Option D Human physiology

Introduction

Human physiology involves examining not only the structures of the human body but also how they function together in harmony. Nerves and hormones work together under the control of the brain to ensure that the heart beats at the correct rate, that digestion is completed by all the right enzymes produced at the right times, and that our breathing rate matches our activity level. After digestion, nutrients are processed, stored or disposed of so that our cells have the resources they need to live, grow and repair themselves. If an emergency arrives, the body is prepared; and if we should move to a high altitude, our physiology is modified so that we adapt to the different conditions.

D1 Human nutrition

The food we eat keeps us alive and provides the nourishment we need to grow, repair our bodies and stay active. A balanced diet gives us all the essential substances that we need in just the right quantities. Our needs differ depending on our age, activities and lifestyle. Some people who do not get the balance right may become overweight, underweight or even seriously ill. The choices people make about what to eat depend on where they live but are also influenced by social issues.

Nutrients

Nutrients are chemical substances, found in foods that are used in the human body. We need a number of nutrients to build our bodies and to stay healthy. We obtain these from the foods we eat. **Essential nutrients** are those that cannot be made in the body and must therefore be included in the diet. Essential nutrients are:
- essential amino acids
- essential fatty acids
- vitamins
- minerals
- water.

Minerals and vitamins are both needed in very small quantities. Their chemical structures are quite different – vitamins are organic compounds, whereas minerals are usually derived from inorganic ions. For example, sodium in the diet is available as Na^+ ions.

Although carbohydrates are a very important part of the human diet, there are no specific carbohydrates that are essential so they are not included in this list.

Nutrient a chemical substance taken in by a living organism and used for growth or metabolism – for humans, nutrients are found in the food we eat

Learning objectives

You should understand that:
- Essential nutrients must be included in the diet because they cannot be synthesised by the body.
- Dietary minerals are chemical elements that are essential nutrients.
- Vitamins are chemically diverse carbon compounds that are essential nutrients.
- Some amino acids and some fatty acids are essential nutrients.
- A lack of essential amino acids affects protein production.
- Malnutrition can be caused by an imbalance, deficiency or excess of nutrients in the diet.
- A centre in the hypothalamus controls appetite.
- Overweight people are more likely to suffer with type II diabetes and hypertension (high blood pressure).
- Starvation can lead to the breakdown of tissue in the body.

Exam tip
Remember that the term 'essential nutrients' does not refer to all substances that the body needs, but only to necessary substances that the body can't synthesise for itself.

Figure D.1 Kwashiorkor is a protein deficiency disease seen in young children, resulting from a diet low in protein, energy and other nutrients. The children do not grow properly and suffer from edema, which causes the swollen appearance of their abdomen.

Malnutrition the insufficient, excessive or imbalanced consumption of nutrients, which leads to health problems

Aspartame

The artificial sweetener aspartame contains phenylalanine, so children with PKU must avoid it. You might have noticed labels on things like chewing gum and diet drinks, warning that the product contains phenylalanine – this warning is aimed at people with PKU, since phenylalanine is not harmful to most people.

Amino acids and proteins

To synthesise all the proteins in a human body, 20 different amino acids are needed. We can make some of these in our cells by converting certain nutrients into amino acids, but there are nine that cannot be synthesised and must be taken in as part of a healthy diet. These are known as **essential amino acids**.

Protein deficiency malnutrition can occur if an individual does not have enough of one or more of these essential amino acids. Protein deficiency can lead to poor growth and lack of energy, as well as loss of body mass. One of the most common conditions associated with protein deficiency is swelling of the abdomen (Figure **D.1**). A lack of protein in the diet prevents blood plasma proteins being produced properly. Blood plasma protein assists with the reabsorption of tissue fluid into blood capillaries and without it fluid remains in the tissues causing **edema** (swelling).

Phenylketonuria

Phenylketonuria (PKU) is a rare genetic metabolic disorder. In the USA, PKU occurs in only 1 in 15 000 births. It is caused by a mutation to a gene on chromosome 12. People who suffer from PKU lack an enzyme that is needed to process the amino acid phenylalanine. They are unable to make the liver enzyme tyrosine hydroxylase, which converts phenylalanine into another non-essential amino acid called tyrosine. Phenylalanine is essential for normal growth but if too much builds up in the blood, brain damage can result. The condition is treatable if it is diagnosed soon after birth. Babies and children with untreated PKU develop serious physical and mental health problems as levels of phenylalanine in their blood rise. In many parts of the world, a simple blood test at birth is used to identify babies with PKU. Children who are identified as having PKU must be given a special diet that is low in protein and especially low in the amino acid phenylalanine. They must avoid many common, high protein foods such as milk and dairy products, nuts, fish and meat. PKU only affects children until puberty. After this, they can have a normal diet.

Malnutrition, starvation or deficiency?

Malnutrition occurs when a person does not eat a balanced diet. The diet may mean the person is deficient in one or more nutrients, or suffers an imbalance from eating an excess of a particular nutrient. A person can eat a lot of food but still be malnourished.

Starvation is different from malnutrition – it occurs when an individual simply does not have enough to eat. Starvation can lead to the breakdown of body tissues as the individual first uses up stored carbohydrate and then protein from body structures as a source of energy for respiration.

A **deficiency** occurs when a person does not have enough of one particular nutrient and suffers health problems as a result.

Vitamins and minerals

Vitamins and minerals are usually listed together in diet information because, although they are both vital for good health, they are both needed only in very small quantities. Vitamins are chemically quite different from minerals and the two nutrient groups come from many different sources. Some key differences are shown in Table **D.1**.

The ability to synthesise vitamins varies in different animals. Most animals can synthesise vitamin C but there are a few notable exceptions including bats, guinea pigs, monkeys, apes and humans, which all need a dietary supply of vitamin C. Humans can synthesise vitamin D in the skin (see below) but cannot synthesise any other vitamins. A range of vitamins must be taken in as part of a healthy diet.

Vitamins are:	Minerals are:
made in plants and animals	substances derived from rocks or found dissolved in water
compounds	elements in ionic form e.g. phosphate (PO_4^-)
organic e.g. vitamin C ($C_6H_8O_6$)	inorganic e.g. iron (Fe^{2+}), calcium (Ca^{2+}), iodine (I^-)

Table D.1 Comparing vitamins and minerals.

Vitamin C

Nutritional labels on food products show the quantities of different nutrients that they contain, together with a recommended daily amount (RDA) for each one. The recommended level for vitamin C is about 50 mg per day. Vitamin C helps to protect the body from infection and is important in keeping bones, teeth and gums healthy and for synthesis of the protein collagen. A shortage of the vitamin leads to the deficiency disease called **scurvy**.

Two main techniques have been used to work out how much vitamin C a person needs each day. The first involves the use of animal tests and the second uses human test subjects.

During tests involving animals, small mammals such as guinea pigs, which cannot manufacture vitamin C, are fed diets containing different levels of the vitamin, while all other nutrients are controlled. Levels of vitamin C in the blood can be measured and the health of the animals is monitored. After a time, animals receiving insufficient vitamin C show signs of deficiency, such as poor collagen in bones and increased rates of infection. The data collected can be used to calculate the amount of vitamin C required by a human.

Humans were directly monitored during a number of medical investigations carried out in Sheffield, UK, during World War II. The subjects were conscientious objectors – pacifists, who were allowed to volunteer for experiments as an alternative to military service. The young men and women were fed diets lacking in vitamin C for 6 weeks but were given supplements of 70 mg of L-ascorbic acid each day. (L-ascorbic acid is the chemical term for vitamin C.) The subjects were then divided into three groups. The first group continued to receive 70 mg of L-ascorbic acid per day, the second was given 10 mg per day and the third group received no L-ascorbic acid at all. After 6–8 months on this regime,

Vitamin C is found in citrus fruits such as oranges and lemons, and strawberries and kiwi fruit are also rich sources. Fresh vegetables also contain vitamin C but the amount is reduced by cooking.

the volunteers deprived of vitamin C developed signs of scurvy while the other two groups did not.

The results indicated that 10 mg of vitamin C per day would be sufficient for good health but it is generally agreed that the recommended level should be higher to account for variation between people and provide a suitable level to protect people from scurvy and infection.

? Test yourself

1 Explain why all the human volunteers were deprived of vitamin C in their diet but given L–ascorbic acid for 6 weeks before the experiments.

Recommended daily amounts

The Vitamin and Mineral Nutrition Information System (VMNIS) was set up in 1991 to strengthen the surveillance of micronutrient deficiencies in the world. Different countries establish different values for RDAs of various nutrients. The RDAs for vitamin C for an adult from various authorities are shown below.

World Health Organization	45 mg day^{-1}
Canada	75 mg day^{-1} for women; 90 mg day^{-1} for men
UK	75 mg day^{-1}
USA	60–95 mg day^{-1}

Human experimentation

Between 1942 and 1946, Professor John Pemberton was a Medical Officer to the Research Team that carried out the medical experiments in Sheffield, including those on vitamin C, and he has written about that research. In his paper, published in the *International Journal of Epidemiology* (2006), he says:

'The Sheffield conscientious objectors demonstrated, once again, how valuable medical knowledge can be obtained by human experimentation, and sometimes in no other way, if volunteers can be found who are willing to undergo considerable discomfort, pain and even serious risks to the health. The contribution of the volunteers to medical knowledge during 1939–45 should not be forgotten.'

Questions to consider

Today, experiments like these would not be permitted under the Helsinki Agreement of 1975, which promotes human rights.

- What are the ethical issues involved in such trials?
- Can experiments in which subjects may be put at risk ever be justified?

A reputation on the line

Linus Pauling (1901–94) was an American biochemist who won two Nobel Prizes for his work. In 1986, in his book *How to Live Longer and Feel Better*, he suggested that very large doses of vitamin C, as high as 1000 mg per day, would provide protection against colds and other minor respiratory tract infections. There was no conclusive experimental evidence to back up his claims but he is believed by many people because of his reputation and fame.

Question to consider

- How important is reputation in deciding whether or not a new theory or proposal is a good one?

Vitamin D

Vitamin D (calciferol) is needed to ensure that sufficient calcium is absorbed in the digestive system to build healthy bones. Vitamin D deficiency can lead to softening or malformation of the bones, a condition known as **osteomalacia** or **rickets** (Figure **D.2**). This condition can be a problem in growing children and breastfeeding mothers whose vitamin D intake is low.

Vitamin D is obtained from foods such as oily fish, particularly salmon and tuna, egg yolk, liver and dairy products including milk, cheese and butter. In some countries, milk is fortified by adding supplements of vitamin D.

Vitamin D is one of the few vitamins that can be made in the body. It is synthesised in the skin when it is exposed to ultraviolet (UV) rays from the sun. Only a short exposure is needed but in some countries at extreme latitudes there is insufficient sunlight in winter months for vitamin D to be made. Fortunately, the liver can store vitamin D that is produced during the summer.

Osteomalacia and rickets

Osteomalacia causes bones to become softened because they do not contain sufficient of two vital minerals – calcium and phosphorus. There are several causes of osteomalacia but most occur as a result of faulty metabolism of vitamin D or phosphorus. **Rickets** is the term used for the condition when it occurs in children, for whom the consequences can be particularly severe because the bones are still growing.

Balancing risks

For vitamin D to be produced, sufficient light must reach the skin. If an individual stays out of the sunshine, or protects the skin with a sun-blocking cream or clothing, they may not receive enough UV rays. On the other hand, excessive exposure to UV light leads to an increased risk of malignant melanoma, a form of skin cancer. It is important to balance the need for sunlight with the risk of too much exposure.

Fair-skinned people should always protect their skin and avoid intense sunlight. To minimise the risk of skin cancer, they should only expose their skin during early morning or late afternoon when the sunlight is less intense. Individuals with darker skin, which is protected by increased amounts of melanin pigment, require more time in sunlight than fair-skinned people to produce the vitamin D they need. The amount of time depends on the intensity of the sunlight, and therefore varies with distance from the equator and with the seasons of the year.

Both exposure to the sun and complete protection from it carry some risks. It is important to consider these risks but impossible to avoid them completely.

Question to consider

- How can conflicting knowledge claims be balanced?

Figure D.2 People who suffer from rickets have bone deformities because vitamin D is vital for the incorporation of calcium and phosphorus into the bone matrix.

Appetite control

The **appetite control centre** is found in the **hypothalamus** at the base of the brain. Its job is to signal to the body when sufficient food has been eaten and the body has reached satiation. The hypothalamus receives information in four important ways:

- When the stomach is full, receptors in the stomach wall send messages to the brain via the vagus nerves.
- When food enters the small intestine, it secretes a peptide hormone called PYY 3-36, which suppresses appetite.
- Another hormone, leptin, is released by adipose (fat) tissue and this also suppresses appetite – a person who has more adipose tissue has more leptin-secreting cells (Subtopic **6.6**).
- Insulin from the pancreas, released as food is absorbed, also suppresses appetite.

Evidence for the importance of the hypothalamus in controlling the feeling of hunger has come from people who have damage in that area of the brain. In many cases, they have severe appetite-control problems being either unable to eat or unable to stop eating. Despite the controls that the hypothalamus provides for us, almost everyone can be encouraged to eat when they are not hungry by the appearance or smells of delicious food, or if we are tempted by enticing advertisements.

Risks associated with excessive body weight

Carbohydrates in the form of sugars and starch are the body's main source of energy, but if the energy is not used for day-to-day activities, the excess is stored either as glycogen in the liver and muscles, or as fat. The body's capacity to store glycogen is limited so eating an excess of carbohydrate means that fat reserves build up and over a long period of time can lead to weight gain and obesity.

Fat contains twice as much energy as carbohydrate, so eating an excess of fatty foods is very likely to lead to obesity. There is also a substantial risk of heart disease and other cardiovascular problems associated with an excess of saturated and *trans* fatty acids in the diet. (You can review the structures of these fats in Subtopic **2.3**.)

Type II diabetes

Type II diabetes is the most common form of diabetes, accounting for nine out of ten cases worldwide. It is also known as late-onset diabetes or non-insulin-dependent diabetes mellitus. Individuals who have the condition develop insulin resistance, which means that the receptor cells that normally respond to insulin fail to be stimulated by it, even though the beta cells in the pancreas still produce insulin (Subtopic **6.6**).

Causes and symptoms

The causes of type II diabetes are not fully understood but there is a strong correlation of risk with weight and diet. High levels of fatty acids in the blood may be a factor causing the condition and people whose diets are high in fat but low in fibre seem to be most at risk. Obesity, associated with a lack of exercise or a genetic makeup that influences fat metabolism, is a key risk factor. The condition is more common in older people but there are an increasing number of cases in overweight children.

Some ethnic groups are more likely to develop type II diabetes and this provides evidence for a genetic link to a predisposition to the condition. Aboriginal Australians, people of Asian and Afro–Caribbean origin, Native Americans and Maori peoples are all at a higher risk.

The symptoms of type II diabetes tend to develop slowly but include:

- high glucose levels in the blood
- glucose in the urine
- frequent need to urinate, which leads to dehydration and increased thirst
- tiredness and fatigue
- some loss of weight.

Hypertension and CHD

The relative amounts of different types of fatty acid in a person's diet can, in many cases, be correlated with health issues. Diets in societies around the world are very different and so is the incidence of coronary heart disease (CHD) and other diet–related illnesses. Diets in Mediterranean and Asian populations, such as those in Greece and Japan, tend to include a high intake of vegetables, fruit and wholegrain products, and lower amounts of fish and red meat, high-fat dairy products and other animal products. These populations have relatively low rates of CHD.

Eating a diet that is high in saturated fatty acids has been shown to have a positive correlation with an increased risk of CHD and other diseases of the circulatory system, including hypertension (high blood pressure). Saturated fatty acids can be deposited inside the arteries, and if the deposits combine with cholesterol they may lead to atherosclerosis, which reduces the diameter of the lumen and leads to hypertension (Figure **D.3**). Reliable evidence suggests that in countries where the typical diet is high in saturated fatty acids, and many high–fat foods, animal products and processed foods are eaten, there is likely to be a high incidence of CHD. Since all fatty acids are high in energy, an excess of these foods in the diet can also lead to obesity, which places a further strain on the heart.

Correlation and cause

Differences in CHD rates between countries may also be due to differences in other CHD risk factors, including physical activity and obesity, and not only be due to diet. It is important to remember that correlation between two variables does not necessarily indicate cause. In addition, dietary patterns vary with gender, socioeconomic status, culture and ethnic group.
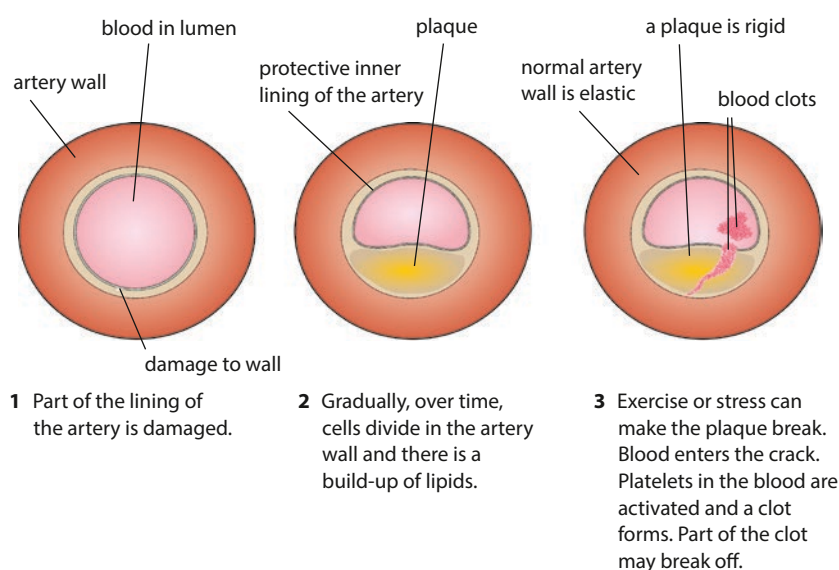

1 Part of the lining of the artery is damaged.

2 Gradually, over time, cells divide in the artery wall and there is a build-up of lipids.

3 Exercise or stress can make the plaque break. Blood enters the crack. Platelets in the blood are activated and a clot forms. Part of the clot may break off.

