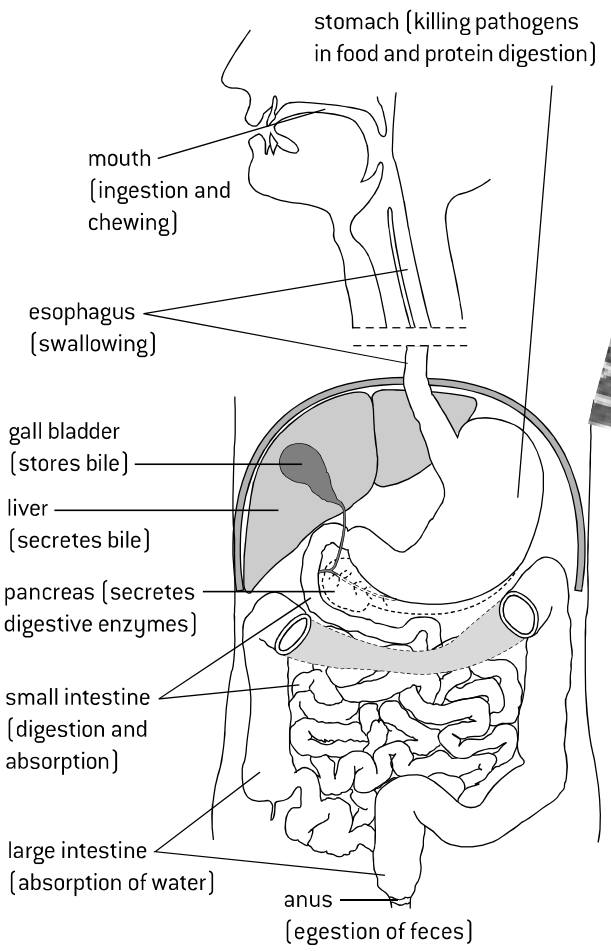
Digestion

THE HUMAN DIGESTIVE SYSTEM



STRUCTURE OF THE SMALL INTESTINE

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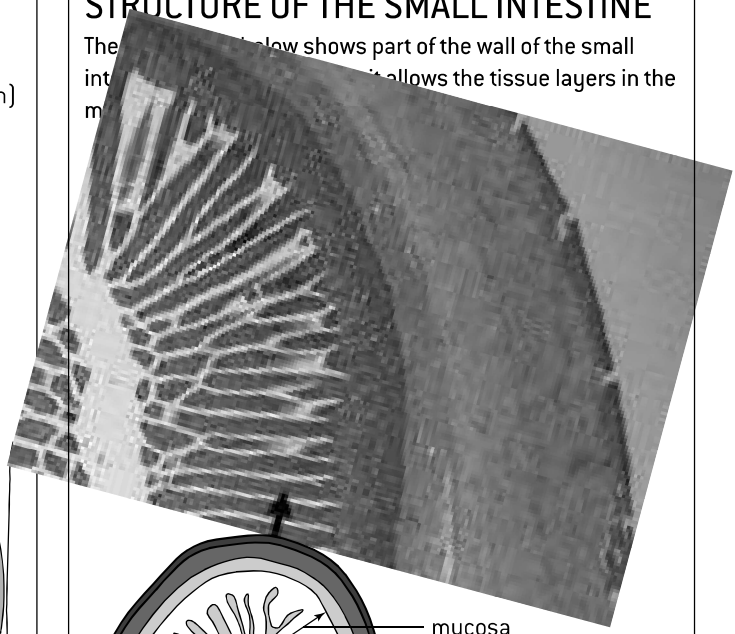
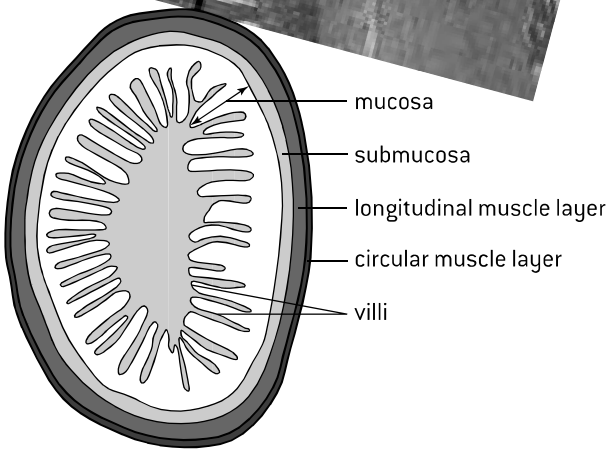




DIGESTION IN THE SMALL INTESTINE

Waves of muscle contraction, called **peristalsis**, pass along the intestine. Contraction of circular muscle behind the food constricts the gut to prevent food from being pushed back towards the mouth.

Contraction of longitudinal muscle where the food is located moves it on along the gut. Contraction of both layers of muscle mixes food with enzymes in the small intestine.

Enzymes digest most macromolecules in food into monomers in the small intestine. These macromolecules include proteins, starch, glycogen, lipids and nucleic acids. Cellulose remains undigested. The pancreas secretes three types of enzyme into the lumen of the small intestine:

lipids (fats and oils) $\xrightarrow{\textbf{lipase}}$ fatty acids + glycerol

polypeptides $\xrightarrow{\textbf{endopeptidase}}$ shorter peptides

starch $\xrightarrow{\textbf{amylase}}$ maltose

The details of starch digestion in the small intestine are explained (right).

DIGESTION OF STARCH

There are two types of molecule in starch: **amylose** and **amylopectin**. They are both polymers of α-glucose linked by 1,4 bonds but in amylose the chains are unbranched and in amylopectin there are some 1,6 bonds that make the molecule branched.

Amylase breaks 1,4 bonds in chains of four or more glucose monomers, so it can digest amylose into maltose but not glucose. Because of the specificity of its active site, amylase cannot break the 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 enzymes in the membranes of microvilli on villus epithelium cells: **maltase** and **dextrinase** digest maltose and dextrins into glucose. Also in the membranes of the microvilli are protein pumps that cause the absorption of the glucose produced by digesting starch.

Blood carrying glucose and other products of digestion flows though villus capillaries to venules in the submucosa 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.

Absorption

INTESTINAL VILLI

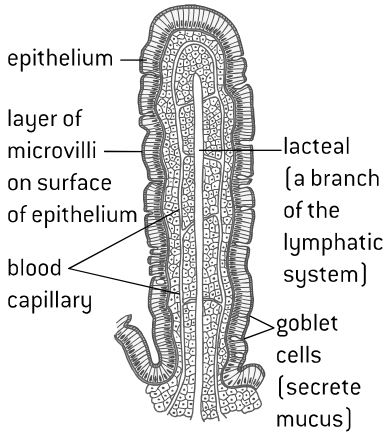
The process of taking substances into cells and the blood is called **absorption**. In the human digestive system nutrients are absorbed by the epithelium, which is the single layer of cells forming the inner lining of the mucosa. The rate of absorption depends on the surface area of this epithelium.

Absorption occurs principally in the small intestine. The small intestine in adults is about seven metres long and 25–30 millimetres wide and there are folds on its inner surface, giving a large surface area of epithelium.

The area of epithelium is further increased by the presence of **villi**, which 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 ten.

The villi absorb mineral ions and vitamins and also monomers formed by digestion such as glucose.

Structure of a villus



METHODS OF ABSORPTION

Different methods of membrane transport are used in epithelium cells to absorb different nutrients:

- **Simple diffusion**, in which nutrients pass down the concentration gradient between phospholipids in the membrane.

  Example – hydrophobic nutrients such as fatty acids and monoglycerides.
- **Facilitated diffusion**, in which nutrients pass down the concentration gradient through specific channel proteins in the membrane.

  Example – hydrophilic nutrients such as fructose.
- **Active transport**, in which nutrients are pumped through the membrane against the concentration gradient by specific pump proteins.

  Example – mineral ions such as sodium, calcium and iron.
- **Endocytosis** (pinocytosis), in which small droplets of the fluid are passed through the membrane by means of vesicles.

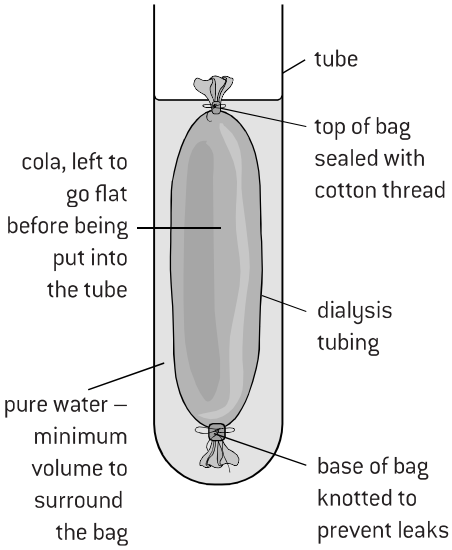
  Example – triglycerides and cholesterol in lipoprotein particles.

