

# Edexcel AS Biology Teacher 2

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These notes may be used freely by A level biology students and teachers, and they may be copied and edited. I would be interested to hear of any comments and corrections.

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# Biology Teacher 2 Specification

## 2.01 Cells, Tissues and Organs

Cell theory is a unifying concept that states that cells are a fundamental unit of structure, function and organisation in all living organisms. In complex organisms, cells are organised into tissues, organs, and organ systems.

## 2.02 Eukaryotic Cells

The ultrastructure of eukaryotic cells and the functions of organelles, including: nucleus, nucleolus, 80S ribosomes, rough and smooth endoplasmic reticulum, mitochondria, centrioles, lysosomes, Golgi apparatus, cell wall, chloroplasts, vacuole and tonoplast.

## 2.03 Prokaryotic Cells

The ultrastructure of prokaryotic cells and the structure of organelles, including: nucleoid, plasmids, 70S ribosomes and cell wall. Distinguish between Gram positive and Gram negative bacterial cell walls. Be able to distinguish between Gram positive and Gram negative bacterial cell walls and why each type reacts differently to some antibiotics.

## 2.04 Microscopy

How magnification and resolution can be achieved using light and electron microscopy. The importance of staining specimens in microscopy.

## 2.05 Cell Membranes and Transport

The structure of the cell surface membrane with reference to the fluid mosaic model.

- How passive transport is brought about by: diffusion; facilitated diffusion (through carrier proteins and protein channels); osmosis. How the properties of molecules affects how they are transported, including solubility, size and charge.
- Water potential = turgor pressure + osmotic potential.
- The process of active transport, including the role of ATP. Phosphorylation of ADP requires energy and that hydrolysis of ATP provides an accessible supply of energy for biological processes.
- Large molecules can be transported into and out of cells through the formation of vesicles, in the processes of endocytosis and exocytosis.

## 2.06 Surface area to volume ratio

How surface area to volume ratio affects transport of molecules in living organisms. Why organisms need a mass transport system and specialised gas exchange surfaces as they increase in size.

## 2.07 Gas exchange

How mammals, fish and insects are adapted for gas exchange. Gas exchange in flowering plants, including the role of stomata, gas exchange surfaces in the leaf and lenticels.

## 2.08 Circulation

The advantages of a double circulatory system in mammals over the single circulatory systems in bony fish, including the facility for blood to be pumped to the body at higher pressure and the splitting of oxygenated and deoxygenated blood.

## 2.09 Heart

The structure of the heart. The sequence of events of the cardiac cycle. Myogenic stimulation of the heart, including the roles of the sinoatrial node (SAN), atrioventricular node (AVN) and bundle of His. Be able to interpret data showing ECG traces and pressure changes during the cardiac cycle.

## 2.10 Blood Vessels

The structure of arteries, veins and capillaries.

## 2.11 Tissue Fluid

Transfer of materials between the circulatory system and cells. How the interchange of substances occurs through the formation and reabsorption of tissue fluid, including the effects of hydrostatic pressure and oncotic pressure. Tissue fluid that is not reabsorbed is returned to the blood via the lymph system.

## 2.12 Blood

The structure of blood as plasma and blood cells, to include erythrocytes and leucocytes (neutrophils, eosinophils, monocytes and lymphocytes). The function of blood as transport, defence, and formation of lymph and tissue fluid.

## 2.13 Gas Transport

The structure of haemoglobin in relation to its role in the transport of respiratory gases, including the Bohr effect. The oxygen dissociation curve of haemoglobin. The similarities and differences between the structures and functions of haemoglobin and myoglobin. The significance of the oxygen affinity of fetal haemoglobin as compared to adult haemoglobin.

## 2.14 Blood Clotting

The role of platelets and plasma proteins in the sequence of events leading to blood clotting, including: platelets form a plug and release clotting factors, including thromboplastin; prothrombin changes to its active form, thrombin; soluble fibrinogen forms insoluble fibrin to cover the wound.

## 2.15 Cardiovascular Disease

The stages that lead to atherosclerosis, its effect on health and the factors that increase the risk of its development.

### **2.16 Transport in plants**

The structure of xylem and phloem tissues in relation to their role in transport.

- How water can be moved through plant cells by the apoplastic and symplastic pathways. How the cohesion-tension model explains the transport of water from plant roots to shoots. How temperature, light, humidity and movement of air affect the rate of transpiration.

- The strengths and weaknesses of the mass-flow hypothesis in explaining the movement of sugars through phloem tissue.

### **2.17 Inorganic ions in Plants**

The role in plants of:

- nitrate ions – to make DNA and amino acids
- phosphate ions – to make ADP and ATP.
- calcium ions – to form calcium pectate for the middle lamellae
- magnesium ions – to produce chlorophyll



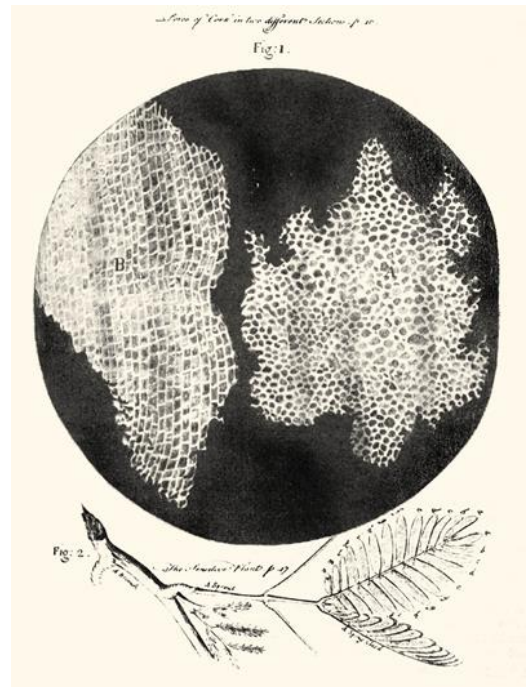
# Cells

## Cell Theory

All living things are made of cells. Cells were first seen in dead plant tissue 1665 by Robert Hooke (who named them after monks' cells in a monastery), and living cells were first observed by Leeuwenhoek a few years later using a primitive microscope. However it wasn't until two centuries later that scientists realised that all living organisms were composed of cells, when Schleiden and Schwann proposed cell theory in 1838.

Cell theory states that:

1. All organisms are composed of one or more cells. All the processes of life (growth, metabolism, reproduction) take place within cells.
2. Cells are the smallest units that can be alive.
3. New cells are always formed by division of old cells and new living cells cannot be spontaneously generated. The first cells must have evolved from non-living structures 4 billion years ago, but the development of "life" took place gradually over millions of years, so there was no definable first cell.



## Unicellular and Multicellular Organisms

Some organisms are made of just a single cell (e.g. bacteria, algae, protozoa, yeast). In these unicellular organisms, the single cell carries out all the process of life. But most organisms are multicellular. They are composed of many cells, which are differentiated to carry out different tasks.

## Prokaryotic and Eukaryotic Cells

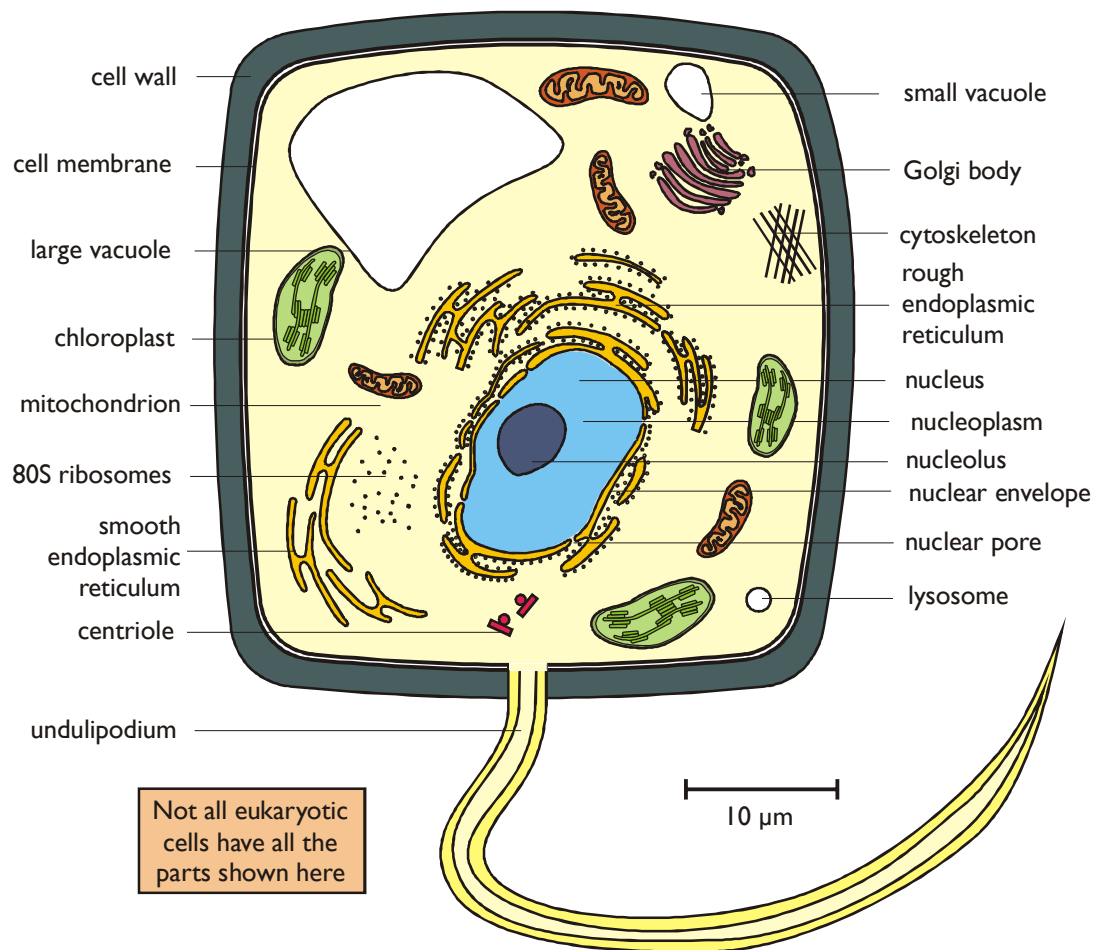
Cells can be classified into two large groups:

- Prokaryotic cells do not have a nucleus, or any interior compartments
- Eukaryotic cells do have a nucleus, and various other interior compartments, called organelles.

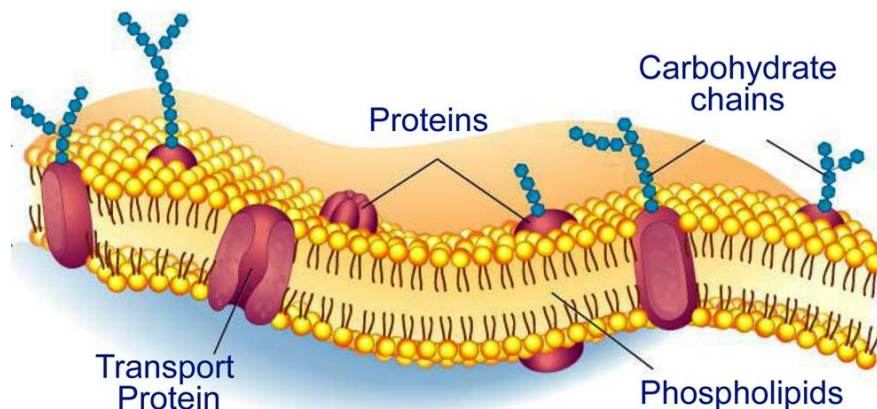
We'll examine these two kinds of cell in detail, based on structures seen in electron micrographs. These show the individual organelles inside a cell.

# Eukaryotic Cells

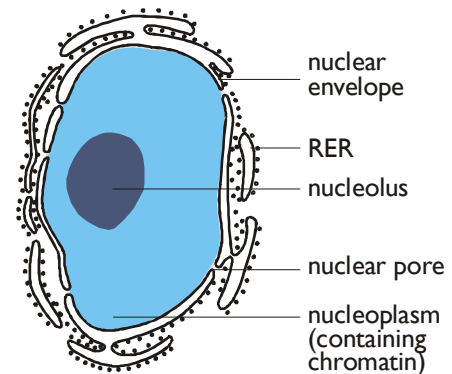
Eukaryotic cells contain a nucleus and numerous other cell organelles.



- **Cell Membrane (or Plasma Membrane).** This is a thin, flexible layer round the outside of all cells made of phospholipids and proteins. It separates the contents of the cell from the outside environment, and controls the entry and exit of materials. The structure and function of the membrane is examined in detail on pxx.

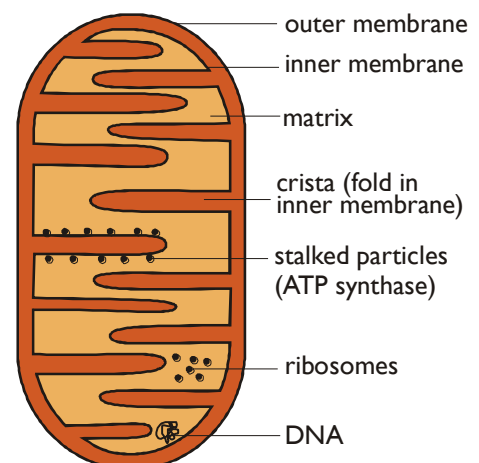


- **Cytoplasm (or Cytosol).** This is the solution within the cell membrane. It contains enzymes for glycolysis (part of respiration) and other metabolic reactions together with sugars, salts, amino acids, nucleotides and everything else needed for the cell to function.
- **Nucleus.** This is the largest organelle. It is roughly spherical and surrounded by a nuclear envelope, which is a double membrane with nuclear pores – large holes containing proteins that control the exit of substances from the nucleus. The interior is called the nucleoplasm, which is full of chromatin – the DNA/protein complex. During cell division the chromatin becomes condensed into discrete observable chromosomes. The nucleolus is a dark region of chromatin, involved in making ribosomes.

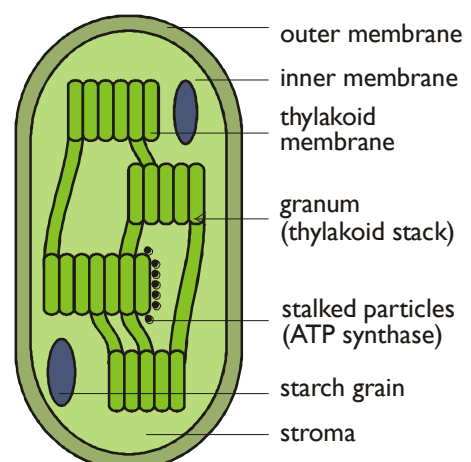


- **Mitochondrion (pl. Mitochondria).** This is a sausage-shaped organelle (8µm long), and is where aerobic respiration takes place and ATP is synthesised in all eukaryotic cells (anaerobic respiration takes place in the cytoplasm). Cells that use a lot of energy (like muscle cells) have many mitochondria.

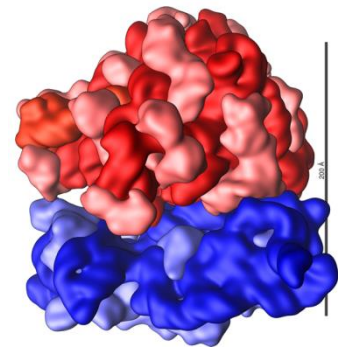
Mitochondria are surrounded by a double membrane: the outer membrane is simple and quite permeable, while the inner membrane is highly folded into cristae, which give it a large surface area. The space enclosed by the inner membrane is called the mitochondrial matrix, and contains small circular strands of DNA. The inner membrane is studded with stalked particles, which are the enzymes that make ATP.



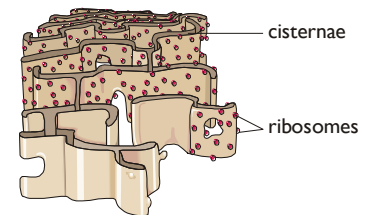
- **Chloroplasts.** Bigger and fatter than mitochondria, chloroplasts are where photosynthesis takes place, so are only found in photosynthetic organisms (plants and algae). Like mitochondria they are enclosed by a double membrane, but chloroplasts also have a third membrane called the thylakoid membrane. The thylakoid membrane is folded into thylakoid disks, which are then stacked into piles called grana. The space between the inner membrane and the thylakoid is called the stroma. The thylakoid membrane contains chlorophyll and chloroplasts also contain starch grains, ribosomes and circular DNA.



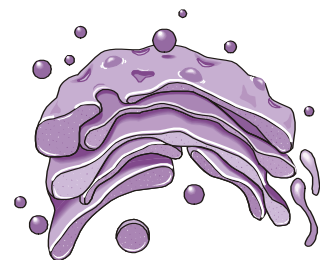
- **Ribosomes.** These are the smallest and most numerous of the cell organelles, and are the sites of protein synthesis. Ribosomes are either found free in the cytoplasm, where they make proteins for the cell's own use, or they are found attached to the rough endoplasmic reticulum, where they make proteins for export from the cell. All eukaryotic ribosomes are of the larger, "80S", type.



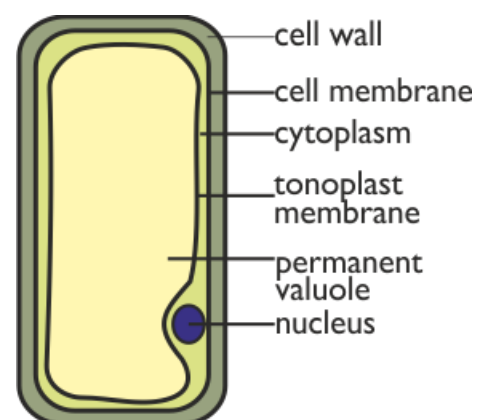
- **Endoplasmic Reticulum (ER).** This is a series of membrane channels involved in synthesising and transporting materials. Rough Endoplasmic Reticulum (RER) is studded with numerous ribosomes, which give it its rough appearance. The ribosomes synthesise proteins, which are processed in the RER (e.g. by enzymatically modifying the polypeptide chain, or adding carbohydrates), before being exported from the cell via the Golgi Body. Smooth Endoplasmic Reticulum (SER) does not have ribosomes and is used to process materials, mainly lipids, needed by the cell.



- **Golgi Body (or Golgi Apparatus).** Another series of flattened membrane vesicles, formed from the endoplasmic reticulum. Its job is to transport proteins destined for extracellular use from the ER to the cell membrane for export. Parts of the RER containing proteins fuse with one side of the Golgi body membranes, while at the other side small vesicles bud off and move towards the cell membrane, where they fuse, releasing their contents to the outside of the cell by exocytosis.

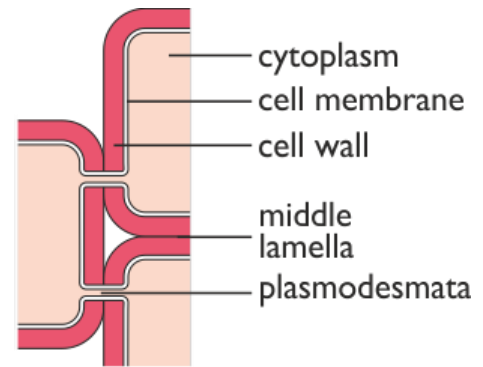


- **Vacuoles.** These are membrane-bound sacs containing water or dilute solutions of salts and other solutes. Most cells can have small vacuoles that are formed as required, but plant cells usually have one very large permanent vacuole that fills most of the cell, so that the cytoplasm (and everything else) forms a thin layer round the outside. Plant cell vacuoles are surrounded by a tonoplast membrane and filled with cell sap. They help to keep the cell rigid, or turgid. Some unicellular protists have feeding vacuoles for digesting food, or contractile vacuoles for expelling water.

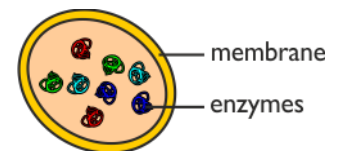




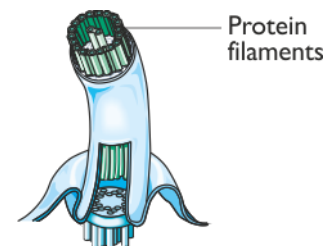
- **Cell Wall.** This is a thick layer outside the cell membrane used to give a cell strength and rigidity and resist osmotic lysis. Cell walls consist of a network of fibres, which give strength but are freely permeable to solutes (unlike membranes). A wickerwork basket is a good analogy. Plant cell walls are made mainly of cellulose, but can also contain hemicellulose, pectin, lignin and other polysaccharides. There are often channels through plant cell walls called plasmodesmata, which link the cytoplasms of adjacent cells. Fungal cell walls are made of chitin.



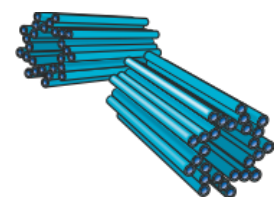
- **Lysosomes.** These are small membrane-bound vesicles formed from the RER containing a cocktail of digestive enzymes. They are used to break down unwanted chemicals, toxins, organelles or even whole cells, so that the materials may be recycled. They can also fuse with a feeding vacuole or a phagosome to digest its contents.



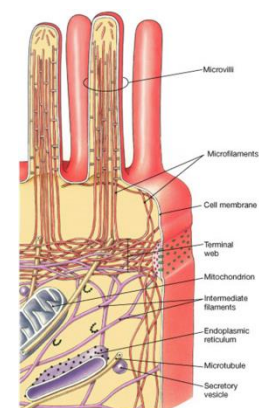
- **Cytoskeleton.** This is a network of protein fibres extending throughout all eukaryotic cells, used for support, transport and motility. The cytoskeleton is attached to the cell membrane and gives the cell its shape, as well as holding all the organelles in position. The cytoskeleton is also responsible for all cell movements, such as cell division, cilia and flagella, cell crawling and muscle contraction in animals.



- **Centrioles.** There are always two centrioles found near the nucleus. They are part of the cytoskeleton and are used in cell division to make the spindle fibres that move the chromosomes.



- **Cilia, Flagella and Microvilli.** These are different finger-like extensions of the cell membrane containing cytoskeleton proteins so they can move. Cilia are short and numerous and are used for moving the cell (e.g. ciliates) or for moving the extracellular fluid (e.g. trachea). Flagella are longer than the cell, there are usually only one or two of them and they are used for motility (e.g. sperm). Microvilli are short extensions found in certain cells such as in the epithelial cells of the intestine and kidney, where they increase the surface area for absorption of materials.



## Comparison of different types of Eukaryotic Cell

	Fungi	Plants	Animals
Nucleus	✓	✓	✓
Mitochondria	✓	✓	✓
Chloroplast	✗	✓	✗
80S ribosome	✓	✓	✓
Vacuoles	✓	✓	✗
Cytoskeleton	✓	✓	✓
Centriole	✓	✓	✓
Plasma membrane	✓	✓	✓
Cell Wall	✓(chitin)	✓(cellulose)	✗

## Cell Organisation

In multicellular organisms the eukaryotic cells are specialised to perform different functions. Thousands of different types of cell have been described, such as red blood cells, smooth muscle cells, adipose cells, B lymphocytes, osteocytes, motor neurones, ova, ciliated epithelial cells, endocrine cells, hepatocytes, palisade mesophyll cells, guard cells, root hair cells, cambium, and countless more.

