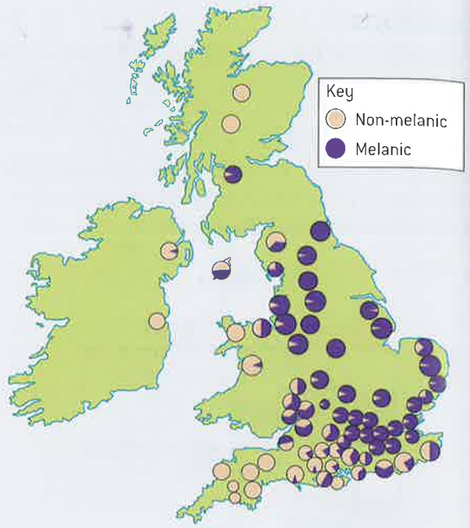
6 The map in figure 14 shows the distribution in the 1950s of two forms of *Biston betularia* in Britain and Ireland. *Biston betularia* is a species of moth that flies at night. It spends the daytime roosting on the bark of trees. The non-melanic form has white wings, peppered with black spots. The melanic form has black wings. Before the industrial revolution, the melanic form was very rare. The prevailing wind direction is from the Atlantic Ocean, to the west.

**a)** State the maximum and minimum percentages of the melanic form. [2]

**b)** Outline the trends in the distribution of the two forms of *Biston betularia*, shown in figure 14. [2]

**c)** Explain how natural selection can cause moths such as *Biston betularia* to develop camouflaged wing markings. [4]

**d)** Suggest reasons for the distribution of the two forms. [2]




▲ Figure 14



# 6 HUMAN PHYSIOLOGY

## Introduction

Research into human physiology is the foundation of modern medicine. Body functions are carried out by specialized organ systems. The structure of the wall of the small intestine allows it to move, digest and absorb food. The blood system continuously transports substances to cells and simultaneously collects waste products. The skin and immune system resist the continuous threat of invasion by pathogens. The lungs are actively ventilated to ensure that gas exchange can occur passively. Neurons transmit the message, synapses modulate the message. Hormones are used when signals need to be widely distributed.

## 6.1 Digestion and absorption

### Understanding

- The contraction of circular and longitudinal muscle layers of the small intestine mixes the food with enzymes and moves it along the gut.
- The pancreas secretes enzymes into the lumen of the small intestine.
- Enzymes digest most macromolecules in food into monomers in the small intestine.
- Villi increase the surface area of epithelium over which absorption is carried out.
- Villi absorb monomers formed by digestion as well as mineral ions and vitamins.
- Different methods of membrane transport are required to absorb different nutrients.

### Applications

- Processes occurring in the small intestine that result in the digestion of starch and transport of the products of digestion to the liver.
- Use of dialysis tubing to model absorption of digested food in the intestine.

### Skills

- Production of an annotated diagram of the digestive system.
- Identification of tissue layers in transverse sections of the small intestine viewed with a microscope or in a micrograph.

### Nature of science

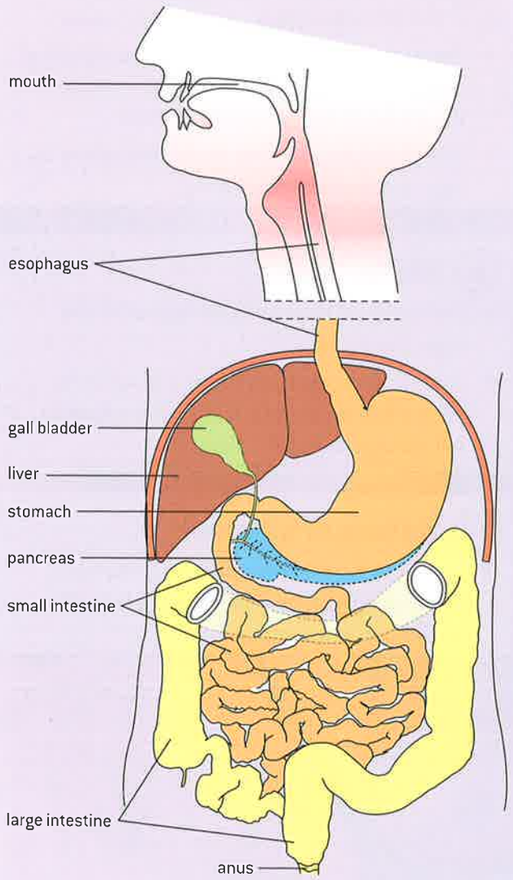
- Use models as representations of the real world: dialysis tubing can be used to model absorption in the intestine.

## Structure of the digestive system

### Production of an annotated diagram of the digestive system.

The part of the human body used for digestion can be described in simple terms as a tube through which food passes from the mouth to the anus. The role of the digestive system is to break down the diverse mixture of large carbon compounds in food, to yield ions and smaller compounds that can be absorbed. For proteins, lipids and polysaccharides digestion involves several stages that occur in different parts of the gut.

Digestion requires surfactants to break up lipid droplets and enzymes to catalyse reactions. Glandular cells in the lining of the stomach and intestines produce some of the enzymes.




▲ Figure 1 The human digestive system

Surfactants and other enzymes are secreted by accessory glands that have ducts leading to the digestive system. Controlled, selective absorption of the nutrients released by digestion takes place in the small intestine and colon, but some small molecules, notably alcohol, diffuse through the stomach lining before reaching the small intestine.

Figure 1 is a diagram of the human digestive system. The part of the esophagus that passes through the thorax has been omitted. This diagram can be annotated to indicate the functions of different parts. A summary of functions is given in table 1 below.

| Structure | Function |
|---|---|
| Mouth | Voluntary control of eating and swallowing. Mechanical digestion of food by chewing and mixing with saliva, which contains lubricants and enzymes that start starch digestion |
| Esophagus | Movement of food by peristalsis from the mouth to the stomach |
| Stomach | Churning and mixing with secreted water and acid which kills foreign bacteria and other pathogens in food, plus initial stages of protein digestion |
| Small intestine | Final stages of digestion of lipids, carbohydrates, proteins and nucleic acids, neutralizing stomach acid, plus absorption of nutrients |
| Pancreas | Secretion of lipase, amylase and protease |
| Liver | Secretion of surfactants in bile to break up lipid droplets |
| Gall bladder | Storage and regulated release of bile |
| Large intestine | Re-absorption of water, further digestion especially of carbohydrates by symbiotic bacteria, plus formation and storage of feces |

▲ Table 1



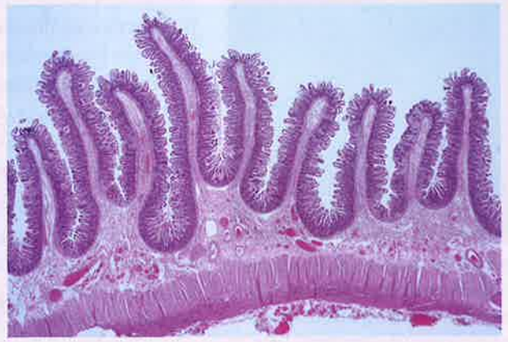


## Structure of the wall of the small intestine

### Identification of tissue layers in transverse sections of the small intestine viewed with a microscope or in a micrograph.

The wall of the small intestine is made of layers of living tissues, which are usually quite easy to distinguish in sections of the wall. From the outside of the wall going inwards there are four layers:

- serosa – an outer coat
- muscle layers – longitudinal muscle and inside it circular muscle
- sub-mucosa – a tissue layer containing blood and lymph vessels
- mucosa – the lining of the small intestine, with the epithelium that absorbs nutrients on its inner surface.



▲ Figure 2 Longitudinal section through the wall of the small intestine. Folds are visible on the inner surface and on these folds are finger-like projections called villi. All of the four main tissue layers are visible, including both circular and longitudinal parts of the muscle layer. The mucosa is stained darker than the sub-mucosa

## Peristalsis

### The contraction of circular and longitudinal muscle layers of the small intestine mixes the food with enzymes and moves it along the gut.

The circular and longitudinal muscle in the wall of the gut is smooth muscle rather than striated muscle. It consists of relatively short cells, not elongated fibres. It often exerts continuous moderate force, interspersed with short periods of more vigorous contraction, rather than remaining relaxed unless stimulated to contract.

Waves of muscle contraction, called peristalsis, pass along the intestine. Contraction of circular muscles behind the food constricts the gut to prevent it from being pushed back towards the mouth. Contraction of longitudinal muscle where the food is located moves it on along the gut. The contractions are controlled unconsciously not by the brain but by the enteric nervous system, which is extensive and complex.

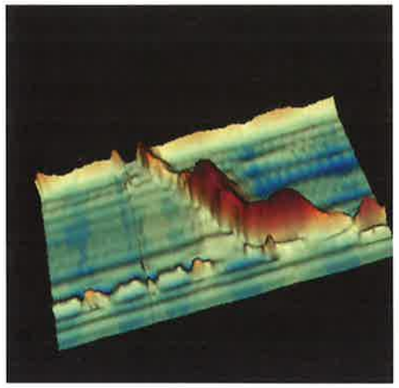
Swallowed food moves quickly down the esophagus to the stomach in one continuous peristaltic wave. Peristalsis only occurs in one direction, away from the mouth. When food is returned to the mouth from the stomach during vomiting, abdominal muscles are used rather than the circular and longitudinal muscle in the gut wall.

In the intestines the food is moved only a few centimetres at a time so the overall progression through the intestine is much slower, allowing time for digestion. The main function of peristalsis in the intestine is churning of the semi-digested food to mix it with enzymes and thus speed up the process of digestion.

**Activity**

**Tissue plan diagrams of the intestine wall**

To practice your skill at identifying tissue layers, draw a plan diagram of the tissues in the longitudinal section of the intestine wall in figure 2. To test your skill further, draw a plan diagram to predict how the tissues of the small intestine would appear in a transverse section.



▲ Figure 3 Three-dimensional image showing the wave of muscle contraction (brown) in the esophagus during swallowing. Green indicates when the muscle is exerting less force. Time is shown left to right. At the top the sphincter between the mouth and the esophagus is shown permanently constricted apart from a brief opening when swallowing starts

## Pancreatic juice

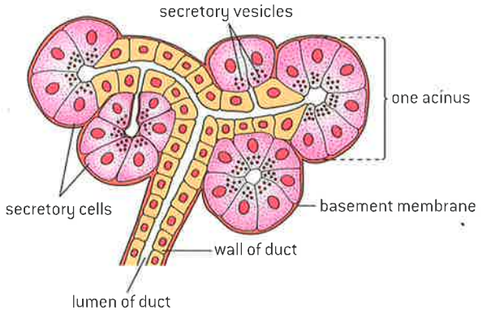
### The pancreas secretes enzymes into the lumen of the small intestine.

The pancreas contains two types of gland tissue. Small groups of cells secrete the hormones insulin and glucagon into the blood. The remainder of the pancreas synthesizes and secretes digestive enzymes into the gut in response to eating a meal. This is mediated by hormones synthesized and secreted by the stomach and also by the enteric nervous system. The structure of the tissue is shown in figure 4. Small groups of gland cells cluster round the ends of tubes called ducts, into which the enzymes are secreted.

The digestive enzymes are synthesized in pancreatic gland cells on ribosomes on the rough endoplasmic reticulum. They are then processed in the Golgi apparatus and secreted by exocytosis. Ducts within the pancreas merge into larger ducts, finally forming one pancreatic duct, through which about a litre of pancreatic juice is secreted per day into the lumen of the small intestine.

Pancreatic juice contains enzymes that digest all the three main types of macromolecule found in food:

- amylase to digest starch
- lipases to digest triglycerides, phospholipids
- proteases to digest proteins and peptides.




▲ Figure 4 Arrangement of cells and ducts in a part of the pancreas that secretes digestive enzymes

## Digestion in the small intestine

### Enzymes digest most macromolecules in food into monomers in the small intestine.

The enzymes secreted by the pancreas into the lumen of the small intestine carry out these hydrolysis reactions:

- starch is digested to maltose by amylase
- triglycerides are digested to fatty acids and glycerol or fatty acids and monoglycerides by lipase
- phospholipids are digested to fatty acids, glycerol and phosphate by phospholipase
- proteins and polypeptides are digested to shorter peptides by protease.

This does not complete the process of digestion into molecules small enough to be absorbed. The wall of the small intestine produces a variety of other enzymes, which digest more substances. Some enzymes produced by gland cells in the intestine wall may be secreted in intestinal juice but most remain immobilized in the plasma membrane of epithelium cells lining the intestine. They are active there and continue to be active when the epithelium cells are abraded off the lining and mixed with the semi-digested food.

- Nucleases digest DNA and RNA into nucleotides.
- Maltase digests maltose into glucose.





- Lactase digests lactose into glucose and galactose.
- Sucrase digests sucrose into glucose and fructose.
- Exopeptidases are proteases that digest peptides by removing single amino acids either from the carboxy or amino terminal of the chain until only a dipeptide is left.
- Dipeptidases digest dipeptides into amino acids.

Because of the great length of the small intestine, food takes hours to pass through, allowing time for digestion of most macromolecules to be completed. Some substances remain largely undigested, because humans cannot synthesize the necessary enzymes. Cellulose for example is not digested and passes on to the large intestine as one of the main components of dietary fibre.

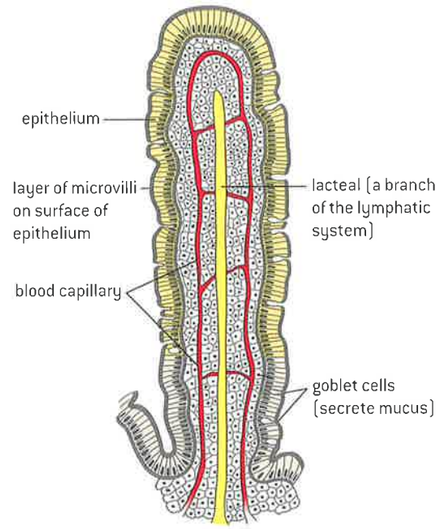
▲ Figure 5 Cystic fibrosis causes the pancreatic duct to become blocked by mucus. Pills containing synthetic enzymes help digestion in the small intestine. The photograph shows one day's supply for a person with cystic fibrosis

## Villi and the surface area for digestion

### Villi increase the surface area of epithelium over which absorption is carried out.

The process of taking substances into cells and the blood is called absorption. In the human digestive system nutrients are absorbed principally in the small intestine. The rate of absorption depends on the surface area of the epithelium that carries out the process. The small intestine in adults is approximately seven metres long and 25–30 millimetres wide and there are folds on its inner surface, giving a large surface area. This area is increased by the presence of villi.

Villi are small finger-like projections of the mucosa on the inside of the intestine wall. A villus is between 0.5 and 1.5 mm long and there can be as many as 40 of them per square millimetre of small intestine wall. They increase the surface area by a factor of about 10.




▲ Figure 6 Structure of an intestinal villus

## Absorption by villi

### Villi absorb monomers formed by digestion as well as mineral ions and vitamins.

The epithelium that covers the villi must form a barrier to harmful substances, while at the same time being permeable enough to allow useful nutrients to pass through.

Villus cells absorb these products of digestion of macromolecules in food:

- glucose, fructose, galactose and other monosaccharides
- any of the twenty amino acids used to make proteins
- fatty acids, monoglycerides and glycerol
- bases from digestion of nucleotides.

They also absorb substances required by the body and present in foods but not needing digestion:

- mineral ions such as calcium, potassium and sodium
- vitamins such as ascorbic acid (vitamin C).

▲ Figure 7 Scanning electron micrograph of villi in the small intestine

Some harmful substances pass through the epithelium and are subsequently removed from the blood and detoxified by the liver. Some harmless but unwanted substances are also absorbed, including many of those that give food its colour and flavour. These pass out in urine. Small numbers of bacteria pass through the epithelium but are quickly removed from the blood by phagocytic cells in the liver.

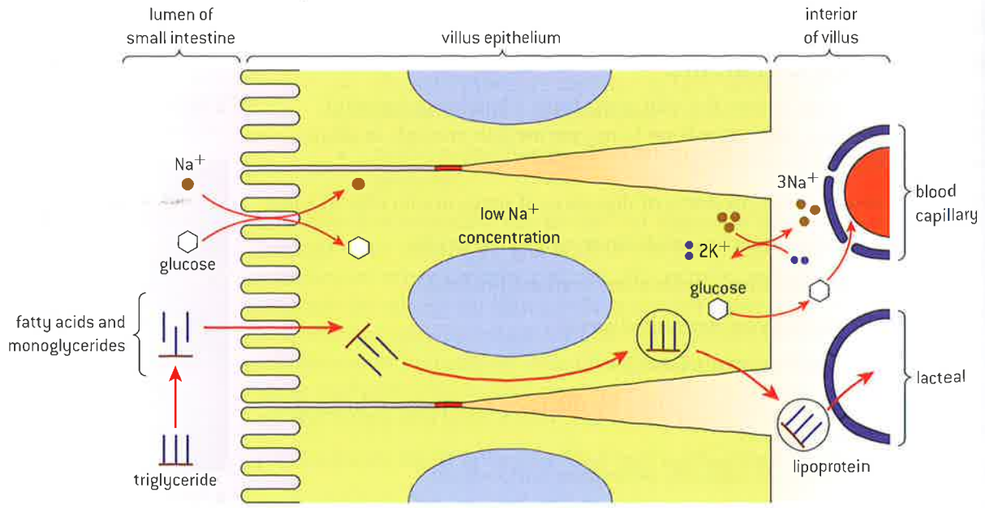
## Methods of absorption

### Different methods of membrane transport are required to absorb different nutrients.

To be absorbed into the body, nutrients must pass from the lumen of the small intestine to the capillaries or lacteals in the villi. The nutrients must first be absorbed into epithelium cells through the exposed part of the plasma membrane that has its surface area enlarged with microvilli. The nutrients must then pass out of this cell through the plasma membrane where it faces inwards towards the lacteal and blood capillaries of the villus.

Many different mechanisms move nutrients into and out of the villus epithelium cells: simple diffusion, facilitated diffusion, active transport and exocytosis. These methods can be illustrated using two different examples of absorption: triglycerides and glucose.

- Triglycerides must be digested before they can be absorbed. The products of digestion are fatty acids and monoglycerides, which can be absorbed into villus epithelium cells by simple diffusion as they can pass between phospholipids in the plasma membrane.
- Fatty acids are also absorbed by facilitated diffusion as there are fatty acid transporters, which are proteins in the membrane of the microvilli.
- Once inside the epithelium cells, fatty acids are combined with monoglycerides to produce triglycerides, which cannot diffuse back out into the lumen.




▲ Figure 8 Methods of absorption in the small intestine





- Triglycerides coalesce with cholesterol to form droplets with a diameter of about 0.2 μm, which become coated in phospholipids and protein.
- These lipoprotein particles are released by exocytosis through the plasma membrane on the inner side of the villus epithelium cells. They then either enter the lacteal and are carried away in the lymph, or enter the blood capillaries in the villi.
- Glucose cannot pass through the plasma membrane by simple diffusion because it is polar and therefore hydrophilic.
- Sodium–potassium pumps in the inwards-facing part of the plasma membrane pump sodium ions by active transport from the cytoplasm to the interstitial spaces inside the villus and potassium ions in the opposite direction. This creates a low concentration of sodium ions inside villus epithelium cells.
- Sodium–glucose co-transporter proteins in the microvilli transfer a sodium ion and a glucose molecule together from the intestinal lumen to the cytoplasm of the epithelium cells. This type of facilitated diffusion is passive but it depends on the concentration gradient of sodium ions created by active transport.
- Glucose channels allow the glucose to move by facilitated diffusion from the cytoplasm to the interstitial spaces inside the villus and on into blood capillaries in the villus.

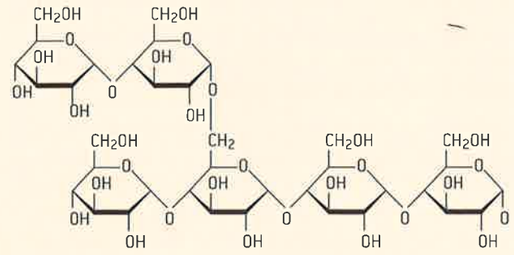
## Starch digestion in the small intestine

### Processes occurring in the small intestine that result in the digestion of starch and transport of the products of digestion to the liver.

Starch digestion illustrates some important processes including catalysis, enzyme specificity and membrane permeability. Starch is a macromolecule, composed of many α-glucose monomers linked together in plants by condensation reactions. It is a major constituent of plant-based foods such as bread, potatoes and pasta. Starch molecules cannot pass through membranes so must be digested in the small intestine to allow absorption.

All of the reactions involved in the digestion of starch are exothermic, but without a catalyst they happen at very slow rates. There are two types of molecule in starch:

- amylose has unbranched chains of α-glucose linked by 1,4 bonds;
- amylopectin has chains of α-glucose linked by 1,4 bonds, with some 1,6 bonds that make the molecule branched.



▲ Figure 9 Small portion of an amylopectin molecule showing six α-glucose molecules, all linked by 1,4 bonds apart from one 1,6 bond that creates a branch

The enzyme that begins the digestion of both forms of starch is amylase. Saliva contains amylase but most starch digestion occurs in the small intestine, catalysed by pancreatic amylase. Any 1,4 bond in starch molecules can be broken by this enzyme, as long as there is a chain of at least four glucose monomers. Amylose is therefore

digested into a mixture of two- and three-glucose fragments called maltose and maltotriose.

Because of the specificity of its active site, amylase cannot break 1,6 bonds in amylopectin. Fragments of the amylopectin molecule containing a 1,6 bond that amylase cannot digest are called dextrins. Digestion of starch is completed by three enzymes in the membranes of microvilli on villus epithelium cells. Maltase, glucosidase and dextrinase digest maltose, maltotriose and dextrins into glucose.

Glucose is absorbed into villus epithelium cells by co-transport with sodium ions. It then moves by facilitated diffusion into the fluid in interstitial spaces inside the villus. The dense network of capillaries close to the epithelium ensures that glucose only has to travel a short distance to enter the blood system. Capillary walls consist of a single layer of thin cells, with pores between adjacent cells, but these capillaries have larger pores than usual, aiding the entry of glucose.

Blood carrying glucose and other products of digestion flows though villus capillaries to venules in the sub-mucosa of the wall of the small intestine. The blood in these venules is carried via the hepatic portal vein to the liver, where excess glucose can be absorbed by liver cells and converted to glycogen for storage. Glycogen is similar in structure to amylopectin, but with more 1,6 bonds and therefore more extensive branching.