There are some more complex methods of transport. For example, glucose is absorbed by sodium co-transporter proteins which move a molecule of glucose together with a sodium ion across the membrane together into the epithelium cells. The glucose can be moved against its concentration gradient because the sodium ion is moving down its concentration gradient. The sodium gradient is generated by active transport of sodium out of the epithelium cell by a pump protein.

MODELLING ABSORPTION WITH DIALYSIS TUBING

Dialysis tubing can be used to model absorption by the epithelium of the intestine. The diagram shows one possible method. Cola drink contains a mixture of substances which can be used to model digested and undigested foods in the intestine. The water outside the bag is tested at intervals to see if substances in the cola have diffused through the dialysis tubing.

The expected result is that glucose and phosphoric acid, which have small-sized particles, diffuse through the tubing but caramel, which consists of larger polymers of sugar, does not.



USING MODELS IN SCIENCE

A model in science is a theoretical representation of the real world. Models sometimes consist of mathematical equations but in biology they often represent a structure or process non-mathematically.

When a model has been proposed predictions are made using it, which are then tested. This is done with experiments or with observations of the real world. If predictions based on a model fit experimental data or observations, the model is trusted more. If the predictions are not as close as they could be, the model is modified.

Sometimes evidence shows that a model or theory is incorrect. This known as falsification. The model or theory must then be discarded and replaced.

Theoretical models used to explain the structure of biological membranes were described in Topic 1. An example of physical models is described above.

The cardiovascular system

HARVEY AND THE CIRCULATION OF BLOOD

Until the 17th century the doctrines of Galen, one of the ancient Greek philosophers, about blood were accepted with little questioning by doctors. Galen taught that blood is produced by the liver, pumped out by the heart and consumed in the other organs of the body.

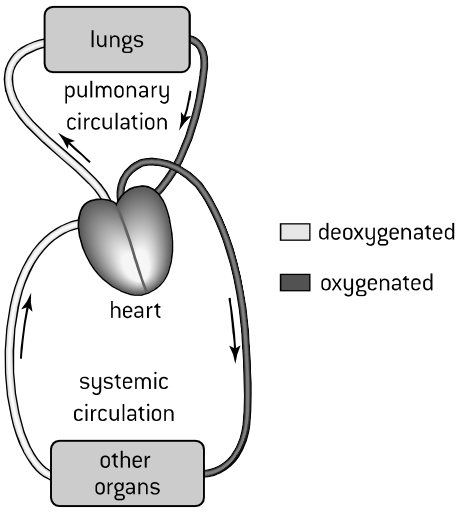
William Harvey is usually credited with the discovery of the circulation of the blood. He had to overcome widespread opposition because Galen's theories were so well established. Harvey published his results and also toured Europe to demonstrate experiments that overturned previous theories and provided evidence for his theory. As a result, his theory that there is a circulation of blood became generally accepted.

Harvey demonstrated that blood flow through vessels is unidirectional with valves to prevent backflow and also that the rate of flow through major vessels is far too high for blood to be consumed in the body after being pumped out by the heart. He showed that the heart pumps blood out in the arteries and that it returns in veins.

William Harvey 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. Microscopes had not been invented by the time that he 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 Harvey had predicted.

THE DOUBLE CIRCULATION

The circulation that Harvey discovered in humans is double: there are separate circulations for the lungs (**pulmonary circulation**) and for other organs of the body (**systemic circulation**).



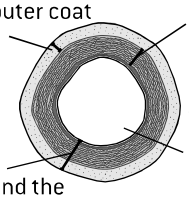
The heart is a double pump with left and right sides. The right side pumps deoxygenated blood to the lungs via the pulmonary artery. Oxygenated blood returns to the left side of the heart in the pulmonary vein. The left side pumps this blood via the aorta to all organs of the body apart from the lungs. Deoxygenated blood is carried back the right side of the heart in the vena cava.

STRUCTURE AND FUNCTION OF BLOOD VESSELS

Blood vessels are tubes that carry blood. There are three main types.

- **Arteries** convey blood pumped out at high pressure by the ventricles of the heart. They carry the blood to tissues of the body.
- **Capillaries** carry blood through tissues. They have permeable walls that allow exchange of materials between the cells of 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.

Arteries

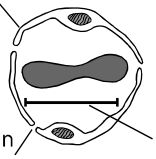


Thick layer containing elastic fibres that maintain high pressure between pumping cycles and muscle that contracts or relaxes to adjust the diameter of the lumen

Narrow lumen to help maintain the high pressures

Capillaries

Wall consists of a single layer of thin cells so the distance for diffusion in or out is small

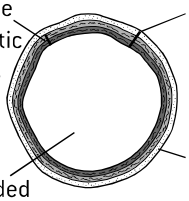


Pores between cells in the wall allow some of the plasma to leak out and form tissue fluid. Phagocytes can also squeeze out

Very narrow lumen – only about 10 μm across so that capillaries fit into small spaces. Many small capillaries have a larger surface area than fewer wider ones would

Veins

Thin layers of tissue with few or no elastic fibres or muscle as blood flow is not pulsatile



Wide lumen is needed to accommodate the low pressure, slow flowing blood. Valves are present at intervals in veins to prevent back-flow

Thin wall allows the vein to be pressed flat by adjacent muscles, helping to move the blood

Outer coat is thin as there is no danger of veins bursting

The heart

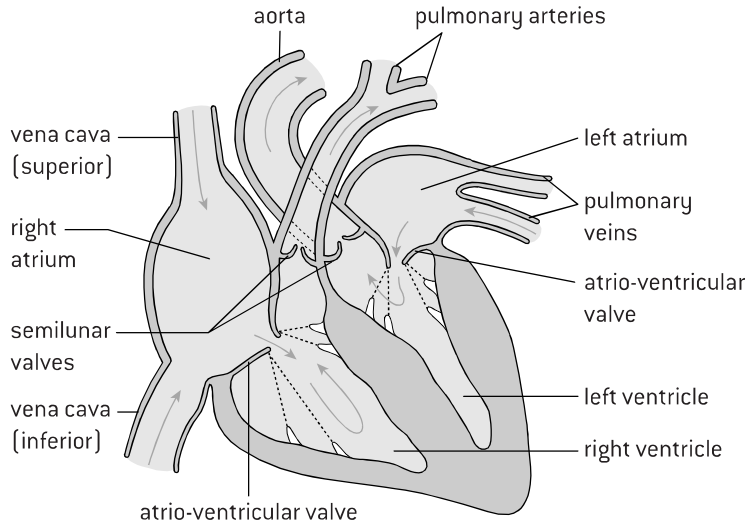
CARDIAC MUSCLE

The walls of the heart are made of **cardiac muscle**, which has a special property – it can contract on its own without being stimulated by a nerve (myogenic contraction).

There are many capillaries in the muscular wall of the heart. The blood running through these capillaries is supplied by the coronary arteries, which branch off the aorta, close to the semilunar valve. The blood brought by the coronary arteries brings nutrients. It also brings oxygen for aerobic cell respiration, which provides energy for cardiac muscle contraction.

Valves in the heart ensure circulation of blood by preventing back-flow. The atria are collecting chambers and the ventricles are pumping chambers.

STRUCTURE OF THE HEART



THE CARDIAC CYCLE

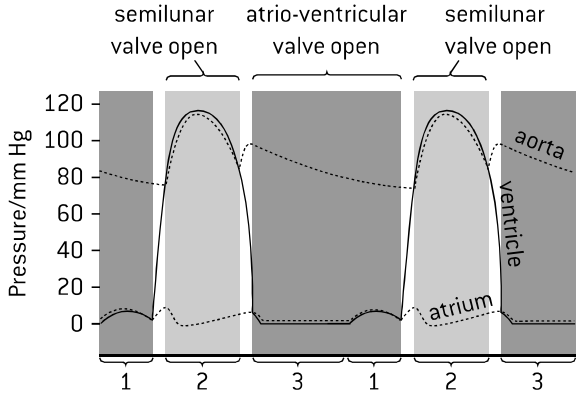
The beating of the heart consists of a cycle of actions:

1. The walls of the atria contract, pushing blood from the atria into the ventricles through the atrio-ventricular valves, which are open. The semilunar valves are closed, so the ventricles fill with blood.
2. The walls of the ventricles contract powerfully and the blood pressure rapidly rises inside them. This first causes the atrio-ventricular valves to close, preventing back-flow to the atria and then causes the semilunar valves to open, allowing blood to be pumped out into the arteries. At the same time the atria start to refill by collecting blood from the veins.
3. The ventricles stop contracting so pressure falls inside them. The semilunar valves close, preventing back-flow from the arteries to the ventricles. When the ventricular pressure drops below the atrial pressure, the atrio-ventricular valves open. Blood entering the atrium from the veins then flows on to start filling the ventricles.

   The next cardiac cycle begins when the walls of the atria contract again.

PRESSURES IN THE CARDIAC CYCLE

The graph below shows pressure changes in the left atrium, the left ventricle and the aorta during the cardiac cycle.



The numbered brackets indicate the three phases of the cardiac cycle described (left).