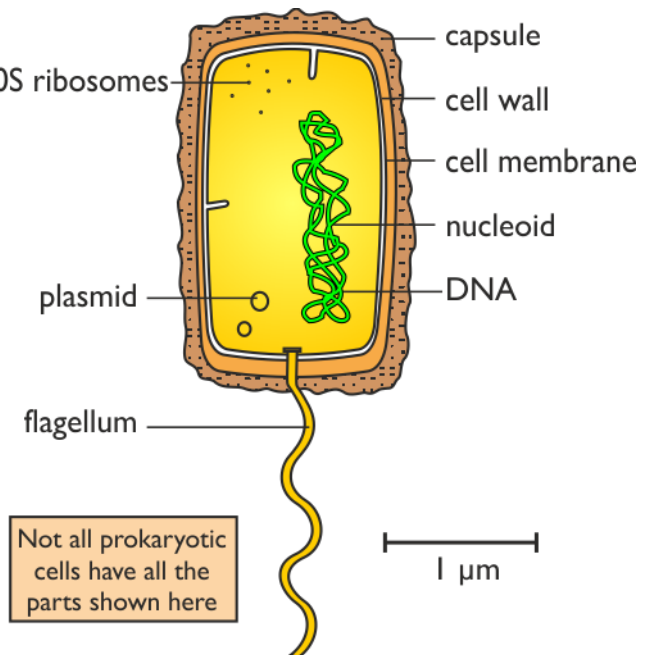
Eukaryotic cells are arranged into:

- **A tissue** is a group of similar cells performing a particular function. Simple tissues are composed of one type of cell, while compound tissues are composed of more than one type of cell. Animal tissues include epithelium (lining tissue), connective, nerve, muscle, blood, glandular. Plant tissues include epidermis, meristem, vascular, mesophyll, cortex.
- **An organ** is a group of physically-linked different tissues working together as a functional unit. For example the stomach is an organ composed of epithelium, muscular, glandular and blood tissues. A plant leaf is also an organ, composed of mesophyll, epidermis and vascular tissues.
- **An organ system** is a group of organs working together to carry out a specific complex function. Humans have seven main systems: the circulatory, digestive, nervous, respiratory, reproductive, urinary and muscular-skeletal systems.

# Prokaryotic Cells

Prokaryotic cells are smaller than eukaryotic cells and do not have a nucleus or indeed any membrane-bound organelles. The prokaryotes comprise the bacteria and archaeabacterial (see unit 2). Prokaryotic cells are much older than eukaryotic cells and they are far more abundant (there are ten times as many bacteria cells in a human than there are human cells). The main features of prokaryotic cells are:

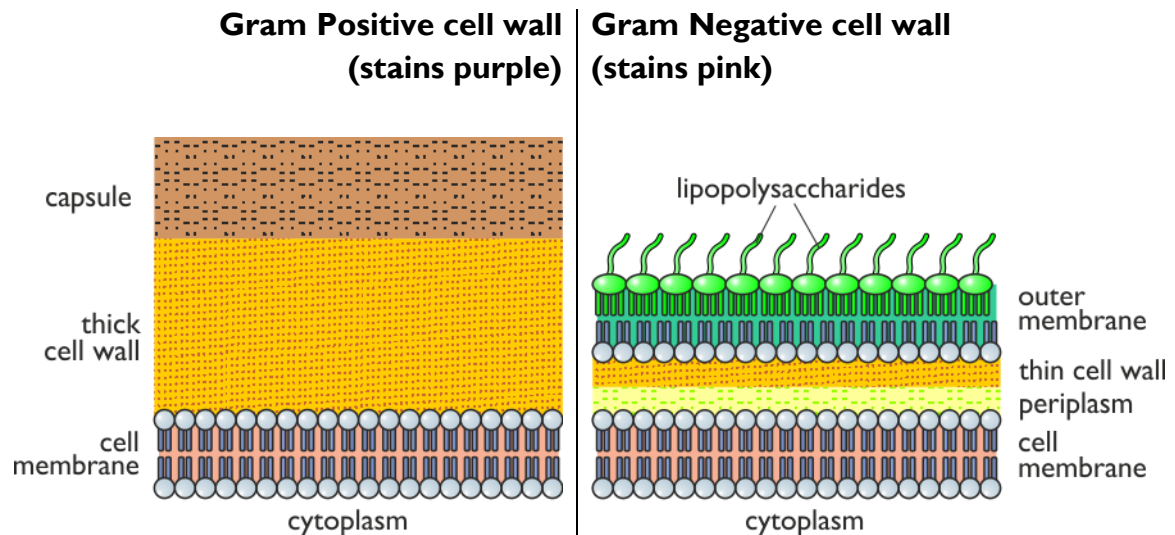
- **Cytoplasm.** Contains all the enzymes needed for all metabolic reactions, since there are no organelles
- **Ribosomes.** The smaller “70S” type, all free in the cytoplasm and never attached to membranes. Used for protein synthesis.
- **Nucleoid.** The region of the cytoplasm that contains DNA. It is not surrounded by a nuclear membrane.
- **DNA.** Always circular (i.e. a closed loop), and not associated with any proteins to form chromatin. Sometimes referred to as the bacterial chromosome to distinguish it from plasmid DNA.



- **Plasmid.** Small circles of DNA, separate from the main DNA loop. Used to exchange DNA between bacterial cells, and also very useful for genetic engineering (see unit 3).
- **Plasma membrane.** Made of phospholipids and proteins, like eukaryotic membranes.
- **Cell Wall.** This is a thick layer outside the cell membrane used to give a cell strength and rigidity and resist osmotic lysis. Made of peptidoglycan (not cellulose), which is a glycoprotein (i.e. a protein/carbohydrate complex, also called murein). There are two types of cell wall: Gram-positive and Gram-negative (see next page).
- **Capsule.** A thick polysaccharide layer outside of the cell wall. Used for sticking cells together, as a food reserve, as protection against desiccation and chemicals, and as protection against phagocytosis. In some species the capsules of many cells fuse together forming a mass of sticky cells called a biofilm. Dental plaque is an example of a biofilm.
- **Flagellum.** A rigid rotating helical-shaped tail used for propulsion. The motor is embedded in the cell membrane and is driven by a  $H^+$  gradient across the membrane. The bacterial flagellum is quite different from the eukaryotic flagellum.

## The Bacterial Cell Wall

There are two kinds of bacterial cell wall, which are identified by the Gram Stain technique when observed under the microscope. Gram positive bacteria stain purple, while Gram negative bacteria stain pink. The technique was discovered by Christian Gram in 1884 and is still used today to identify and classify bacteria. We now know that the different staining is due to two types of cell wall:



Gram positive bacteria have a thick peptidoglycan cell wall outside their cell membrane. The cell wall is very strong and allows these bacteria to withstand severe physical conditions. There may be a capsule outside the cell wall.

Gram negative bacteria have a more complex structure, with a thin layer of periplasm (like cytoplasm but outside the cell), a thin peptidoglycan cell wall, and then a second, outer membrane, which contains lipopolysaccharides instead of phospholipids in its outer layer. This layer resists antibiotics and lysozyme enzymes, so gram negative bacteria are more difficult to kill.

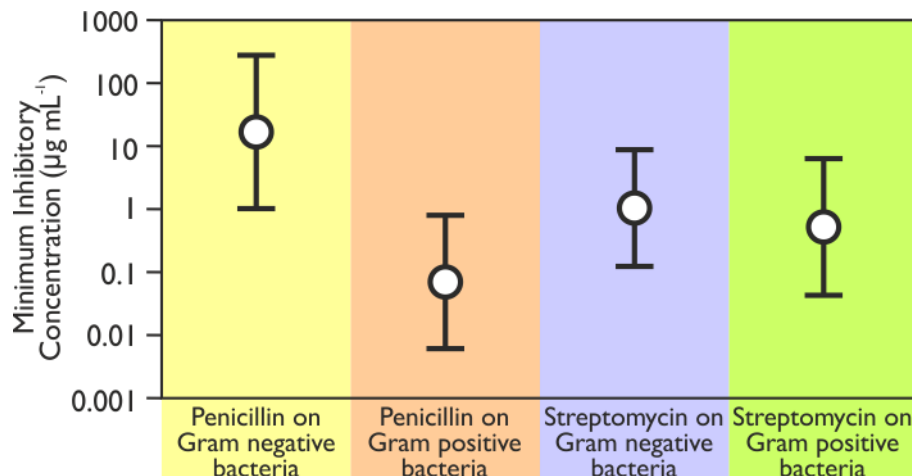
## Bacteria Cells and Antibiotics

Antibiotics are antimicrobial chemicals produced naturally by other microbes (usually fungi or bacteria) and used to treat bacterial infections. Antibiotics are so useful because they are selectively toxic i.e. they kill bacteria growing in human tissue without killing the host human cells. Antibiotics do this by inhibiting enzymes that are unique to prokaryotic cells, such those involved in synthesising the bacterial cell wall or 70S ribosomes. For example:

- penicillin (and related antibiotics ampicillin, amoxicillin and methicillin) Inhibits an enzyme involved in the synthesis of peptidoglycan for bacterial cell wall. This weakens the cell wall, killing bacterial cells by osmotic lysis. The penicillins can't easily cross cell membranes, so they are only effective against Gram-positive bacteria (since the peptidoglycan cell wall is exposed) but not against Gram-negative bacteria (since the wall is behind the outer membrane).

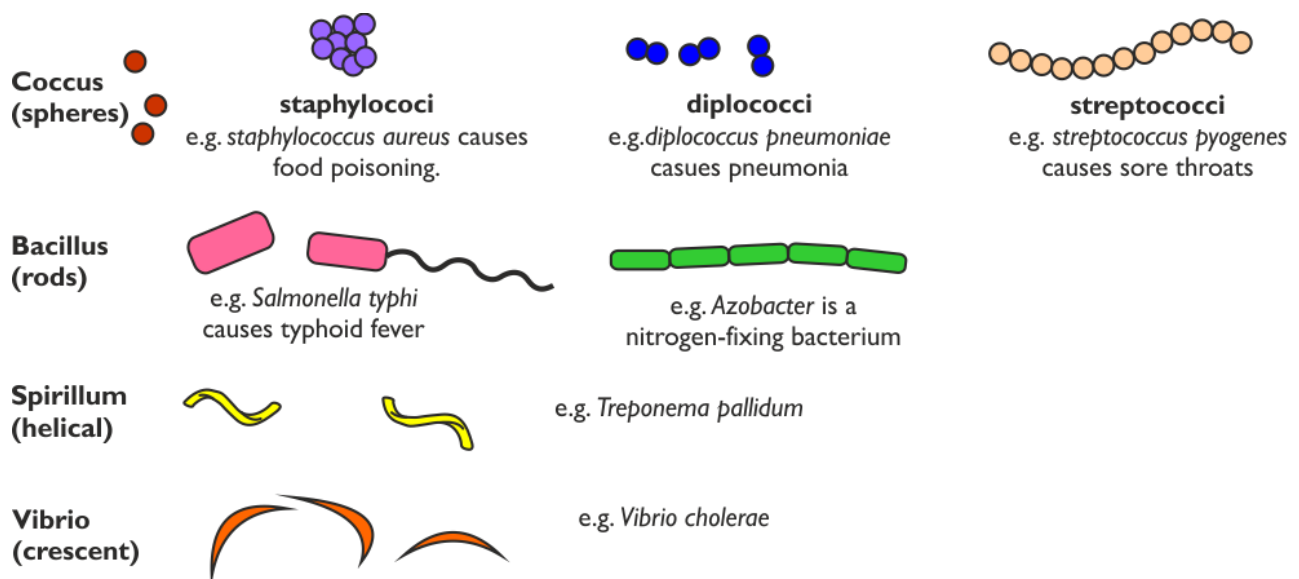
- Streptomycin, tetracycline and erythromycin inhibit enzymes in 70S ribosomes. This stops protein synthesis so prevents cell division. These antibiotics are equally effective against Gram-positive and Gram-negative bacteria, since they both contain the same 70S ribosomes.

These effects are reflected in the concentration of antibiotics required to treat bacterial infections, shown on this chart:



## Bacterial Cell Shapes

Bacteria have a variety of distinctive shapes when seen under a microscope:



## Summary of the Differences Between Prokaryotic and Eukaryotic Cells

Prokaryotic Cells	Eukaryotic cells
small cells (< 5 $\mu\text{m}$ )	larger cells (> 10 $\mu\text{m}$ )
always unicellular	often multicellular
no nucleus or any membrane-bound organelles	always have nucleus and other membrane-bound organelles
DNA is circular, without proteins	DNA is linear and associated with proteins to form chromatin
ribosomes are small (70S)	ribosomes are large (80S)
no cytoskeleton	always has a cytoskeleton
motility by rigid rotating flagellum, made of flagellin	motility by flexible waving undulipodium, made of tubulin
cell division is by binary fission	cell division is by mitosis or meiosis
reproduction is always asexual	reproduction is asexual or sexual
huge variety of metabolic pathways	common metabolic pathways

## Endosymbiosis

Prokaryotic cells are far older and more diverse than eukaryotic cells. Prokaryotic cells have probably been around for 3.5 billion years, while eukaryotic cells arose only about 1 billion years ago. It is thought that eukaryotic cell organelles like nuclei, mitochondria and chloroplasts are derived from prokaryotic cells that became incorporated inside larger prokaryotic cells. This idea is called endosymbiosis, and is supported by these observations:

- organelles contain circular DNA, like bacteria cells.
- organelles contain 70S ribosomes, like bacteria cells.
- organelles have double membranes, as though a single-membrane cell had been engulfed and surrounded by a larger cell.
- organelles reproduce by binary fission, like bacteria.
- organelles are very like some bacteria that are alive today.





# Microscopy

Of all the techniques used in biology microscopy is probably the most important. The vast majority of living organisms are too small to be seen in any detail with the human eye, and cells and their organelles can only be seen with the aid of a microscope. Microscopes have two properties: magnification and resolution.

## Magnification and Resolution

- **Magnification** is a dimensionless number, usually written as a magnification factor, e.g.  $\times 100$ . It simply indicates how much bigger the image is than the original object. By using more lenses microscopes can magnify by a larger amount, but the image may get more blurred, so this doesn't always mean that more detail can be seen.
- **Resolution** is a distance, usually measured in nm. It is the smallest separation at which two separate objects can be distinguished, or resolved. For example if the resolution of a microscope is 50nm, then objects closer together than 50nm cannot be seen as separate objects. The resolution of a microscope is ultimately limited by the wavelength of light used (400-600nm for visible light), so to improve resolution waves with a shorter wavelength is needed. This is how electron microscopes gain resolution.

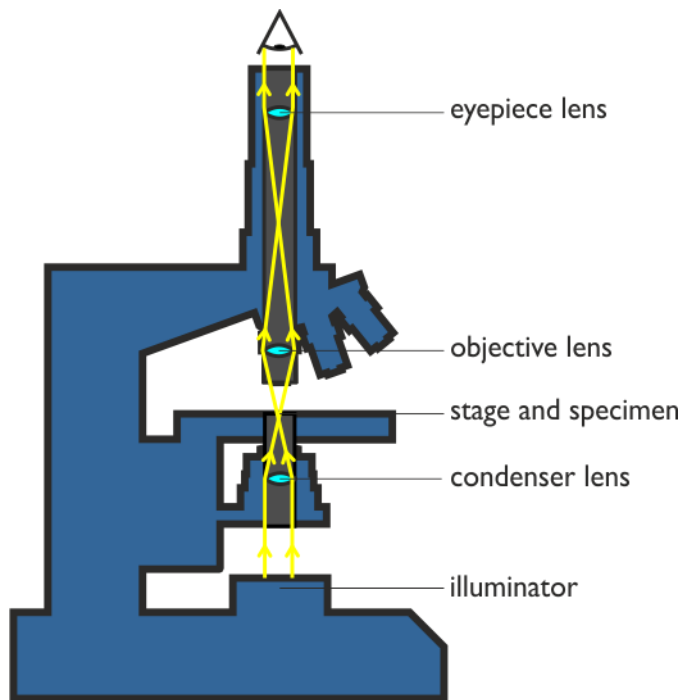
This chart shows the effect of magnification and resolution on the appearance of two small objects.

	Low resolution (a large distance)	High resolution (a small distance)
Low magnification		
High magnification		

There are three common kinds of microscope:

1. Light (or optical) microscope
2. Transmission electron microscope (TEM)
3. Scanning electron microscope (SEM)

## I. The Light Microscope



Light, or optical, microscopes are the oldest, simplest and most widely-used form of microscopy. Specimens are illuminated with visible light, which is focused using glass lenses and viewed using the eye or photographic film. Most light microscopes have three lenses: a condenser lens to focus the light onto the specimen; an objective lens to magnify the image; and an eyepiece lens to focus the image on the eye. The total magnification of a microscope is given by the product of the objective and eyepiece lenses. The resolution of a light microscope is about 200nm, but special optical techniques (like fluorescence microscopy and interference microscopy) can improve this limit down to 1nm.

Specimens can be living or dead but need to be thin so that enough light can be transmitted through them. Most biological specimens will then be invisible, so they usually need to be coloured with a chemical stain to make them stand out. Some common stains are:

- Methylene blue to stain DNA in nuclei
- Iodine to stain starch in plant cells
- Phalloidin to stain the cytoskeleton
- Phloroglucinol to stain lignin in xylem cell walls

## 2. The Transmission Electron Microscope (TEM)

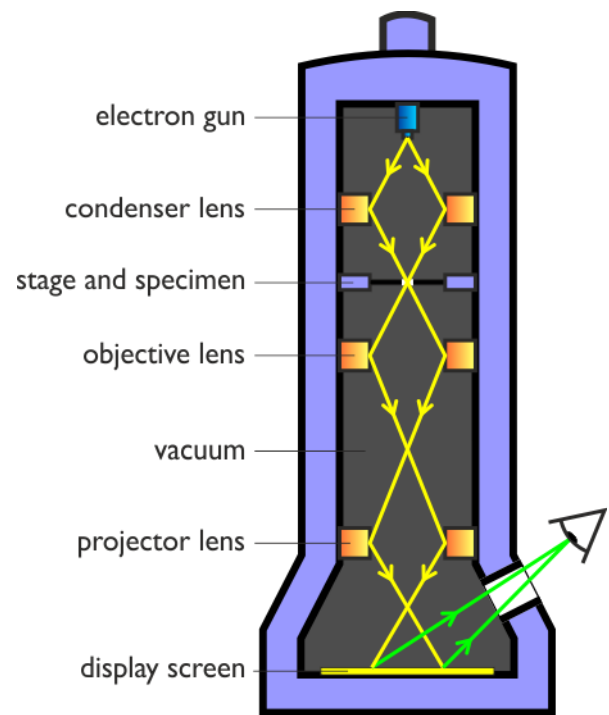
The Transmission Electron Microscope (TEM) uses a beam of electrons, rather than electromagnetic radiation, to "illuminate" the specimen. This may seem strange, but electrons behave like waves and can easily be produced (using a hot wire), focused (using electromagnets) and detected (using a phosphor screen or photographic film). A beam of electrons has an effective wavelength of less than 1nm, so can be used to resolve small sub-cellular ultrastructure. The development of the electron microscope in the 1930s revolutionised biology, allowing organelles such as mitochondria, ER and membranes to be seen in detail for the first time.



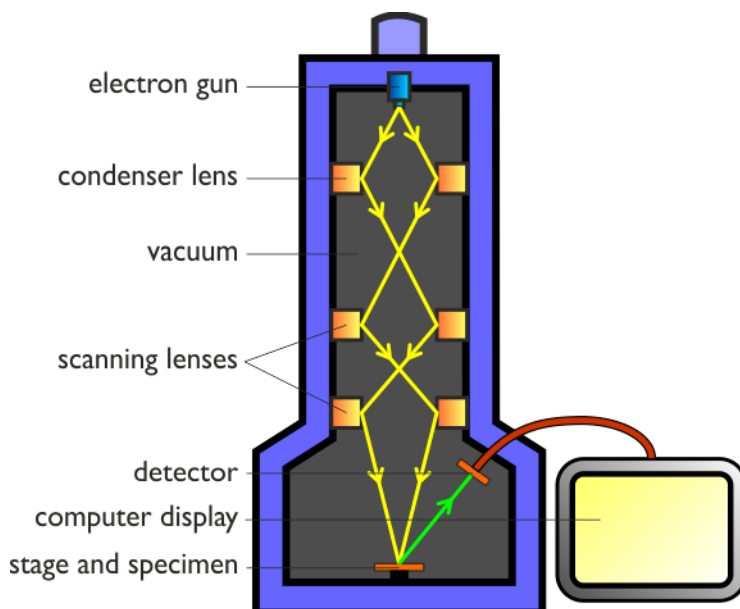
Electron microscope specimens need to be very thin, and to prevent them breaking the specimens have to be embedded in plastic. Biological specimens are usually transparent to electrons, so they also have to be stained with electron-dense heavy metal compounds such as gold, osmium or even uranium salts. These stains aren't coloured, so electron microscope images are always monochrome (though they can be coloured artificially).

The biggest problem with electron microscopy is that there must be a vacuum inside the electron microscope (or the electron beam would be scattered by air molecules), so it can't be used for living organisms. Specimens can also be damaged by the electron beam, so delicate structures and molecules can be destroyed.

There is always a concern that structures observed by an electron microscope are artefacts (i.e. due to the preparation process and not present in the real cell), but improvements in technique have eliminated most of these.



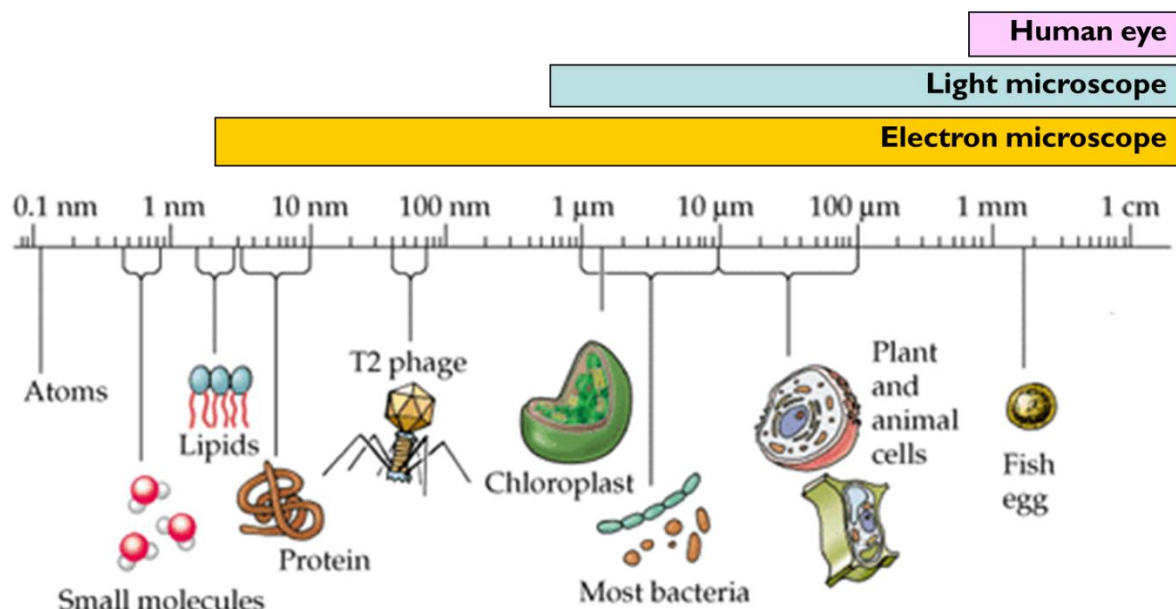
### 3. The Scanning Electron Microscope (SEM)



The scanning electron microscope (SEM) works in a very different way to other microscopes. It scans a fine beam of electrons onto a specimen and detects the electrons scattered back by the surface. The scattered electron signal is then converted into a computer-generated image of the surface of the specimen. These images are fantastically detailed but do not have very high magnification.

## Comparison of Different Microscopes

	Light Microscope	TEM	SEM
<b>Advantages</b>	<ul style="list-style-type: none"> <li>• good magnification (1000x)</li> <li>• can use living specimens</li> <li>• colour images</li> </ul>	<ul style="list-style-type: none"> <li>• high magnification (5 000 000x)</li> <li>• very good resolution (1nm)</li> </ul>	<ul style="list-style-type: none"> <li>• gives 3-dimensional images</li> <li>• don't need thin sections</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>• poor resolution (200nm)</li> <li>• can't see organelles</li> <li>• specimens must be stained</li> </ul>	<ul style="list-style-type: none"> <li>• vacuum, so can't use living specimens</li> <li>• complex specimen preparation – specimens need to be very thin and embedded in plastic</li> <li>• no colour</li> <li>• specimens can be damaged by electron beam, causing artefacts.</li> </ul>	<ul style="list-style-type: none"> <li>• resolution not as good as TEM (10nm)</li> <li>• can't see internal structures</li> </ul>
<b>Uses</b>	<ul style="list-style-type: none"> <li>• tissues, cells and small organisms</li> <li>• videos</li> </ul>	<ul style="list-style-type: none"> <li>• cell organelles, prokaryotes and viruses</li> </ul>	<ul style="list-style-type: none"> <li>• surfaces of living and non-living specimens</li> </ul>



# Magnification Calculations

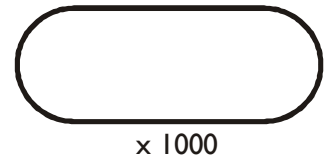
Microscope drawings and photographs (micrographs) are usually magnified, and you have to be able to calculate the actual size of the object from the drawing. There are two ways of doing this:

## 1. Using a Magnification Factor

Sometimes the image has a magnification factor on it. The formula for the magnification is:

$$\text{magnification} = \frac{\text{image length}}{\text{actual length}}, \text{ or } \begin{array}{c} \text{I} \\ \text{M} \quad \text{A} \end{array}$$

For example if this drawing of an object is 40mm long and the magnification is  $\times 1000$ , then the object's actual length is  $\frac{I}{M} = \frac{40}{1000} = 0.04\text{mm} = 40\mu\text{m}$ . Always convert your answer to appropriate units, usually  $\mu\text{m}$  for cells and organelles.