Figure D.3 The development of atherosclerosis in an artery.

Another indicator of the risk of CHD is the level of cholesterol in an individual's blood. **Cholesterol** is a steroid that is synthesised in the liver and found almost exclusively in foods of animal origin. It forms part of the cell membrane and it helps in the transport of substances in and out of cells, communication between cells and the conduction of impulses along nerve cells. Cholesterol is carried in the blood to the liver, where it can either be broken down or excreted in the bile (Subtopic **D3**). Cholesterol is transported around the body in the form of two types of **lipoprotein**.

- **Low–density lipoproteins** (**LDLs**) are often referred to as 'bad cholesterol' because they do not travel easily in the bloodstream and can clog up arteries, causing atherosclerosis, CHD or stroke. Raised LDL levels in the blood frequently occur in people who have high levels of saturated or *trans* fatty acids in their diet.
- **High–density lipoproteins** (**HDLs**) are sometimes known as 'good cholesterol'. HDLs are carried easily in the blood and do not contribute to blockages in the arteries. Evidence also suggests that HDL cholesterol can help to remove LDLs from arteries.

A definite link has been found between the intake of saturated fats in the diet and the level of cholesterol in the blood. High levels of saturated fats in food increase both LDL and total blood cholesterol levels. There is also a clear correlation between saturated fats in the diet and CHD. Medical professionals recommend reducing the intake of saturated fats to reduce blood cholesterol and the risk of a heart attack. However, it may be that reducing the levels of cholesterol in the form of LDLs is more important than reducing the total cholesterol level in the blood.

Starvation

Starvation occurs when an individual simply does not have enough to eat. Starvation can lead to the breakdown of body tissues as the individual first uses stored carbohydrate and then protein from muscles and other tissues as a source of energy.

One extreme case of starvation is **anorexia nervosa**, an eating disorder in which individuals stop eating a balanced diet and become seriously underweight because they have an obsessive fear of gaining body mass. The condition has psychological causes and people with the disorder are unable to appreciate that they have a problem, often perceiving themselves as overweight despite being normal or underweight. The condition affects mostly young women – approximately 90% of cases of anorexia nervosa are in females, with few men or boys being affected.

Among the many consequences of anorexia nervosa are serious disturbances of the endocrine system, anemia, and loss of hair and muscle mass. The lack of food causes dehydration and low blood pressure, which in turn can cause fainting and, in the longer term, damage to the kidneys and liver. In extreme cases, not only voluntary muscle but also heart muscle may be broken down to supply amino acids that can be used for respiration. A shortage of calcium can permanently damage the teeth and weaken bones, while a shortage of other ions can lead to irregular heart beat or even a heart attack.

Nature of science

Falsification of theories – replacement of one theory with another

Early investigations into vitamin C deficiency and scurvy proved unsuccessful because the animals used in the studies were laboratory rats and mice. If these animals were deprived of dietary vitamin C they showed no signs of scurvy. This led to the suggestion that scurvy was exclusively a human condition. It was not until laboratory guinea pigs were studied that the ability of animals to synthesise their own vitamin C was considered. Researchers concluded that scurvy was not exclusive to humans but was limited to those mammals that are unable to synthesise the vitamin in their own bodies.

? **Test yourself**

   2 Define what is meant by 'essential nutrient'.
   3 State where in the body the appetite control centre is located.

D2 Digestion

Digestive juices

Saliva, gastric juice and pancreatic juice

Digestive juices contain many different enzymes and other substances that assist with digestion (Subtopic **6.1**). The contents of secretions from exocrine glands in the mouth, stomach and pancreas are summarised in Table **D.2**.

Digestive juice	Site of production	Contents
saliva	salivary glands in the mouth	• water • mucus • salivary amylase
gastric juice	gastric glands in the stomach wall	• water • mucus • pepsin secreted as pepsinogen • hydrochloric acid
pancreatic juice	exocrine cells in the pancreas	• water • pancreatic amylase • trypsin secreted as trypsinogen • pancreatic lipase • carboxypeptidase chymotrypsin • hydrogencarbonate (HCO_3^-) ions

Table D.2 The contents of saliva, gastric juice and pancreatic juice.

   Pepsin and trypsin are protease enzymes that digest protein and are therefore potentially harmful to the cells that produce them and structures that they come into contact with. In order to prevent damage

Learning objectives

You should understand that:
- The secretion of digestive juices is controlled by nervous and hormonal stimulation.
- Exocrine glands secrete into the lumen of the intestine or onto the surface of the body.
- The volume and content of gastric secretions released into the stomach and small intestine is carefully regulated by nervous and hormonal mechanisms.
- The acidic nature of the stomach provides a favourable environment for some types of hydrolysis and also helps to kill pathogens in ingested food.
- The cells of the epithelium of the villi are adapted to absorb food.
- There is a positive correlation between the rate of transit of material through the large intestine and the fibre content of the material.
- Materials that are not absorbed in the gut are egested.

to the proteins in body cells, both these enzymes are secreted as inactive **precursors**: pepsinogen and trypsinogen, respectively. These are converted to their active form where they are needed, after secretion.

- **Pepsinogen** is converted to **pepsin** in the stomach when in the presence of hydrochloric acid, which is secreted by different cells in the stomach lining. The inner lining of the stomach is protected from both hydrochloric acid and pepsin by a thick layer of mucus.
- **Trypsinogen** is activated by the enzyme enterokinase (or enteropeptidase), which converts trypsinogen to **trypsin**. The activating enzyme is secreted by the walls of the small intestine when food enters from the stomach.

Exocrine glands

Digestive juices are produced in **exocrine glands** in the mouth (salivary glands), in the stomach wall (gastric glands) and in the exocrine tissue of the pancreas. All exocrine glands secrete their products via ducts to where they are needed. Cells of an exocrine gland that produces digestive juices are arranged in a single layer around small ducts that are connected to the intestine. One group of exocrine cells arranged around a duct is called an **acinus** (Figure **D.4**) and one exocrine gland contains many acini. The small ducts join together to form one larger duct, which carries the secretions to their destination.

Exocrine gland cells of the digestive system produce enzymes that are proteins and so the cells contain an extensive rough endoplasmic reticulum, which is the site of protein synthesis. Also visible inside the cells are numerous ribosomes, Golgi apparatus for packaging and processing the enzymes and large numbers of vesicles, which store enzymes before they are secreted by exocytosis into the ducts of the gland. Exocrine cells also contain a clearly visible nucleolus in the nucleus for the production of ribosome subunits, and numerous mitochondria to produce ATP for protein synthesis (Figure **D.5**).

Exam tip

Remember the differences between exocrine and endocrine glands:

- **Exocrine** glands, such as salivary glands and sweat glands, produce secretions that pass along ducts to their site of action. They are not part of the endocrine (hormonal) system.
- **Endocrine** glands secrete hormones directly into the bloodstream and they travel in the circulation to their target organs.
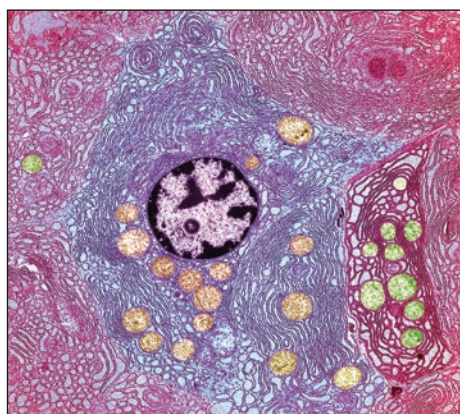

Figure D.5 Coloured electron micrograph of a pancreatic cell showing rough endoplasmic reticulum and many mitochondria.
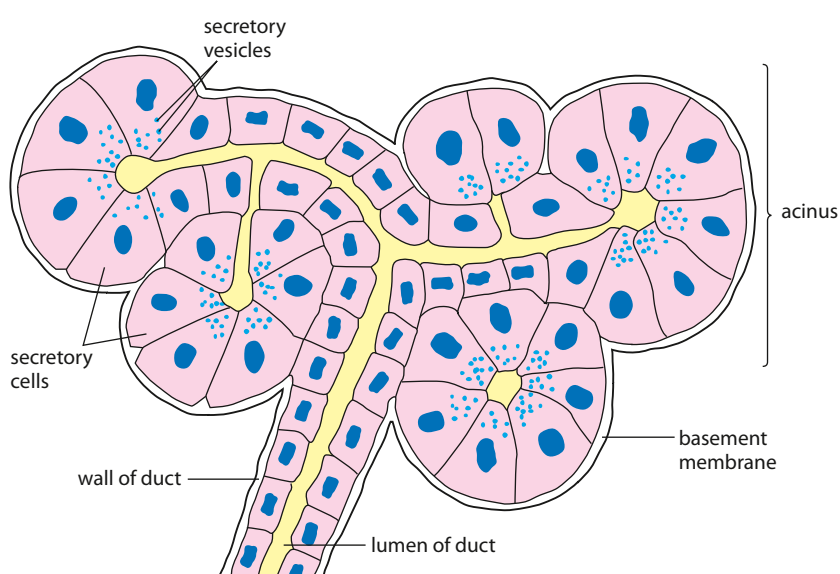

Figure D.4 A group of acini in exocrine tissue of the pancreas.

Stomach acid

Hydrochloric acid released into the stomach maintains the contents at pH 2, which is the optimum pH for the hydrolysis of protein molecules by protease enzymes. The acid conditions denature proteins so that peptide bonds in protein molecules are exposed to protease enzymes. Acidic conditions also kill bacteria that may be present on ingested food.

Gastric acid is produced by cells known as **parietal cells**, which line the stomach. In the plasma membranes of these cells are hydrogen–potassium pumps with ATPase enzymes, which pump H^+ ions from the cell into the stomach lumen. Parietal cells are stimulated to increase acid production when it is needed. Other cells in the stomach release hydrogen carbonate ions, which prevent the contents becoming too acidic, and also produce mucus forming a barrier against the stomach contents so that the lining is not damaged by the acid.

Excess acid in the stomach can cause acid indigestion, which, in mild cases, can be treated with proprietary antacid preparations. But if a person suffers from excess acid for long periods of time, the amount of acid that their stomach produces may need to be controlled. Acid production can be reduced using proton pump inhibitors (PPIs), a group of drugs that are very effective inhibitors of acid secretion, and are used to treat indigestion, acid reflux and stomach ulcers. PPIs work by blocking the hydrogen–potassium pumps and ATPase enzymes in the plasma membranes of the parietal cells, the last step in the H^+ secretion process.

Control of secretion of digestive juices

The production of digestive juices requires energy, and large numbers of mitochondria can be seen in the exocrine cells that produce them (Figure **D.5**). The body controls the secretion of digestive juices so that they are released at the correct time when food is present in the alimentary canal and so that neither enzymes nor energy are wasted. Both the nervous and hormonal systems are involved in controlling the volume and content of digestive juices that are produced.

Experience tells us that the sight or smell of food stimulates the production of saliva, and the nerve impulses that cause this response also stimulate the release of gastric juice in the stomach. Both responses are **reflex actions**. When food enters the stomach, more gastric juice is released as touch and stretch receptors in the stomach wall send impulses to the brain. Chemoreceptors in the stomach lining also send impulses to the brain, which controls the continued stimulation of the gastric glands.

Nerve impulses also pass to **endocrine glands** in the stomach wall that produce the hormone gastrin. Gastrin is released into the bloodstream and stimulates gastric glands to produce more hydrochloric acid and continue the production of gastric juices for periods of several hours. If lipids are present in the stomach, the hormone enterogasterone is also released. This hormone decreases the flow of gastric juice and delays the exit of fat-containing food from the stomach. As partly digested food leaves the stomach, two further hormones – secretin and CCK-PZ (cholecystokinin–pancreozymin) – are released from the small intestine. The effects of these hormones, which are all produced by endocrine glands and released into the bloodstream, are summarised in Table **D.3**.

Exam tip
Sketch a flow diagram to show the interaction of hormones, glands and nerve impulses involved in controlling digestive juices.

Hormone	Site of production	Effect of hormone
gastrin	stomach wall	• stimulates production of hydrochloric acid (HCl) and gastric juices
enterogasterone	stomach wall	• slows flow of gastric juice • slows exit of fats from stomach
secretin	small intestine	• stimulates the pancreas to release hydrogen carbonate (HCO_3^-) ions to neutralise acidic chyme (partly digested food) from the stomach
CCK-PZ (cholecystokinin)	small intestine	• stimulates the release of bile from the gall bladder (Subtopic **D3**) • and the release of pancreatic enzymes into the small intestine

Table D.3 Hormones involved in the control of intestinal secretions.

Important digestive disorders

Helicobacter pylori infection and stomach ulcers

Helicobacter pylori is a spiral-shaped bacterium that is able to grow in the human stomach. Unlike other bacteria, it can tolerate acidic conditions and survives well at the pH values found in the stomach. The organism was brought to the attention of the medical profession in the 1980s by two Australians – Dr Barry Marshall and Dr Robin Warren – who isolated it from the stomach linings of patients who were suffering from stomach ulcers and inflammation of the stomach lining (gastritis). Marshall and Warren proposed that *H. pylori* caused these symptoms. Until this time, stomach ulcers were thought to be caused by the excess secretion of acid, which caused damage to the stomach lining. Ulcers were associated with a stressful lifestyle, which was said to cause excess production of gastric juice. Since the 1980s, plenty of evidence has been gathered to support the hypothesis proposed by Marshall and Warren.

- Ulcers used to be treated with antacid treatments, which relieved the symptoms for relatively short periods of time. Today, antimicrobial drugs that kill bacteria and remove *H. pylori* infection provide long-term relief of symptoms and cure ulcers.
- *H. pylori* is regularly found in patients with both gastritis and ulcers. Many strains of the bacterium produce toxins that cause inflammation of the stomach lining.

Stomach cancer occurs far more frequently in patients who are infected for many years with strains of *H. pylori* than in non-infected people, so the bacterium seems to increase the risk of stomach cancer. But millions of people are infected with these bacteria and most of them do not get stomach cancer so there must be other factors at work. *H. pylori* has not been established as the sole cause of stomach cancer.

Cholera and the effect of cholera toxin

Cholera toxin is produced by virulent strains of the cholera bacterium *Vibrio cholerae*, which can infect the intestine if ingested in contaminated water or food. The toxin binds to surface receptors on mucosal cells of the intestine known as enterocytes. The cells take in the toxin, which disrupts proteins inside the cell leading to over-production of cAMP. cAMP modifies a chloride channel protein in the cell membrane so that chloride ions are pumped out of the cell in a process involving ATP. This efflux of chloride ions is followed by the secretion of water, sodium ions, potassium

ions and hydrogencarbonate ions into the intestine. The cells replace lost water and ions from the blood in a continuous process, so that the overall effect of the toxin can be a loss of up to 2 litres of fluid per hour from the intestine. A person with cholera quickly becomes severely dehydrated, suffering from devastating diarrhea (so-called 'rice water' feces), which can contaminate water and spread the cholera bacteria to others.

Cholera in the world today

The worldwide incidence of cholera is a cause for concern but it is less prevalent today in areas where public sanitation is good and clean water is available. International agreements mean that people must be vaccinated before they travel to infected areas. In 2011, 32% of all cholera cases reported to the WHO were from Africa, which was a considerable reduction from 2001–09, when about 95% of cases were from that continent. Cholera outbreaks can be caused by damage to sanitation systems during times of war, natural disasters such as earthquakes, or when people are displaced from their homes. Following the 2010 earthquake in Haiti, there has been a serious cholera outbreak which began in October that year and has continued. It is thought to be the worst epidemic of cholera for two decades. By August 2013, it had killed over 8000 people and the situation was made worse by the fact that many people were living and being treated in tented camps, without proper sanitation systems.

A paradigm shift

'No one believed it', Staffan Normark, a member of the Nobel Assembly at the Karolinska institute, said at a news conference.

The discovery of *Helicobacter pylori* is an example of a paradigm shift. This term was first used by an American philosopher Thomas Kuhn in his book *The Structure of Scientific Revolutions* (1962). It describes a change in assumptions within a ruling scientific theory. A paradigm shift occurs when there are a significant number of anomalies that counter the accepted paradigm – in this case, the belief that bacteria could not survive in the stomach and that ulcers were caused by excessive acid production. The accepted theory is thrown into a state of crisis until a new paradigm is formed and gains its own followers. For a time, an intellectual 'battle' will occur between the followers of the old and new paradigms.

For some time after Marshall and Warren's initial discovery of *H. pylori* in their patients, the well-established idea that bacteria could not survive in acid conditions persisted, despite evidence to the contrary. The men's proposed hypothesis was outside the mainstream view of the time (even though there had been some anecdotal and published evidence regarding antibiotic treatment of ulcers), and Marshall and Warren had to persevere in the face of considerable scepticism. They tested their theory, gathered evidence to support it, published their results and eventually they overturned the prevailing notion that ulcers were caused by stress and diet, based on the evidence of their experiments. Marshall even decided to deliberately infect himself with the bacterium in 1985 in order to show from his own experience that it caused stomach inflammation, a potential precursor of an ulcer. Their persistence paid off and the two men were awarded Nobel Prize for medicine in 2005 for showing that bacterial infection was to blame for painful ulcers in the stomach and intestine.