CONTROL OF HEART RATE

One region of specialized cardiac muscle cells in the wall of the right atrium acts as the pacemaker of the heart by initiating each contraction. This region is called the **sinoatrial (SA) node**. The SA node sends out an electrical signal that stimulates contraction as it is propagated first through the walls of the atria and then through the walls of the ventricles.

Messages can be carried to the SA node by nerves and hormones.

- Impulses brought from the medulla of the brain by two nerves can cause the SA node to change the heart rate. One nerve speeds up the rate and the other slows it down.
- The hormone epinephrine increases the heart rate to help to prepare the body for vigorous physical activity.

CORONARY ARTERY DISEASE

Coronary artery disease is caused by fatty plaque building up in the inner lining of coronary arteries, which become occluded (narrowed). As this becomes more severe blood flow to cardiac muscle is restricted, causing chest pain. Minerals often become deposited in the plaque making it hard and rough. Various factors have been shown by surveys to be associated with coronary artery disease and are likely causes of it:

- high blood cholesterol levels
- smoking
- high blood pressure (hypertension)
- high blood sugar levels, usually due to diabetes
- genetic factors (thus a family history of the disease).

Defence against infectious disease

BARRIERS TO INFECTION

A **pathogen** is an organism or virus that causes disease. The skin and mucous membranes are the primary defence against pathogens, by forming a barrier preventing entry.

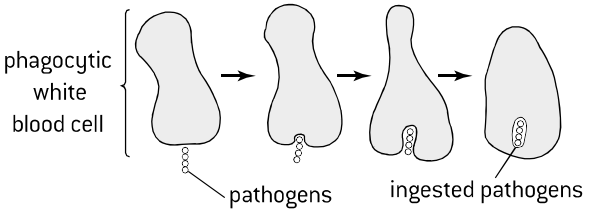
- The outer layers of the skin are tough and form a physical barrier. Sebaceous glands in the skin secrete lactic acid and fatty acids, which make the surface of the skin acidic. This prevents the growth of most pathogenic bacteria.
- Mucous membranes are soft areas of skin that are kept moist with mucus. Mucous membranes are found in the nose, trachea, vagina and urethra. Although they do not form a strong physical barrier, many bacteria are killed by lysozyme, an enzyme in the mucus. In the trachea pathogens tend to get caught in the sticky mucus; cilia then push the mucus and bacteria up and out of the trachea.

Despite these barriers, pathogens sometimes enter the body so other defences are needed. Two types of white blood cell fight infections in the body: **phagocytes** and **lymphocytes**.

PHAGOCYTES

Phagocytes ingest pathogens by endocytosis. The pathogens are then killed and digested inside the cell by enzymes from lysosomes. Phagocytes can ingest pathogens in the blood. They can also squeeze out through the walls of blood capillaries and move through tissues to sites of infection. They then ingest the pathogens causing the infection. Large numbers of phagocytes at a site of infection form pus.

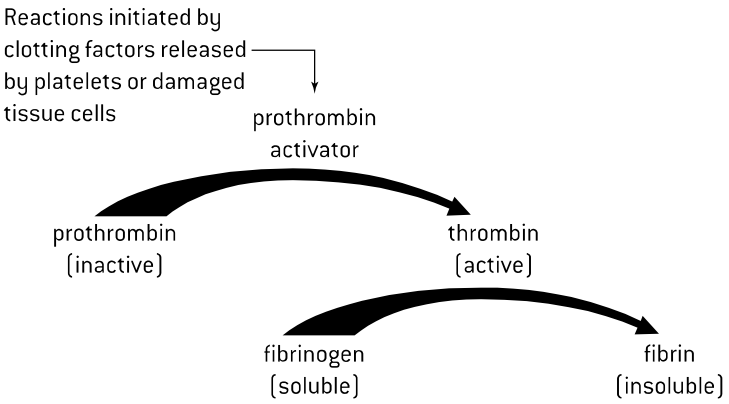
Phagocytes give us what is called **non-specific immunity** to diseases, because a phagocyte does not distinguish between pathogens – it ingests any pathogen if stimulated to do so.

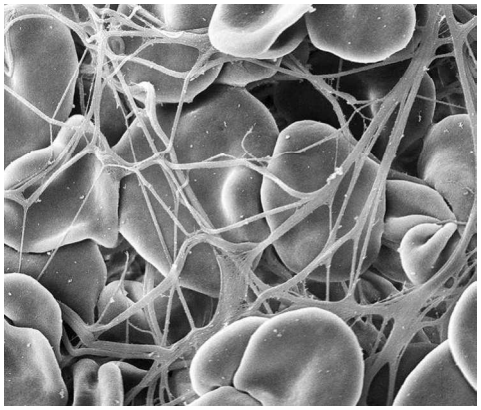


BLOOD CLOTTING

When the skin is cut and blood escapes from blood vessels, a semi-solid blood clot is formed from liquid blood to seal up the cut and prevent entry of pathogens. Platelets have an important role in clotting. Platelets are small cell fragments that circulate with red and white blood cells in blood plasma. The clotting process begins with the release of clotting factors either from damaged tissue cells or from platelets. These clotting factors set off a cascade of reactions in which the product of each reaction is the catalyst of the next reaction.

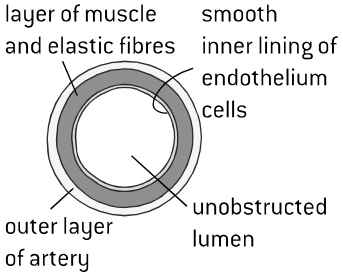
This system helps to ensure that clotting only happens when it is needed and also makes it a very rapid process. In the last reaction fibrinogen, a soluble plasma protein, is altered by the removal of sections of peptide that have many negative charges. This allows the remaining polypeptide to bind to others, forming long protein fibres called fibrin. Fibrin forms a mesh of fibres across wounds. Blood cells are caught in the mesh and soon form a semi-solid clot. If exposed to air the clot dries to form a protective scab, which remains until the wound has healed.

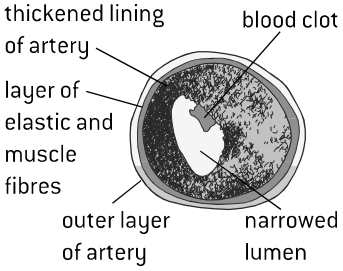




BLOOD CLOTS IN CORONARY ARTERIES

If the deposits of plaque in coronary arteries rupture, blood clots form (**coronary thrombosis**), which may completely block the artery. The consequence of this is that an area of cardiac muscle receives no oxygen and so stops beating in a coordinated way. This is often called a **heart attack**. Uncoordinated contraction of cardiac muscle is **fibrillation**. Sometimes the heart recovers and starts beating again, but severe heart attacks can be fatal as contractions of the heart stop completely.

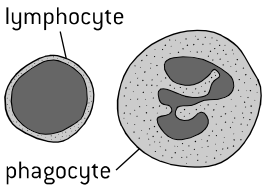




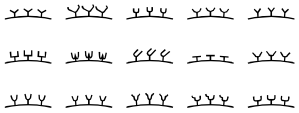
Antibodies and antibiotics

PRODUCTION OF ANTIBODIES

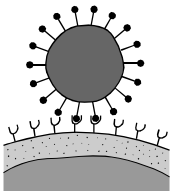
① Antibodies are made by lymphocytes, one of the two main types of white blood cell. Antigens are foreign substances that stimulate the production of antibodies.



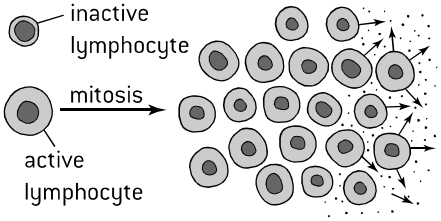
② A lymphocyte can only make one type of antibody so a huge number of different lymphocyte types is needed. Each lymphocyte puts some of the antibody that it can make into its cell surface membrane with the antigen-combining site projecting outwards.



③ When a pathogen enters the body, its antigens bind to the antibodies in the cell surface membrane of one type of lymphocyte.



④ When antigens bind to the antibodies on the surface of a lymphocyte, this lymphocyte become active and divides by mitosis to produce a clone of many identical cells.

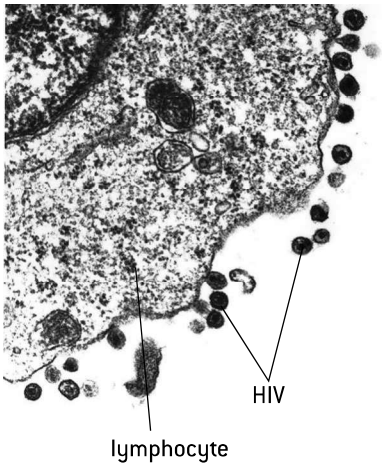


⑤ The cells produced by mitosis are plasma cells. They produce large quantities of the same antibody. The antibody binds to the antigens on the surface of the pathogen and stimulates its destruction. Production of antibodies by lymphocytes is known as specific immunity, because different antibodies are needed to defend against different pathogens. After an infection has been cleared from the body, most of the lymphocytes used to produce the antibodies disappear, but some persist as memory cells. These memory cells can quickly reproduce to form a clone of plasma cells if a pathogen carrying the same antigen is re-encountered.