## Modelling physiological processes

Use models as representations of the real world: dialysis tubing can be used to model absorption in the intestine.

Living systems are complex and when experiments are done on them, many factors can influence the results. It can be very difficult to control all of the variables and analysis of results becomes difficult. Sometimes it is better to carry out experiments using only parts of systems. For example, much research in physiology has been carried out using clones of cells in tissue culture rather than whole organisms.

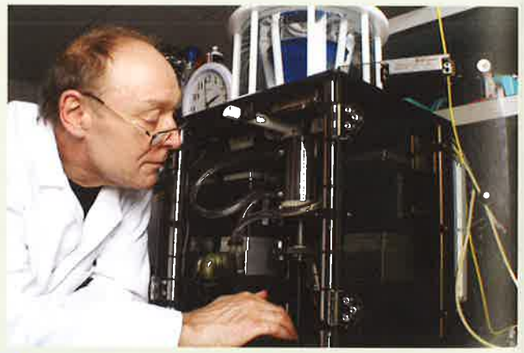


Figure 10 The Dynamic Gastric Model with its inventor, Richard Faulks, adjusting the antrum mechanism

Another approach is to use a model to represent part of a living system. Because it is much simpler, a model can be used to investigate specific aspects of a process. A recent example is the Dynamic Gastric Model, a computer-controlled model of the human stomach that carries out mechanical and chemical digestion of real food samples. It can be used to investigate the effects of diet, drugs, alcohol and other factors on digestion.

A simpler example is the use of dialysis tubing made from cellulose. Pores in the tubing allow water and small molecules or ions to pass through freely, but not large molecules. These properties mimic the wall of the gut, which is also more permeable to small rather than large particles. Dialysis tubing can be used to model absorption by passive diffusion and by osmosis. It cannot model active transport and other processes that occur in living cells





## Modelling the small intestine

Use of dialysis tubing to model absorption of digested food in the intestine.

To make a model of the small intestine, cut a length of dialysis tubing and seal one end by tying a knot in the tubing or tying with a piece of cotton thread. Pour in a suitable mixture of foods and seal the open end by tying with a piece of cotton thread. Two experiments using model intestines made in this way are suggested here:

### 1 Investigating the need for digestion using a model of the small intestine

Set up the apparatus shown in figure 11 and leave it for one hour.

#### Results

To obtain the results for the experiment, take the bags out of each tube, open them and pour the solutions from them into separate test tubes from the liquids in the tubes. You should now have four samples of fluid. Divide each of these samples into two halves and test one half for starch and the other half for sugars.

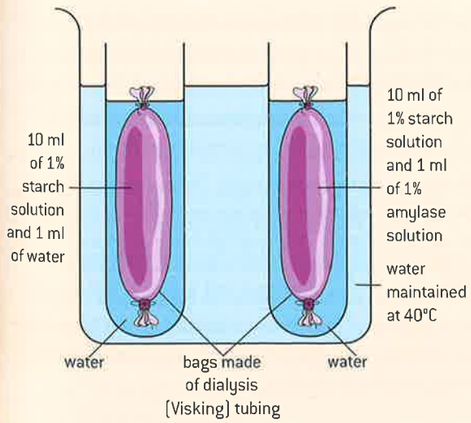



Figure 11 Apparatus for showing the need for digestion

Record all the results in the way that you think is most appropriate.

#### Conclusions and evaluation

State carefully all the conclusions that you can make from your results.

Discuss the strengths and weaknesses of this method of investigating the need for digestion.

Suggest improvements to the method, or suggest an entirely different method of investigating the need for digestion.

### 2 Investigating membrane permeability using a model of the small intestine

Cola drinks contain a mixture of substances with different particle sizes. They can be used to represent food in the small intestine. Dialysis tubing is semi-permeable so can be used to model the wall of the small intestine.

#### Predictions

Cola contains glucose, phosphoric acid and caramel, a complex carbohydrate added to produce a brown colour. Predict which of these substances will diffuse out of the bag, with reasons for your predictions. Predict whether the bag will gain or lose mass during the experiment.

#### Instructions

1 Make the model intestine with cola inside.

2 Rinse the outside of the bag to wash off any traces of cola and then dry the bag.

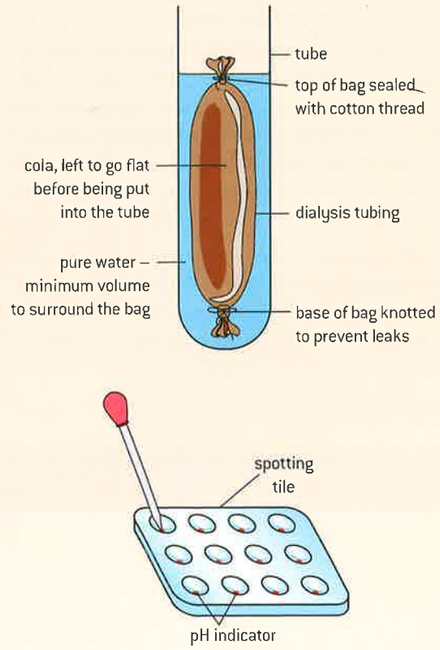



Figure 12 Apparatus for membrane permeability experiment

3 Find the mass of the bag using an electronic balance.

4 When you are ready to start the experiment, place the bag in pure water in a test tube.

5 Test the water around the bag at suitable time intervals. A suggested range is 1, 2, 4, 8 and 16 minutes. At each time lift the bag up and down a few times to mix the water in the tube, then do these tests:

- Look carefully at the water to see whether it is still clear or has become brown.
- Use a dropping pipette to remove a few drops of the water and test them in a spotting tile with a narrow-range pH indicator. Use a colour chart to work out the pH.
- Dip a glucose test strip into the water and record the colour that it turns. Instructions vary for these test strips. Follow the instructions and work out the glucose concentration of the water.

6 After testing the water for the last time, remove the bag, dry it and find its mass again with the electronic balance.

### Conclusions

**a)** Explain the conclusions that you can draw about the permeability of the dialysis tubing from the tests of the water and from the change in mass of the bag. [5]

**b)** Compare and contrast the dialysis tubing and the plasma membranes that carry out absorption in villus epithelium cells in the wall of the intestine. [5]

**c)** Use the results of your experiment to predict the direction of movement of water by osmosis across villus epithelium cells. [5]

## TOK

**What are some of the variables that affect perspectives as to what is "normal"?**

In some adult humans, levels of lactase are too low to digest lactose in milk adequately. Instead, lactose passes through the small intestine into the large intestine, where bacteria feed on it, producing carbon dioxide, hydrogen and methane. These gases cause some unpleasant symptoms, discouraging consumption of milk. The condition is known as lactose intolerance. It has sometimes in the past been regarded as an abnormal condition, or even as a disease, but it could be argued that lactose intolerance is the normal human condition.

The first argument for this view is a biological one. Female mammals produce milk to feed their young offspring. When a young mammal is weaned, solid foods replace milk and lactase secretion declines. Humans who continue to consume milk into adulthood are therefore unusual. Inability to consume milk because of lactose intolerance should not therefore be regarded as abnormal.

The second argument is a simple mathematical one: a high proportion of humans are lactose intolerant.

The third argument is evolutionary. Our ancestors were almost certainly all lactose intolerant, so this is the natural or normal state. Lactose tolerance appears to have evolved separately in at least three centres: Northern Europe, parts of Arabia, the Sahara and eastern Sudan, and parts of East Africa inhabited by the Tutsi and Maasai peoples. Elsewhere, tolerance is probably due to migration from these centres.





# 6.2 The blood system

## Understanding

- Arteries convey blood at high pressure from the ventricles to the tissues of the body.
- Arteries have muscle and elastic fibres in their walls.
- The muscle and elastic fibres assist in maintaining blood pressure between pump cycles.
- Blood flows through tissues in capillaries with permeable walls that allow exchange of materials between cells in the tissue and the blood in the capillary.
- Veins collect blood at low pressure from the tissues of the body and return it to the atria of the heart.
- Valves in veins and the heart ensure circulation of blood by preventing backflow.
- There is a separate circulation for the lungs.
- The heartbeat is initiated by a group of specialized muscle cells in the right atrium called the sinoatrial node.
- The sinoatrial node acts as a pacemaker.
- The sinoatrial node sends out an electrical signal that stimulates contraction as it is propagated through the walls of the atria and then the walls of the ventricles.
- The heart rate can be increased or decreased by impulses brought to the heart through two nerves from the medulla of the brain.
- Epinephrine increases the heart rate to prepare for vigorous physical activity.

## Applications

- William Harvey's discovery of the circulation of the blood with the heart acting as the pump.
- Causes and consequences of occlusion of the coronary arteries.
- Pressure changes in the left atrium, left ventricle and aorta during the cardiac cycle.

## Skills

- Identification of blood vessels as arteries, capillaries or veins from the structure of their walls.
- Recognition of the chambers and valves of the heart and the blood vessels connected to it in dissected hearts or in diagrams of heart structure.

## Nature of science

- Theories are regarded as uncertain: William Harvey overturned theories developed by the ancient Greek philosopher Galen on movement of blood in the body.

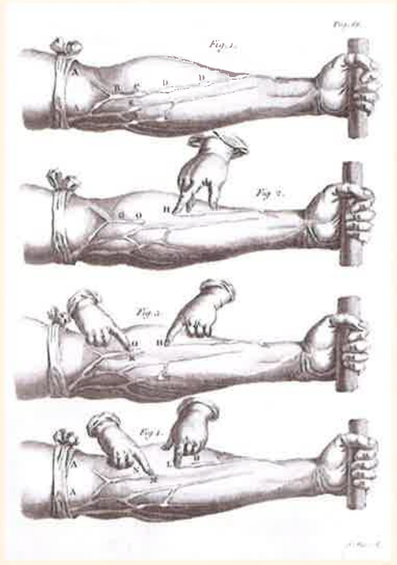
## William Harvey and the circulation of blood

William Harvey's discovery of the circulation of the blood with the heart acting as the pump.

William Harvey is usually credited with the discovery of the circulation of the blood as he combined earlier discoveries with his own research findings to produce a convincing overall theory for blood flow in the body. He overcame widespread opposition by publishing his results and also by touring Europe to demonstrate experiments that falsified previous theories and provided evidence for his theory. As a result his theory became generally accepted.

Harvey demonstrated that blood flow through the larger vessels is unidirectional, with valves to prevent backflow. He also showed that the rate of flow through major vessels was far too high for blood to be consumed in the body after being pumped out by the heart, as earlier theories proposed. It must therefore return to the heart and be recycled. Harvey showed that the heart pumps blood out in the arteries and it returns in veins. He predicted the presence of numerous fine vessels too small to be seen with contemporary equipment that linked arteries to veins in the tissues of the body.

Blood capillaries are too narrow to be seen with the naked eye or with a hand lens. Microscopes had not been invented by the time that Harvey published his theory about the circulation of blood in 1628. It was not until 1660, after his death, that blood was seen flowing from arteries to veins though capillaries as he had predicted.



▲ Figure 1 Harvey's experiment to demonstrate that blood flow in the veins of the arm is unidirectional

## Overturning ancient theories in science

Theories are regarded as uncertain: William Harvey overturned theories developed by the ancient Greek philosopher Galen on movement of blood in the body.

During the Renaissance, interest was reawakened in the classical writings of Greece and Rome. This stimulated literature and the arts, but in some ways it hampered progress in science. It became almost impossible to question the doctrines of such writers as Aristotle, Hippocrates, Ptolemy and Galen.

According to Galen, blood is formed in the liver and is pumped to and fro between the liver and the right ventricle of the heart. A little blood passes into the left ventricle, where it meets air from the lungs and becomes "vital spirits". The vital spirits are distributed to the body by the arteries. Some of the vital spirits flow to the brain, to be converted into "animal spirits", which are then distributed by the nerves to the body.

William Harvey was unwilling to accept these doctrines without evidence. He made careful observations and did experiments, from which he deduced that blood circulates through the pulmonary and systemic circulations. He predicted the existence of capillaries, linking arteries and veins, even though the lenses of the time were not powerful enough for him to see them.





The following extract is from Harvey's book *On the Generation of Animals*, published in 1651 when he was 73.

> *And hence it is that without the due admonition of the senses, without frequent observation and reiterated experiment, our mind goes astray after phantoms and appearances. Diligent observation is therefore requisite in every science, and the senses are frequently to be appealed to. We are, I say, to strive after personal experience, not to rely of the experience of others: without which no one can properly become a student of any branch of natural science. I would not have you therefore, gentle reader, to take anything on trust from me concerning the Generation of Animals: I appeal to your own eyes as my witness and judge. The method of pursuing truth commonly pursued at this time therefore is to be held erroneous and almost foolish, in which so many enquire what things others have said, and omit to ask whether the things themselves be actually so or not.*

## Arteries

Arteries convey blood at high pressure from the ventricles to the tissues of the body.

Arteries are vessels that convey blood from the heart to the tissues of the body. The main pumping chambers of the heart are the ventricles. They have thick strong muscle in their walls that pumps blood into the arteries, reaching a high pressure at the peak of each pumping cycle. The artery walls work with the heart to facilitate and control blood flow. Elastic and muscle tissue in the walls are used to do this.

Elastic tissue contains elastin fibres, which store the energy that stretches them at the peak of each pumping cycle. Their recoil helps propel the blood on down the artery. Contraction of smooth muscle in the artery wall determines the diameter of the lumen and to some extent the rigidity of the arteries, thus controlling the overall flow through them.

Both the elastic and muscular tissues contribute to the toughness of the walls, which have to be strong to withstand the constantly changing and intermittently high blood pressure without bulging outwards (aneurysm) or bursting. The blood's progress along major arteries is thus pulsatile, not continuous. The pulse reflects each heartbeat and can easily be felt in arteries that pass near the body surface, including those in the wrist and the neck.

Each organ of the body is supplied with blood by one or more arteries. For example, each kidney is supplied by a renal artery and the liver by the hepatic artery. The powerful, continuously active muscles of the heart itself are supplied with blood by coronary arteries.

### Activity

**Discussion questions on William Harvey's methods**

1 William Harvey refused to accept doctrines without evidence. Are there academic contexts where it is reasonable to accept doctrines on the basis of authority rather than evidence gathered from primary sources?

2 Harvey welcomed questions and criticisms of his theories when teaching anatomy classes. Suggest why he might have done this.

3 Can you think of examples of the "phantoms and appearances" that Harvey refers to?

4 Why does Harvey recommend "reiteration" of experiments?

5 Harvey practised as a doctor, but after the publication in 1628 of his work on the circulation of the blood, far fewer patients consulted him. Why might this have been?

## Artery walls

Arteries have muscle and elastic fibres in their walls.

The wall of the artery is composed of several layers:

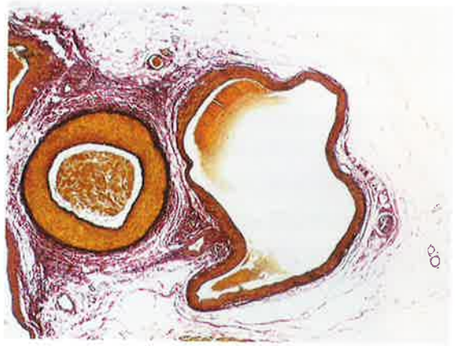
- tunica externa – a tough outer layer of connective tissue
- tunica media – a thick layer containing smooth muscle and elastic fibres made of the protein elastin
- tunica intima – a smooth endothelium forming the lining of the artery.

**Activity**

**Standing on your head**

Pocket valves and vein walls become less efficient with age, causing poor venous return to the heart. Have you ever performed gymnastic moves such as headstands or handstands, or experienced very high g-forces on a ride at an amusement park? Young people can mostly do any of these activities easily but older people may not be able to. What is the explanation?

▲ Figure 5 Which veins in this gymnast will need valves to help with venous return?



▲ Figure 6 Artery and vein in transverse section. The tunica externa and tunica intima are stained more darkly than the tunica media. Clotted blood is visible in both vessels

## Valves in veins

Valves in veins and the heart ensure circulation of blood by preventing backflow.

Blood pressure in veins is sometimes so low that there is a danger of backflow towards the capillaries and insufficient return of blood to the heart. To maintain circulation, veins contain pocket valves, consisting of three cup-shaped flaps of tissue.

- If blood starts to flow backwards, it gets caught in the flaps of the pocket valve, which fill with blood, blocking the lumen of the vein.
- When blood flows towards the heart, it pushes the flaps to the sides of the vein. The pocket valve therefore opens and blood can flow freely.

These valves allow blood to flow in one direction only and make efficient use of the intermittent and often transient pressures provided by muscular and postural changes. They ensure that blood circulates in the body rather than flowing to and fro.

## Identifying blood vessels

Identification of blood vessels as arteries, capillaries or veins from the structure of their walls.

Blood vessels can be identified as arteries, capillaries or veins by looking at their structure. Table 1 below gives differences that may be useful.

| | Artery | Capillary | Vein |
|---|---|---|---|
| Diameter | Larger than 10 μm | Around 10 μm | Variable but much larger than 10 μm |
| Relative thickness of wall and diameter of lumen | Relatively thick wall and narrow lumen | Extremely thin wall | Relatively thin wall with variable but often wide lumen |
| Number of layers in wall | Three layers, tunica externa, media and intima. These layers may be sub-divided to form more layers | Only one layer – the tunica intima which is an endothelium consisting of a single layer of very thin cells | Three layers – tunica externa, media and intima |
| Muscle and elastic fibres in the wall | Abundant | None | Small amounts |
| Valves | None | None | Present in many veins |

▲ Table 1





## The double circulation

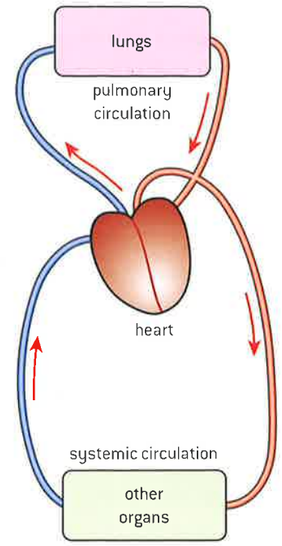
There is a separate circulation for the lungs.

There are valves in the veins and heart that ensure a one-way flow, so blood circulates through arteries, capillaries and veins. Fish have a single circulation. Blood is pumped at high pressure to their gills to be oxygenated. After flowing through the gills the blood still has enough pressure to flow directly, but relatively slowly, to other organs of the body and then back to the heart. In contrast, the lungs used by mammals for gas exchange are supplied with blood by a separate circulation.

Blood capillaries in lungs cannot withstand high pressures so blood is pumped to them at relatively low pressure. After passing through the capillaries of the lungs the pressure of the blood is low, so it must return to the heart to be pumped again before it goes to other organs. Humans therefore have two separate circulations:

- the pulmonary circulation, to and from the lungs
- the systemic circulation, to and from all other organs, including the heart muscles.

Figure 7 shows the double circulation in a simplified form. The pulmonary circulation receives deoxygenated blood that has returned from the systemic circulation, and the systemic circulation receives blood that has been oxygenated by the pulmonary circulation. It is therefore essential that blood flowing to and from these two circulations is not mixed. The heart is therefore a double pump, delivering blood under different pressures separately to the two circulations.

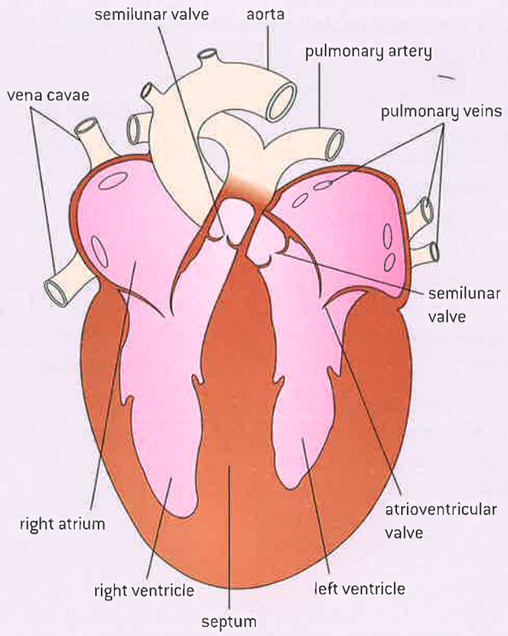



▲ Figure 7 The double circulation

## Heart structure

Recognition of the chambers and valves of the heart and the blood vessels connected to it in dissected hearts or in diagrams of heart structure.

- The heart has two sides, left and right, that pump blood to the systemic and pulmonary circulations.
- Each side of the heart has two chambers, a ventricle that pumps blood out into the arteries and an atrium that collects blood from the veins and passes it to the ventricle.
- Each side of the heart has two valves, an atrioventricular valve between the atrium and the ventricle and a semilunar valve between the ventricle and the artery.
- Oxygenated blood flows into the left side of the heart through the pulmonary veins from the lungs and out through the aorta.




▲ Figure 8 Structure of the heart

- Deoxygenated blood flows into the left side of the heart through the vena cava and out in the pulmonary arteries.

The heart is a complicated three-dimensional structure. The best way to learn about its structure is by doing a dissection. A fresh specimen of a mammalian heart, with blood vessels still attached, a dissecting dish or board and dissecting instruments are needed.

### 1 Arteries and veins

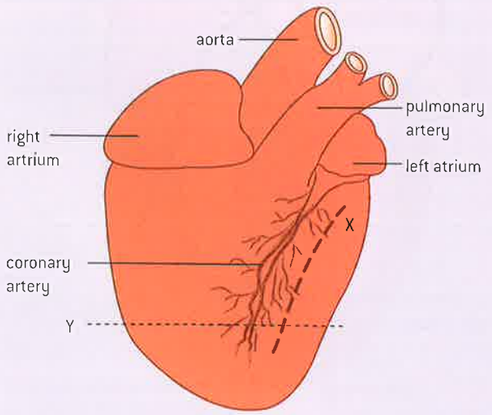
Tidy up the blood vessels attached to the heart by removing membranes and other tissue from around them. Identify the thick-walled arteries and the thin-walled veins.

### 2 Pulmonary artery and aorta

Push a glass rod or other blunt-ended instrument into the heart through the arteries and feel through the wall of the heart to where the end of the rod has reached. Identify the pulmonary artery, through which you will reach the thinner-walled right ventricle, and the aorta, through which you will reach the thicker-walled left ventricle.