Sometimes you have to calculate the magnification. For example if this drawing of an object is 40mm long and its actual length is  $25\mu\text{m}$ , the magnification of the drawing is:  $\frac{I}{A} = \frac{40}{0.025} = \times 1600$ . Remember, the image and actual length must be

in the same units. Magnifications can also be less than one (e.g.  $\times 0.1$ ), which means that the drawing is smaller than the actual object.

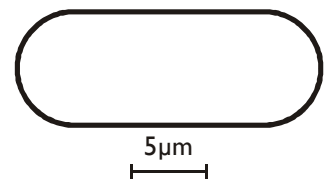


## 2. Using a Scale Bar

Sometimes the picture has a scale bar on it. The formula for calculating the actual length is:

$\text{actual size} = \frac{\text{image length}}{\text{bar length}} \times \text{bar scale}$ . The image size and bar length must be measured in the same units (usually mm), and the actual size will come out in the same units as the bar scale.

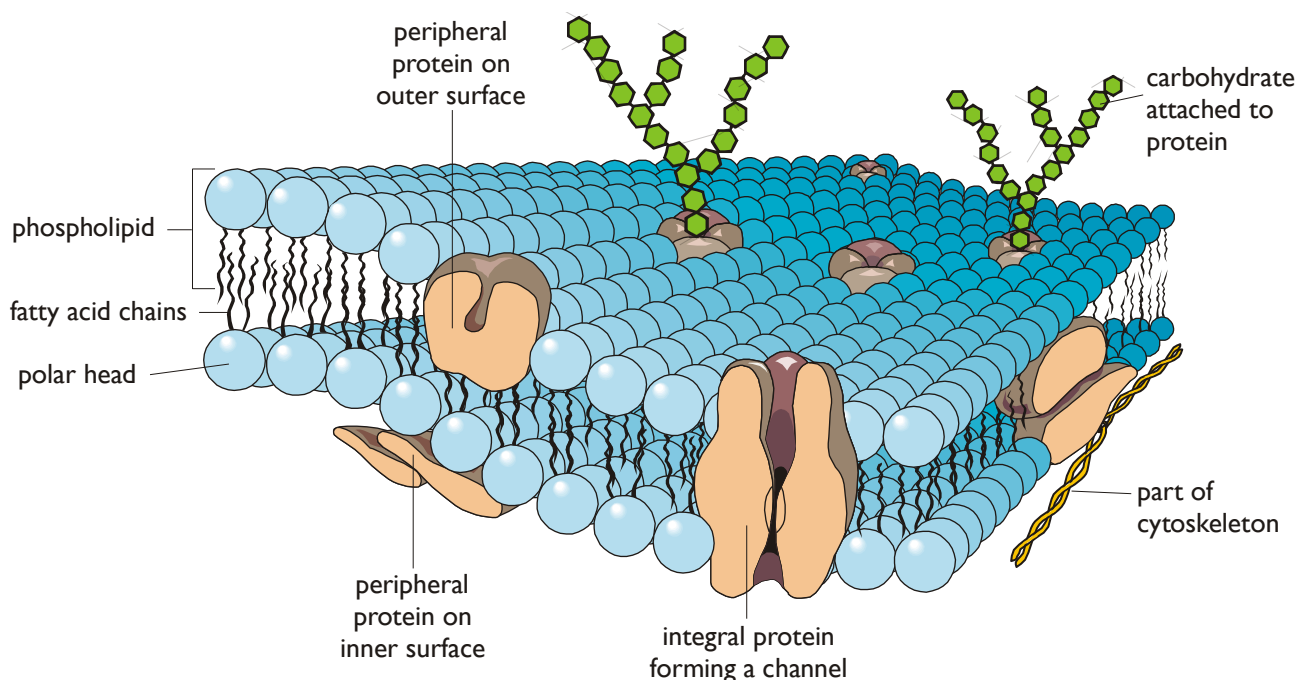
For example if this drawing of an object is 40mm long and the  $5\mu\text{m}$  scale bar is 10mm long, then the object's actual size is:  $\frac{40}{10} \times 5\mu\text{m} = 20\mu\text{m}$ .



It's good to have a rough idea of the size of objects, to avoid silly mistakes. A mitochondrion is not 30mm long! Scale bars make this much easier than magnification factors.

# The Cell Membrane

The cell membrane (or plasma membrane) surrounds all living cells, and is the cell's most important organelle. It controls how substances can move in and out of the cell and is responsible for many other properties of the cell as well. The membranes that surround the nucleus and other organelles are almost identical to the cell membrane. Membranes are composed of phospholipids, proteins and carbohydrates arranged as shown in this diagram.



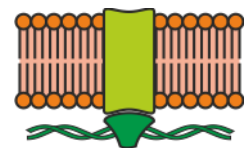
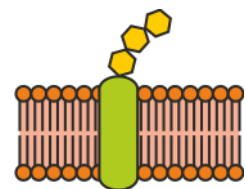
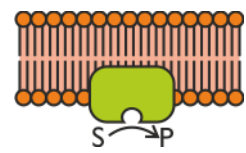
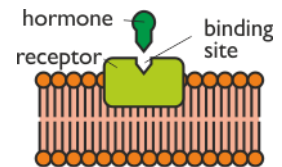
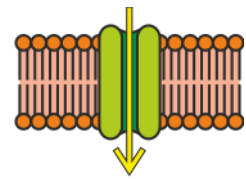
The phospholipids form a thin, flexible sheet, while the proteins "float" in the phospholipid sheet like icebergs, and the carbohydrates extend out from the proteins. This structure is called a fluid mosaic structure because all the components can move around (it's fluid) and the many different components all fit together, like a mosaic.

**The phospholipids** are arranged in a bilayer (i.e. a double layer), with their polar, hydrophilic phosphate heads facing out towards water, and their non-polar, hydrophobic fatty acid tails facing each other in the middle of the bilayer. This hydrophobic layer acts as a barrier to most molecules, effectively isolating the two sides of the membrane. Different kinds of membranes can contain phospholipids with different fatty acids, affecting the strength and flexibility of the membrane, and animal cell membranes also contain cholesterol linking the fatty acids together and so stabilising and strengthening the membrane.

**The proteins** usually span from one side of the phospholipid bilayer to the other (integral proteins), but can also sit on one of the surfaces (peripheral proteins). They can slide around the membrane very quickly and collide with each other, but can never flip from one side to the other. The proteins have hydrophilic amino acids in contact with the water on the outside of membranes, and hydrophobic amino acids in

contact with the fatty chains inside the membrane. Proteins comprise about 50% of the mass of membranes, and are responsible for most of the membrane's properties.

- **Transport proteins.** Most transport of small molecules across the membrane take place through integral proteins. This transport includes facilitated diffusion and active transport (more details below).
- **Receptor proteins.** Receptor proteins must be on the outside surface of cell membranes and have a specific binding site where hormones or other chemicals can bind to form a hormone-receptor complex (like an enzyme-substrate complex). This binding then triggers other events in the cell membrane or inside the cell.
- **Enzymes.** Enzyme proteins catalyse reactions in the cytoplasm or outside the cell, such as maltase in the small intestine (more in digestion).
- **Recognition proteins.** Some proteins are involved in cell recognition. These are often glycoproteins, such as the A and B antigens on red blood cell membranes.
- **Structural proteins.** Structural proteins on the inside surface of cell membranes and are attached to the cytoskeleton. They are involved in maintaining the cell's shape, or in changing the cell's shape for cell motility. Structural proteins on the outside surface can be used in cell adhesion – sticking cells together temporarily or permanently.



**The carbohydrates** are found on the outer surface of all eukaryotic cell membranes, and are attached to the membrane proteins or sometimes to the phospholipids. Proteins with carbohydrates attached are called glycoproteins, while phospholipids with carbohydrates attached are called glycolipids.

*Remember that a membrane is not just a lipid bilayer, but comprises the lipid, protein and carbohydrate parts.*

# Movement across Cell Membranes

The job of the cell membrane is to control what materials can enter and leave cells. There are five main methods by which substances can move across a cell membrane:

## Passive transport methods

1. Lipid Diffusion
2. Facilitated Diffusion
3. Osmosis (Water Diffusion)

## Active transport methods

4. Active Transport
5. Bulk transport

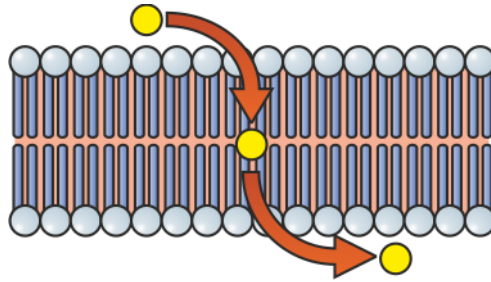
## Passive Transport Methods

Passive processes do not require any energy, other than the thermal energy of the surroundings. Substances move around randomly within cells due to thermal motion, and if there is a concentration difference between two places then the random movement results in a substance diffusing down its concentration gradient from a high to a low concentration. This process is called diffusion.



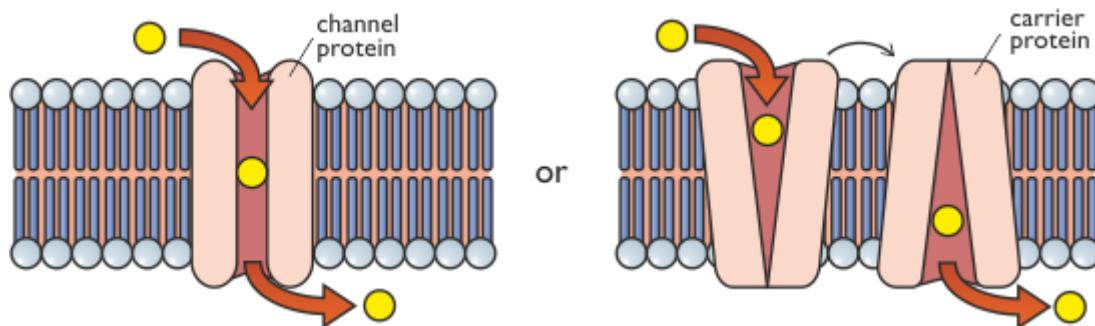
Passive transport is simply diffusion across a cell membrane, so does not require metabolic energy and is simply driven by thermal energy. Substances diffuse in both directions across a membrane, but there is a net movement down a concentration gradient.

## 1. Lipid Diffusion (Simple Diffusion)



A few substances can diffuse directly through the lipid bilayer part of the membrane. The only substances that can do this are hydrophobic (lipid-soluble) molecules such as steroids, and a few extremely small hydrophilic molecules, such as  $\text{H}_2\text{O}$ ,  $\text{O}_2$  and  $\text{CO}_2$ . For these molecules the membrane is no barrier at all. Since lipid diffusion is a passive process, no energy is involved and substances can only move down their concentration gradient. Lipid diffusion cannot be switched on or off by the cell.

## 2. Facilitated Diffusion.

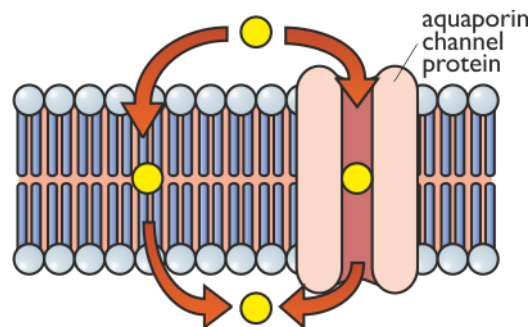


Facilitated Diffusion is the diffusion of substances across a membrane through a trans-membrane transport protein molecule. The transport proteins tend to be specific for one molecule, so substances can only cross a membrane that contains an appropriate protein. This is a passive diffusion process, so no energy is involved and substances can only move down their concentration gradient. There are two kinds of transport protein:

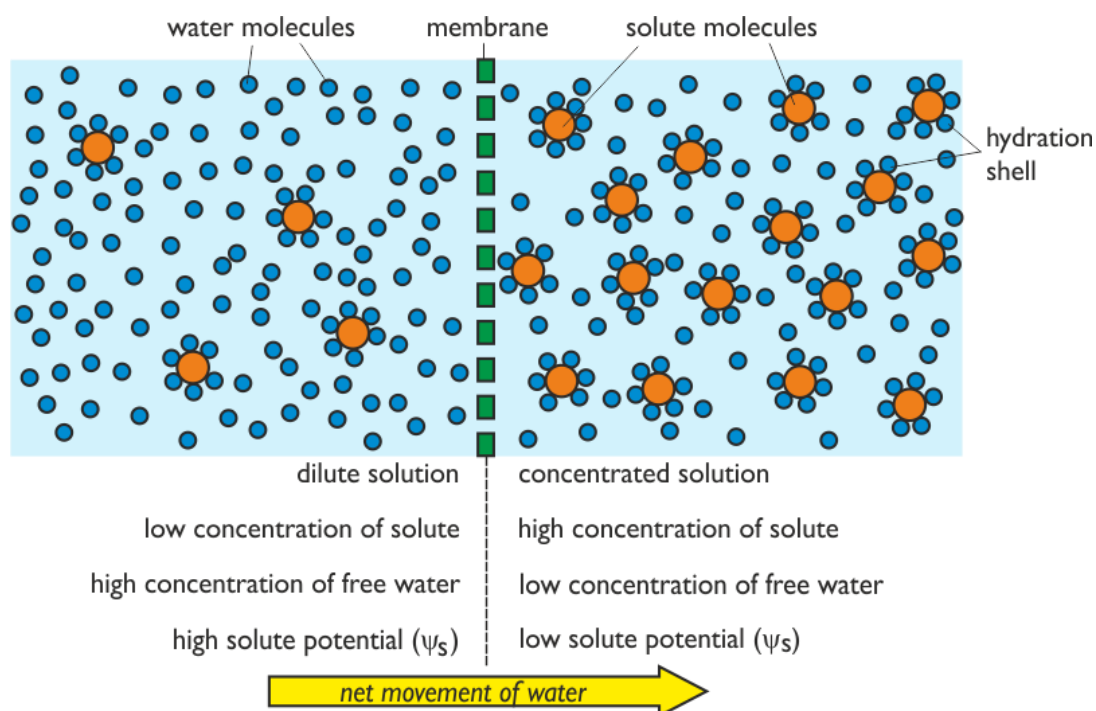
- Channel Proteins form a water-filled pore or channel in the membrane. This allows charged substances to diffuse across membranes. Most channels can be gated (opened or closed), allowing the cell to control the entry and exit of ions. In this way cells can change their permeability to certain ions. Ions like  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{Cl}^-$  diffuse across membranes through specific ion channels.
- Carrier Proteins have a binding site for a specific solute and constantly flip between two states so that the site is alternately open to opposite sides of the membrane. The substance will bind on the side where it is at a high concentration and be released where it is at a low concentration. Important solutes like glucose and amino acids diffuse across membranes through specific carriers. Sometimes carrier proteins have two binding sites and so carry two molecules at once. This is called cotransport, and a common example is the sodium/glucose cotransporter found in the small intestine (see next page). Both molecules must be present for transport to take place.

### 3. Osmosis (Water Diffusion)

Osmosis is the diffusion of water across a membrane. Water can diffuse across a membrane in two ways: partly through the phospholipid bilayer (an example of lipid diffusion) and partly through protein channels called aquaporins (an example of facilitated diffusion).



As we've seen, diffusion takes place down a concentration gradient but, as the solvent in all cells, the total concentration of water is very high (about  $55\text{mol L}^{-1}$ ) and it never changes. However, much of this water is not free to diffuse, since it is bound to solute molecules as a hydration shell. The more concentrated the solution, the more solute molecules there are in a given volume, and the more water molecules are bound in hydration shells, so the fewer free water molecules there are. Two different solutions can be separated by a cell membrane, since membranes are partially-permeable (i.e. the solvent water molecules can pass through easily, but larger solute molecules cannot). So if there is a concentration difference of solutes across a membrane, there will also be a concentration difference of free water molecules across the membrane, so water will diffuse across. This is osmosis. In osmosis water diffuses from a more dilute solution to a more concentrated solution across a partially-permeable membrane.





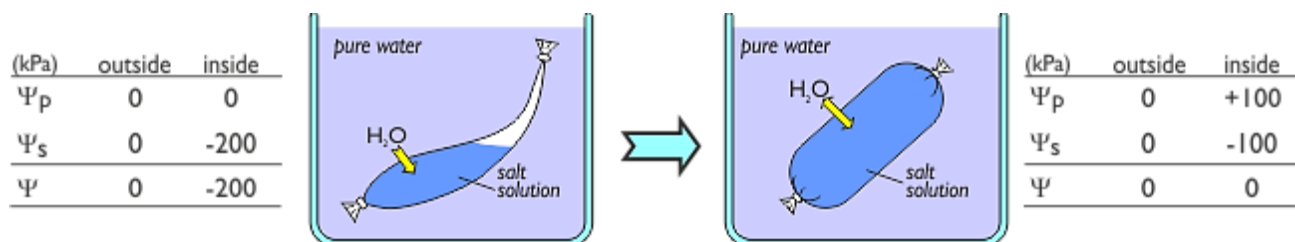
## Water Potential

Osmosis can be quantified using water potential, so we can calculate which way water will move. Water potential is a force and is measured in units of pressure (Pa, or usually kPa), and the rule is that water always "falls" from a high to a low water potential (in other words it's a bit like gravity potential or electrical potential). It is abbreviated by the symbol  $\Psi_w$  or just  $\Psi$  (the Greek letter psi, pronounced "sy").

Water potential is made up of two components: pressure potential ( $\Psi_p$ ) and solute potential ( $\Psi_s$ ).

<b>water potential</b> $\Psi$	=	<b>pressure potential</b> $\Psi_p$	+	<b>solute potential</b> $\Psi_s$
The overall pressure on water. $\Psi$ can be positive or negative. If two compartments are separated by a partially-permeable membrane, then water diffuses from the higher to the lower water potential.	=	Hydrostatic pressure due to an external force. $\Psi_p$ is usually positive, which means a compression force (e.g. due to a cell wall) but it can be negative, which means a tension force (e.g. in xylem vessels). Pressure potential used to be known as <u>turgor pressure</u> , and this term is sometimes still applied to plant cells.	+	Pressure due to dissolved solutes. The higher the solute concentration, the lower the solute potential. $\Psi_s$ is always negative since pure water has $\Psi_s = 0$ , and any solute decreases $\Psi_s$ . Solute potential used to be known as osmotic pressure or <u>osmotic potential</u> , but these terms are obsolete.

In this experiment a Visking tube is used a partially permeable membrane that lets water through but not solute molecules. The experiment illustrates the use of the water potential equation.



A Visking tube bag containing salt solution is placed in a beaker of pure water. The beaker is open to the air, so there are no external forces on the water, so  $\Psi_p=0$  and since pure water has  $\Psi_s=0$  then overall  $\Psi_s=0$ . The Visking bag is floppy (flaccid) so is not generating any pressure so  $\Psi_p=0$ , but the salt solution has a  $\Psi_s=-200\text{kPa}$ , so the overall  $\Psi=-200\text{kPa}$ . So water enters the bag by osmosis, down its water potential gradient.

As water enters the bag it dilutes the salt, raising  $\Psi_s$  to  $-100\text{kPa}$ . The incoming water expands the bag till it can expand no more, and it applies a compression force resisting further entry of water ( $\Psi_p=+100\text{kPa}$ ). At equilibrium the positive pressure potential balances the negative solute potential so the water potential is zero and there is no net movement of water.

We can use water potential to understand the behaviour of cells in different surroundings or solutions.

There are three situations:

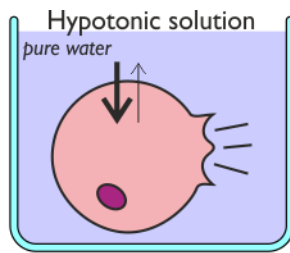
A hypotonic solution      A solution with a lower solute concentration, or higher  $\Psi_s$ , than the cell.

A hypertonic solution      A solution with a higher solute concentration, or lower  $\Psi_s$ , than the cell.

A isotonic solution      A solution with the same solute concentration and  $\Psi_s$  as the cell.

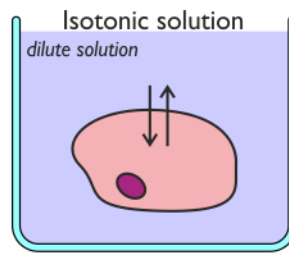
### Cells without cell walls (animal cells)

Since animal cells don't have a cell wall, there is rarely an external force acting on them, so  $\Psi_p$  is almost always zero. Animal cells burst in a hypotonic solution (osmotic lysis) and shrink in a hypertonic solution. The crinkled shape is due to the cytoskeleton.



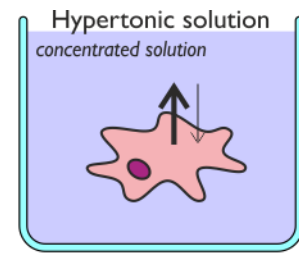
(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	0
$\Psi_s$	0	-200	0
$\Psi$	0	-200	0

Water enters cell. Membrane can't resist pressure, so cell bursts - cell lysis.



(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	0
$\Psi_s$	-200	-200	-200
$\Psi$	-200	-200	-200

Water diffuses equally in both directions, so cell stays normal size.

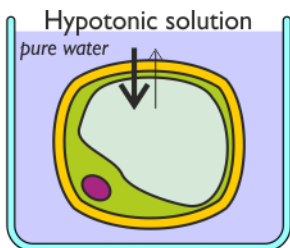


(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	0
$\Psi_s$	-400	-200	-400
$\Psi$	-400	-200	-400

Water leaves cell, so cell shrinks, making cytoplasm more concentrated and decreasing,  $\Psi_s$ .

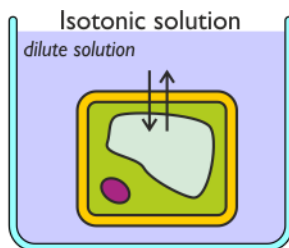
### Cells with cell walls (plant, fungi and bacteria cells)

Cell walls are strong so can apply an external force to the cell, increasing  $\Psi_s$ . In a hypotonic solution plant cells swell until they reach a dynamic equilibrium where the positive pressure potential exactly balances the negative solute potential, so the overall water potential is zero and there is no net movement of water. The cell is turgid and this is the normal state for healthy plant cells. Turgor provides support for leaves and non-woody stems. In isotonic solutions  $\Psi_p=0$  and the cells are flaccid. In hypertonic solutions plant cells act like animal cells, shrinking and pulling away from the cell wall. This is called plasmolysis and would kill the cell.



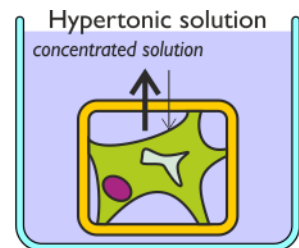
(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	+200
$\Psi_s$	0	-200	-200
$\Psi$	0	-200	0

Water enters cell. Cell wall provides compression force stopping entry of water. This state is called turgor, and is common in plants.



(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	0
$\Psi_s$	-200	-200	-200
$\Psi$	-200	-200	-200

No net diffusion of water: Cell wall is not under pressure. This state is called flaccid.



(kPa)	out side	inside initial	inside final
$\Psi_p$	0	0	0
$\Psi_s$	-400	-200	-400
$\Psi$	-400	-200	-400

Water leaves cell. Cytoplasm shrinks, making contents more concentrated and decreasing  $\Psi_s$ . This state is called plasmolysis.

