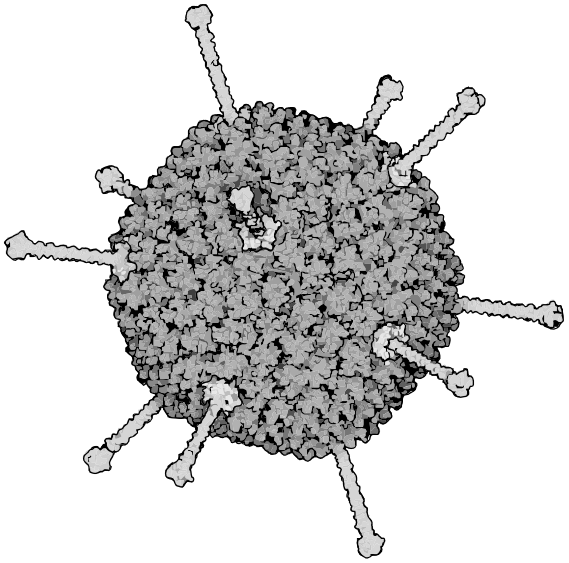
Antigens and allergy

SUBSTANCES ON CELL SURFACES

All living organisms have proteins and other substances in the plasma membranes on the surface of their cells, especially proteins. Some organisms have a cell wall outside their plasma membranes made of polysaccharides or other substances. There is so much variety in the types of substance on the surfaces of cells that every species has unique molecules.

Viruses are not considered living organisms and are not composed of cells, but they also have unique molecules on their surface. The surface of most viruses is a protein coat (capsid). The capsid of some viruses is enveloped in a membrane taken from the plasma membrane of the host cell. The image below shows the capsid of an adenovirus.



Unique surface molecules are used in several ways:

- viruses recognize and bind to their host using molecules on the surface of the host's cells
- living organisms recognize their own cells and cell types using surface molecules
- living organisms recognize cells that are not part of the organism and also viruses by surface molecules that are not present in that organism (foreign). These molecules trigger the production of antibodies, so they are **antigens**.

HOST SPECIFICITY OF PATHOGENS

Some pathogens are species-specific and only infect members of a single species.

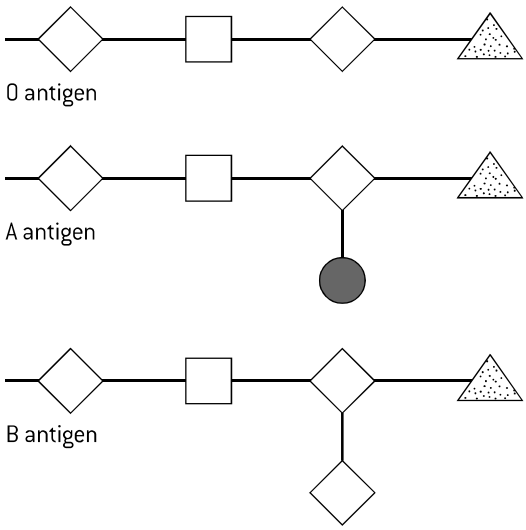
Examples:
Polio, measles and syphilis only affect humans.

Other pathogens can cross species barriers, so can be transmitted from infected members of one species to uninfected members of another species.

Examples:
Tuberculosis can infect both cattle and badgers and can pass in milk from cattle to infect humans; rabies can pass from infected dogs to humans. A disease that can be passed to humans from other animals is called a **zoonosis**.

ANTIGENS ON RED BLOOD CELLS

The ABO blood groups system is based on the presence or absence of a group of glycoproteins in the membranes of red blood cells. Glycoproteins in this group cause antibody production if a person does not naturally possess them, so they are known as antigens. O, A and B antigens are three different versions of the glycoprotein. The O antigen is always present. The A antigen is made by adding an N-acetyl-galactosamine molecule to the O antigen, and the B antigen is made by adding galactose.



Blood group	Antigens present	Antigens that cause antibody production
O	O	A or B (A, B or AB blood)
A	O and A	B (B or AB blood)
B	O and B	A (A or AB blood)
AB	O, A and B	None

HISTAMINE AND ALLERGIES

Two types of cell in the body secrete histamine:

- **basophils**, which are a type of white blood cell
- **mast cells**, which are similar to basophils but are found in connective tissue.

Histamine is secreted in response to local infection and causes the dilation of the small blood vessels in the infected area. The vessels become leaky, increasing the flow of fluid containing immune components to the infected area and allowing these components to leave the blood vessel, resulting in both specific and non-specific immune responses.

Allergies are reactions by the immune system to substances in the environment that are normally harmless, such as pollen, bee stings or specific foods, for example peanuts. Substances in these allergens cause over-activation of basophils and mast cells and therefore excessive secretion of histamine. This causes the symptoms associated with allergies: inflammation of tissues, itching, mucus secretion and sneezing. Histamine is also implicated in the formation of allergic rashes and in the dangerous swelling known as anaphylaxis. To lessen the effects of allergic responses, anti-histamine drugs can be used.

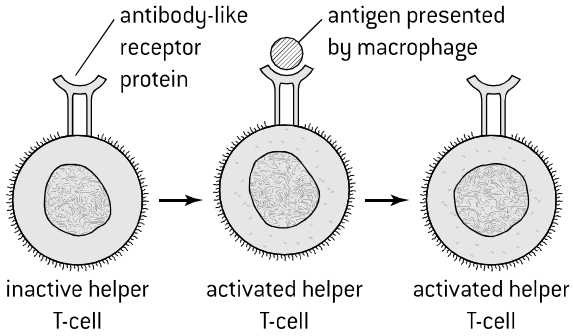
Antibody production

STAGES IN ANTIBODY PRODUCTION

The production of antibodies by the immune system is one of the most remarkable biological processes. When a pathogen invades the body, the immune system gears up to produce large amounts of the specific antibodies needed to combat the pathogen. This process only takes a few days. The production of antibodies by B-cells is shown in a simplified form in Topic 6 and is explained more fully here.

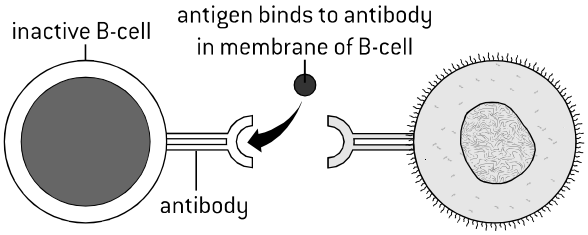
1. **Activation of helper T-cells**

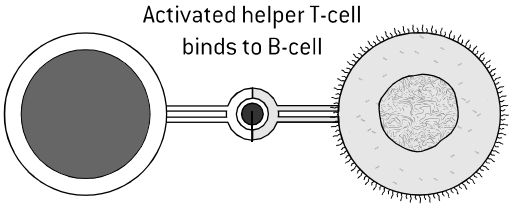
   Helper T-cells have antibody-like receptor proteins in their plasma membrane to which one specific antigen can bind. When the antigen binds, the helper T-cell is activated. The antigen is brought to the helper T-cell by a macrophage – a type of phagocytic white blood.

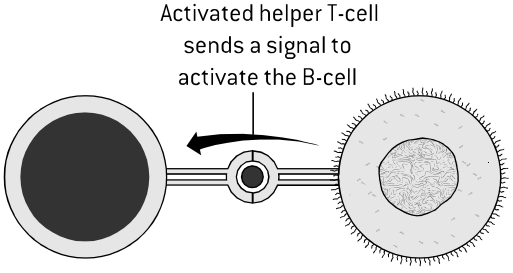


2. **Activation of B-cells**

   Inactive B-cells have antibodies in their plasma membrane. If these antibodies match an antigen, the antigen binds to the antibody. An activated helper T-cell with receptors for the same antigen can then bind to the B-cell. The activated helper T-cell sends a signal to the B-cell, activating it.

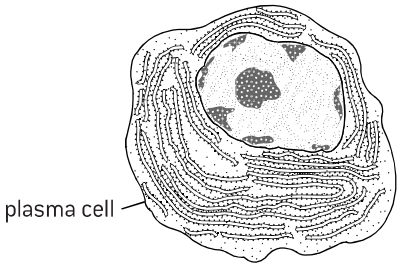






3. **Production of plasma cells**

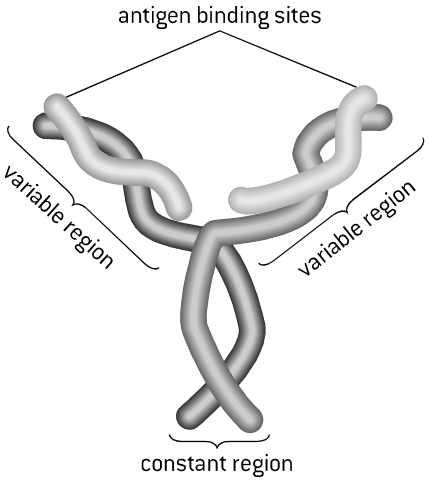
   Activated B-cells start to divide by mitosis to form a clone of cells. These cells become active, with a much greater volume of cytoplasm. They are then known as plasma cells. They have a very extensive network of rough endoplasmic reticulum. This is used for synthesis of large amounts of antibody, which is then secreted by exocytosis.



4. **Production of memory cells**

   Memory cells are B-cells and T-cells that are formed at the same time as activated helper T-cells and B-cells, when a disease challenges the immune system. After the activated cells and the antibodies produced to fight the disease have disappeared, the memory cells persist and allow a rapid response if the disease is encountered again. Memory cells give long-term immunity to a disease.

THE ROLE OF ANTIBODIES



The diagram (above) shows the structure of an antibody molecule (an immunoglobulin). The tips of the variable region are the antigen binding sites. The constant region is the part of the molecule that aids the destruction of the pathogen.

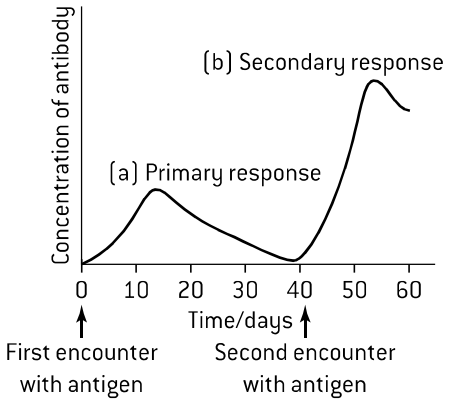
There are different versions of the constant region, which use different tactics to destroy the pathogen. Five are outlined here:

- making a pathogen more recognizable to phagocytes so they are more readily engulfed.
- preventing viruses from docking to host cells
- neutralizing toxins produced by pathogens
- binding to the surface of a pathogen cell and bursting it by causing the formation of pores
- sticking pathogens together (agglutination) so they cannot enter host cells and phagocytes can ingest them more easily.