HIV AND THE IMMUNE SYSTEM

HIV (human immunodeficiency virus) infects a type of lymphocyte that plays a vital role in antibody production. Over a period of years these lymphocytes are gradually destroyed. Without active lymphocytes, antibodies cannot be produced. This condition is called **AIDS (acquired immunodeficiency syndrome)** and, if untreated, leads to death from infections by a variety of pathogens that would normally be controlled easily.

HIV does not survive for long outside the body and cannot easily pass through the skin. Transmission involves the transfer of body fluids from an infected person to an uninfected one:



- Through small cuts or tears in the vagina, penis, mouth or intestine during vaginal, anal or oral sex.
- In traces of blood on hypodermic needles shared by intravenous drug abusers.
- Across the placenta from a mother to a baby, or through cuts during childbirth or in milk during breast-feeding.
- In transfused blood or with blood products such as Factor VIII used to treat hemophiliacs.

ANTIBIOTICS

Antibiotics are chemicals produced by microorganisms, to kill or control the growth of other organisms. For example, *Penicillium* fungus produces penicillin to kill bacteria. Antibiotics work by blocking processes that occur in prokaryotic cells but not eukaryotic cells. There are many differences between human and bacterial cells and each antibiotic blocks one of these processes in bacteria without causing any harm in humans.

Viruses lack a metabolism and instead rely on a host such as a human cell to carry out metabolic processes. It is not possible to block these processes using an antibiotic without also harming the human cells. For this reason viral diseases cannot be treated with antibiotics.

Most bacterial diseases in humans can be treated successfully with antibiotics, but some strains of bacteria have acquired genes that confer resistance to an antibiotic and some strains of bacteria now have multiple resistance.

TESTING PENICILLIN

Penicillin was developed as an antibiotic by Florey and Chain in the late 1930s. Their first test was on eight mice infected with a bacterium that causes a fatal pneumonia. All the four treated mice recovered but the untreated mice died. Initially they only had small quantities of relatively impure penicillin. They tested these on a man that was close to death from a bacterial infection. He started to recover but the antibiotic ran out. Five patients were then tested, all of whom were cured.

Florey and Chain's research would not be regarded as safe enough today. Extensive animal testing of new drugs is first done to check for harmful effects. After this small and then larger doses are tested on healthy, informed humans to see if the drug is tolerated. Only then is the drug tested on patients with the disease and if small scale trials suggest that it is effective, larger scale double-blind trials are carried out on patients to test the drug's effectiveness and look for rare side effects.

Ventilation

THE NEED FOR VENTILATION

Cell respiration happens in the cytoplasm and mitochondria and releases energy in the form of ATP for use inside the cell.

In humans, oxygen is used in cell respiration and carbon dioxide is produced. Humans therefore must take in oxygen from their surroundings and release carbon dioxide.

This process of swapping one gas for another is called **gas exchange**. It happens by diffusion in the alveoli of human lungs, so it depends on concentration gradients of oxygen and carbon dioxide between the air in the alveoli and blood flowing in the adjacent capillaries. To maintain these concentration gradients, the air in the alveoli must be refreshed frequently. The process of bringing fresh air to the alveoli and removing stale air is called **ventilation**.

The diagram of the ventilation system shows how air is carried to and from the alveoli in the trachea, bronchi and bronchioles.

MONITORING VENTILATION IN HUMANS

Ventilation rate is the number of inhalations or exhalations per minute.

Tidal volume is the volume of air taken in or out with each inhalation or exhalation. By monitoring ventilation rate and tidal volume at rest and then during mild and vigorous exercise the effect of ventilation can be investigated.

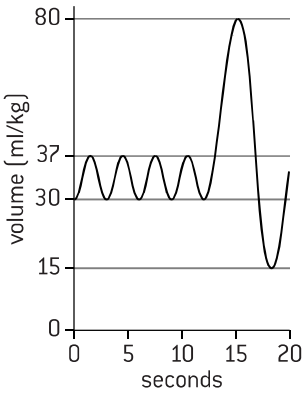
1. **Monitoring ventilation rate**

This can be done by simple observation or using 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 chest belt due to chest expansions.
- The ventilation rate can be deduced and also the relative size of ventilations but not the absolute size.

2. **Monitoring tidal volumes**

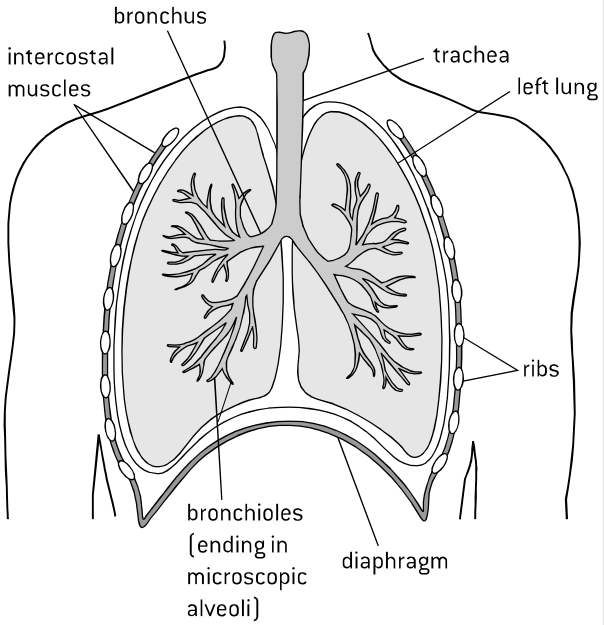
Tidal volumes are measured using a **spirometer**. Simple spirometers can be made using a bell jar, with volumes marked on it, placed in a pneumatic trough. A tube is used to breathe out into the bell jar so the expired volume can be measured. There are many designs of electronic spirometer that doctors use.



The graph (right) shows the type of data that is generated by monitoring ventilation with a spirometer. Tidal volume is deduced by how much the lung volume increases or decreases with each ventilation. Ventilation rate is deduced by counting the number of ventilations in a period on the graph and measuring the time period using the *x*-axis of the graph.

$$\text{Rate} = \frac{\text{number of ventilations}}{\text{time}}$$

THE VENTILATION SYSTEM



VENTILATION OF THE LUNGS

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. Muscles that cause the opposite movement from each other are **antagonistic muscles**.

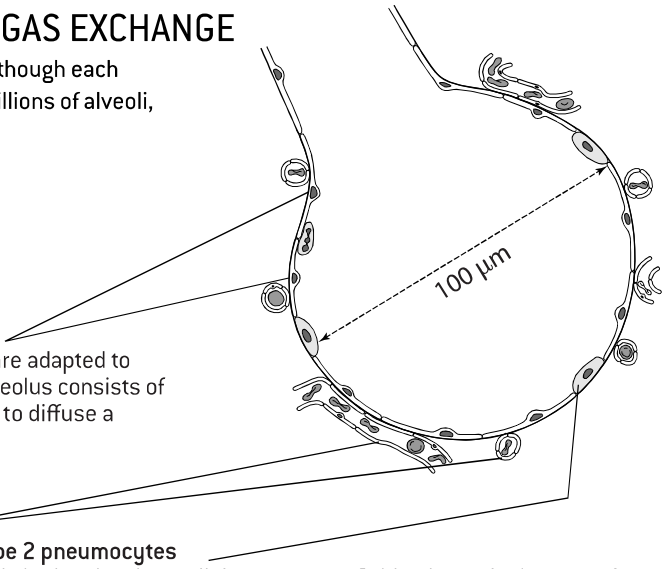
Inhaling	Exhaling
• The external intercostal muscles contract, moving the ribcage up and out	• The internal intercostal muscles contract, moving the ribcage down and in
• The diaphragm contracts, becoming flatter and moving down	• The abdominal muscles contract, pushing the diaphragm up into a dome shape
• These muscle movements increase the volume of the thorax	• These muscle movements decrease the volume of the thorax
• The pressure inside the thorax therefore drops below atmospheric pressure	• The pressure inside the thorax therefore rises above atmospheric pressure
• Air flows into the lungs from outside the body until the pressure inside the lungs rises to atmospheric pressure	• Air flows out from the lungs to outside the body until the pressure inside the lungs falls to atmospheric pressure

Gas exchange

ADAPTATIONS OF AN ALVEOLUS FOR GAS EXCHANGE

Gas exchange surfaces have four properties (below). Although each alveolus is very small, the lungs contain hundreds of millions of alveoli, giving a huge overall surface area for gas exchange.

- permeable to oxygen and carbon dioxide
- a large surface area for diffusion
- thin, so the distance for diffusion is small
- moist, so oxygen can dissolve



Type 1 pneumocytes
Extremely thin and permeable alveolar cells that are adapted to carry out gas exchange. Most of the wall of the alveolus consists of a single layer of these thin cells. Gases only have to diffuse a very short distance to pass through them.

Blood capillaries
The alveolus is covered by a dense network of blood capillaries with low oxygen and high carbon dioxide concentrations. Oxygen therefore diffuses from the air in the alveolus to the blood and carbon dioxide diffuses in the opposite direction.