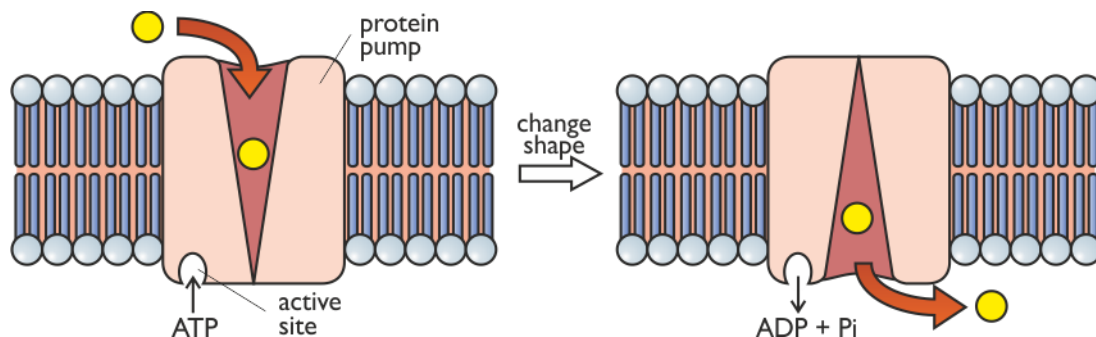
## Active Transport Methods and ATP

Active processes need energy. All the processes that need energy in a cell (including active transport) use a molecule called adenosine triphosphate (ATP) as their immediate source of energy. ATP is synthesised from ADP and phosphate ( $P_i$ ) using energy released from glucose in respiration in mitochondria.



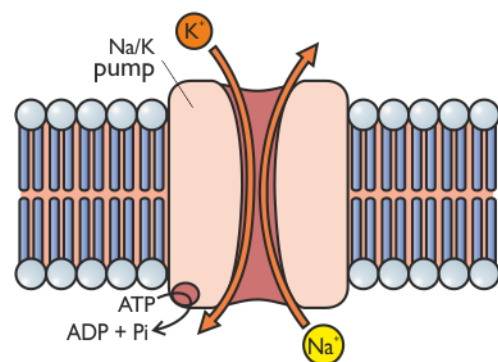
The hydrolysis (splitting) of ATP back to ADP and  $P_i$  releases energy, which can be used to drive processes like muscle contraction, biosynthesis, and active transport. Active transport therefore involves protein molecules that are ATPase enzymes, which catalyse this hydrolysis of ATP to release the energy.

## 4. Active Transport



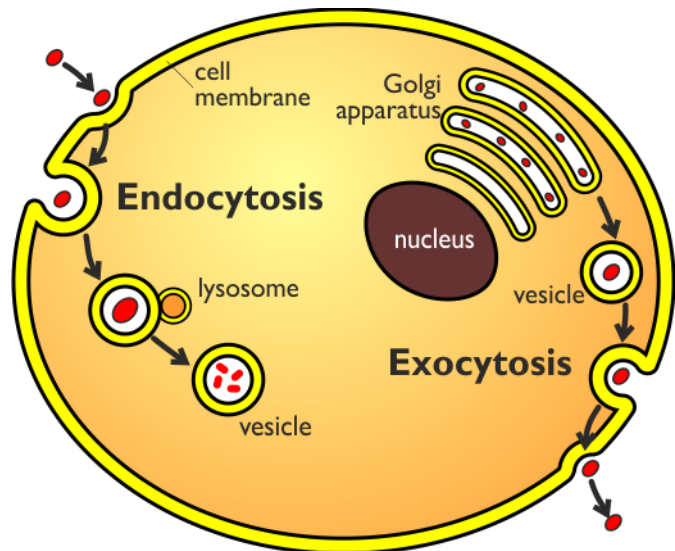
Active transport is the pumping of substances across a membrane by a trans-membrane protein pump molecule, using energy from ATP. These transport proteins are ATPase enzymes, and they have an ATPase active site on their cytoplasm side. The protein binds a molecule of the substance to be transported on one side of the membrane, changes shape using energy from ATP splitting, and releases the molecule on the other side. The proteins are highly specific, so there is a different protein pump for each molecule to be transported. Active transport always occurs in the same direction and can transport substances up their concentration gradient.

A common active transport pump is the sodium/potassium ATPase (Na/K pump), found in all animal cell membranes. This pump continually uses ATP to actively pump sodium ions out of the cell and potassium ions into the cell. This creates ion gradients across the cell membrane, which can be used to regulate water potential and drive other process.



## 5. Bulk Transport

Membrane proteins can only transport fairly small molecules, like ions, glucose and amino acids. But cells also need to transport large macromolecules like proteins and polysaccharides and even small cells. These large objects are transported by bulk transport using membrane vesicles. The synthesis, movement and fusion of the vesicles require metabolic energy in the form of ATP, so this is another active transport process. Transport into a cell is called endocytosis and transport out of a cell is called exocytosis.



### Endocytosis

A part of the membrane folds to form a pocket that deepens and pinches shut to form a vesicle containing whatever material was captured outside the cell.

- Endocytosis of large particles in suspension (such as microbial cells, viruses, dust particles and cellular debris) is called phagocytosis (“cell eating”). Phagocytosis is used by large white blood cells called phagocytes to engulf and destroy pathogens in the blood. They also recycle dead and damaged red blood cells. The vesicle, called a phagosome, often fuses with a lysosome so that the lysozyme enzymes can digest the engulfed particles into small soluble molecules. These molecules are then recycled for cell growth.
- Endocytosis of small volumes of extra-cellular fluid with its dissolved solutes is called pinocytosis (“cell drinking”). Many unicellular protists feed this way, and human cells take up cholesterol-containing lipoproteins (LDLs) from the blood by pinocytosis.

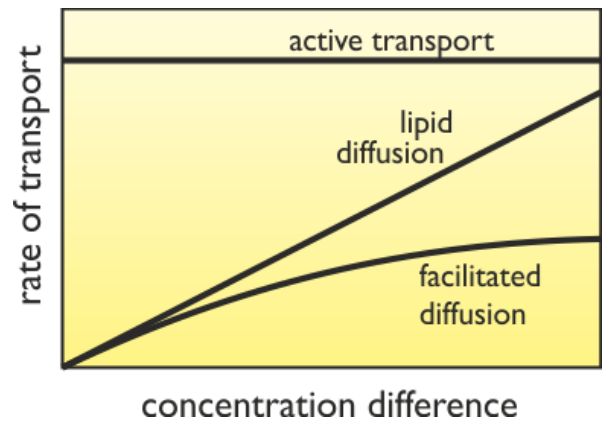
### Exocytosis

This is the reverse of endocytosis. A membrane vesicle fuses with the cell membrane so that its contents are released to the outside. The vesicle is usually formed from the endoplasmic reticulum and the Golgi apparatus, where proteins, lipids and other substances are synthesised and processed for export. Exocytosis is used by secretory cells to secrete hormones into the blood and digestive enzymes into the intestine, and by nerve cells to release neurotransmitter chemicals at synapses (Y13). Exocytosis is also used by plant cells to export the proteins and carbohydrates needed to make the cell wall.

## Effect of concentration difference on rate of transport

The three kinds of transport can be distinguished experimentally by the effect of solute concentration on its rate of transport:

- Lipid diffusion shows a linear relationship. The greater then concentration difference the great the rate of diffusion (see Fick's law  $p \propto x$ ).
- Facilitated diffusion has a curved relationship with a maximum rate. At high concentrations the rate is limited by the number of transport proteins.
- Active transport has a high rate even when there is no concentration difference across the membrane. Active transport stops if cellular respiration stops, since there is no ATP.



## Summary of Membrane Transport

method	uses energy?	which part of membrane?	specific?	concentration gradient
Lipid Diffusion	✗	phospholipid bilayer	✗	↓
Osmosis	✗	phospholipid bilayer	✓	↓
Facilitated Diffusion	✗	proteins	✓	↓
Active Transport	✓	proteins	✓	↑

## Surface Area : Volume Ratio

All organisms need to exchange substances such as food, waste, gases and heat with their surroundings. These substances must diffuse between the organism and the surroundings. The rate of exchange of gases must depend on the organism's surface area that is in contact with the surroundings. The requirements for respiration depends on the mass or volume of the organism, so the ability to meet the requirements depends on (surface area  $\div$  volume), which is known as the surface area : volume ratio.

As organisms get bigger their volume and surface area both get bigger, but not by the same amount. This can be seen by performing some simple calculations concerning different-sized organisms. In these calculations each organism is assumed to be cube-shaped to make the calculations easier. The surface area of a cube with length of side  $L$  is  $6L^2$ , while the volume is  $L^3$ .

organism	length		SA (m <sup>2</sup> )	vol (m <sup>3</sup> )	SA:vol ratio (m <sup>-1</sup> )
bacterium	1 $\mu\text{m}$	(10 <sup>-6</sup> m)	$6 \times 10^{-12}$	10 <sup>-18</sup>	6,000,000:1
amoeba	100 $\mu\text{m}$	(10 <sup>-4</sup> m)	$6 \times 10^{-8}$	10 <sup>-12</sup>	60,000:1
bee	10 mm	(10 <sup>-2</sup> m)	$6 \times 10^{-4}$	10 <sup>-6</sup>	600:1
pig	1 m	(10 <sup>0</sup> m)	$6 \times 10^0$	10 <sup>0</sup>	6:1
whale	100 m	(10 <sup>2</sup> m)	$6 \times 10^4$	10 <sup>6</sup>	0.06:1

So as organisms get bigger their surface area : volume ratio gets smaller. A bacterium is all surface with not much inside, while a whale is all insides with not much surface. This means that as organisms become bigger it becomes more difficult for them to exchange materials with their surroundings. In fact this problem sets a limit on the maximum size for a single cell of about 100 $\mu\text{m}$ . In anything larger than this materials simply cannot diffuse fast enough to support the reactions needed for life.

So how do organisms larger than 100  $\mu\text{m}$  survive? They need three features:

1. Large organisms need to be multicellular, which means that their bodies are composed of many small cells, rather than one big cell. Each cell in a multicellular organism is no bigger than about 30 $\mu\text{m}$ , and so can exchange materials quickly and independently. Each human contains about  $10^{14}$  cells.
2. Large organisms need a mass transport system, which uses energy to pump nutrient solutions quickly around large bodies. Each individual cell can thus be fed quickly. Mass transport systems include the blood systems of animals and the vascular systems of plants.
3. Large organisms need a specialised exchange system with a large surface area. These systems include lungs, gills, intestines, roots and leaves.

# Gas Exchange Systems

Organisms must constantly exchange oxygen and carbon dioxide between their cells and their surroundings for respiration and photosynthesis. The rate at which gases can diffuse through a surface is given by Fick's law:

$$\text{Rate of Diffusion} \propto \frac{\text{surface area} \times \text{concentration difference}}{\text{distance}}$$

Large organisms all have specialised gas exchange systems. Fick's law tells us that, in order to support a fast rate of diffusion, these exchange surfaces must have:

- a large surface area
- a small distance between the source and the destination
- a mechanism to maintain a high concentration gradient across the gas exchange surface.

We shall examine how these requirements are met in the gas exchange systems of humans, fish, insects and plants. This table summarises the main systems.

organism/ system	large surface area	small distance	high concentration gradient
Human lungs	600 million alveoli with a total area of 100m <sup>2</sup>	each alveolus is only one cell thick	constant ventilation replaces the air
Fish gills	feathery filaments with lamellae	lamellae are two cells thick	water pumped over gills in countercurrent to blood
Leaves	surface area of leaves of 1 tree is 200m <sup>2</sup> , surface area of spongy cells inside leaves of 1 tree is 6000m <sup>2</sup> .	gases diffuse straight into leaf cells	wind replaces air round leaves, and photosynthesis counteracts respiration

For comparison, a tennis court has an area of about 260 m<sup>2</sup> and a football pitch has an area of about 5000 m<sup>2</sup>.

## Epithelial Tissue

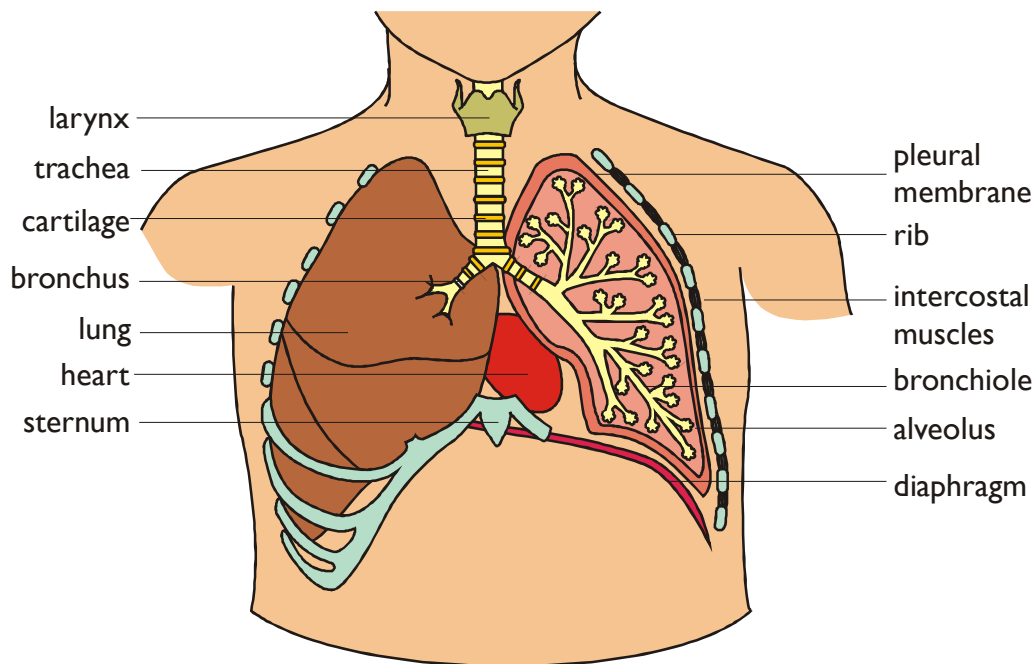
Epithelial tissue is the name given to the layer of cells covering all the external and internal surfaces of the body. Exchange therefore takes place through epithelial tissue and the cells are adapted for exchange. There are many different kinds of epithelial tissue:

- Squamous epithelium is found surrounding the alveoli (see p45). The cells are extremely flattened, like pancakes, and are often so thin that the nucleus makes a bulge.
- Endothelium is found lining capillaries and other blood vessels (see unit 2). These are also flat squamous cells, but on an internal surface (endo=inside).
- Columnar epithelium is found lining the alimentary canal. The cells are thick but have microvilli to give a large surface area for many transport proteins for facilitated diffusion and active transport.
- Ciliated epithelium is found on the trachea and bronchi (see p45). These cells are not adapted for exchange, but for lubrication and protection.
- Epidermis is found on the outer surface of the skin. It forms a tough, impermeable barrier preventing desiccation (water loss) and infection.

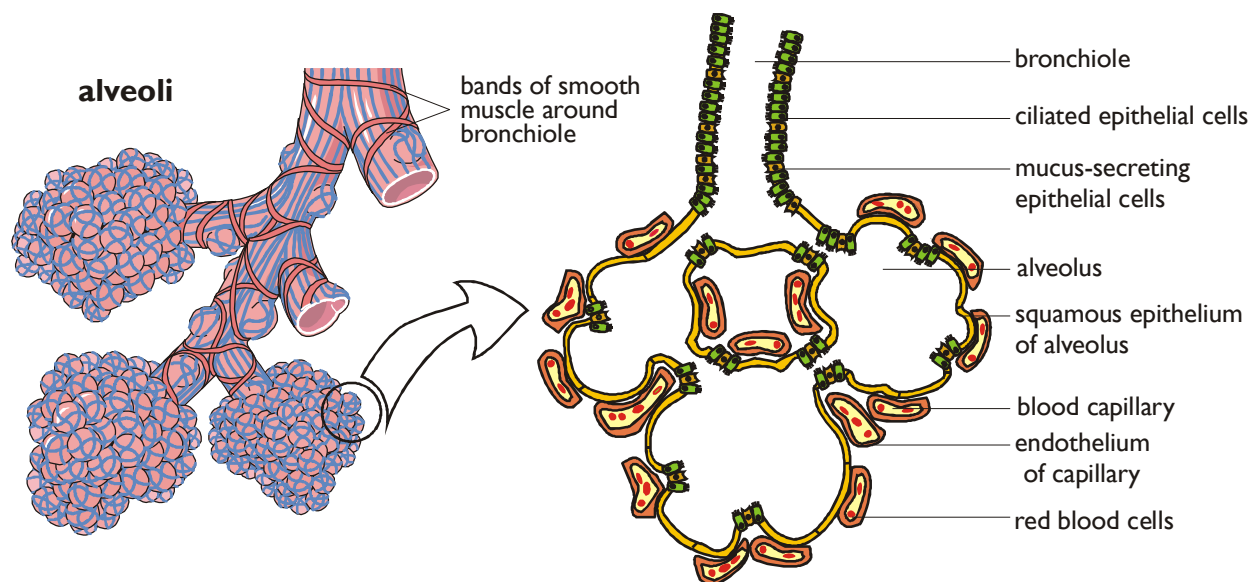


# Gas Exchange in Humans

This diagram shows the gas exchange system in humans:



The gas exchange system is also referred to as the respiratory system, but this can be confusing as respiration takes place in all cells, and is quite distinct from gas exchange. The actual gas exchange surface is on the alveoli inside the lungs.



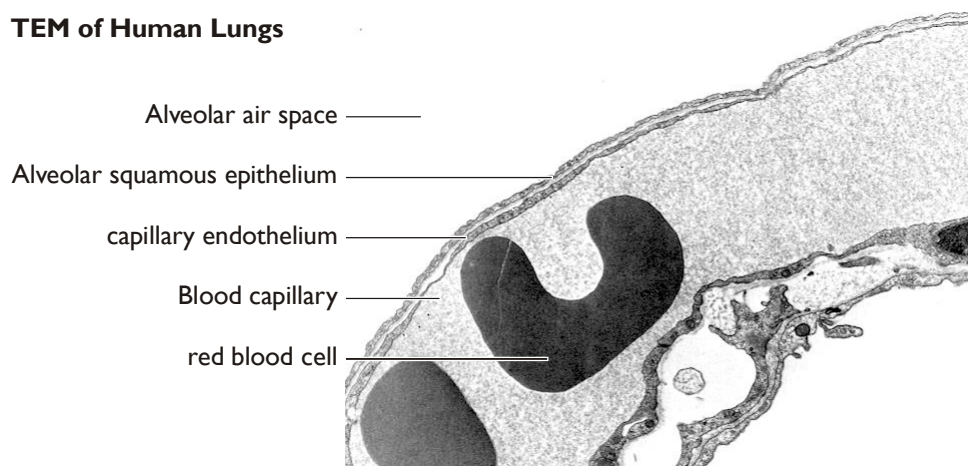
This surface meets the three requirements of Fick's law:

- A large surface area. Although each alveolus is tiny, an average adult has about 600 million alveoli, giving a total surface area of about 100m<sup>2</sup>, so the area is huge.



- A small distance between the source and the destination. The walls of the alveoli are composed of a single layer of flattened squamous epithelial cells, as are the walls of the capillaries, so gases need to diffuse through just two thin cells.
- A mechanism to maintain a high concentration gradient across the gas exchange surface. The steep concentration gradient across the gas exchange surface is maintained in two ways: by blood flow on one side and ventilation on the other side. This means oxygen can always diffuse down its concentration gradient from the air to the blood, while at the same time carbon dioxide can diffuse down its concentration gradient from the blood to the air

### TEM of Human Lungs



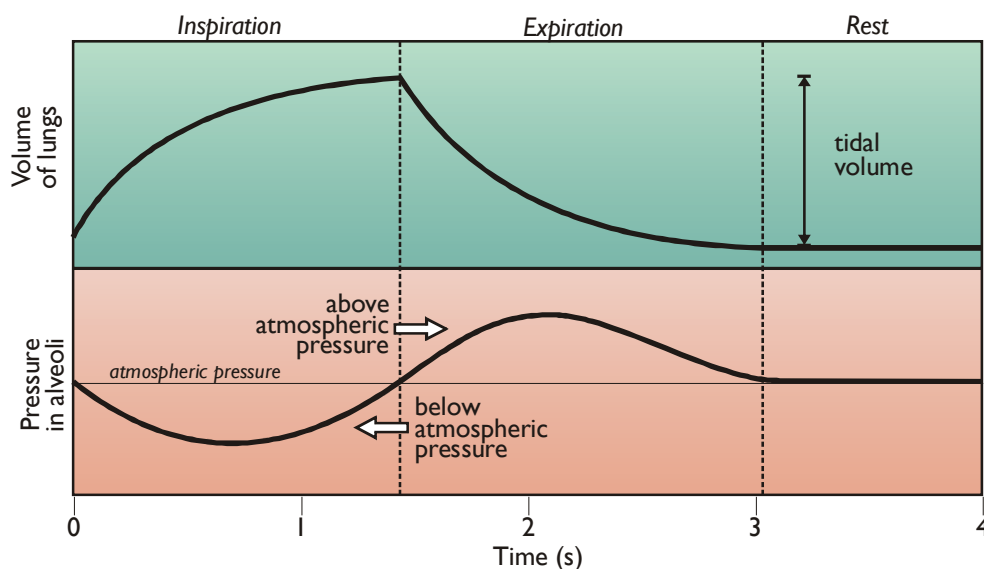
The large surface area and short distance that are ideal for gas exchange also cause a problem: water loss. Water inevitably diffuses down its concentration gradient from the tissue fluid and alveoli cells into the air in the alveoli, so the air in the alveoli is constantly moist. This is why exhaled air contains more water than normal, inhaled air, and this represents a significant loss of water from the body. However, by having the gas exchange surface deep inside the body at the end of long narrow bronchioles, the water loss is minimised. The moist alveolar air means that there is less of a diffusion gradient (and so less water is lost) than if the alveoli were exposed to outside dry air. The epithelial cells secrete a soapy surfactant to reduce the surface tension of the water (due to hydrogen bonds) and make it less "sticky". Without this surfactant the alveoli would collapse, and this can be a problem in premature babies.

Some of the epithelial cells of the bronchioles secrete mucus, which traps bacteria and other microscopic particles that enter the lungs. This mucus is constantly swept upwards by the cilia of the ciliated epithelial cells to the throat, where it is swallowed and any bacteria in it are killed by the acid in the stomach. Phagocyte cells migrate from the blood capillaries to the alveolar air space to kill any bacteria that have not been trapped by the mucus.

## Ventilation

Ventilation means the movement of air over the gas exchange surface (also known as breathing). Lungs are not muscular and cannot ventilate themselves, but instead the whole thorax moves and changes size, due to the action of two sets of muscles: the intercostal muscles and the diaphragm. These movements are transmitted to the lungs via the pleural sac surrounding each lung. The outer membrane is attached to the thorax and the inner membrane is attached to the lungs. Between the membranes is the pleural fluid, which is incompressible, so if the thorax moves, the lungs move too. The alveoli are elastic and collapse if not held stretched by the thorax.

The muscle contractions increase the volume of the thorax, which in turn decreases the pressure in the lungs (by Boyle's law), which in turn causes air to move in. Ventilation in humans is tidal, which means the air flows in and out by the same route. The rule is that *air always flows from a high pressure to a low pressure*. These volume and pressure changes are shown in this graph:



Inspiration	<ul style="list-style-type: none"> <li>The diaphragm contracts and flattens downwards and the external intercostal muscles contract, pulling the ribs up and out.</li> <li>This increases the volume of the thorax and the lungs, and stretches the elastic-walled alveoli.</li> <li>This decreases the pressure of air in the alveoli below atmospheric.</li> <li>Air flows in from high pressure to low pressure.</li> </ul>
Normal expiration	<ul style="list-style-type: none"> <li>The diaphragm relaxes and curves upwards and the external intercostal muscles relax, allowing the ribs to fall.</li> <li>This decreases the volume of the thorax and the lungs, and allows the alveoli and bronchioles to shrink by <u>elastic recoil</u>.</li> <li>This increases the pressure of air in the alveoli above atmospheric.</li> <li>Air flows out from high pressure to low pressure.</li> </ul>
Forced expiration	<ul style="list-style-type: none"> <li>The abdominal muscles contract, pushing the diaphragm upwards</li> <li>The internal intercostal muscles contract, pulling the ribs downward</li> <li>This gives a larger and faster expiration, used in exercise</li> </ul>

## Pulmonary Ventilation

Pulmonary Ventilation is the volume of air ventilating the lungs each minute. It is calculated as the product of the ventilation rate and the tidal volume.

$$\text{pulmonary ventilation} = \text{ventilation rate} \times \text{tidal volume}$$

- The ventilation rate can be calculated from the pressure graph by measuring the time taken for one ventilation cycle and using the formula:

$$\text{ventilation rate (breaths per minute)} = \frac{60}{\text{cycle time (s)}}$$

- The tidal volume is the normal volume of air breathed in each breath (also called the breathing depth). It can be measured from the volume graph.