Questions to consider

1 Marshall and Warren used themselves as experimental subjects to provide evidence to support their hypothesis. Do you think there is a case for carrying out research on human subjects?
2 Discuss the ethical implications of doing research on humans.

Absorption of food

Structure of the small intestine

Absorption of digested food occurs in the ileum, which is part of the small intestine (Subtopic **6.1**). The structure of this region is related to its function. The surface area provided for absorbing food is increased enormously by folding of its inner lining into structures known as villi (Figure **D.6**) and each villus contains capillaries and a lacteal to transport absorbed molecules.

The inner lining of the small intestine is known as the **intestinal mucosa**. It is this layer that is responsible for absorbing food. The longitudinal and circular muscles in the intestine wall contract to move food along.

Villus
(enlarged view)

Small intestine with villi

columnar epithelium cells

Microvilli on surface of epithelial cells

capillary
network

lacteal

This is a light micrograph of a transverse section through the small intestine. Look back at Figure **6.2** (in coursebook), and see if you can identify the tissue layers.

smooth
muscle

arteriole

venule
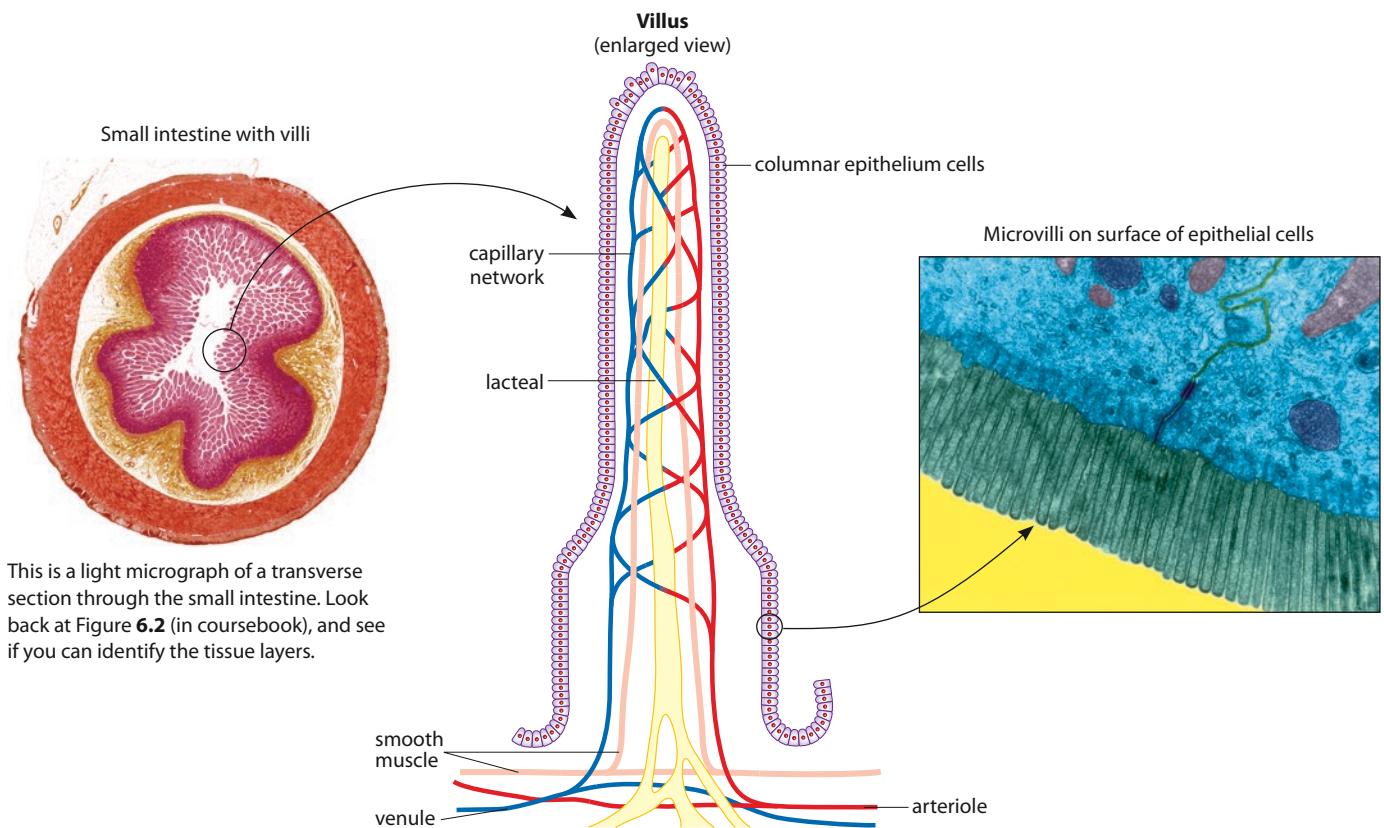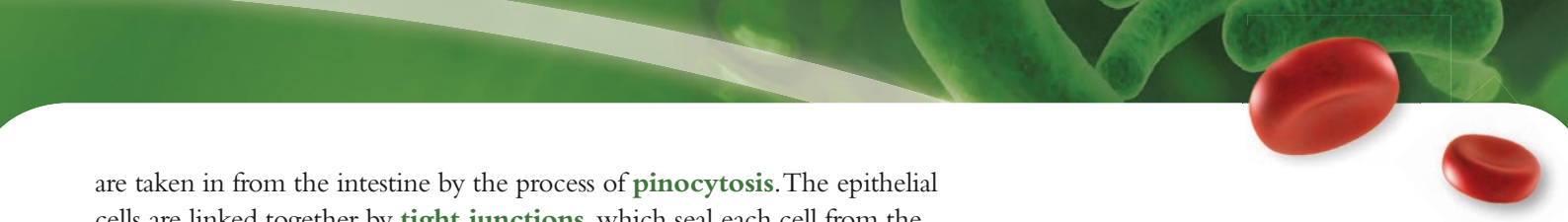
Figure D.6 The structure and microstructure of the small intestine.

Structure of a villus

Each fold of the intestinal mucosa is known as a **villus** and each villus also has many tiny projections known as **microvilli**. These structures produce a very large surface area for the absorption of digested materials.

Digested material must pass through the microvilli of the epithelial cells that make up the villi in order to reach a capillary or lacteal vessel. These epithelial cells contain structures that are vital to the processes of absorption. They have many mitochondria indicating that some absorption occurs using active transport and requires energy. In addition, many vesicles are present and these structures show that some materials

are taken in from the intestine by the process of **pinocytosis**. The epithelial cells are linked together by **tight junctions**, which seal each cell from the adjacent cell. The two adjacent membranes share some proteins and the tight junction between them prevents materials passing in between the cells. Most molecules are forced to pass straight through the cells from the lumen of the small intestine and into capillaries on the other side.

Digested molecules are small enough to pass through the epithelial cells and into the bloodstream. Movement can occur by a number of means (Subtopic **1.4**).

- **Simple diffusion** can occur if molecules are small and can pass through the hydrophobic part of the plasma membrane. For example, short-chain fatty acids and vitamins A, D, E and K are absorbed by simple diffusion.
- **Facilitated diffusion** occurs in the case of molecules such as fructose, which are hydrophilic. Channel proteins in the epithelial cell membrane enable these molecules to move, provided they are small enough and there is a concentration gradient which permits diffusion.
- **Active transport** is used to transport molecules that do not have a sufficiently high concentration gradient to pass by diffusion. Glucose, amino acids and mineral ions are all absorbed by this method. Mitochondria produce the ATP needed for active transport by the membrane pumps.
- **Pinocytosis** also draws in small drops of liquid from the ileum. Each droplet is surrounded by small sections of membrane that invaginate to form a vesicle. The vesicles are taken into the cytoplasm where their contents can be released.

Undigested material

Materials such as cellulose, which cannot be digested or absorbed, pass right through the intestine and are **egested** as part of the solid waste, or feces. Feces contain not only cellulose but also lignin from plant cell walls and bacteria that live in the digestive system and are carried through it. Cells of the intestine wall that are worn away as food travels past them also form part of the feces, as well as bile pigments containing material from the breakdown of red blood cells, which give the feces their familiar colour. The rate at which these materials pass through the large intestine is influenced by the amount of fibre in the feces.

Dietary fibre is found in cereals, fruits and vegetables. Fibre is made up of the indigestible parts or compounds of plants, which pass relatively unchanged through the stomach and intestines. There are two categories of fibre and both are beneficial to the body and important in a healthy diet. Most plant foods contain a mixture of both types.

- **Soluble fibre** includes pectins, gums and mucilage, which are found mainly in fruits, vegetables, oat bran, beans and lentils. Soluble fibre soaks up water like a sponge, which helps to slow down the rate of digestion and helps the contraction of intestinal muscles. This type of fibre lowers LDL ('bad') cholesterol levels (Subtopic **D1**).
- **Insoluble fibre** includes cellulose, hemicelluloses and lignin, which make up the structural parts of plant cell walls and are found in bran, fruit skins, vegetables and wholegrain foods. The most important role of insoluble fibre is to add bulk to feces, which therefore pass through

the colon more easily, preventing constipation and associated problems. Insoluble fibre, which does not absorb water, speeds up the time that food takes to pass through the gut – there is a positive correlation between the amount of insoluble fibre in a person's diet and the rate of transit of materials through the large intestine. This type of fibre helps to reduce the risk of colon cancer.

Nature of science

Serendipity in science – the role of gastric acid in digestion

William Beaumont (1785–1853) was a United States Army doctor. As a result of a chance meeting with a Canadian fur trapper who had been shot in the stomach, he became famous for his studies of digestion in the stomach and is sometimes known as the 'father of gastric physiology'.

The Canadian fur trapper, Alexis St Martin, was wounded in an accident in 1822 and Beaumont was called to treat him. The wound was reported to be 'more than the size of the palm of a man's hand' and, although it healed, a year later small holes were still present in St Martin's skin. Over a period of years, Beaumont was able to lift a flap of skin and observe St Martin's stomach beneath. He not only watched the digestive process, he also extracted gastric juices and studied how they worked. He used extracted gastric juice to digest meat in his laboratory and then compared this with the digestion of a similar piece of meat that he inserted, attached to a string, into St Martin's stomach. Beaumont studied the digestion of a range of foods and also investigated the effect of emotion on digestion. Beaumont and St Martin worked together over a period of years and in 1833, Beaumont published his research as *Experiments and Observations on the Gastric Juices and the Physiology of Digestion*. He described many aspects of the digestive process and even suggested that alcohol could cause damage to the stomach.

The serendipitous meeting of Beaumont and St Martin had an important impact on the understanding of digestion and Beaumont became the first person to observe digestion in the stomach directly. Interestingly, St Martin did not suffer any ill effects from his wound or Beaumont's experiments. He died at the age of 86, outliving Beaumont by almost 30 years.

? Test yourself

4 Outline the importance of the acid conditions in the stomach.
5 Explain how the structure of intestinal epithelial cells is related to their function.
6 State the importance of fibre in the human diet.

D3 Functions of the liver

Structure of the liver

The liver is the largest internal organ in the body and makes up 3–5% of our body weight. It is situated just below the diaphragm and has many important roles including detoxification of poisons, recycling the constituents of worn out erythrocytes, storage of nutrients and the production of bile and plasma proteins.

The liver is an unusual organ because it is supplied by two large blood vessels, rather than one (Figure **D.7**). The first is the hepatic artery, a branch of the aorta, which carries oxygenated blood to the liver, and the second is the hepatic portal vein, which carries blood from the intestine. Blood in the hepatic portal vein is rich in nutrients that have been absorbed by capillaries in the small intestine. Of the total volume of blood in the body, 20% flows through the liver at any time.

The liver is divided into **lobules**, which are rows of **hepatocytes** (liver cells) arranged in a circular pattern around a central vein (Figure **D.8**). Between the rows of cells are **sinusoids**, which are a type of blood capillary that is much larger than the capillaries of other tissues. Blood from branches of both the hepatic portal vein and the hepatic artery flows along the sinusoids. The endothelial cells that line the sinusoids are very thin and well spaced. These structural features help with absorption of substances into the surrounding hepatocytes (Figure **D.8**).

Attached to the walls of the sinusoids are numerous phagocytes called Kupffer cells, which remove and break down bacteria and damaged red blood cells (erythrocytes). Blood from the sinusoids flows into the central veins, which unite to form the hepatic vein. The hepatic vein leaves the liver and joins the vena cava.

Learning objectives

You should understand that:
- Toxins are removed from the blood and detoxified by the liver.
- The liver recycles components of red blood cells (erythrocytes).
- The breakdown of red blood cells (erythrocytes) begins with phagocytosis by Kupffer cells.
- Recycled iron is taken to the bone marrow and used to make hemoglobin in new red blood cells.
- Excess cholesterol is converted to bile salts.
- Plasma proteins are produced in hepatocytes, by the endoplasmic reticulum and Golgi apparatus.
- Blood from the small intestine flows to the liver, which regulates nutrient levels in the blood.
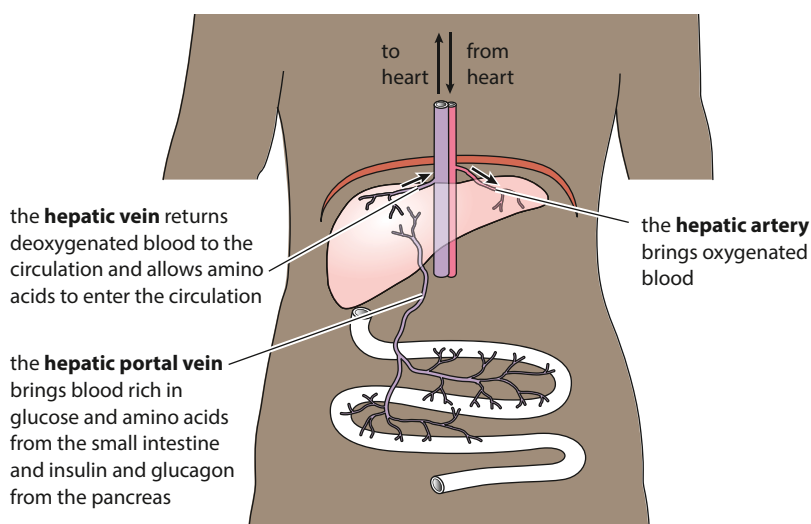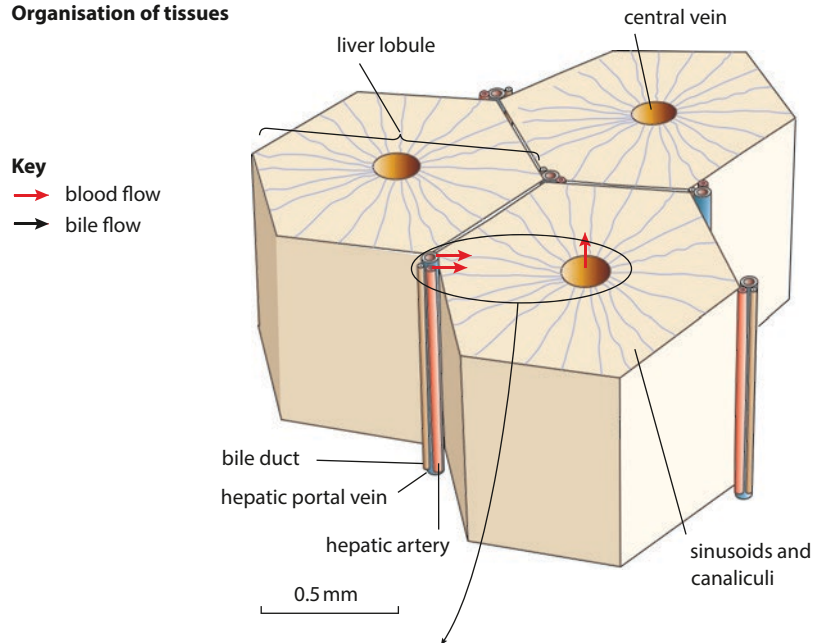- The liver can store certain nutrients that are present in excess.

the **hepatic vein** returns deoxygenated blood to the circulation and allows amino acids to enter the circulation

the **hepatic portal vein** brings blood rich in glucose and amino acids from the small intestine and insulin and glucagon from the pancreas

to heart   from heart

the **hepatic artery** brings oxygenated blood

Figure D.7 Blood supply of the liver.

Organisation of tissues

liver lobule

central vein

Key

→ blood flow

→ bile flow

bile duct

hepatic portal vein

hepatic artery

sinusoids and canaliculi

0.5 mm

Structure

bile to gall bladder

bile canaliculus

hepatocyte

blood to hepatic vein

bile duct

central vein

blood from hepatic portal vein

blood from hepatic artery

sinusoids

Kupffer cell

0.1 mm
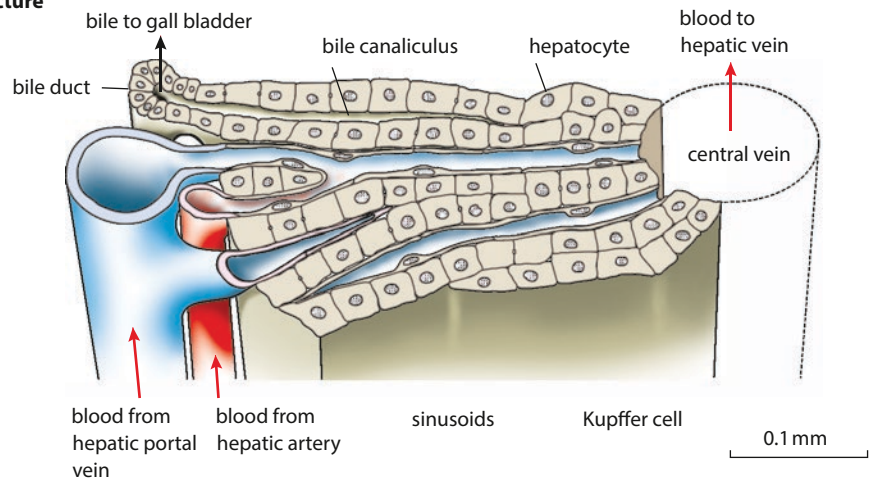
Figure D.8 Structure of a liver lobule.