Type 2 pneumocytes
Cells in the alveolus wall that secrete a fluid to keep the inner surface of the alveolus moist and allow gases to dissolve. The fluid also contains a natural detergent (surfactant), to prevent the sides of the alveoli from sticking together by reducing surface tension.

LUNG CANCER

Epidemiology is the study of the incidence and causes of disease. Surveys are used to look for correlations between disease rates and factors that could be implicated. Correlation does not prove causation but careful analysis can show whether a factor actually causes a disease. The five main causes of lung cancer are these:

- **Smoking** – tobacco smoke contains many mutagens that cause tumours to develop. Smoking causes nearly 90% of lung cancer cases.
- **Passive smoking** – exhaled breath from smokers passes carcinogens on to others, both children and other adults. Smoking bans are reducing this.
- **Air pollution** – the many sources include diesel exhaust fumes, nitrogen oxides from vehicles and smoke from wood and coal fires.
- **Radon gas** – in some areas it leaks out of rocks, especially granite.
- **Asbestos and silica** – dust from these materials causes cancer if deposited in the lungs.

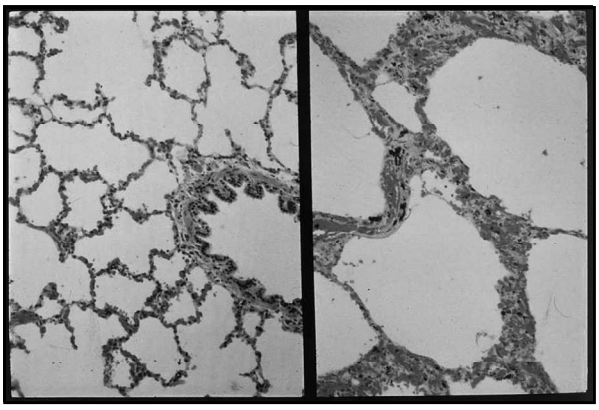
The consequences of lung cancer are:

- difficulties with breathing
- persistent coughing
- coughing up blood
- general fatigue
- chest pain
- loss of appetite
- weight loss

Lung cancer is usually fatal as it is only discovered at a late stage when the primary tumour is large and secondary tumours have already developed elsewhere in the body.

EMPHYSEMA

The main causes of emphysema are smoking and air pollution. Cilia that line the airways and expel mucus are damaged and cease to function, so mucus builds up in the lungs, causing infections. Toxins in cigarette smoke and polluted air cause inflammation and damage to the white blood cells that fight infections in the lungs. A protease (trypsin) is released from inflamed cells and damaged white blood cells. This enzyme digests elastic fibres in the lungs and eventually causes complete breakdown of alveolus walls. Microscopic alveoli (below left) are replaced by progressively larger air sacs with thicker, less permeable walls (below right).

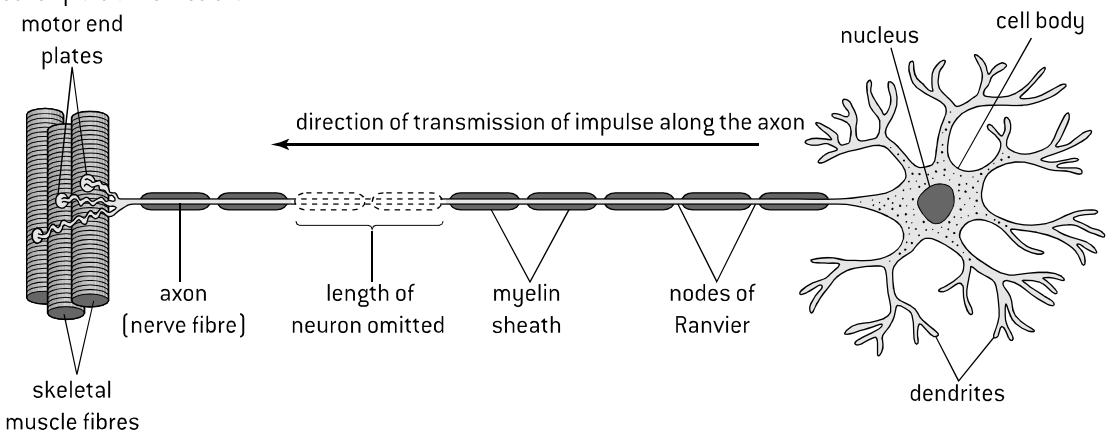


Emphysema is a chronic and progressive disease with serious consequences. The surface area for gas exchange reduces so the oxygen saturation of the blood falls and exercise is more and more difficult. The lungs lose their elasticity, making it increasingly difficult to exhale (shortness of breath). Mucus in the lungs causes coughing and wheezing.

Neurons and synapses

STRUCTURE AND FUNCTION OF NEURONS

The nervous system is composed of cells called **neurons**. These cells carry messages at high speed in the form of electrical impulses. Many neurons are very elongated and carry impulses long distances in a very short time. Myelinated nerve fibres have a myelin sheath with small gaps called **nodes of Ranvier**, allowing the nerve impulse to jump from node to node. This is known as **saltatory conduction** and speeds up the transmission.

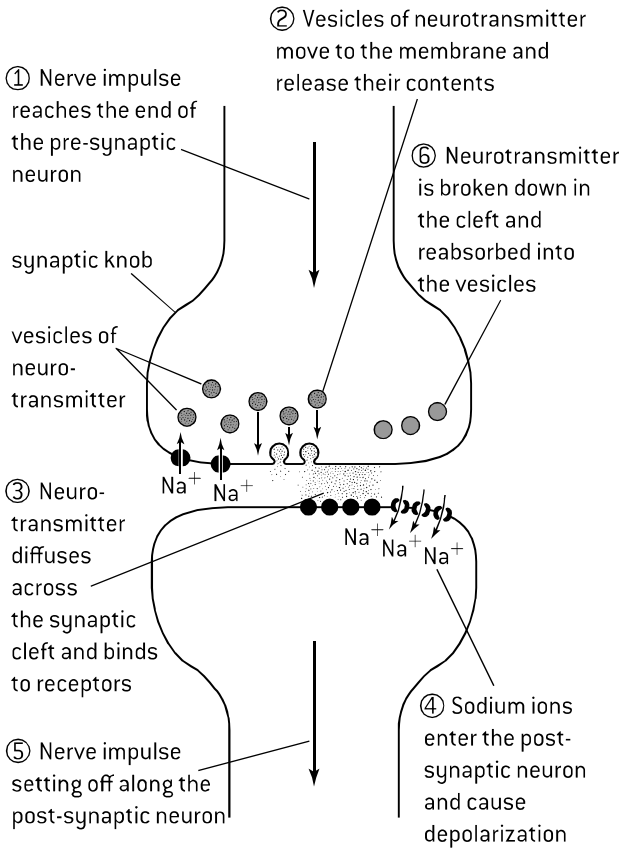


SYNAPSES

A **synapse** is a junction between two neurons or a junction between neurons and receptor or effector cells. The plasma membranes of the neurons are separated by a narrow fluid-filled gap called the synaptic cleft. Messages are passed across the synapse in the form of chemicals called neurotransmitters. The neurotransmitters always pass in the same direction from the pre-synaptic neuron to the post-synaptic neuron.

Many synapses function in the following way.

1. A nerve impulse reaches the end of the pre-synaptic neuron.
2. Depolarization of the pre-synaptic membrane causes vesicles of neurotransmitter to move to the pre-synaptic membrane and fuse with it, releasing the neurotransmitter into the synaptic cleft by **exocytosis**.
3. The neurotransmitter diffuses across the synaptic cleft and binds to receptors in the post-synaptic membrane.
4. The receptors are transmitter-gated sodium channels, which open when neurotransmitter binds. Sodium ions diffuse into the post-synaptic neuron. This causes depolarization of the post-synaptic membrane.
5. The depolarization passes on down the post-synaptic neuron as an action potential.
6. Neurotransmitter in the synaptic cleft is rapidly broken down, to prevent continuous synaptic transmission. The figure (right) shows the events that occur during synaptic transmission.



CHOLINERGIC SYNAPSES

Synapses do not all use the same neurotransmitter but many use **acetylcholine**. They are known as **cholinergic synapses**. The pre-synaptic neuron secretes acetylcholine into the synaptic cleft, which diffuses across the synapse and then binds to receptors in the post-synaptic membrane. The acetylcholine is broken down in the synaptic cleft by the enzyme **cholinesterase**, producing acetyl groups and choline. The choline is reabsorbed by the pre-synaptic neuron.

NEONICOTINOID PESTICIDES

Neonicotinoid pesticides bind to acetylcholine receptors in the post-synaptic membranes of cholinergic synapses in insects. Cholinesterase does not break down these pesticides so they remain bound to the receptors, preventing acetylcholine from binding. They therefore block synaptic transmission, which ultimately kills the insect. Unfortunately honeybees are killed along with insect pests that are the intended target of neonicotinoids.