Vaccination and monoclonal antibodies

VACCINATION

Vaccines contain antigens that trigger immunity to a disease without actually causing the disease in the person who is vaccinated. Most vaccines contain weakened or killed forms of the pathogens. Some vaccines just contain the chemical that acts as the antigen. The vaccine is either injected into the body or sometimes swallowed. The principle of vaccination is that antigens in the vaccine cause the production of the antibodies needed to control the disease. Sometimes two or more vaccinations are needed to stimulate the production of enough antibodies. The figure (right) shows a typical response to a first and second vaccination against a disease. The first vaccination causes a little antibody production and the production of some memory cells. The second vaccination, sometimes called a booster shot, causes a response from the memory cells and therefore faster and greater production of antibodies. Memory cells produced as a result of vaccination should persist to give long-term immunity.



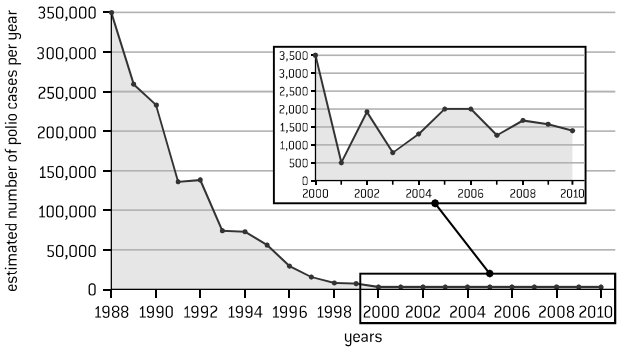
JENNER AND SMALLPOX VACCINATION

Smallpox was the first infectious disease of humans to have been eradicated by vaccination. This was done by a worldwide vaccination programme in the 1960s and 70s, with the last ever case of the disease in 1977. Smallpox was also the first disease for which a vaccine was tested on a human. In 1796 Edward Jenner deliberately infected an 8-year-old boy with cowpox using pus from a blister of a milkmaid with this disease. He then tried to infect the boy with smallpox, but found that he was immune. Cowpox is a less virulent disease caused by viruses similar enough to the smallpox virus for antibodies produced in response to cowpox to give immunity to smallpox. Jenner then tested his procedure on 23 other people including himself.

Today Jenner's tests would be considered ethically unacceptable as they involved a child too young to understand the dangers who could not therefore give informed consent, and he had not first done tests to find out if the vaccine had harmful side-effects.

ANALYSING EPIDEMIOLOGICAL DATA

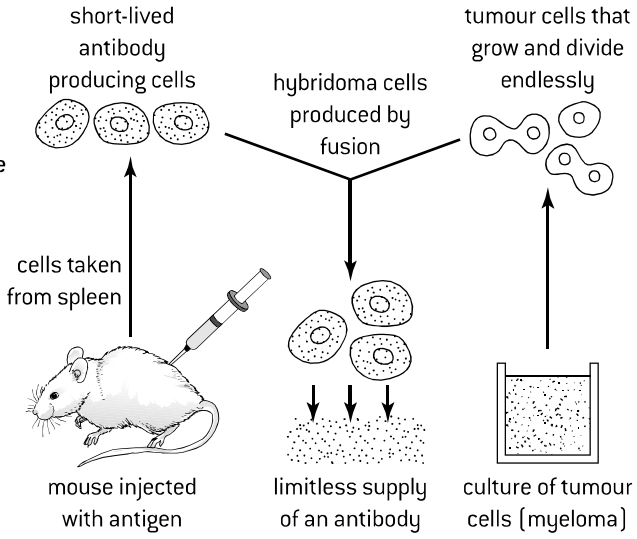
Epidemiology is the study of the distribution, patterns and causes of disease in a population. Epidemiological data can be used to help plan vaccination programmes, such as the programme aimed at eliminating polio. Cases are monitored carefully to find out where further vaccination is required to give the population immunity and prevent further spread of the disease.



PRODUCTION OF MONOCLONAL ANTIBODIES

Large quantities of a single type of antibody can be made using an ingenious technique. Antigens that correspond to a desired antibody are injected into an animal. Plasma cells producing the desired antibody are extracted from the animal. Tumour cells that grow and divide endlessly are obtained from a culture. The **plasma cells** are fused with the **tumour cells** to produce **hybridoma cells**, which divide endlessly to produce a clone of one specific type of hybridoma cell. The hybridoma cells are cultured and the antibodies that they produce are extracted and purified. The antibodies produced by this method are called **monoclonal antibodies** because they are all produced from one clone of hybridoma cells, so are identical.

Monoclonal antibodies are used in many different ways. One use is in pregnancy test kits. The urine of pregnant women contains hCG, a protein secreted by the developing embryo and later by the placenta. Pregnancy test kits contain monoclonal antibodies to which hCG binds. This causes a coloured band to appear, indicating that the hCG was present in the urine sample and the woman who produced the urine is pregnant.

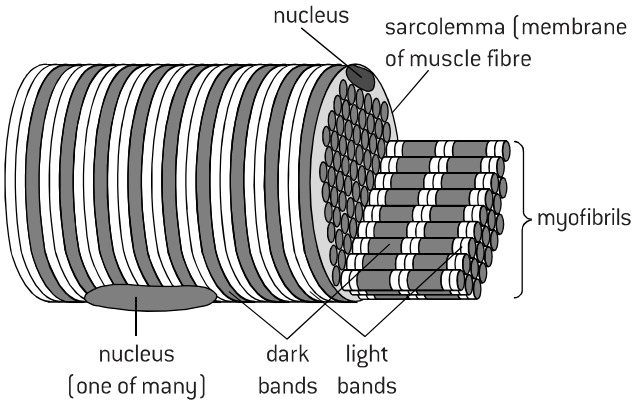


Muscle

STRUCTURE OF SKELETAL MUSCLE

Skeletal muscle is attached to bone and causes movement of animal bodies. It consists of large multinucleate cells called muscle fibres. Within each muscle fibre are cylindrical structures called **myofibrils** and around these is a specialized type of endoplasmic reticulum – the **sarcoplasmic reticulum**. There are also mitochondria between the myofibrils.

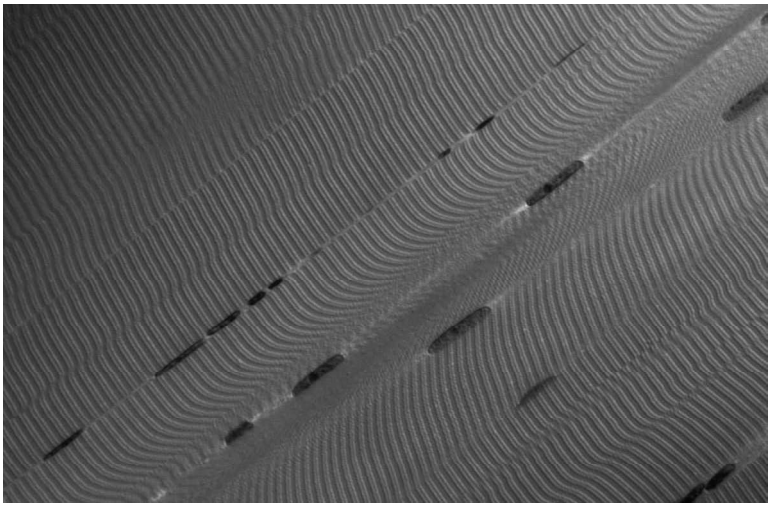
Myofibrils consist of repeating units called sarcomeres, which have light and dark bands. The light and dark bands extend across all the myofibrils in a muscle fibre, giving it a striated (striped) appearance. Each sarcomere is able to contract and exert force.



MEASURING SARCOMERE LENGTHS WITH LIGHT MICROSCOPES

The image on the right is a light micrograph of skeletal muscle fibres showing more than one nucleus per fibre and also light and dark bands. Use these instructions to measure the length of one sarcomere:

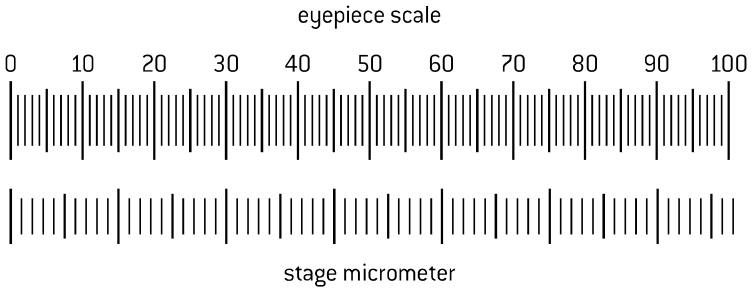
1. Measure the distance in millimetres from the start of one dark band to the start of a dark band ten bands away.
2. Divide by ten to find the length of one sarcomere in the micrograph.
3. Convert this length in millimetres to micrometres by multiplying by a thousand.
4. Find the actual length of a sarcomere by dividing this length by the magnification of the micrograph, which is 200×.



Sarcomere lengths can also be measured using a slide of skeletal muscle and a light microscope with an **eyepiece scale**. As in the method above, it is best to measure the length of ten or more sarcomeres and divide to find the length of one.

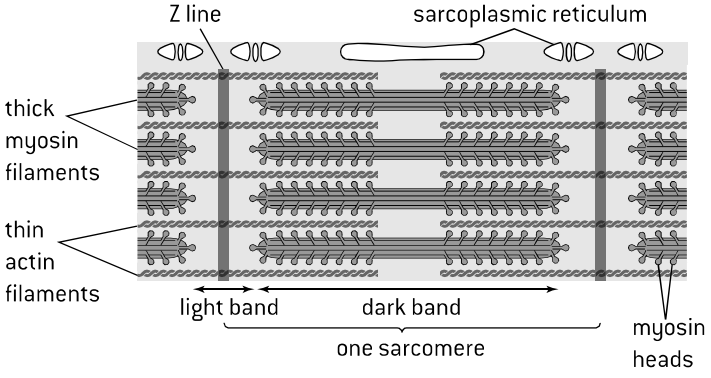
The eyepiece scale does not have units on it and must be **calibrated** using a slide that has an accurate scale of known lengths marked on it. This type of slide is called a **stage micrometer**.

Calibration shows how many micrometres each division of the eyepiece scale represents.