### 3 Dorsal and ventral sides

Lay the heart so that the aorta is behind the pulmonary artery, as in figure 9. The ventral side is now uppermost and the dorsal side underneath. The dorsal side of an animal is its back.




▲ Figure 9 Ventral view of the exterior of the heart

### 4 Left ventricle

Identify the left ventricle. It has a smooth wall, with a tree-like pattern of blood vessels. Using a sharp scalpel, make an incision as shown by the dashed line X in figure 9. This should open up the left ventricle. Look at the thick muscular wall that you have cut through.

### 5 Atrioventricular valve

Extend the incision further towards the atrium if necessary until you can see the two thin flaps of the atrioventricular valve. Tendons attached to the sides of the left ventricle prevent the valve inverting into the atrium.

### 6 Left atrium and pulmonary vein

Identify the left atrium. It will look surprisingly small as there is no blood inside it. The outer surface of its wall has a wrinkled appearance. Extend the incision that you have already made, either with the scalpel or with scissors, to cut through the wall of the left atrium as far as the pulmonary vein. Look at the thin wall of the atrium and the opening of the pulmonary vein or veins (there may be two).

### 7 Aorta

Find the aorta again and measure the diameter of its lumen, in millimetres. Using scissors, cut through the wall of the aorta, starting at its end and working towards the left ventricle. Look at the smooth inner surface of the aorta and try stretching the wall to see how tough it is.

### 8 Semilunar valve

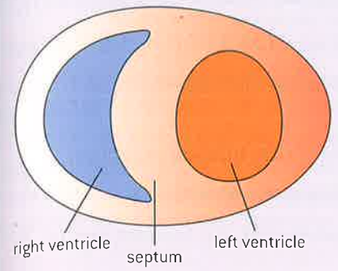
Where the aorta exits the left ventricle, there will be three cup-shaped flaps in the wall. These form the semilunar valve. Try pushing a blunt instrument into the flaps to see how blood flowing backwards pushes the flaps together, closing the valve.

### 9 Coronary artery

Look carefully at the inner surface of the aorta, near the semilunar valve. A small hole should be visible, which is the opening to the coronary arteries. Measure the diameter of the lumen of this artery. The coronary arteries supply the wall of the heart with oxygen and nutrients.








▲ Figure 10 Transverse section through the ventricles

### 10 Septum

Make a transverse section through the heart near the base of the ventricles, along the dotted line marked Y in figure 9. Measure the thickness in millimetres of the walls of the left and right ventricles and of the septum between them (figure 10). The septum contains conducting fibres, which help to stimulate the ventricles to contract.

## Atherosclerosis

### Causes and consequences of occlusion of the coronary arteries.

One of the commonest current health problems is atherosclerosis, the development of fatty tissue called atheroma in the artery wall adjacent to the endothelium. Low density lipoproteins (LDL) containing fats and cholesterol accumulate and phagocytes are then attracted by signals from endothelium cells and smooth muscle. The phagocytes engulf the fats and cholesterol by endocytosis and grow very large. Smooth muscle cells migrate to form a tough cap over the atheroma. The artery wall bulges into the lumen narrowing it and thus impeding blood flow.

Small traces of atheroma are normally visible in children's arteries by the age of ten, but do not affect health. In some older people atherosclerosis becomes much more advanced but often goes unnoticed until a major artery becomes so blocked that the tissues it supplies become compromised.

Coronary occlusion is a narrowing of the arteries that supply blood containing oxygen and nutrients to the heart muscle. Lack of oxygen (anoxia) causes pain, known as angina, and impairs the muscle's ability to contract, so the heart beats faster as it tries to maintain blood circulation with some of its muscle out of action. The fibrous cap covering atheromas sometimes ruptures, which stimulates the formation of blood clots that can block arteries supplying blood to the heart and cause acute heart problems. This is described in sub-topic 6.3.

The causes of atherosclerosis are not yet fully understood. Various factors have been shown to be associated with an increased risk of atheroma but are not the sole causes of the condition:

- high blood concentrations of LDL (low density lipoprotein)
- chronic high blood glucose concentrations, due to overeating, obesity or diabetes

## Activity

**Structure and function of the heart**

Discuss the answers to these questions.

1. Why are the walls of the atria thinner than the walls of the ventricles?
2. What prevents the atrioventricular valve from being pushed into the atrium when the ventricle contracts?
3. Why is the left ventricle wall thicker than the right ventricle wall?
4. Does the left side of the heart pump oxygenated or deoxygenated blood?
5. Why does the wall of the heart need its own supply of blood, brought by the coronary arteries?
6. Does the right side of the heart pump a greater volume of blood per minute, a smaller volume, or the same volume as the left?

### Activity

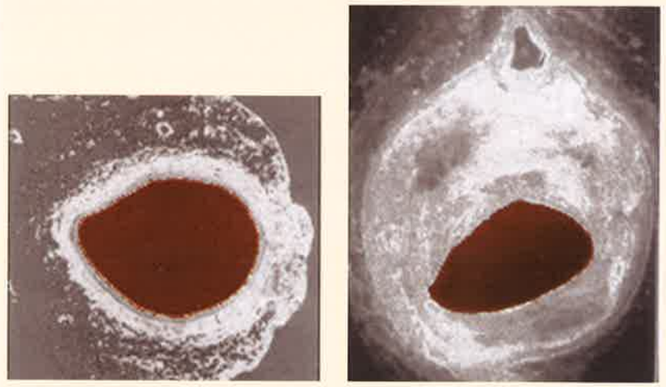
**Carnitine and coronary occusion**

A chemical called carnitine that is found in certain foods is converted into TMAO by bacteria in the gut. Find out what foods contain the highest concentrations of carnitine and discuss whether this finding should influence dietary advice.

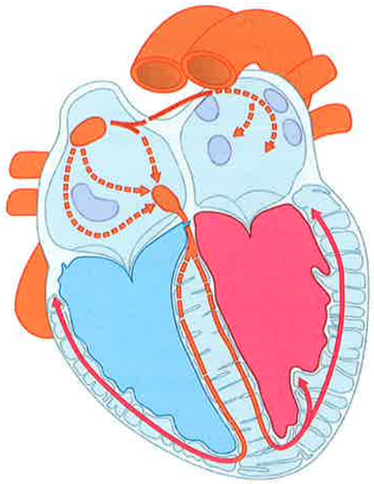
- chronic high blood pressure due to smoking, stress or any other cause
- consumption of *trans* fats, which damage the endothelium of the artery.

There are also some more recent theories that include microbes:

- infection of the artery wall with *Chlamydia pneumoniae*
- production of trimethylamine N-oxide (TMAO) by microbes in the intestine.



▲ Figure 11 A normal artery (left) has a much wider lumen than an artery that is occluded by atheroma (right)



▲ Figure 12 The sinoatrial node

## The sinoatrial node

### The heartbeat is initiated by a group of specialized muscle cells in the right atrium called the sinoatrial node.

The heart is unique in the body as its muscles can contract without stimulation from motor neurons. The contraction is called myogenic, meaning that it is generated in the muscle itself. The membrane of a heart muscle cell depolarizes when the cell contracts and this activates adjacent cells, so they also contract. A group of cells therefore contracts almost simultaneously at the rate of the fastest.

The region of the heart with the fastest rate of spontaneous beating is a small group of special muscle cells in the wall of the right atrium, called the sinoatrial node. These cells have few of the proteins that cause contraction in other muscle cells, but they have extensive membranes. The sinoatrial node therefore initiates each heartbeat, because the membranes of its cells are the first to depolarize in each cardiac cycle.





## Initiating the heartbeat

### The sinoatrial node acts as a pacemaker.

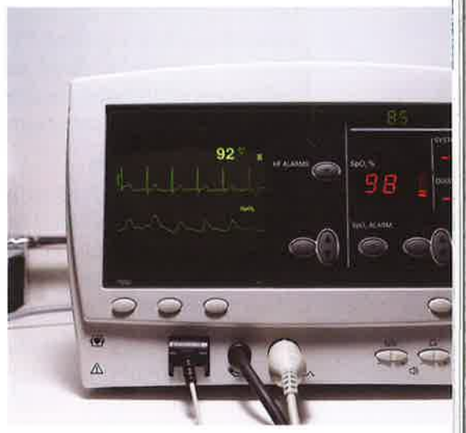
Because the sinoatrial node initiates each heartbeat, it sets the pace for the beating of the heart and is often called the pacemaker. If it becomes defective, its output may be regulated or even replaced entirely by an artificial pacemaker. This is an electronic device, placed under the skin with electrodes implanted in the wall of the heart that initiate each heartbeat in place of the sinoatrial node.

## Atrial and ventricular contraction

### The sinoatrial node sends out an electrical signal that stimulates contraction as it is propagated through the walls of the atria and then the walls of the ventricles.

The sinoatrial node initiates a heartbeat by contracting and simultaneously sends out an electrical signal that spreads throughout the walls of the atria. This can happen because there are interconnections between adjacent fibres across which the electrical signal can be propagated. Also the fibres are branched so each fibre passes the signal on to several others. It takes less than a tenth of a second for all cells in the atria to receive the signal. This propagation of the electrical signal causes the whole of both left and right atria to contract.

After a time delay of about 0.1 seconds, the electrical signal is conveyed to the ventricles. The time delay allows time for the atria to pump the blood that they are holding into the ventricles. The signal is then propagated throughout the walls of the ventricles, stimulating them to contract and pump blood out into the arteries. Details of the electrical stimulation of the heartbeat are included in Option D.



▲ Figure 13 Heart monitor displaying the heart rate, the electrical activity of the heart and the percentage saturation with oxygen of the blood

### TOK

**What matters more in ethical decision making: intent or consequences?**

There are some circumstances in which prolonging the life of an individual who is suffering brings in to question the role of the physician. Sometimes, an active pacemaker may be involved in prolonging the life of a patient and the physician receives a request to deactivate the device. This will accelerate the pace of the patient's death. Euthanasia involves taking active steps to end the life of a patient and it is illegal in many jurisdictions. However, there is a widely accepted practice of withdrawing life-sustaining interventions such as dialysis, mechanical ventilation, or tube feeding from terminally ill patients. This is often a decision of the family of the patient. The withdrawal of life support is seen as distinct from euthanasia because the patient dies of their condition rather than the active steps to end the patient's life in the case of euthanasia. However, the distinction can be subtle. The consequence is the same: the death of the patient. The intent can be the same: to end the patient's suffering. Yet in many jurisdictions, one action is illegal and the other is not.

## The cardiac cycle

### Pressure changes in the left atrium, left ventricle and aorta during the cardiac cycle.

The pressure changes in the atrium and ventricle of the heart and the aorta during a cardiac cycle are shown in figure 15. To understand them it is necessary to appreciate what occurs at each stage of the cycle. Figure 14 below summarizes the events, with timings assuming a heart rate of 75 beats per minute. Typical volumes of blood are shown and also an indication of the direction of blood flow to or from a chamber of the heart.

**0.0 – 0.1 seconds**

- The atria contract causing a rapid but relatively small pressure increase, which pumps blood from the atria to the ventricles, through the open atrioventricular valves.
- The semilunar valves are closed and blood pressure in the arteries gradually drops to its minimum as blood continues to flow along them but no more is pumped in.

**0.1 – 0.15 seconds**

- The ventricles contract, with a rapid pressure build up that causes the atrioventricular valves to close.
- The semilunar valves remain closed.

**0.15 – 0.4 seconds**

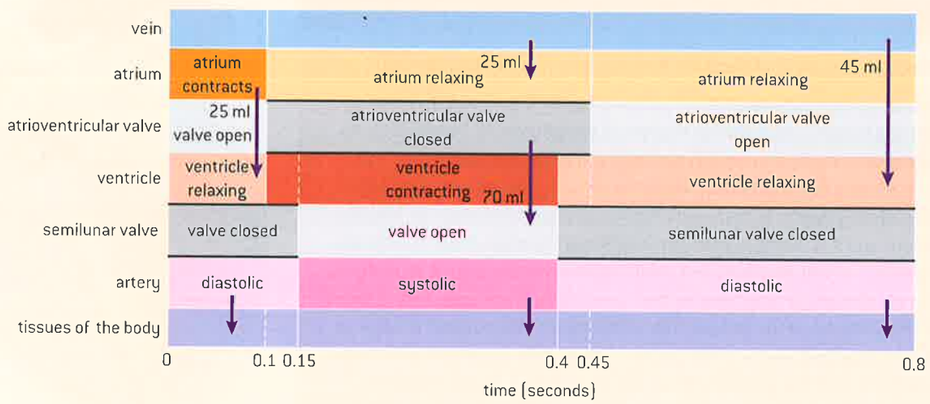
- The pressure in the ventricles rises above the pressure in the arteries so the semilunar valves open and blood is pumped from the ventricles into the arteries, transiently maximizing the arterial blood pressure.
- Pressure slowly rises in the atria as blood drains into them from the veins and they fill.

**0.4 – 0.45 seconds**

- The contraction of the ventricular muscles wanes and pressure inside the ventricles rapidly drops below the pressure in the arteries, causing the semilunar valves to close.
- The atrioventricular valves remain closed.

**0.45 – 0.8 seconds**

- Pressure in the ventricles drops below the pressure in the atria so the atrioventricular valves open.
- Blood from the veins drains into the atria and from there into the ventricles, causing a slow increase in pressure.




▲ Figure 14 One cardiac cycle is represented on the diagram, starting on the left with contraction of the atrium. Vertical arrows show flows of blood to and from the atrium and ventricle





### Data-based questions: Heart action and blood pressures

Figure 15 shows the pressures in the atrium, ventricle and artery on one side of the heart, during one second in the life of the heart.

1 Deduce when blood is being pumped from the atrium to the ventricle. Give both the start and the end times. [2]

2 Deduce when the ventricle starts to contract. [1]

3 The atrioventricular valve is the valve between the atrium and the ventricle. State when the atrioventricular valve closes. [1]

4 The semilunar valve is the valve between the ventricle and the artery. State when the semilunar valve opens. [1]

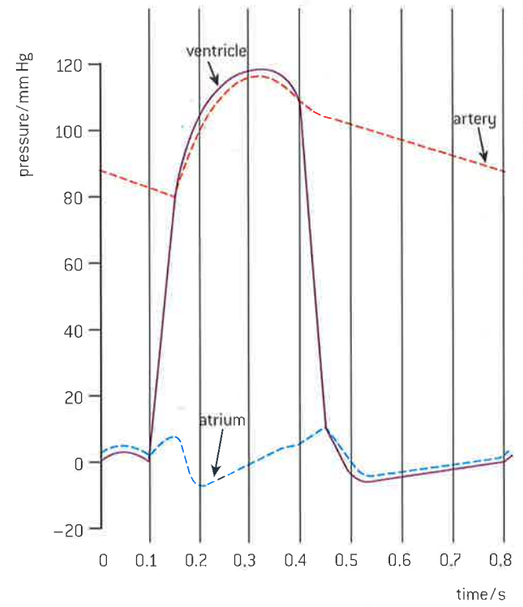
5 Deduce when the semilunar valve closes. [1]

6 Deduce when blood is being pumped from the ventricle to the artery. Give both the start and the end times. [2]

7 Deduce when the volume of blood in the ventricle is:

**a)** at a maximum [1]

**b)** at a minimum. [1]




▲ Figure 15 Pressure changes during the cardiac cycle

## Changing the heart rate

### The heart rate can be increased or decreased by impulses brought to the heart through two nerves from the medulla of the brain.

The sinoatrial node that sets the rhythm for the beating of the heart responds to signals from outside the heart. These include signals from branches of two nerves originating in a region in the medulla of the brain called the cardiovascular centre. Signals from one of the nerves cause the pacemaker to increase the frequency of heartbeats. In healthy young people the rate can increase to three times the resting rate. Signals from the other nerve decrease the rate. These two nerve branches act rather like the throttle and brake of a car.

The cardiovascular centre receives inputs from receptors that monitor blood pressure and its pH and oxygen concentration. The pH of the blood reflects its carbon dioxide concentration.

- Low blood pressure, low oxygen concentration and low pH all suggest that the heart rate needs to speed up, to increase the flow rate of blood to the tissues, deliver more oxygen and remove more carbon dioxide.
- High blood pressure, high oxygen concentration and high pH are all indicators that the heart rate may need to slow down.

**Activity**

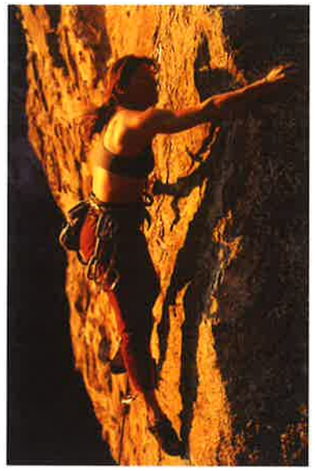
**Listening to heart sounds**

Sounds produced by blood flow can be heard with a simple tube or stethoscope placed on the chest near the heart. The consequences of this whole cardiac cycle for the flow of blood out of the heart can be felt as the pulse in a peripheral artery.

(a)

(b)

▲ Figure 16 Taking the pulse: (a) radial pulse (b) carotid pulse



▲ Figure 17 Adventure sports such as rock climbing cause epinephrine secretion

## Epinephrine

Epinephrine increases the heart rate to prepare for vigorous physical activity.

The sinoatrial node also responds to epinephrine in the blood, by increasing the heart rate. This hormone is also sometimes called adrenalin and is produced by the adrenal glands. The secretion of epinephrine is controlled by the brain and rises when vigorous physical activity may be necessary because of a threat or opportunity. So epinephrine has the nickname "fight or flight hormone".

In the past when humans were hunter-gatherers rather than farmers, epinephrine would have been secreted when humans were hunting for prey or when threatened by a predator. In the modern world athletes often use pre-race routines to stimulate adrenalin secretion so that their heart rate is already increased when vigorous physical activity begins.

# 6.3 Defence against infectious disease

### Understanding

- The skin and mucous membranes form a primary defence against pathogens that cause infectious disease.
- Cuts in the skin are sealed by blood clotting.
- Clotting factors are released from platelets.
- The cascade results in the rapid conversion of fibrinogen to fibrin by thrombin.
- Ingestion of pathogens by phagocytic white blood cells gives non-specific immunity to diseases.
- Production of antibodies by lymphocytes in response to particular pathogens gives specific immunity.
- Antibiotics block processes that occur in prokaryotic cells but not in eukaryotic cells.
- Viral diseases cannot be treated using antibiotics because they lack a metabolism.
- Some strains of bacteria have evolved with genes which confer resistance to antibiotics and some strains of bacteria have multiple resistance.

### Applications

- Causes and consequences of blood clot formation in coronary arteries.
- Effects of HIV on the immune system and methods of transmission.
- Florey and Chain's experiments to test penicillin on bacterial infections in mice.

### Nature of science

- Risks associated with scientific research: Florey and Chain's tests on the safety of penicillin would not be compliant with current protocols on testing.





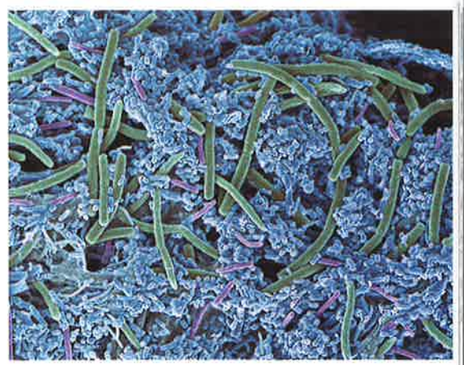
## Skin as a barrier to infection

The skin and mucous membranes form a primary defence against pathogens that cause infectious disease.

There are many different microbes in the environment that can grow inside the human body and cause a disease. Some microorganisms are opportunistic and although they can invade the body they also commonly live outside it. Others are specialized and can only survive inside a human body. Microbes that cause disease are called pathogens.

The primary defence of the body against pathogens is the skin. Its outermost layer is tough and provides a physical barrier against the entry of pathogens and protection against physical and chemical damage. Sebaceous glands are associated with hair follicles and they secrete a chemical called sebum, which maintains skin moisture and slightly lowers skin pH. The lower pH inhibits the growth of bacteria and fungi.

Mucous membranes are a thinner and softer type of skin that is found in areas such as the nasal passages and other airways, the head of the penis and foreskin and the vagina. The mucus that these areas of skin secrete is a sticky solution of glycoproteins. Mucus acts as a physical barrier; pathogens and harmful particles are trapped in it and either swallowed or expelled. It also has antiseptic properties because of the presence of the anti-bacterial enzyme lysozyme.



▲ Figure 1 Scanning electron micrograph of bacteria on the surface of teeth. Mucous membranes in the mouth prevent these and other microbes from invading body tissues

## Cuts and clots

Cuts in the skin are sealed by blood clotting.

When the skin is cut, blood vessels in it are severed and start to bleed. The bleeding usually stops after a short time because of a process called clotting. The blood emerging from a cut changes from being a liquid to a semi-solid gel. This seals up the wound and prevents further loss of blood and blood pressure. Clotting is also important because cuts breach the barrier to infection provided by the skin. Clots prevent entry of pathogens until new tissue has grown to heal the cut.

## Platelets and blood clotting

Clotting factors are released from platelets.

Blood clotting involves a cascade of reactions, each of which produces a catalyst for the next reaction. As a result blood clots very rapidly. It is important that clotting is under strict control, because if it occurs inside blood vessels the resulting clots can cause blockages.

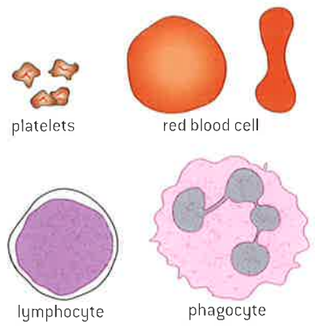
The process of clotting only occurs if platelets release clotting factors. Platelets are cellular fragments that circulate in the blood. They are smaller than either red or white blood cells. When a cut or other injury involving damage to blood vessels occurs, platelets aggregate at the site forming a temporary plug. They then release the clotting factors that trigger off the clotting process.