Nerve impulses

RESTING POTENTIALS

A **resting potential** is the voltage (electrical potential) across the plasma membrane of a neuron when it is not conducting a nerve impulse. There are sodium–potassium pumps in the plasma membranes of axons. They pump sodium out and potassium in, by active transport. Concentration gradients of both sodium and potassium are established across the membrane. The inside of the neuron develops a net negative charge, compared with the outside, because of the presence of chloride and other negatively charged ions. There is therefore a potential (voltage) across the membrane. This is called the resting potential. A typical resting potential is −70mV.

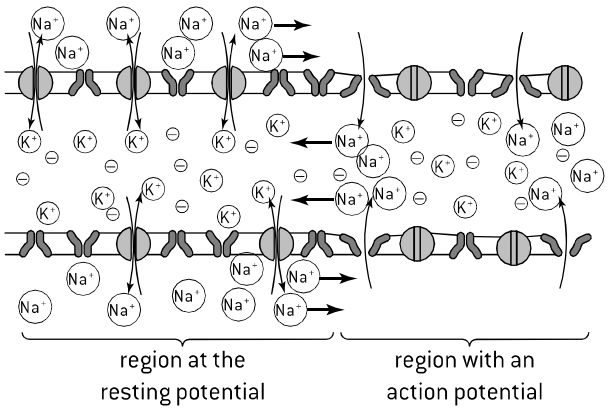
ACTION POTENTIALS

An **action potential** is the depolarization and repolarization of a neuron, due to facilitated diffusion of ions across the membrane through voltage-gated ion channels. If the potential across the membrane rises from −70 to −50 mV, voltage-gated sodium channels open and sodium ions diffuse in down the concentration gradient. The entry of positively charged sodium ions causes the inside of the neuron to develop a net positive charge compared to the outside – the potential across the membrane is reversed. This is **depolarization**.

The reversal of membrane polarity causes potassium channels to open, allowing potassium ions to diffuse out down the concentration gradient. The exit of positively charged potassium ions causes the inside of the neuron to develop a net negative charge again compared with the outside – the potential across the membrane is restored. This is **repolarization**.

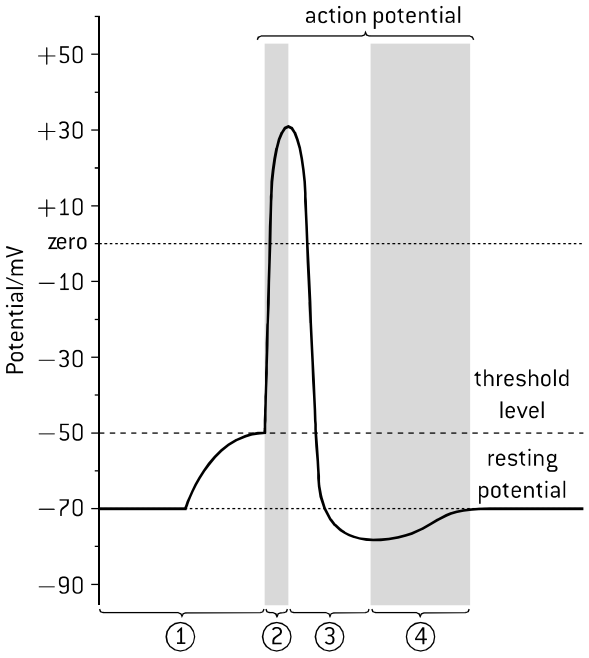
PROPAGATION OF NERVE IMPULSES

A nerve impulse is an action potential that travels along the axon of a neuron from one end to the other. There is an action potential whenever a part of the axon reaches the threshold potential of −50mV. An action potential in one part of the axon triggers an action potential in the next part. This is called the **propagation of the nerve impulse**. It is due to diffusion of sodium ions between a region with an action potential and the next region that is still at the resting potential. The diffusion of sodium ions along the axon, both inside and outside the membrane, is called **local currents**. It changes the voltage across the membrane from the resting potential of −70mV to the threshold potential of −50mV. This causes an action potential, because voltage-gated sodium channels open.



OSCILLOSCOPE TRACES

The changes in membrane potential in axons during an action potential can be measured using electrodes. The results are displayed on an oscilloscope. The figure below shows the type of trace that is obtained.



1. The axon membrane is at a resting potential of −70 mV and then rises to the threshold potential of −50 mV, either due to local currents or to the binding of a neurotransmitter at a synapse.
2. The membrane depolarizes due to voltage-gated Na^+ channels opening and Na^+ ions diffusing in.
3. The membrane repolarizes due to voltage-gated K^+ channels opening and K^+ ions diffusing out.
4. The membrane returns to the resting potential due to pumping of Na^+ ions out and K^+ ions in to the axon. This rebuilds concentration gradients of both types of ion, so another action potential could occur.

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.

This is an excellent example of cooperation and collaboration between groups of scientists, which is an important aspect of the nature of science.

Research breakthroughs are often made in science when different techniques are combined to solve a problem. Scientists from different disciplines meet and exchange ideas both within universities and research institutes and also at international conferences and symposia.

Regulating blood glucose and body temperature

BLOOD GLUCOSE CONCENTRATION

Blood glucose concentration is usually kept between 4 and 8 millimoles per dm^3 of blood. Cells in the pancreas monitor the concentration and secrete the hormones **insulin** or **glucagon** when the level is high or low.

Responses to high blood glucose levels

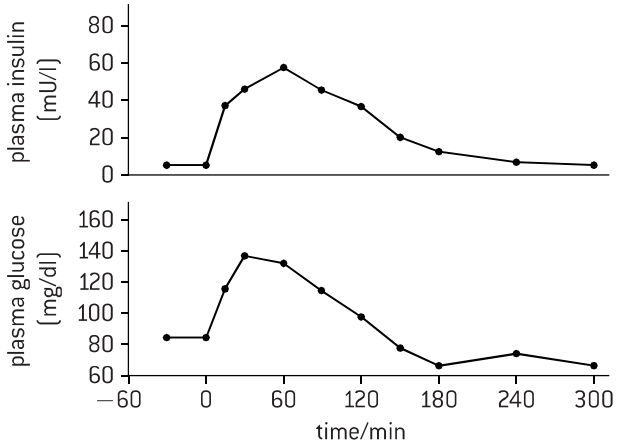
Insulin is secreted by β (beta) cells.

It stimulates the liver and muscle cells to absorb glucose and convert it to glycogen. Granules of glycogen are stored in these cells. Other cells are stimulated to absorb glucose and use it in cell respiration instead of fat. These processes lower the blood glucose level.

Responses to high blood glucose levels

Glucagon is secreted by α (alpha) cells.

It stimulates liver cells to break glycogen down into glucose and release the glucose. This raises the blood glucose level.



The graphs show the results of giving experimental subjects 75 g of glucose at time zero, after an overnight period of fasting.

DIABETES

In some people the control of blood glucose does not work effectively and the concentration can rise or fall beyond the normal limits. The full name for this condition is **diabetes mellitus**. There are two forms of this condition:

Type I diabetes

- The onset is usually during childhood.
- The immune system destroys β cells in the pancreas so the amount of insulin secreted becomes insufficient.
- Blood glucose levels have to be measured regularly and insulin injections, often before meals, are used to control glucose levels.
- Diet cannot by itself control this type of diabetes.

Type II diabetes

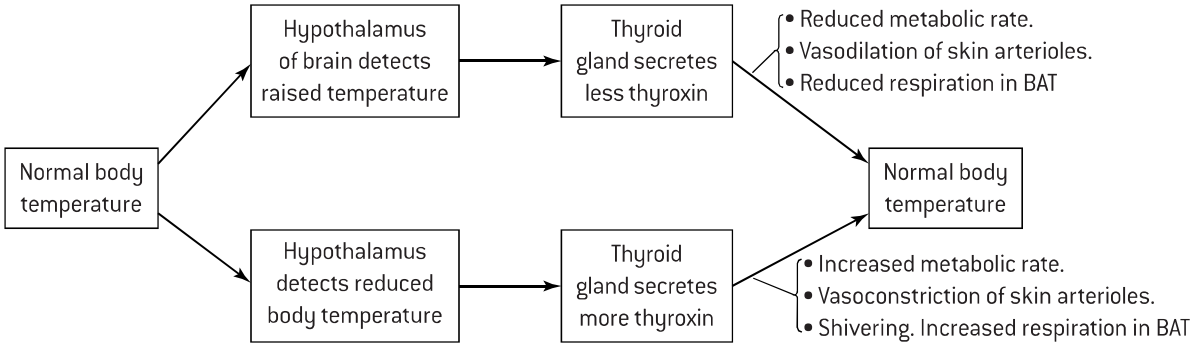
- The onset is usually after childhood.
- Target cells become insensitive to insulin, so insulin injections are not usually an effective treatment.
- Low carbohydrate diets can control the condition.
- Various risk factors increase the rate, particularly diets rich in fat and low in fibre, obesity due to over-eating and lack of exercise and genetic factors that affect fat metabolism.

THYROXIN

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 addition, thyroxin is implicated in heat generation by shivering and by uncoupled cell respiration in brown adipose tissue (BAT).