Liver functions

Detoxification

The liver has an essential role in removing toxins from the blood and **detoxifying** them. Hepatocytes absorb toxins and convert them into non-toxic or less toxic products. Some of the toxins are by-products of metabolic reactions, such as lactate from anaerobically respiring muscles or hydrogen peroxide produced by processes including fatty acid metabolism. These toxins are broken down by the enzyme catalase. Other toxins that the liver processes are ingested substances such as alcohol, food additives and pesticides.

Erythrocyte and hemoglobin breakdown

Red blood cells survive in the bloodstream for about 120 days before they must be replaced with new cells from the bone marrow. At the end of their lives, red blood cells may break into fragments as their membranes become weakened and thus release free hemoglobin into the bloodstream. Cell fragments and hemoglobin are taken in by phagocytosis by the Kupffer cells in the sinusoids of the liver and the component parts of hemoglobin are broken down for recycling or excretion. This is shown in Figure **D.9**.
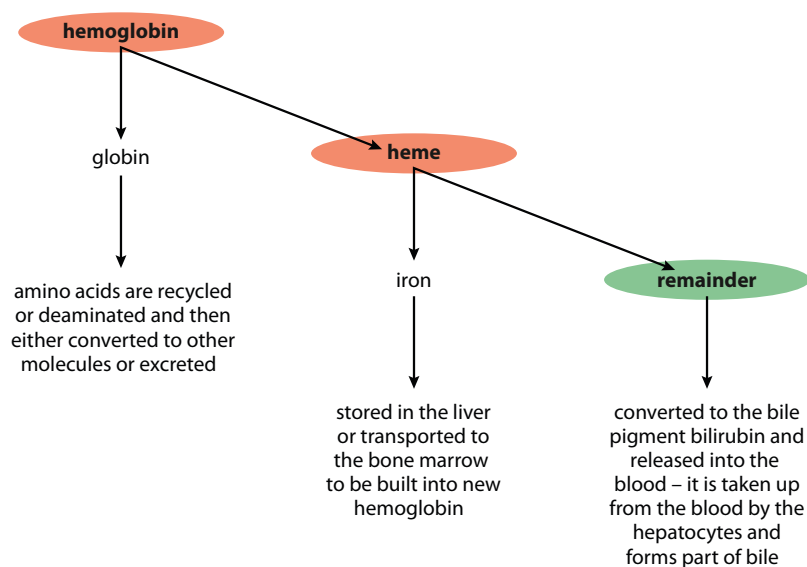
Figure D.9 The breakdown of hemoglobin. Hemoglobin is split into heme groups and globin. Globin is hydrolysed to amino acids, which can be re-used. Iron is removed from the heme group and either stored or taken to the bone marrow where it is used to produce hemoglobin for new red blood cells. The remaining part of the molecule becomes part of bile.

Synthesis

The liver synthesises both plasma proteins and cholesterol. Plasma proteins, found in the blood, play an important part in blood **homeostasis**. They are key to regulating the osmotic balance of body fluids and regulate the movement of water between plasma and tissue fluid, as well as affecting ultrafiltration in the kidney. The plasma proteins synthesised by the endoplasmic reticulum and assembled in the Golgi apparatus of hepatocytes include globulins and albumen and the blood–clotting protein, fibrinogen.

Hepatocytes also synthesise cholesterol, which is essential in membrane structure and is the precursor for several other molecules including the steroid hormones testosterone, estrogen and progesterone. Cholesterol is found in many of the foods of animal origin that we eat but all the cholesterol required by the body is made by the liver.

Cholesterol

The liver can regulate the amount of cholesterol in the blood. If there is sufficient, the liver may stop its synthesis of cholesterol, in a **negative feedback** process. Excess cholesterol is excreted in the bile, but high levels in bile can cause deposits in the gall bladder called gallstones, which obstruct the bile duct. Excess cholesterol in the blood can contribute to blockages in the walls of certain arteries (Figure **D.3**) and lead to cardiovascular disease.

Exam tip

Check you understand the role of cholesterol in the body as well as the link it has to CHD.

Bile

Small channels called bile canaliculi pass between the rows of hepatocytes. Bile is produced in the hepatocytes and secreted into these channels, which connect to form the bile duct. Bile contains bile salts, which are important in the digestion of lipids in the intestine, and bile pigments, which are derived from the breakdown of hemoglobin. Bile is stored in the gall bladder and released when food enters the small intestine.

Vitamin D

Vitamin D is made in the skin when exposed to sunlight (Subtopic **D1**). People who live in areas close to the Poles, where there is little sunlight during winter and the temperature is very cold, cover most of their skin during this time. In this situation, the liver is able to release vitamin D that has been stored during the warmer, summer months, when more skin is exposed to sunlight. However, sunlight contains ultraviolet rays that can cause skin cancer, and so a balance is needed between exposure, to synthesise vitamin D, and protection from the damaging UV.
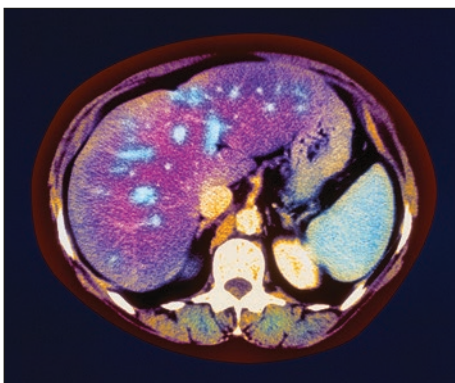

Figure D.10 This is a coloured MRI scan of a person suffering from a fatty liver. The fat deposits can be seen as blue patches in the liver (purple).

Storage and regulation of nutrients

The liver plays a key role in homeostasis. It regulates blood sugar levels and is able to store lipids, iron (from the breakdown of hemoglobin) and the fat-soluble vitamins A and D. Absorbed nutrients are carried in the blood directly from the intestine to the liver via the hepatic portal vein. The blood that leaves the liver contains regulated amounts of nutrients.

One of the most important roles of the liver is to maintain the correct level of glucose in the blood. After a meal containing carbohydrate, the glucose level in the blood will rise, but during exercise it will fall as glucose is respired by the muscles. The liver helps to balance out these fluctuations by storing glucose as **glycogen** in the hepatocytes when levels are high and breaking down and reconverting the glycogen to glucose when the level falls. Two pancreatic hormones insulin and glucagon control this process.

- **Insulin** is released when glucose levels are high and stimulates the hepatocytes to take up glucose and convert it to glycogen.
- **Glucagon** is released when glucose levels are low and stimulates hepatocytes to convert glycogen back to glucose.

Liver damage

Alcohol and the liver

Alcohol, absorbed from the gut, passes straight to the liver in the hepatic portal vein and is absorbed by the hepatocytes. Hepatocytes remove and detoxify the alcohol, but if it is present in large amounts, blood may have to flow through the liver many times before all the alcohol can be absorbed. This makes liver cells very susceptible to damage by alcohol. If large quantities are consumed, fatty deposits begin to build up in the liver lobules, replacing damaged cells, and reducing liver function (Figure **D.10**). The liver can become inflamed, a condition known as alcoholic hepatitis, whose symptoms include nausea and **jaundice**. In the longer term, the liver may become permanently damaged as scar tissue develops in place of damaged blood vessels and hepatocytes. This is called **cirrhosis** of the liver. These areas of the liver are no longer able to function efficiently and if cirrhosis is extensive, liver failure can be the result. Damage like this is fatal unless the liver tissue can be replaced by a transplant.

Causes and consequences of jaundice

Jaundice is caused by a build-up of the pigment bilirubin in the blood and tissues of the body. People with jaundice have yellow skin and whites of the eyes as a result of the liver's inability to metabolise and excrete the bilirubin. They may also have yellowing of mucous membranes in the nose and mouth, dark urine and pale feces.

Bilirubin is a waste product of the breakdown of red blood cells by the liver (Figure **D.9**) and in healthy individuals it is removed in bile. Bile is stored in the gall bladder and is released into the digestive system through the bile duct. Jaundice can occur as a result of any condition that disrupts the movement of bilirubin from the blood to the liver and then out of the body. There are three slightly different types of jaundice that are caused in different ways.

- **Pre-hepatic jaundice** occurs when a condition or infection speeds up the breakdown of red blood cells and increases bilirubin levels in the blood. This type of jaundice can be caused by malaria, sickle cell anemia and thalassemia, as well as some rare genetic conditions.
- **Intra-hepatic jaundice** occurs when the liver is damaged and its cells cannot process bilirubin. This may be due to an infection such as hepatitis, leptospirosis or glandular fever. Cells may also be damaged by exposure to harmful substances, such as alcohol and drugs, including ecstasy and overdoses of paracetamol (also called acetaminophen). Certain chemicals including phenol can also harm hepatocytes.
- **Post-hepatic jaundice** occurs when the bile duct is damaged, inflamed or blocked, so that the gall bladder is unable to send bile to the digestive system. Gallstones can cause this type of jaundice.

> **Exam tip**
> The liver is the body's largest organ. Make a checklist of all the roles it has and problems that occur if it isn't working properly.

Attitudes to knowledge

Alcohol is widely consumed in many parts of the world and in some cultures there are major health and social concerns about the rise of 'binge drinking' in young people. Binge drinking is the consumption of large amounts of alcohol in a short period of time.

Attitudes to both alcohol consumption and the use of certain drugs vary considerably in different cultures, despite widespread knowledge of the well-established correlation between excessive alcohol consumption and liver disease, as well as the longer-term problems of alcohol addiction.

Question to consider
- How is the interpretation and application of knowledge affected by culture?

Nature of science

Public understanding of science – the cholesterol story

Our understanding of health issues changes as new discoveries are made. The link between cholesterol and heart disease is one very good example. As new knowledge about different types of cholesterol – LDL and HDL – has emerged, scientists have been forced to reconsider previously held views and to try and communicate the new information to others.

The fact that heart disease is only partially related to cholesterol levels in the blood has been known since the 1950s. In addition, there have long been clues that dietary cholesterol is not directly linked to developing heart disease. Nevertheless, heart disease and its causes are often misunderstood and many people are confused about the effect of cholesterol and try to avoid all foods that contain it.

Chemically, cholesterol is a fat, but it does not provide the body with energy. Instead, it's an essential building block for molecules, cells and tissues. It forms part of all cellular membranes and is particularly important in nerve cells. It is a component of hormones and skin cells can also convert it to vitamin D in the presence of sunlight, making it a most useful and vital substance.

In metabolic terms, cholesterol in the diet is not directly correlated to cholesterol in the blood but fat in the diet is. Cholesterol that is present in foods such as eggs or shellfish is broken down during digestion and the body manufactures its own cholesterol from fats that we eat.

Our knowledge of cholesterol has changed. New scientific advances have shown that there are different types of cholesterol, some of which have beneficial effects. The public perception of the issue is confused, with some people still believing the original view that 'all cholesterol is bad', while others now think that all the cholesterol in their diet is doing them good. Scientists must be aware that good communication is vital and time is needed for new ideas to be disseminated. Communication of new research must be clear so that people who would benefit from scientific advances do not take the view that 'science keeps changing its mind' and decide not believe any of it.

? Test yourself

7 Outline **three** important roles of the liver.
8 Outline the stages in the breakdown of red blood cells and the fate of the products.
9 State the names of the main blood vessels that enter and leave the liver.

D4 The heart

The structure of cardiac muscle

Heart muscle works throughout our lives and never rests. It requires constant supplies of blood, which carries oxygen and nutrients to it. Three large coronary arteries branch from the aorta and supply heart muscle with oxygen-rich blood (Subtopic **6.2**, Figure **6.8**).

Heart muscle has a unique composition that adapts it for the conduction of waves of excitation from fibre to fibre. It is made up of short, striped muscles fibres, which branch and are also joined together at their ends by linking structures known as intercalated discs. (Figure **D.11**). This arrangement of linkages between cells allows action potentials to spread rapidly and enables the heart muscle fibres to act together and produce a more powerful effort as they contract simultaneously. Blood vessels, found in the spaces between the fibres, are branches of the two coronary arteries, which come from the aorta. In this way the heart is provided with a good blood supply carrying oxygen and glucose for its activity.
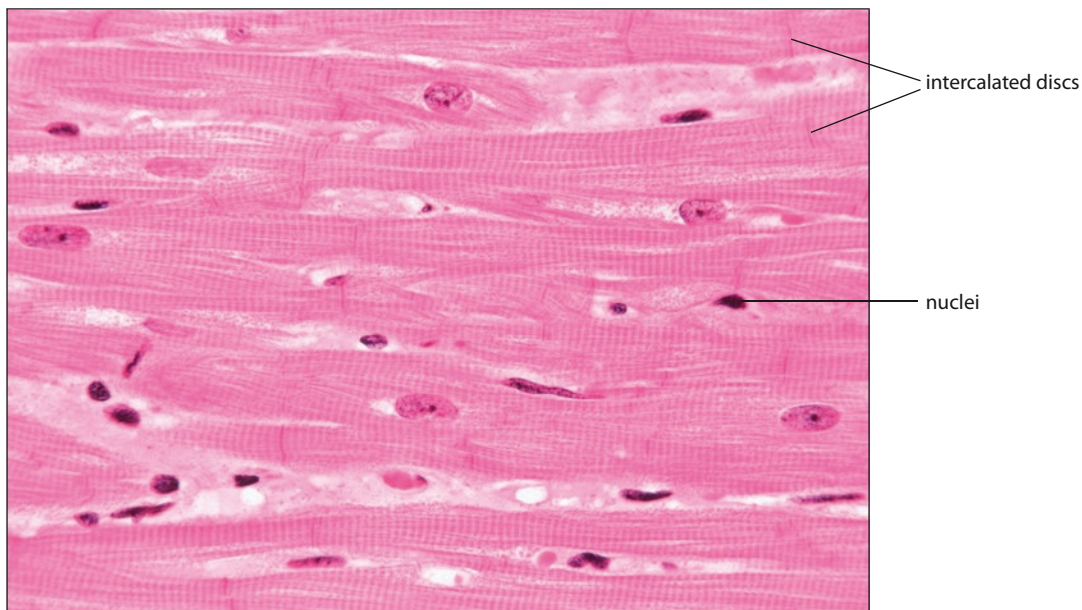
Learning objectives

You should understand that:
- The structure of cells in cardiac muscle enables electrical impulses to be propagated through the heart wall.
- Impulses from the sinoatrial node cannot pass directly from atria to ventricles.
- Impulses are delayed at the atrioventricular node.
- The delay allows time for atrial systole to occur before the atrioventricular valves close.
- Conducting fibres enable the contraction of the entire ventricular wall to be coordinated.
- Normal heart sounds are caused by the closing of the atrioventricular and semilunar valves.

Figure D.11 Stained light micrograph of structure of cardiac muscle showing striations formed by actin and myosin filaments, branching cells and intercalated discs. (×300).

Control of the heart beat

An individual's heart rate changes with the level of their activity, emotions or stress. Heart muscle is unique in that it can contract without stimulation – it is said to be **myogenic**. However, under normal circumstances, heart rate is controlled by nervous or hormonal stimulation. Impulses pass to the pacemaker, the **sinoatrial node** (SAN), in the left atrium via nerves from the medulla oblongata in the brain. The SAN is also stimulated by the hormone epinephrine (adrenalin).

The SAN initiates contraction of the heart. Cells in the SAN produce action potentials that spread through the muscle cells in the walls of the atria and cause atrial **systole** (contraction). The impulses are prevented from passing directly to the ventricles but they do stimulate a group of cells known as the **atrioventricular node** (AVN). This node is situated in the lower part of the atrium, close to the ventricles. The AVN sends out impulses down two bands of conducting fibres that run down the centre of the heart, between the two ventricles, to the base of the heart (Figure **D.12**). From here, fibres branch out between the cells of the thick ventricular walls. As impulses arrive, coordinated contraction occurs across the muscle tissue of the ventricle walls. This sequence of events is known as the **cardiac cycle**.

Heart rate is speeded up during exercise as a rise in carbon dioxide and a fall in the pH of the blood cause impulses to be sent from the medulla in the brain via the sympathetic nerve to the SAN. When exercise stops and blood pH returns to normal, impulses pass via the vagus nerve, which slows the heart rate down. Increasing levels of epinephrine (adrenalin), the 'fight or flight' hormone, are produced at times of stress or anxiety – epinephrine stimulates the SAN to increase the heart rate.

The sympathetic nerves are part of the nervous system that deals with functions such as heart rate, which are automatically controlled by the brain.

