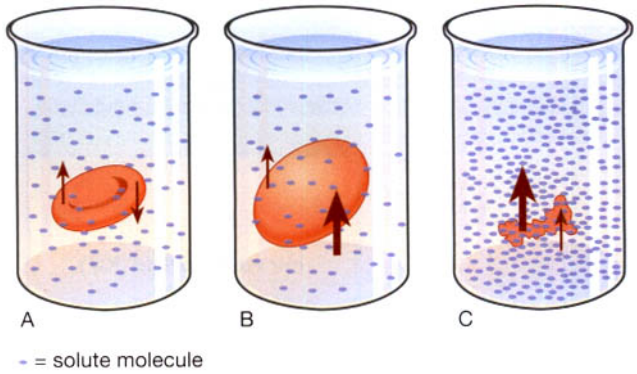


Figure 2.15 The process of osmosis. Net water movement when a red blood cell is suspended in solutions of varying concentrations (tonicity): A. Isotonic solution. B. Hypotonic solution. C. Hypertonic solution.

plasma and red blood cells are too large to cross and therefore remain in the blood.

Osmosis

Osmosis is the movement of water down its concentration gradient across a semipermeable membrane when equilibrium cannot be achieved by diffusion of solute molecules. This is usually because the solute molecules are too large to pass through the pores in the membrane. The force with which this occurs is called the *osmotic pressure*. Water crosses the membrane down its concentration gradient from the side with the lower solute concentration to the side with the greater solute concentration. This dilutes the more concentrated solution, and concentrates the more dilute solution. Osmosis proceeds until equilibrium is reached, at which point the solutions on each side of the membrane are of the same concentration and are said to be *isotonic*. Osmosis can be illustrated using the semipermeable membrane of the red blood cell as an example.

The concentration of water and solutes in the plasma 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 will move down its concentration gradient across the 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*. Conversely, if the plasma water concentration falls so that the plasma becomes more concentrated than the intracellular fluid within the red blood cells (the plasma becomes *hypertonic*), water passively moves by osmosis from the blood cells into the plasma and shrinkage of the blood cells occurs (Fig. 2.15).

BODY FLUIDS

Learning outcomes

After studying this section, you should be able to:

- define the terms intra- and extracellular fluid
- using examples, explain why homeostatic control of the composition of these fluids is vital to body function.

The total body water in adults of average build is about 60% of body weight. This proportion is higher in young people and in adults below average weight. It is lower in the elderly and in obesity in all age groups. About 22% of body weight is extracellular water and about 38% is intracellular water (Fig. 2.16).

Extracellular fluid

The extracellular fluid (ECF) consists of blood, plasma, lymph, cerebrospinal fluid and fluid in the interstitial spaces of the body. Interstitial or intercellular fluid (tissue fluid) bathes all the cells of the body except the outer layers of skin. It is the medium through which substances pass from blood to the body cells, and from the cells to blood. Every body cell in contact with the ECF is directly dependent upon the composition of that fluid for its well-being. Even slight changes can cause permanent damage, and any change is therefore resisted by the body, through one or more of its many control mechanisms; this is homeostasis. For example, a fall in plasma calcium levels

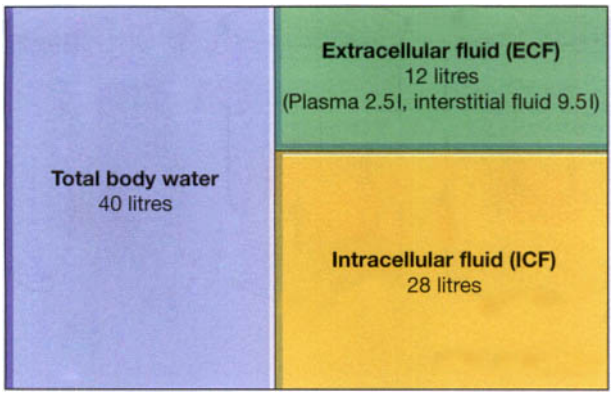


Figure 2.16 Distribution of body water in a 70 kg person.

causes *tetany* (abnormal spasmodic muscle contractions) and convulsions (fits), because of increased excitability of muscle and nervous tissue. Rising blood calcium depresses muscle and nerve function, and can even cause the heart to stop beating. Calcium levels in the ECF are only one of the many parameters under constant, careful adjustment by the homeostatic mechanisms of the body.

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. The composition of ICF can therefore be very different from ECF. Thus, sodium levels are nearly ten times higher in the ECF than in the ICF. This concentration difference occurs because although sodium diffuses into the cell down its concentration gradient there is a pump in the membrane which 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.

3 The cells, tissues and organisation of the body

Cells are the smallest functional units of the body. They are grouped together to form *tissues*, each of which has a specialised function, e.g. blood, muscle, bone. Different tissues are grouped together to form *organs*, e.g. heart, stomach, brain. Organs are grouped together to form *systems*, each of which performs a particular function that maintains homeostasis and contributes to the health of the individual (p. 5). For example, the digestive system is responsible for taking in, digesting and absorbing food and involves a number of organs, including the stomach and intestines.

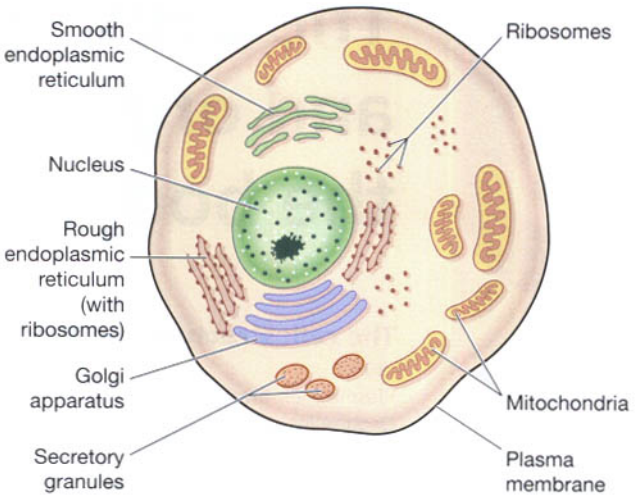


Figure 3.1 The simple cell.

THE CELL: STRUCTURE AND FUNCTIONS

Learning outcomes

After studying this section you should be able to:

- describe the structure of the plasma membrane
- explain the functions of the following organelles: nucleus, mitochondria, ribosomes, endoplasmic reticulum, Golgi apparatus, lysosomes, microtubules and microfilaments
- outline the two types of cell division
- define the term 'mutation'
- compare and contrast active, passive and bulk transport of substances across cell membranes.

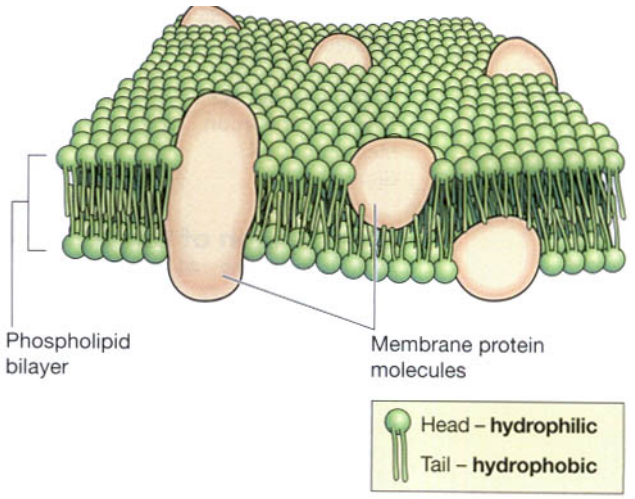


Figure 3.2 The plasma membrane.

The human body develops from a single cell called the *zygote*, which results from the fusion of the ovum (female egg cell) and the spermatozoon (male germ cell). Cell multiplication 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 by a microscope.

A cell consists of a *plasma membrane* inside which there are a number of *organelles* floating in a watery fluid called *cytosol* (Fig. 3.1). Organelles are small structures with highly specialised functions, many of which are contained within a membrane. They include: the *nucleus*, *mitochondria*, *ribosomes*, *endoplasmic reticulum*, *Golgi apparatus*, *lysosomes*, *microfilaments* and *microtubules*.

Plasma membrane

The plasma membrane (Fig. 3.2) consists of two layers of phospholipids (fatty substances (p. 24)) with some protein molecules embedded in them. Those that extend all the way through the membrane may provide channels that allow the passage of, for example, electrolytes and non-lipid-soluble substances.

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'). 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.

The membrane proteins perform several functions:

- branched carbohydrate molecules attached to the outside of some membrane protein molecules give the cell its immunological identity
- they can act as specific receptors for hormones and other chemical messengers
- some are enzymes
- some are involved in transport across the membrane.

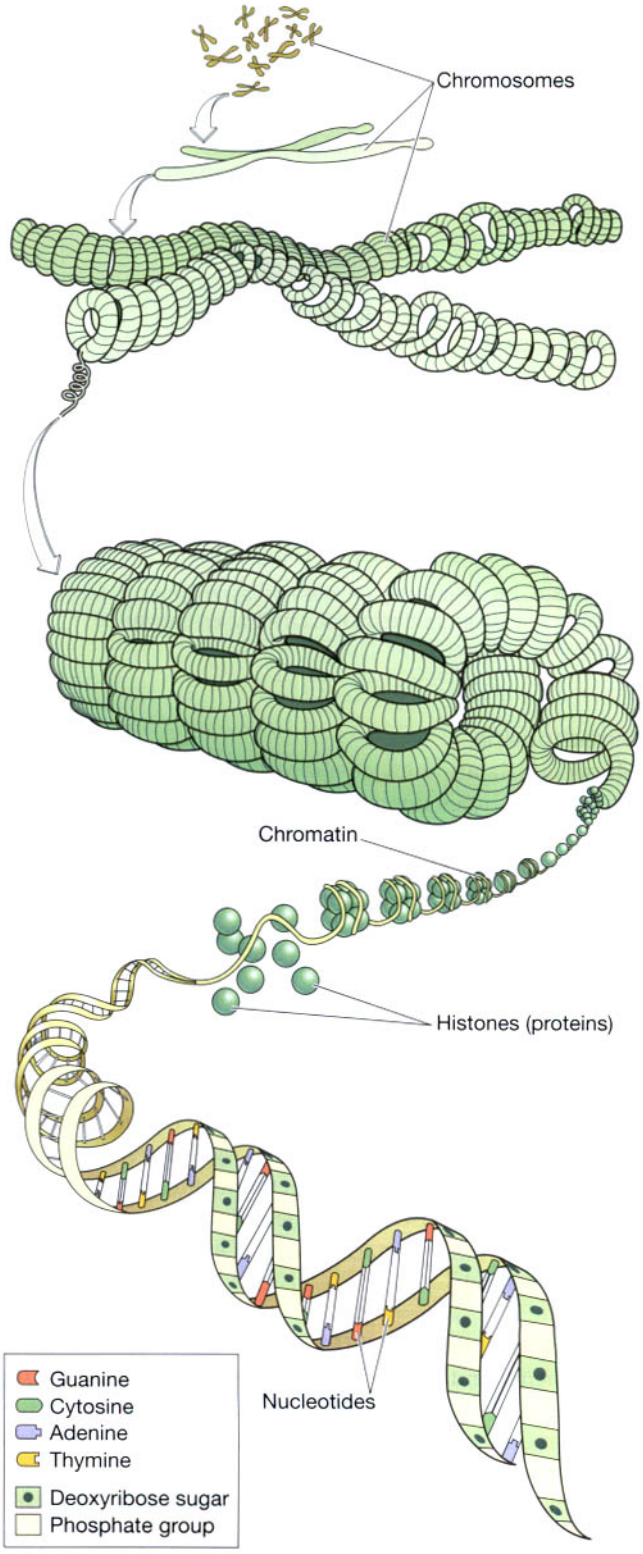
Organelles

Nucleus

Every cell in the body has a nucleus, with the exception of mature erythrocytes (red blood cells). Skeletal muscle and some other cells contain several nuclei. The nucleus is the largest organelle and is contained within a membrane similar to the plasma membrane but it has tiny pores through which some substances can pass between it and the *cytoplasm*, i.e. the cell contents excluding the nucleus.

The nucleus contains the body's genetic material, which directs the activities of the cell. This is built from DNA (p. 24) and proteins called *histones* coiled together forming a fine network of threads called *chromatin*. Chromatin resembles tiny strings of beads. During cell division the chromatin replicates and becomes more tightly coiled forming *chromosomes* (Fig. 3.3).

The functional subunits of chromosomes are called *genes*. Each cell contains the total complement of genes required to synthesise all the proteins in the body but most cells synthesise only the defined range of proteins that are appropriate to their own specialised functions. This means that only part of the *genome* or genetic code is used by each cell. Metabolic processes occur in a series of steps, each of which is catalysed by a specific enzyme (p. 26) and each enzyme can be produced only if the controlling gene is present. This is the 'one gene, one enzyme' concept. Therefore, when a gene is missing the associated enzyme is also missing and the chemical change it should catalyse does not occur (Fig. 3.4). This means that the intermediate metabolite upon which the enzyme should act accumulates. In physiological quantities such metabolites are harmless but when they accumulate they may become toxic. There are a number of diseases caused by such inborn errors of metabolism, e.g. phenylketonuria, abnormal haemoglobin and some immune deficiencies (see later chapters).



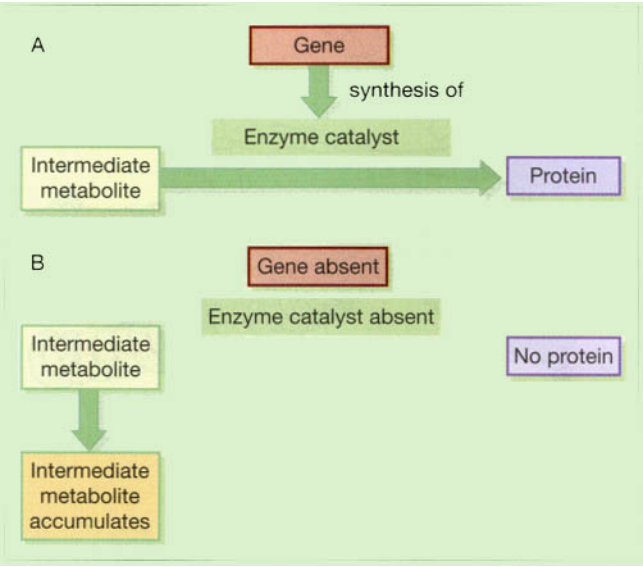


Figure 3.4 The relationship between genes, enzymes and protein synthesis: A. Enzyme synthesised. B. Effect when enzyme not synthesised.

Mitochondria

Mitochondria are sausage-shaped structures in the cytoplasm, sometimes described as the 'power house' of the cell. They are involved in aerobic respiration, the processes by which chemical energy is made available in the cell. This is in the form of ATP, which releases energy when the cell breaks it down (see Fig. 2.12, p. 25). Synthesis of ATP is most efficient in the final stages of aerobic respiration, a process requiring oxygen (p. 315).

Ribosomes

These are tiny granules composed of RNA and protein. They synthesise proteins from amino acids, using RNA as the template (see Fig. 2.11, p. 25). When present in free units or in small clusters in the cytoplasm, the ribosomes make proteins for use within the cell. Ribosomes are also found on the outer surface of rough endoplasmic reticulum (see below).

Endoplasmic reticulum (ER)

Endoplasmic reticulum is a series of interconnecting membranous canals in the cytoplasm. There are two types: smooth and rough. Smooth ER synthesises lipids and steroid hormones, and is also associated with the detoxification of some drugs. Rough ER is studded with ribosomes. These are the site of synthesis of proteins that are 'exported' (extruded) from cells, i.e. enzymes and hormones that pass out of their parent cell to be used by other cells in the body.

Golgi apparatus

The Golgi apparatus consists of stacks of closely folded flattened membranous sacs. It is present in all cells but is larger in those that synthesise and export proteins. The proteins move from the endoplasmic reticulum to the Golgi apparatus where they are 'packaged' into membrane-bound vesicles called *secretory granules*. The vesicles are stored and, when needed, move to the plasma membrane, through which the proteins are exported.

Lysosomes

Lysosomes are one type of secretory vesicle formed by 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 extruded from the cell as waste material.

Lysosomes in white blood cells contain enzymes that digest foreign material such as microbes.

Microfilaments and microtubules

Microfilaments. These are tiny strands of protein that provide structural support and maintain the characteristic shape of the cell.

Microtubules. These are contractile protein structures in the cytoplasm involved in the movement of the cell and of organelles within the cell, the movement of cilia (small projections from the free border of some cells) and possibly the organisation of proteins in the plasma membrane.

Cell division (Fig. 3.5)

There are two types of cell division: *mitosis* and *meiosis*.

Mitosis

Beginning with the fertilised egg, or zygote, cell division is an ongoing process. As the fetus develops in the mother's uterus, its cells multiply and grow into all the specialities that provide the sum total of the body's physiological functions. The life span of most individual cells is limited. Many become worn out and die, and are replaced by identical cells by the process of mitosis.

Mitosis occurs in two stages: replication of DNA, in the form of 23 pairs of chromosomes, then division of the cytoplasm. DNA is the only type of molecule capable of independently forming a duplicate of itself. When the two identical sets of chromosomes have moved to the opposite poles of the parent cell, a 'waist' forms in the cytoplasm, and the cell divides. There is then a complete

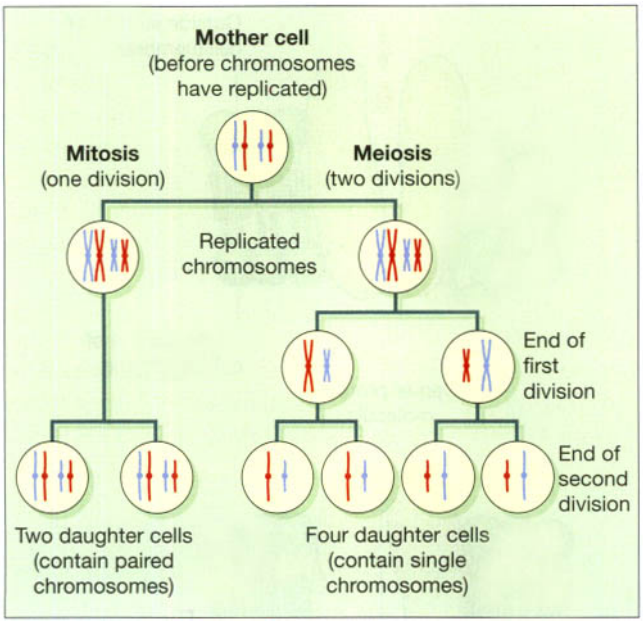


Figure 3.5 Cell division. Simplified diagram of mitosis and meiosis.

set of chromosomes in each daughter cell. The organelles in the cytoplasm of the daughter cells are incomplete at cell division but they develop as the cell grows to maturity.

The frequency with which cell division occurs varies with different types of cell (p. 42).

Meiosis

This is the process of cell division that occurs in the formation of reproductive cells (*gametes*—the ova and spermatozoa). The ova grow to maturity in the ovaries of the female and the spermatozoa in the testes of the male. In meiosis four daughter cells are formed after two divisions. During meiosis the pairs of chromosomes separate and one from each pair moves to opposite poles of the 'parent' cell. When it divides, each of the 'daughter' cells has only 23 chromosomes, called the *haploid number*. This means that when the ovum is fertilised the resultant zygote has the full complement of 46 chomosomes (the *diploid number*), half from the father and half from the mother. Thus the child has some characteristics inherited from the mother and some from the father, such as colour of hair and eyes, height, facial features, and some diseases.

Determination of sex depends upon one particular pair of chromosomes: the *sex chromosomes*. In the female both sex chromosomes are the same size and shape and are called X chromosomes. In the male there is one X chromosome and a slightly smaller Y chromosome. When the ovum is fertilised by an X-bearing spermatozoon the child is female and when it is fertilised by a Y-bearing spermatozoon the child is male.

Sperm X + ovum X → child XX = female
Sperm Y + ovum X → child XY = male

Mutation

Cells are said to mutate when their genetic make-up is altered in any way. Mutation may cause:

- no significant change in cell function
- modification of cell function that may cause physiological abnormality but does not prevent cell growth and multiplication, e.g. inborn errors of metabolism, defective blood clotting
- the death of the cell.

Some mutations occur by chance, which may be accounted for by the countless millions of cell divisions and DNA replications that occur in the body throughout life. Others may be caused by extraneous factors, such as X-rays, ultraviolet rays or some chemicals.

The most important mutations are those that occur in the ova and spermatozoa. Genetic changes in these cells are passed on to subsequent generations although they do not affect the parent.

Transport of substances across cell membranes

Passive transport

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

Diffusion

This was described on page 26. Small substances diffuse down the concentration gradient crossing membranes by:

- dissolving in the lipid part of the membrane, e.g. lipid-soluble substances: oxygen, carbon dioxide, fatty acids, steroids
- passing through water-filled channels, or pores in the membrane, e.g. small water-soluble substances: sodium, potassium, calcium.

Facilitated diffusion

This passive process is utilised by some substances that are unable to 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. 3.6). 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 which can be transported at any time. This is known as the *transport maximum*.

Osmosis

Osmosis is passive movement of water *down its concentration gradient* towards equilibrium across a semipermeable membrane and is explained on page 27.

Active transport

This is the transport of substances *up their concentration gradient* (uphill), i.e. from a lower to a higher concentration. Chemical energy in the form of ATP (p. 25) drives specialised protein carrier molecules that transport substances across the membrane in either direction (see Fig. 3.6). 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.

The sodium pump

This active transport mechanism maintains homeostasis of the electrolytes sodium (Na^+) and potassium (K^+). It may utilise up to 30% of the ATP required for cellular metabolism.

The principal cations are: K^+ intracellularly and Na^+ extracellularly. There is a tendency for these ions to diffuse down their concentration gradients, K^+ outwards and Na^+ into the cell. Homeostasis is maintained as excess Na^+ is pumped out across the cell membrane in exchange for K^+.

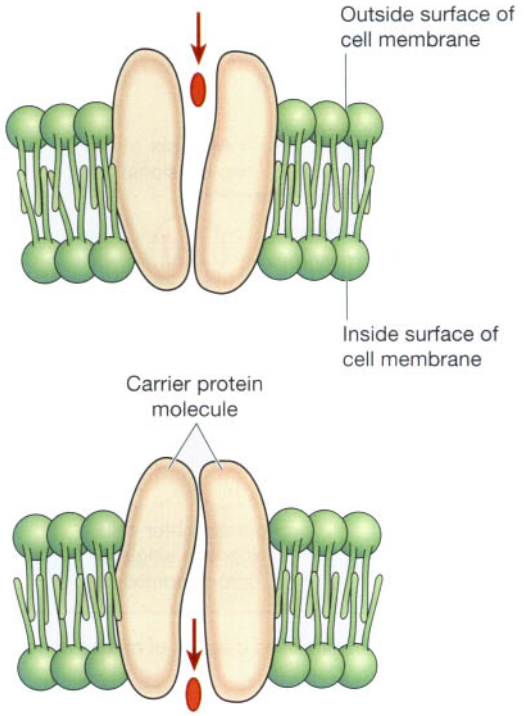


Figure 3.6 Specialised protein carrier molecules involved in facilitated diffusion and active transport.

Bulk transport (Fig. 3.7)

Transfer of particles too large to cross cell membranes occurs by *pinocytosis* or *phagocytosis*. These particles are engulfed by extensions of the cytoplasm which enclose them, forming a membrane-bound vacuole. When the vacuole is small, pinocytosis occurs. In phagocytosis larger particles, e.g. cell fragments, foreign materials, microbes, are taken into the cell. Lysosomes then adhere to the vacuole membrane, releasing enzymes which digest the contents.

Extrusion of waste material by the reverse process through the plasma membrane is called *exocytosis*. Secretory granules formed by the Golgi apparatus usually leave the cell in this way, as do any indigestible residues of phagocytosis.

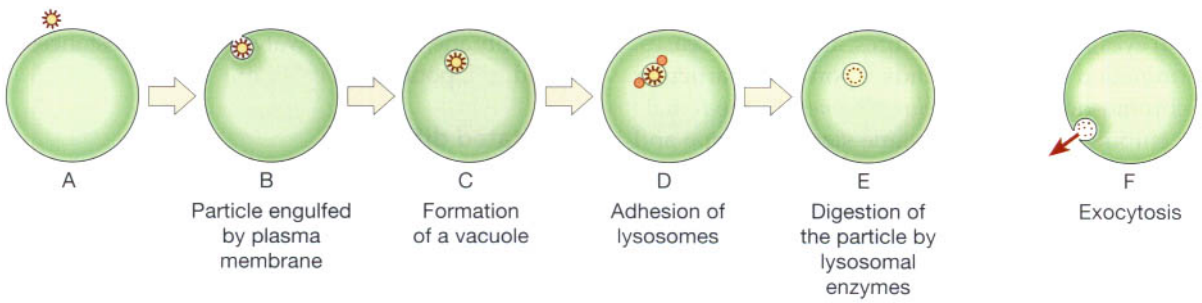


Figure 3.7 Bulk transport across plasma membranes: A–E. Phagocytosis. F. Exocytosis.

TISSUES

Learning outcomes

After studying this section you should be able to:

- describe the structure and functions of these tissues: epithelial, connective, muscle, nervous
- explain the capacity of different types of tissue to regenerate
- outline the structure and functions of membranes
- compare and contrast the structure and functions of exocrine and endocrine glands.

The tissues of the body consist of large numbers of cells and they are classified according to the size, shape and functions of these cells. There are four main types of tissue, each of which has subdivisions.

They are:

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

Epithelial tissue

This group of tissues is found covering the body and lining cavities and tubes. It is also found in glands. The structure of epithelium is closely related to its functions which include:

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

The cells are very closely packed and the intercellular substance, called the *matrix*, is minimal. The cells usually lie on a *basement membrane*, which is an inert connective tissue.

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 is divided into four types. It is usually found on absorptive or secretory surfaces, where the single layer enhances these processes, and not usually 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 are the cells.

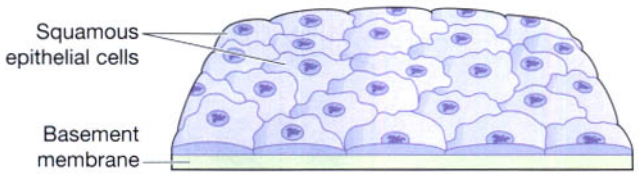


Figure 3.8 Squamous epithelium.

Squamous (pavement) epithelium

This is composed of a single layer of flattened cells (Fig. 3.8). The cells fit closely together like flat stones, forming a thin and very smooth membrane.

Diffusion takes place freely through this thin, smooth, inactive lining of the following structures:

- heart
- blood vessels
- lymph vessels

(where it is also known as endothelium)

- alveoli of the lungs.

Cuboidal (cubical) epithelium

This consists of cube-shaped cells fitting closely together lying on a basement membrane (Fig. 3.9). It forms the tubules of the kidneys and is found in some glands. Cuboidal epithelium is actively involved in secretion, absorption and excretion.

Columnar epithelium

This is formed by a single layer of cells, rectangular in shape, on a basement membrane (Fig. 3.10). It is found

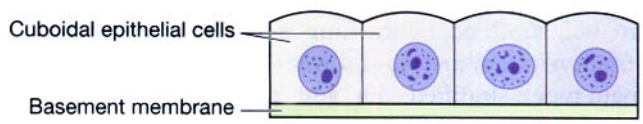


Figure 3.9 Cuboidal epithelium.

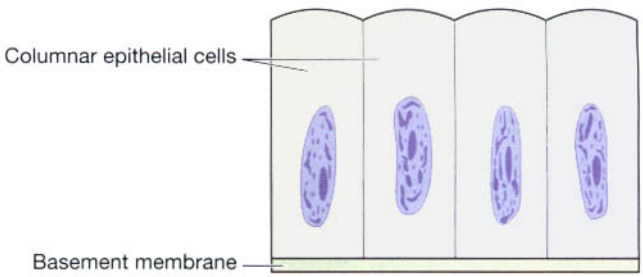


Figure 3.10 Columnar epithelium.

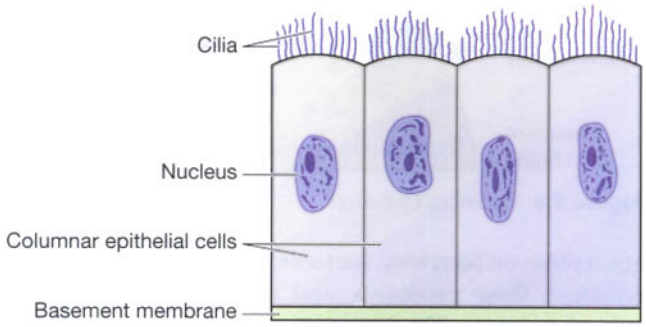


Figure 3.11 Ciliated columnar epithelium.

lining the organs of the alimentary tract and consists of a mixture of cells; some absorb the products of digestion and others secrete *mucus*. Mucus is a thick sticky substance secreted by modified columnar cells called *goblet cells*.

Ciliated epithelium (Fig. 3.11)
This is formed by columnar cells each of which has many fine, hair-like processes, called *cilia*. The cilia consist of microtubules inside the plasma membrane that extends from the free border (luminal border) of the columnar cells. The wave-like movement of many cilia propels the contents of the tubes, which they line in one direction only.

Ciliated epithelium is found lining the uterine tubes and most of the respiratory passages. In the uterine tubes the cilia propel ova towards the uterus (Ch. 19) and in the respiratory passages they propel mucus towards the throat (Ch. 10).

Stratified epithelia

Stratified epithelia consist of several layers of cells of various shapes. The superficial layers grow up from below. 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 (Fig. 3.12)
This is composed of a number of layers of cells of different shapes representing newly formed and mature cells. In the deepest layers the cells are mainly columnar and, as they grow towards the surface, they become flattened and are then shed.

Non-keratinised stratified epithelium. This is found on wet surfaces that may be subjected to wear and tear but are protected from drying, e.g. the conjunctiva of the eyes, the lining of the mouth, the pharynx, the oesophagus and the vagina.

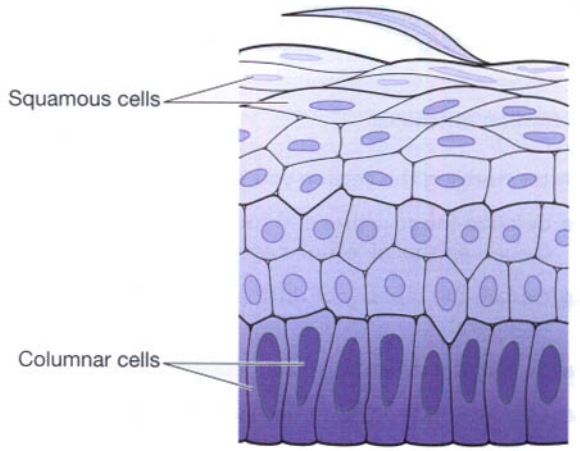


Figure 3.12 Stratified epithelium.

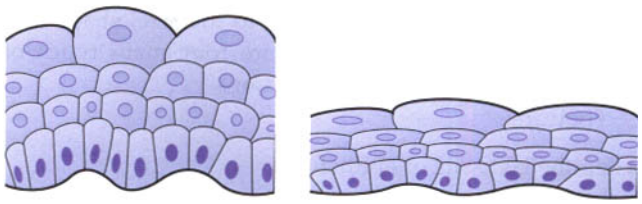


Figure 3.13 Transitional epithelium: A. Relaxed. B. Stretched.

Keratinised stratified epithelium. This is found on dry surfaces that are subjected to wear and tear, i.e. skin, hair and nails. The surface layer consists of dead epithelial cells to which the protein keratin has been added. This forms a tough, relatively waterproof protective layer that prevents drying of the underlying live cells. The surface layer of skin is rubbed off and is replaced from below (Ch. 14).

Transitional epithelium (Fig. 3.13)
This is composed of several layers of pear-shaped cells and is found lining the urinary bladder. It allows for stretching as the bladder fills.

Connective tissue

Connective tissue is the most abundant tissue in the body. The cells forming the connective tissues are more widely separated from each other than those forming the epithelium, and intercellular substance (matrix) is present in considerably larger amounts. There may or may not be fibres present in the matrix, which may be of a semisolid jelly-like consistency or dense and rigid, depending upon the position and function of the tissue.

Major functions of connective tissue are:

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

Cells of connective tissue

Connective tissue, excluding blood (Ch. 4), is found in all organs supporting the specialised tissue. The different types of cell involved include:

- fibroblasts
- fat cells
- macrophages
- leukocytes
- mast cells.

Fibroblasts. Fibroblasts are large flat cells with irregular processes. They produce *collagen* and *elastic fibres* and a matrix of extracellular material. Very fine collagen fibres, sometimes called *reticulin fibres*, are found in very active tissue, such as the liver and lymphoid tissue. Fibroblasts are particularly active in tissue repair (wound healing) where they may bind together the cut surfaces of wounds or form *granulation tissue* following tissue destruction (see p. 367). The collagen fibres formed during healing shrink as they grow old, sometimes interfering with the functions of the organ involved and with adjacent structures.

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. They vary in size and shape according to the amount of fat they contain.

Macrophages. These are 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 as they are actively phagocytic, engulfing and digesting cell debris, bacteria and other foreign bodies. Their activities are typical of those of the macrophage/monocyte defence system, e.g. monocytes in blood, phagocytes in the alveoli of the lungs, Kupffer cells in liver sinusoids, fibroblasts in lymph nodes and spleen and microglial cells in the brain.

Leukocytes. White blood cells (p. 64) are normally found in small numbers in healthy connective tissue but migrate in significant numbers during infection when they play an important part in tissue defence. *Lymphocytes* synthesise and secrete specific *antibodies* into the blood in the presence of foreign material, such as microbes (Ch. 15).

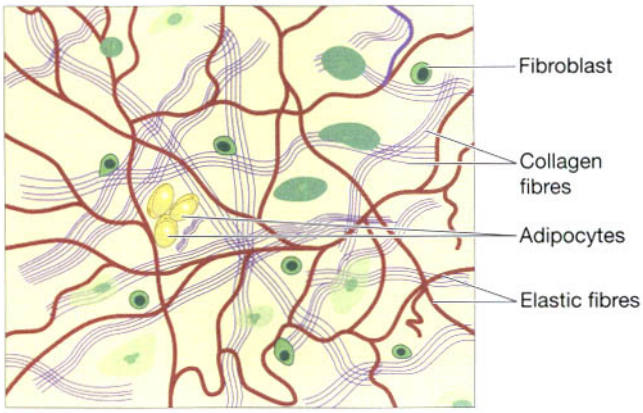


Figure 3.14 Loose (areolar) connective tissue.

Mast cells. These cells are similar to basophil leukocytes (see p. 66). They are found in loose connective tissue and under the fibrous capsule of some organs, e.g. liver and spleen, and in considerable numbers round blood vessels. They produce granules containing *heparin, histamine* and other substances, which are released when the cells are damaged by disease or injury. Histamine is involved in local and general inflammatory reactions, it stimulates the secretion of gastric juice and is associated with the development of allergies and hypersensitivity states (see p. 383). Heparin prevents coagulation of blood, which may aid the passage of protective substances from blood to affected tissues.

Loose (areolar) connective tissue (Fig. 3.14).

This is the most generalised of all connective tissue. The matrix is described as semisolid with many fibroblasts and some fat cells, mast cells and macrophages widely separated by elastic and collagen fibres. It is found in almost every part of the body providing elasticity and tensile strength. It connects and supports other tissues, for example:

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

Adipose tissue (Fig. 3.15).

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

White adipose tissue. This makes up 20 to 25% of body weight in well-nourished adults. The amount of adipose

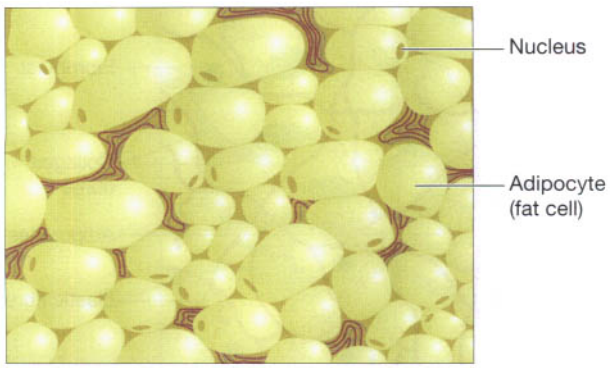


Figure 3.15 Adipose tissue.

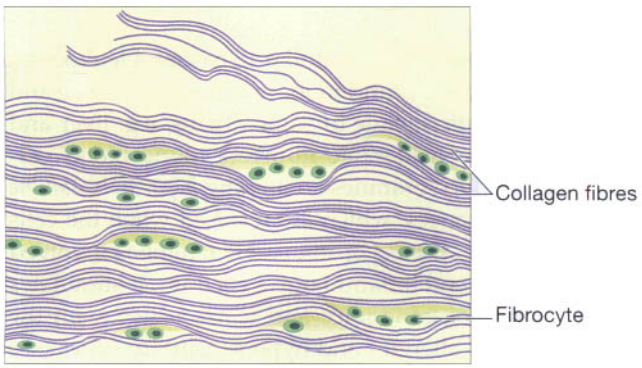


Figure 3.16 Fibrous tissue.

tissue in an individual is determined by the balance between energy intake and expenditure. It is found supporting the kidneys and the eyes, between muscle fibres and under the skin, where it acts as a thermal insulator.

Brown adipose tissue. This is present in the newborn. It has a more extensive capillary network than white adipose tissue. When brown tissue is metabolised, it produces less energy and considerably more heat than other fat, contributing to the maintenance of body temperature. In adults it is present in only small amounts.

Dense connective tissue

Fibrous tissue (Fig. 3.16)

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

- forming the ligaments, which bind bones together
- as an outer protective covering for bone, called *periosteum*

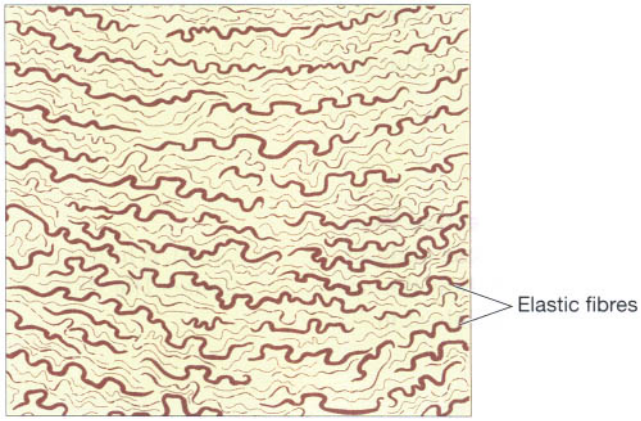


Figure 3.17 Elastic tissue.

- as an outer protective covering of some organs, e.g. the kidneys, lymph nodes and the brain
- forming muscle sheaths, called *muscle fascia*, which extend beyond the muscle to become the tendon that attaches the muscle to bone.

Elastic tissue (Fig. 3.17)

Elastic tissue 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 alteration of shape is required, e.g. in large blood vessel walls, the epiglottis and the outer ears.

Blood

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

Lymphoid tissue (Fig. 3.18)

This tissue has a semisolid matrix with fine branching reticulin fibres. It contains white blood cells (*monocytes* and *lymphocytes*). They are found in blood and in lymphoid tissue in the:

- lymph nodes
- spleen
- palatine and pharyngeal tonsils
- vermiform appendix
- solitary and aggregated nodes in the small intestine
- wall of the large intestine.

Cartilage

Cartilage is a much firmer tissue than any of the other connective tissues; the cells are called *chondrocytes* and

are less numerous. They are embedded in matrix reinforced by collagen and elastic fibres. There are three types:

- hyaline cartilage
- fibrocartilage
- elastic fibrocartilage.

Hyaline cartilage (Fig. 3.19)
Hyaline cartilage appears as a smooth bluish-white tissue. The chondrocytes are in small groups within cell nests and the matrix is solid and smooth. Hyaline cartilage is found:

- on the surface of the parts of the bones that form joints
- forming the costal cartilages, which attach the ribs to the sternum
- forming part of the larynx, trachea and bronchi.

Fibrocartilage (Fig. 3.20)
This consists of dense masses of white collagen fibres in a matrix similar to that of hyaline cartilage with the cells widely dispersed. It is a tough, slightly flexible tissue found:

- as pads between the bodies of the vertebrae, called the intervertebral discs
- 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
- as ligaments joining bones.

Elastic cartilage (Fig. 3.21)
This flexible tissue consists of yellow elastic fibres lying in a solid matrix. The cells lie between the fibres. It forms the pinna or lobe of the ear, the epiglottis and part of the tunica media of blood vessel walls.

Bone

Bone is a connective tissue with cells (osteocytes) surrounded by a matrix of collagen fibres that is strengthened by inorganic salts, especially calcium and phosphate. 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:

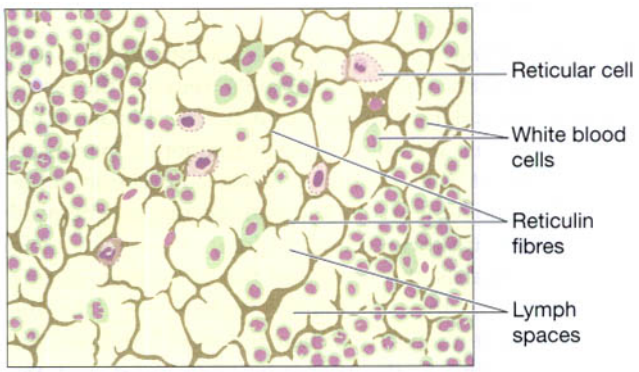


Figure 3.18 Lymphoid tissue.

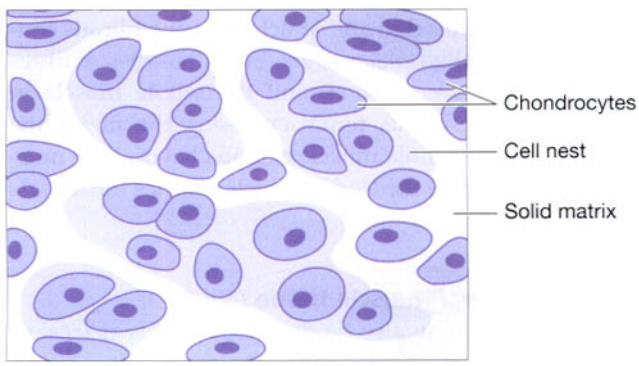


Figure 3.19 Hyaline cartilage.

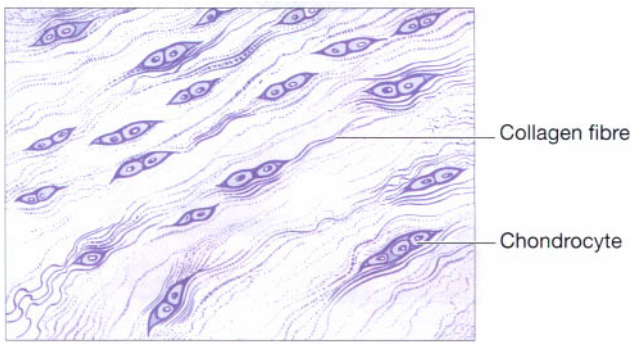


Figure 3.20 Fibrocartilage.

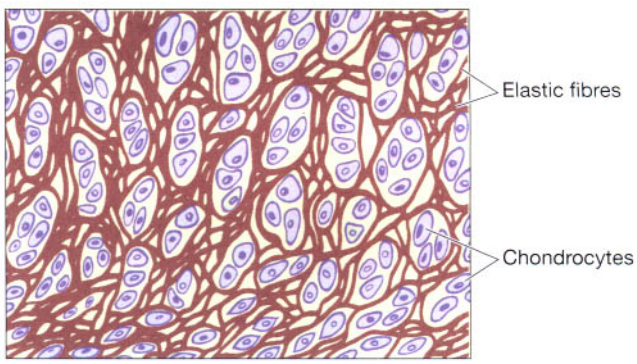


Figure 3.21 Elastic fibrocartilage.