### Activity

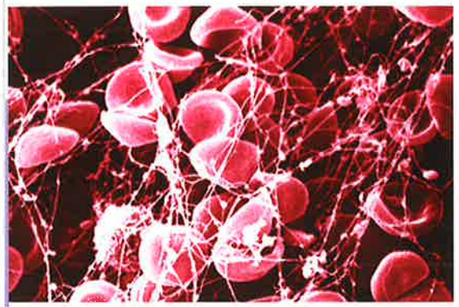
**Imaging human skin**

A digital microscope can be used to produce images of the different types of skin covering the human body. Figure 2 shows four images produced in this way.

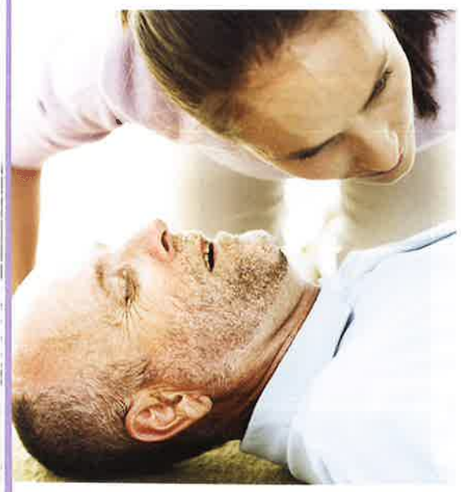
▲ Figure 2




▲ Figure 3 Cells and cell fragments from blood. Lymphocytes and phagocytes are types of white blood cell



▲ Figure 4 Scanning electron micrograph of clotted blood with fibrin and trapped blood cells



▲ Figure 5 Early intervention during a heart attack can save the patient's life so it is important to know what to do by being trained

## Fibrin production

The cascade results in the rapid conversion of fibrinogen to fibrin by thrombin.

The cascade of reactions that occurs after the release of clotting factors from platelets quickly results in the production of an enzyme called thrombin. Thrombin in turn converts the soluble protein fibrinogen into the insoluble fibrin. The fibrin forms a mesh in cuts that traps more platelets and also blood cells. The resulting clot is initially a gel, but if exposed to the air it dries to form a hard scab.

Figure 4 shows red blood cells trapped in this fibrous mesh.

## Coronary thrombosis

Causes and consequences of blood clot formation in coronary arteries.

In patients with coronary heart disease, blood clots sometimes form in the coronary arteries. These arteries branch off from the aorta close to the semilunar valve. They carry blood to the wall of the heart, supplying the oxygen and glucose needed by cardiac muscle fibres for cell respiration. The medical name for a blood clot is a thrombus. Coronary thrombosis is the formation of blood clots in the coronary arteries.

If the coronary arteries become blocked by a blood clot, part of the heart is deprived of oxygen and nutrients. Cardiac muscle cells are then unable to produce sufficient ATP by aerobic respiration and their contractions become irregular and uncoordinated. The wall of the heart makes quivering movements called fibrillation that do not pump blood effectively. This condition can prove fatal unless it resolves naturally or through medical intervention.

Atherosclerosis causes occlusion in the coronary arteries. Where atheroma develops the endothelium of the arteries tends to become damaged and roughened; especially, the artery wall is hardened by deposition of calcium salts. Patches of atheroma sometimes rupture causing a lesion. Coronary occlusion, damage to the capillary epithelium, hardening of arteries and rupture of atheroma all increase the risk of coronary thrombosis.

There are some well-known factors that are correlated with an increased risk of coronary thrombosis and heart attacks:

- smoking
- high blood cholesterol concentration
- high blood pressure
- diabetes
- obesity
- lack of exercise.

Of course correlation does not prove causation, but doctors nonetheless advise patients to avoid these risk factors if possible.





## Phagocytes

Ingestion of pathogens by phagocytic white blood cells gives non-specific immunity to diseases.

If microorganisms get past the physical barriers of skin and mucous membranes and enter the body, white blood cells provide the next line of defence. There are many different types of white blood cell. Some are phagocytes that squeeze out through pores in the walls of capillaries and move to sites of infection. There they engulf pathogens by endocytosis and digest them with enzymes from lysosomes. When wounds become infected, large numbers of phagocytes are attracted, resulting in the formation of a white liquid called pus.

## Antibody production

Production of antibodies by lymphocytes in response to particular pathogens gives specific immunity.

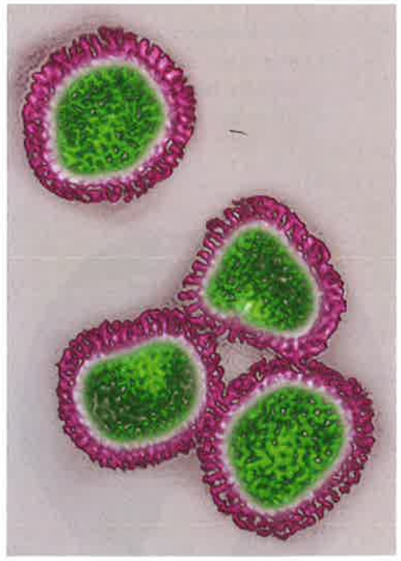
If microorganisms get past the physical barriers of the skin and invade the body, proteins and other molecules on the surface of pathogens are recognized as foreign by the body and they stimulate a specific immune response. Any chemical that stimulates an immune response is referred to as an antigen. The specific immune response is the production of antibodies in response to a particular pathogen. The antibodies bind to an antigen on that pathogen.

Antibodies are produced by types of white blood cell called lymphocytes. Each lymphocyte produces just one type of antibody, but our bodies can produce a vast array of different antibodies. This is because we have small numbers of lymphocytes for producing each of the many types of antibody. There are therefore too few lymphocytes initially to produce enough antibodies to control a pathogen that has not previously infected the body. However, antigens on the pathogen stimulate cell division of the small group of lymphocytes that produce the appropriate type of antibody. A large clone of lymphocytes called plasma cells are produced within a few days and they secrete large enough quantities of the antibody to control the pathogen and clear the infection.

Antibodies are large proteins that have two functional regions: a hypervariable region that binds to a specific antigen and another region that helps the body to fight the pathogen in one of a number of ways, including these:

- making a pathogen more recognizable to phagocytes so they are more readily engulfed
- preventing viruses from docking to host cells so that they cannot enter the cells.

Antibodies only persist in the body for a few weeks or months and the plasma cells that produce them are also gradually lost after the infection has been overcome and the antigens associated with it are no longer present. However, some of the lymphocytes produced during an infection are not active plasma cells but instead become memory cells



▲ Figure 6 Avian influenza viruses. In this electron micrograph of a virus in transverse section, false colour has been used to distinguish the protein coat that is recognized as antigens by the immune system (purple) from the RNA of the virus (green)

that are very long-lived. These memory cells remain inactive unless the same pathogen infects the body again, in which case they become active and divide to produce plasma cells very rapidly. Immunity to an infectious disease involves either having antibodies against the pathogen, or memory cells that allow rapid production of the antibody.

## Human immunodeficiency virus

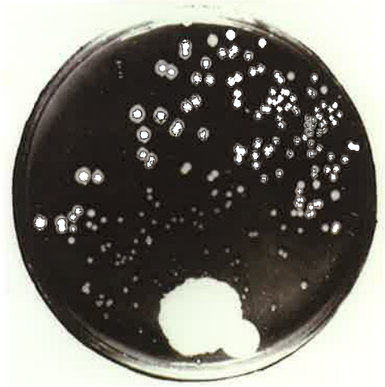
### Effects of HIV on the immune system and methods of transmission.

The production of antibodies by the immune system is a complex process and includes different types of lymphocyte, including helper T-cells. The human immunodeficiency virus (HIV) invades and destroys helper T-cells. The consequence is a progressive loss of the capacity to produce antibodies. In the early stages of infection, the immune system makes antibodies against HIV. If these can be detected in a person's body, they are said to be HIV-positive.

HIV is a retrovirus that has genes made of RNA and uses reverse transcriptase to make DNA copies of its genes once it has entered a host cell. The rate at which helper T-cells are destroyed by HIV varies considerably and can be slowed down by using anti-retroviral drugs. In most HIV-positive patients antibody production eventually becomes so ineffective that a group of opportunistic infections strike, which would be easily fought off by a healthy immune system. Several of these are normally so rare that they are marker diseases for the latter stages of HIV infection, for example Kaposi's sarcoma. A collection of several diseases or conditions existing together is called a syndrome. When the syndrome of conditions due to HIV is present, the person is said to have acquired immune deficiency syndrome (AIDS).

AIDS spreads by HIV infection. The virus only survives outside the body for a short time and infection normally only occurs if there is blood to blood contact between infected and uninfected people. There are various ways in which this can occur:

- sexual intercourse, during which abrasions to the mucous membranes of the penis and vagina can cause minor bleeding
- transfusion of infected blood, or blood products such as Factor VIII
- sharing of hypodermic needles by intravenous drug users.



▲ Figure 7 Fleming's petri dish which first showed the inhibition of bacterial growth by penicillin from a mycelium of *Penicillium*

## Antibiotics

### Antibiotics block processes that occur in prokaryotic cells but not in eukaryotic cells.

An antibiotic is a chemical that inhibits the growth of microorganisms. Most antibiotics are antibacterial. They block processes that occur in prokaryotes but not in eukaryotes and can therefore be used to kill bacteria inside the body without causing harm to human cells. The processes targeted by antibiotics are bacterial DNA replication, transcription, translation, ribosome function and cell wall formation.

Many antibacterial antibiotics were discovered in saprotrophic fungi. These fungi compete with saprotrophic bacteria for the dead organic matter on which they both feed. By secreting antibacterial antibiotics, saprotrophic fungi inhibit the growth of their bacterial competitors. An example is penicillin. It is produced by some strains of the *Penicillium* fungus, but only when nutrients are scarce and competition with bacteria would be harmful.





## Testing penicillin

### Florey and Chain's experiments to test penicillin on bacterial infections in mice.

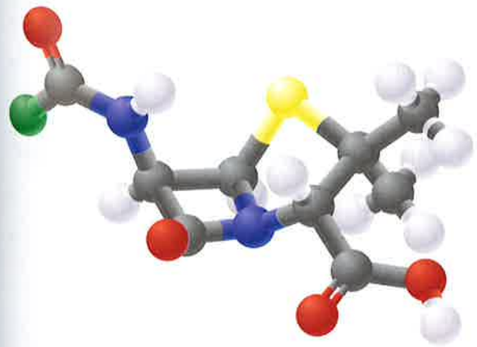
Howard Florey and Ernst Chain formed a research team in Oxford in the late 1930s that investigated the use of chemical substances to control bacterial infections. The most promising of these was penicillin, discovered by Alexander Fleming in 1928. Florey and Chain's team developed a method of growing the fungus *Penicillium* in liquid culture in conditions that stimulated it to secrete penicillin. They also developed methods for producing reasonably pure samples of penicillin from the cultures.

The penicillin killed bacteria on agar plates, but they needed to test whether it would control bacterial infections in humans. They first tested it on mice. Eight mice were deliberately infected with *Streptococcus* bacteria that cause death from pneumonia. Four of the infected mice were given injections with penicillin. Within 24 hours all the untreated mice were dead but the four given penicillin were healthy. Florey and Chain decided that they should next do tests on human patients, which required much larger quantities.

When enough penicillin had been produced, a 43-year-old policeman was chosen for the first human test. He had an acute and life-threatening bacterial infection caused by a scratch on the face from a thorn on a rose bush. He was given penicillin for four days and his condition improved considerably, but supplies of penicillin ran out and he suffered a relapse and died from the infection.

Larger quantities of penicillin were produced and five more patients with acute infections were tested. All were cured of their infections, but sadly one of them died. He was a small child who had an infection behind the eye. This had weakened the wall of the artery carrying blood to the brain and although cured of the infection, the child died suddenly of brain hemorrhage when the artery burst.

Pharmaceutical companies in the United States then began to produce penicillin in much larger quantities, allowing more extensive testing, which confirmed that it was a highly effective treatment for many previously incurable bacterial infections.



▲ Figure 8 Penicillin – the green ball represents a variable part of the molecule

### Activity

**World AIDS Day**

The red AIDS awareness ribbon is an international symbol of awareness and support for those living with HIV. It is worn on World AIDS Day each year – December 1st.

Are you aware how many people in your area are affected and what can be done to support them?

## Penicillin and drug testing

Risks associated with scientific research: Florey and Chain's tests on the safety of penicillin would not be compliant with current protocols on testing.

When any new drug is introduced there are risks that it will prove to be ineffective in some or all patients or that it will cause harmful side effects. These risks are minimized by strict protocols that pharmaceutical companies must follow. Initial tests are performed on animals and then on small numbers of healthy humans. Only if a drug passes these tests is it tested on patients with the disease that the drug is intended to treat. The last tests involve very large numbers of patients to test whether the drug is effective in all patients and to check that there are no severe or common side effects.

There are some famous cases of drugs causing problems during testing or after release.

- Thalidomide was introduced in the 1950s as a treatment for various mild conditions but when it was found to relieve morning sickness in pregnant women it was prescribed for that purpose. The side effects of the drug on the fetus had not been tested and more than 10,000 children were born with birth deformities before the problem was recognized.
- In 2006 six healthy volunteers were given TGN1412, a new protein developed for treatment of autoimmune diseases and leukemia. All six rapidly became very ill and suffered multiple organ failure. Although the volunteers recovered, they may have suffered long-term damage to their immune systems.

It is very unlikely that Florey and Chain would have been allowed to carry out tests on a new drug today with the methods that they used for penicillin. They tested the drug on human patients after only a very brief period of animal testing. Penicillin was a new type of drug and there could easily have been severe side effects. Also the samples that they were using were not pure and there could have been side effects from the impurities.

On the other hand, the patients that they used were all on the point of death and several were cured of their infections as a result of the experimental treatment. Because of expeditious testing with greater risk-taking than would now be allowed, penicillin was introduced far more quickly than would be possible today. During the D-day landings in June 1944 penicillin was used to treat wounded soldiers and the number of deaths from bacterial infection was greatly reduced.

▲ Figure 9 Wounded US troops on Omaha beach 6 June 1944

## Viruses and antibiotics

Viral diseases cannot be treated using antibiotics because they lack a metabolism.

Viruses are non-living and can only reproduce when they are inside living cells. They use the chemical processes of a living host cell, instead of having a metabolism of their own. They do not have their own means of transcription or protein synthesis and they rely on the





host cell's enzymes for ATP synthesis and other metabolic pathways. These processes cannot be targeted by drugs as the host cell would also be damaged.

All of the commonly used antibiotics such as penicillin, streptomycin, chloramphenicol and tetracycline control bacterial infections and are not effective against viruses. Not only is it inappropriate for doctors to prescribe them for a viral infection, but it contributes to the overuse of antibiotics and increases in antibiotic resistance in bacteria.

There are a few viral enzymes which can be used as targets for drugs to control viruses without harming the host cell. Only a few drugs have been discovered or developed to control viruses in this way. These are known as antivirals rather than antibiotics.

## Resistance to antibiotics

Some strains of bacteria have evolved with genes which confer resistance to antibiotics and some strains of bacteria have multiple resistance.

In 2013 the government's chief medical officer for England, Sally Davies, said this:

> *The danger posed by growing resistance to antibiotics should be ranked along with terrorism on a list of threats to the nation. If we don't take action, then we may all be back in an almost 19th-century environment where infections kill us as a result of routine operations. We won't be able to do a lot of our cancer treatments or organ transplants.*

The development of resistance to antibiotics by natural selection is described in sub-topic 5.2. Strains of bacteria with resistance are usually discovered soon after the introduction of an antibiotic. This is not of huge concern unless a strain develops multiple resistance, for example methicillin-resistant *Staphylococcus aureus* (MRSA) which has infected the blood or surgical wounds of hospital patients and resists all commonly used antibiotics. Another example of this problem is multidrug-resistant tuberculosis (MDR-TB). The WHO has reported more than 300,000 cases worldwide per year with the disease reaching epidemic proportions in some areas.

Antibiotic resistance is an avoidable problem. These measures are required:

- doctors prescribing antibiotics only for serious bacterial infections
- patients completing courses of antibiotics to eliminate infections completely
- hospital staff maintaining high standards of hygiene to prevent cross-infection
- farmers not using antibiotics in animal feeds to stimulate growth
- pharmaceutical companies developing new types of antibiotic – no new types have been introduced since the 1980s.

**Activity**

**Distinguishing between bacterial and viral infections**

How can a doctor distinguish between bacterial and viral infections, without prescribing an antibiotic and seeing if it cures the infection?

▲ Figure 10 Many viruses cause a common cold. Children lack immunity to most of them so frequently catch a cold. Antibiotics do not cure them

### Data-based questions: Antibiotic resistance

Bacterial resistance to antibiotics is a direct consequence of the overuse of these drugs. In the USA, currently more than half of the doctor visits for upper respiratory tract infections (URIs) are prescribed antibiotics, despite knowledge that most URIs are caused by viruses.

In the early 1990s, Finnish public health authorities began discouraging the use of the antibiotic erythromycin for URIs in response to rising bacterial resistance to the antibiotic, and the national erythromycin consumption per capita dropped by 43 per cent.

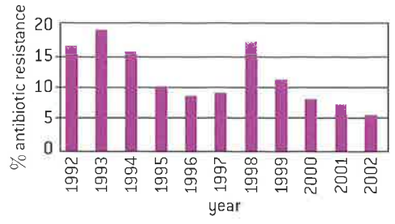
The data in figure 11 shows the incidence in Finland, over a 10-year period, of *Streptococcus pyogenes* strains that are resistant to the antibiotic erythromycin. *S. pyogenes* is responsible for the condition known as "strep throat".

1 **a)** Describe the pattern of erythromycin resistance over the period from 1992 to 2002. [3]

**b)** Suggest a reason for the pattern shown. [2]

2 Calculate the percentage difference in antibiotic resistance between 2002 and 1992. [2]

3 Evaluate the claim that reduction in the use of erythromycin has led to a reduction in the incidence of antibiotic resistance in *S. pyogenes*. [3]




▲ Figure 11 The incidence of *Streptococcus pyogenes* strains that are resistant to the antibiotic erythromycin over a 10-year period in Finland

# 6.4 Gas exchange

## Understanding

- Ventilation maintains concentration gradients of oxygen and carbon dioxide between air in alveoli and blood flowing in adjacent capillaries.
- Type I pneumocytes are extremely thin alveolar cells that are adapted to carry out gas exchange.
- Type II pneumocytes secrete a solution containing surfactant that creates a moist surface inside the alveoli to prevent the sides of the alveolus adhering to each other by reducing surface tension.
- Air is carried to the lungs in the trachea and bronchi and then to the alveoli in bronchioles.
- Muscle contractions cause the pressure changes inside the thorax that force air in and out of the lungs to ventilate them.
- Different muscles are required for inspiration and expiration because muscles only do work when they contract.

## Applications

- External and internal intercostal muscles, and diaphragm and abdominal muscles as examples of antagonistic muscle action.
- Causes and consequences of lung cancer.
- Causes and consequences of emphysema.

## Skills

- Monitoring of ventilation in humans at rest and after mild and vigorous exercise. (Practical 6)

## Nature of science

- Obtain evidence for theories: epidemiological studies have contributed to our understanding of the causes of lung cancer.

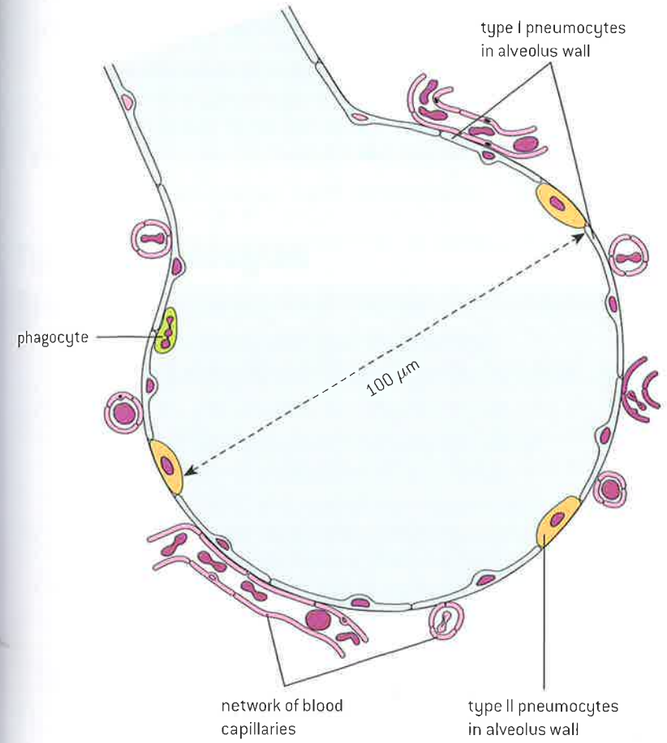




## Ventilation

### Ventilation maintains concentration gradients of oxygen and carbon dioxide between air in alveoli and blood flowing in adjacent capillaries.

All organisms absorb one gas from the environment and release a different one. This process is called gas exchange. Leaves absorb carbon dioxide to use in photosynthesis and release the oxygen produced by this process. Humans absorb oxygen for use in cell respiration and release the carbon dioxide produced by this process. Terrestrial organisms exchange gases with the air. In humans gas exchange occurs in small air sacs called alveoli inside the lungs (figure 1).

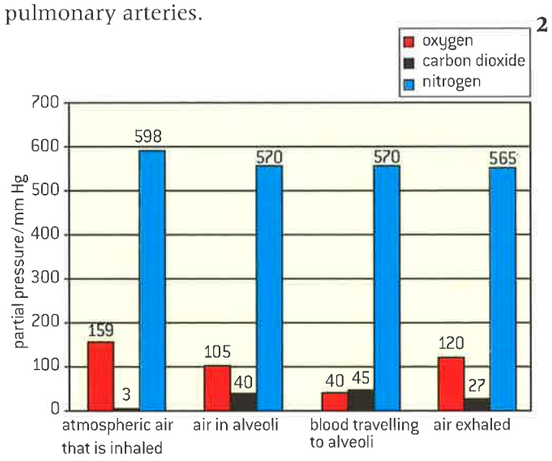



▲ Figure 1

Gas exchange happens by diffusion between air in the alveoli and blood flowing in the adjacent capillaries. The gases only diffuse because there is a concentration gradient: the air in the alveolus has a higher concentration of oxygen and a lower concentration of carbon dioxide than the blood in the capillary. To maintain these concentration gradients fresh air must be pumped into the alveoli and stale air must be removed. This process is called **ventilation**.