Artificial pacemakers

Artificial heart pacemakers are fitted to patients who have a problem with electrical conduction through the heart. This can mean that the heart beats too slowly or too fast. They are also used for patients who have suffered heart failure so that their heart beat is uncoordinated. A typical pacemaker is approximately 4 cm long and weighs about 30 g. Pacemakers are fitted below the collar bone (Figure **D.13**) and have leads that connect to the heart via a vein. Pacemakers are battery powered and generate pulses that stimulate the heart at an appropriate, adequate rate.
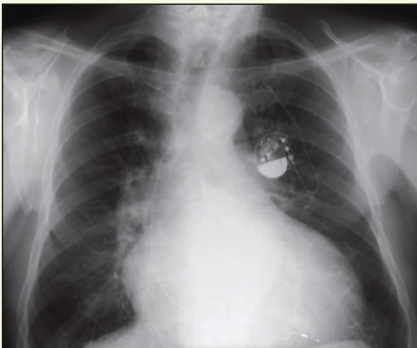
Figure D.13 An X-ray photograph showing a pacemaker in position in a patient.
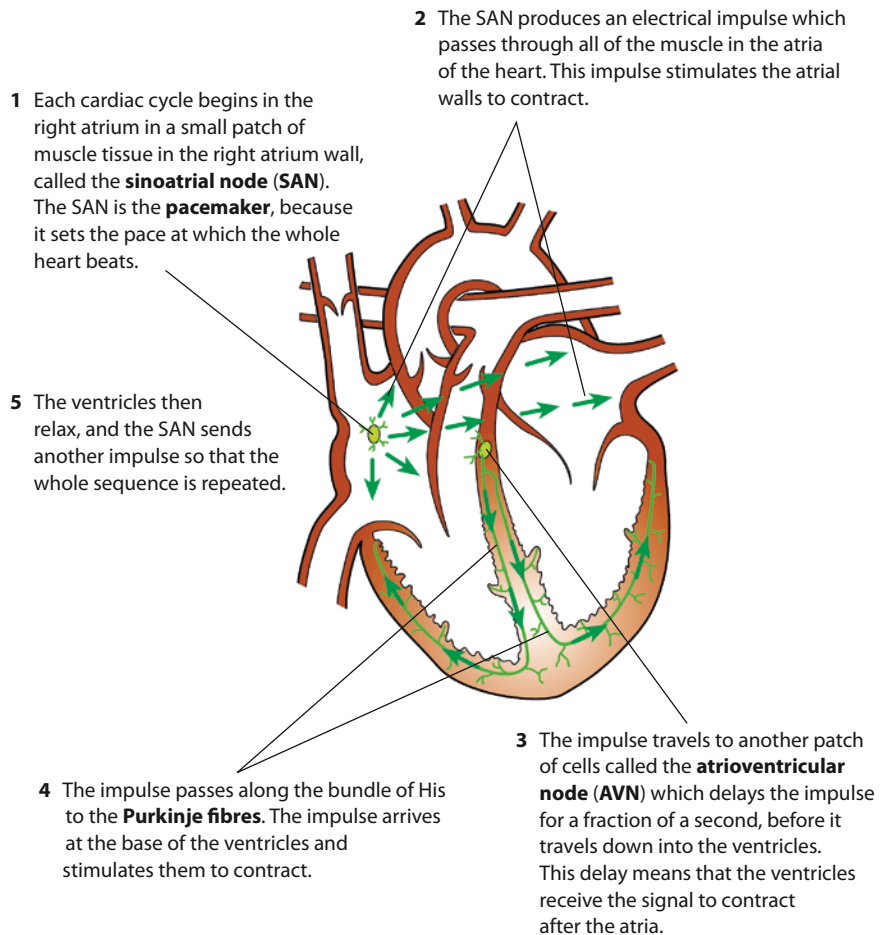
1 Each cardiac cycle begins in the right atrium in a small patch of muscle tissue in the right atrium wall, called the **sinoatrial node** (**SAN**). The SAN is the **pacemaker**, because it sets the pace at which the whole heart beats.

2 The SAN produces an electrical impulse which passes through all of the muscle in the atria of the heart. This impulse stimulates the atrial walls to contract.

5 The ventricles then relax, and the SAN sends another impulse so that the whole sequence is repeated.

3 The impulse travels to another patch of cells called the **atrioventricular node** (**AVN**) which delays the impulse for a fraction of a second, before it travels down into the ventricles. This delay means that the ventricles receive the signal to contract after the atria.

4 The impulse passes along the bundle of His to the **Purkinje fibres**. The impulse arrives at the base of the ventricles and stimulates them to contract.

Figure D.12 How electrical impulses move through the heart.
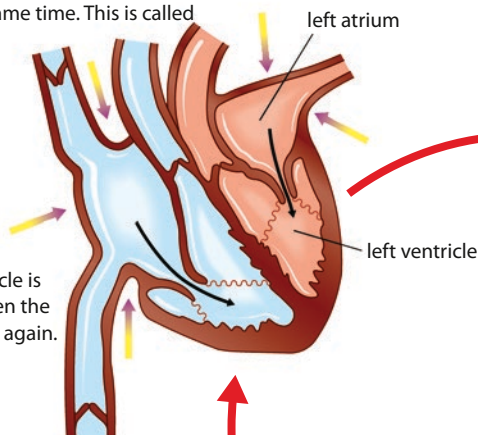
Defibrillators

If a person's heart stops beating properly they may to go into **cardiac arrest**. In such cases, a **defibrillator** can be used to deliver an electric shock to the heart, which will be stimulated into re-establishing its proper rhythm. Defibrillators are not usually used to restart a heart that has stopped completely but are vital in cases when uncoordinated contraction of the ventricular muscle (ventricular fibrillation) makes the ventricles 'quiver' rather than contract fully. Defibrillation can also treat **tachycardia**, a fast heart rhythm that originates in one of the ventricles. A defibrillator consists of a pair of electrodes, which are placed on the patient's chest, and a battery that delivers an electrical impulse between them.
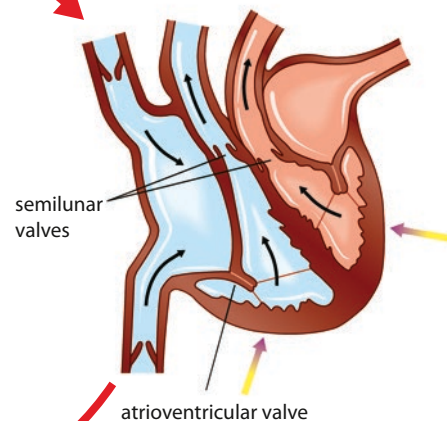
The cardiac cycle

The cardiac cycle describes the events that go to make up one heart beat. The heart rate, normally about 70 beats per minute, is a measure of the frequency of the cardiac cycle. The key structures that are important in the cardiac cycle are the muscles of the walls of the atria and ventricles, the atrioventricular and semilunar valves (Figure **6.6** in Subtopic **6.2**), the sinoatrial node (SAN) or pacemaker, and the atrioventricular node (AVN).

Contraction of the heart is called **systole** and relaxation is known as **diastole** (Figure **D.14**). Atria and ventricles always contract separately, with contraction of the two atria being followed – after a short pause due to the delay of the impulse at the AVN – by contraction of the two ventricles. The four valves, two in the heart and two in the main arteries, keep blood flowing in one direction. As these valves close, they produce the characteristic 'lub–dub' or heart sounds that can be heard through a stethoscope. The two sides of the heart work together so that the 'lub' sound is made as the two atrioventricular valves flap shut after atrial systole, and the 'dub' sound is the closing of the two semilunar valves once ventricular systole is complete.

1 The muscles of the atrium wall contract, pushing blood through the atrioventricular valves into the ventricles. Both atria contract at the same time. This is called atrial systole.

left atrium

left ventricle

5 The whole cycle is repeated when the atria contract again.

2 Blood forced into the ventricles causes the blood pressure inside them to rise, so the atrioventricular valves snap closed. When the ventricles are full, ventricle muscles contract, generating the pressure that drives blood through the semilunar valves into the aorta and the pulmonary artery. This is ventricular systole. A pulse is produced that can be felt in arteries in other parts of the body.

semilunar valves

atrioventricular valve

4 Blood flows into the atria from the veins, opens the atrioventricular valves, and begins to fill the ventricles.
Blood from the body enters the right atrium via the vena cava. Blood from the lungs enters the left atrium from the pulmonary artery.
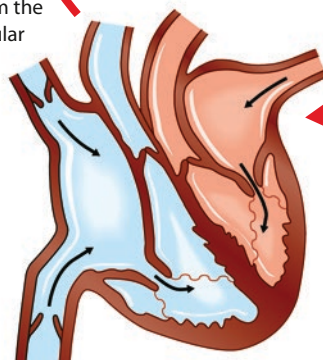
3 Ventricles and atria now relax, and the pressure inside them is low. The semilunar valves are closed by the back pressure of blood in the arteries. This part of the cycle is called diastole.

Key
→ pressure exerted by contraction of muscle
→ movement of blood

Figure D.14 The cardiac cycle.

As the heart beats, the pressure and volume in each of its four chambers change and these changes can been shown on graphs such as the one shown in Figure **D.15**.

At the end of the cardiac cycle, both atria and ventricles are in diastole (relaxed). Blood has been pumped out of the ventricles and blood is re-entering the atria from the pulmonary veins and vena cava. The pressure in the atria is slightly greater than in the ventricles so blood flows through the atria via the atrioventricular valves and into the ventricles. Blood pressure in the arteries is higher than that in the ventricles so the semilunar valves remain closed.

When the ventricles are approximately 70% full a new cardiac cycle begins. It starts with contraction of the walls of the atria, **atrial systole**. Blood is pumped through the atrioventricular valves, filling the ventricles to capacity. The thin walls of the atria do not generate much pressure, but after the contraction is complete, most of the blood from the atria has entered the ventricles.
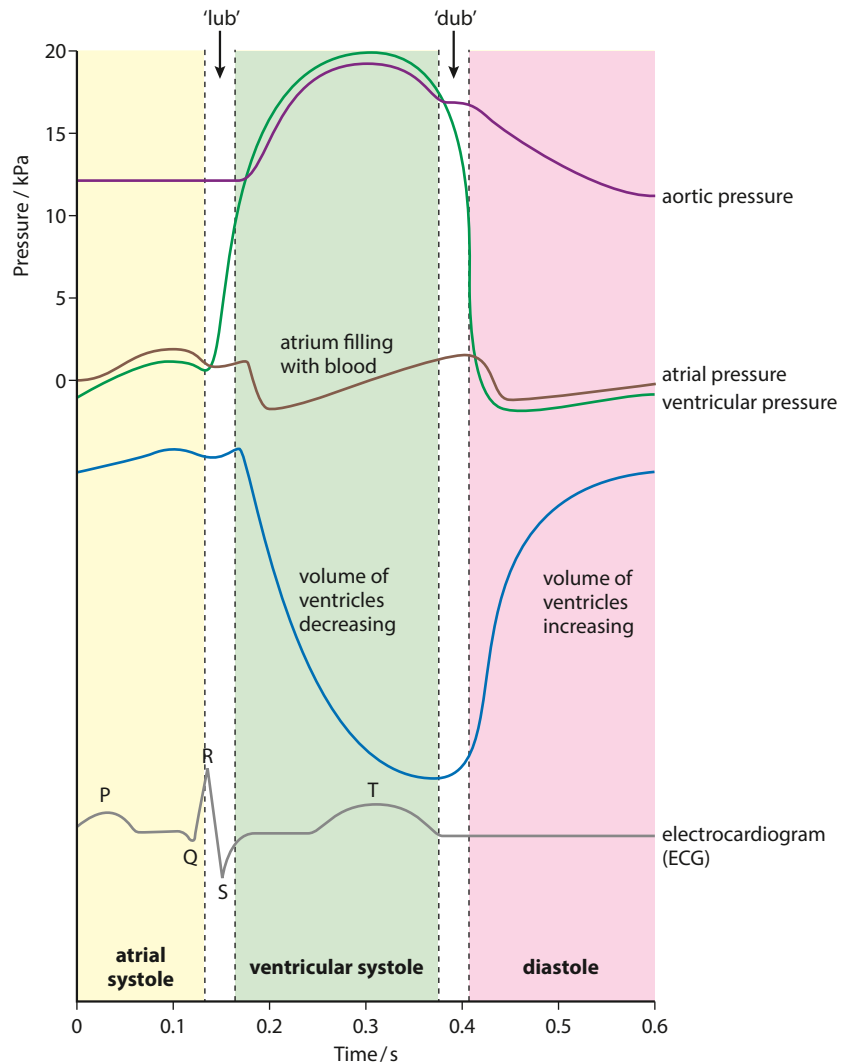
Figure D.15 Pressure and volume changes in the heart during the cardiac cycle, with an electrocardiogram (ECG) trace. An ECG trace records the rhythm and electrical activity of the heart via electrodes attached to the chest.

As **ventricular systole** begins, it produces sufficient pressure to snap the atrioventricular valves closed and produce the first heart sound. As the ventricles contract, pressure inside the chambers rises so that it becomes greater than the pressure in the arteries (the pulmonary artery and aorta) that leave the heart. This pressure forces the semilunar valves open and blood is pumped out of the ventricles into the arteries. At the end of ventricular systole, blood pressure in the ventricles is lower than that in the arteries and the back pressure forces the semilunar valves shut, causing the second heart sound.

When pressure in the ventricles falls below that in the atria, the atrioventricular valves re-open. Blood from the veins flows passively through the atria and into the ventricles. All four chambers of the heart return to diastole and the cycle begins all over again.

Coronary heart disease

Coronary heart disease (CHD) is often caused by damage to the arteries – for example, by **atherosclerosis**. Atherosclerosis is a slow degeneration of the arteries caused by a build-up of material known as **plaque** inside them. Plaque becomes attached to the smooth endothelium lining an artery and can accumulate over many years. Few people suffer from any symptoms before middle age. Fibrous tissue in the lining may become damaged and thickened so that lipids, cholesterol (released from low-density lipoproteins) and cell debris accumulate. Calcium may also be present, causing the artery to loses elasticity and become hard and inflexible. Over time, the diameter of the artery becomes restricted so that blood cannot flow along it properly, leading to **hypertension** (Figure **D.3**). As the rate of flow slows down, blood may clot in the artery, further restricting the movement of blood along it. Clots may also break free and travel to block another smaller artery elsewhere in the body – this is called a **thrombosis**. If any of the three coronary arteries is blocked (Figure **6.8**), an area of the heart muscle will receive less oxygen and cells in that region may stop contracting or even die. A blockage in a coronary artery or one of its branches is known as a **coronary thrombosis** or heart attack. If an artery is blocked in the brain, the clot may cause a **stroke**.

Risk factors associated with CHD

The incidence of heart disease varies from country to country (Table **D.4**) and between individuals. Some factors associated with the likelihood of developing CHD are related to a person's environment. By making personal choices about lifestyle, it is possible to lower the risk of developing CHD. Other factors that increase the risk cannot be controlled. For example, the risk of CHD is affected by:

- **genetic factors** – CHD tends to occur more frequently in some families than others with similar lifestyles
- **the person's sex** – men are more likely to have CHD than women
- **the person's age** – CHD is more prevalent in older people.

Country	Death rate / 100 000
Kiribati	11
France	29
Switzerland	52
Australia	60
Canada	66
UK	68
Germany	75
China	79
USA	80
Brazil	81
Colombia	85
Ghana	120
Poland	122
Rep. of Congo	125
Malaysia	138
Turkey	157
Iran	194
Pakistan	222
Lithuania	233
Afghanistan	328
Ukraine	399

Table D.4 Death rates from CHD per 100 000 people in different countries (from UNESCO and WHO).

Lifestyle factors that increase the risk of CHD include:

- **smoking** – smokers are significantly more likely to suffer from CHD than non-smokers
- **lack of exercise** – a lifestyle involving little physical activity may contribute to obesity and high blood pressure
- **hypertension (high blood pressure)** – causes strain on the heart, which has to work harder to pump blood
- **obesity** – increases the work of the heart; people who are overweight are also more likely to have high blood pressure and high cholesterol levels in their blood
- **diet** – there have been many claims that diet can increase the risk of CHD; for example, there is a positive correlation between intake of saturated fat and CHD, but cause and effect have not been proven. Reliable evidence suggests that in countries where many high-fat foods, animal products and processed foods are eaten, there is likely to be a high incidence of CHD. Since all fatty acids are high in energy, an excess of these foods in the diet can also lead to obesity, which places a further strain on the heart.

There is some correlation between CHD and blood cholesterol levels. Reducing the amount of cholesterol in the diet can reduce blood cholesterol levels to a certain extent. But while LDL cholesterol (low-density lipoprotein) is associated with an increased risk of CHD, HDL cholesterol (high-density lipoprotein) is correlated with a reduced risk. So it is difficult to predict the effect of reducing dietary cholesterol on risk with any certainty.

Many aspects of lifestyle are interrelated and it is very difficult to isolate a single factor that can be said to cause CHD. Research focusing on just one aspect of risk may underestimate the contribution of other important factors. If a person changes one aspect of their lifestyle, other risk factors may become important.
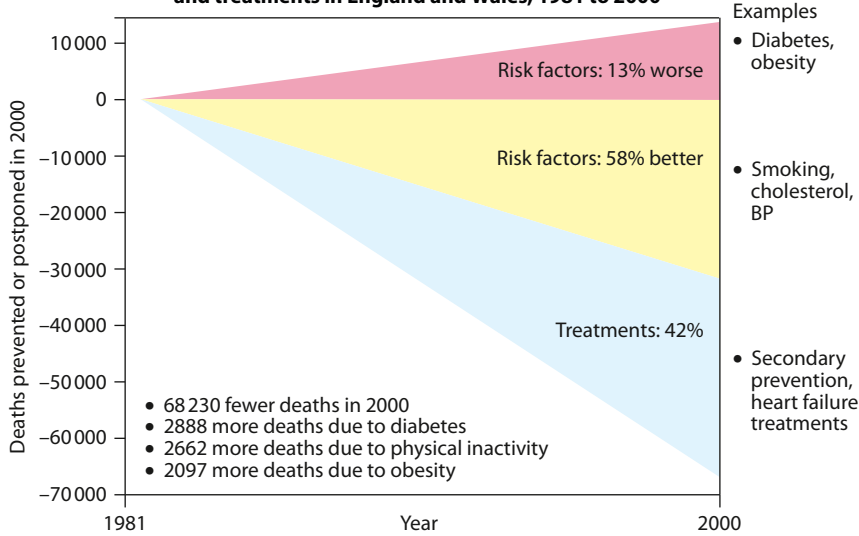
Analysis of data

Medical researchers collect and collate large amounts of data related to heart disease and risk factors. For example, the two graphs shown in Figure **D.16** present data on the prevention and reduction of heart disease in the USA and UK over a period of 30 and 20 years, respectively.