- *compact bone*—solid or dense appearance
- *cancellous or spongy bone*—spongy or fine honeycomb appearance.

These are described in detail in Chapter 16.

Muscle tissue

There are three types of muscle tissue, which consists of specialised contractile cells:

- skeletal muscle
- smooth muscle
- cardiac muscle.

Skeletal muscle tissue (Fig. 3.22)

This may be described as *skeletal, striated, striped* or *voluntary* muscle. It is called voluntary because contraction is under conscious control.

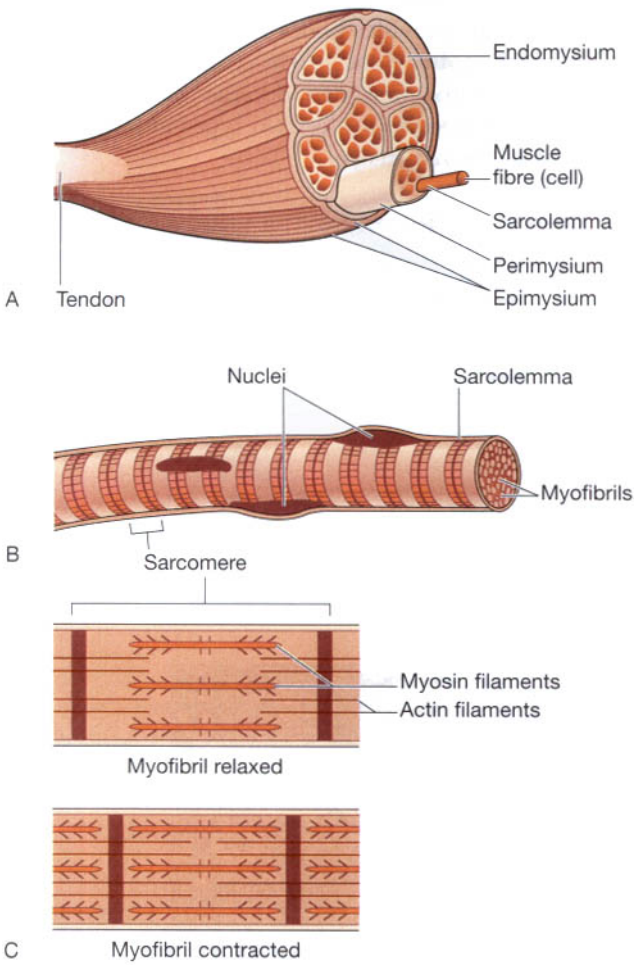


Figure 3.22 Organisation within a skeletal muscle: A. A skeletal muscle and its connective tissue. B. A muscle fibre (cell). C. A myofibril: relaxed and contracted.

When skeletal muscle is examined microscopically the cells are found to be roughly cylindrical in shape and may be as long as 35 cm. Each cell, commonly called a fibre, has several nuclei situated just under the *sarcolemma* or cell membrane of each muscle fibre. The muscle fibres lie parallel to one another and, when viewed under the microscope, they show well-marked transverse dark and light bands, hence the name striated or striped muscle.

Sarcoplasm, the cytoplasm of muscle fibres, contains:

- bundles of *myofibrils*, which consist of filaments of contractile proteins including *actin* and *myosin*
- many mitochondria, which generate chemical energy (ATP) from glucose and oxygen by aerobic respiration
- *glycogen*, a carbohydrate store which is broken down into glucose when required
- *myoglobin*, a unique oxygen-binding protein molecule, similar to haemoglobin in red blood cells, which stores oxygen within muscle cells.

A myofibril has a repeating series of dark and light bands, consisting of units called *sarcomeres*. A sarcomere represents the smallest functional unit of a skeletal muscle fibre and consists of:

- thin filaments of actin
- thick filaments of myosin.

The *sliding filament theory* explains the finding that sarcomeres shorten but the filaments remain the same length when skeletal muscle contracts. The thin actin filaments slide past the thick myosin filaments, increasing the overlap of the filaments when contraction takes place. The movement of filaments occurs as chemical cross-bridges are formed and broken, moving the actin filaments towards the centre of the sarcomere during contraction. As the sarcomeres shorten, so does the skeletal muscle involved. When the muscle relaxes the cross-bridges break, the filaments slide apart and the sarcomeres return to their original length (Fig. 3.22C).

A muscle consists of a large number of muscle fibres. In addition to the sarcolemma mentioned previously, each fibre is enclosed in and attached to fine fibrous connective tissue called *endomysium*. Small bundles of fibres are enclosed in *perimysium*, and the whole muscle in *epimysium*. The fibrous tissue enclosing the fibres, the bundles and the whole muscle extends beyond the muscle fibres to become the *tendon*, which attaches the muscle to bone or skin.

Smooth (visceral) muscle tissue (Fig. 3.23)

Smooth muscle may also be described as *non-striated* or *involuntary*. It is not under conscious control. It is found in the walls of hollow organs:

- regulating the diameter of blood vessels and parts of the respiratory tract
- propelling contents of the ureters, ducts of glands and alimentary 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. There is no distinct sarcolemma but a very fine membrane surrounds each fibre. Bundles of fibres form sheets of muscle, such as those found in the walls of the above structures.

Cardiac muscle tissue (Fig. 3.24)

This type of muscle tissue is found exclusively in the wall of the heart. It is not under conscious control but, when viewed under a microscope, cross-stripes characteristic of voluntary muscle can be seen. Each fibre (cell) has a nucleus and one or more branches. 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*, can be seen as lines which are thicker and darker than the ordinary cross-stripes. This arrangement gives cardiac muscle the appearance of a sheet of muscle rather than a very large number of individual fibres. The end-to-end continuity of cardiac muscle cells has significance in relation to the way the heart contracts. A wave of contraction spreads from cell to cell across the intercalated discs which means that cells do not need to be stimulated individually.

Function of muscle tissue

Muscle functions by alternate phases of contraction and relaxation. When the fibres contract they become thicker and shorter. Skeletal muscle fibres are stimulated by *motor nerve impulses* originating in the brain or spinal cord (p. 151 and p. 158) and ending at the *neuromuscular junction* (p. 145). Smooth and cardiac muscle have the intrinsic ability to initiate contraction. In addition, contraction is stimulated by *autonomic nerve impulses*, some hormones and local metabolites. When muscle fibres contract they follow the *all or none law*; i.e. each fibre contracts to its full capacity or not at all. The *strength* of contraction, e.g. lifting a weight, depends on the *number* of fibres contracting at the same time. When effort is sustained, groups of fibres contract in series. Contraction of smooth muscle is slower and more sustained than skeletal muscle.

In order to contract when it is stimulated, a muscle fibre must have an adequate blood supply to provide sufficient oxygen, calcium and nutritional materials and to remove waste products.

Muscle tone

This is a state of partial contraction of muscles. It is achieved by the contraction of a few muscle fibres at a time. Skeletal muscle tone is essential for maintenance of posture in the sitting and standing positions. The muscle is stimulated to contract through a system of *spinal reflexes*. Stretching of a muscle or its tendon stimulates the reflex action (Ch. 7). A degree of muscle tone is also maintained by smooth and cardiac muscle.

Muscle fatigue

If a muscle is stimulated to contract at very frequent intervals, its response gradually becomes depressed and will in time cease. Fatigue is prevented during sustained muscular effort because the fibres usually contract in series. All the fibres of a muscle rarely contract at the same time but if maximum effort is made it can be sustained, if for only a short time.

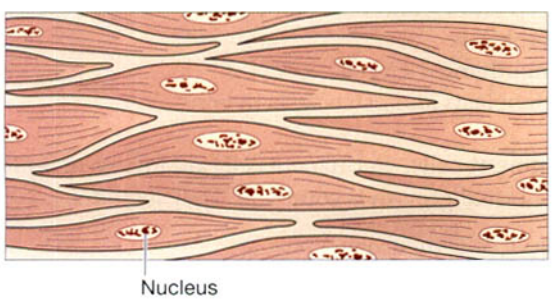


Figure 3.23 Smooth muscle fibres.

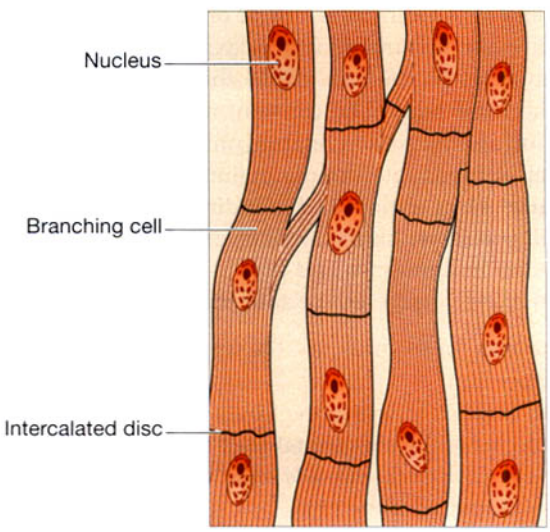


Figure 3.24 Cardiac muscle fibres.

Energy source for muscle contraction

The chemical energy (ATP) which muscles require is usually derived from the breakdown (catabolism) of carbohydrate and fat. Protein molecules inside the fibres are used to provide energy when supplies of carbohydrate and fat are deficient. Each molecule undergoes a series of changes and, with each change, small quantities of energy are released. For the complete breakdown of these molecules and the release of all the available energy an adequate supply of oxygen is required. If the individual undertakes excessive exercise, the oxygen supply may be insufficient to meet the metabolic needs of the muscle fibres. This may result in the accumulation of intermediate metabolic products, such as lactic acid. Where the breakdown process and the release of energy are complete, the waste products are carbon dioxide and water (Ch. 12).

Not all the chemical energy (ATP) used by muscle fibres is converted into mechanical energy during contraction. Some is lost as heat.

Further features of skeletal muscle

The skeletal muscles are those which produce body movements. Each muscle consists of a fleshy part made up of striped fibres and tendinous parts consisting of fibrous tissue, usually at both ends of the fleshy part. The muscle is attached to bone or skin by these tendons. When the tendinous attachment of a muscle is broad and flat it is called an *aponeurosis*.

To be able to produce movement at a joint, a muscle or its tendon must stretch across the joint. When a muscle contracts, its fibres shorten and it pulls one bone towards another, e.g. bending the elbow.

The muscles of the skeleton are arranged in groups, some of which are *antagonistic* to each other. To produce movement at a joint, one muscle or group of muscles contracts while the antagonists relax; e.g. to bend the knee the muscles on the back of the thigh contract and those on the front relax. The constant adjustment of the contraction and relaxation of antagonistic groups of muscles is well demonstrated in the maintenance of balance and posture when sitting and standing. These adjustments usually occur without conscious effort.

Individual muscles and groups of muscles have been given names that reflect certain characteristics, e.g.:

- the *shape* of the muscle—the trapezius is shaped like a trapezium
- the *direction* in which the fibres run—the oblique muscles of the abdominal wall
- the *position* of the muscle—the tibialis in the leg is associated with the tibia
- the *movement* produced by contraction of the muscle—flexors, extensors, adductors
- the *number of points of attachment* of a muscle—the biceps muscle has two tendons at one end
- the *names of the bones to which the muscle is attached*—the carpi radialis muscles are attached to the carpal bones in the wrist and to the radius in the forearm.

A more detailed description of skeletal muscles is given in Chapters 17 and 18.

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 support the neurones.

These are described in detail in Chapter 7.

Tissue regeneration

When tissue regeneration occurs it is essential that some of the original cells are available to replicate by mitosis. The extent to which regeneration is possible depends on the normal rate of physiological turnover of particular types of cell. Those with a rapid turnover regenerate most effectively. There are three types.

Labile cells. Labile cells are those in which replication is normally a continuous process. They include cells in:

- epithelium of e.g. skin, mucous membrane, secretory glands, ducts, uterus lining
- bone marrow
- blood
- spleen and lymphoid tissue.

Stable cells. Stable cells have retained the ability to replicate but do so infrequently.

They include:

- liver, kidney and pancreatic cells
- fibroblasts
- smooth muscle cells
- osteoblasts and osteoclasts in bone.

Permanent cells. Permanent cells are unable to replicate after normal growth is complete. They include:

- nerve cells (neurones)
- skeletal and cardiac muscle.

Membranes

Membranes are sheets of epithelial tissue and their supporting connective tissue that cover or line internal structures or cavities. The main membranes are:

- mucous
- serous
- synovial.

Mucous membrane

This is the moist lining of the alimentary tract, respiratory tract and genitourinary tracts and is sometimes referred to as the *mucosa*. The membrane consists of epithelial cells, some of which produce a secretion called *mucus*, a slimy tenacious fluid. As it accumulates the cells become distended and finally burst, discharging the mucus on to the free surface. As the cells fill up with mucus they have the appearance of a goblet or flask and are known as *goblet cells* (Fig. 3.25). Organs lined by mucous membrane have a moist slippery surface. Mucus protects the lining membrane from mechanical and chemical injury and in the respiratory tract it traps inhaled foreign 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 within the cavity. The two layers are separated by *serous fluid* secreted by the epithelium. There are three sites where serous membranes are found:

- the *pleura* lining the thoracic cavity and surrounding the lungs (p. 251)
- the *pericardium* lining the pericardial cavity and surrounding the heart (p. 83)
- the *peritoneum* lining the abdominal cavity and surrounding abdominal organs (p. 284).

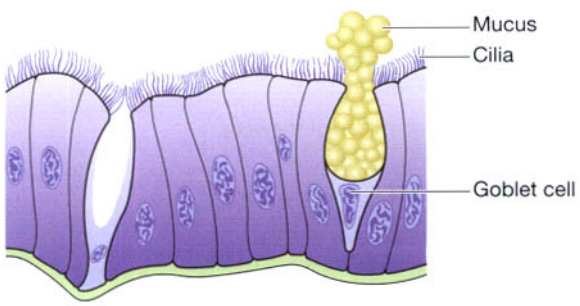


Figure 3.25 Ciliated columnar epithelium with goblet cells.

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

Synovial membrane

This membrane is found lining the joint cavities and surrounding tendons, which could be injured by rubbing against bones, e.g. over the wrist joint. It is made up of a layer of fine, flattened epithelial cells on a layer of delicate connective tissue.

Synovial membrane secretes clear, sticky, oily *synovial fluid*, which acts as a lubricant to the joints and helps to maintain their stability (Ch. 17).

Glands

Glands are groups of epithelial cells which produce specialised secretions. Glands that discharge their secretion on to the epithelial surface of an organ, either directly or through a *duct*, are called *exocrine glands*. Exocrine glands vary considerably in size, shape and complexity as shown in Figure 3.26. Other glands discharge their secretions into blood and lymph. These are called *endocrine glands* (ductless glands) and their secretions are *hormones* (see Ch. 9).

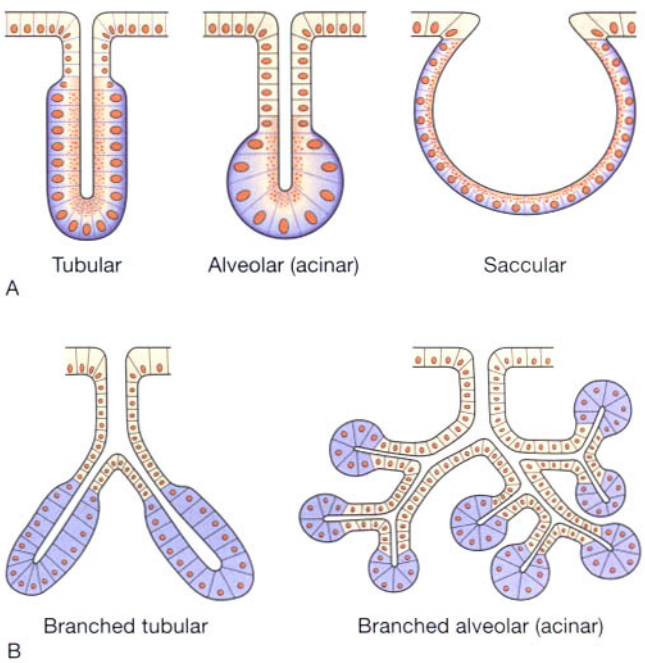


Figure 3.26 Exocrine glands: A. Simple glands. B. Compound (branching) glands.

ORGANISATION OF THE BODY

Learning outcomes

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.

In this part of the chapter a brief account is given of some anatomical terms and the names and positions of bones. A more detailed account of the bones, muscles and joints is given in Chapters 16, 17 and 18.

Anatomical terms

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

Median plane. When the body, in the anatomical position, is divided *longitudinally* through the midline into right and left halves it has been divided in the median plane.

Table 3.1 lists the paired directional terms used in anatomy.

The skeleton

The skeleton is the bony framework of the body. It forms the cavities and fossae that protect some structures, forms the joints and gives attachment to muscles. A detailed description of bones is given in Chapter 16. Table 3.2 lists the terminology related to the skeleton.

The skeleton is described in two parts: *axial* and *appendicular* (Fig. 3.27).

The axial skeleton (axis of the body) consists of:

- skull
- vertebral column
- sternum or breast bone
- ribs.

The appendicular skeleton (appendages attached to the axis of the body) consists of:

- the bones of the upper limbs, the two clavicles and the two scapulae
- the bones of the lower limbs and the two innominate bones of the pelvis.

Axial skeleton

Skull

The skull is described in two parts, the *cranium*, which contains the brain, and the *face*. It consists of a number of bones which develop separately but fuse together as they mature. The only movable bone is the mandible or lower jaw. The names and positions of the individual bones of the skull can be seen in Figure 3.28.

Table 3.1 Paired directional terms used in anatomy

Directional term	Meaning
Medial	Structure is nearer to the midline. *The heart is medial to the humerus*
Lateral	Structure is 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	Part of the body being described is nearer the front of the body. *The sternum is anterior to the vertebrae*
Posterior or dorsal	Part of the body being described is nearer the back of the body. *The vertebrae are posterior to the sternum*
Superior	Structure nearer the head. *The skull is superior to the scapulae*
Inferior	Structure further from the head. *The scapulae are inferior to the skull*

Table 3.2 Terminology related to the skeleton

Term	Meaning
Articulating surface	The part of the bone that enters into 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 joint, e.g. 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

Functions of the skull

The various parts of the skull have specific and different functions:

- The *cranium* protects the delicate tissues of the brain.
- The *bony eye sockets* provide the eyes with some protection against injury and give attachment to the muscles which move the eyes.
- The *temporal bone* protects the delicate structures of the ear.
- Some bones of the face and the base of the skull give resonance to the voice because they have cavities called *sinuses*, containing air. The sinuses have tiny openings into the nasal cavity.
- The bones of the face form the walls of the posterior part of the nasal cavities. They keep the air passage open, facilitating breathing.
- The *maxilla* and the *mandible* provide alveolar ridges in which the teeth are embedded.
- The mandible is the only movable bone of the skull and chewing food is the result of raising and lowering the mandible by contracting and relaxing some muscles of the face, the muscles of mastication.

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 cartilage. The vertebral column is described in five parts and the bones of each part are numbered from above downwards (Figs 3.27 and 3.29):

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

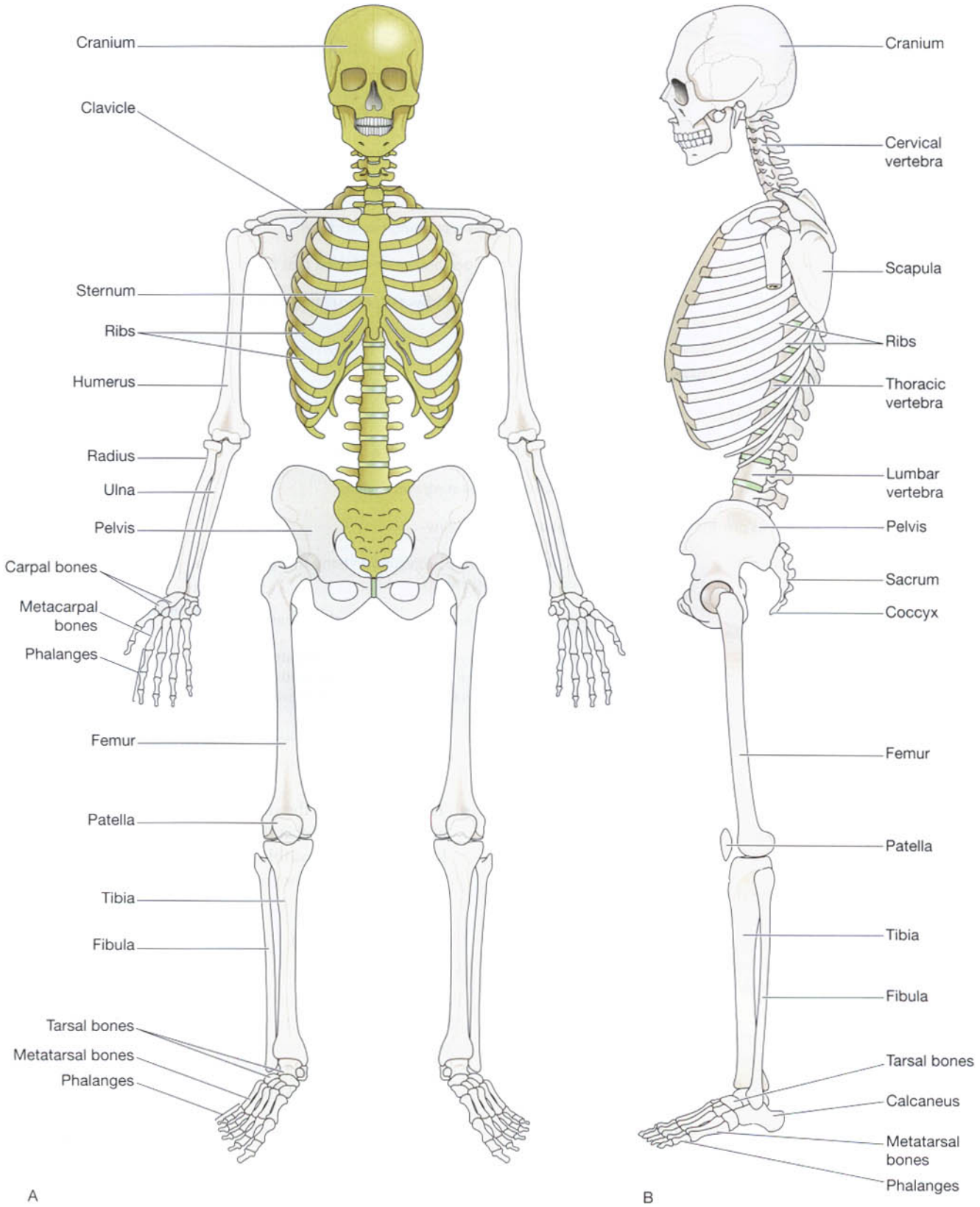


Figure 3.27 The bony skeleton: A. Anterior view: axial skeleton – gold, appendicular skeleton – brown. B. Lateral view.

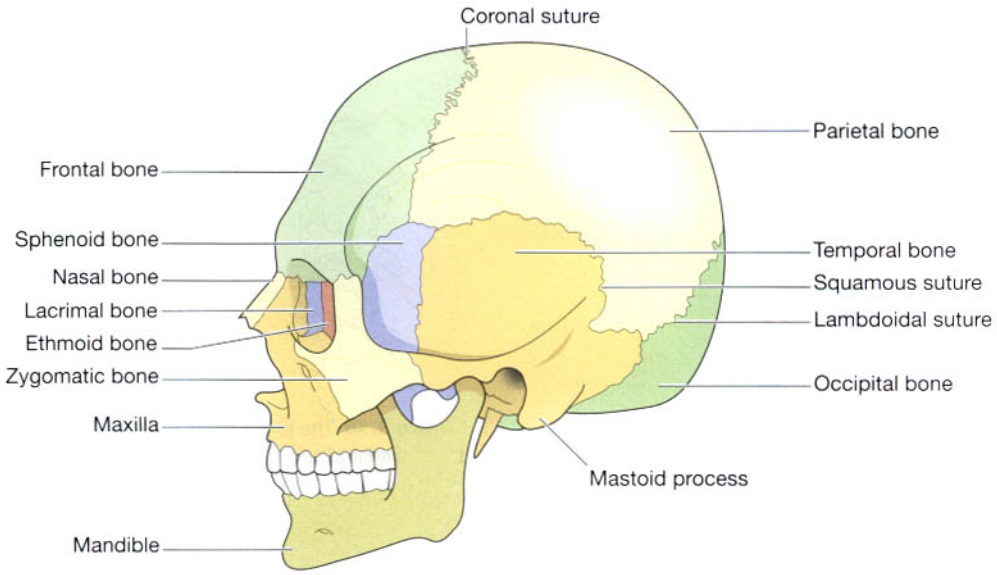


Figure 3.28 The skull: bones of the cranium and face.

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

The *sacrum* consists of five vertebrae fused into one bone which 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 which articulates with the sacrum above.

Functions of the vertebral column

The vertebral column has several important functions:

- It protects the spinal cord. In each bone there is a hole or *foramen* and when the vertebrae are arranged one above the other, as shown in Figure 3.29, the foramina form a canal. The spinal cord, which is an extension of nerve tissue from the brain, lies in this canal (Fig. 3.30).
- Adjacent vertebrae form openings (intervertebral foramina) through which spinal nerves pass from the spinal cord to all parts of the body (Fig. 3.30). There are 31 pairs of spinal nerves.
- In the thoracic region the ribs articulate with the vertebrae forming joints which move during respiration.

Thoracic cage

The thoracic cage is formed by:

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

The arrangement of the bones can be seen in Figure 3.31.

Functions of the thoracic cage

The functions of the thoracic cage are as follows:

- It protects the thoracic organs. The bony framework protects the heart, lungs, large blood vessels and other structures.
- It forms joints between the upper limbs and the axial skeleton. The upper part of the sternum, the *manubrium*, articulates with the clavicles forming the only joints between the upper limbs and the axial skeleton.
- It gives attachment to the muscles of respiration:
  - *intercostal muscles* occupy the spaces between the ribs and when they contract the ribs move upwards and outwards, increasing the capacity of the thoracic cage, and inspiration (breathing in) occurs.
  - the *diaphragm* is a dome-shaped muscle which separates the thoracic and abdominal cavities. It is attached to the bones of the thorax and when it contracts it assists with inspiration. Structures which extend from one cavity to the other pass through the diaphragm
- It enables breathing (ventilation) to take place.

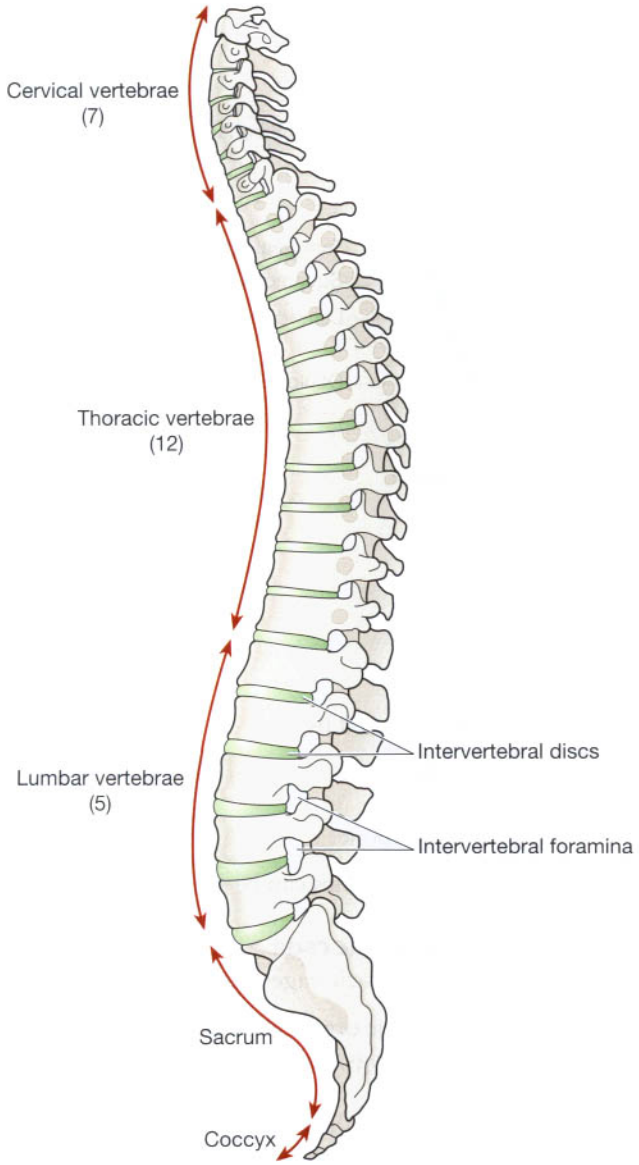


Figure 3.29 The vertebral column – lateral view.

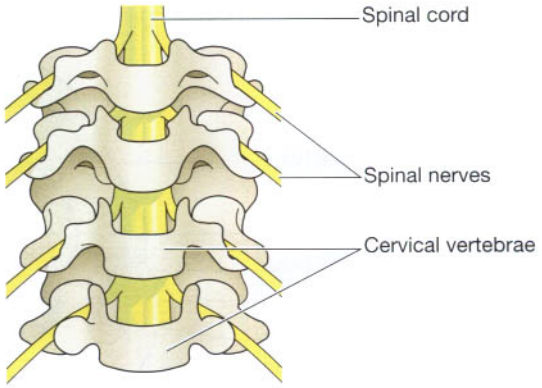


Figure 3.30 The lower cervical vertebrae separated to show the spinal cord and spinal nerves (in yellow).

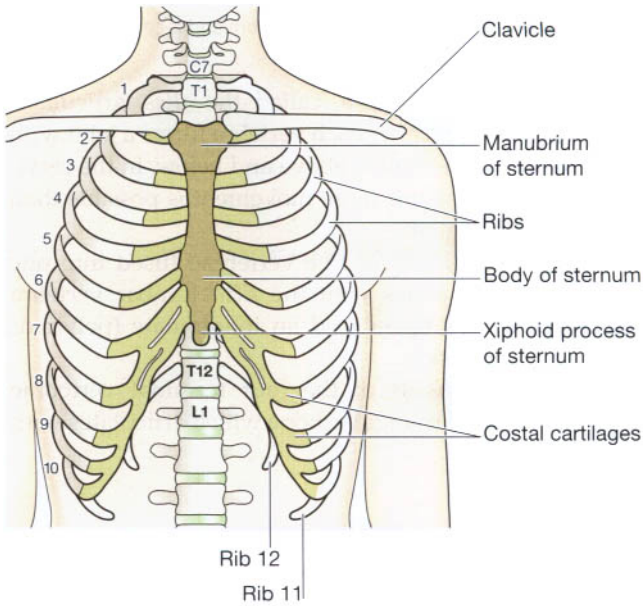


Figure 3.31 The structures forming the walls of the thoracic cage.

Appendicular skeleton

The appendages are:

- the upper limbs and the shoulder girdles
- the lower limbs and the innominate bones of the pelvis.

The names of the bones involved, their position and their relationship to other bones are shown in Figure 3.27.

Functions of the appendicular skeleton

The appendicular skeleton has two functions.

- *Voluntary movement*. The bones, muscles and joints of the limbs are involved in voluntary movement. This may range from the very fine movements of the fingers associated with writing to the coordinated movement of all the limbs associated with running and jumping.
- *Protection of delicate structures*. Structures such as blood vessels and nerves lie along the length of bones of the limbs and are protected from injury by the muscles and skin. These structures are most vulnerable where they cross joints and where bones can be felt near the skin.

Cavities of the body

The organs that make up the systems of the body are contained in four *cavities*:

- cranial
- thoracic
- abdominal
- pelvic.

Cranial cavity

The cranial cavity contains the *brain*, and its boundaries are formed by the bones of the skull (Fig. 3.32):

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.

Thoracic cavity

This cavity is situated in the upper part of the trunk. Its boundaries are formed by a bony framework and supporting muscles (Fig. 3.33):

Anteriorly – the sternum and costal cartilages of the ribs
Laterally – 12 pairs of ribs and the intercostal muscles
Posteriorly – the thoracic vertebrae and the intervertebral discs between the bodies of the vertebrae

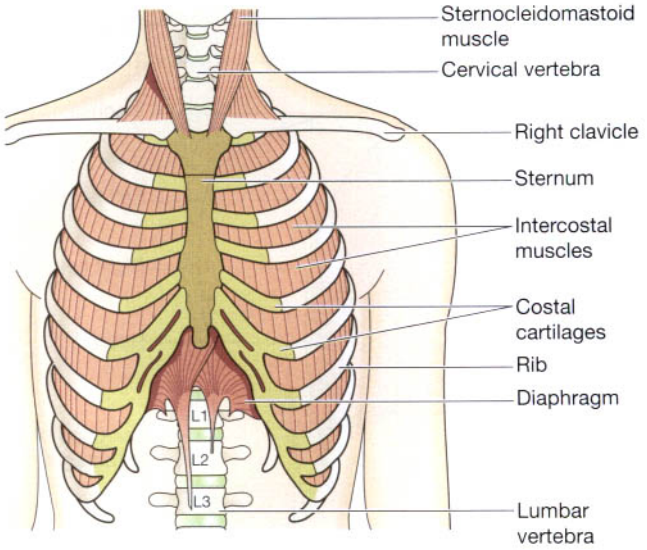


Figure 3.33 Structures forming the walls of the thoracic cavity and associated structures.

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 (Fig. 3.34):

- the trachea, 2 bronchi, 2 lungs
- the heart, aorta, superior and inferior vena cava, numerous other blood vessels
- the oesophagus

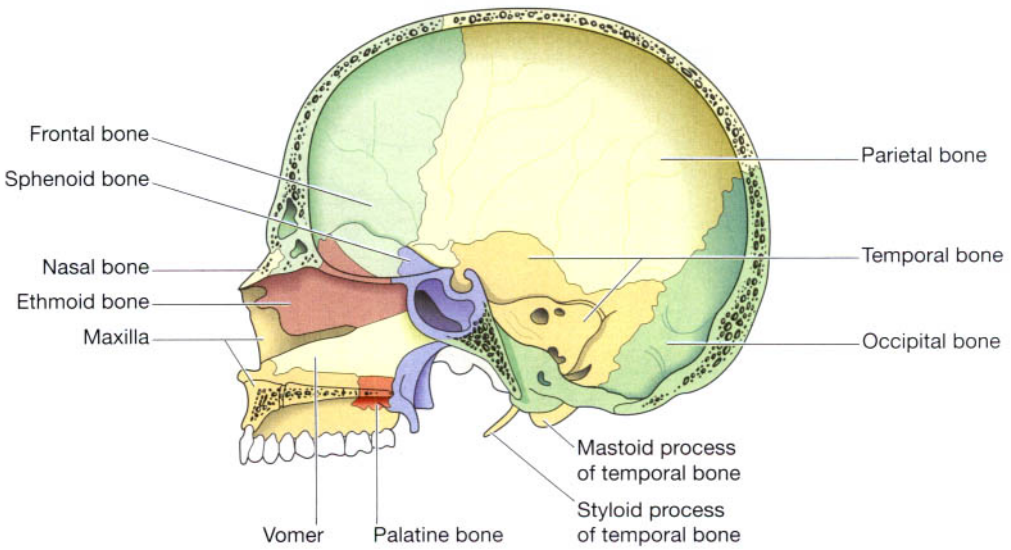


Figure 3.32 Bones forming the right half of the cranium and the face – viewed from the left.

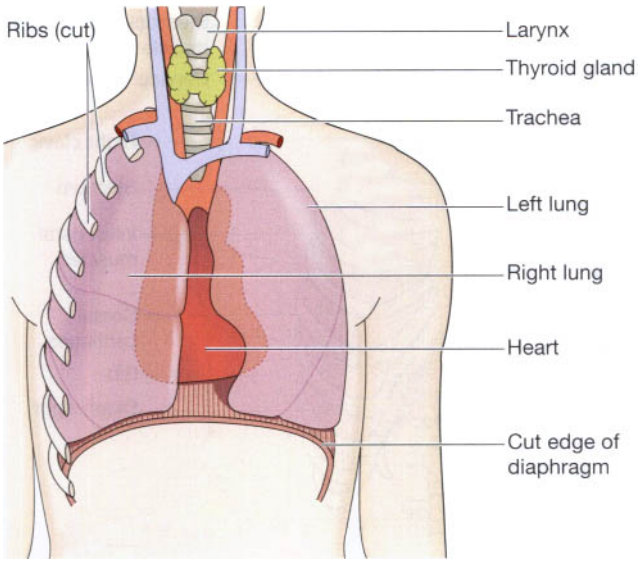


Figure 3.34 Some of the main structures in the thoracic cavity and the root of the neck.

- lymph vessels and lymph nodes
- nerves.

The *mediastinum* is the name given to the space between the lungs including the structures found there, such as the heart, oesophagus and blood vessels.

Abdominal cavity

This is the largest cavity in the body and is oval in shape (Figs 3.35 and 3.36). It is situated in the main part of the trunk and its boundaries are:

Superiorly – the diaphragm, which separates it from the thoracic cavity
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 – the pelvic cavity with which it is continuous.

By convention, the abdominal cavity is divided into the nine regions shown in Figure 3.37. This facilitates the description of the positions of the organs and structures it contains.

Contents

Most of the space in the abdominal cavity is occupied by the organs and glands involved in the digestion and absorption of food (Figs 3.35 and 3.36). These are:

- the stomach, small intestine and most of the large intestine
- the liver, gall bladder, bile ducts and pancreas.

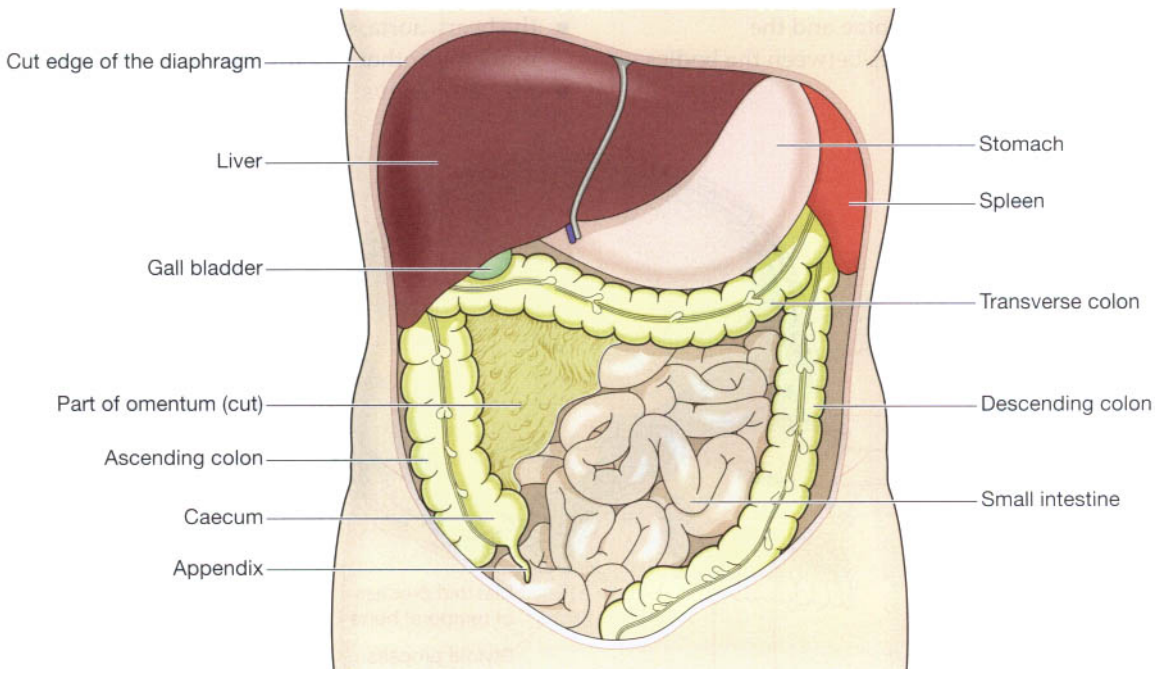


Figure 3.35 Organs occupying the anterior part of the abdominal cavity and the diaphragm (cut).

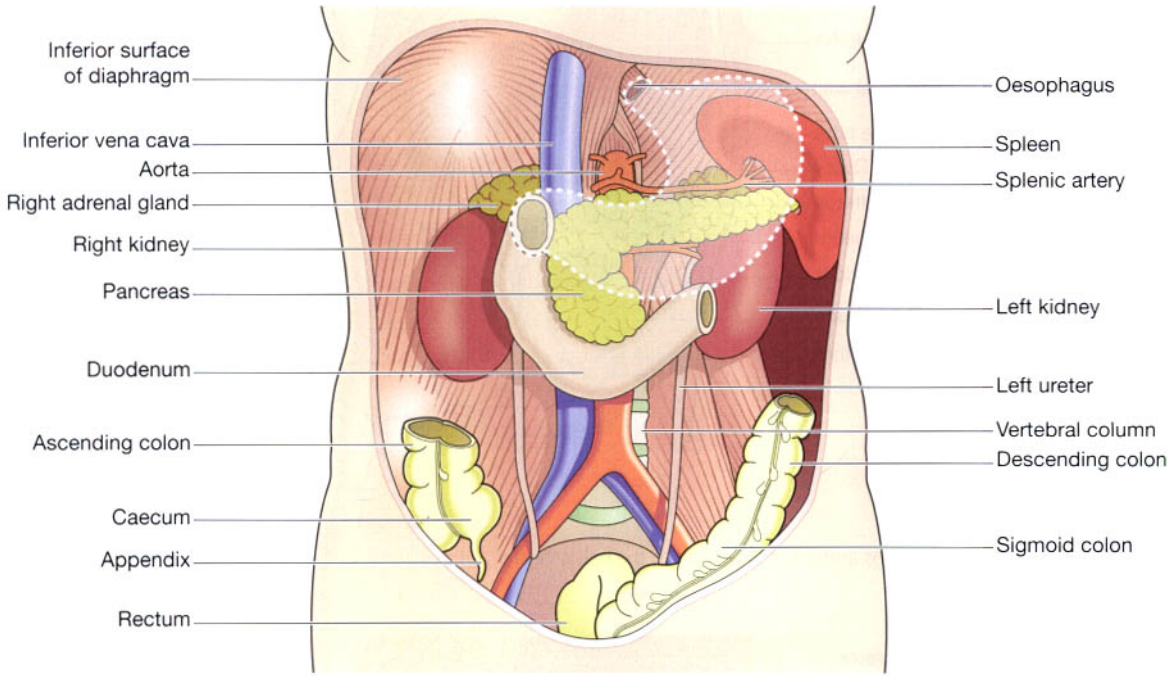


Figure 3.36 Organs occupying the posterior part of the abdominal cavity and the diaphragm (cut). The broken line shows the position of the stomach.

Other structures include:

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

Pelvic cavity

The pelvic cavity is roughly funnel shaped and extends from the lower end of the abdominal cavity (Figs 3.38 and 3.39). The boundaries are:

Superiorly – it is continuous with the abdominal cavity
Anteriorly – the pubic bones
Posteriorly – the sacrum and coccyx
Laterally – the innominate 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
- urinary bladder, lower parts of the ureters and the urethra

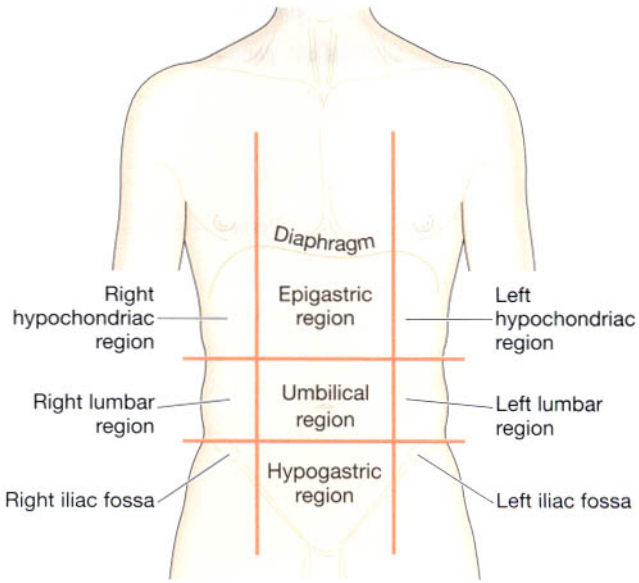


Figure 3.37 Regions of the abdominal cavity.