## Data-based questions: Concentration gradients

Figure 2 shows the typical composition of atmospheric air, air in the alveoli and gases dissolved in air returning to the lungs in the pulmonary arteries.




▲ Figure 2 Partial pressures of gases in the pulmonary system

1 Explain why the oxygen concentration in the alveoli is not as high as in fresh air that is inhaled. [2]

2 **a)** Calculate the difference in oxygen concentration between air in the alveolus and blood arriving at the alveolus. [1]

**b)** Deduce the process caused by this concentration difference. [1]

**c)** **(i)** Calculate the difference in carbon dioxide concentration between air inhaled and air exhaled. [1]

**(ii)** Explain this difference. [2]

**d)** Despite the high concentration of nitrogen in air in alveoli, little or none diffuses from the air to the blood. Suggest reasons for this. [2]

## Ventilation experiments

Monitoring of ventilation in humans at rest and after mild and vigorous exercise. (Practical 6)

In an investigation of the effect of exercise on ventilation, the type or intensity of exercise is the independent variable and the ventilation parameter that is measured is the dependent variable.

- A simple approach for the independent variable is to choose levels of activity ranging from inactive to very active, such as lying down, sitting and standing, walking, jogging and sprinting. A more quantitative approach is to do the same activity at different measured rates, for example running at different speeds on a treadmill. This allows the ventilation parameters to be correlated with work rate in joules per minute during exercise.

Ventilation of the lungs is carried out by drawing some fresh air into the lungs and then expelling some of the stale air from the lungs. The volume of air drawn in and expelled is the tidal volume. The number of times that air is drawn in or expelled per minute is the ventilation rate.

Either or both of these can be the dependent variable in an investigation of the effect of exercise on ventilation rate. They should be measured after carrying on an activity for long enough to reach a constant rate. The example methods given below include a simple and a more advanced technique that could be used for the investigation.

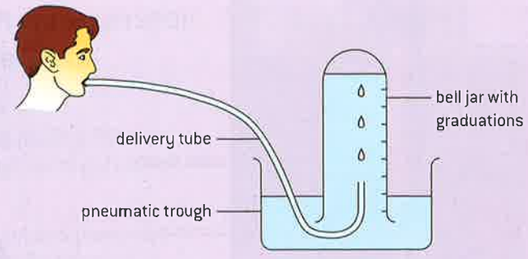
**1 Ventilation rate**

- The most straightforward way to measure ventilation rate is by simple observation. Count the number of times air is exhaled or inhaled in a minute. Breathing should be maintained at a natural rate, which is as slow as possible without getting out of breath.
- Ventilation rate can also be measured by data logging. An inflatable chest belt is placed around the thorax and air is pumped in with a bladder. A differential pressure sensor is then used to measure pressure variations inside the belt due to chest expansions. The rate of ventilations can be deduced and the relative size of ventilations may also be recorded.

**2 Tidal volume**

- Simple apparatus is shown in figure 3. One normal breath is exhaled through the delivery tube into a vessel and the volume is measured. It is not safe to use this apparatus for repeatedly inhaling and exhaling air as the $CO_2$ concentration will rise too high.
- Specially designed spirometers are available for use with data logging. They measure flow rate into and out of the lungs and from these measurements lung volumes can be deduced.

To ensure that the experimental design is rigorous, all variables apart from the independent and dependent variables should be kept constant. Ventilation parameters should be measured several times at all levels of exercise with each person in the trial. As many different people as possible should be tested.




▲ Figure 3





## Type I pneumocytes

Type I pneumocytes are extremely thin alveolar cells that are adapted to carry out gas exchange.

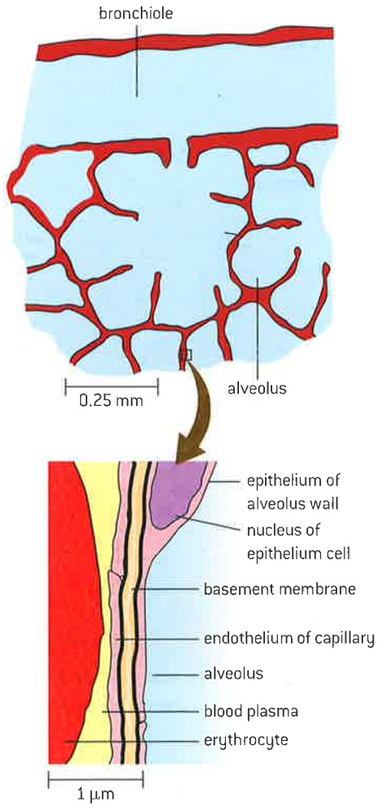
The lungs contain huge numbers of alveoli with a very large total surface area for diffusion. The wall of each alveolus consists of a single layer of cells, called the epithelium. Most of the cells in this epithelium are Type I pneumocytes. They are flattened cells, with the thickness of only about 0.15 µm of cytoplasm.

The wall of the adjacent capillaries also consists of a single layer of very thin cells. The air in the alveolus and the blood in the alveolar capillaries are therefore less than 0.5 µm apart. The distance over which oxygen and carbon dioxide has to diffuse is therefore very small, which is an adaptation to increase the rate of gas exchange.

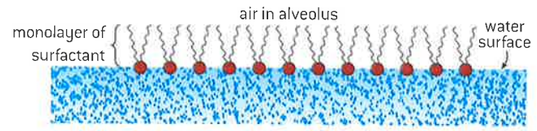
## Type II pneumocytes

Type II pneumocytes secrete a solution containing surfactant that creates a moist surface inside the alveoli to prevent the sides of the alveolus adhering to each other by reducing surface tension.

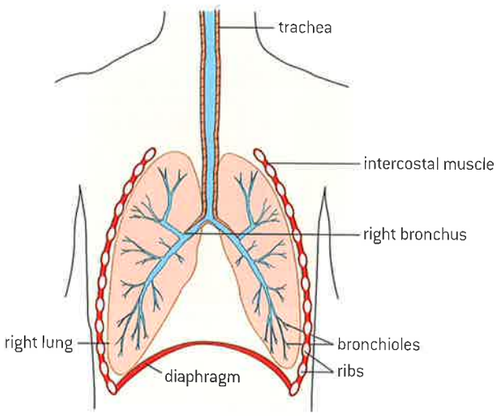
Type II pneumocytes are rounded cells that occupy about 5% of the alveolar surface area. They secrete a fluid which coats the inner surface of the alveoli. This film of moisture allows oxygen in the alveolus to dissolve and then diffuse to the blood in the alveolar capillaries. It also provides an area from which carbon dioxide can evaporate into the air and be exhaled.



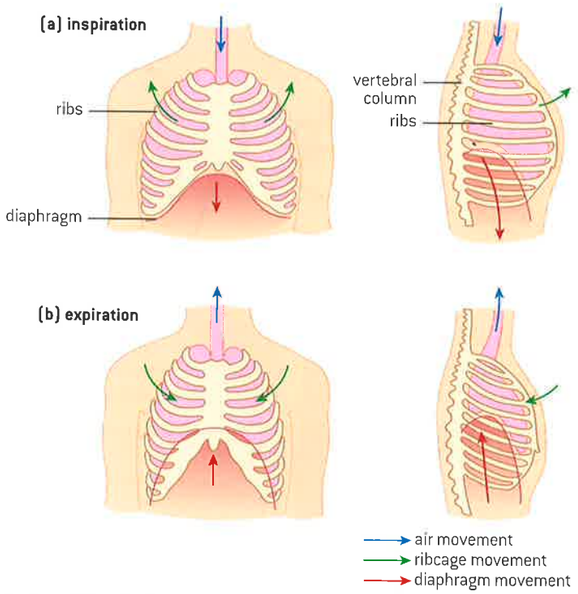

▲ Figure 4 Structure of alveoli




▲ Figure 5 Pulmonary surfactant molecules on the surface of the film of moisture lining the alveoli




▲ Figure 6 The ventilation system




▲ Figure 7 Ventilation of the lungs

The fluid secreted by the Type II pneumocytes contains a pulmonary surfactant. Its molecules have a structure similar to that of phospholipids in cell membranes. They form a monolayer on the surface of the moisture lining the alveoli, with the hydrophilic heads facing the water and the hydrophobic tails facing the air. This reduces the surface tension and prevents the water from causing the sides of the alveoli to adhere when air is exhaled from the lungs. This helps to prevent collapse of the lung.

Premature babies are often born with insufficient pulmonary surfactant and can suffer from infant respiratory distress syndrome. Treatment involves giving the baby oxygen and also one or more doses of surfactant, extracted from animal lungs.

## Airways for ventilation

**Air is carried to the lungs in the trachea and bronchi and then to the alveoli in bronchioles.**

Air enters the ventilation system through the nose or mouth and then passes down the trachea. This has rings of cartilage in its wall to keep it open even when air pressure inside is low or pressure in surrounding tissues is high. The trachea divides to form two bronchi, also with walls strengthened with cartilage. One bronchus leads to each lung.

Inside the lungs the bronchi divide repeatedly to form a tree-like structure of narrower airways, called bronchioles. The bronchioles have smooth muscle fibres in their walls, allowing the width of these airways to vary. At the end of the narrowest bronchioles are groups of alveoli, where gas exchange occurs.

## Pressure changes during ventilation

**Muscle contractions cause the pressure changes inside the thorax that force air in and out of the lungs to ventilate them.**

Ventilation of the lungs involves some basic physics. If particles of gas spread out to occupy a larger volume, the pressure of the gas becomes lower. Conversely, if a gas is compressed to occupy a smaller volume, the pressure rises. If gas is free to move, it will always flow from regions of higher pressure to regions of lower pressure.





During ventilation, muscle contractions cause the pressure inside the thorax to drop below atmospheric pressure. As a consequence, air is drawn into the lungs from the atmosphere (inspiration) until the lung pressure has risen to atmospheric pressure. Muscle contractions then cause pressure inside the thorax to rise above atmospheric, so air is forced out from the lungs to the atmosphere (expiration).

## Antagonistic muscles

**Different muscles are required for inspiration and expiration because muscles only do work when they contract.**

Muscles can be in two states: contracting and relaxing.

- Muscles do work when they contract by exerting a pulling force (tension) that causes a particular movement. They become shorter when they do this.
- Muscles lengthen while they are relaxing, but this happens passively – they do not lengthen themselves. Most muscles are pulled into an elongated state by the contraction of another muscle. They do not exert a pushing force (compression) while relaxing so do no work at this time.

Muscles therefore can only cause movement in one direction. If movement in opposite directions is needed at different times, at least two muscles will be required. When one muscle contracts and causes a movement, the second muscle relaxes and is elongated by the first. The opposite movement is caused by the second muscle contracting while the first relaxes. When muscles work together in this way they are known as an antagonistic pair of muscles.

Inspiration and expiration involve opposite movements, so different muscles are required, working as antagonistic pairs.

▲ Figure 8 Different muscles are used for bending the leg at the knee and for the opposite movement of straightening it

### Antagonistic muscle action in ventilation

**External and internal intercostal muscles, and diaphragm and abdominal muscles as examples of antagonistic muscle action.**

Ventilation involves two pairs of opposite movements that change the volume and therefore the pressure inside the thorax:

| | Inspiration | Expiration |
|---|---|---|
| Diaphragm | Moves downwards and flattens | Moves upwards and becomes more domed |
| Ribcage | Moves upwards and outwards | Moves downwards and inwards |

Antagonistic pairs of muscles are needed to cause these movements.

| | Inspiration | Expiration |
|---|---|---|
| Volume and pressure changes | The volume inside the thorax increases and consequently the pressure decreases | The volume inside the thorax decreases and consequently the pressure increases |

| | | | |
|---|---|---|---|
| Movement of the diaphragm | Diaphragm | The diaphragm contracts and so it moves downwards and pushes the abdomen wall out | The diaphragm relaxes so it can be pushed upwards into a more domed shape |
| | Abdomen wall muscles | Muscles in the abdomen wall relax allowing pressure from the diaphragm to push it out | Muscles in the abdomen wall contract pushing the abdominal organs and diaphragm upwards |
| Movement of the ribcage | External intercostal muscles | The external intercostal muscles contract, pulling the ribcage upwards and outwards | The external intercostal muscles relax and are pulled back into their elongated state. |
| | Internal intercostal muscles | The internal intercostal muscles relax and are pulled back into their elongated state | The internal intercostal muscles contract, pulling the ribcage inwards and downwards |

## Epidemiology

### Obtain evidence for theories: epidemiological studies have contributed to our understanding of the causes of lung cancer.

Epidemiology is the study of the incidence and causes of disease. Most epidemiological studies are observational rather than experimental because it is rarely possible to investigate the causes of disease in human populations by carrying out experiments.

As in other fields of scientific research, theories about the causes of a disease are proposed. To obtain evidence for or against a theory, survey data is collected that allows the association between the disease and its theoretical cause to be tested. For example, to test the theory that smoking causes lung cancer, the smoking habits of people who have developed lung cancer and people who have not are needed. Examples of very large epidemiological surveys that provided strong evidence for a link between smoking and lung cancer are included in sub-topic 1.6.

A correlation between a risk factor and a disease does not prove that the factor causes the disease. There are usually confounding factors which also have an effect on the incidence. They can cause spurious associations between a disease and a factor that does not cause it. For example, an association has repeatedly been found by epidemiologists between leanness and an increased risk of lung cancer. Careful analysis showed that among smokers leanness is not significantly associated with an increased risk. Smoking reduces appetite and so is associated with leanness and of course smoking is a cause of lung cancer. This explains the spurious association between leanness and lung cancer.

To try to compensate for confounding factors it is usually necessary to collect data on many factors apart from the one being investigated. This allows statistical procedures to be carried out to take account of confounding factors and try to isolate the effect of single factors. Age and sex are almost always recorded and sometimes epidemiological surveys include only males or females or only people in a specific age range.

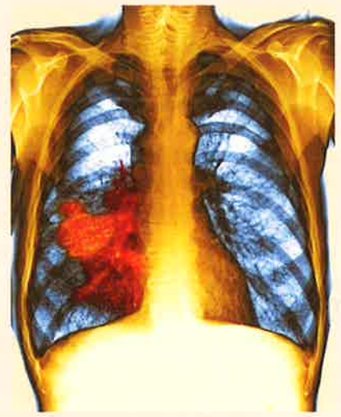
## Causes of lung cancer

### Causes and consequences of lung cancer.

Lung cancer is the most common cancer in the world, both in terms of the number of cases and the number of deaths due to the disease. The general causes of cancer are described in sub-topic 1.6. The specific causes of lung cancer are considered here.







▲ Figure 9 A large tumour (red) is visible in the right lung. The tumour is a bronchial carcinoma

- Smoking causes about 87% of cases. Tobacco smoke contains many mutagenic chemicals. As every cigarette carries a risk, the incidence of lung cancer increases with the number smoked per day and the number of years of smoking.
- Passive smoking causes about 3% of cases. This happens when non-smokers inhale tobacco smoke exhaled by smokers. The number of cases will decline in countries where smoking is banned indoors and in public places.
- Air pollution probably causes about 5% of lung cancers. The sources of air pollution that are most significant are diesel exhaust fumes, nitrogen oxides from all vehicle exhaust fumes and smoke from burning coal, wood or other organic matter.
- Radon gas causes significant numbers of cases in some parts of the world. It is a radioactive gas that leaks out of certain rocks such as granite. It accumulates in badly ventilated buildings and people then inhale it.
- Asbestos, silica and some other solids can cause lung cancer if dust or other particles of them are inhaled. This usually happens on construction sites or in quarries, mines or factories.

The consequences of lung cancer are often very severe. Some of them can be used to help diagnose the disease: difficulties with breathing, persistent coughing, coughing up blood, chest pain, loss of appetite, weight loss and general fatigue.

In many patients the tumour is already large when it is discovered and may also have metastasized, with secondary tumours in the brain or elsewhere. Mortality rates are high. Only 15% of patients with lung cancer survive for more than 5 years. If a tumour is discovered early enough, all or part of the affected lung may be removed surgically. This is usually combined with one or more courses of chemotherapy. Other patients are treated with radiotherapy.

The minority of patients who are cured of lung cancer, but have lost some of their lung tissue, are likely to continue to have pain, breathing difficulties, fatigue and also anxiety about the possible return of the disease.

## Emphysema

### Causes and consequences of emphysema.

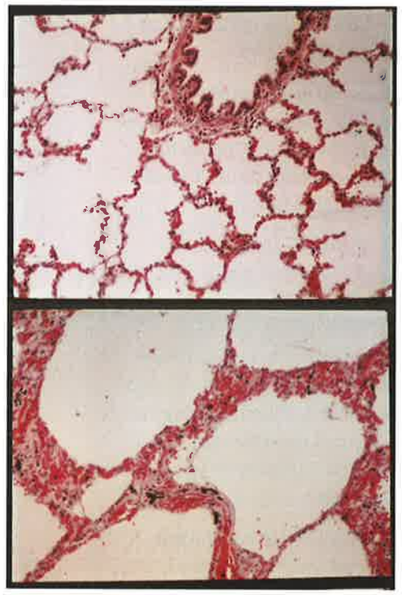
In healthy lung tissue each bronchiole leads to a group of small thin-walled alveoli. In a patient with emphysema these are replaced by a smaller number of larger air sacs with much thicker walls. The total surface area for gas exchange is considerably reduced and the distance over which diffusion of gases occurs is increased, and so gas exchange is therefore much less effective. The lungs also become less elastic, so ventilation is more difficult.

The molecular mechanisms involved are not fully understood, though there is some evidence for these theories:

- Phagocytes inside alveoli normally prevent lung infections by engulfing bacteria and produce elastase, a protein-digesting enzyme, to kill them inside the vesicles formed by endocytosis.
- An enzyme inhibitor called alpha 1-antitrypsin (A1AT) usually prevents elastase and other proteases from digesting lung tissue. In smokers, the number of phagocytes in the lungs increases and they produce more elastase.
- Genetic factors affect the quantity and effectiveness of A1AT produced in the lungs.

In about 30% of smokers digestion of proteins in the alveolus wall by the increased quantity of proteases is not prevented and alveolus walls are weakened and eventually destroyed.

Emphysema is a chronic disease because the damage to alveoli is usually irreversible. It causes low oxygen saturation in the blood and higher than normal carbon dioxide concentrations. As a result the patient lacks energy and may eventually find even tasks such as climbing stairs too onerous. In mild cases there is shortness of breath during vigorous exercise but eventually even mild activity causes it. Ventilation is laboured and tends to be more rapid than normal.



▲ Figure 10 Healthy lung tissue (top) and lung tissue showing emphysema (bottom)

**Data-based questions:** Emphysema and gas exchange

Figure 10 shows healthy lung tissue and tissue from a lung with emphysema, at the same magnification. Smoking usually causes emphysema. Breathing polluted air makes the disease worse.

1 a) Place a ruler across each micrograph and count how many times the edge of the ruler crosses a gas exchange surface. Repeat this several times for each micrograph, in such a way that the results are comparable. State your results using suitable units. [3]

b) Explain the conclusions that you draw from the results. [3]

2 Explain why people who have emphysema feel tired all the time. [3]

3 Suggest why people with emphysema often have an enlarged and strained right side of the heart. [1]





# 6.5 Neurons and synapses

## Understanding

- Neurons transmit electrical impulses.
- The myelination of nerve fibres allows for saltatory conduction.
- Neurons pump sodium and potassium ions across their membranes to generate a resting potential.
- An action potential consists of depolarization and repolarization of the neuron.
- Nerve impulses are action potentials propagated along the axons of neurons.
- Propagation of nerve impulses is the result of local currents that cause each successive part of the axon to reach the threshold potential.
- Synapses are junctions between neurons and between neurons and receptor or effector cells.
- When pre-synaptic neurons are depolarized they release a neurotransmitter into the synapse.
- A nerve impulse is only initiated if the threshold potential is reached.

## Applications

- Secretion and reabsorption of acetylcholine by neurons at synapses.
- Blocking of synaptic transmission at cholinergic synapses in insects by binding of neonicotinoid pesticides to acetylcholine receptors.

## Skills

- Analysis of oscilloscope traces showing resting potentials and action potentials.

## Nature of science

- Cooperation and collaboration between groups of scientists: biologists are contributing to research into memory and learning.

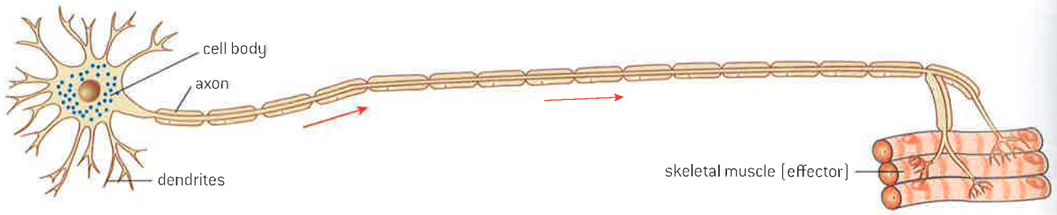
## Neurons

### Neurons transmit electrical impulses.

Two systems of the body are used for internal communication: the endocrine system and the nervous system. The endocrine system consists of glands that release hormones. The nervous system consists of nerve cells called neurons. There are about 85 billion neurons in the human nervous system. Neurons help with internal communication by transmitting nerve impulses. A nerve impulse is an electrical signal.

Neurons have a cell body with cytoplasm and a nucleus but they also have narrow outgrowths called nerve fibres along which nerve impulses travel.

- Dendrites are short branched nerve fibres, for examples those used to transmit impulses between neurons in one part of the brain or spinal cord.
- Axons are very elongated nerve fibres, for example those that transmit impulses from the tips of the toes or the fingers to the spinal cord.




▲ Figure 1 Neuron with dendrites that transmit impulses to the cell body and an axon that transmits impulses a considerable distance to muscle fibres

▲ Figure 2 Nerve fibres (axons) transmitting electrical impulses to and from the central nervous system are grouped into bundles

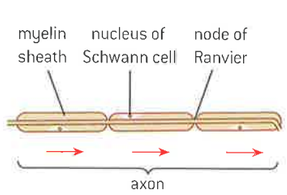
## Myelinated nerve fibres

### The myelination of nerve fibres allows for saltatory conduction.

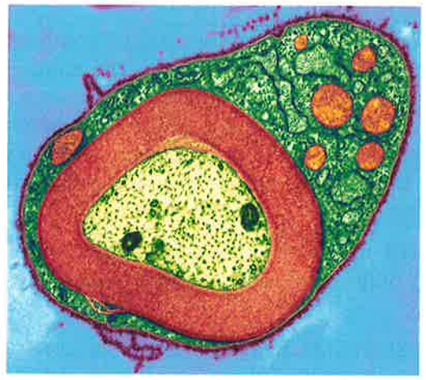
The basic structure of a nerve fibre along which a nerve impulse is transmitted is very simple: the fibre is cylindrical in shape, with a plasma membrane enclosing a narrow region of cytoplasm. The diameter in most cases is about 1 μm, though some nerve fibres are wider than this. A nerve fibre with this simple structure conducts nerve impulses at a speed of about 1 metre per second.