The upper graph shows the reductions in CHD deaths as a result of campaigns to reduce smoking and the effect of health programmes which screen and treat high risk patients. The lower graph shows the results of similar programmes in the USA.
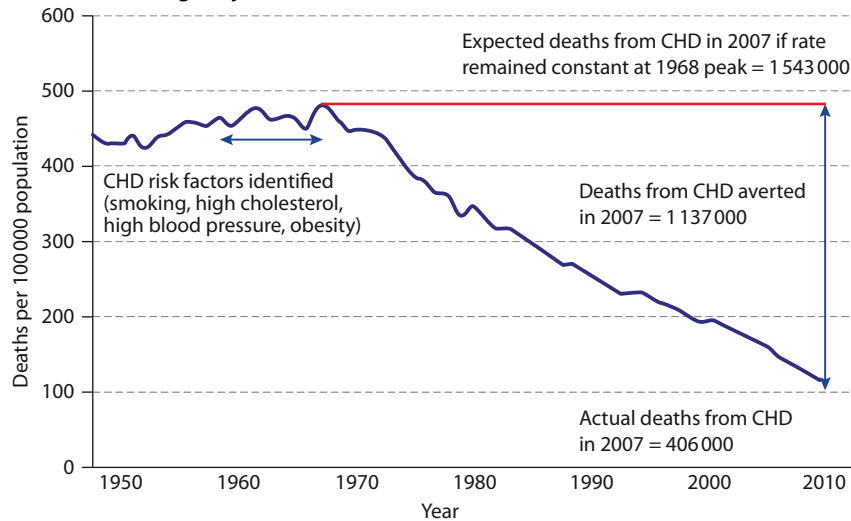
Consider how important data like these are. Why do you think long term studies are vital to medical research? Why is it important to include data from large numbers of people? How can this information be used to help in planning public health strategies and education?

CHD deaths prevented or postponed by risk factor changes and treatments in England and Wales, 1981 to 2000

Examples
- Diabetes, obesity

Risk factors: 13% worse

Risk factors: 58% better

- Smoking, cholesterol, BP

Treatments: 42%

- Secondary prevention, heart failure treatments

- 68 230 fewer deaths in 2000
- 2888 more deaths due to diabetes
- 2662 more deaths due to physical inactivity
- 2097 more deaths due to obesity

y-axis: Deaths prevented or postponed in 2000 (10 000, 0, −10 000, −20 000, −30 000, −40 000, −50 000, −60 000, −70 000)

x-axis: Year (1981 to 2000)

Source: B. Unal *et al* in *Circulation*, (2004).

Age-adjusted death rates for CHD in the United States of America

Expected deaths from CHD in 2007 if rate remained constant at 1968 peak = 1 543 000

CHD risk factors identified (smoking, high cholesterol, high blood pressure, obesity)

Deaths from CHD averted in 2007 = 1 137 000

Actual deaths from CHD in 2007 = 406 000

y-axis: Deaths per 100 000 population (0, 100, 200, 300, 400, 500, 600)

x-axis: Year (1950, 1960, 1970, 1980, 1990, 2000, 2010)

Source: *Vital Statistics of the United States,* CDC/National Centre for Health Statistics.

Figure D.16 Graphs showing age-adjusted death rates from CHD in the UK and USA in recent decades.

Nature of science

Scientific advance follows technical innovation – the stethoscope

Our understanding of the way the heart works took a big step forward following the invention of the stethoscope by René Laennec (1781–1826) in France in 1816. His device was a simple wooden tube, similar to an ear trumpet, which had only one earpiece that he used to listen to a patient's breathing. It was not until the mid 1800s that a flexible stethoscope with two earpieces first appeared, and the first instrument for commercial sale was designed by the American physician George Cammann in 1852. Since that time, the stethoscope has become one of a doctor's most important tools.

The invention of the stethoscope gave doctors a chance to listen to a person's heart and lungs, and for the first time they were able to detect faults in internal anatomy that could cause symptoms of disease. Today, stethoscopes are not only used to listen to the chest but also other parts of the body such as the bowels, and the heart of a fetus during pregnancy. Learning to listen for and diagnose the sounds is an important part of any doctor's training.

Symbols of knowledge

Symbols are often used as a form of non-verbal communication. The heart is used as a symbol in many different cultures. In the Egyptian Book of the Dead a heart was shown being weighed as a measure of worthiness to enter into paradise. In the Bible, the heart has been used as a devotional image for many centuries. It has also appeared on playing cards since the 1400s. In Japan, the oldest heart symbol known is one on a helmet from the 1550s where it was used to represent the goddess of archers. In Chinese, the symbol for a heart is the same one used to mean feelings and the mind. In the contemporary world, a heart is best known as a symbol of love.

Questions to consider

- Why is the heart a symbol of love?
- Do symbols make communication easier or do they exclude those who do not understand them?
- How are symbols used in other areas of knowledge?

? Test yourself

10 Outline the risk factors for coronary thrombosis.

11 Describe what happens to the chambers of the heart during atrial systole, ventricular systole and diastole.

12 Define the term 'myogenic'.

13 Using the information in Figure **D.16** and your knowledge of heart disease, state the most important factors contributing to the fall in deaths from CHD in the USA and UK in recent decades.

D5 Hormones and metabolism (HL)

The body is under the control of two systems: the nervous system and the endocrine system. These are mostly independent of one another but there are situations in which the two work together to control activities such as heart rate (Subtopics **6.2** and **D.4**).

The chemical structures of hormones

Hormones are chemical substances that are secreted directly into the bloodstream from endocrine glands found throughout the body (Figure **D.17**).

Since hormones circulate in the bloodstream, they come into contact with all cells in the body but only cells that have specific, genetically determined receptors will respond. These **target cells** have receptors on the plasma membrane that recognise and bind to the hormone.

Different hormones have different chemical structures and can be divided into three categories as shown in Table **D.5**.

Chemical category of hormone	Examples
steroids derived from cholesterol	testosterone, progesterone
proteins	insulin, FSH, LH
tyrosine derivative	thyroxin – each thyroxin molecule has four iodine atoms

Table D.5 The different chemical forms of hormones.
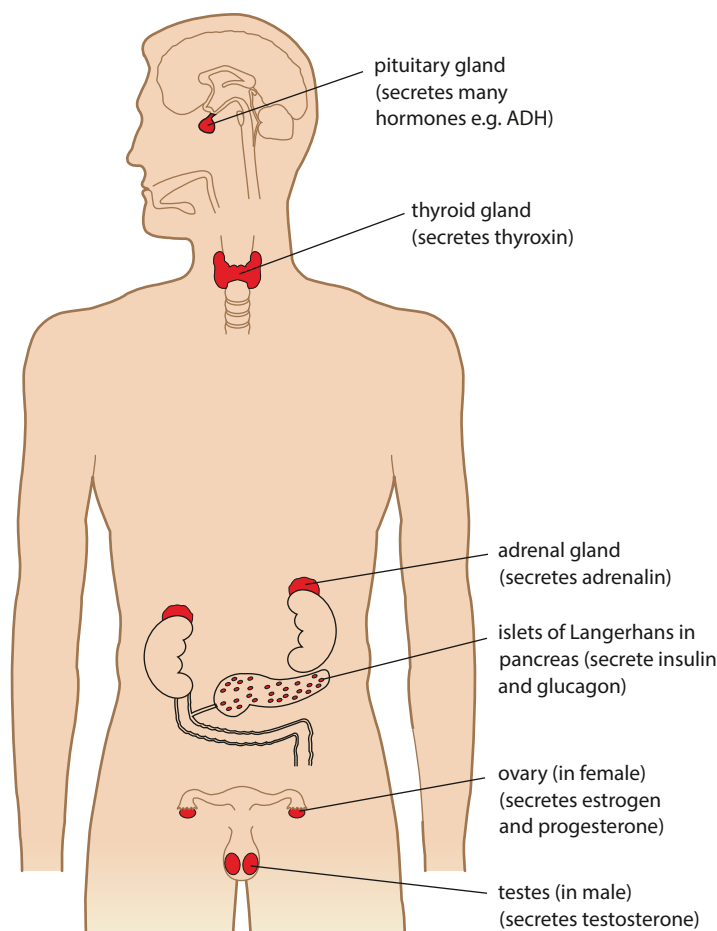
Figure D.17 Endocrine glands of the body.

How hormones control cells

Protein hormones and steroid hormones control their target cells in different ways (Figure **D.18**).

Protein hormones bind to a surface receptor, very often a glycoprotein, but do not enter the cell. Instead, the binding process triggers the release of a second messenger chemical which cascades from the cytoplasmic side of the plasma membrane and this messenger controls the activity of the cell. This may be achieved by regulating the activity of a specific enzyme in the cell, either activating it or inhibiting it.

Steroid hormones do enter target cells as they can easily pass through the plasma membrane. They bind to a specific receptor in the cytoplasm forming a hormone–receptor complex, which is transported through a nuclear pore into the nucleus. Here, the hormone regulates the process of transcription of one or more specific genes.
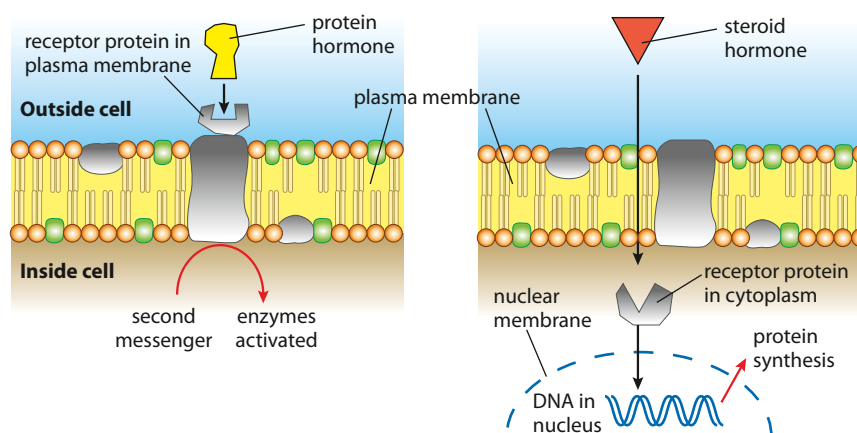
Figure D.18 The modes of action of protein and steroid hormones.

The hypothalamus and the pituitary gland

The **hypothalamus** is a small area of the brain that monitors hormone levels and indirectly controls functions including body temperature, hunger and sleep. It links the hormonal and nervous systems and secretes releasing hormones that regulate the hormones of the anterior pituitary gland. It has a range of receptors of its own, which allow it to act independently, but it also receives information from other parts of the brain.

The **pituitary gland**, situated just below the hypothalamus (Figure **D.19**), is made up of two different parts – the anterior and posterior lobes. The posterior lobe develops from the brain and has neurons connecting it directly to the brain. The anterior lobe develops separately and has no direct neural connection with the brain.

The hypothalamus has to communicate with each lobe of the pituitary gland in a different way.

- The hypothalamus contains the cell bodies of many **neurosecretory cells**, which have their terminal ends in the posterior lobe of the pituitary. A neurosecretory cell is simply a neuron that has been modified to secrete and store a large quantity of hormone at the terminal end of the cell body. Surrounding the terminal ends of the neurosecretory cells is a capillary network so that when the cells receive

Portal veins always connect two capillary networks. The hepatic portal vein has branches at both ends, in the liver and in the digestive system. The portal vein that connects the hypothalamus and the pituitary gland also has branches in both structures.
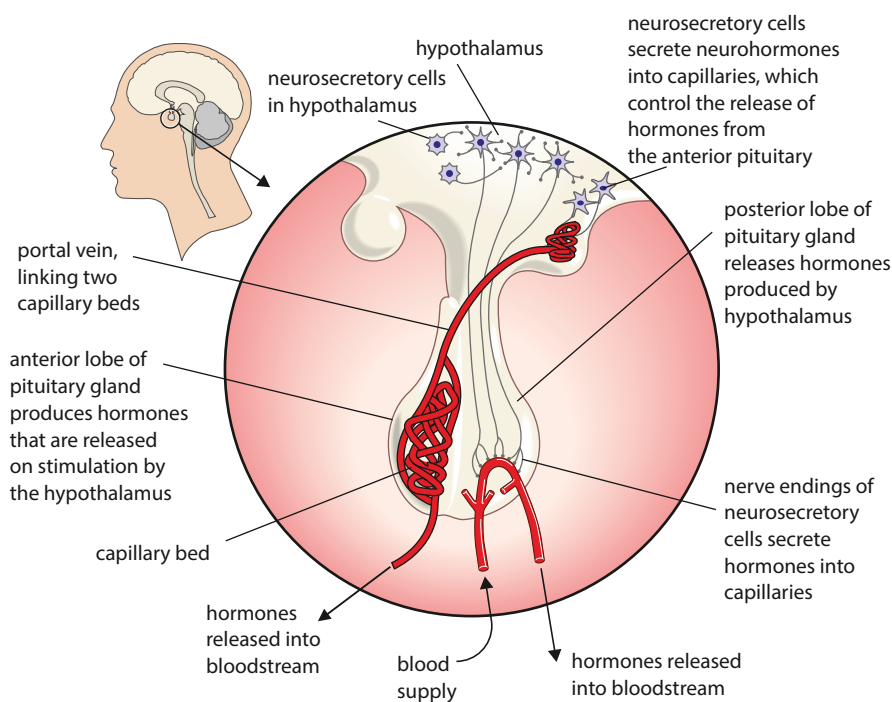
Figure D.19 The hypothalamus and pituitary gland.

Diagram labels:
- hypothalamus
- neurosecretory cells in hypothalamus
- neurosecretory cells secrete neurohormones into capillaries, which control the release of hormones from the anterior pituitary
- portal vein, linking two capillary beds
- posterior lobe of pituitary gland releases hormones produced by hypothalamus
- anterior lobe of pituitary gland produces hormones that are released on stimulation by the hypothalamus
- capillary bed
- nerve endings of neurosecretory cells secrete hormones into capillaries
- hormones released into bloodstream
- blood supply
- hormones released into bloodstream

the appropriate information they can release the hormone directly into the blood. Two examples of posterior lobe hormones released in this way are antidiuretic hormone (ADH) and oxytocin.

- Control of the anterior lobe of the pituitary is regulated by another set of neurosecretory cells in the hypothalamus. These cells end in a different capillary bed just above the pituitary gland. The blood from these capillaries flows into a portal vein, which passes into capillaries within the anterior lobe of the pituitary. These neurosecretory cells secrete releasing hormones (RH), which control the release of the hormones from the cells of the anterior lobe. One example is gonadotrophin releasing hormone (GnRH), which controls the release of follicle stimulating hormone (FSH) and luteinising hormone (LH).

Pituitary hormones

Hormones from the pituitary gland control reproduction, growth and changes that take place as the body develops. They are also important in homeostasis. The hormones produced and secreted by the anterior and posterior pituitary glands are summarised in Table **D.6**.

The secretions from neurosecretory cells are often called hormones. They are more correctly termed **neurohormones** because they are not produced by endocrine glands. These neurohormones are usually peptides that travel as droplets along the axons of the cell.

Hormone	Secreted by	Effect on the body
human growth hormone (HGH or somatotrophin)	anterior pituitary	controls growth and metabolism
thyroid stimulating hormone (TSH)	anterior pituitary	stimulates the thyroid gland to produce thyroxin, which increases metabolic rate
adreno-corticotropic hormone (ACTH)	anterior pituitary	produced in response to stress – targets the adrenal gland to produce corticosteroid hormones
follicle stimulating hormone (FSH)	anterior pituitary	targets the reproductive system – stimulates follicular development in the ovary and meiotic division of primary spermatocytes in the testes (Subtopic **11.4**)
luteinising hormone (LH)	anterior pituitary	targets ovaries and testes to produce sex hormones (Subtopic **11.4**)
prolactin	anterior pituitary	stimulates milk production by the mammary glands and estrogen production by ovaries
oxytocin	posterior pituitary	stimulates contraction of the uterus wall during childbirth and milk release during suckling
antidiuretic hormone (ADH)	posterior pituitary	important in the homeostatic regulation of blood plasma – causes reabsorption of water from the collecting ducts of the kidneys (Subtopic **11.3**)

Table D.6 Hormones produced and secreted by the anterior and posterior pituitary glands.

Hormonal changes and control of milk secretion

During the second and third trimesters of pregnancy (3–9 months), the placenta produces progesterone and estrogen, which suppress the menstrual cycle and promote the growth of breast tissue for **lactation** (milk production).

As the end of pregnancy approaches, the level of progesterone produced by the placenta falls (Figure **D.20**) and this signals the onset of the uterine contractions known as labour. At this time, the hormone **oxytocin** is secreted by the posterior lobe of the pituitary gland. Oxytocin stimulates the uterus muscles to contract and is controlled by **positive feedback**. A small contraction of the uterus muscle stimulates the release of further oxytocin, which in turn stimulates more and stronger contractions until the baby is born. Oxytocin is also important in the control of milk release from the mammary glands.