STRUCTURE OF A SARCOMERE

A sarcomere is a subunit of a myofibril. At either end is a Z line to which narrow actin filaments are attached. The actin filaments stretch inwards towards the centre of the sarcomere. Between them, there are thicker myosin filaments, which have heads that form cross-bridges by binding to the actin. The part of the sarcomere containing myosin is the dark band and the part containing only actin filaments is the light band. The figure (right) shows the structure of a sarcomere.

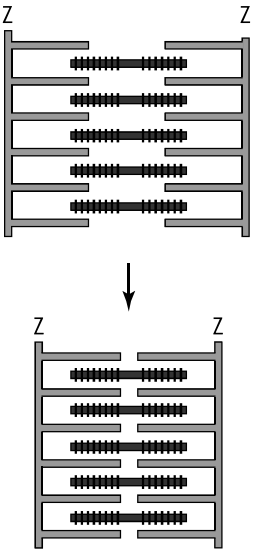


Muscle contraction

SLIDING FILAMENTS AND CONTRACTION

The contraction of the skeletal muscle is achieved by the **sliding of actin and myosin filaments** over each other. This pulls the ends of the sarcomeres together, making the muscle shorter.

The sliding of the filaments is an active process and requires the use of energy from **ATP**. The hydrolysis of one molecule of ATP provides enough energy for a myosin filament to slide a small distance along an actin filament. A repeated cycle of events is used to contract muscle sufficiently to move part of an animal body in the desired way.



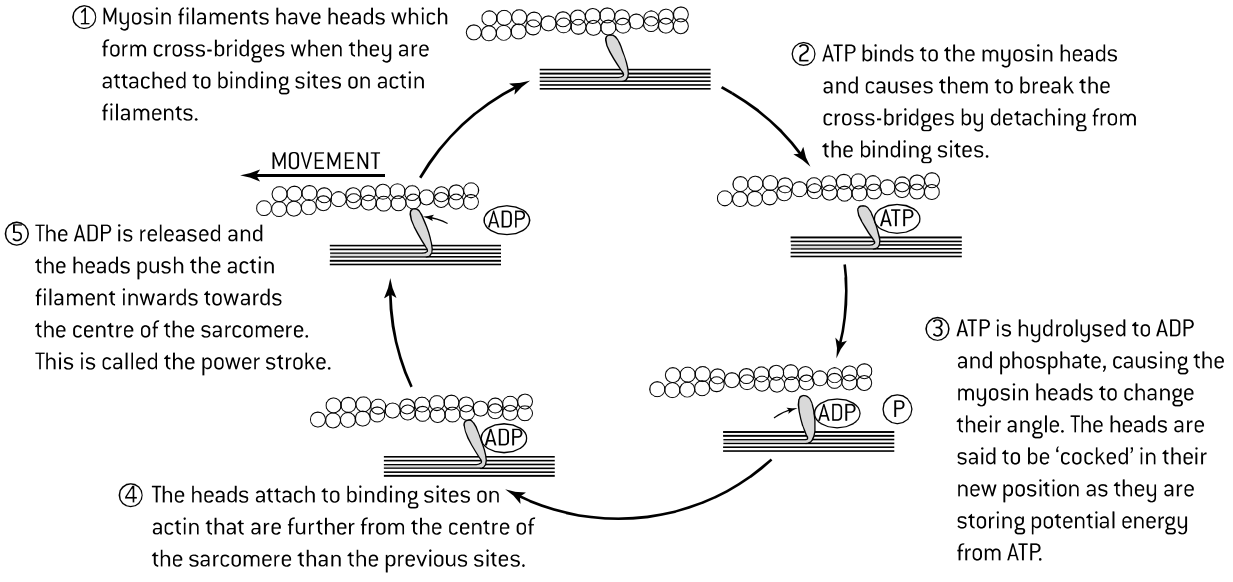
CONTROL OF MUSCLE CONTRACTION

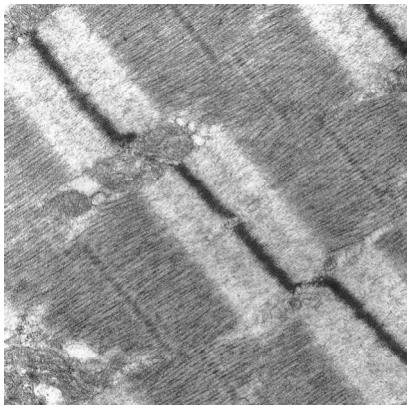
When a motor neuron stimulates a striated muscle fibre, **calcium ions** are released from the sarcoplasmic reticulum inside the fibre. The calcium binds to **troponin**, a protein that is associated with the actin filaments in muscle. The calcium causes the shape of troponin to change and this causes the movement of **tropomyosin**, another protein associated with actin, exposing binding sites on actin. This allows myosin heads to form cross-bridges by binding to actin.

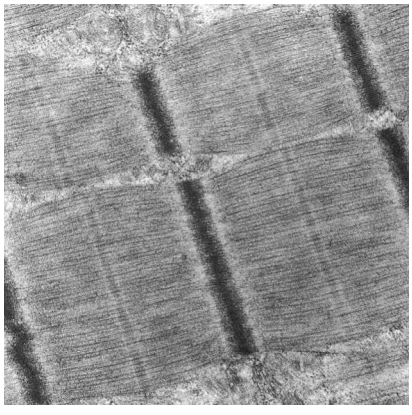
Radioactive calcium (^{45}Ca) has been used to investigate the control of muscle contraction. For example, using autoradiography it was shown that radioactive calcium is concentrated in the region of overlap between actin and myosin filaments in contracted muscle, but not in relaxed muscle. This is because calcium ions are bound to troponin, allowing cross-bridge formation and sliding of filaments.

THE MECHANISM OF MUSCLE CONTRACTION

The sliding of actin filaments over myosin filaments towards the centre of the sarcomere is achieved by a repeated cycle of stages, in which cross-bridges are formed and broken and energy is released by the hydrolysis of ATP.







CONTRACTED AND RELAXED MUSCLE FIBRES IN ELECTRON MICROGRAPHS

Contraction of striated (skeletal) muscle makes the light bands narrower and the sarcomeres shorter. The electron micrographs show relaxed muscle with wide light bands (far left) and fully contracted muscle with very narrow light bands (near left).

Movement

MUSCLES AND MOVEMENT

Muscles provide the forces that move animal bodies. As muscles only exert force when they contract and not when they relax and lengthen, a muscle can only cause a movement in one direction. For opposite movements there has to be a pair of muscles that exert force in opposite directions – an **antagonistic pair** of muscles.

Muscles are typically elongated structures, with tendons forming attachments at both ends. One end of the muscle is the anchorage, which is a firm point of attachment that does not move when the muscle contracts. Bones are used as **anchorages** in humans and other vertebrates. In insects and other arthropods the exoskeleton provides the anchorage. The opposite end of the muscle from the anchorage is the **insertion**. Bones and exoskeletons are again used for muscle insertions. Muscle contraction causes the bone or section of exoskeleton forming the insertion to move, together with surrounding tissues. Bones and exoskeleton can change the size and direction of the force exerted by a muscle, so they act as **levers**.

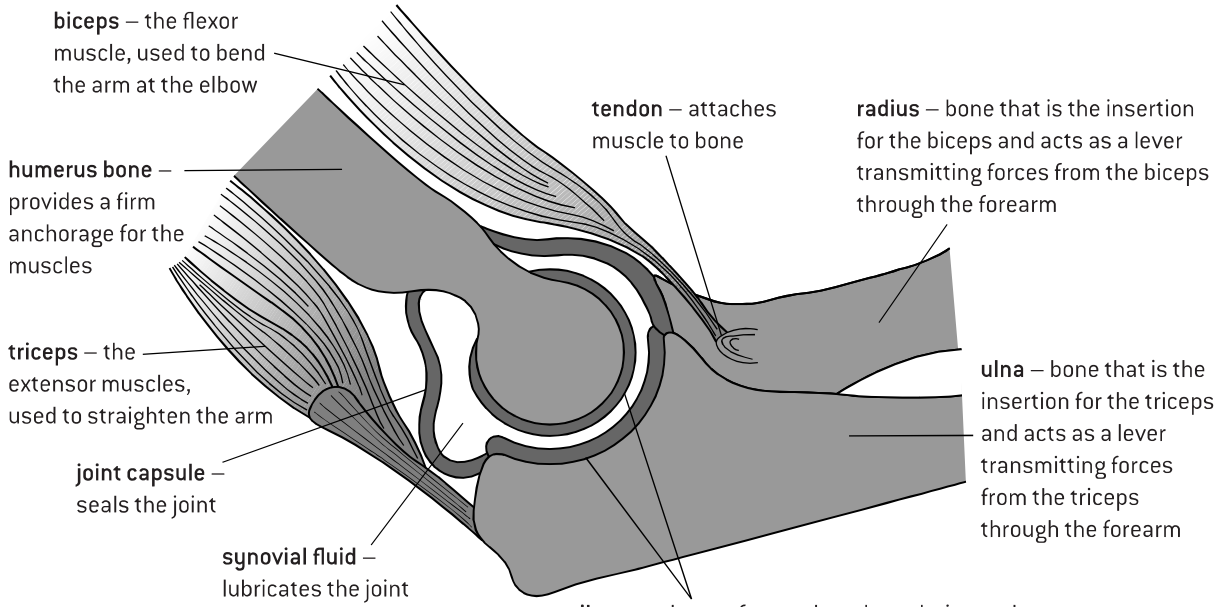
SYNOVIAL JOINTS

Junctions between bones are called **joints**. Some joints are fixed, such as joints between the plates of bone in the skull. Other joints allow movement (articulation). Most of these are **synovial joints**. They have three main parts:

- **Cartilage** covering the surface of the bones to reduce friction where they could rub against each other.
- **Synovial fluid** between the cartilage-covered surfaces, to lubricate the joint and further reduce friction.
- **Joint capsule** that seals the joint and holds in the synovial fluid.

There are also **ligaments** which are tough cords of tissue connecting the bones on opposite sides of a joint. They restrict movement and help to prevent dislocation. Ligaments ensure that certain movements can occur at a synovial joint but not others. For example the elbow allows considerable movement in one plane: bending (flexion) or straightening (extension), but little movement in the other two planes.

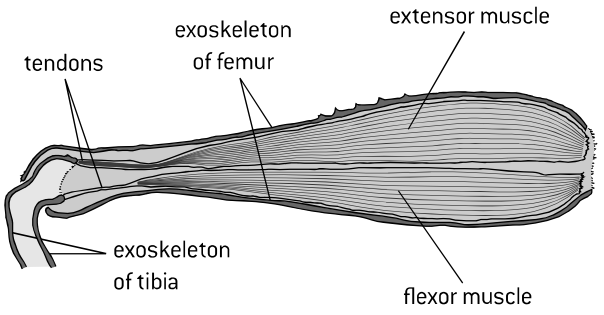
THE ELBOW JOINT



ANTAGONISTIC MUSCLES IN AN INSECT LEG

Insects have many joints in their legs, most of which move on one plane and can either flex (bend) or extend (straighten). A pair of antagonistic muscles causes these opposite movements.