- in the female, the organs of the reproductive system: the uterus, uterine tubes, ovaries and vagina (Fig. 3.38)
- in the male, some of the organs of the reproductive system: the prostate gland, seminal vesicles, spermatic cords, deferent ducts (vas deferens), ejaculatory ducts and the urethra (common to the reproductive and urinary systems) (Fig. 3.39).

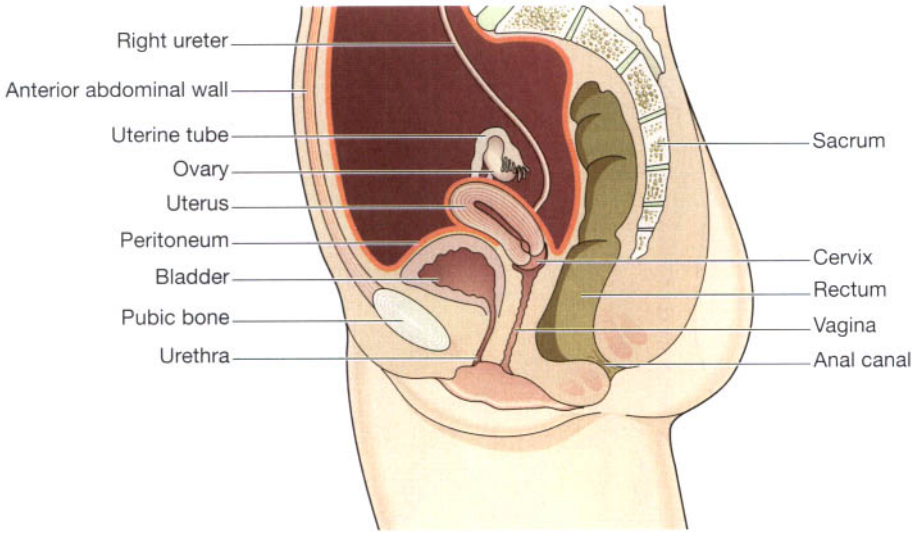


Figure 3.38 Female reproductive organs and other structures in the pelvic cavity.

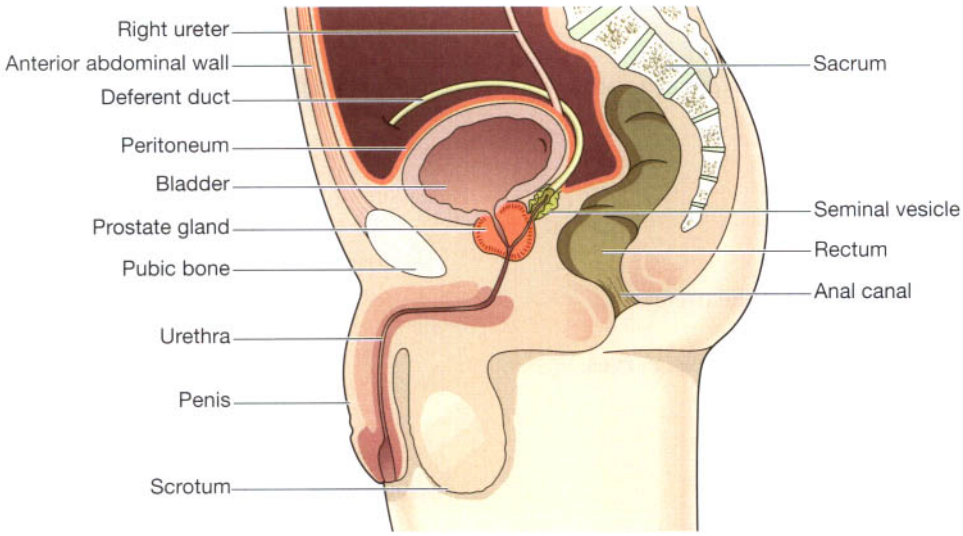


Figure 3.39 Male reproductive organs and other structures in the pelvic cavity.

DISORDERS OF CELLS AND TISSUES

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'
- outline causes of death in malignant disease
- compare and contrast the effects of benign and malignant tumours.

Neoplasms or tumours

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 although a clear distinction is not always possible (see Table 3.3). Benign tumours only rarely change their character and become malignant.

Causes of neoplasms

Some factors are known to precipitate the changes found in tumour cells but the reasons for the uncontrolled cell multiplication are not known. The process of change is *carcinogenesis* and the agents precipitating the change are *carcinogens*. Carcinogenesis may be of genetic and/or environmental origin and a clear-cut distinction is not always possible.

Carcinogens

Environmental agents known to cause malignant changes in cells do so by progressive irreversible disorganisation and modification of the chromosomes and genes. It is impossible to specify a maximum 'safe dose' of a carcinogen. A small dose may initiate change but this may not be enough to cause malignancy unless there are repeated doses within a limited period of time that have a cumulative effect. In addition there are widely varying latent periods between exposure and evidence of malignancy.

Table 3.3 **Differences between benign and malignant tumours**

Benign	Malignant
Slow growth	Rapid growth
Cells well differentiated	Cells poorly differentiated
Usually encapsulated	Not encapsulated
Does not spread	Spreads: – by local infiltration – via lymph – via blood – via body cavities
Recurrence is rare	Recurrence is common

There may also be other unknown factors. Environmental carcinogens include chemicals, irradiations and oncogenic viruses.

Chemical carcinogens

Some chemicals are carcinogens when absorbed; others are modified after absorption and become carcinogenic. Some known chemical carcinogens are:

- aniline dyes
- arsenic compounds
- asbestos
- benzene derivatives
- cigarette smoke
- nickel compounds
- some fuel oils
- vinyl chloride.

Radiation carcinogens

Exposure to ionising radiation including X-rays, radioactive isotopes, environmental radiations and ultraviolet rays in sunlight may cause malignant changes in some cells and kill others. The cells are affected during mitosis so those normally undergoing continuous controlled division are most susceptible. These labile tissues include skin, mucous membrane, bone marrow, lymphoid tissue and gametes in the ovaries and testes.

Oncogenic viruses

Viruses, some consisting of DNA and some of RNA, are known to cause malignant changes in animals and there are indications of similar involvement in humans. Viruses enter cells and the addition of DNA or RNA to the host cell's nucleus causes mutation. The mutant cells may be malignant.

Host factors

Internal body factors of the host can influence susceptibility to tumours. These include:

- race
- diet
- age
- inherited factors.

Tumours of individual structures are described in the appropriate chapters.

Growth of tumours

Normally cells divide in an orderly manner. Neoplastic cells have escaped from the normal controls and they multiply in a disorderly manner forming a tumour. Blood vessels grow with the proliferating cells, but in some malignant tumours the blood supply does not keep pace with growth and *ischaemia* (lack of blood supply) leads to tumour cell death, called *necrosis*. If the tumour is near the surface, this may result in skin ulceration and infection. In deeper tissues there is fibrosis; e.g. retraction of the nipple in breast cancer is due to the shrinkage of fibrous tissue in a necrotic tumour. The mechanisms controlling the life span of tumour cells are poorly understood.

Cell differentiation

Differentiation of cells into types with particular structural and functional characteristics occurs at an early stage in fetal development; e.g. epithelial cells develop different characteristics from lymphocytes. Later, when cell replacement occurs, daughter cells have the same appearance, functions and genetic make-up as the parent cell. In benign tumours the cells from which they originate are easily recognised; i.e. tumour cells are *well differentiated*. Tumours with well-differentiated cells are usually benign but some may be malignant. Malignant tumours grow beyond their normal boundaries and show varying levels of differentiation:

- *mild dysplasia* – this means the tumour cells have retained most of their normal features and their parent cells can usually be identified
- *anaplasia* – this means the tumour cells have lost most of their normal features and their parent cells cannot be identified.

Encapsulation and spread of tumours

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

Malignant tumours are not encapsulated. They spread locally by infiltration, and tumour fragments may spread to other parts of the body in blood or lymph. Some spreading cells may be phagocytosed but others lodge in tissues away from the primary site and grow into *secondary tumours* (metastases).

Local spread

Benign tumours enlarge and may cause pressure damage to local structures. They do not spread to other parts of the body.

Benign or malignant tumours may:

- damage nerves, causing pain and loss of nerve control of other tissues and organs supplied by the damaged nerves
- compress adjacent structures causing e.g. ischaemia (lack of blood), necrosis (death of tissue), blockage of ducts, organ dysfunction or displacement, or pain due to pressure on nerves.

Additionally *malignant tumours* grow into and infiltrate surrounding tissues and they may:

- erode blood and lymph vessel walls, causing spread of tumour cells to other parts of the body.

Lymphatic spread

This occurs when malignant tumours grow into lymph vessels. Groups of tumour cells break off and are carried to lymph nodes where they lodge and may grow into secondary tumours. There may be further spread through the lymphatic system, and to blood because lymph eventually enters the subclavian veins.

Blood spread

This occurs when the walls of a blood vessel are eroded by a malignant tumour. A *thrombus* (blood clot) may form at the site and *emboli* consisting of fragments of tumour and blood clot enter the bloodstream. These emboli block small blood vessels, cause *infarcts* (areas of dead tissue) and metastatic tumours develop. Phagocytosis of tumour cells in the emboli is unlikely to occur because these are protected by 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 site of the original tumour and the anatomy of the circulatory system, although the reasons why some organs develop metastases more frequently than others are not always clear.

Table 3.4 **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
Many organs	Lungs

Body cavities spread

This occurs when a tumour penetrates the wall of a cavity. The peritoneal cavity is most frequently involved. If, for example, a malignant tumour in an abdominal organ penetrates 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; e.g. a pleural tumour binds the visceral and parietal layers together, limiting expansion of the lung.

Table 3.4 shows common sites of primary tumours and their metastases.

Effects of tumours

Pressure effects

Both benign and malignant tumours may cause pressure damage to adjacent structures, especially if in a confined space. The effects depend on the site of the tumour 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 cause ischaemia, necrosis, blockage of ducts, organ dysfunction or displacement, pain due to invasion of nerves or pressure on nerves.

Hormonal effects

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 are markedly dysplastic malignant tumours. High levels of hormones are found in the bloodstream as secretion occurs in the absence of the normal stimulus and homeostatic control mechanism. Some malignant tumours produce *uncharacteristic hormones*. The cells of the tumour do not appear to originate from the appropriate endocrine gland. There is evidence of this phenomenon but the reasons for it are unclear. Endocrine glands may be destroyed by invading tumours, causing hormone deficiency.

Cachexia

This is the severe weight loss accompanied by progressive weakness, loss of appetite, wasting and anaemia that is usually associated with advanced cancer. The severity is usually indicative of the stage of development of the disease. The causes are not clear.

Causes of death in malignant disease

Infection

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

Organ failure

A tumour may destroy so much tissue that an organ cannot function. Severe damage to vital organs, such as lungs, brain, liver and kidneys, are common causes of death.

Carcinomatosis

When there is widespread metastatic disease associated with cachexia, severe physiological and biochemical disruption follows. In time, this results in loss of the homeostatic control mechanisms necessary to maintain life.

Haemorrhage

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

2

Communication

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4 The blood

Blood is a connective tissue. It provides one of the means of communication between the cells of different parts of the body and the external environment, e.g. it carries:

- oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs for excretion
- nutrients from the alimentary tract to the tissues and cell wastes to the excretory organs, principally the kidneys
- hormones secreted by endocrine glands to their target glands and tissues
- heat produced in active tissues to other less active tissues
- protective substances, e.g. antibodies, to areas of infection
- clotting factors that coagulate blood, minimising its loss from ruptured blood vessels.

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.

Blood in the blood vessels is always in motion. The continual flow maintains a fairly constant environment for the body cells.

Blood volume and the concentration of its many constituents are kept within narrow limits by homeostatic mechanisms.

COMPOSITION OF BLOOD

Learning outcomes

After studying this section, you should be able to:

- describe the chemical composition of plasma
- discuss the structure, function and formation of red blood cells, including the systems used in medicine 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.

Blood is composed of a straw-coloured transparent fluid, *plasma*, in which different types of cells are suspended. Plasma constitutes about 55% and cells about 45% of blood volume (Fig. 4.1A).

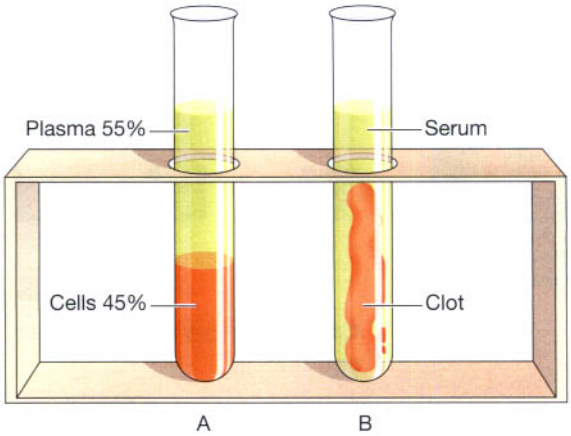


Figure 4.1 A. The proportions of blood cells and plasma in whole blood separated by gravity. B. A blood clot in serum.

Plasma

The constituents of plasma are water (90 to 92%) and dissolved substances, including:

- plasma proteins: albumins, globulins (including *antibodies*), fibrinogen, clotting factors
- inorganic salts (mineral salts): sodium chloride, sodium bicarbonate, potassium, magnesium, phosphate, iron, calcium, copper, iodine, cobalt
- nutrients, principally from digested foods, e.g. monosaccharides (mainly glucose), amino acids, fatty acids, glycerol and vitamins
- organic waste materials, e.g. urea, uric acid, creatinine
- hormones
- enzymes, e.g. certain clotting factors
- gases, e.g. oxygen, carbon dioxide, nitrogen.

Plasma proteins

Plasma proteins, which make up about 7% of plasma, are normally retained within the blood, because they are too big to escape through the capillary pores into the tissues. They are largely responsible for creating the osmotic pressure of blood (normally 25 mmHg or 3.3 kPa*), which keeps plasma fluid within the circulation. If plasma protein levels fall, because of either reduced production or loss from the blood vessels, osmotic pressure is also reduced, and fluid moves into the tissues (oedema) and body cavities.

*1 kilopascal (kPa) = 7.5 millimetres of mercury (mmHg)
1 mmHg = 133.3 Pa = 0.133 kPa

Albumins. These are formed in the liver. They are the most abundant plasma proteins and their main function is to maintain a normal plasma osmotic pressure. Albumins also act as carrier molecules for lipids and steroid hormones.

Globulins. Most are formed in the liver and the remainder in lymphoid tissue. Their main functions are:

- as antibodies (immunoglobulins), which are complex proteins produced by lymphocytes that play an important part in immunity. They bind to, and neutralise, foreign materials (antigens) such as micro-organisms (see also p. 380).
- transportation of some hormones and mineral salts; e.g. thyroglobulin carries the hormone thyroxine and transferrin carries the mineral iron
- inhibition of some proteolytic enzymes, e.g. α_2 macroglobulin inhibits trypsin activity.

Clotting factors. These are substances essential for coagulation of blood (p. 67). *Serum* is plasma from which clotting factors have been removed (Fig. 4.1B).

Fibrinogen. This is synthesised in the liver and is essential for blood coagulation.

Plasma viscosity (thickness) is due to plasma proteins, mainly albumin and fibrinogen. Viscosity is used as a measure of the body's response to some diseases.

Inorganic salts (mineral salts)

These are involved in a wide variety of activities, including cell formation, contraction of muscles, transmission of nerve impulses, formation of secretions and maintenance of the balance between acids and alkalis. In health the blood is slightly alkaline. Alkalinity and acidity are expressed in terms of pH, which is a measure of hydrogen ion concentration, or $[H^+]$ (p. 21 and Fig. 2.6). The pH of blood is maintained between 7.35 and 7.45 by an ongoing complicated series of chemical activities, involving buffering systems.

Nutrients

Food is digested in the alimentary tract and the resultant nutrients are absorbed, e.g. monosaccharides, amino acids, fatty acids, glycerol and vitamins. Together with mineral salts they are required by all body cells to provide energy, heat, materials for repair and replacement, and for the synthesis of other blood components and body secretions.

Organic waste products

Urea, creatinine and uric acid are the waste products of protein metabolism. They are formed in the liver and conveyed in blood to the kidneys for excretion. Carbon dioxide, released by all cells, is conveyed to the lungs for excretion.

Hormones (Ch. 8)

These are chemical compounds synthesised by endocrine glands. Hormones pass directly from the cells of the glands into the blood which transports them to their target tissues and organs elsewhere in the body, where they influence cellular activity.

Gases

Oxygen, carbon dioxide and nitrogen are transported round the body in solution in plasma. Oxygen and carbon dioxide are also transported in combination with haemoglobin in red blood cells (p. 256). Most oxygen is carried in combination with haemoglobin and most carbon dioxide as bicarbonate ions dissolved in plasma. Atmospheric nitrogen enters the body in the same way as other gases and is present in plasma but it has no physiological function (p. 255).

Cellular content of blood

There are three types of blood cells (see Fig. 1.5, p. 8).

- erythrocytes or red cells
- thrombocytes or platelets
- leukocytes or white cells.

All blood cells originate from *pluripotent stem cells* and go through several developmental stages before entering the blood. Different types of blood cells follow separate lines of development. The process of blood cell formation is called *haemopoiesis* (Fig. 4.2) and takes place within red bone marrow. For the first few years of life, red marrow occupies the entire bone capacity and, over the next 20 years, is gradually replaced by fatty yellow marrow that has no erythropoietic function. In adults, erythropoiesis is confined to flat bones, irregular bones and the ends (*epiphyses*) of long bones, the main sites being the sternum, ribs, pelvis and skull.

Erythrocytes (red blood cells)

These are circular biconcave non-nucleated discs with a diameter of about 7 microns. Measurements of red cell numbers, volume and haemoglobin content are routine and useful assessments made in clinical practice (Table 4.1). The symbols in brackets are the abbreviations commonly used in laboratory reports.

Erythrocyte count. This is the number of erythrocytes per litre (l) or per cubic millimetre (mm^3) of blood.

Packed cell volume or haematocrit. This is the volume of red cells in 1 litre or 1 mm^3 of whole blood.

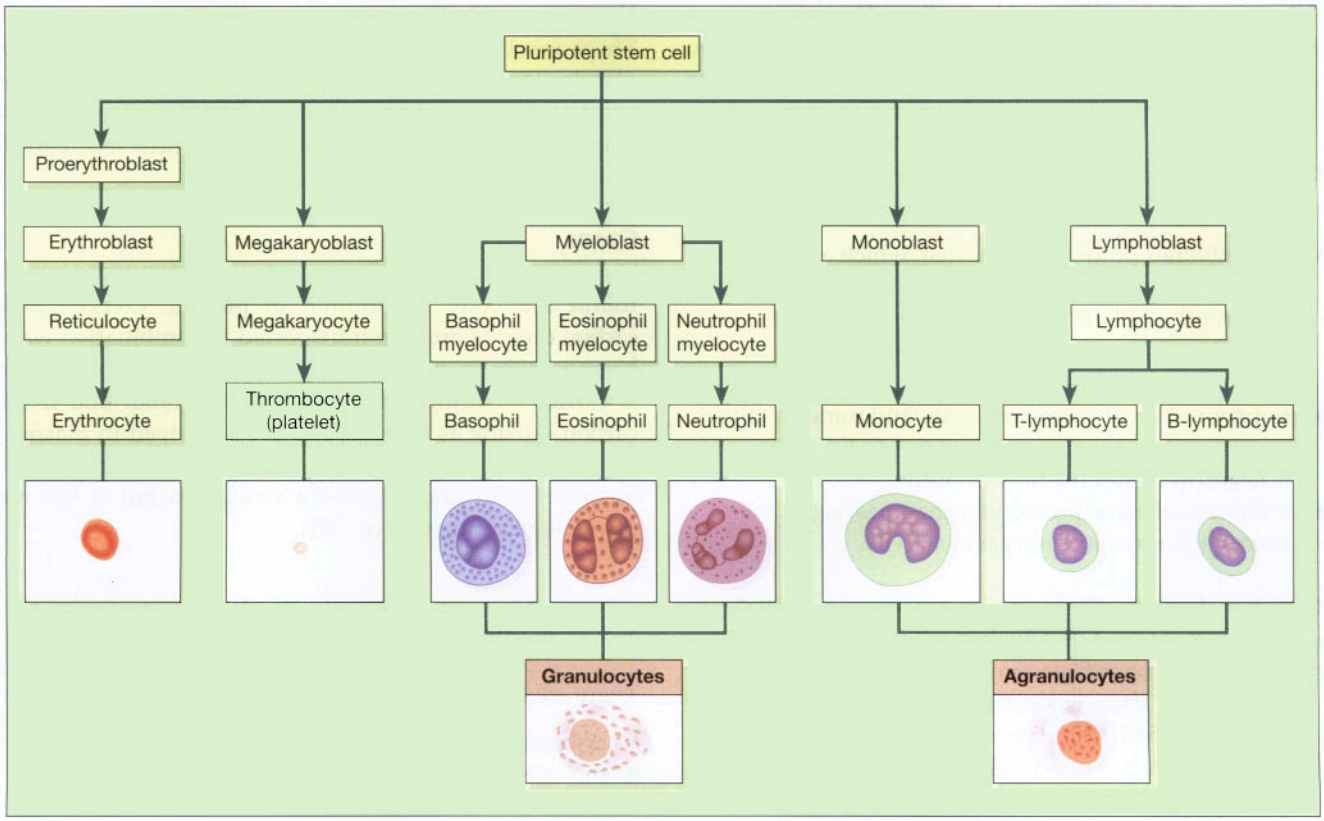


Figure 4.2 Haemopoiesis: stages in the development of blood cells.

Mean cell volume. This is the average volume of cells, measured in femtolitres (fl = 10^{-15} litre).

Haemoglobin. This is the weight of haemoglobin in whole blood, measured in grams per 100 ml.

Mean cell haemoglobin. This is the average amount of haemoglobin in each cell, measured in picograms (pg = 10^{-12} gram).

Mean cell haemoglobin concentration. This is the amount of haemoglobin in 100 ml of red cells.

Development and life span of erythrocytes

Erythrocytes are formed in red bone marrow, which is present in the ends of long bones and in flat and irregular bones. They pass through several stages of development before entering the blood. Their life span in the circulation is about 120 days.

Table 4.1 Erythrocytes – normal values

Measure	Normal values
Erythrocyte count	
Male	4.5×10^{12}/l to 6.5×10^{12}/l (4.5 to 6.5 million/mm^3)
Female	4.5×10^{12}/l to 5×10^{12}/l (4.5 to 5 million/mm^3)
Packed cell volume (PCV)	0.4 to 0.5 l/l (40 to 50/mm^3)
Mean cell volume (MCV)	80 to 96 fl
Haemoglobin (Hb)	
Male	13 to 18 g/100 ml
Female	11.5 to 16.5 g/100 ml
Mean cell haemoglobin (MCH)	27 to 32 pg/cell
Mean cell haemoglobin concentration (MCHC)	30 to 35 g/100 ml of cells

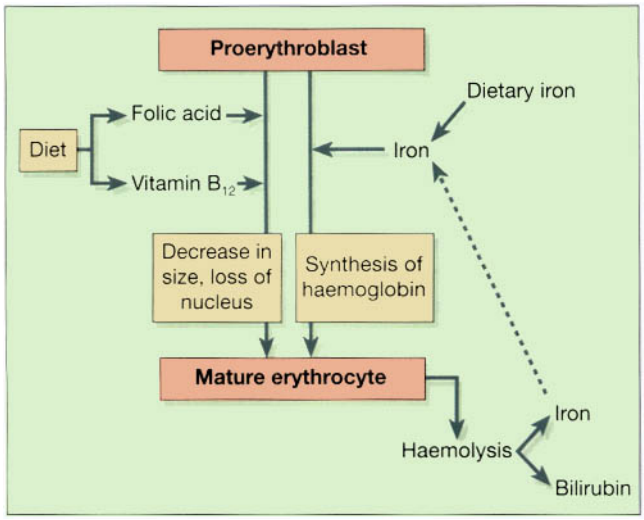


Figure 4.3 Maturation of the erythrocyte.

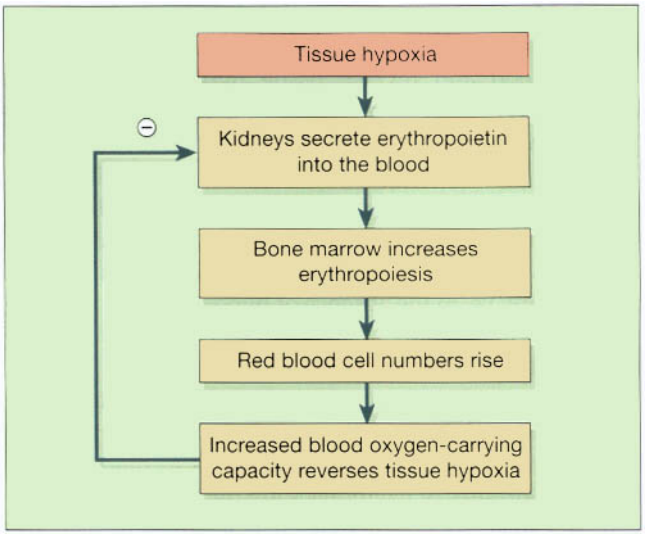


Figure 4.4 Control of erythropoiesis: the role of erythropoietin.

The process of development of red blood cells from pluripotent stem cells takes about 7 days and is called *erythropoiesis* (Fig. 4.2). It is characterised by two main features:

- maturation of the cell
- formation of haemoglobin inside the cell (Fig. 4.3).

Maturation of the cell. During this process the cell decreases in size and loses its nucleus. These changes depend on a number of factors, especially the presence of vitamin B_{12} and folic acid. These are present in sufficient quantity in a normal diet containing dairy products, meat and green vegetables. If the diet contains more than is needed, they are stored in the liver. Absorption of vitamin B_{12} depends on a glycoprotein called *intrinsic factor* secreted by parietal cells in the gastric glands. Together they form the *intrinsic factor–vitamin* B_{12} complex (IF–B_{12}). During its passage through the intestines, the bound vitamin is protected from enzymatic digestion, and is absorbed in the terminal ileum.

The effects of deficient intake of vitamin B_{12} do not appear for several years because there are large stores in the liver.

Folic acid is absorbed in the duodenum and jejunum where it undergoes change before entering the blood. Signs of deficiency are apparent within a few months.

Deficiency of either vitamin B_{12} or folic acid leads to impaired red cell production.

Formation of haemoglobin. Haemoglobin is a complex protein, consisting of *globin* and an iron-containing substance called *haem*, and is synthesised inside developing erythrocytes in red bone marrow.

Haemoglobin in mature erythrocytes combines with oxygen to form *oxyhaemoglobin*, giving arterial blood its characteristic red colour. In this way the bulk of oxygen absorbed from the lungs is transported around the body to maintain a continuous oxygen supply to all cells. Haemoglobin is also involved, to a lesser extent, in the transport of carbon dioxide from the body cells to the lungs for excretion.

Each haemoglobin molecule contains four atoms of iron. Each atom can carry one molecule of oxygen, therefore one haemoglobin molecule can carry up to four molecules of oxygen. Haemoglobin is said to be saturated when all its available binding sites for oxygen are filled. When oxygen levels are low, only partial saturation is possible.

Control of erythropoiesis

The number of red cells remains fairly constant, which means that the bone marrow produces erythrocytes at the rate at which they are destroyed. This is due to a homeostatic negative feedback mechanism (Fig. 4.4).

The primary stimulus to increased erythropoiesis is *hypoxia*, i.e. deficient oxygen supply to body cells. This occurs when:

- the oxygen-carrying power of blood is reduced by e.g. haemorrhage or excessive erythrocyte breakdown (*haemolysis*) due to disease
- the oxygen tension in the air is reduced, as at high altitudes.

Hypoxia increases erythrocyte formation by stimulating the production of the hormone *erythropoietin*, mainly by the kidneys. Erythropoietin stimulates an increase in the production of proerythroblasts and the release of

increased numbers of reticulocytes into the blood. These changes increase the oxygen-carrying capacity of the blood and reverse tissue hypoxia, the original stimulus. When the tissue hypoxia is overcome, erythropoietin production declines (Fig. 4.4). When erythropoietin levels are low, red cell formation does not take place even in the presence of hypoxia, and *anaemia* (the inability of the blood to carry adequate oxygen for body needs) develops. It is believed that erythropoietin regulates normal red cell replacement, i.e. in the absence of hypoxia.

Destruction of erythrocytes

The life span of erythrocytes is about 120 days and their breakdown, or *haemolysis*, is carried out by *phagocytic reticuloendothelial cells*. These cells are found in many tissues but the main sites of haemolysis are the spleen, bone marrow and liver. As erythrocytes age, changes in their cell membranes make them more susceptible to haemolysis. Iron released by haemolysis is retained in the body and reused in the bone marrow to form haemoglobin (Fig. 4.3). *Biliverdin* is formed from the protein part of the erythrocytes. It is almost completely reduced to the yellow pigment *bilirubin*, before it is bound to plasma globulin and transported to the liver (see Fig. 12.41, p. 310). In the liver it is changed from a fat-soluble to a water-soluble form before it is excreted as a constituent of bile.

Blood groups

Individuals have different types of antigen on the surfaces of their red blood cells. These antigens, which are inherited, determine the individual's *blood group*. In addition, individuals 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 *transfusion reaction*. The main signs are clumping of red blood cells, haemolysis, shock and kidney failure. These antibodies circulate in the bloodstream and the ability to make them, like the antigens, is genetically determined and not associated with acquired immunity (see also Ch. 15).

If individuals are transfused with blood of the same group, i.e. possessing the same antigens on the surface of the cells, 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 mount an attack upon them 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 population has either A-type antigens (blood group A), B-type antigens (blood group B) or both (blood group AB) on their red cell surface. The remaining 45% have neither A nor B type antigens (blood group O). The corresponding antibodies are called anti-A and anti-B. Blood group A individuals cannot make anti-A (and therefore do not have these antibodies in their plasma), since otherwise a reaction to their own cells would occur; they do, however, make anti-B. Blood group B individuals, for the same reasons, make only anti-A. Blood group AB make neither, and blood group O make both anti-A and anti-B (Fig. 4.5).

Because blood group AB people make neither anti-A nor anti-B antibodies, they are known as *universal recipients*: transfusion of either type A or type B blood into these individuals is 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 be safely transfused into A, B, AB or O types; group O is known as the *universal donor*.

The Rhesus system

The red blood cell membrane antigen important here is the Rhesus (Rh) antigen, or Rhesus factor. 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 are capable of making anti-Rhesus antibodies, but are stimulated to do so only in certain circumstances, e.g. in pregnancy (p. 71), or as the result of an incompatible blood transfusion.

Leukocytes (white blood cells)

These cells have an important function in defending the body against microbes and other foreign materials. Leukocytes are the largest blood cells and they account for about 1% of the blood volume. They contain nuclei and some have granules in their cytoplasm. There are two main types (Table 4.2):

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

Granulocytes (polymorphonuclear leukocytes)

During their formation, *granulopoiesis*, they follow a common line of development through *myeloblast* to *myelocyte* before differentiating into the three types (Figs 4.2 and

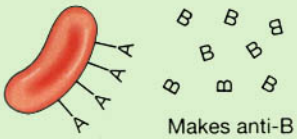
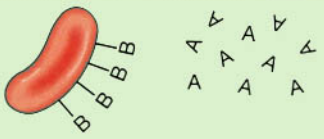
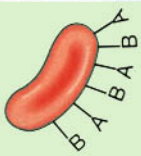
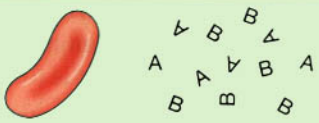
Blood group	Antigen + antibody(ies) present	As donor, is	As recipient, is
A	 Antigen A; Makes anti-B	Compatible with: A and AB Incompatible with: B and O, because both make anti-A antibodies that will react with A antigens	Compatible with: A and O Incompatible with: B and AB, because type A makes anti-B 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 4.5 The ABO system of blood grouping: antigens, antibodies and compatibility.

4.6). All granulocytes have multilobed nuclei in their cytoplasm. Their names represent 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.

Neutrophils

Their main function is to protect against any foreign material that gains entry to the body, mainly microbes, and to remove waste materials, e.g. cell debris. They are attracted in large numbers to any area of infection by chemical substances, released by damaged cells, called *chemotaxins*. Neutrophils pass through the capillary walls in the affected area by *amoeboid movement* (Fig. 4.7). Thereafter they engulf and kill the microbes by *phagocytosis* (Fig. 4.8). Their granules are *lysosomes* that contain enzymes that digest the engulfed material. The pus that may form in the affected area consists of dead tissue cells, dead and live microbes, and phagocytes killed by microbes.

There is a physiological increase in circulating neutrophils following strenuous exercise and in the later stages of normal pregnancy. Numbers are also increased in:

Table 4.2 Numbers of different types of leukocyte in adult blood

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

- microbial infection
- tissue damage, e.g. inflammation, myocardial infarction, burns, crush injuries
- metabolic disorders, e.g. diabetic ketoacidosis, acute gout
- leukaemia
- heavy smoking
- use of oral contraceptives.

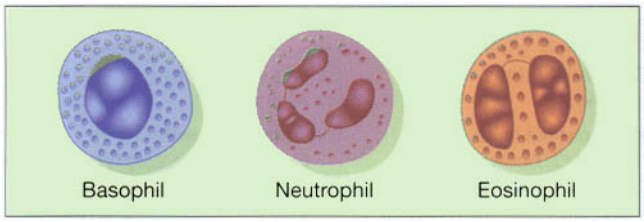


Figure 4.6 The granulocytes (granular leukocytes).

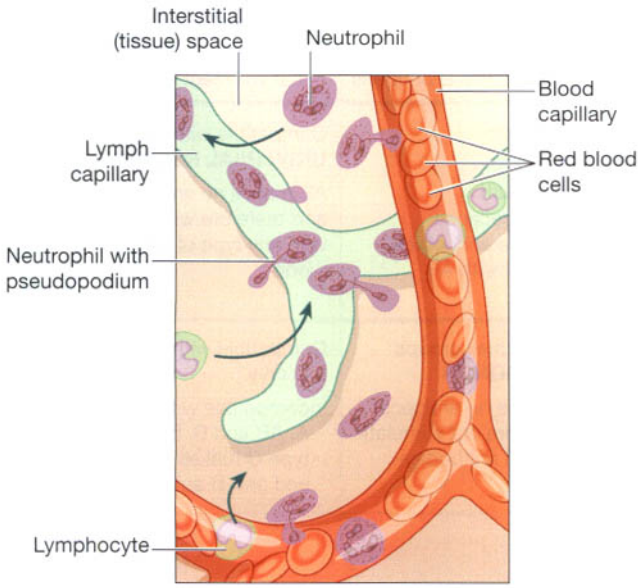


Figure 4.7 Amoeboid movement of leukocytes.

Eosinophils

Eosinophils, although capable of phagocytosis, are less active in this 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 certain toxic chemicals, stored in their granules, which they release when the eosinophil binds an infecting organism.

Eosinophils are often found at sites of allergic inflammation, such as the asthmatic airway and skin allergies. There, they promote tissue inflammation by releasing their array of toxic chemicals, but they may also dampen down the inflammatory process through the release of other chemicals, such as an enzyme that breaks down histamine (p. 376).

Basophils

Basophils, which are closely associated with allergic reactions, contain cytoplasmic granules packed with *heparin* (an anticoagulant), *histamine* (an inflammatory agent) and other substances that promote inflammation. Usually the stimulus that causes basophils to release the contents of their granules is an *allergen* (an antigen that causes allergy) of some type. This binds to antibody-type receptors on the basophil membrane. A cell type very similar to basophils, except that it is found in the tissues, not in the circulation, is the *mast cell*. Mast cells release their granule contents within seconds of binding an allergen, which accounts for the rapid onset of allergic symptoms following exposure to, for example, pollen in hay fever.

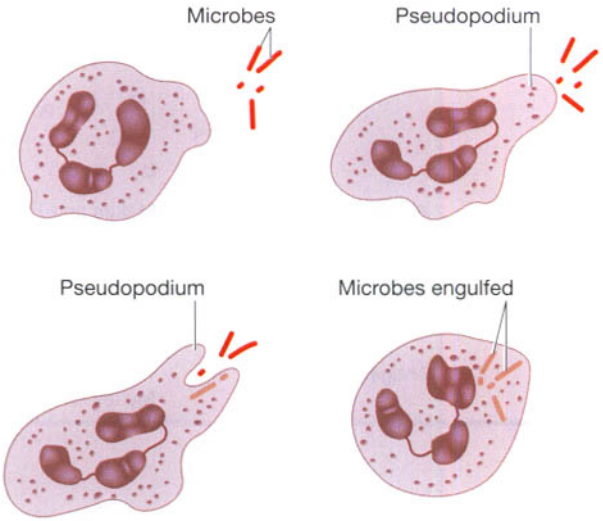


Figure 4.8 Phagocytic action of neutrophils.

Agranulocytes

The types of leukocyte with a large nucleus and no granules in their cytoplasm are *monocytes* and *lymphocytes* and they make up 25% to 50% of all leukocytes (Figs 4.2 and 4.9).

Monocytes

These are large mononuclear cells that originate in red bone marrow. Some circulate in the blood and are actively motile and phagocytic while others migrate into the tissues where they develop into *macrophages*. Both types of cell produce *interleukin 1* which:

- acts on the hypothalamus, causing the rise in body temperature associated with microbial infections
- stimulates the production of some globulins by the liver
- enhances the production of activated T-lymphocytes.

Macrophages have important functions in inflammation (p. 375) and immunity.

The monocyte–macrophage system. This system, which is sometimes called the *reticuloendothelial system*, consists of the body's complement of monocytes and

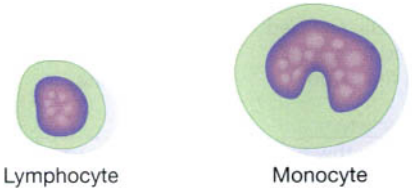


Figure 4.9 The agranulocytes.

macrophages. Some macrophages are mobile whereas others are fixed. These include:

- *histiocytes* in connective tissues
- *microglia* in the brain
- *Kupffer cells* in the liver
- *alveolar macrophages* in the lungs
- *sinus-lining macrophages* (reticular cells) in the spleen, lymph nodes and thymus gland
- *mesangial cells* in the glomerulus of nephrons in the kidney
- *osteoclasts* in bone.

Macrophages function in close association with monocytes in the blood and with lymphocytes which influence their activity. They are actively phagocytic and if they encounter large amounts of foreign or waste material, they tend to multiply at the site and 'wall off' the area, isolating the material, e.g. in the lungs when foreign material has been inhaled. Their numbers are increased in microbial infections, collagen diseases and some non-infective bowel conditions.

Lymphocytes

Lymphocytes are smaller than monocytes and have large nuclei. They circulate in the blood and are present in great numbers in lymphatic tissue such as lymph nodes and the spleen. Lymphocytes develop from pluripotent stem cells in red bone marrow, then travel in the blood to lymphoid tissue elsewhere in the body where they are *activated*, i.e. they become immunocompetent which means they are able to respond to *antigens* (foreign material). Examples of antigens include:

- cells regarded by lymphocytes as abnormal, e.g. those that have been invaded by viruses, cancer cells, tissue transplant cells
- pollen from flowers and plants
- fungi
- bacteria
- some large molecule drugs, e.g. penicillin, aspirin.

Although all lymphocytes originate from one type of stem cell, when they are activated in lymphatic tissue, two distinct types of lymphocyte are produced—*T-lymphocytes* and *B-lymphocytes*. The specific functions of these two types are discussed in Chapter 15.

Thrombocytes (platelets)

These are very small non-nucleated discs, 2 to 4 μm in diameter, derived from the cytoplasm of megakaryocytes in red bone marrow (Fig. 4.2). They contain a variety of substances that promote blood clotting, which causes *haemostasis* (cessation of bleeding).

The normal blood platelet count is between 200×10^9/l and 350×10^9/l (200 000 to 350 000/mm^3). The control of platelet production is not yet entirely clear but it is believed that one stimulus is a fall in platelet count and that a substance called *thrombopoietin* is involved. The life span of platelets is between 8 and 11 days and those not used in haemostasis are destroyed by macrophages, mainly in the spleen.

Haemostasis

When a blood vessel is damaged, loss of blood is stopped and healing occurs in a series of overlapping processes, in which platelets play a vital part.

1. Vasoconstriction. When platelets come in contact with a damaged blood vessel, their surface becomes sticky and they adhere to the damaged wall. They then release *serotonin* (5-hydroxytryptamine), which constricts (narrows) the vessel, reducing blood flow through it. Other chemicals that cause vasoconstriction, e.g. thromboxanes, are released by the damaged vessel itself.

2. Platelet plug formation. The adherent platelets clump to each other 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 by which many platelets rapidly arrive at the site of vascular damage and quickly form a temporary seal—the *platelet plug*.

3. Coagulation (blood clotting). This is a complex process that also involves a positive feedback system and only a few stages are included here. The factors involved are listed in Table 4.3. Their numbers represent the order in which they were discovered and not the order of participation in the clotting process. Blood clotting results in formation of an insoluble thread-like mesh of *fibrin* which traps blood cells and is much stronger than the rapidly formed platelet plug. In the final stages of this process *prothrombin activator* acts on the plasma protein *prothrombin* converting it to thrombin.

Thrombin then acts on another plasma protein *fibrinogen* and converts it to fibrin (Fig. 4.10).

Prothrombin activator can be formed by two processes which often occur together: the extrinsic and intrinsic

Table 4.3 Blood clotting factors

I	Fibrinogen
II	Prothrombin
III	Tissue factor (thromboplastin)
IV	Calcium (Ca^{2+})
V	Labile factor, proaccelerin, Ac-globulin
VII	Stable factor, proconvertin
VIII	Antihaemophilic globulin (AHG), antihaemophilic factor A
IX	Christmas factor, plasma thromboplastin component (PTA), antihaemophilic factor B
X	Stuart Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihaemophilic factor C
XII	Hageman factor
XIII	Fibrin stabilising factor

(There is no Factor VI)

Vitamin K is essential for synthesis of Factors II, VII, IX and X

pathways (Fig. 4.10). The *extrinsic pathway* occurs rapidly (within seconds) when there is tissue damage outside the circulation. 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 confined to the circulation. It is triggered by damage to a blood vessel lining (endothelium) and the effects of platelets adhering to it. After a time the clot shrinks, squeezing out *serum*, a clear sticky fluid that consists of plasma from which clotting factors have been removed.

4. Fibrinolysis. After the clot has formed the process of removing it and healing the damaged blood vessel begins. The breakdown of the clot, or fibrinolysis, is the first stage. An inactive substance called *plasminogen* is present in the clot and is converted to the enzyme *plasmin* by activators released from the damaged endothelial cells. Plasmin initiates the breakdown of fibrin to soluble products that are treated as waste material and removed by phagocytosis. As the clot is removed, the healing process restores the integrity of the blood vessel wall.