In a person with normal physiology, cooling triggers increased thyroxin secretion by the thyroid gland, which stimulates heat production. Recent research has also suggested that thyroxin causes constriction of vessels that carry blood from the core to the skin, reducing heat loss. Thyroxin thus regulates the metabolic rate and also helps to control body temperature.



Leptin and melatonin

LEPTIN AND OBESITY

A strain of mice was discovered in the 1950s that feed ravenously, become inactive and gain mass, mainly through increased **adipose tissue**. They grow to a body mass 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 discovered that the wild-type allele of this gene supported the synthesis of a new hormone. It was named **leptin**, and was also found in humans. Leptin is a protein hormone secreted by **adipose cells** (fat storage cells). If the amount of adipose tissue in the body increases, the concentration of leptin in the blood rises. 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 causing long-term **appetite inhibition** and reduced food intake.

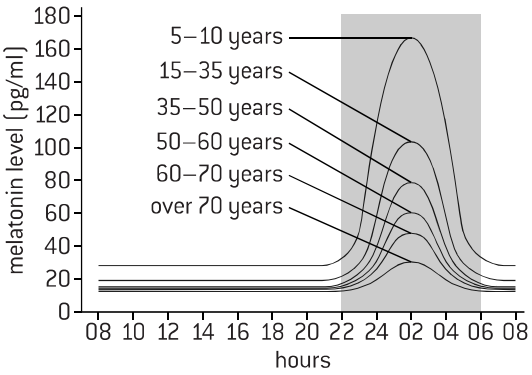
When *ob/ob* mice were injected with leptin their appetite declined, energy expenditure increased and body mass dropped by 30% in a month. Trials were therefore done to see if leptin injections would control obesity in humans. A large clinical trial was carried out. 73 obese volunteers injected themselves 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 the results of the group receiving the highest dose 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 because human physiology differs from that of mice and other rodents. Further research has shown that most cases of obesity in humans are due not to insufficient leptin secretion but to target cells in the hypothalamus being resistant to leptin. They therefore fail to respond to it, even at high concentrations. Injections of extra leptin therefore fail to control obesity in these patients.

Obesity in humans is only due to mutations in the leptin gene in a very small proportion of cases. Trials in these obese people have shown significant weight loss while the leptin injections are being given. However, leptin is a short-lived protein and has to be injected several times a day, so most patients offered this treatment have refused it.

MELATONIN AND JET LAG

Humans are adapted to live in a 24-hour cycle and have circadian rhythms in behaviour that fit this cycle. Ganglion cells in the retina detect whether it is light or dark and send impulses to the supra-chiasmatic nuclei (SCN) in the hypothalamus. Neurones in the SCN control secretion of the hormone melatonin by the pineal gland. Melatonin secretion increases in the evening and drops to a low level at dawn. As the hormone is rapidly removed from the blood by the liver, concentrations rise and fall rapidly after a change in secretion.



The graph shows that melatonin secretion declines with age, helping to explain how sleep patterns become more irregular as we grow older.

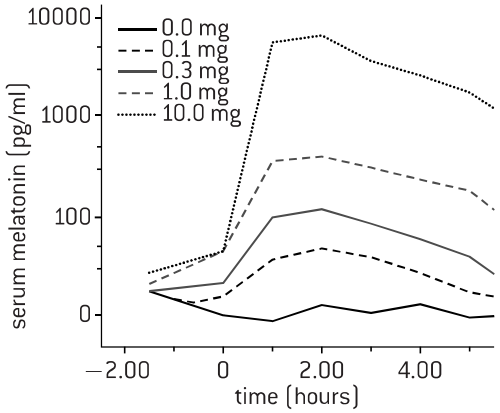
The body's circadian rhythms are disrupted by travelling rapidly between time zones. These symptoms are often experienced:

- sleep disturbance
- headaches
- fatigue
- irritability.

Together they are known as jet lag. They are caused by the SCN and pineal gland continuing to set a circadian rhythm to suit the timing of day and night at the point of departure rather than the destination. This only lasts for a few days, during which time impulses sent by ganglion cells to the SCN when they detect light help the body to adjust to the new regime.

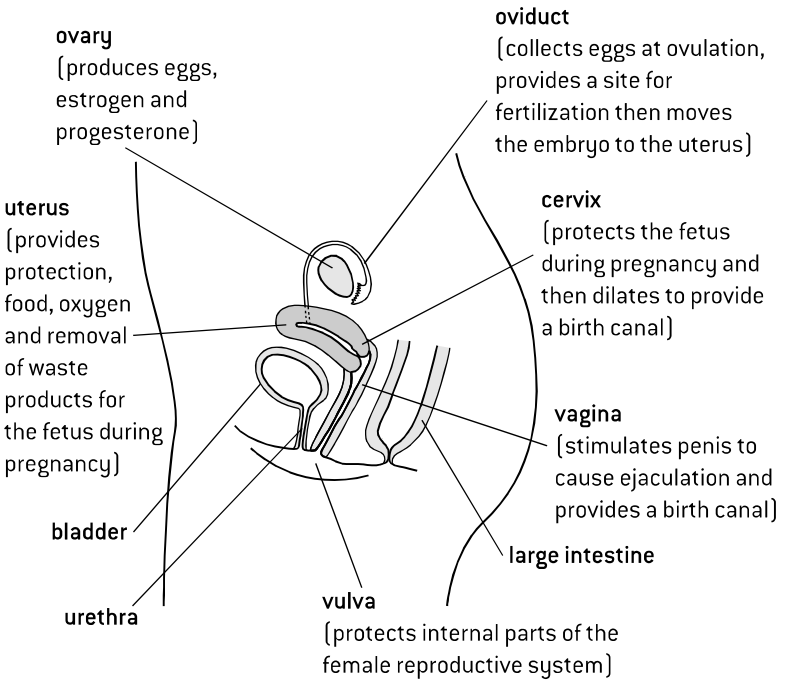
Melatonin is sometimes used to try to prevent or reduce jet lag. It is taken orally at the time when sleep should ideally be commencing. Most trials of melatonin have shown that it is effective at promoting sleep and helping to reduce jet lag, especially if flying eastwards and crossing five or more time zones.

The graph below shows blood plasma concentrations of melatonin in the hours after ingesting different doses at time zero.



Reproductive systems

THE FEMALE REPRODUCTIVE SYSTEM



SEX DETERMINATION

Human reproduction involves the fusion of a sperm and an egg. Embryos all initially develop in a similar way. Embryonic gonads are formed that could become either ovaries or testes. The presence or absence of a single gene (SRY) decides which developmental pathway is followed. This gene codes for TDF (testis determining factor), a gene regulation protein. By binding to specific DNA sites TDF stimulates the expression of genes for testis development.

SRY is located on the Y chromosome, so there are two possibilities for an embryo:

♂ SRY is present in an embryo if the sex chromosomes are XY. The embryonic gonads therefore develop into testes and the fetus becomes male.

♀ SRY is absent in an embryo if the sex chromosomes are XX. TDF is therefore not produced, so the embryonic gonads develop as ovaries and the fetus becomes female.

STEROID HORMONES

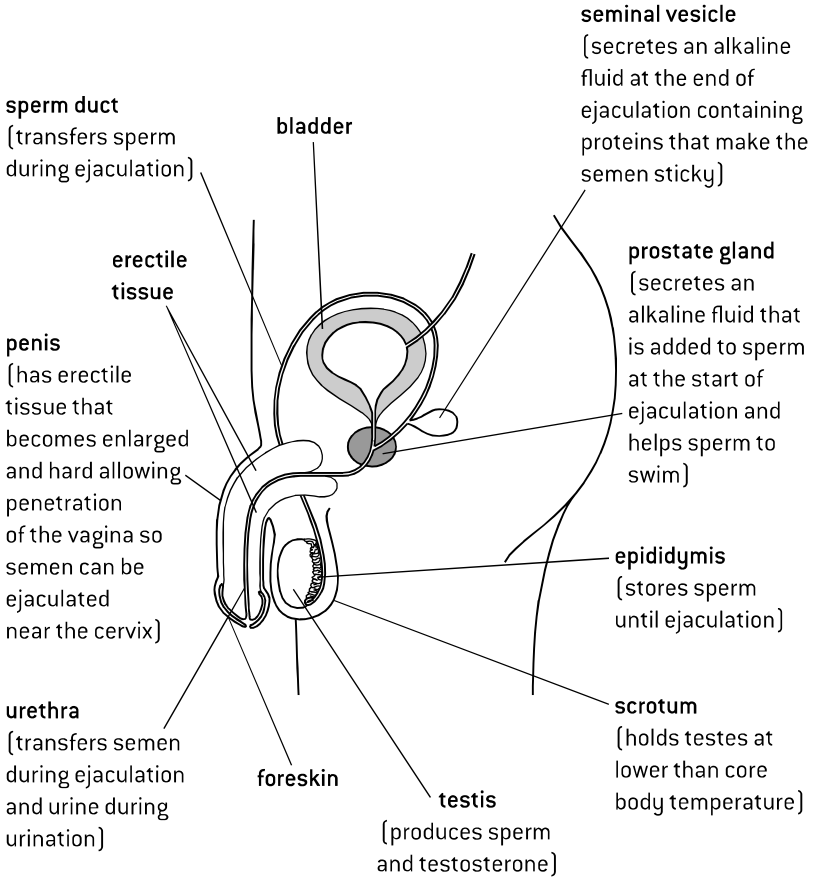
Testosterone, estrogen and progesterone are all steroids.