Both the ventilation rate and the tidal volume can be varied by the body. When the body exercises the pulmonary ventilation can increase so that

- oxygen can diffuse from the air to the blood faster
- carbon dioxide can diffuse from the blood to the air faster

These changes allow aerobic respiration in muscle cells to continue for longer.

	ventilation rate (breaths min <sup>-1</sup> )	tidal volume (cm <sup>3</sup> breath <sup>-1</sup> )	pulmonary ventilation (cm <sup>3</sup> min <sup>-1</sup> )
at rest	12	500	6 000
at exercise	18	1000	18 000

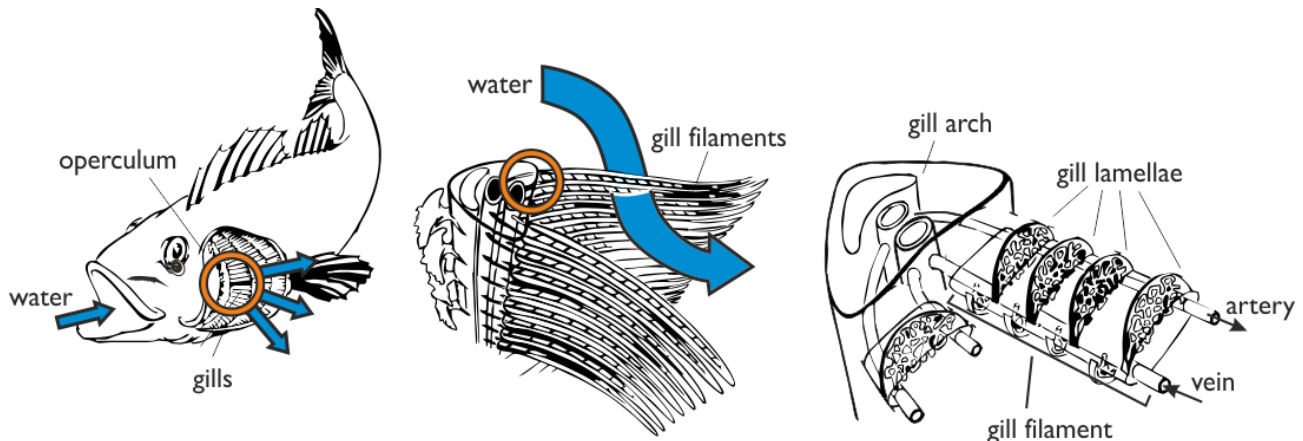
## Gas Exchange, Ventilation and Respiration

These words describe three quite different processes! Gas exchange is when certain gases (usually oxygen and carbon dioxide) diffuse between the environment and the blood. Ventilation is a muscular movement that helps to speed up gas exchange. Ventilation increases the rate of gas exchange by increasing the concentration difference across the respiratory surface, which increases the rate of diffusion by Fick's law. Respiration is the oxidation of glucose by a series of chemical reactions that take place in all living cells. This table summarises the differences:

Gas Exchange	Ventilation
uses diffusion	uses mass flow
passive (no energy needed)	active (thorax muscles use ATP energy)
gases move down their own concentration gradients (so can be in different directions)	all gases in air move together in one direction
slow	quick

## Gas Exchange in Fish

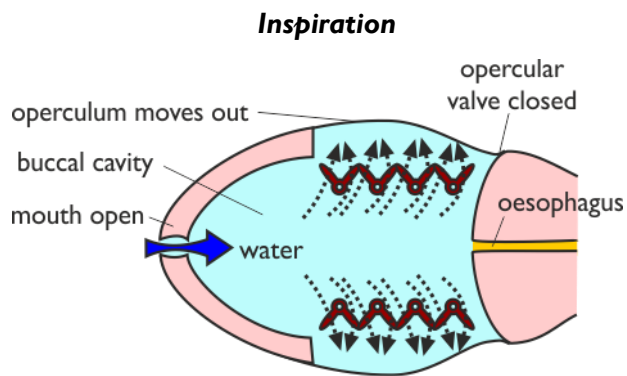
Gas exchange is more difficult for fish than for mammals because the concentration of dissolved oxygen in water is less than 1%, compared to 20% in air. Fish have developed specialised gas-exchange organs called gills, which are composed of thousands of filaments. The filaments in turn are covered in feathery lamellae each only a few cells thick containing blood capillaries. This structure gives a large surface area and a short distance for gas exchange.



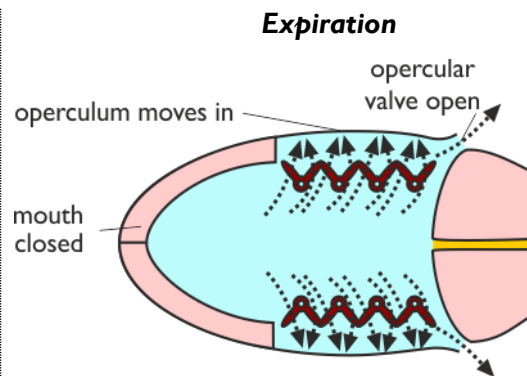
Water flows over the filaments and lamellae, and oxygen can diffuse down its concentration gradient the short distance between water and blood. Carbon dioxide diffuses the opposite way down its concentration gradient. The gills are covered by muscular flaps called opercula on the side of a fish's head. The gills are so thin that they cannot support themselves without water, so if a fish is taken out of water the gills collapse and the fish suffocates.

## Ventilation in Fish

Fish ventilate their gills with sea water to maintain the gas concentration gradient. But, unlike humans, fish ventilation is one-way rather than tidal. Water enters through the mouth but exits through the opercula valves. This one-way ventilation is necessary because water is denser and more viscous than air, so it would take too much energy to change its momentum every breath. Some fish (like tuna, mackerels and anchovies) swim constantly with their mouths open, using their swimming movement to ventilate their gills, but most fish use their mouth muscles for ventilation, which means they can ventilate even when not swimming.

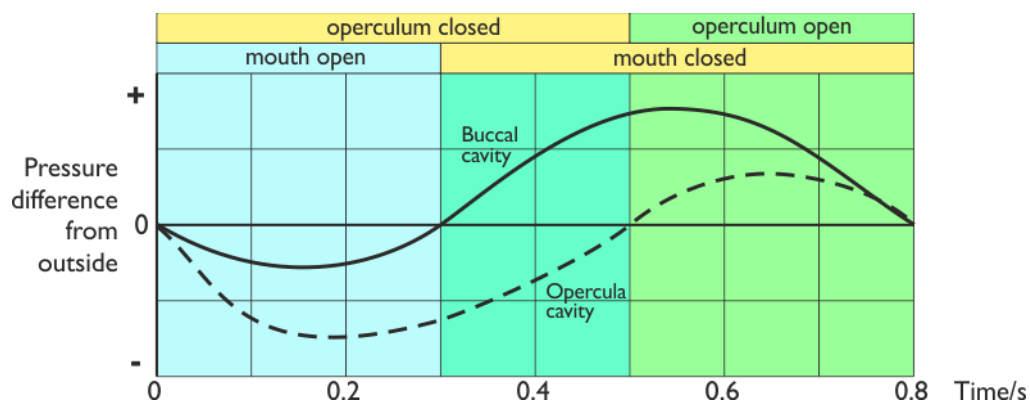


1. The mouth opens.
2. The muscles in the mouth contract, lowering the floor of the mouth, and the opercula muscles contract, pushing the opercula outwards.
3. This increases the volume of the buccal cavity and the opercular cavity.
4. This decreases the pressure of water in the buccal cavity below the outside water pressure.
5. The outside water pressure closes the opercular valve.
6. Water flows in through the open mouth and over the gills from high pressure to low pressure.



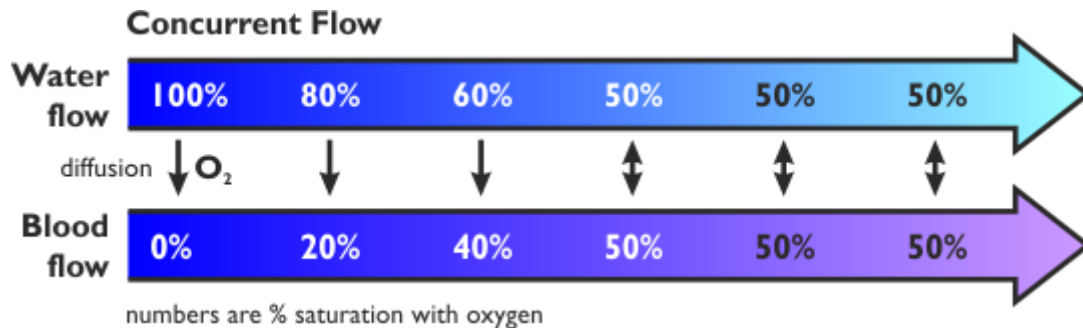
1. The mouth closes.
2. The mouth and opercular muscles relax, raising the floor of the buccal cavity.
3. This decreases the volume of the buccal cavity.
4. This increases the pressure of water in the buccal cavity above the outside water pressure.
5. This pressure forces the opercula valves open.
6. Water flows out over the gills and through the opercula valve from high pressure to low pressure.

These pressure changes are shown in this graph. The rule is that water always flows from a high pressure to a low pressure. This graph shows that water flows in one direction only.

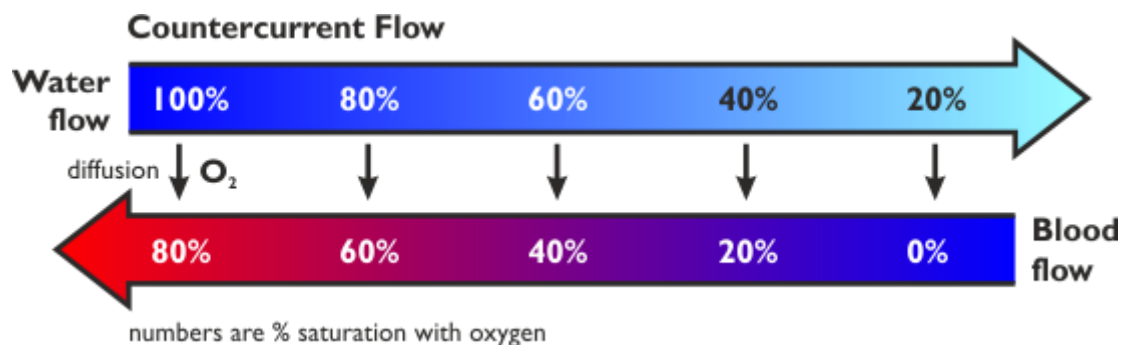


## Counter Current Exchange

Because fish have a one-way flow, they can make use of another trick to improve their efficiency of gas exchange: a counter current system. If water and blood flowed past each other in the same direction (parallel or concurrent flow) then the oxygen concentration in the water and blood quickly becomes the same, so no further diffusion can take place, and only 50% of the oxygen can be extracted from the water:

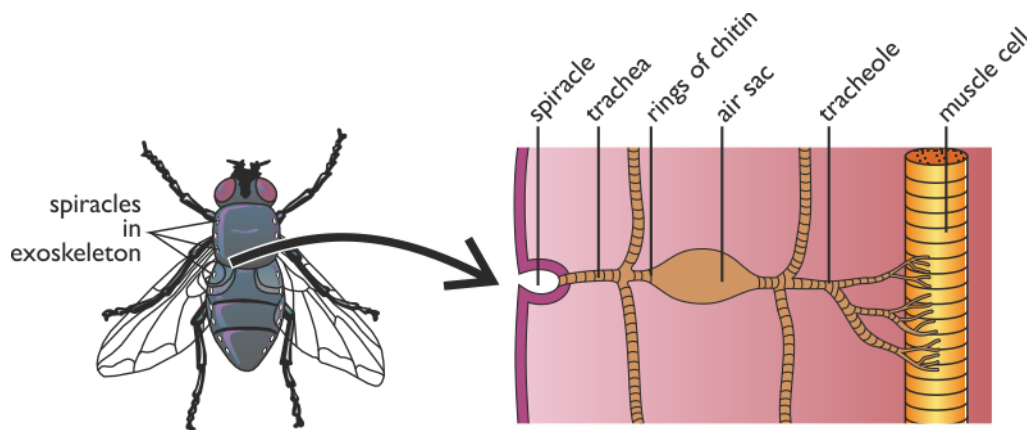


In the countercurrent system the blood flows towards the front of the fish in the gill lamellae while the water flows towards the back. This means that there is always a higher concentration of oxygen in the water than in the blood, so oxygen continues to diffuse into the blood along the whole length of the lamellae. Using this system fish gills can extract about 80% of the dissolved oxygen from the water:



# Gas Exchange in Insects

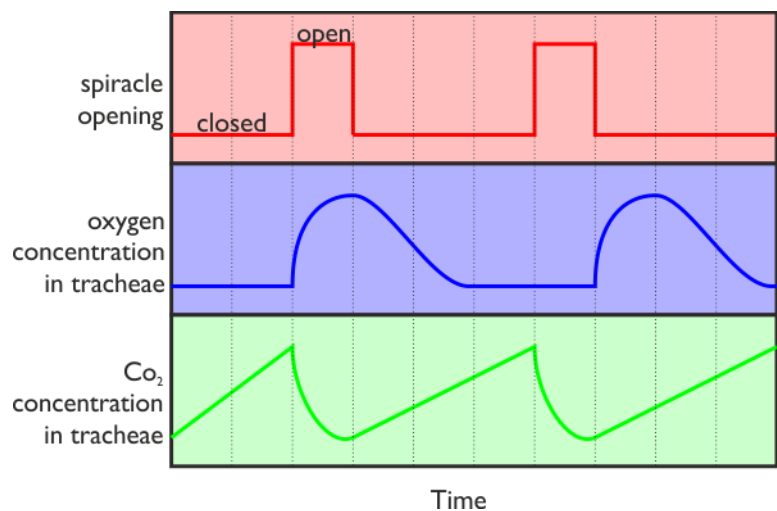
Insects are fairly small, but they are also very active, so they need to respire quickly. They have a rigid exoskeleton, which is waterproof to prevent the insects drying out, but it also prevents gas exchange. Insects increase their rate of gas exchange by having openings in the exoskeleton called spiracles, which lead to a network of tubes called tracheae, which branch into many smaller tracheoles that carry air directly to the cells. These tracheae and tracheoles are held open by rings of hard chitin (a polysaccharide). The tracheoles penetrate deep into the insects tissues, carrying air quickly and directly to every cell. At the ends of the tracheoles oxygen diffuses directly into the cells, and carbon dioxide diffuses out, down their concentration gradients.



## Insect Ventilation

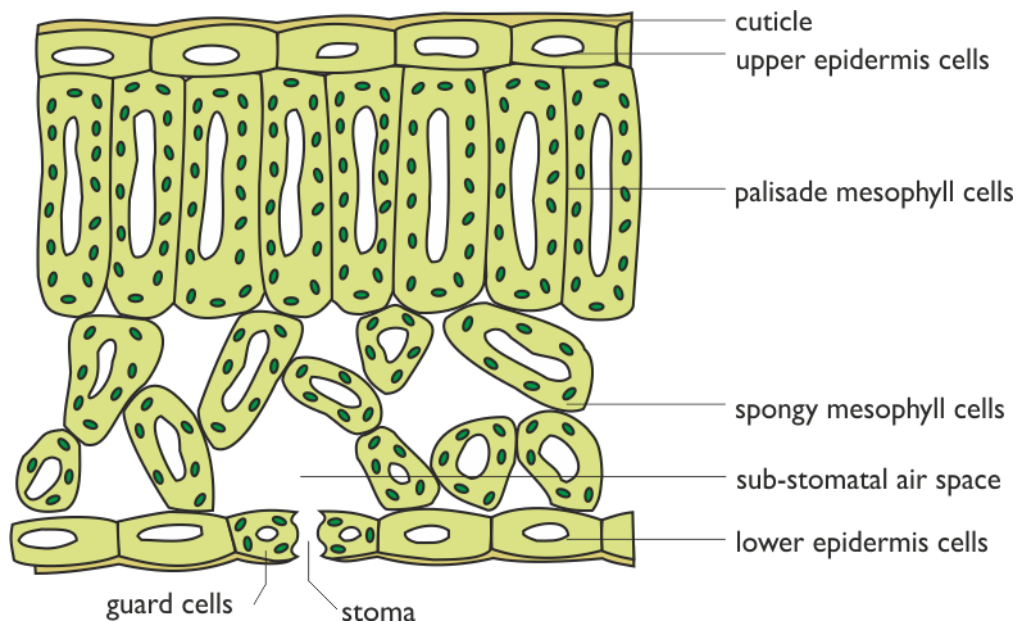
Small insects can rely entirely on diffusion through the tracheoles to obtain enough oxygen for respiration, but larger and more active insects, like houseflies and grasshoppers, ventilate their tracheal system by using muscles to squeeze their abdomen and so suck air in and out of the spiracles. This increases the concentration gradient and so the rate of gas exchange.

To counteract problems of water loss insects can close their spiracles using a muscular valve. The opening and closing is controlled by the nervous system, which detects a build-up of  $\text{CO}_2$  in the tracheae. Some insects also have spines or hairs around the spiracles to increase humidity and so reduce evaporation.



# Gas Exchange in Plants

All plant cells respire all the time, and during the day many plant cells also photosynthesise, so plants also need to exchange gases. The main gas exchange surfaces in plants are the spongy mesophyll cells in the leaves. Leaves of course have a huge surface area, and the irregular-shaped, loosely-packed spongy cells increase the area for gas exchange by a factor of about 20.



So leaves meet all the requirements of Fick's law for fast gas exchange.

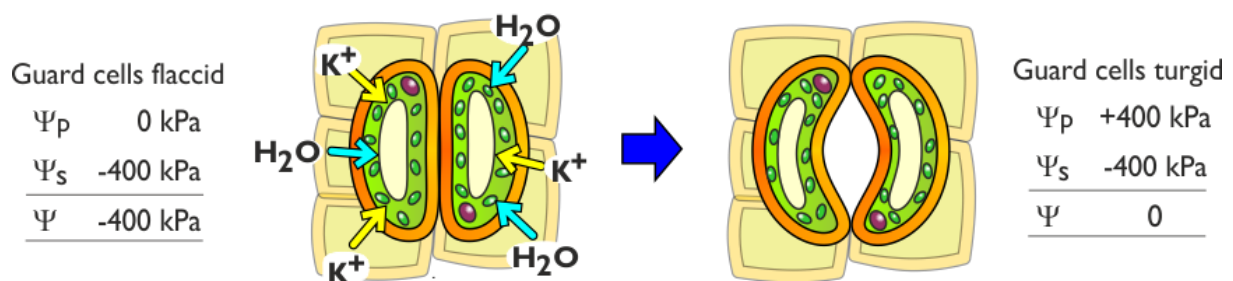
- The spongy cells have a huge surface area
- Leaves are thin and there is a very short diffusion distance between the stomata and the spongy cells.
- Leaves are ventilated simply by being exposed, so the air surrounding them is constantly being replaced in all but the stillest days. In addition, during the hours of daylight photosynthesis increases the oxygen concentration in the sub-stomatal air space, and decreases the carbon dioxide concentration. These increase the concentration gradients for these gases, speeding up the rate of diffusion.



## Stomata

The upper surface of a leaf is covered in a waxy cuticle that prevents water loss, but it also prevents diffusion of gases. Gases enter and leave the leaf through pores called stomata (singular stoma), which are usually in the lower surface of the leaf. There are often several thousand stomata per square centimetre of leaf surface. Stomata open onto sub-stomatal air spaces, from which gases can diffuse into the spongy and palisade mesophyll cells.

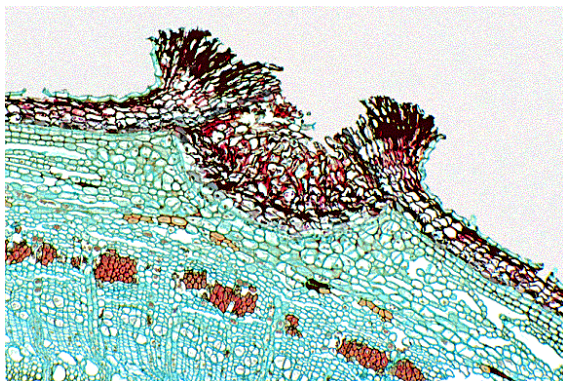
Stomata are formed by two guard cells, which can change shape to open and close the stomata. When the guard cells are flaccid the stoma is closed. To open the stoma,  $K^+$  ions are actively pumped into the guard cells, lowering the solute potential ( $\Psi_s$ ). So water diffuses in by osmosis, making the guard cells turgid. The guard cells elongate as they expand (since their cell wall has rings that prevent them from getting fatter), forcing them apart to form the pore.



## Lenticels

Leaf cells exchange gases for respiration and photosynthesis through stomata, but how do cells in the rest of a plant exchange gases? In small stems diffusion from the outside is often fast enough, given that cells in plant stems and roots have a low metabolic rate. But large, woody stems have impermeable layers of bark and cork, limiting gas exchange. These woody stems have structures called lenticels, which are loosely-packed cells with air spaces between them. These lenticels serve the same function as stomata in leaves (though they cannot be controlled).

Lenticel under the light microscope x50



Lenticels on a tree trunk



# The Evolution of Circulatory Systems

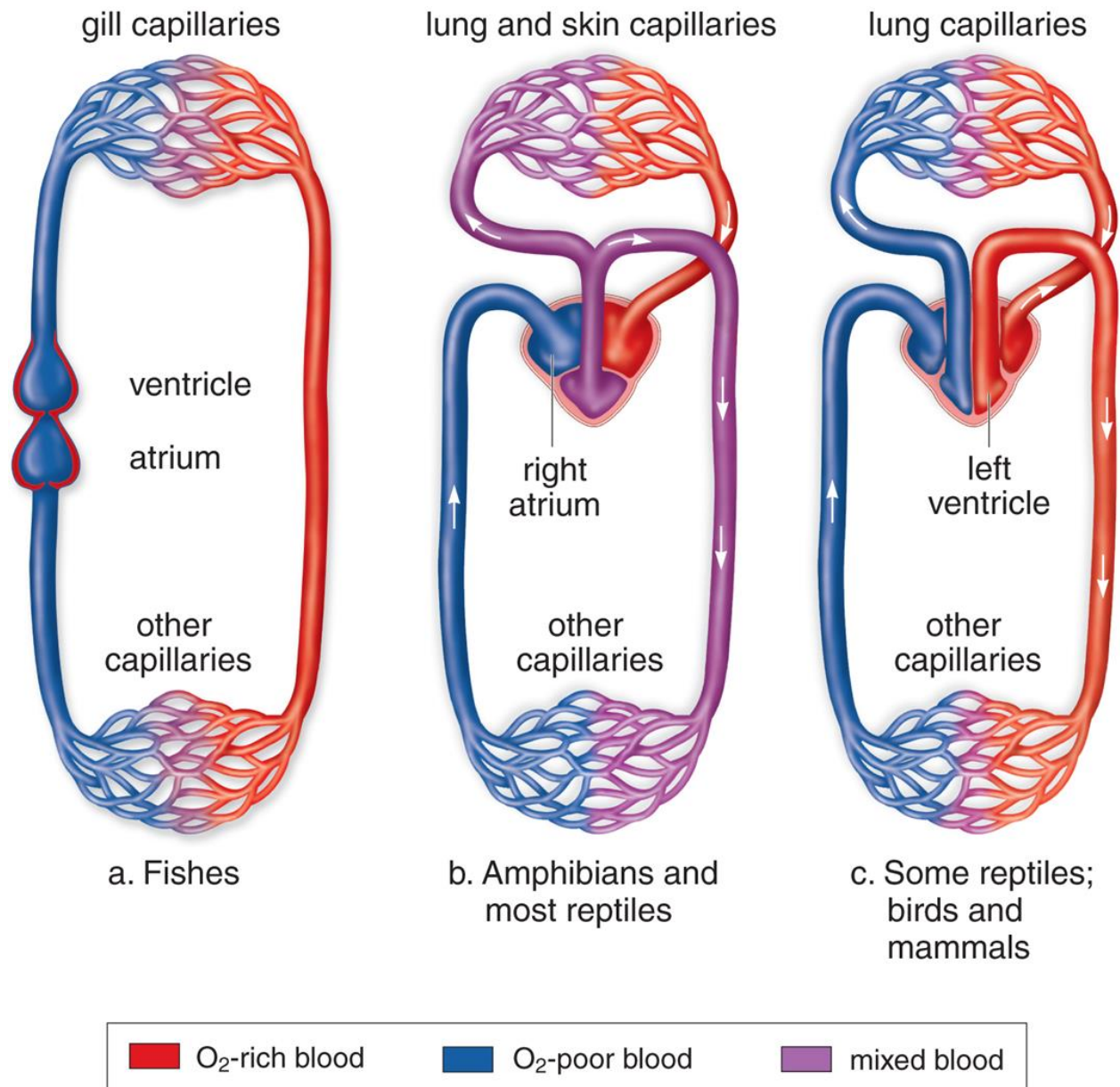
We saw earlier that large organisms need a mass transport system to carry gases, nutrients and waste around their bodies quickly. It is important to be clear about the differences between mass transport and diffusion:

- In mass transport (aka mass flow, bulk transport) a fluid (liquid or gas) moves in a particular direction due to a force. The fluid and everything dissolved or suspended in it move in the same direction at the same speed, like a river carrying everything with it. Mass flow is completely independent of concentration differences. Mass flow requires energy, but it is fast, especially over large distances. Examples of mass flow include: circulatory systems in animals, xylem and phloem systems in plants, filter feeder currents, and ventilation.
- In diffusion solutes move in random directions due to their thermal energy. If there is a concentration difference then the random movement results in the substance diffusing down its concentration gradient. Diffusion is very slow and is only useful over small distances ( $< 100 \mu\text{m}$ ). It cannot be used to move substances over large distances in living organisms.