After birth, blood levels of the hormone **prolactin**, from the anterior pituitary gland, increase. This hormone stimulates milk production by the mammary glands. As a baby suckles, prolactin secretion is maintained and oxytocin is also released from the posterior pituitary gland. Oxytocin is necessary for the milk–ejection reflex, or 'let-down', to occur – it causes contraction of the smooth muscle cells that squeeze milk into the duct system of the breasts. The two hormones continue to be released in proportion to the amount of milk the baby consumes as it suckles so that the supply is matched to the demand. When the baby is weaned and no longer takes milk, the levels of these hormones decrease.
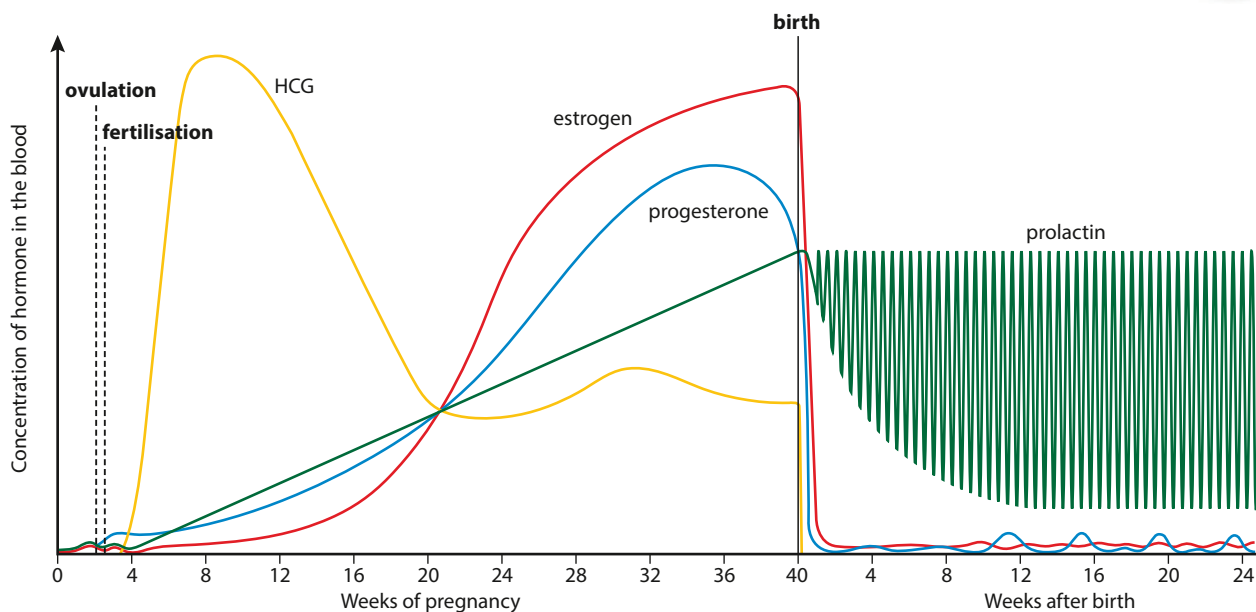
Figure D.20 Changes in the levels of hormones during pregnancy and birth. Oxytocin is not shown, but peaks during birth and then drops, continuing to rise and fall less dramatically each time the baby feeds. Prolactin levels also fluctuate regularly with the baby's feeding pattern.

Human growth hormone use by athletes

Human growth hormone (HGH) has been used by some athletes to promote muscle growth – particularly in power sports such as bodybuilding, swimming and weight lifting – in an attempt to improve performance. The hormone was declared a banned substance by the Olympic Committee in 1989 but there is evidence that it is still used. In the USA, HGH is available with a doctor's prescription.

Scientific evidence about the effect of HGH on muscles is mixed. The hormone appears to reduce body fat and increase lean body mass, but does not seem to increase the strength of muscles. It has been shown to build up connective tissue in muscles, making them appear larger and also increasing the ability of the muscle to resist injury and repair itself quickly. But none of these effects make the muscle physically stronger. Researchers in a 2010 study funded by the World Anti-Doping Agency in Sydney, Australia, reported that HGH could provide an energy boost in short-duration events such as running or swimming – but the study failed to find any evidence of HGH use producing an increase in power, strength or endurance.

Despite the results of such studies, and HGH's side-effects – which can include muscle and joint pain and swelling – some athletes still use the hormone. Part of its attraction may lie in the fact that, because it is a naturally occurring substance, it is hard to detect in the body.

Nature of science

Cooperation and collaboration – the international effort to eliminate iodine deficiency

People living far from the coast or those who have little seafood in their diet may suffer from a shortage of iodine. Iodine is needed to synthesise the hormone **thyroxine**, which regulates growth and controls metabolism. Without iodine, the thyroid gland can become enlarged, producing a swelling known as **goitre**.

Iodine deficiency disorder (IDD) is a serious problem for babies whose mothers were iodine deficient during pregnancy. Unborn babies with IDD can suffer brain damage and have poor mental development after birth. The most severe cases lead to **cretinism**, which UNICEF estimated affected more than 11 million people worldwide in 2000.

Goitre and cretinism are rare in Europe and the Americas because in these regions sodium iodide (NaI) has been added to table salt since the early part of the twentieth century. In the Mid-Western states of the USA, iodine added to salt in the 1920s reduced the incidence of goitre in children from 40% to 10% in just 4 years.

UNICEF has been involved in efforts to eliminate iodine deficiency since the 1950s. The organisation has persuaded and assisted many governments to iodise salt in an effort to eliminate IDD. It has provided salt iodisation equipment and iodine supplements to many countries. At the time of the World Summit for Children in 1990, only about 20% of households in the world used iodised salt and the campaign was stepped up. By the end of 2000, this figure had risen to around 70%. This global progress has meant that by the 21st century more than 91 million newborn children were protected against significant losses in learning ability caused by IDD.

? Test yourself

14 List the **three** chemical categories of hormones.

15 State which hormone type:
   a enters the cell directly
   b binds to a cell surface receptor.

16 Describe the effect of oxytocin in the control of milk secretion.

D6 Transport of respiratory gases (HL)

Oxygen dissociation curves

The oxygen content of air is measured as a **partial pressure**. In a mixture of gases, each component gas exerts a pressure (the partial pressure) in proportion to its percentage in the mixture. It is calculated as follows.

For normal dry air at sea level, atmospheric pressure is 101.3 kPa. The partial pressure of oxygen, which makes up 21% of the air, is:

$$\frac{21}{100} \times 101.3\,\text{kPa} = 21.3\,\text{kPa}$$

The partial pressures of other gases in dry air at sea level are shown in Table **D.7**.

Gas	Approximate percentage composition / %	Partial pressure / kPa
oxygen	21	21.3
carbon dioxide	0.0035	negligible
nitrogen	79	80.0

Table D.7 The partial pressures of gases in dry air at sea level. At high altitude, the pressure of air falls but the percentage of oxygen in the air remains approximately the same. At 5000 m, the partial pressure of oxygen is 11.5 kPa; at 10 000 m, it falls to just 5.5 kPa.

Oxygen is transported from the lungs to respiring tissues bound to the hemoglobin molecules that fill red blood cells. Each hemoglobin molecule can bind four oxygen molecules via the iron in the heme groups it contains (Figure **D.21**). When hemoglobin comes into contact with normal air, containing approximately 21% oxygen, it binds readily with oxygen molecules and becomes almost 100% saturated.

It follows that in an area of the body where there is a lot of oxygen (a high partial pressure), such as the lungs, most hemoglobin molecules will be carrying the maximum amount of oxygen and will be fully saturated. However, in areas where the oxygen level is lower, fewer hemoglobin molecules carry their maximum complement of oxygen and the hemoglobin may be only 50% saturated. As blood travels from the lungs to actively respiring tissues, the amount of oxygen bound to hemoglobin changes as the partial pressure of oxygen decreases. Hemoglobin readily releases oxygen where the partial pressure is lower, so it acts as an oxygen delivery service for respiring cells. Figure **D.22** shows the percentage saturation of hemoglobin at different oxygen concentrations and is known as an **oxygen dissociation curve**.

The steep S-shape of the dissociation curve shows how the affinity of hemoglobin changes at different partial pressures of oxygen. At a partial pressure of 10 kPa, which might be found in the lungs, hemoglobin is 95% saturated. At a partial pressure of 4 kPa, found in the tissues, hemoglobin does not bind with oxygen and will release it, so saturation falls to only about 50%. About half of the oxygen collected by hemoglobin in the lungs is released at this low partial pressure to supply the needs of actively respiring cells.

Partial pressure the proportion of the total pressure that is due to one component of a mixture of gases

The **pascal** (Pa) is the SI unit of pressure, named after the French physicist and philosopher Blaise Pascal. It is a measure of force per unit area, defined as 1 newton per square metre.
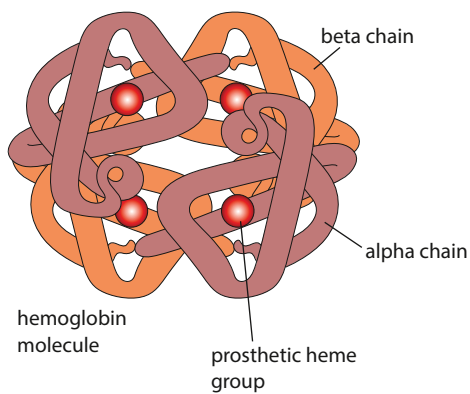1000 Pa = 1 kilopascal (kPa).

Figure D.21 Hemoglobin is a protein that has quaternary structure. It consists of four subunits bound together – two α chains and two β chains – each of which contains an iron-containing heme group.
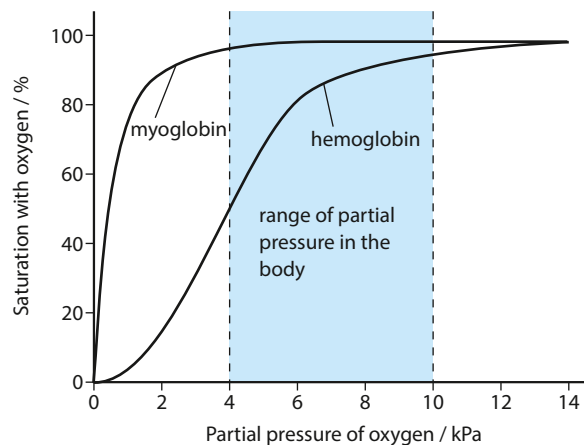

Figure D.22 Dissociation curves for hemoglobin and myoglobin. The curves are constructed using the normal range (at sea level) of partial pressure of oxygen in the body. The partial pressure of oxygen in alveolar air is about 14 kPa due to the presence of water vapour, which forms about 6% of alveolar air.

Sigmoid curve

The sigmoid shape (S-shape) of a dissociation curve is due to the allosteric effect that occurs when the first molecule of oxygen binds to hemoglobin. Once the first oxygen molecule has bound to one of the heme groups in hemoglobin, the shape of the molecule changes making it much easier for other oxygen molecules to bind. The steep slope of the curve shows that as the partial pressure of oxygen rises, hemoglobin readily becomes saturated.

Fetal hemoglobin

Whereas adult hemoglobin is composed of two α and two β chains, fetal hemoglobin is composed of two α and two γ (gamma) chains. Fetal hemoglobin must be able to collect oxygen from the mother's hemoglobin across the placenta. Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin because the γ chain has fewer positive charges than the adult hemoglobin β chain. At birth, a baby's blood contains between 50% and 90% fetal hemoglobin. During the first 6 months of life, adult hemoglobin synthesis begins and production of fetal hemoglobin stops.

Myoglobin is another oxygen–binding protein found in muscle cells. Each myoglobin molecule has only one heme group and can bind to just one oxygen molecule. It is used to store oxygen, which is released as oxygen supply falls and the muscles begin to respire anaerobically. The dissociation curve for myoglobin (Figure **D.22**) is to the left of the curve for hemoglobin. At almost all partial pressures of oxygen, myoglobin remains saturated. It is still fully saturated with oxygen at partial pressures well below those that cause hemoglobin to release oxygen, and myoglobin can hold onto oxygen until the partial pressure falls extremely low. It provides a 'reserve supply' of oxygen during vigorous activity because oxygen is only released when the partial pressure falls to 1 or 2 kPa, and this reserve means that muscles can continue to respire aerobically for longer.

Fetal hemoglobin

The molecular structure of hemoglobin in the blood of a fetus is different from that of an adult. The dissociation curve for fetal hemoglobin lies to the left of the adult curve for all partial pressures of oxygen (Figure **D.23**). This tells us that fetal hemoglobin has a higher affinity for oxygen than maternal (adult) hemoglobin, whatever the concentration of oxygen. In the capillaries of the placenta, the partial pressure of oxygen is low. Here the mother's adult hemoglobin releases oxygen, which is easily picked up and bound to fetal hemoglobin. At a partial pressure of 4 kPa, the mother's hemoglobin is only 50% saturated, but fetal hemoglobin becomes approximately 70% saturated. The fetal hemoglobin carries the oxygen to the baby's body and releases it into the respiring fetal tissues.
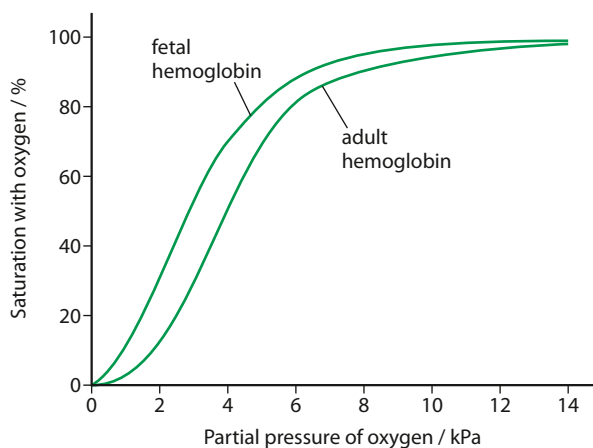
Figure D.23 Graph showing dissociation curves for adult and fetal hemoglobin.

Transport of carbon dioxide in the blood

Carbon dioxide produced during aerobic respiration is carried back to the lungs by the blood. It diffuses into capillaries close to respiring cells and is transported in one of three ways.

- About 70% of carbon dioxide enters red blood cells and is converted to HCO_3^- (hydrogencarbonate) ions.
- About 7% remains in the blood and is transported dissolved in plasma.
- The remainder is bound to hemoglobin.

Carbon dioxide reacts with water to form carbonic acid, which dissociates to form hydrogencarbonate ions and hydrogen ions:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The hydrogen ions bind to plasma proteins and this process has a buffering effect, preventing an excessive fall in pH in the blood. This reaction in the plasma is slow, but most of the carbon dioxide (about 70%) diffuses into the red blood cells where the reaction is catalysed by the enzyme carbonic anhydrase.

The hydrogen carbonate ions that are formed move out of the red blood cells via special channel proteins by facilitated diffusion. Hydrogencarbonate ions are exchanged for chloride ions, so the balance of charges on each side of the membrane is maintained. This is known as the **chloride shift** (Figure **D.24**).

The hydrogen ions remaining in the red blood cells bind reversibly to hemoglobin and prevent the pH of the cell falling, a process known as pH **buffering**.

Some carbon dioxide binds to hemoglobin. Each hemoglobin molecule can combine with one carbon dioxide molecule to form carbaminohemoglobin but, as it does so, it must release its oxygen. As carbaminohemoglobin is formed, oxygen is released into actively respiring tissues, just where it is needed. When red blood cells reach the lungs, the carbaminohemoglobin releases carbon dioxide, which is exhaled and hemoglobin is available again to collect oxygen. About 20% of carbon dioxide produced by respiration is carried in this way. As hydrogen ions and carbon dioxide bind to hemoglobin they cause the Bohr shift, which is described below.
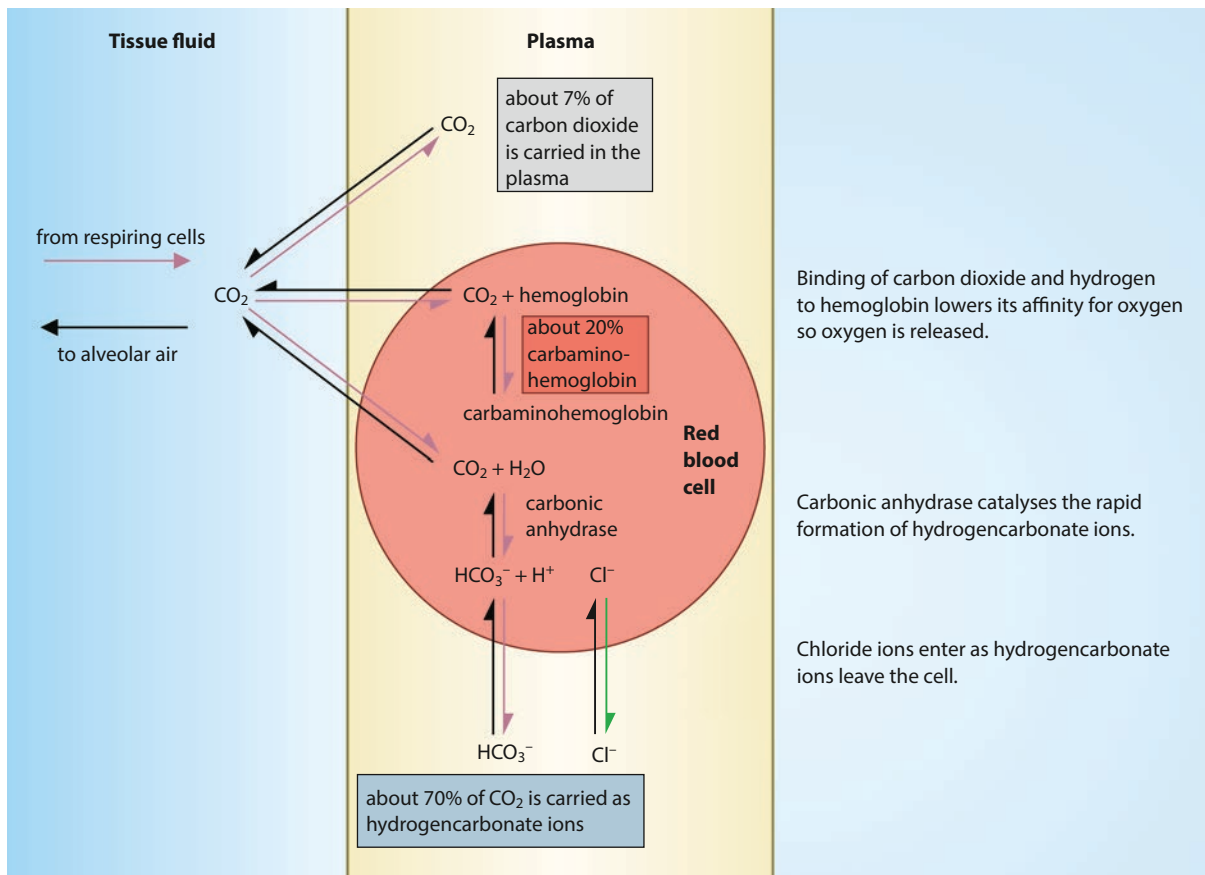
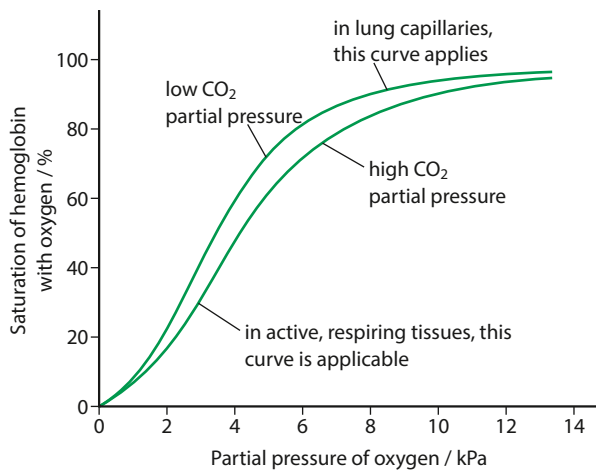**Figure D.24** Carbon dioxide transport in the blood and the chloride shift.