Testosterone is produced by developing testes in the fetus. It causes pre-natal development of male genitalia, including the penis, sperm duct and prostate gland. During puberty testosterone production increases. It stimulates development of male secondary sexual characteristics during puberty, including growth of the testes, penis and pubic hair. Testosterone also stimulates sperm production from puberty onwards.

Estrogen causes pre-natal development of female reproductive organs if testosterone is not present. These organs include the oviduct, uterus and vagina. Raised levels of estrogen during puberty cause development of female secondary sexual characteristics, including growth of breasts and pubic hair.

Progesterone prepares the uterus during the menstrual cycle for the implantation of an embryo and has important roles in supporting a pregnancy.

THE MALE REPRODUCTIVE SYSTEM



Conception and pregnancy

THE MENSTRUAL CYCLE

Between puberty and the menopause, women who are not pregnant follow a cycle called the menstrual cycle. This cycle is controlled by hormones FSH and LH, produced by the pituitary gland, and estrogen and progesterone, produced by the ovary. Both positive and negative feedback control is used in the menstrual cycle. During each menstrual cycle an **oocyte** (egg) matures inside a fluid-filled sac in the ovary called a **follicle**. The egg is released when the follicle bursts open during **ovulation**.

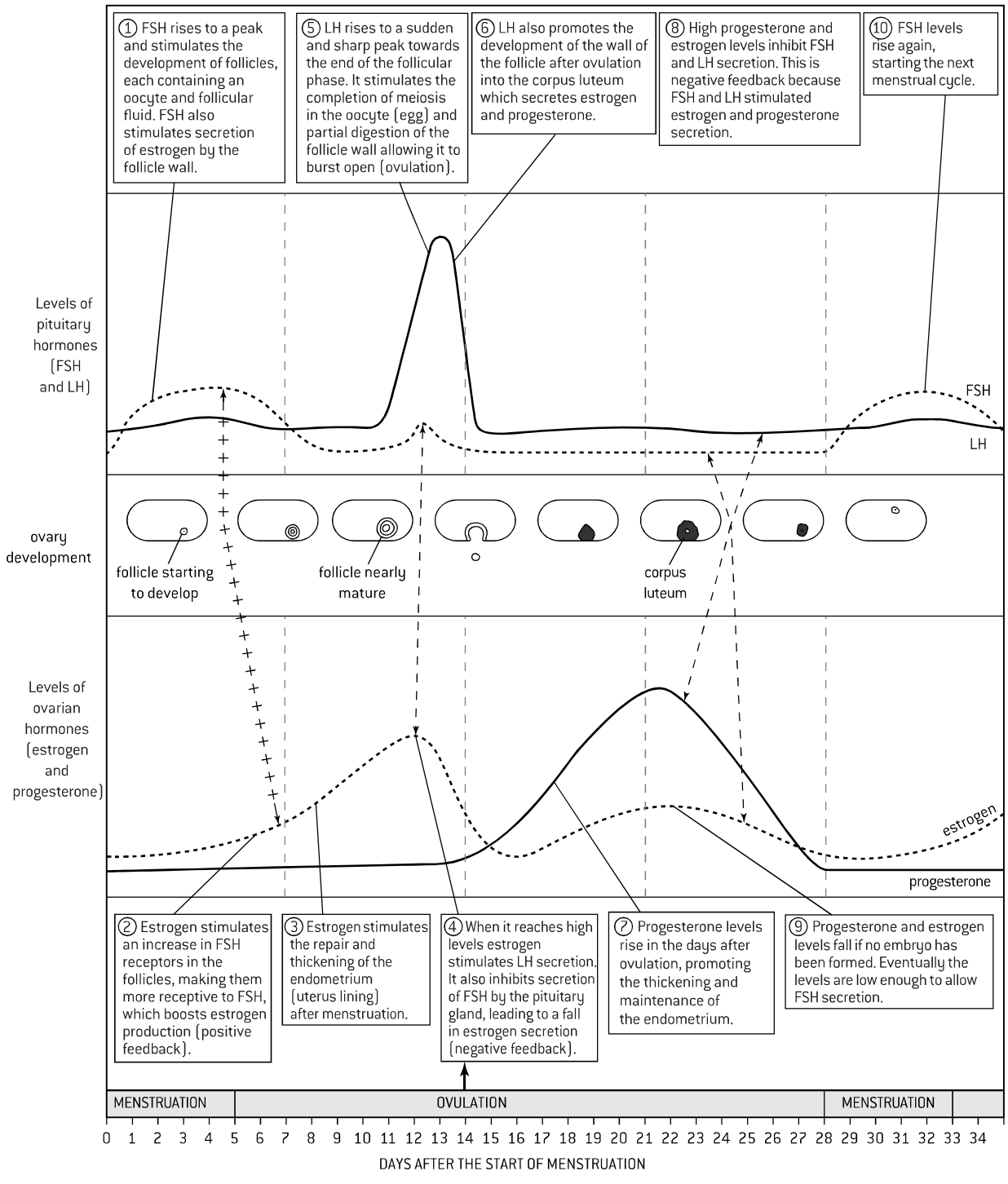
FEEDBACK CONTROL

In feedback systems, the level of a product feeds back to control the rate of its own production.

Negative feedback has a stabilizing effect because a change in levels always causes the opposite change. A rise in levels feeds back to decrease production and reduce the level. A decrease in levels feeds back to increase production and raise the level.

Positive feedback tends to lead to sudden rises or falls, because a rise causes further rises and a fall causes further falls.

STAGES OF THE MENSTRUAL CYCLE



Research into reproduction

IN VITRO FERTILIZATION

Pioneering research in the second half of the 20th century led to the development of **in vitro fertilization**, often abbreviated to IVF. It has been used extensively to overcome fertility problems in either the male or female parent. The following procedures are usually used:

1. **Down-regulation**

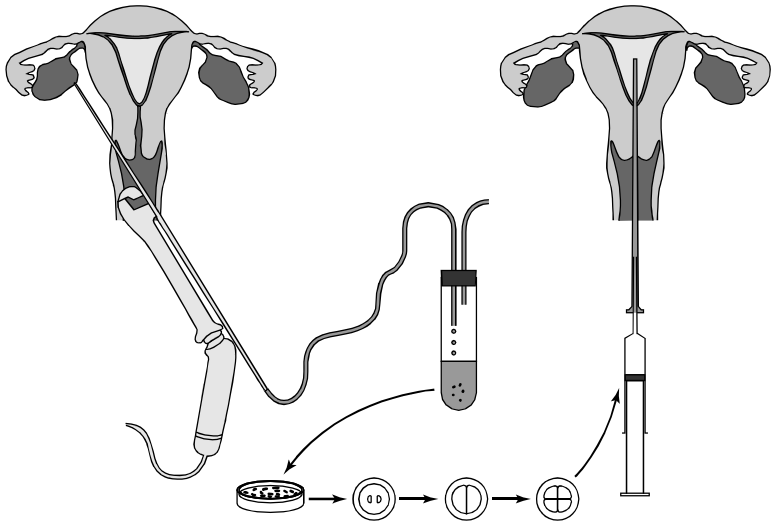
The woman takes a drug each day, usually as a nasal spray, to stop her pituitary gland secreting FSH or LH. Secretion of estrogen and progesterone therefore also stops. This suspends the normal menstrual cycle and allows doctors to control the timing and amount of egg production in the woman's ovaries.

2. **Artificial doses of hormones**

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 than during a normal menstrual cycle, so far more follicles develop than usual. Twelve is not unusual and there can be as many as twenty follicles. This stage of IVF is therefore called superovulation.

3. **Egg retrieval and fertilization**

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.



The diagrams above show egg retrieval from the ovaries, culture of eggs after in vitro fertilization and implantation of 4-cell embryos into the uterus.

4. **Establishing a pregnancy**

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.

HARVEY AND THE DISCOVERY OF SEXUAL REPRODUCTION

William Harvey's discovery of the circulation of blood in the 17th century shows that he was a brilliant research scientist and yet he made little progress in another area that interested him very much: reproduction in humans and other animals. 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 (copulation), but only found signs of anything developing in females two or more months after the start of the mating season.

He regarded his experiments with deer as proof that Aristotle's theory of reproduction was false, which it certainly is. However Harvey concluded that offspring cannot be the result of mating, which is also false. The problem for Harvey was that the gametes, the process of fertilization and early stages of embryo development are too small to see with the naked eye or a hand lens, and effective microscopes were not available when he was working. An effective microscope was not invented until 17 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. He was unlucky in his choice of experimental animal because embryos in the deer that he used remain microscopically small for an unusually long period.

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.