Mass transport systems have developed greater complexity as animals have evolved and become larger and more active.

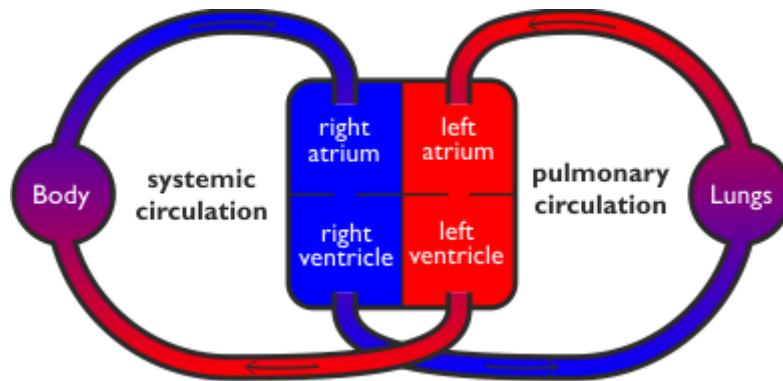
1. Small invertebrates, like sponges, jellyfish and flatworms, don't need a mass transport system at all. Their body walls are so thin that their cells can meet all their needs through diffusion.
2. Many invertebrates, like arthropods and molluscs, have an open circulatory system, where cells are bathed in a fluid called haemolymph. The fluid is pumped around the body by a simple muscular heart so that nutrients are distributed to all cells.
3. Vertebrates have a closed circulatory system, where blood is confined to vessels distinct from the tissue fluid. Fish have a simple single circulatory system. They have a two-chambered heart with muscular walls that contract to pump blood. The blood first passes through the gills, where it is oxygenated, then passes on to the rest of the body. Thus the body cells receive well-oxygenated blood. The disadvantage of this single circulatory system is that the blood loses pressure as it flows through the gills, so it flows slowly through the body tissues, resulting in slow gas exchange.
4. Amphibians and reptiles have lungs instead of gills, and they have a double circulatory system that pumps blood separately to the lungs and the rest of the body. However, they only have a three-chambered heart, so the oxygenated and deoxygenated blood mix in the single ventricle, so gas exchange is not very efficient.
5. Mammals and birds have a double circulatory system, with a four-chambered heart. One side of the heart pumps blood to the lungs only and is called the pulmonary circulation, while the other side of the heart pumps blood to the rest of the body – the systemic circulation. This double circulatory system is

more efficient as the oxygenated and deoxygenated blood don't mix, and the blood in the systemic circulation is pumped to the body's cells at high pressure, allowing for fast gas exchange. This in turn permits fast respiration and a more active, warm-blooded lifestyle. Mammals and birds evolved from different reptile ancestors, so their four-chambered hearts evolved independently – an example of convergent evolution.

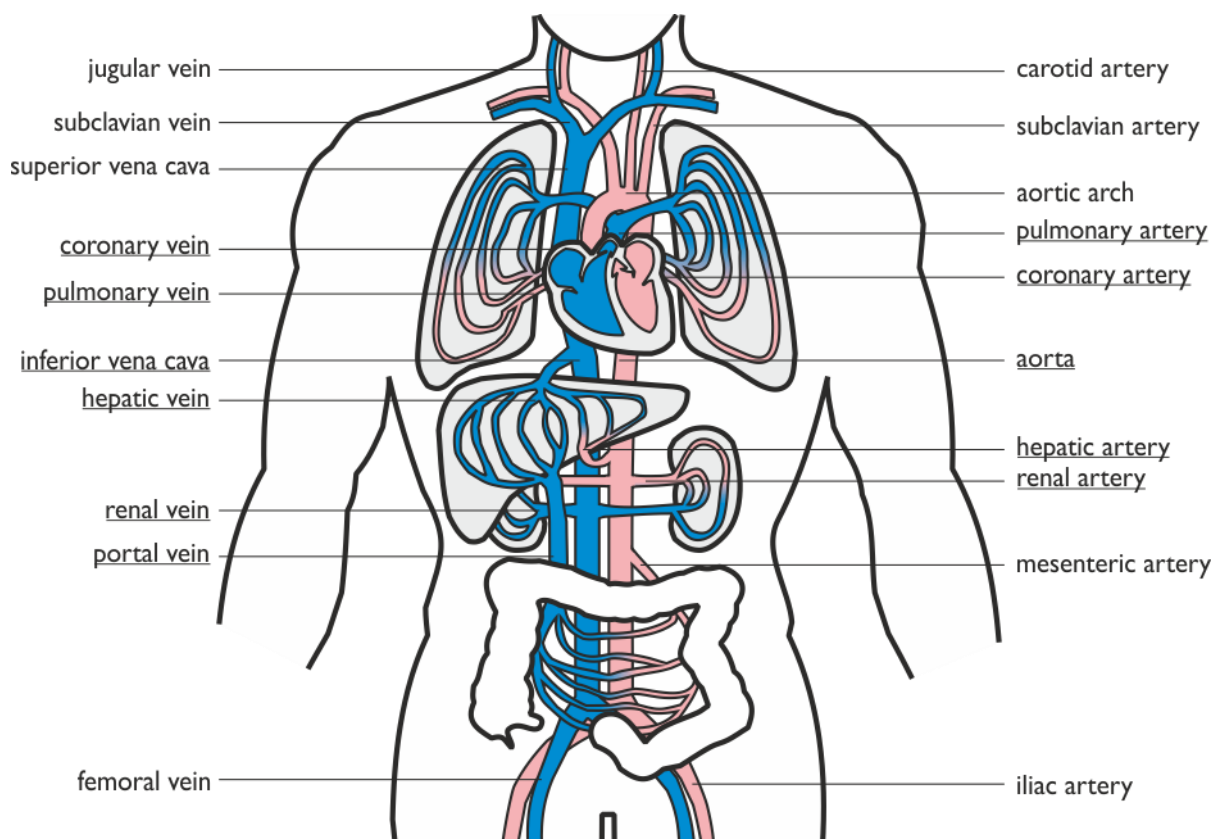


# The Human Circulatory System

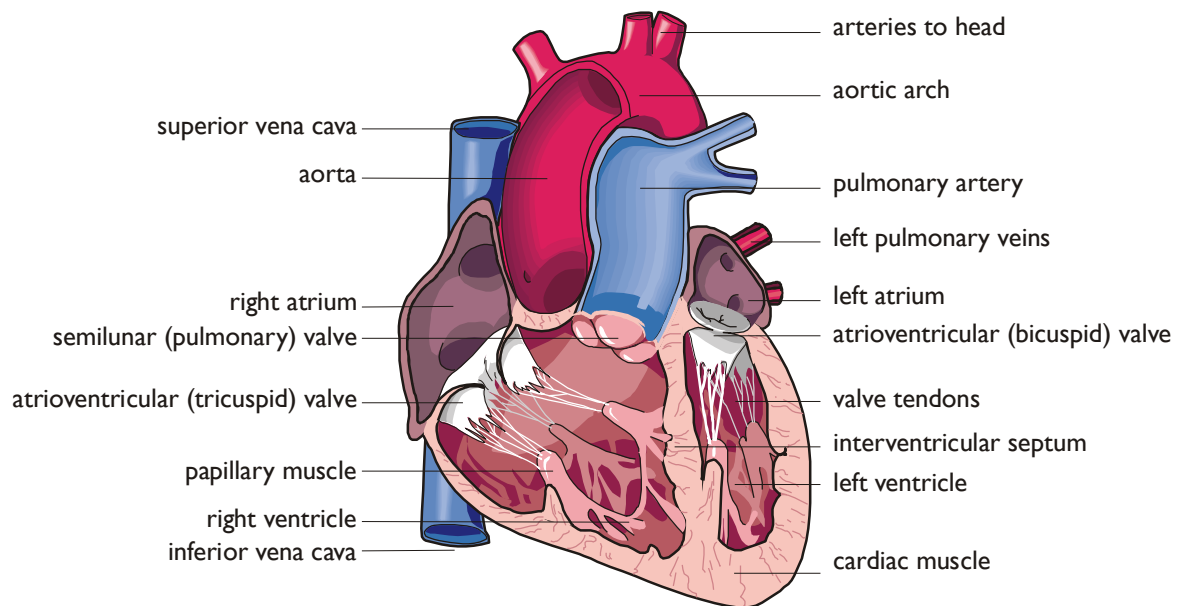
Humans have a double circulatory system with a 4-chambered heart. In humans the right side of the heart pumps blood to the lungs only and is called the pulmonary circulation, while the left side of the heart pumps blood to the rest of the body – the systemic circulation.



The circulation of blood round the body was first observed by Ibn-Al-Nafis (1213-1288) in Cairo and independently rediscovered by William Harvey in England in 1628. Until then people assumed that blood ebbed and flowed through the same tubes, because they hadn't seen capillaries. This diagram illustrates the blood vessels to the main organs. The underlined vessels are listed in the specification.



# The Heart



The human heart has four chambers: two thin-walled atria on top, which receive blood, and two thick-walled ventricles underneath, which pump blood. Veins carry blood into the atria and arteries carry blood away from the ventricles. Between the atria and the ventricles are atrioventricular valves, which prevent back-flow of blood from the ventricles to the atria. The left valve has two flaps and is called the bicuspid (or mitral) valve, while the right valve has 3 flaps and is called the tricuspid valve. The valves are held in place by valve tendons ("heart strings") attached to papillary muscles, which contract at the same time as the ventricles, holding the valves closed. There are also two semi-lunar valves in the arteries (the only examples of valves in arteries) called the pulmonary and aortic valves.

The left and right halves of the heart are separated by the inter-ventricular septum. The walls of the right ventricle are 3 times thinner than on the left and it produces less force and pressure in the blood. This is partly because the blood has less far to go (the lungs are right next to the heart), but also because a lower pressure in the pulmonary circulation means that less fluid passes from the capillaries to the alveoli. The internal volume of the left and right ventricles is the same.

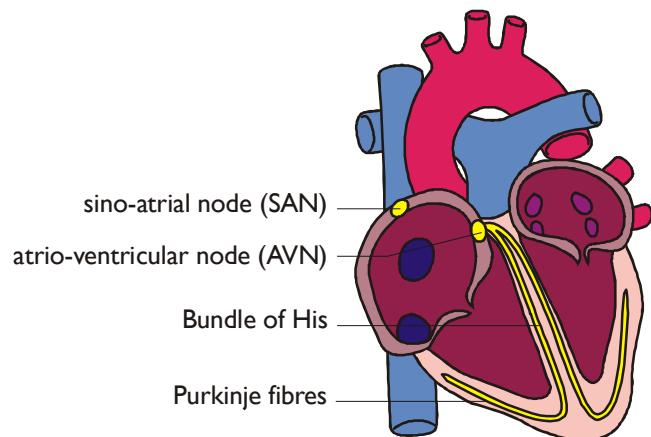
The heart is made of cardiac muscle, composed of cells called myocytes. When myocytes receive an electrical impulse they contract together, causing a heartbeat. Since myocytes are constantly active, they have a great requirement for oxygen, so are fed by numerous capillaries from two coronary arteries. These arise from the aorta as it leaves the heart. Blood returns via the coronary sinus, which drains directly into the right atrium.



## The Cardiac Cycle

Cardiac muscle contracts about 75 times per minute, pumping around 75 cm<sup>3</sup> of blood from each ventricle each beat (the stroke volume). It does this continuously for up to 100 years.

Cardiac muscle is myogenic, which means that it can contract on its own, without needing nerve impulses. Contractions are initiated within the heart by the sino-atrial node (SAN, or pacemaker) in the right atrium. This extraordinary tissue acts as a clock, and contracts spontaneously and rhythmically about once a second, even when surgically removed from the heart.

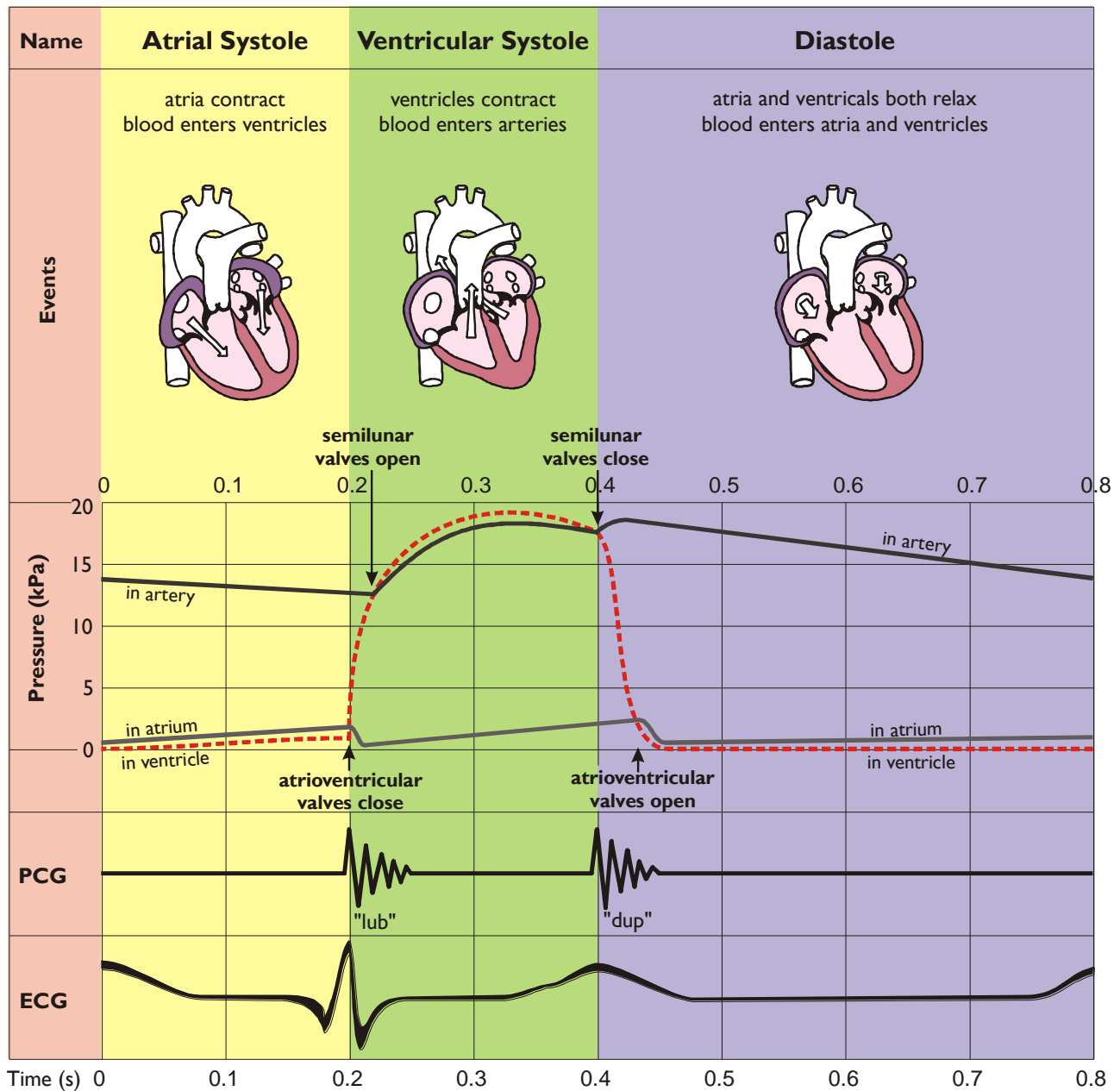


There is a complicated sequence of events at each heartbeat called the cardiac cycle. The cardiac cycle has three stages:

- 1. Atrial Systole.** The SAN contracts and transmits electrical impulses throughout the atria, which both contract, pumping blood into the ventricles. The ventricles are electrically insulated from the atria, so they do not contract at this time. The blood can't flow back into the veins because of the valves in the veins.
- 2. Ventricular Systole.** The electrical impulse passes from the atrioventricular node (AVN) to the Purkinje (or Purkyne) fibres, with a short but important delay of about 0.1s. The Purkinje fibres pass down through the interventricular septum as the bundle of His, which is insulated from the surrounding muscle cells, so the ventricles do not contract yet. At the base of the ventricles the Purkinje fibres spread out and initiate ventricular contraction. The ventricles therefore contract shortly after the atria, from the bottom up, squeezing blood upwards into the arteries. The blood can't go into the atria because of the atrioventricular valves, which are forced shut with a "lub" sound.
- 3. Diastole.** The atria and the ventricles relax, while the atria fill with blood. The semilunar valves in the arteries close as the arterial blood pushes against them, making a "dup" sound.

The events of the three stages are shown in the chart below. The pressure changes show most clearly what is happening in each chamber. Blood flows because of pressure differences, and it **always flows from a high pressure to a low pressure**, if it can. So during atrial systole the atria contract, making the atrium pressure higher than the ventricle pressure, so blood flows from the atrium to the ventricle. The artery

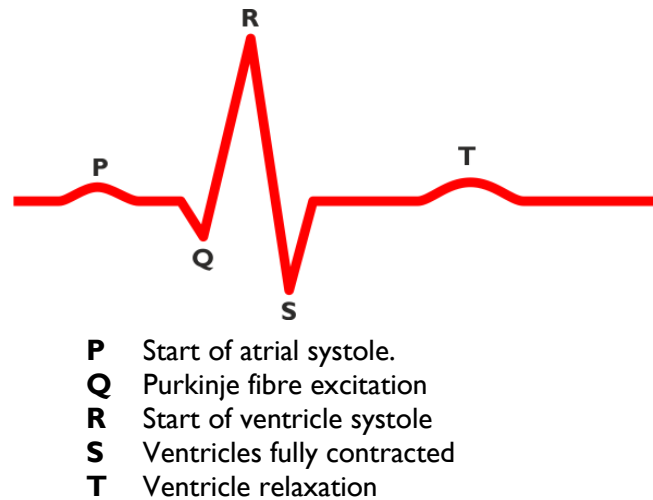
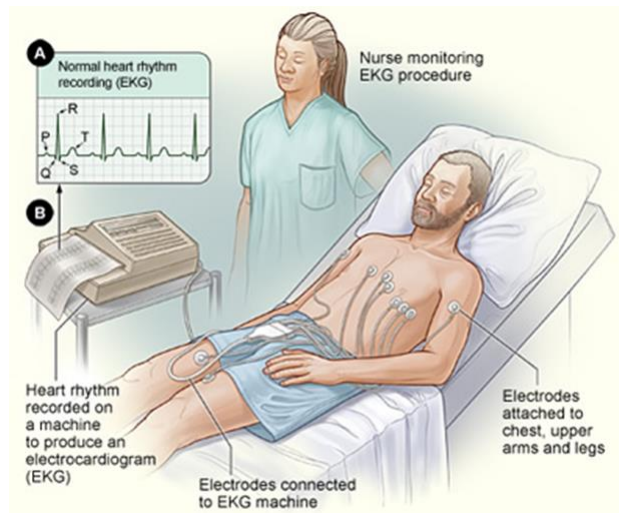
pressure is higher still, but blood can't flow from the artery back into the heart due to the semi-lunar valves. The valves are largely passive: they are opened by blood flowing through them the right way and are forced closed when blood tries to flow through them the wrong way. Whenever lines cross in the pressure graph it means that a valve opens or closes.



This diagram just shows one side of the heart. The two sides have identical traces except that the pressures in the right side are lower than those in the left side. The PCG (or phonocardiogram) is a recording of the sounds the heart makes. The cardiac muscle itself is silent and the sounds are made by the valves closing. The first sound (lub) is due to the atrioventricular valves closing and the second (dup) is due to the semi-lunar valves closing.

## Electrocardiogram (ECG)

The electrocardiogram (or ECG) is a recording of the electrical activity of the heart. It is made by placing ten electrode patches on the skin and recording electrical activity from the heart that reaches the skin. Although it is fairly crude, the ECG is simple and non-invasive. There is a characteristic pattern of peaks and troughs each cycle, labelled PQRS, which are caused by specific events in the cardiac cycle.



Changes in these ECG waves can be used to help diagnose problems with the heart, such as tachycardia (fast heartbeat) or myocardial infarction (heart attack).

## Cardiac Output

Cardiac Output is the amount of blood flowing through the heart each minute. It is calculated as the product of the heart rate and the stroke volume:

$$\text{cardiac output} = \text{heart rate} \times \text{stroke volume}$$

- The heart rate can be calculated from the pressure graph by measuring the time taken for one cardiac cycle and using the formula:

$$\text{heart rate (beats per minute)} = \frac{60}{\text{cycle time (s)}}$$

- The stroke volume is the volume of blood pumped in each beat.

Both the heart rate and the stroke volume can be varied by the body. When the body exercises the cardiac output can increase dramatically so that

- oxygen and glucose can get to the muscles faster
- carbon dioxide and lactate can be carried away from the muscles faster
- heat can be carried away from the muscles faster

	heart rate (beats min <sup>-1</sup> )	stroke volume (cm <sup>3</sup> beat <sup>-1</sup> )	cardiac output (cm <sup>3</sup> min <sup>-1</sup> )
at rest	75	75	5 600
at exercise	180	120	22 000

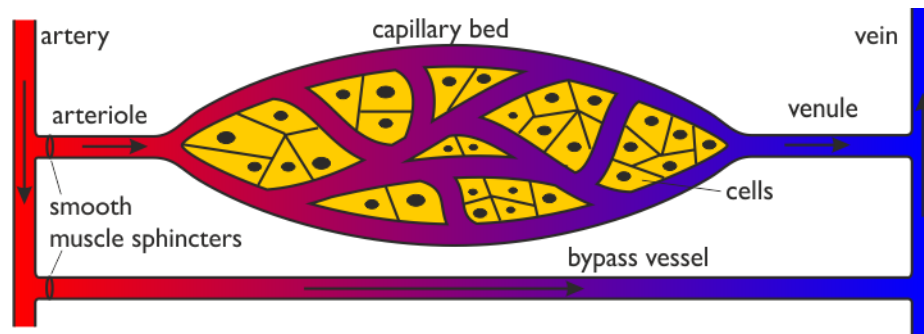


# Blood Vessels

Blood circulates in a series of different kinds of blood vessels as it circulates round the body.