For example in the legs of crickets there are two large muscles inside the femur. The tendons at the distal ends of these muscles are attached to opposite sides of the exoskeleton of the tibia, so one of them is a flexor of the joint between the femur and tibia and the other is an extensor.



Excretion and osmoregulation

EXCRETION

Metabolic pathways are chains and cycles of reactions in living cells used to build up and break down biochemicals.

In all organisms the metabolic pathways produce waste products that would be toxic if they were allowed to accumulate in cells, so they must be removed.

The removal from the body of potentially toxic waste products of metabolic pathways is **excretion**.

OSMOREGULATION

Water moves into and out of cells by osmosis. The direction in which water moves is determined by hydrostatic pressure and solute concentration. If the pressures are equal, water moves from a lower to a higher solute concentration by osmosis. Living organisms can control the movement of water by adjusting the solute concentrations of their cells and body fluids. This is **osmoregulation** – control of the internal solute concentration of a living organism.

NITROGENOUS WASTE PRODUCTS

Three nitrogenous compounds are excreted by animals: ammonia, urea and uric acid. The table below shows which of these compounds are excreted by the main groups of animal:

Waste product	Groups in which this is the main nitrogenous waste product
Ammonia	freshwater fish amphibian larvae
Urea	marine mammals terrestrial mammals marine fish adult amphibians
Uric acid	birds insects

Two trends can be seen in this table.

1. The type of type of nitrogenous waste in animals is correlated with **habitat**.
   - **Ammonia** is toxic and has to be excreted as a very dilute solution, so a large volume of water is required. It is therefore only excreted by animals that live in water, where abundant supplies of water are always available.
   - **Urea** is less toxic, so can be excreted as a more concentrated solution, with less loss of water. Conversion of ammonia to urea requires energy but it is worthwhile if an animal needs to conserve water.
   - **Uric acid** is not toxic even when concentrated so much that it precipitates to form a semi-solid paste. Conversion of ammonia to uric acid requires much energy, but it is worthwhile for animals that live in arid habitats so need to conserve as much water as possible. It also benefits animals that fly, as a concentrated paste of uric acid contains less water than dilute urine, reducing body mass during flight.
2. The type of nitrogenous waste in animals is correlated with **evolutionary history**. For example, mammals excrete urea, even though some mammals such as beavers and otters live in aquatic habitats and do not need to conserve water and presumably could excrete ammonia in a large volume of dilute urine, but instead they excrete urea, like terrestrial mammals.

OSMOCONFORMERS AND OSMOREGULATORS

Many marine organisms allow their internal solute concentration to fluctuate with that of the water around them – they do not attempt to maintain constant internal solution concentrations. These organisms are **osmoconformers**.

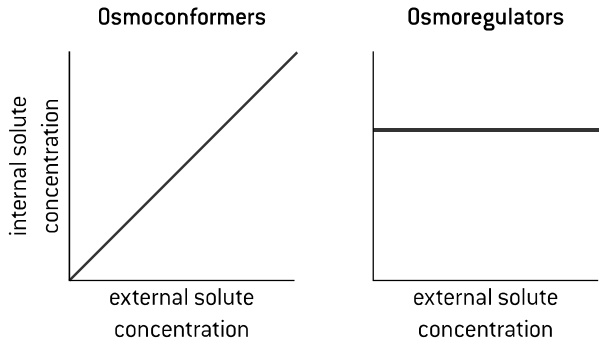
Examples: squids and sea squirts.

A disadvantage of being an osmoconformer is that cells inside the body may not contain the ideal solute concentration for body processes.

Most terrestrial organisms are **osmoregulators** because they maintain a constant internal solute concentration, whatever the external solute concentration.

Example: humans.

A disadvantage of being an osmoregulator is that energy has to be used to keep solute concentrations in the body constant.



DEHYDRATION AND OVER-HYDRATION

To explain dehydration and over-hydration in osmoregulators, three terms are required:

isotonic – a solute concentration equal to that of normal body fluids; **hypotonic** – a lower solute concentration than normal body fluids; **hypertonic** – a higher solute concentration than normal body fluids.

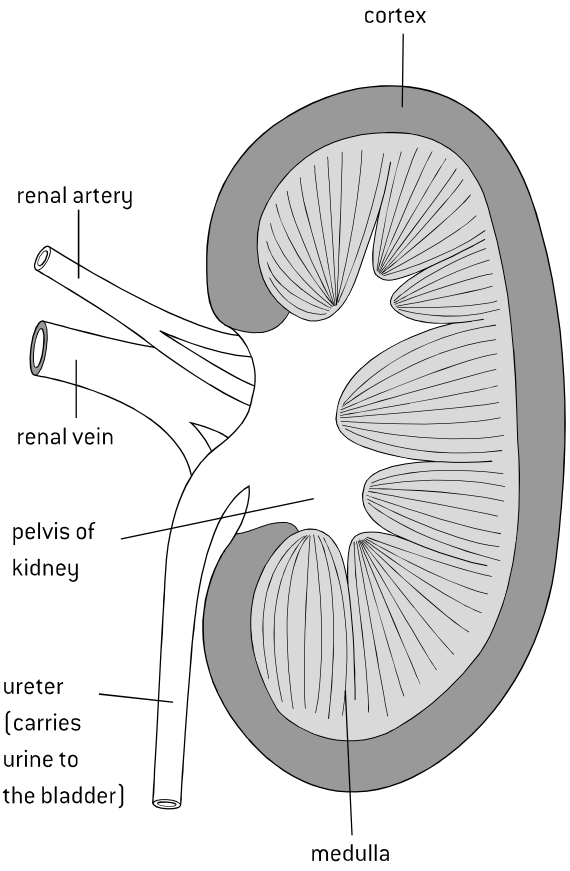
Dehydration is due to loss of water from the body, but not an equivalent quantity of solutes, so body fluids become hypertonic. The consequences are thirst, small quantities of dark coloured urine, lethargy, a raised heart rate, low blood pressure and in severe cases seizures, brain damage and death. **Over-hydration** is due to excessive intake of water, so the body fluids become hypotonic. The consequences are behaviour changes, confusion, drowsiness, delirium, blurred vision, muscle cramps, nausea and in acute cases seizures, coma and death.

Kidney structure and ultrafiltration

STRUCTURE AND FUNCTIONS OF THE KIDNEY

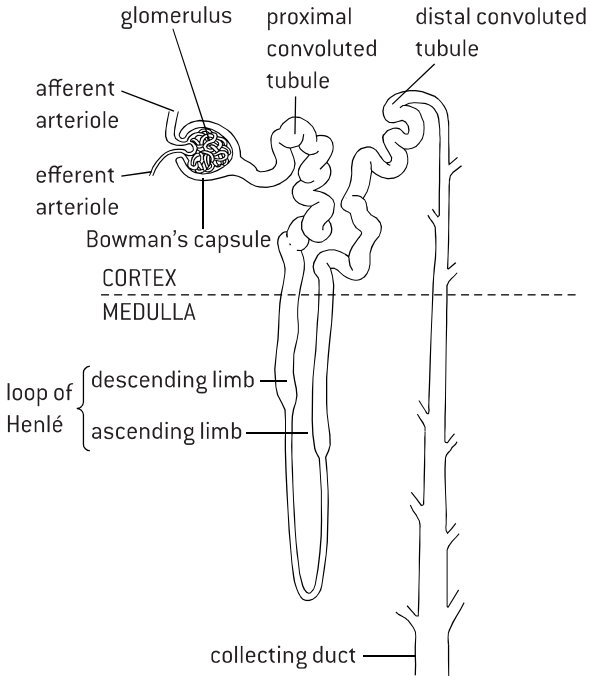
The kidney has two functions, excretion and osmoregulation.

The diagram (below) shows the structure of the kidney. The **cortex** and **medulla** contain many narrow tubes called **nephrons**. The renal pelvis consists of spongy tissue into which urine drains from collecting ducts.



STRUCTURE OF THE NEPHRON

The figure (below) shows the structure of a nephron, together with the associated **glomerulus**. A group of nephrons join up to form one **collecting duct**.



- The glomerulus and Bowman's capsule produce a filtrate from the blood by **ultrafiltration**.
- The proximal convoluted tubule transfers useful substances from the filtrate back into the blood by **selective reabsorption**.
- The loop of Henlé establishes high solute concentrations in the medulla, so hypertonic urine can be produced.
- The distal convoluted tubule adjusts individual solute concentrations and the pH of the blood.
- The collecting duct carries out **osmoregulation** by varying the amount of water reabsorbed.

ULTRAFILTRATION IN THE GLOMERULUS

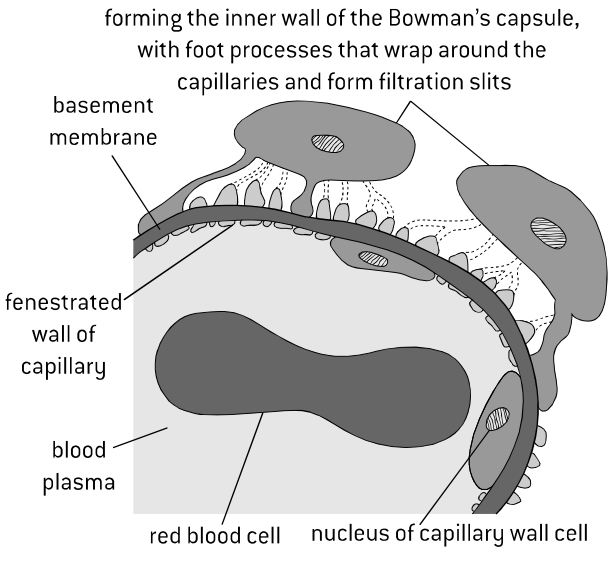
The glomerulus is a knot-like ball of blood capillaries. All capillaries let some fluid leak out but 20% of the plasma escapes from glomerulus capillaries which is a very large amount. There are two reasons:

- very high blood pressure, because the vessel taking blood away from the glomerulus is narrower than the vessel bringing blood
- many large pores (fenestrations) in the capillary walls.

These pores would allow any molecules through, but there are two filters beyond the pores that only small to medium sized particles can pass through (68,000 molecular mass or less):

- **basement membrane** – a gel on the outside of the capillary, with small gaps through a mesh of protein fibres
- **filtration slits** – narrow gaps between the foot process of **podocyte** cells where they wrap around the capillaries.