Some nerve fibres are coated along most of their length by a material called myelin. It consists of many layers of phospholipid bilayer. Special cells called Schwann cells deposit the myelin by growing round and round the nerve fibre. Each time they grow around the nerve fibre a double layer of phospholipid bilayer is deposited. There may be 20 or more layers when the Schwann cell stops growing.

There is a gap between the myelin deposited by adjacent Schwann cells. The gap is called a node of Ranvier. In myelinated nerve fibres the nerve impulse can jump from one node of Ranvier to the next. This is called saltatory conduction. It is much quicker than continuous transmission along a nerve fibre so myelinated nerve fibres transmit nerve impulses much more rapidly than unmyelinated nerve fibres. The speed can be as much as 100 metres per second.




▲ Figure 3 Detail of a myelinated nerve fibre showing the gaps between adjacent Schwann cells (nodes of Ranvier)



▲ Figure 4 Transverse section of axon showing the myelin sheath formed by the Schwann cell's membrane wrapped round the axon many times (red)





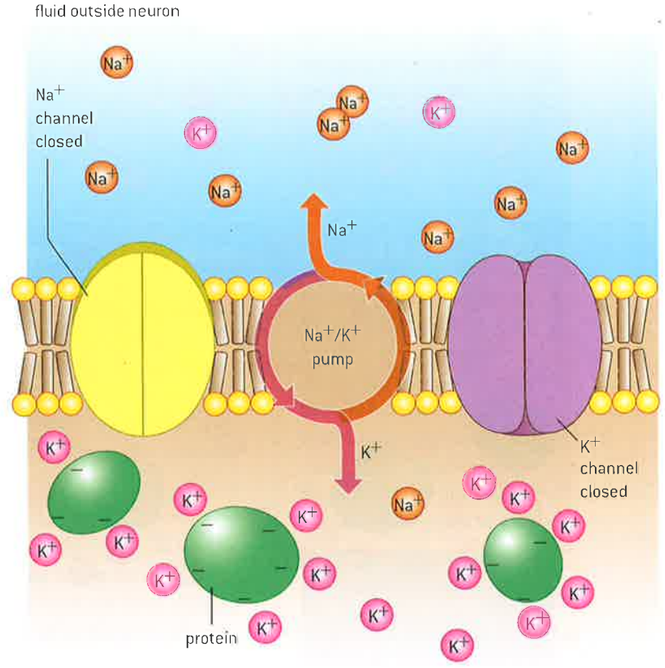
## Resting potentials

### Neurons pump sodium and potassium ions across their membranes to generate a resting potential.

A neuron that is not transmitting a signal has a potential difference or voltage across its membrane that is called the resting potential. This potential is due to an imbalance of positive and negative charges across the membrane.

- Sodium–potassium pumps transfer sodium ($Na^+$) and potassium ($K^+$) ions across the membrane. $Na^+$ ions are pumped out and $K^+$ ions are pumped in. The numbers of ions pumped is unequal – when three $Na^+$ ions are pumped out, only two $K^+$ ions are pumped in, creating concentration gradients for both ions.
- Also the membrane is about 50 times more permeable to $K^+$ ions than $Na^+$ ions, so $K^+$ ions leak back across the membrane faster than $Na^+$ ions. As a result, the $Na^+$ concentration gradient across the membrane is steeper than the $K^+$ gradient, creating a charge imbalance.
- In addition to this, there are proteins inside the nerve fibre that are negatively charged (organic anions), which increases the charge imbalance.

These factors together give the neuron a resting membrane potential of about −70 mV.




▲ Figure 5 The resting potential is generated by the sodium–potassium pump

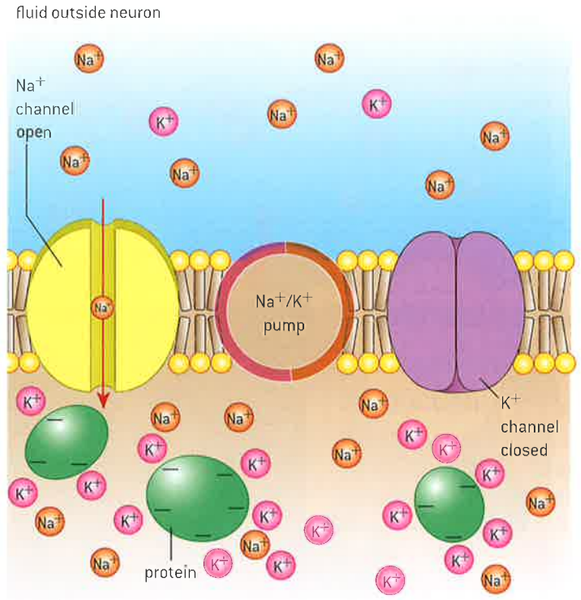
## Action potentials

### An action potential consists of depolarization and repolarization of the neuron.

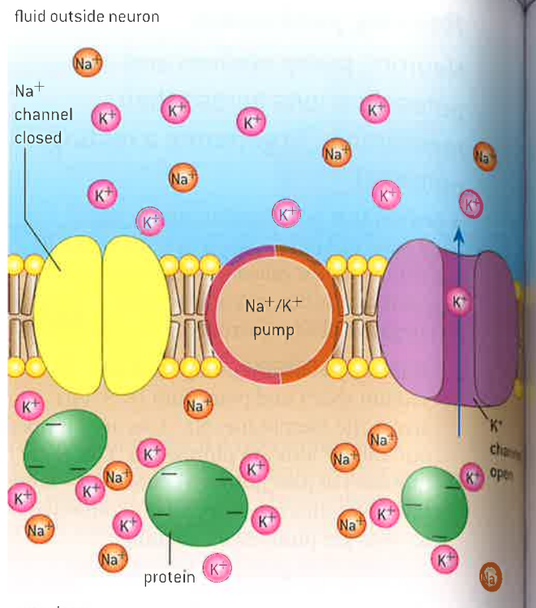
An action potential is a rapid change in membrane potential, consisting of two phases:

- depolarization – a change from negative to positive
- repolarization – a change back from positive to negative.

Depolarization is due to the opening of sodium channels in the membrane, allowing $Na^+$ ions to diffuse into the neuron down the concentration gradient. The entry of $Na^+$ ions reverses the charge imbalance across the membrane, so the inside is positive relative to the outside. This raises the membrane potential to a positive value of about +30 mV.




▲ Figure 6 Neuron depolarizing




▲ Figure 7 Neuron repolarizing

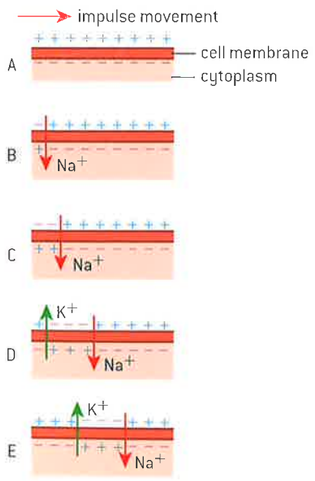
Repolarization happens rapidly after depolarization and is due to the closing of the sodium channels and opening of potassium channels in the membrane. This allows potassium ions to diffuse out of the neuron, down their concentration gradient, which makes the inside of the cell negative again relative to the outside. The potassium channels remain open until the membrane has fallen to a potential close to −70 mV. The diffusion of potassium repolarizes the neuron, but it does not restore the resting potential as the concentration gradients of sodium and potassium ions have not yet been re-established. This takes a few milliseconds and the neuron can then transmit another nerve impulse.

## Propagation of action potentials

### Nerve impulses are action potentials propagated along the axons of neurons.

A nerve impulse is an action potential that starts at one end of a neuron and is then propagated along the axon to the other end of the neuron. The propagation of the action potential happens because the ion movements that depolarize one part of the neuron trigger depolarization in the neighbouring part of the neuron.

Nerve impulses always move in one direction along neurons in humans and other vertebrates. This is because an impulse can only be initiated at one terminal of a neuron and can only be passed on to other neurons or




▲ Figure 8 Action potentials are propagated along axons





different cell types at the other terminal. Also, there is a refractive period after a depolarization that prevents propagation of an action potential backwards along an axon.

## Local currents

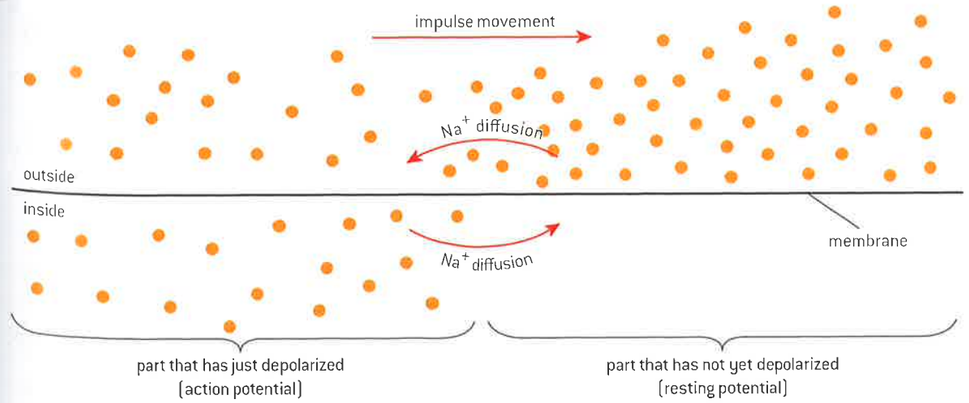
### Propagation of nerve impulses is the result of local currents that cause each successive part of the axon to reach the threshold potential.

The propagation of an action potential along an axon is due to movements of sodium ions. Depolarization of part of the axon is due to diffusion of sodium ions into the axon through sodium channels. This reduces the concentration of sodium ions outside the axon and increases it inside. The depolarized part of the axon therefore has different sodium ion concentrations to the neighbouring part of the axon that has not yet depolarized. As a result, sodium ions diffuse between these regions both inside and outside the axon.

Inside the axon there is a higher sodium ion concentration in the depolarized part of the axon so sodium ions diffuse along inside the axon to the neighbouring part that is still polarized. Outside the axon the concentration gradient is in the opposite direction so sodium ions diffuse from the polarized part back to the part that has just depolarized. These movements are shown in figure 10. They are called local currents.

Local currents reduce the concentration gradient in the part of the neuron that has not yet depolarized. This makes the membrane potential rise from the resting potential of −70mV to about −50 mV. Sodium channels in the axon membrane are voltage-gated and open when a membrane potential of −50mV is reached. This is therefore known as the threshold potential. Opening of the sodium channels causes depolarization.

Thus local currents cause a wave of depolarization and then repolarization to be propagated along the axon at a rate of between one and a hundred (or more) metres per second.



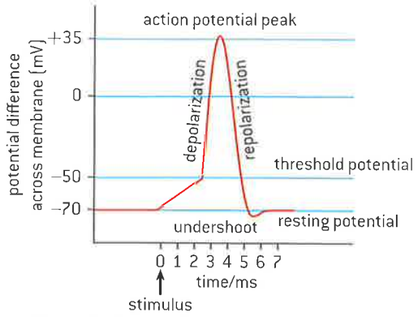

▲ Figure 10 Local currents

### Activity

**Neurons in a sea anemone and an anemonefish**

Anemonefish have a nervous system similar to ours, with a central nervous system and neurons that transmit nerve impulses in one direction only. Sea anemones have no central nervous system. Their neurons form a simple network and will transmit impulses in either direction along their nerve fibres. They both protect each other from predators more effectively than they can themselves. Explain how they do this.

▲ Figure 9 Anemonefish among the tentacles of a sea anemone




▲ Figure 11 Changes in membrane polarity during an action potential

## Analysing oscilloscope traces

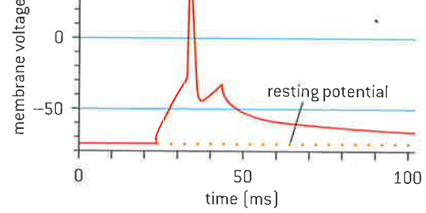
### Analysis of oscilloscope traces showing resting potentials and action potentials.

Membrane potentials in neurons can be measured by placing electrodes on each side of the membrane. The potentials can be displayed using an oscilloscope. The display is similar to a graph with time on the x-axis and the membrane potential on the y-axis. If there is a resting potential, a horizontal line appears on the oscilloscope screen at a level of −70 mV, assuming that this is the resting potential of the neuron.

If an action potential occurs, a narrow spike is seen, with the rising and falling phases showing the depolarization and repolarization. The oscilloscope trace may also show the potential rising before the depolarization until the threshold potential is reached. The repolarization does not usually return the membrane potential to −70 mV immediately and there is a phase in which the potential changes gradually until the resting potential is reached.

**Data-based questions:** Analysing an oscilloscope trace

The oscilloscope trace in figure 12 was taken from a digital oscilloscope. It shows an action potential in a mouse hippocampal pyramidal neuron that happened after the neuron was stimulated with a pulse of current.




▲ Figure 12

1 State the resting potential of the mouse hippocampal pyramidal neuron. [1]

2 Deduce with a reason the threshold potential needed to open voltage-gated sodium channels in this neuron. [2]

3 Estimate the time taken for the depolarization, and the repolarization. [2]

4 Predict the time taken from the end of the depolarization for the resting potential to be regained. [2]

5 Discuss how many action potentials could be stimulated per second in this neuron. [2]

6 Suggest a reason for the membrane potential rising briefly at the end of the repolarization. [1]

## Synapses

### Synapses are junctions between neurons and between neurons and receptor or effector cells.

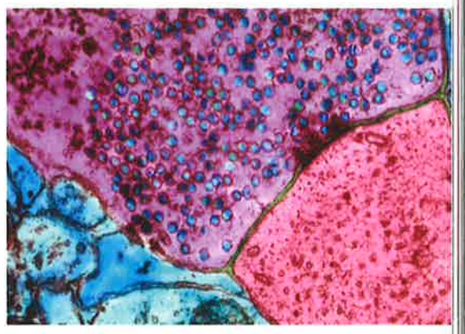
Synapses are junctions between cells in the nervous system. In sense organs there are synapses between sensory receptor cells and neurons. In both the brain and spinal cord there are immense numbers of synapses between neurons. In muscles and glands there are synapses between neurons and





muscle fibres or secretory cells. Muscles and glands are sometimes called effectors, because they effect (carry out) a response to a stimulus.

Chemicals called neurotransmitters are used to send signals across synapses. This system is used at all synapses where the pre-synaptic and post-synaptic cells are separated by a fluid-filled gap, so electrical impulses cannot pass across. This gap is called the synaptic cleft and is only about 20 nm wide.



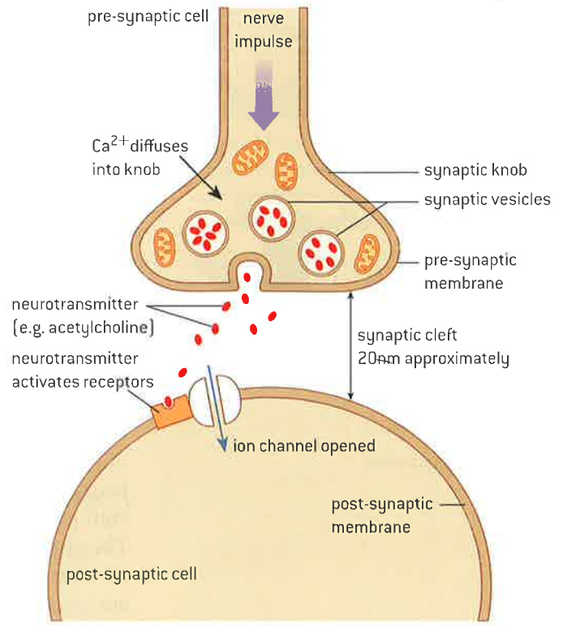
▲ Figure 13 Electron micrograph of a synapse. False colour has been used to indicate the pre-synaptic neuron (purple) with vesicles of neurotransmitter (blue) and the post-synaptic neuron (pink). The narrowness of the synaptic cleft is visible

## Synaptic transmission

### When pre-synaptic neurons are depolarized they release a neurotransmitter into the synapse.

Synaptic transmission occurs very rapidly as a result of these events:

- A nerve impulse is propagated along the pre-synaptic neuron until it reaches the end of the neuron and the pre-synaptic membrane.
- Depolarization of the pre-synaptic membrane causes calcium ions ($Ca^{2+}$) to diffuse through channels in the membrane into the neuron.
- Influx of calcium causes vesicles containing neurotransmitter to move to the pre-synaptic membrane and fuse with it.
- Neurotransmitter is released into the synaptic cleft by exocytosis.
- The neurotransmitter diffuses across the synaptic cleft and binds to receptors on the post-synaptic membrane.
- The binding of the neurotransmitter to the receptors causes adjacent sodium ion channels to open.
- Sodium ions diffuse down their concentration gradient into the post-synaptic neuron, causing the post-synaptic membrane to reach the threshold potential.
- An action potential is triggered in the post-synaptic membrane and is propagated on along the neuron.
- The neurotransmitter is rapidly broken down and removed from the synaptic cleft.




▲ Figure 14 A nerve impulse is propagated across a synapse by the release, diffusion and post-synaptic binding of neurotransmitter

**Data-based questions:** Parkinson's disease

Dopamine is one of the many neurotransmitters that are used at synapses in the brain. In Parkinson's disease, there is a loss of dopamine-secreting neurons, which causes slowness in initiating movement, muscular rigidity and in many cases shaking. Figure 15 shows the metabolic pathways involved in the formation and breakdown of dopamine.

1 Explain how symptoms of Parkinson's disease are relieved by giving the following drugs:

**a)** L-DOPA [1]

**b)** selegeline, which is an inhibitor of monoamine oxidase-B (MAO-B) [1]

**c)** tolcapone, which is an inhibitor of catechol-O-methyl transferase (COMT) [1]

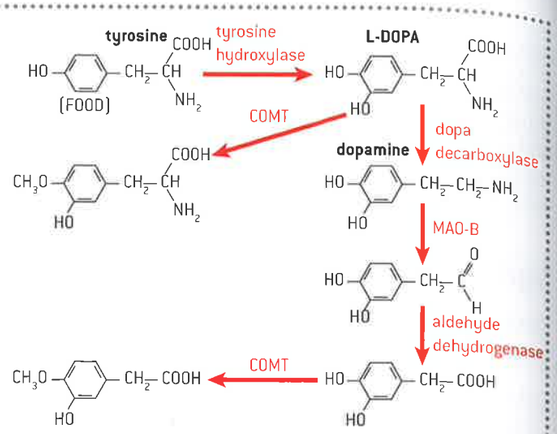
**d)** ropinirole, which is an agonist of dopamine [1]

**e)** safinamide, which inhibits reuptake of dopamine by pre-synaptic neurons. [1]

**2** Discuss how a cure for Parkinson's disease might in the future be developed by:

**a)** stem cell therapy [3]

**b)** gene therapy. [2]

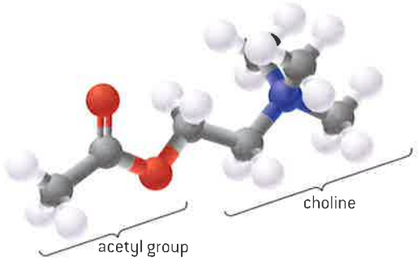



▲ Figure 15 The formation and breakdown of L-DOPA and dopamine. The enzymes catalysing each step are shown in red

## Acetylcholine

### Secretion and reabsorption of acetylcholine by neurons at synapses.

Acetylcholine is used as the neurotransmitter in many synapses, including synapses between neurons and muscle fibres. It is produced in the pre-synaptic neuron by combining choline, absorbed from the diet, with an acetyl group produced during aerobic respiration. The acetylcholine is loaded into vesicles and then released into the synaptic cleft during synaptic transmission.




▲ Figure 16 Acetylcholine

The receptors for acetylcholine in the post-synaptic membrane have a binding site to which acetylcholine will bind. The acetylcholine only remains bound to the receptor for a short time, during which only one action potential is initiated in the post-synaptic neuron. This is because the enzyme acetylcholinesterase is present in the synaptic cleft and rapidly breaks acetylcholine down into choline and acetate. The choline is reabsorbed into the pre-synaptic neuron, where it is converted back into active neurotransmitter by recombining it with an acetyl group.

## Neonicotinoids

### Blocking of synaptic transmission at cholinergic synapses in insects by binding of neonicotinoid pesticides to acetylcholine receptors.

Neonicotinoids are synthetic compounds similar to nicotine. They bind to the acetylcholine receptor in cholinergic synapses in the central nervous system of insects. Acetylcholinesterase does not break down neonicotinoids, so the binding is irreversible. The receptors are blocked, so acetylcholine is unable to bind and synaptic transmission is prevented. The consequence in insects is paralysis and death. Neonicotinoids are therefore very effective insecticides.

One of the advantages of neonicotinoids as pesticides is that they are not highly toxic to humans and other mammals. This is because a much greater proportion of synapses in the central nervous system are cholinergic in insects than in mammals and also because neonicotinoids bind much less strongly to acetylcholine receptors in mammals than insects.

Neonicotinoid pesticides are now used on huge areas of crops. In particular one neonicotinoid, imidacloprid, is the most widely used insecticide in the world. However, concerns have been raised about the effects of these insecticides on honeybees and other beneficial insects. There has been considerable controversy over this and the evidence of harm is disputed by the manufacturers and some government agencies.





## Threshold potentials

### A nerve impulse is only initiated if the threshold potential is reached.

Nerve impulses follow an all-or-nothing principle. An action potential is only initiated if the threshold potential is reached, because only at this potential do voltage-gated sodium channels start to open, causing depolarization. The opening of some sodium channels and the inward diffusion of sodium ions increases the membrane potential causing more sodium channels to open – there is a positive feedback effect. If the threshold potential is reached there will therefore always be a full depolarization.