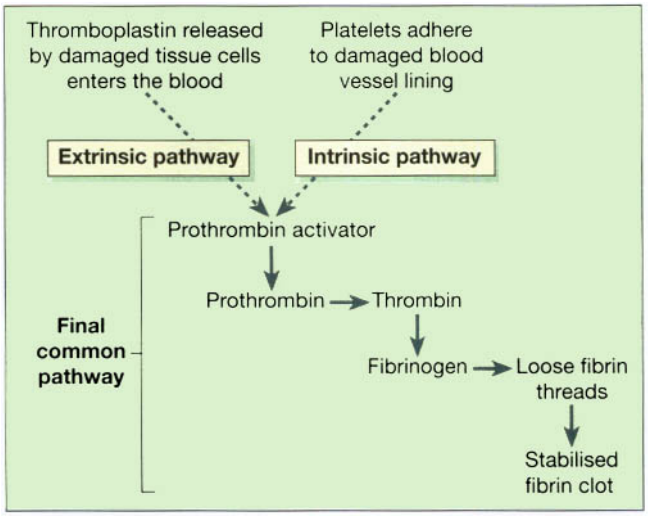
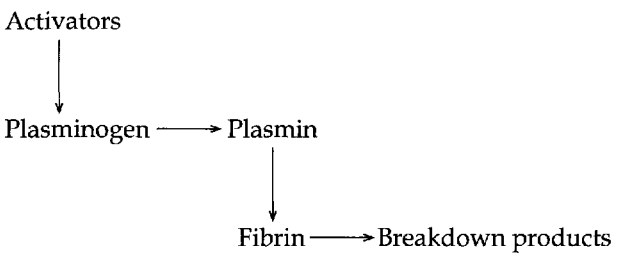


Figure 4.10 Stages of blood clotting (coagulation).



Control of coagulation

The process of blood clotting relies heavily on several processes that are self-perpetuating—that is, once started, a positive feedback mechanism promotes their continuation. For example, thrombin is a powerful stimulator of its own production. The body therefore possesses several mechanisms to control and limit the coagulation cascade; otherwise once started the clotting process would spread throughout the circulatory system, far beyond requirements. The main controls are:

- the perfect smoothness of normal blood vessel lining; platelets do not adhere to this surface
- the binding of thrombin to a special thrombin receptor on the cells lining blood vessels; once bound, thrombin is inactivated
- the presence of natural anticoagulants, e.g. heparin, in the blood, which inactivate clotting factors.

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

In anaemia there is not enough haemoglobin available to carry sufficient oxygen from the lungs to supply the needs of the tissues. It occurs when the rate of production of mature cells entering the blood from the red bone marrow does not keep pace with the rate of haemolysis. The classification of anaemia is based on the cause:

- impaired erythrocyte production
  - iron deficiency
  - megaloblastic anaemias
  - hypoplastic anaemia
- increased erythrocyte loss
  - haemolytic anaemias
  - *normocytic* anaemia.

Red cells may appear abnormal when examined microscopically. Characteristic changes are listed in Table 4.4. Signs and symptoms of anaemia relate to the inability of the blood to supply body cells with enough oxygen, and may represent adaptive measures. Examples include:

- tachycardia; the heart rate increases to improve blood supply and speed circulation
- palpitations (an awareness of the heartbeat), or angina pectoris (p. 121); these are caused by the increased effort of the overworked heart muscle
- breathlessness on exertion; when oxygen requirements increase, respiratory rate and effort rise in an effort to meet the greater demand.

Iron deficiency anaemia

This is the most common form of anaemia in many parts of the world. The normal daily requirement of iron intake in men is about 1 to 2 mg derived from meat and highly coloured vegetables. The normal daily requirement in women is 3 mg. The increase is necessary to compensate for loss of blood during menstruation and to meet the needs of the growing fetus during pregnancy. Children, during their period of rapid growth, require more than adults.

The amount of haemoglobin in each cell is regarded as below normal when the MCH is less than 27 pg/cell. The anaemia is regarded as severe when the haemoglobin level is below 9 g/dl blood. It is caused by deficiency of iron in the bone marrow and may be due to dietary deficiency, excessively high requirement or malabsorption. Usually more than one factor is involved, e.g. loss of blood and malabsorption.

In this type of anaemia erythrocytes are microcytic and hypochromic because their haemoglobin content is low.

Normal requirements, deficient intake

Because of the relative inefficiency of iron absorption, deficiency occurs frequently, even in individuals whose requirements are normal. The likelihood of deficiency increases if the daily diet is restricted in some way, as in poorly planned vegetarian diets, or in calorie-controlled 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, since the liver carries only a few months' store and milk is a poor source of iron.

Table 4.4 Terms used to describe changes in red blood cells

Term	Definition	Example
Normocytic	Cells normal sized	Acute haemorrhage
Microcytic	Cells smaller than normal	Iron deficiency
Macrocytic	Cells bigger than normal	Vitamin B_{12} or folic acid deficiency
Hypochromic	Cells paler than normal	Iron deficiency anaemia
Haemolytic	Rate of cell destruction raised	Autoimmune disease Sickle cell anaemia

High requirements, normal or deficient intake

This type of anaemia occurs in pregnancy, when iron requirements are increased both for fetal growth and to support the additional load on the mother's cardiovascular system. It may also occur as a result of chronic blood loss, the causes of which include:

- chronic peptic ulcers
- menorrhagia
- intestinal ulceration
- haemorrhoids
- carcinoma.

Malabsorption

Iron absorption is usually increased following haemorrhage but may be reduced in abnormalities of the stomach, duodenum or jejunum including:

- resection of stomach or upper part of the small intestine
- hypochlorhydria, e.g. in malignant disease, Addisonian pernicious anaemia.

Megaloblastic anaemias

Maturation of erythrocytes is impaired when deficiency of vitamin B_{12} and/or folic acid occurs (Fig. 4.3) and abnormally large erythrocytes (megaloblasts) are found in the blood. During normal erythropoiesis (Fig. 4.2) 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. When deficiency of vitamin B_{12} and/or folic acid occurs, the rate of DNA and RNA synthesis is reduced, delaying cell division. The cells can therefore grow larger than normal between divisions. Circulating cells are immature, larger than normal and some are nucleated (MCV >94 fl). The haemoglobin content of each cell is normal or raised. The cells are fragile and their life span is reduced to between 40 and 50 days. Depressed 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 occurs more often in females than males, usually between 45 and 65 years of age. It is an autoimmune disease in which auto-antibodies destroy intrinsic factor (IF) and parietal cells in the stomach.

Dietary deficiency of vitamin B_{12}

This is rare, except in true vegans, i.e. when no animal products are included in the diet. The store of vitamin B_{12} is such that deficiency takes several years to appear.

Other causes of vitamin B_{12} deficiency

These include the following.

- *Gastrectomy* – this leaves fewer cells available to produce IF after partial resection of the stomach.
- *Chronic gastritis, malignant disease and ionising radiation* – these damage the gastric mucosa including the parietal cells that produce IF.
- *Blind loop syndrome* – this occurs when the contents of the small intestine are slow moving or static, allowing microbes to colonise the small intestine and use or destroy the intrinsic factor–vitamin B_{12} (IF–B_{12}) complex before it reaches the terminal ileum where it is absorbed. Blind loops of bowel occur in diverticular disease (p. 328) and are left after some surgical procedures.
- *Malabsorption of intrinsic factor–vitamin B_{12} complex* – this may follow resection of terminal ileum or inflammation of the terminal ileum, e.g. Crohn's disease or tropical sprue.

Complications of vitamin B_{12} deficiency anaemia

These may appear before the signs of anaemia. They include:

- subacute combined degeneration of the spinal cord in which nerve fibres in the posterior and lateral columns of white matter become demyelinated. Vitamin B_{12} is essential for the secretion and maintenance of myelin (p. 142 and p. 186).
- ulceration of the tongue and glossitis.

Folic acid deficiency anaemia

Deficiency in the bone marrow causes a form of megaloblastic anaemia not associated with degeneration of the spinal cord. It may be due to:

- dietary deficiency, e.g. in infants if there is delay in establishing a mixed diet, in alcoholics, in anorexia and in pregnancy when the requirement is raised
- malabsorption from the jejunum caused by e.g. coeliac disease, tropical sprue or anticonvulsant drugs
- interference with use by e.g. cytotoxic and anticonvulsant drugs.

Hypoplastic and aplastic anaemias

Hypoplastic and aplastic anaemias are due to varying degrees of bone marrow failure. Bone marrow function is reduced in hypoplastic anaemia, and absent in aplastic anaemia. Since the bone marrow produces leukocytes and platelets as well as erythrocytes, *leukopenia* (low

white cell count) and *thrombocytopenia* (low platelet count) are likely to accompany diminished red cell numbers. 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 often idiopathic, but the known causes include:

- drugs, e.g. cytotoxic drugs, some anti-inflammatory and anticonvulsant drugs, some sulphonamides and antibiotics
- ionising radiation
- some chemicals, e.g. benzene and its derivatives
- chronic nephritis
- viral disease, including hepatitis
- invasion of bone marrow by, e.g., malignant disease, leukaemia or fibrosis.

Haemolytic anaemias

These occur when red cells are destroyed while in circulation or are removed prematurely from the circulation because the cells are abnormal or the spleen is overactive.

Congenital haemolytic anaemias

In these diseases genetic abnormality leads to the synthesis of abnormal haemoglobin and increased red cell membrane friability, reducing cell oxygen-carrying capacity and life span. 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. A high proportion of abnormal molecules makes the sickling permanent. The life span of cells is reduced by early haemolysis. Sickle cells do not move smoothly through the small blood vessels. This tends to increase the viscosity of the blood, reducing the rate of blood flow and leading to intravascular clotting, ischaemia and infarction. The anaemia is due to early haemolysis of irreversibly sickled cells.

Blacks are more affected than other races. Some affected individuals have a degree of immunity to malaria because the life span of the sickled cells is less than the time needed for the malaria parasite to mature inside the cells.

Complications. Pregnancy, infection and dehydration predispose to the development of 'crises' due to intravascular clotting and ischaemia, causing severe pain in long bones, chest or the abdomen. The formation of gallstones (*cholelithiasis*) and inflammation of the gall bladder (*cholecystitis*) also occurs (p. 336).

Thalassaemia

There is reduced globin synthesis with resultant reduced haemoglobin production and increased friability of the cell membrane, leading to early haemolysis. Severe cases may cause death in infants or young children. This condition is most common in Mediterranean countries.

Haemolytic disease of the newborn

In this disorder, the mother's immune system makes antibodies to the baby's red blood cells, causing haemolysis and phagocytosis of fetal erythrocytes. The antigen system involved is usually (but not always) the Rhesus (Rh) antigen.

A Rh^- mother carries no Rh antigen on her red blood cells, but she has the capacity to produce anti-Rh antibodies. If she conceives a child fathered by a 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. Because they carry an antigen (the Rh antigen) foreign to the mother, her immune system will be stimulated to produce neutralising antibodies to it. The red cells of second and subsequent Rh^+ babies are attacked by these maternal antibodies, which can cross the placenta and enter the fetal circulation (Fig. 4.11). In the most severe cases, the baby dies in the womb from profound anaemia. In less serious circumstances, the baby is born with some degree of anaemia, which is corrected with blood transfusions.

The disease is much less common than it used to be, because it was discovered that if a Rh^- mother is given an injection of anti-Rh antibodies within 72 hours of the delivery of a Rh^+ baby, her immune system does not make its own anti-Rh antibodies to the fetal red cells. Subsequent pregnancies are therefore not affected. The anti-Rh antibodies given to the mother bind to, and neutralise, any fetal red cells present in her circulation before her immune system becomes sensitised to them.

Acquired haemolytic anaemias

In this context acquired means haemolytic anaemia in which no familial or racial factors have been identified. There are several causes.

Chemical agents

These substances cause early or excessive haemolysis, e.g.:

- some drugs, especially when taken long term in large doses, e.g. phenacetin, primaquine, sulphonamides
- chemicals encountered in the general or work environment, e.g. lead, arsenic compounds

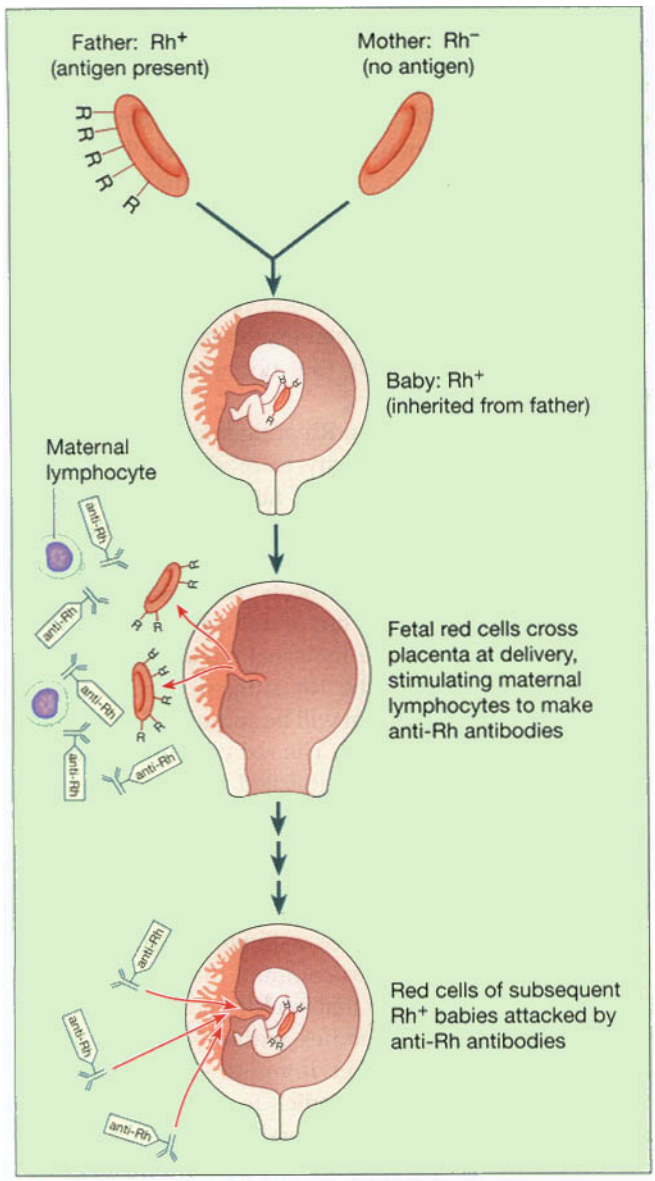


Figure 4.11 The immune processes involved in haemolytic disease of the newborn.

- toxins produced by microbes, e.g. *Streptococcus pyogenes, Clostridium welchii.*

Autoimmunity

In this disease 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. carcinoma, 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. 4.5, p. 65). However, if individuals receive a transfusion of blood possessing antigens different from their own, their immune system will recognise them as foreign, make antibodies to them and destroy them (transfusion reaction). This adverse reaction between the blood of incompatible recipients and donors leads to haemolysis within the recipient's cardiovascular system. The breakdown products of haemolysis lodge in, and block, the filtering mechanism of the nephron, impairing kidney function. Other principal signs of a transfusion reaction include fever, chills, lumbar pain and shock.

Other causes of haemolytic anaemia

These include:

- parasitic diseases, e.g. malaria
- ionising radiation, e.g. X-rays, radioactive isotopes
- destruction of blood trapped in tissues in, e.g., severe burns, crushing injuries
- physical damage to cells by, e.g., artificial heart valves, kidney dialysis machines.

Normocytic normochromic anaemia

In this type the cells are normal but the numbers are reduced and the proportion of reticulocytes in the blood may be increased as the body tries to restore erythrocyte numbers to normal. This occurs:

- in many chronic disease conditions, e.g. in chronic inflammation
- following severe haemorrhage
- in haemolytic disease.

Polycythaemia

There are an abnormally large number of erythrocytes in the blood. This increases blood viscosity, slows the rate of flow and increases the risk of intravascular clotting, ischaemia and infarction.

Relative increase in erythrocyte count

This occurs when the erythrocyte count is normal but the blood volume is reduced by fluid loss, e.g. excessive serum exudate from extensive superficial burns.

True increase in erythrocyte count

Physiological. Prolonged hypoxia stimulates erythropoiesis and the number of cells released into the normal volume of blood is increased. This occurs in people living

at high altitudes where the oxygen tension in the air is low and the partial pressure of oxygen in the alveoli of the lungs is correspondingly low. Each cell carries less oxygen so more cells are needed to meet the body's oxygen needs.

Pathological. The reason for this increase in circulating red cells, sometimes to twice the normal number, is not known. It may be secondary to other factors that cause hypoxia of the red bone marrow, e.g. cigarette smoking, pulmonary disease, bone marrow cancer.

Polycythaemia rubra vera

In this primary condition of unknown cause there is abnormal excessive production of the erythrocyte precursors, i.e. *myeloproliferation*. This raises the haemoglobin level and the haematocrit (relative proportion of cells to plasma). The blood viscosity is increased and may lead to hypertension and cerebral, coronary or mesenteric thrombosis. Aplastic anaemia and leukaemia may also be present.

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

This is the name of the condition in which the total blood leukocyte count is less than $4 \times 10^9/l$ ($4000/mm^3$).

Granulocytopenia (neutropenia)

This is a general term used to indicate an abnormal reduction in the numbers of circulating granulocytes (polymorphonuclear leukocytes), commonly called neutropenia because 40 to 75% of granulocytes are neutrophils. A reduction in the number of circulating granulocytes occurs when production does not keep pace with the normal removal of cells or when the life span of the cells is reduced. Extreme shortage or the absence of granulocytes is called *agranulocytosis*. A temporary reduction occurs in response to inflammation but the numbers are usually quickly restored. Inadequate granulopoiesis may be caused by:

- drugs, e.g. cytotoxic drugs, phenylbutazone, phenothiazines, some sulphonamides and antibiotics
- irradiation damage to granulocyte precursors in the bone marrow by, e.g., X-rays, radioactive isotopes
- diseases of red bone marrow, e.g. leukaemias, some anaemias
- severe microbial infections.

In conditions where the spleen is enlarged, excessive numbers of granulocytes are trapped, reducing the number in circulation. Neutropenia predisposes to severe infections that can lead to tissue necrosis, septicaemia and death. Septicaemia is the presence of significant numbers of active pathogens in the blood. The pathogens are commonly *commensals*, i.e. microbes that are normally present in the body but do not usually cause infection, such as those in the bowel.

Leukocytosis

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

Pathological leukocytosis exists when a blood leukocyte count of more than $11 \times 10^9/l$ ($11\,000/mm^3$) is sustained and is not consistent with the normal protective function. One or more of the different types of cell is involved.

Leukaemia

Leukaemia is a malignant proliferation of white blood cell precursors by 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 but in some cases it may be normal or even low. The proliferation of immature leukaemic blast cells crowds out other blood cells formed in bone marrow, causing anaemia, thrombocytopenia and leukopenia (pancytopenia).

Causes of leukaemia

Some causes of leukaemia are known but many cases cannot be accounted for. Some people may have a genetic predisposition that is triggered by environmental factors. Known causes include:

Ionising radiation. Radiation such as that produced by X-rays and radioactive isotopes causes malignant changes in the precursors of white blood cells. The DNA of the cells may be damaged and some cells 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 encountered in the general or work environment alter the DNA of the white cell precursors in the bone marrow. These include benzene and its derivatives, asbestos, cytotoxic drugs, chloramphenicol.

Viral infections.

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 (Fig. 4.2 and Table 4.5).

Acute leukaemias

These types usually have a sudden onset and affect the poorly differentiated and immature 'blast' cells (Fig. 4.2). They are aggressive tumours that reach a climax within a few weeks or months. The rapid progress of bone marrow invasion impairs its function and culminates in anaemia, haemorrhage and susceptibility to infection. The mucous membranes of the mouth and upper gastrointestinal tract are most commonly affected.

Acute myeloblastic leukaemia. This occurs at any age, but most commonly between 25 and 60 years.

Acute lymphoblastic leukaemia. This disease is most common in children under 10 years, although a number of cases may occur up to about 40 years of age.

Chronic leukaemias

These conditions are less aggressive than the acute forms and the leukocytes are more differentiated, i.e. at the 'cyte' stage (Fig. 4.2).

Chronic granulocytic leukaemia. There is a gradual increase in the number of immature granulocytes in the blood. In the later stages, anaemia, secondary haemorrhages, infections and fever become increasingly severe. It is slightly more common in men than women and usually occurs between the ages of 20 and 40 years. Although treatment may appear to be successful, death usually occurs within about 5 years.

Table 4.5 Types of leukaemia and the cells involved

Type of leukaemia	Type of cell involved
Myeloid (myelogenous myeloblastic)	Granulocytes, myelocytes, myeloblasts
Lymphocytic	Lymphocytes, lymphoblasts
Monocytic	Monocytes

Chronic lymphocytic leukaemia. There is enlargement of the lymph nodes and hyperplasia of lymphoid tissue throughout the body. The lymphocyte count is considerably higher than normal. Lymphocytes accumulate in the bone marrow and there is progressive anaemia and thrombocytopenia. It is three times more common in males than females and it occurs mainly between the ages of 50 and 70 years. Death is usually due to repeated infections of increasing severity, with great variations in survival times.

HAEMORRHAGIC DISEASES

Learning outcomes

After studying this section, you should be able to:

- indicate the main causes and effects of thrombocytopenia
- relate levels of vitamin K to clotting disorders
- explain the term disseminated intravascular coagulation, including its principal causes
- describe the physiological deficiencies present in the haemophilias
- explain the pattern of inheritance of haemophilia.

Thrombocytopenia

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

Reduced platelet production

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

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

Increased platelet destruction

A reduced platelet count occurs when production of new cells does not keep pace with destruction of damaged and worn out cells. This occurs in disseminated intravascular coagulation (see below) 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. Antiplatelet antibodies are formed that coat platelets, leading to platelet destruction and their removal from the circulation. 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. The severity of the disease varies from mild bleeding into the skin to severe haemorrhage. When the platelet count is very low there may be severe bruising, haematuria, gastrointestinal or cranial haemorrhages.

Secondary thrombocytopenic purpura. This may occur in association with red bone marrow diseases, excessive irradiation and some drugs, e.g. digoxin, chlorthiazides, quinine, sulphonamides.

Vitamin K deficiency

Vitamin K is required by the liver for the synthesis of many clotting factors and therefore deficiency predisposes to impairment of haemostasis (p. 67).

Haemorrhagic disease of the newborn

Spontaneous haemorrhage from the umbilical cord and intestinal mucosa occurs in babies when the stored vitamin K obtained from the mother before birth has been used up and the intestinal bacteria needed for its synthesis in the infant's bowel are not yet established. This is most likely to occur when the baby is premature.

Deficient absorption in adults

Vitamin K is fat soluble and bile salts are required in the colon for its absorption. Deficiency may occur when there is liver disease, prolonged obstruction to the biliary tract or in any other disease where fat absorption is impaired, e.g. coeliac disease.

Dietary deficiency

This is rare because a sufficient supply of vitamin K is usually synthesised in the intestine by bacterial action. However, deficiency may occur during treatment with drugs that sterilise the bowel.

Disseminated intravascular coagulation (DIC)

DIC is a common complication of a number of other disorders. The coagulation system is activated within the blood vessels, leading to formation of intravascular clots and deposition of fibrin within the tissues. Because of this consumption of clotting factors and platelets there is a consequent tendency to haemorrhage. The causes of DIC include:

- severe shock, especially when due to microbial infection
- septicaemia when endotoxins are released by Gram-negative bacteria
- severe trauma
- premature separation of placenta when amniotic fluid enters maternal blood
- acute pancreatitis when digestive enzymes are released into the blood
- malignant tumours with widely dispersed metastases.

Congenital disorders

The haemophilias

In each body cell, except gametes, there are 46 chromosomes arranged in 23 pairs, of which one pair are sex chromosomes. In the female, the two sex chromosomes are identical and are called X chromosomes. In the male, each cell has one X chromosome and one Y chromosome.

Female – XX
Male – XY

Each gamete (ovum and spermatozoon) has only 23 chromosomes, one from each of the 23 pairs. This means that each ovum has an X chromosome and each spermatozoon has either an X *or* a Y chromosome.

Fusion of an ovum with a spermatozoon carrying an X chromosome results in the conception of a female child, whereas if the spermatozoon bears a Y chromosome the child is male.

The Y chromosome is shorter than, and therefore carries fewer genes than, the X chromosome. 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 the synthesis of clotting factors VIII and IX is one example, and is therefore carried on X chromosomes only. If the gene is abnormal on one of a female's two X chromosomes, she is most likely to have a normal gene on her other X chromosome, which ensures production of normal clotting factors. A female who carries the faulty gene, even though the disease is not expressed in her, may pass the faulty gene on to her children and is said to be a *carrier*. If the gene is abnormal in a male, who has only one copy of the gene since he has only one X chromosome, he will therefore have haemophilia. Haemophilia is inherited as shown in Figure 4.12. This illustrates the possible genetic combinations of the children of a carrier mother (one normal gene and one faulty gene) and a normal father (one normal gene).

Sufferers from haemophilia experience repeated episodes of severe and prolonged bleeding at any site, with little evidence of trauma. Recurrent bleeding into joints is common, causing severe pain and, in the long term, cartilage is damaged.

The two main forms of haemophilia differ only in the clotting factor involved; the clinical picture in both is identical.

Haemophilia A. In this disease, factor VIII is abnormal and is less biologically active.

Haemophilia B (Christmas disease). This is the less common sex-linked genetic haemorrhagic disease. Factor IX is deficient, resulting in deficiency of thromboplastin.

von Willebrand's disease. In this disease a deficiency in the von Willebrand factor causes low levels of factor VIII. As the inheritance is not sex-linked, haemorrhages due to defective clotting occur equally in males and females.

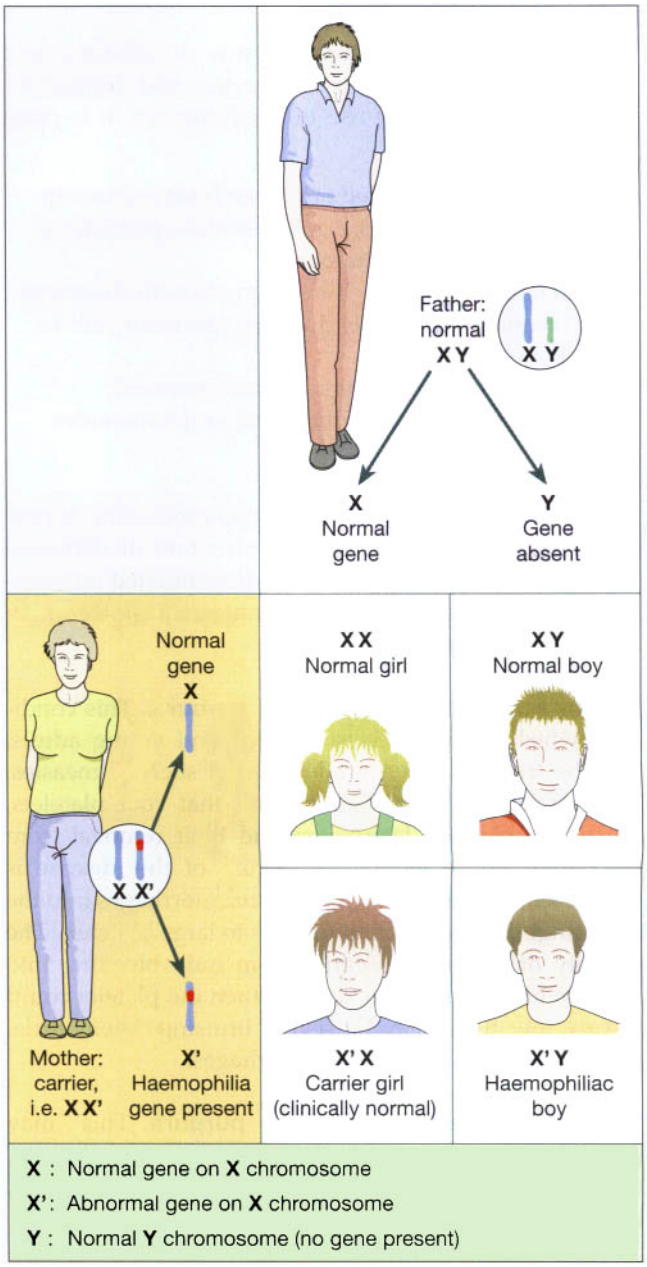


Figure 4.12 Transmission of the sex-linked haemophilia gene between generations.

5 The cardiovascular system

The cardiovascular system is divided for descriptive purposes into two main parts.

1. The *circulatory system*, consisting of the *heart*, which acts as a pump, and the *blood vessels* through which the *blood* circulates
2. The *lymphatic system*, consisting of *lymph nodes* and *lymph vessels*, through which colourless *lymph* flows.

The two systems communicate with one another and are intimately associated.

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

- the pulmonary circulation
- the systemic circulation.

The right side of the heart pumps blood to the lungs (the pulmonary circulation) where gas exchange occurs; i.e. CO_2 leaves the blood and enters the lungs, and O_2 leaves the lungs and enters the blood. The left side of the heart pumps blood into the systemic circulation, which supplies the rest of the body. Here, tissue wastes are passed into the blood for excretion, and body cells extract nutrients and O_2.

The circulatory system ensures a continuous flow of blood to all body cells, and its function is subject to continual physiological adjustments in order to maintain an adequate blood supply. Should the supply of oxygen and nutrients to body cells become inadequate, tissue damage occurs and cell death may follow.

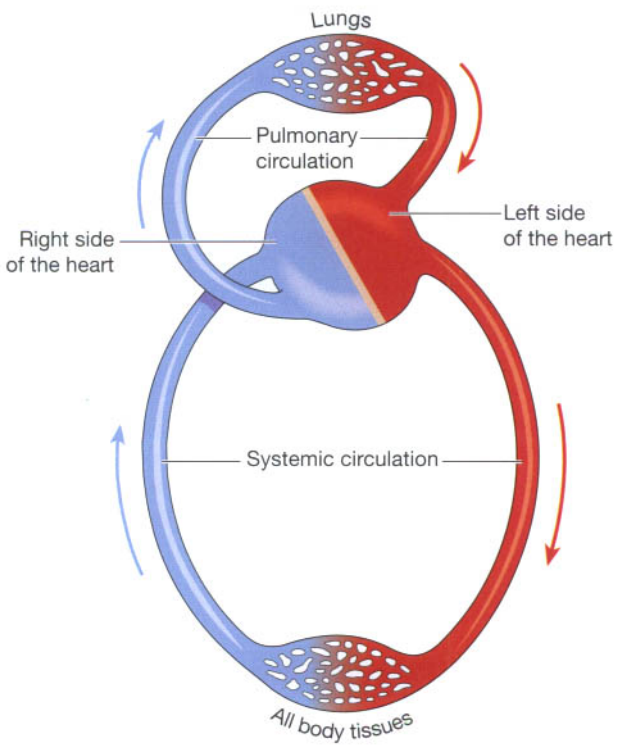


Figure 5.1 The relationship between the pulmonary and the systemic circulations.

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
- indicate the main factors controlling blood vessel diameter
- explain the mechanisms by which exchange of nutrients, gases and wastes occurs between the blood and the tissues.

The heart pumps blood into vessels that vary in structure, size and function, and there are several types: arteries, arterioles, capillaries, venules and veins (Fig. 5.2).

Arteries and arterioles

These are the blood vessels that transport blood away from the heart. They vary considerably in size and their walls consist of three layers of tissue (Fig. 5.3):

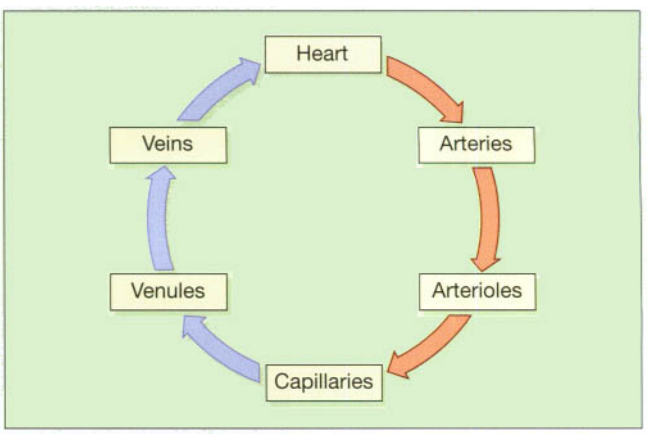


Figure 5.2 The relationship between the heart and the different types of blood vessel.

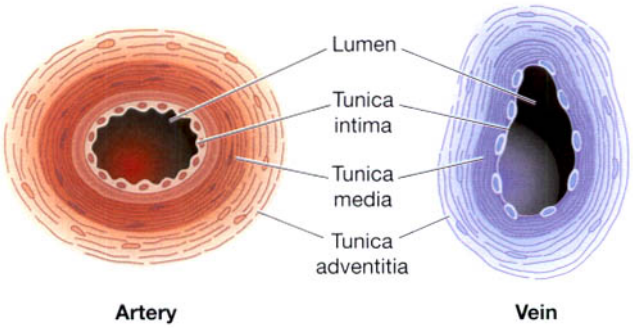


Figure 5.3 Structures of an artery and a vein.

- *tunica adventitia* or outer layer of fibrous tissue
- *tunica media* or middle layer of smooth muscle and elastic tissue
- *tunica intima* or inner lining of squamous epithelium called *endothelium*.

The amount of muscular and elastic tissue varies in the arteries depending upon their size. In the large arteries, sometimes called elastic arteries, the tunica media consists of more elastic tissue and less smooth muscle. These proportions gradually change 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. Arteries have thicker walls than veins and this enables them to withstand the high pressure of arterial blood.

Anastomoses and end-arteries

Anastomoses are arteries that form a link between main arteries supplying an area, e.g. the arterial supply to the palms of the hand (p. 102) and soles of the feet, the brain, the joints and, to a limited extent, the heart muscle. If one artery supplying the area is occluded anastomotic arteries provide a *collateral circulation*. This is most likely to provide an adequate blood supply when the occlusion occurs gradually, giving the anastomotic arteries time to dilate.

End-arteries are the arteries with no anastomoses or those beyond the most distal anastomosis, e.g. the branches from the circulus arteriosus (circle of Willis) in the brain or the central artery to the retina of the eye. When an end-artery is occluded the tissues it supplies die because there is no alternative blood supply.

Veins and venules

The veins are the blood vessels that return blood at low pressure to the heart. The walls of the veins are thinner than those of arteries but have the same three layers of tissue (Fig. 5.3). They are thinner because there is less muscle and elastic tissue in the tunica media. When cut, the veins collapse while the thicker-walled arteries remain open.

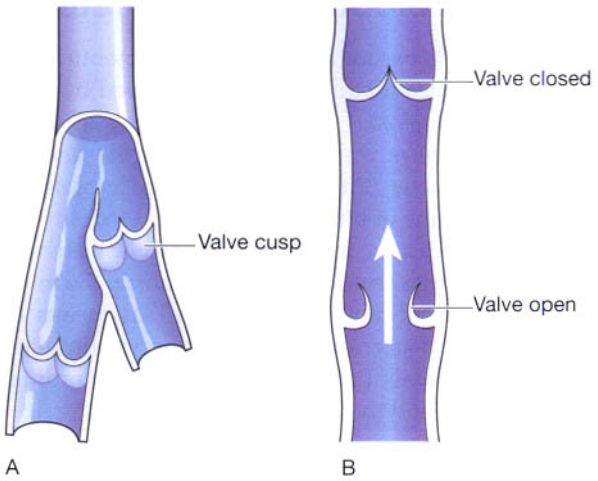


Figure 5.4 Interior of a vein: A. The valves and cusps. B. The direction of blood flow through a valve.

When an artery is cut blood spurts at high pressure while a slower, steady flow of blood escapes from a vein.

Some veins possess *valves*, which prevent backflow of blood, ensuring that it flows towards the heart (Fig. 5.4). 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. Valves are absent in very small and very large veins in the thorax and abdomen. They are formed by a fold of tunica intima strengthened by connective tissue. The cusps are *semilunar* in shape with the concavity towards the heart.

The smallest veins are called *venules*.

Capillaries and sinusoids

The smallest arterioles break up into a number of minute vessels called *capillaries*. Capillary walls consist of a single layer of endothelial cells through which water and other small-molecule substances can pass. Blood cells and large-molecule substances such as plasma proteins do not normally pass through capillary walls. The capillaries form a vast network of tiny vessels which link the smallest arterioles to the smallest venules. Their diameter is approximately that of an erythrocyte (7 μm). The capillary bed is the site of exchange of substances between the blood and the tissue fluid, which bathes the body cells.

Sinusoids are wider than capillaries and have extremely thin walls separating blood from the neighbouring cells. In some there are distinct spaces between the endothelial cells. Among the endothelial cells there may be many phagocytic macrophages, e.g. Kupffer cells in the liver. Sinusoids are found in bone marrow, endocrine glands, spleen and liver. Because of their larger lumen the blood pressure in sinusoids is lower than in capillaries and there is a slower rate of blood flow.

Control of blood vessel diameter

All blood vessels except capillaries have smooth muscle fibres in the tunica media which are supplied by nerves of the *autonomic nervous system*. These nerves arise from the *vasomotor centre* in the *medulla oblongata* and they change the diameter of the lumen of blood vessels, controlling the volume of blood they contain. Medium-sized and small arteries have more muscle than elastic tissue in their walls. In large arteries, such as the aorta, the middle layer is almost entirely elastic tissue. This means that small arteries and arterioles respond to nerve stimulation whereas the diameter of large arteries varies according to the amount of blood they contain.

Vasodilatation and vasoconstriction

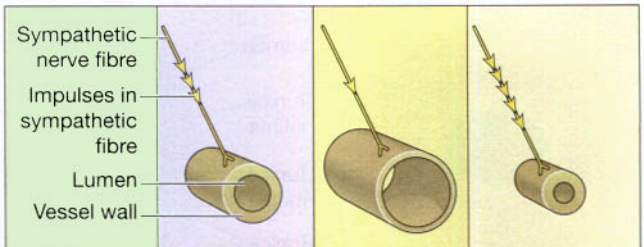
Sympathetic nerves supply the smooth muscle of the tunica media of blood vessels. There is no parasympathetic nerve supply to most blood vessels and therefore the diameter of the vessel lumen and the tone of the smooth muscle is determined by the degree of sympathetic nerve stimulation. There is always some nerve input to the smooth muscle in the vessel walls which can then be increased or decreased (Fig. 5.5). Decreased nerve stimulation causes the smooth muscle to relax, thinning the vessel wall and enlarging the lumen. This process is called *vasodilatation* and results in increased blood flow under less resistance. Conversely, when nervous activity is increased the smooth muscle of the tunica media contracts and thickens; this process is called *vasoconstriction*.

The blood vessels primarily responsible for providing resistance to blood flow are the small arterioles, the walls of which consist mainly of smooth muscle. A small change in their lumen results in considerable alteration in blood flow to the part of the body they supply. Arterioles provide the *peripheral resistance* to the flow of blood and are therefore called resistance vessels. This is important in maintaining homeostasis of blood pressure (p. 91).

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 involved. The most important factor in relation to flow of blood along vessels is peripheral resistance. The length of the vessels and viscosity of blood could also contribute but in health these are constant and are therefore not significant determinants of changes in blood flow.

Autoregulation

The accumulation of metabolites in local tissues also influences the degree of dilatation of arterioles. This mechanism ensures that local blood flow is increased or decreased in response to tissue need. For example in:



	Resting situation	Vasodilatation	Vasoconstriction
Sympathetic stimulation	Moderate	Decreased	Increased
Smooth muscle	Moderate tone	Relaxed	Contracted
Thickness of vessel wall	Moderate	Thinner	Thicker
Diameter of lumen	Moderate	Increased	Decreased
Peripheral resistance in arterioles	Moderate	Decreased	Increased

Figure 5.5 The relationship between sympathetic stimulation and blood vessel diameter.

- exercise; e.g. lactic acid accumulation in muscle causes vasodilatation
- hypoxia; vasodilatation follows an episode of reduced tissue blood flow
- tissue damage; e.g. in inflammation, mediators such as histamine, prostaglandins and bradykinin lead to vasodilatation (p. 376),
- situations where the circulation to vital organs, such as the brain and heart, is threatened.

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*. Vessels with thin walls and the endothelium of the others receive oxygen and nutrients by diffusion from the blood passing through them.

Internal respiration

Internal respiration (Fig. 5.6) is the exchange of gases between capillary blood and local body cells.

Oxygen is carried from the lungs to the tissues in chemical combination with haemoglobin as *oxyhaemoglobin*. The exchange in the tissues takes place between blood at the arterial end of the capillaries and the tissue

fluid and then between the tissue fluid and the cells. The process involved is that of diffusion from a higher concentration of oxygen in the blood to a lower concentration in the cells, i.e. down the concentration gradient.

Oxyhaemoglobin is an unstable compound and breaks up (dissociates) easily to liberate oxygen. Factors that increase dissociation include raised carbon dioxide content of tissue fluid, raised temperature and 2,3 diphosphoglycerate (DPG), a substance present in red blood cells. In active tissues there is an increased production of carbon dioxide and heat which leads to an increased availability of oxygen. In this way oxygen is available to the tissues in greatest need.

DPG is produced in red blood cells and causes haemoglobin to give up its oxygen more readily. Erythrocyte production of DPG increases in anaemia and other conditions, promoting oxygen release to the tissues.

Carbon dioxide is one of the waste products of cell metabolism and, towards the venous end of the capillary, it diffuses into the blood down the concentration gradient. Blood transports carbon dioxide to the lungs for excretion by three different mechanisms:

- dissolved in the water of the blood plasma—7%
- in chemical combination with sodium in the form of sodium bicarbonate—70%
- remainder in combination with haemoglobin—23%.

Cell nutrition

The nutrients required by the cells of the body are transported round the body in the blood plasma. In passing from the blood to the cells, the nutrients pass through the semipermeable capillary walls into the tissue fluid which bathes the cells, then through the cell membrane into the cell. The mechanism of the transfer of water and other substances from the blood capillaries depends mainly upon diffusion, osmosis and active transport.

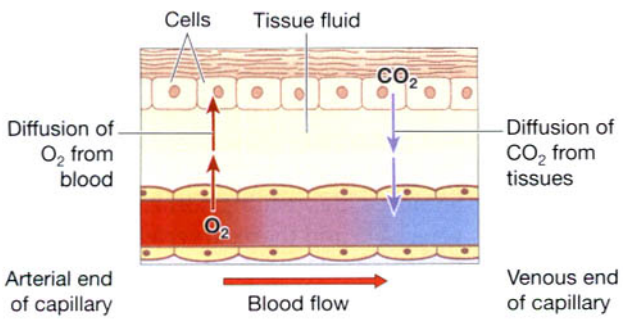


Figure 5.6 The exchange of gases in internal respiration.

Diffusion (p. 26)

The capillary walls consist of a single layer of epithelial cells that constitutes a *semipermeable membrane* which allows substances with small molecules to pass through into tissue fluid, and retains large molecules in the blood. Diffusible substances include dissolved oxygen and carbon dioxide, glucose, amino acids, fatty acids, glycerol, vitamins, mineral salts and water.

Osmosis (p. 27)

Osmotic pressure across a semipermeable membrane draws water from a dilute to a more concentrated solution in an attempt to establish a state of equilibrium. The force of the osmotic pressure depends on the *number of non-diffusible* particles in the solutions separated by the membrane. The main substances responsible for the osmotic pressure between blood and tissue fluid are the plasma proteins, especially albumin.

Capillary fluid dynamics

At the arterial end the capillary blood pressure, i.e. *hydrostatic pressure*, is about 35 mmHg (5 kPa). This causes the forward movement of blood and forces some water and solutes of small enough molecular size to pass out of the capillaries into the tissue spaces. The *osmotic pressure* in the capillaries is about 25 mmHg (3 kPa). This pressure draws water into the capillaries and is exerted mainly by plasma proteins of molecular size too large to pass through the capillary walls. The net outward pressure of 10 mmHg is the difference between the hydrostatic and osmotic pressures (Figs 5.7 and 5.8).