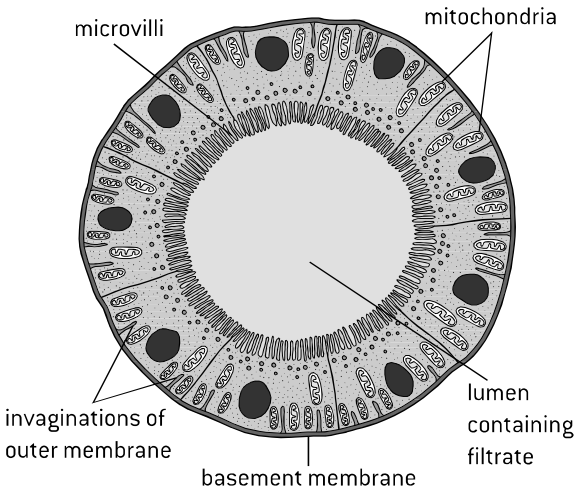
The filtrate that enters the Bowman's capsule contains all substances in blood plasma except plasma proteins.



Urine production and osmoregulation

SELECTIVE REABSORPTION

Large volumes of glomerular filtrate are produced – about one litre every 10 minutes by the two kidneys. As well as waste products, the filtrate contains substances that the body needs, which must be reabsorbed into the blood. Most of this selective reabsorption happens in the **proximal convoluted tubule**. The wall of the nephron consists of a single layer of cells. In the proximal convoluted tubule the cells have **microvilli** projecting into the lumen (right), giving a large surface area for absorption. Pumps in the membrane reabsorb useful substances by **active transport**, using ATP produced by **mitochondria** in the cells. All of the glucose in the filtrate is reabsorbed. About 80% of the mineral ions, including sodium, are reabsorbed. Active transport of solutes makes the total solute concentration higher in the cells of the wall than in the filtrate in the tubule. Water therefore moves by osmosis from the filtrate to the cells and on into the adjacent blood.



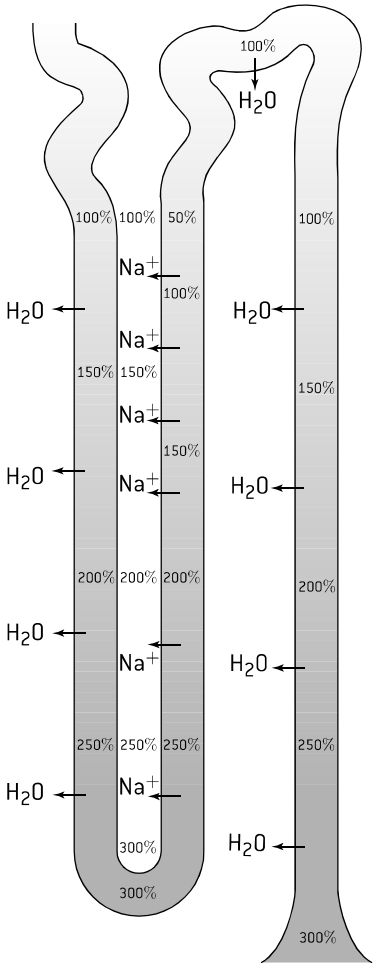
ROLE OF THE LOOP OF HENLÉ

Glomerular filtrate flows deep into the medulla in descending limbs of the loops of Henlé and then back out to the cortex in ascending limbs. Descending limbs and ascending limbs are opposite in terms of permeability. Descending limbs are very permeable to water but are relatively impermeable to sodium ions. Ascending limbs are very permeable to sodium ions but are relatively impermeable to water.

Ascending limbs pump sodium ions from the filtrate into the medulla by active transport, creating a high solute concentration in the medulla. As the filtrate flows down the descending limb into this region of high solute concentration, some water is drawn out by osmosis. This dilutes the fluids in the medulla slightly. However the filtrate that leaves the loop of Henlé is more dilute than the fluid entering it, showing that the overall effect of the loop of Henlé is to increase the solute concentration of the medulla. This is the role of the loop of Henlé – to create an area of higher solute concentrations in the medulla than in normal body fluids (hypertonic).

After the loop of Henlé, the filtrate passes through the distal convoluted tubule, where the ions can be exchanged between the filtrate and the blood to adjust blood levels. It then passes into the collecting duct.

The diagram shows movements of water and sodium ions in the loop of Henlé and the collecting duct. Concentrations of solutes inside and outside the nephron are shown as a percentage of normal blood solute concentration.



Movements of water and sodium ions in the loop of Henlé and the collecting duct. Solute concentrations inside and outside the nephron are shown as a percentage of normal blood solute concentration

ADH AND OSMOREGULATION

Osmoregulation is the control of solute concentrations in the body fluids, especially the blood plasma. The collecting duct has an important role in osmoregulation. If the water content of the blood is too low, the pituitary gland secretes ADH (anti-diuretic hormone), which is also sometimes called vasopressin. This hormone makes the cells of the collecting duct increase the permeability of their plasma membranes to water. The cells do this by putting water channels, called aquaporins, into their membranes. As the filtrate passes down the collecting duct through the medulla, the high solute concentration of the medulla causes much of the water in the filtrate to be reabsorbed by osmosis. ADH is secreted when the internal solute concentration of body fluids is too high and, as it causes a small volume of concentrated urine to be produced, the result is that the blood plasma becomes more dilute.

If the solute concentration of body fluids is too low, ADH is not secreted and the collecting duct becomes much less permeable to water by removal of aquaporins from its membranes. Only a small amount of water is reabsorbed as the filtrate passes down the collecting duct and a large volume of dilute urine is produced, making the solute concentration of the blood higher.

Kidney function and kidney failure

FILTRATE AND URINE CONCENTRATIONS

The table below shows differences in composition between blood in the glomerulus, filtrate at various points in the nephron and urine.

	Concentration (mg per 100ml)		
	Plasma proteins	Glucose	Urea
Blood in glomerulus	740	90	30
Glomerular filtrate	0	90	30
Filtrate at start of loop of Henlé	0	0	90
Filtrate at end of loop of Henlé	0	0	200
Urine with ADH	0	0	1800
Urine without ADH	0	0	180

BLOOD IN THE RENAL ARTERY AND VEIN

The composition of blood is altered as it flows through the kidney, so there are differences between blood in the renal artery and vein.

	Comparison of concentrations		Reason for difference between renal artery and vein
	Renal artery	Renal vein	
oxygen	higher	lower	aerobic respiration to provide ATP for kidney function
carbon dioxide	lower	higher	
glucose	slightly higher	slightly lower	use of glucose in aerobic respiration
urea	higher	about 20% lower	excretion of urea in urine
plasma proteins	equal		not added or removed
sodium and chloride ions	variable	always at normal levels	kidney raises or lowers concentrations to normalize them

URINE TESTS

Samples of urine are easily obtained and can be tested for the presence of abnormalities that are indicators of disease:

Blood cells – their presence is caused by a variety of diseases including infections and some cancers.

Glucose – almost always indicates diabetes.

Proteins – very small amounts of protein in the urine are normal because some proteins such as the hormones hCG and insulin are small enough to be filtered out of the blood, but larger amounts of proteins in urine are a sign of kidney disease.

Drugs – many drugs pass out of the body in the urine so tests can show if a person is a drug abuser, either for recreational reasons or to gain unfair advantage in sports competitions.

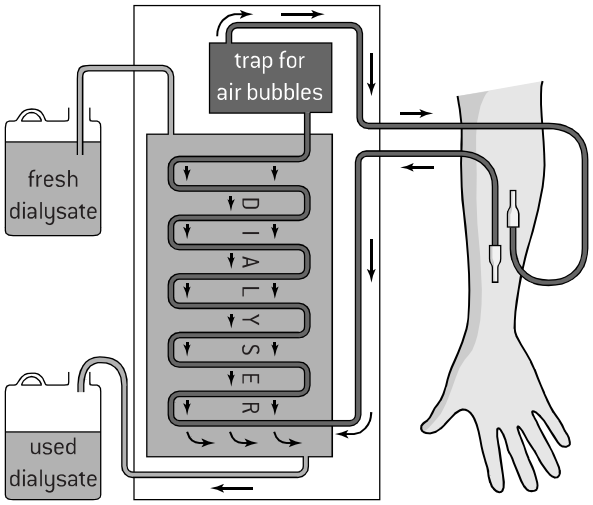
TREATMENT OF KIDNEY FAILURE

Kidney failure is a serious condition because toxins build up in the body and solute concentrations are not maintained at the normal level. Untreated kidney failure makes the patient feel increasingly ill and is eventually fatal. There are two approaches to the treatment of kidney failure.

1. **Hemodialysis**

   Blood is drawn out of a vein in the arm and passed though a kidney machine for 3 to 4 hours, 3 times per week. The blood flows next to a semi-permeable dialysis membrane with dialysate (dialysis fluid) on the other side. Pores through the membrane allow small particles to diffuse in either direction, but plasma proteins and cells are retained in the blood. Dialysate has these features:

   - no urea or other waste products so they diffuse from the blood to the fluid
   - ideal concentrations of glucose and other metabolites so ideal concentrations are achieved in the blood by diffusion to or from the fluid
   - high calcium and low potassium concentrations to extract potassium and add calcium to the blood
   - hydrogencarbonate ions (HCO_3^-) to reduce the acidity of the blood
   - a total solute concentration that will cause excess water to be removed from the blood by osmosis across the dialysis membrane.



2. **Kidney transplants**

   Dialysis can keep patients alive for years, but a better long-term treatment is a kidney transplant. Sometimes a living donor provides one of their two kidneys for transplant and in other cases the kidneys of a person who has recently died are donated to two patients needing a transplant. It is essential that the donor and recipient are in the same blood group and their tissues match as closely as possible to minimize the chance of rejection of the kidney by the recipient's immune system. The new kidney is grafted in to the lower abdomen with the renal artery, renal vein and ureter connected to the recipient's blood vessels and bladder.