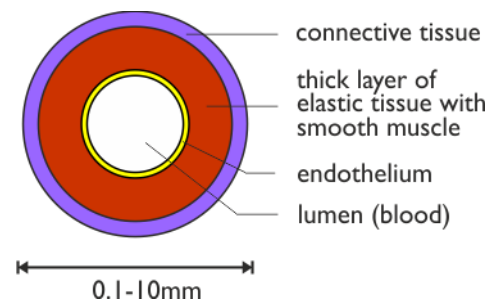
Heart → Aorta → Arteries → Arterioles → Capillaries → Venules → Veins → Vena Cava → Heart

The purpose of these different vessels is to deliver blood to capillary beds, where substances are exchanged between cells and blood. No cell in the body is more than 100µm away from a capillary.

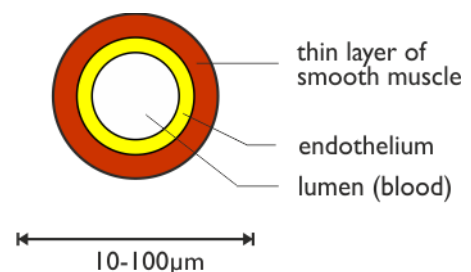


Each kind of vessel is adapted to its function.

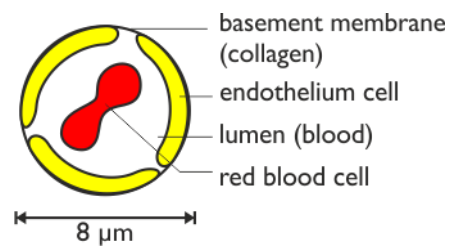
**Arteries** carry blood from the heart to every tissue in the body. They continually branch into smaller and smaller vessels. Arteries have thick walls (over 100 cells thick) composed mainly of elastic tissue allowing the artery to expand without bursting and so withstand the high pressure of blood from the heart. The arteries close to the heart are particularly elastic and expand during systole and recoil again during diastole, helping to even out the pulsating blood flow.



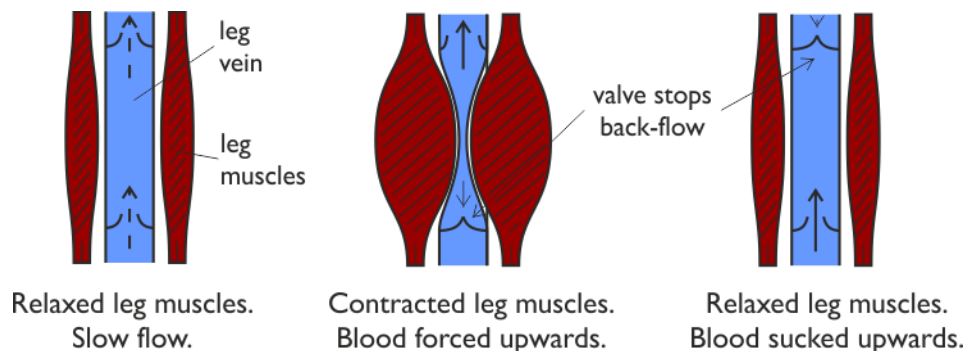
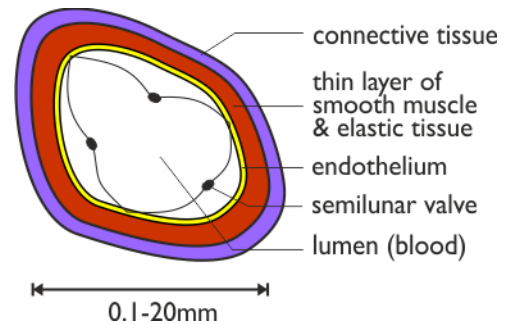
**Arterioles** are the smallest arteries. Each arteriole leads to one capillary bed. Arterioles have thinner walls (about 10 cells thick), composed mainly of smooth muscle tissue to regulate the blood flow to the capillary bed. The muscles can contract (vasoconstriction) to close off the capillary beds; or relax (vasodilation) to open up the capillary bed. These changes are happening constantly under the involuntary control of the medulla in the brain, and are most obvious in the capillary beds of the skin, causing the skin to change colour from pink (skin arterioles dilated) to blue (skin arterioles constricted). There is not enough blood to fill all the body's capillaries, and at any given time up to 20% of the body's capillary beds are closed off.



**Capillaries** are where the transported substances actually enter and leave the blood. Capillaries are very narrow and their walls are composed of single squamous endothelial cells with gaps between them, making capillaries very permeable. There are a vast number of capillaries ( $10^8$  m in one adult!), so they have a huge surface area : volume ratio, helping the rapid diffusion of substances between blood and cells.



**Veins** carry blood from every tissue in the body to the heart. The smallest veins, called venules, collect the blood from capillary beds and feed into larger veins. The blood has lost almost all its pressure in the capillaries, so it is at low pressure inside veins and is moving slowly. Veins therefore don't need thick walls and they have a larger lumen than arteries, to reduce the resistance to flow. They also have semi-lunar valves to stop the blood flowing backwards. It is particularly difficult for blood to flow upwards through the legs to heart, and the flow is helped by contractions of the leg and abdominal muscles:

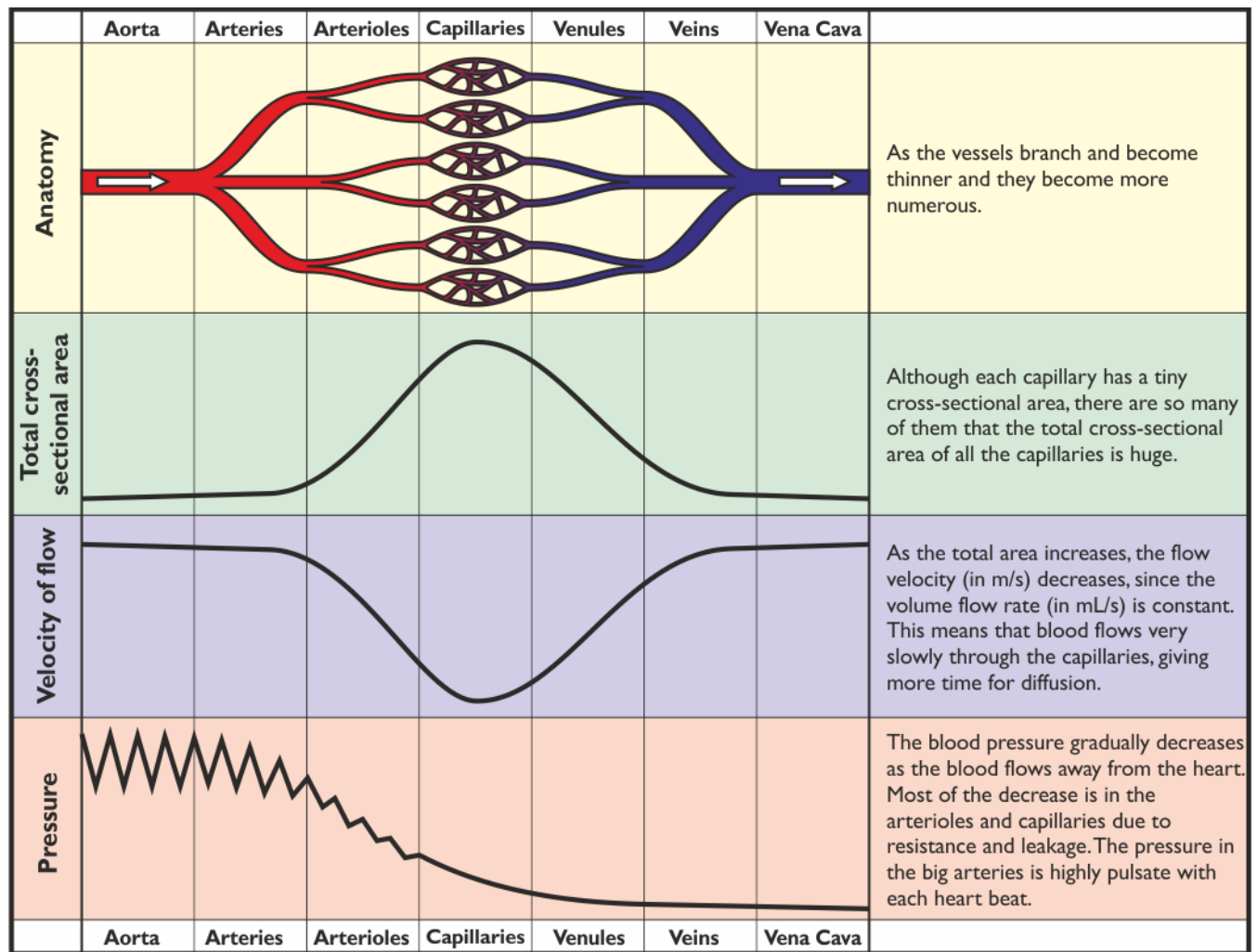


The body relies on constant contraction of these muscles to get the blood back to the heart, and this explains why soldiers standing still on parade for long periods can faint, and why sitting still on a long flight can cause swelling of the ankles and Deep Vein Thrombosis (DVT or “economy class syndrome”), where small blood clots collect in the legs.

Note the correct words:

<b>Muscles</b>	contract and relax
<b>Elastic tissues</b>	stretch and recoil
<b>Tubes</b>	constrict and dilate

This diagram shows some of the changes that take place as the blood flows round the body.

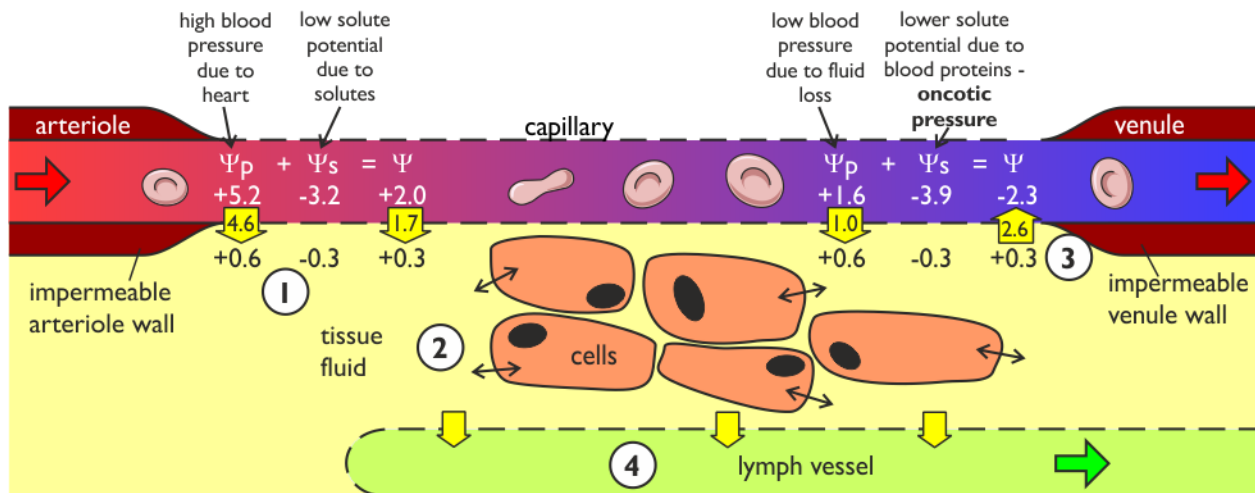


### Summary of Different Blood vessels

Arteries	Arterioles	Capillaries	Veins
Function is to carry blood from the heart to the tissues	Function is to carry blood from arteries to one capillary bed	Function is to allow exchange of materials between the blood and the tissues	Function is to carry blood from tissues to the heart
Thick walls with elastic layers to resist high pressure	Thick walls with smooth muscle to control flow to capillary bed	Very thin, permeable walls, only one cell thick to allow exchange of materials	Thin walls, mainly collagen, since blood at low pressure
Small lumen	Small lumen	Very small lumen. Blood cells must distort to pass through.	Large lumen to reduce resistance to flow
No valves (except in heart)	No valves	No valves	Many valves to prevent back-flow
Blood at high pressure	Blood pressure falls	Blood pressure falls	Blood at low pressure
Blood usually oxygenated (except in pulmonary circulation)	Blood usually oxygenated (except in pulmonary circulation)	Blood changes from oxygenated to deoxygenated (except in pulmonary circulation)	Blood usually deoxygenated (except in pulmonary circulation)

## Tissue Fluid (Interstitial Fluid)

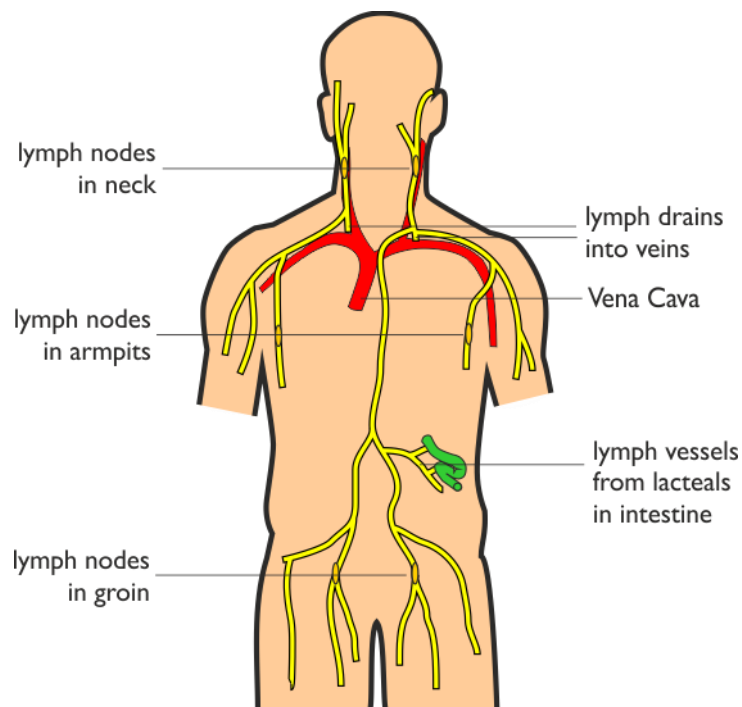
No exchange of materials takes place in the arteries and veins, whose walls are too thick and impermeable. Substances are all exchanged between the blood and the cells in capillary beds, but they do not actually move directly between the blood and the cell: they first diffuse into the tissue fluid (or interstitial fluid) that surrounds all cells, and then diffuse from there to the cells. Hydrostatic pressure, diffusion and osmosis all play a part in the formation and removal of tissue fluid.



1. At the arterial end of the capillary bed there is still fairly high hydrostatic pressure ( $\Psi_p$ ) in the blood, due to the contraction of the heart, so blood plasma is forced out through the permeable walls of the capillary. Cells and proteins are too big to leave the capillary, so they remain in the blood. There is also a water potential ( $\Psi$ ) gradient here, but it doesn't matter as the capillary wall is permeable to solutes, so osmosis cannot happen. So tissue fluid is formed by pressure filtration, not diffusion or osmosis.
2. This fluid now forms tissue fluid surrounding the cells. Materials are exchanged between the tissue fluid and the cells by all four methods of transport across a cell membrane: gases and lipid-soluble substances (such as steroids) cross by lipid diffusion; water crosses by osmosis; ions cross by facilitated diffusion; and glucose and amino acids cross by active transport.
3. At the venous end of the capillary bed there is a much lower hydrostatic pressure ( $\Psi$ ) in the blood, since it has lost so much plasma. There is also a lower solute potential ( $\Psi_s$ ) since the blood has lost a lot of water but retained its soluble proteins, so it is effectively a concentrated protein solution. This solute potential is called the oncotic pressure, since the pressure is due mainly to large proteins rather than small solutes.  $\Psi_p$  and  $\Psi_s$  combine to make a water potential ( $\Psi$ ) gradient back into the capillary, so most of the water returns to the blood down this gradient by osmosis. Solutes (such as carbon dioxide, urea, salts, etc.) are not affected by water potential, but also enter the blood by diffusion, down their individual concentration gradients.
4. Not all the fluid that left the blood returns to it, so there is excess tissue fluid. This excess drains into lymph vessels, which are found in all capillary beds. Lymph vessels have very thin walls, like capillaries, and tissue fluid can easily diffuse inside, forming lymph.

## The Lymphatic System

The lymphatic system consists of a network of lymph vessels flowing alongside the veins. The vessels lead towards the heart, where the lymph drains back into the blood system near the superior vena cava. There is no pump, but there are numerous semi-lunar valves, and lymph is helped along by contraction of body muscles, just as in veins.



The lymphatic system has three different functions:

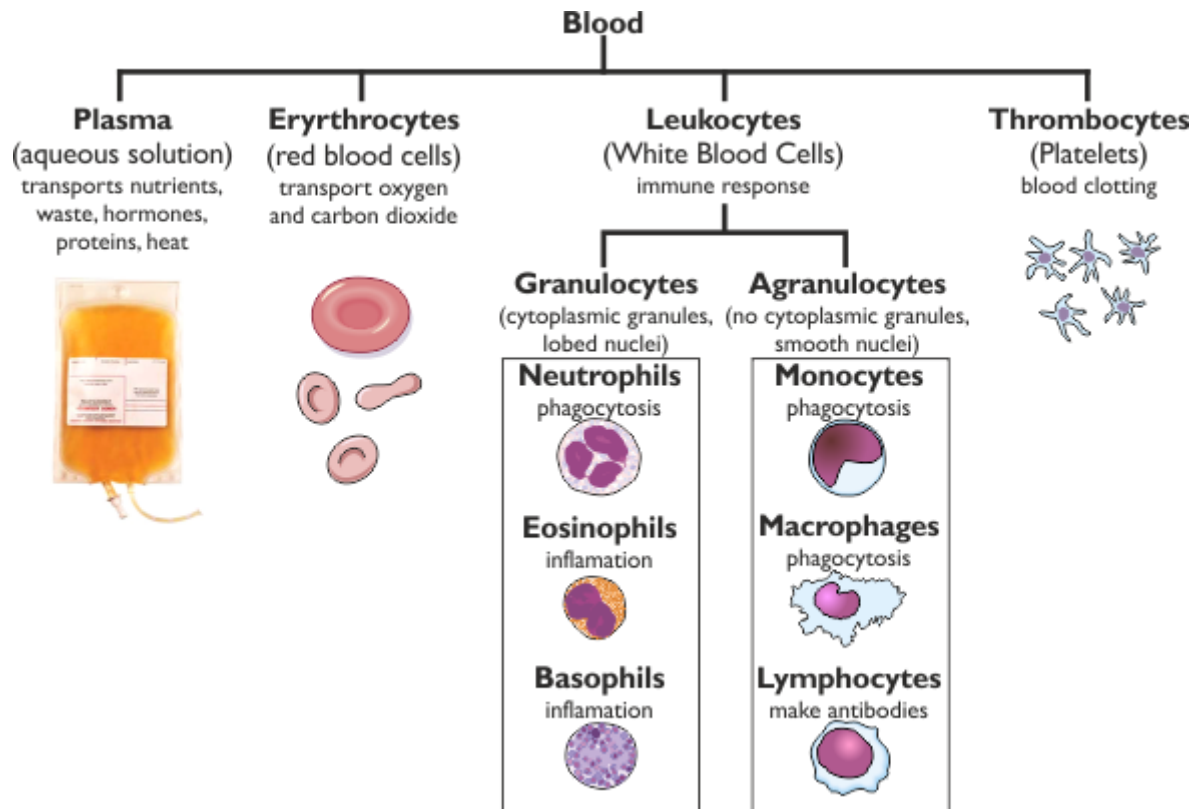
- It drains excess tissue fluid
- It absorbs fats from the small intestine, via the lacteals inside each villus.
- It is part of the immune system. There are networks of lymph vessels at various places in the body (such as tonsils and armpits) called lymph nodes where white blood cells develop. These become swollen if more white blood cells are required to fight an infection.

Remember the difference between these four fluids:

Plasma	The liquid part of blood. It contains dissolved glucose, amino acids, salts and vitamins; and suspended proteins and fats.
Serum	Purified blood plasma, with blood clotting proteins removed, used in hospitals for blood transfusions.
Tissue Fluid	The solution surrounding cells. Its composition is similar to plasma, but with fewer proteins (which stay in the blood capillaries).
Lymph	The solution inside lymph vessels. Its composition is similar to tissue fluid, but with more fats (from the digestive system).

# Blood

Blood is a complex mixture of solutes and cells. It is actually classed as a tissue, since it is composed of a number of similar cells, which are suspended in an aqueous solution called plasma. The main components are shown in this diagram:



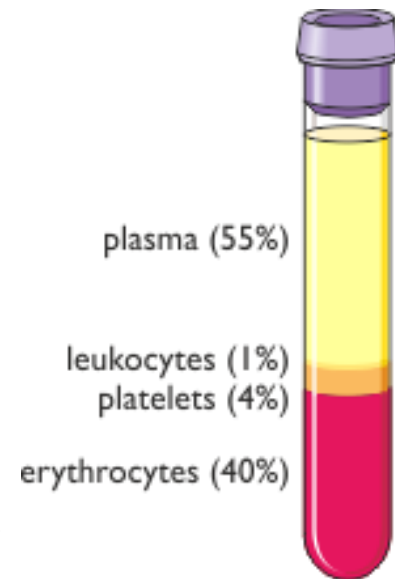
## Plasma

Plasma is the liquid part of blood, comprising about 55% of blood by volume. Plasma is a pale yellow-coloured aqueous solution containing numerous dissolved solutes, all being transported from one part of the body to another.

- Nutrients (e.g. glucose, amino acids, vitamins, lipids, nucleotides)
- Waste e.g. urea, lactic acid
- Ions (e.g.  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{HPO}_4^{2-}$ ,  $\text{SO}_4^{2-}$ ) These help control the solute potential of the blood and some also help buffer the blood pH.
- Hormones Transported from glands to target organs
- Proteins (eg albumins and blood clotting factors, antigens and antibodies)
- Water.
- Heat.

## Erythrocytes (Red Blood Cells)

Erythrocytes are by far the most numerous of the blood cells, with about 5 million in each  $\text{mm}^3$  of blood. Erythrocytes are formed from blood stem cells in the bone marrow (the soft centres of large hollow bones), and have a limited life of about 120 days. Mature erythrocytes lose their nuclei, mitochondria and other organelles and are just packed with the red protein haemoglobin. It is the erythrocytes that give blood its red colour.



## Leukocytes (White Blood Cells)

Leukocytes are larger than erythrocytes but there are far fewer of them (only 5000 per  $\text{mm}^3$  of blood). Like erythrocytes they are formed in bone marrow, but some finish developing in the lymph nodes or thymus gland. Leukocytes are all part of the immune system, killing pathogens in the blood and tissue fluid. We'll study leukocytes and the immune system in detail in Y13. There are several different kinds of leukocyte, usually classified by their appearance:

- **Granulocytes** have visible vesicles or granules in their cytoplasm containing signalling molecules that can control other parts of the immune system. They have characteristic lobed nuclei. They include neutrophils (which are phagocytes and comprise 70% of all white blood cells); eosinophils (which stain orange with the stain eosin and stimulate the inflammatory response); and basophils (which have a two-lobed nucleus and secrete histamines that stimulate inflammation).
- **Agranulocytes** have clear cytoplasm without granules and large unlobed nuclei. They include monocytes (which are large phagocytic cells); macrophages (which are phagocytes formed from monocytes); and lymphocytes (which are small leukocytes responsible for the specific immune response).

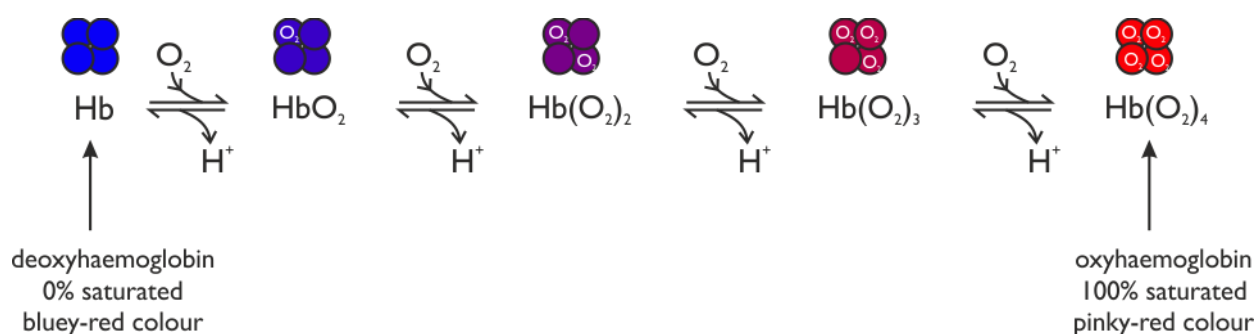
## Thrombocytes (platelets)

Platelets are cell fragments without nuclei, formed by fragmentation of large cells called megakaryocytes in the bone marrow. There are 400,000 platelets per  $\text{mm}^3$  of blood and they are responsible for blood clotting.