At the venous end of the capillaries hydrostatic pressure is reduced to about 15 mmHg (2 kPa) and the osmotic pressure remains the same, at 25 mmHg (3 kPa). The net

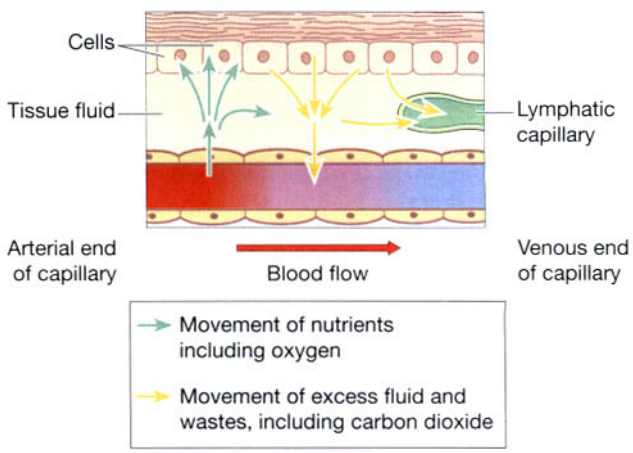


Figure 5.7 Diffusion of nutrients and waste products between capillaries and cells.

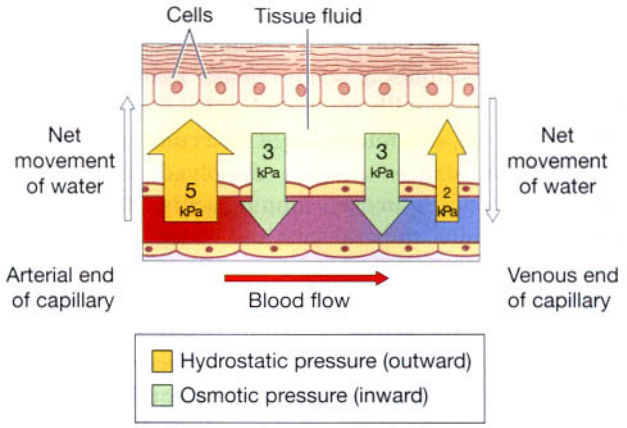


Figure 5.8 Effect of capillary pressures on water movement between capillaries and cells.

force moving water and solvents into the capillaries is again the difference between the two pressures, i.e. 10 mmHg.

This transfer of substances, including water, to the tissue spaces is a dynamic process. As blood flows slowly through the large network of capillaries from the arterial to the venous end, there is constant change. Not all the water and cell waste products return to the blood capillaries. The excess is drained away from the tissue spaces in the minute *lymph capillaries* which originate as blind-end tubes with walls similar to, but more permeable than, those of the blood capillaries (Fig. 5.7). Extra tissue fluid and some cell waste materials enter the lymph capillaries and are eventually returned to the bloodstream (Ch. 6).

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.

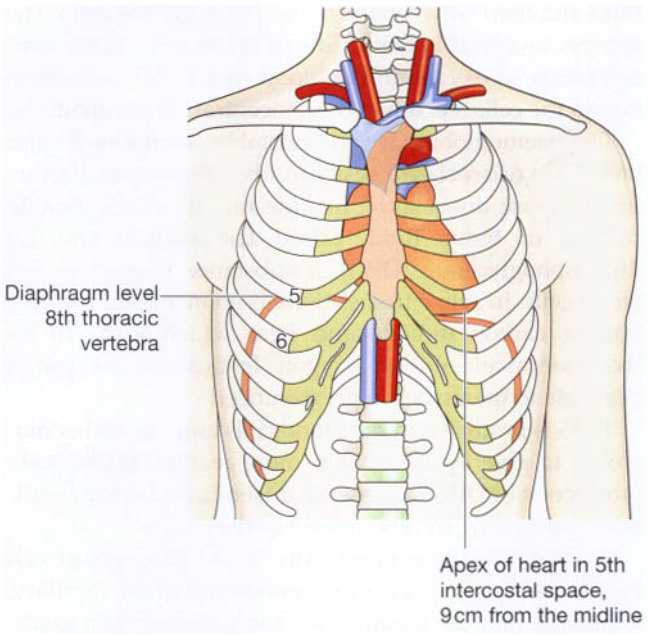


Figure 5.9 Position of the heart in the thorax.

The heart is a roughly cone-shaped hollow muscular organ. It is about 10 cm long and is about the size of the owner's fist. It weighs about 225 g in women and is heavier in men (about 310 g).

Position

The heart lies in the thoracic cavity in the mediastinum between the lungs (Fig. 5.9). It lies obliquely, a little more to the left than the right, and presents a *base* above, and an *apex* below. The apex is about 9 cm to the left of the midline at the level of the 5th intercostal space, i.e. a little below the nipple and slightly nearer the midline. The base extends to the level of the 2nd rib.

Organs associated with the heart (Fig. 5.10)

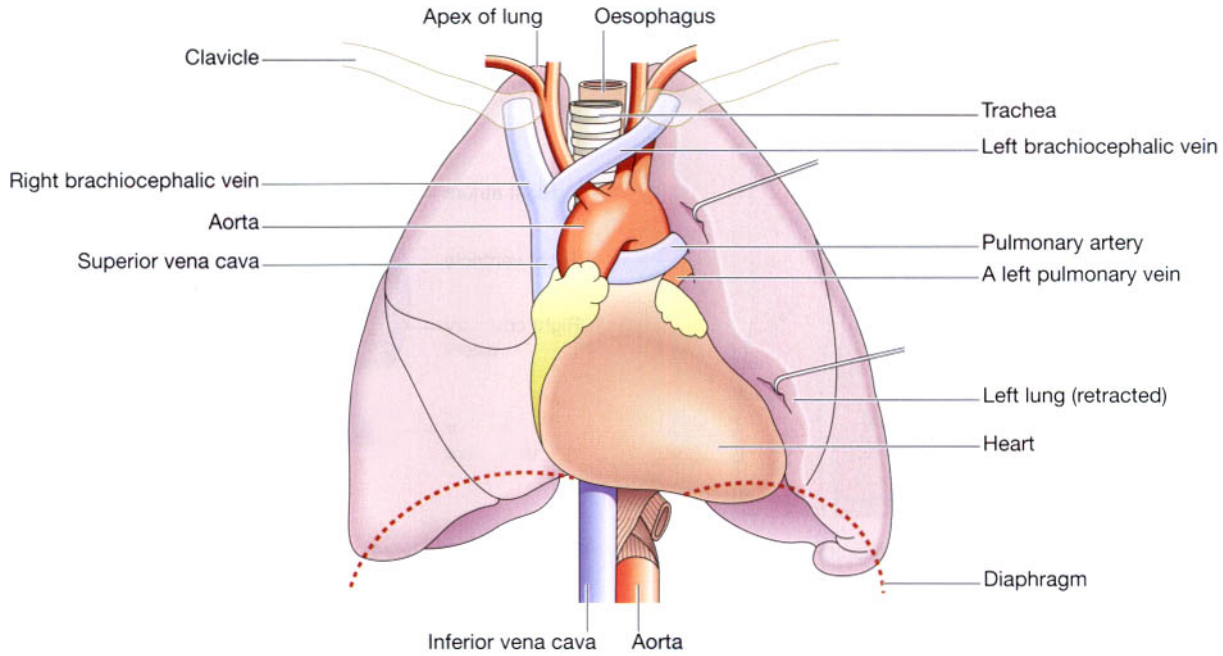
Inferiorly – the apex rests on the central tendon of the diaphragm

Superiorly – the great blood vessels, i.e. the aorta, superior vena cava, pulmonary artery and pulmonary veins

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 is composed of three layers of tissue (Fig. 5.11): pericardium, myocardium and endocardium.

Pericardium

The pericardium is made up of two sacs. The outer sac consists of fibrous tissue and the inner of a continuous double layer of serous membrane.

The outer fibrous sac is continuous with the tunica adventitia of the great blood vessels above and is adherent to the diaphragm below. Its inelastic, fibrous nature prevents overdistension of the heart.

The outer layer of the serous membrane, the *parietal pericardium*, lines the fibrous sac. The inner layer, the *visceral pericardium*, or epicardium, which is continuous with the parietal pericardium, is adherent to the heart muscle. A similar arrangement of a double membrane forming a closed space is seen also with the pleura, the membrane enclosing the lungs (see Fig. 10.16, p. 251).

The serous membrane consists of flattened epithelial cells. It secretes serous fluid into the space between the visceral and parietal layers which allows smooth movement between them when the heart beats. The space between the parietal and visceral pericardium is only a *potential space*. In health the two layers are in close association, with only the thin film of serous fluid between them.

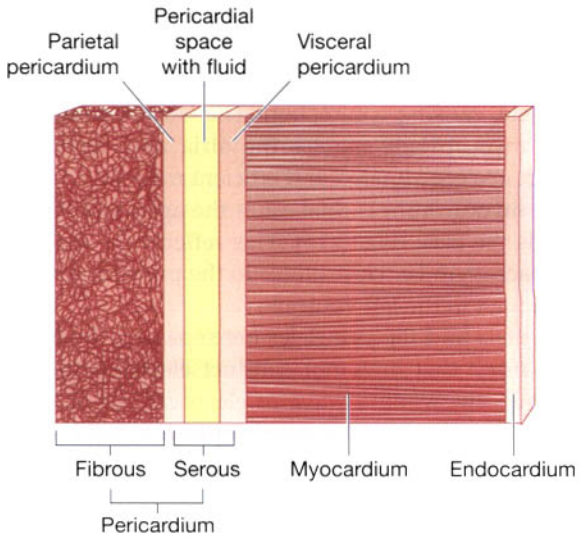


Figure 5.11 Layers of the heart wall.

Myocardium

The myocardium is composed of specialised cardiac muscle found only in the heart (Fig. 5.12). It is not under voluntary control but, like skeletal muscle, cross-stripes are seen on microscopic examination. Each fibre (cell) has a nucleus and one or more branches. The ends of the cells and their branches are in very close contact with the ends and branches of adjacent cells. Microscopically these

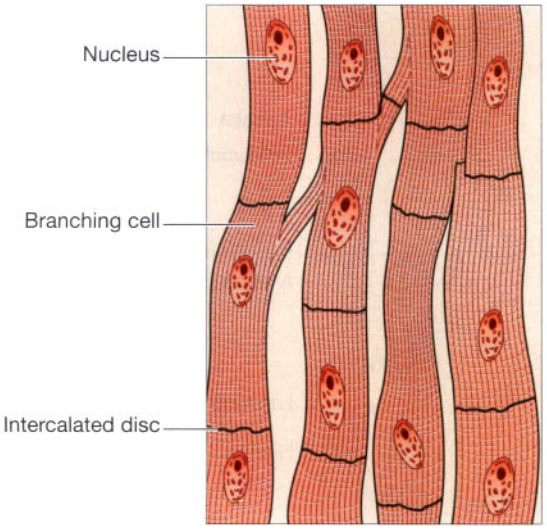


Figure 5.12 Cardiac muscle, with fibres separated.

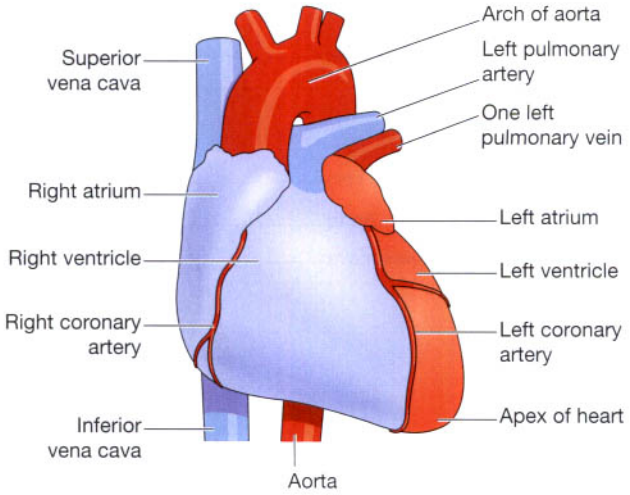


Figure 5.13 The heart and the great vessels, viewed from the front.

'joints', or *intercalated discs*, can be seen as thicker, darker lines than the ordinary cross-stripes. This arrangement gives cardiac muscle the appearance of being a sheet of muscle rather than a very large number of individual cells. Because of the end-to-end continuity of the fibres, each one does not need to have 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, causing contraction. The 'sheet' arrangement of the myocardium enables the atria and ventricles to contract in a coordinated and efficient manner.

The myocardium is thickest at the apex and thins out towards the base (Fig. 5.15). This reflects the amount of work each chamber contributes to the pumping of blood. It is thickest in the left ventricle.

The atria and the ventricles are separated by a *ring of fibrous tissue* that does not conduct electrical impulses. Consequently, when a wave of electrical activity passes over the atrial muscle, it can only spread to the ventricles through the conducting system which bridges the fibrous ring from atria to ventricles (p. 87).

Endocardium

This forms the lining of the myocardium and the heart valves. It is a thin, smooth, glistening membrane which permits smooth flow of blood inside the heart. It consists of flattened epithelial cells, continuous with the endothelium that lines the blood vessels.

Interior of the heart

The heart is divided into a right and left side by the *septum* (Fig. 5.14), a partition consisting of myocardium

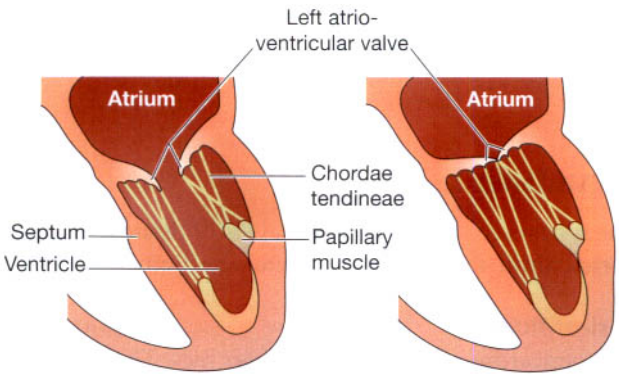


Figure 5.14 The left atrioventricular valve: A. Valve open. B. Valve closed.

covered by endocardium. After birth blood cannot cross the septum from one side to the other. Each side is divided by an *atrioventricular valve* into an upper chamber, the *atrium*, and a lower chamber, the *ventricle* (Fig. 5.15). The atrioventricular valves are formed by double folds of endocardium strengthened by a little fibrous tissue. The *right atrioventricular valve* (tricuspid valve) has three flaps or *cusps* and the *left atrioventricular valve* (mitral valve) has two cusps.

The valves between the atria and ventricles open and close passively according to changes in pressure in the chambers. They open when the pressure in the atria is greater than that in the ventricles. During *ventricular systole* (contraction) the pressure in the ventricles rises above that in the atria and the valves snap shut preventing backward flow of blood. The valves are prevented

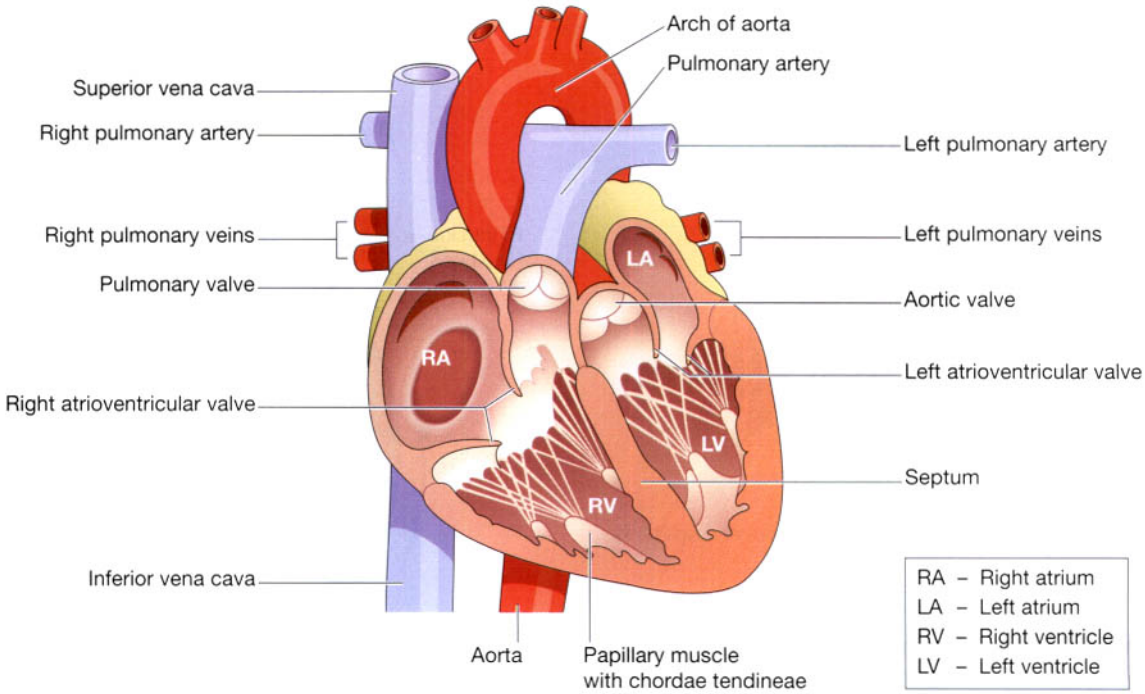


Figure 5.15 Interior of the heart.

from opening upwards into the atria by tendinous cords, called *chordae tendineae*, which extend from the inferior surface of the cusps to little projections of myocardium covered with endothelium, called *papillary muscles* (Fig. 5.14).

Flow of blood through the heart

(Fig. 5.16)

The two largest veins of the body, the *superior* and *inferior venae cavae*, empty their contents into the right atrium. This blood passes via the right atrioventricular valve into the right ventricle, and from there it is pumped into the *pulmonary artery* or *trunk* (the only artery in the body which carries deoxygenated blood). The opening of the pulmonary artery is guarded by the *pulmonary valve*, formed by three *semilunar cusps*. This valve prevents the back flow of blood into the right ventricle when the ventricular muscle relaxes. After leaving the heart the pulmonary artery divides into *left* and *right pulmonary arteries*, which 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 atrioventricular valve into the left ventricle, and from there it is pumped into the aorta, the first artery of

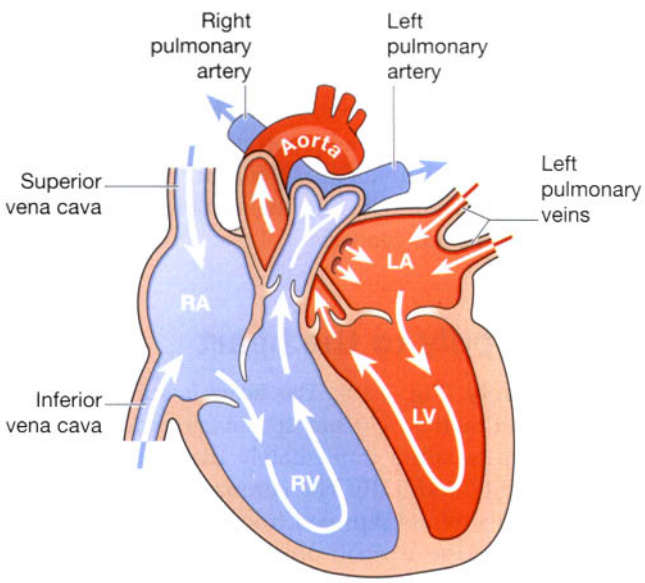


Figure 5.16 Direction of blood flow through the heart.

the general circulation. The opening of the aorta is guarded by the *aortic valve*, formed by three *semilunar cusps* (Fig. 5.17).

From this sequence of events it can be seen that the blood passes from the right to the left side of the heart via the lungs, or pulmonary circulation (Fig. 5.18). However, it should be noted that both atria contract at the same

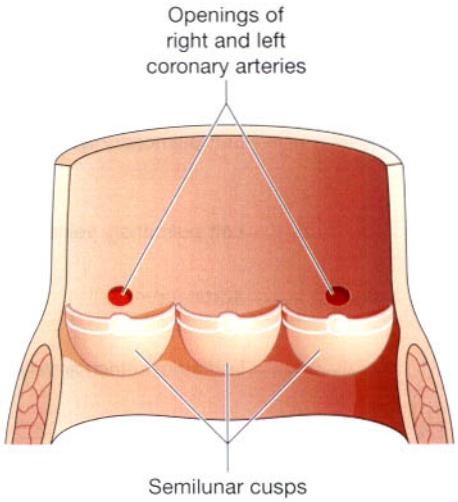


Figure 5.17 The aorta cut open to show the semilunar cusps of the aortic valve.

time and this is followed by the simultaneous contraction of both ventricles.

The muscle layer of the walls of the atria is very thin in comparison with that of the ventricles (Fig. 5.16). This is consistent with the amount of work it does. The atria, usually assisted by gravity, only propel the blood through the atrioventricular valves into the ventricles, whereas the ventricles actively pump the blood to the lungs and round the whole body. The muscle layer is thickest in the wall of the left ventricle.

The pulmonary trunk leaves the heart from the upper part of the right ventricle, and the aorta leaves from the upper part of the left ventricle.

Blood supply to the heart

Arterial supply (Fig. 5.19). 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 5.17 and 5.19). The coronary arteries receive about 5% of the blood pumped from the heart, although the heart comprises a small proportion of body weight. This large blood supply, especially to the left ventricle, highlights the importance of the heart to body function. The coronary arteries traverse the heart, eventually forming a vast network of capillaries.

Venous drainage. Most of the venous blood is collected into several small veins that join to form the *coronary sinus* which opens into the right atrium. The remainder passes directly into the heart chambers through little venous channels.

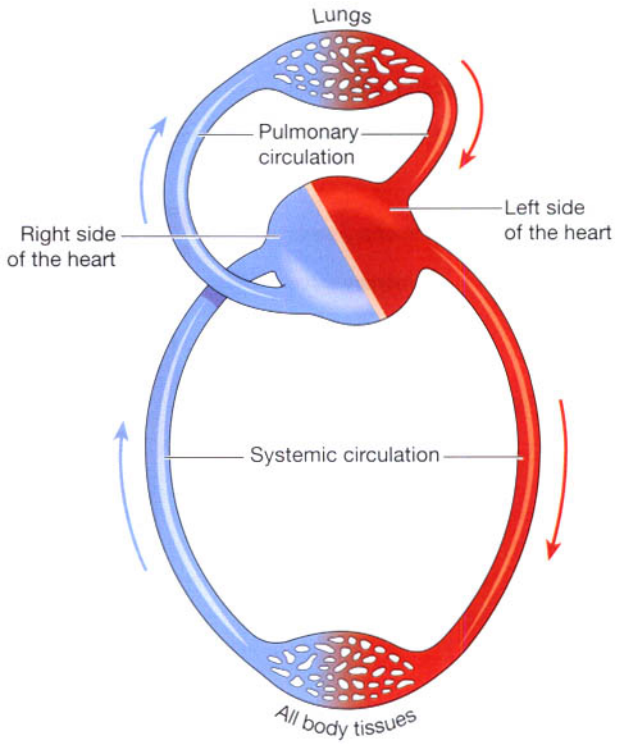


Figure 5.18 The relationship between the systemic and pulmonary circulations.

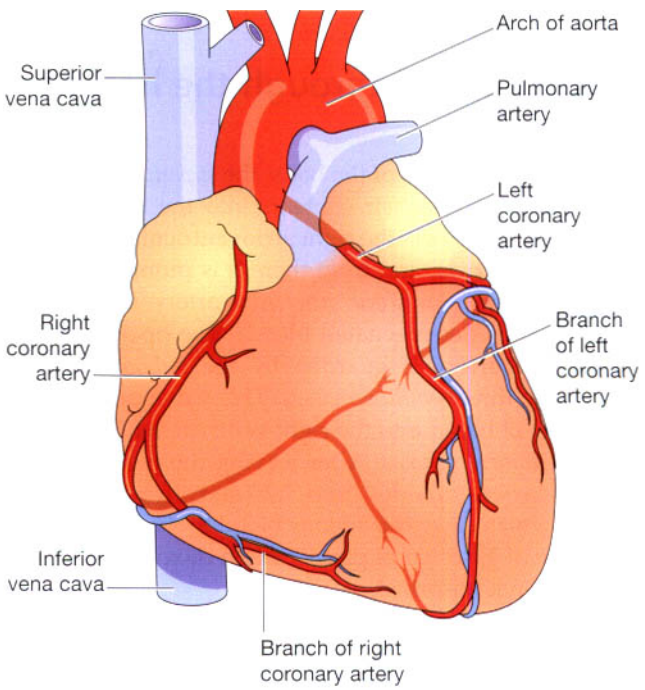
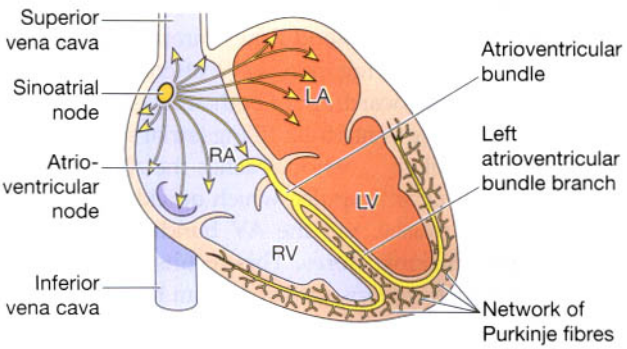


Figure 5.19 The coronary arteries.



Conducting system of the heart

The heart has an intrinsic system whereby the cardiac muscle is automatically stimulated to contract without the need for a nerve supply from the brain (Fig. 5.20). However, the intrinsic system can be stimulated or depressed by nerve impulses initiated in the brain and by circulating chemicals including hormones.

There are small groups of specialised neuromuscular cells in the myocardium which initiate and conduct impulses causing coordinated and synchronised contraction of the heart muscle.

Sinoatrial node (SA node)

This small mass of specialised cells is in the wall of the right atrium near the opening of the superior vena cava. The SA node is the *'pace-maker'* of the heart because it normally initiates impulses more rapidly than other groups of neuromuscular cells.

Atrioventricular node (AV node)

This small mass of neuromuscular tissue is situated in the wall of the atrial septum near the atrioventricular valves. Normally the AV node is stimulated by impulses that sweep over the atrial myocardium. However, it too is capable of initiating impulses that cause contraction but at a slower rate than the SA node.

Atrioventricular bundle (AV bundle or bundle of His) This is a mass of specialised fibres that originate from the AV node. The AV bundle crosses the fibrous ring that separates atria and ventricles then, 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 fine fibres, called the *Purkinje fibres*. The AV bundle, bundle branches and Purkinje fibres convey electrical impulses from the AV node to the apex of the myocardium where the wave of ventricular contraction begins, then sweeps upwards and outwards, pumping blood into the pulmonary artery and the aorta.

Nerve supply to the heart

In addition to the intrinsic impulses generated within the conducting system described above, the heart is influenced by autonomic nerves originating in the *cardiovascular centre* in the *medulla oblongata* which reach it through the autonomic nervous system. These consist of *parasympathetic* and *sympathetic nerves* and their actions are antagonistic to one another.

The *vagus nerves* (parasympathetic) supply mainly the SA and AV nodes and atrial muscle. Parasympathetic stimulation reduces the rate at which impulses are produced, decreasing the rate and force of the heart beat.

The *sympathetic nerves* supply the SA and AV nodes and the myocardium of atria and ventricles. Sympathetic stimulation *increases* the rate and force of the heart beat.

Factors affecting heart rate

Autonomic nervous system. As described above, the rate at which the heart beats is a balance of sympathetic and parasympathetic activity and this is the most important factor in determining heart rate.

Circulating chemicals. The hormones adrenaline and noradrenaline, secreted by the adrenal medulla, have the same effect as sympathetic stimulation, i.e. they increase the heart rate. Other hormones including thyroxine increase heart rate by their metabolic effect. Some drugs, dissolved gases and electrolytes in the blood may either increase or decrease the heart rate.

Position. When the person is upright, the heart rate is usually faster than when lying down.

Exercise. Active muscles need more blood than resting muscles and this is achieved by an increased heart rate and selective vasodilatation.

Emotional states. During excitement, fear or anxiety the heart rate is increased. Other effects mediated by the sympathetic nervous system may be present (see Fig. 7.43, p. 171).

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.

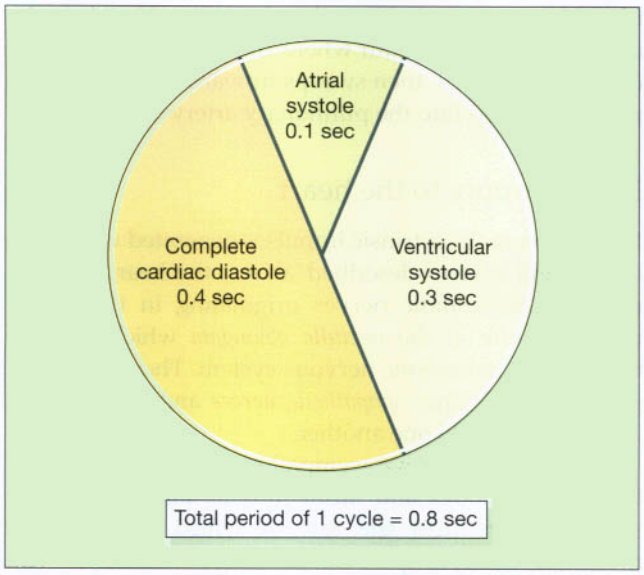


Figure 5.21 The stages of one cardiac cycle.

Temperature. The heart rate rises and falls with body temperature.

Baroreceptor reflex. See page 92.

The cardiac cycle

The function of the heart is to maintain a constant circulation of blood throughout the body. The heart acts as a pump and its action consists of a series of events known as the *cardiac cycle* (Fig. 5.21).

During each heartbeat, or cardiac cycle, the heart contracts and then relaxes. The period of contraction is called *systole* and that of relaxation, *diastole*.

Stages of the cardiac cycle

The normal number of cardiac cycles per minute ranges from 60 to 80. Taking 74 as an example each cycle lasts about *0.8 of a second* and consists of:

- *atrial systole*—contraction of the atria
- *ventricular systole*—contraction of the ventricles
- *complete cardiac diastole*—relaxation of the atria and ventricles.

It does not matter at which stage of the cardiac cycle a description starts. For convenience the period when the atria are filling has been chosen.

The superior vena cava and the inferior vena cava transport deoxygenated blood into the right atrium *at the same time* as the four pulmonary veins convey oxygenated blood into the left atrium. The atrioventricular valves are open and blood flows through to the ventricles. 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 s). When the wave of contraction reaches the AV node it is stimulated to emit an 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 which 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 s). The high pressure generated during ventricular contraction is greater than that in the aorta and forces the atrioventricular valves to close, preventing backflow of blood into the atria.

After contraction of the ventricles there is *complete cardiac diastole*, a period of *0.4 seconds*, when atria and ventricles are relaxed. During this time the myocardium recovers until it is able to contract again, and the atria refill in preparation for the next cycle.

The valves of the heart and of the great vessels open and close according to the pressure within the chambers of the heart. The AV valves are open while the ventricular muscle is relaxed during atrial filling and systole. When the ventricles contract there is a gradual increase in the pressure in these chambers, and when it rises above atrial pressure the atrioventricular valves close. When the ventricular pressure rises above that in the pulmonary artery and in the aorta, the pulmonary and aortic valves 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 (Fig. 5.22). This figure also shows how the walls of the aorta and other elastic arteries stretch and recoil in response to blood pumped into them.

Heart sounds

The individual is not usually conscious of his heartbeat, but if the ear or the diaphragm of a stethoscope is placed on the chest wall a little below the left nipple and slightly nearer the midline the heartbeat can be heard.

Two sounds, separated by a short pause, can be clearly distinguished. They are described in words as *'lub dup'*. The first sound, *'lub'*, is fairly loud and is due to the closure of the atrioventricular valves. This corresponds with ventricular systole. The second sound, *'dup'*, is softer and is due to the closure of the aortic and pulmonary valves. This corresponds with atrial systole.

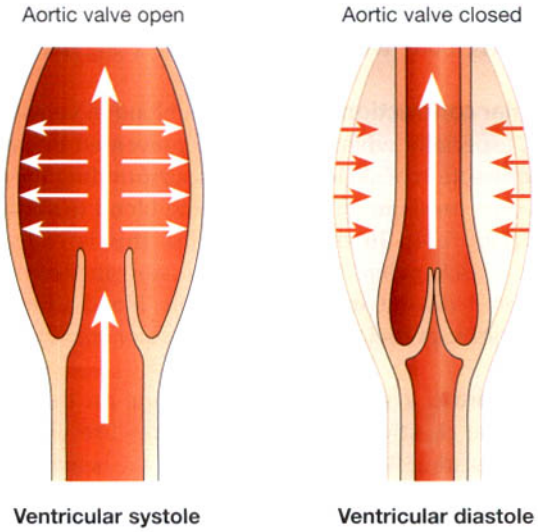


Figure 5.22 Diagram showing the elasticity of the walls of the aorta.

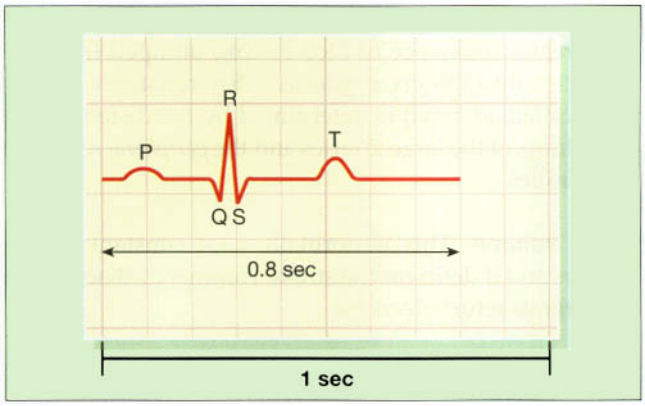


Figure 5.23 Electrocardiogram of one cardiac cycle.

Electrical changes in the heart

As the body fluids and tissues are good conductors of electricity, the electrical activity within the heart can be detected by attaching electrodes to the surface of the body. The pattern of electrical activity may be displayed on an oscilloscope screen or traced on paper. The apparatus used is an *electrocardiograph* and the tracing is an *electrocardiogram* (ECG).

The normal ECG tracing shows five waves which, by convention, have been named P, Q, R, S and T (Fig. 5.23).

The P wave arises when the impulse from the SA node sweeps over the atria.

The QRS complex represents the very rapid spread of the impulse from the AV node through the AV bundle and the Purkinje fibres and the electrical activity of the ventricular muscle.

The T wave represents the relaxation of the ventricular muscle.

The ECG described above originates from the SA node and is known as *sinus rhythm*. The rate of sinus rhythm is 60 to 100 beats per minute. A faster heart rate is called *tachycardia* and a slower heart rate, *bradycardia*.

By examining the pattern of waves and the time interval between cycles and parts of cycles, information about the state of the myocardium and the cardiac conduction system is obtained.

Cardiac output

The cardiac output is the amount of blood ejected from the heart. The amount expelled by each contraction of the ventricles 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 per minute, the cardiac output is 5 l/minute. This can be greatly increased to meet the demands of exercise to around 25 l/minute, and in athletes up to 35 l/minute. This increase during exercise is called the *cardiac reserve*.

When increased blood supply is needed to meet increased tissue requirements of oxygen and nutrients, heart rate and/or stroke volume can be increased.

Stroke volume

The stroke volume is determined by the volume of blood in the ventricles immediately before they contract, i.e. the ventricular end-diastolic volume (VEDV), sometimes called *preload*. This depends on the amount of blood returning to the heart through the superior and inferior venae cavae (the *venous return*). Increased VEDV leads to stronger myocardial contraction, and more blood is expelled. In turn the stroke volume and cardiac output rise. This capacity to increase the stroke volume with increasing VEDV is finite, and when the limit is reached, i.e. the cardiac output cannot match the venous return, the cardiac output decreases and the heart begins to fail (p. 119). Other factors that increase myocardial contraction include:

- increased stimulation of the sympathetic nerves innervating the heart
- hormones, e.g. adrenaline, noradrenaline, thyroxine.

Arterial blood pressure. This affects the stroke volume as 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.

Blood volume. This is normally kept constant by the kidneys and if deficient the stroke volume, cardiac output and venous return decrease.

Venous return

Venous return is the major determinant of cardiac output and, normally, the heart pumps out all blood returned to it. The force of contraction of the left ventricle ejecting blood into the aorta is not sufficient to return the blood through the veins and back to the heart. Other factors are involved.

The position of the body. Gravity assists the venous return from the head and neck when standing or sitting and offers less resistance to venous return from the lower parts of the body when an individual is lying flat.

Muscular contraction. Back flow of blood in veins of the limbs, especially when standing, is prevented by valves. The contraction of skeletal muscles surrounding the deep veins puts pressure on them, pushing blood towards the heart (Fig. 5.24). In the lower limbs, this is called the *skeletal muscle pump*. When the pressure in deep veins is lowered during muscle relaxation, blood flows into them from superficial veins through *communicating veins*.

The respiratory pump. During inspiration the expansion of the chest creates a negative pressure within the thorax, assisting flow of blood towards the heart. In addition, when the diaphragm descends during inspiration, the increased intra-abdominal pressure pushes blood towards the heart.

A summary of the factors that alter cardiac output is given in Box 5.1.

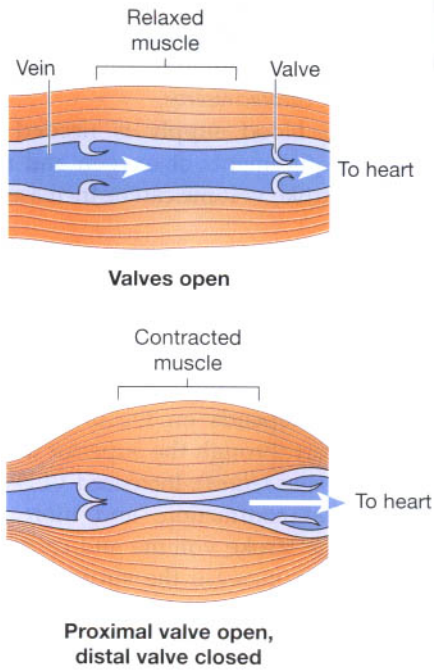


Figure 5.24 The flow of blood through a vein, aided by the contraction of skeletal muscle.

Box 5.1 Summary of factors affecting cardiac output

Cardiac output = Stroke volume × Heart rate

Factors affecting stroke volume:

- VEDV (ventricular end-diastolic volume)
- Venous return
  - position of the body
  - skeletal muscle pump
  - respiratory pump
- Strength of myocardial contraction
- Blood volume.

Factors affecting heart rate:

- Autonomic nerve stimulation
- Circulating chemicals
- Activity and exercise
- Emotional states
- Gender
- Age
- Body temperature
- Baroreceptor reflex.

BLOOD PRESSURE

Learning outcomes

After studying this section, you should be able to:

- define the term blood pressure
- describe the main control mechanisms for regulation of blood pressure.

Blood pressure is the force or pressure which the blood exerts on the walls of the blood vessels.

The systemic arterial blood pressure, usually called simply arterial blood pressure, is the result of the discharge of blood from the left ventricle into the already full aorta.

When the left ventricle contracts and pushes blood into the aorta the pressure produced within the arterial system is called the *systolic blood pressure*. In adults it is about 120 mmHg (millimetres of mercury) or 16 kPa (kilopascals).

When *complete cardiac diastole* occurs and the heart is resting following the ejection of blood, the pressure within the arteries is called *diastolic blood pressure*. In an adult this is about 80 mmHg or 11 kPa. The difference between systolic and diastolic blood pressures is the *pulse pressure*.

These figures vary according to the time of day, the posture, gender and age of the individual. During bedrest at night the blood pressure tends to be lower. 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 in the following manner:

$$BP = \frac{120}{80}\ \text{mmHg or } BP = \frac{16}{11}\ \text{kPa}$$

The elasticity of the artery walls. There is a considerable amount of elastic tissue in the arterial walls, especially in large arteries. Therefore, when the left ventricle ejects blood into the already full aorta, it distends, then the elastic recoil pushes the blood onwards. This distension and recoil occurs throughout the arterial system. During cardiac diastole the elastic recoil of the arteries maintains the diastolic pressure (Fig. 5.22).

Systemic arterial blood pressure maintains the essential flow of substances into and out of the organs of the body. Control of blood pressure especially to the vital organs is essential to maintain homeostasis.

The blood pressure is maintained within normal limits by fine adjustments. Blood pressure is determined by cardiac output and peripheral resistance:

$$\text{Blood pressure} = \frac{\text{Cardiac}}{\text{output}} \times \frac{\text{Peripheral}}{\text{resistance}}$$

Cardiac output

The cardiac output is determined by the stroke volume and the heart rate. Factors that affect the heart rate and stroke volume are described above, and they may increase or decrease cardiac output and, in turn, blood pressure. An increase in cardiac output raises both the systolic and diastolic pressure. An increase in stroke volume increases systolic pressure more than it does diastolic pressure.

Peripheral or arteriolar resistance

Arterioles are the smallest arteries and they have a tunica media composed almost entirely of smooth muscle which responds to nerve and chemical stimulation. Constriction and dilatation of the arterioles are the main determinants of peripheral resistance (p. 80). Vasoconstriction causes blood pressure to rise and vasodilatation causes it to fall.

When elastic tissue in the tunica media is replaced by inelastic fibrous tissue as part of the ageing process, blood pressure rises.

Dilatation and constriction of arterioles occurs selectively around the body, resulting in changes in the blood flow through organs according to their needs. The highest priorities are the blood supply to the brain and the heart muscle, and in an emergency, supplies to other parts of the body are reduced in order to ensure an adequate supply to these organs. Generally, changes in the amount of blood flowing to any organ depend on how active it is. A very active organ needs more oxygen and nutrients than a resting organ and it produces more waste materials for excretion.

Control of blood pressure (BP)

Blood pressure is controlled in two ways:

- short-term control, on a moment-to-moment basis, which mainly involves the baroreceptor reflex, to be discussed below, and also chemoreceptors and circulating hormones
- long-term control, which involves regulation of blood volume by the kidneys and the renin–angiotensin–aldosterone system (p. 223).

The cardiovascular centre (CVC) is a collection of interconnected neurones in the brain and is situated

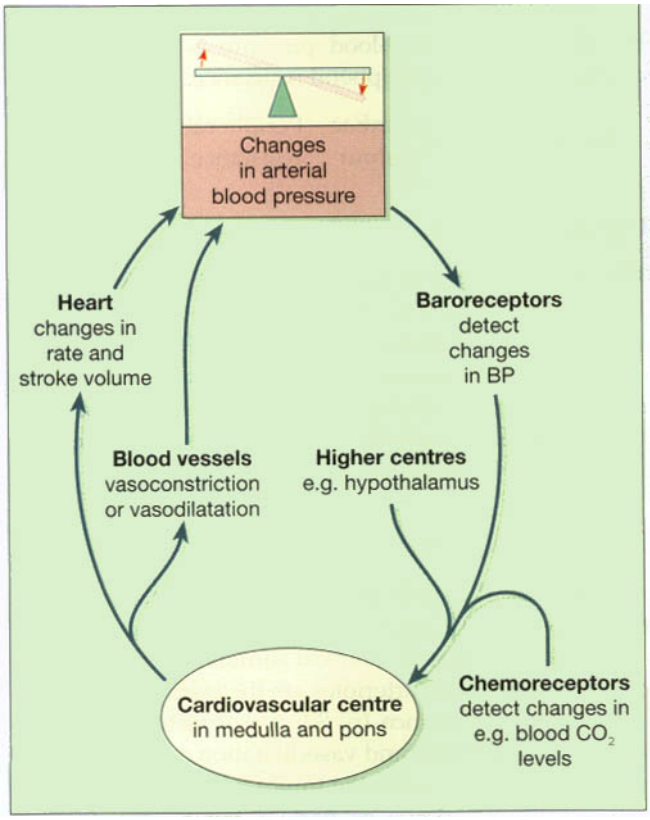


Figure 5.25 Summary of the main mechanisms in blood pressure control.

within the medulla and pons. The CVC receives, integrates and coordinates inputs from:

- baroreceptors (pressure receptors)
- chemoreceptors
- higher centres in the brain.