Excretion and osmoregulation in animals

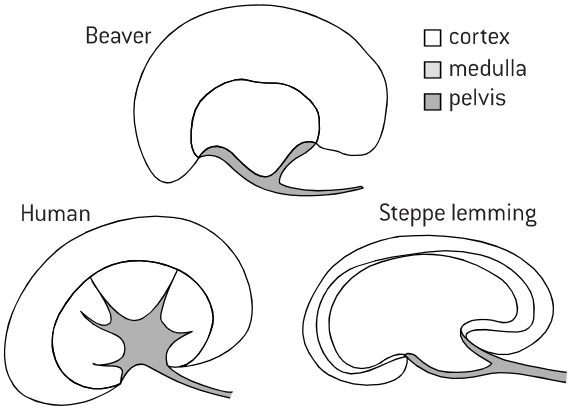
EXCRETION AND WATER CONSERVATION

The maximum solute concentration of urine varies considerably between species. This observation led to research into the kidney physiology of different species and in particular how desert animals are able to conserve water by producing very concentrated urine. This research revealed some of the basic physiology of all mammalian kidneys so is a good example of how curiosity about a particular phenomenon can lead to progress in science.

The table below shows the maximum solute concentration (MSC) and concentration factor of urine (CF) and the habitat:

Species	MSC (mOsm dm^{-3})	CF	Habitat
beaver	520	×2	aquatic
human	1200	×4	intermediate
brown rat	2900	×9	intermediate
kangaroo rat	5500	×18	desert
hopping mouse	9400	×25	desert

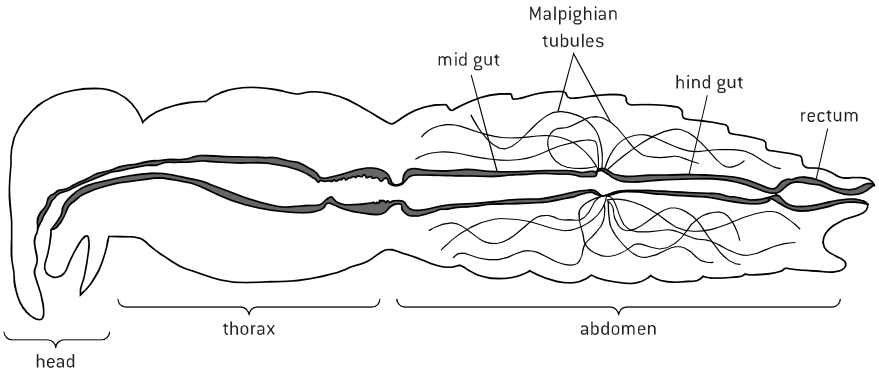
Longitudinal sections through the kidneys of mammals of aquatic, desert and intermediate habitats show significant differences. One example of each is shown (below). These species show a general trend in mammals: there is a positive correlation between the thickness of the medulla compared to the overall size of the kidney, and the need for water conservation. This is because a thicker medulla allows the loops of Henlé and collecting ducts to be longer, so more water can be reabsorbed and the urine can be made more concentrated.



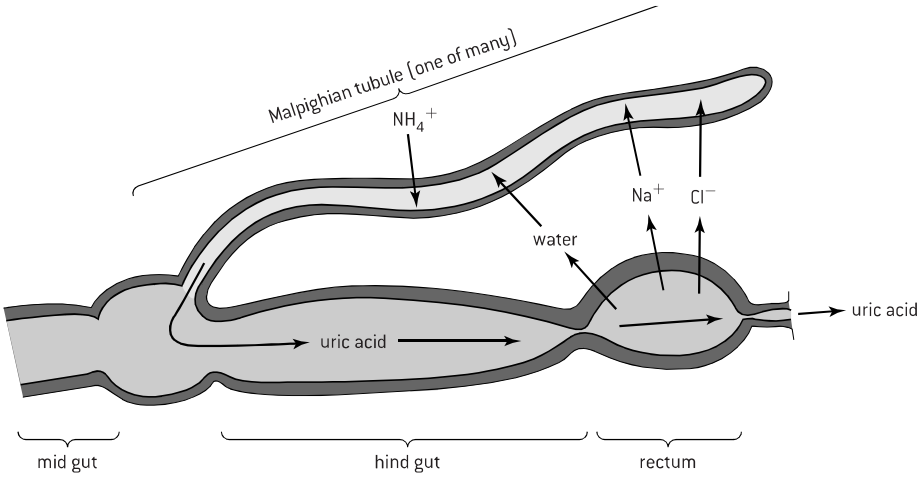
THE MALPIGHIAN TUBULE SYSTEM

The circulatory system of insects uses hemolymph rather than blood. Hemolymph is pumped by a vessel that runs from the abdomen forwards through the thorax to the head. Branches of this vessel carry the hemolymph to different parts of the body and it is then released and is free to flow gradually through tissues until being drawn back into the vessel for re-pumping. Body cells are therefore bathed in hemolymph and release waste products into it.

Between the midgut and hindgut of insects there is a ring of narrow blind-ended ducts, called **Malpighian tubules**, which extend through the body cavity of the insect. Cells in the tubule walls extract waste products from the hemolymph and pass them into the lumen of the tubule. Ammonia is extracted and converted by Malpighian tubule cells into uric acid.



To create a flow of fluid that will carry uric acid and other waste products along the Malpighian tubules to the hindgut, cells in the tubule wall transfer mineral ions by active transport from the hemolymph to the lumen of the tubule and water follows passively by osmosis. The solution that is produced in this way drains into the lumen of the hindgut where it mixes with the semi-digested food. The mixture is carried on to the last section of the gut – the rectum. Mineral ions are pumped by cells in the wall of the rectum from the feces in the rectum to the hemolymph and again water follows passively by osmosis. By moving solutes and water into and out of the hemolymph, the Malpighian tubules and rectum together prevent dehydration and achieve osmoregulation.

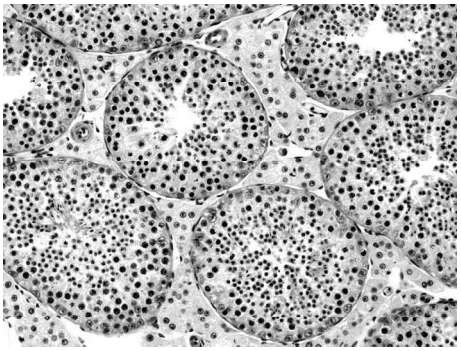


Spermatogenesis

STAGES IN GAMETOGENESIS

Spermatogenesis is the production of male gametes in the testes. Oogenesis is production of female gametes in the ovaries. Both processes have the same basic stages:

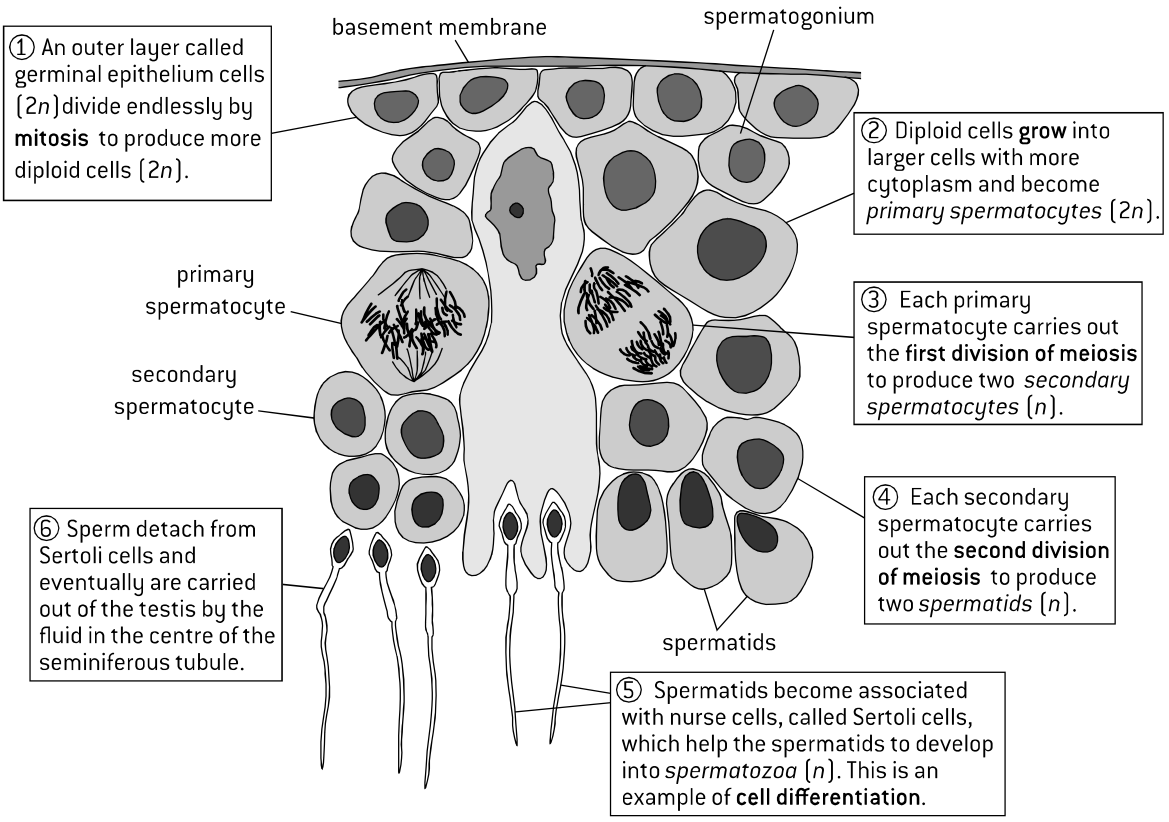
- mitosis to generate large numbers of diploid cells
- cell growth so the cells have enough resources to undergo two divisions of meiosis
- meiosis to produce haploid cells
- differentiation so the haploid cells develop into gametes with structures needed for fertilization.



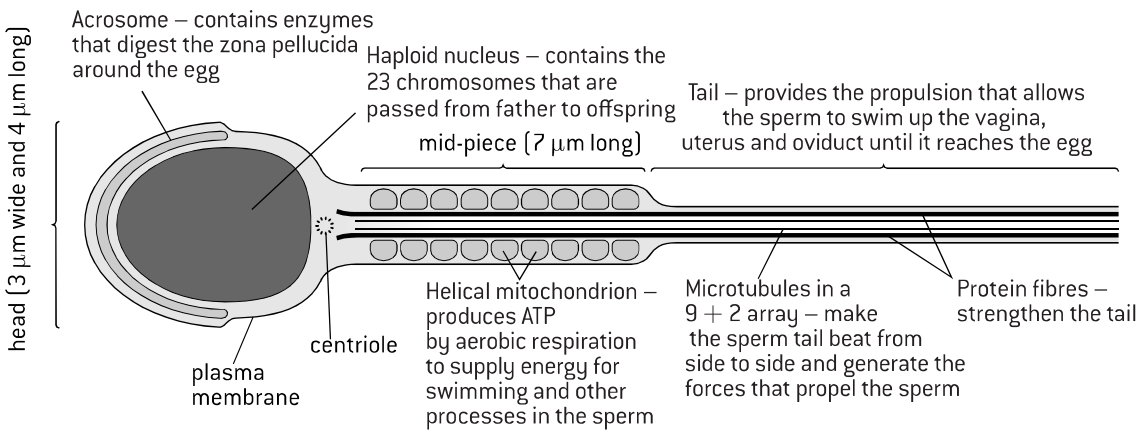
The micrograph (left) shows the testis tissue. Most of it is seminiferous tubules. The tubule walls produce sperm.