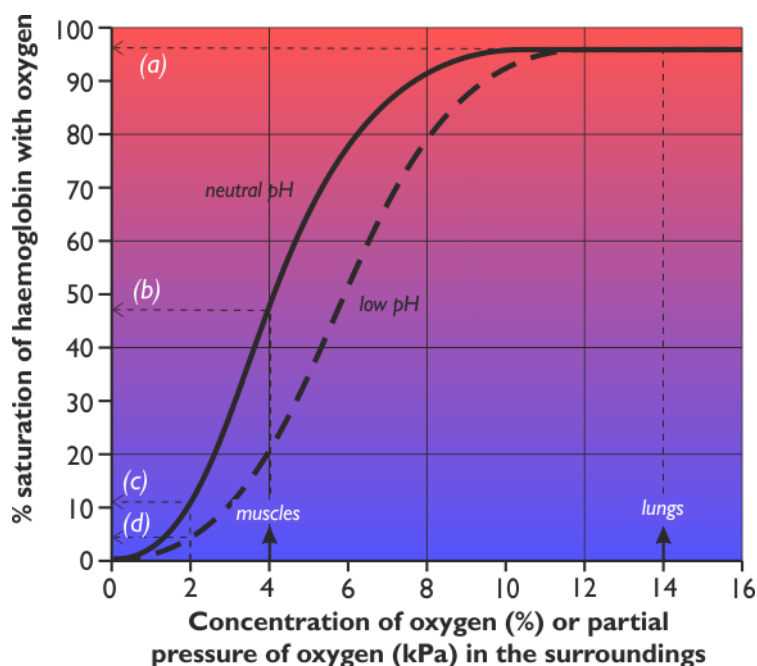


# Transport of Oxygen

Oxygen is carried in red blood cells bound to the protein haemoglobin. A red blood cell contains about 300 million haemoglobin molecules and there are 5 million red blood cells per  $\text{cm}^3$  of blood. The result of this is that blood can carry up to 20% oxygen, whereas pure water can only carry 1%. The haemoglobin molecule consists of four polypeptide chains, with a haem prosthetic group at the centre of each chain. Each haem group contains one iron atom, and one oxygen molecule binds to each iron atom. So one haemoglobin molecule can bind up to four oxygen molecules. This means there are 4 binding steps, as shown in this chemical equation:



A sample of blood can therefore be in any state from completely deoxygenated (0% saturated) to fully oxygenated (100% saturated). Since deoxyhaemoglobin and oxyhaemoglobin are different colours, it is easy to measure the % saturation of a sample of blood in a colorimeter. As the chemical equation shows, oxygen drives the reaction to the right, so the more oxygen there is in the surroundings, the more saturated the haemoglobin will be. This relation is shown in the oxygen dissociation curve:



The concentration of oxygen in the surroundings can be measured as a % (there's about 20% oxygen in air), but it's more correct to measure it as a partial pressure ( $PO_2$ , measured in kPa). Luckily, since the pressure of one atmosphere is about 100 kPa, the actual values for  $PO_2$  and % $O_2$  are the same (e.g. 12%  $O_2$  has a  $PO_2$  of 12 kPa).



The graph is read by starting with an oxygen concentration in the environment surrounding the blood capillaries on the horizontal axis, then reading off the state of the haemoglobin in the blood that results from the vertical axis.

This curve has an S (or sigmoid) shape, and shows several features that help in the transport of oxygen in the blood:

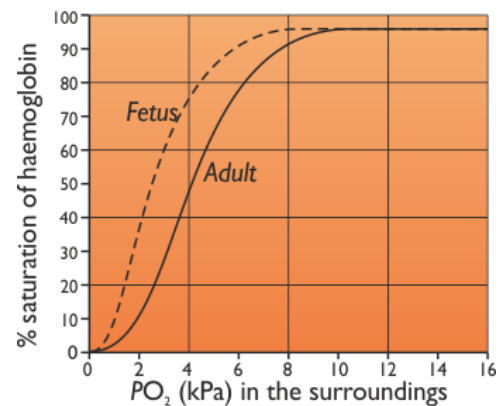
- In the alveoli of the lungs oxygen is constantly being brought in by ventilation, so its concentration is kept high, at around 14 kPa. As blood passes through the capillaries surrounding the alveoli the haemoglobin binds oxygen to become almost 100% saturated (point *a*). Even if the alveolar oxygen concentration falls a little the haemoglobin stays saturated because the curve is flat here.
- In tissues like muscle, liver or brain, oxygen is used by respiration, so its concentration is low, typically about 4 kPa. At this  $PO_2$  the haemoglobin is only 50% saturated (point *b*), so it unloads about half its oxygen (i.e. from about 100% saturated to about 50% saturated) to the cells, which use it for respiration.
- In tissues that are respiring quickly, such as contracting muscle cells, the  $PO_2$  drops even lower, to about 2 kPa, so the haemoglobin saturation drops to about 10% (point *c*), so almost 90% of the oxygen is unloaded, providing more oxygen for the muscle cells.
- Actively-respiring tissues also produce a lot of  $CO_2$ , which dissolves in tissue fluid to make carbonic acid and so lowers the pH. The chemical equation on the previous page shows that hydrogen ions drive the reaction towards the deoxyhaemoglobin state, so low pH reduces the % saturation of haemoglobin at any  $PO_2$ . This is shown on the graph by the dotted line, which is lower than the normal dissociation curve. This downward shift is called the Bohr effect, after the Danish scientist who first discovered it. So at a  $PO_2$  of 2kPa, the actual saturation is nearer 5% (point *d*), so 95% of the oxygen loaded in the lungs is unloaded in respiring tissues.

Remember that oxygen can only diffuse in and out of the blood from capillaries, which are permeable. Blood in arteries and veins is “sealed in”, so no oxygen can enter or leave the blood whatever the conditions surrounding the blood vessel. So as haemoglobin travels from the lungs to a capillary bed in a body tissue and back to the lungs, it “switches” from one position on the dissociation curve to another position, without experiencing the intermediate stages of the curve.

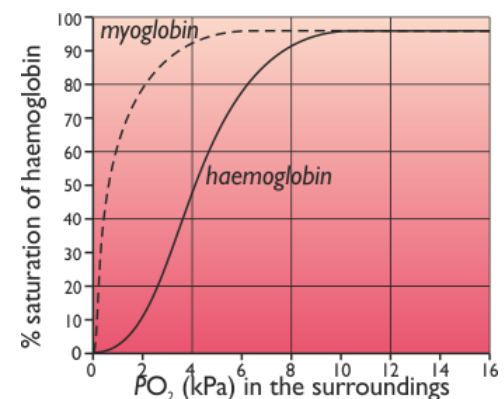
## Different Haemoglobins

Different animals possess different types of haemoglobin with different oxygen transporting properties. These properties are related to the animal's way of life, so they are an adaptation that helps the animal survive in its environment.

A **human fetus** obtains its oxygen from the placenta not the lungs. In the placenta the mother's and fetus's capillary beds are intertwined (but the bloods don't mix). Fetal haemoglobin is a different kind from the "adult" form, with a higher affinity for oxygen at low partial pressures, so its oxygen dissociation curve is shifted up. So this different haemoglobin allows oxygen to diffuse from the mother's blood to the fetus, yet still be unloaded in the fetal tissues. Fetal haemoglobin is gradually replaced by "adult" haemoglobin during the first year after birth.



Myoglobin is a protein found only in muscle cells. It is like a single haemoglobin chain, with a single haem group, and it also binds oxygen. It is myoglobin that gives red meat its colour. As the dissociation curve shows, myoglobin has a higher affinity for oxygen, especially at low partial pressures. So in muscle cells oxygen will unload from haemoglobin and bind to myoglobin. Oxygen will only be unloaded from myoglobin at very low partial pressures, when muscle cells are respiring rapidly. So myoglobin acts as an oxygen store, making oxygen available when needed.

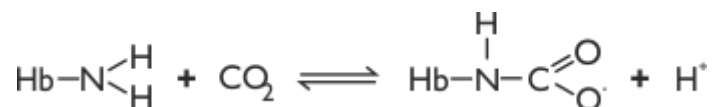


# Transport of Carbon Dioxide

Carbon dioxide is carried between respiring tissues and the lungs by two main methods:

## 1. As Carbamino Haemoglobin (13%)

Carbon dioxide can bind to amino groups in haemoglobin molecules, forming carbamate ions:



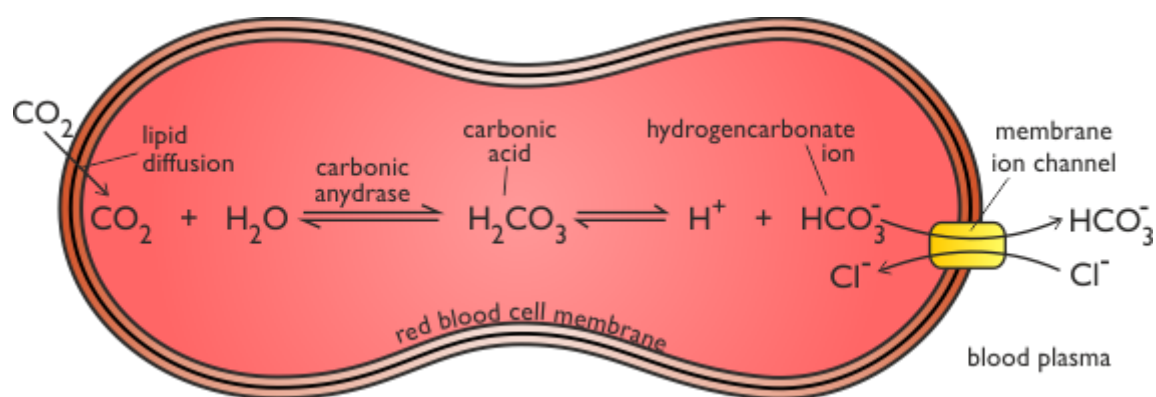
Since there are so many haemoglobin molecules in red blood cells, and each one has many amino groups, quite a lot of  $\text{CO}_2$  can be carried this way.

## 2. As Hydrogen Carbonate ions (85%)

Carbon dioxide reacts with water to form carbonic acid, which immediately dissociates to form a hydrogen carbonate (or bicarbonate) ion and a proton ( $\text{H}^+$ ).



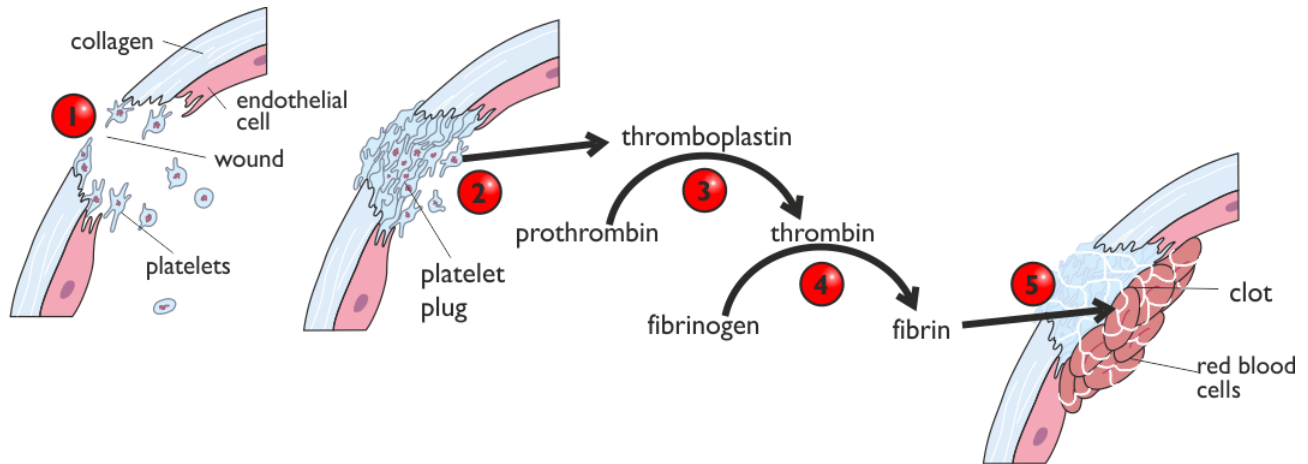
Hydrogen carbonate is very soluble, so a lot of  $\text{CO}_2$  can be carried this way. However, the reaction in water is very slow, but fortunately red blood cells contain the enzyme carbonic anhydrase, which catalyses the reaction with water by a factor of  $10^8$  times.



In both cases the reactions are reversible and the direction of the reactions is governed by the  $\text{CO}_2$  concentration (remember enzymes will catalyse reactions in either direction). So in most tissues, where  $\text{CO}_2$  is high due to respiration, the reactions go to the right, absorbing  $\text{CO}_2$ . In the lungs, where  $\text{CO}_2$  is low due to ventilation, the reactions go to the left, releasing  $\text{CO}_2$ . In tissues a proton is released by these reactions, so this lowers the pH of actively respiring tissues. This proton binds to haemoglobin, and is the cause of the Bohr effect. The low pH is also one cause of muscle fatigue.

# Blood Clotting (haemostasis)

Any cut in the skin that reaches a blood vessel is potentially very hazardous, since blood could be lost to the outside and pathogens could get in. So one of the most important jobs of blood is to quickly seal any wound or injury. This process is called blood clotting, blood coagulation, or haemostasis.

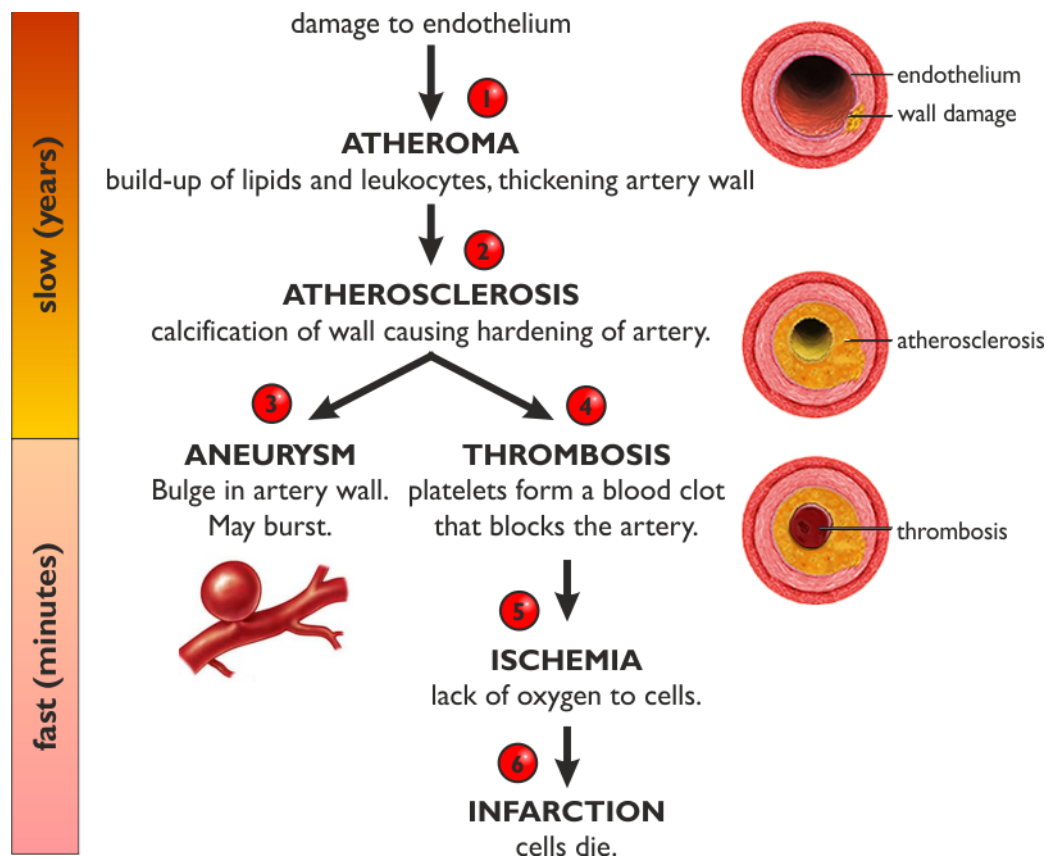


1. Clotting is initiated when blood starts to leak out of a blood vessel. The platelets in the blood come into contact with collagen fibres outside the endothelial cells lining the blood vessels and this contact causes the platelets to secrete chemical messengers.
2. The messengers attract more platelets and then cause the platelets to change shape and stick together at the wound to form a platelet plug. The plug blocks the gap temporarily and the activated platelets in the plug release the enzyme thromboplastin.
3. Thromboplastin catalyses the conversion of the plasma protein prothrombin into another enzyme thrombin.
4. Thrombin catalyses the conversion of another soluble plasma protein fibrinogen into the insoluble fibrous protein fibrin.
5. Fibrin forms strong fibres between the platelets in the plug. This fibre mesh makes the plug stronger and also traps red blood cells to form a large solid clot (or thrombus) that seals the wound. The clotting process also stimulates cell division in the surrounding tissue, causing the wound to gradually heal permanently.

This sequence of events may seem complicated but it serves the very useful purpose of amplification. Imagine each platelet releases 10 molecules of thromboplastin every second; each thromboplastin releases 10 molecules of thrombin; and each thrombin releases 10 molecules of fibrin. Each step amplifies the response 10 times, so overall each platelet releases 1000 fibrin molecules. So this complicated cascade mechanism ensures that a clot is formed much more quickly than a simpler mechanism. In fact this is a simplified version of the clotting cascade and the real cascade has at least 13 steps!

# Cardiovascular Disease

Cardiovascular disease (CVD) is a general term that describes a disease of the heart or blood vessels. Cardiovascular diseases include coronary heart disease, stroke, peripheral arterial disease, and aortic disease, and are responsible 33% of all deaths in the UK, more than any other single cause. Cardiovascular disease is usually caused by blocked arteries due to atherosclerosis – hardening of the arteries.



1. The sequence starts with damage to an artery, caused by factors such as high blood pressure, tobacco smoke or just age. The damage causes cholesterol and other insoluble lipids to collect in the wall of the artery and stimulates an inflammatory response, where leukocytes collect at the site of the damage. Together these form a plaque or atheroma, which narrows the lumen of the artery, restricting blood flow and raising blood pressure.
2. Over time the atheroma can collect minerals (like calcium) and become calcified, hardening the wall of the artery and making it less elastic. This hardening is atherosclerosis.
3. The atherosclerosis weakens the wall of the artery, so the pressure of blood causes a local swelling called an aneurism. If the wall is particularly weak the aneurism may burst causing blood loss and probable death.
4. The atherosclerosis stimulates the platelets to initiate the blood clotting cascade, so a blood clot forms inside the artery, called a thrombosis. The thrombosis can grow quickly to block the whole artery.

Alternatively, the clot can break loose to form an embolism which travels round the bloodstream and may become lodged elsewhere.

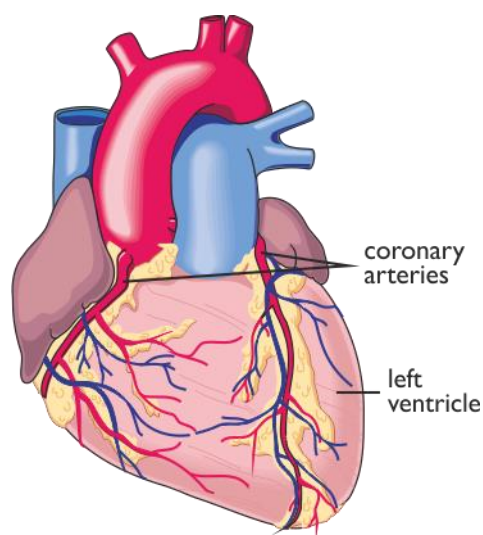
5. If the thrombosis blocks the artery then oxygen will not reach the cells “downstream” of the blockage. This is called ischaemia and the cells cannot respire aerobically.

6. If the ischemia is prolonged the cells will die. This death is called an infarction. The severity of the infarction depends on the location of the thrombosis. If it is on a small artery then only a few cells will die, but if it is on a large artery to an important organ then the infarction could be fatal.

Atherosclerosis can occur in any artery and so infarctions can affect any tissue. But the two most important and serious examples are in the arteries feeding the heart and the brain.

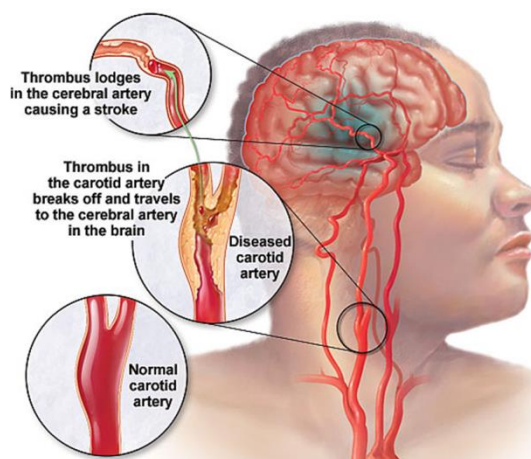
### Myocardial Infarction (Heart Attack).

A myocardial infarction or heart attack is caused by atherosclerosis in a coronary artery. These are the arteries on the surface of the heart that feed the cardiac muscle cells so that they can respire and contract. There are two coronary arteries that arise directly from the aorta, and these split into numerous smaller arteries and arterioles and finally a network of capillaries, where exchange with the cardiac cells actually takes place. Cardiac muscle is incapable of anaerobic respiration so a myocardial infarction quickly kills the affected cells. The severity of the heart attack depends on how far along the coronary artery the thrombosis is. If only a small part of one ventricle is killed then the patient will recover, but a thrombosis early in the coronary artery will always be fatal.



### Stroke

A stroke is caused by atherosclerosis in an artery in the brain. There are two carotid arteries carrying blood from the aorta to the head and these split into cerebral arteries in the brain. Like cardiac muscle, the brain is incapable of anaerobic respiration so an infarction quickly kills the affected brain cells. A small infarction that kills just a few brain cells may affect specific brain functions, such as speech, memory, or paralysis of a particular part of the body. But a blockage in large artery to the brain is likely to be fatal.



## Risk Factors for Cardiovascular Disease

There are a number of risk factors that can increase the likelihood of coronary heart disease. The more of the factors that apply, the greater the risk of a heart attack. The factors can be classified in two groups – non-modifiable risks (that cannot be changed) and modifiable risks (that can be changed):

### Non-modifiable Risk factors

- **Genetics.** Your genes affect all your characteristics, including susceptibility to disease. Genes affect characteristics like blood pressure and fat metabolism, so genes undoubtedly affect the chance of atherosclerosis and cardiovascular disease. This doesn't mean that, for some people, CVD is inevitable; it just means some people have to be even more careful about their lifestyle risk factors.
- **Age.** Blood vessels lose their elasticity with age and are more likely to accumulate minor damage, so atherosclerosis and CVD are more likely.
- **Sex.** Statistics show that men are significantly more likely to develop atherosclerosis and CVD than women. This is probably due to the presence of oestrogen in the blood, which reduces the build-up of cholesterol.

### Modifiable Risk factors

- **Smoking.** Smokers are between two and six times more likely to suffer from CVD than non-smokers, so there is a strong correlation. There is also causation: nicotine in cigarette smoke increases heart rate and blood pressure, increasing the risk of atherosclerosis.
- **Diet.** High levels of saturated fat increase the amount of cholesterol carried in the blood and so increase the risk of atherosclerosis. High levels of salt increase blood pressure and so increase the risk of aneurism. However, dietary fibre and vitamin C reduce the risk of heart disease.
- **Stress.** Stress causes the release of cytokines that trigger an inflammatory response in blood vessels leading to atheroma. It also raises blood pressure.