The CVC sends autonomic nerves (both sympathetic and parasympathetic) to the heart and blood vessels. It controls BP by slowing down or speeding up the heart rate and by dilating or constricting blood vessels. Activity in these fibres is essential for control of blood pressure (Fig. 5.25). The two divisions of the autonomic nervous system, the sympathetic and the parasympathetic systems, are described more fully in Chapter 7. Their actions relating to the heart and blood vessels are summarised in Table 5.1.

Table 5.1 The sympathetic and parasympathetic nervous systems

	Sympathetic stimulation	Parasympathetic stimulation
Heart	↑Rate ↑Strength of contraction	↓Rate ↓Strength of contraction
Blood vessels	Most constrict	There is little parasympathetic innervation to most blood vessels

Baroreceptors

These are nerve endings sensitive to pressure changes (stretch) within the vessel, situated in the arch of the aorta and in the carotid sinuses (Fig. 5.26) and are the body's principal moment-to-moment regulatory mechanism for controlling blood pressure. A rise in blood pressure in these arteries stimulates the baroreceptors, increasing their input to the CVC. The CVC responds by increasing parasympathetic nerve activity to the heart; this slows the heart down. At the same time, sympathetic stimulation to the blood vessels is inhibited, causing vasodilatation. The net result is a fall in systemic blood pressure. Conversely, if pressure within the aortic arch and carotid sinuses falls, the rate of baroreceptor discharge also falls. The CVC responds by increasing sympathetic drive to the heart to speed it up. Sympathetic activity in blood vessels is also increased, leading to vasoconstriction. Both these measures counteract the falling blood pressure. Baroreceptor control of blood pressure is also called the *baroreceptor reflex* (Fig. 5.26).

Chemoreceptors

These are nerve endings situated in the carotid and aortic bodies. They are primarily involved in control of respiration (p. 256). They are sensitive to changes in the levels of carbon dioxide, oxygen and the acidity of the blood (pH). Their input to the CVC influences its output only when severe disruption of respiratory function occurs or when arterial BP falls to less than 80 mmHg. The effects are outlined in Figure 5.27.

Higher centres in the brain

Input to the CVC from the higher centres is influenced by emotional states such as fear, anxiety, pain and anger that may stimulate changes in blood pressure.

The hypothalamus in the brain controls body temperature and influences the CVC which responds by adjusting the diameter of blood vessels in the skin—an important mechanism in determining heat loss and retention (p. 365).

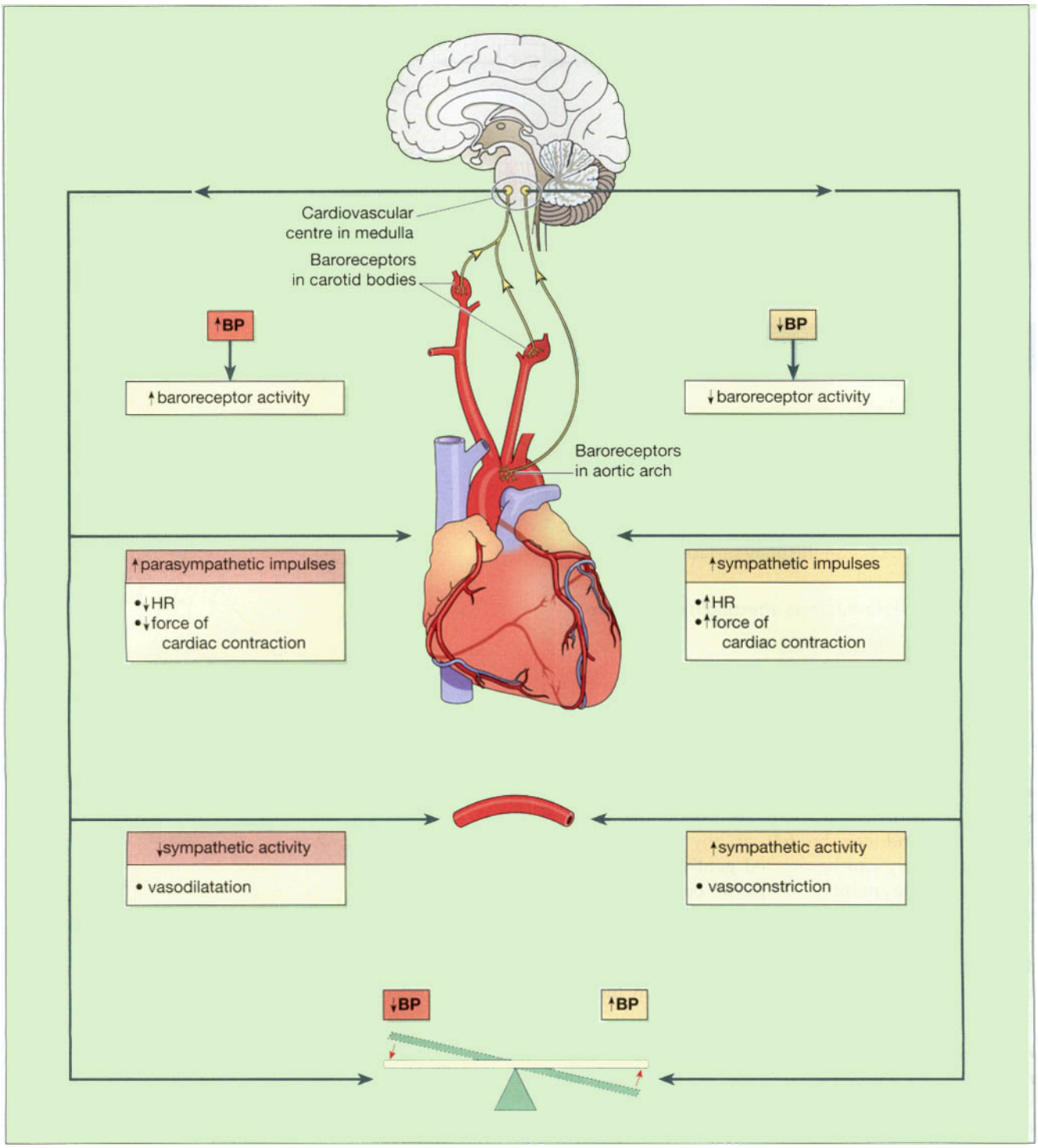


Figure 5.26 The baroreceptor reflex.

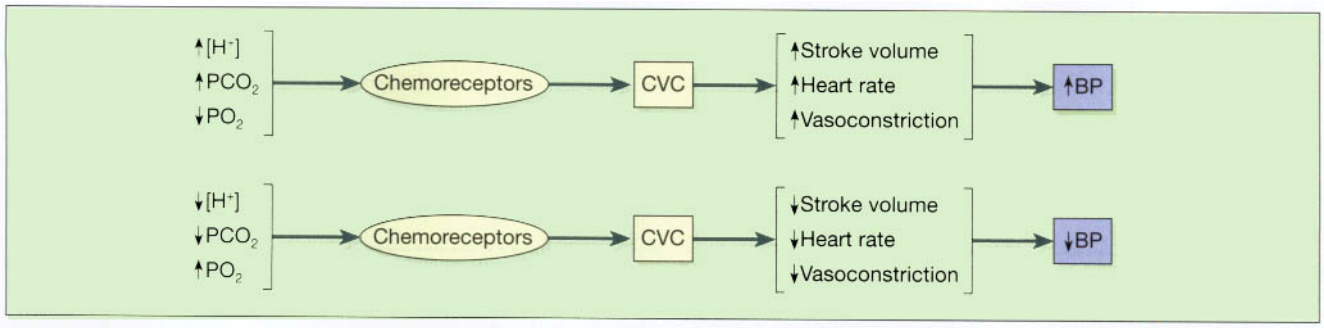


Figure 5.27 The relationship between stimulation of chemoreceptors and arterial blood pressure.

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 rate.

The pulse is a wave of distension and elongation felt in an artery wall due to the contraction of the left ventricle forcing about 60 to 80 millilitres of blood through the already full aorta and into the arterial system. When the aorta is distended, a wave passes along the walls of the arteries and can be felt at any point where a superficial artery can be pressed gently against a bone (Fig. 5.28). The number of pulse beats per minute normally represents the heart rate and varies considerably in different people and in the same person at different times. An average of 60 to 80 is common at rest. Information that may be obtained from the pulse includes:

- *the rate* at which the heart is beating
- *the regularity* with which the heartbeats occur, i.e. the length of time between beats should be the same
- *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* — the artery wall should feel soft and pliant under the fingers.

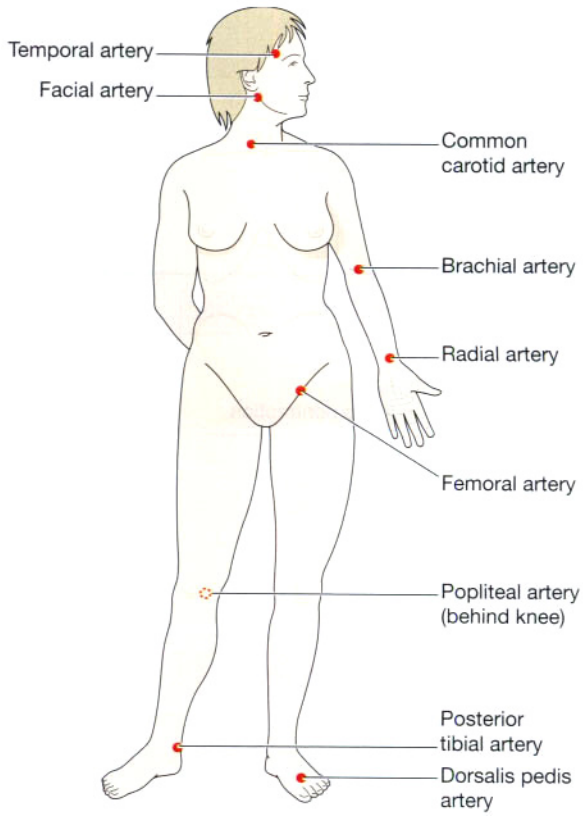


Figure 5.28 The main pulse points.

Factors affecting the pulse rate

In health, the pulse rate and the heart rate are identical. Factors influencing heart rate are summarised on page 87. In certain circumstances, the pulse may be less than the heart rate. This may occur, for example, if:

- the arteries supplying the peripheral tissues are narrowed or blocked and the blood therefore is not pumped through them with each heartbeat
- the heart is diseased or failing, and is unable to generate enough force, with each contraction, to circulate blood to the peripheral arteries.

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, including the heart itself
- describe the venous drainage involved in returning blood to the heart from the body
- describe the arrangement of blood vessels relating to the portal circulation
- explain the physiological importance of the portal circulation.

Although circulation of blood round the body is continuous (Fig. 5.18) it is convenient to describe it in two parts:

- pulmonary circulation
- systemic or general circulation.

Pulmonary circulation

This consists of the circulation of blood from the right ventricle of the heart to the lungs and back to the left atrium. In the lungs, carbon dioxide is excreted and oxygen is absorbed.

The pulmonary artery or trunk, carrying *deoxygenated blood*, leaves the upper part of the right ventricle of the heart. It passes upwards and divides into left and right pulmonary arteries at the level of the 5th thoracic vertebra.

The left pulmonary artery runs to the root of the left lung where it divides into two branches, one passing into each lobe.

The right pulmonary artery passes to the root of the right lung and divides into two branches. The larger branch carries blood to the middle and lower lobes, and the smaller branch to the upper lobe.

Within the lung these arteries divide and subdivide into smaller arteries, arterioles and capillaries. The interchange of gases takes place between capillary blood and air in the alveoli of the lungs (p. 255). In each lung the capillaries containing oxygenated blood join up and eventually form two veins.

Two pulmonary veins leave each lung, returning oxygenated blood to the left atrium of the heart. During atrial systole this blood passes 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 is returned to the right atrium of the heart by the *superior* and *inferior venae cavae*. Figure 5.32 shows the general positions of the aorta and the main arteries of the limbs. Figure 5.33 provides an overview of the venae cavae and the veins of the limbs.

The circulation of blood to the different parts of the body will be described in the order in which their arteries branch off the aorta.

Aorta

The aorta (Fig. 5.29) begins at 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 a little to the left of the thoracic vertebrae. At the level of the 12th thoracic vertebra it passes behind the diaphragm then downwards in the abdominal cavity to the level of the 4th lumbar vertebra, where it divides into the *right* and *left common iliac arteries*.

Throughout its length the aorta gives off numerous branches. Some of the branches are *paired*, i.e. there is a right and left branch of the same name, for instance, the right and left renal arteries supplying the kidneys, and some are single or *unpaired*, e.g. the coeliac artery.

Thoracic aorta

This part of the aorta is above the diaphragm and is described in three parts:

- ascending aorta
- arch of the aorta
- descending aorta in the thorax.

Ascending aorta

This is about 5 cm long and lies behind the sternum.

The right and left coronary arteries are its only branches and they arise from the aorta just above the level of the aortic valve (Fig. 5.17).

Arch of the aorta

The arch of the aorta is a continuation of the ascending aorta. It begins behind the manubrium of the sternum

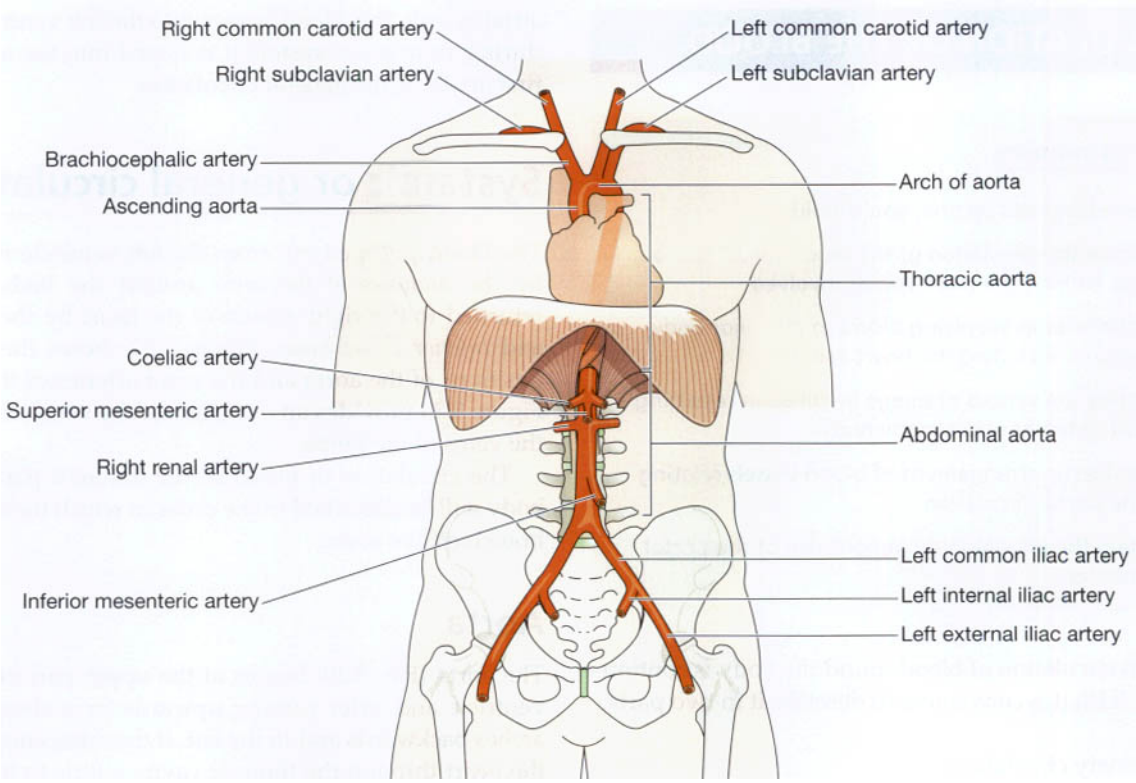


Figure 5.29 The aorta and its main branches.

and runs upwards, backwards and to the left in front of the trachea. It then passes downwards to the left of the trachea and is continuous with the descending aorta.

Three branches are given off from its upper aspect (Fig. 5.30):

- brachiocephalic artery or trunk
- left common carotid artery
- left subclavian artery.

The brachiocephalic artery is about 4 to 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.*

Circulation of blood to the head and neck

Arterial supply

The paired arteries supplying the head and neck are the *common carotid arteries* and the *vertebral arteries* (Fig. 5.31).

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 fascia, called the *carotid sheath.* At the level of the upper border of the thyroid cartilage they divide into:

- external carotid artery.
- internal carotid artery.

The carotid sinuses are slight dilatations at the point of division (bifurcation) of the common carotid arteries 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 vasomotor centre in the medulla oblongata (p. 92).

The carotid bodies are two small groups of specialised cells, called *chemoreceptors,* one lying in close association with each common carotid artery at its bifurcation. They are supplied by the glossopharyngeal nerves and their cells are stimulated by changes in the carbon dioxide and oxygen content of blood. The resultant nerve impulses initiate reflex adjustments of respiration through the respiratory centre in the medulla oblongata.

External carotid artery (Fig. 5.31). This artery supplies the superficial tissues of the head and neck, via a number of branches.

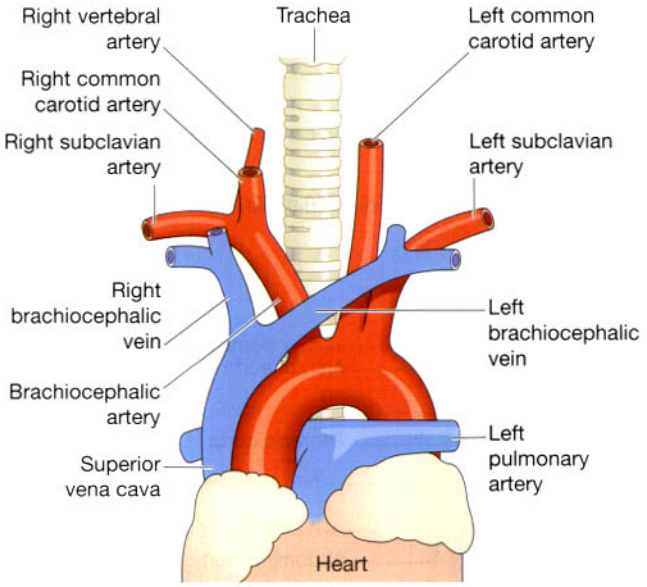


Figure 5.30 The arch of the aorta and its branches.

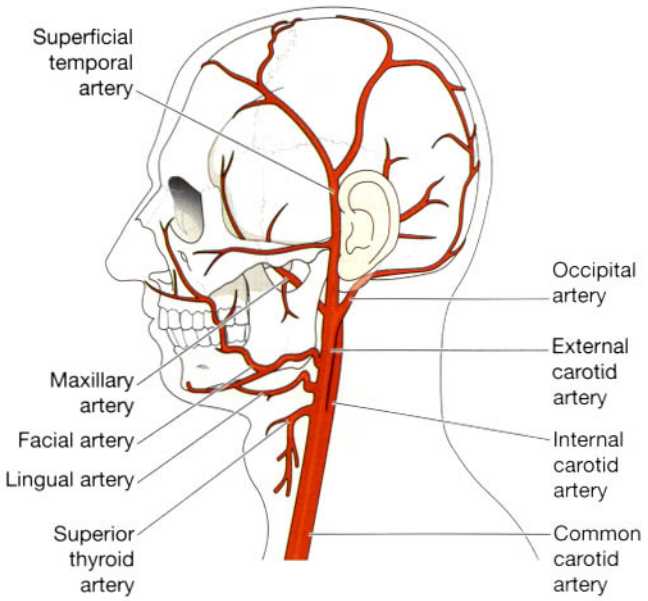


Figure 5.31 Main arteries of the left side of the head and neck.

- The *superior thyroid artery* supplies the thyroid gland and adjacent muscles.
- The *lingual artery* supplies the tongue, the lining membrane of 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 and structures in the mouth. The pulse may be felt where the artery crosses the jaw bone.
- 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 pulse may be felt in front of the upper part of the ear.
- The *maxillary artery* supplies the muscles of mastication and 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) (Fig. 5.34) which supplies the greater part 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). The greater part of the brain is supplied with arterial blood by an arrangement of arteries called the *circulus arteriosus* or the *circle of Willis* (Fig. 5.34). Four large arteries contribute to its formation: two *internal carotid arteries* and two *vertebral arteries* (Fig. 5.35). 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, then join to form the *basilar artery*. The arrangement in the circulus arteriosus (circle of Willis) is such that the brain as a whole receives an adequate blood supply when a contributing artery is damaged and during extreme movements of the head and neck.

Anteriorly, *two anterior cerebral arteries* arise from the internal carotid arteries and are joined by the *anterior communicating artery*.

Posteriorly, *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 by a *posterior communicating artery*, completing the circle. The *circulus arteriosus* is therefore formed by:

- 2 anterior cerebral arteries
- 2 internal carotid arteries
- 1 anterior communicating artery
- 2 posterior communicating arteries
- 2 posterior cerebral arteries
- 1 basilar artery.

From this circle, the *anterior cerebral arteries* pass forward to supply the anterior part of the brain, the *middle cerebral arteries* pass laterally to supply the sides of the

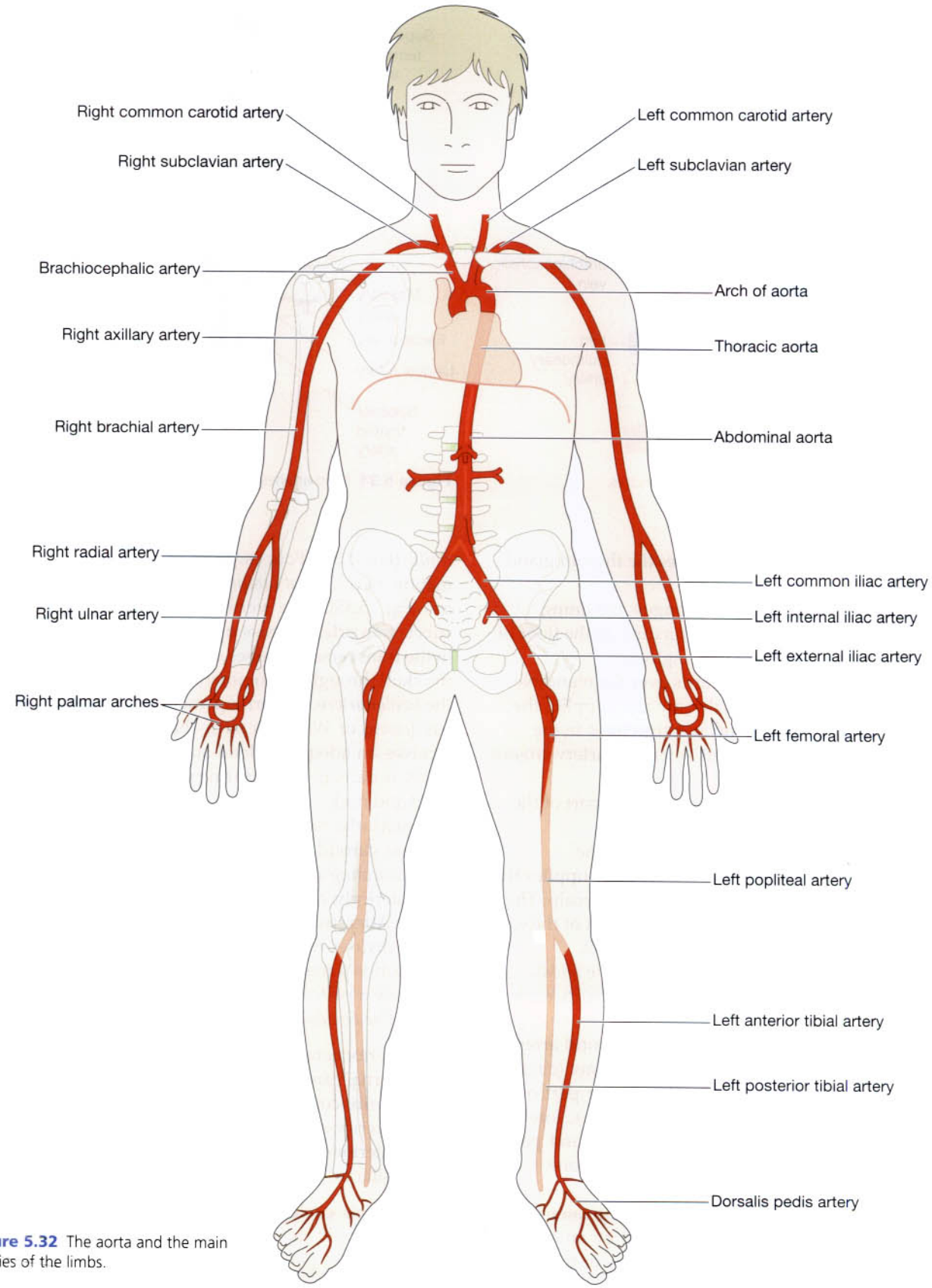


Figure 5.32 The aorta and the main arteries of the limbs.

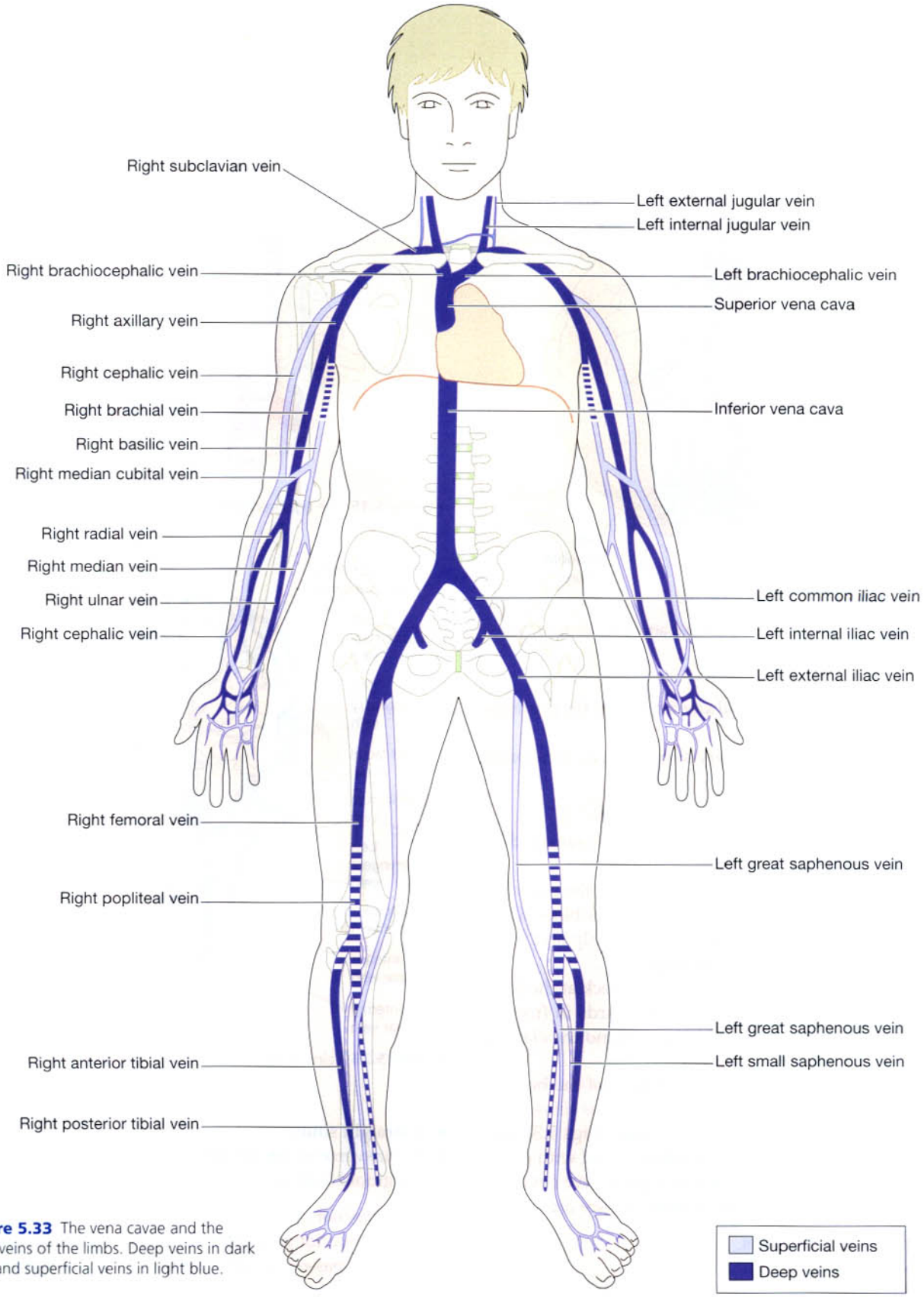


Figure 5.33 The vena cavae and the main veins of the limbs. Deep veins in dark blue and superficial veins in light blue.

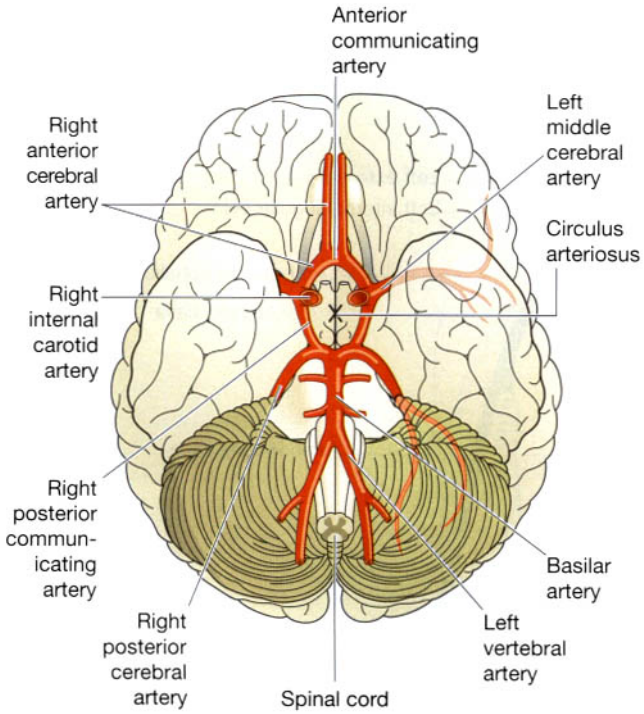


Figure 5.34 Arteries forming the circulus arteriosus (circle of Willis) and its main branches to the brain.

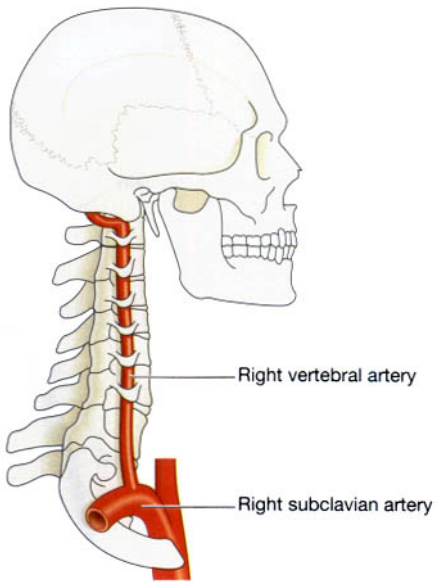


Figure 5.35 The right vertebral artery.

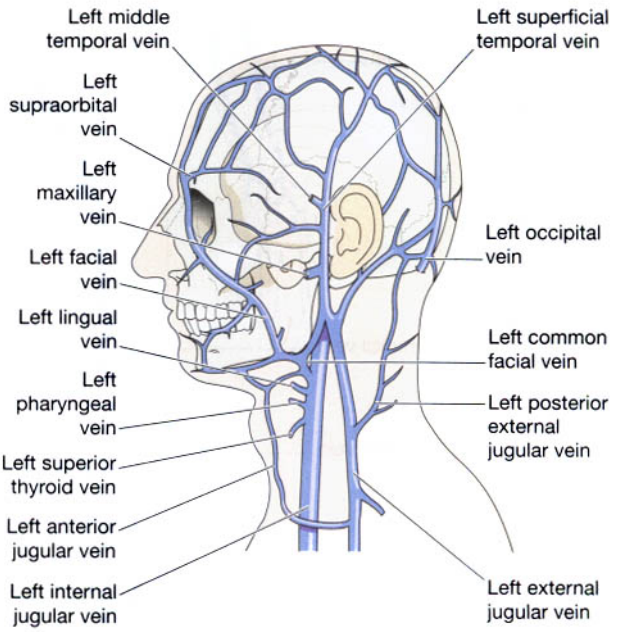


Figure 5.36 Veins of the left side of the head and neck.

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 from the head and neck

The 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. 5.36).

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, then behind the clavicle before entering the *subclavian vein*.

The venous blood from the deep areas of the brain is collected into channels called the *dural venous sinuses*.

The dural venous sinuses of the brain (Figs 5.37 and 5.38) are formed by layers of dura mater lined with endothelium. The dura mater is the outer protective covering of the brain (p. 147). The main venous sinuses are:

- 1 superior sagittal sinus
- 1 inferior sagittal sinus
- 1 straight sinus
- 2 transverse or lateral sinuses
- 2 sigmoid sinuses.

The *superior sagittal sinus* carries the venous blood from the superior part of the brain. It begins in the frontal region and passes directly backwards in the midline of

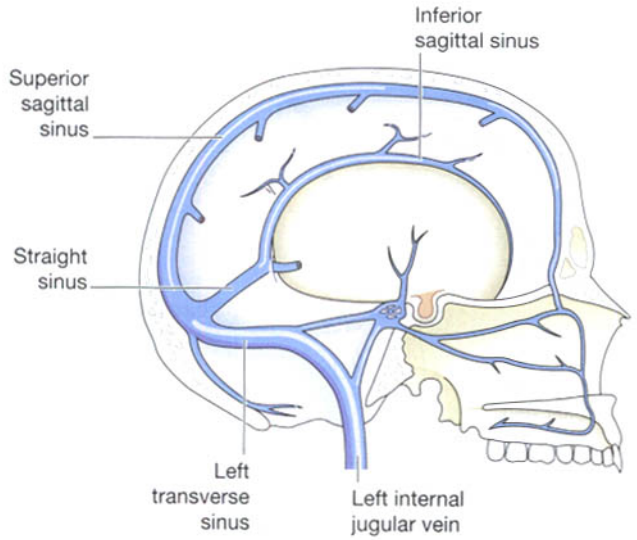


Figure 5.37 Venous sinuses of the brain viewed from the right.

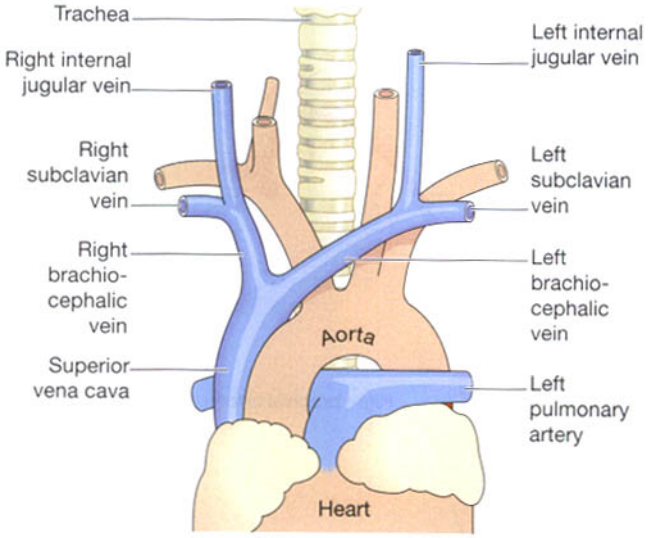


Figure 5.39 The superior vena cava and the veins which form it.

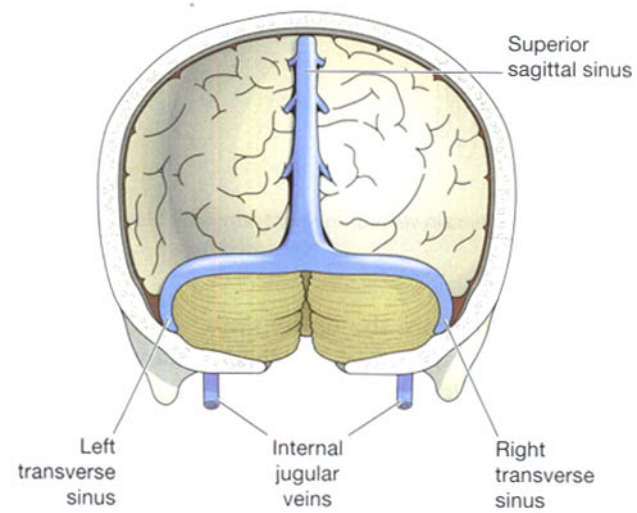


Figure 5.38 Venous sinuses of the brain viewed from above.

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 forward 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 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. 5.39).

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 ends in the right atrium of the heart.

Circulation of blood to the upper limb

Arterial supply

The subclavian arteries. The right subclavian artery arises from the brachiocephalic artery; the left branches from the arch of the aorta. They are slightly arched and pass behind the clavicles and over the first ribs before entering the axillae, where they continue as the *axillary arteries* (Fig. 5.40).

Before entering the axilla each subclavian artery gives off two branches: the *vertebral artery*, which passes upwards to supply the brain, and the *internal thoracic artery*, which supplies the breast and a number of structures in the thoracic cavity.

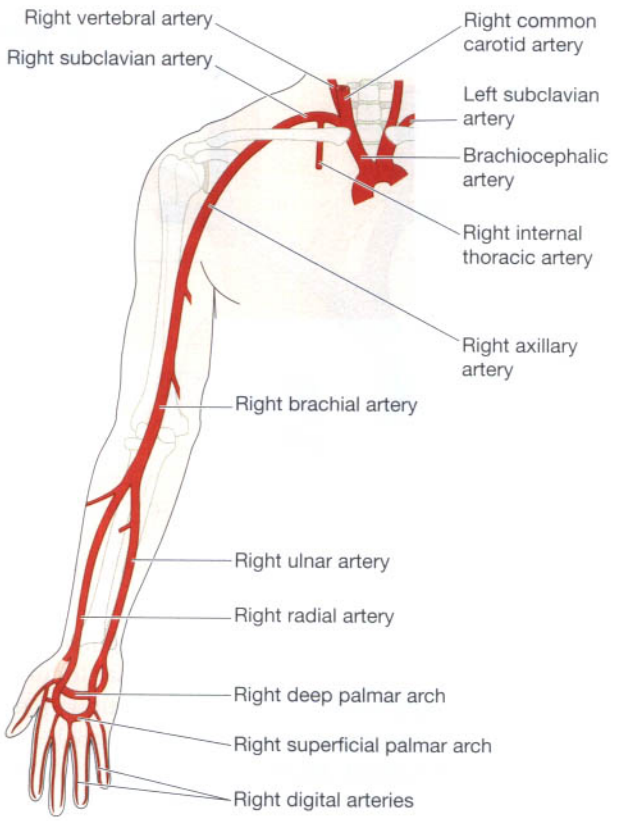


Figure 5.40 The main arteries of the right arm.

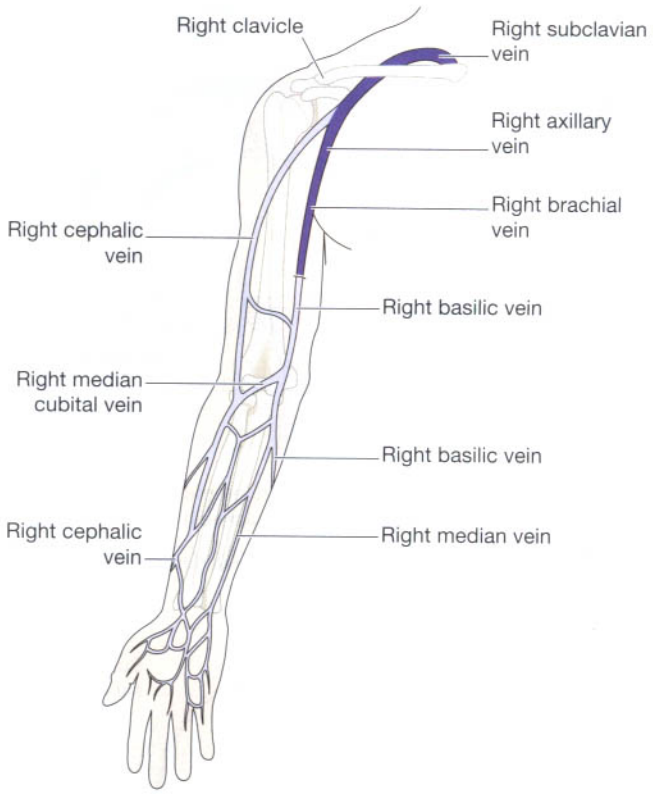


Figure 5.41 The main veins of the right arm. Dark blue indicates deep veins.

The *axillary artery* is a continuation of the subclavian artery and lies in the axilla. The first part lies deeply; then it runs more superficially to become the *brachial artery*.

The *brachial artery* is a continuation of the axillary artery. It 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 *radial* and *ulnar arteries*.

The *radial artery* passes down the radial or lateral side of the forearm to the wrist. Just above the wrist it lies superficially and can be felt in front of the radius, where the radial pulse is palpable. The artery then passes between the first and second metacarpal bones and enters the palm of the hand.

The *ulnar artery* runs downwards on the ulnar or medial 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.

Branches from the axillary, brachial, radial and ulnar arteries supply all the structures in the upper limb.

Venous return from the upper limb

The veins of the upper limb are divided into two groups: deep and superficial veins (Fig. 5.41).

The *deep veins* follows 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 can be easily seen. 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 receives 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 receives blood from the medial aspect of the hand, forearm and arm. There are many small veins which link the cephalic and basilic veins.

The *median vein* is a small vein that is 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 when the subclavian and internal jugular veins unite. 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 terminates in the right atrium. It is about 7 cm long and passes downwards along the right border of the sternum.

Descending aorta in the thorax

This part of the aorta is continuous with the arch of the aorta and begins at the level of the 4th thoracic vertebra. It extends downwards on the anterior surface of the bodies of the thoracic vertebrae (Fig. 5.42) 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* which supply the walls of the thoracic cavity and the organs within the cavity, including:

- *bronchial arteries* that supply the bronchi and their branches, connective tissue in the lungs and the lymph nodes at the root of the lungs
- *oesophageal arteries* that supply the oesophagus
- *intercostal arteries* that run along the inferior border of the ribs and supply the intercostal muscles, some muscles of the thorax, the ribs, the skin and its underlying connective tissues.

Venous return from the thoracic cavity

Most of the venous blood from the organs in the thoracic cavity is drained into the *azygos vein* and the *hemiazygos vein* (Fig. 5.43). Some of the main veins which join them are the *bronchial, oesophageal* and *intercostal veins*. The azygos

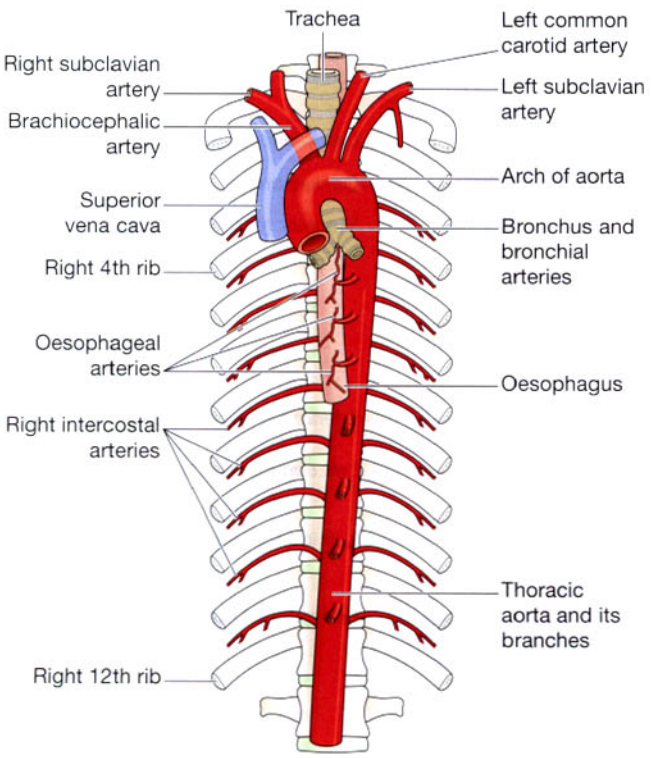


Figure 5.42 The aorta and its main branches in the thorax.