STAGES IN SPERMATOGENESIS

The five stages of spermatogenesis are shown in this diagram of cells in the wall of the seminiferous tubule.



STRUCTURE OF HUMAN SPERM



Oogenesis

STAGES IN OOGENESIS

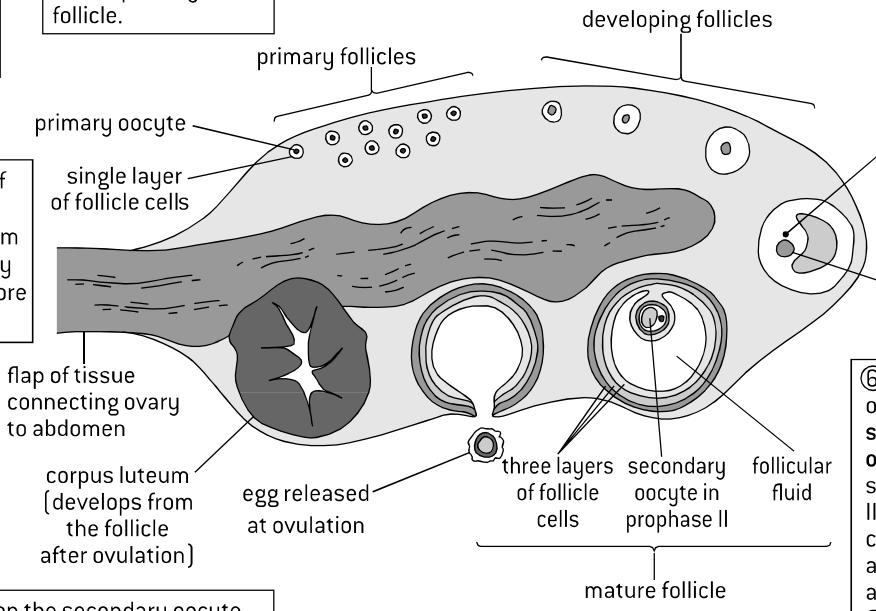
① In the ovaries of a female fetus, germinal epithelium cells ($2n$) divide by **mitosis** to form more diploid cells ($2n$).

② Diploid cells **grow** into larger cells called *primary oocytes* ($2n$).

③ Primary oocytes start the **first division of meiosis** but stop during prophase I. The primary oocyte and a single layer of follicle cells around it form a primary follicle.

④ When a baby girl is born the ovaries contain about 400,000 primary follicles.

⑤ Every menstrual cycle a few primary follicles start to develop. The primary oocyte completes the first division of meiosis, forming two haploid nuclei. The cytoplasm of the primary oocyte is **divided unequally** forming a large secondary oocyte(n) and a small polar cell (n).

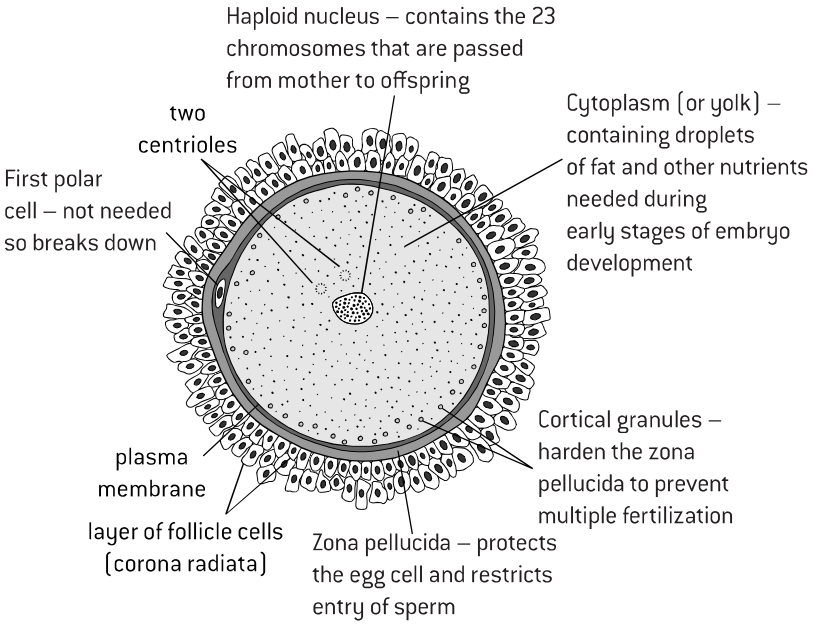


⑥ The secondary oocyte starts the **second division of meiosis** but stops in prophase II. The follicle cells meanwhile are proliferating and follicular fluid is forming.

⑦ When the mature follicle bursts, at the time of ovulation, the egg that is released is actually still a secondary oocyte.

⑧ After fertilization the secondary oocyte completes the second division of meiosis to form an ovum(with a haploid nucleus already inside it) and a second polar cell or body. The first and second polar bodies do not develop and eventually **degenerate**.

STRUCTURE OF A MATURE HUMAN EGG



Diameter of egg cell = 110 μm

COMPARING OOGENESIS AND SPERMATOGENESIS

There are some significant differences between spermatogenesis and oogenesis:

1. Millions of sperm are produced by men each day from puberty onwards and they can be released frequently by ejaculation. From puberty until menopause women who are not pregnant produce and release just one egg every 28 days.
2. Nearly all the cytoplasm is removed during the latter stages of spermatogenesis so sperm contain very little. Egg cells have more cytoplasm than any other human cell. The mitochondria of the zygote are all derived from the cytoplasm of the egg cell. The egg cell destroys the helical mitochondria of the sperm after fertilization.

Fertilization

INTERNAL AND EXTERNAL FERTILIZATION

In some species females release unfertilized eggs and males put their sperm over the eggs, so fertilization takes place outside the body. This is **external fertilization**.

Examples:
salmon and other fish, frogs and other amphibians.

In other species the male passes his sperm into the female's body and fertilization takes place there. This is **internal fertilization**.

Examples:
pythons and other reptiles, albatrosses and other birds, humans and other mammals.

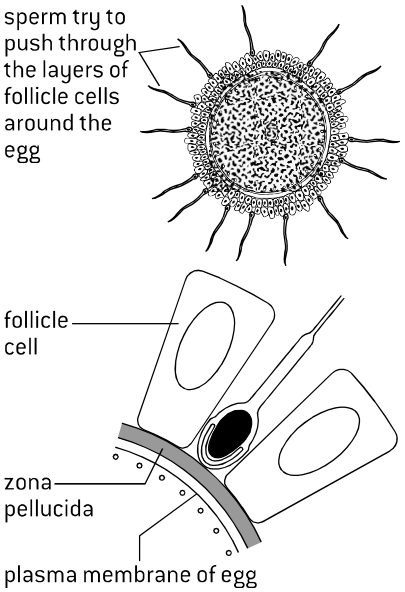
AVOIDING POLYSPERMY

A diploid zygote is produced when one haploid sperm fuses with a haploid egg – this is fertilization. Fusion of two or more sperm with an egg cell results in a cell that has three of each chromosome type (triploid), or more. This is called polyspermy. Cells produced in this way often die and those that survive are almost always sterile. There are therefore mechanisms in fertilization that normally prevent polyspermy.

DECLINING MALE FERTILITY

During the last fifty years the average number of sperm per unit volume of human semen has fallen by 50% and it continues to drop by about 2% per year. Various factors may be contributing to this, but one is the presence in the environment of estrogen and progesterone since the introduction of the female contraceptive pill. The effects of these chemicals on male fertility were not tested before the contraceptive pill started to be used by millions of women. There are also steroids that are chemically related to these female sex hormones in a wide range of products including plastics, food packaging and furniture. Again, adequate testing has not been done. The enormous drop in male fertility shows how essential it is to test for harmful side effects before scientific or technological developments are introduced.

STAGES IN THE FERTILIZATION OF A HUMAN EGG



1. **Arrival of sperm**

   Sperm are attracted by a chemical signal and swim up the oviduct to reach the egg. Fertilization is only successful if many sperm reach the egg.

2. **Binding**

   The first sperm to break through the layers of follicle cells binds to the zona pellucida. This triggers the acrosome reaction.

3. **Acrosome reaction**

   The contents of the acrosome are released, by the separation of the acrosomal cap from the sperm. Enzymes from the acrosome digest a route for the sperm through the zona pellucida, allowing the sperm to reach the plasma membrane of the egg.

4. **Fusion**

   The plasma membranes of the sperm and egg fuse and the sperm nucleus enters the egg and joins the egg nucleus. Fusion causes the cortical reaction.

5. **Cortical reaction**

   Small vesicles called cortical granules move to the plasma membrane of the egg and fuse with it, releasing their contents by exocytosis. Enzymes from the cortical granules cause cross-linking of glycoproteins in the zona pellucida, making it hard and preventing polyspermy.

6. **Mitosis**

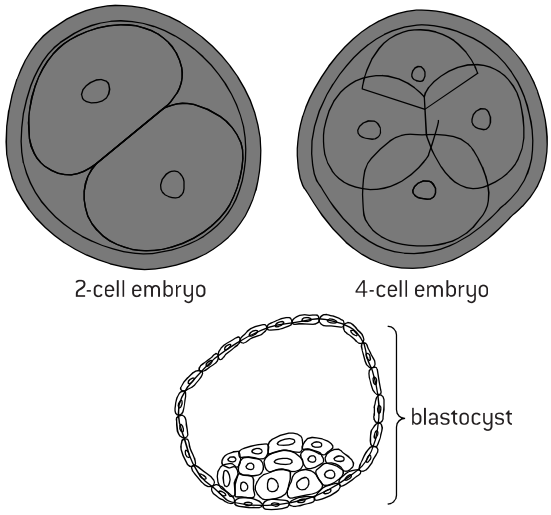
   The nuclei from the sperm and egg do not fuse together. Instead, both nuclei carry out mitosis, using the same centrioles and spindle of microtubules. A two-cell embryo is produced.