At a synapse, the amount of neurotransmitter secreted following depolarization of the pre-synaptic membrane may not be enough to cause the threshold potential to be reached in the post-synaptic membrane. The post-synaptic membrane does not then depolarize. The sodium ions that have entered the post-synaptic neuron are pumped out by sodium–potassium pumps and the post-synaptic membrane returns to the resting potential.

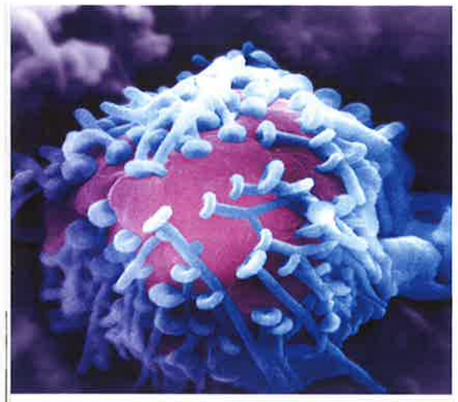
A typical post-synaptic neuron in the brain or spinal cord has synapses not just with one but with many pre-synaptic neurons. It may be necessary for several of these to release neurotransmitter at the same time for the threshold potential to be reached and a nerve impulse to be initiated in the post-synaptic neuron. This type of mechanism can be used to process information from different sources in the body to help in decision-making.

### Activity

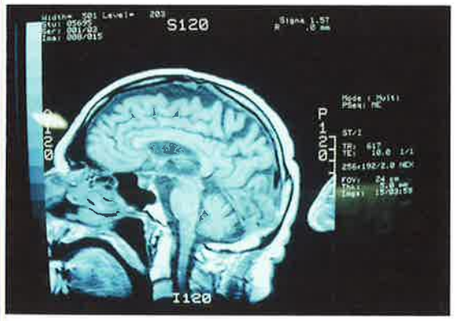
**Research updates on neonicotinoids**

There are currently intense research efforts to try to discover whether neonicotinoids are to blame for collapses in honeybee colonies. What are the most recent research findings and do they suggest that these insecticides should be banned?

▲ Figure 17 Research has shown that the neonicotinoid pesticide imidacloprid reduces growth of bumblebee colonies



▲ Figure 18 Many synapses are visible in this scanning electron micrograph between the cell body of one post-synaptic neuron and a large number of different pre-synaptic neurons (blue)




▲ Figure 19 Memory and learning are functions of the cerebrum—the folded upper part of the brain

## Research into memory and learning

Cooperation and collaboration between groups of scientists: biologists are contributing to research into memory and learning.

Higher functions of the brain including memory and learning are only partly understood at present and are being researched very actively. They have traditionally been investigated by psychologists but increasingly the techniques of molecular biology and biochemistry are being used to unravel the mechanisms at work. Other branches of science are also making important contributions, including biophysics, medicine, pharmacology and computer science.

The Centre for Neural Circuits and Behaviour at Oxford University is an excellent example of collaboration between scientists with different areas of expertise. The four group leaders of the research team and the area of science that they originally studied are:

- Professor Gero Miesenböck – medicine and physiology
- Dr Martin Booth – engineering and optical microscopy
- Dr Korneel Hens – chemistry and biochemistry
- Professor Scott Waddell – genetics, molecular biology and neurobiology.

The centre specializes in research techniques known as optogenetics. Neurons are genetically engineered to emit light during synaptic transmission or an action potential, making activity in specific neurons in brain tissue visible. They are also engineered so specific neurons in brain tissue respond to a light signal with an action potential. This allows patterns of activity in the neurons of living brain tissue to be studied.

There are many research groups in universities throughout the world that are investigating memory, learning and other brain functions. Although there is sometimes competition between scientists to be the first group to make a discovery, there is also a strongly collaborative element to scientific research. This extends across scientific disciplines and national boundaries. Success in understanding how the brain works will undoubtedly be the achievement of many groups of scientists in many countries throughout the world.





# 6.6 Hormones, homeostasis and reproduction

## Understanding

- Insulin and glucagon are secreted by α and β cells in the pancreas to control blood glucose concentration.
- Thyroxin is secreted by the thyroid gland to regulate the metabolic rate and help control body temperature.
- Leptin is secreted by cells in adipose tissue and acts on the hypothalamus of the brain to inhibit appetite.
- Melatonin is secreted by the pineal gland to control circadian rhythms.
- A gene on the Y chromosome causes embryonic gonads to develop as testes and secrete testosterone.
- Testosterone causes prenatal development of male genitalia and both sperm production and development of male secondary sexual characteristics during puberty.
- Estrogen and progesterone cause prenatal development of female reproductive organs and female secondary sexual characteristics during puberty.
- The menstrual cycle is controlled by negative and positive feedback mechanisms involving ovarian and pituitary hormones.

## Applications

- Causes and treatment of type I and type II diabetes.
- Testing of leptin on patients with clinical obesity and reasons for the failure to control the disease.
- Causes of jet lag and use of melatonin to alleviate it.
- The use in IVF of drugs to suspend the normal secretion of hormones, followed by the use of artificial doses of hormones to induce superovulation and establish a pregnancy.
- William Harvey's investigation of sexual reproduction in deer.

## Skills

- Annotate diagrams of the male and female reproductive system to show names of structures and their functions.

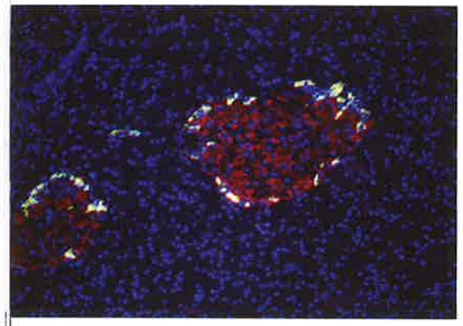
## Nature of science

- Developments in scientific research follow improvements in apparatus: William Harvey was hampered in his observational research into reproduction by lack of equipment. The microscope was invented 17 years after his death.

## Control of blood glucose concentration

Insulin and glucagon are secreted by α and β cells in the pancreas to control blood glucose concentration.

Cells in the pancreas respond to changes in blood glucose levels. If the glucose concentration deviates substantially from the set point of about 5 mmol $L^{-1}$, homeostatic mechanisms mediated by the pancreatic hormones insulin and glucagon are initiated.



▲ Figure 1 Fluorescent light micrograph of the pancreas showing two islets of Langerhans surrounded by exocrine gland tissue. Alpha cells in the islets are stained yellow and beta cells are stained red

The pancreas is effectively two glands in one organ. Most of the pancreas is exocrine glandular tissue that secretes digestive enzymes into ducts leading to the small intestine. There are small regions of endocrine tissue called islets of Langerhans dotted through the pancreas that secrete hormones directly into the blood stream. The two cell types in the islets of Langerhans secrete different hormones.

- Alpha cells (α cells) synthesize and secrete glucagon if the blood glucose level falls below the set point. This hormone stimulates breakdown of glycogen into glucose in liver cells and its release into the blood, increasing the concentration.
- Beta cells (β cells) synthesize insulin and secrete it when the blood glucose concentration rises above the set point. This hormone stimulates uptake of glucose by various tissues, particularly skeletal muscle and liver, in which it also stimulates the conversion of glucose to glycogen. Insulin therefore reduces blood glucose concentration. Like most hormones, insulin is broken down by the cells it acts upon, so its secretion must be ongoing. Secretion begins within minutes of eating and may continue for several hours after a meal.

## Diabetes

### Causes and treatment of type I and type II diabetes.

Diabetes is the condition where a person has consistently elevated blood glucose levels even during prolonged fasting, leading to the presence of glucose in the urine. Continuously elevated glucose damages tissues, particularly their proteins. It also impairs water reabsorption from urine while it is forming in the kidney, resulting in an increase in the volume of urine and body dehydration. If a person needs to urinate more frequently, is constantly thirsty, feels tired and craves sugary drinks, they should test for glucose in the urine to check whether they have developed diabetes.

There are two main types of this disease:

- Type I diabetes, or early-onset diabetes, is characterized by an inability to produce sufficient quantities of insulin. It is an autoimmune disease arising from the destruction of beta cells in the islets of Langerhans by the body's own immune system. In children and young people the more severe and obvious symptoms of the disease usually start rather suddenly. The causes of this and other autoimmune diseases are still being researched.
- Type II diabetes, sometimes called late-onset diabetes, is characterized by an inability to process or respond to insulin because of a deficiency of insulin receptors or glucose transporters on target cells. Onset is slow and the disease may go unnoticed for many years. Until the last few decades, this form of diabetes was very rare in people under 50 and common only in the over 65s. The causes of this form of diabetes are not well understood but the main risk factors are sugary, fatty diets, prolonged obesity due to habitual overeating and lack of exercise, together with genetic factors that affect energy metabolism.

The treatment of the two types of diabetes is different:

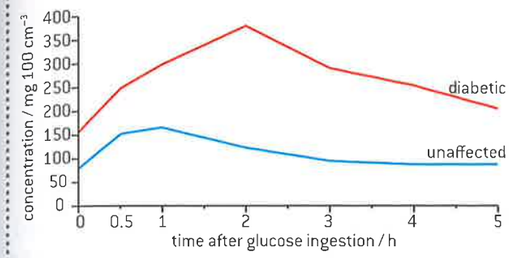
- Type I diabetes is treated by testing the blood glucose concentration regularly and injecting insulin when it is too high or likely to become too high. Injections are often done before a meal to prevent a peak of blood glucose as the food is digested and absorbed. Timing is very important because insulin molecules do not last long in the blood. Better treatments are being developed using implanted devices that can release exogenous insulin into the blood as and when it is necessary. A permanent cure may be achievable by coaxing stem cells to become fully functional replacement beta cells.
- Type II diabetes is treated by adjusting the diet to reduce the peaks and troughs of blood glucose. Small amounts of food should be eaten frequently rather than infrequent large meals. Foods with high sugar content should be avoided. Starchy food should only be eaten if it has a low glycemic index, indicating that it is digested slowly. High-fibre foods should be included to slow the digestion of other foods. Strenuous exercise and weight loss are beneficial as they improve insulin uptake and action.





### Data-based questions: The glucose tolerance test

The glucose tolerance test is a method used to diagnose diabetes. In this test, the patient drinks a concentrated glucose solution. The blood glucose concentration is monitored to determine the length of time required for excess glucose to be cleared from the blood.




▲ Figure 3 A person with diabetes and an unaffected person give very different responses to the glucose tolerance test

With reference to figure 3, compare the person with normal glucose metabolism to the person with diabetes with respect to:

**a)** The concentration of glucose at time zero, i.e. before the consumption of the glucose drink.

**b)** The length of time required to return to the level at time zero.

**c)** The maximum glucose level reached.

**d)** The time before glucose levels start to fall.

### Activity

**Foods for type II diabetics**

Discuss which of the foods in figure 2 are suitable for a person with type II diabetes. They should be foods with a low glycemic index.

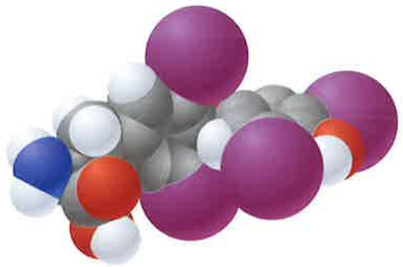
▲ Figure 2

## Thyroxin

### Thyroxin is secreted by the thyroid gland to regulate the metabolic rate and help control body temperature.

The hormone thyroxin is secreted by the thyroid gland in the neck. Its chemical structure is unusual as the thyroxin molecule contains four atoms of iodine. Prolonged deficiency of iodine in the diet therefore prevents the synthesis of thyroxin. This hormone is also unusual as almost all cells in the body are targets. Thyroxin regulates the body's metabolic rate, so all cells need to respond but the most metabolically active, such as liver, muscle and brain are the main targets.

Higher metabolic rate supports more protein synthesis and growth and it increases the generation of body heat. In a person with normal physiology, cooling triggers increased thyroxin secretion by the thyroid gland, which stimulates heat production so body temperature rises.



▲ Figure 4 Structure of thyroxin with atoms of iodine shown purple

Thyroxin thus regulates the metabolic rate and also helps to control body temperature.

The importance of thyroxin is revealed by the effects of thyroxin deficiency (hypothyroidism):

- lack of energy and feeling tired all the time
- forgetfulness and depression
- weight gain despite loss of appetite as less glucose and fat are being broken down to release energy by cell respiration
- feeling cold all the time because less heat is being generated
- constipation because contractions of muscle in the wall of the gut slow down.
- impaired brain development in children.

## Leptin

### Leptin is secreted by cells in adipose tissue and acts on the hypothalamus of the brain to inhibit appetite.

Leptin is a protein hormone secreted by adipose cells (fat storage cells). The concentration of leptin in the blood is controlled by food intake and the amount of adipose tissue in the body. The target of this hormone is groups of cells in the hypothalamus of the brain that contribute to the control of appetite. Leptin binds to receptors in the membrane of these cells. If adipose tissue increases, blood leptin concentrations rise, causing long-term appetite inhibition and reduced food intake.

▲ Figure 5 Mouse with obesity due to lack of leptin and a mouse with normal body mass

The importance of this system was demonstrated by research with a strain of mice discovered in the 1950s that feed ravenously, become inactive and gain body weight, mainly through increased adipose tissue. They grow to a body weight of about 100 grams, compared with wild type mice of 20–25 grams. Breeding experiments showed that the obese mice had two copies of a recessive allele, *ob*. In the early 1990s it was shown that the wild-type allele of this gene supported the synthesis of a new hormone that was named leptin. Adipose cells in mice that have two recessive *ob* alleles cannot produce leptin. When *ob*/*ob* mice were injected with leptin their appetite declined, energy expenditure increased and body mass dropped by 30% in a month.

### Leptin and obesity

#### Testing of leptin on patients with clinical obesity and reasons for the failure to control the disease.

The discovery that obesity in mice could be caused by a lack of leptin and cured by leptin injections soon led to attempts to treat obesity in humans in this way. Amgen, a biotechnology company based in California, paid $20 million for the commercial rights to leptin and a large clinical trial was carried out. Seventy-three obese volunteers injected themselves either with one of several leptin doses or with a placebo. A double blind procedure was used, so neither the researchers nor the volunteers knew who was injecting leptin until the results were analysed.





The leptin injections induced skin irritation and swelling and only 47 patients completed the trial. The eight patients receiving the highest dose lost 7.1 kg of body mass on average compared with a loss of 1.3 kg in the 12 volunteers who were injecting the placebo. However, in the group receiving the highest dose the results varied very widely from a loss of 15 kg to a gain of 5 kg. Also any body mass lost during the trial was usually regained rapidly afterwards. Such disappointing outcomes are frequent in drug research – the physiology of humans is different in many ways from mice and other rodents.

In contrast to *ob*/*ob* mice, most obese humans have exceptionally high blood leptin concentrations. The target cells in the hypothalamus may have become resistant to leptin so fail to respond to it, even at high concentrations. Appetite is therefore not inhibited and food intake is excessive. More adipose tissue develops, causing a rise in blood leptin concentration but the leptin resistance prevents inhibition of appetite. Injection of extra leptin inevitably fails to control obesity if the cause is leptin resistance, just as insulin injections alone are ineffective with early-stage type II diabetes.

A very small proportion of cases of obesity in humans are due to mutations in the genes for leptin synthesis or its various receptors on target cells. Trials in people with such obesity have shown significant weight loss while the leptin injections are continuing. However leptin is a short-lived protein and has to be injected several times a day and consequently most of those offered this treatment have refused it. Also leptin has been shown to affect the development and functioning of the reproductive system, so injections are not suitable in children and young adults. All in all leptin has not fulfilled its early promise as a means of solving the human obesity problem.

## Melatonin

### Melatonin is secreted by the pineal gland to control circadian rhythms.

Humans are adapted to live in a 24-hour cycle and have rhythms in behaviour that fit this cycle. These are known as circadian rhythms. They can continue even if a person is placed experimentally in continuous light or darkness because an internal system is used to control the rhythm.

Circadian rhythms in humans depend on two groups of cells in the hypothalamus called the suprachiasmatic nuclei (SCN). These cells set a daily rhythm even if grown in culture with no external cues about the time of day. In the brain they control the secretion of the hormone melatonin by the pineal gland. Melatonin secretion increases in the evening and drops to a low level at dawn and as the hormone is rapidly removed from the blood by the liver, blood concentrations rise and fall rapidly in response to these changes in secretion.

The most obvious effect of melatonin is the sleep-wake cycle. High melatonin levels cause feelings of drowsiness and promote sleep through the night. Falling melatonin levels encourage waking at the end of the night. Experiments have shown that melatonin contributes to the night-time drop in core body temperature, as blocking the rise in melatonin levels reduces it and giving melatonin artificially during the day causes a drop in core temperature. Melatonin receptors have been discovered in the kidney, suggesting that decreased urine production at night may be another effect of this hormone.

When humans are placed experimentally in an environment without light cues indicating the time of day, the SCN and pineal gland usually

▲ Figure 6 Until a baby is about three months old it does not develop a regular day-night rhythm of melatonin secretion so sleep patterns do not fit those of the baby's parents

maintain a rhythm of slightly longer than 24 hours. This indicates that timing of the rhythm is normally adjusted by a few minutes or so each day. A special type of ganglion cell in the retina of the eye detects light of wavelength 460–480 nm and passes impulses to cells in the SCN. This indicates to the SCN the timing of dusk and dawn and allows it to adjust melatonin secretion so that it corresponds to the day-night cycle.

### Jet lag and melatonin

Causes of jet lag and use of melatonin to alleviate it.

Jet lag is a common experience for someone who has crossed three or more time zones during air travel. The symptoms are difficulty in remaining awake during daylight hours and difficulty sleeping through the night, fatigue, irritability, headaches and indigestion. The causes are easy to understand: the SCN and pineal gland are continuing to set a circadian rhythm to suit the timing of day and night at the point of departure rather than the destination.

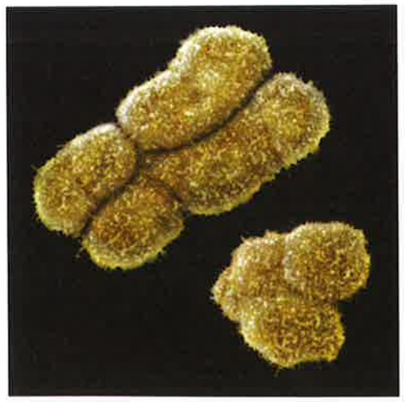
Jet lag only lasts for a few days, during which impulses sent by ganglion cells in the retina to the SCN when they detect light help the body to adjust to the new regime. Melatonin is sometimes used to try to prevent or reduce jet lag. It is taken orally at the time when sleep should ideally be commencing. Most trials of melatonin have shown that it is effective at promoting sleep and helping to reduce jet lag, especially if flying eastwards and crossing five or more time zones.

## Sex determination in males

A gene on the Y chromosome causes embryonic gonads to develop as testes and secrete testosterone.

Human reproduction involves the fusion of a sperm from a male with an egg from a female. Initially the development of the embryo is the same in all embryos and embryonic gonads develop that could either become ovaries or testes. The developmental pathway of the embryonic gonads and thereby the whole baby depends on the presence or absence of one gene.

- If the gene SRY is present, the embryonic gonads develop into testes. This gene is located on the Y chromosome, so is only present in 50% of embryos. SRY codes for a DNA-binding protein called TDF (testis determining factor). TDF stimulates the expression of other genes that cause testis development.
- 50% of embryos have two X chromosomes and no Y so they do not have a copy of the SRY gene. TDF is therefore not produced and the embryonic gonads develop as ovaries.



▲ Figure 7 X and Y chromosomes

## Testosterone

Testosterone causes prenatal development of male genitalia and both sperm production and development of male secondary sexual characteristics during puberty.

The testes develop from the embryonic gonads in about the eighth week of pregnancy, at the time when the embryo is becoming a fetus and is about 30mm long. The testes develop testosterone-secreting cells at an early stage and these produce testosterone until about the fifteenth week





of pregnancy. During the weeks of secretion, testosterone causes male genitalia to develop, which are shown in figure 8.

At puberty the secretion of testosterone increases. This stimulates sperm production in the testes, which is the primary sexual characteristic of males. Testosterone also causes the development of secondary sexual characteristics during puberty such as enlargement of the penis, growth of pubic hair and deepening of the voice due to growth of the larynx.

## Sex determination in females

Estrogen and progesterone cause prenatal development of female reproductive organs and female secondary sexual characteristics during puberty.

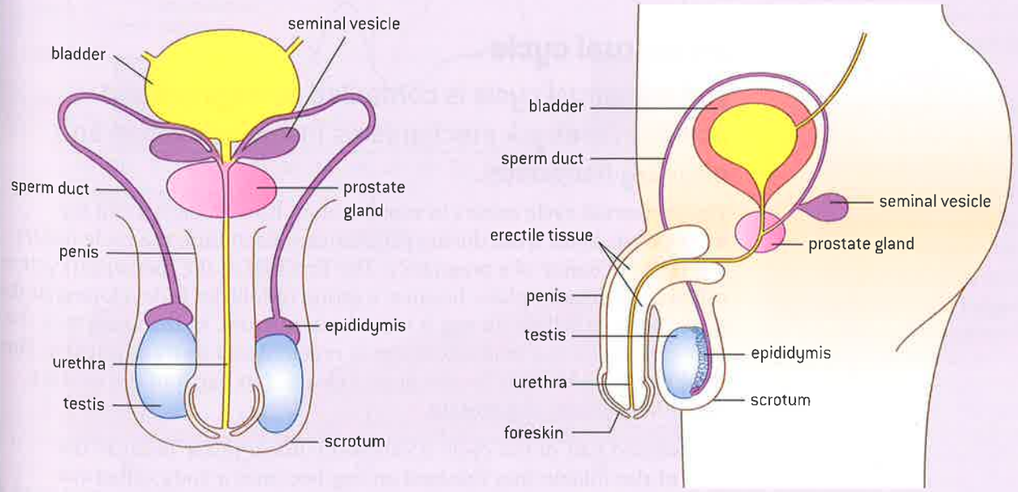
If the gene SRY is not present in an embryo because there is no Y chromosome, the embryonic gonads develop as ovaries. Testosterone is therefore not secreted, but the two female hormones, estrogen and progesterone, are always present in pregnancy. At first they are secreted by the mother's ovaries and later by the placenta. In the absence of fetal testosterone and the presence of maternal estrogen and progesterone, female reproductive organs develop which are shown in figure 9.