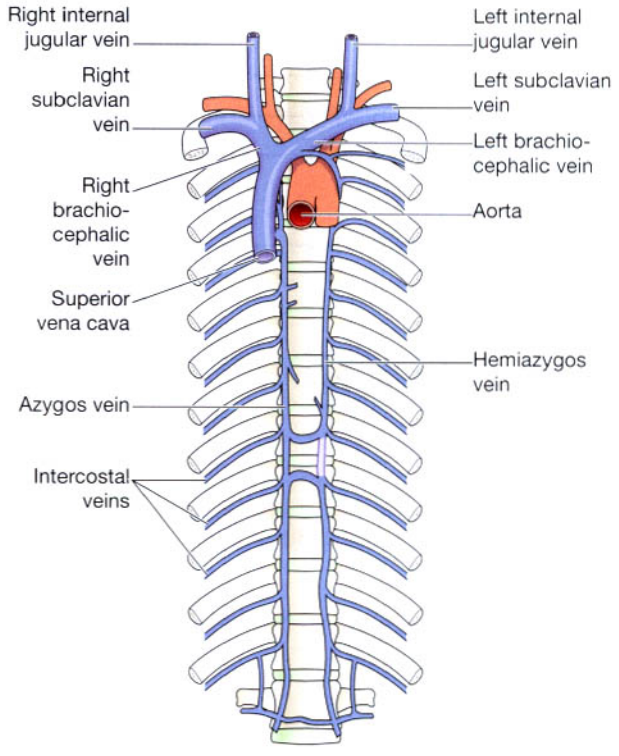


Figure 5.43 The superior vena cava and the main veins of the thorax.

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. 12.50, p. 321).

Abdominal aorta

The abdominal aorta is a continuation of the thoracic aorta. The name changes when the aorta enters the abdominal cavity by passing behind the diaphragm at the level of the 12th thoracic vertebra. It descends in front of the bodies of the vertebrae to the level of the 4th lumbar vertebra, where it divides into the *right* and *left common iliac arteries* (Fig. 5.44).

When a branch of the abdominal aorta supplies an organ it is only named here and is described in more detail in association with the organ. However, illustrations showing the distribution of blood from the coeliac, superior and inferior mesenteric arteries are presented here (Figs 5.45 and 5.46).

Many branches arise from the abdominal aorta, some of which are *paired* and some *unpaired*.

Paired branches

- *Inferior phrenic arteries* supply the diaphragm.
- *Renal arteries* supply the kidneys and give off branches, the *suprarenal arteries*, to supply the adrenal glands.
- *Testicular arteries* supply the testes in the male.
- *Ovarian arteries* supply the ovaries in the female.

The testicular and ovarian arteries are much longer than the other paired branches. This is because the testes and the ovaries begin their development in the region of the kidneys. As they grow they descend into the scrotum and the pelvis respectively and are accompanied by their blood vessels.

Unpaired branches

The *coeliac artery* (Fig. 5.44) is a short thick artery about 1.25 cm long. It arises immediately below the diaphragm and divides into three branches:

- *left gastric artery*: supplies the stomach
- *splenic artery*: supplies the pancreas and the spleen
- *hepatic artery*: supplies the liver, gall bladder and parts of the stomach, duodenum and pancreas.

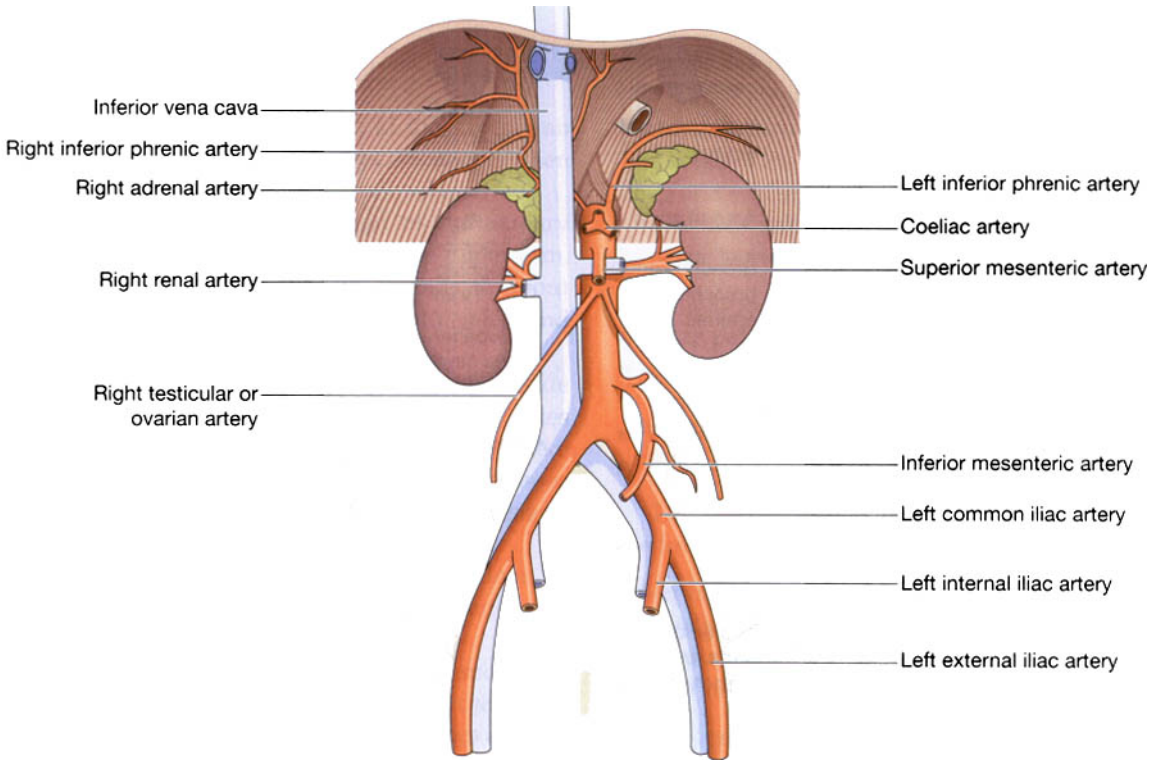


Figure 5.44 The abdominal aorta and its branches.

The *superior mesenteric artery* (Fig. 5.44) branches from the aorta between the coeliac artery and the renal arteries. It supplies the whole of the small intestine and the proximal half of the large intestine.

The *inferior mesenteric artery* (Fig. 5.44) 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 from the abdominal organs

The *inferior vena cava* is formed when *right* and *left common iliac veins* join at the level of the body of the 5th lumbar vertebra. This is the largest vein in the body and it conveys blood from all parts of the body below the diaphragm to the right atrium of the heart. It passes through the central tendon of the diaphragm at the level of the 8th thoracic vertebra.

Paired testicular, ovarian, renal and adrenal veins join the inferior vena cava.

Blood from the remaining organs in the abdominal cavity passes through the liver via the *portal circulation* before entering the inferior vena cava (Fig. 5.45).

Portal circulation

In all the parts of the circulation which have been described previously, 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 passes from the capillary beds of the abdominal part of the digestive system, the spleen and pancreas to the liver. It passes through a second capillary bed, the hepatic sinusoids, in the liver before entering the general circulation via the inferior vena cava. In this way blood with a high concentration of nutrients, absorbed from the stomach and intestines, goes to the liver first. In the liver certain modifications take place, including the regulation of nutrient supply to other parts of the body.

Portal vein

This is formed by the union of the following veins (Figs 5.47 and 5.48), each of which drains blood from the area supplied by the corresponding artery:

- splenic vein
- inferior mesenteric vein
- superior mesenteric vein
- gastric veins
- cystic vein.

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 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, 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* which drains venous blood from the gall bladder joins the portal vein.

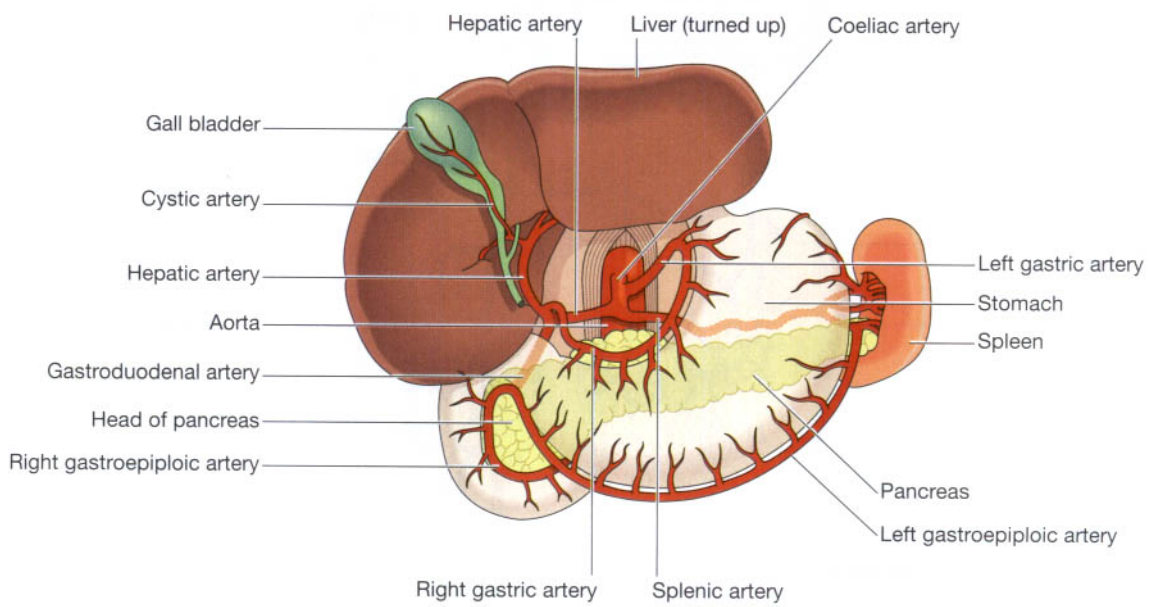


Figure 5.45 The coeliac artery and its branches, and the inferior phrenic arteries.

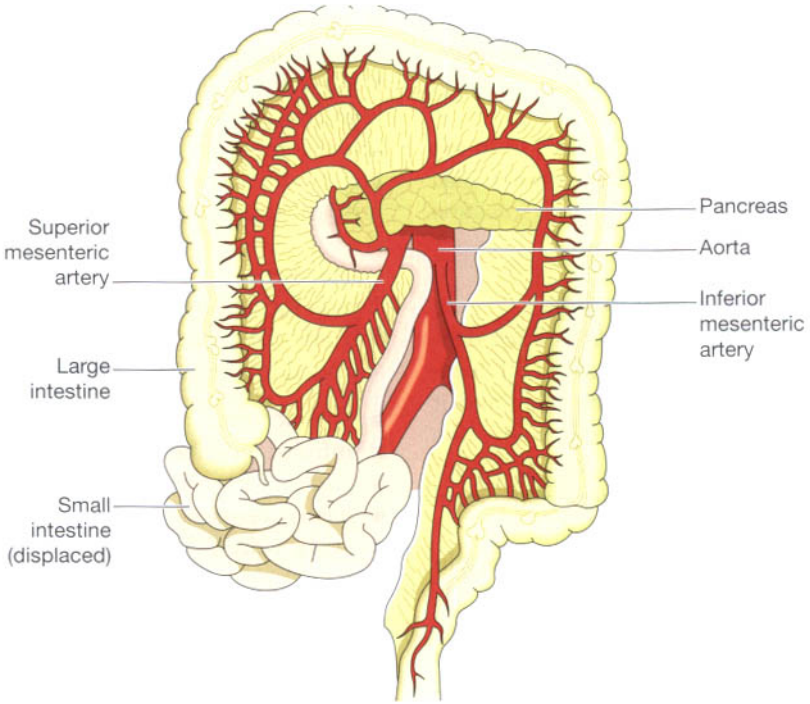


Figure 5.46 The superior and inferior mesenteric arteries and their branches.

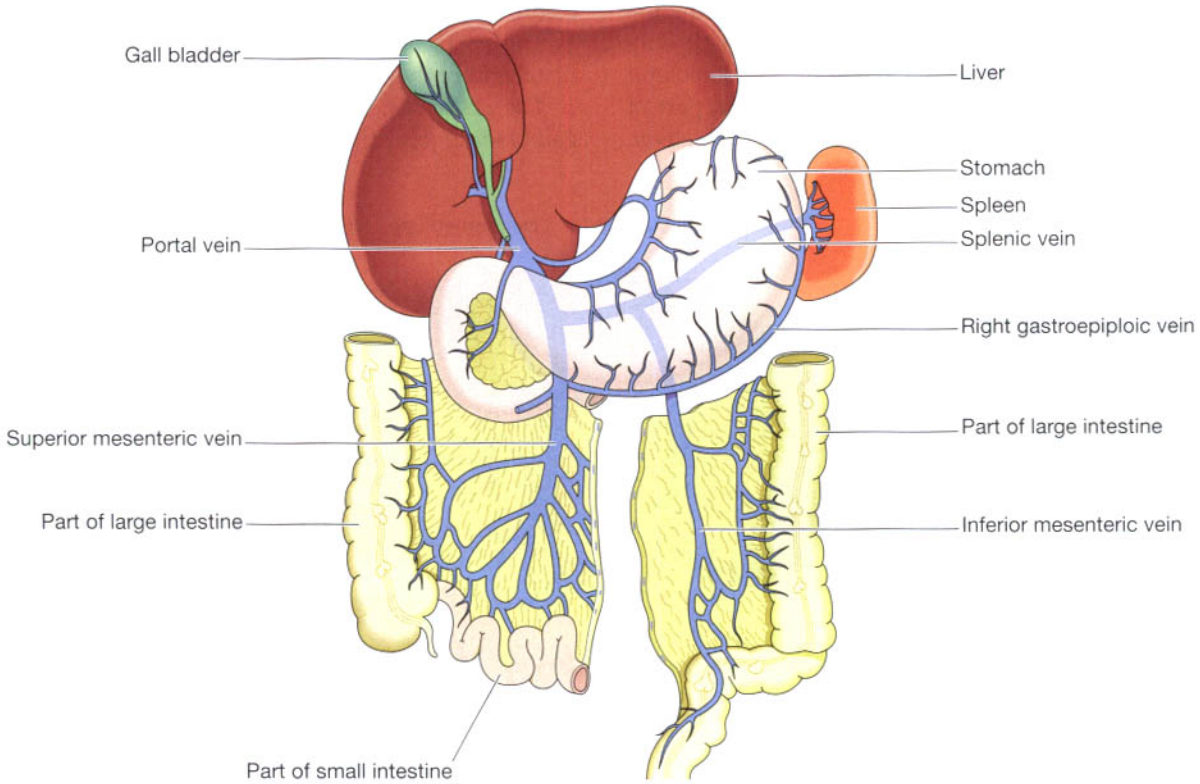


Figure 5.47 Venous drainage from the abdominal organs and the formation of the portal vein.

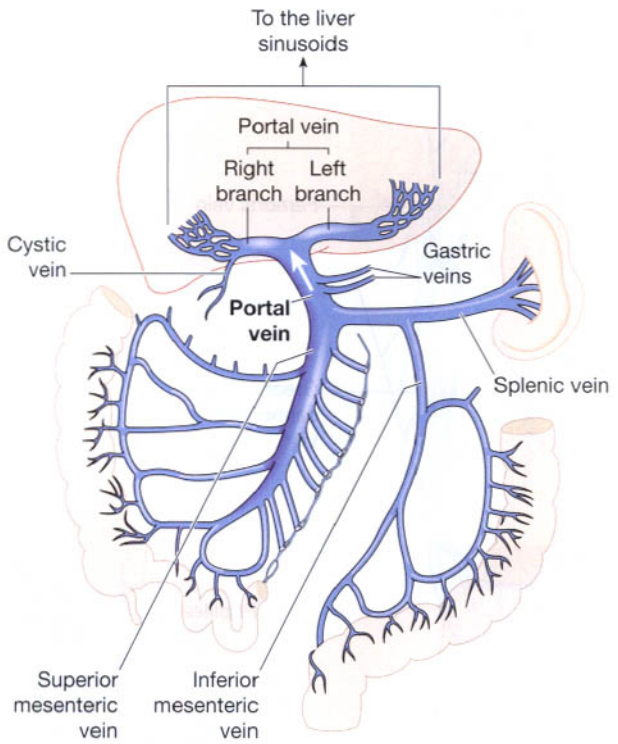


Figure 5.48 The portal vein – formation and termination.

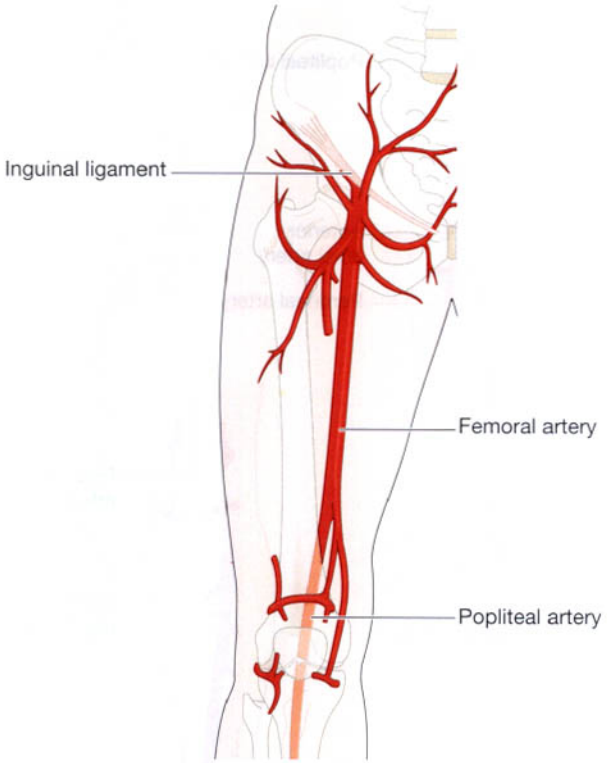


Figure 5.49 The femoral artery and its main branches.

Hepatic veins

These are very short veins that leave the posterior surface of the liver and, almost immediately, enter the inferior vena cava.

Circulation of blood to the pelvis and lower limb

Arterial supply

Common iliac arteries. The right and left common iliac arteries are formed when the abdominal aorta divides at the level of the 4th lumbar vertebra (Fig. 5.32). In front of the sacroiliac joint each divides into:

- internal iliac artery
- external iliac artery.

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. 5.49) begins at the midpoint of the inguinal ligament and extends downwards in front of the thigh; then it 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. 5.50) passes through the popliteal fossa behind the knee. 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. 5.50) 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*.

The *dorsalis pedis artery* is a continuation of the anterior tibial artery and passes over the dorsum of the foot, supplying arterial blood to the structures in this area. It ends by passing 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. 5.50) 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*.

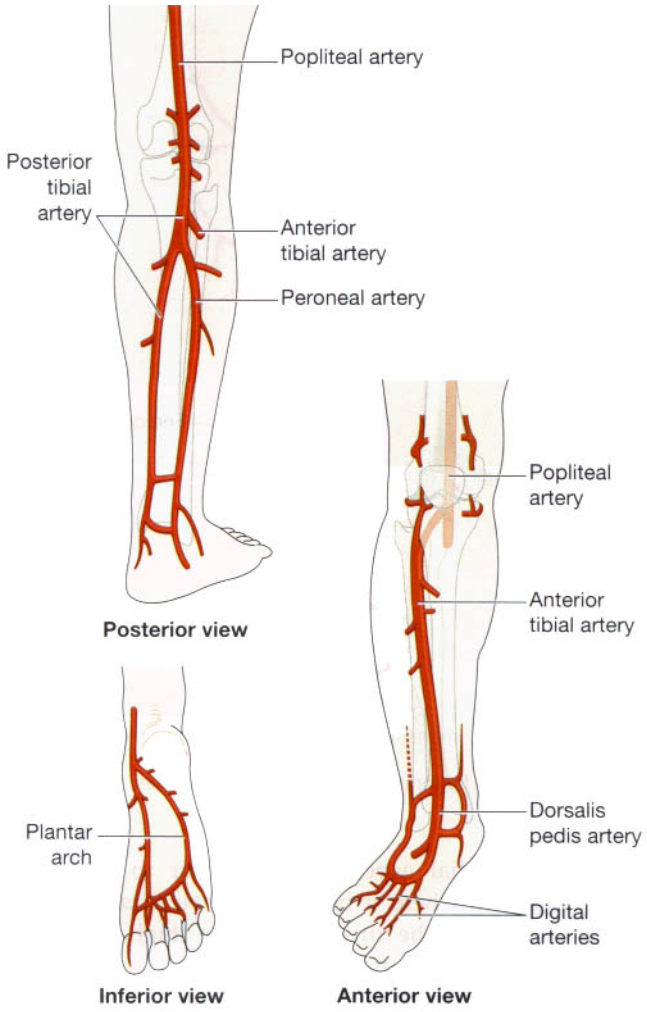


Figure 5.50 The right popliteal artery and its main branches.

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.

Venous return

There are both deep and superficial veins in the lower limb (Fig. 5.31). 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. Backward flow is prevented by a large number of valves. Superficial veins receive less support by surrounding tissues than deep veins.

Deep veins. The deep veins accompany the arteries and their branches and have the same names. They are:

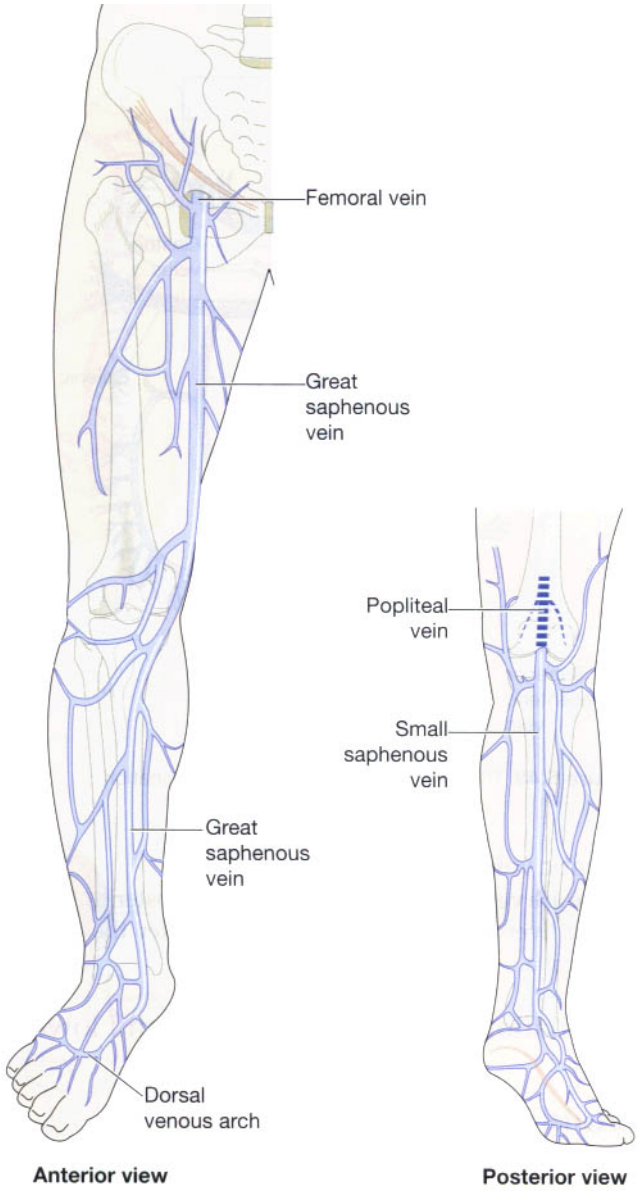


Figure 5.51 Superficial veins of the leg.

- digital veins
- plantar venous arch
- posterior tibial vein
- anterior tibial vein
- popliteal vein
- femoral vein
- external iliac vein
- internal iliac vein
- common iliac vein.

The *femoral vein* ascends in the thigh to the level of the inguinal ligament where it becomes the external iliac vein.

The *external iliac vein* is 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* receives tributaries from several veins which drain the organs of the pelvic cavity.

The *two common iliac veins* begin at the level of the sacroiliac joints. They ascend obliquely and end a little to the right of the body of the 5th lumbar vertebra by uniting to form the *inferior vena cava.*

Superficial veins (Fig. 5.51). The two main superficial veins draining blood from the lower limbs are:

- small saphenous vein
- great saphenous vein.

The *small saphenous vein* begins behind the ankle joint where many small veins which 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 up the inner side of the thigh. Just below the inguinal ligament it joins the *femoral vein.*

Many *communicating veins* join the superficial veins, and the superficial and deep veins of the lower limb.

SUMMARY OF THE MAIN BLOOD VESSELS

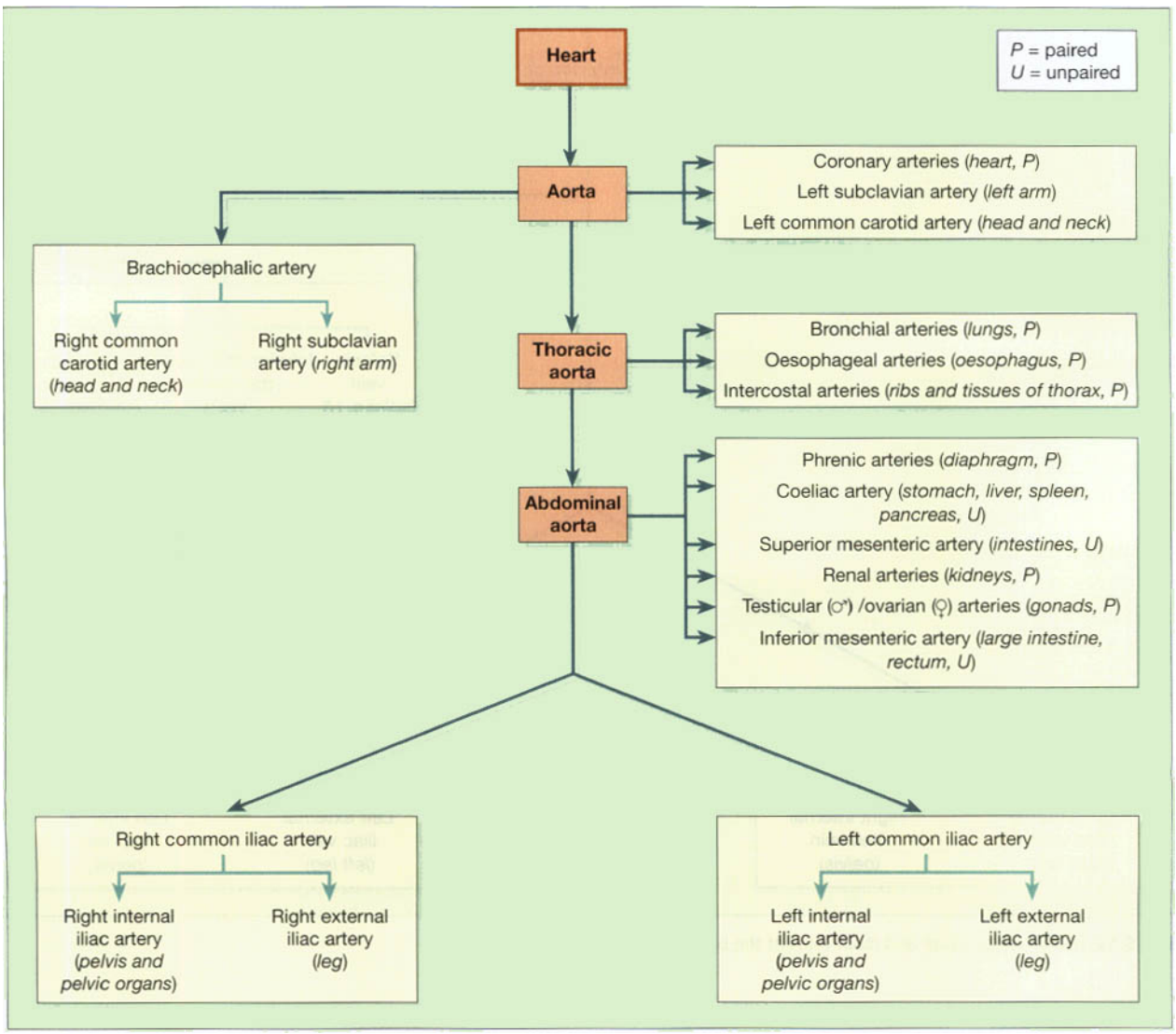


Figure 5.52 A. The aorta and main arteries of the body.

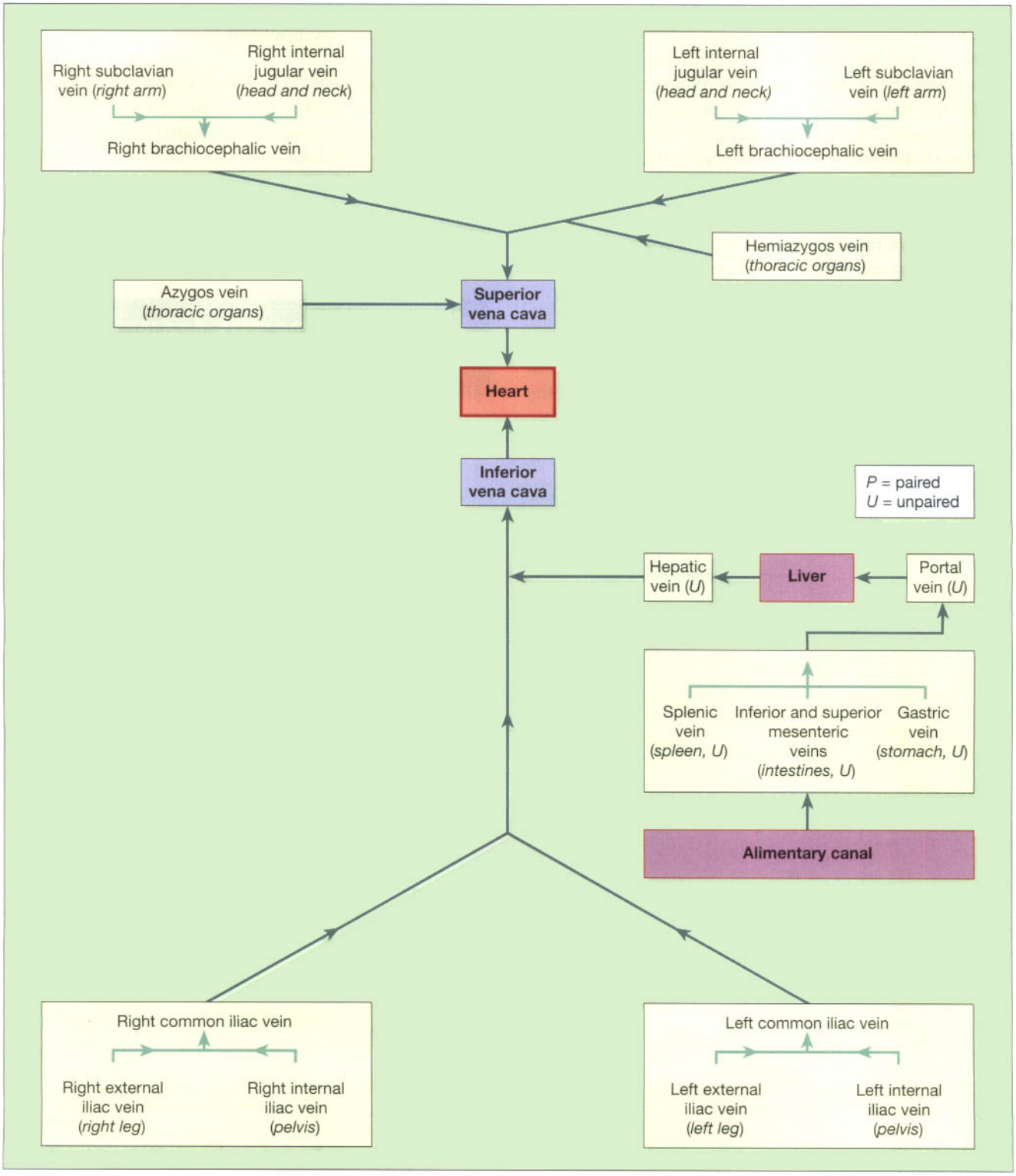


Figure 5.52 B. The venae cavae and main veins of the body.

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 occurs when the metabolic needs of cells are not being 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. A number of different types of shock are described:

- hypovolaemic
- cardiogenic
- septic
- neurogenic
- anaphylactic.

Hypovolaemic shock

This occurs when the blood volume is reduced by 15 to 25%. Reduced venous return and in turn cardiac output may occur following:

- severe haemorrhage—whole blood is lost
- extensive superficial burns—serum is lost and blood cells at the site of the burn are destroyed
- severe vomiting and diarrhoea—water and electrolytes are lost
- perforation of an organ allowing its contents to enter the peritoneal cavity (peritonitis).

Cardiogenic shock

This occurs in acute heart disease when the damaged heart muscle cannot maintain an adequate cardiac output, e.g. in myocardial infarction.

Septic shock (bacteraemic, endotoxic)

This is caused by severe infections in which endotoxins are released into the circulation from dead Gram-negative bacteria, e.g. *Enterobacteria, Pseudomonas*.

The mode of action of the toxins is not clearly understood. It may be that they cause an apparent reduction in the blood volume because of vasodilatation and pooling of blood in the large veins. This reduces the venous return to the heart and the cardiac output.

Neurogenic shock (vasovagal attack, fainting)

The causes include sudden acute pain, severe emotional experience, spinal anaesthesia and spinal cord damage. Parasympathetic nerve impulses reduce the heart rate, and in turn, the cardiac output. The venous return may also be reduced by the pooling of blood in dilated veins. These changes effectively reduce the blood supply to the brain, causing fainting. The period of unconsciousness is usually of short duration.

Anaphylactic shock

In allergic reactions an antigen interacts with an antibody and a variety of responses can occur (p. 383). In severe cases, the chemicals released, e.g. histamine, bradykinin, produce widespread vasodilatation and constriction of bronchiolar smooth muscle (bronchospasm). The vasodilatation profoundly reduces the venous return and cardiac output resulting in tissue hypoxia. Bronchospasm reduces the amount of air entering the lungs, increasing tissue hypoxia.

Physiological changes during shock

In the short term these are associated with physiological attempts to restore an adequate blood circulation. If the state of shock persists, the longer-term changes may be irreversible.

Immediate or reactive changes

As the blood pressure falls, a number of reflexes are stimulated and hormone secretions increased in an attempt to restore homeostasis. These raise the blood pressure by increasing peripheral resistance, the blood volume and the cardiac output. The changes include:

1. vasoconstriction, following:
   a. stimulation of the baroreceptors in the aortic arch and carotid sinuses
   b. sympathetic stimulation of the adrenal glands which causes increased secretion of adrenaline and noradrenaline
   c. stimulation of the renin–angiotensin–aldosterone system by diminished blood flow to the kidneys (p. 223)

2. increased heart rate, following sympathetic stimulation
3. water retention by the kidney, following increased release of antidiuretic hormone by the posterior lobe of the pituitary gland, increasing salt and water retention.

In shock of moderate severity the circulation to the heart and brain is maintained, in the short term. Restlessness, confusion and coma occur as circulation to the brain is impaired. If shock is very severe there may not be time for the above changes to be effective. The severe hypoxia that occurs disrupts cell metabolism. In the absence of adequate oxygen, cellular metabolism switches to less efficient anaerobic pathways, large amounts of lactic acid are formed and hydrogen ions accumulate, reaching dangerous levels in a few minutes. These are the changes that lead to the severe metabolic acidosis which occurs immediately prior to and following cardiac arrest.

Long-term changes associated with shock

If the state of shock is not reversed, hypoxia and low blood pressure cause irreversible brain damage and capillary dilatation and a vicious circle of events is established.

Hypoxia. When this persists there is cell damage and a release of chemical substances that increase the permeability of the capillaries. More fluid enters the interstitial spaces, leading to further hypovolaemia, further reduction in blood pressure and increased hypoxia.

Low blood pressure. As the blood pressure continues to fall, cerebral and myocardial hypoxia becomes progressively more marked and the reduced blood flow encourages the formation of thrombi and infarcts. There is acute renal failure and a marked reduction in the secretion of urine, leading to the retention of damaging metabolic waste products. If effective treatment is not possible these irreversible changes become progressively more severe and eventually may cause death.

DISEASES OF BLOOD VESSELS

Learning outcomes

After studying this section, you should be able to:

- discuss the main causes, effects and complications of arterial disease, including atheroma, arteriosclerosis and aneurysm
- explain the main causes of venous thrombosis
- 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

Patchy changes (*atheromatous plaques*) develop in the tunica intima of large and medium-sized arteries. These consist of accumulations of cholesterol and other lipid compounds, excess smooth muscle and fat-filled monocytes (foam cells). The plaque is covered with a fibrous cap. As plaques grow they spread along the artery wall forming swellings that protrude into the lumen. Eventually the whole thickness of the wall and long sections of the vessel may be affected (Fig. 5.53). Plaques may rupture, exposing subintimal materials to the blood. This may cause thrombosis and vasospasm and will compromise blood flow.

Arteries most commonly involved are those in the heart, brain, kidneys, small intestine and lower limbs.

Causes of atheroma

The origin of atheromatous plaques is uncertain. *Fatty streaks* present in artery walls of infants are usually absorbed but their incomplete absorption may be the origin of atheromatous plaques in later life.

Atherosclerosis is considered to be a disease of older people because it is usually in these age groups that clinical signs appear. Plaques, however, start to form in childhood in developed countries.

The incidence of atheroma is widespread in developed countries. Why atheromatous plaques develop is not yet clearly understood but the predisposing factors appear to exert their effects over a long period. This may mean that the development of atheroma can be delayed or even

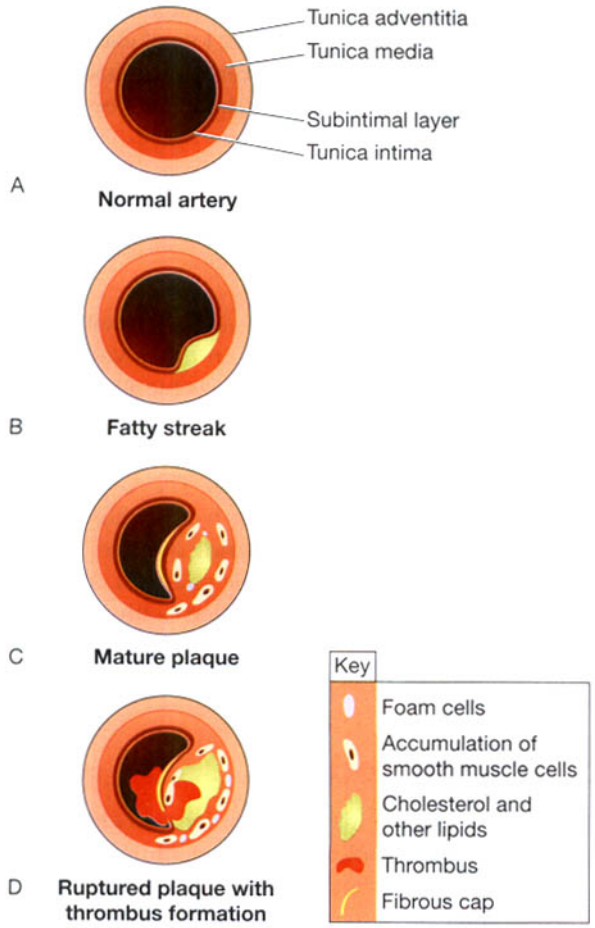


Figure 5.53 Stages in the development of an atheromatous plaque.

arrested by a change in lifestyle. Predisposing factors include:

- heredity – family history
- gender – males are more susceptible than females until after the menopause
- increasing age
- hypertension
- diabetes mellitus
- smoking, especially cigarettes
- excessive emotional stress in work or home environment
- diet, e.g. high intake of refined carbohydrates and/or cholesterol and saturated fatty acids (from animal fats)
- obesity
- sedentary lifestyle
- excessive alcohol consumption.

Effects of atheroma

Arteries may be partially or completely blocked by atheromatous plaques alone, or by plaques combined with a thrombus. This may reduce or completely block the blood supply. The effects depend on the site and size of the artery involved and the extent of collateral circulation. Commonly the arteries affected are those in the heart, abdomen and pelvis.

Narrowing of an artery

The tissues distal to the narrow point become ischaemic. The cells may receive enough blood to meet their minimum needs, but not enough to cope with an increase in metabolic rate, e.g. when muscle activity is increased. This causes acute cramp-like ischaemic pain. Cardiac muscle and skeletal muscles of the lower limb are most commonly affected. Ischaemic pain in the heart is called *angina pectoris* (p. 121), and in the lower limbs, *intermittent claudication*.

Occlusion of an artery

When an artery is completely blocked, the tissues it supplies rapidly undergo degeneration and die from *ischaemia* which leads to *infarction*. The extent of tissue damage depends on:

- the size of the artery occluded
- the amount and type of tissue involved
- the extent of collateral circulation, e.g. in the brain the circulus arteriosus (circle of Willis) provides extensive collateral blood vessels while in the heart there are very few.

When a coronary artery is occluded *myocardial infarction* (p. 121) occurs. Occlusion of arteries in the brain causes cerebral ischaemia and this leads to *cerebral infarction* (stroke).

Complications of atheroma

Thrombosis and infarction

If the fibrous cap overlying a plaque breaks down, platelets are activated by the damaged cells and a blood clot (thrombus) forms, blocking the artery and causing ischaemia and infarction. Pieces of the clot (emboli) may break off, travel in the bloodstream and lodge in small arteries distal to the clot, causing small infarcts (areas of dead tissue).

Haemorrhage

When calcium salts are deposited in the plaques, the artery walls become brittle, rigid and unresponsive to rises in blood pressure and may rupture, causing haemorrhage.

Aneurysm formation

When the arterial wall is weakened by spread of the plaque between the layers of tissue, a local dilatation

(aneurysm) may develop (see below). This may lead to thrombosis and embolism, or the aneurysm may rupture causing severe haemorrhage. The most common sites affected are the aorta and the abdominal and pelvic arteries.

Arteriosclerosis

This is a progressive degeneration of arterial walls, associated with ageing and accompanied by hypertension.

Large and medium arteries

The tunica media is infiltrated with fibrous tissue and calcium. This causes the vessels to lose their elasticity. The lumen dilates and they become tortuous (Fig. 5.54). Loss of elasticity increases systolic blood pressure, and the *pulse pressure* (the difference between systolic and diastolic pressure).

Small arteries and arterioles

Hyaline thickening of the tunica media and tunica intima causes narrowing of the lumen and they become tortuous (Fig. 5.54). These arteries are the main determinants of peripheral resistance (p. 80) and narrowing of their lumens increases peripheral resistance and blood pressure. Ischaemia of tissues supplied by affected arteries may occur. In the limbs, the resultant ischaemia predisposes to gangrene which is particularly serious in people with diabetes mellitus.