Pregnancy and childbirth

EARLY EMBRYO DEVELOPMENT AND IMPLANTATION

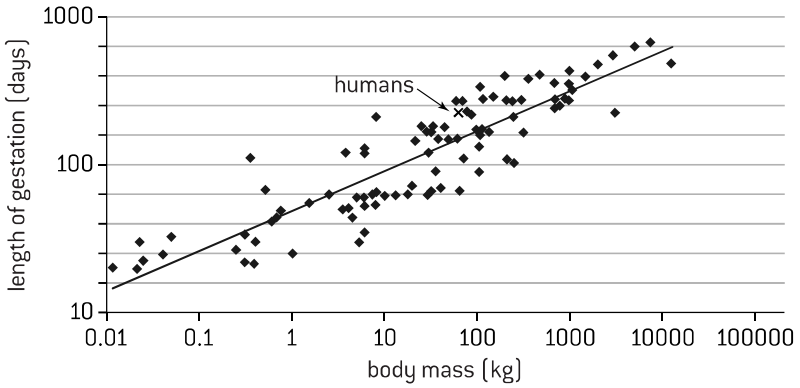
If a couple want to have a child, they have sexual intercourse without using any method of contraception. Semen is ejaculated into the vagina and sperm that it contains swim through the cervix, up the uterus and into the oviducts. If there is an egg in the oviducts, a sperm can fuse with it to produce a zygote.

The zygote produced by fertilization in the oviduct is a new human individual. It starts to divide by mitosis to form a 2-cell embryo, then a 4-cell embryo (right) and so on until a hollow ball of cells called a **blastocyst** is formed. While these early stages in the development of the embryo are happening, the embryo is transported down the oviduct to the uterus. When it is about 7 days old, the embryo implants itself into the **endometrium** (the lining of the wall of the uterus), where it continues to grow and develop. If implantation does not occur then the embryo is not supplied with enough food and the pregnancy does not continue.



ANIMAL SIZE AND DURATION OF GESTATION

The graph below shows the relationship between body mass and duration of gestation (pregnancy) in a wide range of species of mammal. Both scales are logarithmic. The cross is the data point for humans (266 day gestation and 60kg body mass). Although there is a positive correlation overall between body mass and duration of gestation, there are examples of species that have the same length of gestation but body masses differing by more than two orders of magnitude. In animals with a relatively long gestation the offspring are more advanced in their development when they are born than animals with a short gestation time in relation to adult body mass.



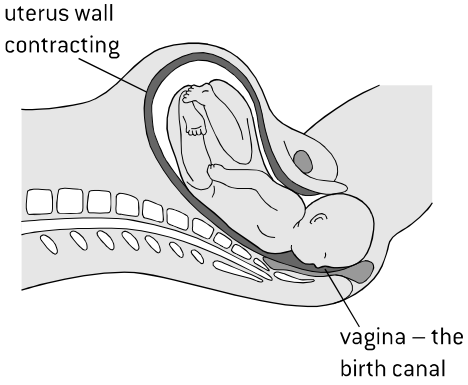
HORMONAL CONTROL OF PREGNANCY

Human embryos secrete the hormone **hCG** (human chorionic gonadotrophin) from a very early stage. hCG stimulates the ovary to maintain the secretion of **progesterone** during the first three months of pregnancy. Progesterone causes the uterus lining to continue to thicken so it can support the embryo after implantation.

By about the 12th week of pregnancy the ovary stops secreting progesterone, but by this time the **placenta** has developed and takes over the task of secreting the progesterone that is needed to sustain the pregnancy until the time of childbirth (labour). The placenta also secretes **estrogen**.

HORMONAL CONTROL OF CHILDBIRTH

Through the 9 months of pregnancy, rising levels of the hormone **progesterone** ensure that the uterus develops and sustains the growing fetus. It also prevents uterine contractions and so prevents spontaneous abortions. The level of progesterone starts to fall in the last third of the pregnancy and more steeply shortly before the end. This allows the mother's body to secrete another hormone – **oxytocin**. There is also a rise in **estrogen**, which causes an increase in the number of oxytocin receptors on the muscle in the uterus wall. When oxytocin binds to these receptors it causes the muscle to contract. Uterine contractions stimulate the secretion of more oxytocin. The uterine contractions therefore become stronger and stronger. This is an example of **positive feedback**.

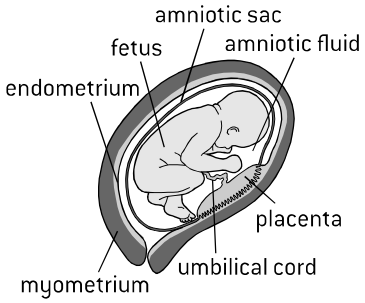


While the muscle in the wall of the uterus is contracting, the cervix relaxes and becomes wider. The amniotic sac bursts and the amniotic fluid is released. Finally, often after many hours of contractions, the baby is pushed out through the cervix and the vagina. The umbilical cord is cut and the baby begins its independent life. Contractions continue for a time until the placenta is expelled as the afterbirth. The diagram shows the baby's head emerging during childbirth.

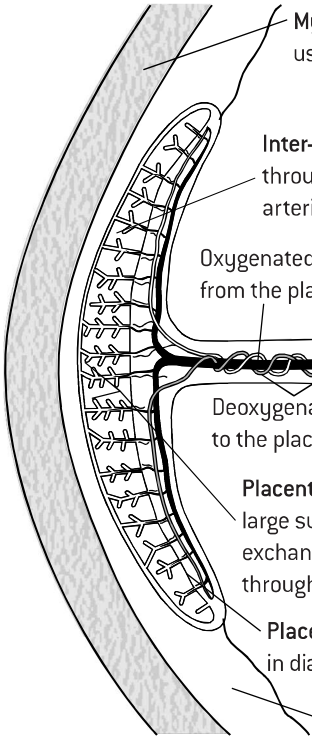
Structure and function of the placenta

FUNCTION OF THE PLACENTA

By the time that the embryo is about 8 weeks old, it starts to develop bone tissue and is known from then onwards as a **fetus**. The fetus develops a placenta and an umbilical cord. The placenta is a disc-shaped structure, with many projections called placental villi embedded in the uterus wall. In the placenta the blood of the fetus flows close to the blood of the mother in the uterus wall. This facilitates the exchange of materials between maternal and fetal blood.



STRUCTURE OF THE PLACENTA



Myometrium – muscular wall of the uterus, used during childbirth.

Inter-villous spaces – maternal blood flows through these spaces, brought by uterine arteries and carried away by uterine veins.

Oxygenated fetal blood flows back to the fetus from the placenta along the **umbilical vein**.

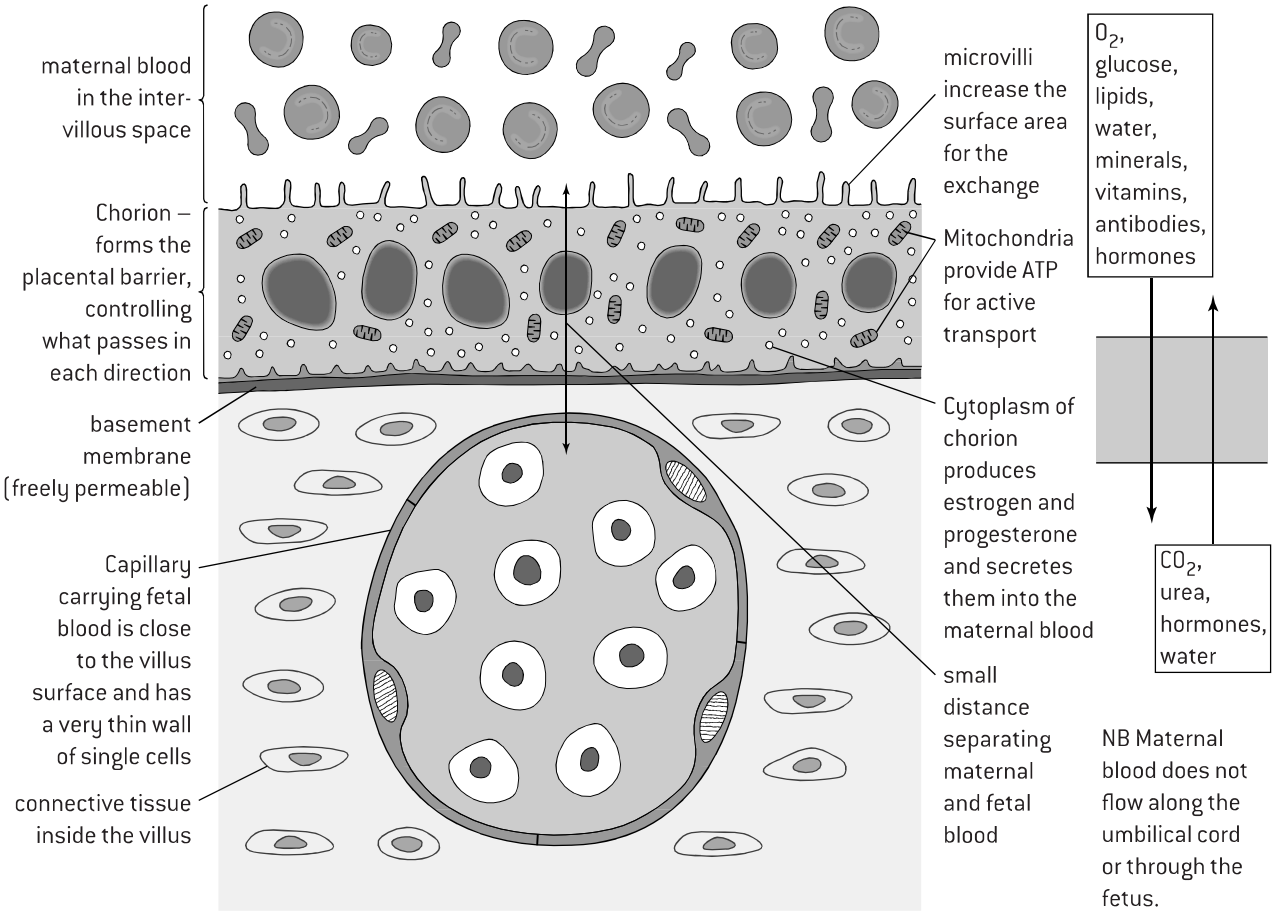
Deoxygenated fetal blood flows from the fetus to the placenta along two umbilical arteries.

Placental villi – small projections that give a large surface area ($14m^2$) for gas exchange and exchange of other materials. Fetal blood flows through capillaries in the villi.

Placenta – a disc-shaped structure, 185 mm in diameter and 20 mm thick when fully grown.

Endometrium – the lining of the uterus, into which the placenta grows.

EXCHANGE OF MATERIALS ACROSS THE PLACENTA



NB Maternal blood does not flow along the umbilical cord or through the fetus.