Figure D.25 The effect of carbon dioxide concentration on hemoglobin saturation: the Bohr shift.

The Bohr shift

The affinity of hemoglobin for oxygen is not only affected by the partial pressure of oxygen, but also reduced in the presence of high carbon dioxide concentrations. As the partial pressure of carbon dioxide rises, the ability of hemoglobin to combine with oxygen falls and so the dissociation curve moves to the right. This effect is known as the **Bohr shift**. It is caused when hydrogen ions produced from carbonic acid combine with hemoglobin. Figure **D.25** shows the effect of two different partial pressures of carbon dioxide on the oxygen dissociation curve. In an environment where the partial pressure of carbon dioxide is high, such as in actively respiring tissue, the curve moves to the right – which means that, at any given oxygen partial pressure, oxygen is more likely to dissociate from hemoglobin if the partial pressure of carbon dioxide is high. This effect promotes the release of oxygen in active tissues where respiration is producing high levels of carbon dioxide, so cells receive the oxygen they need.

Ventilation rate and exercise

When a person exercises, their ventilation rate and tidal volume (depth of breathing) increase. Muscles need oxygen for aerobic respiration and as the rate of exercise increases, so does the rate of oxygen consumption. Blood returning to the lungs also has a higher level of carbon dioxide, produced as a result of the increased activity. An increase in ventilation rate and tidal volume draws in more fresh air to maintain the concentration gradient between the alveolar air and the blood. Thus oxygen can be absorbed at a faster rate and the body can get rid of the additional carbon dioxide produced. These changes in ventilation are adjusted to match the body's metabolic needs.

Ventilation rate is controlled by the breathing centre of the **medulla oblongata** in the brain stem, which receives nerve impulses from sensory cells in different parts of the body. The breathing centre responds to match ventilation rate to activity levels (Figure **D.26**). **Chemoreceptors** in the inner wall of the aorta and carotid arteries respond to an increase in carbon dioxide in the blood. This excess carbon dioxide forms carbonic acid that cannot be buffered and so the pH of the blood falls. Impulses are passed to the medulla, which increases the ventilation rate by sending motor impulses to the intercostal muscles and diaphragm to increase their
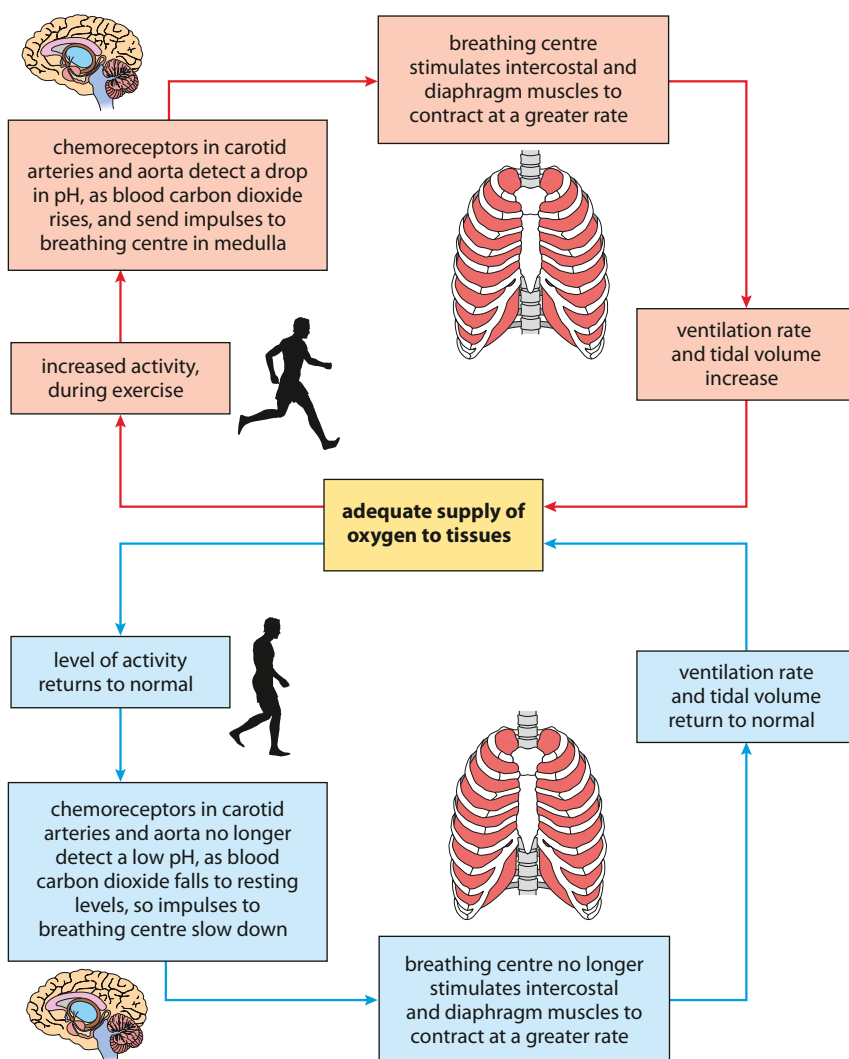

Figure D.26 The control of breathing.

rate of contraction (Subtopic **6.4**). The breathing centre contains similar chemoreceptors, which also respond to deviations of blood pH from the normal level. An increase in ventilation rate causes carbon dioxide to be removed from the body at a faster rate and blood pH returns to its normal level of between 7.35 and 7.45.

After exercise, as the level of carbon dioxide in the blood falls, ventilation rate decreases.

Gas exchange at high altitude

At high altitude, the percentage of oxygen in the air is the same as it is as sea level, but because air pressure is lower, the partial pressure of oxygen is reduced. At these lower partial pressures, hemoglobin does not become fully saturated with oxygen so that when a person moves suddenly from low to high altitude they may experience 'altitude sickness'. Symptoms include headache, nausea, dizziness and breathlessness as well as an increased heart rate. Altitude sickness can be avoided by travelling to high altitude gradually over a period of days so that the body has the opportunity to acclimatise.

During acclimatisation, the body adjusts both the ventilation and circulatory systems to cope with the lower oxygen availability. Ventilation rate increases temporarily and adjustments to the circulatory system ensure that the rate of oxygen delivery to the tissues increases. Over a period of weeks, the number of red blood cells and thus the concentration of hemoglobin steadily increase and the density of capillaries in the lungs and muscles also rises. After long periods at high altitude, the size of the lungs and the tidal volume increase so that the volume of air breathed can be 25% greater than at sea level. Once these adjustments have been made, heart and ventilation rates can return to their previous levels. People who live permanently at high altitude have a larger lung capacity and surface area for gas exchange, as well as a greater concentration of myoglobin in their muscles. Animals from high-altitude environments, such as llamas and vicunas, are also adapted to cope with the lower oxygen availability.

Some athletes choose to train at high altitude to develop increased levels of red blood cells and myoglobin. These adaptations are retained for a short time when they return to sea level and can improve athletic performance.

Causes and treatment of emphysema

Emphysema is a chronic obstructive pulmonary disease (COPD), which slowly destroys the alveoli in the lungs (Figure **D.27**) so that their bunch-like structure is lost and they eventually burst, becoming large, irregular sacs, which trap air in the lungs. The area available for gas exchange is reduced, so that insufficient oxygen reaches the blood, eventually leading to low oxygen levels (hypoxemia) and high levels of carbon dioxide (hypercapnia) building up in the blood. Emphysema also damages the elastic fibres in the lungs so that airways collapse during exhalation and air cannot be expelled properly. The main symptom of emphysema is shortness of breath, which usually begins gradually, so a person may not realise they have the disease at first, but in more advanced stages of emphysema the lungs become so damaged that sufferers become short of breath even while resting.
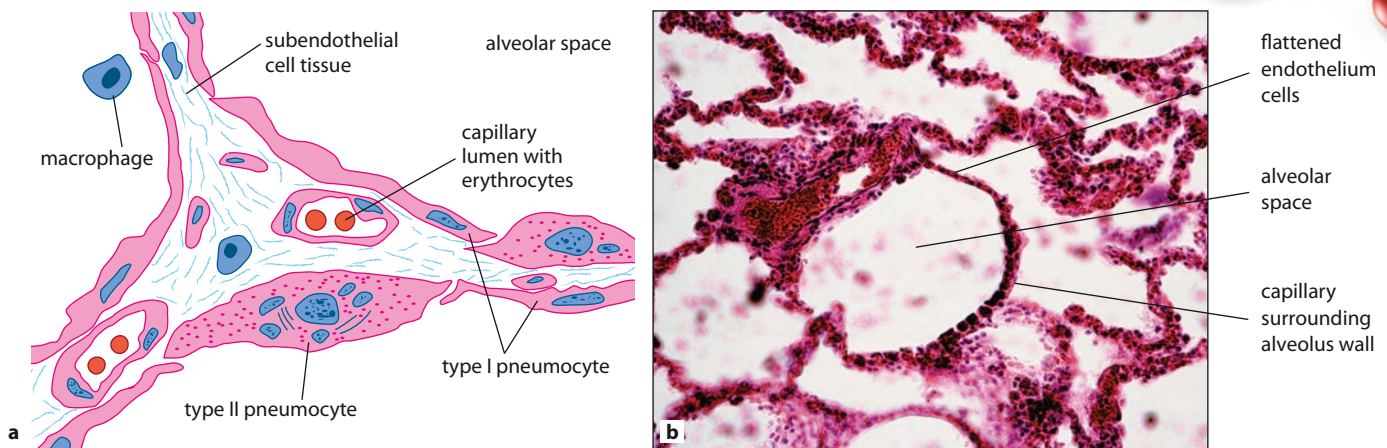
Figure D.27 a Enlarged diagram showing part of an alveolus. Pneumocytes line the alveoli where their secretions assist with gas exchange. They are easily damaged by smoking. **b** In this stained micrograph of healthy lung tissue, the structure of the alveoli, with capillaries running adjacent to the alveolar epithelium, is clear. The proximity of the red blood cells to the alveolar walls makes gas exchange highly efficient.

The most common cause of emphysema is smoking, although long-term exposure to air pollution, industrial pollutants and coal or silica dust can also be causes. Treatments can be used to reduce some of the problems of emphysema, but the damage it causes is permanent. At present, there are no drug treatments that can alter the rate of decline in lung function. The most important single factor in treatment is for the person to give up smoking so that lung damage is slowed down. Other treatments include bronchial dilators, delivered via an inhaler. These medicines relax the muscles in the bronchi and ease a person's breathing, in a similar way to treatments for asthma. In more severe cases patients are treated with oxygen therapy, and inhale oxygen from a cylinder either continuously or during periods of exercise.

Nature of science

Scientific understanding drives technical advance – athletics training

Athletes have always understood that regular training, with repetition of specific exercises to increase fitness, has an effect on the muscles and the cardiac and ventilation systems. The maximum ventilation rate during exercise can increase by 10–15% as a result of training, which will also lead to an increase in the vital capacity and development of new capillaries in the alveoli. These factors lead to a higher rate of oxygen absorption and of carbon dioxide removal. After regular training the heart becomes stronger and can pump the necessary blood to working muscles. If an athlete trains at high altitude, additional red blood cells form to carry the oxygen that is needed for improved performance.

Today elite athletes are more likely to use specific training regimes designed for them by sports scientists and physiologists who study individual athletes to maximise their performances. Precise measurement of metabolic products such as creatine in the blood, as well as the number of red blood cells a sample contains may make a difference of vital seconds or minutes to an athlete's performance.

But knowledge of science can be used in other ways, which many regard as undesirable. Erythropoietin (EPO) is a hormone that is naturally produced by the kidneys to stimulate red blood cell production in bone marrow. It is also used as a performance-enhancing substance by some athletes. Artificially increasing the proportion of red blood cells in the blood is known as **blood doping**. It can be achieved by transfusion – an athlete stores a blood sample in advance, and then some time later, just before a competition or event, receives a transfusion of his or her own red blood cells. Alternatively, an athlete may receive an injection of EPO (which can be produced by genetic engineering) to stimulate additional red blood cell production.

Is EPO OK?

Both professional and amateur athletes have been known to use EPO and there has been much debate about the acceptability of this practice. EPO has been used for blood doping in competitive endurance sports such as cycling, rowing and marathons. Until recently, there was no way to test for it directly, but in 2000 French chemists developed a method of distinguishing pharmaceutical EPO from the natural hormone normally present in an athlete's urine. This was accepted by the World Anti-Doping Agency and now EPO tests are conducted on both blood and urine samples at international events.

Some argue that, since it is possible to increase red blood cell counts by training at high altitude or sleeping in low-oxygen environments, it should be acceptable to achieve the same results by taking an injection of EPO.

EPO is also used therapeutically to treat patients who have kidney failure and cannot produce it naturally.

Questions to consider

- Can the use of EPO be regarded as cheating?
- What constitutes an acceptable level of risk for professional athletes when using substances such as EPO?
- Is the case of EPO any different from other substances used to enhance athletic performance?
- How might the views of medical practitioners and those of spectators differ in relation to the effects of EPO?

? Test yourself

17 Define 'partial pressure'.
18 Explain what is meant by the term 'Bohr shift' and why it is important in supplying oxygen to respiring tissues.
19 Describe how fetal hemoglobin differs from adult hemoglobin in its affinity for oxygen.

Exam-style questions

1 Outline the cause and treatment of phenylketonuria (PKU). **[5]**

2 Distinguish between the mode of action of steroid and protein hormones. **[2]**

3 Explain why pepsin is initially synthesised as an inactive precursor and how it is subsequently activated. **[3]**

4 Outline the importance of acidic conditions in the stomach. **[3]**

5 Explain how the structural features of the epithelium cells of a villus are related to their function. **[5]**

6 Outline how blood is brought to the liver, circulates through the liver, and then leaves the liver. **[4]**

7 **a** Describe the process of erythrocyte and hemoglobin breakdown in the liver. **[5]**

  b Outline the role of the liver in the storage of nutrients. **[2]**

8 Explain the events of the cardiac cycle including systole, diastole and heart sounds. **[6]**

9 **a** Define the term 'partial pressure'. **[1]**

  b Outline how the body acclimatises to high altitudes. **[3]**

10 The information in the graph shows blood pressure changes in the left ventricle and the aorta during two cardiac cycles.
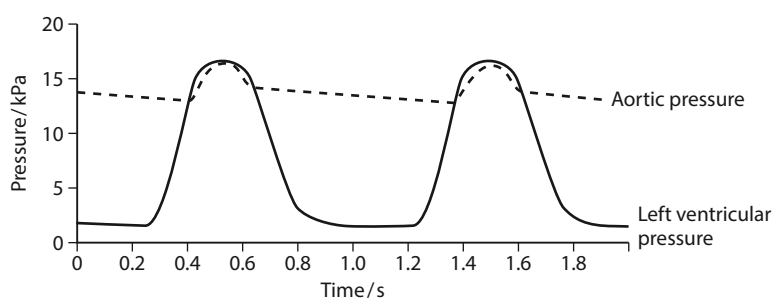
  a Draw an arrow on the graph to show when the atrioventricular valves close. **[1]**

  b Calculate the heart rate shown by the graph. **[2]**

  c What is the maximum pressure in the left ventricle during the cardiac cycle? **[1]**

  d The pressure in the right ventricle rises to a maximum of about 3.2 kPa during the cardiac cycle. Suggest reasons why this pressure is different from that in the left ventricle. **[3]**

  e State **two** reasons why the pressure in the left ventricle falls to a lower level than the pressure in the aorta. **[2]**