During puberty the secretion of estrogen and progesterone increases, causing the development of female secondary sexual characteristics. These include enlargement of the breasts and growth of pubic and underarm hair.

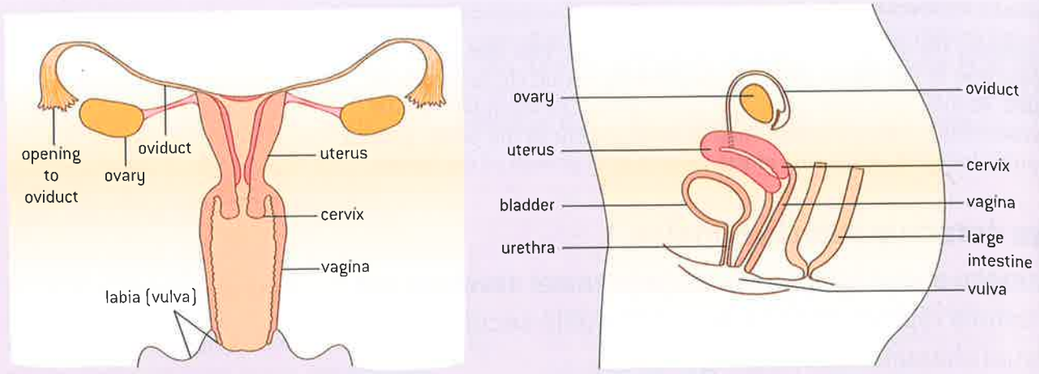
### Male and female reproductive systems

Annotate diagrams of the male and female reproductive system to show names of structures and their functions.

The tables on the next page indicate functions that should be included when diagrams of male and female reproductive systems are annotated.




▲ Figure 8 Male reproductive system in front and side view




▲ Figure 9 Female reproductive system in front and side view

**Male reproductive system**

| | |
|---|---|
| Testis | Produce sperm and testosterone |
| Scrotum | Hold testes at lower than core body temperature |
| Epididymis | Store sperm until ejaculation |
| Sperm duct | Transfer sperm during ejaculation |
| Seminal vesicle and prostate gland | Secrete fluid containing alkali, proteins and fructose that is added to sperm to make semen |
| Urethra | Transfer semen during ejaculation and urine during urination |
| Penis | Penetrate the vagina for ejaculation of semen near the cervix |

**Female reproductive system**

| | |
|---|---|
| Ovary | Produce eggs, estrogen and progesterone |
| Oviduct | Collect eggs at ovulation, provide a site for fertilization then move the embryo to the uterus |
| Uterus | Provide for the needs of the embryo and then fetus during pregnancy |
| Cervix | Protect the fetus during pregnancy and then dilate to provide a birth canal |
| Vagina | Stimulate penis to cause ejaculation and provide a birth canal |
| Vulva | Protect internal parts of the female reproductive system |

## Menstrual cycle

### The menstrual cycle is controlled by negative and positive feedback mechanisms involving ovarian and pituitary hormones.

The menstrual cycle occurs in most women from puberty until the menopause, apart from during pregnancies. Each time the cycle occurs it gives the chance of a pregnancy. The first half of the menstrual cycle is called the follicular phase because a group of follicles is developing in the ovary. In each follicle an egg is stimulated to grow. At the same time the lining of the uterus (endometrium) is repaired and starts to thicken. The most developed follicle breaks open, releasing its egg into the oviduct. The other follicles degenerate.

The second half of the cycle is called the luteal phase because the wall of the follicle that released an egg becomes a body called the corpus luteum. Continued development of the endometrium prepares

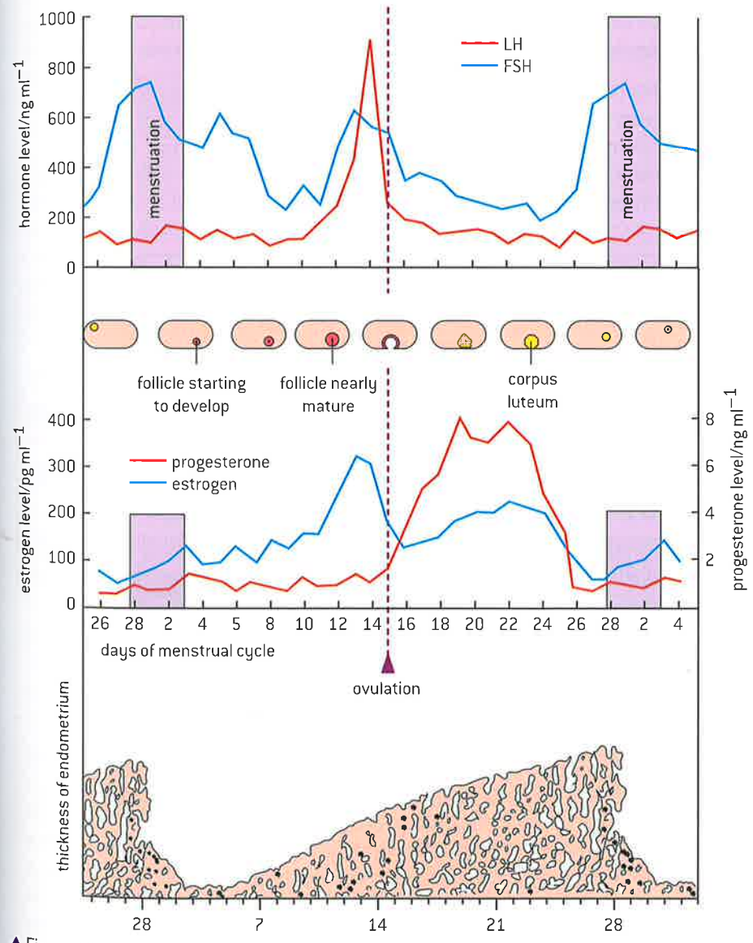




it for the implantation of an embryo. If fertilization does not occur the corpus luteum in the ovary breaks down. The thickening of the endometrium in the uterus also breaks down and is shed during menstruation.

Figure 10 shows hormone levels in a woman over a 36-day period, including one complete menstrual cycle. The pattern of changes is typical for a woman who is not pregnant. The hormone levels are measured in mass per millilitre. The actual masses are very small, so progesterone, FSH and LH are measured in nanograms (ng) and estrogen is measured in picograms (pg). Figure 10 also shows the state of the ovary and of the endometrium.

The four hormones in figure 10 all help to control the menstrual cycle by both negative and positive feedback. FSH and LH are protein hormones produced by the pituitary gland that bind to FSH and LH receptors in the membranes of follicle cells. Estrogen and progesterone are ovarian hormones, produced by the wall of the follicle and corpus




▲ Figure 10 The menstrual cycle

## TOK

**To what extent do motives matter when judging the morality of an act?**

Human eggs can be obtained by using FSH to stimulate the ovaries, then collecting eggs from the ovaries using a micropipette. Women have sometimes undergone this procedure to produce eggs for donation to another woman who is unable to produce eggs herself.

Recently stem-cell researchers have used eggs in therapeutic cloning experiments. The nucleus of an egg is removed and replaced with a nucleus from an adult. If the resulting cell developed as an embryo, stem cells could be removed from it and cloned. It might then be possible to produce tissues or organs for transplanting to the adult who donated the nucleus. There would be no danger of tissue rejection because the stem cells would be genetically identical to the recipient.

There is a shortage of eggs both for donation to other women and for research. In 2006, scientists in England got permission to offer women cut-price IVF treatment, if they were willing to donate some eggs for research. In Sweden only travel and other direct expenses can be paid to egg donors, and in Japan egg donation is banned altogether.

1 Is there a distinction to be drawn between donating eggs for therapeutic cloning experiments and donating eggs to a woman who is unable to produce eggs herself, for example because her ovaries have been removed? Can the same act be judged differently depending on motives?

luteum. They are absorbed by many cells in the female body, where they influence gene expression and therefore development.

- FSH rises to a peak towards the end of the menstrual cycle and stimulates the development of follicles, each containing an oocyte and follicular fluid. FSH also stimulates secretion of estrogen by the follicle wall.
- Estrogen rises to a peak towards the end of the follicular phase. It stimulates the repair and thickening of the endometrium after menstruation and an increase in FSH receptors that make the follicles more receptive to FSH, boosting estrogen production (positive feedback). When it reaches high levels estrogen inhibits the secretion of FSH (negative feedback) and stimulates LH secretion.
- LH rises to a sudden and sharp peak towards the end of the follicular phase. It stimulates the completion of meiosis in the oocyte and partial digestion of the follicle wall allowing it to burst open at ovulation. LH also promotes the development of the wall of the follicle after ovulation into the corpus luteum which secretes estrogen (positive feedback) and progesterone.
- Progesterone levels rise at the start of the luteal phase, reach a peak and then drop back to a low level by the end of this phase. Progesterone promotes the thickening and maintenance of the endometrium. It also inhibits FSH and LH secretion by the pituitary gland (negative feedback).

### Data-based questions: The female athlete triad

The female athlete triad is a syndrome consisting of three interrelated disorders that can affect female athletes: osteoporosis, disordered eating and menstrual disorders. Osteoporosis is reduced bone mineral density. It can be caused by a diet low in calcium, vitamin D or energy, or by low estrogen levels. Figure 11 shows the bone mineral density in two parts of the femur for female runners who had different numbers of menstrual cycles per year. The t-score is the number of standard deviations above or below mean peak bone mass for young women.

1 **a)** Outline the relationship between number of menstrual cycles per year and bone density. [3]

**b)** Compare the results for the neck of the femur with the results for the trochanter. [3]

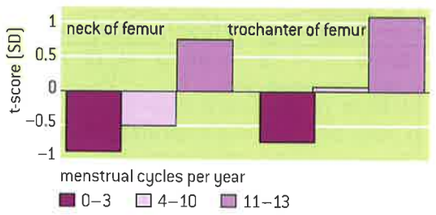
2 Explain the reasons for some of the runners having:

**a)** higher bone density than the mean [2]

**b)** lower bone density than the mean. [4]

3 **a)** Suggest reasons for female athletes having few or no menstrual cycles. [2]

**b)** Suggest one reason for eating disorders and low body weight in female athletes. [1]




▲ Figure 11 Bone mass in women grouped by number of menstrual cycles





## In vitro fertilization

The use in IVF of drugs to suspend the normal secretion of hormones, followed by the use of artificial doses of hormones to induce superovulation and establish a pregnancy.

The natural method of fertilization in humans is *in vivo*, meaning that it occurs inside the living tissues of the body. Fertilization can also happen outside the body in carefully controlled laboratory conditions. This is called *in vitro* fertilization, almost always abbreviated to IVF. This procedure has been used extensively to overcome fertility problems in either the male or female parent.

There are several different protocols for IVF, but the first stage is usually down-regulation. The woman takes a drug each day, usually as a nasal spray, to stop her pituitary gland secreting FSH or LH. Secretion of estrogen and progesterone therefore also stops. This suspends the normal menstrual cycle and allows doctors to control the timing and amount of egg production in the woman's ovaries.

Intramuscular injections of FSH and LH are then given daily for about ten days, to stimulate follicles to develop. The FSH injections give a much higher concentration of this hormone than during a normal menstrual cycle and as a consequence far more follicles develop than usual. Twelve is not unusual and there can be as many twenty follicles. This stage of IVF is therefore called superovulation.

When the follicles are 18 mm in diameter they are stimulated to mature by an injection of HCG, another hormone that is normally secreted by the embryo. A micropipette mounted on an ultrasound scanner is passed through the uterus wall to wash eggs out of the follicles. Each egg is mixed with 50,000 to 100,000 sperm cells in sterile conditions in a shallow dish, which is then incubated at 37 °C until the next day.

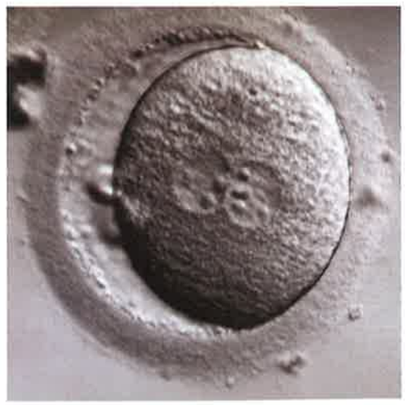
If fertilization is successful then one or more embryos are placed in the uterus when they are about 48 hours old. Because the woman has not gone through a normal menstrual cycle extra progesterone is usually given as a tablet placed in the vagina, to ensure that the uterus lining is maintained. If the embryos implant and continue to grow then the pregnancy that follows is no different from a pregnancy that began by natural conception.

## William Harvey and sexual reproduction

William Harvey's investigation of sexual reproduction in deer.

William Harvey is chiefly remembered for his discovery of the circulation of the blood, but he also had a lifelong obsession with how life is transmitted from generation to generation and pioneered research into sexual reproduction. He was taught the "seed and soil" theory of Aristotle, according to which the male produces a seed, which forms an egg when it mixes with menstrual blood. The egg develops into a fetus inside the mother.

William Harvey tested Aristotle's theory using a natural experiment. Deer are seasonal breeders and only become sexually active during the autumn. Harvey examined the uterus of female deer during the mating season by slaughtering and dissecting them. He expected to find eggs developing in the uterus immediately after mating, but only found signs of anything developing in females two or more months after the start of the mating season.



▲ Figure 12 IVF allows the earliest stages in a human life to be seen. This micrograph shows a zygote formed by fertilization. The nuclei of the egg and sperm are visible in the centre of the zygote. There is a protective layer of gel around the zygote called the fertilization membrane


▲ Figure 13 William Harvey's book on the reproduction of animals *Exercitationes de Generatione Animalium* published in 1651

He regarded his experiments with deer as proof that Aristotle's theory of reproduction was false and concluded "the fetus doth neither proceed from the seed of male or female in coition, nor yet from any commixture of that seed". Although Aristotle's "seed and soil" theory was false, Harvey's conclusion that the fetus did not result from events during coitus (sexual intercourse) was also false.

Harvey was well aware that he had not discovered the basis of sexual reproduction: "neither the philosophers nor the physicians of yesterday or today have satisfactorily explained, or solved the problem of Aristotle."

## Improvements in apparatus and research breakthroughs

Developments in scientific research follow improvements in apparatus: William Harvey was hampered in his observational research into reproduction by lack of equipment. The microscope was invented seventeen years after his death.

Harvey was understandably reluctant to publish his research into sexual reproduction, but he did eventually do so in 1651 when he was 73 years old in his work *Exercitationes de Generatione Animalium*. He knew that he had not solved the mystery of sexual reproduction:

> *When I plainly see nothing at all doth remain in the uterus after coition, ... no more than remains in the braine after sensation, ... I have invented this Fable. Let the learned and ingenious flock of men consider of it; let the supercilious reject it: and for the scoffing ticklish generation, let them laugh their swinge. Because I say, there is no sensible thing in the uterus after coition; and yet there is a necessity, that something should be there, which may render the animal fruitful.*

William Harvey failed to solve the mystery because effective microscopes were not available when he was working, so fusion of gametes and subsequent embryo development remained undiscovered. He was unlucky with his choice of experimental animal because embryos in the deer that he used remain microscopically small for an unusually long period. Microscopes were invented seventeen years after Harvey's death, allowing the discovery of sperm, eggs and early stage embryos.

Scientific research has often been hampered for a time by deficiencies in apparatus, with discoveries only being made following improvements. This will continue into the future and we can look forward to further transformations in our understanding of the natural world as new techniques and technology are invented.





## Questions

1 Using the data in table 1:

**a)** outline the relationship between the age of the mother and the success rate of IVF [3]

**b)** outline the relationship between the number of embryos transferred and the chance of having a baby as a result of IVF [3]

**c)** discuss how many embryos fertility centres should be allowed to transfer. [4]

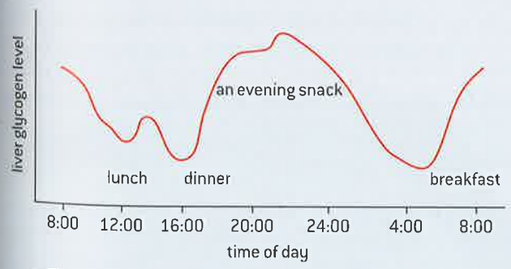
| Age of mother | Percentage of pregnancies per IVF cycle according to the number of embryos transferred | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | | 3 | | |
| | single | single | twins | single | twins | triplets |
| < 30 | 10.4 | 20.1 | 9.0 | 17.5 | 3.6 | 0.4 |
| 30–34 | 13.4 | 21.8 | 7.9 | 18.2 | 7.8 | 0.6 |
| 35–39 | 19.1 | 19.1 | 5.0 | 17.4 | 5.6 | 0.6 |
| > 39 | 4.1 | 12.5 | 3.5 | 12.7 | 1.7 | 0.1 |

▲ Table 1

2 Figure 14 shows variations in liver glycogen over the course of one day.

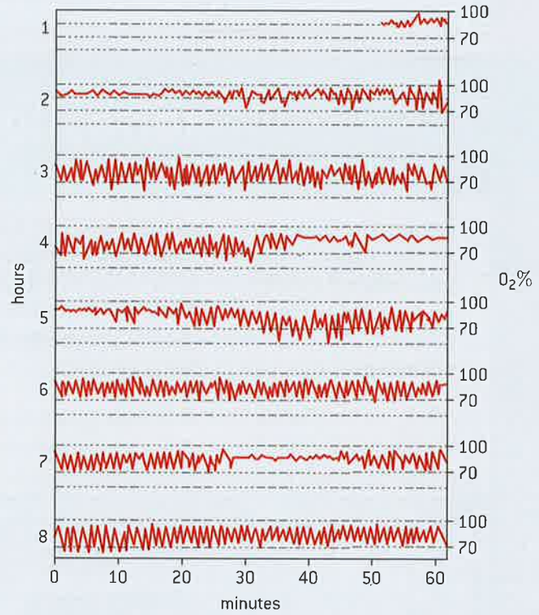
**a)** Explain the variation in liver glycogen. [3]

**b)** Evaluate the contribution of glycogen to blood sugar homeostasis. [2]




▲ Figure 14

3 Sometimes the ventilation of the lungs stops. This is called apnea. One possible cause is the blockage of the airways by the soft palate during sleep. This is called obstructive sleep apnea. It has some potentially harmful consequences, including an increased risk of accidents during the daytime as a result of disrupted sleep and tiredness. Figure 15 shows the percentage oxygen saturation of arterial blood during a night of sleep in a patient with severe obstructive sleep apnea.




▲ Figure 15

**a)** Hour 8 shows a typical pattern due to obstructive sleep apnea.

(i) Explain the causes of falls in saturation. [2]

(ii) Explain the causes of rises in saturation. [2]

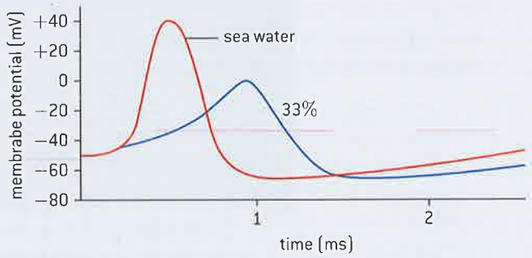
(iii) Calculate how long each cycle of falling and rising saturation takes. [2]

**b)** Estimate the minimum oxygen saturation that the patient experienced during the night, and when it occurred. [2]

**c)** Deduce the sleep patterns of the patient during the night when the trace was taken. [2]

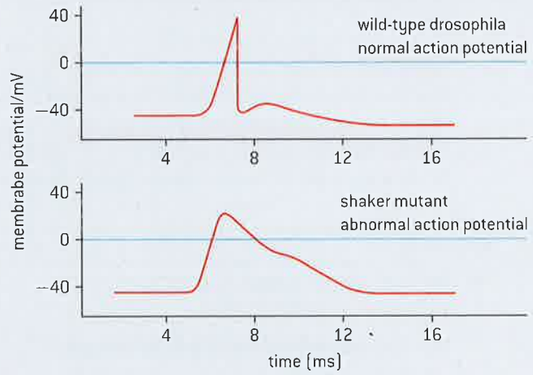
4 The action potential of a squid axon was recorded, with the axon in normal sea water. The axon was then placed in water with a $Na^+$ concentration of one-third of that of sea water.

The action potential was recorded again. Figure 16 shows these recordings.




▲ Figure 16

5 Geneticists discovered a mutant variety of fruit fly that shakes vigorously when anaesthetized with ether. Studies have shown that the shaker mutant has $K^+$ channels that do not function properly. Figure 17 shows action potentials in normal fruit flies and in shaker mutants.




▲ Figure 17

**a)** Using only the data in figure 17, outline the effect of reduced $Na^+$ concentration on:
(i) the magnitude of depolarization [2]
(ii) the duration of the action potential. [2]

**b)** Explain the effects of reduced $Na^+$ concentration on the action potential. [3]

**c)** Discuss the effect of reduced $Na^+$ concentration on the time taken to return to the resting potential. [2]

**d)** Compare the action potentials of shaker and normal fruit flies. [3]

**e)** Explain the differences between the action potentials.



# 7 NUCLEIC ACIDS (AHL)

## Introduction

The discovery of the structure of DNA revolutionized biology. Information stored in a coded form in DNA is copied onto mRNA. The structure of DNA is ideally suited to its function. Information transferred from DNA to mRNA is translated into an amino acid sequence.

## 7.1 DNA structure and replication

### Understanding

- DNA structure suggested a mechanism for DNA replication.
- Nucleosomes help to supercoil the DNA.
- DNA replication is continuous on the leading strand and discontinuous on the lagging strand.
- DNA replication is carried out by a complex system of enzymes.
- DNA polymerases can only add nucleotides to the 3' end of a primer.
- Some regions of DNA do not code for proteins but have other important functions.

### Applications

- Rosalind Franklin's and Maurice Wilkins' investigation of DNA structure by X-ray diffraction.
- Tandem repeats are used in DNA profiling.
- Use of nucleotides containing dideoxyribonucleic acid to stop DNA replication in preparation of samples for base sequencing.

### Nature of science

- Making careful observations: Rosalind Franklin's X-ray diffraction provided crucial evidence that DNA is a double helix.

### Skills

- Analysis of results of the Hershey and Chase experiment providing evidence that DNA is the genetic material.
- Utilization of molecular visualization software to analyse the association between protein and DNA within a nucleosome.