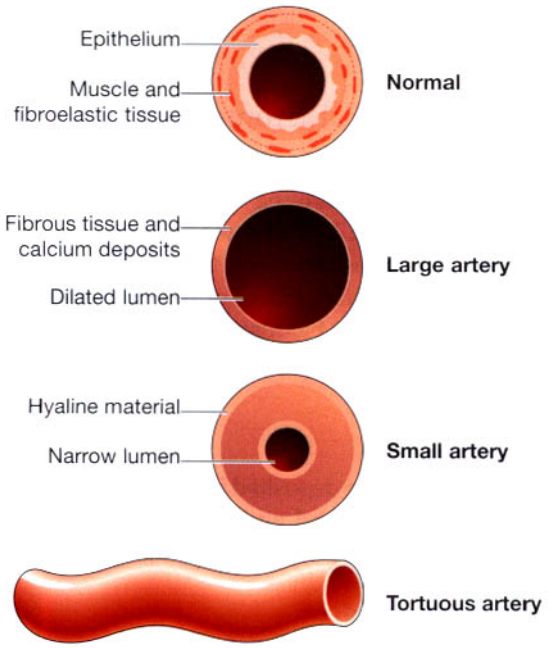


Figure 5.54 Arteriosclerotic arteries.

Senile arteriosclerosis. This is a condition affecting elderly people in which the progressive loss of elasticity and reduced arterial lumen leads to cerebral ischaemia and loss of mental function. There may or may not be evidence of hypertension.

Thromboangiitis obliterans (Buerger's disease)

In this condition there is acute inflammation with thrombosis of the small arteries mainly in the lower limbs. It occurs most commonly in men between the ages of 20 and 40 years and is associated with heavy cigarette smoking. The condition may be caused by an immune response to an antigen, possibly a tobacco protein. The condition may become chronic and the vessel walls become fibrosed, lose their elasticity and do not dilate during exercise. The individual suffers from acute ischaemic pain and, as the disease progresses, the distance walked with comfort is gradually reduced. In the long term the skin may ulcerate and, in extreme cases, gangrene may develop.

Polyarteritis nodosa

This is a connective tissue disorder associated with inflammation of the tunica media of medium-sized arteries in any part of the body. The most common sites are the heart, kidneys, alimentary tract, liver, pancreas and nervous system. It is acute at first but frequently becomes chronic. Necrosis and rupture of blood vessels may occur in the acute phase followed by thrombosis, ischaemia, infarction and death. It is believed to be caused by an immune reaction. In most cases the antigen is not known but it may be a virus or drug such as a sulphonamide or antibiotic.

Aneurysms

Aneurysms are abnormal local dilatations of arteries which vary considerably in size (Fig. 5.55). The causes are not clear but predisposing factors include atheroma, hypertension and defective formation of collagen in the arterial wall.

Fusiform or spindle-shaped distensions occur mainly in the abdominal aorta and less commonly in the iliac arteries. They are usually associated with atheromatous changes.

Saccular aneurysms bulge out on one side of the artery. When they occur in the relatively thin-walled arteries of the circulus arteriosus (circle of Willis) in the brain they are sometimes called 'berry' aneurysms. They may be

associated with defective collagen production, with atheromatous changes or be congenital.

Dissecting aneurysms occur mainly in the arch of the aorta due to infiltration of blood between the endothelium and tunica media, beginning at a site of endothelial damage.

Microaneurysms are fusiform or saccular aneurysms, occurring in small arteries and arterioles in the brain. They are associated with hypertension. Recurring small strokes (transient ischaemic attacks) are commonly due to thrombosis in the aneurysm or to haemorrhage when an aneurysm ruptures.

Complications of aneurysms

Haemorrhage

A ruptured aneurysm may cause sudden death or disability of varying severity, depending on the size and site of the artery.

Pressure

Localised swelling may cause pressure affecting adjacent tissues including organs, blood vessels and nerves.

Thrombosis and embolism

A blood clot (thrombus) may form in an artery where the endothelium has been damaged by an aneurysm. A piece of clot (embolus) may break off and travel in the bloodstream until it lodges in a small artery distal to the aneurysm and obstructs the blood flow, causing ischaemia and infarction.

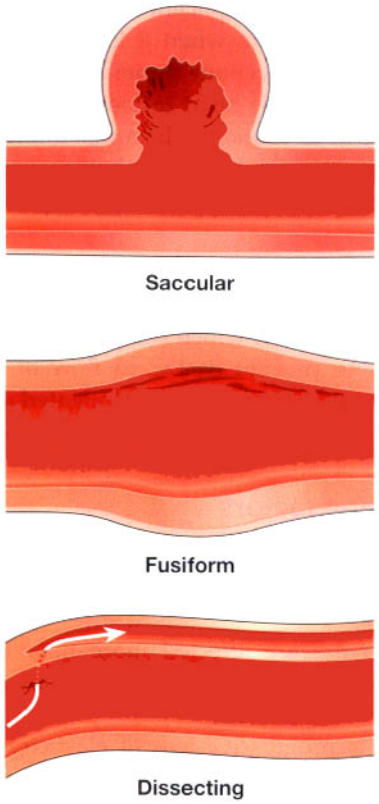


Figure 5.55 Types of aneurysm.

Venous thrombosis

This may be *superficial thrombophlebitis* or *deep vein thrombosis*.

Superficial thrombophlebitis

In this acute inflammatory condition a thrombus forms in a superficial vein and the tissue around the affected vein becomes red and painful. The most common causes are:

- intravenous infusion
- varicosities in the saphenous vein.

Deep vein thrombosis (DVT)

A thrombus forms in a deep vein commonly in the lower limb, pelvic or iliac veins, but occasionally in an upper limb. The thrombus may affect a long section of the vein and, after some days, fibrinolysis (p. 68) may enable recanalisation through the blockage. Deep vein thrombosis may be accompanied by pain and swelling, but is often asymptomatic. There are several predisposing factors.

Reduced rate of blood flow. This may be caused by:

- immobility associated with prolonged bedrest
- pressure on veins in the popliteal region by, e.g., a pillow under the knees in bed or sitting in a chair for long periods, as in long journeys
- pressure on a vein by an adjacent tumour
- prolonged low blood pressure, as in shock.

Changes in the blood. These may trigger intravascular clotting, e.g.:

- increased blood viscosity in, e.g., dehydration, polycythaemia (p. 72)
- increased adhesiveness of platelets, e.g. associated with the use of some oral contraceptive drugs, and in some malignant diseases.

Damage to the blood vessel wall. This can result in intravascular clotting, e.g.:

- accidental injury
- surgery.

The most common complication of DVT is *pulmonary embolism*, which occurs when a large piece or several small fragments of a venous thrombus become detached and travel through the heart to lodge in the pulmonary artery or one of its branches. It causes infarction of lung tissue. A massive pulmonary embolism usually causes sudden collapse and death.

Varicose veins

A varicosed vein is one which is so dilated that the valves do not close to prevent backward flow of blood. Such veins lose their elasticity, become elongated and tortuous and fibrous tissue replaces the tunica media.

Predisposing factors

Heredity. There appears to be a familial tendency but no abnormal genetic factor has been identified.

Gender. Females are affected more than males, especially following pregnancy.

Age. There is progressive loss of elasticity in the vein walls with increasing age so that elastic recoil is less efficient.

Obesity. Superficial veins in the limbs are supported by subcutaneous areolar tissue. Excess adipose tissue may not provide sufficient support.

Gravity. Standing for long periods with little muscle contraction tends to cause pooling of blood in the lower limbs and pelvis.

Pressure. Because of their thin walls, veins are easily compressed by surrounding structures, leading to increased venous pressure distal to the site of compression.

Sites and effects of varicose veins

Varicose veins of the legs

When valves in the anastomosing veins between the deep and superficial veins in the legs become incompetent the venous pressure in the superficial veins rises. In the long term they stretch and become chronically dilated because the superficial veins are not supported by much tissue. Such areas are seen externally as *varicosities* (Fig. 5.56). 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, and haemorrhage occurs.

The skin over a varicose vein may become poorly nourished due to stasis of blood, leading to the formation of *varicose ulcers* usually on the medial aspects of the leg just above the ankle.

Haemorrhoids

Sustained pressure on the veins at the junction of the rectum and anus leads to increased venous pressure, valvular incompetence and the development of haemorrhoids (Fig. 5.56). The most common causes are chronic constipation, and the increased pressure in the pelvis towards the end of pregnancy. Slight bleeding may occur each time stools are passed and, in time, may cause anaemia. Severe haemorrhage is rare.

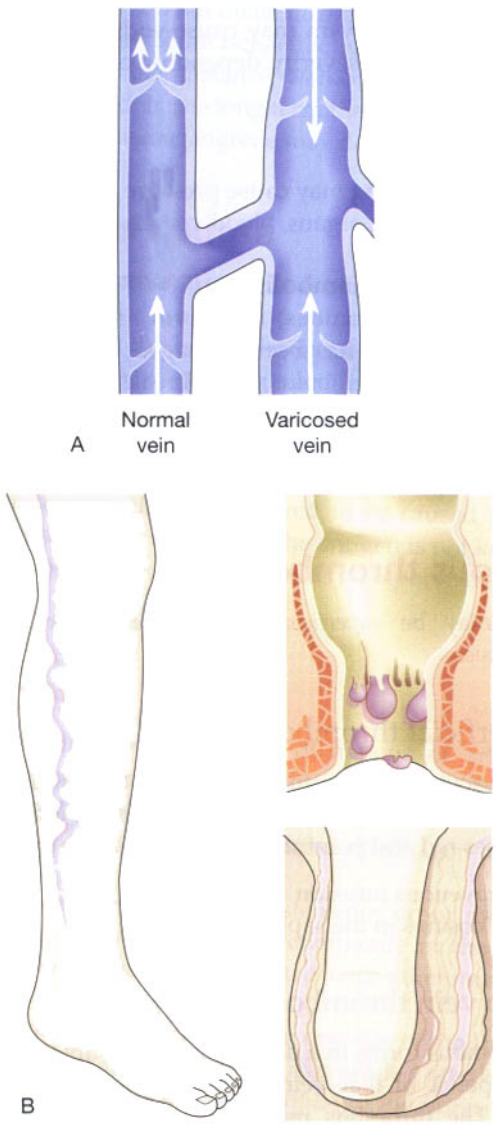


Figure 5.56 A. Normal and varicosed veins. B. Common sites for varicosities – the leg, scrotum (varicocele) and anus (haemorrhoids).

Scrotal varicocele

Each spermatic cord is surrounded by a plexus of veins that may become varicosed (Fig. 5.56), especially in men whose work necessitates standing for long periods. If the varicocele is bilateral the increased temperature due to venous congestion may cause depressed spermatogenesis and result in infertility.

Oesophageal varices

The veins involved are at the lower end of the oesophagus. When the venous pressure in the liver rises, there is a rise in pressure in the anastomosing veins between the left gastric vein and the azygos vein. Sustained pressure causes varicosities to develop in the oesophagus (see Fig. 12.50, p. 321). The commonest causes of increased portal vein pressure are cirrhosis of the liver and right-sided cardiac failure. If the pressure continues to rise, inelastic varicosed veins may rupture causing severe haemorrhage, and possibly death.

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 not true tumours but are sufficiently similar to be classified as such. They consist of an excessive growth of blood vessels arranged in an uncharacteristic manner and 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.

Capillary 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 to 3 years, atrophy may begin and by the end of 5 years in about 80% of cases the tumours have disappeared.

Cavernous haemangiomas. Blood vessels larger than capillaries grow in excess of normal needs in a localised area and are interspersed with collagen fibres. They are dark red in colour and may be present in the skin, though more commonly in the liver. They grow slowly, do not regress and may become large and unsightly.

THROMBOSIS, EMBOLISM AND INFARCTION

Learning outcomes

After studying this section, you should be able to:

- define the terms thrombosis, embolism and infarction
- explain, in general terms, the effects of the above on the body.

A *thrombus* is an intravascular blood clot, causing *thrombosis*. It may partially or completely occlude an artery or vein, interfering with the circulation of blood.

Factors which predispose to thrombus formation include:

- an abnormality of the normally smooth endothelium, e.g. ruptured atheromatous plaque
- abnormal blood flow in a vessel, especially venous stasis
- increased coagulability of the blood.

If a fragment of thrombus, called an *embolus*, becomes detached, it travels in the bloodstream until it lodges in and blocks a smaller vessel. The tissue supplied by the vessel becomes ischaemic and dies; this is *infarction*.

An *embolus* is a mass of any material carried in the bloodstream and large enough to block a blood vessel. Most emboli consist of fragments of thrombi but other materials include:

- fragments of atheromatous plaques
- fragments of vegetations from heart valves, e.g. infective endocarditis
- tumour fragments that may cause metastases
- amniotic fluid, during childbirth
- fat, from extensive bone fractures
- air, iatrogenic or following puncture of a blood vessel in the lung by a broken rib
- nitrogen in decompression sickness – 'the bends'
- pus from an abscess
- clumps of platelets with adherent microbes.

Emboli in veins move towards the heart and lodge in the smaller vessels of the lungs or the liver (an important cause of metastases in tumours of the alimentary tract). Those in arteries travel away from the heart and lodge in smaller arteries or arterioles.

The effects of an embolus are determined by the site and size of the blood vessel occluded, not its composition. Common serious consequences include:

- myocardial infarction (p. 121)
- cerebral infarction (p. 180)
- pulmonary embolism (p. 116).

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 there is excess tissue fluid, which causes swelling. It may occur in internal organs or in superficial tissues when there is disruption of the mechanisms that maintain homeostasis (p. 81).

Sites of oedema

When oedema is present in the superficial tissues *pitting* of the surface may be observed, i.e. an indentation in the skin remains after firm finger pressure has been applied. The sites at which superficial oedema is observed may be influenced by gravity and the position of the individual. When the individual is in the standing or sitting position the oedema is observed in the lower limbs, beginning in the feet and ankles. Patients on bedrest tend to develop oedema in the sacral area. This may be described as *dependent oedema*.

In *pulmonary oedema*, venous congestion in the lungs, or increased vessel permeability results in accumulation of fluid in the tissue spaces and in the alveoli. This reduces the area available for gaseous exchange and results in *dyspnoea* (breathlessness), cyanosis and expectoration of frothy sputum. The most common causes of pulmonary oedema are:

- cardiac failure
- inhalation of irritating gases
- inflammation
- intravenous infusion of excess fluid.

Causes of oedema

Increased venous hydrostatic pressure

Congestion of the venous circulation increases venous hydrostatic pressure, reducing the 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
- external pressure on a limb due to, e.g., prolonged sitting or tight garments.

Decreased plasma osmotic pressure

When there is depletion of plasma proteins, less fluid returns to the circulation at the venous end of the capillary (Fig. 5.57B). Causes include:

- acute nephritis when the kidneys excrete protein
- nephrotic syndrome (p. 352)
- liver failure (p. 335)
- malnourishment where protein intake is very low.

Impaired lymphatic drainage

Some fluid returns to the circulation via the lymphatic system and when flow is impaired, oedema develops (Fig. 5.57C). Causes include:

- malignancy causing blockage of lymph nodes
- surgical removal of lymph nodes
- destruction of lymph nodes by chronic inflammation.

Increased small vessel permeability

In inflammation (p. 375), chemical mediators increase small vessel permeability in the affected area. Plasma proteins then leave the circulation (Fig. 5.57D) and the increased tissue osmotic pressure draws fluid into the area causing swelling of the affected tissue. This type of oedema also occurs in allergic reactions, e.g. anaphylaxis, asthma, hay fever.

Ascites and effusions

Ascites. This is the name given to the accumulation of excess fluid in the peritoneal cavity. The most common causes are:

- liver disease (p. 333)
- obstruction of lymph vessels in the abdominal cavity
- acute inflammation.

Pleural effusion. This is excess serous fluid in the pleural cavity. The most common causes are:

- heart failure due to increased blood pressure in the pulmonary circulation
- inflammation of the pleural membrane.

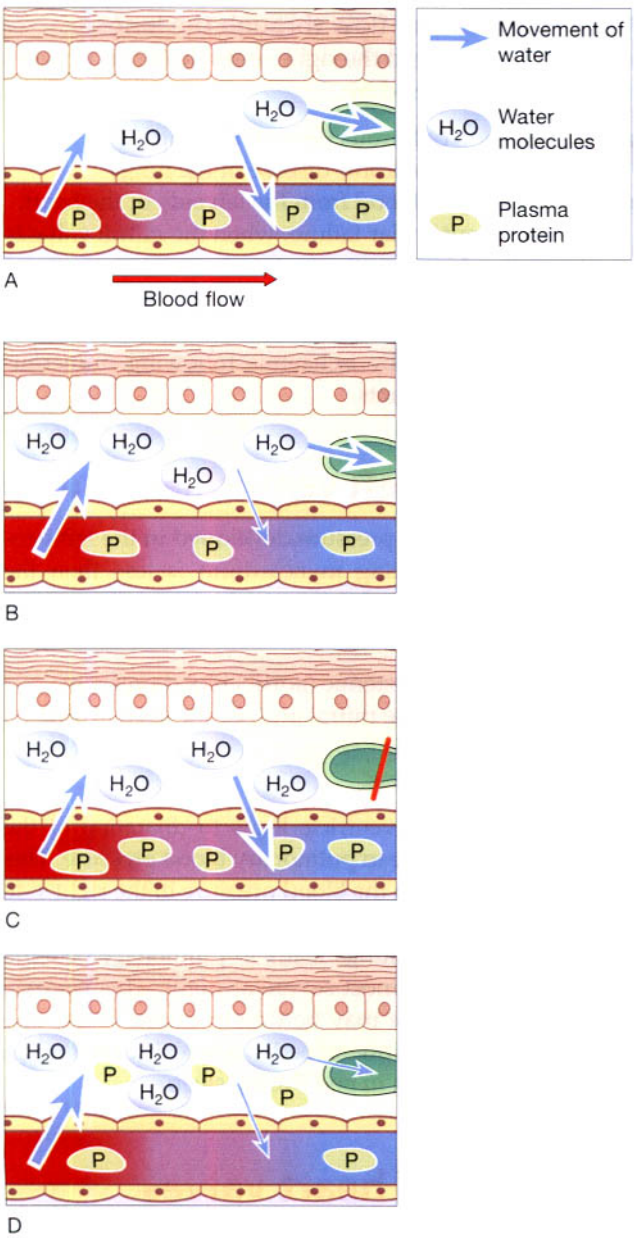


Figure 5.57 Mechanisms of oedema formation: A. Normal distribution of tissue fluid. B, C and D. Different mechanisms of oedema formation. Arrows indicate direction of movement of water.

DISEASES OF THE HEART

Learning outcomes

After studying this section, you should be able to:

- describe the consequences of failure of either or both sides of the heart
- explain the physiological 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
- outline rheumatic heart disease and its effects on cardiac function
- explain the underlying pathophysiology of pericarditis
- describe, with reference to standard ECG trace, the main cardiac arrhythmias
- describe the principal congenital abnormalities of the heart.

Cardiac failure

The heart is described as failing when the cardiac output is unable to maintain the circulation of sufficient blood to meet the needs of the body. In mild cases, cardiac output is adequate at rest and becomes inadequate only when increased cardiac output is required, e.g. in exercise. Heart failure may affect either side of the heart, but since both sides of the heart are part of one circuit, when one half of the pump begins to fail it frequently leads to increased strain on, and eventual failure of, the other half. The main clinical manifestations depend on which side of the heart is most affected.

Compensatory mechanisms in heart failure

When heart failure happens acutely, 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 fibres enlarge and increase in number, which makes the walls of the chambers thicker
- the heart chambers enlarge
- decreased renal blood flow activates the renin–angiotensin–aldosterone system (p. 223), which leads to salt and water retention. This increases blood volume and cardiac workload. The direct vasoconstrictor action of angiotensin 2 increases peripheral resistance and puts further strain on the failing heart.

Acute cardiac failure

A sudden decrease in output of blood from both ventricles causes acute reduction in the oxygen supply to all the tissues. Recovery from the acute phase may be followed by chronic failure, or death may occur due to anoxia of vital centres in the brain. The commonest causes are:

- severe damage to an area of cardiac muscle due to ischaemia caused by sudden occlusion of one of the larger coronary arteries by atheroma or atheroma with thrombosis
- pulmonary embolism
- acute toxic myocarditis
- severe cardiac arrhythmia
- rupture of a heart chamber or valve cusp
- severe malignant hypertension.

Chronic cardiac failure

This develops gradually and in the early stages there may be no symptoms because certain compensatory changes occur as described above. When further compensation is not possible there is a gradual decline in myocardial efficiency. Underlying causes include:

- chronic hypertension, myocardial fibrosis, valvular disease, lung diseases, anaemia
- previous acute cardiac failure
- degenerative changes of old age.

Right-sided (congestive) cardiac failure

The right ventricle fails when pressure developed within it by the contracting myocardium is less than the force needed to push blood through the lungs.

When compensation has reached its limit, and the ventricle is not emptying completely, the right atrium and venae cavae become congested with blood and this is followed by congestion throughout the venous system. The organs affected first are the liver, spleen and kidneys. *Oedema* (p. 118) of the limbs and *ascites* (excess fluid in the peritoneal cavity) usually follow.

This problem may be caused by increased vascular resistance in the lungs, weakness of the myocardium and/or stenosis and incompetence of valves in the heart or great vessels.

Resistance to blood flow through the lungs

When this is increased the right ventricle has more work to do. It may be caused by:

- the formation of fibrous tissue following inflammation or chronic disease of the lungs
- back pressure of blood from the left side of the heart, e.g. in left ventricular failure, when the mitral valve is stenosed and/or incompetent.

Weakness of the myocardium

This may be caused by ischaemia following numerous small myocardial infarcts.

Left-sided or left ventricular failure

This occurs when the pressure developed in the left ventricle by the contracting myocardium is less than the pressure in the aorta and the ventricle cannot then pump out all the blood it receives. Causes include:

- excessively high systemic (aortic) blood pressure
- incompetence of the mitral and/or the aortic valve
- aortic valve stenosis
- myocardial weakness.

Failure of the left ventricle leads to dilatation of the atrium and an increase in pulmonary blood pressure. This is followed by a rise in the blood pressure in the right side of the heart and eventually systemic venous congestion.

Congestion in the lungs leads to pulmonary oedema and dyspnoea, often most severe at night. This *paroxysmal nocturnal dyspnoea* may be due to raised blood volume as fluid from peripheral oedema is reabsorbed when the patient 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 left atrioventricular 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 (p. 88). Damaged valves generate abnormal heart sounds called *murmurs*. A severe valve disorder results in heart failure. The most common causes of valve defects are rheumatic fever, fibrosis following inflammation and congenital abnormalities.

Stenosis

This is the narrowing of a valve opening, impeding blood flow through the valve. It occurs when inflammation and encrustations roughen the edges of the cusps so that they stick together, narrowing the valve opening. When healing occurs fibrous tissue is formed which shrinks as it ages, increasing the stenosis and leading to incompetence.

Incompetence

Sometimes called *regurgitation*, this is a functional defect caused by failure of a valve to close completely, allowing blood to flow back into the ventricle when it relaxes.

Ischaemic heart disease

Ischaemic heart disease is due to the effects of atheroma, causing narrowing or occlusion of one or more branches of the coronary arteries. The narrowing is caused by atheromatous plaques (p. 112). Occlusion may be by plaques alone, or plaques complicated by thrombosis. The overall effect depends on the size of the coronary artery involved and whether it is narrowed or occluded. Narrowing of an artery leads to *angina pectoris*, and occlusion to *myocardial infarction*, i.e. an area of dead tissue.

When atheroma develops slowly, a *collateral arterial blood supply* may have time to develop and effectively supplement or replace the original. This consists of the dilatation of normally occurring anastomotic arteries joining adjacent branch arteries. When sudden severe narrowing or occlusion of an artery occurs the anastomotic arteries dilate but may not be able to supply enough blood to meet the needs of the myocardium.

Angina pectoris

This is sometimes called *angina of effort* because increased cardiac output required during extra physical effort causes severe ischaemic pain in the chest. The pain may also radiate to the arms, neck and jaw. Other factors which may precipitate angina include:

- cold weather
- exercising after a heavy meal
- strong emotions.

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, e.g. 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 development of the disease the chest pain stops when the cardiac output returns to its resting level soon after the extra effort stops.

Myocardial infarction

An *infarct* is an area of tissue that has died because of lack of oxygenated blood (p. 117). The myocardium is affected when a branch of a coronary artery is occluded. The commonest cause is an atheromatous plaque complicated by thrombosis. The extent of myocardial damage depends on the size of the blood vessel and site of the infarct. The damage is permanent because cardiac muscle cannot regenerate and the dead tissue is replaced with non-functional fibrous tissue. Speedy restoration of blood flow through the blocked artery using clot-dissolving (thrombolytic) drugs can greatly reduce the extent of the permanent damage and improve prognosis, but treatment must be started within a few hours of the infarction occurring. The effects and complications are greatest when the left ventricle is involved.

Myocardial infarction is usually accompanied by very 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 arrhythmias, especially *ventricular fibrillation*, due to disruption of the cardiac conducting system
- cardiac failure, caused by impaired contraction of the damaged myocardium and, in severe cases, cardiogenic shock
- rupture of a ventricle wall, usually within 2 weeks of the original episode
- pulmonary or cerebral embolism originating from a mural clot within a ventricle, i.e. a clot that forms inside the heart over the area of dead tissue
- pericarditis
- angina pectoris
- recurrence.

Rheumatic heart disease

Rheumatic fever

This autoimmune disease occurs 2 to 4 weeks after a throat infection, caused by *Streptococcus pyogenes* (beta-haemolytic Group A). The antibodies developed to combat the infection damage the heart. The microbes are not present in the heart lesion and the same infection in other parts of the body is very rarely followed by rheumatic fever. How the antibodies damage the heart is not yet understood. Children and young adults are most commonly affected.

Death rarely occurs in the acute phase but after recovery there may be permanent damage to the heart valves, eventually leading to disability and possibly cardiac failure.

Effects on the endocardium

The endocardium becomes inflamed and oedematous and tiny pale areas called *Aschoff's bodies* appear which, when they heal, leave thick fibrous tissue. Thrombotic fibrous nodules consisting of platelets and fibrin form on the free borders of the cusps of the heart valves. When healing occurs the fibrous tissue formed shrinks as it ages, distorting the shape of the cusps and causing stenosis and incompetence of the valve. The mitral and aortic valves are commonly affected, the tricuspid valve sometimes and the pulmonary valve rarely.

Effects on the myocardium

Aschoff's bodies form on the connective tissue between the cardiac muscle fibres. As in the endocardium, healing is accompanied by fibrosis which may interfere with myocardial contraction.

Effects on the pericardium

Inflammation leads to the accumulation of exudate in the pericardial cavity. Healing is accompanied by fibrous thickening of the pericardium and adhesions form between the two layers. In severe cases the layers may fuse, obliterating the cavity. Within this inelastic pericardium the heart may not be able to expand fully during diastole, leading to reduced cardiac output, generalised venous congestion and oedema.

Sydenham's chorea

This usually occurs between the ages of 5 and 15 years. The causes are unknown but it is commonly associated with streptococcal throat infection, rheumatic fever or endocarditis. There are rapid, uncoordinated, involuntary muscle movements. In mild cases recovery takes place within about 4 weeks. In some cases the initial recovery may be followed by recurrences.

Choreiform movements may occasionally occur during pregnancy, in women taking contraceptive pills and following cerebrovascular lesions, especially in the elderly.

Subclinical rheumatic heart disease

Valvular incompetence developing in older people who have a history of rheumatic fever many years previously is believed to be due to repeated subclinical attacks. These attacks are not associated with repeated episodes of sore throat so it is assumed that the original disease has remained active in a subclinical form. In some cases there is no history of rheumatic fever.

Infective endocarditis

Pathogenic organisms in the blood may colonise any part of the endocardium but the most common sites are on or near the heart valves and round the margins of congenital heart defects. These areas are susceptible to infection because they are exposed to fast-flowing blood that may cause mild trauma.

The main predisposing factors are bacteraemia, depressed immune response and heart abnormalities.

Bacteraemia

Microbes may or may not multiply while in the bloodstream and, if not destroyed by phagocytes or antibodies, they tend to adhere to platelets and form tiny infected emboli. Inside the heart the emboli are most likely to settle on already damaged endocardium. Vegetations consisting of platelets and fibrin surround the microbes and seem to protect them from normal body defences and antibiotics. Because of this, infection may be caused by a wide range of microbes, including some of low pathogenicity, e.g.:

- non-haemolytic streptococci, e.g. following tooth extraction, tonsillectomy
- *Escherichia coli* and other normal bowel inhabitants, e.g. following intestinal surgery
- *Staphylococcus aureus*, e.g. from boils and carbuncles
- microbes from infections of, e.g., the biliary, urinary, respiratory tracts
- microbes accidentally introduced during medical and nursing procedures, e.g. cystoscopy, bladder catheterisation, arterial and venous cannulation, surgery, wound dressing
- low-virulence microbes that cause infection in people with reduced immune response.

Depressed immune response

This enables low-virulence bacteria, viruses, yeasts and fungi to become established and cause infection. These are organisms always present in the body and the environment. Depression of the immune systems may be caused by:

- cytotoxic drugs
- ionising radiation, e.g. X-rays used in cancer treatment
- anti-inflammatory drugs, e.g. corticosteroids
- malignant diseases, e.g. leukaemia, tumours of lymphoid tissue
- sharing of syringes by drug addicts, spreading human immunodeficiency virus (HIV).

Heart abnormalities

The sites most commonly infected are already abnormal in some way, e.g. valve cusps damaged by earlier attacks of rheumatic fever, endothelium damaged by the fast flow of blood through a narrow opening, such as a stenosed valve or congenital septal defect.

Acute infective endocarditis

This is a severe febrile illness usually caused by high-virulence microbes, commonly *Staphylococcus aureus*. Vegetations grow rapidly and pieces may break off, becoming infected emboli. These settle in other organs where the microbes grow, destroying tissue and forming pus. The effects depend on the organ involved, e.g. brain or kidney infection may cause death in a few days. The causative microbes rapidly destroy heart valves, impairing their function and resulting in acute heart failure.

Subacute infective endocarditis

This endocarditis is usually caused by low-virulence microbes, e.g. non-haemolytic streptococci or some staphylococci. Infected emboli may settle in any organ but do not cause suppuration and rarely cause death. Microbes in the vegetations seem to be protected by surrounding platelets and fibrin from normal body defences and antibiotics. Healing by fibrosis further distorts the shape of the valve cusps, increasing the original stenosis and incompetence. Heart failure may develop later.

Cardiac arrhythmias

The heart rate is normally initiated by intrinsic impulses generated in the SA node. The rhythm is determined by the route of impulse transmission through the conducting system. The heart rate is usually measured as the pulse, but to determine the rhythm, an electrocardiogram (ECG) is required (Fig. 5.58A). 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 (p. 88) gives rise to *normal sinus rhythm* which has a rate between 60 and 100 beats per minute.

Sinus bradycardia. This is sinus rhythm below 60 beats per minute. This may occur during sleep and is common in athletes. It is an abnormality when it follows myocardial infarction or accompanies raised intracranial pressure (p. 177).

Sinus tachycardia. This is sinus rhythm above 100 beats per minute when the individual is at rest. This accompanies exercise and anxiety; but is an indicator of some disorders, e.g. fever, hyperthyroidism, 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. 5.58B). Ventricular fibrillation and asystole cause sudden and complete loss of cardiac output, i.e. *cardiac arrest* and death.

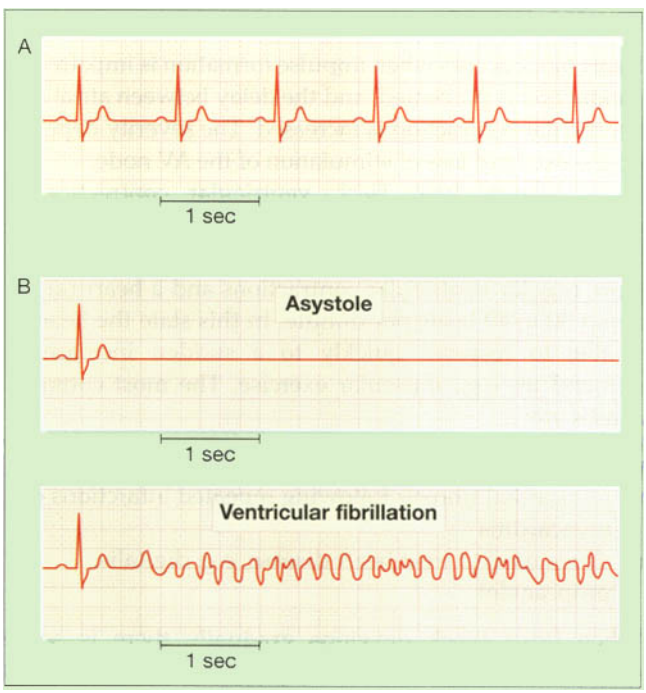


Figure 5.58 ECG traces: A. Normal sinus rhythm. B. Life-threatening arrhythmias.

Fibrillation

This is the contraction of the cardiac muscle fibres in a disorderly sequence. The chambers do not contract as a whole and the pumping action is disrupted.

In *atrial fibrillation* contraction of the atria is uncoordinated and rapid, pumping is ineffective and stimulation of the AV node is disorderly. Ventricular contraction becomes rapid and rhythm and force irregular; although an adequate cardiac output and blood pressure may be maintained, the pulse is irregular. The causes of increased excitability and disorganised activity are not always clear but predisposing conditions include:

- ischaemic heart disease
- degenerative changes in the heart due to old age
- thyrotoxicosis
- rheumatic heart disease.

In *ventricular fibrillation* there is disorganised and very rapid contraction causing disruption of ventricular function. Blood is not pumped from the heart into either the pulmonary or the systemic circulation. No pulses can be felt, consciousness is lost and breathing stops. The ECG shows an irregular chaotic trace with no recognisable wave pattern (Fig. 5.58B). If normal heart action cannot be restored quickly, death follows due to cerebral anoxia.

Heart block

Heart block occurs when impulse formation is impaired or conduction is prevented, and 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*, ventricular contraction is entirely independent of impulses initiated by the SA node. Impulses generated by the AV node result in slow, regular ventricular contractions and a heart rate of about 30 to 40 beats per minute. In this state the heart is unable to respond quickly to a sudden increase in demand by, e.g., muscular exercise. The most common causes are:

- acute ischaemic heart disease
- myocardial fibrosis following repeated infarctions or myocarditis
- drugs used to treat heart 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.

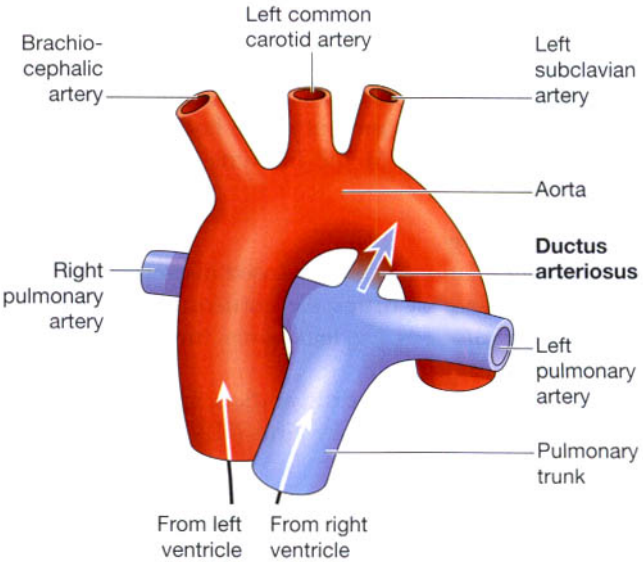


Figure 5.59 The position of the ductus arteriosus in the fetus. The arrow indicates the direction of flow of blood from the pulmonary circulation into the aorta.

Congenital abnormalities

Abnormalities in 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. Sometimes, there are no symptoms in early life and the abnormality is recognised only when complications appear.

Patent ductus arteriosus

Before birth the ductus arteriosus, joining the arch of the aorta and the pulmonary artery, allows blood to pass from the pulmonary artery to the aorta (Fig. 5.59). It carries blood pumped into the pulmonary trunk by the right ventricle into the aorta, bypassing the pulmonary circulation. At birth, when the pulmonary circulation is established, the ductus arteriosus should close completely. If it remains patent, blood regurgitates from the aorta to the pulmonary artery where the pressure is lower, reducing the volume entering the systemic circulation and increasing the volume of blood in the pulmonary circulation. This leads to pulmonary congestion and eventually cardiac failure.

Atrial septal defect

Before birth most oxygenated blood from the placenta enters the left atrium from the right atrium through the

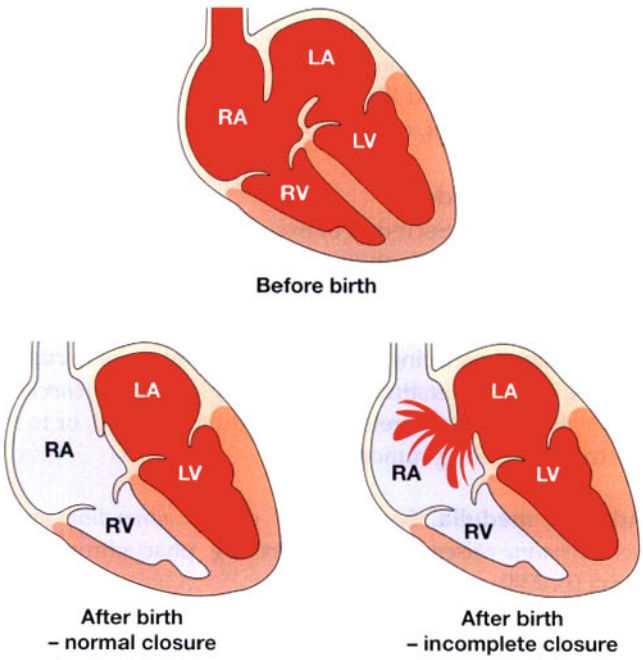


Figure 5.60 Atrioseptal valve: normal and defective closure after birth.

foramen ovale in the septum. There is a valve-like structure across the opening consisting of two partly overlapping membranes. The 'valve' is open when the pressure in the right atrium is higher than in the left. This diverts blood flow from the right to the left side of the heart, bypassing the pulmonary circulation. After birth, when the pulmonary circulation is established and the pressure in the left atrium is the higher, the two membranes come in contact, closing the 'valve'. Later the closure becomes permanent due to fibrosis (Fig. 5.60).

When the membranes do not overlap an opening between the atria remains patent after birth. In many cases it is too small to cause symptoms in early life but they may appear later. 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 gains access to 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 leads to hypertension in the upper body (which is supplied by arteries arising from the aorta proximal to the narrowing) because increased force of contraction of the heart is needed to push the blood through the coarctation. There is hypotension in the rest of the body.

Fallot's tetralogy

A characteristic combination of four congenital cardiac abnormalities, called the tetralogy of Fallot, 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.

DISORDERS OF BLOOD PRESSURE

Learning outcomes

After studying this section, you should be able to:

- define the term hypertension
- identify normal and abnormal blood pressure recordings, taking into account the age of the individual
- 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
- describe the term hypotension.

Hypertension

The term hypertension is used to describe blood pressure that is sustained at a higher than the generally accepted 'normal' maximum level for a particular age group, e.g.:

- at 20 years – 140/90 mmHg
- at 50 years – 160/95 mmHg
- at 75 years – 170/105 mmHg.

Arteriosclerosis (p. 114) contributes to increasing blood pressure with age but is not the only factor involved.

Hypertension is described as *essential* (primary, idiopathic) or *secondary to other diseases*. Irrespective of the cause, hypertension commonly affects the kidneys (p. 353).

Essential hypertension

This means hypertension of unknown cause. It accounts for 85 to 90% of all cases and is subdivided according to the rate at which the disease progresses.

Benign (chronic) hypertension

The rise in blood pressure is usually slight to moderate and continues to rise slowly over many years. Sometimes complications are the first indication of hypertension, e.g. heart failure, cerebrovascular accident, myocardial infarction. Occasionally the rate of progress increases and the hypertension becomes malignant. Predisposing factors include:

- inherited tendency
- obesity
- excessive alcohol intake
- cigarette smoking
- lack of exercise.

Malignant (accelerated) hypertension

The blood pressure is already elevated and continues to rise rapidly over a few months. Diastolic pressure in excess of 120 mmHg is common. The effects are serious and quickly become apparent, e.g. haemorrhages into the retina, papilloedema (oedema around the optic disc), encephalopathy (cerebral oedema) and progressive renal disease, leading to cardiac failure.

Secondary hypertension

Hypertension resulting from other diseases accounts for 10 to 15% of all cases.

Kidney diseases

Raised blood pressure is a complication of many kidney diseases. The vasoconstrictor effect of excess *renin* released by damaged kidneys is one causative factor but there may be others, as yet unknown.

Endocrine disorders

Adrenal cortex. Secretion of excess *aldosterone* and *cortisol* stimulates the retention of excess sodium and water by the kidneys, raising the blood volume and pressure. Oversecretion of aldosterone (Conn's syndrome) is due to a hormone-secreting tumour. Oversecretion of cortisol may be due to overstimulation of the gland by *adrenocorticotrophic hormone* secreted by the pituitary gland, or to a hormone-secreting tumour.

Adrenal medulla. Secretion of excess *adrenaline* and *noradrenaline* raises blood pressure, e.g. phaeochromocytoma (p. 234).

Stricture of the aorta

Hypertension develops in branching arteries proximal to the site of a stricture. In *congenital coarctation* the stricture is between the ductus arteriosus and the left subclavian artery causing hypertension in the head, neck and right arm. Compression of the aorta by an adjacent tumour may cause hypertension proximal to the stricture.

Hypertension may be a complication of some drug treatment, e.g.:

- corticosteroids
- non-steroidal anti-inflammatory drugs
- oral contraceptives.

Effects and complications of hypertension

The effects of long-standing and progressively rising blood pressure are serious. Hypertension predisposes to atherosclerosis and has specific effects on particular organs.

Heart

The rate and force of cardiac contraction are increased to maintain the cardiac output against a sustained rise in arterial pressure. The left ventricle hypertrophies and begins to fail when compensation has reached its limit. This is followed by back pressure and accumulation of blood in the lungs (pulmonary congestion), hypertrophy of the right ventricle and eventually to right ventricular failure. Hypertension also predisposes to ischaemic heart disease (p. 121) and aneurysm formation (p. 114).

Brain

Stroke, caused by cerebral haemorrhage, is common, the effects depending on the position and size of the ruptured vessel. 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 possibly death.

Hypertensive encephalopathy. Hypertensive encephalopathy is a rare condition in which hypertension is accompanied by neurological disturbance, e.g. papilloedema, difficulty with speech, paraesthesia, convulsions and loss of consciousness. It is usually reversed when hypertension is controlled.

Kidneys

Essential hypertension causes kidney damage. If sustained for only a short time recovery may be complete. Otherwise the kidney damage causes further hypertension owing to activation of the renin–angiotensin–aldosterone system (p. 223), progressive loss of kidney function and kidney failure.

Pulmonary hypertension

Raised blood pressure in the pulmonary circulation is secondary to:

- changes in blood vessels, described above
- chronic diseases of the respiratory system
- diseases of the heart, e.g. congenital defects of the septum, stenosis and incompetence of the mitral or aortic valve, heart failure
- diseases of other organs that cause raised pressure in the left side of the heart, e.g. cirrhosis of the liver, thrombosis of the portal vein.

Hypotension

This usually occurs as a complication of other conditions, e.g.:

- shock (p. 111)
- Addison's disease (p. 233).

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 syncope (fainting) is due to sudden reduction in blood pressure on standing up quickly from a sitting or lying position. It occurs most commonly in the elderly. It may be caused by delay in response of the baroreceptors in the carotid sinuses to the gravitational effects of standing up. It may also occur when patients are being treated with antihypertensive drugs, especially when the most appropriate dose is being established.